Acute increases in serum creatinine after starting ACE inhibitor-based therapy and effects of its continuation on major clinical outcomes in type 2 diabetes: the ADVANCE trial

Short title: Increasing creatinine after starting ACEI

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Abstract

Discontinuation of angiotensin converting enzyme (ACE) inhibitor is recommended if patients experience ≥30% acute increase in serum creatinine after starting this therapy. However, the long term effects of its continuation or discontinuation on major clinical outcomes after increases in serum creatinine are unclear.

In the ADVANCE trial, 11,140 diabetes patients were randomly assigned to perindopril-indapamide or placebo after a 6-week active run-in period. The current study included 11,066 participants with two serum creatinine measurements recorded prior to and during the active run-in period (3 weeks apart). Acute increase in creatinine was determined using these two measurements and classified into four groups: increases in serum creatinine of <10%, 10-19%, 20-29%, and ≥30%. The primary study outcome was the composite of major macrovascular events, new or worsening nephropathy, and all-cause mortality.

An acute increase in serum creatinine was associated with an elevated risk of the primary outcome (p for trend <0.001). The hazard ratios were 1.11 (95% CI 0.97 to 1.28) for those with an increase of 10-19%, 1.34 (1.07 to 1.66) for 20-29%, and 1.44 (1.15 to 1.81) for ≥30%, compared with <10%. However, there was no evidence of heterogeneity in the benefit of randomized treatment effects on the outcome across subgroups defined by acute serum creatinine increase (p for heterogeneity = 0.94).

Acute increases in serum creatinine after starting perindopril-indapamide were associated with greater risks of subsequent major clinical outcomes. However, continuation of ACE inhibitor-based therapy reduced the long-term risk of major clinical outcomes, irrespective of acute increase in creatinine.

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Inhibition of the renin-angiotensin system (RAS) confers significant cardiorenal protective benefits and is considered an important component of treatment in people at high-risk of developing adverse cardiovascular and renal outcomes, including those with type 2 diabetes.[1-5] However, treatment with RAS inhibitors is also associated with acute increases in serum creatinine or a sudden decline in glomerular filtration rate, largely attributed to a RAS inhibition-induced decline in intraglomerular pressure.[1, 4-6] Thus discontinuation is recommended if patients experience ≥30% increase in serum creatinine.[7] Cessation of RAS inhibitors in response to such elevations may have important consequences for subsequent cardiovascular and renal risk with any potential cardiorenal protective effects from RAS inhibitors nullified.

There have been few studies assessing the relationship between RAS inhibition-induced acute changes in serum creatinine and longer-term clinical outcomes, and overall conclusions reached by prior studies have been conflicting. In addition, many of the prior studies were conducted in specific populations (e.g. patients with left ventricular systolic dysfunction and heart failure),[8-12] with limited generalizability to the broader population at high risk of cardiovascular disease. Conventionally, large acute increases in serum creatinine or fall in kidney function following RAS inhibition have been believed to be predictive of longer-term renal benefit with earlier, relatively smaller studies (n=40 [6] to 1,435 [13]) supporting these associations. Conversely, more recent studies have reported increased adverse cardiovascular and renal events associated with initial changes in serum creatinine or estimated glomerular filtration rate (eGFR).[14, 15] However, the long term effects of continuation or discontinuation of that therapy on major cardiovascular and renal outcomes after increases in serum creatinine are unclear.

We evaluated the associations of acute increases in serum creatinine after starting an ACE inhibitor-based therapy, and the subsequent effects of its continuation or discontinuation, with major clinical outcomes using data from the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial.

Methods

Study design and population

ADVANCE was a 2x2 factorial randomized controlled trial evaluating the effects of blood pressure (BP) lowering and intensive blood glucose lowering treatment on vascular outcomes in patients with type 2 diabetes. Detailed descriptions of the design have been published previously.[16-18] In brief, 12,877 potentially eligible participants entered a 6-week pre-randomization active run-in period during which all patients received a fixed-dose combination of the ACE inhibitor perindopril (2 mg) and the diuretic indapamide (0.625 mg). In participants previously taking ACE inhibitors, ACE inhibitors other than perindopril ceased and open-label perindopril (2 or 4 mg per day) was offered instead. All other treatments were continued at the discretion of the treating physician. Overall, a total of 11,140 individuals with type 2 diabetes aged ≥55 years at high risk of cardiovascular events (recruited from 215 centers in 20 countries) who adhered to, and tolerated, the 6-week perindopril-indapamide run-in therapy were randomized to a fixed-dose combination of perindopril (2 mg) and indapamide (0.625 mg) or matching placebo, and also to either a gliclazide (modified release)-based intensive glucose control regimen aiming to achieve a hemoglobin A1c ≤6.5 %, or standard glucose control based on local guidelines. The dose of randomized perindopril and indapamide treatment was doubled to 4 mg and 1.25 mg, respectively, 3 months after randomization. Ethics approval was obtained from the

institutional review board of each center, and all participants provided written informed consent.

Serum creatinine was measured (in μmol/L) before and during the active run-in period (3 weeks apart), 4 and 12 months after randomization, subsequent annual intervals and at the end of trial follow-up. Acute increases in serum creatinine were defined as the difference between the first two measurements, classified into 4 groups: <10%, 10-19%, 20-29%, and ≥30%. Only participants with these two measurements were included in these secondary analyses.

Study outcomes and follow-up

The primary study outcome of interest was the composite of major macrovascular events (defined as the composite of nonfatal and fatal myocardial infarction, nonfatal and fatal stroke or cardiovascular death), new or worsening nephropathy (defined as the development of macroalbuminuria, doubling of serum creatinine to a level of ≥200 μmol/L, requirement for renal-replacement therapy, or renal death) and all-cause mortality. Secondary outcomes included the individual components of the primary outcome: 1) major macrovascular events, 2) new or worsening nephropathy and 3) all-cause mortality. Participants were followed from their visit at trial randomization until the earliest of the first study event, death or the end of follow-up (Figure 1). Study events recorded during the randomized treatment phase were reviewed and validated by an independent end-point adjudication committee.

Statistical analysis

Continuous variables are reported as means with standard deviation (SD) for variables with approximately symmetric distributions. Results for variables with skewed distributions

are presented as median and interquartile interval and were transformed into natural logarithms before analysis. Linear trends across categories were tested by linear regression analysis and logistic regression analysis, as appropriate. Patient characteristics associated with acute elevations of serum creatinine over three weeks prior to randomization were assessed using multivariable linear regression models.

We described the time course of mean creatinine values graphically according to levels of acute increase in creatinine. Since some study participants had used ACE inhibitors before registering with ADVANCE, we also plotted this time course separately for those with and without prior ACE inhibitor use, as well as by randomized treatment.

Cox regression models were used to estimate hazard ratios (HRs) and their corresponding 95% CIs relating the level of acute creatinine increase to outcomes. Models were adjusted for age, sex and region of residence (Asia or other), duration of diabetes mellitus, history of macrovascular disease, current smoking, current alcohol consumption, body mass index, hemoglobin A1c, total cholesterol, triglyceride, eGFR (calculated using the CKD-EPI creatinine equation[19]), systolic BP, urine albumin-to-creatinine ratio (UACR) at registration, randomized blood pressure–lowering intervention, and randomized glucose control intervention. We also assessed continuous change in serum creatinine increase using restricted cubic spline regression models with knots placed at -10, 0, 10, 20, 30, and 40% increase. Unadjusted and multiple-adjusted linear regression models were used to explore the factors associated with an acute creatinine increase.

The effects of randomized treatment on outcomes were assessed by unadjusted Cox regression models according to subgroups defined by acute increases in serum creatinine, based on the intension-to-treat principle. Heterogeneity in the treatment effects between subgroups was tested by adding interaction terms to the relevant Cox models. We explored

potential modification of the association between acute serum creatinine increases (≥30% vs. <30%) and randomized treatment effects according to subsets of participants categorized by baseline eGFR (≥90, 60-89, and <60 ml/min/1.73m^2) and prior ACE inhibitor use at registration.

Statistical analyses were performed with SAS 7.11 (SAS Institute, Cary NC, USA) and Stata software (release 13, StataCorp, College Station, TX, USA). A two-sided p-value <0.05 was considered statistically significant.

Results

Patient characteristics

Of the 11,140 participants in the ADVANCE trial, 11,066 participants (99.3%) were eligible for inclusion in the present analysis. The mean age of the cohort was 66 years (SD 6), 42.5% were female and 32.1% had a history of macrovascular disease at registration (Table 1). The mean and median values of eGFR and UACR at registration were 75 ml/min/1.73m^2 (SD 18) and 15.0 μg/mg (inter-quartile range, 7.1-39.8), respectively, and the proportion of patients with eGFR <60 ml/min/1.73m^2 was 21.7%.

Changes in serum creatinine

Of the 11,066 participants included in the analysis, 530 (5%) experienced an increase in serum creatinine ≥30% over 3 weeks post registration; increases of 20-29%, 10-19% and <10% were observed in 5%, 16% and 75% of the study cohort, respectively, and the mean increase was 2.4 μmol/l (SD, 25.8). Participants with greater increases of serum creatinine were more often women (p for trend <0.001; Table 1), had higher levels of hemoglobin A_{1c} (p for trend=0.003) and eGFR (p for trend <0.001) and had an increased heart rate (p for trend <0.001).

Follow-up creatinine levels did not show substantial differences, irrespective of the levels of acute increase in serum creatinine (Figure S1 and S2).

Those already using ACE inhibitors had higher values of creatinine at registration (Figure S3A). Among participants subsequently randomized to the perindopril-indapamide treatment group, serum creatinine levels throughout the trial follow-up remained higher, compared with those subsequently randomized to placebo, regardless of ACE inhibitor use at registration. Although serum creatinine levels increased rapidly during the first 3 weeks after starting perindopril-indapamide, the change plateaued within a year in both randomized groups (Figure S3B).

Older age, longer duration of diabetes, presence of macrovascular disease, and higher levels of eGFR and UACR (p values for all variables <0.001) were predictive of acute serum creatinine increase (Table S1).

Association between acute increase in serum creatinine and clinical outcomes

Over a median follow-up of 4.4 years, 1,669 patients (15.1%) developed the primary outcome. There were 991 (8.9%) major macrovascular events, 396 (3.6%) new or worsening nephropathy events, and 869 (7.7%) deaths.

Acute increase in serum creatinine was subsequently associated with an elevated risk of the primary outcome (p for trend <0.001; Figure 2). The HRs were 1.11 (95% CI 0.97-1.28) for those with an increase of 10-19%, 1.34 (1.07-1.66) for those with 20-29% increase, and 1.44 (1.15-1.81) for those with ≥30% increase, compared with those with <10% increase. Similar associations were observed for major macrovascular events alone, new or worsening nephropathy alone, and all-cause mortality alone. Overall results were similar when analyses were repeated using continuous assessments of acute serum creatinine increase (Figure 3).

Randomized treatment effect of perindopril-indapamide according to acute increase in serum creatinine over 3 weeks prior to randomization

Overall, treatment with perindopril-indapamide therapy, compared with placebo, significantly reduced the risk of the primary outcome (HR 0.89, 95% CI: 0.81-0.98) and all-cause mortality (HR 0.85, 95% CI: 0.75-0.97). There was no evidence of heterogeneity of the effect of randomized treatment for any of the four outcomes shown in Figure 4 across subgroups defined by acute increase in serum creatinine (p for heterogeneity≥0.74).

Consistent results were observed when we assessed participants according to eGFR levels at registration (Figure S4) and ACE inhibitor use at registration (Figure S5).

Discussion

In this analysis of 11,066 patients with type 2 diabetes from a large RCT evaluating the effects of ACE inhibitor-based therapy, increased levels of acute serum creatinine after starting ACE inhibitor-based therapy were associated with greater risk of subsequent major clinical outcomes. However, the beneficial effects of perindopril-indapamide therapy were consistent across differing levels of acute increases of serum creatinine including increases of ≥30%. Our findings suggest that while initial short-term increases in serum creatinine beyond 30% (and indeed even 20%) are associated with less favorable prognosis, continuation of ACE inhibitor-based therapy in those who experience these levels of increase may be beneficial and reduce the long-term risk of major clinical outcomes.

Prior studies

A recent population-based study showed increased incidence of adverse cardiovascular and renal events associated with increases in serum creatinine of ≥30% in adults commencing ACE inhibitor or ARB treatment (incidence rate ratio for end-stage renal

disease in patients with serum creatinine increase ≥30% vs <30%: 3.43, 95% CI: 2.40 to 4.91).[14] On the other hand, prior studies in relatively small cohorts (n=40 [6] and 1,435 [13]) have shown initial decreases in eGFR to be associated with longer-term renal benefit. Our findings are largely consistent with the former study,[14] and differ from the latter two studies.[6, 13] Although the reason for the differences in the results is unclear, differences in patient populations (e.g. mean eGFR in RENAAL was 40 ml/min/1.73m^2) may explain these differences. However, neither of these previous studies assessed the randomized treatment effects of RAS inhibitors on subsequent outcomes according to levels of short-term RAS inhibitor-induced serum creatinine change.

In a recent analysis of two randomized trials (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial [ONTARGET] and the Telmisartan Randomized AssessmeNt Study in ACE iNtoleranT subjects with cardiovascular Disease [TRANSCEND]),[15] among 9,340 patients, 2-week changes in eGFR after commencement of treatment with telmisartan (40 or 80 mg) or ramipril (5 mg) were associated with increased risk (although, mostly not statistically significant) of cardiovascular and renal events. In addition, in a smaller subgroup of patients who received telmisartan (n=3217 to 5384), subsequent treatment effects of telmisartan did not significantly vary according to acute telmisartan-induced change in eGFR (e.g. p values for interaction for cardiovascular events and new micro- or macro albuminuria= 0.63 and 0.18, respectively). Our results also support continuation of RAS inhibitors even when patients experience an increase in serum creatinine, although careful monitoring of kidney function would then be appropriate.

Plausible explanations

There are several potential pathophysiological mechanisms explaining the association between acute increase in serum creatinine after starting ACE inhibitor-based therapy and

adverse clinical outcomes. First, acute increase in serum creatinine may reflect pre-existing renovascular and systemic vascular disease, which lead to long-term increased risk of cardiovascular disease. Second, the greater increases in serum creatinine may be attributed to increased glomerular filtration pressure (i.e. hyperfiltration) at baseline, which was associated with increased risk of cardiovascular disease.[20] Indeed, we observed a significant relationship between history of macrovascular disease, higher eGFR at baseline and acute increase in serum creatinine (Table S1). GFR of patients with these two conditions may be dependent on higher glomerular filtration pressure by angiotensin-induced constriction of the efferent glomerular arteriole, and thus leading to GFR reduction in response to the reduced glomerular pressure by RAS blockade-induced dilation. Taken together, acute increase in serum creatinine may be a risk marker of cardiovascular disease, and further investigation and intervention for the underlying risks should be considered once patients experience it.

Study strengths and limitations

Our study has assessed the potential differential impact of acute rises in serum creatinine following ACE inhibitor-based therapy on longer-term randomized ACE inhibitor-based treatment effects based on 1) a large participant population derived from an international, multicenter RCT assessing the effects of perindopril-indapamide combination therapy and 2) evaluation of the relationship between acute increases in serum creatinine and subsequent major clinical outcomes using categorical and continuous assessments of serum creatinine change.

However, our study has some limitations. First, our study cohort was derived from a clinical trial of patients with type 2 diabetes and thus results may not be representative of broader populations. Second, the rate of end-stage renal disease events in ADVANCE was relatively low (0.1% per year), possibly due to the fact that most had relatively well-

preserved kidney function (78.3% of the study participants had an eGFR of ≥60 ml/min/1.73m^2), which limited our ability to assess the effect of continued ACE inhibitor-based therapy treatment in patients who experience acute serum creatinine elevations of ≥30% on long-term renal outcome outcomes. Third, our study is complicated by the inclusion of subjects (43% of the total) who were already taking an ACE inhibitor at registration. However, these subjects showed similar changes in creatinine during the study, and similar effects of randomized therapy, to those who were not taking ACE inhibitors when the active run-in period began. Finally, randomized treatment of ADVANCE consisted of a combination of the ACE inhibitor perindopril and the diuretic indapamide. Thus, we cannot exclude the possibility that the diuretic contributed to the effects observed.

Perspectives

Acute increases in serum creatinine following treatment with fixed-dose perindopril-indapamide combination therapy in patients with type 2 diabetes were associated with greater risk of subsequent major clinical outcomes including major macrovascular and renal events and all-cause mortality. However, the beneficial effects of continuing long-term randomized treatment on major outcomes were consistent irrespective of the magnitude of acute increases in serum creatinine. This suggests that, even in patients with diabetes who experience more than a 30% acute increase in serum creatinine, the benefits of continuing ACE inhibitor-based therapy outweigh the risks.

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Novelty and Significance

What Is New?

- This secondary analysis of a randomized controlled trial, involving 11,066 patients with diabetes, showed that acute increases in serum creatinine after starting angiotensin converting enzyme (ACE) inhibitor-based therapy were associated with greater risks of subsequent major macrovascular, renal events and all-cause mortality.
- However, similar beneficial randomised treatment effects of the same therapy were observed, irrespective of the degree of acute increase in creatinine.

What Is Relevant?

- Discontinuation of ACE inhibitor is recommended if patients experience ≥30% acute increase in serum creatinine after starting this therapy.
- However, the long term effects of its continuation or discontinuation on major clinical outcomes after increases in serum creatinine are unclear.

Summary

Acute increases in serum creatinine after starting perindopril-indapamide were associated with greater risks of subsequent major clinical outcomes. However, continuation of ACE inhibitor-based therapy reduced the long-term risk of major clinical outcomes, irrespective of acute increase in creatinine.

Table 1: Characteristics of study participants at registration

	Acute increase in serum creatinine				
	≥30%	20-29%	10-19%	<10%	P value for trend
Number of participants	530 (4.8)	538 (4.9)	1,730 (15.6)	8,268 (74.7)	-
Demographic factors					
Age (years)	65 (6)	65 (6)	66 (6)	66 (6)	0.10
Female (n, %)	276 (52)	243 (45)	678 (39)	3,504 (42)	0.003
Residence in Asia (n, %)	326 (62)	261 (49)	560 (32)	2,985 (36)	<0.001
Medical and lifestyle history					
Duration of diabetes mellitus (years)	8.2 (6.5)	8.6 (6.5)	8.3 (6.6)	7.8 (6.3)	0.001
History of macrovascular disease at baseline (n, %)	165 (31)	180 (33)	582 (34)	2,628 (32)	0.52
Current smoking (n, %)	77 (15)	73 (14)	238 (14)	1,284 (16)	0.10
Current alcohol drinking (n, %)	108 (20)	139 (26)	563 (33)	2,557 (31)	<0.001
Risk factors					
SBP (mmHg)	145 (22)	146 (22)	146 (22)	145 (21)	0.22
DBP (mmHg)	80 (11)	80 (11)	81 (11)	81 (11)	0.54
Heart rate (bpm)	77 (11)	75 (12)	74 (12)	74 (12)	<0.001
Hemoglobin A_{1c} (%)	7.7 (1.7)	7.6 (1.6)	7.5 (1.5)	7.5 (1.5)	0.003
Total cholesterol (mmol/l)	5.3 (1.2)	5.1 (1.2)	5.1 (1.2)	5.2 (1.2)	0.32
Triglycerides* (mmol/l)	1.6 (1.1-2.2)	1.6 (1.1-2.4)	1.6 (1.1-2.3)	1.7 (1.2-2.3)	0.08
Body mass index (kg/m^2)	27.5 (5.1)	28.0 (5.5)	28.6 (5.2)	28.4 (5.2)	0.002
eGFR ($ml/min/1.73m^2$)	89 (18)	81 (17)	78 (16)	72 (17)	<0.001
UACR (µg/mg)	15.9 (7.8-49.5)	18.6 (8.0-48.2)	15.9 (7.1-43.3)	14.5 (7.1-38.0)	<0.001
Randomized treatments (n, %)					
Perindopril-indapamide	262 (49)	272 (51)	883 (51)	4,109 (50)	0.67
Intensive blood glucose control	260 (49)	274 (51)	861 (50)	4,138 (50)	0.83
Blood glucose-lowering treatments (n, %)					
Oral hypoglycemic agents†	496 (94)	489 (91)	1,562 (90)	7,510 (91)	0.17
Insulin	8 (2)	7 (1)	25 (1)	119 (1)	0.99
BP-lowering treatments (n, %)					
β-blocker	105 (20)	128 (24)	426 (25)	2,052 (25)	0.03
Calcium-channel blocker	179 (34)	176 (33)	522 (30)	2,531 (31)	0.14
Diuretics‡	112 (21)	113 (21)	360 (21)	2,032 (25)	<0.001
Angiotensin-converting enzyme inhibitors†	209 (39)	214 (40)	706 (41)	3,624 (44)	0.002
Angiotensin II receptor blockers	30 (6)	34 (6)	132 (8)	407 (5)	0.008
Other antihypertensive agents	77 (15)	70 (13)	177 (10)	1,056 (13)	0.99
Any BP-lowering agents†	378 (71)	398 (74)	1,293 (75)	6,244 (76)	0.03
Changes in risk factors					
First serum creatinine (µmol/L)	68.1 (21.0)	78.3 (22.3)	82.9 (27.0)	89.0 (24.8)	<0.001
Second serum creatinine (µmol/L)	113.3 (103.1)	96.9 (27.5)	94.3 (30.9)	85.8 (24.1)	<0.001

Mean values and their corresponding standard deviations (SDs) are presented for continuous variables unless described otherwise; *median values (interquartile interval [IQI[) are presented for triglycerides and urine albumin-creatinine-ratio (UACR), categorical variables are presented as numbers and percentages (n, %); eGFR=estimated glomerular

filtration rate; SBP=systolic blood pressure; †Randomized treatment with gliclazide was not included; ‡Randomized treatment with perindopril-indapamide was not included.

Figure legend

Figure 1: Identification of the cohort and study design

Figure 2: The association between acute increase in serum creatinine over 3 weeks prior to randomization and clinical outcomes over 4.4 years post randomization

Models were adjusted for age, sex, region of residence, duration of diabetes, history of macrovascular diseases, smoking habit, drinking habit, body mass index, hemoglobin A_{1c} level, total cholesterol, log-transformed triglyceride, estimated glomerular filtration rate (eGFR), systolic blood pressure and log-transformed urine albumin-to-creatinine ratio at registration, randomized blood pressure–lowering intervention, and randomized glucose control intervention.

Patients with missing values in covariates were excluded.

Figure 3: Spline curves assessing the association between continuous acute increases in serum creatinine and study outcomes

A) Combined major macrovascular events, new or worsening nephropathy, and all-cause mortality, B) major macrovascular events, C) new or worsening nephropathy, D) all-cause mortality; the circles represent the points at which knots were placed (-10, 0, 10, 20, 30, and 40% increase). The areas shaded in grey represent the 95% confidence intervals.

Models were adjusted for age, sex, region of residence, duration of diabetes, history of macrovascular diseases, smoking habit, drinking habit, body mass index, hemoglobin A_{1c}, total cholesterol, log-transformed triglyceride, estimated glomerular filtration rate, systolic

blood pressure, log-transformed urine albumin-to-creatinine ratio at registration, randomized blood pressure–lowering intervention, and randomized glucose control intervention.

Figure 4: Randomized treatment effects on clinical outcomes over 4.4 years post randomization according to acute increase in serum creatinine over 3 weeks prior to randomization

Active: perindopril-indapamide.

Figure 1

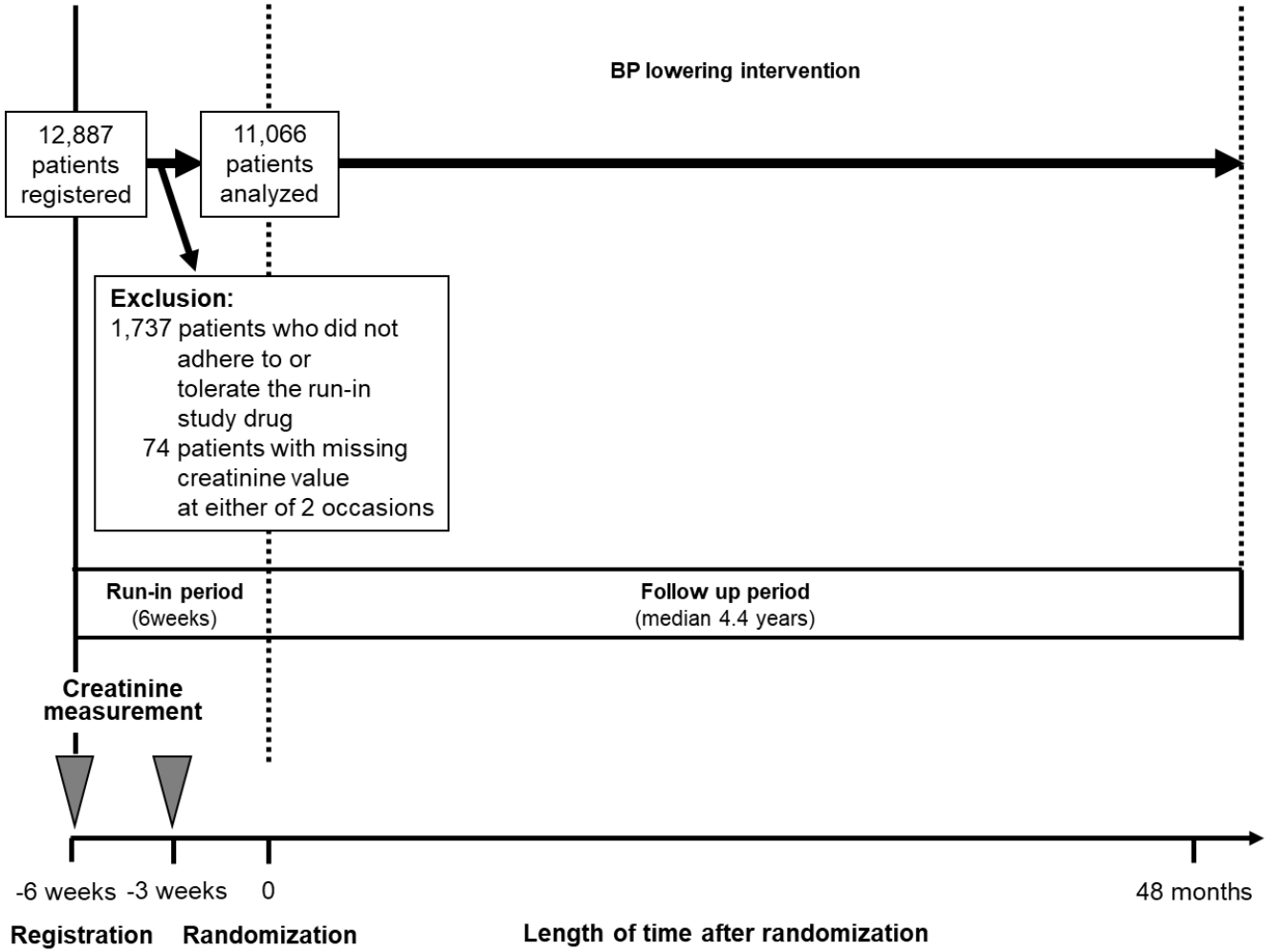

BP lowering intervention
12,887 patients registered
11,066 patients analyzed
Exclusion:
1,737 patients who did not adhere to or tolerate the run-in study drug
74 patients with missing creatinine value at either of 2 occasions
Run-in period (6weeks)
Follow up period (median 4.4 years)
Creatinine measurement
-6 weeks
-3 weeks
0
48 months
Registration
Randomization
Length of time after randomization

Figure 2

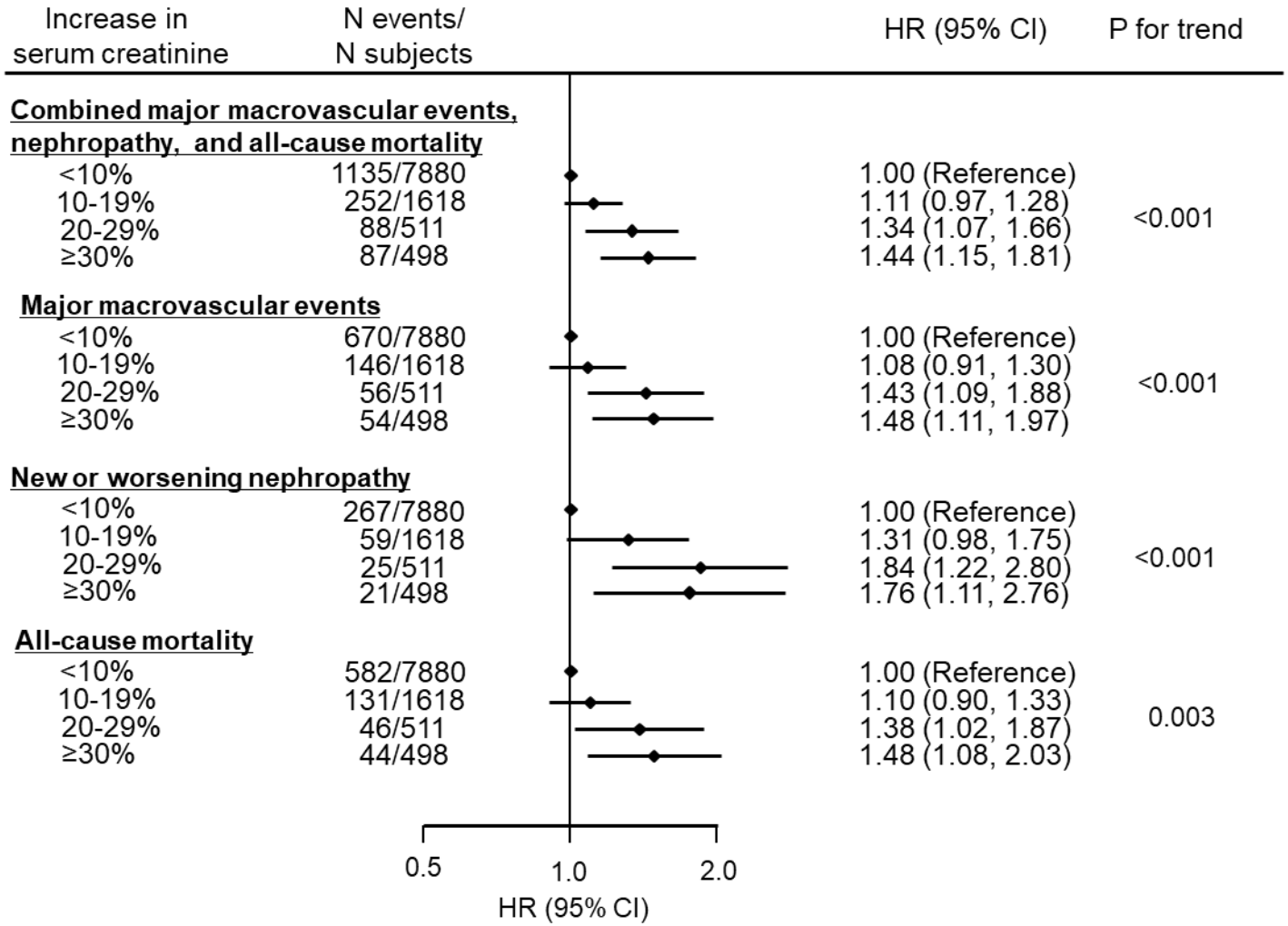

Increase in serum creatinine
N events/ N subjects
HR (95% CI)
P for trend
Combined major macrovascular events, nephropathy, and all-cause mortality
<10% 1135/7880 1.00 (Reference)
10-19% 252/1618 1.11 (0.97, 1.28)
20-29% 88/511 1.34 (1.07, 1.66)
≥30% 87/498 1.44 (1.15, 1.81)
<0.001
Major macrovascular events
<10% 670/7880 1.00 (Reference)
10-19% 146/1618 1.08 (0.91, 1.30)
20-29% 56/511 1.43 (1.09, 1.88)
≥30% 54/498 1.48 (1.11, 1.97)
<0.001
New or worsening nephropathy
<10% 267/7880 1.00 (Reference)
10-19% 59/1618 1.31 (0.98, 1.75)
20-29% 25/511 1.84 (1.22, 2.80)
≥30% 21/498 1.76 (1.11, 2.76)
<0.001
All-cause mortality
<10% 582/7880 1.00 (Reference)
10-19% 131/1618 1.10 (0.90, 1.33)
20-29% 46/511 1.38 (1.02, 1.87)
≥30% 44/498 1.48 (1.08, 2.03)
0.003
0.5
1.0
2.0
HR (95% CI)

Figure 3

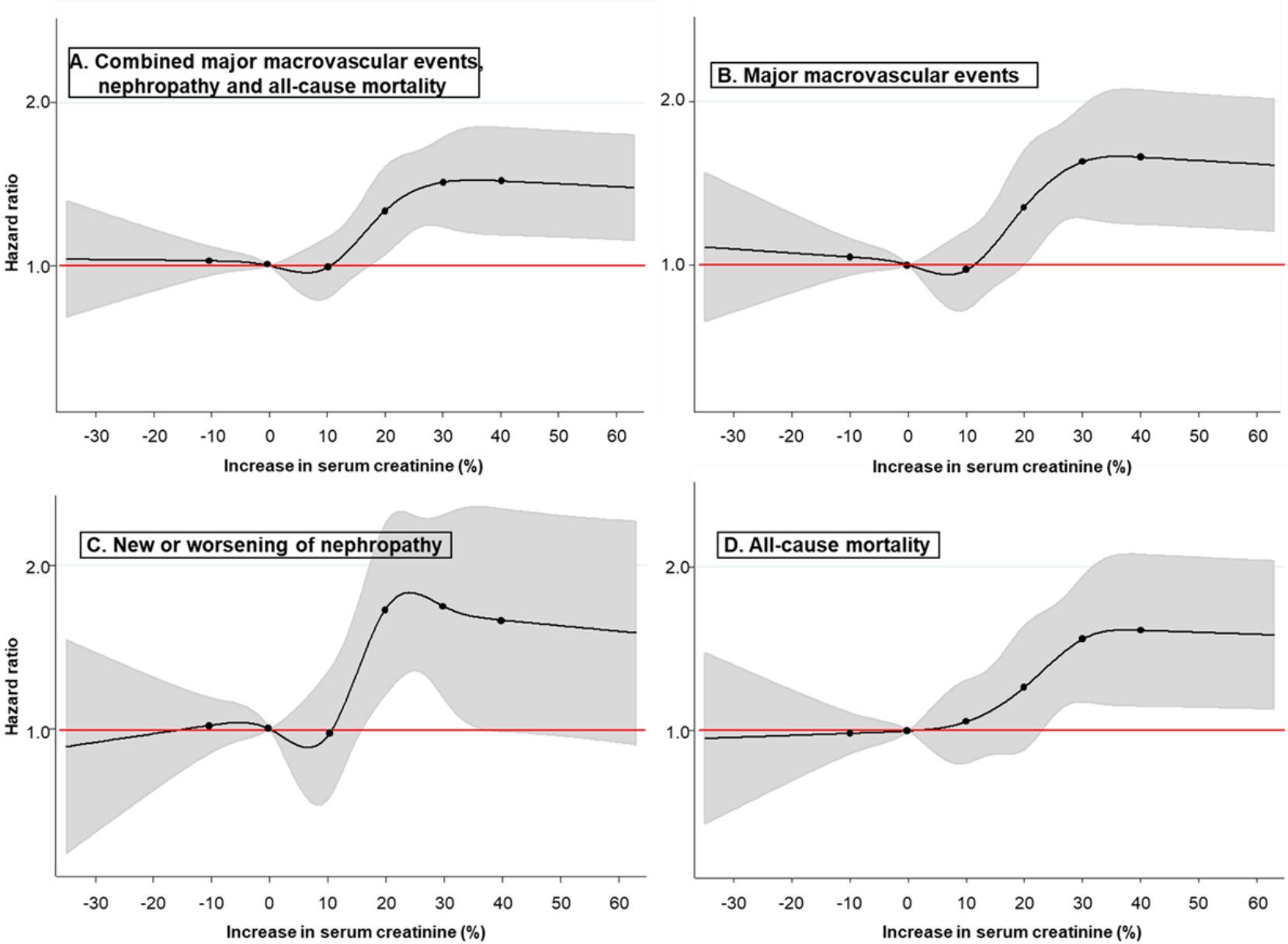
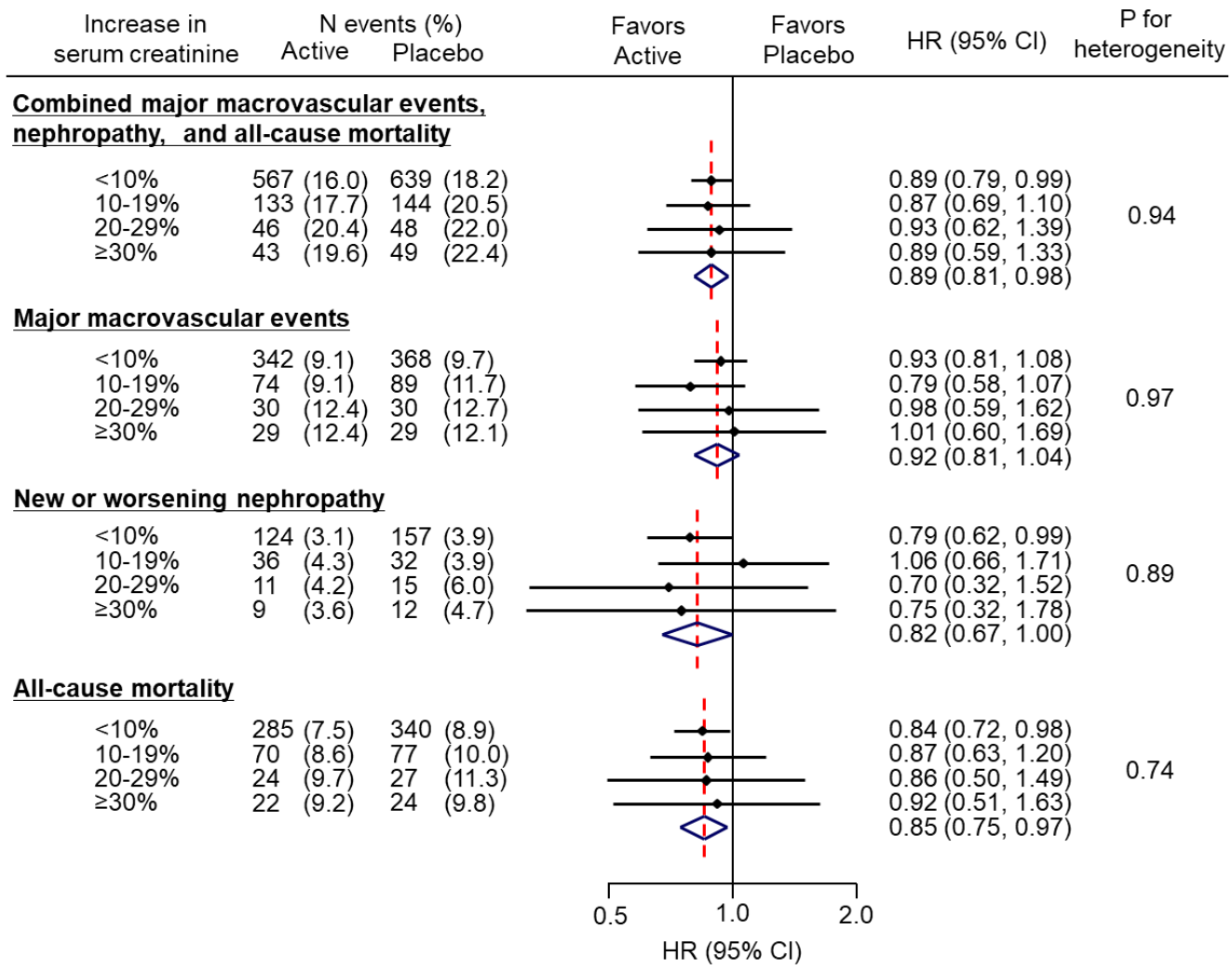

A. Combined major macrovascular events, nephropathy and all-cause mortality
B. Major macrovascular events
C. New or worsening of nephropathy
D. All-cause mortality
Hazard ratio
2.0
1.0
-30 -20 -10 0 10 20 30 40 50 60
Increase in serum creatinine (%)

Figure 4


Increase in serum creatinine
N events (%) Active
Placebo
Favors Active
Favors Placebo
HR (95% CI)
P for heterogeneity
Combined major macrovascular events, nephropathy, and all-cause mortality
<10% 567 (16.0) 639 (18.2) 0.89 (0.79, 0.99)
10-19% 133 (17.7) 144 (20.5) 0.87 (0.69, 1.10)
20-29% 46 (20.4) 48 (22.0) 0.93 (0.62, 1.39)
≥30% 43 (19.6) 49 (22.4) 0.89 (0.59, 1.33)
0.89 (0.81, 0.98)
0.94
Major macrovascular events
<10% 342 (9.1) 368 (9.7) 0.93 (0.81, 1.08)
10-19% 74 (9.1) 89 (11.7) 0.79 (0.58, 1.07)
20-29% 30 (12.4) 30 (12.7) 0.98 (0.59, 1.62)
≥30% 29 (12.4) 29 (12.1) 1.01 (0.60, 1.69)
0.92 (0.81, 1.04)
0.97
New or worsening nephropathy
<10% 124 (3.1) 157 (3.9) 0.79 (0.62, 0.99)
10-19% 36 (4.3) 32 (3.9) 1.06 (0.66, 1.71)
20-29% 11 (4.2) 15 (6.0) 0.70 (0.32, 1.52)
≥30% 9 (3.6) 12 (4.7) 0.75 (0.32, 1.78)
0.82 (0.67, 1.00)
0.89
All-cause mortality
<10% 285 (7.5) 340 (8.9) 0.84 (0.72, 0.98)
10-19% 70 (8.6) 77 (10.0) 0.87 (0.63, 1.20)
20-29% 24 (9.7) 27 (11.3) 0.86 (0.50, 1.49)
≥30% 22 (9.2) 24 (9.8) 0.92 (0.51, 1.63)
0.85 (0.75, 0.97)
0.74
0.5
1.0
2.0
HR (95% CI)