

Dysregulated Coagulation in Haemodialysis - Vascular access and Cerebrovascular disease

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Abstract

Uraemia confers a prothrombotic tendency in tandem with a bleeding diathesis through platelet dysfunction that is most evident in patients with renal failure who are dependent on haemodialysis. This form of renal replacement therapy accentuates this clinical paradox by its procoagulant nature and the use of regular anticoagulation to prevent dialysis circuit and vascular access thrombotic dysfunction. This thesis evaluates such dysregulated coagulation in the extracorporeal circuit, the central venous catheter and dialyser, and in the twin substrates of cerebrovascular disease, thromboembolism and haemorrhage.

Firstly the comparative effect of catheter site on thrombosis is evaluated by the jugular and translumbar routes before examining catheter type as a determinant in a randomised, controlled clinical trial. Subsequently novel use of catheter flow monitoring as a predictive tool for thrombotic dysfunction is presented and the efficacy of thrombolytic therapies assessed. Lastly a prospective pharmacokinetic evaluation of tinzaparin in dialysis circuit anticoagulation which revealed a novel influence of gender on anti-factor Xa activity.

Stroke incidence and risk is examined in one of the largest studies to date before two specific risk factors for thromboembolic stroke are examined, intracranial arterial calcification and transient ischaemic attack. A potential association between intracranial arterial calcification and this stroke subtype is described for the first time in haemodialysis and results from the first prospective screening study for transient ischaemic attack in haemodialysis are presented. Finally renal dysfunction is shown to be a determinant of thrombolytic efficacy in acute ischaemic stroke.

All these studies advance our understanding of thrombotic catheter dysfunction, its thrombolytic management and the behaviour of tinzaparin in haemodialysis. In addition they afford unique insights into cerebrovascular disease in haemodialysis that challenge traditional paradigms of a pathology with high incidence in these patients.

TABLE OF CONTENTS

Acknowledgements	10
Contributors	11
Index of Figures.....	12
Index of Tables	14
Abbreviations	16
1. General introduction	19
1.1. Overview of chronic kidney disease	20
1.1.1. Definitions.....	20
1.1.2. Dialysis for end-stage renal disease.....	21
1.1.3. Vascular Access for Haemodialysis.....	22
1.2. Coagulation in clinical practice.....	24
1.2.1. The physiology of coagulation.....	24
1.2.2. Therapeutics of anticoagulation	29
1.3. Anticoagulation in haemodialysis	32
1.3.1. Haemodialysis circuit anticoagulation.....	32
1.3.2. Prevention of catheter thrombosis	33
1.3.3. Thrombolytics for catheter dysfunction.....	34
1.3.4. Uraemia and coagulation.....	36
1.4. Cerebrovascular disease and renal impairment	38
1.4.1. Stroke is a cerebral vascular disease.....	38
1.4.2. Renal impairment as a vascular risk factor	39
1.4.3. Cerebrovascular disease in end-stage renal disease	40
1.5. Conclusions and thesis outline.....	41
2. Catheter site as a determinant of CVC thrombosis	42
2.1. Introduction	43
2.1.1. CVC insertion technique and choice of site	43
2.1.2. Understanding and assessing catheter function.....	44
2.1.3. Fibrin sheath formation and thrombosis	45
2.1.4. Clinical management of catheter dysfunction	46

2.1.5.	The TesioCath™ twin catheter system for haemodialysis	46
2.1.6.	The translumbar approach to CVC placement.....	46
2.2.	Methods	48
2.2.1.	Subjects and data abstraction	48
2.2.2.	Approach to central venous catheter use	49
2.2.3.	Protocol and technique of CVC insertion	50
2.2.4.	CVC care and microbiological screening	51
2.2.5.	Dialysis adequacy and protocols.....	52
2.2.6.	Definitions of infective episodes and management protocols.....	53
2.2.7.	Statistical methods	54
2.3.	Results	56
2.3.1.	Internal jugular CVCs	56
2.3.2.	Translumbar CVCs.....	61
2.4.	Conclusions	65
2.4.1.	Internal jugular CVCs	65
2.4.2.	Translumbar CVCs.....	69
2.4.3.	Study limitations.....	71
2.4.4.	Influence of access site.....	72
3.	Catheter type as a determinant of CVC thrombosis	73
3.1.	Introduction	74
3.1.1.	Catheter design and function.....	74
3.1.2.	TesioCath™ performance.....	75
3.1.3.	LifeCath Twin™ central venous catheter	77
3.1.4.	Procoagulant profiles and catheter function.....	79
3.1.5.	Hypotheses and aims of the study	80
3.2.	Methods	81
3.2.1.	Study design and participants	81
3.2.2.	Catheter insertion and periprocedural care	81
3.2.3.	Haemodialysis prescription and targets.....	82
3.2.4.	Catheter care protocols.....	84
3.2.5.	Mechanical complications – definitions and management.....	84
3.2.6.	Infective complications – definitions and management.....	85
3.2.7.	Procoagulant profile testing	85
3.2.8.	Outcomes and sample size calculation	86

3.2.9.	Statistical methods	86
3.3.	Results	88
3.3.1.	Cohort characteristics	88
3.3.2.	Catheter function	89
3.3.3.	Patient survival and hospitalisation.....	91
3.3.4.	Infective complications.....	92
3.3.5.	Prevalence of procoagulant profiles.....	92
3.4.	Conclusions	94
3.4.1.	Thrombotic catheter dysfunction	94
3.4.2.	Catheter blood flow rates	95
3.4.3.	Patient survival and complications.....	96
3.4.4.	The role of procoagulants	97
3.4.5.	The influence of CVC design on thrombotic dysfunction	97
4.	Thrombotic catheter dysfunction, thrombolytics and flow monitoring	98
4.1.	Introduction	99
4.1.1.	Defining catheter dysfunction	99
4.1.2.	Catheter locking solutions.....	99
4.1.3.	Thrombolytics for catheter dysfunction.....	101
4.1.4.	Urokinase for CVC dysfunction	102
4.1.5.	Catheter flow monitoring in practice.....	103
4.1.6.	Hypotheses and aims of the study	105
4.2.	Methods	106
4.2.1.	Study design and participants	106
4.2.2.	Definitions of catheter dysfunction	107
4.2.3.	Thrombolytic management of catheter dysfunction.....	107
4.2.4.	Derivation of the CathRisk index.....	107
4.2.5.	Statistical methods	107
4.3.	Results	109
4.3.1.	Cohort characteristics	109
4.3.2.	Catheter dysfunction	110
4.3.3.	Catheter performance characteristics.....	112
4.3.4.	Predictors of thrombotic dysfunction.....	115
4.4.	Conclusions	117
4.4.1.	Catheter function and outcomes	117

4.4.2.	Efficacy of thrombolytic therapy	120
4.4.3.	Catheter flow monitoring	122
4.4.4.	Study limitations.....	122
4.4.5.	Future considerations.....	123
5.	Tinzaparin pharmacokinetics in haemodialysis circuit anticoagulation ...	124
5.1.	Introduction	125
5.1.1.	Low molecular weight heparins in ESRD	125
5.1.2.	Pharmacokinetic monitoring	126
5.1.3.	Study rationale and aims	127
5.2.	Methods	128
5.2.1.	Subjects.....	128
5.2.2.	Study protocol.....	129
5.2.3.	Sample analysis.....	130
5.2.4.	Statistical analysis	131
5.3.	Results	132
5.3.1.	Study cohort demographics.....	132
5.3.2.	Anti-Xa activity profile.....	132
5.3.3.	Determinants of 1-hour anti-Xa activity	135
5.3.4.	Effect of tinzaparin on routine coagulation parameters.....	135
5.3.5.	Effect of tinzaparin on antithrombin-III levels	136
5.3.6.	Safety and efficacy	137
5.4.	Conclusions	138
5.4.1.	Comparative assessments of anti-Xa activity	138
5.4.2.	Pleiotropic effects of tinzaparin	139
5.4.3.	Effect of gender	140
5.4.4.	Changes in antithrombin-III and fibrinogen	140
5.4.5.	Study limitations.....	141
5.4.6.	Future considerations.....	141
6.	Determinants of stroke risk in maintenance haemodialysis	142
6.1.	Introduction	143
6.1.1.	Epidemiology of stroke in ESRD	143
6.1.2.	Prevalence of stroke subtypes	145
6.1.3.	Risk factors for stroke in ESRD.....	145
6.1.4.	Aims of the study	146

6.2. Methods	147
6.2.1. Study design	147
6.2.2. Study variables and definitions	147
6.2.3. Outcome measures	147
6.2.4. Statistical methods	148
6.3. Results	150
6.3.1. Characteristics of study cohort	150
6.3.2. Overall stroke incidence	150
6.3.3. Ischaemic and haemorrhagic strokes	152
6.3.4. Risk of incident stroke	154
6.3.5. Mortality after acute stroke	155
6.4. Conclusions	158
6.4.1. Incidence of stroke	158
6.4.2. Haemorrhagic and ischaemic stroke subtypes	159
6.4.3. Impact of stroke on patient survival	160
6.4.4. Risk factors for stroke in HD	161
6.4.5. Study limitations	162
6.4.6. Perspectives for future evaluation	163
7. Intracranial arterial calcification and ischaemic stroke	165
7.1.1. Overview of the biology of arterial calcification	166
7.1.2. End-stage renal disease promotes vascular calcification	167
7.1.3. Clinical effects of vascular calcification	168
7.1.4. Intracranial arterial calcification and stroke	169
7.1.5. Hypotheses and aims of the study	169
7.2. Methods	171
7.2.1. Study design	171
7.2.2. Study variables and definitions	172
7.2.3. Scoring of IAC	172
7.2.4. Statistical methods	174
7.3. Results	176
7.3.1. Clinical factors associated with IAC	176
7.3.2. Clinical factors influencing severity of IAC	176
7.3.3. IAC severity as a predictor of acute ischaemic stroke	177
7.3.4. IAC severity and association with patient survival	178

7.4. Conclusions	179
7.4.1. High prevalence of IAC	179
7.4.2. Factors influencing burden of IAC	180
7.4.3. IAC and acute ischaemic stroke	181
7.4.4. Study limitations	182
7.4.5. Future considerations	182
8. Screening for transient ischaemic attack in haemodialysis	184
8.1. Introduction	185
8.1.1. Defining transient ischaemic attacks (TIA)	185
8.1.2. Clinical relevance of TIA	185
8.1.3. Risk scoring for TIA	186
8.1.4. Hypotheses and aims of the study	187
8.2. Methods	188
8.2.1. Study design	188
8.2.2. Screening questionnaire	189
8.3. Results	190
8.3.1. Study cohort	190
8.4.1. Incidence of TIA in haemodialysis	192
8.4.2. Questionnaire validity	193
8.4.3. Future considerations	194
9. Thrombolysis for acute ischaemic stroke and renal impairment	195
9.1.1. Thrombolysis for acute ischaemic stroke	196
9.1.2. Measures of efficacy of thrombolysis	197
9.1.3. Safety of systemic thrombolysis in ESRD	198
9.1.4. Efficacy of thrombolysis in CKD	199
9.1.5. Hypotheses and aims of the study	199
9.2. Methods	201
9.2.1. Study design	201
9.2.2. Thrombolytic therapy	202
9.2.3. Outcome measures	204
9.2.4. Statistical methods	204
9.3. Results	205
9.3.1. Study cohort	205
9.3.2. Efficacy of thrombolytic therapy	206

9.3.3.	Complications of thrombolysis.....	207
9.3.4.	Hospitalisation and discharge destination	208
9.4.	Conclusions	209
9.4.1.	Renal function affects outcome after thrombolysis.....	209
9.4.2.	Incidence of intracranial haemorrhage	210
9.4.3.	Mortality with thrombolysis.....	211
9.4.4.	Study limitations.....	211
9.4.5.	Future approaches	211
10.	Appendices	213
10.1.	Tinzaparin use for maintenance haemodialysis	213
10.2.	TIA screening questionnaire.....	214
10.3.	ABCD2 scoring template	215
10.4.	Publications deriving from this work	216
11.	References	253

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Index of Figures

1.1	Growth in number of prevalent dialysis patients in the UK (1982-2009) according to modality	22
1.2	Schematic representation of platelet and blood vessel endothelium interactions	25
1.3	The coagulation cascade	26
1.4	Fibrinolytic cascade	28
1.5	Relationship between blood flow rate and urea clearance at different dialysate flow rates for a theoretical dialyser	32
1.6	Schematic representation of recirculation	35
2.1	Cumulative patient survival for internal jugular CVC cohort	57
2.2	Cumulative assisted primary internal jugular CVC site patency	58
2.3	Prior CVC history in patients presenting to surgical or interventional radiology teams for CVC insertion	59
2.4	Dialysis adequacy (spKt/V) achieved by translumbar CVCs over the time of the study	62
2.5	Cumulative assisted primary catheter site patency for translumbar TesioCaths	63
3.1	The LifeCath Lock device	77
3.2	LifeCath Twin™ catheters	78
3.3	VyTes trial flow diagram	83
3.4	Maximal flow rates during the first six haemodialysis (HD) sessions following CVC insertion	89
3.5	Maximal achieved flow rates from both CVCs during 12 months of follow up	90
4.1	Distribution of blood flow rates achieved by study cohort	110
4.2	Relationship between pre-treatment BFR and improvement in flow rates with urokinase locking	111
4.3	Performance of TesioCaths in catheter-naïve patients	112
4.4	Trends in BFR:AP performance ratios in two newly inserted CVCs	113
4.5	Performance characteristics of a failing CVC and effect of catheter replacement on performance parameters	114

4.6	Changes in BFR:AP ratio with time in a dysfunctional CVC requiring thrombolytic therapy	115
4.7	Changes in performance parameters of two catheter types at defined nominal blood flow rates (Qb)	118
5.1	Anti-Xa activity of tinzaparin across different weight bands	133
5.2	Variation in anti-Xa activity of tinzaparin with ethnicity	134
5.3	Effect of gender on anti-Xa activity after adjusting for weight	134
5.4	Influence of gender and weight on 1-hour anti-Xa activity	135
5.5	Correlation between APTT and anti-Xa activity	136
5.6	Effect of gender on antithrombin-III levels	137
6.1	Effect of renal impairment according CKD stage on stroke incidence (from USRDS 2009 Report)	143
6.2	Actuarial survival of haemodialysis patients after acute stroke	155
7.1	Overview of study groups and CT imaging selection	171
7.2	CT calcification patterns, from paper by Woodcock et al. (1999)	174
7.3	Effect of haemodialysis vintage on IAC load	177
8.1	Renal function in patients referred to a local TIA clinic	193

Index of Tables

1.1	Classification of stages of chronic kidney disease	20
2.1	Protocols for empirical treatment of access-related infections	53
2.2	Internal jugular CVC cohort demographics	56
2.3	Regression analysis of factors affecting primary assisted TesioCath™ site patency	60
2.4	Translumbar study cohort characteristics	61
2.5	Infective and mechanical complications of translumbar CVCs	64
2.6	Major studies examining outcomes with the TesioCath™ system for maintenance haemodialysis	65
2.7	Summary of studies using urokinase infusion for CVC dysfunction	68
2.8	Summary of major studies reporting on series of translumbar CVCs for haemodialysis	69
2.9	Comparative outcomes using the TesioCath™ system for haemodialysis via the internal jugular and translumbar routes	72
3.1	Summary of published RCTs to date comparing function in tunnelled CVCs for haemodialysis	75
3.2	Baseline characteristics of VyTes study participants	88
3.3	Secondary outcomes in the VyTes study	91
3.4	Procoagulant antibody results in VyTes	93
4.1	Summary of clinical studies reporting on urokinase for CVC dysfunction (1995-2011)	104
4.2	Thrombolytics and CVC performance cohort characteristics	109
4.3	Predictors of thrombotic dysfunction requiring urokinase	116
4.4	Incidence of thrombotic catheter dysfunction in major studies of CVCs inserted via conventional routes	119
5.1	Pharmacokinetic studies of tinzaparin in HD circuit anticoagulation	127
5.2	Inclusion and exclusion criteria for tinzaparin evaluation	129
5.3	Tinzaparin study protocol including sample collections	130

5.4	Mean dry weights of tinzaparin study groups according to ethnicity	132
5.5	Comparative anti-Xa activity between our study and the study by Hainer et al. (2002)	133
6.1	Major published studies on stroke incidence in haemodialysis patients	144
6.2	Comparative demographics of study cohorts	151
6.3	Patient characteristics and clinical features at time of stroke according to subtype	153
6.4	Risk factors for first (incident) stroke	154
6.5	Association of new acute stroke and baseline clinical characteristics on age-adjusted survival in the study cohort	156
6.6	Association between risk factors at time of acute stroke and subsequent mortality	157
7.1	Characteristics of IAC study population	173
7.2	Predictors of new ischaemic stroke	178
8.1	Demographic characteristics of TIA study cohort	190
8.2	Intra-class coefficients for TIA symptom reporting	191
9.1	Comparisons between studies examining the effect of CKD on outcomes of acute ischaemic stroke treated with systemic thrombolysis	200
9.2	CKD and Stroke Thrombolysis study cohort characteristics	205
9.3	Baseline characteristics of thrombolysed patients with and without renal dysfunction	206
9.4	Multivariate analysis of factors associated with a significant effect in NIHSS score improvement following thrombolytic therapy	207

Abbreviations

ADP	Adenosine phosphate
AF	Atrial fibrillation
AP	Arterial pressure
APTT	Activated partial thromboplastin time
AVF	Arteriovenous fistula
AVG	Arteriovenous graft
BFR	Blood flow rate
BMP	Bone morphogenetic protein
BP	Blood pressure
Ca ²⁺	Calcium
cAMP	Cyclic adenosine monophosphate
CBG	Capillary blood glucose
CDC	Centre for Diseases Control
CI	Confidence interval
CKD	Chronic kidney disease
CRB	Catheter-related bacteraemia
CRP	C-reactive protein
CrVD	Cerebrovascular disease
CT	Computed tomography
CVC	Central venous catheter
CVS	Central venous stenosis
eGFR	Estimated glomerular filtration rate
ESA	Erythropoiesis-stimulating agent
ESRD	End-stage renal disease
FBC	Full blood count
FDA	Food and Drug Administration
FGF	Fibroblast growth factor
GCS	Glasgow coma scale
GFR	Glomerular filtration rate
GP	Glycoprotein
HASU	Hyperacute stroke unit
HD	Haemodialysis
HES	Hospital episode statistics
HR	Hazard ratio
IAC	Intracranial arterial calcification
ICD	International Classification of Disease
ICH	Intracranial haemorrhage
IHD	Ischaemic heart disease
INR	International Normalised Ratio

IRTC	Imperial Renal and Transplant Centre
LDL	Low density lipoprotein
LMWH	Low molecular weight heparin
MDRD	Modification of Diet in Renal Disease
MGP	Matrix Gla protein
MRI	Magnetic resonance imaging
mRS	Modified Rankin scale
MRSA	Methicillin-resistant Staphylococcus aureus
NHS	National Health Service
NIHSS	National Institutes of Health Stroke Scale
NKF-K/DOQI	National Kidney Federation – Kidney Disease Outcomes Quality Initiative
OR	Odds ratio
PACS	Picture Archiving and Communications System
PAI	Plasminogen activator inhibitor
PAR	Protease-activated receptor
PAS	Patient administration system
PCI	Primary coronary intervention
PD	Peritoneal dialysis
PDGF	Platelet-derived growth factor
PF	Platelet factor
PTH	Parathyroid hormone
PVD	Peripheral vascular disease
PWV	Pulse wave velocity
RCT	Randomised controlled trial
RRT	Renal replacement therapy
Qb	Blood flow rate (through a haemodialyser)
Qd	Dialysate flow rate
SD	Standard deviation
spKt/V	Single-pool Kt/V
TAFI	Tissue activatable fibrinolysis inhibitor
TFPI	Tissue factor plasminogen inhibitor
TIA	Transient ischaemic attack
TNF	Tumour necrosis factor
tPA	Tissue plasminogen activator
UF	Ultrafiltration
UFH	Unfractionated heparin
UK	United Kingdom
US	United States
USRDS	United States Renal Data Service
VEGF	Vascular endothelial growth factor

VP	Venous pressure
VSMC	Vascular smooth muscle cell
vWF	von Willebrand factor

1. General introduction

The background to the management of end-stage renal disease with haemodialysis is introduced with specific reference to central venous catheters as a form of enduring vascular access. The physiology of coagulation in health and uraemia is then summarised to provide a basis for its therapeutic manipulation in haemodialysis to maintain patency of the extracorporeal circuit and the vascular access. The introduction concludes with an examination of stroke in haemodialysis patients as a clinically relevant correlate of both sides of the coagulation spectrum – thrombosis and haemorrhage.

1.1. Overview of chronic kidney disease

1.1.1. Definitions

Chronic kidney disease (CKD) is defined by consensus as an enduring impairment of renal function lasting more than 3 months and is classified into 5 distinct stages according to estimated glomerular filtration rate, eGFR (National Kidney Foundation 2002). In the United Kingdom 5-8% of the population has CKD Stage 3 or greater (Ahmad et al. 2006), a prevalence similar to that reported in the United States (Coresh et al. 2003). National guidelines have been developed to improve detection of CKD and to guide management including referral to specialist nephrology services (Joint Specialty Committee for Renal Disease of the Royal College of Physicians of London and Renal Association 2006).

Stage	eGFR (ml/min/1.73m ²)	Additional criteria
1	>90	Structural abnormalities on imaging ; persistent albuminuria or haematuria
2	60-89	after exclusion of urological causes
3	30-59	-
4	15-29	-
5	<15	-

Table 1.1. Classification of stages of chronic kidney disease. Adapted (Feehally et al. 2008).

CKD Stage 5 or end-stage renal disease (ESRD) is a clinical state of irreversible renal impairment that is managed either through palliative symptom control (conservative care) or renal replacement therapy (RRT) in the form of transplantation and dialysis (haemodialysis and peritoneal dialysis). Compared to dialysis, transplantation confers a better prognosis with significantly longer patient survival and a markedly better quality of life. However despite a steady rise in national transplantation rates, the number of patients reaching ESRD and receiving dialysis in the UK continues to increase and consumes a disproportionate amount of the UK National Health Service (NHS) budget. The reasons for this are manifold but in the main relate to a progressively ageing population with a greater comorbid burden, the

increasing prevalence of diabetes and obesity in the community as well as a greater availability and demand for dialysis therapies.

1.1.2. Dialysis for end-stage renal disease

Dialysis is a life-sustaining blood purification therapy that aims to replace native renal function by maintaining electrolyte, fluid and acid-base homeostasis. This is achieved through convective and diffusive movement of solutes between the patient's blood and a buffered solution (dialysate) across a semipermeable membrane. In peritoneal dialysis (PD) the dialysis membrane is the patient's peritoneum whereas in haemodialysis (HD) synthetic membranes have been manufactured for this purpose. Salt and water clearance (ultrafiltration) is achieved using an osmotic gradient in PD and by the application of a transmembrane pressure gradient in HD.

The dominant dialysis modality in the UK at present is unit-based haemodialysis performed three times weekly, a frequency of treatment required to control uraemic symptoms since the nascence of HD in 1964 (Scribner et al. 2004). Over time the type and milieu of dialysis delivery in the UK has shifted from home therapies (PD, home HD) to dedicated in-centre HD (Figure 1.1) reflecting an increase in dialysis provision for the expanding number of patients with ESRD as well as the influence of global socioeconomic factors (Grassmann et al. 2005). Most HD patients in the UK accordingly receive dialysis thrice weekly with a treatment time of 3-5 hours despite innovations in the frequency, duration and technology of HD therapies (Power et al. 2009a).

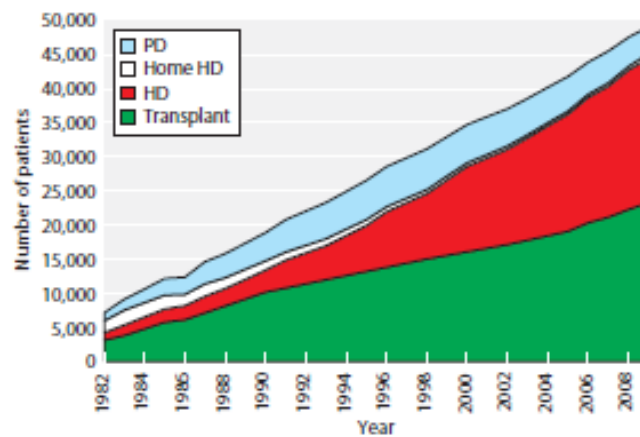


Figure 1.1. Growth in number of prevalent dialysis patients in the UK (1982-2009) according to modality (Tomson and Maggs 2010).

1.1.3. Vascular Access for Haemodialysis

The delivery of regular HD requires the maintenance of durable vascular access which must be able to support the high blood flow rates required to effect adequate dialytic clearance during the relatively short treatment session. This can be achieved by the formation of arteriovenous conduits that are created surgically by anastomosing the patient's vessels (arteriovenous fistula, AVF) or by interposing a segment of prosthetic material (arteriovenous graft, AVG). Alternatively large-bore dialysis lines (central venous catheters, CVCs) can be inserted into a large vein and used for HD. All these forms of vascular access can act as portals for infection and are prone to dysfunction through native blood vessel stenosis and thrombosis.

Comparatively AVFs have the best longevity and lowest rates of access-related infection but are dependent on adequate, adaptable vasculature for formation as well as maturation, that is the progressive dilation and muscular transformation of the venous segment (arterialisation) that allows for future repeated venepuncture (Dixon 2006). Arteriovenous grafts can be used where the patient's native vasculature is inadequate for AVF formation with a shorter time-to-use period but are prone to frequent stenosis and thrombosis requiring recurrent endovascular intervention. In addition infection of prosthetic AVGs may require removal and complex vascular surgery. CVCs are relatively easily placed and removed, and in contrast to AVFs and

AVGs, can be placed without surgery and used immediately. They are however prone to thrombosis and are associated with the highest rates of access-related infection and central venous stenosis. In addition a number of studies have implicated CVCs as independent predictors of mortality in haemodialysis patients (Lacson E Jr et al. 2009;Pisoni et al. 2009).

National and international guidelines discourage use of CVCs as long-term dialysis access and advocate preferential use of AVFs and thereafter AVGs (Fluck and Kumwenda 2008;NKF-K/DOQI 2001;Tordoir et al. 2007). Nonetheless over 50% of patients still start HD with a CVC and this is the enduring form of vascular access in up to 35% of patients (Rayner and Pisoni 2010). Unfavourable vascular anatomy, patient choice, female sex, ischaemic heart disease, peripheral vascular disease, obesity and white race have all been associated with enduring CVC use (Duncan et al. 2004;Graham et al. 2008;Quarello et al. 2006;Reddan et al. 2002;Wasse et al. 2008). CVCs therefore need to deliver adequate dialysis for the long-term and with minimal associated complications (infective and mechanical).

Achievement of dialysis adequacy is dependent on dialytic molecular clearance and ultrafiltration (UF) which in turn require optimal haemodialyser function and blood flows through the extracorporeal circuit (vascular access, associated tubing and haemodialyser). Clinical strategies directed at maintaining patency of the extracorporeal circuit and CVC access have been paramount from the nascence of haemodialysis with use of compounds with anticoagulant properties and in the case of CVCs, thrombolytics to overcome access thrombosis.

1.2. Coagulation in clinical practice

1.2.1. The physiology of coagulation

Haemostasis is the process whereby a haemostatic clot forms at sites of vascular injury to prevent ongoing blood loss. This is a tightly controlled process involving interactions between the injured vascular endothelium, circulating platelets and activation of a cascade of coagulation proteins (factors) that results in localised thrombus formation which is controlled by opposing fibrinolytic pathways that ultimately effect dissolution of the thrombus after a period of time allowing for tissue repair. The balance between the two processes is crucial to avoid pathological thrombosis (e.g. deep vein thrombosis, pulmonary embolism, myocardial and cerebral infarction) or uncontrolled haemorrhage leading to loss of organ perfusion and circulatory shock.

Blood coagulation conceptually occurs in a series of phases: (1) Platelet activation and aggregation, (2) Activation of the coagulation cascade and formation of fibrin, (3) Termination of coagulation and (4) Clot dissolution. These are outlined in more detail below.

1. Platelet activation at the site of blood vessel injury

Circulating platelets adhere to areas of activated endothelium and exposed subendothelial matrix leading to their activation and further platelet aggregation.

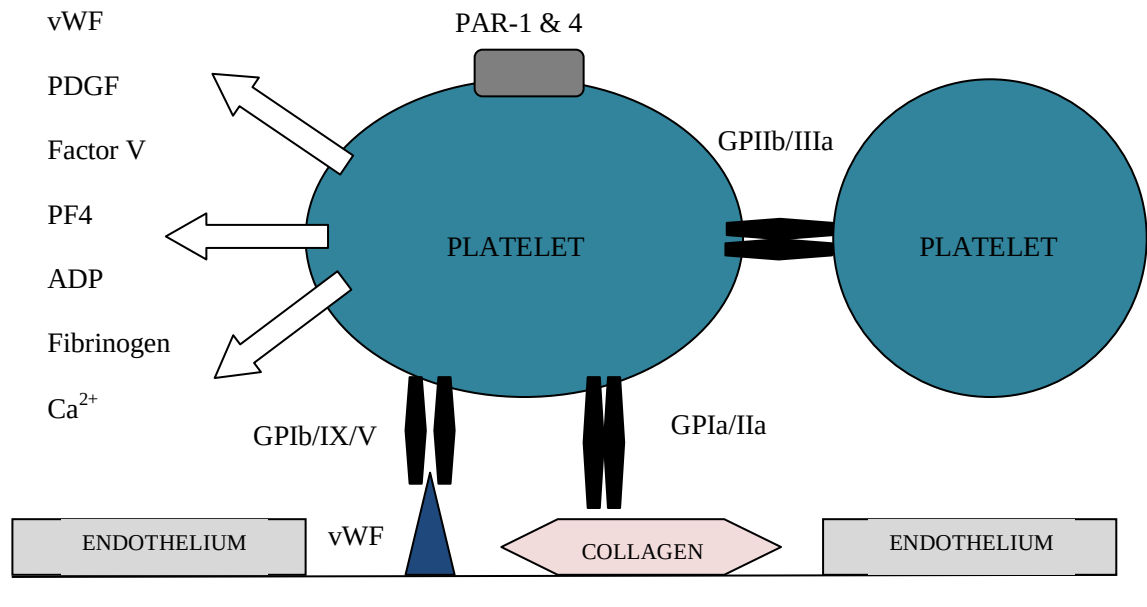


Figure 1.2. Schematic representation of platelet and blood vessel endothelium interactions. Platelets bind to exposed collagen either directly or via von Willebrand factor (vWF) at areas of endothelial injury via membrane-bound glycoproteins GPIb and GPIIa/IIa or GPIb/IX/V and GPIIb/IIIa respectively. Platelet activation leads to the release of variety of mediators that amplify the activation response and recruit additional platelets – most importantly thromboxane A₂ and adenosine phosphate (ADP). Platelet-platelet adhesion and activation occurs via GPIIb/IIIa activation and binding of fibrinogen. The platelet membrane also contains protease-activated receptors (PARs) that bind thrombin leading to activation.

2. Activation of the coagulation cascade at the site of the platelet plug

Activation of the coagulation cascade via the extrinsic pathway leads to the formation of thrombin which converts circulating soluble fibrinogen into insoluble fibrin strands that enmesh and stabilise the platelet plug. The contribution of the intrinsic pathway is unclear: it is not required for normal haemostasis but may play a role in thrombosis. The physiological activator of the contact system is also uncertain but has been suggested to be both collagen and polyphosphate released from platelets.

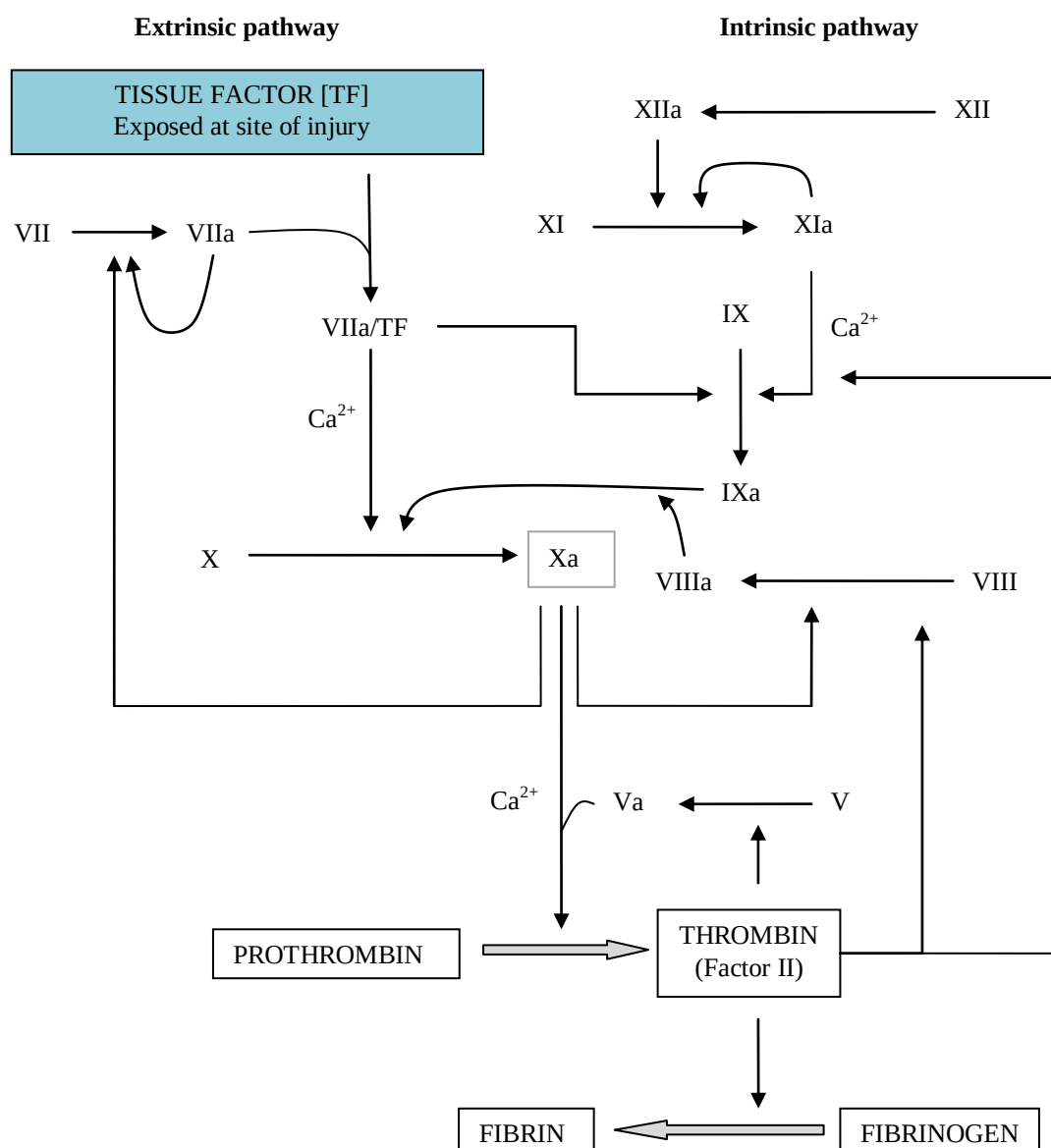


Figure 1.3. The coagulation cascade.

Activation of the extrinsic pathway is initiated by exposure of tissue factor at sites of injury, and activation of the intrinsic pathway by exposure of blood to negatively charged molecules of the subendothelium. Polymerisation and crosslinking of fibrin occurs in the presence of activated factor XIII (not depicted in Figure 1.3).

3. Limitation and localisation of thrombosis

Platelets are deactivated by endothelial prostacyclin and nitric oxide. The endothelium also secretes tissue factor pathway inhibitor (TFPI) which inhibits Factor X activation. Thrombin diffusing away from the site of injury is captured by endothelial cell thrombomodulin which then mediates activation of protein C. Antithrombin, protein C and protein S act as inactivators of a number of key coagulation factors (e.g. Factor IXa, Xa, XIa, Va and VIIIa).

4. Clot dissolution - fibrinolysis

Fibrin is lysed through the action of plasmin in a cascade that is regulated by the presence of inhibitors at specific stages.

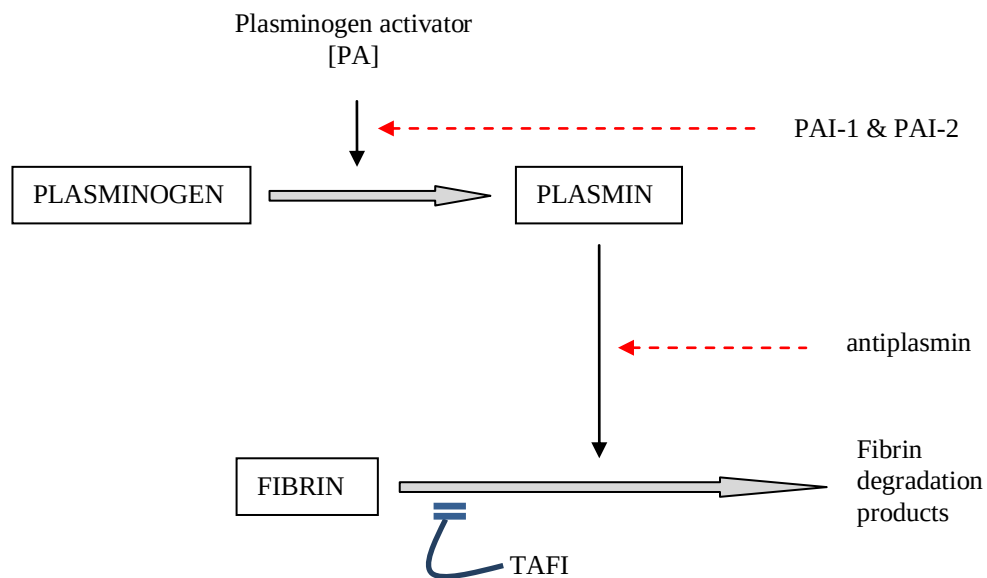


Figure 1.4. Fibrinolytic cascade. Fibrin is broken down by the action of plasmin that is formed by activation of circulating plasminogen. This process is regulated by inhibitors (red dashed lines) with TAFI acting to prevent fibrin breakdown by restricting plasminogen binding. Abbreviations: PAI, plasminogen activator inhibitor; TAFI, tissue activatable fibrinolysis inhibitor.

1.2.2. Therapeutics of anticoagulation

Pharmacological inhibition of coagulation is desirable in a number of clinical scenarios such as in ischaemic heart disease, prevention and treatment of deep vein thrombosis (DVT) and pulmonary embolism, the prevention of thromboembolic stroke in established atrial fibrillation, in patients with prosthetic heart valves and to maintain the patency of extracorporeal circuits used for cardiac surgery as well as renal replacement therapies.

In clinical practice this is achieved through inhibition of platelet function, limiting thrombin production and use of fibrinolytic agents. The major drugs in clinical use shall be reviewed briefly in turn.

[I] Platelet function inhibitors

- a. Aspirin. Irreversible inactivation of cyclo-oxygenase 1 by aspirin impairs platelet synthesis of thromboxane A₂ which leads to reduced stimulation by some agonists (e.g. ADP, adrenaline). The clinical effect on bleeding time can last up to 1 week.
- b. Dipyridamole. Inhibition of cAMP phosphodiesterase by this agent leads to raised cAMP levels within platelets and inhibits platelet activation. It also blocks adenosine uptake and breakdown.
- c. Clopidogrel. The metabolites of this drug inhibit platelet aggregation by blocking the platelet P₂Y₁₂ receptor and also appear to impair fibrinogen binding to the GPIIb/IIIa receptor. Clinical effects may last 4-10 days.
- d. Abciximab, tirofiban, eptifibatide. These agents bind to the GPIIb/IIIa receptor and inhibit its function leading to reduced platelet-platelet aggregation and binding to fibrinogen.

[II] Limiting thrombin production

- e. Heparins. Endogenous heparans as well as synthetic heparins (unfractionated, low-molecular weight, fondaparinux) bind to a dedicated site on the antithrombin molecule and induce a conformational change in the molecule that accelerates its ability to inactivate thrombin more than 1000-fold.

- f. Activated protein C. Administered as an infusion in critical care scenarios for severe sepsis, protein C inactivates the factors Va and VIIIa (figure 6). In so doing it inhibits formation of factor Xa along the extrinsic and common pathways and thus inhibits resultant thrombin formation. Concerns about excess haemorrhagic complications have limited its use despite initial enthusiasm in severe sepsis.
- g. Warfarin. This oral vitamin-K antagonist inhibits γ -carboxylation of factors II, VII, IX and X and remains the mainstay of oral anticoagulation in clinical practice.
- h. Direct thrombin inhibitors. Agents like argatroban and dabigatran bind directly to active sites on the thrombin molecule rather than forming complexes with antithrombin to exert a clinical effect. They are contraindicated in advanced renal impairment (creatinine clearance $<30\text{ml/min/1.73m}^2$).
- i. Rivaroxaban. This oral direct factor Xa inhibitor is currently approved for use in DVT prophylaxis following orthopaedic surgery in Europe and Canada but is similarly contraindicated in severe renal impairment.

[III] Fibrinolytic agents

- j. Tissue-type plasminogen activator (tPA). This enzyme circulates naturally in small amounts the plasma complexed with its inhibitor (PAI-1) and is released locally by the vascular endothelium. Synthetic tPA (alteplase) is administered as an infusion for thrombolysis in myocardial infarction, ischaemic stroke and arterial thromboembolism.
- k. Urokinase. This naturally occurring enzyme is present throughout the body and in high concentrations in the urine. Synthetic forms are similarly available.

The majority of these agents are used extensively in patients with ESRD for non-dialytic indications (e.g. antiplatelet therapy in ischaemic heart disease or warfarin in chronic atrial fibrillation). However despite numerous clinical trials in the general population the efficacy and side-effect profile of these agents has been relatively poorly characterised in patients with ESRD. Furthermore the effect of uraemia on

intrinsic coagulation which will be discussed later has the potential to significantly alter their safety-efficacy profile.

In addition patients on haemodialysis are further exposed to anticoagulants with specific therapeutic intent relating to their treatment – patency and function of the dialysis circuit and their vascular access. This introduction will now briefly discuss the rationale behind each approach and focus on CVCs which form the vascular access studied in this thesis.

1.3. Anticoagulation in haemodialysis

1.3.1. Haemodialysis circuit anticoagulation

Synthetic extracorporeal surfaces are thrombogenic (Gawaz et al. 1999) and as a result the HD circuit is dependent on anticoagulation to maintain adequate patency for blood flow and dialytic clearance. The effect of haemodialysis is traditionally expressed through solute clearance (Sargent and Gotch 1980) which is achieved predominantly by diffusive transport across a semipermeable synthetic dialysis membrane and to a much lesser extent by convective transport occurring during UF. Diffusive movement is driven by a concentration gradient between plasma and dialysate that is maintained by the application of counter-current flow between the two fluids. In addition membrane pore size, surface charge characteristics and the flow mechanics (e.g. velocity, cellular composition) at the interface of the two fluids affect the rate of molecular movement across the membrane (Clark and Ronco 2001). On average maximal solute clearance is achieved with a dialysate flow rate that is twice the blood flow rate through the dialyser and there is no significant benefit to increasing the rates of either component after a certain point. The approximate relationship between blood flow and solute clearance for a theoretical dialyser is shown in Figure 1.5.

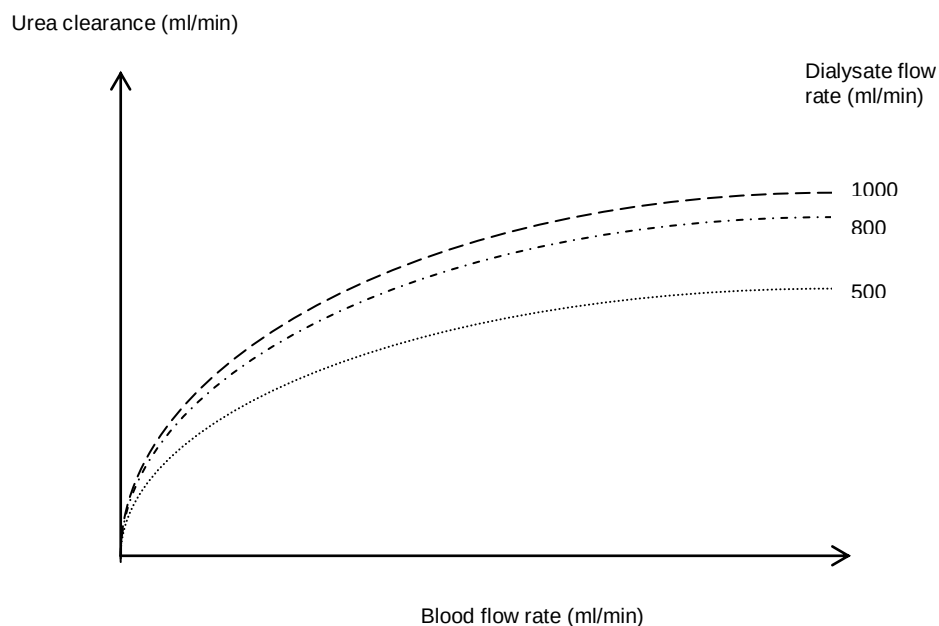


Figure 1.5. Relationship between blood flow rate and urea clearance at different dialysate flow rates for a theoretical dialyser.

Performance of a dialyser in vivo is different to its performance in vitro as documented by the manufacturer. Deposition of plasma proteins and cellular fragments on the surface and in the pores of the dialysis membrane alters its characteristics during haemodialysis (Clark et al. 2007). Taken together these effects increase resistance to flow, reduce the effective surface area for diffusion and ultimately reduce dialysis adequacy. This is compounded by extracorporeal thrombus formation occurring by activation of inflammatory and procoagulant pathways as blood passes over the synthetic surfaces of the haemodialysis circuit. Ultimately lack of effective blood flow leads to circuit clotting with loss of the blood volume in the discarded extracorporeal tubing and loss of effective treatment time.

In clinical practice HD circuit anticoagulation was largely achieved using heparins delivered into the inflow limb of the circuit with the intention of achieving regional effect (Davenport 2006;Fischer 2007). Nonetheless a degree of systemic effect is inevitable despite strategies to minimise this such as continuous dose-titration (Seifert et al. 1986). Until the advent of low molecular-weight heparins (LMWHs) unfractionated heparin was the mainstay of anticoagulation. Use of LMWHs has been shown to offer equivalent circuit anticoagulant efficacy but is less labour intensive with some benefit reported terms of lipid and potassium control (Bramham et al. 2008). As a class they have differing pharmacokinetic and pharmacodynamic properties (Brophy et al. 2006;Malyszko et al. 2004;Naumnik et al. 2003) but accumulate in renal failure and are less well characterised in ESRD with less experience of use.

1.3.2. Prevention of catheter thrombosis

The tips of CVCs have additional side holes to allow for bidirectional, smooth, low-resistance flow of blood (Ash 2008). This interface between blood and prosthetic surface is a nidus for clot formation that may occlude the lumen of the side hole and/or propagate into the internal lumen of the CVC leading to progressive downstream obstruction to flow and eventual total occlusion (Twardowski 1998b). As a result unfractionated heparin has been widely used as a prophylactic luminal “locking” solution to prevent CVC thrombosis during the interdialytic period.

Systemic overspill of any locking solution is inevitable and relates to the rate of instillation, the presence and orientation of side holes in the CVC and the density of that solution with respect to blood. Systemic heparinisation is seen in CVCs locked with heparin and relates to the volume and concentration of solution used (Pepper et al. 2007; Thomson et al. 2011). Regular inadvertent heparinisation may have clinical consequences in patients at high risk of bleeding (e.g. following recent surgery, recent haemorrhage) and as a result alternatives such as sodium citrate are used (Karaaslan et al. 2001; Yevzlin et al. 2007). Sodium citrate has been reported to exert equivalent anticoagulant efficacy to heparin in most studies (Lok et al. 2007; Stas et al. 2001) and has an additional antimicrobial effect but is still prone to symptomatic overspill which can be marked (Power et al. 2009b).

1.3.3. Thrombolytics for catheter dysfunction

Catheter dysfunction is characterised by increased resistance to flow through the vascular access and may relate to the formation of thrombus within the lumen, over the side holes or around the catheter tip causing adherence to the vessel wall (Twardowski 1998b). In clinical practice this leads to interruption of treatment by automated circuits in the HD machine and the reinstitution of therapy for the remainder of the session at lower blood flow rates. The net result is impaired dialytic clearance which may be compounded by increased catheter recirculation.

Recirculation describes the phenomenon whereby a proportion of the blood flow leaving the dialyser outlet re-enters the haemodialysis circuit via the dialyser inlet without distributing to the systemic circulation (Figure 1.6). Recirculation increases with closer apposition between the inlet and outlet lumens of the dialysis access decreases (dialysis needles or CVC lumens) and in the presence of downstream flow limitation due to vessel stenosis or thrombosis (Figure 1.6).

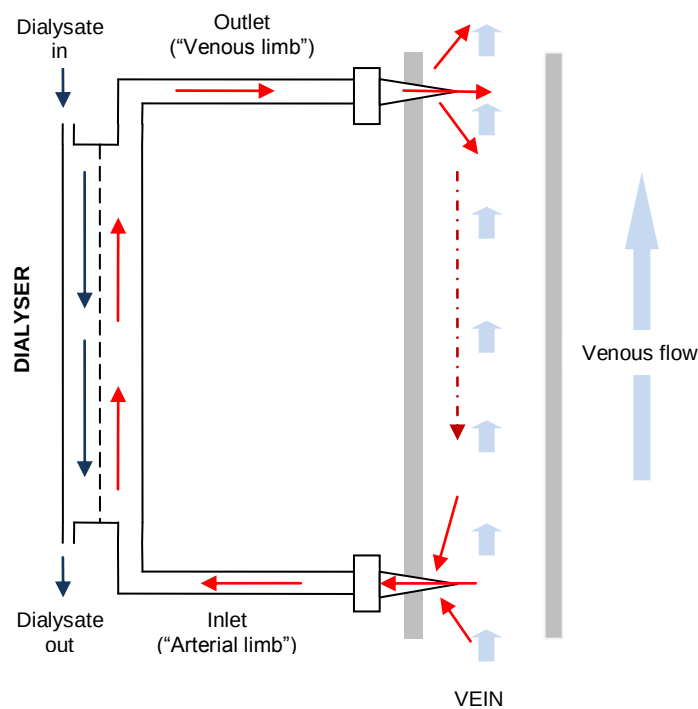


Figure 1.6. Schematic representation of recirculation. Dark red dashed arrow demonstrates retrograde flow of dialysed blood re-aspirated into dialyser inlet and accounting for recirculation.

Treatment of occluded or dysfunctional CVCs has involved the use of thrombolytics such as urokinase or tPA using a variety of protocols for intraluminal administration (Mokrzycki and Lok 2010). These include “dwells”, progressive “pushes” or slow infusions with the aim of achieving clot lysis and restoration of function that is often transient (Donati et al. 2011;Hemmelgarn et al. 2011;Tumlin et al. 2010). Ultimately replacement of the CVC is required following failure of these approaches to restore function. Although pre-emptive strategies for dysfunction involving access monitoring and timely intervention have shown benefit in in AVGs (Schild 2010) and to a lesser extent in AVFs (Zasuwa et al. 2010), there are no such data published in CVCs.

1.3.4. Uraemia and coagulation

It has long been recognized that renal failure manifests a bleeding diathesis with prolongation of bleeding time (Andrassy and Ritz 1985; Stewart and Castaldi 1967) and higher rates of haemorrhagic complications particularly gastrointestinal bleeding and subdural haematoma (Leonard and Shapiro 1975; Tseng and Lin 2008). This is multifactorial and believed to relate to the effects of uraemic toxins on coagulation function, renal anaemia and administered medication (e.g. anticoagulation for haemodialysis, antiplatelet therapy for vascular disease).

It has been shown that there is progressive platelet dysfunction as renal function declines (Di Minno et al. 1985), with manifest abnormalities in platelet activation and degranulation as well as platelet aggregation (Eknoyan and Brown, III 1981). Calcium-dependent platelet function is impaired (Ware et al. 1989), dense granule content is decreased, platelet ADP and serotonin stores are reduced and there is an impaired platelet response to thrombin stimulation (Di Minno et al. 1985). In addition platelet-platelet interactions are impaired as are platelet-endothelial interactions (Castillo et al. 1986) with a reduced GPIIb/IIIa complex activation in response to von Willebrand factor (Escolar et al. 1990). Dialysis improves some of these abnormalities (Galbusera et al. 2009; Stewart & Castaldi 1967), a finding which implicates uraemic toxins, such as guanidinosuccinic acid, as pathogens (Horowitz et al. 1970; Noris and Remuzzi 1999).

Anaemia is highly prevalent in advanced renal impairment and reflects inadequate haematopoiesis, increased red cell turnover and intercurrent occult bleeding (Fishbane and Nissenson 2010). A reduced haematocrit exerts an adverse rheological effect by reducing vessel shear wall stress and platelet-vessel wall impaction that acts as a cellular activating signal (Valeri et al. 2007). Furthermore haemoglobin acts as a scavenger for endothelial nitrous oxide which acts as a platelet inhibitor and vasodilator (Kim-Shapiro et al. 2006). Correction of anaemia, either by blood transfusion or by recombinant human erythropoietin, has been shown to reduce the bleeding time in uraemia (Gordge et al. 1990; Livio et al. 1982).

Use of antithrombotic agents such as antiplatelet drugs and other anticoagulants (e.g. heparins for haemodialysis circuit anticoagulation, warfarin) will clearly increase the baseline bleeding tendency in uraemia which itself can enhance their pharmacodynamic effects (Gaspari et al. 1987). Other medicines can exert

idiosyncratic effects such as the beta-lactam antibiotics (e.g. benzylpenicillin) which attenuate platelet function through interaction with the ADP receptor (Shattil et al. 1980).

It is worth noting that paradoxically the coagulation cascade is activated in uraemic patients with elevated levels of fibrinogen, factor VIII and decreased levels of proteins C and S (Mercier et al. 2001; Pawlak et al. 2003; Vaziri et al. 1994). This confers a procoagulant profile in uraemia that is enhanced by reduced ADAMTS13 activity, the enzyme that degrades Willebrand factor (Mannucci et al. 2001). These effects lead to the clinical manifestation of an increased risk of DVT in patients with non-dialysis CKD (Folsom et al. 2010; Wattanakit et al. 2008). In the absence of regional anticoagulation haemodialysis is itself a prothrombotic intervention with activation of complement, platelets and the coagulation cascade as blood passes over synthetic surfaces (Huang et al. 2009).

As a result of these competing effects there is dysregulated coagulation in ESRD with the clinical imperative of navigating through the Scylla of thrombosis leading to dialytic failure and vital organ occlusion, and the Charybdis of haemorrhage leading to circulatory failure and lack of organ perfusion. In this introduction I will next consider cerebrovascular disease as a highly relevant and poignant clinical correlate of both these extremes in haemodialysis patients.

1.4. Cerebrovascular disease and renal impairment

1.4.1. Stroke is a cerebral vascular disease

Stroke is defined by the World Health Organisation (1980) as “rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin”. It is caused by an interruption in the blood supply to a section of the brain either as a result of vessel occlusion by thrombus (ischaemic stroke) or as a result of bleeding from a vessel (haemorrhagic stroke). Risk factors for stroke closely mirror those for cardiac and peripheral vascular disease (Donnan et al. 2008). Established non-modifiable risk factors are increasing age, a positive family history, male gender and non-Caucasian ethnicity (Markus et al. 2007). Hypertension remains the major modifiable risk factor for both stroke subtypes with stroke risk increasing in proportion to both systolic and diastolic blood pressure parameters (Prospective studies collaboration 1995; Sharma and Hakim 2011). Atherosclerotic risk factors such as smoking, diabetes mellitus and hypercholesterolaemia (particularly in people aged 45 years or less) confer a greater risk of ischaemic stroke whereas high alcohol use, a bleeding diathesis and blood vessel wall fragility (e.g. as a result of congenital aneurysm or amyloid angiopathy typically in the elderly) predispose to haemorrhagic stroke (Berger et al. 1998; O'Donnell et al. 2010).

Stroke remains the second leading cause of death in industrialised countries. Stroke aetiology significantly influences 30-day mortality with rates 8-15% for ischaemic stroke rising to 40-60% for haemorrhagic strokes (Heuschmann et al. 2011; Thorvaldsen et al. 1995; Weir et al. 2001). It is the leading cause of disability in the Western world and is associated with a substantial economic burden accounting for £8 million in healthcare costs in England (UK Department of Health 2010) and consuming 25% long-term care beds (UK Department of Health 2005).

1.4.2. Renal impairment as a vascular risk factor

Numerous epidemiological studies have implicated renal impairment as an independent cardiovascular risk factor (Sarnak et al. 2003;Stenvinkel 2010). The pathogenesis for this phenomenon has not been fully elucidated but may relate to factors specific to the uraemic milieu as well as the over-representation of traditional risk factors such as ageing, established vascular disease, hypertension and diabetes in patients with renal disease (McCullough et al. 2007). In uraemia accelerated atherosclerosis and a distinct form of vascular calcification involving the media rather than the intima has been observed (Drueke and Massy 2010;London et al. 2005). This pathology becomes more prevalent and progressive with decline in renal function and reaches its zenith in patients with ESRD (Guerin et al. 2000;Nakano et al. 2010;Toussaint et al. 2008).

Perturbations in bone mineral metabolism become more prevalent as renal dysfunction progresses with elevations in fibroblast growth factor 23 (FGF-23), hyperparathyroidism and hyperphosphataemia (Cunningham et al. 2011). Hypercalcaemia may occur as a result of secondary hyperparathyroidism and/or calcium loading from use of calcium-based phosphate binders (Block et al. 2005). Declining GFR as well as these factors above have been independently associated with vascular calcification in renal impairment (Shroff and Shanahan 2007). The underlying pathophysiology appears to have at its core a transdifferentiation of medial vascular smooth muscle cells to an osteoblastic phenotype with deposition of osseous extracellular matrix (Reynolds et al. 2004;Shroff et al. 2010).

Arterial calcification predisposes to adverse cardiovascular events as well as increased mortality in all stages of renal impairment (Mizobuchi et al. 2009;Verbeke et al. 2011). Increased vascular stiffness leads to increases in pulse pressure, aortic pulse wave velocity and adverse pressure waveform transmission that adversely affect cardiac function and remodelling (London 2003). It can be hypothesised that similar mechanisms may underlie the extracranial and intracranial arterial changes seen in patients with advanced renal impairment such increased carotid intima medial thickness (Tanaka et al. 2010), vascular calcification (Bugnicourt et al. 2009) and extensive small vessel disease on cerebral imaging (Savazzi et al. 2001).

1.4.3. Cerebrovascular disease in end-stage renal disease

Stroke incidence increases with each stage of CKD and reaches a peak in those patients with end-stage renal disease. Although stroke is one of the leading causes of death in patients with ESRD and the primary cause of disability in this subpopulation there is little published data on its epidemiology, underlying pathophysiology as well as the safety and efficacy of established treatments for this condition. There is even less published on the effect of renal impairment on functional outcomes after established stroke and the prognostic effect of a stroke event on patient survival. Patients with advanced renal impairment have been excluded from major randomized controlled trials on primary and secondary stroke prevention and to date renal function has not been examined in historical and current trials of thrombolytic agents in acute ischaemic stroke (Lindley R., personal communication).

There is evidence to suggest that the pathophysiological processes behind stroke in ESRD are subtly different to the general population. The prevalence of haemorrhagic stroke is higher (25-30% vs. 15-20%) with a greater background prevalence of cerebral microbleeds (Iseki et al. 1993; Kawamura et al. 1998; Shima et al. 2010). The benefits of statins for lipid-lowering in primary prevention are unclear (Fellstrom et al. 2009; Wanner et al. 2005) and the high prevalence of intracranial arterial calcification (Bugnicourt et al. 2009) may abrogate any clinical benefit from antiplatelet therapy in secondary prevention.

1.5. Conclusions and thesis outline

The coagulation system is dysregulated in end-stage renal disease due to the direct effects of uraemia as well iatrogenic factors such as the haemodialysis procedure itself and prescribed thrombolytics, antiplatelet agents and anticoagulants.

In this thesis I will firstly examine thrombotic and haemorrhagic complications associated with the use of CVCs as a definitive form of vascular access in HD patients. I will examine the comparative function and complications associated with CVCs inserted via the internal jugular and translumbar routes. In a prospective, randomized controlled trial of 2 types of CVC I will then analyse the effect of catheter type and prothrombotic factors on long-term catheter function. Finally I will explore the efficacy of a thrombolytic lock regime on restoring catheter patency and the potential value of catheter flow monitoring in predicting dysfunction.

Subsequently I will focus on cerebral haemorrhagic and thrombotic complications in HD patients. This thesis will examine the incidence and risk factors for stroke in HD patients. It will then assess the prevalence and potential pathogenetic influence of intracranial arterial calcification on ischaemic stroke and appraise the potential effect of screening for transient ischaemic attack on stroke incidence. I will conclude by analysing the effect of renal impairment on the clinical efficacy of thrombolytic therapy in the emergency treatment of acute ischaemic stroke.

2. Catheter site as a determinant of CVC thrombosis

This chapter presents two studies of the function and thrombotic complications of CVCs used for haemodialysis. Medium-term outcomes such as the need for thrombolytic therapy and access replacement are compared between a conventional route, the internal jugular, and the more complex translumbar route.

2.1. Introduction

2.1.1. CVC insertion technique and choice of site

The central venous haemodialysis catheter is a flexible, tubular device made of synthetic polymer with large bore lumens (typically 12-14 French, or 4-4.7mm) capable of sustaining high flow rates required for effective haemodialysis. They require insertion into large central veins due to their diameter and the volume of blood that they process. A multitude of CVCs are available commercially and typically consist of either a single, dual-lumen design or a twin catheter system.

Real-time ultrasound guidance for venous puncture is current standard of care replacing the “landmark” method which relied on the use of anatomical landmarks for localisation. The vein is punctured with an introducer needle and a long guidewire is inserted through it and down the length of the vein to maintain anatomical position during the subsequent manoeuvres (Seldinger technique). The introducer needle is then removed and a firmer, wider dilator is used to create a tract through the subcutaneous tissues and into the vein. In the case of temporary CVCs this dilator is removed and the catheter slid down the guidewire into position in the vein. Where tunnelled, cuffed CVCs are inserted the dilator is broader and designed as a peel-away sheath through which the catheter is inserted into the vein before being withdrawn. A section of the tunnelled CVC that includes the cuff segment passes through the subcutaneous tissues of the anterior thoracic wall before exiting through the skin (the exit site).

Over three decades ago the subclavian approach was favoured although it soon became apparent that rates of central venous stenosis were unacceptably high. A landmark study showed that rates of central venous stenosis in subclavian CVCs were 32% higher than that in CVCs inserted via the internal jugular route (Schillinger et al. 1991). As a result the internal jugular route has become the preferred initial approach although associated rates of central venous stenosis are not insignificant reaching 40-45% (MacRae et al. 2005a; Taal et al. 2004). Insertion through the right rather than the left internal jugular is preferred due to the ease afforded by the absence of anatomical bends with this approach to the superior vena caval/right atrial junction. The angulations of the venous passage with the left-sided approach as well as the smaller cross-sectional area of the left internal jugular vein have been

implicated in the higher complication rates at insertion (Lin et al. 1998;Salgado et al. 2004) as well as higher rates of central venous stenosis.

2.1.2. Understanding and assessing catheter function

The function of CVCs for haemodialysis is to provide durable vascular access delivering effective fluid performance with minimal infective and traumatic complications. This is a holistic definition and international guidelines often refer to catheter function as a measure of its mechanical effectiveness, i.e. its ability to provide set blood flow rates and dialytic adequacy.

The blood flow rate through a catheter relates to the haemodialyser pump speed settings and resistance to flow. The latter depends on a number of factors such the luminal cross-sectional area throughout the length of the CVC, the cross-sectional shape of the catheter, the number and orientation of side holes, the position of the catheter tip with respect to adjacent structures (venous wall, cardiac wall) and the presence of external, flow-limiting pathology (e.g. fibrin strands or sheath, mural thrombus). Different designs have been used to improve and maintain good mechanical function such as twin-catheter systems (e.g. TesioCath™), split-tip dual lumen catheters (e.g. AshSplit™) and even self-centering dual-lumen catheters (e.g. Centros™). The fluid mechanical principles behind catheter function and design have been reviewed extensively elsewhere (Ash 2008).

CVC malfunction is defined as a “failure to attain and maintain an extracorporeal blood flow sufficient to perform haemodialysis without significantly lengthening the haemodialysis treatment” (NKF-K/DOQI 2006). There is no consensus regarding the minimum blood flow rate (Q_b) that defines this with rates of 250-300ml/min being suggested. Other than malposition and catheter kinking the pathology that underpins CVC malfunction is often complex and involves element of fibrin sheath formation, intraluminal and mural thrombosis and venous stenosis. Furthermore the temporal relationship between malfunction and catheter-related infection suggests a contributory effect of the bacterial biofilm on the surface of the CVC in these processes.

2.1.3. Fibrin sheath formation and thrombosis

An extraluminal sheath of fibrin develops within 24 hours of CVC insertion and can extend along the whole length of the CVC by 7 days (Hoshal, Jr. et al. 1971). The sheath consists initially of fibrin, albumin and other serum proteins including coagulation factors. A layer of collagen is subsequently deposited as smooth muscle cells migrate into it from the vessel wall and it undergoes endothelialisation (Mehall et al. 2002). The triggering insult is believed to be catheter-induced endothelial trauma, inflammation and response to injury (Forauer et al. 2006). This mechanical injury occurs as a result of guidewire placement and catheter insertion, and ongoing movement due to respiration, posture and even the haemodialysis procedure itself. Mature fibrin sheaths can form sleeves that persist following CVC removal and require mechanical guidewire disruption prior to catheter replacement to avoid recurrent dysfunction (Oliver et al. 2007).

The prosthetic nature of CVC material promotes thrombosis with some evidence that silicone is less thrombogenic than other polymers (Curelaru et al. 1983). Catheter-induced endothelial injury results in thrombosis through mechanisms already discussed in Section 1.2.1. Autopsy studies show venous endothelial denudation with tethering mural thrombus and fibrin formation at the site of CVC tip apposition (Forauer and Theoharis 2003). Thrombosis is further favoured by the inflammatory response to injury and flow stagnation as a result of fibrin sheaths. Thrombus can form on the catheter tip and side-holes and propagate intraluminally as well as extend along the vessel wall. Although perceived as the primary thrombotic pathology in CVCs, intraluminal thrombus is not responsible for significant catheter obstruction (Twardowski 1998b) whereas extraluminal thrombus and fibrin adjacent to the catheter are. Clinical strategies to combat these include prophylactic anticoagulation (in the form of either oral anticoagulation or intraluminal heparin locks) and using thrombolytic agents to treat overt catheter dysfunction. A recent study using alteplase as a routine interdialytic catheter locking solution reduces not only the incidence of catheter dysfunction but also the rate of catheter-related bacteraemia (Hemmelgarn et al. 2011) suggesting a relationship between fibrin sheath, bacterial biofilm and dysfunction.

2.1.4. Clinical management of catheter dysfunction

The management of dysfunctional CVCs in clinical practice involves a number of manoeuvres in sequence. Typically the patient's position is changed to improve the catheter's orientation in the vein and forceful flushes of normal saline are used to expel any small thrombi that may have occluded the side holes. A chest radiograph can be performed to ensure there is no malposition or kinking of the CVC. Persisting one-way flow in a catheter lumen can prompt the dialysis staff to "reverse the lines" (i.e. to change the lumens attached to the "arterial" and "venous" limbs of the haemodialysis circuit). Ongoing dysfunction is then managed with the installation of an intraluminal solution of thrombolytic. A continuous infusion of thrombolytic is subsequently used if required before catheter replacement is carried out. Many studies have been performed with variations in thrombolytic type and dose, methods of delivery and criteria for treatment and these will be discussed in greater depth in Chapter 4.

2.1.5. The TesioCath™ twin catheter system for haemodialysis

This eponymous CVC consists of two separate 10Fr catheters inserted parallel to each other into a central vein and requiring two separate venous punctures for guidewire placement, catheter insertion and two separate tunnelling procedures (Tesio et al. 1994). The performance of the TesioCath™ for haemodialysis has been reported in a number of studies although these are limited by relatively low patient numbers (Wivell et al. 2001) or a short period of follow-up (Wang et al. 2006). A recent large study from another UK unit showed that the number of previous catheters and the laterality of insertion influenced the longevity of CVCs including TesioCaths™ (Fry et al. 2008). Nonetheless the long-term performance of this catheter with modern haemodialysis techniques remains poorly described.

2.1.6. The translumbar approach to CVC placement

Initially described over twenty years ago (Ortuno et al. 1971) the translumbar approach to cannulating the inferior vena cava (IVC) has been used in adult and paediatric patients to place haemodialysis access in cases where the upper body

venous circulation has become impassable (Rajan et al. 1998;Rodriguez-Cruz et al. 2007). It is a safe approach when used by radiologists with expertise although prior series report poor long-term function (Lund et al. 1995). There is however no data on CVC function and outcomes in modern cohorts using this approach and no consistent characterisation of thrombotic complications.

The aims of the first section of this thesis are to characterise and compare the performance, thrombotic and other complications of a single type of CVC (TesioCath™) inserted for long-term haemodialysis via a conventional route (i.e. the internal jugular approach) and via an unconventional route such as the translumbar approach that is required when upper body venous passages are exhausted.

2.2. Methods

2.2.1. Subjects and data abstraction

The Imperial Renal and Transplant Centre (IRTC) provides specialist renal care for a population of over 2.1 million people in a large urban centre. It acts as the admission unit for a haemodialysis programme of just under 1,500 patients delivered by eight satellite units and one hospital unit with a high prevalence (77%) of CVC use. All aspects of haemodialysis care are subject to a centralised consultant-led audit on a monthly basis including dialysis adequacy, access type and infection, water quality and anaemia management.

Electronic records are maintained on all patients receiving renal replacement therapy at the IRTC. These include:

- (a) Monthly reports on patients initiating haemodialysis treatment, transferring dialysis modality or withdrawing from dialysis, receiving a renal transplant and transferring care out of centre.
- (b) Monthly reports submitted by each haemodialysis unit with full haematological, biochemical data and haemodialysis parameters for each patient. These include erythropoietin dose, dialysis adequacy (spKt/V), dialysis flow rates, treatment time and dry weight.
- (c) Dialysis clinic letters.
- (d) Electronic records of dialysis parameters for each haemodialysis session extending to 1996 (Proton renal system).
- (e) Electronic records of all day case procedures in the renal directorate.
- (f) Electronic hospital discharge summaries covering all inpatient admissions.
- (g) Data available in the hospital Patient Administration System (PAS) encoding patient comorbidities and hospital episode data such as procedures and clinical outcome.
- (h) Radiological data including source images available on the hospital Picture Archiving and Communications System (PACS).

As well as electronic sources, clinical case notes (paper records) were examined for additional information and corroboration. All these sources were used to generate and validate a data set extending from 1st January 1999 to 1st March 2010 that included all patients receiving haemodialysis at the IRTC and included survival results, treatment duration, access type and duration, laboratory and radiological results, comorbidity coding as well as antiplatelet and anticoagulant use. This core

dataset was used as the basis for individualised datasets that were tailored for separate studies in this thesis.

This chapter presents data from a retrospective analysis of two overlapping cohorts:

- (a) A cohort of 433 patients receiving an internal jugular TesioCath™ CVC from 1st January 1999 – 1st April 2008.
- (b) Patients who had a translumbar inferior vena caval TesioCath™ inserted from 1st January 1999 - 16th June 2008.

2.2.2. Approach to central venous catheter use

All patients opting for haemodialysis were assessed clinically for AVF formation by a consultant nephrologist and referred for further assessment by a consultant surgeon as appropriate. TesioCaths™ (12 Fr Bio-Flex Tesio Catheter, MedComp Inc, Harleysville, Pennsylvania) were inserted in incident patients with no suitable vessels for successful AVF formation, those requiring immediate vascular access, patients unable to wait for AVF maturation or those unwilling to have AVFs formed. In prevalent haemodialysis patients the indication for CVC placement was inadequate or failed access via an existing AVF, AVG or CVC as well as patient choice.

Central venous mapping using conventional iodinated venography was only performed in patients with clinical signs suggestive of central venous stenosis (e.g. upper limb or facial swelling, plethoric facies, change in vocal quality) or in patients with a history of multiple jugular CVC insertions. In all patients temporary venous access for haemodialysis using an uncuffed CVC was obtained by the femoral vein only (to preserve upper body venous patency) and was in place for not more than a few days to reduce infective and thrombotic complications.

Translumbar inferior vena caval CVCs were inserted when all other AVF options and CVC approaches in the superior vena caval circulation were exhausted. Specifically bilateral brachiocephalic venous and/or superior vena caval occlusion not amenable to venoplasty and the absence of large, accessible thoracic collateral veins for CVC placement were indications for the translumbar approach. Prior to insertion the patency of the inferior vena cava was confirmed by conventional venography using the transfemoral route.

2.2.3. Protocol and technique of CVC insertion

Before insertion of a tunnelled, cuffed CVC both incident and prevalent haemodialysis patients were screened for methicillin-resistant *Staphylococcus aureus* (MRSA) carriage with nasal and axillary swabs according to hospital protocol. Those with MRSA carriage received 2% mupirocin ointment nasally (Bactroban ® Nasal Ointment, GlaxoSmithKline UK, Uxbridge, UK) four times daily. All other patients were treated with 0.1% chlorhexidine and 0.5% neomycin cream nasally (Naseptin ® Nasal Cream, Alliance Pharmaceuticals, Chippenham, UK) four times daily. These were started before CVC insertion and continued for 1 week after insertion.

Preprocedural single doses of antibiotics were given on the day of CVC insertion in all cases although the protocol varied according to the time period studied. From 1999 to 2005 patients received clarithromycin 250mg orally (or vancomycin 500mg intravenously if MRSA positive on screening) and ciprofloxacin 250mg orally. In the period from 2005 all patients received 500mg vancomycin intravenously and 250mg of ciprofloxacin orally.

All internal jugular TesioCaths™ were inserted by members of the surgical team with experience in the technique or by interventional radiologists under sterile conditions in operating theatres or in the interventional suite of the radiology department. Catheter insertion was achieved using an insertion point between the sternal and clavicular heads of the sternocleidomastoid muscle and correct placement was guided by ultrasound and x-ray fluoroscopy. All TesioCaths™ were inserted percutaneously using a two-guidewire technique and with no deep dissection to the vein. The tip of the “venous” catheter was placed about 3cm caudal to the right atrial margin visible on x-ray. The tip of the “arterial” catheters was placed 3cm cephalic to the tip of the “venous” catheter. The cuffs were individually tunnelled from the point of the percutaneous puncture to lie within the tunnel 3cm from the exit site and maintaining a separation of at least 1cm between the venous and arterial catheters. A post-procedural chest x-ray was performed to exclude pneumothorax and assess catheter tip position in all cases.

Catheter and central venograms were not routinely performed in cases of CVC replacement. Catheter venograms were performed as clinically indicated at the

discretion of the interventional radiologist. The surgical teams did not perform venography in any instance. If required mechanical fibrin sheath disruption using a guidewire was performed by the attendant interventional radiologist.

All translumbar CVCs were inserted by one experienced interventional radiologist. Two 75cm 10Fr single-lumen Bio-Flex TesioCaths™ were inserted under fluoroscopic guidance into the IVC with local anaesthesia and moderate intravenous sedation (Power et al. 2010c). The catheter tips were positioned using fluoroscopy to lie in the right atrium or the right atrial/inferior vena caval junction. The catheters were tunnelled using two discrete tracts to the right flank with the skin exit points aimed at the anterior axillary line and above the level of the belt.

Following insertion and flushing with normal saline to ensure adequate flow, all catheters were filled with 5000iu/ml unfractionated heparin (Monoparin sodium heparin, 5000iu/ml, CP Pharmaceuticals, Wrexham, UK) to the volume of each catheter lumen. 46.7% sodium citrate (DuraLock C™, MedComp) was used instead as a catheter lock in postoperative patients, patients with an overt bleeding diathesis and in those with heparin allergy or sensitivity. Antibiotic catheter locks were not used in any patient.

2.2.4. CVC care and microbiological screening

All CVCs were handled by trained staff using aseptic technique. The exit site was cleaned at the start of each dialysis session with 4% chlorhexidine gluconate solution (Hibiscrub®, Molnlycke Healthcare, Manchester, UK) for 1 minute before being allowed to dry in air and a new bio-occlusive dressing was then applied over it. 2% mupirocin ointment (Bactroban ®) was applied routinely to the exit site before the new dressing in 4/9 satellite dialysis units; no antibacterial ointment was applied in the remaining 5/9 units. The catheter hubs, clamps and distal portions of the catheter limbs were cleaned with 4% chlorhexidine solution and allowed to dry both before and after connection to the dialyser in all satellite units.

Quarterly screening of all patients for nasal and exit site carriage of MRSA was adopted as routine practice at our centre in 2007. All patients returning to their satellite dialysis unit after an inpatient admission were screened. Patients with

positive swabs were treated four times daily for a 5-day course with topical 2% mupirocin ointment nasally and to the exit site.

2.2.5. Dialysis adequacy and protocols

All patients in the study were dialysed three times weekly using low to medium flux synthetic haemodialysers. Specifically AM-BIO-1000Wet haemodialysers (Asahi Kasei Medical Europe GmbH, Frankfurt, Germany) were used with Gambro AK-100 or AK-200 (Gambro AB, Stockholm, Sweden) dialysis machines during 1999-2005 and Braun Dialog machines from 2005 (B. Braun Medical Inc., Bethlehem, PA, USA). Dialysis session length ranged from 2.5 – 5 hours. Dialysis adequacy was measured by single-pool Kt/V (spKt/V) on a monthly basis by using the Daugirdas method (Daugirdas 1993). Dialysis prescription was tailored to achieve a spKt/V $\geq$ 1.6. In patients failing to achieve this target, haemodialyser size was increased, blood flows were increased, dialysate flow rates were adjusted to $\geq$ 500ml/min and access recirculation assessed by a urea-based method and if necessary consideration given to access replacement.

The target blood flow for CVCs was $\geq$ 350ml/min. CVC dysfunction was identified by consistently suboptimal blood flow of <250ml/min and/or declining dialysis adequacy (defined as three consecutive falls in monthly spKt/V irrespective of magnitude). Catheter displacement or kinking was excluded by plain chest x-ray. Subsequently 5000 units of urokinase were instilled into each catheter lumen for 2 hours as a locking solution and dialysis was re-attempted on an outpatient basis. If this failed then patients were admitted to the ward for 12-hour intraluminal infusion of 12,500 units of urokinase using an infusion protocol previously described by Webb and colleagues (Webb et al. 2001). Contrary to the protocol by Webb et al. (2001), oral anticoagulation was not used with intent to improve blood flow rates. Similarly antiplatelet agents were not instituted for this indication. Failure of thrombolytic infusion mandated catheter replacement.

2.2.6. Definitions of infective episodes and management protocols

The definitions used in the studies aimed to be clinically relevant and allied to established reporting standards to aid comparison with published series. Pyrexia was defined as a tympanic temperature of $\geq 38^{\circ}\text{C}$, and all patients with pyrexia with or without a systemic inflammatory response were investigated with exit site swabs, multiple blood cultures drawn from the catheter itself and the peripheral veins, and urine and sputum culture where appropriate to circumstances. Samples were obtained before starting antibiotics to maximise diagnostic yield. Sepsis was presumed to be catheter-related if there was no clinical or microbiological evidence of another source. Empirical antibiotic treatment pre-empted microbiological confirmation of infection and followed a defined protocol (Table 2.1). Subsequent therapy was tailored to antibiotic sensitivities. Proven or suspected CVC infections were treated for a minimum duration of 2 weeks. Catheter-related bacteraemia (CRB) was defined according to established reporting standards (Silberzweig et al. 2003). Catheter salvage (i.e. treatment of infection without routine early catheter replacement) was attempted where clinically appropriate. Catheter-related sepsis was defined as the clinical presence of sepsis with growth of organisms in the blood or the catheter tip (in cases where catheter removal occurred) with no evidence of alternative source of infection. This definition is similar to published reporting standards (Silberzweig et al. 2003).

1999-2005

Sepsis, tunnel infection	Vancomycin 500mg & ceftazidime [†] 2g IV
Exit site infection	Clarithromycin 250mg bd & ciprofloxacin 250mg bd PO

2005-2010

Sepsis, tunnel infection	Vancomycin 500mg & meropenem 2g ^{*†} IV
Exit site infection	Vancomycin 500mg IV & ciprofloxacin 250mg bd PO

Table 2.1. Protocols for empirical treatment of access-related infections. All intravenous agents were administered post dialysis.

Abbreviations: IV, intravenously ; PO, orally ; bd, twice daily. * Tazocin 4.5g bd IV substituted for in-patients. [†] In the event of penicillin allergy, ciprofloxacin 250mg bd was substituted.

Exit site swabs were taken if there was exudate with or without pain, crusting, erythema or induration at the exit site. Infection limited to the exit site in the absence of pyrexia was treated initially with an empirical choice of oral agents and subsequently tailored according to determined antibiotic sensitivities for a minimum of 2 weeks. Febrile patients were treated as for systemic sepsis as described in Table 2.1.

Tunnel infections were defined by pain, redness or induration along the subcutaneous course of the CVC and were treated from the outset with intravenous antibiotics. The choice of agent was adjusted when culture results were available with the addition of a second appropriate oral agent for a minimum of 6 weeks. Persisting infection was indication for TesioCath™ removal.

Patients with pyrexia and exhibiting a systemic inflammatory response (core temperature > 38°C, tachycardia or tachypnoea, leucocytosis >12x10⁹/ml), relative hypotension or a persistent tunnel infection were admitted to our centre for ongoing care. Bacteraemia alone did not qualify the patient for admission. The catheter was only removed in the patient had hypotension requiring inotrope support, persistent bacteraemia, or refractory tunnel infection for >3 days despite targeted intravenous antibiotic therapy. Where appropriate a new TesioCath™ was inserted into the contralateral side once the bloodstream was cleared of infection for at least 48 hours.

2.2.7. Statistical methods

Parametric data were analysed using Student's t test, categorical variables were compared using chi-square or Fisher's exact test as appropriate and timeline incidence data using a Poisson model. Kaplan-Meier survival analysis was made on an intention-to-treat basis for patient survival censoring for change in dialysis access or modality, transplantation and transfer to another centre as well as for assisted primary CVC patency censoring for death with a functioning TesioCath, change in dialysis access or modality, transplantation and transfer to another centre. Statistical significance was defined by a p-value <0.05.

STATISTICA 9.0 (StatSoft Inc, Tulsa, OK, USA), StatsDirect 2.7.4. (StatsDirect, Altrincham, Cheshire, UK) and STATA 10.0 (StataCorp LP, College Station, TX, USA) were used to perform statistical analysis.

These studies were approved by our research governance board as audit/service evaluation and so waived the requirement for informed consent.

2.3. Results

2.3.1. Internal jugular CVCs

Four hundred and thirty-three patients undergoing 759 TesioCath™ insertions were examined spanning a total of 552,035 catheter days follow-up. The mean length of follow-up was 23.8 ± 23.3 months. The demographics of the study cohort are given in Table 2.2. Over a third of insertions (274 catheters, 36%) occurred in incident haemodialysis patients. In total 416/759 (55%) insertions were performed by the surgical team and the remainder by interventional radiologists. Twenty-nine insertions (4%) were unsuccessful (10 radiological, 19 surgical) and required a further procedure which was successful in all cases. There was one death as a result of asystolic arrest in the context of normokalaemia in a patient with ischaemic cardiomyopathy during otherwise successful radiological insertion. There were no other periprocedural complications.

	n	%
Mean age [years]	59.7 ± 15.2	
Patients aged >70 years	124	28.6
Male	247	57
Incident : Prevalent	222 : 221	
Mean dialysis vintage [months] *	39.1 ± 42.6	
Ethnicity		
White	209	48
African-Caribbean	86	20
South Asian	133	31
Diabetic	108	25

Table 2.2. Internal jugular CVC cohort demographics (n=433). * Describes prevalent dialysis patients only. Values expressed as mean $\pm$ standard deviation.

Cumulative patient survival rates were 85%, 72%, 63% and 48% at 1, 2, 3, and 5 years respectively (Figure 2.1). Diabetes had no significant effect on patient survival (log rank $p=0.26$).

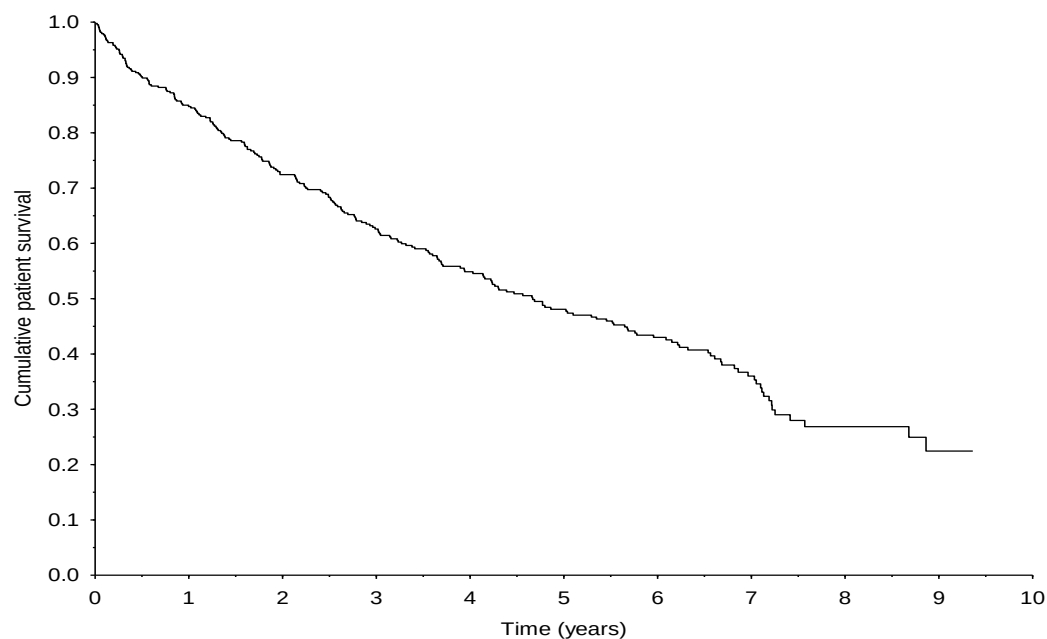


Figure 2.1. Cumulative patient survival for internal jugular CVC cohort. Data censored for death, transplantation, change of dialysis modality or access type and transfer to another centre.

Over the study period, 73 (17%) patients received a kidney transplant, three changed dialysis modality, 36 patients transferred to another centre and 232 of 433 (54%) died. The mean spKt/V achieved in patients during the study period was 1.6 ± 0.3 .

Median assisted primary CVC site patency was 3.2 years with cumulative patency of 76.1% at 1 year, 62.2% at 2 years and 42.6% at 5 years (Figure 2.2). Co-existent diabetes did not significantly affect assisted primary CVC site patency (log rank $p=0.07$) or time to first CVC failure (log rank $p=0.18$). In patients receiving their first CVC cumulative assisted primary site patency was not significantly different in incident compared with prevalent patients (as defined by more than 30 days on haemodialysis; log rank $p=0.09$) however median assisted primary site patency declined with each subsequent CVC insertion (3.41 vs. 3.19 and 2.02 years for first, second and third CVC respectively).

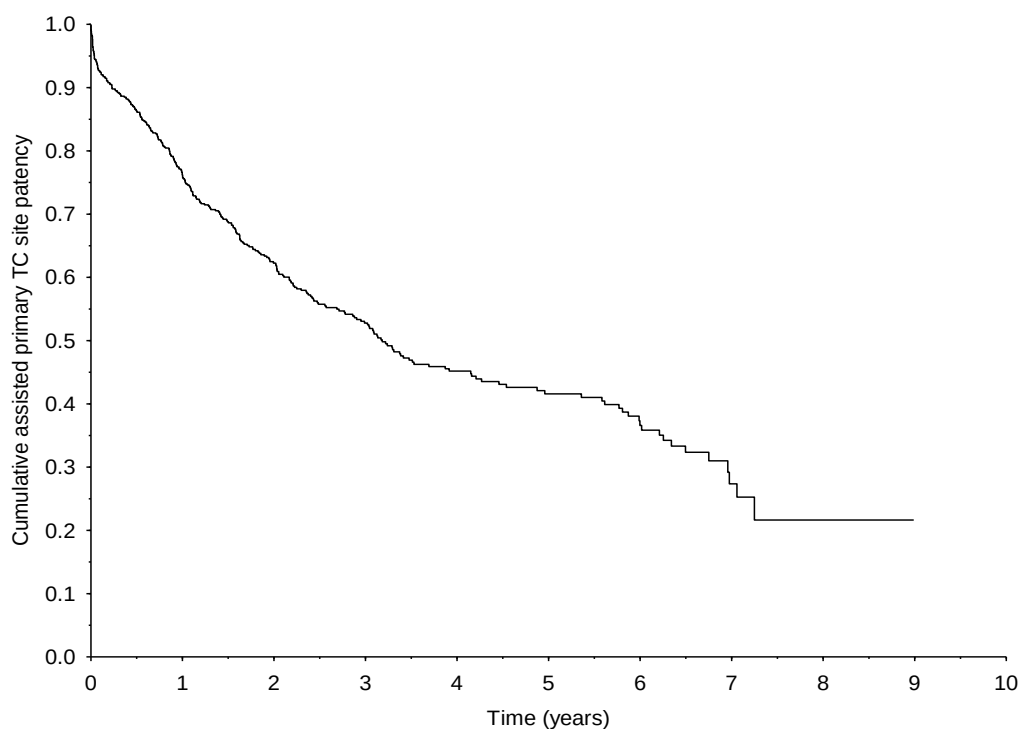


Figure 2.2. Cumulative assisted primary internal jugular CVC site patency. Data censored for death, transplantation, change in dialysis modality or access type and transfer to another centre.

Interventional radiology insertions were associated with worse CVC patency than surgical insertions on univariate and multivariate analysis (hazard ratio [HR] 1.41, 95% confidence interval [CI] 1.13 – 1.77). However a greater proportion of patients presenting to the radiologists had a history of prior CVCs (49% vs. 38%, $p=0.002$). The distribution of prior CVC insertions is shown in Figure 2.3. Diabetes, ischaemic heart disease, cerebrovascular disease, patient ethnicity and age were not significantly associated with worse CVC patency (Table 2.3).

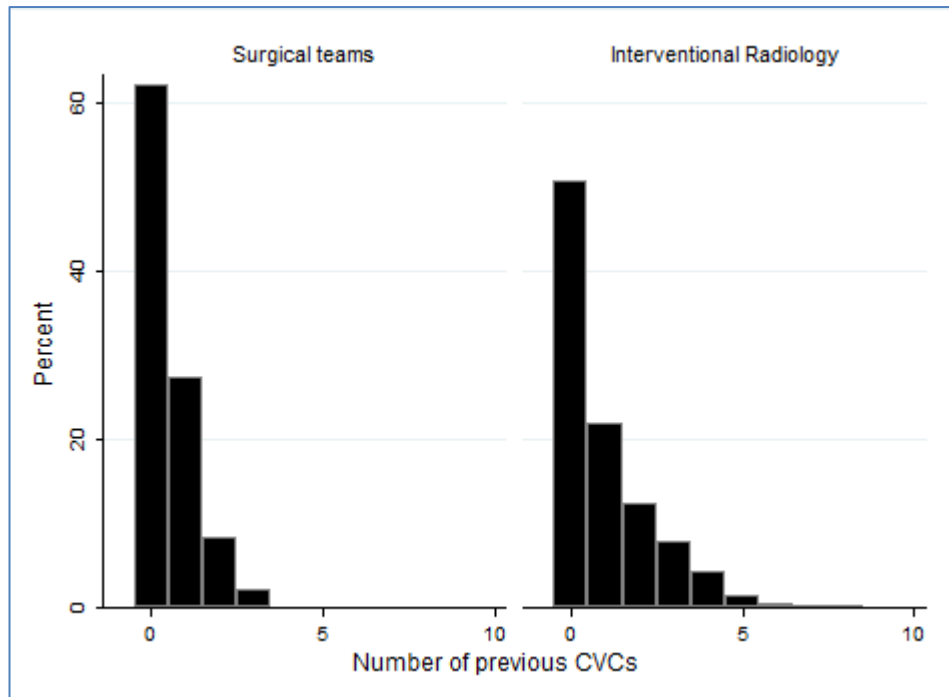


Figure 2.3. Prior CVC history in patients presenting to surgical or interventional radiology teams for CVC insertion.

There were 195 admissions for CVC dysfunction during the study period at a rate of 0.35 per 1000 catheter days (95% CI, 0.31 – 0.41). A total of 164 of 195 (84%) admissions were a result of suboptimal flow not resolving with the use of urokinase catheter locks. Elective CVC replacement was performed in 41 of 164 (25%) cases. Urokinase infusion was used in the remainder and was successful on 53 of 123 (43%) occasions. In addition, 31 of 759 (4%) TesioCaths™ dislodged and required replacement at a rate of 0.06 per 1000 catheter days (95% CI, 0.04 -0.08). Twenty-two (5%) patients required venoplasty of central venous stenoses over the course of the study period (11 lesions in the right and nine in the left brachiocephalic veins were treated as well as seven lesions in the upper superior vena cava). No patient had more than one procedure.

Factor	Univariate analysis		Multivariate analysis	
	Hazard ratio	p value	Hazard ratio	p value
Age [yrs]	1.00 [0.99 - 1.00]	0.3	-	
Caucasian ethnicity	0.98 [0.78 – 1.22]	0.8	-	
Diabetes mellitus	1.29 [1.02 – 1.64]	0.03	1.24 [0.98 – 1.57]	0.07
Hypertension	1.05 [0.83 - 1.32]	0.7	-	
IHD	0.84 [0.67 – 1.06]	0.1	-	
CrVD	0.98 [0.75 – 1.27]	0.9	-	
PVD	0.90 [0.65 – 1.23]	0.5	-	
Any previous CVC	1.22 [0.97 – 1.52]	0.09	1.15 [0.92 – 1.44]	0.2
Insertion by IR	1.44 [1.16 – 1.79]	0.001	1.41 [1.13 – 1.77]	0.002

Table 2.3. Regression analysis of factors affecting primary assisted TesioCath™ site patency. Hazard ratios expressed with 95% confidence intervals in square brackets. Abbreviations: IR, interventional radiology.

A total of 425 infective episodes were identified, 88% with a defined source. Of these, 115 (27%) were proven to relate to vascular access with a further 118 (28%) presumed to. The overall incidence of catheter-related infection was 0.42 per 1000 catheter days (95% CI, 0.37 – 0.48) comprising 46 episodes of exit-site infection at a rate of 0.08 per 1000 catheter days (95% CI, 0.06 – 0.11) and 187 episodes of catheter-related bacteraemia at a rate of 0.34 per 1000 catheter days (95% CI, 0.29 – 0.39). There were 176 admissions for catheter-related sepsis, a rate of 0.31 per 1000 catheter days (95% CI, 0.27 - 0.37).

2.3.2. Translumbar CVCs

Thirty-nine TesioCaths™ were inserted in 26 patients with a total experience of 15,864 catheter days follow-up. The mean length of follow-up was 13.3 ± 15.5 months (range 0.2 – 81.6). Thirty-five percent of patients were over 65 years old and 31% were diabetic (Table 2.4). Diabetes mellitus was the cause of ESRD for 3/26 patients. Mean age at insertion for diabetics was 65.1 ± 11.1 vs. 60.2 ± 12.5 years in non-diabetics ($p=0.3$). Overall patients were established on haemodialysis for 5.9 ± 3.2 years on average before they required a translumbar CVC. Twenty-one of twenty-six (81%) of patients had at least one arteriovenous access (AVF or AVG) prior to receiving a translumbar CVC. Patients had a mean of 4.2 vascular accesses prior to requiring a translumbar CVC (mean 3.0 ± 1.3 CVCs, 1.0 ± 0.9 AVFs, 0.5 ± 0.7 AVGs). All patients had bilateral brachiocephalic venous occlusions and 9/26 had concurrent superior vena caval occlusion.

	n	%
Mean age at insertion [years]	61.9 ± 12.1	
Male	11	42
Mean dialysis vintage [years]	5.9 ± 3.2	
Ethnicity		
White	14	54
African-Caribbean	6	23
South Asian	6	23
Comorbidities		
Diabetes mellitus	8	31
Hypertension	15	58
Ischaemic heart disease	7	27
Peripheral vascular disease	3	12

Table 2.4. Translumbar study cohort characteristics. Values expressed as mean $\pm$ standard deviation.

Cumulative patient survival was 81.5% at 1 year, 68.1% at 2 years and 51% at 3 years censoring for change of dialysis modality, transplantation and transfer to another unit. No patients died as a result of lack of vascular access options or CVC-related infection. Diabetic comorbidity did not significantly affect patient survival (log rank $p=0.4$). Patient survival in this cohort was not significantly different at these time points to that of the internal jugular cohort described in Section 2.3.1 (log rank

p=0.3). Of note both cohorts were similar with respect to age and major comorbid conditions but different with respect to gender predominance.

All CVCs were placed successfully with immediate function yielding post-insertion blood flow rates of ≤ 300 ml/min. Catheter tips rested in the right atrium in 18/37 cases and the right atrial/inferior vena caval junction in 20 cases reflecting patient habitus as well as upper venous anatomy. Subsequent mean monthly blood flow rate for all catheters was 300 ± 3 ml/min (range 100 – 450 ml/min; mean 307 ml/min). The mean spKt/V was 1.5 ± 0.4 over the course of the study. There was a trend to a higher mean spKt/V (from 1.2 to 1.6) over time reflecting an increase in the minimum targeted spKt/V at our unit from 1.4 to 1.6 (Figure 2.4). A spKt/V ≥ 1.2 was achieved in 87.2% patients and a spKt/V ≥ 1.4 was achieved in 71.8%.

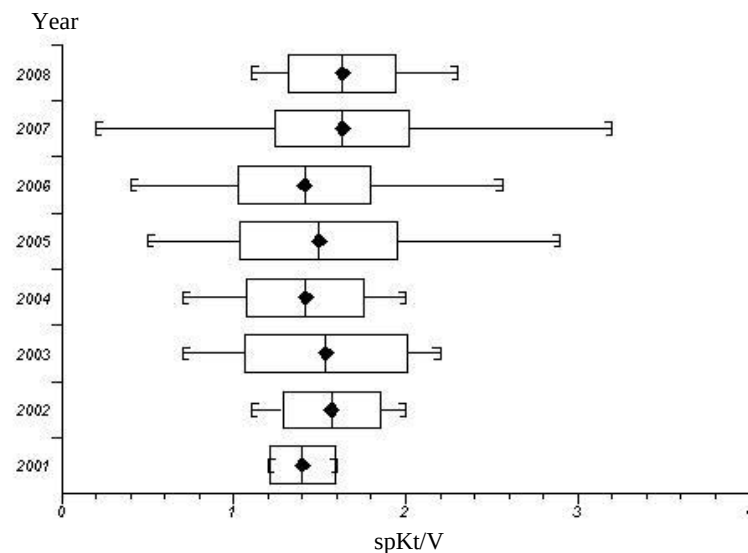


Figure 2.4. Dialysis adequacy (spKt/V) achieved by translumbar CVCs over the time of the study. Box = mean, standard deviation, 25-75%; T-bars = minimum and maximum values.

Cumulative assisted primary CVC site patency was 73.2% at 1 year, 33.4% at 2 years and 27.9% at 3 years censoring for death, change in dialysis modality, transplantation and transfer to another unit (Figure 2.5). The presence of diabetes did not significantly affect CVC patency (log rank p=0.09). The insertion of one catheter was associated with a self-limiting retroperitoneal haematoma that was managed conservatively and no blood transfusion was required. A second retroperitoneal bleed occurred following catheter displacement. There were no other major complications.

During the study period four of thirty-nine (10%) catheters dislodged and required replacement. Catheter dysfunction requiring urokinase infusion occurred in 10 catheters, a rate of 0.63 per 1000 catheter days (95% CI, 0.30 – 1.16). Nine of thirty-nine (23%) catheters required replacement for persistent dysfunction (Table 2.5).

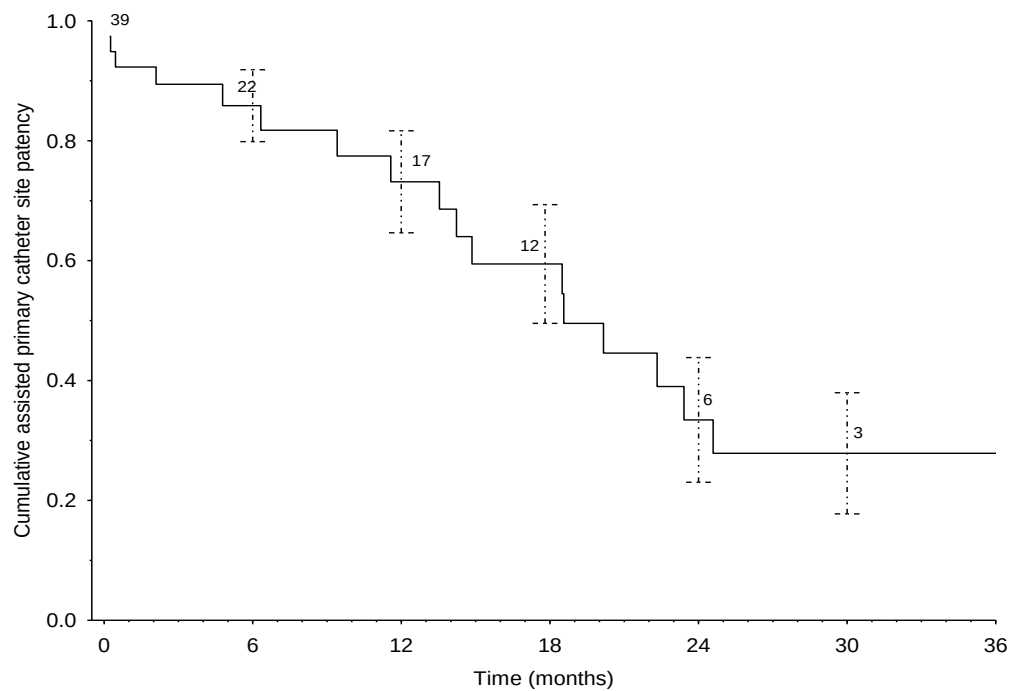


Figure 2.5. Cumulative assisted primary catheter site patency for translumbar TesioCaths™. Numbers at risk shown in black font.

The incidence of catheter-related infection was 2.84 per 1000 catheter days (95% CI, 2.07 – 3.80). There were 32 episodes of exit-site infection including 1 pseudomonal tunnel infection. There were 13 episodes of CRB at a rate of 0.82 per 1000 catheter days. Nine of nineteen (47%) hospital admission for infection were due to proven or presumed catheter-related sepsis.

	Incidence rate	95% CI
Catheter-related bacteraemia	0.82	0.44 – 1.40
Exit-site infections	2.01	1.38 – 2.85
All-cause hospital admission	3.97	3.05 – 5.08
Hospital admission due to CVCs	1.45	0.92 – 2.16
Access infection-related hospital admission	0.57	0.20 – 1.08
Access dysfunction-related	0.88	0.48 – 1.48

Table 2.5. Infective and mechanical complications of translumbar CVCs. Incidence rates expressed as events per 1000 catheter days. Abbreviations: CI, confidence interval.

2.4. Conclusions

Both these retrospective studies demonstrate that TesioCaths™ deliver an adequate haemodialysis dose with rates of access-related infection that in absolute terms are low compared to published series and with no compromise to patient survival when compared to national registry data. Compared to internal jugular CVCs, translumbar CVCs have higher rates of thrombotic dysfunction and lower primary catheter patency rates as well as higher rates of catheter-related infection. This section will appraise these findings in turn before discussing hypotheses that warrant further study.

2.4.1. Internal jugular CVCs

The current study is one of the largest published series examining the function of a specific CVC (TesioCath™) for maintenance haemodialysis with prior studies varying in cohort size and duration of follow-up (Table 2.6). For the purpose of this discussion the term CVC will relate to the TesioCath™ catheter type unless otherwise stated.

Authors	Publication year	TesioCaths™ [n]	Jugular placement	Total follow-up [catheter days]
Power et al.	2011	759	All	552,035
Wang et al.	2006	303	All *	74,876
Wivell et al.	2001	184	183	13,200
Webb et al.	2002	100	74	13,749
Perini et al.	2000	79	79	4,367
Prabhu et al.	1997	82	82	7,046

Table 2.6. Major studies examining outcomes with the TesioCath™ system for maintenance haemodialysis.

* This is presumed although not stated.

A large single-centre UK study by Fry and colleagues has not been included in Table 2.6. It reported on over 212,000 catheter days of follow-up using 3 different types of CVC including 359 TesioCaths™ (Fry et al. 2008). However this series includes a substantial number of femoral catheters (n=120, 15% total study cohort) and the authors do not report outcomes or length of follow-up according to catheter type. Wang et al. (2006) present a large U.S. series with clear access route protocols (internal jugular, then femoral and finally translumbar) but do not explicitly state the location of the CVCs on which they finally report.

Cumulative assisted primary patency rates in this study are higher than those reported to date. Wang et al. (2006) studied 303 CVCs in 200 patients and reported patency rates of 60% at 1 year, 51.5% at 2 years and 51.5% at 3 years. The study by Wivell et al. (2001) in 132 patients had much shorter follow-up (to 1.5 years) and reported an even worse patency rate of 45% at 1 year. Although Fry et al. (2008) do not report patency rates at set time points, analysis of the Kaplan-Meier curves suggests TesioCath™ patency rates of 69%, 44% and 30% at 1, 2 and 3 years respectively. The enhanced patency rates in our study occurred despite the relatively low efficacy of urokinase infusions compared to other studies: 43% vs. 95% (Webb et al. 2001) and 82% (Twardowski 1998a). Furthermore catheter dysfunction was defined by a blood flow less than 200ml/min in the U.S. studies by Wang et al. (2006) and Wivell et al. (2001) as opposed to a more stringent 250ml/min in our study and yet the incidence of dysfunction was higher in their cohorts (8.8 and 0.8 per 1,000 catheter days respectively vs. 0.35 per 1,000 catheter days in our study). Differences in reported patency rates may therefore relate to a number of other factors such as the different populations studied and unquantified centre-specific differences in surgical, radiological and haemodialysis staff experience. The higher prevalence of diabetes (46% vs. 25%) in the study by Wang et al. (2006) may have adversely affected catheter patency although this was not observed in this study. Both Wivell et al. (2001) and Wang et al. (2006) described U.S. populations with different ethnic case mixes which may have had an effect on outcomes – 37% patients in the study by Wang et al. (2006) were African-Caribbean as opposed to 20% in our study. Adoption of a catheter salvage policy as opposed has been shown to be successful in approximately two-thirds of cases at our centre, with no additional adverse effect on patient survival or infective complications (Ashby et al. 2009). This approach is likely to have had a positive effect on assisted primary access site patency rates in our study.

The other significant difference in clinical outcomes between this study and published TesioCath™ cohorts is in the incidence of access-related infection. It is possible that differences in catheter dysfunction reported above may relate causally to differences in rates of access-related infection, comprising both local infection (at the exit site or tunnel) as well as CRB which can lead to systemic sepsis syndrome and sequelae such as infective endocarditis, discitis or osteomyelitis (Lok 2006;Nassar and Ayus 2001). Studies report CRB incidence at 2-5 cases per 1,000 catheter days with considerable variation between centres and countries (Allon 2004;Lee et al. 2005;Pisoni et al. 2009). A recent Center for Disease Control (CDC) study found access-related bacteraemia rates of 0.07, 0.15 and 1.01 per 1,000 access days for AVF, AVG and tunnelled CVCs respectively (Klevens et al. 2008). Antimicrobial catheter locks have been used to reduce CRB rates further (to 0.3 – 1.1 per 1,000 catheter days) albeit in centres with relative high CRB rates in the control groups. We found no additional efficacy of 46.7% sodium citrate in a prospective, randomized controlled trial at our centre (Power et al. 2009b). Low CRB rates in the present study (0.34 per 1,000 catheter days) without the routine use of an antimicrobial catheter lock are consistent with results from other centres (Spector et al. 2008;Zhang et al. 2009). Adherence to a defined peri-procedural catheter insertion and care protocol including antibiotics may be contributory. The use of 4% chlorhexidine rather than the recommended standard of 2% (O'Grady et al. 2002;Valles et al. 2008) may have helped further but there are no trials comparing the two in haemodialysis. Intranasal mupirocin at catheter insertion, screening and treatment for MRSA at the exit site, pre-emptive antibiotic starts where clinically indicated and the experience of haemodialysis nursing staff in a programme with a high CVC prevalence may have further influenced CRB rates favourably.

The relatively low efficacy (43%) of urokinase infusion at restoring adequate function (i.e. ability to sustain flows >250ml/min) in our study is striking. Assessing prior literature reveals significant differences in protocol (Table 2.7).

Study	Year	Urokinase lock	Urokinase infusion	Efficacy
Power et al.	2011	5,000 units each limb for 2hrs	12,500 units each limb over 12hrs	43%
Shavit et al.	2010	Not stated	125,000 units each limb over 90mins	97%
Webb et al.	2001	5,000 units each limb for 4 hrs	25,000 units each limb over 12hrs	95% overall (77% first infusion)
Twardowski	1998	5,000 – 9,000 units each limb for 1hr	125,000 units each limb over 1.5hrs 250,000 units intradialytically over 3hrs	78% 81 → 90% with repeated use
Peska et al.	1997	Not stated	50,000 units each limb over 30mins	68%

Table 2.7. Summary of studies using urokinase infusion for CVC dysfunction. Efficacy is defined as sustained haemodialysis with blood flow rates ≥ 250 ml/min following treatment. Studies allowed for multiple urokinase infusions.

There is clearly a relationship between the urokinase dose delivered and lytic efficacy in the studies listed which included a variety of CVCs that may have influenced results. The dose and duration of prior intraluminal urokinase locks may have biased outcomes with infusions and efficacy modulated by catheter design. The low rates of urokinase efficacy in our study probably relates to the relatively low doses used due to prevailing concerns amongst clinicians at our centre about bleeding in haemodialysis patients.

There was a near exponential decrease in the primary assisted catheter site patency rates with each subsequent CVC insertion suggesting an influence from established structural pathology (Figure 2.3) such as central venous stenosis or pre-existing fibrin sheath or thrombus. The prevalence of symptomatic central venous stenosis in the cohort described in this study was 5% although the prevalence of occult stenosis may indeed have been higher (Taal et al. 2004). Nonetheless despite a high prevalence of CVC use at our centre this figure is low and may reflect the low infection rates (Hernandez et al. 1993), avoidance of temporary internal jugular CVCs

and TesioCath™ design. Clearly the patency rates of catheters inserted by radiologists were lower than those inserted by surgical teams (41% increased risk of CVC loss) and likely represents bias by indication as these catheters were inserted in situations deemed to be more challenging (e.g. numerous previous CVCs, presence of a cardiac pacemaker, established central venous stenosis).

2.4.2. Translumbar CVCs

The data from our study represents one of the largest and most detailed series in the available literature (Table 2.8) and demonstrates good patency and access flow rates. Prior series were limited by small cohort size (Biswal et al. 2000;Lund et al. 1995) or lack of data on catheter function (Rajan et al. 1998).

Authors	Year	CVCs for HD [n]	Data on flow [Y/N]	Follow-up [catheter days]
Power et al.	2009	39	Y	15,864
Biswal et al	2000	10	N	2,252
Rajan et al.	1998	54	N	<i>Not reported</i>
Lund et al.	1995	15	Y	2,076

Table 2.8. Summary of major studies reporting on series of translumbar CVCs for haemodialysis.

Mean assisted primary catheter site patency (73% at 1 year) was much longer than that reported by Biswal et al. (2000) and exceeds the rate of 17% at 1 year reported by Lund et al. (1995). Patient demographics and comorbidities are not reported in detail in either paper and may have accounted for some of the differences seen. Although Biswal et al. (2000) reported on a series of 10 TesioCath™ CVCs, Lund et al. (1995) used two different CVC types in their series and it is possible that catheter design further affected outcomes.

Lund et al. (1995) report in limited detail in their study on the achieved flow rates (stating it to be between 200 and 300ml/min) in 15 catheters that were inserted for haemodialysis and two for plasmapheresis. As such our study is the first to report in detail on the achieved flow rates. A mean blood flow rate of 300ml/min delivered by

the translumbar TesioCaths™ in our study is comparable that delivered by a historic series of similar internal jugular CVCs (291ml/min; Duncan et al. 2004). Clearly achieved blood flow rates will reflect the local target for dialysis adequacy and there are no comparative data on this aspect of performance in translumbar CVCs. The catheters in this study achieved the desired increases in dialysis adequacy with a mean spKt/V exceeding the mean urea reduction ratio of 61% in the TesioCath™ series of Wivell et al. (2001) and equivalent to that for internal jugular CVCs (Duncan et al. 2004).

Catheter thrombosis requiring thrombolytic infusion occurred at lower rate than in the study by Lund et al. (1995), 0.63 vs. 3.3 per 1,000 catheter days. This may be because they report thrombosis in single double-lumen catheters as opposed to the twin single-lumen TesioCaths™, two of the CVCs in their series were used for plasmapheresis, and it is unclear whether they used a catheter locking solution and if so what it contained. In addition the catheters used in the study by Lund et al. (1995) reflect older technology with a step-tip configuration that may have contributed to the difference seen. Of course the phenotype of patients requiring translumbar CVCs is likely to be significantly different to patients requiring access via a conventional route. Such patients may have endothelial dysfunction or a procoagulant state that predisposed them to increased rates of access loss. This may further compromise subsequent access function although there are no available studies to confirm this.

Interestingly, rates of all-cause mechanical dysfunction in this study (i.e. thrombosis and displacement) were comparable to those reported in internal jugular TesioCaths™ by Wang et al. (2006), 0.88 vs. 0.8 per 1,000 catheter days. Overall 10% of CVCs dislodged in our series, which is similar to the 13% reported by Biswal et al. (2000), but remains a significant proportion of inserted accesses and relates to their site of insertion. The rate of complications associated with this route was low in this study and is in keeping with prior literature (Biswal et al. 2000; Markowitz et al. 1998).

CRB rates again may have influenced rates of thrombotic dysfunction by occurring at a lower rate than that in the series by Lund et al. (1995), 0.82 vs. 1.4 per 1,000 catheter days. This is similar to the rate of 0.81 per 1,000 catheter days reported in a large UK single-centre series by Winnett et al. (2008) and lower than that published by Wivell et al. (2001) and Wang et al. (2006): 2.3 and 1.4 per 1,000 catheter days respectively. In the context of our centre however this represents a higher rate of

CRB than for internal jugular CVCs which probably reflects the anatomical site of insertion where the patient lies on the exit site and it subjected to more mechanical stress.

The transfemoral route would appear to be a useful first option where there is preserved lower body venous patency as it is associated with fewer periprocedural complications than either translumbar or transhepatic routes (Smith et al. 2004;Stavropoulos et al. 2003). However it is associated with lower patency rates (mean of 85 days vs. 406 days in this study) and with higher rates of infection, 5.2 per 1,000 catheter days (Zaleski et al. 1999). In addition this route has a high rate of ipsilateral deep venous thrombosis reaching 25% (Maya and Allon 2005). Although better outcomes have been reported in a more recent series using TesioCaths™, rates of thrombosis (12% of cohort) and infection (1.77 per 1,000 catheter days) remain disproportionately high with disappointing assisted patency rates of 54% at 1 year in a centre that prophylactically locked the lumens with urokinase (Bertoli et al. 2010). As a result this approach is not favoured at our centre.

2.4.3. Study limitations

These studies benefit from direct comparisons of outcomes using standardised definitions and protocolised delivery of care within a single centre and using CVCs with a single design type. Data has been validated using multiple sources to deliver an accurate dataset for analysis. The clinical outcomes reflect daily clinical practice and as such are applicable to this scenario. However such retrospective studies have inherent limitations.

The use of a large unselected cohort as in the internal jugular CVC study would help minimise bias although there is clear confounding by indication in the cohort of patients requiring translumbar access. The cohort size in the translumbar CVC study remains small in absolute terms and conclusions from the data need to be interpreted in that light. It can be suggested that results obtained in one centre with a high degree of expertise in using CVCs may be limited in their applicability to other centres. Finally a retrospective approach can suggest associations and lead to the generation of hypotheses but inherently cannot prove causality and other factors that were not explored in these studies may have influenced outcomes.

Significantly neither study reported on the incidence of catheter dysfunction resolving with thrombolytic locks alone. The internal jugular CVC study did not explore the potential effect of laterality on patency rates, which has been clearly demonstrated in other studies (Fry et al. 2008). Furthermore these studies did not comprehensively explore the temporal association between infection and thrombotic dysfunction.

2.4.4. Influence of access site

Access site remains a powerful determinant of subsequent CVC function and complications. Compared to the internal jugular route, translumbar CVCs are associated with equivalent short-term, although lower long-term, patency rates and higher rates of infection and mechanical dysfunction (Table 2.9). Rates of catheter-related bacteraemia and dysfunction are just over 2-fold higher in translumbar CVCs, a finding that suggests a possible shared pathophysiology.

Access site	Cumulative primary assisted CVC site patency			CRB rate	Displacement rate	Thrombolytic infusion rate
	1 yr	2 yrs	3 yrs			
Internal jugular	76%	62%	55%	0.34	0.06	0.29
Translumbar	73%	33%	28%	0.82	0.25	0.63

Table 2.9. Comparative outcomes using the TesioCath™ system for haemodialysis via the internal jugular and translumbar routes. Rates are expressed as events per 1,000 catheter days.

Despite concerns with the use of CVCs for long-term vascular access in HD patients, the survival data reported in these two studies is at least comparable and sometimes better than national registry data which contains populations with a much lower prevalence of this access form (Ansell et al. 2010;US Renal Data System 2007). The infection rates reported in the internal jugular CVC series are comparable to those reported with AVGs (Klevens et al. 2008;Taylor et al. 2002) and as such challenge assertions that this form of arteriovenous access is comparable to an autogenous fistula particularly where access type is used to determine healthcare remuneration policies.

3. Catheter type as a determinant of CVC thrombosis

This chapter presents the results of a prospective randomized controlled study (VyTes) using two comparable CVCs for haemodialysis – the TesioCath™ and the Vygon LifeCath Twin™. Catheter function, outcomes and complications are assessed as well as the prevalence and potential impact of procoagulant profiles on thrombotic catheter dysfunction.

3.1. Introduction

3.1.1. Catheter design and function

Since the inception of tunnelled CVCs for long-term haemodialysis in the 1960s there have been numerous designs available for commercial use that attempt to combine ease of insertion with long-term durability, performance, ease of use and safety. An extensive review of catheter materials design and fluid mechanics is beyond the scope of this text but can be found in an extensive review (Ash 2008).

There are 2 broad categories of tunnelled CVC for haemodialysis: those with twin catheters placed in parallel, such as the Canaud and Tesio catheters (Canaud et al. 1998; Tesio et al. 1994), and those with a single catheter containing both lumens such as the PermCath™ designed by Quinton (Schwab et al. 1988) and the SplitCath™ designed by Ash (Ash et al. 2002). Most variations in the single body design relate to the cross-sectional luminal shape (e.g. D-shape vs. circular) and the conformation of the distal end of the catheter which can be either as a step-tip (e.g. HemoGlide™ catheter) or split-tip (e.g. SplitCath™ and HemoSplit™).

The overall intent of these changes in design is to deliver high blood flow rates while minimising recirculation as well as vessel trauma that may lead to thrombosis. Ultimately assessments of design superiority are best made in the setting of well-designed prospective randomized controlled trials (RCTs). It is surprising that given the breadth of experience in haemodialysis with CVCs for over more than five decades, there are relatively few such published studies (Table 3.1).

Authors	Year	Catheter types	Catheter number	Follow-up
O'Dwyer et al.	2005	AshSplit™ PermCath™	69	18 months
Schwab et al.	2002	TesioCath™ LifeSite™	70	6 months
Trerotola et al.	2002	SplitCath™ Opti-Flow™	132	6 months
Trerotola et al.	2001	Hickman™ AshSplit™	24	6 weeks
Richard et al.	2001	TesioCath™ AshSplit™ Opti-Flow™	113	12 months

Table 3.1. Summary of published RCTs to date comparing function in tunnelled CVCs for haemodialysis.

3.1.2. TesioCath™ performance

Our centre has favoured the TesioCath™ twin catheter system despite the need for two separate venous punctures and subcutaneous tunnels. Clinical experience of long-term patency and dialytic adequacy has been detailed already in Chapter 2 without focusing on aspects of catheter performance such as blood flow rates and catheter recirculation.

The first detailed analysis of TesioCath™ performance examined 82 CVCs over a 12 month period and was published over a decade ago (Prabhu et al. 1997). This study demonstrated attainment of high blood flow rates (400ml/min) with acceptable recirculation rates (mean 4.6%±0.5%) that are comparable to other catheters (Trerotola et al. 1999). Reaching such high flow rates in CVCs is often limited by high venous pressures (typically over 300mmHg) and the performance of the TesioCath™ in this respect is attributed to the number and orientation of side holes on the distal tip giving low resistance to flow. A subsequent study of 67 Tesio catheter pairs (Perini et al. 2000) highlighted the immediate performance of these CVCs which constitutes a well-recognised drawback - immediate post-insertion flow rates were lower than on subsequent HD sessions (mean 286ml/min, minimum 160ml/min during the first HD session; mean 300ml/min on subsequent sessions).

This characteristic of the Tesio catheter was highlighted by Wivell et al. (2001) in their series: "... for reasons that are not apparent, the Tesio catheters do not provide

blood flows adequate for dialysis until at least 24 hours after placement, a problem that is noted on the package insert.”. It has been speculated (though not proven) that the soft, flexible nature of the polymer used in the design of CVCs allows for comfort and ease of insertion but the intrinsic deformability of the catheter makes it prone to extrinsic compression from an acutely oedematous subcutaneous tunnel. TesioCaths™ in their study delivered a mean flow rate of 281ml/min and an average recirculation rate of 6.1%.

Another feature of Tesio catheter design is the cuff configuration– an ovoid shape with a strip of Dacron in the middle, rather like a rugby football. This allows for smoother insertion through the subcutaneous tunnel but has been anecdotally considered suboptimal for tethering the CVC in position making it more prone to displacement than catheters with classic cuboidal cuffs. Three studies have reported specifically on TesioCath™ displacement. No displacement over a one year period was reported by Prabhu et al. (1997) while Wivell et al. (2001) reported a displacement rates of 0.38 per 1,000 catheter days and rates of 0.06 per 1,000 catheter days was reported from our centre (Power et al. 2011). There is no data on displacement in the few comparative studies between TesioCaths™ and other CVCs.

With the exception of the series by Prabhu et al. (1997) prior studies did not target high-end (>300ml/min) flow rates for maintenance haemodialysis and, other than the study by Perini et al. (2000), did not detail dialysis adequacy. As such a rigorous prospective assessment of TesioCath™ performance with modern dialysis practices is still absent in the literature.

3.1.3. LifeCath Twin™ central venous catheter

The LifeCath Twin™ CVC for haemodialysis (Vygon UK, Swindon, Wilts, UK) consists of two separate 10Fr lumens that are inserted using two separate venous punctures and dilations and lie in parallel along two separate subcutaneous tunnels. The technique of insertion is as for the TesioCath™ (described in Section 2.2.3). However there are a number of differences in design compared to the TesioCath™ that are described below:

(a) Stiffer polymer

The polyurethane polymer material used for the design of the LifeCath Twin™ remains flexible but is stiffer and less deformable than the TesioCath™, a design change which is said to allow for high flow rates ($\geq 400\text{ml/min}$) from the first dialysis post-insertion (personal communication, Vygon UK).

(b) Cuff design reduces catheter displacement

These catheters have a cuboidal cuff fully coated in Dacron that is claimed to offer better tethering within the subcutaneous tunnel and less displacement compared to the Tesio catheter system (personal communication, Vygon UK).

(c) Different hub locking device

Although similar in principle, the LifeCath Lock device is structurally different to the equivalent hub locking device in the Tesio catheters both in the design of the locking components as well as having a longer metallic introducer component (Figure 3.1).

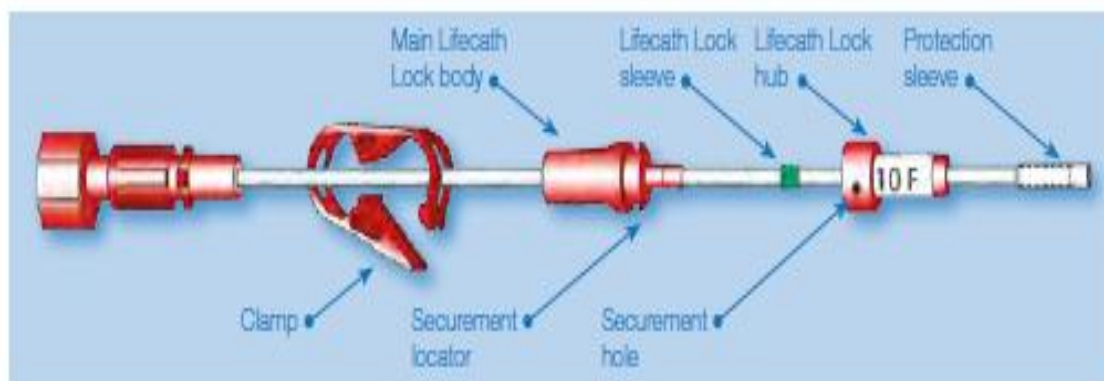


Figure 3.1. The LifeCath Lock device (from Vygon UK).

(d) Sidehole design

Compared to the TesioCath™, the LifeCath Twin™ has a similar number of sideholes (6) at the distal end intended to reduce resistance to flow but they are placed in a subtly different spiral orientation to the TesioCath™ (Figure 3.2). On inspection they are just <1mm smaller than those on the TesioCath™.

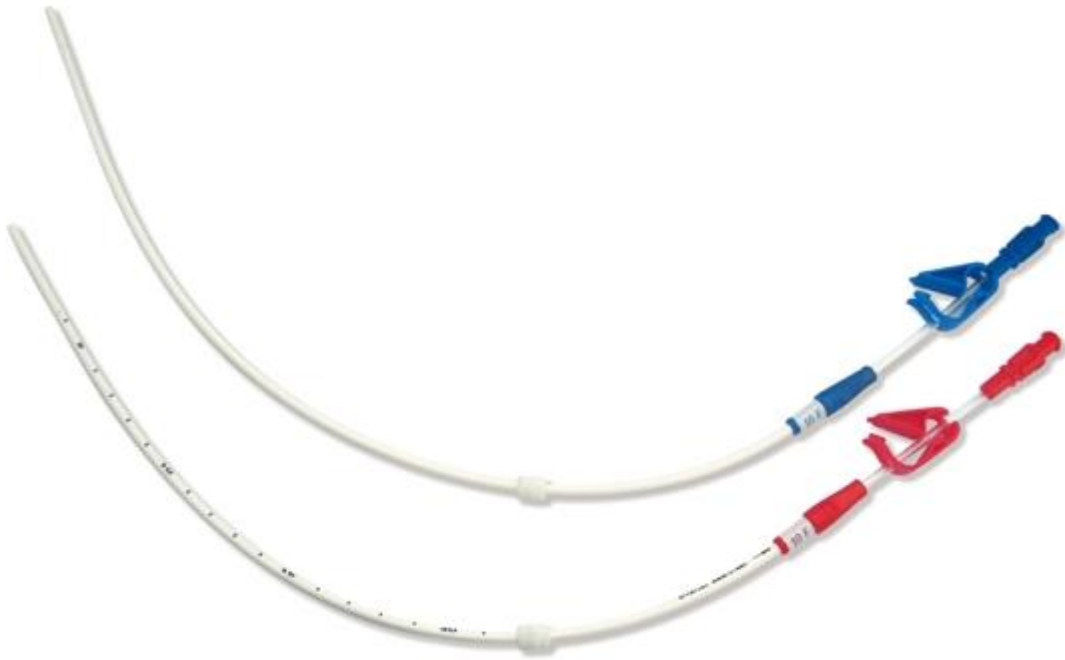


Figure 3.2. LifeCath Twin™ catheters (from Vygon UK).

The manufacturer claims that the LifeCath Twin can deliver blood flow rates greater than 400ml/min consistently: "... flow rate pressure at 0.41 Bar (calculated for the complete catheter before the length is adjusted by the physician): 473 ml/min ..." (Vygon UK). Despite its current use in clinical practice there are no published clinical trials using the LifeCath Twin for maintenance haemodialysis and the assertions regarding performance remain unvalidated.

3.1.4. Procoagulant profiles and catheter function

The role of thrombophilic phenotypes in catheter thrombosis remains poorly characterised as almost all studies in haemodialysis have examined patients with arteriovenous access (grafts and/or fistulae), have heterogeneous methodology with conflicting results. Greater rates of access thrombosis occurred with the 4G/5G polymorphism of the plasminogen activator inhibitor-type 1 (PAI-1) gene (Lazo-Langner et al. 2006; Trimarchi et al. 2008) and the C677T polymorphism of the methylenetetrahydrofolate reductase (MTHFR) gene (Fekih-Mrissa et al. 2011; Fukasawa et al. 2003). A role for elevated lipoprotein(a) levels (Hojs et al. 2002; Knoll et al. 2005), platelet factor 4-heparin antibodies (Carrier et al. 2007; O'shea et al. 2003), anticardiolipin antibodies (Adler et al. 2001; Chuang et al. 2005; George et al. 1999; Gultekin et al. 2005) and hyperhomocysteinaemia (Manns et al. 1999) remains unclear. Furthermore levels of many thrombophilic factors such as PAI-1, factor VIII, antiprothrombin, anticardiolipin and anti- β 2-glycoprotein-1 (GP1) levels are elevated in haemodialysis controls (Molino et al. 2004; Molino et al. 2005; Sands et al. 2001).

These studies require careful interpretation as a number of distinct pathophysiological processes underpin arteriovenous access dysfunction and thrombosis such as neointimal hyperplasia, endothelial trauma, stasis, altered endothelial shear wall stress, systemic hypotension, circulating volume and pharmacotherapy (Chang et al. 2011; Dember et al. 2008; Paulson et al. 2002). The degree of influence a procoagulant profile exerts is unclear and can logically be considered additive to the above factors. Interpretation of outcomes from the single study that included CVCs (n=30) is limited by the finding that catheter use was an independent predictor of access thrombosis ($p < 0.01$) with a stronger predictive power than any of the seven thrombophilic gene polymorphisms studied (Brophy et al. 2009).

To date studies in patients on haemodialysis have looked for the presence of IgG and IgM anticardiolipin and anti- β 2-GP-1 antibodies without screening for the IgA subclass. Pilot data from our centre suggested that the IgA, but not IgG or IgM subclass of anticardiolipin antibodies and the IgA and IgG subclasses of anti- β 2-GP-1 are predictive of thrombotic events in patients with CKD (Goel et al. 2009a; Goel et al. 2009b). The prevalence of these antibodies in patients on haemodialysis has not

been described to date neither has any potential association with catheter thrombosis been explored.

3.1.5. Hypotheses and aims of the study

The primary aims of the present study were to rigorously assess the immediate and long-term dialytic performance of the TesioCath™ and the LifeCath Twin™ in a randomized controlled trial. Parameters of performance included blood flow rates, dialytic adequacy as well as the incidence of periprocedural and subsequent complications (infective and mechanical). Based on available data it was hypothesised that the LifeCath Twin™ would perform better at the first dialysis but that subsequent function and complication rates were equivalent between the two catheter types.

The secondary aims of the study were to assess participants for procoagulant profiles and to test the hypothesis that patients with diagnosed procoagulant phenotypes experienced greater rates of catheter dysfunction.

3.2. Methods

3.2.1. Study design and participants

This was a single-centre, open-label, controlled parallel-group trial with balanced (1:1) randomisation carried out at the Imperial Renal and Transplant Centre, London (Figure 3.3).

Eligible participants were adult patients (aged 18 years or older) incident to haemodialysis and opting to receive a CVC as medium to long-term vascular access for maintenance therapy with no prior history of tunnelled cuffed catheter insertion. Participants must have been able to give informed consent and expected to survive more than 12 months after insertion. Participants had to be medically fit for the procedure – i.e. able to lie flat with no evidence of haemodynamic instability (heart rate >55 and <120 beats per minute, systolic blood pressure >95mmHg) and no severe bleeding diathesis as judged clinically. Furthermore eligible participants had to be free of evidence of active infection, i.e. no recent positive blood cultures, fever, C-reactive protein level >100mg/l.

3.2.2. Catheter insertion and periprocedural care

After obtaining written consent participants were randomised to receive either a TesioCath™ (Bio-Flex Tesio Catheter, MedCOMP Inc., Harleysville, Penn., USA) or a LifeCath Twin™ (Vygon UK, Swindon, Wilts, UK) for vascular access. Simple 1:1 randomisation was performed using a concealed allocation technique involving opaque, sequentially numbered, sealed envelopes that were opened by the enrolling physician.

Prior to insertion all patients were screened for methicillin-resistant *Staphylococcus aureus* (MRSA) carriage with nasal and axillary swabs according to hospital protocol. Those with MRSA carriage received 2% mupirocin ointment nasally (Bactroban® Nasal Ointment, GlaxoSmithKline UK, Uxbridge, UK) four times daily. All other patients were treated with 0.1% chlorhexidine and 0.5% neomycin cream nasally (Naseptin® Nasal Cream, Alliance Pharmaceuticals, Chippenham, UK) four times daily for a total of 5 days.

Preprocedural single doses of antibiotics were given on the day of CVC insertion in all cases - 1g of vancomycin intravenously and 250mg of ciprofloxacin orally.

CVCs were inserted predominantly by an experienced interventional nephrologist and also by senior members of the surgical team with experience in the technique in sterile conditions in the operating theatres. The insertion technique for both CVCs was identical and has been described in Section 2.2.3.

3.2.3. Haemodialysis prescription and targets

Haemodialysis was performed via the newly inserted CVC within 12 hours of insertion in all cases. In order to avoid disequilibrium phenomena in incident patients our protocol is for the first haemodialysis session to last 2 hours with blood flow rates (Q_b) of 250ml/min and dialysate flow rates (Q_d) of 500ml/min, the second session lasting 3 hours with Q_b 300ml/min and Q_d 500ml/min. All subsequent sessions were of 3.5-5 hours duration with $Q_b \geq 350$ ml/min and Q_d 800ml/min. In this study the target blood flow rate was 450ml/min. This was recorded as achieved in the first haemodialysis session in incident patients if this flow rate was maintained uninterrupted for 10 minutes, and in the second session for 20 minutes. In all subsequent dialysis sessions this target was achieved following maintenance of target flow rate for over 90 minutes. Attending clinicians were permitted to prescribe a different blood flow rate if clinically indicated. In cases where the target flow rate was not achieved, the maximum flow rate achieved for at least 50% of the dialysis session was recorded. Maximum blood flow rates were recorded for the first six haemodialysis sessions post-insertion and thereafter monthly.

All patients in the study were dialysed thrice weekly using medium flux synthetic haemodialysers (Nipro Sureflux®-E, Nipro Europe, Zaventem, Belgium) and Braun Dialog dialysis machines (B. Braun Medical Inc., Bethlehem, PA, USA). Dialysis adequacy was measured by single-pool Kt/V (spKt/V) on a monthly basis by using the Daugirdas method (Daugirdas 1993). Dialysis prescription was tailored to achieve a $spKt/V \geq 1.6$ in all patients with the option to increase haemodialyser surface area as required. Failure to achieve this minimum dialysis adequacy led to assessment of access recirculation using a urea-based method and consideration of catheter replacement.

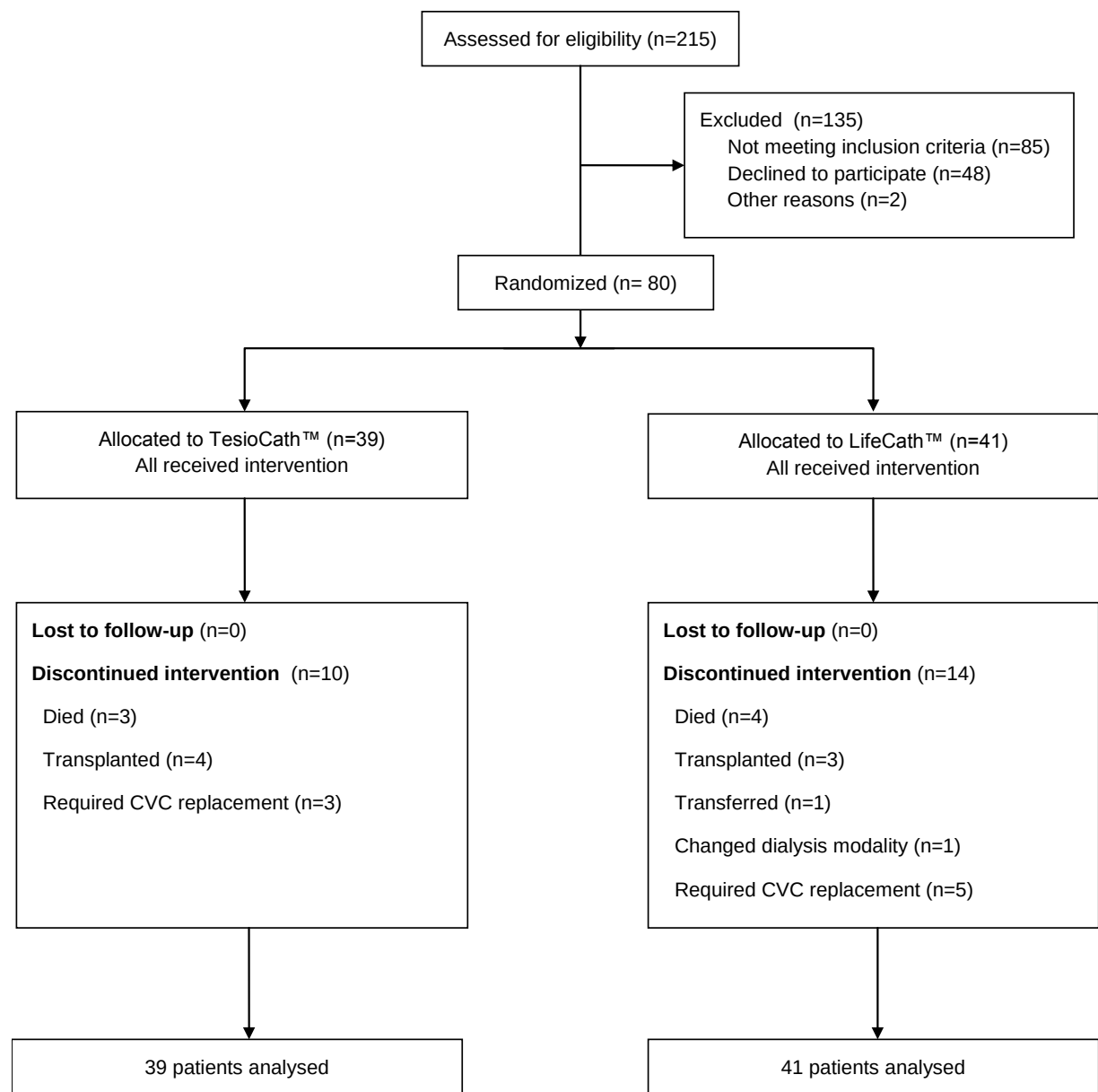


Figure 3.3. VyTes trial flow diagram.

3.2.4. Catheter care protocols

All CVCs were handled by trained staff using aseptic technique according to the protocols defined in Section 2.2.4.

Quarterly screening for nasal and exit site carriage of MRSA was carried out in all patients. In addition all patients returning to their satellite dialysis unit after an inpatient admission were screened. Patients with positive swabs were treated four times daily for a 5-day course with topical 2% mupirocin ointment nasally and to the exit site.

3.2.5. Mechanical complications – definitions and management

CVC dysfunction was defined by consistently suboptimal blood flow of <250ml/min and/or declining dialysis adequacy (defined as three consecutive falls in monthly spKt/V irrespective of magnitude) despite simple outpatient manoeuvres such as brisk saline flushes and reversing the lumens.

Catheter displacement or kinking was assessed by plain chest radiography and managed by catheter repositioning or replacement as deemed clinically necessary. Cuff extrusion was always an indication for prompt catheter replacement. All catheters requiring replacement were inserted via separate venous punctures and subcutaneous tunnels.

Dysfunction not attributable to catheter displacement or deformation was classified as thrombotic in origin. Initially 5000 units of urokinase were instilled into each catheter lumen for 2 hours as a locking solution and dialysis was re-attempted. If this failed then patients were admitted to the ward for 12-hour intraluminal infusion of 12,500 units of urokinase using an infusion protocol as previously described in Section 2.2.5 before dialysis was re-attempted. A maximum of two infusions were attempted before catheter replacement was performed for ongoing significant dysfunction (i.e. blood flow rates persistently <250ml/min).

3.2.6. Infective complications – definitions and management

Pyrexia was defined as a tympanic temperature of $\geq 38^{\circ}\text{C}$, and all pyrexial patients with or without a systemic inflammatory response were investigated with exit site swabs, multiple blood cultures drawn from the catheter itself and the peripheral veins, and urine and sputum culture where appropriate to circumstances. The definitions and management of infective episodes were as previously described in Section 2.2.6.

3.2.7. Procoagulant profile testing

Anticardiolipin IgG and IgM antibodies and lupus anticoagulant status are assayed routinely at our centre at least once in patients assessed or listed for renal transplantation. In addition serum from study participants was additionally sampled after a minimum of 30 days on maintenance haemodialysis to be representative of a clinical steady state. These samples were frozen and stored prior to testing following conclusion of the study.

Samples were tested using an APTUS automated analyser (Sigma Diagnostics, Sigma-Aldrich Ltd, Gillingham, Dorset, UK) with commercially available enzyme-linked immunosorbent assay (ELISA) kits. We assayed for anticardiolipin IgG, IgM and IgA antibodies as well as for anti- $\beta 2$ -GP-1 IgG and IgM using dedicated 96-well kits (Diamedix®, Miami, FL, USA). Study funding allowed for two IgA and IgG & IgM anticardiolipin ELISA kits but only one anti- $\beta 2$ -GP-1 IgG & IgM kit.

We therefore tested for all anticardiolipin antibody subclasses in all available samples ($n=76$). All patients with at least one sample testing equivocal or positive in any subclass had all their samples tested for anti- $\beta 2$ -GP1 antibodies to look for any consistent association representing a procoagulant diathesis. A total of 40 anti- $\beta 2$ -GP1 antibody tests were performed using sera from patients with a prior history of arteriothrombotic disease (e.g. ischaemic stroke, myocardial infarction, peripheral vascular disease) as well as from patients chosen at random.

3.2.8. Outcomes and sample size calculation

The primary outcome measure in this study was the achievement of a maximum blood flow rate of 450ml/min during the first haemodialysis session after insertion. Based on an expected incidence of the primary endpoint of 25% with TesioCaths™ and 70% with LifeCath Twin™ CVCs we calculated that a sample size of 80 patients would have 98% power to detect a significant difference between the two CVC types (with a two-sided type 1 error of 5%). Even allowing for an anticipated dropout rate of 10% a sample size of 70 patients would retain over 90% power.

Secondary outcome measures included peri-procedural complications, maximum blood flow rates during the first six haemodialysis sessions as well as on a monthly basis, the incidence of infective complications, the incidence of catheter displacement and thrombotic dysfunction.

All participants were followed up for 12 months or until transplantation, change of dialysis access (including change of CVC), change of dialysis modality or dialysis withdrawal, death or transfer to another unit.

The trial adhered to the principles of the Declaration of Helsinki and was approved by our local Research Ethics Committee (Ealing & West London Research Ethics Committee Trial Number 08/H0710/24) and is registered with ClinicalTrials.gov (ID: NCT01022359).

3.2.9. Statistical methods

Descriptive statistics are expressed as the mean $\pm$ standard deviation or median with the interquartile range (IQR) as appropriate. Continuous and categorical variables were compared using Student's t-test and the chi-square or the Mann-Whitney U test respectively, as appropriate. Timeline incidence data were analysed by using a Poisson model and expressed with 95% confidence intervals (CI). Kaplan-Meier survival analysis was performed on an intention-to-treat basis for patient, CVC and adverse-event-free survival censoring for death with a functioning CVC, change in dialysis access or modality, transplantation, dialysis withdrawal and transfer to

another centre. STATA 10.0 (StataCorp LP, College Station, TX, USA) was used to perform statistical analysis. Statistical significance was defined as $p < 0.05$.

3.3. Results

3.3.1. Cohort characteristics

The study cohort comprised 80 patients, 69% male, mean age of 61.0±16.1 years and with a total of 24,179 catheter days follow-up. Overall 36/80 (45%) patients were of South Asian, 43% White and 10% African-Caribbean ethnicity reflecting the demographics of the population served by our centre. The prevalence of major comorbidities in the study cohort was representative of our patient population (Power et al. 2009b) with 38/80 (48%) patients diabetic and 26/80 (33%) having ischaemic heart disease. There were no significant differences between treatment groups at time of randomisation (Table 3.2).

	TesioCath™ (n=39)	LifeCath Twin™ (n=41)	p
Age [years]	63.3 ± 15.6	58.9 ± 16.4	0.22
Male	29 [74%]	26 [63%]	0.29
Ethnicity			
White	16 [41%]	18 [44%]	0.79
African-Caribbean	2 [5%]	6 [15%]	0.26
South Asian	20 [51%]	16 [39%]	0.27
Other	1 [3%]	1 [2%]	0.99
Comorbidities			
Diabetes mellitus	18 [46%]	20 [49%]	0.81
Hypertension	32 [82%]	32 [78%]	0.67
IHD	16 [41%]	10 [24%]	0.11
CrVD	10 [26%]	6 [15%]	0.22
PVD	5 [13%]	5 [12%]	0.93

Table 3.2. Baseline characteristics of VyTees study participants. Values expressed as mean ± standard deviation or number [percent] unless noted otherwise.

3.3.2. Catheter function

All CVCs were inserted successfully with no need for immediate repositioning. There were no peri-procedural complications. All patients received their first haemodialysis session within 12 hours of insertion.

Significantly more LifeCath™ catheters reached the primary endpoint compared to TesioCaths™ (44% vs. 10%, $p=0.001$). LifeCath™ CVCs delivered a significantly higher maximal flow rate (Qb) at the first dialysis after insertion compared to TesioCaths™ (mean $383\pm82\text{ml/min}$ vs. $277\pm79\text{ml/min}$, $p<0.001$). Despite convergence in performance (Figure 3.4) statistically significant differences persisted until the fourth haemodialysis session (mean Qb 379 ± 43 vs. $361\pm48\text{ml/min}$, $p=0.08$).

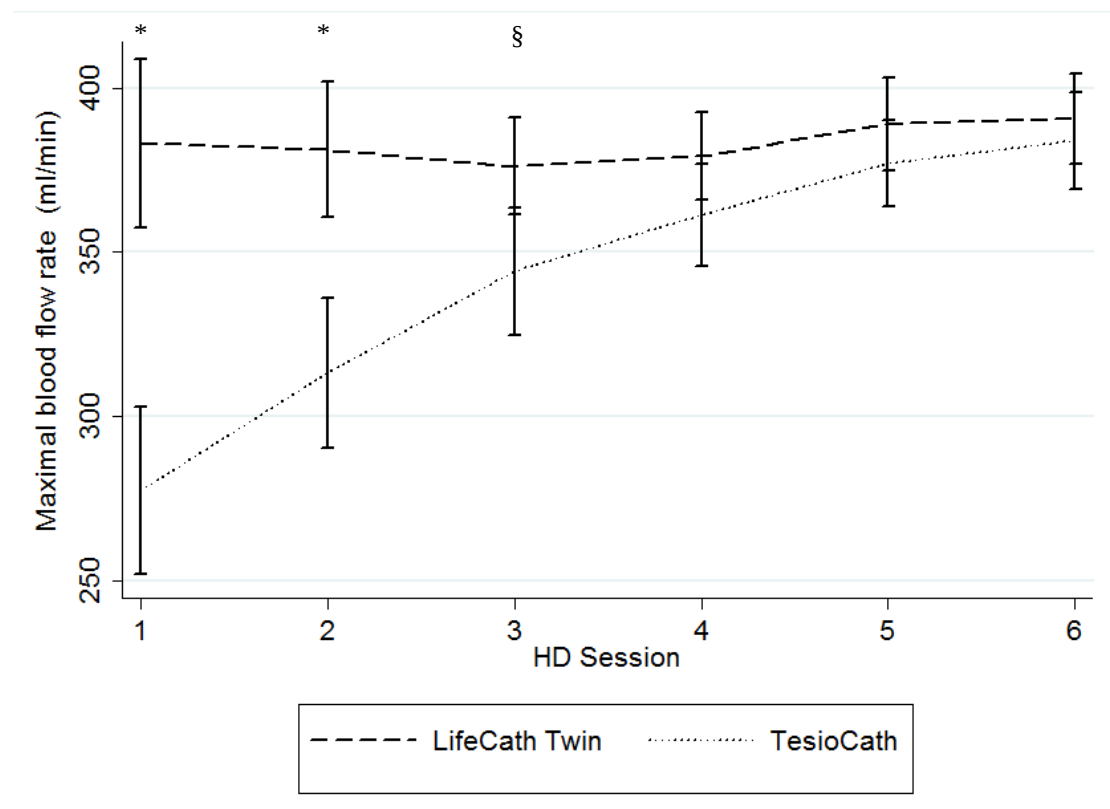


Figure 3.4. Maximal flow rates during the first six haemodialysis (HD) sessions following CVC insertion. Mean values are depicted at each time point with 95% confidence limits. * $p<0.001$, § $p=0.01$

Both CVCs performed to a similar level during subsequent follow up, consistently achieving Qb in excess of 400ml/min (Figure 3.5) and delivering equivalent levels of dialysis adequacy ($p=0.07$). The overall rate of catheter dysfunction in the cohort was 2.8 per 1,000 catheter days (95% CI 2.1-3.5). Although there were no significant differences in urokinase lock use between groups (Table 3.3), the LifeCath™ group had a significantly higher need for urokinase infusions (6 vs. none in the TesioCath™ group, $p=0.01$). These were given as 3 sequential infusions in 2 CVCs with persistent dysfunction which required replacement (and received the default CVC at our centre, the TesioCath™). On follow-up these patients subsequently had further thrombotic catheter failure requiring replacement within 4 weeks.

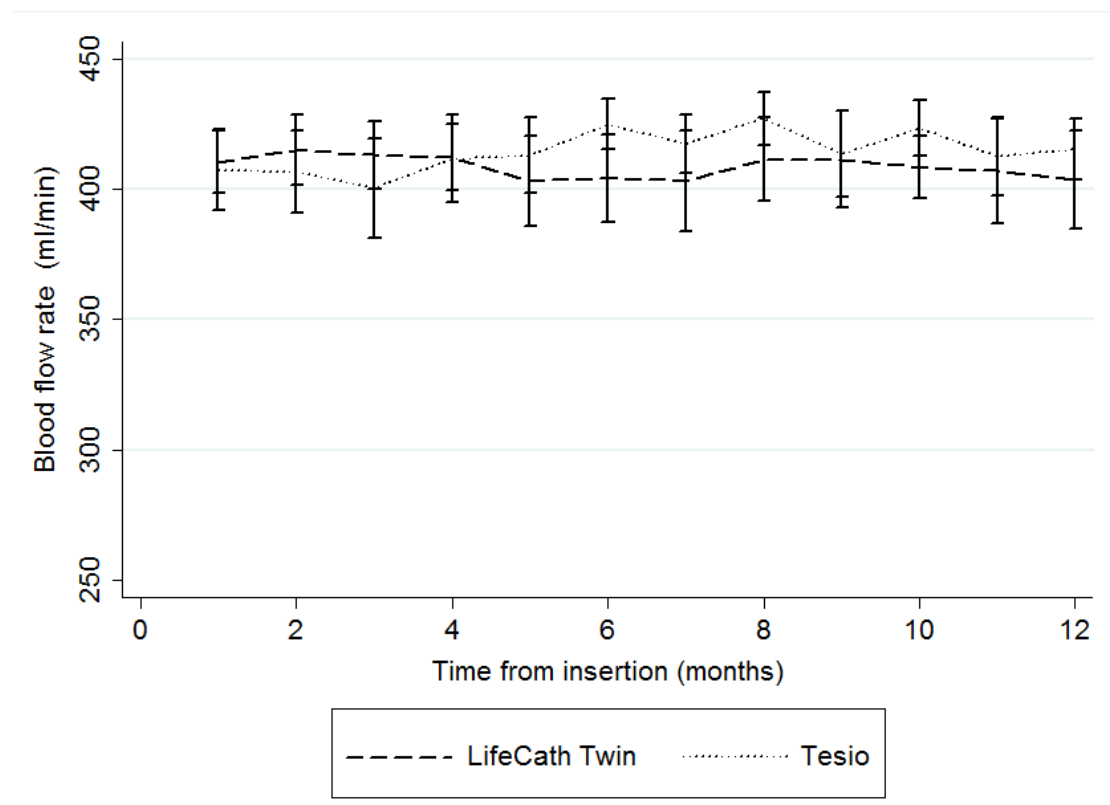


Figure 3.5. Maximal achieved flow rates from both CVCs during 12 months of follow up. Mean values are depicted at each time point with 95% confidence limits.

Catheter displacement occurred once in each group (one patient pulled out the CVC and in the other a patient experienced recurrence of catheter displacement for reasons that remain unclear).

3.3.3. Patient survival and hospitalisation

There was no significant difference in patient survival between the two groups (log rank $p=0.65$). 4 patients died during follow-up in the LifeCath™ group (2 from sudden cardiac death, 1 from myocardial infarction and 1 from pulmonary sepsis) and 3 in the TesioCath™ group (1 from myocardial infarction, 1 following severe haemorrhagic stroke, 1 due to extensive metastatic malignancy that was diagnosed 9 months following CVC insertion). Rates of hospitalisation for CVC-related complications (infective and mechanical) were significantly higher in patients randomised to the LifeCath Twin™ catheter (Table 3.3, $p=0.02$) due to the disparity in need for 12-hour urokinase infusions. There was no significant difference in rates of all-cause hospital admission between the two groups ($p=0.14$) or in the mean length of stay (8.6 ± 1.9 vs. 11.4 ± 2.6 days, $p=0.13$).

	TesioCath™	LifeCath Twin™	p
Deaths (/1000 patient years)	88 (18-257)	124 (34-319)	0.7
Mean spKt/V	1.81 ± 0.29	1.85 ± 36	0.07
Mean Qb (ml/min)	413 ± 46	411 ± 43	0.5
All-cause hospitalisations	2.3 (1.6-3.3)	3.3 (2.4-4.6)	0.1
CVC-related admissions	0.24 (0.05-0.70)	0.94 (0.47-1.68)	0.02
Catheter-related bacteraemia	0.40 (0.13-0.94)	0.51 (0.19-1.12)	0.7
Exit site infections	0.24 (0.05-0.70)	0.09 (0.002-0.48)	0.4
Urokinase locks	2.4 (1.6-3.4)	3.2 (2.2-4.4)	0.3
Urokinase infusions	0	0.51 (0.19-1.11)	0.01

Table 3.3. Secondary outcomes in the VyTes study. Values are expressed as event rate per 1,000 catheter days with 95% confidence intervals in brackets unless stated otherwise.

3.3.4. Infective complications

Twelve hospitalisations in each group occurred as a result of infection. Of these 4 (16%) were attributable to the CVC with 2 patients in the LifeCath™ group and 1 patient in the TesioCath™ group requiring admission for CRB , and 1 patient in the TesioCath™ group having a tunnel infection. There were no significant differences in rates of exit site infection and CRB between the two groups ($p=0.7$ and 0.4 respectively). All episodes were treated successfully with catheter salvage.

3.3.5. Prevalence of procoagulant profiles

76 samples from 56 patients were tested for anticardiolipin IgG, IgM and IgA antibodies with data available on IgG & IgM status from a further 7 patients. Due to a technical error with the analyser reliable data were available on 40/76 IgG tests and 48/76 IgM tests. All IgA tests were performed without technical issues (Table 3.4).

Just one study patient tested IgG positive 6 months following enrolment. He was concurrently IgM positive but tested negative with respect to both subclasses in two subsequent samples. Interestingly he was anticardiolipin IgA positive in all three samples. In total 7 patients were IgM positive – only one patient had repeat samples available and was negative on retesting as already described. Two IgM positive patients (29%) were concurrently IgA positive. Four patients tested positive for anticardiolipin IgA and a further two were equivocal. All patients ($n=2$) with repeat samples remained positive in subsequent tests.

No patient tested positive for anti- β 2-GP1 IgG. Just one patients tested positive for the IgM subclass with three patients yielding equivocal results. Of 41 patients tested for lupus anticoagulant all were negative.

Antibody	Subclass	Patients tested	Positive	Negative
Anticardiolipin	IgM	49	7 [14.3%]	42 [85.7%]
	IgG	46	1 [2.2%]	45 [97.8%]
	IgA	56	4 [7.1%]	52 [92.9%]
Anti-β2-GP-1	IgM	36	0	0
	IgG	36	1 [2.8%]	35 [97.2%]

Table 3.4. Procoagulant antibody results in VyTes.

3.4. Conclusions

The LifeCath Twin™ CVC is able to deliver greater blood flow rates than the TesioCath™ CVC during the first three haemodialysis sessions. Thereafter the two CVC types are equivalent in mechanical function and dialytic efficacy with no significant differences in the rates of infective complications.

3.4.1. Thrombotic catheter dysfunction

Overall rates of thrombotic catheter dysfunction in this study were low and comparable to prior series with a variety of catheter types (Grudzinski et al. 2007; Lok et al. 2007). Insertions in incident haemodialysis patients naïve to large-bore jugular venous cannulation is likely to have resulted in overall lower rates of catheter dysfunction compared to studies including prevalent patients. A rate of 2.4 per 1,000 catheter days in the TesioCath™ group in this study is comparable to those reported in prior studies with the Tesio catheter (1.4, 1.7 and 5.5 per 1,000 catheter days in the studies by Prabhu et al. 1997, Perini et al. 2000 and Wivell et al. 2001 respectively).

Although design differences are likely to explain flow function in the immediate post-insertion period these do not translate into significantly different performance in the medium to long-term and do not appear to effect differences in thrombotic occlusive pathology. The presence of numerous side holes at the catheter tip is implicated in greater loss of locking solution and admixture with blood leading to thrombus formation with occlusion (Mankus et al. 1998) although the outcomes from this study would appear to counter claims of high rates of infection and thrombosis in CVCs with side holes (Tal et al. 2006). Despite an increased size of side-holes the TesioCath™ group did not require more thrombolytic lock administration. Indeed it can be hypothesised that thrombolytic locks may be more efficacious with increased lock leakage as a greater volume would come into contact with the fibrin and thrombus around the catheter tip. Though intuitively appealing, this hypothesis has not been tested specifically despite indirect support from PreCLOT study outcomes that used routine alteplase locks (Hemmelgarn et al. 2011).

Urokinase infusions were required in 2 patients in the LifeCath™ group who accounted for 37% total urokinase lock use and received 3 infusions each prior to catheter replacement. 12-hour urokinase infusion resulted in the restoration of adequate function ($Q_b \geq 250\text{ml/min}$) in 4/6 (67%) cases. This was greater than reported in our retrospective series (Power et al. 2011) and yet lower than the 77-100% reported in previous studies (Table 2.7). In each case function declined thereafter and re-treatment or CVC replacement was required in keeping with published experience (Clase et al. 2001; Lok et al. 2006).

3.4.2. Catheter blood flow rates

The LifeCath Twin™ delivered significantly higher maximum blood flow rates during the 1st-3rd haemodialysis sessions following insertion compared to the TesioCath™. Both CVCs are of equal diameter (10Fr) and are adjusted following insertion to achieve comparable lengths, a factor that theoretically could influence resistance to flow. The reasons for this initial difference in flow may relate to differences in deformability between the two CVCs. This is suggested by the convergence of performance with time, paralleling resolution of post-traumatic tissue oedema in the subcutaneous tunnel. Any other factors such as “biolization” (i.e. protein coating of the surface of the CVC leading to greater resistance to clotting; cf. Ash 2007) would likely have an equal influence on both CVCs and any effect of side-hole orientation and number would persist over time.

Both CVC types were able to consistently deliver high blood flow rates over 12 months follow-up. Despite the product characteristics of both CVCs stating that they can achieve Q_b of 400-450ml/min no studies to date have reported in detail on function and outcome with either CVC at these rates. It has been considered that compared to AVFs the use CVC limits the Q_b “ceiling”. Results from this study would refute this. Recirculation in both CVCs was between 4 and 7% and similar to 4.6% reported by Prabhu et al. (1997) who targeted a flow rate of 400ml/min. Perini et al. (2000) reported on blood flow rates in their Tesio catheter series but do not provide a treatment target. The mean Q_b in their study was just over 300ml/min suggesting they prescribed flow rates lower than the present study.

This study examined nominal blood pump flow rates as an outcome measure rather than measuring the actual flow rate within the CVC (e.g. by an ultrasonic technique).

It is established that there is a disparity between the two rates in CVCs (Trerotola et al. 1999) which for the Tesio catheter has been quantified as a mean difference of 36ml/min (Prabhu et al. 1997 at blood pump flow rates similar to those used in our study (mean 388 ml/min). In clinical practice blood pump flow rates remain a cardinal measure of CVC flow performance and dialytic adequacy a measure of delivered dose. It is reassuring therefore to note that dialysis adequacy was high in the cohort as a whole with no significant difference between the two groups.

Although in theory high blood flow rates through a CVC could predispose to haemolysis and venous endothelial injury from increased turbulent blood flow there is no evidence of harm or haemodynamic instability. We did not observe any evidence of haemolysis or symptomatic central venous stenosis (CVS) during the period of follow-up although this may have been too short to detect the latter. Nonetheless data from our retrospective series suggests that attainment of flow rates 350-400ml/min does not lead to a high incidence of symptomatic CVS (Power et al. 2011).

3.4.3. Patient survival and complications

Cumulative patient survival at 1 year was 90% (95% CI 80-95%) and comparable to that of incident patients in our retrospective TesioCath™ series (Power et al. 2011). The relatively low number of deaths during the period of follow-up (n=7) precludes a valid survival analysis to examine factors such as CVC allocation although overall there was no significant difference in mortality rates between the two groups (Table 3.3).

Overall rates of catheter-related infection were low and consistent with prior data from our centre (Power et al. 2009b;Power et al. 2010a;Power et al. 2011) with no significant differences between groups despite the absence of routine antimicrobial catheter locks. We found no association between catheter dysfunction and infection in this study although a true effect is likely to have been obscured by the low rates of both events.

Catheter displacement was not a significant problem and was not associated with a specific catheter type contrary to our initial hypothesis. The duration of follow-up as

well as the total number of CVCs and patients examined in this study may have minimised any true effect and this study was not adequately powered to examine this endpoint.

3.4.4. The role of procoagulants

It is difficult to draw valid conclusions from the antibody screening results performed in this study. Overall 1/61 (1.6%) patients were anticardiolipin IgG positive, 7/61 (11.5%) were IgM positive and 4/56 (7.1%) were IgA positive. None of the 36 patients tested were anti- β 2-GP1 IgG positive and 1/36 (2.8%) tested positive for IgM. The low prevalence of anticardiolipin antibody positivity in this study is in keeping with data from the general population (Vila et al. 1994) as well as from haemodialysis cohort (Lazo-Langner et al. 2006). Repeat testing, typically 6 months apart, is advised to reduce the risk of false positives as evidenced by one patient in this study (Wilson et al. 1999). The prevalence of anticardiolipin IgA antibodies in HD is unknown and this data represents the first such characterisation. It remains unclear whether this subclass confers any additional risk of thrombosis above that of “traditional” antiphospholipid antibodies (Carmo-Pereira et al. 2003).

The overall small sample size and low rates of CVC thrombotic events make clinical correlation of antibody results unreliable. Of note, none of the patients requiring thrombolytics were positive any of the antibodies tested.

3.4.5. The influence of CVC design on thrombotic dysfunction

Although catheter design affects hydraulic performance *in vivo* this study does not demonstrate a significant effect on rates of thrombotic dysfunction which suggests that intrinsic pathophysiological mechanisms are dominant in the evolution and manifestation of this clinical problem. It can be hypothesised that pre-emptive approaches such as flow monitoring as well as judicious early use of thrombolytics can achieve better long-term catheter function. With no publications on flow surveillance as a clinical tool to describe the natural history of CVCs and predict thrombotic dysfunction this novel approach was examined in the next chapter of the thesis.

4. Thrombotic catheter dysfunction, thrombolytics and flow monitoring

This chapter presents results of a longitudinal analysis of thrombolytic use in an extended cohort of CVCs to ascertain the incidence of thrombotic dysfunction and the efficacy of urokinase lock use. Dialytic measures of catheter function are then examined and a novel scheme for catheter flow surveillance is described before its applicability in determining the risk of thrombotic dysfunction is assessed.

4.1. Introduction

4.1.1. Defining catheter dysfunction

Definitions of CVC dysfunction are heterogeneous in prior literature with criteria based on blood flow rate (BFR), haemodialysis circuit pressures (arterial and venous) and changes in parameters of dialysis adequacy. The NKF/KDOQI (2006) guideline definition lacks specificity and offers a BFR criterion (minimum 300ml/min) derived by consensus opinion rather than evidence. Lack of standardised definitions with discrete criteria in the field of vascular access has prompted a recent initiative to address this (Lee et al. 2011b). The authors define CVC dysfunction as "... the first occurrence of either (1) peak blood flow of 200ml/minute or less for 30 minutes during a dialysis treatment, (2) mean blood flow of 250ml/minute or less during two consecutive dialysis treatments, or (3) inability to initiate dialysis owing to inadequate blood flow, after attempts to restore patency have been attempted.". This parallels definitions in the PreCLOT study (Hemmelgarn et al. 2011) and accurately encapsulates clinical practice with focus on blood flow performance as the primary measure of CVC function. Low and/or declining BFRs are judged as the hallmark of CVC dysfunction that, if not positional in origin, is attributed to thrombotic pathology and treated with thrombolytics, fibrin sleeve disruption and ultimately catheter replacement. Clearly the reported incidence of dysfunction will depend on the stringency of the definition used and all aspects of catheter care and management which include the choice of catheter locking solution as well as the approaches taken to treating dysfunction.

4.1.2. Catheter locking solutions

In clinical practice the intraluminal volume of CVCs is filled with a "locking" solution during the intradialytic period to reduce the incidence of thrombosis, and depending on the compound, also exert an antibacterial effect. Standard of care has involved unfractionated heparin of varying concentrations (1,000 U/ml-10,000 U/ml) and most commonly 5,000 U/ml. Alternative anticoagulant solutions such as tinzaparin (Malo et al. 2010), alteplase (Gittins et al. 2007;Schenk et al. 2000), and varying concentrations of trisodium citrate (Grudzinski et al. 2007;Power et al. 2009b;Weijmer et al. 2005) have been used. Trisodium citrate exerts both an

anticoagulant and antibacterial effect through its avid chelation of free calcium ions (Weijmer et al. 2002). Composite solutions with dual action such as taurolidine/citrate (Solomon et al. 2010), gentamicin/heparin (McIntyre et al. 2004) and methylene blue/methylparaben/ citrate (Maki et al. 2011) have also been examined.

Leakage of the lock solution has been shown to occur in most, if not all, tunnelled CVCs including TesioCaths™ (Pepper et al. 2007). This is more pronounced in non-tunnelled CVCs, occurs from the time of instillation and can persist for 30 minutes thereafter. It is common practice to overfill the CVC by about 20% to ensure adequate delivery of the anticoagulant locking solution to the catheter tip although this can cause an eventual loss of up to 40% of the total volume (Sungur et al. 2007). In the same study using five types of non-tunnelled CVC showed that leakage occurred even with underfilling the lumen by 20%. Lock leakage potentially diminishes the therapeutic efficacy of the solution and can lead to side-effects from systemic distribution.

Leakage of heparin lock results in systemic anticoagulation which may be clinically significant and last for up to 4 hours (Karaaslan et al. 2001; Polaschegg and Shah 2003). A retrospective study of 143 patients reported a greater risk of haemorrhagic complications with 5,000 U/ml heparin compared to 1,000 U/ml heparin or citrate in the comparator group (Yevzlin et al. 2007). A more recent retrospective study of 105 patients did not find a significant difference in bleeding events with 5,000 U/ml heparin compared to 1,000 U/ml but noted greater rates of CVC dysfunction with the lower concentration (Ivan et al. 2010). Nonetheless use of lower concentration heparin (1,000 U/ml) has been shown to be economically advantageous (Holley and Bailey 2007) and the American Society for Diagnostic and Interventional Radiology recommends its use for heparin-based CVC locking (Moran and Ash 2008)

Lower rates of bleeding complications have been reported with sodium citrate locks compared to heparin (MacRae et al. 2008; Weijmer et al. 2005) and less biofilm formation (Bosma et al. 2010). Leakage results in dose-dependent side-effects (e.g. perioral paraesthesiae, metallic taste). In a RCT comparing 46.7% sodium citrate vs. 5,000 U/ml heparin locks we found that 54% of citrate-treated patients had adverse symptoms (Power et al. 2009b).

Thrombolytics such as urokinase and alteplase have been used extensively for the treatment of CVC dysfunction but reports on their use as a locking solution have

been limited to small studies until recently (Schenk et al. 2000). A large RCT randomised 225 patients to receive alteplase 1mg once-weekly or heparin 5,000 U/ml thrice-weekly and found lower rates of CRB and dysfunction in the alteplase group (Hemmelgarn et al. 2011) with no significant difference in bleeding rates.

Studies on the use of warfarin and/or antiplatelet agents are few and limited by relatively small numbers and heterogeneous treatment (Coli et al. 2006; Mokrzycki et al. 2001; Zellweger et al. 2005). They have yielded conflicting results and suggest, at best, modest benefit with warfarin therapy to an INR>2.0 but with the attendant higher risk of bleeding compared to standard heparin locks (Obialo et al. 2003).

4.1.3. Thrombolytics for catheter dysfunction

Alteplase, reteplase and urokinase are the major thrombolytics in clinical use for the treatment of CVC dysfunction. Recent placebo-controlled studies have assessed tenecteplase, another recombinant tPA with greater fibrin specificity than alteplase as well as increased resistance to PAI-1 (Tumlin et al. 2010). Streptokinase is no longer used given its antigenicity and side-effects with recurrent use.

Administration of thrombolytics in clinical practice has involved three main methods:

- (1) “Locking” - the thrombolytic agent is instilled slowly into the CVC to fill the intraluminal volume and allowed to dwell for a variable length of time before being withdrawn fully and dialysis re-attempted.
- (2) “Push-locking” – the intraluminal volume of the CVC is filled with the thrombolytic solution and the active front of the solution advanced at regular intervals (typically 10-20 minutes) by progressive “pushes” of 0.9% saline. The total duration of this procedure is 30-60 minutes depending on the number of saline pushes.
- (3) Infusion – the thrombolytic agent is infused through the CVC lumens at a steady rate using volumetric pumps. This method allows for delivery of a higher total dose of thrombolytic as well as maintenance of an active front at the catheter tip and side-holes.

The short-term efficacy of these treatments varies between 50% and 90% although comparisons between studies are very limited by heterogeneity in design, definitions, dose, catheter type and protocol (Clase et al. 2001; Lok et al. 2006; Mokrzycki & Lok

2010). Repeated use is often required with a median 15-30 days of additional function gained as each treatment delivers diminishing returns (Little and Walshe 2002). This is intuitively in keeping with the underlying pathophysiology of a recurrent fibrin sleeve with thrombosis. As the majority of data derives from North American populations it is limited with respect to urokinase following its withdrawal from the North American market (1999 – 2002) following an FDA advisory. To date there are just 12 publications examining urokinase for CVC dysfunction with no inclusion in systematic reviews on this subject (Clase et al. 2001; Mokrzycki & Lok 2010). There are only two small comparative studies between urokinase and alteplase. The first is limited by small numbers (n=37) and significant baseline differences between groups (Eyrich et al. 2002) but found that urokinase was less efficacious than alteplase (35% vs. 70%). The second study (Zacharias et al. 2003) compared the efficacy of alteplase in patients who had previously received urokinase (n=14) and found greater success rate, defined by a BFR>200ml/min, with alteplase particularly in completely occluded CVCs (88% vs. 43%).

4.1.4. Urokinase for CVC dysfunction

Urokinase has been in use for over 15 years and despite the dominance of other thrombolytics in North American markets following the prior FDA advisory, it remains in established use in Europe. Efficacy data from prior literature is summarised in Table 4.1. Overall rates of CVC dysfunction with heparin locks vary between 4.0 and 5.5 per 1,000 catheter days and the efficacy of urokinase at improving BFR is of the order of 75-95% (Peska et al. 1997; Seddon et al. 1998; Shavit et al. 2010; Twardowski 1998a; Webb et al. 2001; Zacharias et al. 2003). No significant bleeding complications are reported with high-dose urokinase although safety concerns remain given the small cohorts involved.

There are currently no randomised studies on the efficacy of different urokinase protocols and no large RCTs comparing urokinase to other thrombolytics. With the exception of Little and Walshe (2002), data on CVC performance following thrombolytic use is limited to the immediate post-treatment period.

4.1.5. Catheter flow monitoring in practice

Vascular access surveillance is advocated in national and international guidelines for all access types especially AVFs and AVGs. It can take the form of physical assessment, recirculation and dialysis adequacy measurements, as well as flow and pressure monitoring. In arteriovenous accesses the rationale is to identify the failing access early and institute pre-emptive interventional treatment to prevent sequelae of access failure such as occlusion and life-threatening hyperkalaemia. Such approaches have been investigated extensively for AVGs and to a lesser extent for AVFs. Randomised studies in AVGs showed no benefit despite a wealth of observational data supporting surveillance. In contrast two randomised studies in AVFs demonstrated lower rates of access failure in the surveillance group. However rates of restenosis after intervention were high in both AVGs and AVFs, a finding that has tempered enthusiasm for pre-emptive endovascular therapies.

In contrast there are no published studies to date on CVC surveillance techniques and the role of flow monitoring in predicting dysfunction. There is a complex curvilinear relationship between the BFR and the limb pressures in the HD circuit (venous pressure, VP, and arterial pressure, AP) which has been demonstrated *ex vivo* in a dual-lumen CVC using a haemofiltration machine (Naka et al. 2008). Such a relationship will be influenced by catheter length, elasticity, orientation, luminal diameter, the number and orientation of side-holes, blood rheology (determined by the haematocrit and concentration of serum proteins), and the structure of the vein around the catheter tip. Despite the high prevalence of CVC use in clinical practice there are no *in vivo* data on flow parameters defining function. A functional ratio of BFR to AP is offered as an indicator of CVC dysfunction in just one publication to date (Besarab and Pandey 2011). Although the authors suggest a number of parameters for surveillance they have not analysed outcomes comprehensively at their centre nor have they undertaken a pre-emptive approach to CVC dysfunction (Besarab A. Personal communication 2011).

Study	No. of CVCs	Definition of dysfunction	Protocol type	Treatment duration	Total dose [IU in each lumen]	Definition of success	Success	Notes
Suhocki et al. 1996	121	BFR<200ml/min or BFR<300ml/min in 2 consecutive sessions	Dwell / Push-lock	30 mins	5,000 U/ml	BFR≥300ml/min 1 st session post-treatment	74%	
Peska et al. 1997	22	BFR<250ml/min	Infusion off HD	20 mins each lumen	70,000	Change in BFR during 1 st HD after infusion	Improved BFR in 86%. 64% CVCs attained BFR≥250ml/min	If occluded, a guidewire was passed through the catheter prior to thrombolytic administration
Twardowski 1998	104	BFR<400ml/min with AP<350mmHg	Infusion during HD	1.5 hours each lumen	125,000	BFR>400ml/min 1 st session post-treatment	81%	36% required subsequent infusion on HD
Seddon et al. 1998	Not stated	BFR<200ml/min	Push-lock	1hr	2,500 U/ml	BFR>200ml/min 1 st session post-treatment	74%	
Webb et al. 2001	23	"Blood flow inadequate to support haemodialysis"	Infusion off HD	12 hours each lumen	12,500	"Adequate blood flow"	95%	Warfarin started after infusion (INR target 2-2.5)
Eyrich et al. 2002	10	BFR<200ml/min	Push-lock	1hr	5,000 U/ml	BFR>300ml/min 1 st session post-treatment	35%	
Zacharias et al. 2003	66	BFR<200ml/min	Push-lock	30 mins	5,000 U/ml	BFR≥200ml/min 1 st session post-treatment	43-75%	Lower patency rates in completely occluded CVCs
Shavit et al. 2010	37	Total CVC occlusion	Infusion off HD	1.5 hours each lumen	125,000	BFR>250ml/min 1 st session post-treatment	97%	

Table 4.1. Summary of clinical studies reporting on urokinase for CVC dysfunction (1995-2011). Abbreviations: BFR, blood flow rate; HD, haemodialysis. Only the major protocol used in the study by Twardowski (1998) is included here.

Markers of progressive dysfunction and incipient CVC failure can allow for pre-emptive thrombolytic therapy. To date there are no studies examining the effect of pre-emptive therapy on catheter outcomes. It can be hypothesised that an early approach to catheter dysfunction may reduce treatment costs, infections and prolong primary CVC patency rates. Indeed studies of thrombolytics as routine catheter locks suggest that this may be the case (Hemmelgarn et al. 2011;McGill et al. 2008).

4.1.6. Hypotheses and aims of the study

The primary aim of this study was to derive a dynamic index of CVC function based on the relationship between blood flow rate and transduced pressures in the arterial and venous limbs of the haemodialysis circuit. We describe use of this index (CathRisk) with reference to specific clinical scenarios and hypothesised that this index could be used for CVC surveillance and trends in its value precede overt CVC dysfunction.

The second aims of this study were to derive the absolute risk factors predictive of CVC dysfunction including a threshold value for CathRisk, and to ascertain the efficacy of thrombolytic locks in clinical practice using with Tesio catheter system.

4.2. Methods

4.2.1. Study design and participants

This was a retrospective cohort study of all patients receiving maintenance, thrice-weekly haemodialysis via a TesioCath™ at a single satellite haemodialysis unit at our centre (Northwick Park Renal Centre) from 1st October 2008 to 31st January 2011. This allowed for a uniform approach to CVC care, dialysis protocols and data capture as well as treatment of catheter dysfunction. Patients using a different CVC type (e.g. LifeCath™) were excluded from analysis.

Paper and electronic records relating to inpatient and outpatient episodes were examined as well as dialysis data. Patient characteristics were captured at study entry and included age, sex, ethnicity, cause of end-stage renal disease as well as major comorbid conditions: diabetes mellitus, hypertension (persistent postdialysis blood pressure [BP] $\geq 140/90$ mmHg in the context of clinical euvolaemia and/or an enduring requirement for antihypertensive therapy), ischaemic heart disease (presence of ongoing anginal chest pain, prior myocardial infarction or coronary intervention percutaneously and/or with bypass grafting), peripheral vascular disease (clinical and/or radiological evidence of aortic or distal arterial atheroembolic disease) and cerebrovascular disease (stroke or transient ischaemic attack). Dialysis data was extracted from a real-time electronic record (Proton, Clinical Computing Ltd.) that was updated daily by dialysis staff. Analysed variables were pre- and post-dialysis BP readings, patient dry weight and interdialytic weight gain, ultrafiltration volume and rate, treatment time, maximum BFR, the AP and VP at that flow rate.

All patients in the study were dialysed three times weekly using low to medium flux synthetic haemodialysers (AM-BIO-1000Wet, Asahi Kasei Medical Europe GmbH, Frankfurt, Germany and Nipro Sureflux®-E series, Nipro Europe, Zaventem, Belgium) and Braun Dialog haemodialysis machines (B. Braun Medical Inc., Bethlehem, PA, USA). Dialysis session length ranged from 2.5 – 5 hours and dialysis prescription tailored as described in Section 2.2.5.

4.2.2. Definitions of catheter dysfunction

The target blood flow for CVCs was ≥ 350 ml/min and dysfunction defined by consistently suboptimal BFRs < 250 ml/min and/or declining dialysis adequacy (defined as three consecutive falls in monthly spKt/V irrespective of magnitude). Catheter displacement or kinking was excluded by plain chest x-ray.

4.2.3. Thrombolytic management of catheter dysfunction

We used a urokinase lock regimen of 5000 U instilled into each catheter lumen for 2 hours as a dwell. This was subsequently aspirated and dialysis re-attempted. Failure to achieve adequate function was an indication for further urokinase locks. Repeated failure was managed 12-hour intraluminal infusion of 12,500 units of urokinase as described in Section 2.2.5.

4.2.4. Derivation of the CathRisk index

We decided to examine the relationship between flow rate and inflow access pressure (AP) as a standard ratio with prior precedent (Besarab & Pandey 2011). We then examined the change in this ratio over time in incident and prevalent patients and correlated this ratio to thrombotic events during the period of follow-up. We used a threshold BFR:AP ratio of 0.9 for high risk of CVC dysfunction as it corresponded to two standard deviations from the distribution mean and was comparable to prior suggested performance parameters (Besarab & Pandey 2011). CathRisk, an indicator variable, was positive when BFR:AP was less than 0.9.

4.2.5. Statistical methods

Descriptive statistics are expressed as the mean $\pm$ standard deviation or median with interquartile range (IQR) as appropriate. Continuous and categorical variables were compared using Student's t test and the chi-square or Mann-Whitney U test respectively as appropriate. Timeline incidence data were analysed using a Poisson model and expressed with 95% CI. Kaplan-Meier survival analysis was made on an

intention-to-treat basis for primary access site patency, censoring for death with a functioning CVC, change in dialysis access or modality, transplantation and transfer to another centre. Univariate and multivariate logistic regression was used to determine the risk of catheter dysfunction (defined by a need for urokinase lock and/or infusion) associated with factors of interest such as gender, ethnicity, CVC vintage, major comorbid conditions, dry weight, static peridialytic blood pressure parameters, interdialytic weight gain, UF rate and CathRisk positivity. STATA 10.0 (StataCorp LP, College Station, TX, USA) was used to perform statistical analysis. Statistical significance was defined by $p < 0.05$.

Ethical approval for this study was granted as an audit/service evaluation as per national guidelines (NHS National Research Ethics Service 2009).

4.3. Results

4.3.1. Cohort characteristics

The study cohort comprised of 164 patients, 58% male with a mean age of 62.7 ± 15.1 years (Table 4.2). 78 patients (47%) were incident to haemodialysis and prevalent patients had been receiving this therapy for a median of 3.2 years (IQR 1.6-4.8 years). A total of 40,333 HD sessions in 224 TesioCaths™ were examined spanning a total period of 108,114 catheter days follow-up and median 430 days per CVC (IQR 270-833 days). 132 catheters were the first such access type with overall cumulative assisted primary catheter site patency of 89% at 6 months, 81% at 1 year and 67% at 2 years.

	N [%]
Mean age [years]	62.7 ± 15.1
Male	96 [58%]
Ethnicity	
White	54 [33%]
African-Caribbean	24 [15%]
South Asian	85 [52%]
Other	1 [0.6%]
Comorbidities	
Diabetes mellitus	74 [45%]
Hypertension	75 [46%]
Ischaemic heart disease	49 [30%]
Cerebrovascular disease	24 [15%]
Peripheral vascular disease	18 [11%]

Table 4.2. Thrombolytics and CVC performance cohort characteristics.

Patients dialysed for an average of 4.3 ± 0.5 hours with a mean BFR of 402 ± 53 ml/min (Figure 4.1). Blood pressures were well controlled in this cohort with average predialysis levels of 141 ± 25 / 79 ± 15 mmHg and postdialysis levels of 135 ± 26 / 76 ± 14 mmHg in the context of mean interdialytic weight gains of 1.9 ± 1.1 kg.

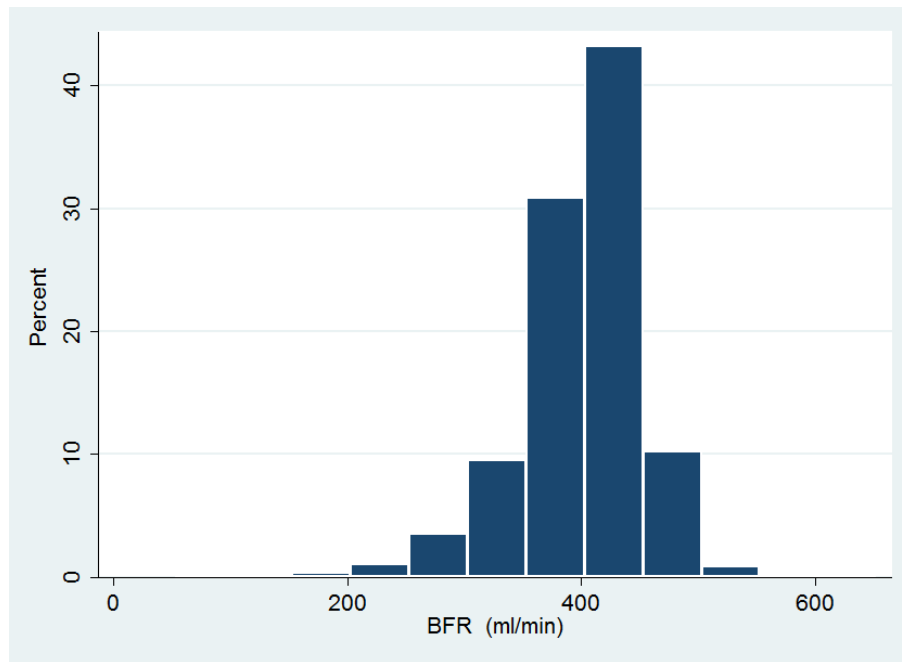


Figure 4.1. Distribution of blood flow rates achieved by study cohort.

4.3.2. Catheter dysfunction

Eighty-seven percent of HD sessions occurred at target blood flow rates. In total 594/40,333 (15%) HD sessions studied occurred at BFRs of ≤ 250 ml/min. Thrombolytics were used overall on 253 occasions at a rate of 5.5 per 1,000 catheter days (95% CI 5.1-6.0). The majority of these administrations were locks with just 6/253 (2%) being infusions and were administered at mean BFRs of 299 ± 72 mmHg.

Urokinase locks caused an improvement in BFR ≥ 40 ml/min in 78/253 (31%) cases and delivered BFRs > 250 ml/min on 43/89 (48%) occasions where pre-treatment flow rates were below this threshold. Locks led to greater BFR improvement when used in more advanced flow dysfunction (on average 4.7 ± 0.6 ml/min per 10 ml/min BFR, $p < 0.001$; Figure 4.2).

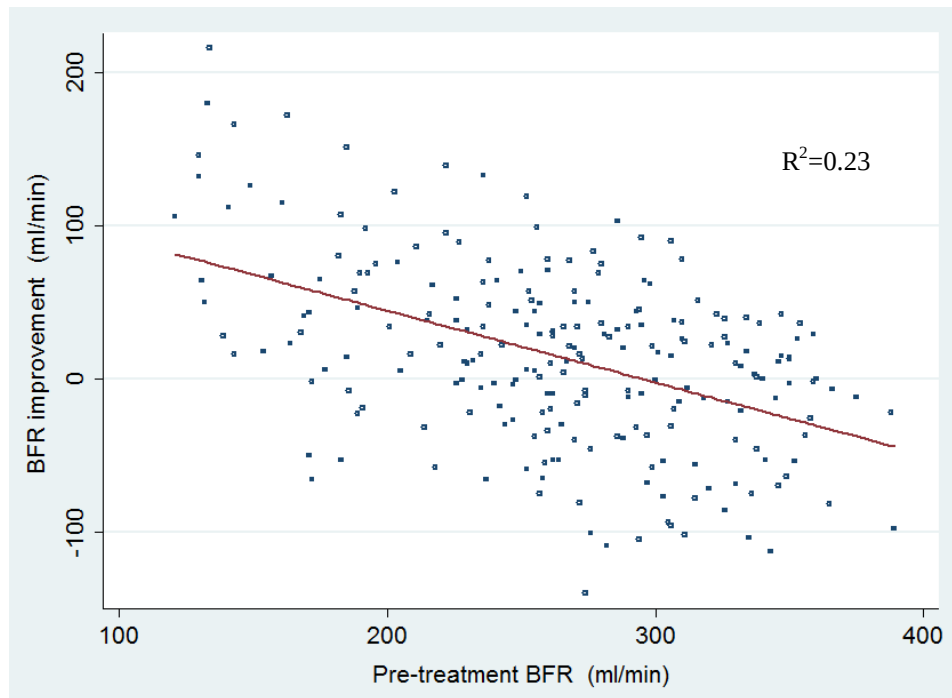


Figure 4.2. Relationship between pre-treatment BFR and improvement in flow rates with urokinase locking.

The BFR improvement seen with urokinase locks diminishes slowly over a 2 week period after treatment (mean 2.3 ± 0.9 ml/min with each HD session after adjusting for pre-treatment flow).

Urokinase infusion improved blood flows on 4/6 (67%) occasions although clinically significant increases (>40 ml/min) occurred on 50% occasions. Median BFR improved following urokinase infusion from 252 to 373 ml/min although given the relatively small sample size and variability in response this did not reach statistical significance ($p=0.2$).

4.3.3. Catheter performance characteristics

Mean achieved BFR during the first year after insertion in catheter-naïve patients was 409 ± 52 ml/min and performance of these CVCs degraded with time (mean 3.5 ± 0.6 ml/min/year, $p < 0.001$) in keeping with clinical experience (Figure 4.3).

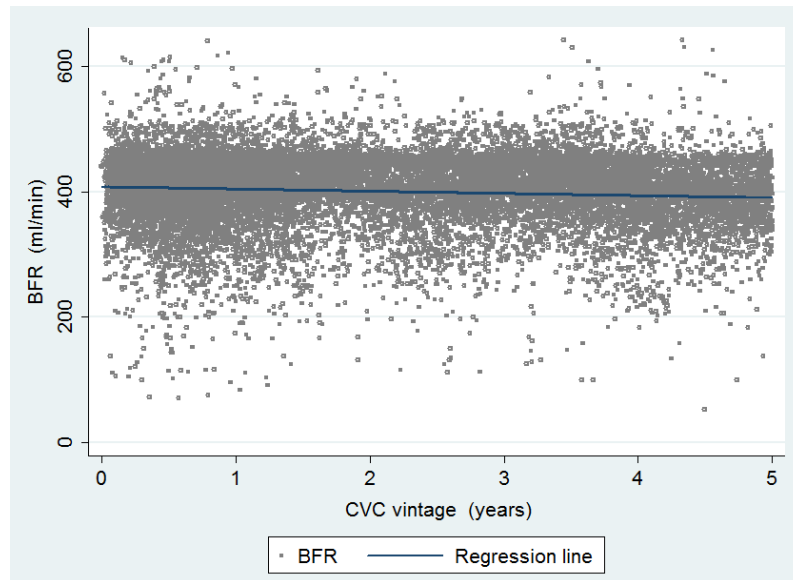
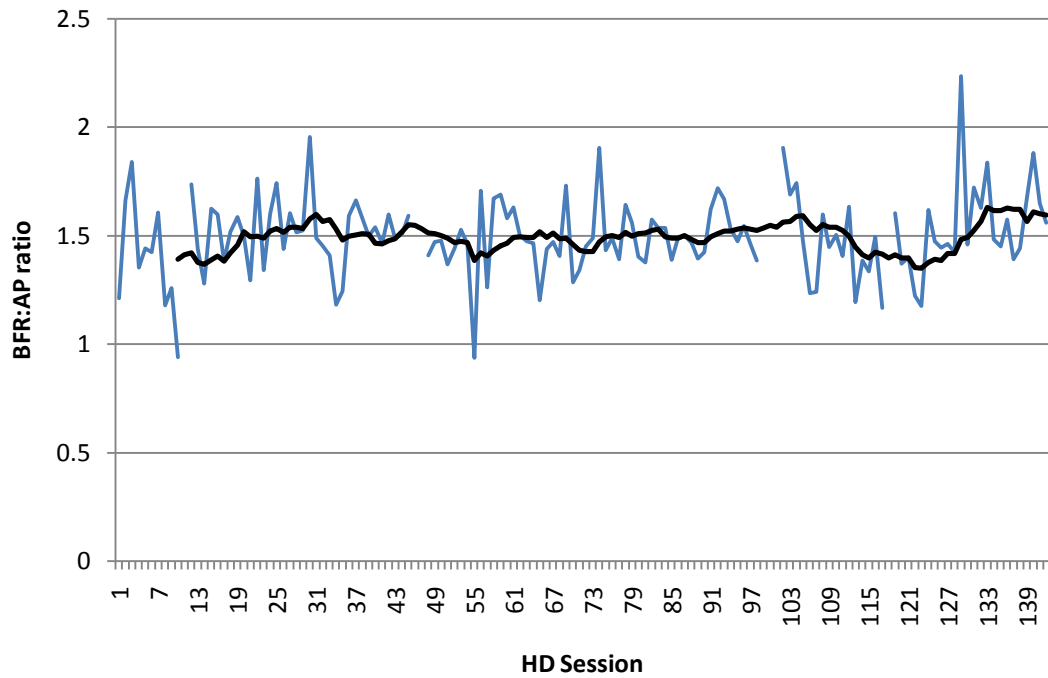
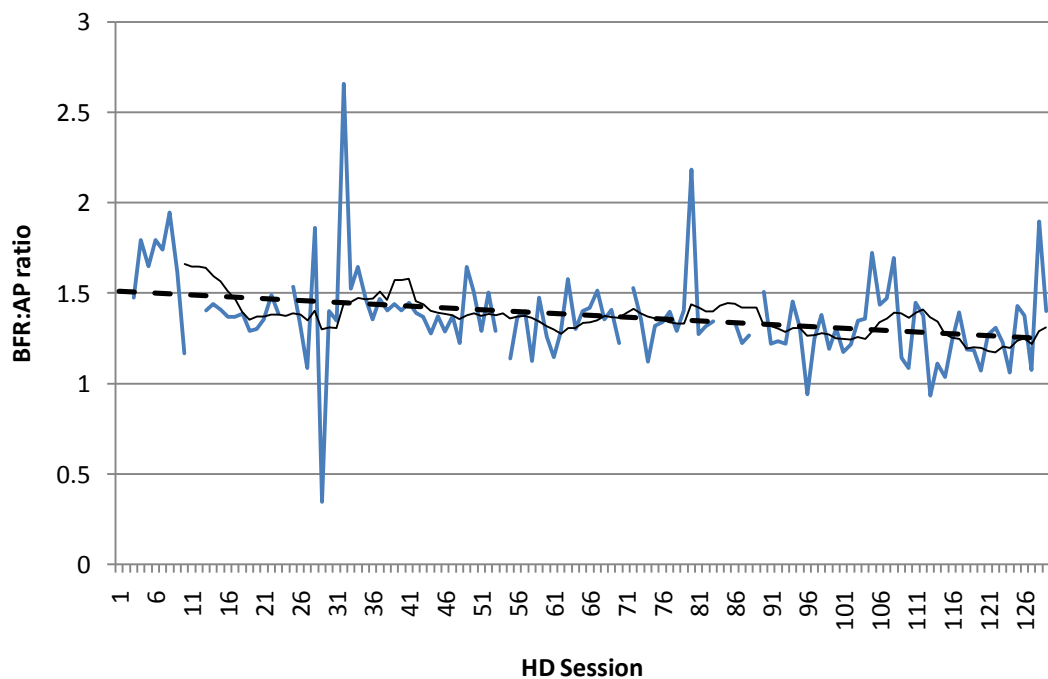


Figure 4.3. Performance of TesioCaths in catheter-naïve patients.

There was a degree of session-to-session variability in flow-pressure characteristics which is biologically plausible but in well-functioning CVCs the time-averaged BFR:AP ratios (i.e. over the last 10 HD sessions) represented the clinical picture better. The function of newly inserted CVCs varied according to the patient, with catheters manifesting ongoing good performance achieving BFR:AP ratios of 1.3-1.6 and those with eventual dysfunction displaying a progressive deterioration in this indicator (Figures 4.4a and b respectively).



Figures 4.4(a) & (b). Trends in BFR:AP performance ratios in two newly inserted CVCs: (a) with good function, shown above, (b) with progressive deterioration leading to dysfunction requiring intervention, shown below. Blue lines represent actual BFR:AP values, solid black lines the time-averaged value and the dashed black line in 4.4(b) the linear trend.



Wider variations in this performance index occurred over time superimposed on a general trend indicative of suboptimal function in some and the underlying reasons for this are not clear (Figure 4.5). This might represent developing, partially occlusive thrombus that is dislodged at intervals with ongoing background fibrin sheath development. Catheter replacement results in performance characteristics indicative of good function (i.e. BFR:AP ~ 1.5 ; Figure 4.5).

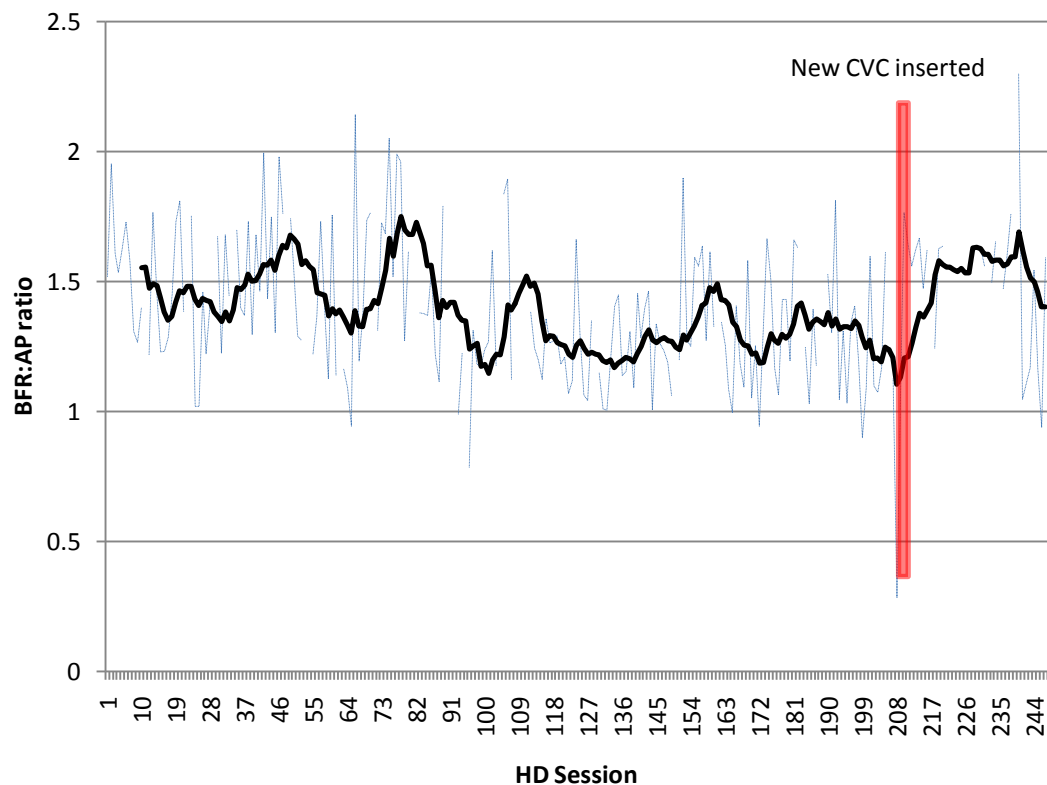


Figure 4.5. Performance characteristics of a failing CVC and effect of catheter replacement on performance parameters. Blue line represents actual BFR:AP values, solid black line the time-averaged values.

Dysfunctional CVCs yield lower BFR:AP ratios with sharp declines in this prior to episodes that requiring thrombolytics (Figure 4.6).

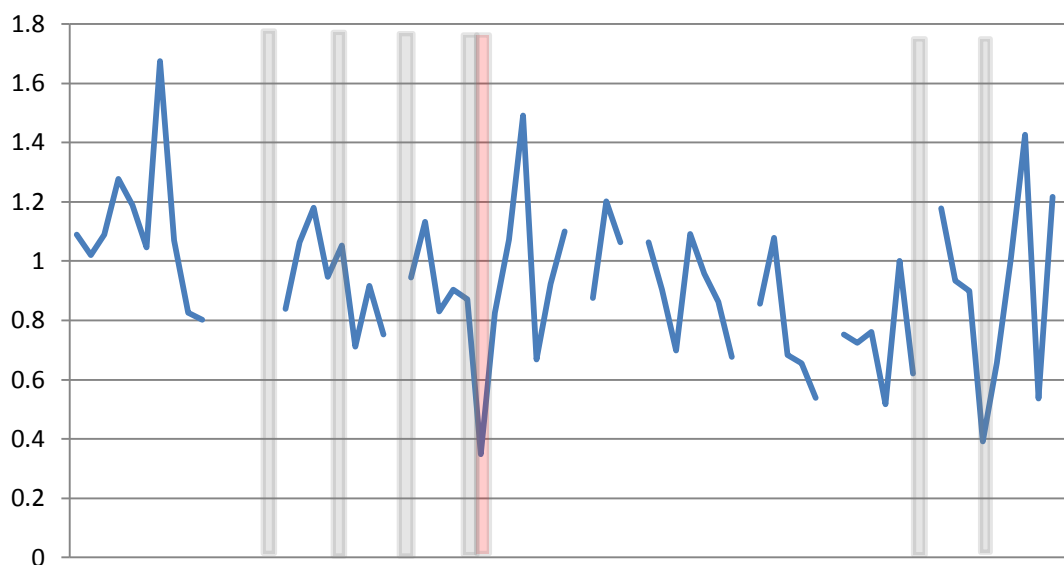


Figure 4.6. Changes in BFR:AP ratio (y-axis) with time in a dysfunctional CVC requiring thrombolytic therapy. Urokinase locks indicated by the grey bars and infusion by the red bar.

After inspection of CVC performance characteristics in this cohort I speculated that CVCs operating with BFR:AP values ≤ 1.0 are already dysfunctional and, on the whole, would progress to needing thrombolytic salvage. I therefore examined factors predicting this outcome including a nominal variable, CathRisk, which was positive when BFR:AP was < 0.9 .

4.3.4. Predictors of thrombotic dysfunction

The risk of needing thrombolytics was significantly associated with greater dry weight (4% per kg, $p=0.009$), catheter vintage (2% per month, $p=0.003$), UF rate (70% per l.hr^{-1} , $p=0.05$) and reduced on average by 72% ($p=0.03$) in the presence of a diagnosis of hypertension (Table 4.3). On multivariate analysis the most significant factor predictive of dysfunction was CathRisk positivity (OR 7.83, 95% CI 5.40-11.36, $p<0.001$).

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Demographic characteristics						
Male gender	0.73	0.26-2.06	0.55	-	-	-
Ethnicity						
White	1.43	0.49-4.18	0.51	-	-	-
South Asian	0.45	0.16-1.28	0.13	-	-	-
African-Caribbean	1.87	0.47-7.39	0.38	-	-	-
Comorbidities						
Diabetes mellitus	0.67	0.24-1.87	0.44	-	-	-
Hypertension	0.23	0.08-0.69	0.009	0.28	0.09-0.86	0.03
IHD	1.55	0.52-4.60	0.43	-	-	-
CrVD	0.76	0.18-3.26	0.72	-	-	-
PVD	1.17	0.24-5.75	0.85	-	-	-
Dry weight [kg]	1.04	1.01-1.08	0.005	1.04	1.01-1.07	0.009
Dialytic parameters						
CVC vintage [/month]	1.02	1.01-1.03	<0.001	1.02	1.01-1.03	0.003
Predialysis BP [/mmHg]						
SBP	0.99	0.99-1.00	0.07	1.00	0.99-1.01	0.69
DBP	0.99	0.98-0.99	0.02	0.99	0.97-1.00	0.13
Postdialysis BP [/mmHg]						
SBP	0.99	0.98-0.99	0.006	0.99	0.98-1.00	0.19
DBP	0.99	0.98-0.99	0.03	0.99	0.98-1.01	0.82
IDWG [kg]	0.98	0.84-1.13	0.78	-	-	-
UF Rate [l.hr ⁻¹]	1.69	1.02-2.79	0.04	1.70	0.99-2.90	0.05
CathRisk +ve *	6.47	4.58-9.12	<0.001	7.83	5.40-11.35	<0.001

Table 4.3. Predictors of thrombotic dysfunction requiring urokinase. Abbreviations: BP, blood pressure; IDWG, interdialytic weight gain. CathRisk defined by BFR:AP ratio <0.9.

4.4. Conclusions

This is the largest and most comprehensive study to our knowledge of the flow performance characteristics of TesioCaths™. We have assessed a specific index, the ratio between BFR and AP, as an indicator of CVC function and for the first time demonstrated its clinical correlation to the natural history of this access form. As such we have proposed an evidence-based system for flow monitoring in CVCs and proposed a novel framework of risk assessment to help predict CVC dysfunction.

4.4.1. Catheter function and outcomes

The cumulative assisted primary patency rates for TesioCaths™ in this study (81% and 67% at 1 and 2 years respectively) were marginally higher than those reported earlier (76% and 62% respectively, Power et al. 2009b) despite similar incident patient numbers, older age (mean 62.7 vs. 59.7 years), and a higher proportion of diabetics (45% vs. 25%) in this series. This may reflect centre-specific changes in dialysis practice or variables not accounted for in these studies. As discussed previously (see section 2.4.1) these patency rates exceed those reported in prior TesioCath™ series (Wang et al. 2006; Wivell et al. 2001) as well as those published in comparative studies: 48% at 1 year (Rosenblatt et al. 2006); 69% and 44% at 1 and 2 years respectively (Fry et al. 2008). Although Perini et al. (2000) report a patency rate of 92% at 6 months, this is in a small number of catheters at risk at this time point (n=9) with no longer follow-up data.

Flow performance of CVCs in this study is comparable to the findings of Prabhu et al. (1997) with 95% of their cohort (n=75) reaching BFRs of 375ml/min in all HD sessions and exceeds a series reporting mean BFRs of 252ml/min (Ibrik et al. 2006). The present study constitutes the largest and most comprehensive series on TesioCath™ flow performance in the literature to my knowledge and demonstrates consistent long-term achievement of flow rates over 400ml/min. The flow rates reported in this study constitute nominal blood flow rates (Q_b) rather than effective blood flow (Q_{eff}) rates derived by ultrasonic dilution methods. Studies have shown a disparity between the two values (Figure 4.7) that progressively increase at higher BFRs (Trerotola et al. 1999). Prabhu et al. (1997) reported a mean Q_b 388±6ml/min

with a measured Q_{eff} $352 \pm 8 \text{ ml/min}$, representing a mean error of 36 ml/min . This provided the rationale for our definition of flow improvement with thrombolysis (i.e. improvement in $\text{BFR} \geq 40 \text{ ml/min}$). Use of nominal BFRs reflects routine clinical practice and is in keeping with overwhelming majority of studies reporting on catheter function. I have not reported on recirculation rates in this series as this is not routinely measured at our centre. Studies in dual-lumen CVCs demonstrate design-dependent increases in recirculation as Q_b increases (Trerotola et al. 1999).

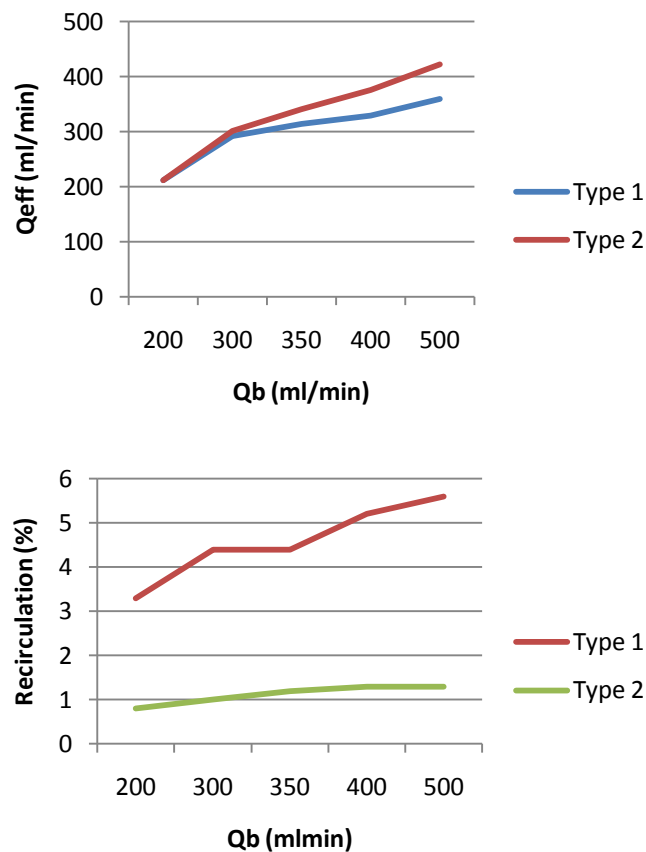


Figure 4.7. Changes in performance parameters of two catheter types at defined nominal blood flow rates (Q_b). Top: Relationship between effective blood flows (Q_{eff}) and Q_b . Bottom: Changes in recirculation with increasing Q_b . Adapted from Trerotola et al. (1999).

Prabhu et al. (1997) reported mean recirculation of 4.6% at mean Q_b 418 ml/min without assessment at set flow rates. The benefit of aiming for higher BFRs in routine practice may be abrogated by increasing recirculation.

The incidence of thrombotic dysfunction in this study is comparable to other large series including this catheter type (Table 4.4). Higher rates of thrombotic dysfunction with TesioCaths™ may relate to greater loss of locking solution with this design although this remains speculative. Other significant factors such as the type and concentration of locking solution used, definitions of dysfunction as well as the initial thrombolytic efficacy would affect the total number episodes in such analyses. Heterogeneity in all these between studies influences the validity of comparisons.

Study	Catheter type	Follow-up (catheter days)	CVCs (n)	Dysfunction rate [/1,000 catheter days]
Current series	Tesio	108,114	224	5.5
Solomon et al. (2010)	AS (65), TC (29) & others	17,771	114	6.6
Power et al. (2009b)	Tesio	36,497	232	6.3
Winnett et al. (2008)	AS	55,915	413	2.4
Lok et al. (2007)	U-C (95% cohort)	34,354	353	4.4
Ibrik et al. (2006)	Tesio	18,324	210	4.2
Rosenblatt et al. (2006)	Tesio	6,433	34	6.6
Wang et al. (2006)	Tesio	60,378	303	0.8
Weijmer et al. (2005)	AS (44), HC (24), TC (5), NCC (19)	9,379	98	4.5
Wivell et al. (2001)	Tesio	13,200	184	9.8
Perini et al. (2000)	Tesio	4,367	67	5.5
Prabhu et al. (1997)	Tesio	7,046	82	1.6

Table 4.4. Incidence of thrombotic catheter dysfunction in major studies of CVCs inserted via conventional routes. Abbreviations of catheter types: AS, Ash-Split; HC, Hemo-Cath; TC, TesioCath; LS, LifeSite; NCC, Neostar Circle-C; U-C, Uldall-Cook.

Analyses reporting overall rates do not account for event clustering (e.g. multiple doses in patients with suboptimal responses to thrombolytics, as in Section 3.3.2) or potential protocol violations. It is therefore reassuring that the incidence rates

reported in the present study are similar to those in a RCT at our centre (Power et al. 2009b).

Recurrent dysfunction is attributed to fibrin sheath formation as well as evolving central venous stenosis. In a large study of CVCs removed for either for infection or mechanical dysfunction (n=334), 76% had demonstrable fibrin sheaths (Alomari and Falk 2007), a prevalence similar to that reported in a RCT on the impact of fibrin sheath disruption on patency (Oliver et al. 2007). It is interesting to note that 30% patients with recurrent dysfunction in the study by Oliver et al. (2007) did not have a fibrin sheath on venography but the authors do not provide information on what the underlying pathology was. I examined 12 TesioCaths™ removed for persistent dysfunction and found no intraluminal thrombus (unpublished data) while noting thrombotic occlusion of a single side hole in one catheter suggesting that extraluminal pathology (fibrin, mural thrombus) is the dominant source of dysfunction.

4.4.2. Efficacy of thrombolytic therapy

Urokinase locks were used in 43% sessions with documented BFR <250ml/min suggesting either some protocol deviation or efficacy of non-thrombolytic methods but reflects clinical practice. The efficacy of urokinase locks in this study was 48% and lower than reported before (Table 4.1). Suhocki et al. (1996) reported 74% efficacy with 5,000U urokinase administered either as a 30-minute dwell or as a push-lock. Prior studies reported success rates of 95% and 81% respectively (Moss et al. 1990; Schwab et al. 1988). By contrast less encouraging results were reported in other series with urokinase dwells (15%, Twardowski 1998a) and push-locks (35%, Eyrich et al. 2002; 43-75%, Zacharias et al. 2003) with large variations likely relating to methodology. It can be hypothesised that push-locks would be more efficacious than dwells by delivering a higher total dose of active urokinase to the catheter tip and promoting outflow through the tip and side-holes. Intuitively this should result in more extensive fibrinolysis and better immediate to medium-term function. However there are no randomised studies comparing these two methods with any thrombolytic.

Similar short dwell (30-60 minute) protocols using alteplase reported success rates of 93% (Eyrich et al. 2002), 77% (MacRae et al. 2005b), and 85-92% (Zacharias et al. 2003). Increasing the dwell time from 2 to 48 hours in one RCT (MacRae et al.

2005b) did not affect short term patency, 77% vs. 79%. The efficacy of 2-8 hour dwells was 75% in another large trial of thrombolytic locks (Little & Walshe 2002) and push-locking did not improve success rates (Daeiagh et al. 2000; Meers and Toffelmire 1999).

Greater efficacy in similar protocols using alteplase rather than urokinase could relate to differential effects on clot lysis (Ouriel et al. 1995) or inherent differences in fibrin specificity. Urokinase, or urokinase-type plasminogen activator (uPA), is administered as the single-chain form (sc-uPA) which is converted to two-chain uPA (tc-uPA) by plasmin-mediated proteolytic cleavage. sc-uPA has <0.5% the plasminogen-activating efficiency of tc-uPA (Lijnen et al. 1990) but is the only subtype that can initiate fibrin-specific clot lysis (Gurewich et al. 1984). It has greater activity when bound to partially degraded rather than intact fibrin (Fleury et al. 1993) and its actions lead to plasmin generation with positive feedback conversion of sc-uPA to tc-uPA that leads to accelerated plasmin generation and clot lysis. This feedback loop is predominantly under PAI-1 control.

Differences in catalytic activity that depend on fibrin structure may underlie clinical differences in thrombolytic efficiency in uraemia. Two studies have shown differences in fibrin clot structure in ESRD patients (Sjoland et al. 2007; Undas et al. 2008). Clots in these patients were more compact with smaller fibrin network pore sizes, more rigid and less susceptible to fibrinolysis with alteplase *in vitro*. It is possible that given its mode of action urokinase is less effective at lysing such clots than alteplase although there are no published comparative studies and *in vivo* performance may differ.

The nature of the occlusive substrate remains a significant confounder as it has been presumed but never demonstrated in the majority of studies including this. Although the performance of thrombolytics has been discussed with respect to activity on thrombus, their action on fibrin sheaths has not been characterised. The term “fibrin sheath” is a misnomer as these are mixed cellular and non-cellular endothelialised structures with significant collagen deposition (Forauer et al. 2006) that would resist thrombolytics. Animal models have shown that at the distal ends of these sheaths there is thrombus at different stages of organisation (Xiang et al. 2001). It is presumed that the efficacy of thrombolytics in CVCs is directed at this sheath-related thrombus as well as peri-catheter mural thrombus (Xiang et al. 1998). The gradual organisation of these mural thrombi with smooth muscle cell infiltration and

deposition of collagen may predispose to lytic resistance and persistent and/or recurrent dysfunction. The graded relation we described between the degree of dysfunction and thrombolytic efficacy may in fact reflect this underlying pathology.

4.4.3. Catheter flow monitoring

This current study constitutes the first comprehensive analysis in the literature of pressure flow monitoring in CVCs and its relation to access dysfunction. The NKF-K/DOQI guidelines (2006) offer extensive protocols for access flow surveillance and advocate using this to detect dysfunction early but their recommendations are limited to AVFs and AVGs and they provide no suggestions for CVCs. It is intuitive that changes in access pressures indicate progressive resistance to flow due to the development of occlusive pathology and that monitoring could predict dysfunction as in AVGs (Besarab et al. 1991; Sullivan et al. 1993).

The descriptive analysis of changes in CVC pressure-flow characteristics constitutes a framework for understanding the natural history of catheter function in HD patients and could permit development of predictive models. This novel approach allows for pre-emptive thrombolytic therapy and if effective could prevent disruption to HD schedules, hospitalisation and catheter loss. A derived risk threshold BFR:AP of 0.9 is comparable to studies in AVGs where a ratio of 0.75 was proposed (Besarab 2006) and adopted in the 2006 NKF/K-DOQI guidelines. The present CVC threshold is based on a large cohort with long follow-up thus minimising sample sampling bias. As a value it seems reasonable given the smaller luminal diameter of CVCs compared to AVGs. The absolute threshold may vary according to catheter type as twin systems may have separate or conjoined fibrin sheaths and variable dynamics influencing flow resistance and thrombus formation. These results therefore require validation in other CVC types.

4.4.4. Study limitations

As before retrospective studies cannot prove a cause and effect relationship and one is unable to exclude confounding due to unmeasured variables and this analysis is open to bias by indication as suggested by the association between diagnosed hypertension and CVC dysfunction. In keeping with appropriate statistical practice I

have not performed a validation analysis of this score on the derivation cohort and so we cannot comment on the predictive power of such an approach as opposed to one based on conventional parameters such as BFR. An assessment using a single centre and a single catheter type could limit the applicability of these findings.

4.4.5. Future considerations

Although this study suggested a role for access flow surveillance in CVCs the predictive power of such approaches, including CathRisk, require formal assessment in subsequent prospective studies. It can be speculated that predictive flow modelling to guide pre-emptive thrombolytic therapy may lead to cost-effective thrombolytic use with less catheter dysfunction and bacteraemia and clinical trials to test this are required.

5. Tinzaparin pharmacokinetics in haemodialysis circuit anticoagulation

This chapter presents the results of a pilot study of the anti-Xa profile of intravenous tinzaparin used for routine HD circuit anticoagulation. Novel findings relating to variability of effect are discussed with reference to prior literature and gaps in the evidence base highlighted as a stimulus for further study in an anticoagulant being used increasingly frequently in Europe in patients with ESRD as recommended by European Best Practice Guidelines.

5.1. Introduction

5.1.1. Low molecular weight heparins in ESRD

Commercial use of low molecular weight heparins (LMWHs) began in the mid-1980s with more extensive development in Europe compared to North America. Since then their licensed use has extended to treatment and prophylaxis of deep vein thrombosis and pulmonary embolism, post-surgical thromboprophylaxis, anticoagulation in acute coronary syndromes and to prevent extracorporeal circuit thrombosis in HD. Until their introduction unfractionated heparin (UFH) was used for adequate anticoagulation in HD. UFH requires constant monitoring as its clinical effect is modulated by its complex kinetics and binding to plasma proteins the levels of which vary over time. As a result a plethora of protocols with different loading and maintenance doses, point-of-care testing and target heparinisation levels have been adopted.

LMWHs offer a more consistent pharmacodynamic profile than UFH with equivalent efficacy in maintaining HD circuit patency (Lim et al. 2004). As their license for use does not require pharmacokinetic monitoring they offer a more attractive alternative to UFH in this setting. Other advantages are that they are less likely to induce hyperkalaemia compared to UFH (Hottelart et al. 1998) and amelioration of lipid profile (Al-Saran et al. 2010). On these grounds they are recommended as the anticoagulant of choice in the current European Best Practice Guidelines for HD (Tordoir et al. 2007). LMWHs are given as a single bolus injection into the inflow ("arterial") limb of the HD circuit prior to initiation of dialysis and so require less nursing time to administer than UFH. Dalteparin, enoxaparin and tinzaparin are the three most studied LMWHs to date with tinzaparin the most commonly used in Western Europe and Canada although it is not licensed for use in HD in the U.S.

LMWHs are manufactured by depolymerisation of porcine heparin and each type consists of a multitude of fragments of variable molecular weight (4-8 kDa). The bioavailability, pharmacodynamics and pharmacokinetics of each LMWH are determined by the amount and length of each constituent fragment (Boneu et al. 1988; Mousa 2002). As a result each LMWH offers a unique anticoagulant profile and they cannot be used interchangeably.

During haemodialysis they are not cleared through the haemodialyser and anuric patients rely on hepatic clearance. The half-life in ESRD is highest for enoxaparin (24 hours), dalteparin and then tinzaparin (Davenport 2008; Polkinghorne et al. 2002). Use of enoxaparin for HD has been tempered by studies showing persistence of effect up to 48 hours after injection and a bleeding risk extending to 10 hours after injection (Guillet et al. 2003). The haemodialysis community has subsequently focused on tinzaparin as the LMWH of choice for intermittent HD.

5.1.2. Pharmacokinetic monitoring

Tinzaparin exerts an anticoagulant effect by binding to antithrombin and potentiating inhibition of factors Xa and IIa (thrombin). The bioavailability of the anti-Xa potentiating fractions (those with shorter lengths) exceeds that of the anti-IIa potentiating fractions leading to an anti-Xa:IIa ratio of 1.9 when compared with UFH; by comparison enoxaparin has an anti-Xa:IIa effect of 3.9 (Davenport 2008). Like other LMWHs, tinzaparin further inhibits factor Xa formation by stimulating endothelial release of TFPI (Mousa et al. 2003). Despite significant variations in relative anti-Xa and anti-IIa effects between LMWHs, it is the former measure that has been adopted by the European Pharmacopoeia Commission as the indicator of therapeutic potency.

The efficacy of tinzaparin in delivering adequate HD circuit anticoagulation has been reported on in a number of studies using clinically-derived outcomes such as the incidence of clots in the venous chamber of the circuit, total circuit occlusion or overt haemorrhage (Bramham et al. 2008; Davenport 2006; Egfjord et al. 1998). However just three studies report pharmacokinetic data using this LMWH in HD, which is surprising given its widespread use (Hainer et al. 2002; Lord et al. 2002; Simpson et al. 1996). These have varied in dose determination (fixed or weight-based), cohort size and design and are summarised below (Table 5.1). Only the study by Hainer et al. (2002) reported on anti-IIa activity.

Study	Cohort size	Dose	Samples per patient
Christidou et al. 2005	10	3,500IU	3
Hainer et al. 2002	12	75IU/kg – mean 6,480IU	11
Lord et al. 2002	10	3,500-4,500IU	4
Simpson et al. 1996	8	2,139-2,339	5

Table 5.1. Pharmacokinetic studies of tinzaparin in HD circuit anticoagulation. The cohort size refers to the number of patients in whom a pharmacokinetic analysis was performed.

At present there is no comprehensive body of data available to inform clinical practice in situations where accurate regulation of the intensity of anticoagulation is essential, such as in the post-surgical period, in bridging anticoagulation for patients with prosthetic heart valves undergoing invasive procedures or following haemorrhagic events. There are no defined anti-Xa targets available to direct dosing of tinzaparin and dose adjustments are largely empirical.

5.1.3. Study rationale and aims

Following conversion from UFH to tinzaparin as HD circuit anticoagulation at our centre we noticed a sharp increase in the number of haemorrhagic strokes which was out of keeping with the previous five years and occurred predominantly in patients of South Asian ethnicity. No studies examining any LMWH had considered a potential association between anticoagulant effect and ethnicity and we hypothesised that such an influence may have led to our experience. The significant multi-ethnic nature of our HD population parallels that of other large, urban UK units and any potential ethnic variations in tinzaparin effect would therefore be clinically relevant. We temporarily reverted to our prior protocol using UFH before evaluating the anticoagulant effect of tinzaparin as used at our centre.

5.2. Methods

5.2.1. Subjects

We carried out this evaluation in clinically stable patients established (>90 days) on maintenance HD and receiving this therapy three times weekly in two satellite HD units at our centre (Northwick Park and Brent Renal Centres) between 1st February – 1st April 2010. All patients received a set dose of 2,500U tinzaparin for evaluation. The inclusion and exclusion criteria are listed in Table 5.2, and incorporate our established guidelines for the delivery of circuit anticoagulation on HD (October 2008) as well as additional criteria for this evaluation. Specifically we wished to standardise haemodialyser type as this appeared to influence the total dose required to prevent circuit clotting (Egffjord et al. 1998), avoid confounding by differences in HD technique and not include patients with uncontrolled hypertension as this group had experienced the majority of haemorrhagic strokes (see Section 6). Patients had to be already receiving a minimum of 4 hours of HD per session as we wished to examine anti-Xa effect extending to this time point.

We divided the cohort into 3 groups of 12 patients based on target dry weight to account for the weight-dependent nature of tinzaparin effect: <60kg, 60-80kg and >80kg. Each weight group comprised 4 patients of White ethnicity, 4 of South Asian ethnicity and 4 of African-Caribbean ethnicity. Given the high prevalence of CVC use at our centre we opted to examine only patients with using this vascular access form and developed a set evaluation protocol for all patients (Section 5.2.2).

INCLUSION CRITERIA	EXCLUSION CRITERIA
On maintenance HD [3x/week]	Known allergies/intolerances to tinzaparin/enoxaparin or their constituents
Able to give informed verbal consent	Evidence of overt sepsis (fever>38°C)
Aged ≥18 years	First dialysis or urea level ≥40mmol/l
Achieving spKt/V≥1.4	Thrombocytopaenia including heparin-induced thrombocytopaenia (HIT)
Achieving BFRs≥300ml/min	Septicaemia
Dialysing with standard, mid-flux membranes	Liver failure
Minimum HD session length of 4 hours	On anticoagulation therapy, such as warfarin, with target INR≥2
	Suspicion of active bleeding following downward haemoglobin trend
	Due for/received surgery within 48 hours
	Any trauma including suspicion of head injury
	Uncontrolled hypertension [>200/100mmHg]
	Known clotting factor abnormalities (deficiencies or excess)
	On haemodiafiltration
	Requiring enoxaparin anticoagulation prior to study entry

Table 5.2. Inclusion and exclusion criteria for tinzaparin evaluation. Established unit guidelines are shaded grey.

5.2.2. Study protocol

We evaluated the effect of a single dose of tinzaparin 2,500U (Innohep®, Leo Pharma, Princes Risborough, Bucks, UK) in each patient with sampling during that HD session as well as one sample being taken just prior to starting the next HD session 48 hours later. Prior to evaluation each patients underwent a washout period to ensure UFH did not affect results through use in the HD circuit or as a CVC lock. As well as modifying the HD session just prior to the test session, we opted to

perform the evaluation during the first session of the week to allow 72 hours to elapse between the two. This is represented in Table 5.3 below.

	HD session									
	1	2	3				4			
CVC lock	46.7% citrate	46.7% citrate	46.7% citrate				Routine			
Anticoagulation	UFH	Heparin-free	Tinzaparin				Routine			
	Sample times [hrs into HD]									
			0	1	2	4	0	1	2	4
PT, APTT, Fbg	-	-	X	X	X	X	X	-	-	-
AT-III	-	-	X	X	X	X	-	-	-	-
Anti-Xa	-	-	X	X	X	X	X	-	-	-

Table 5.3. Tinzaparin study protocol including sample collections. Abbreviations: HD, haemodialysis; PT, prothrombin time; APTT, activated partial thromboplastin time; Fbg, fibrinogen; AT-III, antithrombin-III.

We collected information on any complications associated with HD sessions 3 and 4 such as circuit thrombosis, CVC dysfunction, patient symptoms and bleeding.

5.2.3. Sample analysis

All samples were delivered within 3 hours of collection to the coagulation laboratories of the Department of Haematology at the Hammersmith Hospital for analysis. Samples were tested using the Sysmex CA 7000 analyser (Sysmex UK, Milton Keynes, Bucks, UK). Anti-Xa assays were performed using Coamatic® Heparin kits (Quadrantech Diagnostics Ltd, Epsom, Surrey, UK) and antithrombin levels assayed using Berichrom® Antithrombin kits (Siemens Healthcare Diagnostics, Camberley, Surrey, UK).

5.2.4. Statistical analysis

Descriptive statistics are expressed as the mean $\pm$ standard deviation or median with interquartile range (IQR) as appropriate. Continuous and categorical variables were compared using Student's t test and the chi-square or Mann-Whitney U test respectively as appropriate. Analysis of variance (ANOVA) was used to compare differences between groups. Univariate and multivariate regression analysis was used to examine the relationship of anti-Xa activity and factors of interest such as age, gender, ethnicity, and weight. STATA 10.0 (StataCorp LP, College Station, TX, USA) was used to perform statistical analysis. Statistical significance was defined by $p < 0.05$.

Ethical approval for this study was granted as this constituted a service evaluation as defined by national guidelines (NHS National Research Ethics Service 2009).

5.3. Results

5.3.1. Study cohort demographics

In total 36 patients were evaluated and of these 32 formed the cohort under analysis. Four patients were excluded due to protocol violations - one patient did not receive tinzaparin despite its prescription and three patients had evidence of ongoing UFH contamination in the form of marked APTT prolongation on their initial (time 0) sample. The mean age of the study cohort was 68.6 ± 13.1 years with slight male preponderance (56%). Mean patient dry weight was 74.6 ± 18.3 kg. There were no statistically significant differences in age or weight between ethnic subgroups (Table 5.4) and no differences in gender distribution ($p=0.8$).

	Ethnicity			P
	White	South Asian	African-Caribbean	
Weight band				
<60kg	57.5 ± 1.7	52.6 ± 10.1	56.7 ± 1.3	0.5
60-80kg	73.0 ± 4.5	69.3 ± 2.3	67.5 ± 8.4	0.4
>80kg	89.3 ± 6.0	102.6 ± 6.3	96.8 ± 14.5	0.2

Table 5.4. Mean dry weights of tinzaparin study groups according to ethnicity. Results presented as mean value $\pm$ standard deviation.

5.3.2. Anti-Xa activity profile

The plasma anti-Xa activity profile with tinzaparin was dose-dependent and displayed as similar time course across the three weight bands (Figure 5.1). This was in keeping with published data (Hainer et al. 2002). Anti-Xa activity at 1 hour after administration was 0.49 ± 0.13 IU/ml and concordant with a mean of 0.51 IU/ml at this time point extrapolated from the analysis by Hainer et al. (2002) after dose adjustment for comparison. Mean activity at subsequent time points were also in keeping with prior results (Table 5.5).

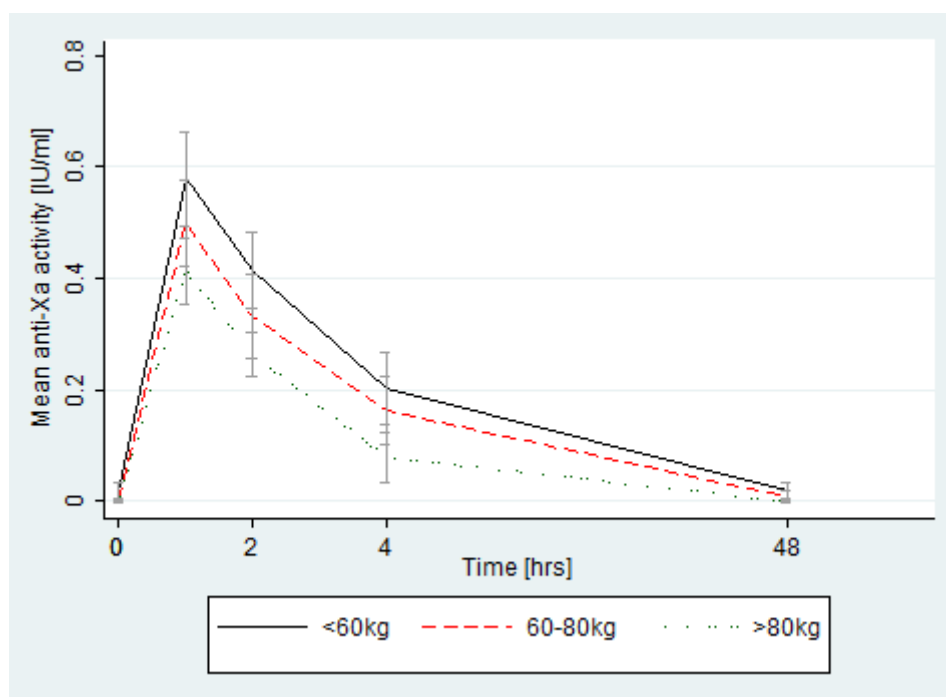


Figure 5.1. Anti-Xa activity of tinzaparin across different weight bands.

By 4 hours into HD the level of anti-Xa activity was low and there was no residual effect of tinzaparin by the start of the next HD session.

	Anti-Xa activity [IU/ml]			
Time points [hours]	1	2	4	48
Current study	0.49	0.33	0.14	0
Hainer et al. 2002 *	0.51	0.38	0.24	0

Table 5.5. Comparative anti-Xa activity between our study and the study by Hainer et al. (2002). Values from this study are extrapolated from graphical representations as absolute values are not given in the manuscript and adjusted for comparison to reflect the average dosing regime in the present study (mean 33.5IU tinzaparin/kg).

There were no significant differences in anti-Xa activity throughout between ethnic groups after adjusting for weight (Figure 5.2).

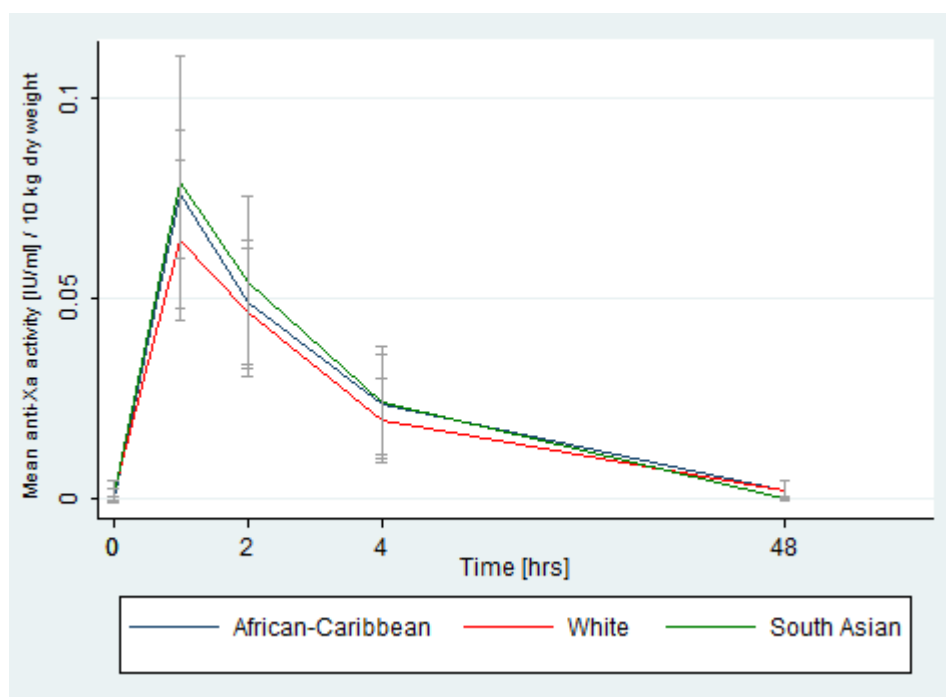


Figure 5.2. Variation in anti-Xa activity of tinzaparin with ethnicity.

Overall female patients had significantly lower dry weights compared to males (mean 67.5 vs. 79.5kg, $p < 0.001$). After adjusting for dry weight mean anti-Xa activity was still higher in female patients across all time points during the evaluation session ($p \leq 0.01$ at all points, Figure 5.3).

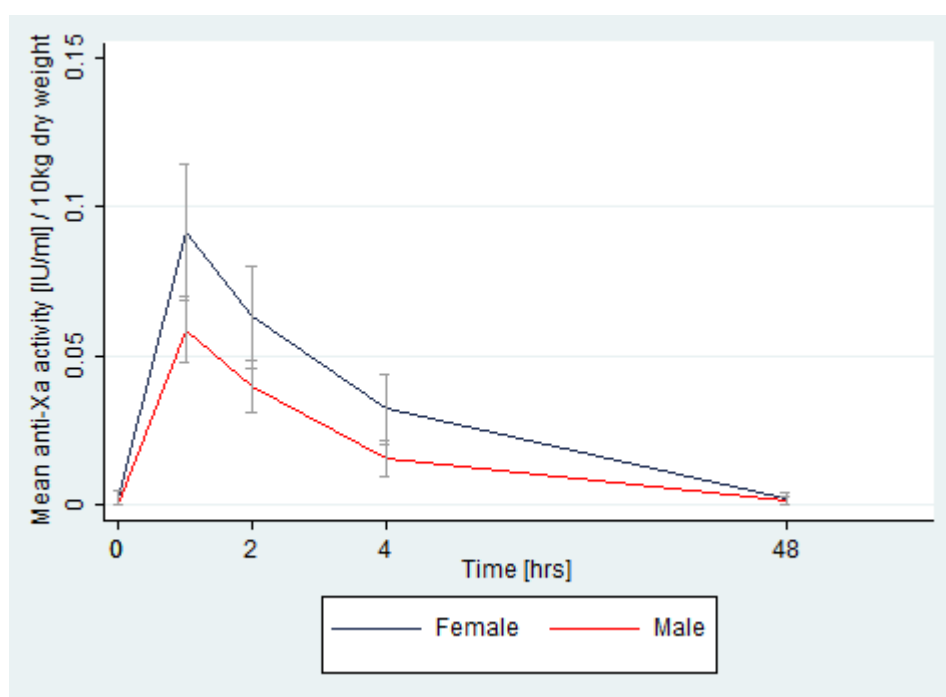


Figure 5.3. Effect of gender on anti-Xa activity after adjusting for weight.

5.3.3. Determinants of 1-hour anti-Xa activity

Patient dry weight as well as gender independently predicted peak (1 hour) anti-Xa activity ($p=0.001$ and 0.03 respectively). Patient ethnicity did not have a significant effect ($p=0.3$).

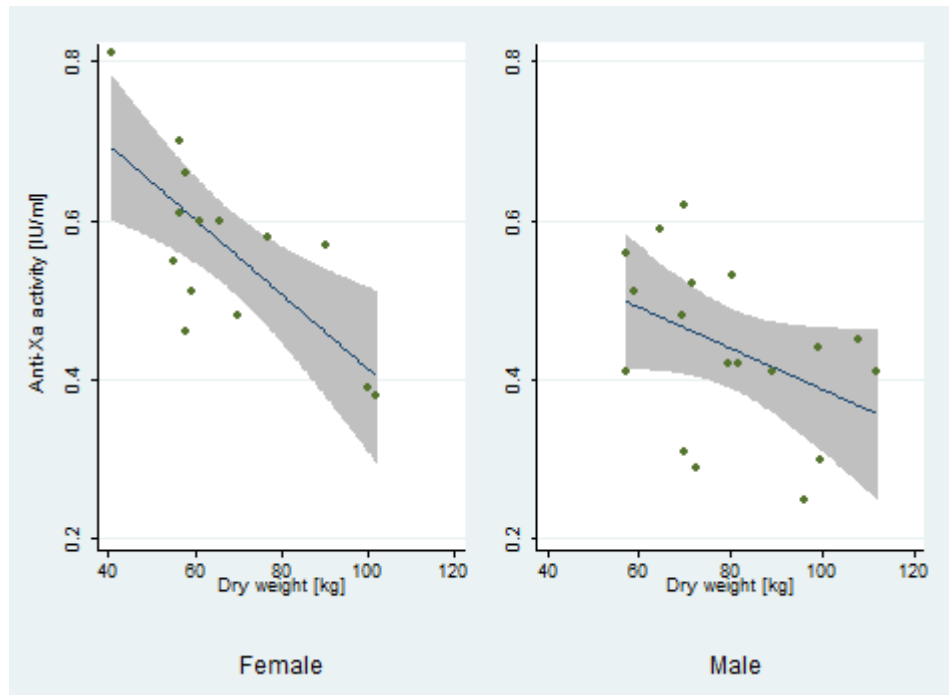


Figure 5.4. Influence of gender and weight on 1-hour anti-Xa activity.

5.3.4. Effect of tinzaparin on routine coagulation parameters

In keeping with its mode of action tinzaparin had no effect on prothrombin time (PT) which remained within normal limits throughout (mean 10.9 ± 0.7 seconds). Indicative of its anti-IIa activity, tinzaparin caused prolongation of the activated partial thromboplastin time (APTT) at 1 hour (mean 43.5 ± 9.9 seconds) but this returned within normal limits by 2 hours (mean 33.8 ± 6.7 seconds). On average APTT rose above the upper limit of normal (35.5 seconds in our laboratories) when anti-Xa activity exceeded 0.25 IU/ml.

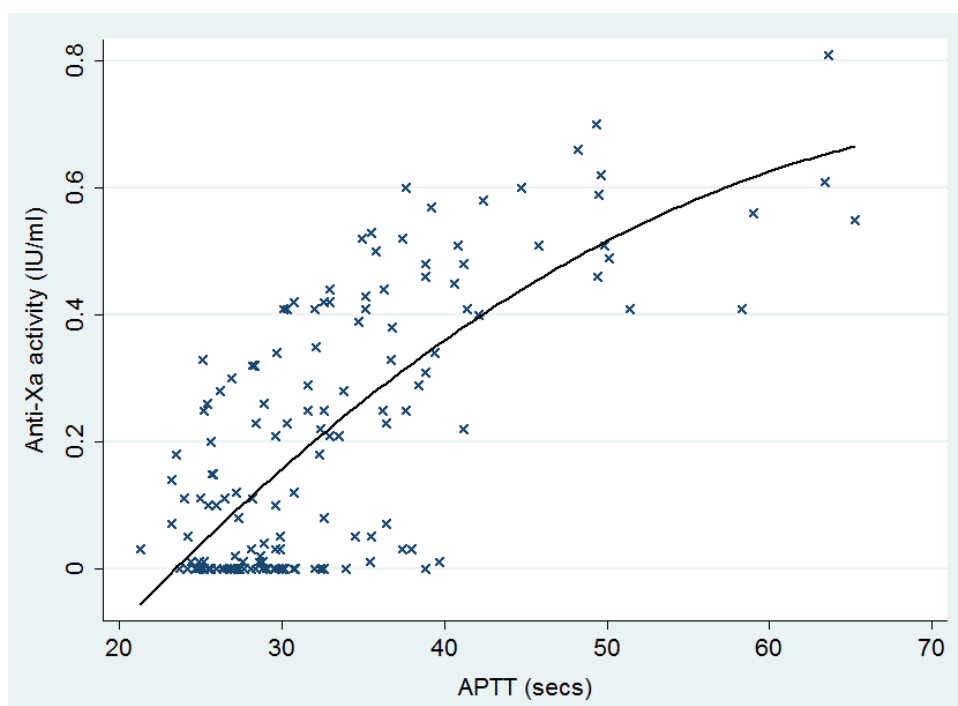


Figure 5.5. Correlation between APTT and anti-Xa activity. Absolute values represented by crosses, fitted line represented in black.

Fibrinogen levels rose with time on HD (mean 3.56 ± 0.95 g/l at baseline vs. 3.82 ± 0.98 g/l at 4 hours) which may represent progressive haemoconcentration as a result of UF. On multivariate analysis levels were higher in females (mean difference 0.30 ± 0.05 g/dl, $p=0.05$). Fibrinogen levels correlated with patient ethnicity such that African-Caribbean patients had the lowest levels and those of South Asian ethnicity had the highest (mean 1.07 g/l higher, $p<0.001$). There was no interaction between anti-Xa activity and fibrinogen levels ($p=0.6$).

5.3.5. Effect of tinzaparin on antithrombin-III levels

Antithrombin-III levels did not correlate with anti-Xa level ($p=0.1$) but were on average significantly higher in females (mean difference 0.1 ± 0.2 IU/ml, $p<0.001$).

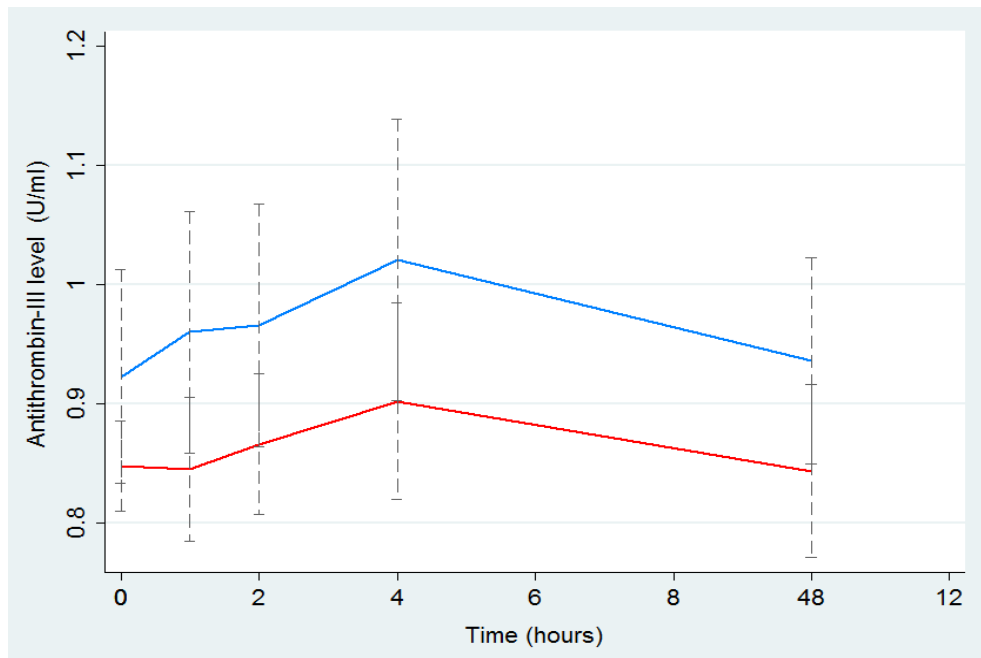


Figure 5.6. Effect of gender on antithrombin-III levels. Males represented by the red line, females by the blue line.

Levels displayed an upwards trend with time on HD ($p=0.06$) and varied with ethnicity in a similar manner to plasma fibrinogen levels such that South Asian patients had the highest and African-Caribbean patients the lowest levels ($p=0.04$).

5.3.6. Safety and efficacy

No episodes of catheter dysfunction or circuit thrombosis were noted. Patients did not express any unexpected symptoms during this time and there were no minor or major bleeding episodes.

5.4. Conclusions

Tinzaparin exerts consistent anti-Xa activity between ethnic subgroups with a time profile that appears adequate for intermittent HD with mean session lengths around 4 hours and with no evidence of accumulation. We discerned a significant differential effect of gender on anti-Xa activity that represents a novel finding.

5.4.1. Comparative assessments of anti-Xa activity

To date only one published study looked comprehensively at the pharmacokinetic (anti-Xa and anti-IIa) profile of tinzaparin in HD patients (Hainer et al. 2002). The authors tested activity of both effects at 0, 0.25, 0.5, 0.75, 1, 2, 3, 4 hours as well as at 6, 8 and 12 hours after administration. Although HD session length (median 3.75 hours) was similar to ours there are significant differences. They used high-flux haemodialysers in a smaller (12 vs. 32 patients) and considerably younger (mean age 50.7 vs. 68.6 years) cohort than our own. Nonetheless, after adjusting for dosing differences, the mean anti-Xa activity reported in their study is remarkably similar to that in our study at similar time points. This supports the prevailing opinion regarding consistency of effect.

Significant bleeding complications are associated with LMWHs when administered without dose-adjustment for renal impairment (Farooq et al. 2004) and this risk correlates with anti-Xa activity (Kuczka et al. 2009). The paucity of large pharmacokinetic studies of tinzaparin in ESRD is therefore surprising. Our study constitutes the largest assessment of anti-Xa activity during the first hour of HD which likely confers the highest haemorrhagic risk as it coincides with the greatest BP levels. Hainer et al. (2002) provide a detailed analysis of the first hour of HD albeit in 12 patients. Simpson et al. (1996) provide data on just 8 patients dialysed with very low flows (mean Qb 200ml/min, mean Qd 500ml/min) using dialysers already primed with tinzaparin. Although they report anti-Xa activity at hourly intervals they do not detail the tinzaparin doses and weights of this subgroup. Other pharmacokinetic studies are similarly limited by small sample sizes, incomplete reporting and heterogeneous HD practices. These include a Greek study measuring anti-Xa activity at 0, 2 and 4 hours with 3,500IU tinzaparin (Christidou et al. 2005) and a Canadian study using 3,500-4,500IU tinzaparin (Lord et al. 2002) describing anti-Xa activity at baseline, mid-dialysis, the end of HD and prior to the next session. Lord

et al. (2002) do not provide specific times for the mid-dialysis sample, do not quantify the dose used referring to it as a “satisfying dosage”, and do not provide the weights for the patients used in their evaluation subgroup.

Hainer et al. (2002) dosed according to weight (75IU/kg) delivering a mean tinzaparin dose of 6480IU compared to 2500IU used in our study. This is in contrast to the relatively low doses (mean 2,139-2,186IU) used by Simpson et al. (1996) although they used circuits already primed with anticoagulant. Use of fixed-dose tinzaparin regimens has been suggested by Davenport (2008) allowing for ease of administration. With a mean HD session length of 4 hours Davenport reported that just under 80% patients had uneventful dialyses with 2500IU tinzaparin with a small proportion (<5%) requiring doses in excess of 4500IU (Davenport 2008). Dialyser flux and composition may have influenced the dose required to avoid the clinical endpoint of circuit thrombosis. In the only study examining this effect Egfjord et al. (1998) reported a two-fold difference in the dose of tinzaparin required with three haemodialysers to prevent clotting during HD (2,571 – 5,020IU).

5.4.2. Pleiotropic effects of tinzaparin

The different effects of LMWHs on the coagulation cascade are not accounted for by measuring just one parameter such as anti-Xa activity. For LMWHs with a significant anti-IIa effect, such as tinzaparin, this may be more clinically significant. Only the study by Hainer et al. (2002) provided a pharmacokinetic analysis of this but described just three characteristics: peak activity (0.85IU/ml), the time to peak activity (16 minutes) and the observed half-life (96 minutes) after IV administration. In their study the ratio of anti-Xa:anti-IIa effect at peak was 1.5 with the anti-IIa effect decaying 43% faster (Hainer et al. 2002). Such kinetics may not be valid in mid-flux HD, as at our centre, and require further evaluation.

LMWHs exert other anticoagulant effects through a variety of mechanisms such as TFPI release and decreases in circulating vWF. The anti-Xa activity of enoxaparin has been correlated to alterations in the physical properties of blood clots *in vitro*, an effect modulated by the presence of uraemia (Brophy et al. 2004). Repeated use of enoxaparin for maintenance HD causes less depletion of TFPI compared to UFH (Naumnik et al. 2003) and is associated with less platelet reactivity *in vitro* (Aggarwal et al. 2004). Studies in HD patients reveal variations between LMWHs in their ability

to release TFPI (Naumnik et al. 2011) and despite use of anti-Xa activity as a surrogate for clinical effect, studies suggest this correlates poorly with pharmacodynamic effect in these patients (Brophy et al. 2006). There is no comparative data involving tinzaparin that is published to date.

5.4.3. Effect of gender

The finding of a significant effect of gender on peak anti-Xa activity in ESRD patients in our study represents the first such report in the literature regarding any LMWH to date. This relationship was not known or evaluated by the manufacturer (Leo Pharma UK, personal communication) and may have significant consequences when using fixed-dose tinzaparin in women with very low weights on HD. The reasons for this effect are not established and may relate to differences in body composition that are unaccounted for in this analysis. Tinzaparin is predominantly distributed in the plasma with a volume of distribution of 3.1-5l, similar to the total adult intravascular volume. Although no gender differences were reported in studies in the general (non-dialysis) population, dialysis patients have greater volumes of total body water compared to age and gender-matched controls (Basile et al. 2008) with data to suggest that females have significantly lower relative tissue hydration (Van Biesen W. et al. 2011) and which may account for differences in tinzaparin distribution. In the absence of comparative data in HD patients this remains a hypothesis.

5.4.4. Changes in antithrombin-III and fibrinogen

We report effects of gender and ethnicity on antithrombin-III levels that parallel data from non-dialysis populations (Gader et al. 1995; Tait et al. 1990). Similar relationships exist with regards to fibrinogen levels (Kaptoge et al. 2007). We speculate that progressive rises in the measured values of these variables relate to ultrafiltration although we did not measure that parameter in the present study and so cannot rule out a direct effect from exposure to the extracorporeal circuit.

5.4.5. Study limitations

Although the present study is the largest pharmacokinetic evaluation of tinzaparin in HD to date, the cohort size nonetheless remains relatively small and may have influenced outcomes. The anti-IIa profile of tinzaparin was not measured in this study and any potential effect of ethnicity on this parameter cannot be excluded. Similarly any differences in other anticoagulant effects such as TFPI release are unknown. This study evaluated a single dose of 2,500IU and therefore the profile of higher doses is not characterised and although there was no evidence of a residual anti-Xa effect at the subsequent HD session the effect of repeated doses was not characterised and one cannot comment on the degree of anti-Xa activity after 4 hours. Finally conclusions from this study cannot be extrapolated to provide data for longer HD sessions and in other ethnic groups.

5.4.6. Future considerations

Despite its increasing use for HD circuit anticoagulation the pharmacokinetics and pharmacodynamics of tinzaparin remain relatively poorly characterised in ESRD with the uncertain effects of higher doses on different HD schedules and modalities and no correlation between anti-Xa levels and clinical outcomes. The absence of comparative pharmacokinetic studies between UFH regimes and tinzaparin in HD mean that judgements about equivalent intensities of anticoagulation and dose-titration to targets are not feasible. This is particularly important in clinical scenarios characterised by higher than average bleeding risk in a population exposed to anticoagulation regularly thrice weekly and with a baseline haemorrhagic diathesis. In our opinion it is essential to characterise these areas in greater detail with larger, comprehensive pharmacokinetic evaluations to allow for tailored anticoagulation in haemodialysis patients.

As a result a larger, funded, prospective evaluation of all three set doses of tinzaparin (2500, 3500 and 4500IU) has been developed using a larger cohort of 58 patients. Anti-Xa and anti-II activity of tinzaparin will be measured at 0, 0.25, 0.5, 1, 2, 4 and 48 hours to obtain a better understanding of tinzaparin kinetics in HD.

6. Determinants of stroke risk in maintenance haemodialysis

This chapter presents the results of a study evaluating the incidence of thrombotic (ischaemic) and haemorrhagic stroke in a large patient cohort as well as its effect on patient survival. Demographic and clinical factors of interest are evaluated to provide a clinical framework for risk appraisal.

6.1. Introduction

6.1.1. Epidemiology of stroke in ESRD

Stroke is the leading cause of long-term disability and the second and third leading causes of death in the U.S. and U.K. respectively (Hill 2009; Lloyd-Jones et al. 2010). The incidence of stroke progressively increases with declining eGFR and reaches a peak in CKD Stage 5 (US Renal Data System 2009) with rates 5-10 times higher than in the general population (Kawamura et al. 1998; Seliger et al. 2003a; Sozio et al. 2009).

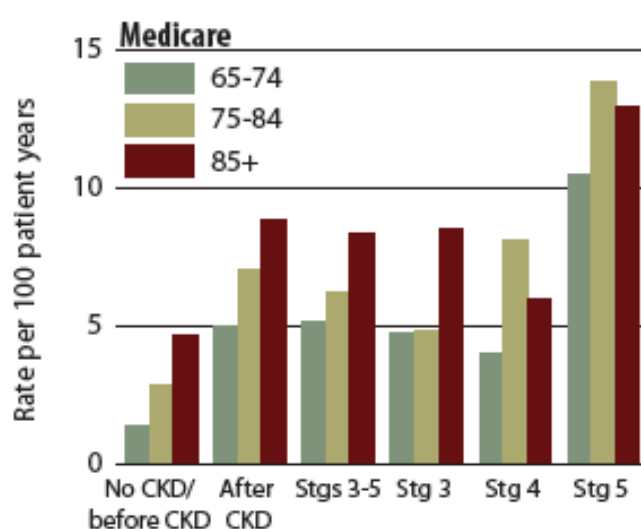


Figure 6.1. Effect of renal impairment according CKD stage on stroke incidence (from USRDS 2009 Report). Data derived from populations eligible for Medicare.

The prognosis of HD patients following stroke is appalling with 60% patients aged 75-84 years dying within one year and over half experiencing walking disability (US Renal Data System 2009). This propensity for stroke has been related to the higher prevalence of risk factors such as hypertension and diabetes that are over-represented in dialysis patients. In addition, factors specific to ESRD such as an accelerated calcific arteriosclerosis, uraemic toxemia, increased systemic inflammation and use of anticoagulation to maintain flow in the extracorporeal circuit have been cited as additional risk strata although proof of causation has been elusive (Sozio et al. 2011).

Epidemiological data in HD patients has derived largely from U.S. and Japanese cohorts and is summarised in Table 6.1. Only one study from a single Spanish centre provides a European perspective but is limited to the evaluation of ischaemic stroke alone and involves relatively small patient numbers and follow-up (Sanchez-Perales et al. 2010). Rates of stroke in patients on peritoneal dialysis (PD) are even less well characterised with just two studies reporting on this pathology (Pai et al. 2004; Toyoda et al. 2004) in cohorts of 16 and 12 patients respectively. One analysis of U.S. registry data (Seliger et al. 2003b) reported no difference in stroke risk in patients on PD compared to those on HD despite contradictory data (Toyoda et al. 2004). In keeping with data from Seliger et al. (2003b) PD was not associated with a higher risk of stroke or carotid endarterectomy in a recent U.S. prospective cohort study (Sozio et al. 2009).

Study	Era	Numbers (n)	Stroke events (n)	Stroke incidence	Predominant subtype
Iseki et al. 1993	1988-1991	1,609 (all HD)	41	12.5	H (4x)
Kawamura et al. 1998	1971-1994	1,064 (all HD)	85	13.2	H (2.5x)
Iseki et al. 2000	1988-1998	3,741 (all HD)	271	17.2	H (1.7x)
Seliger et al. 2003	1993-1999	8,920 (89% HD)	915	33.1	I (5.5x)
Toyoda et al. 2005	1980-2002	1,740 (all HD)	151	13.0	I ‡
Sozio et al 2009	1995-2004	1,041 (74% HD)	200	49	I (6.7x)
Chan et al. 2009	2003-2007	1,671 (all HD) *	102	45	I (3x)
Sanchez-Perales et al. 2010	1999-2005	449 (81% HD)	30†	24.1	Ischaemic only

Table 6.1. Major published studies on stroke incidence in haemodialysis patients.

Note: Stroke incidence reported as number of events per 1,000 patient years.

Abbreviations: HD, haemodialysis; H, haemorrhagic; I, ischaemic.

* All patients had atrial fibrillation.

† Only ischaemic events were reported.

‡ In the contemporary cohort ischaemic strokes predominated whereas the older cohort (1980-1996) had a higher incidence of haemorrhagic events.

6.1.2. Prevalence of stroke subtypes

Patients on HD have a higher prevalence of haemorrhagic stroke (reaching 30%) compared to the general population. This was particularly marked in early Japanese studies (Iseki et al. 1993;Iseki and Fukiyama 1996;Kawamura et al. 1998) reporting haemorrhagic stroke in 72%-80%. This may reflect uncontrolled hypertension in these cohorts with predialysis BPs averaging 172/90mmHg in one study (Kawamura et al. 1998) as well as a genetic predisposition to these subtypes (Yamada et al. 2008). Ethnic variations in stroke incidence and subtype are well described in the general population (Gunaratne et al. 2009;Mak et al. 2009b;Markus et al. 2007) and may relate to socioeconomic factors as well as genotypic variations (Tzourio et al. 2008).

6.1.3. Risk factors for stroke in ESRD

Four studies reporting stroke incidence in ESRD patients have critically evaluated the risk factors associated with this pathology. These have consistently identified increasing age as an independent risk factor for all-cause stroke as well as attributing risk to a diagnosis of hypertension (Iseki & Fukiyama 1996;Seliger et al. 2003b), low serum albumin levels (Seliger et al. 2003b) and diabetes mellitus (Sanchez-Perales et al. 2010;Seliger et al. 2003b;Sozio et al. 2009). The risk associated with atrial fibrillation was examined in just one study (Sanchez-Perales et al. 2010) where it increased ischaemic stroke risk over 3-fold. The effect of ethnicity was evaluated in just two studies, both from the U.S., and found that white ethnicity was associated with a higher stroke risk (Seliger et al. 2003b;Sozio et al. 2009). The potential effect of a wide breadth of haematological and biochemical variables has not been evaluated to date. More pertinently there are no studies reporting on the effect of erythropoietin dose and sensitivity on stroke risk in HD patients in contrast to compelling data from non-dialysis populations in large RCTs (Pfeffer et al. 2009;Singh et al. 2006).

6.1.4. Aims of the study

There are relatively few data on stroke epidemiology in Western HD populations with small cohorts reflecting modern HD practices and outcomes. Just one study to date provides a European perspective but is limited to evaluating of one subtype.

A comprehensive examination of the characteristics and incidence of stroke, risk factors at baseline and the effect of stroke on patient survival in a large and multi-ethnic urban UK haemodialysis population was performed to understand better the mechanisms behind stroke in this high risk population.

6.2. Methods

6.2.1. Study design

The study cohort comprised of all prevalent and incident (i.e. starting treatment during the course of the study) patients on HD at our centre who were established for more than 90 days on thrice weekly maintenance HD from 1st January 2002 to 1st June 2009. Paper and electronic records relating to outpatient and inpatient episodes were examined, and laboratory, radiological and dialysis data were analysed. Stroke was defined as an acute neurological event lasting more than 24 hours in duration accompanied by compatible findings on neuroimaging (computed tomography and/or magnetic resonance imaging). Ischaemic stroke was defined using the International Classification of Disease, Ninth Revision (ICD-9) coding criteria 433.1 and 434.1 and radiological confirmation of infarction was mandated. Haemorrhagic stroke was defined as intracerebral and/or subarachnoid haemorrhage (ICD-9 codes 430, 431 and 432.9). Subdural haematoma (ICD-9 codes 432.0 and 432.1) was excluded from this analysis.

6.2.2. Study variables and definitions

Patient characteristics were captured at dialysis initiation and included age, sex, ethnicity, cause of ESRD, major comorbid conditions as defined in Section 4.2.1 including a diagnosis of atrial fibrillation. Similarly treatment details were recorded including time on HD therapy and erythropoiesis-stimulating agent (ESA), aspirin, clopidogrel and warfarin use.

6.2.3. Outcome measures

The primary outcome measure was the incidence of fatal and non-fatal hospitalised stroke (ischaemic and haemorrhagic). For patients identified with acute stroke during the study period, additional laboratory data were examined at the time of the event (haemoglobin, platelet count, coagulation profile, albumin, cholesterol, ferritin, bone profile and parathyroid hormone) and pre- and post-dialysis BP was assessed (the average of 3 BP readings at that event was taken as representative).

Secondary outcome measures included overall survival in the study cohort as well as survival after acute stroke according to subtype.

6.2.4. Statistical methods

Descriptive statistics are expressed as the mean $\pm$ standard deviation. Continuous and categorical variables were compared using t-tests and chi-square or the Mann-Whitney U test respectively. Timeline incidence data were analysed using a Poisson model and expressed with 95% confidence intervals (CIs). Patient survival analysis was performed using the Kaplan-Meier method and comparisons made using the log-rank test.

To identify factors significantly associated with first (incident) all-cause stroke as well as each stroke subtype, a competing-risks approach was used to account for the higher rate of mortality compared to stroke in dialysis patients. Age-adjusted Cox regression models were used, including variables such as sex, comorbid conditions (as previously described), and vascular access type and censoring for death, change in dialysis modality or transplant, transfer out of centre, dialysis therapy withdrawal and loss to follow-up. Time origin was defined as the date of HD therapy initiation. Patients with a history of prior stroke were excluded from this analysis.

Subsequently the influence of these baseline clinical factors on mortality in the entire study cohort was examined using Cox models in which new acute stroke was incorporated as a time-dependent variable. Factors influencing subsequent survival in patients with first (incident) stroke were also examined using Cox models including variables captured at time of event including age, sex, comorbid conditions, BP, C-reactive protein level $>3\text{mg/l}$, ferritin level, total cholesterol level, albumin level $>35\text{g/l}$, haemoglobin level and erythropoietin dose.

All models met assumptions of proportionality. Factors identified by univariate analysis with $p < 0.1$ were examined using multivariate analysis. A backwards selection procedure was applied to this multivariate model to identify risk factors of significance.

Statistical significance was defined by $p < 0.05$ from two-sided tests. All statistical analyses were performed using STATA 10.0 (StataCorp LP, College Station, TX, USA).

Ethical approval for this study was granted as an audit and service evaluation according to national guidelines (NHS National Research Ethics Service 2009).

6.3. Results

6.3.1. Characteristics of study cohort

There were 2,474 maintenance HD patients during the period under study with 9,541 patient-years of follow-up. Of these 2,384 patients (96%) had complete demographic and clinical data. This formed the study cohort with a total of 7,326 patient-years of follow-up and mean follow-up of 3.0 ± 2.1 years per patient (Table 6.2).

A total of 17% cohort received a kidney transplant, with 5% transferring care out of centre during the period of study. Characteristics of this group were representative of national cohorts reported by the UK Renal Registry (Caskey et al. 2010) except for significant representation of South Asian and African-Caribbean patients and a significant proportion of patients dependent on CVCs as definitive vascular access.

6.3.2. Overall stroke incidence

There were 145 strokes during the study period. Eighteen of 145 events (12%) occurred within the first 90 days of HD treatment (13 ischaemic and 5 haemorrhagic) and were excluded from analysis. A total of 127 strokes were studied in depth in 121 patients with an overall incidence of 17.3 per 1,000 patient years (95% CI 14.5 - 20.6). Twelve patients had experienced at least one acute stroke before 2002, leaving 109 strokes as the first event for patients in the period of study.

Compared with the general HD population, patients who experienced stroke were significantly older at the time of HD initiation (62.9 ± 12.7 vs. 58.2 ± 15.9 years, $p=0.01$) with a mean age of 64.5 ± 12.5 years at the time of their stroke. Diabetes was the cause of ESRD in 61/121 (51%) patients with stroke, hypertension in 12% and polycystic kidney disease in 3%. Patients with stroke had a higher prevalence of diabetes, ischaemic heart disease (IHD) and established cerebrovascular disease. Stroke was not more prevalent in patients with atrial fibrillation. There were significantly more strokes in patients treated with clopidogrel (15.7% vs. 9.3%, $p=0.02$) but no propensity to haemorrhagic over ischaemic events was detected. There was a lower prevalence of AVF use in the stroke group (Table 6.2).

	Total population [n=2384]	Stroke cohort [n=121]	Non-stroke cohort [n=2263]	P value
Mean age $\pm$ SD (yrs)	58.2 $\pm$ 15.9	62.9 $\pm$ 12.7	58.0 $\pm$ 16.0	0.009
Prevalent patients (%) [¶]	28.0	23.1	28.2	0.2
Mean HD vintage [*]	3.4 $\pm$ 3.2	1.6 $\pm$ 1.4	3.5 $\pm$ 3.2	0.002
Ethnicity				
White	1008 [42.3%]	48 [39.7%]	960 [42.4%]	0.6
African-Caribbean	440 [18.4%]	24 [19.8%]	416 [18.4%]	0.7
South Asian	808 [33.9%]	43 [35.5%]	765 [33.8%]	0.7
Other	128 [5.4%]	6 [5.0%]	122 [5.4%]	0.8
Co-morbidities				
Diabetes	919 [38.5%]	61 [50.4%]	858 [37.9%]	0.006
Ischemic heart disease	764 [32.0%]	49 [40.5%]	715 [31.6%]	0.04
Hypertension	1374 [57.6%]	73 [60.3%]	1301 [57.5%]	0.5
PVD	304 [12.7%]	13 [10.7%]	291 [12.9%]	0.5
Prior CrVD	204 [8.5%]	36 [29.7%]	168 [7.4%]	<0.001
Atrial fibrillation	197 [8.3%]	14 [11.6%]	183 [8.1%]	0.2
Antiplatelet and Anticoagulant Treatment				
Aspirin	881 [36.9%]	53 [43.8%]	828 [36.6%]	0.1
Clopidogrel	229 [9.6%]	19 [15.7%]	210 [9.3%]	0.02
Warfarin	73 [3.1%]	0	73 [3.2%]	0.04
Vascular access				
AVF	642 [26.2%]	16 [13.2%]	626 [27.7%]	<0.001
AVG	11 [0.5%]	0	11 [0.5%]	0.9
CVC	1731 [72.6%]	105 [86.8%]	1626 [71.9%]	<0.001

TABLE 6.2. Comparative demographics of study cohorts.

Notes: ¶ As of study start (1st January 2002). * Prevalent patients only.

Abbreviations: SD, standard deviation

6.3.3. Ischaemic and haemorrhagic strokes

Overall 68% (86 of 121) of all strokes were ischaemic with an incidence of 11.7 per 1,000 patient years (95% CI 9.4 - 14.5) and 32% were haemorrhagic with an incidence of 5.6 per 1,000 patient years (95% CI 4.0 - 7.6). Patients with haemorrhagic strokes were significantly younger than those with ischaemic stroke (mean age 59.9 ± 13.4 vs. 67.5 ± 11.7 years, $p=0.004$).

Forty-five percent of ischaemic strokes occurred in patients of white ethnicity and most haemorrhagic events (54%) occurred in South Asian patients (Table 6.3). On subanalysis by ethnic group there were no significant differences in any demographic or clinical features listed in Table 6.3. Patients with haemorrhagic stroke, irrespective of ethnicity, had significantly higher diastolic BPs both pre- and post-dialysis and a trend to higher systolic readings. There were no other significant differences between subtype groups in comorbidities, haematological or biochemical profiles (including markers of metabolic bone disease, nutrition and inflammation), HD treatment (including spKt/V and dry weight), or ESA treatment. There was no significant difference in antiplatelet agent use between the two groups and no patient who experienced a stroke was on warfarin therapy.

	Ischaemic [n=86]	Haemorrhagic [n=41]	p value
Age at stroke onset (yrs)	67.5 ± 11.7	59.9 ± 13.4	0.004
Ethnicity			
White	39 [45.3%]	11 [26.8%]	0.04
African-Caribbean	19 [22.1%]	5 [12.2%]	0.3
South Asian	25 [29.1%]	22 [53.7%]	0.007
Other	3 [3.5%]	3 [7.9%]	0.4
Comorbidities			
Diabetes	50 [57.5%]	24 [58.5%]	0.9
IHD	41 [47.1%]	13 [31.7%]	0.09
Hypertension	55 [63.2%]	33 [80.5%]	0.06
PVD	12 [13.8%]	3 [7.3%]	0.4
Laboratory parameters			
Hb (g/dl)	12.0 ± 1.7	11.9 ± 1.9	0.9
Plt (x10 ⁹ /l)	193 ± 79	186 ± 63	0.6
PT (secs)	11.8 ± 1.8	11.8 ± 1.5	0.8
APTT (secs)	34.8 ± 13.5	32.6 ± 12.3	0.7
Fbg (g/l)	4.10 ± 0.88	4.00 ± 0.94	0.5
Cholesterol (mmol/l)	3.7 ± 0.9	3.4 ± 1.0	0.2
Albumin (g/l)	32 ± 6	33 ± 5	0.3
Corr. calcium (mmol/l)	2.28 ± 0.22	2.34 ± 0.15	0.1
Phosphate (mmol/l)	1.31 ± 0.43	1.25 ± 0.55	0.5
CRP (mg/l)	32 ± 23	27 ± 16	0.5
Ferritin (mcg/l)	597 ± 285	798 ± 1213	0.7
Hemodialysis Treatment			
HD vintage (yrs)	2.9 ± 2.3	3.1 ± 2.8	0.9
Dry weight (kg)	66.4 ± 13.6	62.4 ± 14.7	0.2
Pre-SBP (mmHg)	156 ± 29	168 ± 32	0.06
Pre-DBP (mmHg)	82 ± 18	92 ± 19	0.008
Post-SBP (mmHg)	151 ± 31	162 ± 25	0.07
Post-DBP (mmHg)	79 ± 17	89 ± 12	0.02
ESA Treatment			
Dose (mcg)*	54.2 ± 26.0	48.2 ± 26.6	0.3
Dose per kg (mcg/kg)*	0.85 ± 0.44	0.75 ± 0.45	0.33
Antiplatelet Treatment			
Aspirin	35 [40.7%]	11 [26.8%]	0.1
Clopidogrel	10 [11.6%]	1 [2.4%]	0.1
Aspirin & Clopidogrel	6 [7.0%]	3 [7.3%]	0.9

TABLE 6.3. Patient characteristics and clinical features at time of stroke according to subtype.

Data expressed as mean ± standard deviation. Numbers expressed with percentages in parentheses. Abbreviations: Hb, haemoglobin; Plt, platelet count; PT, prothrombin time; APTT, activated partial thromboplastin time; Fbg, fibrinogen; Pre- denotes predialysis; Post- denotes postdialysis; SBP, systolic blood pressure; DBP, diastolic blood pressure; Corr. , corrected; CRP, C-reactive protein; ESA, erythropoiesis-stimulating agent.

*All patients received darbepoetin once weekly IV.

6.3.4. Risk of incident stroke

Incident (first ever) stroke occurred in 109 patients at a rate of 14.9 per 1,000 patient years (95% CI, 12.2 – 17.9). Eighty-two events were ischaemic and 27 haemorrhagic with incidence rates of 11.2 per 1,000 patient years (95% CI 8.9 – 13.9) and 3.7 per 1,000 patient years (95% CI 2.5 – 5.4) respectively.

Univariate analysis identified older age, diabetes, prior cerebrovascular disease (all $p < 0.001$), hypertension ($p = 0.01$), ischaemic heart disease ($p = 0.02$) and use of antiplatelet therapy ($p = 0.04$) as risk factors for incident stroke (Table 6.4). On multivariate analysis only diabetes mellitus remained independently associated with incident stroke risk.

Risk factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age at HD start (/yr)	1.03	1.01 – 1.04	<0.001	1.02	0.99 – 1.03	0.1
Male gender	1.25	0.85 – 1.83	0.3	-	-	-
Ethnic background						
African-Caribbean	<i>reference</i>					
White	1.41	0.82 – 2.43	0.2	-	-	-
South Asian	1.41	0.81 – 2.45	0.2	-	-	-
Comorbidities						
Diabetes	2.82	1.93 – 4.14	<0.001	1.92	1.29 – 2.85	0.001
Hypertension	1.67	1.21 – 2.49	0.01	1.34	0.90 – 2.01	0.2
PVD	1.29	0.77 – 2.13	0.3	-	-	-
IHD	1.59	1.09 – 2.31	0.02	1.07	0.72 – 1.61	0.7
Established CrVD*	5.92	4.09 – 8.59	<0.001	4.54	3.07 – 6.72	<0.001
Therapies						
Aspirin	1.48	1.02 – 2.14	0.04	0.96	0.65 – 1.43	0.9
Clopidogrel	1.70	1.03 – 2.82	0.04	1.11	0.65 – 1.88	0.7
Warfarin	0.52	0.13 – 2.12	0.4	-	-	-

TABLE 6.4. Risk factors for first (incident) stroke [n=109].

*Defines clinically manifest cerebrovascular disease (transient ischemic attack) prior to study period.

Multivariate analysis identified diabetes mellitus (HR 1.85, 95% CI 1.13 – 3.03, $p=0.01$) and prior cerebrovascular disease in the form of TIA (HR 5.48, 95% CI 3.40 – 8.82, $p<0.001$) as the only factors associated with risk of incident ischaemic stroke. By contrast increased risk of first haemorrhagic stroke appeared associated with the presence of hypertension (HR 4.26, 95% CI 1.51 – 12.0, $p=0.06$) and to a lesser extent with prior cerebrovascular disease (HR 2.31, 95% CI 1.04 – 5.17, $p=0.04$) but not ethnicity.

6.3.5. Mortality after acute stroke

A total of 726 of 2,384 (30.5%) patients died during the study period, of whom 55 (7.6%) died after acute stroke. Specifically mortality was 24% at 1 year after acute stroke, 46% at 2 years and 60% at 3 years compare with 6%, 12% and 19% respectively in incident HD patients at our centre. Haemorrhagic stroke was associated with markedly higher mortality at 30 days after the acute event (32% vs. 7% for ischaemic stroke, $p<0.001$). Comparatively one-year mortality was 39% vs. 19% at 1 year, 51% vs. 44% at 2 years and 79% vs. 53% at 3 years for haemorrhagic vs. ischaemic stroke (Figure 6.2).

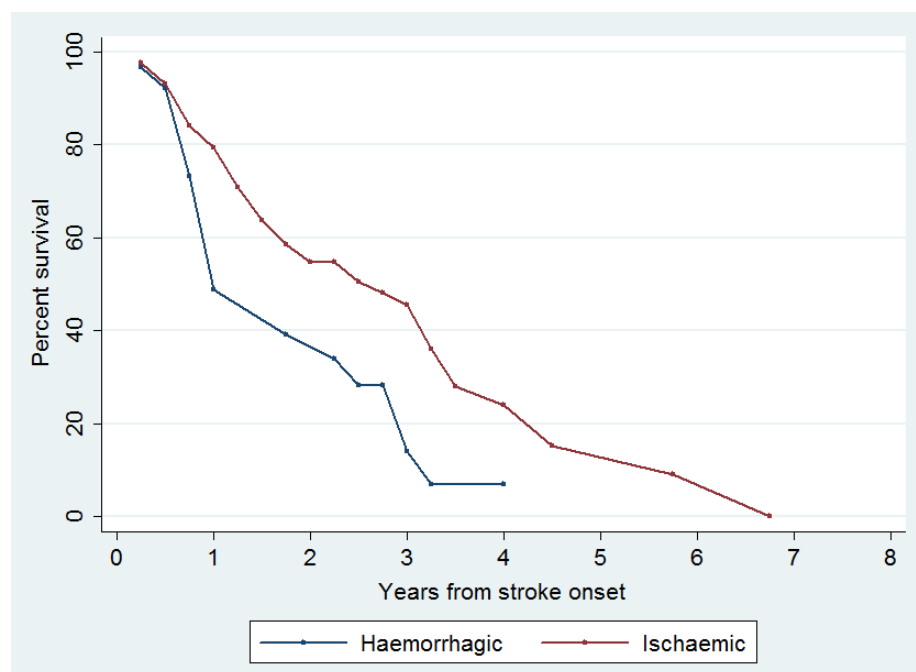


Figure 6.2. Actuarial survival of haemodialysis patients after acute stroke.

6.3.6. Impact of acute stroke on patient survival

Multivariate analysis of the entire study cohort (Table 6.5) showed that an acute stroke had a profound impact on survival (HR 3.26, 95% CI 2.47 – 4.30, $p<0.001$). In addition diabetes mellitus ($p<0.001$), peripheral vascular disease ($p<0.001$) and male sex ($p=0.005$) were associated with worse survival. In counterpoint African-Caribbean ethnicity ($p<0.001$) and aspirin use ($p<0.001$) were associated with better survival.

Risk factors	Univariate analysis			Multivariate analysis		
	HR	95% C.I.	P value	HR	95% C.I.	P value
Acute stroke	3.44	2.61 – 4.53	<0.001	3.26	2.47 – 4.30	<0.001
Male gender	1.25	1.08 – 1.45	0.003	1.24	1.06 – 1.43	0.005
Ethnicity						
White	<i>referent</i>			<i>referent</i>		
African-Caribbean	0.66	0.53 – 0.83	<0.001	0.67	0.54 – 0.88	<0.001
South Asian	0.86	0.73 – 1.02	0.09	0.86	0.72 – 1.02	0.08
Other	0.58	0.29 – 1.17	0.1	-	-	-
Comorbidities						
Diabetes	1.43	1.23 – 1.66	<0.001	1.39	1.19 – 1.62	<0.001
Hypertension	1.02	0.88 – 1.19	0.7	-	-	-
PVD	1.73	1.46 – 2.06	<0.001	1.59	1.33 – 1.90	<0.001
IHD	1.17	1.01 – 1.36	0.04	1.10	0.93 – 1.30	0.3
Prior CrVD	1.14	0.96 – 1.36	0.1	-	-	-
Antiplatelet Treatment						
Aspirin	0.80	0.69 – 0.93	0.003	0.71	0.61 – 0.83	<0.001
Clopidogrel	0.96	0.76 – 1.21	0.7	-	-	-

TABLE 6.5. Association of new acute stroke and baseline clinical characteristics on age-adjusted survival in the study cohort (n=2,384).

In a subanalysis of patients experiencing their first ever stroke (n=109), a serum albumin level >35g/l and aspirin use at the time of stroke were associated with a lower subsequent risk of death ($p=0.007$ and $p=0.03$ respectively), whereas a C-reactive protein level >3mg/l was associated with worse post-stroke survival ($p=0.002$). Factors such as age at the time of stroke, diabetes, ischaemic heart disease, ethnicity, sex, haemoglobin level and dose of darbepoetin did not significantly affect mortality (Table 6.6).

Risk factors	Univariate analysis			Multivariate analysis		
	HR	95% C.I.	P value	HR	95% C.I.	P value
Age (years)	1.01	0.98 – 1.03	0.6	-	-	-
Male gender	1.03	0.59 – 1.80	0.9	-	-	-
HD vintage (years)	1.11	0.82 – 1.51	0.5			
Comorbidities						
Diabetes	1.30	0.76 – 2.22	0.3	-	-	-
Hypertension	1.20	0.68 – 2.12	0.5	-	-	-
PVD	1.97	1.01 – 3.82	0.05	1.64	0.80 – 3.33	0.2
IHD	1.09	0.65 – 1.84	0.7	-	-	-
Prior CrVD	1.35	0.67 – 2.76	0.4	-	-	-
Antiplatelet Treatment						
Aspirin	0.54	0.31 – 0.92	0.03	0.54	0.30 – 0.96	0.03
Clopidogrel	1.84	0.87 – 3.90	0.1	1.50	0.69 – 3.27	0.3
Albumin >35g/l	0.42	0.23 – 0.80	0.008	0.38	0.19 – 0.76	0.007
Haemoglobin (g/dl)	0.92	0.78 – 1.08	0.3	-	-	-
ESA dose / kg weight	0.82	0.52 – 1.25	0.3	-	-	-
CRP >3.0 mg/l	1.40	1.15 – 1.70	0.001	1.36	1.12 – 1.64	0.002
Ferritin (mcg/l)	1.00	0.99 – 1.00	0.6	-	-	-
Cholesterol (mmol/l)	0.86	0.63 – 1.18	0.3	-	-	-
Predialysis SBP (mmHg)	1.00	0.99 – 1.01	0.7	-	-	-
Predialysis DBP (mmHg)	0.99	0.97 – 1.02	0.5	-	-	-
Postdialysis SBP (mmHg)	1.00	0.99 – 1.00	0.4	-	-	-
Postdialysis DBP (mmHg)	1.00	0.98 – 1.01	0.6	-	-	-

TABLE 6.6. Association between risk factors at time of acute stroke and subsequent mortality.

6.4. Conclusions

The data presented constitutes the largest European study regarding stroke incidence in HD patients which is almost ten-fold higher in this group compared to general population. This is similar to published series (Kawamura et al. 1998; Seliger et al. 2003b; Toyoda et al. 2005; Sozio et al. 2009; Sanchez-Perales et al. 2010) and further emphasises the large burden of cerebrovascular disease in patients on dialysis therapies (Delmez et al. 2006; Kim et al. 2007; Naganuma et al. 2011c).

6.4.1. Incidence of stroke

An overall stroke incidence of 17.3 events per 1,000 patient years is significantly lower than rates published from U.S. cohorts (33 - 49 per 1,000 patient years) and below that reported by Sanchez-Perales et al. (2010), 24 per 1,000 patient years. Rates of stroke at our centre were more comparable to those in Japanese cohorts (13.0-17.2 per 1,000 years) that offer an insight into the evolution of stroke epidemiology in HD patients by providing over 20 years of data (Toyoda et al. 2005). More contemporary cohorts had higher overall rates of stroke (17.2 vs. 13.2 & 13.1 events per 1,000 patient years) despite improvements in BP metrics (Kawamura et al. 1998; Iseki et al. 2000; Toyoda et al. 2005). The reasons for such wide disparities in incidence rates are unclear although the study cohorts have varied with regards to demographic and clinical characteristics.

Ischaemic stroke remains the most common subtype in all series including the present study and national trends suggest an increasing prevalence (Sozio et al. 2009; Seliger et al. 2003b; Toyoda et al. 2005). It is interesting that in the Japanese HD population a trend away from haemorrhage was described by Toyoda et al. (2005) which was attributed to more conservative dialysis circuit anticoagulation, better BP control (mean BP on admission 195/97mmHg in 1980-1996 vs. 179/87mmHg in 1997-2002, $p < 0.005$) and a more Westernised lifestyle. This latter effect which remains unquantified may act as a powerful driver to rising ischaemic, stroke rates in Japanese registry studies and may, in part, explain the particularly high incidence in U.S. series.

Sozio et al. (2009) reported an incidence of stroke at 49 per 1,000 patient years in a dialysis population including patients on both HD and PD and which probably had a

greater arteriopathic burden than our own despite a similar prevalence of prior cerebrovascular disease (17% vs. 16% respectively). Notably their cohort had a higher prevalence of diabetes (54% vs. 39%), ischaemic heart disease (44% vs. 32%) and peripheral vascular disease (26% vs. 13%) at baseline. Chan et al. (2009) reported on a selected group of patients (all had atrial fibrillation) who were older (mean age 72 vs. 58 years in our study) and had again a higher prevalence of diabetes and coronary disease.

Furthermore the higher incidence of all-cause stroke in the U.S. may reflect the much higher percentage of African-American patients in their cohorts comprising 24-80% of the dialysis population (Seliger et al. 2003b; Sozio et al. 2009) as well as the relative paucity of South Asian patients (<5% dialysis population). Although patient ethnicity was not associated with an increased risk of stroke in our study, African-American ethnicity was frequently associated with higher risk in the general population (Kittner et al. 1990). Seliger et al. (2003b) identified African-American ethnicity as an independent risk factor for stroke in patients with no documented cardiovascular disease but this was not the case when the authors explored this in patients with this disease. The investigators speculated that it could be related to under-diagnosis of this condition in this subgroup (Seliger et al. 2003b). In contrast the study by Sozio et al. (2009) found that African-American ethnicity was associated with a 36% lower risk of stroke although they offered no potential explanations. It is likely that socioeconomic factors associated with ethnicity rather than ethnically-prevalent genotypic factors are dominant influences and belie these apparently contradictory results. No other studies in HD examined the potential effect of ethnicity on stroke and this is the first to report specifically on rates in South Asian patients.

6.4.2. Haemorrhagic and ischaemic stroke subtypes

In this study haemorrhagic strokes accounted for 32% events and were more prevalent in younger, more hypertensive patients. More than half the patients with haemorrhagic strokes were of South Asian ethnicity, suggesting an ethnic predisposition to this type of stroke. This contrasted with the predominance of ischaemic strokes in white patients. We did not find inter-ethnic differences in BP profile, serum albumin, dialysis adequacy, haematological parameters or ESA dose. Despite the relatively small numbers involved this novel finding supports the concept of a genetic predisposition to stroke subtypes (Markus et al. 2007; Yamada et al.

2008; Mak et al. 2009). The pathogenic mechanism of haemorrhagic stroke in HD patients may be classic hypertensive intracerebral haemorrhage or a haemorrhagic conversion of a prior ischaemic stroke exacerbated by dialysis anticoagulation. The higher prevalence of cerebral microbleeds in HD patients (Yokoyama et al. 2005) and their association with subsequent intracerebral haemorrhage explain the pathophysiology of this stroke subtype in HD (Watanabe 2007). The deposition of beta-amyloid in the intracerebral vasculature, cerebral amyloid angiopathy, is associated with intracerebral haemorrhage (Raposo et al. 2011; Vasilevko et al. 2010) and microbleeds (Dierksen et al. 2010). Whether HD patients are more prone to this pathology than age-matched controls is speculative – there are no autopsy or imaging studies in the literature. One study showed higher levels in HD patients compared to patients without renal impairment but found that HD provided good clearance with a 4 hour session (Kitaguchi et al. 2011). Plaques of cerebral amyloid angiopathy comprise of other constituents such as cystatin C which is markedly elevated in HD (Lee et al. 2009).

Irrespective of ethnicity patients with haemorrhagic strokes presented with significantly higher BP compared to those with ischaemic events both pre- and post-dialysis, a finding in keeping with published data. Hypertension remains an established modifiable risk factor for all stroke subtypes and remains a significant treatment challenge (Iseki et al. 2000; Seliger et al. 2003b; Toyoda et al. 2005). Sodium loading both intradialytically and from dietary intake promotes hypertension through thirst (with volume expansion) as well as through non-volume dependent mechanisms (Hamlyn and Manunta 2011; Penne et al. 2010). A “Westernised” diet high in salt and high-fructose corn syrup as typified in the U.S. may be contributing to higher rates of hypertension-driven stroke in countries increasingly adopting this aspect of lifestyle (Soleimani and Alborzi 2011). We and others have shown that modification of dietary sodium intake and tailoring of dialysate sodium leads to BP improvements in the short to medium-term (Power et al. 2010d) and may lead to better outcomes in the long-term although this remains unproven (Ok 2010).

6.4.3. Impact of stroke on patient survival

Acute stroke constitutes a highly significant clinical event for HD patients, conferring a 3-fold higher risk of death in the present study independently of the effect of traditional risk factors. Overall patient survival at 1 year after all-cause stroke was

69%. The prognosis for haemorrhagic stroke has been extremely poor with case fatality rates reaching 90% in other series (Sozio et al. 2009; Iseki et al. 2000). This study reaffirms this with a higher fatality rate of 32% vs. 7% at 30 days ($p<0.001$) and 39% vs. 19% at 1 year ($p<0.001$). This difference between haemorrhagic and ischaemic stroke parallels experience in the general population (Qureshi et al. 2009). Interestingly mortality rates from haemorrhagic stroke in this study of HD patients were comparable to those reported in large, population studies (Flaherty et al. 2006; Weimar et al. 2003). Functional status or quality of life following acute stroke were not assessed so it is not possible to comment on these important outcome measures which remain undescribed in HD patients to date.

6.4.4. Risk factors for stroke in HD

Prior cerebrovascular disease is the dominant risk factor for stroke in this study (Table 6.4) and independently increased risk more than 4-fold. Although previous studies report a higher prevalence of this factor in patients who subsequently experienced a stroke, its effect has not been fully evaluated (Sozio et al. 2009; Sanchez-Perales et al. 2010). This finding suggests that appropriate screening and treatment measures for prior TIA may strongly influence subsequent stroke incidence in the HD population in a manner similar to the general population (Rothwell et al. 2007a). This hypothesis prompted the subsequent study described in Chapter 8. Diabetes mellitus was the only other clinical factor associated with a higher risk of stroke and is in keeping with prior literature. These findings corroborate results from large population series highlighting the importance of smoking and alcohol excess as further risk factors which were not characterised in this work (O'Donnell et al. 2010).

Although aspirin treatment did not associate with an increased risk of all-cause stroke, clopidogrel treatment was associated with higher risk in this study. This needs to be interpreted with caution due to the relatively small numbers involved and potential confounding by indication. Antiplatelet treatment did not predispose to haemorrhagic stroke, and there were insufficient numbers on warfarin to comment with validity on its influence on stroke risk unlike Chan et al. (2009). In contrast, aspirin treatment was associated with decreased mortality following stroke on univariate and multivariate analysis, an effect not seen with clopidogrel treatment. Although causality cannot be inferred from associations, particularly given the small

numbers involved in this study, this finding is in keeping with recent studies in the general population (Berger et al. 1998;Steinhubl et al. 2009).

The data presented confirmed the association between low serum albumin (<35g/l) and elevated C-reactive protein level, markers of malnutrition-inflammation syndrome, and worse patient survival (Delmez et al. 2006) although inflammatory status *per se* has not been found to predispose to stroke in HD patients (Sozio et al. 2011).

Although ESAs were associated with increased risk of stroke in non-dialysis patients in TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy), there are fewer data for patients on HD therapy (Pfeffer et al. 2009). Patients presenting with stroke in our study were receiving a slightly higher mean monthly dose of darbepoetin compared to the TREAT cohort (52 vs. 44µg/week), but due to incomplete long-term ESA data for the entire cohort, a rigorous examination of the associations between ESA dose and stroke incidence could not be performed. A recent post hoc analysis of the TREAT data suggested that ESA use and not dose *per se* influenced the risk of stroke (Skali et al. 2010). No dose-dependent effect of ESAs on survival after stroke was seen and there were no significant differences in ESA doses in patients presenting with ischaemic as opposed to haemorrhagic subtypes, suggesting that ESAs do not influence this aspect of stroke manifestation.

6.4.5. Study limitations

The strengths of this study include a large cohort size, long follow-up and uniform dialysis practices over time. One is limited to reporting associations and not proofs of causality because of the retrospective nature of this study which is prone to confounding by unidentified influences. Furthermore each stroke subtype consists of multiple difference pathophysiological entities that may vary in causation and are not addressed as such in this analysis. Risk is calculated on the basis of comorbid conditions, biological factors and treatment at baseline. Their variability over time has not been measured and this is a limitation in keeping with all published studies to date. However this study affords a clinician a measure of risk based on factors that can be measured at a single visit.

6.4.6. Perspectives for future evaluation

The dearth of clinical trials on stroke prevention in HD patients is in sharp relief to the high incidence and poor prognosis associated with this lesion. The AURORA (Assessment of Survival and Cardiovascular Events) study of 2,776 HD patients randomly assigned to placebo or 10mg rosuvastatin showed no effect of statin therapy on the incidence of non-fatal strokes (12 vs. 11 per 1,000 patient years, $p=0.4$). Overall incidence rates of stroke were not reported, the prevalence of established cerebrovascular disease was unclear and 44% strokes were fatal (Fellstrom et al. 2009). Results from AURORA and 4D (Die Deutsche Diabetes Dialyse Studie, Wanner et al. 2005) were counterintuitive to our understanding of the prophylactic benefit of statin therapy in high-risk individuals based on studies in the general population (Everett et al. 2010). The recent publications of results from SHARP (Study of Heart and Renal Protection) in which stroke was a component of the composite primary endpoint, indicate that simvastatin and ezetimibe have a significant beneficial effect on stroke incidence irrespective of the level of low-density lipoprotein cholesterol (Sharp Collaborative Group 2010). Diabetes, older age and established cerebrovascular disease are non-modifiable risk factors for stroke in a number of studies including this one.

Uncontrolled hypertension in dialysis patients is a significant modifiable risk factor for stroke, especially haemorrhagic events (Iseki et al. 2003; Seliger et al. 2003b; Toyoda et al. 2005). In the absence of large and appropriately powered prospective trials there is neither a recommended target level nor a form of treatment for BP control at present nor evidence-based consensus on what measure of BP to use (e.g. peridialytic, 24-hour ambulatory or home BP readings). Given the impact of stroke in HD patients large collaborative trials are mandated to provide a similar base of evidence as in the general population with which to treat hypertension and significantly affect the incidence of this condition (ALLHAT Collaborative Research Group 2000; Chapman et al. 2004; Hansson et al. 1998; Ninomiya et al. 2008).

Potential roles for systemic inflammation, anaemia management with ESAs and control of bone mineral metabolism remain unclear but it is likely that for efficacy interventions would need to be targeted in the pre-dialysis phase of the patients' clinical course. Ethnic and genotypic predispositions to stroke in HD patients are incompletely understood but are suggested by our findings of an unexpectedly high prevalence of haemorrhagic stroke in South Asian patients. Comprehensive analysis

of large DNA banks, as used in the BRAINS (Bio-Repository of DNA IN Stroke) study, should help provide some answers in the future (Yadav et al. 2011). Finally changes in HD treatment parameters directed at retarding and even reversing uraemic arterial calcification may be more efficacious at reducing stroke incidence than conventional pharmacotherapy (e.g. statins) that is directed at atherosclerotic substrates. In this regard we explored a potential association between calcification and stroke in the next chapter.

7. Intracranial arterial calcification and ischaemic stroke

This chapter presents a study exploring the factors associated with intracranial arterial calcification (IAC) in HD patients and its effect on the risk of ischaemic stroke. A potential pathophysiological link is proposed based on the findings with reference to prior literature.

7.1. Introduction

7.1.1. Overview of the biology of arterial calcification

Arterial calcification is an active process that occurs with increasing age as well as a number of diseases such as diabetes and renal failure. Calcification commonly occurs in the arterial intima, typically co-localising with atheromatous plaques, and can also occur in the media. In the latter location it leads to the classic lesion of Mönckeberg's sclerosis seen in uraemia but also prevalent in diabetes and ageing (Davies and Hruska 2001). Central to the pathophysiology of this process is the presence of osteoblast-like cells within the vessel wall.

The origin of these cells is uncertain with some models suggesting they are the result of stimulated, phenotypic change of resident vascular smooth muscle cells (VSMCs) and others implicating circulating pluripotent stem cells or transdifferentiated, resident pericytes (Johnson et al. 2006). VSMCs can undergo osteogenic differentiation in response to stimuli such as oxidative stress and bone morphogenetic proteins, BMPs (Hruska et al. 2005) as well as high calcium and inorganic phosphate levels (Reynolds et al. 2004). Such transformed cells deposit extracellular matrix and promote calcification in a manner comparable to ossification in native bone.

Intimal calcification occurs at the site of atherosclerotic plaques in a milieu of inflammation, oxidative stress and macrophage infiltration. BMP-2 expression is increased in response to multiple stimuli convergent in plaque formation such as oxidative stress (Mody et al. 2001), intraluminal hypoxia (Bouletreau et al. 2002), foam cells (Dhore et al. 2001), high tumour necrosis factor (TNF α) levels (Csiszar et al. 2005) and oxidised-low density lipoprotein (LDL). Intimal arterial calcification has a higher prevalence in patients with ESRD and occurs at an earlier age (Goodman et al. 2000). Renal failure is *per se* associated with higher levels of TNF α (Spoto et al. 2011) and oxidative stress (Kaya et al. 2011; Lee et al. 2011a) however there are conflicting studies regarding the relationship between dyslipidaemia and vascular calcification (Krasniak et al. 2007; Tamashiro et al. 2001).

Medial arterial calcification is classically initiated by the release of membrane-bound vesicles from VSMCs as well as by the presence of their apoptotic bodies (Proudfoot et al. 2001) the persistence of which is favoured by the presence of modified lipids

(Proudfoot et al. 2002). Haemodialysis has been shown to trigger VSMC apoptosis although the mechanism is unclear (Shroff et al. 2008). Released membrane-bound bodies act as focal points for the deposition of calcium and phosphate in the form of hydroxyapatite (Reynolds et al. 2004), a key stage in the initiation of vascular calcification. In health, vascular calcification is regulated through the actions of calcification inhibitors that circulate in the serum and are expressed constitutively by VSMCs. These include matrix-Gla protein (MGP), inorganic pyrophosphate, osteopontin, osteoprotegerin and fetuin-A.

Calcification is accompanied by neovascularisation at the lesional sites through a process hypothesised to involve vascular endothelial and VSMCs as well as pericytes and circulating osteoprogenitors under the influence of factors such as BMP-2, BMP-4 and vascular endothelial growth factor, VEGF (Collett and Canfield 2005). The purpose of such neoangiogenesis remains unclear but may promote delivery of circulating cells and cytokines to allow development and maturation of the calcific lesion. Importantly the degree of neoangiogenesis has been correlated with risk of atherosclerotic carotid artery plaque necrosis and rupture (Hiyama et al. 2010; McCarthy et al. 1999).

7.1.2. End-stage renal disease promotes vascular calcification

Arterial calcification is highly prevalent in ESRD and has a graded relationship with adverse survival (London et al. 2003). The remarkably high prevalence of this condition in dialysis patients is explained only in part by the relative over-representation of diabetes in this group. A number of other factors specific to ESRD and uraemia have been identified. As discussed above ESRD is typified by a state of greater oxidative stress and systemic inflammation promoting calcification. Progressive impairment of phosphate excretion as renal function declines leads to compensatory elevations in fibroblast growth factor 23 (FGF-23) and overt hyperphosphataemia. Phosphate has been shown to promote phenotypic change in VSMCs *in vitro* through a sodium-phosphate cotransporter, Pit-1, which is upregulated in uraemia (Giachelli 2003; Mizobuchi et al. 2006) and which itself promotes Cbfa1 expression (an osteogenic transcription factor). Phosphate also promotes VSMC vesicle release and expression of osteopontin and alkaline phosphatase (Chen et al. 2002). Similar effects are reported with hypercalcaemia (Giachelli 2003) that often accompanies uncontrolled secondary hyperparathyroidism

in advanced renal failure which may be promoted by the use of calcium-containing oral phosphate binders used to control hyperphosphataemia (e.g. calcium carbonate/acetate). FGF-23 has been independently associated with calcification in HD patients (Nasrallah et al. 2010;Tamei et al. 2011) as well as other uraemic toxins that promote this process (Moe et al. 2003).

In synergy with the active promotion of vascular calcification in ESRD there is a reduction of the intensity of inhibition of these pathways. MGP inhibits BMP-2 (Bostrom et al. 2001) and requires vitamin-K dependent γ -carboxylation to be fully functional in this regard. Dialysis patients have elevated BMP-2 concentrations in the serum in tandem with a high prevalence of vitamin K deficiency reaching 93% (Pilkey et al. 2007;Sweatt et al. 2003). Warfarin acts as a vitamin K antagonist and use of this anticoagulant (e.g. for maintenance of vascular access patency) may accelerate widespread vascular calcification and has been associated with calciphylaxis (Mazhar et al. 2001;Schurgers et al. 2004). Levels of fetuin-A, a circulating inhibitor that prevents hydroxyapatite crystallisation, are lower in HD patients than the general population and associated with greater arterial calcific burden (Kirkpantur et al. 2009;Schlieper et al. 2009;Westenfeld et al. 2009). Elevated levels of leptin, an adipocytokine may contribute to vascular calcification by direct effects on VSMCs as well as increasing oxidative stress (Mallamaci et al. 2005;Parhami et al. 2001).

7.1.3. Clinical effects of vascular calcification

Intimal arterial calcification is a marker of atherosclerotic disease and predictive of pathological sequelae such as myocardial infarction and death (Sangiorgi et al. 1998;Wilson et al. 2001). Medial calcification adversely affects the mechanical properties of the vascular tree by causing arteriosclerosis, or vascular stiffening, which affects arterial pulse waveforms and velocity (Haydar et al. 2004;London 2003).

In health, left ventricular systole generates a forward pressure wave whose characteristics are dependent on the nature of the contracting left ventricle, blood rheology, and the compliance of the arterial tree. It propagates along the artery until it reaches branch points, turbulent flow or points where the luminal diameter changes. At those loci it is reflected backwards. The resultant pressure wave in the vessel wall is the summation of those two waveforms. In early diastole with appropriately elastic

arteries the reflected wave returns to the central circulation and augments coronary arterial inflow. Arterial stiffening increases pulse-wave velocity (PWV) and results in a more acute reflected wave arriving earlier (late systole) to the central circulation and increasing cardiac workload as well as impairing coronary perfusion (DeLoach and Townsend 2008). Aortic stiffness has been shown to be an independent predictor of all-cause and cardiovascular mortality in the general population as well as patients with ESRD (Blacher et al. 1999;Laurent et al. 2001).

7.1.4. Intracranial arterial calcification and stroke

IAC reflects the total atherosclerotic burden in individuals and has been associated recently with an increased incidence of stroke in the general population (Chen et al. 2007;Suzuki et al. 2007). It is associated with increasing age and diabetes mellitus like other forms of vascular calcification (Mak et al. 2009a) and has been associated with overall cerebral white matter disease but a precise pathophysiological mechanism correlating the two has not been elucidated (Bos et al. 2011). It is associated with greater mortality following ischaemic stroke but this may be an epiphenomenon of the vascular risk associated with extensive calcification (Bugnicourt et al. 2011).

Recent data have shown an increasing prevalence of IAC with each stage of CKD in patients presenting to hospital with stroke-like symptoms (Bugnicourt et al. 2009). The authors found the highest degree of IAC in those with CKD Stage 4 & 5 however patient numbers were very small in that subgroup (n=10). To date there are no large cohort studies providing an epidemiological assessment and quantification of this phenomenon in HD.

7.1.5. Hypotheses and aims of the study

Incidence rates of ischaemic stroke parallel both declining renal function in the general population and the increasing prevalence of IAC (Abramson et al. 2003). We hypothesised that HD patients have a high prevalence of IAC on computed tomographic (CT) brain scanning and the degree of IAC can predict ischaemic stroke

in this group of patients. Such analysis may provide clues into the pathophysiology of stroke in a group of patients with heavy arterial calcific burdens and a manifest high incidence of this disease.

7.2. Methods

7.2.1. Study design

This was a retrospective study of all patients on maintenance HD at our centre from 1st October 2005 to 31st May 2009 and who had a CT scan of the head performed for any neurological indication (acute confusion in 32% cases, motor symptoms in 23%, seizures in 19% and a drop in conscious level in 16%). In total 2,225 patients were established (>90 days) on HD during this time with 4,302 total patient years follow up (Table 7.1). Five hundred and twenty-nine head CT scans were performed of which 490 (93%) were in established HD patients (Figure 7.1). Sixty of these were diagnostic of acute ischaemic stroke, an overall incidence of 13.9 per 1,000 patient years (95% CI 10.6 – 18.0). In the remaining 430 scans, no focal lesions were identified in 75%, there was evidence of old cerebral infarction in 105/430 (24%) scans and a metastatic neoplasm was found in 1 patient.

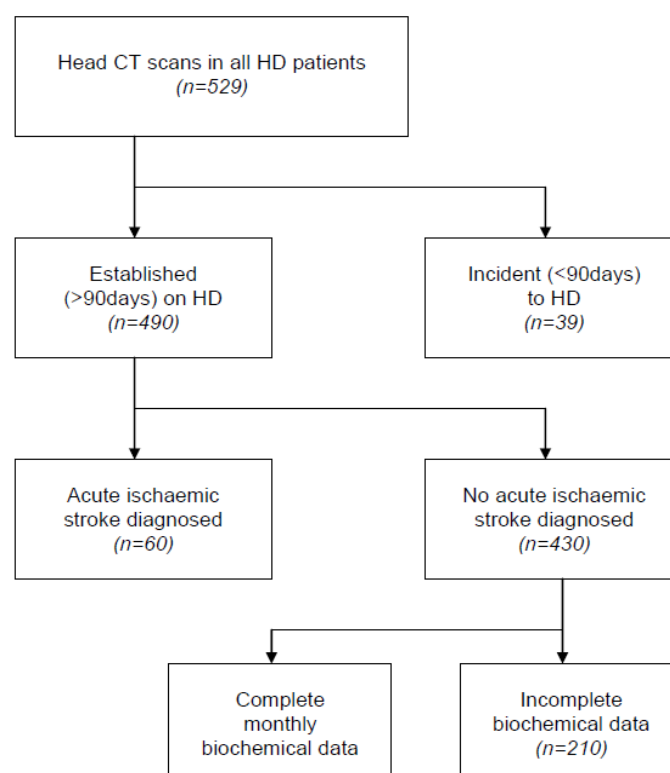


Figure 7.1. Overview of study groups and CT imaging selection.

For analysis of the relationship between laboratory variables and the severity of IAC, a subgroup of scans in patients without evidence of acute ischaemic stroke and who had complete data available for 6 months before image acquisition was examined (n=220, Figure 7.1). The characteristics of this subgroup were representative of the larger, non-stroke cohort in terms of age, haemodialysis vintage, ethnicity, comorbidity profiles and IAC load.

All patients were dialysed three times weekly using mid- to low-flux synthetic haemodialysers over a mean session length of 4.2 hours. Dialysis adequacy measurements and targets were as detailed before (see Section 2.2.5).

7.2.2. Study variables and definitions

The effects of age, gender and ethnicity were analysed. Comorbid conditions were defined as detailed previously (Section 6.2.2). The use of antiplatelet or anticoagulant medication (warfarin) was recorded. Laboratory variables included mean serum calcium, phosphate and parathyroid hormone (PTH) levels over the 6 month period prior to each CT scan acquisition. Acute ischaemic stroke was defined as an acute neurological event >24 hours in duration associated with evidence of infarction on neuroimaging (CT and/or MRI). Haemorrhagic stroke and subdural haematoma were excluded from this analysis.

7.2.3. Scoring of IAC

Bone window CT brain images were analysed to identify IAC at the level of the carotid siphon using a semi-quantitative scale correlating CT findings at this level with conventional angiographic studies (Woodcock, Jr. et al. 1999).

	Whole dialysis population (n=2225)	CT scan cohort (490 scans)	P value	No IAC present (n=76)	IAC present (n=414)	P value	Mean IAC load – Factor present	Mean IAC load – Factor absent	P value
Age (yrs)	59.0 ± 15.8	62.8 ± 14.3	<0.001	48.6 ± 18.0	65.5 ± 11.8	<0.001	-	-	-
Proportion male	61%	61%	0.9	57%	62%	0.4	3.3 ± 1.9	3.4 ± 2.0	0.4
HD vintage (yrs)	-	3.0 ± 3.1	-	2.0 ± 2.3	3.2 ± 3.1	0.002	-	-	-
Ethnicity									
White	951 [43%]	227 [46%]	0.2	30 [39%]	196 [47%]	0.3	-	-	-
African-Caribbean	400 [18%]	103 [21%]	0.1	20 [26%]	87 [21%]	0.4	-	-	-
South Asian	862 [39%]	158 [32%]	0.005	26 [35%]	131 [32%]	0.7	-	-	-
Comorbidities									
Diabetes	877 [39%]	245 [50%]	<0.001	22 [29%]	222 [54%]	<0.001	4.2 ± 1.5	3.6 ± 1.5	<0.001
IHD	713 [32%]	214 [44%]	<0.001	13 [17%]	201 [49%]	<0.001	4.1 ± 1.5	3.3 ± 1.8	<0.001
Hypertension	1244 [60%]	320 [65%]	<0.001	49 [64%]	269 [65%]	0.9	3.3 ± 1.9	3.3 ± 2.0	0.9
Prior CrVD	344 [16%]	201 [41%]	<0.001	14 [18%]	187 [45%]	<0.001	3.9 ± 1.7	3.5 ± 1.9	0.03
PVD	253 [11%]	82 [17%]	0.001	1 [1%]	81 [20%]	<0.001	4.4 ± 1.4	3.4 ± 1.8	<0.001
Acute stroke (n=60)	-	-	-	3 [5%]	57 [95%]	0.02	3.9 ± 1.6	3.2 ± 2.0	0.01

Table 7.1. Characteristics of IAC study population.

Data expressed as mean values ± standard deviation.

The authors had identified 4 discrete patterns of calcification (Figure 7.2) which they classified descriptively and correlated with the degree of luminal stenosis on digital subtraction angiography.

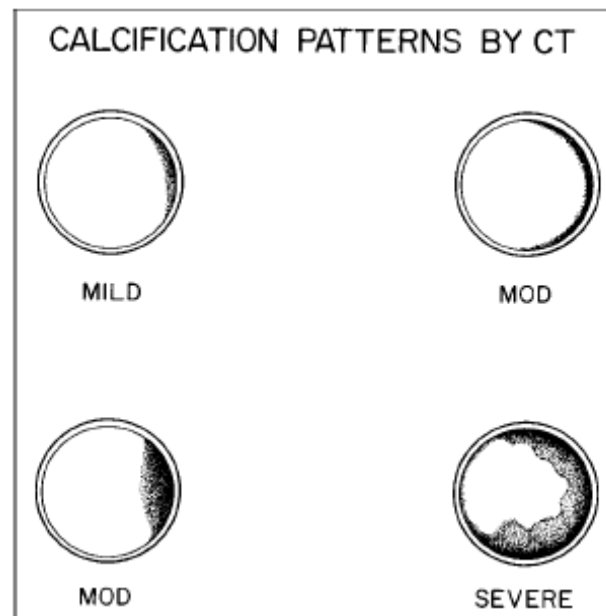


Figure 7.2. CT calcification patterns, from paper by Woodcock et al. (1999).

This classification was subsequently validated and converted into a numerical grading system (Erbay et al. 2007). In keeping with the system used by Erbay et al. (2007) we scored calcification in each carotid siphon as Grade 0 – absent, Grade 1 – thin, discontinuous, Grade 2 – thin, continuous or thick, discontinuous, and Grade 3 – thick, continuous. The overall severity of IAC was expressed as the sum of the carotid siphon calcification scores. The CT images were scored by two observers (Drs Power & Haydar) with good inter-observer agreement (Cohen's alpha 0.74). In cases of disparity the images were rescored on review with consensus.

7.2.4. Statistical methods

Descriptive statistics were expressed as the mean $\pm$ standard deviation. Continuous and categorical variables were compared using Student's t test and the chi-square or Mann-Whitney U test respectively, as appropriate. Timeline incidence data were analysed using a Poisson model and expressed with 95% CI. The relationship

between IAC load and bone profile parameters was examined using Cusick's test for trend.

Univariate and multivariate logistic regression was used to examine the effect of IAC load and factors of interest such as patient age, HD vintage, diabetes, ischemic heart disease, hypertension, pre-existing cerebrovascular disease and peripheral arterial disease in predicting new ischemic stroke in the study cohort. In addition linear regression was used to examine the association between these factors and the quantified IAC load. A mixed effects model was used to account for the fact some patients had more than one scan during the study period. Factors identified by univariate analysis with a p-value <0.1 were then examined using a multivariate model. A backwards selection procedure was then applied to this model to identify risk factors of significance. There was no significant interaction of effect between the factors in the final model.

The effect of IAC severity and comorbidities on patient survival was examined using multivariate Weibull survival models adjusting for patient age and censoring for change in dialysis modality, transplantation, dialysis withdrawal and loss to follow up. For this analysis IAC severity was dichotomised as either low-grade (summated score 1-3) or high-grade (summated score 4-6).

All analyses were performed using STATA 11.0 (StatCorp, College Station, TX, USA). Statistical significance was defined throughout by $p < 0.05$.

Ethical approval for this study was granted as an audit and service evaluation according to national guidelines (NHS National Research Ethics Service 2009).

7.3. Results

7.3.1. Clinical factors associated with IAC

Three hundred and fifty-five (83%) scans in the non-stroke group displayed IAC. The presence of IAC was significantly associated with age, time on HD (vintage), and diabetes, coronary and peripheral arterial disease (Table 7.1). Patient gender and ethnicity did not appear to influence the presence of IAC.

IAC was more prevalent in patients presenting with acute ischaemic stroke (95% vs 83%, $p=0.02$) and more severe (Table 7.1). These patients had a significantly higher prevalence of prior diagnosed cerebrovascular disease (63% vs. 38%, $p<0.001$) but were otherwise similar to the non-stroke group in terms of demographic and comorbid profile.

7.3.2. Clinical factors influencing severity of IAC

The severity of IAC increased significantly with patient age ($p<0.001$) and HD vintage ($p<0.001$), an effect that became statistically significant from 4 years on treatment ($p=0.04$, Figure 7.3). The presence of peripheral vascular disease, diabetes mellitus and ischaemic heart disease (all $p<0.001$ on multivariate analysis) were independently associated with greater IAC severity (regression coefficients 0.94, 0.85 and 0.62 respectively). Male gender was associated with significantly less severe IAC (coefficient -0.38, $p=0.01$). A diagnosis of hypertension and the use of antiplatelet agents had no effect on IAC severity.

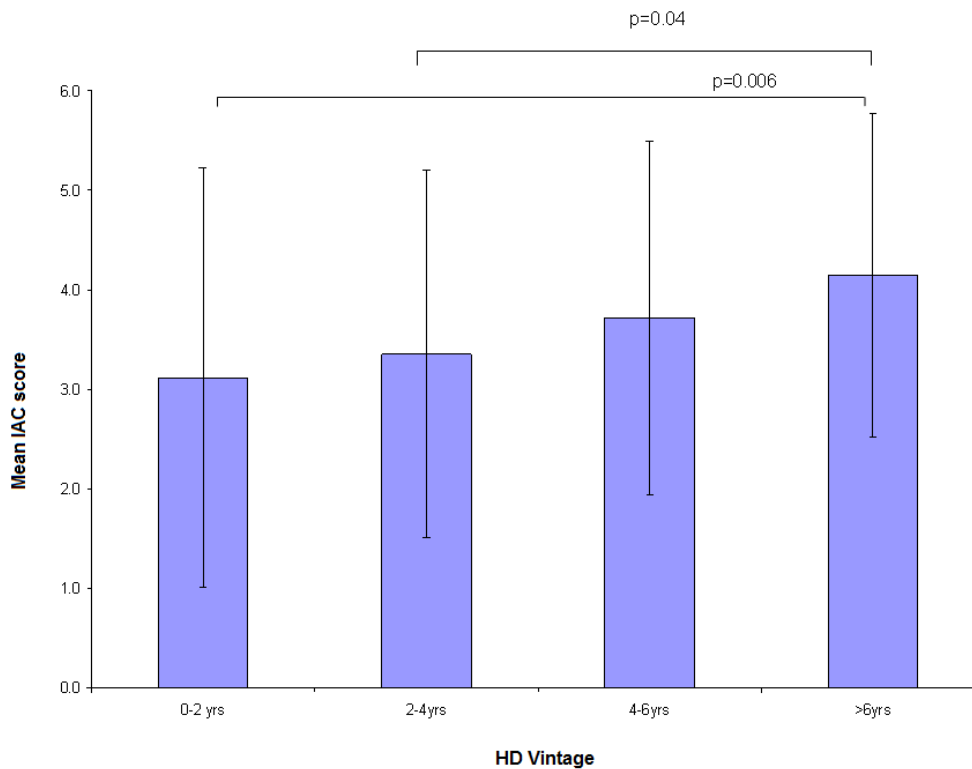


Figure 7.3. Effect of haemodialysis vintage on IAC load.

Higher serum phosphate (p for trend=0.045) and calcium-phosphate product (p for trend=0.03) were significantly associated with a greater IAC load. There was no significant relationship with serum albumin ($p=0.4$) or PTH ($p=0.5$).

7.3.3. IAC severity as a predictor of acute ischaemic stroke

Eighty-seven patients in the study cohort had multiple CT scans for analysis ($n=225$), of which 14 were diagnostic of new ischaemic stroke. Of all the clinical factors examined (Table 7.2), greater IAC severity was an independent predictor of ischaemic stroke ($p=0.05$) and paradoxically diabetes mellitus was protective ($p=0.01$), with haemodialysis vintage and the presence of prior cerebrovascular disease displaying a trend to significance ($p=0.06$).

	Univariate analysis			Multivariate analysis		
Risk Factor	Coefficient	95% CI	P value	Coefficient	95% CI	P value
Age (years)	0.01	-0.03 – 0.05	0.6	-		-
Prior HD (/year)	-0.19	-0.45 – 0.06	0.1	-0.30	-0.53 – 0.01	0.06
Male gender	0.09	-1.07 – 1.24	0.9	-		-
Diabetes mellitus	-1.09	-2.31 – 0.13	0.08	-1.76	-3.11 – -0.40	0.01
IHD	-0.81	-2.03 – 0.40	0.2	-		-
Hypertension	0.36	-0.98 – 1.70	0.6	-		-
CrVD	1.12	-0.09 – 2.34	0.07	1.26	-0.04 – 2.57	0.06
PVD	-1.07	-3.17 – 1.01	0.3	-		-
Aspirin use	-0.75	-2.08 – 0.58	0.3	-		-
Clopidogrel use	-0.49	-2.06 – 1.07	0.5	-		-
IAC load	0.23	-0.09 – 0.55	0.2	0.39	0 – 0.80	0.05

Table 7.2. Predictors of new ischaemic stroke.

7.3.4. IAC severity and association with patient survival

The presence of high-grade IAC was significantly associated with a higher age-adjusted risk of death (HR 2.17, 95% CI 1.22 – 3.87, $p=0.008$) in contrast to the lack of association seen with low-grade IAC (HR 0.84, 95% CI 0.58 – 1.49, $p=0.6$). Longer HD vintage was also independently associated with a greater risk of death (HR 1.01, 95% CI 1.00 – 1.01, $p=0.02$) but other major comorbid conditions such as the occurrence of new ischaemic stroke (HR 1.07, 95% CI 0.64 – 1.78, $p=0.8$), diabetes mellitus (HR 0.98, 95% CI 0.64 – 1.49, $p=0.9$), ischaemic heart disease (HR 0.92, 95% CI 0.61 – 1.39, $p=0.7$) and peripheral vascular disease (HR 0.96, 95% CI 0.56 – 1.67, $p=0.9$) were not.

7.4. Conclusions

In the largest study to date describing IAC in HD patients we found a high prevalence of this pathology (83%) comparable in magnitude to data from the coronary circulation, 70-90%. This data suggested a correlation with acute ischaemic stroke although this needs cautious interpretation given the low number of events studied in that subanalysis.

7.4.1. High prevalence of IAC

Historical as well as emerging data have correlated decreasing renal function and increasing arterial calcification in the coronary circulation (Budoff et al. 2011;Coylewright et al. 2011), the aorta (Iijima et al. 2010), and the extracranial carotid circulation (Pelisek et al. 2010). Prior studies have shown that IAC is more prevalent in patients with renal impairment compared to those with normal renal function (Bugnicourt et al. 2009), and increases in proportion to CKD stage.

Since the publication of our data a Japanese group has published their experience of the prevalence and distribution of IAC in a cross-sectional analysis of 107 HD patients (Iwasa et al. 2011). They found IAC prevalence similar to our own (88%) which was higher than a control group of 43 patients without renal disease (54%). Unlike the present study but in keeping with the study by Bugnicourt et al. (2009) they examined the posterior and anterior intracerebral circulation, and found that in HD patients the anterior circulation was the dominant vascular tree affected by increased IAC (the posterior circulation had no significant difference in IAC with respect to controls).

There were clear associations between the presence of IAC and increasing age, time on HD as well as major comorbidities. This is in keeping with data from the general population (Mak et al. 2009a) and in non-dialysis CKD patients (Bugnicourt et al. 2009). The relationship we described between IAC and increasing age, HD vintage, diabetes and overt arterial disease has been demonstrated in coronary tree in HD patients (Block et al. 2005).

7.4.2. Factors influencing burden of IAC

This data forms the first quantitative assessment of IAC in HD patients in the literature. Diabetes mellitus associated with greater IAC in keeping with the influence of this disease on vascular calcification in patients with normal and impaired renal function (Nakamura et al. 2009). We also found greater IAC in patients with established coronary and peripheral vascular disease reflecting the shared underlying pathology (Leskinen et al. 2009; Sumida et al. 2010).

Of interest is that higher serum phosphate concentration and calcium-phosphate product were associated with more severe IAC. Potential mechanisms for the effect of hyperphosphataemia have already been discussed. While calcium has been shown to stimulate phenotypic change in VSMCs in vitro (Reynolds et al. 2004) we found no association between serum calcium levels and IAC severity in our study. This may have been influenced by the relatively low serum concentrations in our patients treated with predominantly non-calcium-based phosphate binders in an attempt to minimise calcium loading. Indeed clinical studies have reported less vascular calcification with the use of phosphate binders such as sevelamer (Block et al. 2005) and lanthanum carbonate (Toussaint et al. 2011). We could not find an association between PTH levels and IAC although published data link high as well as low levels of PTH with vascular calcification (Raggi et al. 2002).

The apparent protective effect of male gender on the severity of IAC is notable. This contrasts with studies describing an association between male gender and a higher prevalence of extracranial vascular calcification (Jean et al. 2009; Wang et al. 2009). One may hypothesise that IAC may be subject to similar variations in gonadal steroid receptor expression as shown in a study of the coronary circulation (Liu et al. 2005). However a retrospective analysis such as our own is prone to confounding by a number of unidentified factors.

The degree of IAC in the general population has been correlated with the degree of angiographically-proven intracranial atherosclerosis (Kassab et al. 2009; Taoka et al. 2006) although this is a feature of analysis of large arteries as opposed to smaller, stenosed intracranial vessels (Homburg et al. 2011). This contrasts with studies of the coronary circulation where the degree of calcification correlates poorly with luminal stenosis on formal angiography (Sharples et al. 2004). IAC correlates with

cerebral atrophy (Erbay et al. 2008) and white matter disease burden (Chung et al. 2010) while reflecting disease in the extracranial carotid circulation (Lee et al. 2003).

7.4.3. IAC and acute ischaemic stroke

A relationship between IAC and ischaemic stroke has been suggested in a study of Chinese general medical patients by Chen et al. (2007) who reported an independent association (OR 3.17, 95% CI 1.26 - 8.03) while a comparative study of 72 Japanese patients found no such association (Taoka et al. 2006). The current study forms the first such assessment in HD patients. In keeping with data from non-dialysis populations we found a significantly higher prevalence of IAC in patients presenting with acute ischaemic stroke (95%) compared to other diagnoses, and reported a novel relationship between the degree of IAC severity and the risk of new ischaemic stroke that just reaches statistical significance. Separate linear regression analysis of the relationship between a diagnosis of acute ischaemic stroke and IAC severity at the time of scanning in the entire cohort showed that a significant association was present on univariate analysis ($p=0.03$) but not on multivariate analysis ($p=0.08$). The high prevalence of IAC, sample size and uncharacterised confounding factors may have affected the level of statistical significance.

The biological hypothesis that IAC is associated with stroke remains attractive. The cerebral circulation in HD patients represents a vascular bed especially vulnerable to perturbations in blood flow. Experimental models suggest that uraemia impairs cerebral autoregulation (New et al. 2003) while HD alters cerebral haemodynamics and has been shown to reduce middle cerebral arterial blood flow during and after therapy (Stefanidis et al. 2005). Diabetic patients appear prone to worse haemodynamic homeostasis intradialytically independently of UF (Ishida et al. 1999). We hypothesise that IAC may influence ischaemic stroke risk through adverse modulation of arterial waveform transmission to the blood-brain barrier, adverse arterial flow patterns causing vascular remodelling or by promoting atherosclerotic plaque instability and distal embolization.

A significant limitation of our study was the lack of evaluation of the extracranial carotid circulation and as such cannot attribute risk of stroke simply to intracranial findings. HD patients display greater carotid intimal medial thickening than non-dialysis patients and those with normal renal function, a finding correlated with levels

of systemic inflammation (Recio-Mayoral et al. 2011). Extracranial carotid atherosclerotic plaque has been shown to be more calcified and structurally unstable with more areas of rupture in patients with renal impairment compared to those with normal renal function (Pelisek et al. 2010). Calcification with neoangiogenesis, possibly augmented with the use of erythropoietin therapy may further influence plaque stability and promote rupture of unstable atherosclerotic plaques which is the initiating event in thrombosis with distal atheroembolism causing ischaemic stroke.

7.4.4. Study limitations

Although large, this study describes associations and cannot prove causality. Confounding, undescribed differences may have existed to explain the associations seen, such as phosphate binder and vitamin D analogue use. The study cohort underwent CT scanning for a neurological indication rather than planned, interval screening and the results would therefore be prone to indication bias. Prospective study using this modality is hampered by the unethical nature of sequential exposure to significant ionising radiation with no conclusive therapies available to treat the findings. Although a theoretically attractive alternative for imaging, MRI is time-consuming, more expensive and cannot identify calcium.

This study was unable to differentiate between intimal and medial calcification using CT imaging and the relative contribution of these could not be determined. Finally as discussed above we assessed carotid siphon calcification alone and therefore would have missed posterior cerebral circulation lesions.

7.4.5. Future considerations

Although IAC is highly prevalent in HD patients and may influence stroke risk it is uncertain whether IAC causes pathological blood flow and leads to, or augments, cerebrovascular brain injury. Dynamic cerebral blood flow assessment, using global brain imaging as well as middle cerebral artery flow measures, is required both on and off haemodialysis to better characterise the haemodynamic effects of this therapy and evaluate the influence IAC has on this parameter. Imaging modalities such positron-emission tomography can identify vascular inflammation (Pugliese et

al. 2010) and may help in the evaluation of carotid disease in ESRD patients although such use requires validation.

Oral anticoagulation with warfarin may exacerbate IAC although we did not have enough patients on this therapy to comment in this study. It is likely that newer oral anticoagulants such as direct thrombin inhibitors would not exert a similar effect on the vasculature, a relevant issue given the waning popularity of warfarin (Rahme et al. 2011). It is often prescribed in patients with chronic atrial fibrillation (AF) to reduce the risk of ischaemic (cardioembolic) stroke based on data from the general population (Holmes 2010). The efficacy of warfarin in preventing thromboembolic stroke in the setting of AF in HD patients has not been proven, which is in keeping with the absence of randomised-controlled trials examining primary or secondary stroke prevention in HD.

We proceeded to examine the impact of two aspects of stroke management in HD patients that were defined from trials in the general population: addressing transient ischaemic attack (TIA) as a stroke prevention strategy, and the use of systemic thrombolysis for early acute ischaemic stroke.

8. Screening for transient ischaemic attack in haemodialysis

An evaluation of targeted screening for episodes of TIA in HD patients is presented in this chapter in a study aimed at determining the true prevalence of this condition as a basis for stroke prevention measures in those who screening positive.

8.1. Introduction

8.1.1. Defining transient ischaemic attacks (TIA)

Transient ischaemic attack is a clinical diagnosis defined by a rapidly developing loss of focal cerebral function lasting less than 24 hours with no apparent non-vascular cause (Landi 1992). It shares the same pathophysiology as stroke but is typified by faster, complete symptom resolution. Diffusion-weighted magnetic resonance imaging (DWI) has allowed better characterisation of the ischaemic cerebral territory (Kidwell et al. 1999; Nagura et al. 2003) and questioned the arbitrary 24-hour timeframe which was devised on the belief that by this point brain injury would be detectable on microscopy (Albers et al. 2002). Indeed 50% of patients with DWI evidence of ischaemia in the setting of TIA progress to display evidence of infarction (Inatomi et al. 2005; Purroy et al. 2004). Currently all patients with acute neurological symptoms are assessed on an emergency basis by a dedicated acute stroke team and triaged accordingly.

8.1.2. Clinical relevance of TIA

About 70,000 TIAs are diagnosed annually in the United Kingdom (Johnston et al. 2007) although incidence rates in dialysis populations are unknown. TIA is significant risk factor for subsequent stroke with 4-20% experiencing a stroke within 90 days, the majority within the first 48 hours (Daffertshofer et al. 2004; Lisabeth et al. 2004; Lovett et al. 2003).

A number of interventions in the general population have been shown to reduce stroke risk following TIA such as antiplatelet therapy (Antithrombotic Trialists Collaboration 2002; CAPRIE Steering Committee 1996), control of hypertension (PROGRESS Collaborative Group 2001), statins (Amarenco et al. 2006), warfarin for atrial fibrillation and carotid endarterectomy for symptomatic carotid stenosis (Rothwell et al. 2003). The impact of comparable treatments in ESRD patients remains undefined due to scant data and clinical management remains based on trials that have traditionally excluded these cohorts. A post hoc analysis of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) reported an 82% reduction in 2-year stroke risk following surgery in patients with CKD 3 who had

similar rates of perioperative stroke and mortality compared to those with normal eGFR (Mathew et al. 2010). In contrast maximal medical therapy led to higher stroke rates in the CKD group. However as in prior studies endarterectomy in CKD patients was associated with a higher incidence of cardiac events (Ayerdi et al. 2001;Sidawy et al. 2008).

8.1.3. Risk scoring for TIA

A number of clinical scoring systems have been developed and validated for risk stratification of stroke following TIA such as the California score and the ABCD score (Johnston et al. 2000;Rothwell et al. 2005). The ABCD score is calculated as the sum of:

A ge ≥60 years	1 point
B P ≥140/90mmHg	1 point
C linical features	
Unilateral weakness	2 points
Disturbance without weakness	1 point
No disturbance	0 points
D uration of symptoms	
≥ 60 minutes	2 points
10-59 minutes	1 point
<10 minutes	0 points

The presence of diabetes mellitus (1 point) was added in a later version to generate the ABCD2 score (Johnston et al. 2007) and subsequent publications have suggested that the presence of infarction on imaging (CT or DWI) is prognostically significant with 7-day stroke rates of 7.1% in those with infarction and 0.4% in those without (Giles et al. 2010).

Parallel use of these scoring systems with rapid access TIA clinics offering specialist assessment and treatment has been shown to reduce the risk of recurrent stroke in the general population (Lavalley et al. 2007;Rothwell et al. 2007b).

8.1.4. Hypotheses and aims of the study

It is not known whether TIA precedes stroke in HD patients in the same manner as in the general population and the effect of standard interventions remains unproven in a population characterised by different vascular disease and recurrent exposure to anticoagulation by virtue of their treatment for renal failure. Given the particularly high rates of ischaemic stroke in HD patients we hypothesised, in the absence of comparative data, that they would experience similarly high rates of TIA. We aimed to determine the true incidence of this condition with intent to refer for further assessment and reduce future stroke incidence.

8.2. Methods

8.2.1. Study design

Following heightened awareness of the impact that stroke was having on patients under our care (Chapter 6) we initiated a prospective screening programme of all patients receiving maintenance HD at a single dialysis unit at our centre (Northwick Park Renal Centre) over a 12 month period starting from 1st November 2009. This came soon after a well-publicised initiative by the UK Department of Health to improve stroke awareness nationally, the Stroke: Act F.A.S.T. campaign (Department of Health, February 2009).

The FAST acronym aims to identify key symptoms suggestive of stroke: **F**acial weakness, **A**rm weakness, **S**peech problems, and underscore the importance of prompt, emergency medical attention: **T**ime to call 999. Poor public awareness and difficulties getting to hospital have been identified as two factors causing delays in stroke intervention (Wester et al. 1999). The simple message conveyed by F.A.S.T has been shown to capture 89% strokes and TIAs (Kleindorfer et al. 2007). We decided to use the impetus generated by the national campaign and incorporated the key principles of the F.A.S.T symptomatology into the screening questionnaires.

Prior to starting all dialysis unit nursing staff were given educational sessions on the nature and incidence of stroke in HD patients as well as the principles behind the F.A.S.T. campaign with the use of written information and audio-visual presentations. All patients were given verbal as well as written information (A4 leaflets as well as “credit-card”-shaped summary leaflets to carry on their person) about stroke symptoms and how to report them. Translators were used as necessary. Posters were distributed throughout the patient areas (waiting room, dialysis areas) to further reinforce key issues and provide a visual cue to reporting.

All studies to date have derived incidence rates based on self-presentations to medical practitioners. Given the lack of studies using a population-based symptom-screening approach the true incidence of TIA is likely to be even higher given the inherent ascertainment bias in published series.

8.2.2. Screening questionnaire

Screening was performed by dialysis nursing staff once weekly on the first haemodialysis session of the week, using a dedicated questionnaire. This comprised all elements of the F.A.S.T screen and included further questions in an attempt to improve diagnostic yield (Appendix 9.2) such as screening for associated sensory symptoms, visual symptoms, correlates of intracranial pathology (headache, confusion) and any emergency medical presentations.

All positive responses to the questionnaires were referred to the senior sister for the unit and contextualised within the patient's symptom complex given possible overlap (e.g. distal paraesthesiae in patients with established diabetic peripheral sensory neuropathy). If symptoms suggested a new event then the case was cascaded to the consultant in charge who referred the patient urgently to a dedicated, rapid-access TIA clinic as appropriate, with ABCD2 risk scoring (Appendix 9.3). No pre-emptive antiplatelet therapy was started prior to neurological review.

8.2.3. Statistical methods

Descriptive statistics were expressed as the mean $\pm$ standard deviation. Timeline incidence data were analysed using a Poisson model and expressed with 95% CI. A measure of the consistency of responses to the same question over time by each patient, the intra-class coefficient, made using a repeated-measured analysis. All analyses were performed using STATA 10.0 (StatCorp, College Station, TX, USA).

As clinical surveillance in keeping with national guidelines (NHS National Research Ethics Service 2009) as well as aligned to a publicised national public health strategy the need for formal research ethic committee approval was waived by our research governance board.

8.3. Results

8.3.1. Study cohort

A total of 304 patients were screened from 1st November 2009 – 1st November 2010 spanning a total of 2,594 patient months follow-up. During this time 9,504 questionnaires were administered (mean 32 ± 14 per patient). The characteristics of the study cohort are given in Table 8.1 below.

	N [%]
Mean age (years)	65.7 ± 14.0
Male	184 [60.3%]
Median HD vintage (years)	1.8
Ethnicity	
White	103 [34%]
South Asian	160 [53%]
African-Caribbean	37 [12%]
Comorbidities	
Diabetes mellitus	133 [44%]
Hypertension	154 [51%]
Ischaemic heart disease	82 [27%]
Cerebrovascular disease	44 [14%]
Peripheral vascular disease	24 [8%]

Table 8.1. Demographic characteristics of TIA study cohort.

The average HD session length was 4.3 ± 0.4 hours with a mean UF volume of 1.9 ± 1.2 litres per treatment. Achieved dialysis adequacy was high with a mean spKt/V of 2.0 ± 0.3 . Overall BP was well controlled with mean values predialysis of 140/78 mmHg, and post-dialysis of 134/75mmHg. Patients were treated with a mean darbepoetin dose of 38 ± 23 mcg per week achieving a mean haemoglobin of 12.2 ± 0.9 g/dl.

8.3.2. Incidence of stroke and TIA

In total six strokes occurred during the screening period of which 5 were ischaemic representing an average rate of 23.1 per 1,000 patient years. No patients screened

positive for a TIA despite predicting a rate of 4.2 per 1,000 patient years (95% CI 1.4 – 9.7 per 1,000 patient years) using general population data showing a ratio of stroke to TIA of 4:1 (Giles and Rothwell 2009).

One ischaemic stroke was preceded by symptoms compatible with a TIA although this was ascertained retrospectively after hospitalisation and not during screening.

8.3.3. Symptom reporting

These unexpected findings led me to carry out a subanalysis of 590 questionnaires reported by a sample of 20 patients (with 4,587 patient days follow-up) to examine patterns and consistency of reporting (Table 8.2). None had a confirmed TIA or stroke during the period of follow-up.

Symptom	Intra-class coefficient	95% CI
Pins and needles	0.93	0.85 – 0.97
Facial / Limb numbness	0.90	0.76 – 0.96
Arm weakness	0.99	0.98 – 0.99
Leg weakness	0.96	0.89 – 0.94
Facial weakness	0.95	0.91 – 0.98
Visual disturbance	0.95	0.28 – 0.98
Headache	0.92	0.59 – 0.97
Problem with speech	0.94	0.86 – 0.97
Confusion	0.99	0.99 – 1.00

Table 8.2. Intra-class coefficients for TIA symptom reporting.

Although the inter-class coefficients (ICCs) for each symptom were high (>0.9), there was considerable variability, within patients that never had TIA, in reporting paraesthesiae (pins & needles and facial/limb numbness), visual disturbance and headache as evidenced by the wide confidence intervals. This suggests symptom fluctuation that could relate to dialysis schedules, patient psychology, BP variability or “fatiguability” from repeated questioning, and casts doubt on the ability of these questions to detect true positive and negative responses.

8.4. Conclusions

Systematic screening for symptoms correlating to TIA in HD patients did not result in a positive diagnosis over 12 months and did not identify those subsequently experiencing stroke. The reasons for this require further evaluation in light of the ongoing National Stroke Strategy in the UK.

8.4.1. Incidence of TIA in haemodialysis

The true incidence of TIA in HD patients remains unquantified. In its most recent iteration the USRDS report for 2011 combines stroke and TIA as a single measure and the UK Renal Registry has no data on this pathology (Dr Damian Fogarty, personal communication). The classic 4:1 ratio between stroke and TIA in the general population remains to be validated in HD patients. It is possible that the pathophysiology of ischaemic stroke in HD is distinct from that of the general population thereby diminishing the impact of TIA in these patients. However current data is inadequate to make such an assertion and a larger cohort and longer follow-up is required.

I performed an exploratory analysis of eGFR in patients attending a specialist TIA clinic at our centre over a 7 month period (July 2010 – January 2011) showing that 39/241 (16%) referrals occurred in those with an eGFR<60ml/min (Figure 8.1) of which the overwhelming majority had CKD stage 3. Two were on HD and a further 2 patients had CKD stage 4. One of the 2 HD patients had a stroke mimic, and the other was diagnosed with TIA.

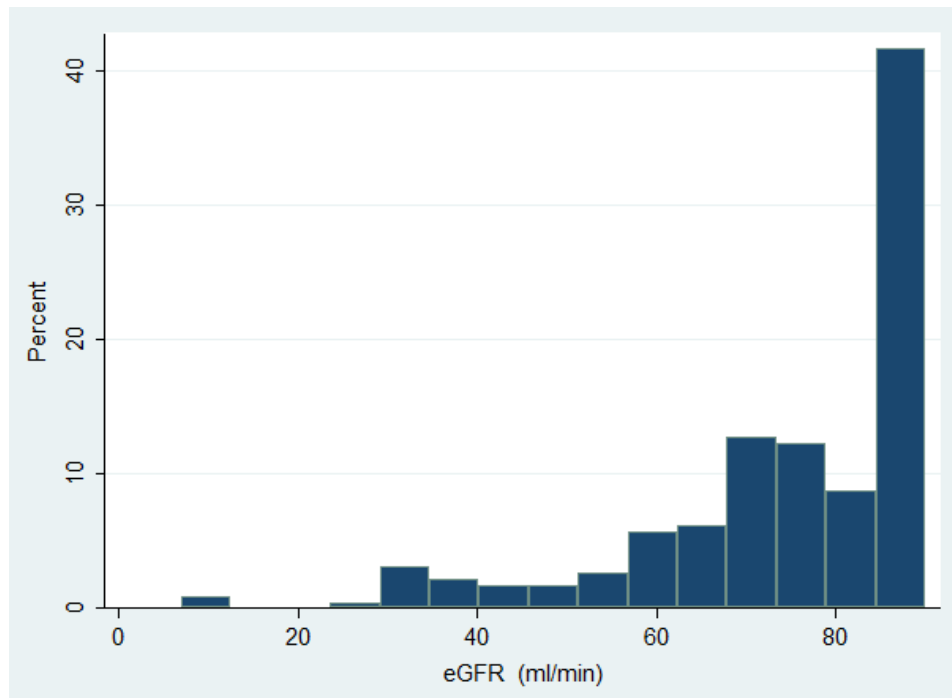


Figure 8.1. Renal function in patients referred to a local TIA clinic.

Patients in this study had well controlled hypertension and modest interdialytic weight gains which would mitigate their risk for cerebrovascular events and diminish the power of this study to detect significant events. They were predominantly of South Asian ethnicity and, as such, do not reflect the demographics of the UK population as a whole (Banerjee et al. 2010).

8.4.2. Questionnaire validity

To date there are very few questionnaires validated for use in population-based TIA detection. The Wilkinson questionnaire was validated in a U.K. population and found to perform poorly as a screening tool yielding just 32% agreement with specialist clinic diagnoses (Wilson et al. 2005). Despite attempts to generate a clinically-relevant, symptom-inclusive questionnaire in this study, it has not been validated in the general population or in HD patients, which is a significant limitation. Although the F.A.S.T tool performs as well as the ROSIER scoring system in capturing cerebrovascular events in emergency department presentations (Whiteley et al. 2011) it performs poorly as a means of recall-based symptom reporting (Bray et al. 2010) with significant false positivity (Moynihan et al. 2010).

The high symptom burden of HD patients which frequently includes paraesthesiae, generalised weakness and headache is likely to have confounded the reliability of these results (Murtagh et al. 2007a;Murtagh et al. 2007b). In a RCT of sodium restriction on BP in patients in the same dialysis unit, 74% reported fatigue/weakness, 35% paraesthesiae and 54% headache (Power et al, 2010c).The wide variability in intra-patient reporting of those components in this study is in keeping with that finding. Other factors such as depression and anxiety, cultural background and values, and levels of health literacy may have influenced symptom reporting (Weisbord et al. 2005;Weisbord et al. 2008). High prevalence of antiplatelet agent use in HD (52%, Table 6.2) and regular exposure to heparin anticoagulation is representative of HD populations but very likely reduced event rates.

8.4.3. Future considerations

We found a very low incidence of TIA in the first study screening for TIA in HD patients to date. Larger regional and national studies are needed to determine the true incidence of TIA in HD patients before ascertaining the safety and efficacy of traditional treatments in stroke reduction in this high-risk group. To this effect we are collaborating with the UK Renal Registry to use hospital episode statistics (HES) to capture a national perspective of stroke and TIA in dialysis patients.

9. Thrombolysis for acute ischaemic stroke and renal impairment

This chapter examines the effect of renal impairment on the safety and efficacy of systemic thrombolysis for acute ischaemic stroke. Although end-stage renal disease is not a licensed contraindication to the use of alteplase for acute stroke, the lack of evidence regarding safety and efficacy was a stimulus to review outcomes in terms of the National Institutes of Health Stroke Scale (NIHSS) score, a validated measure of neurological deficit.

9.1. Introduction

9.1.1. Thrombolysis for acute ischaemic stroke

Ischaemic stroke accounts for approximately 80% strokes in the general population and occurs as a result of thrombotic arterial occlusion. Cerebral parenchymal ischaemia and subsequent infarction occur in a time-dependent manner in the absence of recanalization (Donnan et al. 2008). A number of acute therapies directed at achieving rapid arterial recanalization have been developed including mechanical embolectomy and thrombolysis delivered either locally with the use of an intra-arterial catheter, or systemically into the peripheral venous circulation (Alexandrov 2010). Following outcomes from a seminal RCT of thrombolysis with alteplase within 3 hours of symptom onset in ischaemic stroke (NINDS rt-PA Stroke Study Group 1995) subsequent studies refined its use particularly with respect to the optimal treatment timeframe. Results from ECAS-III (Hacke et al. 2008) as well as large, observational data (Bluhmki et al. 2009) confirmed efficacy and safety to 4.5 hours after symptom onset and an ongoing RCT, the third International Stroke Trial, IST-3, is attempting to validate suggestions from meta-analyses that this timeframe can be extended to 6 hours (Sandercock et al. 2008). Pertinently none of the studies to date examined participants' renal function nor have they assessed the effects of treatment in renal impairment.

Emergency thrombolysis has transformed stroke services in the U.K. with development of specialised stroke centres assessing all patients presenting with symptoms suggestive of acute stroke (UK Department of Health 2007). Thrombolysis is administered and monitored in dedicated hyperacute stroke units (HASUs). Service implementation is audited regularly using predefined measures that include treatment timings and organisational parameters (e.g. Royal College of Physicians Stroke Improvement National Audit Programme, SINAP).

9.1.2. Measures of efficacy of thrombolysis

The original NINDS rt-PA study (1995) used three established, validated functional outcome measures – the Barthel index (Mahoney and Barthel 1965), a measure of functional ability with respect to activities of daily living; the modified Rankin scale (van Swieten et al. 1988), an measure of functional disability across a breadth of vital parameters; and the Glasgow outcome scale (Teasdale et al. 1978). They also used a 42-point measure of neurological deficit (NIHSS) that assesses eleven specific categories and can be used serially with good reproducibility (Lyden et al. 1994). The same measures were used in ECASS-III (Hacke et al. 2008) and are incorporated in IST-3. The NINDS rt-PA study (1995) used improvement in NIHSS at 24 hours after treatment as the primary outcome measure whereas ECASS-III used the modified Rankin score at 90 days.

Safety data including the incidence of intracranial and extracranial haemorrhage was incorporated in study protocols and remains an integral part of quality assurance with thrombolytics. Haemorrhagic risk has been determined in clinical trials and is reflected in the license restrictions for alteplase which include:

- Intracranial haemorrhage
- Suspicion of subarachnoid haemorrhage even if CT scan is negative
- Age <18years or >80 years
- Time of symptom onset >4.5 hours (6 hours in IST-3), or unknown
- Thrombocytopenia
- Deranged coagulation at baseline, including currently on heparin
- Major surgery or trauma within 21 days
- Previous stroke or serious head injury within 3 months
- Other major disorders associated with an increased bleeding risk

It may be argued that the uraemic state of ESRD is associated with an increased risk of bleeding even with normal APTT values, however this was not an exclusion for one of our HD patients involved in a multi-centre RCT (Lindley 2010).

9.1.3. Safety of systemic thrombolysis in ESRD

There is surprisingly little data on the safety of systemic thrombolytic therapies in ESRD. Thrombolysis was the treatment of choice for acute myocardial infarction before the advent of catheter-based endoluminal therapies – PCI, primary coronary intervention. A literature review reveals just one publication reporting on the safety of this treatment in dialysis patients - a retrospective, 12-month analysis of 1,155 U.S. dialysis patients prevalent in 1994 showing no increased risk of bleeding (Newsome et al. 2005). This study did not differentiate between dialysis modalities nor did it specify the dose and type of thrombolytic. The manufacturer of alteplase (Actilyse®, Boehringer Ingelheim GmbH) was unable to provide safety/efficacy data in ESRD patients.

There were no publications on use of alteplase for acute ischaemic stroke in ESRD prior to our publication (Power et al. 2010b). Only three published studies examined outcomes with alteplase for ischaemic stroke according to degree of renal function. A Swiss series included no dialysis patients and just 49 in total with CKD 3 or greater (Lyrer et al. 2008) while another U.S. study reported on a cohort including 20 patients with CKD 3 or greater (Agrawal et al. 2010). This latter study had 3 patients with an eGFR<15ml/min but it is unclear whether they were on dialysis or not.

To date the largest study is Japanese with registry data describing 186 patients with an eGFR <60ml/min (Naganuma et al. 2011a). They had 4 patients on maintenance HD which they went on to describe in a separate publication (Naganuma et al. 2011b) however they used a lower dose of alteplase than recommended (0.6mg/kg vs. 0.9mg/kg) which significantly limits the applicability of their data despite evidence of efficacy (Yamaguchi et al. 2006). Nonetheless intraventricular haemorrhage occurred in 1 out of 4 patients in their series (Naganuma et al. 2011b).

9.1.4. Efficacy of thrombolysis in CKD

In summary, at present, published data on a total of 5 HD patients suggests that alteplase is efficacious at reducing the neurodeficit associated with acute ischaemic stroke with significant intracerebral haemorrhage occurring in 20%. Clearly this sample size is inadequate in drawing conclusions and much larger studies are required to address this issue.

Overall the results from two studies comparing patients with renal impairment (defined by presenting eGFR) to those with maintained renal function suggest that CKD is an independent predictor of suboptimal outcome but is not associated with a higher risk of haemorrhagic complications (Lyrer et al 2008; Naganuma et al. 2011). By contrast the study by Agrawal et al. (2010) did not find an association between CKD and worse functional outcome (modified Rankin score at discharge). It must be appreciated that there is considerable heterogeneity in terms of the definitions, outcome measures and dose of thrombolytic used between the studies (Table 9.1). All used the 4-variable MDRD equation to derive eGFR.

9.1.5. Hypotheses and aims of the study

Given the dearth of evidence regarding the efficacy of alteplase in renal impairment, particularly with dose regimens in established use in Europe and the U.S., I decided to review outcomes with systemic thrombolytic therapy delivered in two large, urban HASUs to which we provide renal services.

I hypothesised that renal impairment affects the therapeutic efficacy of thrombolysis and that advanced uraemia confers a higher risk of haemorrhagic complications that reaches its zenith in HD patients.

Study	Alteplase dose (mg/kg)	Cohort size (n)	CKD Patients (n)	CKD definition	Primary outcome	Secondary outcomes	Era
Lyrer et al. 2008	0.9	196	138 [49]*	eGFR<90	mRS at 3 months	Recurrent stroke Symptomatic ICH	1998-2006
Agrawal et al. 2010	0.9	74	20	eGFR<60	mRS 3-6 at discharge	ICH Death	2005-2009
Naganuma et al. 2011	0.6	578	186	eGFR<60	ICH	mRS at 3 months Survival at 3 months	2005-2008

Table 9.1. Comparisons between studies examining the effect of CKD on outcomes of acute ischaemic stroke treated with systemic thrombolysis.

Abbreviations: mRS, modified Rankin score; ICH, intracranial haemorrhage

Notes: * using eGFR≤60ml/min as a cutoff.

9.2. Methods

9.2.1. Study design

A review of outcomes recorded prospectively during the course of routine clinical practice was performed in two HASUs in the London area (Charing Cross Hospital [CXH] and Northwick Park Hospital [NPH]) to which we provide renal support. Alteplase was administered using defined protocols at each centre and all eligible patients were included in this analysis. A pilot study was performed at the CXH HASU in the first instance with subsequent co-opting of the NPH HASU. As a result the study periods were 1st December 2009-1st April 2011 and 1st August 2009-1st January 2011 at the respective units.

Electronic and paper records relating to each patient episode were examined to derive baseline demographic data (age, gender, ethnicity) and the presence of comorbidities. These included diabetes mellitus, ischaemic heart disease (defined as a history of angina, myocardial infarction or coronary revascularisation), hypertension, prior cerebrovascular disease (stroke and/or transient ischaemic attack), peripheral vascular disease (clinical and/or radiological evidence of aortic or distal arterial atherosclerotic disease), atrial fibrillation (paroxysmal or chronic).

Renal function was derived using the serum creatinine obtained on admission. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation (Levey et al. 2009). This method was chosen in preference to MDRD to improve accuracy of classification across all subgroups especially those with MDRD-eGFR $\geq$ 60ml/min (Stevens et al. 2010). In the absence of prior creatinine levels, renal imaging and urinalysis results CKD was defined by an eGFR $<$ 60ml/min.

Time to treatment was the time between symptom onset and alteplase administration. All patients were assessed on arrival to the emergency room by a senior stroke physician and neurodeficit recorded using NIHSS score on admission and 24 hours after treatment.

9.2.2. Thrombolytic therapy

Both centres had standardised protocols for emergency thrombolysis. Following emergency transfer to the dedicated stroke centre all patients reporting acute neurological symptoms suggestive of acute stroke had emergency non-contrast CT imaging performed and were reviewed in the emergency department by an on-call team of physicians (stroke physicians or neurologists). All patients had the following basic assessments performed: weight, temperature, blood pressure (BP), heart rate and electrocardiogram, capillary blood glucose (CBG) and their Glasgow Coma Scale (GCS) score recorded.

Intravenous access was obtained and urgent blood tests performed including a full blood count (FBC), coagulation screen, renal and liver function, electrolytes and C-reactive protein. All patients were assessed for eligibility for thrombolytic therapy and were excluded if they met any of the criteria listed below.

- i. Symptom onset unclear
- ii. More than 4.5 hours (or 6 hours if enrolling in IST-3) from onset
- iii. Age <18 years or >80 years
- iv. Uncontrolled hypertension – systolic BP>185mmHg or diastolic BP>110mmHg despite treatment
- v. Severe dysglycaemia - CBG≤3.5mM or >20mM despite treatment
- vi. GCS score <8
- vii. Minor symptoms / evidence of resolution
- viii. Seizure as the first event
- ix. Severe sudden-onset headache at symptom onset (suggestive of subarachnoid haemorrhage)
- x. Proven/suspected pregnancy
- xi. Any past history of spontaneous intracranial haemorrhage
- xii. Known proliferative retinopathy
- xiii. Previous stroke / serious head injury within the past 3 months
- xiv. Gastrointestinal ulcer / haemorrhage or urinary tract haemorrhage within 3 months
- xv. Cardiac massage, obstetric delivery or arterial puncture at a non-compressible site within 14 days.
- xvi. Lumbar puncture within 7 days

- xvii. Intracranial arteriovenous malformation or untreated aneurysm
- xviii. Pancreatitis, oesophageal varices, aortic aneurysm, active hepatitis or liver cirrhosis
- xix. Bacterial endocarditis, infective pericarditis or post-infarct pericarditis
- xx. Any evidence of active, internal bleeding or recent unexplained fall in haemoglobin
- xxi. Heparin within the past 48 hours, or on warfarin, or any clotting abnormality
- xxii. Known (or strongly suspected) iron deficient anaemia or thrombocytopaenia
- xxiii. NIHSS>25, or patient totally dependent on others for care prior to current event
- xxiv. Any evidence of intracranial haemorrhage (intracerebral, subarachnoid, subdural, extradural)
- xxv. Non-ischaemic lesion to explain symptom (e.g. abscess, tumour)
- xxvi. Evidence of infarct in greater than one-third of middle cerebral artery territory
- xxvii. If FBC available: Hb <10g/dl ; Platelets <100x10⁹/l.
- xxviii. If clotting available: INR>1.3 seconds ; APTT >34 seconds

Thrombolysis was administered with the agreement of the duty stroke consultant in the high-dependency areas of the HASU in each centre with appropriate haemodynamic and clinical monitoring. Alteplase was prescribed at a dose of 0.9mg/kg to a maximum dose of 90mg, with 10% total dose administered as a 2-minute infusion and the remainder over 60 minutes. No dose adjustment was made according to renal function. All antiplatelet therapy was withheld from admission to 24 hours after thrombolysis.

Infusion of alteplase was stopped immediately in the event of suspected intracranial haemorrhage (e.g. fall in GCS, increasing focal neurological deficit, seizures, meningism, and pupillary asymmetry) and immediate repeat CT scanning and blood tests performed. Interval CT imaging was repeated per protocol 24 hours in all patients.

9.2.3. Outcome measures

The primary outcome measure was the change in NIHSS score from admission to 24 hours after treatment.

Secondary outcomes included the incidence of intracranial haemorrhage (asymptomatic and symptomatic), the incidence of extracranial bleeding, discharge destination and death during the index hospitalisation.

9.2.4. Statistical methods

Descriptive statistics were expressed as the mean $\pm$ standard deviation and the median with interquartile range (IQR) as appropriate. Continuous and categorical variables were compared using Student's t test and the chi-square or Mann-Whitney U test respectively, as appropriate.

Univariate and multivariate linear regression analysis was used to examine the effect of factors of interest such as eGFR, age, gender, ethnicity, comorbid conditions on the degree of improvement in NIHSS score. Factors identified by univariate analysis with a p-value <0.1 were then examined using a multivariate model and tests for interaction of terms were performed. A backwards selection procedure was then applied to this model to identify risk factors of significance. Similarly logistic regression analysis was used to examine the association between these factors and the risk of intracranial haemorrhage and death.

All analyses were performed using STATA 10.0 (StatCorp, College Station, TX, USA). Statistical significance was defined by $p < 0.05$.

The need for formal research ethic committee approval was waived by our research governance board as this study constituted a service evaluation in keeping with national guidelines (NHS National Research Ethics Service 2009).

9.3. Results

9.3.1. Study cohort

A total of 275 patients received thrombolytic therapy of which 76 had CKD stage 3 or greater. Complete demographic and clinical data were available in 229 (83%) cases forming the cohort under analysis (Table 9.2).

	n [%]
Mean age (years)	70.0 ± 13.0
Male	59%
Ethnicity	
White	152 [66.4]
South Asian	50 [21.8]
African-Caribbean	19 [8.3]
Other	8 [3.5]
Comorbidities	
Diabetes mellitus	54 [24.1]
Hypertension	156 [69.6]
Ischaemic heart disease	62 [27.7]
Diagnosed cerebrovascular disease	41 [18.3]
Peripheral vascular disease	6 [2.7]
Atrial fibrillation	55 [24.6]
eGFR (ml/min)	
≥90	58 [25.3]
60 to 89	106 [46.3]
30 to 59	54 [23.6]
15 to 29	10 [4.4]
<15	1 [0.4]

Table 9.2. CKD and Stroke Thrombolysis study cohort characteristics.

Overall 65 patients (28%) had an eGFR<60ml/min, including one HD patient, and comprised the CKD subgroup. Compared to patients with no renal dysfunction, CKD patients were significantly older ($p<0.001$) with a greater prevalence of diabetes, ischaemic heart disease and hypertension (Table 9.3). There were no significant baseline differences in gender, ethnic case mix or established cerebrovascular disease ($p=0.4$).

	CKD (n=65)	No CKD (n=164)	p
Mean age (years)	78.0 ± 7.0	66.7 ± 13.4	<0.001
Male (%)	55.4	60.4	0.5
Ethnicity (n, %)			
White	45 [69.2]	107 [65.2]	0.6
South Asian	15 [23.1]	35 [21.3]	0.8
African-Caribbean	2 [3.1]	17 [10.4]	0.07
Other	3 [4.6]	5 [3.0]	0.4
Comorbidities (%)			
Diabetes mellitus	24 [36.9]	30 [18.3]	0.003
Hypertension	54 [83.1]	102 [62.2]	0.002
Ischaemic heart disease	27 [41.5]	35 [21.3]	0.002
Diagnosed cerebrovascular disease	14 [11.0]	27 [16.5]	0.4
Peripheral vascular disease	2 [3.1]	4 [2.4]	0.9
Atrial fibrillation	21 [32.3]	34 [20.7]	0.06

Table 9.3. Baseline characteristics of thrombolysed patients with and without renal dysfunction (eGFR<60ml/min).

The median eGFR of patients with CKD was 44.3ml/min (IQR 36.7 – 52.2ml/min). There were no significant differences in the time to treatment from symptom onset (221±66 vs. 220±70 minutes, p=0.9) although patients with CKD had a higher median NIHSS score at presentation than those with no renal dysfunction, 10 (IQR 7-14) vs. 8 (IQR 6-14) respectively, p=0.05.

9.3.2. Efficacy of thrombolytic therapy

The difference in median NIHSS scores between the CKD and non-CKD groups persisted to 24 hours from treatment - 6 (IQR 3-11) vs. 3 (IQR 1-8) respectively, p=0.004. NIHSS score at baseline (p<0.001) and ischaemic heart disease (p=0.02) were independently associated with a greater thrombolytic improvement in the NIHSS score. In contrast CKD led to an almost 2-point diminution of this effect (Table 9.4, p=0.006).

Factor	Coefficient	95% CI	P value
NIHSS score at baseline	0.2	0.1 – 0.3	<0.001
CKD	-1.9	-3.3 – 0.6	0.006
Ischaemic heart disease	1.6	0.2 – 2.9	0.02

Table 9.4. Multivariate analysis of factors significantly associated with changes in NIHSS score following thrombolytic therapy.

Age had no significant effect on the primary outcome although there was a suggestion of greater benefit with thrombolysis in the 70-80 year age band (coefficient 1.2, $p=0.06$) compared to the younger age bands. Patient ethnicity, major comorbid conditions and the time to treatment did not significantly affect outcome.

When modelled as a continuous variable, higher eGFR was independently associated with a greater post-thrombolytic improvement in NIHSS score (OR 1.03 per 10ml/min, 95% CI 1.00 – 1.06, $p=0.03$).

9.3.3. Complications of thrombolysis

Intracranial haemorrhage (ICH) occurred in 4 patients in the CKD group and 11 in the non-CKD group (prevalence 6.2% vs. 6.7% respectively, $p=0.9$). Symptomatic ICH occurred in 3/4 cases in the CKD group and 6/11 in the non-CKD. Higher NIHSS score at baseline was the only factor associated with an increased risk of symptomatic and asymptomatic ICH on multivariate analysis (OR 1.12, 95% CI 1.03 – 1.23, $p=0.004$).

Twelve patients died following thrombolysis, representing 5% of the total cohort, with 6 of these in the CKD groups and 6 in the non-CKD group. Those that died were significantly older (mean age 77 vs. 70 years, $p=0.01$) and had a higher prevalence of diabetes (50% vs. 22%, $p=0.05$). A higher NIHSS score at baseline was independently associated with a higher risk of death following treatment (OR 1.24, 95% CI 1.10 – 1.40, $p<0.001$) reflecting its effect on the probability of ICH. The presence of CKD was not associated with a higher risk of death ($p=0.07$).

2 patients developed extracranial bleeding following thrombolysis. The first experienced self-limited thoracic and abdominal wall haematomas (eGFR 39ml/min) while the second had recurrent epistaxis and vaginal bleeding that resolved spontaneously (eGFR 79ml/min).

9.3.4. Hospitalisation and discharge destination

There was a trend to longer hospitalisation in patients with CKD (mean length of stay 11.9 vs. 7.9 days, $p=0.07$) although this did not reach statistical significance. CKD was not associated with a lower chance of home discharge following thrombolysis. The admission NIHSS score was the only significant factor influencing this outcome after adjusting for ICH (OR for home discharge 0.91, 95% CI 0.87 – 0.96, $p<0.001$).

9.4. Conclusions

9.4.1. Renal function affects outcome after thrombolysis

This study demonstrates that renal impairment independently influences the degree of neurological improvement in patients treated with alteplase for acute ischaemic stroke. These findings are consistent with data from other series (Lyrer et al 2008; Naganuma et al. 2011) and represent the first analysis of outcomes with a 4.5 hour timeframe rather than 3 hours as in prior publications (Agrawal et al. 2010; Lyrer et al. 2008; Naganuma et al. 2011).

In keeping with other series patients with renal dysfunction were on average significantly older and had a higher prevalence of co-existent ischaemic heart disease and atrial fibrillation (Agrawal et al. 2010; Naganuma et al. 2011). However there are significant differences in cohort characteristics which may have influenced outcomes and limit comparisons. Firstly Naganuma et al. (2011) reported on a cohort with distinct, homogeneous ethnic composition in contrast to this one and the U.S. series of Agrawal et al. (2010). 50% of patients with renal dysfunction in the study by Agrawal et al. (2010) were diabetic compared to 37% in this study and 20% in the study of Naganuma et al. (2011). The latter study found no significant difference in diabetes prevalence between groups in contrast to this series and that of Agrawal et al. (2010). Finally overall rates of ischaemic heart disease were lower in the series of Naganuma et al. (2010) compared to this cohort (13% vs. 27%, $p < 0.001$). Lyrer et al. (2008) provide comorbidity data for the whole cohort but do not stratify this according to renal function and provide no absolute NIHSS scores making it difficult to use their data for comparative analyses.

There were no significant differences between subgroups in NIHSS scores at presentation in the studies by Agrawal et al. (2010) and Naganuma et al. (2011) in contrast to the present findings. Notably median NIHSS scores at presentation were higher than those in this study (non-CKD group: 12 & 12 vs. 8 respectively; CKD group: 14 & 13 vs. 10 respectively) but may reflect differences in hospital transit times which are not recorded or effects of other unmeasured confounders.

The mechanism whereby renal impairment may attenuate the improvement of neurodeficit with alteplase is unclear. Retrospective studies such as this are hypothesis-generating and cannot prove causality as evidenced by the seemingly

counterintuitive benefit afforded by a diagnosis of ischaemic heart disease. This result suggests residual confounding by factors such as the prescription of antiplatelet therapy and lipid lowering drugs. A post hoc analysis of data from the Northwick Park HASU showed that there were no differences in prescription of antiplatelet agents between groups although renal dysfunction was associated with a greater statin prescription (62% vs. 33%, $p=0.02$). There is conflicting evidence regarding the influence of statins on outcomes after thrombolysis (Alvarez-Sabin et al. 2007; Miedema et al. 2010) and one study suggests they increase risks of ICH (Martinez-Ramirez et al. 2011).

Renal impairment lead to clinically significant differences in the efficacy of thrombolysis by modulating thrombus mechanics and PAI-1 levels, as discussed in section 4.4.2. CKD is associated with greater subclinical cerebrovascular disease burden (Ueda et al. 2011). This may compromise collateral blood flow around infarcts which is known to influence recanalization rates (Bang et al. 2011; Shuaib et al. 2011). It is possible that patients with renal impairment have larger infarct volumes and/or proportionately smaller ischaemic penumbrae that are responsive to reperfusion (Heiss 2011). There are no published data to confirm or refute any of these hypotheses at present.

9.4.2. Incidence of intracranial haemorrhage

Renal impairment did not associate with a higher risk of ICH in keeping with published results from Agrawal et al. (2010). In counterpoint Naganuma et al. (2011) reported higher rates of ICH (27%) in patients with renal dysfunction despite using a lower dose of alteplase. Rates of ICH were lower in the present series than those from the Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Registry (SITS-ISTR) study reporting rates of 14-16% for any ICH using 0.9mg/kg alteplase (Ahmed et al. 2010). These disparities may relate to more experience with alteplase in the present era, variability in pre-treatment BP and glucose profiles that are known to influence ICH risk (Wahlgren et al. 2008) or confounding from occult factors affecting patient selection. The association between NIHSS score at baseline and a higher risk of ICH that was discerned is in compatible with evidence from the SITS-MOST study (Wahlgren et al. 2008).

9.4.3. Mortality with thrombolysis

The overall mortality rate of 5% is comparable with data from the SITS-ISTR registry (Ahmed et al. 2010) showing rates of 7% in groups treated within 3 and 3-4.5 hours and is compatible with outcomes in the series by Agrawal et al. (2010).

9.4.4. Study limitations

Like any retrospective study associations cannot infer causation and remain prone to multiple confounders such as selection bias, confounding by treatment indication, observer bias as regards NIHSS scoring and unmeasured variables (such as admission glucose level or blood pressure) known to influence outcomes with thrombolysis. Despite being the largest European cohort to date, sample size remains relatively small compared to international stroke registries. Use of data from just two units cannot rule out centre-specific treatment effects that may have biased outcomes.

Outcomes at 24 hours were analysed and the medium and long-term effects of thrombolytic therapy remain unknown. NIHSS score was the sole outcome measure and cannot account for valuable information gained by assessing functional status using validated scores such as the modified Rankin scale.

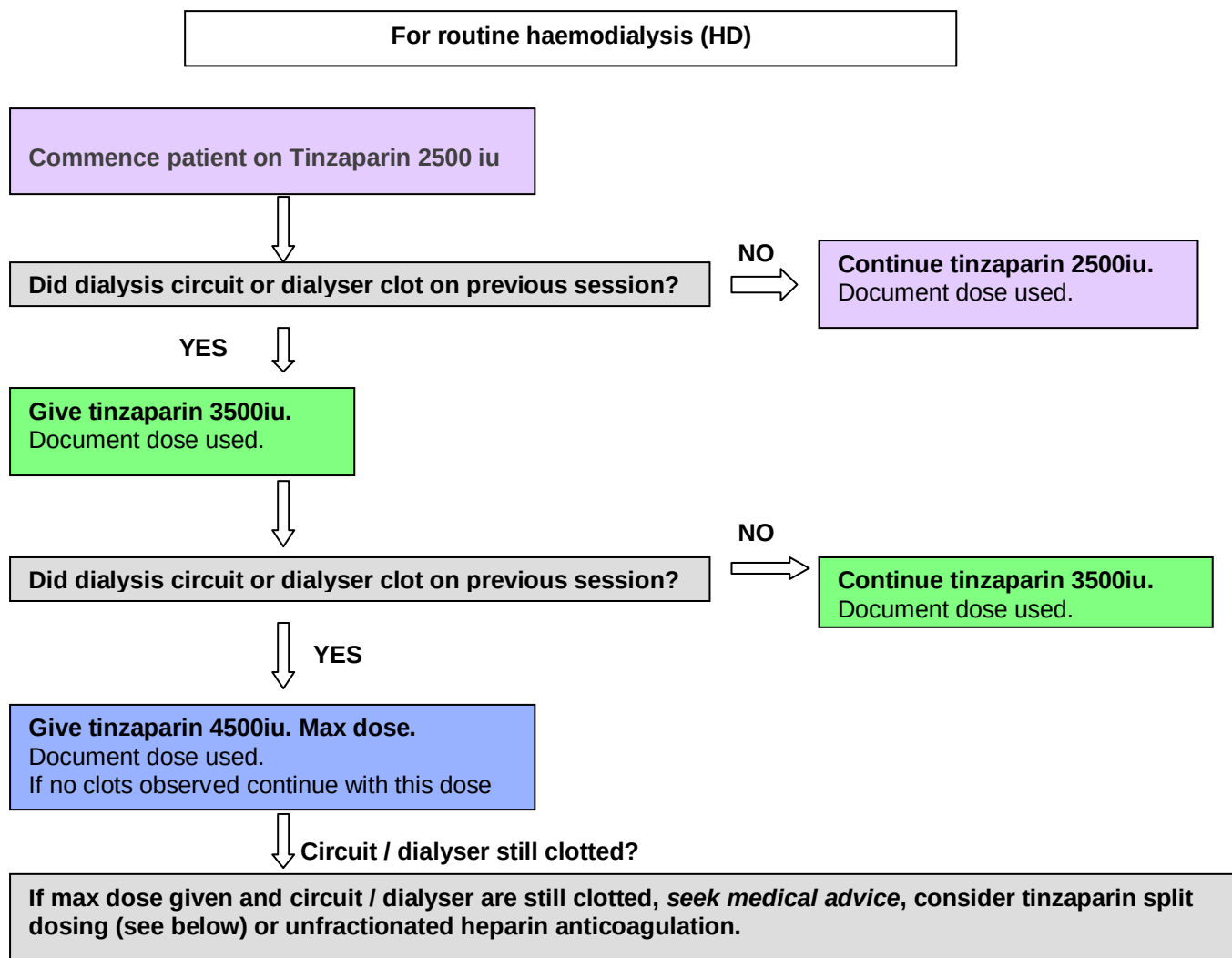
9.4.5. Future approaches

Current data from this study provides a rich number of hypotheses for further evaluation. Stroke burden in patients with advanced renal dysfunction is just beginning to be evaluated. The number of patients with advanced CKD receiving thrombolysis in the UK remains unquantified and the safety – efficacy profile of the therapy is not confirmed. The relationship between renal function and stroke outcomes such as neurological deficit, functional status, psychosocial functioning, healthcare resource need and rehabilitation potential is unknown. It is unclear whether any modulation of alteplase delivery is required for patients with advanced renal impairment.

The effect of renal impairment on stroke characteristics, topography, perfusion dynamics and reperfusion time course are not known. We aim to perform a London-wide analysis of thrombolysis outcomes in patients with renal impairment with parallel volumetric analysis of stroke volume and proteinuria to better characterise the influence of CKD on outcomes and allow for development of interventional trials to improve stroke care.

10. Appendices

10.1. Tinzaparin use for maintenance haemodialysis



10.2. TIA screening questionnaire

PATIENT ID

NORTHWICK PARK TIA SCREENING TOOL

DATE / / 09/10		
	Y	N
PINS AND NEEDLES	☐	☐ LEFT / RIGHT (delete as appropriate)
NUMBNESS IN FACE / LIMBS	☐	☐ LEFT / RIGHT (delete as appropriate)
WEAKNESS ARM	☐	☐ LEFT / RIGHT (delete as appropriate)
LEG	☐	☐ LEFT / RIGHT (delete as appropriate)
FACE	☐	☐ LEFT / RIGHT (delete as appropriate)
VISUAL DISTURBANCE	☐	☐
HEADACHE	☐	☐
PROBLEM WITH SPEECH	☐	☐
CONFUSION	☐	☐
HAVE YOU VISITED A&E OVER THE LAST WEEK	☐	☐
Other comments:		
SIGNATURE _____		

DATE / / 09/10		
	Y	N
PINS AND NEEDLES	☐	☐ LEFT / RIGHT (delete as appropriate)
NUMBNESS IN FACE / LIMBS	☐	☐ LEFT / RIGHT (delete as appropriate)
WEAKNESS ARM	☐	☐ LEFT / RIGHT (delete as appropriate)
LEG	☐	☐ LEFT / RIGHT (delete as appropriate)
FACE	☐	☐ LEFT / RIGHT (delete as appropriate)
VISUAL DISTURBANCE	☐	☐
HEADACHE	☐	☐
PROBLEM WITH SPEECH	☐	☐
CONFUSION	☐	☐
HAVE YOU VISITED A&E OVER THE LAST WEEK	☐	☐
Other comments:		
SIGNATURE _____		

DATE / / 09/10		
	Y	N
PINS AND NEEDLES	☐	☐ LEFT / RIGHT (delete as appropriate)
NUMBNESS IN FACE / LIMBS	☐	☐ LEFT / RIGHT (delete as appropriate)
WEAKNESS ARM	☐	☐ LEFT / RIGHT (delete as appropriate)
LEG	☐	☐ LEFT / RIGHT (delete as appropriate)
FACE	☐	☐ LEFT / RIGHT (delete as appropriate)
VISUAL DISTURBANCE	☐	☐
HEADACHE	☐	☐
PROBLEM WITH SPEECH	☐	☐
CONFUSION	☐	☐
HAVE YOU VISITED A&E OVER THE LAST WEEK	☐	☐
Other comments:		
SIGNATURE _____		

10.3. ABCD2 scoring template

ABCD² Scoring- stroke risk post TIA

Age $\geq$ 60yr 1 point ☐

Blood Pressure $\geq$ 140/90 1 point ☐
(please record pre and post HDx BPs)

Clinical Features (*maximum score of 2 points*)

- unilateral weakness	2 points	} ☐
- speech disturbance	1 point	
- other	0 points	

Duration of symptoms

- $\geq$ 60minutes	2 points	} ☐
- 10-59 minutes	1 point	
- < 10min	0 points	

Diabetes 1point ☐

Total Score

Total points

0-3	low risk
4-5	moderate risk
6-7	high risk

10.4. Publications deriving from this work

10.4.1. Original research

Power A., Singh S., Ashby D., Hamady M., Moser S., Gedroyc W., Taube D., Duncan N., Cairns T. Translumbar central venous catheters for long-term haemodialysis. *Nephrol Dial Transplant* (2010); 25(5): 1588-1595.

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Translumbar central venous catheters for long-term haemodialysis

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Abstract

Background. Vascular access for haemodialysis is achieved by tunneled central venous catheter (CVC) in

at least 23% of prevalent patients in the UK, Canada and the USA. Use of CVCs is associated with an increased incidence of venous stenosis that can progressively limit fu-

ture vascular access routes. Lack of conventional venous access routes mandates the use of alternative strategies such as the translumbar approach.

Methods. We retrospectively analysed patients at our centre requiring translumbar inferior vena caval CVCs (Tesio-Cath) for haemodialysis in the period 1999–2008. Written and electronic records capturing dialysis adequacy and complications, hospital admissions and laboratory data were examined.

Results. Thirty-nine pairs of translumbar CVCs were inserted in 26 patients with 15 864 catheter days follow-up, mean patient age 61.9 ± 12.1 years, 31% diabetic, 15% with ischaemic heart disease. All insertions were successful. Insertion of one CVC was associated with a self-limiting retroperitoneal haematoma. No patients died of a catheter-related cause or through lack of vascular access. Cumulative assisted primary catheter site patency was 81% at 6 months and 73% at 1 year (median 18.5 months). Good dialysis adequacy was achieved throughout (mean single-pool Kt/V 1.5 ± 0.4). The incidence of access-related infection was 2.84/1000 catheter days (exit site infection rate 2.02/1000 catheter days; catheter-related bacteraemia rate 0.82/1000 catheter days). Catheter dysfunction (need for thrombolytic infusion or catheter change) led to 0.88 admissions per 1000 catheter days.

Conclusion. Translumbar inferior vena caval CVCs can offer relatively safe and effective long-term haemodialysis access in patients with no other options.

Keywords: haemodialysis ; inferior vena cava; tunnelled venous catheter; vascular access

Introduction

Long-term haemodialysis requires the formation and maintenance of effective vascular access. The use of arteriovenous fistulae (AVF) is widely advocated where possible based upon a lower rate of complications [1–3]. Despite this, a large proportion of haemodialysis patients start and continue haemodialysis with a central venous catheter (CVC). Twenty-three to seventy-three percent of the patients started haemodialysis with a CVC, and 23–41% of the established patients continued with a CVC in an analysis of the Dialysis Outcomes and Practice Patterns Study [4]. Several factors contribute to enduring CVC use including patient and clinician preference [5,6] and a lack of access options related to female gender [7,8], a history of prior venous catheterisation [4] and the presence of diabetes [8].

CVCs are associated with an increased risk of access-related infection compared to AVFs and prosthetic grafts [9]. Rates of catheter-related infection have, however, been decreasing over the past decade with the use of newer catheter technology and catheter care protocols [10–12]. Endoluminal thrombosis [13] and a risk of central venous stenosis [14,15] remain a concern for a proportion of patients. As the number of accessible venous routes diminishes, achieving effective venous access becomes more challenging. Elaborate vascular surgical procedures have evolved to bypass stenoses with the interposition of

prosthetic graft material to create a patent arteriovenous circuit that supports haemodialysis [16,17]. Extensive surgery may not be acceptable or feasible, and concerns exist about poor long-term patency and infection rates. Unconventional approaches are possible when all surgical and endovascular options for arteriovenous access creation or maintenance are exhausted. One option is to insert a CVC via an unconventional approach into a central vein, and amongst others, transhepatic and transrenal routes into the inferior vena cava (IVC) have been described in the literature [18–20].

The translumbar approach to cannulation of the IVC was first described over 20 years ago [21]. Since then, there have been a number of reports of this approach for haemodialysis access in the paediatric and adult literature [22–25]. A series of 17 catheters was published demonstrating good safety with poor long-term access survival (17% patency at 1 year) [25]. We have favoured this unconventional approach and describe a large and comprehensive series with long follow-up of the translumbar route for long-term haemodialysis access.

Subjects and methods

This retrospective study identified all patients who had a translumbar inferior vena caval CVC of a single type, the Bio-Flex™ Tesio® Cath (MedComp, Harleysville, PA, USA) inserted from 1st January 1999 to 16th June 2008 at our centre. The West London Renal and Transplant Centre provides renal services to a population of over 2 million people, caring for a total of 1200 maintenance haemodialysis patients who receive their treatment with the same protocol for care applied across nine satellite dialysis units. All aspects of haemodialysis care are subject to a centralised consultant-led audit on a monthly basis including dialysis adequacy, access type and infection, water quality and anaemia management. Paper and electronic records relating to inpatient episodes were examined, and laboratory, radiological and dialysis data were analysed.

Dialysis access

All patients were considered for formation of an AVF, and this was encouraged when suitable vessels existed. CVCs were inserted when there was a lack of suitable vessels for first or subsequent access formation determined by clinical examination and independent surgical review if doubt existed. Some patients chose to have a CVC from the outset through a perception of ease-of-use, despite advocating the advantages of AVF. Translumbar inferior vena caval CVCs were inserted when other AVF and CVC approaches had been exhausted in the superior vena caval circulation. Screening for central venous occlusion was conducted using conventional central venography and/or computed tomographic (CT) angiography. Bilateral brachiocephalic venous and/or superior vena caval occlusion and the absence of large, accessible thoracic collateral veins for CVC placement were indications for the translumbar approach. Patency of the IVC was confirmed by conventional venography via the transfemoral route.

Translumbar CVC insertion

All translumbar CVCs were inserted by one experienced interventional radiologist (MH). Two 75 cm, 10 Fr single lumen Bio-Flex™ Tesio® Cath lines were inserted under fluoroscopic guidance into the IVC. All patients received local anaesthesia and moderate sedation. An angiographic 0.035-in guidewire was inserted into the IVC to act as a marker using a 4-French (Fr) sheath via a common femoral venous approach under ultrasound and fluoroscopic guidance. The patient was then placed in the prone position with 25° elevation of the right side. The puncture site was chosen approximately one hand-breadth (8–10 cm) from the midline on the right side of the patient as determined by palpation of the lumbar spinous processes and the lower level of L3 vertebra (a point just cephalad to the right iliac

crest) to avoid puncturing the renal vein. A micropuncture was made with a 21-gauge (G) Accustick(TM) II Introducer System (Boston Scientific, Natick, MA, USA) into the IVC under fluoroscopic guidance with an angle of approach towards the anterior aspect of the L3 vertebra and the guidewire target. In the case of bi-iliac venous occlusion, the IVC was punctured directly below level of the renal veins under CT guidance obviating the need for a guidewire target. Upon aspiration of venous blood, position of the needle tip was confirmed with contrast. A 0.018-in wire was subsequently inserted into the IVC, and a 5-Fr dilating sheath was introduced over this into the IVC. Then an Amplatz stiff 0.035-in wire (Boston Scientific, Natick, MA, USA) was inserted via the sheath, and over this, a peel-away 8-Fr dilating sheath (Cook Inc, Bloomington, IN, USA) was introduced. A second Amplatz stiff 0.035-in wire was inserted next to the first one through the original 8-Fr sheath and IVC puncture site, and two peel-away 11-Fr dilating sheaths were introduced over both wires. The CVC lines were then inserted over the wires and individually advanced with the tips confirmed to be in the right atrium or right atrial/inferior vena caval junction by fluoroscopic imaging. The lines and cuffs were then tunneled by creating two discrete tracts using the tunnelling devices from the venous entry site to the right flank with the skin exit points aimed at the anterior axillary line and above the level of the belt. Each catheter was then filled with 5000 iu/ml unfractionated heparin to the volume of the catheter lumen.

CVC care

All CVCs were handled by trained staff using aseptic technique. The exit site was cleaned at the start of each dialysis session with 4% chlorhexidine gluconate solution (Hibiscrub[®], Molnlycke Healthcare, Manchester, UK) for 1 min before being allowed to dry in air and a new bio-occlusive dressing was then applied. Two percent mupirocin (Bactroban[®] Nasal Ointment, GlaxoSmithKline UK, Uxbridge, UK) was applied routinely to the exit site before the new dressing in 4/9 satellite dialysis units; no antibacterial ointment was applied in the remaining 5/9 satellite units. The catheter hubs, clamps and distal portions of the catheter limbs were cleaned with 4% chlorhexidine gluconate solution and allowed to dry both before and after connection to the dialyser in all satellite units. Five percent heparin was used as a catheter lock in most cases (Monoparin[®] sodium heparin 5000 iu/ml; CP Pharmaceuticals, Wrexham, UK). Citrate (46.7%; DuraLock CTM, MedComp, Harleysville, PA, USA) was used as an alternative catheter lock in patients with active bleeding, heparin sensitivity and in the immediate post-operative period. No antibiotic catheter locks were used.

Microbiological screening

Quarterly screening of all patients for nasal and exit site carriage of methicillin-resistant *Staphylococcus aureus* was adopted as routine practice at our centre in 2007. All patients returning to their satellite dialysis unit after an inpatient admission were screened with additional swabs of their throat, axilla and groin. Patients with positive nasal or exit site swabs were treated four times daily for a 5-day course with topical 2% mupirocin ointment nasally and to the exit site.

Dialysis adequacy

Patients were dialysed three times weekly using low-flux synthetic AM-BIO-1000Wet haemodialysers (Asahi Kasei Medical Europe GmbH, Frankfurt, Germany) with Gambro AK-100 or AK-200 (Gambro AB, Stockholm, Sweden) dialysis machines during 1999–2005 and Braun Dialog machines (B. Braun Medical Inc, Bethlehem, PA, USA) from 2005. Dialysis session length ranged from 2.5 to 5 h. Dialysis adequacy was measured by single-pool Kt/V (spKt/V) on a monthly basis using the Daugirdas method [26]. Dialysis prescription was tailored to achieve a spKt/V of ≥ 1.6 . In patients failing to achieve this target, haemodialyser size was increased, blood flows were increased to ≥ 350 ml/min, dialysate flow rates were adjusted to ≥ 500 ml/min and access recirculation was assessed by a urea-based method and if necessary access was changed.

Systemic sepsis

Pyrexia was defined as a tympanic temperature of $\geq 38^{\circ}\text{C}$, and all patients with pyrexia with or without a systemic inflammatory response were investigated with exit-site swabs, multiple blood cultures drawn from the

catheter itself and from peripheral veins and urine and sputum culture where appropriate to circumstances. Samples were obtained prior to starting antibiotics. Sepsis was presumed to be catheter-related if there was no clinical or microbiological evidence of another source. Antibiotic starts pre-empted microbiological confirmation of infection and followed a defined protocol. Subsequent therapy was tailored to antibiotic sensitivities, and proven or suspected CVC infections were treated for a minimum duration of 2 weeks. Catheter-related bacteraemia (CRB) was defined as per established standards [27]. Catheter salvage was attempted where clinically appropriate. Catheter-related sepsis was defined as the clinical presence of sepsis with growth of organisms in the blood and/or the catheter tip (where catheter removal occurred) with no evidence of alternative source of infection and similar to established reporting standards [27]. Catheter-related infection resulting in hypotension requiring inotropic support, persistent bacteraemia despite antibiotics and tunnel infection lasting more than 3 days despite targeted intravenous antibiotic therapy were indications for catheter removal.

CVC infection—exit-site infection

Exit-site swabs were taken if there was exudate with or without pain, crusting, erythema or induration at the exit site. Infection limited to the exit site and in the absence of pyrexia was treated with oral agents according to determined antibiotic sensitivities for a minimum of 2 weeks. Febrile patients were treated as for systemic sepsis described above.

CVC infection—tunnel infection

Tunnel infections were defined by pain, redness or induration along the subcutaneous course of the line, with or without exudates at the exit site and were treated from the outset with intravenous vancomycin and oral ciprofloxacin. These antibiotics were adjusted when culture results were available with the addition of a second appropriate oral antibiotic for a minimum of 6 weeks. Persisting infection was an indication for CVC removal as detailed above.

CVC dysfunction

The target blood flow for CVCs was ≥ 350 ml/min. CVC dysfunction was identified by consistently suboptimal blood flow of <250 ml/min and/or declining dialysis adequacy. Three consecutive falls in monthly spKt/V, irrespective of magnitude, defined declining dialysis adequacy. Catheter displacement or kinking was excluded by plain X-ray. Subsequently, 5000 units of urokinase was instilled into each lumen for 2 h as a locking solution, and dialysis was re-attempted on an outpatient basis. If this failed, patients were admitted to the ward for a 12-h intraluminal infusion of 12 500 units urokinase as previously described [28]. Failure of thrombolytic strategies mandated catheter replacement. Oral antiplatelet or anticoagulant agents were not used with intent to improve blood flow rate.

Statistics

Parametric data were analysed using Student's *t*-test, categorical variables were compared using chi-square or Fisher's exact test as appropriate and timeline incidence data were analysed using a Poisson model. Kaplan–Meier survival analysis was made on an intention-to-treat basis for patient survival and CVC-assisted primary catheter site patency [29]. Statistical significance was defined by $P < 0.05$. STATISTICA 9.0 (StatSoft Inc, Tulsa, OK, USA) and StatsDirect 2.7.4 (StatsDirect, Altrincham, Cheshire, UK) were used to perform statistical analysis.

Results

Thirty-nine pairs of translumbar inferior vena caval CVCs were inserted in 26 patients, with experience of 15 864 catheter days total follow-up. The mean length of follow-up was 13.3 ± 15.5 months (range 0.2–81.6). Thirty-five percent of the patients were over 65 years old, with similar numbers of whites ($n = 14$) and non-whites ($n = 12$). Diabetes mellitus was the cause of end-stage renal disease for 3/26 patients.

Table 1. Patient baseline characteristics and diagnosed comorbidities

Patient number	26
Mean age at insertion (years)	61.9 ± 12.1
Sex (male:female)	11:15
Ethnicity (white:Afro-Caribbean:South Asian)	14:6:6 (54%, 23%, 23%)
Diabetes mellitus	8 (31%)
Hypertension	15 (58%)
Ischaemic heart disease	7 (27%)
Peripheral vascular disease	3 (12%)
Mean dialysis vintage (years)	5.9 ± 3.2

Values expressed as mean ± standard deviation

Mean age at insertion for diabetics was 65.1 ± 11.1 vs 60.2 ± 12.5 years in non-diabetics ($P = 0.3$); both groups were of equivalent haemodialysis vintage, 4.7 ± 2.4 vs 6.2 ± 3.6 years, respectively ($P = 0.3$). Overall, patients were established on haemodialysis for a mean duration of 5.9 ± 3.2 years before they required a translumbal catheter (range 0–12.9 years) (Table 1). Twenty-one of twenty-six (81%) patients had at least one arteriovenous haemodialysis access (AVF or Arteriovenous graft, AVG) prior to receiving a translumbal CVC. Patients had a mean of 4.2 vascular accesses prior to requiring a translumbal CVC (mean 3.0 ± 1.3 CVCs, 1.0 ± 0.9 AVFs, 0.5 ± 0.7 AVGs). All patients had bilateral brachiocephalic venous occlusions, and 8/26 had concurrent superior vena caval occlusion.

Catheter function and dialysis adequacy

All translumbal CVCs were placed successfully and functioned immediately after insertion with immediate blood flow rates that did not exceed 300 ml/min. Catheter tips rested in the right atrium in 18/37 cases and the right atri-

al/inferior vena caval junction in 20 cases reflecting patient habitus as well as upper venous anatomy. Subsequent mean monthly blood flow rate for all catheters was 300 ± 3 ml/min (range 100–450 ml/min; median 307 ml/min). The mean spKt/V was 1.5 ± 0.4 over the course of the study. There was a trend to a higher mean spKt/V (from 1.2 to 1.6) over time reflecting an increase in the target for minimum spKt/V at our unit from 1.4 to 1.6 (Figure 1). An spKt/V ≥ 1.2 was achieved in 87.2% of patients, and an spKt/V ≥ 1.4 was achieved in 71.8%.

Patient survival

Cumulative patient survival was 81.5% at 1 year, 68.1% at 2 years and 51% at 3 years, censoring for change of dialysis modality, transplantation and transfer to another unit. No patients died as a result of lack of vascular access options or CVC related infection. Diabetic comorbidity did not significantly affect patient survival (logrank $\chi^2 = 0.593$, $P = 0.4$).

By comparison, there was no significant difference in cumulative patient survival between the translumbal CVC cohort and a previously published cohort of 435 patients with jugular CVCs from our centre [30]—84.7% at 1 year, 71.4% at 2 years and 63.0% at 3 years (logrank $\chi^2 = 1.10$, $P = 0.3$) (Figure 2). Of note, both cohorts were similar with respect to age and major comorbid conditions but different with respect to gender predominance (Table 2).

Translumbal CVC patency

Cumulative assisted primary CVC site patency was 73.2% at 1 year, 33.4% at 2 years and 27.9% at 3 years, censoring

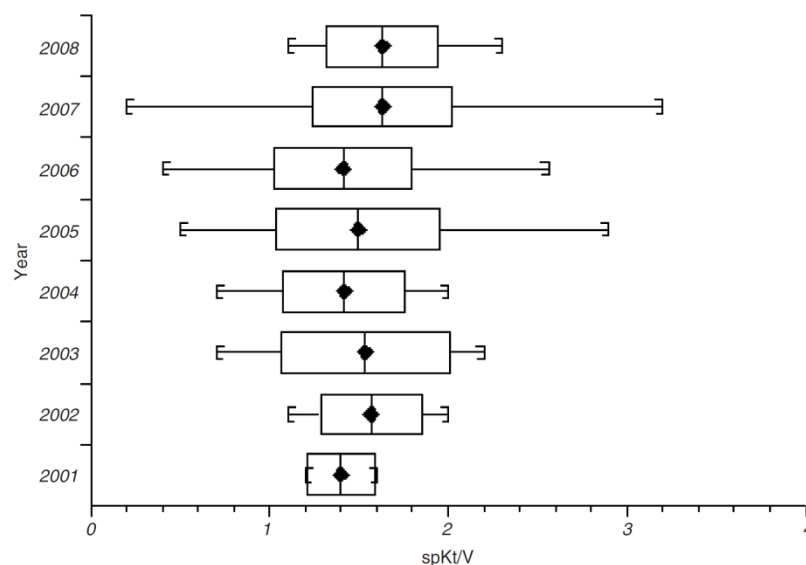


Fig. 1. Dialysis adequacy achieved by translumbal CVCs over time of study. Abbreviation: spKt/V, single-pool Kt/V. Box = mean, standard deviation, 25 to 75%; T-bars = minimum and maximum values.

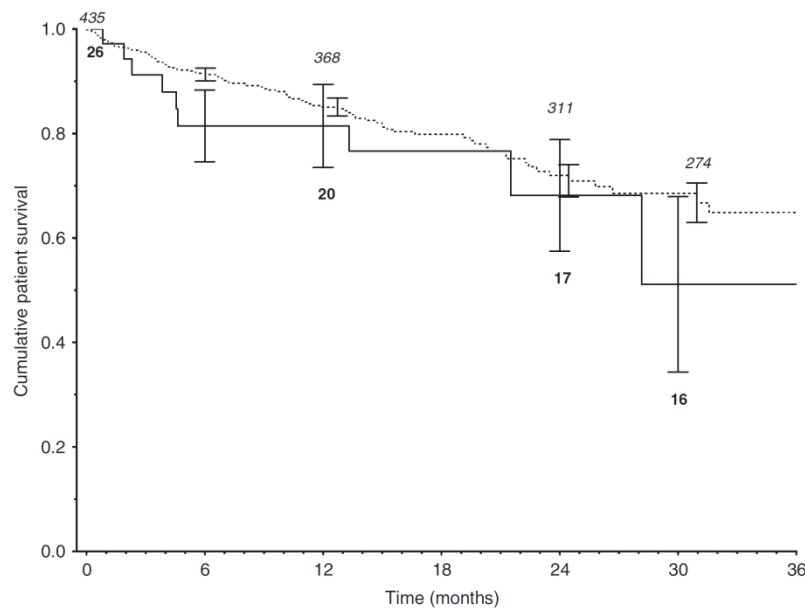


Fig. 2. Cumulative patient survival with CVCs characterized by site of insertion. Translumbar CVCs, solid line; internal jugular CVCs, Duncan *et al.* [30], dashed line. Numbers at risk shown in bold—translumbar CVCs and italics—internal jugular CVCs. Differences in patient demographics described in Table 2.

for death with functioning CVC, change in dialysis modality, transplantation and transfer to another unit (Figure 3). The presence of diabetes did not significantly affect CVC patency (logrank $\chi^2 = 2.96$, $P = 0.09$). By comparison, the jugular CVC cohort from our centre [30] had an assisted primary CVC site patency of 77.8% at 1 year and 44.0% at 3 years. The difference between the two groups did not reach statistical significance (logrank $\chi^2 = 1.58$, $P = 0.2$) (Figure 4).

Sepsis

The incidence of catheter-related infection was 2.84/1000 catheter days (95% confidence interval, CI, 2.07–3.80) (Table 3). There were 32 episodes of exit-site infection (including one *Pseudomonas* tunnel infection). There were 13 episodes of CRB, a rate of 0.82/1000 catheter days. Bacteraemia was due to two organisms in 2/13 episodes.

Table 2. Comparison of patient characteristics with jugular CVC cohort described by Duncan *et al.* [30]

	Translumbar cohort	Jugular cohort (30)	<i>P</i> value
Patient number	26	435	
Mean age at CVC insertion (years)	61.9 $\pm$ 12.1	59.3 $\pm$ 15.2	0.49
Male sex	11 (42%)	308 (71%)	0.002
Diabetes mellitus	8 (31%)	113 (26%)	0.59
Hypertension	15 (58%)	268 (63%)	0.69
Ischaemic heart disease	7 (27%)	161 (31%)	0.30
Peripheral vascular disease	3 (12%)	71 (16%)	0.75

There were 19 hospital admissions for all-cause infection. Nine of nineteen (47%) were due to proven or presumed catheter-related sepsis (Table 3). The mean duration of admission due to catheter-related sepsis was 12.7 ± 10.9 days (range 2–34 days). Eleven of fifteen (73%) of pathogenic isolates were Gram-positive bacteria.

Catheter dysfunction

Four of thirty-nine (10.3%) catheters dislodged and required replacement. Catheter dysfunction requiring urokinase infusion occurred in 10 catheters, a rate of 0.63/1000 catheter days (95% CI, 0.30–1.16). Nine of thirty-nine (23.1%) catheters required replacement for persistent dysfunction (Table 3).

Bleeding complications

The insertion of one catheter was associated with a self-limiting retroperitoneal haematoma that was managed conservatively and no blood transfusion required. A second retroperitoneal bleed occurred following catheter displacement. There were no other complications.

Discussion

The number of patients receiving haemodialysis in the US is increasing on an annual basis, reaching nearly 320 000 by the end of 2006 [31]. Despite national and international guidelines and initiatives such as Fistula First [32] recommending the AVF as the vascular access of choice [1–3],

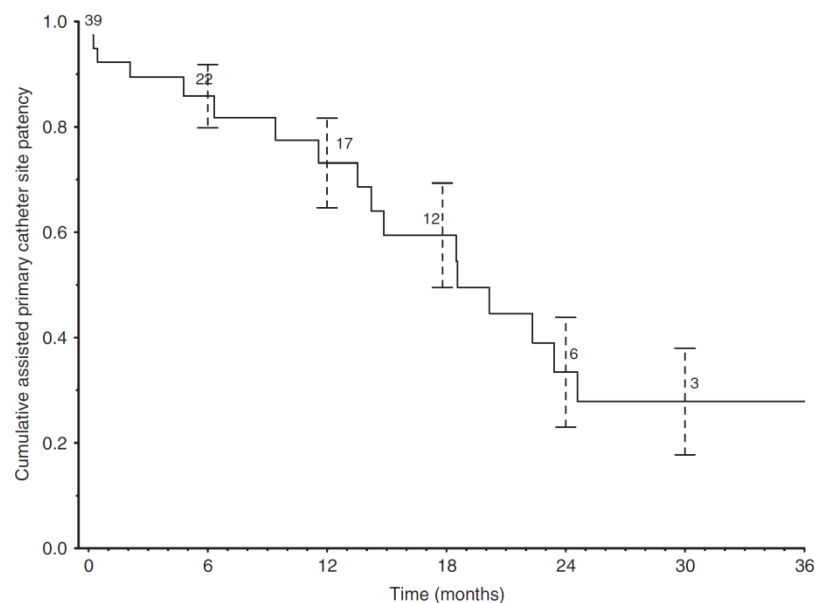


Fig. 3. Cumulative translumbar CVC survival. Numbers at risk shown in black font.

the number of haemodialysis patients using CVCs increased by 50% in the US 1998–2004 [33]. The problem posed by difficult vascular access in patients dependent on CVCs is likely to increase. There is a small number of studies to date reporting on translumbar catheters for haemodialysis [22,25,34].

Cumulative 1- and 2-year haemodialysis patient survival of 81.5 and 68.1% in this series is comparable to contemporary UK Renal Registry data of 80.9 and 69.0% [35] and to US Renal Data Service (USRDS) data of 79.2 and 65.4%, respectively [31]. However, patient survival is less than that of a contemporary cohort dialysing via internal jugular

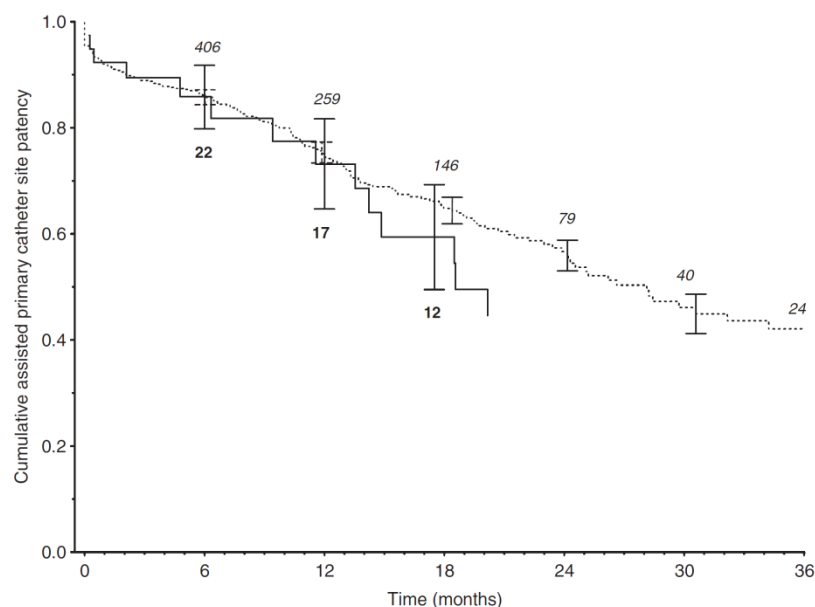


Fig. 4. Cumulative CVC survival characterized by site of insertion. Translumbar CVCs, solid line; internal jugular CVCs, Duncan *et al.* [30], dashed line. Numbers at risk shown in bold—translumbar CVCs and italics—internal jugular CVCs. Differences in patient demographics described in Table 2.

Table 3. Infective and mechanical complications

	Incidence rate
Catheter-related bacteraemia	0.82 (0.44–1.40)
Exit-site infections	2.01 (1.38–2.85)
All-cause hospital admission	3.97 (3.05–5.08)
Access-related hospital admission due to CVCs	1.45 (0.92–2.16)
All infection-related hospital admission	1.19 (0.72–1.87)
Access infection-related hospital admission	0.57 (0.2–1.08)
Access dysfunction-related	0.88 (0.48–1.48)

Incidence rates as events/1000 catheter days with 95% confidence intervals.

CVCs at our centre [30]. Patients requiring translumbar access had a longer haemodialysis vintage and therefore very likely carried a higher burden of comorbidity including cardiovascular disease.

Mean assisted primary catheter site patency was much longer than that reported by Biswal *et al.* in a series of 10 translumbar CVCs [34] and exceeds that reported by Lund *et al.* (17% at 1 year) [25]. Patient demographics and comorbidities are not reported in detail in either paper and may have accounted for some of the differences seen. Catheter patency is lower than for the contemporary cohort with internal jugular access [30]. This is not unexpected as patients requiring translumbar access have a history of recurrent access dysfunction which likely compromises further access function.

We report good access flow rates for translumbar haemodialysis catheters. Lund *et al.* report in limited detail an achieved flow rate of between 200 and 300 ml/min in a series of 15 catheters that were inserted for haemodialysis and two for plasmapheresis [25]. The mean blood flow rate of 300 ml/min in our series is comparable to that reported in a series of 184 internal jugular TesioCaths (291 ml/min) [36]. Achieved blood flow rates will reflect the local target for dialysis adequacy. There is no comparative published data on dialysis adequacy with translumbar haemodialysis access. Translumbar CVCs in this study achieved desired increases in dialysis adequacy with a mean spKt/V exceeding the mean urea reduction ratio of 61% published by Wivell *et al.* [36] and equivalent to that for internal jugular TesioCaths at our centre [30].

CRB occurred at a rate of 0.82/1000 catheter days in this series, lower than reported by Lund *et al.*, 1.4/1000 catheter days [25]. Only one episode of CRB required CVC removal. There is no data on infection in the study by Biswal *et al.* [34]. Our rate is similar to the rate of 0.81/1000 catheter days reported in a large single-centre UK study of all CVC types [12] and lower when compared with other studies of internal jugular TesioCaths, 2.3/1000 catheter days [36] and 1.4/1000 catheter days [37]. It is however higher than the rate of 0.34/1000 catheter days in a cohort of 759 CVCs followed up over 9.5 years at our centre 1999–2008 (unpublished data). This relatively higher rate of CRB associated with the translumbar approach is probably a result of the anatomical site of insertion where the patient lies on the exit site and it is subject to more mechanical stress.

Catheter thrombosis requiring an infusion of thrombolytic occurred at a much lower rate than 3.3/1000 catheter days in the study by Lund *et al.* [25]. This difference may be because they report thrombosis in single double-lumen catheters versus our twin single-lumen catheters, two of their catheters were used for plasmapheresis, and they do not state whether they used a catheter locking solution. Furthermore, the CVCs used in that study reflect older technology with step-tip configuration which may also have been contributory.

All-cause mechanical catheter dysfunction requiring thrombolytic infusion or catheter replacement occurred at a rate comparable to the rate of 0.8/1000 catheter days in the series of 303 internal jugular by Wang *et al.* [37]. This is higher than the rate of 0.33/1000 catheter days reported by Duncan *et al.* [30]. It could be anticipated that translumbar catheters are more prone to mechanical dislodgement because of the site of insertion. The phenotype of patients requiring translumbar CVCs may differ, they may have endothelial dysfunction or procoagulant states that predisposed them to increased rates of access loss and this warrants further study. The possible effects of variation in patient demographics, co-morbidities, dialytic protocols and administered therapies (e.g. anticoagulants) cannot be excluded when comparing different cohorts and may account for some of the differences seen.

The rate of complications associated with translumbar CVC insertion was low in this series in keeping with previous studies. Retroperitoneal haematoma is a recognized rare complication of this procedure, occurring in one patient in both the published series by Biswal *et al.* [34] and Markowitz *et al.* [38].

The transhepatic route can be used in cases of infrarenal caval occlusion, but is complicated by a high rate of catheter thrombosis (24/1000 catheter days) [19] and displacement (14–16%) [19,20]. The transfemoral route would appear to be a useful first option where there is preserved lower body venous patency as it is associated with fewer periprocedural complications than either the translumbar or transhepatic routes [39,40]. We do not opt for this approach at our centre; assisted primary CVC site patency is lower for this approach (mean of 85 days [40] versus a mean of 250 days [34] and 406 days in this study) with an associated higher rate of infection, 5.2/1000 catheter days [40]. In addition, there is a high rate of ipsilateral deep venous thrombosis reaching 25% in one series [39].

We report in detail on the translumbar route for maintenance haemodialysis access and demonstrate high-adequacy dialysis with low rates of catheter-related infection. Outcomes reported may have been influenced by recruitment bias and reflect practice at a single centre. The catheter care protocols used, a policy of clinically appropriate catheter salvage with empirical broad-spectrum antibiotics and prior experience with translumbar catheters may also have influenced outcome. Abnormally high proportions of CVCs result from basic problems in the choice, creation and maintenance of arteriovenous accesses, and this series serves to highlight an extreme on the spectrum of the complications of enduring catheter use for haemodialysis. As such, it reinforces the primacy of arteriovenous access as the vascular access form of choice in haemodialysis

where this is possible. However, the translumbar route can be a useful option in patients with exhausted upper body venous access requiring CVCs for haemodialysis and can offer better patency and infection rates than the transfemoral route.

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Conflict of interest statement. We have no conflicts of interest to declare. The results of this paper have not been published previously in whole or in part, except in abstract format. We have had no involvements that might raise the question of bias in the work reported or in the conclusions, implications or opinions stated.

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Case Report

Successful thrombolysis for acute ischaemic stroke in haemodialysis

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Abstract

Stroke is a leading cause of death worldwide and is associated with significant morbidity in survivors. Early thrombolytic therapy in acute ischaemic stroke has been shown to dramatically improve patient outcomes. Although the age-adjusted incidence of stroke is 5–10 times greater in haemodialysis patients, the use of thrombolysis for this indication in this group of patients has not been described to date. We present a case where alteplase was used successfully for acute ischaemic stroke in a patient established on maintenance haemodialysis in the setting of an international randomized controlled trial and advocate caution with the use of systemic thrombolytics despite the favourable outcome seen with this case.

Keywords: alteplase; haemodialysis; stroke

Introduction

Intravenous rtPA remains the only proven treatment for acute ischaemic stroke in the general population. Patients with end-stage renal disease (ESRD) on dialysis have a 5–10-fold higher incidence of stroke than the general population with an overall incidence rate of 13–33 per 1000 patient-years [1,2]. Haemorrhagic stroke subtype is more frequent in patients on dialysis ($\geq 30\%$) [3]. This may reflect the bleeding diathesis of uraemia [4] as well as the effects of anticoagulation for vascular access and dialysis circuit patency, the prevalence and degree of hypertension, and the established ethnic variations.

Patients with ESRD have been traditionally excluded from the large prospective randomized controlled trials that form the evidence base for treatment of vascular disease, including stroke, in the general population. The paradoxical effect of this apparent ‘renalism’ [5] is to potentially restrict access to beneficial therapies in a cohort that would have derived the greatest benefit. In addition, extrapolating outcome data derived from studies in the general population to patients on haemodialysis is not always fruitful. In one of the few adequately powered large prospective randomized controlled trials in haemodialysis (HD), atorvastatin did not reduce the incidence of stroke in

stark contrast to studies in the general population [6]. At present, the use of thrombolytic therapy for acute ischaemic stroke in HD patients has not been described.

Case report

We present the case of a 73-year-old male of South Asian ethnicity. He had a prior diagnosis of progressive chronic kidney disease secondary to obstructive uropathy and recurrent urosepsis, and a hydronephrotic left kidney requiring insertion of a J-J ureteric stent in June 2009. In addition, he had type 2 diabetes mellitus, ischaemic heart disease (myocardial infarction March 2009) and a diagnosis of hypertension. He did not have a history of cardiac dysrhythmia, a prothrombotic diathesis or cerebrovascular disease. There was no family history of renal or cerebrovascular disease. He was not on maintenance antiplatelet agents or oral anticoagulants. He was a non-smoker and did not consume any alcohol. Following emergency admission to the intensive care unit with pulmonary oedema, oliguria and a serum creatinine of 10.2 mg/dL (899 $\mu\text{mol/L}$), he was established on maintenance thrice weekly HD via a right internal jugular tunnelled cuffed central venous catheter (TesioCathTM, MedComp, Harleysville, PA, USA) 2.5-months prior to presentation with an acute stroke.

He presented to his local emergency department with acute right hemiparesis and aphasia of a 90-min duration. He had undergone routine HD 24-h with no complications prior to presentation. On arrival, his blood pressure (BP) was 190/87 mmHg, capillary blood glucose was 86.5 mg/dL (4.8 mmol/L) and his Glasgow Coma Score (GCS) was 15/15. He was in sinus rhythm on his electrocardiogram. An urgent CT scan of his brain revealed an acute ischaemic stroke affecting the superior parasagittal cortex of the left frontal lobe. There was no evidence of intracranial haemorrhage. At that point, he was transferred immediately to his local acute stroke centre. On arrival, his BP was 176/75 mmHg. Clinical examination revealed a mild right facial droop, evidence of a right hemiparesis (power 3/5 in the upper limb and power 0/5 in the lower limb) with increased muscle tone in the upper limb, lower limb hyperreflexia and an upgoing plantar response in the lower limb.

He was dysphasic with receptive and expressive elements. No cardiac murmurs or carotid bruits were detected, and he was clinically euvoelaemic. Calculated total NIH stroke score was 8. His laboratory examinations are presented in Table 1.

There were no absolute contraindications to thrombolysis, and he was eligible for trial enrolment. Following informed consent, he underwent randomization and received 54 mg rtPA (0.9 mg/kg—weight estimated at 60 kg) as per trial protocol (10% bolus followed by an infusion). rtPA (Actilyse™, Boehringer Ingelheim Ltd, Bracknell, Berkshire, UK) was delivered at 4-h after symptom onset. A repeat CT brain scan was performed 24-h after thrombolysis which showed a small area of haemorrhagic transformation within the original infarct and no other interval change (Figure 1). He remained clinically stable although required sodium valproate (600 mg b.d.) and clobazam (5 mg o.d.) for intermittent left upper limb myoclonus which responded well to therapy. Echocardiography revealed only borderline left ventricular hypertrophy. A 24-h Holter during the interdialytic period revealed sinus rhythm with a 1-h paroxysm of asymptomatic atrial fibrillation that terminated spontaneously. There was no significant carotid stenosis on Doppler ultrasonography. Four days after admission, he was transferred to our specialist renal stroke rehabilitation unit where he was an inpatient for the following month. During this time, power in his upper limb improved to 4/5 proximally and 3/5 distally, and in his lower limb to 4/5 proximally. His dysphasia improved, but he was left with a residual mild expressive deficit. He was discharged home 5 weeks after his initial admission and remains stable on maintenance HD.

Discussion

rtPA (alteplase) is a glycoprotein that becomes activated on binding to fibrin, converting plasminogen to plasmin and leading to fibrinolysis. It is rapidly cleared from the circulation following administration undergoing predominantly hepatic clearance. When administered within 3-h of symptom onset in the seminal placebo-controlled National Institute of Neurological Disorders and Stroke (NINDS) rtPA study, it resulted in a significantly better neurological outcome at 3 months [7]. Analysis of pooled results of six randomized controlled trials of intravenous rtPA showed that



Fig. 1. Single representative axial section through the brain post-thrombolysis. Within the parasagittal cortex of the left frontal lobe in the anterior cerebral artery territory is an ischaemic infarct with a small amount of haemorrhagic transformation (area of increased attenuation marked with the arrow).

the best outcomes occurred in patients treated within 2-h of symptom onset and suggested a benefit extending to 4.5-h. This was confirmed in a subsequent randomized controlled trial, ECASS III [8]. Although mortality did not differ between the two groups, 52.4% patients in the rtPA arm recovered with no disability after 90% vs 45.2% in the placebo arm ($P = 0.04$). There was, however, a higher rate of symptomatic intracerebral haemorrhage in the rtPA arm (2.4% vs 0.2%, $P = 0.008$) in keeping with prior studies. A Cochrane systematic review suggested a benefit associated with rtPA up to 6-h from symptom onset [9], and this is currently under study [10].

Use of rtPA is contraindicated in cases where there is a 'known haemorrhagic diathesis' or severe uncontrolled arterial hypertension (defined as 185/110 mmHg) as well as 'administration of heparin within the previous 48-h and a thromboplastin time exceeding the upper limit of normal for laboratory'. The manufacturer advises caution in 'all situations where there is a high risk of haemorrhage' [11].

The use of warfarin in HD patients with atrial fibrillation or for maintenance of arteriovenous graft patency will preclude some patients from receiving rtPA despite a study demonstrating a higher incidence of stroke in patients on this therapy. High rates of coronary and peripheral arterial disease and its treatment with percutaneous interventions in ESRD lead to a significant proportion of patients on single or dual maintenance antiplatelet therapy. Clinicians need to be aware of the high rates of occult gastrointestinal bleeding in HD patients as well as considering uraemia as a state of mild haemorrhagic diathesis. Heparin is routinely used

Table 1. Laboratory tests at time of presentation

Haemoglobin	15.9 g/dL
Total leucocyte count	$7.5 \times 10^9/\text{mL}$
Platelet count	$161 \times 10^9/\text{mL}$
Sodium	136 mmol/L
Potassium	4.7 mmol/L
Urea	12.2 mmol/L
Creatinine	462 $\mu\text{mol/L}$
Albumin	44 g/L
Total cholesterol	2.2 mmol/L
C-reactive protein	2 mg/L
INR	1.1
APTT	27.8 s
Fibrinogen	4.00 g/L

for dialysis circuit anticoagulation. Although the effect of unfractionated heparin can be monitored using the activated partial thromboplastin time (APTT), this is not the case for low-molecular-weight heparins (e.g. tinzaparin and enoxaparin) that are increasingly used for this indication.

To our knowledge, this is the first reported case of intravenous thrombolysis for treatment of acute ischaemic stroke in a haemodialysis patient. The outcome for this patient was favourable; however, we would advise extreme caution with the use of rtPA (alteplase) and treatment delivered on a case-by-case basis.

Conflict of interest statement. None declared.

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Intracranial arterial calcification is highly prevalent in hemodialysis patients but does not associate with acute ischemic stroke

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Abstract

Intracranial arterial calcification (IAC) is associated with ischemic stroke in the general population but this relationship has not been examined in hemodialysis patients. We examined the factors associated with IAC and its relationship with acute ischemic stroke in this population. We retrospectively studied 490 head computed tomographic scans from 2225 hemodialysis patients presenting with neurological symptoms at our center (October 2005–May 2009). Intracranial arterial calcification was graded using a validated scoring system. Multivariate regression was used to examine the factors associated with the presence of IAC, its severity, and its ability to predict acute ischemic stroke. Weibull's survival models analyzed the relationship between IAC severity and survival. Ninety-five percent of patients with ischemic stroke had IAC vs. 83% in the nonstroke group ($P=0.02$). Intracranial arterial calcification severity increased with age ($P<0.001$), hemodialysis vintage ($P<0.001$), serum phosphate ($P<0.05$), and major comorbidities. In patients with multiple computed tomographic scans during the study period, increased IAC severity at baseline was predictive of acute ischemic stroke ($P=0.05$) on logistic regression analysis. High-grade and not low-grade IAC was associated with worse survival ($P=0.008$). Intracranial arterial calcification is highly prevalent in hemodialysis patients, especially in those with acute ischemic stroke. Its severity is prognostically significant and associated with risk factors for vascular calcification and may confer a greater risk of acute ischemic stroke. The mechanisms underlying the high incidence of ischemic stroke in this patient group require further comprehensive study.

Key words: Cardiovascular disease, hemodialysis, stroke, vascular calcification

INTRODUCTION

Accelerated atherosclerosis and medial arterial calcification are the hallmarks of uremic vascular pathophysiology in chronic kidney disease (CKD).¹ This pathology

becomes more prevalent as renal function declines, reaching a peak in patients with end-stage renal disease. The nature and progression of vascular calcification in the coronary and peripheral arterial vasculature of patients on dialysis has been well characterized and is associated with adverse cardiac events and higher mortality.^{2,3}

The incidence of stroke in the hemodialysis population is 5–10 times higher than that in the general population, with rates reaching 33 per 1000 patient-years.⁴ Ischemic subtypes predominate, as is the case in the general population but the prevalence of hemorrhagic events is

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higher, reaching 30%.^{5,6} Prior studies have associated increasing age, diabetes mellitus, hypertension, and malnutrition with a higher incidence of stroke.⁷

Intracranial arterial calcification has been associated with an increased incidence of stroke in the general population.⁸ The prevalence of IAC increases with each stage of CKD in patients presenting to the hospital with stroke-like symptoms,⁹ a finding that parallels data describing an increasing incidence of stroke with declining renal function.¹⁰ It can be hypothesized that IAC may either be a surrogate marker for stroke risk or may be directly involved in its pathogenesis. There are no large studies examining IAC in hemodialysis patients to date. The factors influencing the prevalence and severity of IAC in this patient group are not known and its relationship with ischemic stroke is unclear.

SUBJECTS AND METHODS

Study population

This retrospective cohort study identified all patients receiving hemodialysis (HD) at our center from 1 October 2005 to 31 May 2009 and who had a computed tomographic (CT) scan of the head performed for any neurological indication (acute confusion in 32% cases, motor symptoms in 23%, seizures in 19%, and a drop in conscious level in 16%). Two thousand two hundred twenty-five patients were established (>90 days) on maintenance hemodialysis during the study period with 4302 total patient years follow-up (Table 1). Five hundred twenty-nine head CT scans were performed, of which 490 (93%) were in established HD patients (Figure 1). Sixty of these were diagnostic of acute ischemic stroke, with an overall incidence of 13.9 per 1000 patient years (95% confidence intervals [95% CI], 10.6–18.0). In the remaining 430 scans, no focal lesions were identified in 75%, there was evidence of old cerebral infarction in 105/430 (24%) scans, and a metastatic neoplasm was found in 1 patient. For analysis of the relationship between laboratory variables and the severity of IAC, we examined a subgroup of scans in patients without evidence of acute ischemic stroke and who had complete data available for 6 months before image acquisition (n=220, Figure 1). The characteristics of this subgroup were representative of the larger nonstroke cohort in terms of age, hemodialysis vintage, ethnicity and comorbidity profiles, and IAC load. All patients were dialyzed 3 times weekly using low-flux synthetic hemodialyzers, with a mean dialysis session length of 4.2 hours. Dialysis adequacy was measured by single-pool Kt/V (spKt/V) using the Daugirdas

method and dialysis prescription was tailored monthly to achieve a target spKt/V of ≥ 1.6 .¹¹

Study variables and definitions

The effects of age, gender, and ethnicity were analyzed. The presence of hypertension was defined by a postdialysis blood pressure $> 140/90$ mmHg and/or the need for antihypertensive medication and ischemic heart disease by a history of myocardial infarction, angina, or coronary intervention). Other comorbidities of interest were diabetes mellitus, peripheral vascular disease, and cerebrovascular disease defined by stroke or transient ischemic attack. The use of antiplatelet or anticoagulant medication (warfarin) was also recorded. Laboratory variables included the mean serum calcium, phosphate, and parathyroid hormone (PTH) levels over the 6 months before each CT scan acquisition. Acute ischemic stroke was defined as an acute neurological event > 24 hours in duration associated with evidence of infarction on neuroimaging (CT and/or MRI). Subdural hematoma and hemorrhagic stroke were excluded from the analysis.

Scoring of vascular calcification

Bone window CT brain images were analyzed to identify IAC at the level of the carotid siphon. A semiquantitative scale has been described for IAC based on original work correlating IAC on CT with conventional carotid angiography.^{12,13} Specifically, calcification in each carotid siphon was scored as Grade 0—absent, Grade 1—thin, discontinuous, Grade 2—thin, continuous or thick, discontinuous, and Grade 3—thick, continuous. The overall severity of IAC was expressed as the sum of the carotid siphon calcification scores. The interobserver agreement between 2 of the authors was good (Cohen's κ 0.74). In cases of disparity, images were rescored by a consensus review.

Statistical analysis

All analyses were carried out using Stata 11.0 (StatCorp, College Station, TX, USA). Descriptive statistics are expressed as the mean $\pm$ standard deviation. Continuous and categorical variables were compared using Student's *t* test and the chi-square or the Mann-Whitney *U* test, respectively, as appropriate. Timeline incidence data were analyzed using a Poisson model and expressed with 95% CI. The relationship between IAC load and bone profile parameters was examined using Cuzick's test for trend.

Table 1 Characteristics of the study population receiving hemodialysis at our center

	Whole dialysis population (n=2225)	CT scan cohort (490 scans)	P value	No IAC present (n=76)	IAC present (n=414)	P value	Mean IAC load		P value
							Factor present	Factor absent	
Age (y)	59.0 ± 15.8	62.8 ± 14.3	<0.001	48.6 ± 18.0	65.5 ± 11.8	<0.001			
Proportion male	61%	61%	0.9	57%	62%	0.4	3.3 ± 1.9	3.4 ± 2.0	0.4
HD vintage (y)		3.0 ± 3.1		2.0 ± 2.3	3.2 ± 3.1	0.002	—	—	—
Ethnicity									
White	951 (43%)	227 (46%)	0.2	30 (39%)	196 (47%)	0.3			
African—Caribbean	400 (18%)	103 (21%)	0.1	20 (26%)	87 (21%)	0.4			
South Asian	862 (39%)	158 (32%)	0.005	26 (35%)	131 (32%)	0.7			
Comorbidities									
Diabetes	877 (39%)	245 (50%)	<0.001	22 (29%)	222 (54%)	<0.001	4.2 ± 1.5	3.6 ± 1.5	<0.001
IHD	713 (32%)	214 (44%)	<0.001	13 (17%)	201 (49%)	<0.001	4.1 ± 1.5	3.3 ± 1.8	<0.001
Hypertension	1244 (60%)	320 (65%)	<0.001	49 (64%)	269 (65%)	0.9	3.3 ± 1.9	3.3 ± 2.0	0.9
Prior CrVD	344 (16%)	201 (41%)	<0.001	14 (18%)	187 (45%)	<0.001	3.9 ± 1.7	3.5 ± 1.9	0.03
PVD	253 (11%)	82 (17%)	0.001	1 (1%)	81 (20%)	<0.001	4.4 ± 1.4	3.4 ± 1.8	<0.001
Acute stroke (n=60)				3 (5%)	57 (95%)	0.02	3.9 ± 1.6	3.2 ± 2.0	0.01

Data expressed as mean values ± standard deviation.

CrVD=cerebrovascular disease; HD=hemodialysis; IAC=intracranial arterial calcification; IHD=ischemic heart disease; PVD=peripheral vascular disease.

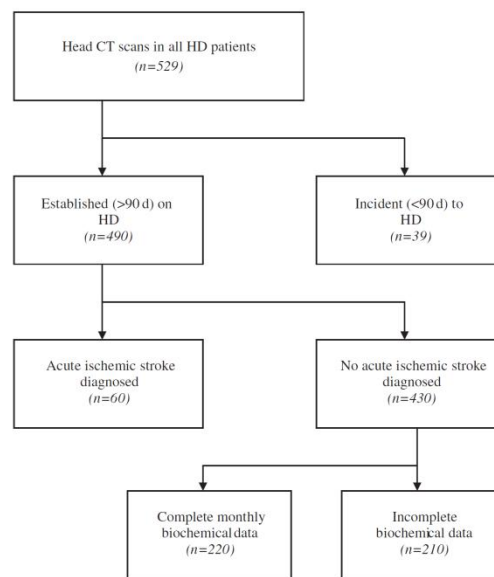


Figure 1 Overview of the study groups and CT imaging selection. CT=computed tomography; HD=hemodialysis.

Univariate and multivariate logistic regression was used to examine the effect of IAC load and clinical factors of interest such as patient age, dialysis vintage, diabetes, ischemic heart disease, hypertension, pre-existing cerebrovascular disease, and peripheral arterial disease in predicting new ischemic stroke in the study cohort. In addition, linear regression was used to examine the association between these factors and the quantified IAC load. As some patients had more than 1 scan during the study period, a mixed-effects model was used. The factors identified by univariate analysis with a P value <0.1 were then examined using a multivariate model. A backwards selection procedure was then applied to this model to identify risk factors of significance. There was no significant interaction of effect between the factors in the final model.

The effect of IAC severity and comorbidities on patient survival was examined using multivariate Weibull's survival models adjusting for patient age and censoring for change in dialysis modality, transplantation, dialysis withdrawal, and loss to follow-up. For this analysis, IAC severity was dichotomized as either low grade (summed score 1–3) or high grade (summed score 4–6). Statistical significance was defined by $P < 0.05$.

RESULTS

Clinical factors associated with the presence of IAC

355/430 (83%) scans in the nonstroke group displayed IAC. The presence of IAC was significantly associated with patient age, time on hemodialysis (hemodialysis vintage) and diabetes, coronary, and peripheral arterial disease (Table 1). Patient gender and ethnicity did not appear to influence the presence of IAC.

Intracranial arterial calcification was more prevalent in patients presenting with acute ischemic stroke (57/60, 95%, vs. 83%, $P=0.02$) and more severe (Table 1). These patients had a significantly higher prevalence of prior diagnosed cerebrovascular disease (63% vs. 38%, $P < 0.001$) but otherwise equivalent demographic profiles and comorbidities.

Clinical factors influencing IAC severity

The severity of IAC increased significantly with patient age ($P < 0.001$) and hemodialysis vintage ($P < 0.001$), an effect that became statistically significant from 4 years on treatment ($P=0.04$). The presence of peripheral vascular

disease, diabetes mellitus, and ischemic heart disease (all $P < 0.001$ on multivariate analysis) were independently associated with greater IAC severity (regression coefficients 0.94, 0.85, and 0.62, respectively). Male gender was associated with significantly less severe IAC (coefficient -0.38 , $P=0.01$). A diagnosis of hypertension and the use of antiplatelet agents had no significant effect on IAC severity.

Higher serum phosphate (P for trend=0.045) and calcium-phosphate product (P for trend=0.03) were significantly associated with a greater IAC load. There was no significant relationship with serum calcium ($P=0.41$) or PTH ($P=0.48$).

IAC severity as a predictor of acute ischemic stroke

Eighty-seven patients in the study cohort had multiple CT scans ($n=225$) for analysis, of which 14 were diagnostic of new ischemic stroke (Table 2). Of all the clinical factors examined, greater IAC severity was an independent predictor of ischemic stroke ($P=0.05$) and paradoxically diabetes mellitus was protective ($P=0.01$), with hemodialysis vintage and the presence of prior cerebrovascular disease displaying a trend to significance ($P=0.06$).

IAC severity and association with patient survival

The presence of high-grade IAC was significantly associated with a higher age-adjusted risk of death (hazard ratio, HR 1.17, 95% CI 1.22–3.87, $P=0.008$) in contrast

to the lack of association seen with low-grade IAC (HR 0.84, 95% CI 0.58–1.49, $P=0.56$). Longer hemodialysis vintage was also independently associated with a greater risk of death (HR 1.01, 95% CI 1.00–1.01, $P=0.02$) but other major comorbid conditions such as the occurrence of new ischemic stroke (HR 1.07, 95% CI 0.64–1.78, $P=0.79$), diabetes mellitus (HR 0.98, 95% CI 0.64–1.49, $P=0.92$), ischemic heart disease (HR 0.92, 95% CI 0.61–1.39, $P=0.70$), and peripheral vascular disease (HR 0.96, 95% CI 0.56–1.67, $P=0.89$) were not.

DISCUSSION

This is the largest study of intracerebral arterial calcification in hemodialysis patients. We describe a high prevalence of IAC in our hemodialysis population (83%), similar in magnitude to studies of the coronary circulation (70–90%). While the coronary circulation remains the most thoroughly studied for arterial calcification in both the general and the hemodialysis population, calcification in the cerebral arterial circulation is not well studied. A high prevalence of IAC in patients with CKD with increasing IAC scores from CKD Stage 1 to 3 has been demonstrated.⁹ The prevalence of IAC was higher in patients presenting with stroke compared with those presenting other neurological symptoms. But only 10 patients in this study had CKD 4–5 and therefore no comment can be made on the relationship with hemodialysis.

We have described the association of the presence or absence of IAC with demographic factors and major

Table 2 Predictors of new ischemic stroke

Risk factor	Predictors of new ischemic stroke			
	Univariate analysis		Multivariate analysis	
	Coefficient [95% CI]	P value	Coefficient [95% CI]	P value
Age (y)	0.01 [−0.03–0.05]	0.6		
Prior HD (y)	−0.19 [−0.45–0.06]	0.1	−0.30 [−0.53–0.01]	0.06
Male gender	0.09 [−1.07–1.24]	0.9		
Diabetes mellitus	−1.09 [−2.31–0.13]	0.08	−1.76 [−3.11–−0.40]	0.01
IHD	−0.81 [−2.03–0.40]	0.2		
Hypertension	0.36 [−0.98–1.70]	0.6		
CrVD	1.12 [−0.09–2.34]	0.07	1.26 [−0.04–2.57]	0.06
PVD	−1.07 [−3.17–1.01]	0.3		
Aspirin use	−0.75 [−2.08–0.58]	0.3		
Clopidogrel use	−0.49 [−2.06–1.07]	0.5		
IAC load	0.23 [−0.09–0.55]	0.2	0.39 [0–0.80]	0.05

CrVD=cerebrovascular disease; HD=hemodialysis; IAC=intracranial arterial calcification; IHD=ischemic heart disease; PVD=peripheral vascular disease.

comorbidities on hemodialysis. Data from the general population demonstrate an association of IAC with increasing age as well as diabetes mellitus.¹⁴ These are also implicated in patients with CKD in addition to dyslipidemia, ischemic heart disease, and peripheral vascular disease.⁹ We demonstrate the relationship between the presence or absence of IAC and increasing age, increasing hemodialysis vintage, the presence of diabetes, and established cardiac and peripheral arterial disease. Published studies examining the extracerebral arterial vasculature in hemodialysis patients are congruous with this.¹⁵

In addition, we have graded IAC and are able to comment on the effect of IAC severity. Our data suggest an independent association between high-grade IAC and adverse survival on hemodialysis. Intracranial arterial calcification severity increases with hemodialysis vintage, a phenomenon related to senescence and to chronic exposure to the proinflammatory state of end-stage renal disease and the hemodialysis process itself.¹⁶ Diabetes mellitus and established cardiac and peripheral arterial disease were associated with more severe IAC in our study.

Particularly interesting is that higher serum phosphate concentration and calcium-phosphate product were associated with more severe IAC. This could result from a direct effect of hyperphosphatemia on vascular calcification as has been *in vitro*, where phosphate can induce transdifferentiation of vascular smooth muscle cells to an osteoblastic phenotype causing mineralization.¹⁷ While calcium has a similar effect *in vitro*, we found no association with serum calcium in our study. This may have been influenced by the relatively low serum concentrations in our patients as we avoid calcium loading with a high use of noncalcium-based phosphate binders. We could not find an association between PTH levels and IAC, although published data link high as well as low levels of PTH with vascular calcification.¹⁸

The apparent protective effect of male gender on the severity of IAC is also notable. This is in contrast to studies describing an association between male gender and a higher prevalence of extracranial vascular calcification.^{19,20} We speculate that there may be a different pathogenetic mechanism affecting intracranial circulation potentially relating to differential gonadal steroid receptor expression²¹ but concede that unidentified factors in our analysis may be confounding.

While the degree of IAC in the general population correlates with the degree of angiographically proven intracranial atherosclerosis,^{22,23} the association between IAC and acute ischemic stroke is less clear. In a study of Chinese general medical patients, Chen et al.⁸ found that IAC was an independent predictor of ischemic stroke (odds

ratio 3.17), whereas a comparative Japanese study of 72 patients reported no such association.²³ These studies reported a higher proportion of calcification (50–80%) affecting the internal carotid circulation.

The potential association between IAC and acute ischemic stroke in hemodialysis patients has not been examined to date. In keeping with data from nondialysis populations, we found a significantly higher prevalence of IAC in patients presenting with acute ischemic stroke (95%). We report a novel relationship between the degree of IAC severity and the risk of new ischemic stroke in hemodialysis patients that just reaches statistical significance, although these data need to be interpreted with caution, given the sample size involved and the event rate (14 new strokes), which reflects the nature of retrospective study in the absence of a regular CT screening protocol. Separate linear regression analysis of the relationship between a diagnosis of acute ischemic stroke and IAC severity at the time of scanning in the entire cohort showed that a significant association was present on univariate analysis ($P=0.03$) in our study but not on multivariate analysis ($P=0.08$). The high prevalence of the presence of IAC, sample size, and confounding factors may have affected the level of statistical significance.

The biological hypothesis that IAC is associated with stroke remains attractive. Cerebral circulation in hemodialysis patients represents a vascular bed especially vulnerable to perturbations in blood flow. Experimental models suggest that uremia may impair cerebral autoregulation. Hemodialysis alters cerebral hemodynamics and has been shown to reduce middle cerebral arterial blood flow during and after therapy.²⁴ Diabetic patients appear to have worse hemodynamic homeostasis intradialytically independent of ultrafiltration.²⁵ We hypothesize that IAC may influence ischemic stroke risk through adverse modulation of arterial waveform transmission to the blood-brain barrier, adverse arterial flow patterns causing vascular remodeling, or by promoting atherosclerotic plaque instability and distal embolization.

While large, there are limitations to our retrospective study, which describes associations and cannot conclusively prove causality. Confounding undescribed differences may have existed to explain the associations seen, for example phosphate binder and vitamin D analog use. The cohort analyzed underwent CT scanning for a neurological indication rather than a planned interval screening and the results may be influenced by indication bias. We reported on calcification in the anterior cerebral circulation only and while this is recognized to be the prime site for isolated posterior cerebral circulation calcification has not been quantified.

In conclusion, IAC is highly prevalent in hemodialysis patients and may influence stroke risk in this vulnerable population. There are no randomized-controlled trials examining primary or secondary stroke prevention in this population and a number of rigorous studies suggest that traditional cardiovascular risk factor management derived from nondialysis patients is not applicable.²⁶ We recommend the avoidance of excessive calcium loading, management of hyperphosphatemia, and maintenance of appropriate bone turnover to retard the progression of vascular calcification but adequately powered randomized studies are required to assess the effect of such risk factor modifications on stroke incidence.

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We have no conflicts of interest to declare. We have had no involvements that might raise the question of bias in the work reported or in the conclusions, implications, or opinions stated.

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Long-term Tesio Catheter Access for Hemodialysis Can Deliver High Dialysis Adequacy with Low Complication Rates

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ABSTRACT

Purpose: The use of central venous catheters for long-term hemodialysis has been associated with increased mortality and high prevalence of infection and venous stenosis. However, because central venous catheters still constitute a significant proportion of vascular access in prevalent populations, even in the Fistula-First era, the authors examined the long-term patient outcomes and performance of this vascular access type to inform current clinical practice.

Materials and Methods: The authors conducted a retrospective cohort study of 433 patients on maintenance hemodialysis in a dialysis program from January 1999 through April 2008 all using twin-catheter Tesio Caths (TCs) (MedCOMP, Harleysville, Pennsylvania). Written and electronic records were examined with respect to laboratory indices as well as mortality, access-related infection, need for thrombolytic infusion, access revision and dialysis adequacy.

Results: A total of 759 TCs were inserted with 552,035 catheter days follow-up. Thirty-six percent of insertions were in patients incident to dialysis (< 90 days). Mean single-pool Kt/V was 1.6 ± 0.3 . Cumulative cohort survival rates were 85%, 72%, and 48% at 1, 2, and 5 years, respectively. No patients died as a result of lack of vascular access. Cumulative assisted primary access site patencies were 76%, 62%, and 42% at 1, 2, and 5 years, respectively. The prevalence of symptomatic central venous stenosis was 5%. Catheter-related bacteremia occurred at a rate of 0.34 per 1,000 catheter days.

Conclusions: Appropriate use of TCs with protocolized care can deliver effective long-term hemodialysis with good adequacy and rates of access-related infection approaching those seen with arteriovenous grafts.

ABBREVIATIONS

AVF = arteriovenous fistulae, AVG = arteriovenous graft, CI = confidence interval, CRB = catheter-related bacteremia, CVC = central venous catheter, HR = hazard ratio, MRSA = methicillin-resistant *Staphylococcus aureus*, spKt/V = single-pool Kt/V, TC = Tesio Cath

Effective hemodialysis is dependent on maintaining durable and safe vascular access capable of sustaining flow delivering high-adequacy treatment with a low incidence of complications. All such vascular access is prone to dysfunction through vessel thrombosis and stenosis as well as

acting as a portal for infection. Arteriovenous fistulae (AVF) have the best longevity and lowest rates of access-related infection but are dependent on adequate, adaptable vasculature for formation and maturation (1). Arteriovenous grafts (AVGs) can be used where the patient's native vasculature is inadequate for AVF formation with a shorter time-to-use period but are prone to frequent stenosis and thrombosis requiring endovascular intervention. Infection of prosthetic AVGs may require removal and surgery. Central venous catheters (CVCs) are relatively easily placed and removed and, in contrast to AVFs and AVGs, can be placed without surgery and used immediately. They are, however, prone to thrombosis and are associated with the highest rates of access-related infection and venous stenosis (2) As such they have been seen as a double-edged sword (3) Despite international guidelines advocating use

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of AVFs as the primary access type (4,5), there is considerable variation in implementation (6). Female sex, the presence of ischemic heart disease and peripheral vascular disease, obesity, and white race have all been cited as predisposing to CVC use (7–9). A pragmatic approach to CVCs has been described in patients awaiting live-donor kidney transplantation or with unsuitable vascular anatomy for AVFs and in patients unwilling to have either AVF or AVG formation (10,11). Until the complications associated with CVCs are reduced to a level comparable with other forms of vascular access it is difficult to recommend their enduring use in long-term hemodialysis patients. To this effect, we examined the complications and outcomes of CVC use in a large cohort at our center over an extended period (over 9 years).

MATERIALS AND METHODS

Our center provides specialist renal care for a population of 2.1 million people in a large urban center. It acts as the admission unit for a hemodialysis program of 1,260 patients delivered by eight satellite units and one hospital unit and with a high prevalence of CVC use. We retrospectively studied outcomes of a cohort of 433 patients receiving a Tesio Cath (TC) (Bio-Flex Tesio Catheter, MedCOMP Inc, Harleysville, Pennsylvania) for vascular access as previously described from January 1, 1999 to April 1, 2008. The study was approved by the Institutional Review Board at our institution, which waived the requirement for informed consent.

All patients were assessed clinically for AVF formation by a consultant nephrologist and referred for further assessment by a consultant surgeon as appropriate. The indication for TC placement in incident patients was a lack of suitable vessels for successful AVF creation, immediate requirement for enduring vascular access for hemodialysis in patients unable to wait for AVF maturation, or patient choice. In prevalent patients the indication was inadequate or failed access via an existing AVF, AVG, or CVC or patient choice.

Central venous mapping by conventional venography was only performed for patients with clinical signs suggestive of central venous stenosis or with a history of multiple uncuffed or cuffed CVC insertions. Temporary venous access for hemodialysis using an uncuffed venous catheter was obtained via the femoral vein only and was in place for not more than a few days.

TC Insertions

Before TC insertion, both incident and prevalent hemodialysis patients were screened for methicillin-resistant *Staphylococcus aureus* (MRSA) carriage with nasal and axillary swabs according to local protocol. Those with MRSA carriage received 2% mupirocin ointment nasally (Bactroban Nasal Ointment, GlaxoSmithKline UK, Uxbridge, United Kingdom) four times daily. All other patients were treated with 0.1% chlorhexidine and 0.5% neo-

mycin cream nasally (Naseptin Nasal Cream, Alliance Pharmaceuticals, Chippenham, United Kingdom) four times daily. These were started before TC insertion and were continued for 1 week after insertion.

Preprocedural single doses of antibiotics were given on the day of TC insertion in all cases. In the period from 1999–2005, our local protocol used clarithromycin, 250 mg orally (vancomycin, 500 mg intravenously, if the patient was MRSA positive on screening), and ciprofloxacin, 250 mg orally. From 2005–2008 all patients received 500 mg of vancomycin intravenously and 250 mg of ciprofloxacin orally.

All TCs (12-F Bio-Flex Tesio Catheter) were inserted by experienced surgeons or interventional radiologists under sterile conditions in operating theatres or in the interventional suite of the radiology department. Catheter placement was via the internal jugular vein in all cases, with an insertion point between the sternal and clavicular heads of the sternocleidomastoid muscle. Ultrasound and x-ray fluoroscopy were used in all cases to guide correct placement. All TCs were inserted percutaneously with no deep dissection to the vein using a two-guide wire technique. The tip of the “venous” catheter was placed about 3 cm caudal to the right atrial margin visible on x-ray. The tip of the “arterial” catheter was placed 3 cm cephalic to the tip of the “venous” catheter. The cuffs were individually tunneled from the point of the percutaneous puncture to lie within the tunnel 3 cm from the exit site and maintaining a separation of at least 1 cm between the venous and arterial catheters. A postprocedural erect chest x-ray was performed to exclude pneumothorax and assess TC tip position.

Catheter and central venograms were not routinely performed in cases of TC replacement. Catheter venograms were performed as clinically indicated at the discretion of the interventional radiologist, and mechanical fibrin sheath disruption using a guide wire was performed if required. Surgical teams did not perform venography in any instance.

TC Care

TCs were locked according to the dead space of each catheter with heparin, 5,000 U/mL (Monoparin sodium heparin, 5000 IU/mL, CP Pharmaceuticals, Wrexham, United Kingdom) between dialysis sessions. A volume of 46.7% sodium citrate (DuraLock C, MedCOMP) was used as a catheter lock in postoperative patients, patients with a bleeding diathesis, and in those with heparin allergy or sensitivity. Antibiotic catheter locks were not used. The exit site was cleaned at each dialysis session with sterile normal saline followed by 4% chlorhexidine gluconate solution (Hibiscrub, Molnlycke Healthcare, Manchester, United Kingdom) and allowed to air dry before the application of a bio-occlusive dressing. Patients did not receive prophylactic antimicrobial therapy to the exit site. Routine systemic antiplatelet or oral anticoagulant agents were not used to improve blood flow rates.

Quarterly screening of all patients for nasal and exit site carriage of MRSA was adopted as routine practice at our center in 2007. All patients returning to their satellite

Table 1. Protocols for Empirical Treatment of Access-related Infections

Infection	Protocol
1999–2005	
Sepsis, tunnel infection	Vancomycin 500 mg and ceftazidime† 2 g IV postdialysis
Exit site infection	Clarithromycin 250 mg bd and ciprofloxacin 250 mg bd PO
2005–2008	
Sepsis, tunnel infection	Vancomycin 500 mg and meropenem 2 g*† IV postdialysis
Exit site infection	Vancomycin 500 mg IV postdialysis and ciprofloxacin 250 mg bd PO

Note.—bd = twice daily, IV = intravenously; PO = orally.

* Tazocin 4.5 g bd IV substituted for in-patients.

† In the event of penicillin allergy, ciprofloxacin 250 mg bd was substituted.

dialysis unit after an inpatient admission were screened with additional swabs of their throat, axilla, and groin. Patients with positive nasal or exit site swabs were treated four times daily for a 5-day course with topical 2% mupirocin ointment nasally and to the exit site.

TC Infection

Pyrexia was defined as a tympanic temperature of $\geq 38^{\circ}\text{C}$, and all patients with pyrexia with or without a systemic inflammatory response were investigated with exit site swabs, multiple blood cultures drawn from the catheter itself and from peripheral veins, and urine and sputum culture where appropriate to circumstances. Samples were obtained before starting antibiotics. Sepsis was presumed to be catheter related if there was no clinical or microbiologic evidence of another source. Empirical antibiotic treatment preempted microbiologic confirmation of infection and followed a defined protocol (Table 1). Subsequent therapy was tailored to antibiotic sensitivities, and proven or suspected TC infections were treated for a minimum duration of 2 weeks. Catheter-related bacteremia (CRB) is defined per established standards (12). Catheter salvage was attempted where clinically appropriate. Catheter-related sepsis was defined as the clinical presence of sepsis with growth of organisms in the blood or the catheter tip (where catheter removal occurred) with no evidence of alternative source of infection and similar to established reporting standards (12).

Exit site swabs were taken if there was exudate with or without pain, crusting, erythema, or induration at the exit site. Infection limited to the exit site in the absence of pyrexia was treated initially with an empirical choice of oral agents and subsequently according to determined antibiotic sensitivities for a minimum of 2 weeks (Table 1). Febrile patients were treated as for systemic sepsis described above.

Tunnel infections were defined by pain, redness, or induration along the subcutaneous course of the line, with

or without exudates at the exit site, and were treated from the outset with intravenous antibiotics per protocol (Table 1). The doses of these antibiotics were adjusted when culture results were available with the addition of a second appropriate oral antibiotic for a minimum of 6 weeks. Persisting infection was an indication for TC removal as detailed above.

Patients with pyrexia exhibiting systemic inflammatory response (core temperature $> 38^{\circ}\text{C}$, tachycardia or tachypnea, leucocytosis $> 12 \times 10^9/\text{mL}$), relative hypotension, or a persistent tunnel infection were admitted to our center for ongoing care. Bacteremia alone did not qualify the patient for admission. The catheter was only removed if the patient had hypotension requiring inotrope support, persistent bacteremia, or refractory tunnel infection for > 3 days despite targeted intravenous antibiotic therapy. Where appropriate, a new TC was inserted in the contralateral internal jugular vein once the bloodstream was cleared of infection for at least 48 hours.

TC Dysfunction

The target blood flow was ≥ 350 mL/min. TC dysfunction was identified by consistently suboptimal blood flow of < 250 mL/min or declining dialysis adequacy. Three consecutive decreases in monthly Kt/V, irrespective of magnitude, defined declining dialysis adequacy. In the first instance, catheter displacement or kinking was excluded by plain x-ray. Subsequently, 5,000 units of urokinase was instilled into each lumen for 2 hours as a locking solution, and dialysis was reattempted on an outpatient basis. If this failed, patients were admitted to the ward for a 12-hour intraluminal infusion of 12,500 units of urokinase as previously described (13). Failure of thrombolytic strategies mandated catheter replacement. Oral antiplatelet or anticoagulant agents were not used with intent to improve blood flow rate.

Dialysis Adequacy

Patients underwent dialysis three times weekly using low-flux synthetic AM-BIO-1000 Wet hemodialyzers (Asahi Kasei Medical Europe GmbH, Frankfurt, Germany). Dialysis session length ranged from 2.5–5 hours. Dialysis adequacy was measured by single-pool Kt/V (spKt/V) on a monthly basis using the Daugirdas method (14). Dialysis prescription was tailored to achieve a target spKt/V of ≥ 1.4 (1999–2005) and ≥ 1.6 (2005–2008). In patients failing to achieve this target, hemodialyzer size was increased, blood flows were increased to ≥ 350 mL/min, dialysate flow rates were adjusted to ≥ 500 mL/min, and access recirculation was assessed by a urea-based method, and, if necessary, access was changed. Dialysis length could be extended to a maximum of 5 hours.

Statistics

Parametric data were analysed using Student *t* test, and timeline incidence data were analyzed using a Poisson model. Kaplan-Meier survival analysis was made on an

Table 2. Patient Demographics

	<i>n</i>	%
Total patient number	433	
Mean patient age (y)	59.7 ± 15.2	
Patients > 70 y	124	28.6
Male	247	57.0
Incident:Prevalent	222:211	
Mean dialysis vintage (mo)*	39.1 ± 42.6	
Ethnicity		
White	209	48.3
Afro-Caribbean	86	19.9
Indo-Asian	133	30.7
Other	5	1.2
Diabetic	108	24.9

* Describes prevalent dialysis patients.

intention-to-treat basis for patient survival censoring for change in dialysis access or modality, transplantation, and transfer to another center and also for assisted primary TC patency (12) censoring for death with a functioning TC, change in dialysis access or modality, transplantation, and transfer to another center. Statistical significance was defined as $P < .05$. STATISTICA 9.0 (StatSoft Inc, Tulsa, Oklahoma) and STATA 10.0 (StataCorp LP, College Station, Texas) were used to perform statistical analysis.

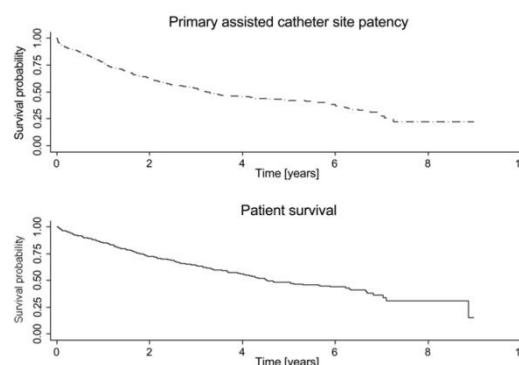
RESULTS

A total of 759 TCs were inserted in 433 patients, with experience of 552,035 catheter days total follow-up. The mean length of follow-up was 23.8 ± 23.3 months. Patient demographics are described in **Table 2**.

A total of 416 of 759 (54.8%) TC insertions were performed by surgeons and the remainder by interventional radiologists, with 274 of 759 (36.1%) in incident hemodialysis patients. The mean patient age at insertion was 60.0 ± 15.0 years (range, 15.4–89.5 years). A total of 29 of 759 (3.8%) insertions were unsuccessful (10 radiologic, 19 surgical) and required a further procedure, which was successful in all cases. There was one death as a result of asystolic arrest in the context of normokalemia in a patient with ischemic cardiomyopathy during successful radiologic insertion. There were no other periprocedural complications.

Patient Survival

Cumulative patient survival rates were 84.7%, 72.4%, 62.6%, and 48.1% at 1, 2, 3, and 5 years, respectively (**Fig 1**). Diabetes had no significant effect on patient survival (log rank $P = .26$). Cumulative survival rates of incident patients were 87%, 75%, and 57% at 1, 2, and 5 years, respectively, which compares favorably with UK data (82%, 71%, and 44%, respectively) (15) and US data

**Figure 1.** Cumulative assisted primary access site patency and patient survival censored for death, transplantation, change of dialysis modality or access type, and transfer to another center.**Table 3.** Mortality of Incident Hemodialysis Patients in Study Cohort Compared with Incident Cohort from USRDS 2007 Report

	Deaths per 1,000 Patient Years at Risk		
	1 Year	2 Years	3 Years
Current study	143	154	152
USRDS (2007)	247	211	214

Note.—USRDS = United States Renal Data Service. Rates expressed as deaths per 1,000 patient years at risk to allow for comparison of data. From reference 16.

(16) (**Table 3**). Over the study period, 73 of 433 (16.8%) patients received a kidney transplant, three changed dialysis modality, 36 patients transferred to another center, and 232 of 433 (53.6%) died. The mean spKt/V during the study period was 1.6 ± 0.3 .

TC Patency

Median-assisted primary TC site patency was 3.2 years, with cumulative patency of 76.1% at 1 year, 62.2% at 2 years, and 41.6% at 5 years (**Fig 1**). The presence of diabetes did not significantly affect assisted primary TC site patency (log rank, $P = .07$) or time to first TC failure (log rank, $P = .18$). In patients receiving their first TC, cumulative assisted primary site patency was not significantly different in incident compared with prevalent patients (defined as more than 30 days on hemodialysis; log rank, $P = .09$). However, median-assisted primary site patency declined with each subsequent TC insertion (3.41 vs 3.19 and 2.02 years for first, second, and third TCs, respectively).

Interventional radiology TC insertion was associated with worse TC patency on univariate and multivariate analysis (hazard ratio [HR], 1.41; 95% confidence interval [CI], 1.13–1.77). However, a greater proportion of patients presenting to the radiologists had previous TCs (49% vs 38%,

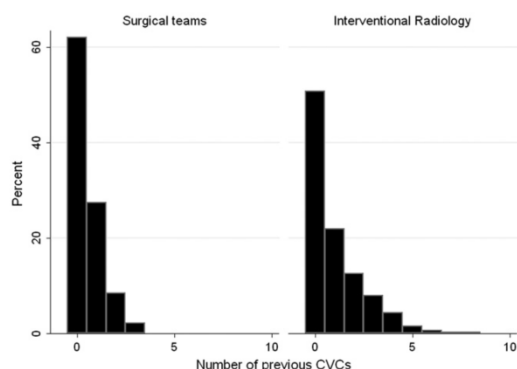


Figure 2. Prior CVC history in patients presenting to surgical or interventional radiology teams for TC insertion.

$P = .002$). The distribution of prior catheter insertions is shown in **Fig 2**. Diabetes, ischemic heart disease, cerebrovascular disease, peripheral vascular disease, patient ethnicity, and age were not significantly associated with worse TC patency (**Table 4**).

TC Sepsis

A total of 425 infective episodes were identified, 88% with a defined source. Of these, 115 (27%) were proven to relate to vascular access with a further 118 (28%) presumed to. The incidence of overall catheter-related infection was 0.42 per 1,000 catheter days (95% CI, 0.37–0.48) comprising 46 episodes of exit-site infection at a rate of 0.08 per 1,000 catheter days (95% CI, 0.06–0.11) and 187 episodes of catheter-related bacteremia at a rate of 0.34 per 1,000 catheter days (95% CI, 0.29–0.39).

There were 176 admissions for catheter-related sepsis at a rate of 0.31 per 1,000 catheter days (95% CI, 0.27–0.37) with a mean duration of admission of 8.1 ± 13.9 days (range, 1–92 days). TC removal was required in 30 of 233 (12.9%) cases of catheter-related infection. Eight patients died secondary to catheter-related sepsis (*S. aureus* [$n = 5$, one of which was methicillin resistant], coagulase-negative *Staphylococcus* [$n = 1$], gram-negative organisms [$n = 2$]). There were four episodes of metastatic catheter-related infection (three cases of infective endocarditis [one fatal] and 1 case of discitis). Catheter salvage was not attempted in any case of metastatic infection.

TC Dysfunction

There were 195 admissions for TC dysfunction during the study period at a rate of 0.35 per 1,000 catheter days (95% CI, 0.31–0.41). A total of 164 of 195 (84%) admissions were a result of suboptimal flow not resolving with the use of urokinase catheter locks. Elective TC replacement was performed in 41 of 164 (25%) cases. Urokinase infusion was used in the remainder and was successful on 53 of 123 (43%) occasions. In addition, 31 of 759 (4%) TCs dis-

lodged and required replacement at a rate of 0.06 per 1,000 catheter days (95% CI, 0.04–0.08). Twenty-two (5%) patients required venoplasty for central venous stenoses over the course of the study period (11 lesions in the right and nine in the left brachiocephalic veins were treated as well as seven lesions in the upper superior vena cava.) No patient had more than one procedure.

DISCUSSION

CVC use for hemodialysis has been associated with high rates of access-related infection and subsequent complications as well as venous stenosis, which may compromise future arteriovenous access formation (1,17,18). As a result, their use is discouraged in national and international guidelines, with initiatives in place to favor AVF formation (4,5,19,20).

Access-related infection comprises both local infection (at the catheter exit site or tunnel) as well as bacteremia relating to the catheter itself. Bacteremia can lead to systemic sepsis syndrome and sequelae such as infective endocarditis, septic arthritis, discitis, or osteomyelitis (2,21). Studies report an incidence of CRB at 2–5 cases per 1,000 catheter days with considerable variation between centers and countries (22–24). A recent Centers for Disease Control study found access-related bacteremia rates of 0.2, 0.4, and 3.1 per 100 patient-months for AVF, AVG, and tunneled CVCs, respectively (equating to 0.07, 0.15, and 1.01 per 1,000 access days, respectively, in this study) (25). Antimicrobial catheter locks have been used to reduce CRB rates further (0.3–1.1 per 1,000 catheter days) albeit in centers with relatively high CRB rates in the control groups (26,27). We found no additional efficacy of 46.7% sodium citrate in a prospective, randomized, controlled trial at our center (28). In this study, we found low rates of CRB without the routine use of antimicrobial catheter locking solutions, in keeping with published results from other centers (29,30). Adherence to a defined periprocedural catheter insertion and care protocol may be contributory. Use of 4% chlorhexidine, rather than the 2% concentrate, which is the recommended standard (31,32), may have further helped reduce infection rates. There are no trials comparing the two concentrations in CVCs for hemodialysis. Antibiotic cover and intranasal Naseptin at catheter insertion, screening and treatment for MRSA at the CVC exit site (33), preemptive antibiotic starts where clinically indicated, and the experience of hemodialysis nursing staff may have further influenced CRB rates favorably. Criteria for standardizing reporting of access-related infection are available (12,34), and yet there is heterogeneity of definitions used in published studies. We have used standardized definitions to allow appropriate comparisons.

Cumulative assisted primary patency rates over both the short and long term in this study are higher than those of previously published studies of TCs despite relatively low thrombolytic infusion efficacy (43% vs 95% [13] and

Table 4. Regression Analysis of Factors Affecting Primary Assisted TC Site Patency

Factor	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio	P Value	Hazard Ratio	P Value
Age (y)	1.00 [0.99–1.00]	.3	—	
Caucasian ethnicity	0.98 [0.78–1.22]	.8	—	
Diabetes mellitus	1.29 [1.02–1.64]	.03	1.24 [0.98–1.57]	.07
Hypertension	1.05 [0.83–1.32]	.7	—	
IHD	0.84 [0.67–1.06]	.1	—	
CrVD	0.98 [0.75–1.27]	.9	—	
PVD	0.90 [0.65–1.23]	.5	—	
Any previous CVC	1.22 [0.97–1.52]	.09	1.15 [0.92–1.44]	.2
Insertion by IR	1.44 [1.16–1.79]	.001	1.41 [1.13–1.77]	.002

Note.—Hazard ratios expressed with 95% confidence intervals in square brackets.

CrVD = cerebrovascular disease, IHD = ischemic heart disease, IR = interventional radiology, PVD = peripheral vascular disease.

82% [3513]), which may relate to the protocol used. Wivell et al (36) reported on 184 TCs in 132 patients with a 1-year cumulative assisted primary patency of 45%. Wang et al (37) studied 303 TCs in 200 patients and reported assisted primary patency rates of 60% at 1 year, 51.5% at 2 years, and 51.5% at 3 years. The higher prevalence of diabetes (46% vs 25%) in the study by Wang et al (37) may have adversely affected catheter patency, although they do not report this. Furthermore, the reported incidence of TC dysfunction in both studies was higher than that in our series (8.8 [36] and 0.8 [37] per 1,000 catheter days, respectively, vs 0.34 per 1,000 catheter days in our study). The cause for this is unclear but may relate to the level of experience of the hemodialysis staff at our center, which has much experience with catheter use as well as different definitions of CVC flow dysfunction and catheter locks used. Additionally, both studies above describe US populations with different ethnic casemixes, which may have affected catheter outcomes. A total of 37% of patients in the study by Wang et al (37) were African American as opposed to 20% in this study.

The use of CVCs for hemodialysis access has been associated with increased mortality in observational studies (38,39) and may relate to the vascular comorbidities of a patient population not suitable for arteriovenous access as well as the higher rates of infection associated with this form of hemodialysis access. Cumulative patient survival in our study compares very favourably with those in the UK registry data with a lower prevalence of CVC use (35% at 6 months, 30% at 1 year) (40). Improved patient survival at our center may relate to lower rates of CVC-related infection, coronary angiographic screening of transplant-listed patients older than 50 years, and our ethnic casemix that may be associated with longer survival on hemodialysis (41). We have previously shown that appropriate use of catheter salvage as opposed to replacement can be successful in approximately two thirds of cases (42), with no additional adverse effect of this strategy on patient survival or infective complications in contrast to published series

(43). Adoption of catheter salvage is likely to have had a positive effect on catheter patency rates reported above.

Long-term use of CVCs has been associated with central venous stenosis (44,45), although such lesions are also found in patients with no history of prior central catheters (46,47). The prevalence of symptomatic central venous stenosis in our cohort was 5%, although the prevalence of occult stenosis may be higher (47). This is in keeping with our current cohort (2005–2009 prevalence 7%, unpublished data). It is possible that low infection rates (48), the avoidance of temporary internal jugular hemodialysis catheters, and CVC design are contributory. The effect of radiologic rather than surgical insertion of TCs on assisted catheter patency possibly represents bias by indication, as these catheters were inserted in situations deemed to be more challenging (eg, numerous previous CVCs, presence of a cardiac pacemaker, established central venous stenosis). No patients died as a result of lack of vascular access throughout the study period.

Our study demonstrates excellent long-term outcomes using the TC system with good patient survival and hemodialysis adequacy and with low rates of CVC-related infection and symptomatic venous stenosis. Notably access-related bacteremia rates in this study are comparable with those reported with AVGs (25,49). Our data suggest that TCs can offer a viable, long-term alternative vascular access option in situations in which AVFs or AVGs are unsuitable or undesired.

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Appraising Stroke Risk in Maintenance Hemodialysis Patients: A Large Single-Center Cohort Study

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Background: Stroke incidence in hemodialysis patients is up to 10 times greater than in the general population and is associated with a worse prognosis. Factors influencing stroke risk by subtype and subsequent prognosis are poorly described in the literature.

Study Design: Retrospective single-center cohort study.

Setting & Participants: 2,384 established maintenance hemodialysis patients at a single center from January 1, 2002, to June 1, 2009.

Predictor: Patient demographics, comorbid conditions.

Outcomes: Incidence of acute stroke (*International Classification of Diseases, 9th Revision* codes 430, 431, 432.9, 433.1, and 434.1 with evidence of compatible neuroimaging), patient survival.

Measurements: Cumulative patient survival, incidence of acute fatal and nonfatal stroke.

Results: 127 strokes occurred during 9,541 total patient-years of follow-up. First (incident) stroke occurred at a rate of 14.9/1,000 patient years (95% CI, 12.2-17.9) with a predominance of ischemic compared with hemorrhagic subtypes (11.2 vs 3.7/1,000 patient-years). 54% of hemorrhagic strokes occurred in patients of South Asian ethnicity compared with ischemic strokes, which occurred predominantly in white patients (45% of events). Diabetes mellitus (HR, 1.92; 95% CI, 1.29-2.85; $P = 0.001$) and prior cerebrovascular disease (HR, 4.54; 95% CI, 3.07-6.72; $P < 0.001$) were independently associated with incident cerebrovascular accident on multivariate analysis. Acute stroke was associated with worse patient survival (HR, 3.26; 95% CI, 2.47-4.30; $P < 0.001$) and overall 1-year mortality of 24%, which was significantly worse in patients with hemorrhagic events (39% vs 19% mortality for ischemic subtypes). Serum albumin level >3.5 g/L (HR, 0.38; 95% CI, 0.19-0.76; $P = 0.007$) and C-reactive protein level >3.0 mg/l (HR, 1.36; 95% CI, 1.12-1.64; $P = 0.002$) influenced survival after stroke on multivariate analysis.

Limitations: Retrospective analysis of data cannot prove causality.

Conclusions: The high incidence of stroke in hemodialysis patients is associated with high mortality, especially hemorrhagic subtypes. Strict management of hypertension, better appreciation of hemodialysis anticoagulation, and large-scale interventional studies are urgently required to direct prevention and treatment of this significant disease.

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INDEX WORDS: Stroke; hemodialysis; ethnicity; hemorrhage.

Stroke (cerebrovascular accident [CVA]) is the leading cause of long-term disability and the second and third leading causes of death in the United States and United Kingdom, respectively.^{1,2} The incidence of CVA in the dialysis population is 5-10 times higher than in the general population and is associated with a worse prognosis.³⁻⁵ This propensity for CVA has been related to the higher prevalence of risk factors recognized in the general population, such as hypertension and diabetes mellitus, and moreover, factors specific to patients on renal replacement therapy for end-stage renal disease; namely, accelerated calcific arteriosclerosis, the effect of uremic toxins, dialysis techniques, vascular access, and use of anticoagulants to maintain flow in the extracorporeal circuit.

Effective treatments also may differ greatly, and although therapeutic trials of statins show benefit in CVA prevention in the general population, trials in dialysis populations have not been as successful.^{6,7} The use of warfarin in patients with atrial fibrillation reduces the risk of thromboembolic CVA in the gen-

eral population⁸; however, one study has suggested that with hemodialysis (HD), warfarin leads to increased risk of CVA.⁹

There are notable differences in the type of CVA in HD patients versus the general population, with a higher prevalence of hemorrhagic CVA. This is particularly marked in early Japanese studies, which may reflect uncontrolled hypertension in these cohorts.^{3,10}

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as well as a genetic predisposition.¹¹ Ethnic variations in CVA incidence and subtype are well described in the general population¹²⁻¹⁴ and may relate to socioeconomic factors and genotypic variations.¹⁵ Most available studies describe dialysis populations from the United States and Japan only.^{3-5,10,16-18} There are relatively few US data restricted to HD populations and even fewer European data.

Our large study aimed to comprehensively examine the characteristics and incidence of CVA, risk factors at baseline, and effect of CVA on patient survival in a large and multiethnic urban population in the United Kingdom.

METHODS

Study Design

We studied the entire cohort of prevalent and incident HD patients at our center who were established for more than 90 days on thrice-weekly maintenance HD therapy during the study period from January 1, 2002, through June 1, 2009. Paper and electronic records relating to outpatient and inpatient episodes were examined, and laboratory, radiologic, and dialysis data were analyzed. CVA was an acute neurologic event more than 24 hours in duration with compatible findings on neuroimaging (computed tomography and/or magnetic resonance imaging). Ischemic CVA was defined by the *International Classification of Diseases, Ninth Revision (ICD-9)*: coding criteria 433.1 and 434.1), and radiologic confirmation of infarction was mandated. Hemorrhagic CVA was defined as intracerebral and/or subarachnoid hemorrhage (*ICD-9* codes 430, 431, and 432.9). Subdural hematoma (*ICD-9* codes 432.0 and 432.1) was excluded from the analysis.

Patient characteristics were captured at dialysis therapy initiation and included age, sex, ethnicity, cause of end-stage renal disease, diagnosis of diabetes mellitus, hypertension (persistent postdialysis blood pressure [BP] $\geq 140/90$ mm Hg in the context of clinical euolemia and/or an enduring requirement for antihypertensive therapy), ischemic heart disease (presence of current anginal chest pain, prior myocardial infarction, or coronary intervention with percutaneous and/or bypass grafting), peripheral vascular disease (clinical and/or radiologic evidence of aortic or distal arterial atherosclerotic disease), and cerebrovascular disease (CVA or transient ischemic attack). Similarly, treatment details were recorded, including time on HD therapy and erythropoiesis-stimulating agent (ESA), aspirin, clopidogrel, and warfarin use.

Outcome was defined as the incidence of fatal and nonfatal hospitalized CVAs. For patients identified with acute CVA during the study period, additional laboratory data were examined at the time of the event (hemoglobin, platelet count, coagulation profile, albumin, cholesterol, ferritin, bone profile, and parathyroid hormone) and pre- and postdialysis BP was assessed (the average of 3 BP readings at that event was taken as representative).

Statistical Analyses

Descriptive statistics are expressed as mean $\pm$ standard deviation. Continuous and categorical variables were compared using *t* test and χ^2 or Mann-Whitney *U* test, respectively. Timeline incidence data were analyzed using a Poisson model and expressed with 95% confidence intervals (CIs). Patient survival analysis was performed using the Kaplan-Meier method and comparisons were made using log-rank test.

To identify factors significantly associated with first (incident) all-cause CVA as well as each stroke subtype (ischemic and hemor-

rhagic), we used a competing-risks approach to account for the higher rate of mortality compared with stroke in dialysis patients. Age-adjusted Cox regression models were used, including variables such as sex, comorbid conditions (as previously described), and vascular access type and censoring for death, change in dialysis modality or transplant, transfer out of center, dialysis therapy withdrawal, and loss to follow-up. Time origin was defined as the date of HD therapy initiation. Patients with a history of stroke were excluded from this analysis.

Subsequently, the influence of these baseline clinical factors on mortality in the entire study cohort was examined using Cox models in which new acute stroke was incorporated as a time-dependent variable. Factors influencing subsequent survival in patients with first (incident) stroke also were examined using Cox models including variables captured at time of event, including age, sex, comorbid conditions, BP, C-reactive protein level >3 mg/L, ferritin level, total cholesterol level, albumin level >3.5 g/dL, hemoglobin level, and erythropoietin dose.

All models met assumptions of proportionality. Factors identified by univariate analysis with $P < 0.1$ were examined using multivariate analysis. A backwards selection procedure was applied to this multivariate model to identify risk factors of significance.

$P < 0.05$ from 2-sided tests was defined as statistically significant. All statistical analyses were performed using STATA software, version 10.1 (StataCorp, www.stata.com).

RESULTS

There were 2,474 maintenance HD patients during the period under study, with 9,541 patient-years of follow up. Of these, 2,384 patients (96%) had complete demographic and clinical data. This formed the study cohort, with a total of 7,326 patient-years of follow-up and mean follow-up of 3.0 ± 2.1 years per patient (Table 1). A total of 17% of the cohort received a kidney transplant, with 5% transferring care out of center during the period of study. Characteristics of this group were representative of national cohorts reported by the UK Renal Registry, except for significant representation of South Asian and black patients and a significant proportion of patients dependent on central venous catheters as definitive vascular access.¹⁹

There were 145 CVAs during the study period. Eighteen of 145 CVAs (12%) occurred within the first 90 days of HD treatment (13 ischemic and 5 hemorrhagic) and were excluded from analysis. A total of 127 CVA events were studied in depth in 121 patients with an overall incidence of 17.3/1,000 patient-years (95% CI, 14.5-20.6). Twelve patients had experienced at least one acute stroke before 2002, leaving 109 CVAs as the first event for patients in the period of study.

Compared with the general HD population, patients who experienced CVA were significantly older at time of dialysis therapy initiation (62.9 ± 12.7 vs 58.2 ± 15.9 years; $P = 0.01$), with a mean age at the time of CVA of 64.5 ± 12.5 years. Diabetes was the cause of end-stage renal disease in 61 of 121 (51%) patients

Table 1. Comparative Demographics of Study Cohorts

	Total Population (N = 2,384)	Stroke Cohort (n = 121)	Nonstroke Cohort (n = 2,263)	P
Age (y)	58.2 ± 15.9	62.9 ± 12.7	58.0 ± 16.0	0.009
Prevalent patients ^a	28.0	23.1	28.2	0.2
HD vintage ^b	3.4 ± 3.2	1.6 ± 1.4	3.5 ± 3.2	0.002
Ethnicity				
White	1,008 (42.3)	48 (39.7)	960 (42.4)	0.6
African-Caribbean	440 (18.4)	24 (19.8)	416 (18.4)	0.7
South Asian	808 (33.9)	43 (35.5)	765 (33.8)	0.7
Other	128 (5.4)	6 (5.0)	122 (5.4)	0.8
Comorbid conditions				
Diabetes	919 (38.5)	61 (50.4)	858 (37.9)	0.006
IHD	764 (32.0)	49 (40.5)	715 (31.6)	0.04
Hypertension	1,374 (57.6)	73 (60.3)	1,301 (57.5)	0.5
PVD	304 (12.7)	13 (10.7)	291 (12.9)	0.5
Prior CrVD	204 (8.5)	36 (29.7)	168 (7.4)	<0.001
Atrial fibrillation	197 (8.3)	14 (11.6)	183 (8.1)	0.2
Antiplatelet/anticoagulant treatment				
Aspirin	881 (36.9)	53 (43.8)	828 (36.6)	0.1
Clopidogrel	229 (9.6)	19 (15.7)	210 (9.3)	0.02
Warfarin	73 (3.1)	0	73 (3.2)	0.04
Vascular access				
AVF	642 (26.2)	16 (13.2)	626 (27.7)	<0.001
AVG	11 (0.5)	0	11 (0.5)	0.9
CVC	1,731 (72.6)	105 (86.8)	1,626 (71.9)	<0.001

Note: Continuous variables are shown as mean ± standard deviation; categorical variables, as percentage or number (percentage).

Abbreviations: AVF, arteriovenous fistula; AVG, arteriovenous graft; CrVD, cerebrovascular disease; CVC, central venous catheter; HD, hemodialysis; IHD, ischemic heart disease; PVD, peripheral vascular disease.

^aAs of study start (January 1, 2002).

^bPrevalent patients only.

with CVA; hypertension, in 15 of 121 (12%); and polycystic kidney disease, in 4 of 121 (3%). Patients with CVA had a higher prevalence of diabetes, ischemic heart disease, and established cerebrovascular disease. CVA was not more prevalent in patients with atrial fibrillation. There were significantly more CVA events in the group receiving clopidogrel (15.7% vs 9.3%; $P = 0.02$), but no propensity to hemorrhagic over ischemic CVA was detected. There was a lower prevalence of arteriovenous fistula use in the CVA group (Table 1).

Overall, 68% (86 of 121) of all CVAs were ischemic, with an incidence of 11.7/1,000 patient-years (95% CI, 9.4-14.5), and 32% (41 of 121) were hemorrhagic, with an incidence of 5.6/1,000 patient-years (95% CI, 4.0-7.6). Patients with hemorrhagic CVA were significantly younger than those with ischemic CVA (mean age, 59.9 ± 13.4 vs 67.5 ± 11.7 years; $P = 0.004$; Table 2). Of ischemic CVAs, 45% occurred in patients of white ethnicity and most hemorrhagic CVAs (54%) occurred in South Asian patients. On subanalysis by ethnic group, there were no significant differences in any demographic or clinical features listed in Table 2. Patients with hemorrhagic CVA

irrespective of ethnicity had significantly higher diastolic BPs both pre- and postdialysis and a trend to higher systolic readings (Table 2). There were no other significant differences between the ischemic and hemorrhagic groups in comorbid conditions, hematologic or biochemical profiles (including markers of metabolic bone disease, nutrition, and inflammation), HD treatment (including Kt/V and HD dry weight), or ESA treatment. There was no significant difference in antiplatelet agent use between the 2 groups and no patient who experienced a CVA was on warfarin therapy.

Patients who experienced their first (incident) CVA during the study period were examined separately. Incident CVA occurred in 109 patients at a rate of 14.9/1,000 patient-years (95% CI, 12.2-17.9); 82 events were ischemic and 27 were hemorrhagic. The rate of incident ischemic CVA was 11.2/1,000 patient-years (95% CI, 8.9-13.9), and hemorrhagic CVA, 3.7/1,000 patient-years (95% CI, 2.5-5.4). Univariate analysis identified older age, diabetes mellitus, prior cerebrovascular disease (all $P < 0.001$), hypertension ($P = 0.01$), presence of ischemic heart disease ($P = 0.02$), and use of antiplatelet therapy ($P = 0.04$) as

Table 2. Patient Characteristics and Clinical Features of Patients at Time of CVA by Subtype

	Ischemic CVA (n = 86)	Hemorrhagic CVA (n = 41)	P
Age at CVA onset (y)	67.5 ± 11.7	59.9 ± 13.4	0.004
Ethnicity			
White	39 (45.3)	11 (26.8)	0.04
African-Caribbean	19 (22.1)	5 (12.2)	0.3
South Asian	25 (29.1)	22 (53.7)	0.007
Other	3 (3.5)	3 (7.9)	0.4
Comorbid conditions			
Diabetes	50 (57.5)	24 (58.5)	0.9
IHD	41 (47.1)	13 (31.7)	0.09
Hypertension	55 (63.2)	33 (80.5)	0.06
PVD	12 (13.8)	3 (7.3)	0.4
Laboratory parameters			
Hemoglobin (g/dL)	12.0 ± 1.7	11.9 ± 1.9	0.9
Platelet count (× 10 ⁹ /L)	193 ± 79	186 ± 63	0.6
Prothrombin time (s)	11.8 ± 1.8	11.8 ± 1.5	0.8
APTT (s)	34.8 ± 13.5	32.6 ± 12.3	0.7
Fibrinogen (g/L)	4.10 ± 0.88	4.00 ± 0.94	0.5
Cholesterol (mmol/L)	3.7 ± 0.9	3.4 ± 1.0	0.2
Albumin (g/dL)	3.2 ± 0.6	3.3 ± 0.5	0.3
Corrected Ca (mmol/L)	2.28 ± 0.22	2.34 ± 0.15	0.1
Phosphate (mmol/L)	1.31 ± 0.43	1.25 ± 0.55	0.5
CRP (mg/L)	32 ± 23	27 ± 16	0.5
Ferritin (μg/L)	597 ± 285	798 ± 1,213	0.7
Hemodialysis treatment			
HD vintage (y)	2.9 ± 2.3	3.1 ± 2.8	0.9
Dry weight (kg)	66.4 ± 13.6	62.4 ± 14.7	0.2
Pre-HD SBP (mm Hg)	156 ± 29	168 ± 32	0.06
Pre-HD DBP (mm Hg)	82 ± 18	92 ± 19	0.008
Post-HD SBP (mm Hg)	151 ± 31	162 ± 25	0.07
Post-HD DBP (mm Hg)	79 ± 17	89 ± 12	0.02
ESA treatment			
Dose (μg) ^a	54.2 ± 26.0	48.2 ± 26.6	0.3
Dose per weight (μg/kg) ^a	0.85 ± 0.44	0.75 ± 0.45	0.3
Antiplatelet treatment			
Aspirin	35 (40.7)	11 (26.8)	0.1
Clopidogrel	10 (11.6)	1 (2.4)	0.1
Aspirin & clopidogrel	6 (7.0)	3 (7.3)	0.9

Note: Continuous data expressed as mean ± standard deviation; categorical data given as number (percentage). Conversion factors for units: corrected Ca in mmol/L to mg/dL, ×4.008; phosphate in mmol/L to mg/dL, ×3.097; albumin and hemoglobin in g/dL to g/L, ×10; cholesterol in mmol/L to mg/dL, ×38.67. No conversion necessary for ferritin in μg/L and ng/mL.

Abbreviations: APTT, activated partial thromboplastin time; Ca, calcium; CRP, C-reactive protein; CVA cerebrovascular accident; DBP, diastolic blood pressure; ESA, erythropoiesis-stimulating agent; HD, hemodialysis; IHD, ischemic heart disease; PVD, peripheral vascular disease; SBP, systolic blood pressure.

^aAll patients received darbepoetin once weekly intravenously.

risk factors for incident CVA (Table 3). On multivariate analysis, only diabetes mellitus and prior cerebrovascular disease remained independently associated

with incident CVA risk. Diabetes mellitus (hazard ratio [HR], 1.85; 95% CI, 1.13-3.03; *P* = 0.01) and prior cerebrovascular disease (HR, 5.48; 95% CI, 3.40-8.82; *P* < 0.001) were the only factors associated with risk of first ischemic CVA on multivariate analysis. In contrast, increased risk of first hemorrhagic CVA was associated with the presence of hypertension (HR, 4.26; 95% CI, 1.51-12.00; *P* = 0.06) and, to a lesser extent, prior cerebrovascular disease (HR, 2.31; 95% CI, 1.04-5.17; *P* = 0.04).

A total of 726 of 2,384 (30.5%) patients died during the study period, of whom 55 (7.6%) died after acute CVA. Specifically, mortality was 24% at 1 year after acute CVA, 46% at 2 years, and 60% at 3 years compared with 6%, 12%, and 19%, respectively, in incident HD patients at our center. Hemorrhagic CVA was associated with markedly higher mortality at 30 days after the acute event (32% vs 7% for ischemic CVA; *P* < 0.001). One-year mortality was 39% versus 19% at 1 year, 51% versus 44% at 2 years, and 79% versus 53% at 3 years.

Multivariate survival analysis of the entire study cohort (Table 4) showed that the occurrence of acute stroke during the study period had a profound negative effect on survival (HR, 3.26; 95% CI, 2.47-4.30; *P* < 0.001). Additionally, diabetes mellitus (*P* < 0.001), peripheral vascular disease (*P* < 0.001), and male sex (*P* = 0.005) were associated with worse patient survival, whereas African-Caribbean ethnicity (*P* < 0.001) and aspirin use (*P* < 0.001) were associated with better survival. In a subanalysis of patients experiencing their first ever stroke (*n* = 109; Table 5), serum albumin level >3.5 g/dL and aspirin use at time of acute stroke were associated a lower subsequent risk of death (*P* = 0.007 and *P* = 0.03, respectively), whereas C-reactive protein level >3.0 mg/L was associated with worse poststroke survival (*P* = 0.002). Factors such as age at CVA onset, diabetes, ischemic heart disease, sex, ethnicity, hemoglobin level, and darbepoetin dose did not significantly affect mortality.

DISCUSSION

In the largest European study of CVA incidence in HD patients to our knowledge, we report an almost 10-fold higher incidence of CVA compared with the general population.²⁰ This order of magnitude is similar to published series and further emphasizes the large burden of cerebrovascular disease for patients on dialysis therapy.^{3,5,16-18,21} Furthermore, we show the profound impact of acute stroke on HD patient survival that is in itself an order of magnitude greater than other traditional risk factors.

The published literature describes cohorts with different demographic and clinical characteristics that make comparisons difficult, with most work done in

Table 3. Risk Factors for First (Incident) Stroke

Risk Factors	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age at HD start (/y)	1.03 (1.01-1.04)	<0.001	1.02 (0.99-1.03)	0.1
Male sex	1.25 (0.85-1.83)	0.3	—	—
Ethnic background				
African-Caribbean	1.00 (reference)			
White	1.41 (0.82-2.43)	0.2	—	—
South Asian	1.41 (0.81-2.45)	0.2	—	—
Comorbid conditions				
Diabetes	2.82 (1.93-4.14)	<0.001	1.92 (1.29-2.85)	0.001
Hypertension	1.67 (1.21-2.49)	0.01	1.34 (0.90-2.01)	0.2
PVD	1.29 (0.77-2.13)	0.3	—	—
IHD	1.59 (1.09-2.31)	0.02	1.07 (0.72-1.61)	0.7
Established CrVD ^a	5.92 (4.09-8.59)	<0.001	4.54 (3.07-6.72)	<0.001
Therapies				
Aspirin	1.48 (1.02-2.14)	0.04	0.96 (0.65-1.43)	0.9
Clopidogrel	1.70 (1.03-2.82)	0.04	1.11 (0.65-1.88)	0.7
Warfarin	0.52 (0.13-2.12)	0.4	—	—

Note: N = 109.

Abbreviations: CI, confidence interval; CrVD, cerebrovascular disease; HD, hemodialysis; HR, hazard ratio; IHD, ischemic heart disease; PVD, peripheral vascular disease.

^aDefines clinically manifest CrVD (transient ischemic attack) before study period.

US and Japanese populations (Table 6). As in our study, ischemic CVA remains the most common subtype in dialysis patients in all series and national trends suggest an increasing prevalence.^{5,17,18} In the Japanese HD population, this trend away from hemor-

rhage was described by Toyoda et al¹⁸ and attributed to more conservative dialysis circuit anticoagulation, better BP control (mean BP on admission, 195/97 mm Hg in 1980-1996 vs 179/87 mm Hg in 1997-2002; $P < 0.005$), and a more Westernized lifestyle. We

Table 4. Association of New Acute CVA and Baseline Clinical Characteristics on Age-Adjusted Mortality in the Study Cohort

Risk Factors	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P	HR (95% CI)	P
Acute stroke	3.44 (2.61-4.53)	<0.001	3.26 (2.47-4.30)	<0.001
Male sex	1.25 (1.08-1.45)	0.003	1.24 (1.06-1.43)	0.005
Ethnicity				
White	1.00 (reference)		1.00 (reference)	
African-Caribbean	0.66 (0.53-0.83)	<0.001	0.67 (0.54-0.88)	<0.001
South Asian	0.86 (0.73-1.02)	0.09	0.86 (0.72-1.02)	0.08
Other	0.58 (0.29-1.17)	0.1	—	—
Comorbid conditions				
Diabetes	1.43 (1.23-1.66)	<0.001	1.39 (1.19-1.62)	<0.001
Hypertension	1.02 (0.88-1.19)	0.7	—	—
PVD	1.73 (1.46-2.06)	<0.001	1.59 (1.33-1.90)	<0.001
IHD	1.17 (1.01-1.36)	0.04	1.10 (0.93-1.30)	0.3
Prior CrVD	1.14 (0.96-1.36)	0.1	—	—
Antiplatelet treatment				
Aspirin	0.80 (0.69-0.93)	0.003	0.71 (0.61-0.83)	<0.001
Clopidogrel	0.96 (0.76-1.21)	0.7	—	—

Note: N = 2,384.

Abbreviations: CI, confidence interval; CrVD, cerebrovascular disease; CVA, cerebrovascular accident; HR, hazard ratio; IHD, ischemic heart disease; PVD, peripheral vascular disease.

Table 5. Association of Risk Factors at Time of Acute CVA and Subsequent Mortality

Risk Factors	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age (/y)	1.01 (0.98-1.03)	0.6	—	—
Male sex	1.03 (0.59-1.80)	0.9	—	—
HD vintage (/y)	1.11 (0.82-1.51)	0.5	—	—
Comorbid conditions				
Diabetes	1.30 (0.76-2.22)	0.3	—	—
Hypertension	1.20 (0.68-2.12)	0.5	—	—
PVD	1.97 (1.01-3.82)	0.05	1.64 (0.80-3.33)	0.2
IHD	1.09 (0.65-1.84)	0.7	—	—
Prior CrVD	1.35 (0.67-2.76)	0.4	—	—
Antiplatelet treatment				
Aspirin	0.54 (0.31-0.92)	0.03	0.54 (0.30-0.96)	0.03
Clopidogrel	1.84 (0.87-3.90)	0.1	1.50 (0.69-3.27)	0.3
Albumin >3.5 g/dL	0.42 (0.23-0.80)	0.008	0.38 (0.19-0.76)	0.007
Hemoglobin (/1 g/dL)	0.92 (0.78-1.08)	0.3	—	—
ESA dose per weight (/1 µg/kg)	0.82 (0.52-1.25)	0.3	—	—
CRP >3.0 mg/L	1.40 (1.15-1.70)	0.001	1.36 (1.12-1.64)	0.002
Ferritin (/1 µg/L)	1.00 (0.99-1.00)	0.6	—	—
Cholesterol (/1 mmol/L)	0.86 (0.63-1.18)	0.3	—	—
Pre-HD SBP (/1 mm Hg)	1.00 (0.99-1.01)	0.7	—	—
Pre-HD DBP (/1 mm Hg)	0.99 (0.97-1.02)	0.5	—	—
Post-HD SBP (/1 mm Hg)	1.00 (0.99-1.00)	0.4	—	—
Post-HD DBP (/1 mm Hg)	1.00 (0.98-1.01)	0.6	—	—

Note: Conversion factors for units: albumin and hemoglobin in g/dL to g/L, $\times 10$; cholesterol in mmol/L to mg/dL, $\times 38.67$. No conversion necessary for ferritin in µg/L and ng/mL.

Abbreviations: CI, confidence interval; CRP, C-reactive protein; CrVD, cerebrovascular disease; DBP, diastolic blood pressure; ESA, erythropoiesis-stimulating agent; HD, hemodialysis; HR, hazard ratio; IHD, ischemic heart disease; PVD, peripheral vascular disease; SBP, systolic blood pressure.

report an overall CVA incidence of 17.3/1,000 patient-years and in keeping with the Japanese literature,^{10,18} but markedly lower than US rates.^{5,9,17} Sozio et al⁵ report a high incidence of CVA at 49/1,000 patient

years in their HD and peritoneal dialysis population, which probably had a greater arteriopathic burden with a similar prevalence of prior cerebrovascular disease compared with our own (17% vs 16%, respec-

Table 6. Major Published Studies on CVA in Hemodialysis Patients

Study	Design	Era	Dialysis Patients (n)	No. CVA Events	CVA Incidence	Predominant Subtype
Iseki et al (1993) ³²	Prospective cohort	1988-1991	1,609 (all HD)	41	11.5	Hemorrhagic (4×)
Kawamura et al (1998) ³	Retrospective cohort	1971-1994	1,064 (all HD)	85	13.2	Hemorrhagic (2.5×)
Iseki et al (2000) ¹⁰	Prospective cohort	1988-1998	3,741 (all HD)	271	17.2	Hemorrhagic (1.7×)
Seliger et al (2003) ¹⁷	Retrospective, USRDS	1993-1999	8,920 (89% HD)	915	33.1	Ischemic (5.5×)
Toyoda et al (2005) ¹⁸	Retrospective cohort	1980-2002	1,740 (all HD)	151	13.0	Ischemic in contemporary cohort ^a
Sozio et al (2009) ⁵	Prospective cohort, CHOICE	1995-2004	1,041 (74% HD)	200	49	Ischemic (6.7×)
Chan et al (2009) ⁹	Retrospective cohort	2003-2007	1,671 (all HD and w/ AF)	102	45	Ischemic (3×)
Sanchez-Perales (2010) ²¹	Retrospective cohort	1999-2005	449 (81% HD)	30 (all ischemic)	24.1	Ischemic subtype only

Note: The study by Delmez et al¹⁶ was not included because it did not report on CVA incidence or subtype.

Abbreviations: AF, atrial fibrillation; CHOICE, Choices for Healthy Outcomes in Caring for ESRD; CVA, cerebrovascular accident; HD, hemodialysis; USRDS, US Renal Data System.

^aOlder cohort (1980-1996) had higher incidence of hemorrhagic CVA.

tively), but a greater prevalence of diabetes (54% vs 39%), ischemic heart disease (44% vs 32%), and peripheral vascular disease (26% vs 13%). Chan et al⁹ reported on a selected older group of HD patients (mean age, 72 vs 58 years in our study), all of whom had atrial fibrillation and a higher prevalence of diabetes and coronary disease. Predictably, overall CVA incidence also was high in this group of patients enriched with risk factors for vascular events at 45/1,000 patient-years, but is unlikely to be representative of the HD population as a whole.

The higher incidence of all-cause CVA in the United States may reflect the much higher percentage of African American patients in US cohorts (28%-40% of the dialysis population)^{5,17} and the relative paucity of patients of South Asian ethnicity (<5% of the dialysis population). Although patient ethnicity was not associated independently with an overall increased risk of CVA in our study, African American ethnicity frequently has been associated with a higher risk of stroke in the general population.²² In HD patients, Seliger et al¹⁷ studied US Renal Data System data and identified African American ethnicity as an independent risk factor for stroke in patients who had no documented cardiovascular disease, but this was not the case in those with this diagnosis. The reason for this is unclear, and the investigators speculated that it could relate to underdiagnosis of this condition in this subgroup.

Hemorrhagic CVAs accounted for 32% of events and were more prevalent in younger and more hypertensive patients. More than half the patients with hemorrhagic CVAs were of South Asian ethnicity, suggesting an ethnic predisposition to this type of CVA. This contrasted with the predominance of ischemic CVAs in white patients. We did not show inter-ethnic differences in BP profile, serum albumin level, dialysis adequacy, hematologic parameters, or ESA dose. Despite the relatively small numbers involved, this novel finding gives support to the idea of a genetic predisposition to CVA subtypes.^{11,13,14} The pathogenic mechanism may be classic hypertensive intracerebral hemorrhage or hemorrhagic conversion of a prior ischemic CVA exacerbated by dialysis anticoagulation. Irrespective of ethnicity, patients with hemorrhagic CVA presented with significantly higher BP compared with those with ischemic events both pre- and postdialysis, a finding in keeping with published data. Hypertension is an established modifiable risk factor that remains a significant treatment challenge.^{10,17,18}

Acute stroke constitutes a highly significant clinical event for HD patients, conferring a 3-fold higher risk of death in our study independently of the effects of traditional risk factors. Overall patient survival at 1

year after all-cause CVA was 69%. The prognosis for hemorrhagic CVA has been extremely poor, with case fatality rates reaching 90% in reported series.^{5,10} Our data reaffirm this with a higher fatality rate of 32% versus 7% at 30 days ($P < 0.001$) and 39% versus 19% at 1 year ($P < 0.001$).

Although previous studies report a higher prevalence of prior cerebrovascular disease in patients who subsequently experienced a CVA, the effect of this factor has not been fully evaluated previously.^{5,21} It is the dominant comorbid risk factor for CVA in our study (Table 3) and independently increased the risk more than 4-fold. This finding suggests that appropriate screening and treatment measures for prior transient ischemic attack may strongly influence subsequent CVA incidence in the dialysis population in a manner similar to the general population.²³ Diabetes mellitus was the only other clinical factor associated with higher risk of CVA (Table 3) and is in keeping with published studies.^{5,21}

Although aspirin treatment did not associate with an increased risk of all-cause CVA, clopidogrel treatment was associated with higher risk in our study, although this result needs to be interpreted with caution due to the relatively small numbers involved and potential confounding by indication. Neither antiplatelet treatment predisposed to hemorrhagic over ischemic CVA, and we did not have sufficient numbers for warfarin anticoagulation to comment with validity on its influence on CVA risk, unlike the cohort described by Chan et al.⁹

In contrast, aspirin treatment was associated with decreased mortality after CVA on univariate and multivariate analysis, an effect not seen with clopidogrel treatment. Although causality cannot be inferred from associations, particularly given the small numbers involved in this study, this finding is in keeping with recent studies in the general population.^{24,25} In addition, we confirm the association between low serum albumin level (<35 g/dL) and elevated C-reactive protein level, markers of malnutrition-inflammation syndrome, and worse survival.¹⁶ Although ESA use was associated with increased risk of stroke in nondialysis patients in TREAT (Trial to Reduce Cardiovascular Events With Aranesp Therapy),²⁶ there are fewer data for patients on HD therapy. Patients presenting with stroke in our study were receiving a slightly higher mean monthly dose of darbepoetin compared with the TREAT cohort (52 vs 44 $\mu\text{g}/\text{wk}$), but due to incomplete long-term ESA data for the entire cohort, rigorous examination of the associations between ESA dose and stroke incidence could not be performed. A recent post hoc analysis of TREAT data suggested that ESA use per se and not dose used influenced the risk of stroke.²⁷ We found no effect of ESA dose on

survival poststroke and there were no significant differences in ESA doses in patients presenting with ischemic as opposed to hemorrhagic stroke, suggesting that ESAs do not influence stroke subtype.

The strengths of this study include the large cohort size, long follow-up period, and uniform dialysis practices over time. We are limited to reporting associations and not causation because of the retrospective nature of this study, and these may be confounded by unidentified influences. Furthermore, each stroke subtype consists of multiple different pathophysiologic entities that may vary in causation and are not addressed as such in our analysis. Risk is calculated on the basis of comorbid conditions, biological factors, and treatment at baseline. Their variability over time has not been measured and this is a limitation in keeping with all published studies to date. However, our work allows a clinician a measure of risk based on factors that can be measured at a single clinic visit.

Clinical trials of CVA prevention in dialysis patients are urgently required given the high incidence and poor prognosis associated with this lesion. The AURORA (Assessment of Survival and Cardiovascular Events) Study of 2,776 HD patients randomly assigned to placebo or 10 mg of rosuvastatin showed no effect of statin therapy on the incidence of nonfatal CVA (12 vs 11/1,000 patient-years; $P = 0.42$).⁶ Overall incidence rates of CVA were not reported, the prevalence of established cerebrovascular disease is unclear, and notably, 76 of 174 (44%) CVAs were fatal. Results from AURORA and 4D (Die Deutsche Diabetes Dialyse Studie)⁷ were counterintuitive to our understanding of the prophylactic effect of statin therapy in patients with CVA based on studies of the general population.²⁸ The recent publication of results from SHARP (Study of Heart and Renal Protection), in which CVA was a component of the composite primary end point, indicate that statin and ezetimibe have a significant beneficial effect on the incidence of CVA irrespective of low-density lipoprotein cholesterol level.²⁹ Diabetes, older age, and established cerebrovascular disease are nonmodifiable risk factors for CVA in a number of studies, including our own.^{3,5,17,18,21} As in the general and chronic kidney disease populations,^{30,31} uncontrolled hypertension in dialysis patients is a significant modifiable risk factor for CVA, particularly hemorrhagic events.^{17,18,32} In the absence of appropriately powered large prospective trials, there is neither a recommended target level nor a form of treatment for BP control at present or evidence-based consensus on what measure of BP to use (eg, peridialytic, 24-hour ambulatory, or home BP readings), and we recommend appropriate clinical judgment. No studies to date of CVA in dialysis

patients have addressed this issue; therefore, the potential role of erythropoietin is unclear.

In the largest European study of CVAs in maintenance HD patients to date, we find a high incidence of events in this population that is associated with diabetes and prior cerebrovascular disease and appears to be influenced by ethnic factors, with a predilection of hemorrhagic CVAs in patients of South Asian ethnicity. CVA has a negative impact on patient survival, which is most marked with hemorrhagic events. The potential role of systemic inflammation, anemia, and bone mineral metabolism management is unclear. Large collaborative studies of the effect of clinical interventions, such as BP control, are required, with the aim of reducing the incidence of this significant pathologic state that affects dialysis patients worldwide.

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