ORIGINAL RESEARCH

Relationship Between Plasma 8-OH-Deoxyguanosine and Cardiovascular Disease and Survival in Type 2 Diabetes Mellitus: Results From the ADVANCE Trial

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Background—8-Oxo-2′-deoxyguanosine (8-oxo-2′-dG) is a biomarker of oxidative DNA damage that is associated with cardiovascular disease and premature mortality in the general population. Although oxidative stress has a proven role in cardiovascular complications in diabetes mellitus, evidence for a relationship between plasma 8-oxo-2′-dG and major cardiovascular outcomes in diabetes mellitus is weak.

Methods and Results—A case-cohort study was performed in 3766 participants with prevalent diabetes mellitus in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial (ClinicalTrials.gov number NCT00145925). The hazard ratios for mortality and major acute cardiovascular events were derived using Cox regression models. During a median of 5 years of follow-up, 695 (18.4%) participants in this enriched cohort died (including 354 deaths from cardiovascular disease). Individuals with higher levels of 8-oxo-2′-dG were more likely to die. After adjusting for cardiovascular disease risk factors, the hazard ratio for a 1-SD increase in plasma 8-oxo-2′-dG was 1.10 (95% confidence interval, 1.01–1.20; P=0.03). This was driven by an independent association between plasma 8-oxo-2′-dG and cardiovascular death (hazard ratio, 1.23; 95% confidence interval, 1.10–1.37 [P<0.001]). By contrast, no association was seen between 8-oxo-2′-dG and noncardiovascular disease death (of which cancer was the major single cause). 8-Oxo-2′-dG was also not significantly associated with either nonfatal myocardial infarction or nonfatal stroke.

Conclusions—In adults with type 2 diabetes mellitus, increased levels of 8-oxo-2′-dG are independently associated with all-cause mortality and cardiovascular mortality in adults with longstanding type 2 diabetes mellitus who participated in the ADVANCE trial, consistent with the role of oxidative damage in the development and progression of cardiovascular decompensation in diabetes mellitus.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00145925. **(*J Am Heart Assoc*. 2018;7: e008226. DOI: 10.1161/JAHA.117.008226.)**

Key Words: cardiovascular outcomes • mortality • oxidative stress • survival analysis • type 2 diabetes mellitus

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It is well established that increased production of reactive oxygen species and the failure of endogenous antioxidant defenses against them results in a state of oxidative stress in diabetes mellitus and oxidative damage that contributes directly to the development and progression of diabetic complications.[1] One useful biomarker of oxidative DNA

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An accompanying Appendix S1 is available at http://jaha.ahajournals.org/content/7/13/e008226/DC1/embed/inline-supplementary-material-1.pdf

*A complete list of the ADVANCE Collaborative Group is provided in Appendix S1.

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Clinical Perspective

What Is New?

- Although type 2 diabetes mellitus is associated with oxidative stress, this is the first large prospective study to confirm an independent association between cardiovascular mortality and oxidative DNA damage in this setting.

What Are the Clinical Implications?

- There remains an unmet need to modulate oxidative damage and validate its utility to reduce mortality in adults with type 2 diabetes mellitus.

damage is 8-oxo-2′-deoxyguanosine (8-oxo-2′-dG), an oxidized derivative of deoxyguanosine and one of the most abundant oxidative products of cellular DNA.[2,3] Urinary 8-oxo-2′-dG has been independently associated with cardiovascular disease (CVD) in population cohorts[4–6] and long-term survival in patients with advanced CKD,[7] heart failure (HF),[8,9] or cancer.[2,3] Yet, despite the recognized role of oxidative stress in diabetic complications, previous studies reported that spot urinary levels of 8-oxo-2′-dG at diagnosis were not associated with subsequent mortality in Danish patients with type 2 diabetes mellitus.[10,11] This surprising finding may reflect the challenges of quantitative urinalysis in patients with type 2 diabetes mellitus in the community, especially when patients are poorly controlled (with polyuria and hyperfiltration) or have renal disease. To minimize these challenges, 8-oxo-2′-dG can also be measured in stored plasma samples, although as a renally cleared metabolite, adjustment must be made for the simultaneous estimated glomerular filtration rate (eGFR).

In the present study, we explore the association between levels of circulating 8-oxo-2′-dG and key adverse outcomes (death and cardiovascular events) in a nested case-cohort study of adults with type 2 diabetes mellitus who participated in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial[12–14] (ClinicalTrials.gov number NCT00145925).

Methods

Study Sample

The ADVANCE trial has been described in detail previously.[12–14] High-risk patients with type 2 diabetes mellitus were recruited from 20 countries in Asia, Australasia, Canada, and Europe. Participants were also required to be 55 years or older and have a history of CVD or ≥1 additional cardiovascular risk factor. The study included 2 randomized comparisons: a double-blind assessment of the efficacy of a fixed combination of perindopril and indapamide (2/0.625 mg for 3 months increasing, if tolerated, to 4/1.25 mg) versus placebo, and an open-label evaluation of an intensive glucose-lowering regimen using modified release gliclazide, with a target glycated hemoglobin of ≤6.5%, versus standard guideline-based glycemic control. A total of 11 140 participants were randomized and the median duration of follow-up was 5 years. Approval for the trial was obtained from each center's institutional review board, and all participants provided written and informed consent.

Nonfasting blood samples were taken at baseline, anticoagulated with EDTA and stored centrally at −80°C for a median of 7.8 years before analyses. Stored plasma samples were available from all countries involved in ADVANCE, except China and India, giving a total base population of 7376 patients. A case-cohort study population was constructed from a random sample of 3500 individuals, taken from these 7376 participants, plus all additional individuals who had a CVD event or a microvascular complication or died during follow-up (n=697).

Baseline data included demographic and clinical information, including age at diagnosis, presence and severity of diabetic complications, antidiabetic therapy, and other regular medications. Weight, height, urinary albumin/creatinine ratio, serum creatinine, fasting lipid levels, and glycated hemoglobin were also measured at baseline. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[15] Levels of baseline high-sensitivity cardiac troponin T, NT-proBNP (N-terminal pro–brain natriuretic peptide), and high sensitivity C-reactive protein were also measured on stored samples.[16–18] Plasma 8-oxo-2′-dG was measured by ELISA (StressMarq Biosciences Inc). The data and study materials will not be made available to other researchers for purposes of reproducing the results or replicating this analysis.

Study End Points

The 4 primary study end points were all-cause death, CVD death, non–CVD death, and major macrovascular events (cardiovascular death, nonfatal myocardial infarction [MI], or nonfatal stroke). Secondary outcomes were nonfatal MI, stroke, and admission to hospital for HF. All possible primary outcomes and deaths (cardiovascular and otherwise) were reviewed by an end point adjudication committee (comprising cardiologists, neurologists, endocrinologists, nephrologists, and ophthalmologists) whose members were blinded to randomized treatment assignments. Cardiovascular death was defined as any death in which the proximate or the underlying cause of death was caused by a disease of the circulatory system (*International Classification of Diseases, Tenth Revision* [*ICD-10*], codes of I10–I14, I20–I25, I26, I27.9,

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I28, I50–I52, I60–I67, I69, I70–I79, I80–I89) or a sudden death (*ICD-10* codes of R96.0, R96.1, I46.1, R98). Using the supporting documents, the committee either confirmed or refuted the initial diagnosis reported by the site investigators using standardized definitions. If the initial diagnosis made by the site investigator was refuted, an alternative diagnosis was provided.[19]

Statistical Analyses

Baseline characteristics were summarized by ordinal categories defined by the thirds of 8-oxo-2′-dG. Tests for linear trend were performed, across the thirds of each biomarker, to identify possible covariates associated with 8-oxo-2′-dG using linear regression. Hazard ratios for log-linear effects of 8-oxo-2′-dG levels on each of the 3 studied outcomes were obtained from weighted Cox regression models for case-cohort analyses.[18] Nonfatal outcomes were analyzed using a Fine and Gray competing risk model, treating death from any cause as the competing event.[20] Results were expressed per unit SD of 8-oxo-2′-dG (3.5 ng/mL). Four models with different sets of potential confounding variables were fitted for each of the biomarker/outcome combinations: model 1 with age, sex, and randomized treatment; model 2 with, additionally, eGFR; model 3 with, additionally, albumin to creatinine ratio, duration of diabetes mellitus, current smoking, systolic blood pressure, body mass index, glycated hemoglobin, plasma glucose, total and high-density lipoprotein cholesterol, triglycerides, and history of macrovascular complications; and model 4 with, additionally, high-sensitivity C-reactive protein, troponin, and NT-proBNP. Analyses were also performed stratified by predefined characteristics at baseline: age (>67 years versus ≤67 years), sex, a history of macrovascular complications, a history of microvascular complications, eGFR

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Table 1. Baseline Demographic, Clinical, and Laboratory Data Classified by Thirds of 8-oxo-2′-dG

Characteristic	First Third (n=1256)	Second Third (n=1254)	Third Third (n=1240)	Total (N=3766)	*P* for Trend
Male sex, No. (%)	689/1256 (54.9)	801/1254 (63.9)	800/1256 (63.7)	2290/3766 (60.8)	<0.0001
Current smoking, No. (%)	192/1256 (15.3)	188/1254 (15.0)	190/1256 (15.1)	570/3766 (15.1)	0.9113
History of a macrovascular event, No. (%)	395/1256 (31.4)	433/1254 (34.5)	488/1256 (38.9)	1316/3766 (34.9)	0.0001
Age, mean (SD), y	66.65 (6.46)	66.95 (6.60)	67.13 (6.75)	66.91 (6.61)	0.0686
Body mass index, mean (SD), kg/m^2	29.32 (4.94)	30.09 (5.34)	30.68 (5.44)	30.03 (5.27)	<0.0001
Duration of diabetes mellitus, mean (SD), y	8.09 (6.33)	8.02 (6.51)	7.56 (6.50)	7.89 (6.45)	0.0389
History of heart failure, No. (%)	47/1256 (3.7)	50/1254 (4.0)	74/1256 (5.9)	171/3766 (4.5)	0.01
Moderate or vigorous activity, No. (%)	612/1256 (48.7)	625/1254 (49.8)	585/1256 (46.6)	1822/3766 (48.4)	0.2812
Aspirin or other antiplatelet agent, No. (%)	576/1256 (45.9)	603/1254 (48.1)	673/1256 (53.6)	1852/3766 (49.2)	0.0001
Statin or other lipid-lowering agent, No. (%)	528/1256 (42.0)	549/1254 (43.8)	591/1256 (47.1)	1668/3766 (44.3)	0.0114
β-Blocker, No. (%)	346/1256 (27.5)	384/1254 (30.6)	412/1256 (32.8)	1142/3766 (30.3)	0.0042
ACEI or ARB, No. (%)	724/1256 (57.6)	733/1254 (58.5)	777/1256 (61.9)	2234/3766 (59.3)	0.0314
Systolic BP, mean (SD), mm Hg	147.94 (21.56)	147.87 (21.03)	146.76 (22.25)	147.52 (21.62)	0.1712
Diastolic BP, mean (SD), mm Hg	81.89 (10.95)	82.03 (10.66)	80.82 (11.08)	81.58 (10.91)	0.0142
Total cholesterol, mean (SD), mmol/L	5.16 (1.14)	5.11 (1.27)	5.13 (1.12)	5.13 (1.17)	0.5528
HDL cholesterol, mean (SD), mmol/L	1.26 (0.34)	1.21 (0.32)	1.20 (0.33)	1.22 (0.33)	<0.0001
Triglycerides, mean (SD), mmol/L	1.79 (1.02)	1.90 (1.14)	2.18 (1.41)	1.96 (1.21)	<0.0001
Glycated hemoglobin, mean (SD), %	7.56 (1.52)	7.38 (1.44)	7.30 (1.32)	7.41 (1.43)	<0.0001
Urinary ACR, median (IQI), mg/mmol	48.21 (110.18)	52.80 (122.27)	65.60 (137.73)	55.55 (124.10)	0.0007
Glucose, mean (SD), mmol/L	8.66 (2.81)	8.44 (2.60)	8.31 (2.76)	8.47 (2.73)	0.0013
eGFR, mean (SD), mL/min per 1.73 m^2	75.53 (15.38)	72.24 (16.60)	66.63 (17.49)	71.47 (16.91)	<0.0001
hs-CRP, median (IQI), mg/L	3.37 (6.86)	3.58 (7.08)	3.94 (6.76)	3.63 (6.91)	0.0393
hs-cTNT, median (IQI), pg/mL	7.47 (19.41)	8.61 (11.66)	11.06 (25.26)	9.04 (19.64)	<0.0001
NT-proBNP, median (IQI), pg/mL	190.22 (396.45)	220.75 (532.26)	381.15 (1404.1)	264.09 (900.59)	<0.0001

8-oxo-2′-dG indicates 8-OH-deoxyguanosine; ACEI, angiotensin-converting enzyme inhibitor; ACR, albumin creatinine ratio; ARB, angiotensin receptor blocker; BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; hs-cTNT, high-sensitivity cardiac troponin T; IQI, interquartile interval; NT-proBNP, N-terminal pro–brain natriuretic peptide.

Table 2. HRs (95% CIs) Per 1 SD (3.5 ng/mL) Higher 8-oxo-2′-dG for Major and Composite End Points

	HR (95% CI)	*P* Value
Model 1		
All-cause death	1.16 (1.07–1.25)	<0.001
Cardiovascular death	1.26 (1.14–1.38)	<0.001
Noncardiovascular death	1.05 (0.94–1.17)	0.42
Major macrovascular events	1.11 (1.03–1.20)	0.006
Total CVD	1.15 (1.07–1.23)	<0.001
Model 2		
All-cause death	1.10 (1.02–1.19)	0.012
Cardiovascular death	1.19 (1.08–1.31)	<0.001
Noncardiovascular death	1.01 (0.90–1.13)	0.87
Major macrovascular events	1.06 (0.98–1.15)	0.16
Total CVD	1.09 (1.01–1.17)	0.027
Model 3		
All-cause death	1.10 (1.01–1.20)	0.031
Cardiovascular death	1.23 (1.10–1.37)	<0.001
Noncardiovascular death	0.98 (0.86–1.11)	0.705
Major macrovascular events	1.08 (0.99–1.18)	0.080
Total CVD	1.11 (1.02–1.20)	0.014
Model 4		
All-cause death	1.09 (0.99–1.19)	0.068
Cardiovascular death	1.20 (1.07–1.34)	0.002
Noncardiovascular death	0.98 (0.86–1.11)	0.714
Major macrovascular events	1.06 (0.97–1.16)	0.177
Total CVD	1.09 (1.00–1.18)	0.041

Model 1: adjusted for age, sex, and randomized treatment groups. Model 2: model 1 plus estimated glomerular filtration rate (by Chronic Kidney Disease Epidemiology Collaboration equation). Model 3: model 2 plus duration of diabetes mellitus, current smoking, systolic blood pressure, body mass index, albumin to creatinine ratio, plasma glucose, glycated hemoglobin, total cholesterol, high-density lipoprotein cholesterol, triglycerides, and history of macrovascular complications. Model 4: model 3 plus high-sensitivity C-reactive protein, troponin, and N-terminal pro–brain natriuretic peptide. 8-oxo-2′-dG indicates 8-OH-deoxyguanosine; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.

< or ≥60 mL/min per 1.73 m^2, and glycated hemoglobin < or ≥7%, adjusted for the variables described in model 3.

Model 3 was used for the primary analysis. Cumulative survival plots were produced from the random subcohort, adjusting as in model 3. Log-likelihood ratio tests were conducted to test the nonlinearity effect of 8-oxo-2′-dG level on outcomes by comparing a model with categorical biomarkers and a model with continuous biomarkers. We tested the proportional hazards assumption by adding an interaction between the exposure and time. All analyses were performed using SAS software and a *P* value of <0.05 was considered to confer statistical significance.

Results

Of the 4197 participants in the case-cohort study, blood samples from 431 (10%) were missing or unsuitable for analysis. The remaining 3766 patients in this cohort had a mean age of 66.9 years and a mean duration of diabetes mellitus of 7.9 years (Table 1); 92% were white. A total of 1316 (34.9%) had a history of previous macrovascular disease.

At baseline, circulating levels of 8-oxo-2′-dG were highly correlated with eGFR (r^2=−0.24, *P*<0.001), consistent with its primary route of excretion by the kidney. After adjusting for eGFR, 8-oxo-2′-dG remained higher in participants with cardiac risk factors, including male sex, poor glycemic control, obesity, current smoking, atherogenic dyslipidemia, elevated systolic blood pressure, a prolonged duration of diabetes mellitus, and higher urinary albumin/creatinine ratio at baseline. Circulating levels of the cardiac marker NT-proBNP were also higher in participants with the highest levels of 8-oxo-2′-dG at baseline, even after adjusting for renal clearance of both substrates (r^2=0.26).

During a median of 5 years of follow-up, 695 (18.4%) participants in this enriched cohort died (including 354 deaths from CVD). After adjusting for age, sex, and randomized treatment (Table 2) or after additionally adjusting for eGFR (model 2) and a wide range of other risk factors (model 3), individuals with higher levels of 8-oxo-2′-dG were more likely to die (Figure 1A). Further adjustment for high-sensitivity C-reactive protein, troponin T, and NT-proBNP further attenuated this association.

The association between 8-oxo-2′-dG and all-cause mortality outcomes was driven by the independent association between 8-oxo-2′-dG and CVD death, which remained significant after adjusting for other potentially confounding variables (Table 2; Figure 1B). Notably, no association was seen between 8-oxo-2′-dG and non–CVD death (of which cancer was the major single cause) (Table 2; Figure 1C). There was no evidence of nonproportionality of hazards (*P*=0.70 for all-cause death, 0.19 for cardiovascular death, 0.09 for noncardiovascular death).

The association between 8-oxo-2′-dG and all-cause and cardiovascular mortality outcomes was not significantly different across strata of age, sex, history of vascular disease, renal function, or glycemic control (Figure 2). There was no evidence of nonlinearity (*P*>0.05) between 8-oxo-2′-dG and mortality outcomes. There was no clear association between 8-oxo-2′-dG and specific causes of documented CVD death (MI, stroke, or HF), although the power to perform this kind of subanalysis is limited because of the low number of fatal cardiovascular events.

During follow-up, 680 (18.0%) participants experienced a major macrovascular event. Unlike survival and CVD mortality,

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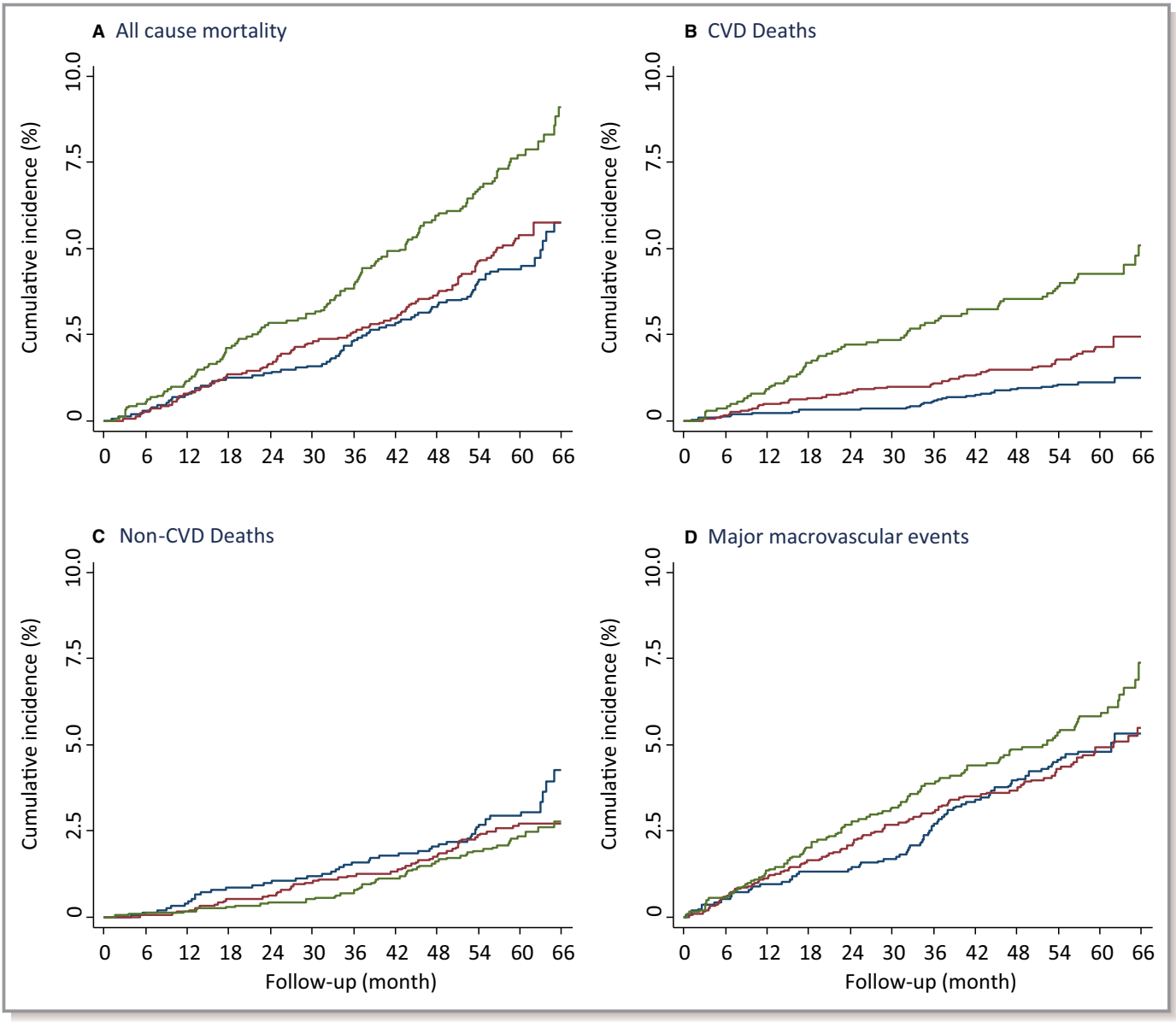


Figure 1. Cumulative survival curves for all primary outcomes by quarter of 8-oxo-2′-deoxyguanosine (8-oxo-2′-dG), adjusted as in model 3 in Table 1. Blue, red, and green lines correspond, in this order, to increasing tertiles of 8-ox-dG. CVD indicates cardiovascular disease.

the unadjusted association between 8-oxo-2′-dG with major macrovascular events (MI, stroke, admission for HF) was eliminated after adjusting for only eGFR (Table 2; Figure 1D). Again, there was no evidence of nonproportionality of hazards (P=0.77 for major macrovascular events). 8-Oxo-2′-dG was also not significantly associated with either nonfatal MI, nonfatal stroke, or hospitalization for HF, after adjusting for other risk factors (Table 3).

Discussion

Oxidative stress is recognized as a clear antecedent of end-organ dysfunction and disease, and diabetes mellitus is associated with increased levels of oxidative stress.[1] In this study, we demonstrate that 8-oxo-2′-dG, a marker of oxidative damage, is independently associated with all-cause mortality and cardiovascular mortality in adults with longstanding type 2 diabetes mellitus who participated in the ADVANCE trial. This finding is consistent with smaller observational studies linking survival of patients with diabetes mellitus to other markers of oxidative stress, including oxidized RNA,[10,11] derivatives of reactive oxygen metabolite,[19] advanced autoxidation products,[2,20] and F-isoprostanes.[2,20] However, this is the first large prospective study to confirm an independent association between mortality and 8-oxo-2′-dG in type 2 diabetes mellitus.

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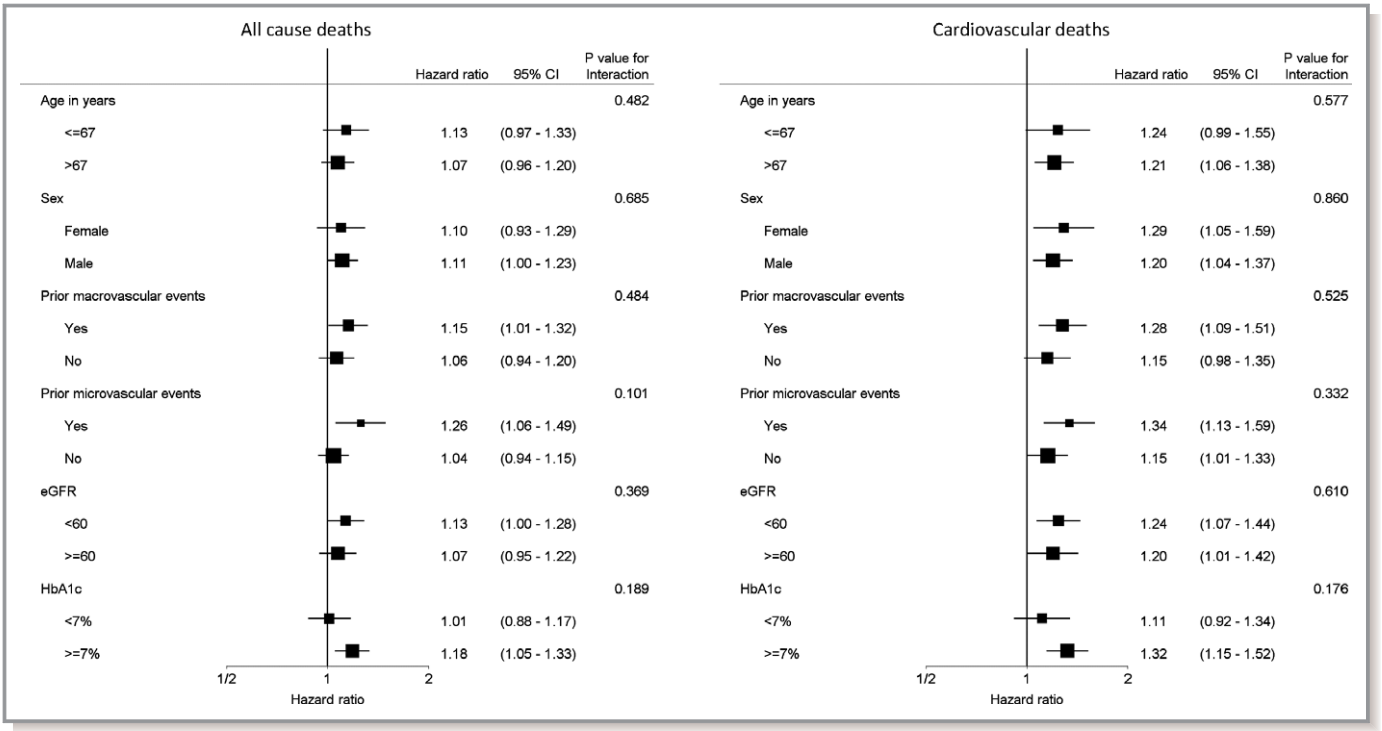


Figure 2. Hazard ratios (with 95% confidence intervals [CIs]) for all-cause and cardiovascular death by predefined subgroups, adjusted as in model 3 in Table 1. eGFR indicates estimated glomerular filtration rate; HbA1c, glycated hemoglobin.

Because of the inherent reactivity of reactive oxygen species, oxidative stress is most easily evaluated by quantitation of oxidative modifications, of which 8-oxo-2′-dG is a highly relevant, stable, and easily measured by-product. Although widely considered a marker of oxidative DNA damage, 8-oxo-2′-dG may also partly reflect the rate of its liberation via DNA repair mechanisms[1,21,22] and oxidatively damaged 2′-deoxyguanosine from the nucleotide pool. 8-Oxo-2′-dG is also clearly associated with kidney function. In most previous studies, the failure to adjust for renal clearance clearly undermines conclusions based on free 8-oxo-2′-dG levels in the circulation or urine.[21] Certainly, in our study, some of the association between plasma 8-oxo-2′-dG levels and mortality was explained by the confounding effect of renal impairment. Although we have specifically adjusted for eGFR in this analysis (model 2), and the association between 8-oxo-2′-dG and mortality remained significant after this adjustment, it is possible we still may have underestimated the role of kidney disease in outcomes, as kidney disease itself may be considered a cause of oxidative stress. Consistent with this hypothesis, the ratio of plasma 8-oxo-2′-dG to eGFR rose as eGFR levels fell in participants in this study.

Recent studies have suggested that 8-oxo-2′-dG may be associated with both the presence of HF and its severity and prognosis.[6,8] Although few patients had an overt history of HF in our ADVANCE cohort, an association between 8-oxo-2′-dG and cardiac function has also been reported in patients with hypertension without overt heart disease.[23] Consistent with this hypothesis, plasma levels of NT-proBNP were independently associated with 8-oxo-2′-dG in our cohort, suggesting that 8-oxo-2′-dG may also be a marker of oxidative injury in the heart and occult cardiac dysfunction in our cohort, therein partly explaining the association of 8-oxo-2′-dG and cardiovascular mortality. Indeed, it has been suggested that 8-oxo-2′-dG and NT-proBNP may be markers of the same process, as oxidative damage may be causally related to cardiac dysfunction. However, even after adjusting for NT-proBNP and TNT in our multivariate models, the association between 8-oxo-2′-dG and cardiovascular mortality remained significant (P=0.01), suggesting that the link is more complex.

Although 8-oxo-2′-dG was associated with major macrovascular events after adjusting for age and sex, this association disappeared after adjusting for eGFR. As oxidative stress is a key mechanism by which these risk factors may be linked to mortality outcomes, such adjustment may not reflect the true role of oxidative damage in the development and progression of CVD. Despite the clear association of 8-oxo-2′-dG with the risk of CVD death, there was no such association with the combination of fatal and nonfatal CVD (major macrovascular events). This is despite the greater power for the latter, owing to the larger number of events. This unusual pattern was also observed in the recent EMPA-REG outcomes trial[24] where CVD death was reduced without a reduction in

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Table 3. HRs (95% CIs) Per 1 SD (3.5 ng/mL) Higher 8-oxo-2′-dG for Fatal and Nonfatal Individual Cardiovascular End Points

	Fatal Events		Nonfatal Events*	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Model 1				
Myocardial infarction	1.25 (0.98–1.60)	0.070	1.02 (0.89–1.17)	0.771
Stroke	1.17 (0.95–1.45)	0.136	0.97 (0.83–1.13)	0.692
Heart failure	1.43 (1.17–1.74)	<0.001	1.23 (1.10–1.37)	<0.001
Model 2				
Myocardial infarction	1.20 (0.92–1.56)	0.170	0.96 (0.83–1.10)	0.567
Stroke	1.12 (0.91–1.37)	0.288	0.92 (0.79–1.08)	0.325
Heart failure	1.35 (1.09–1.68)	0.006	1.11 (0.98–1.26)	0.103
Model 3				
Myocardial infarction	1.30 (0.96–1.76)	0.091	0.95 (0.81–1.11)	0.497
Stroke	1.21 (0.99–1.48)	0.065	0.97 (0.82–1.16)	0.761
Heart failure	1.35 (0.97–1.88)	0.076	1.12 (0.97–1.30)	0.132
Model 4				
Myocardial infarction	1.31 (0.97–1.77)	0.081	0.93 (0.80–1.10)	0.407
Stroke	1.20 (0.98–1.46)	0.081	0.95 (0.80–1.13)	0.534
Heart failure	1.28 (0.87–1.86)	0.208	1.10 (0.95–1.27)	0.207

Model 1: adjusted for age, sex, and randomized treatment groups. Model 2: model 1 plus estimated glomerular filtration rate (by Chronic Kidney Disease Epidemiology Collaboration equation). Model 3: model 2 plus duration of diabetes mellitus, current smoking, systolic blood pressure, body mass index, albumin to creatinine ratio, plasma glucose, glycated hemoglobin, total cholesterol, high-density lipoprotein cholesterol, triglycerides, and history of macrovascular complications. Model 4: model 3 plus high-sensitivity C-reactive protein, troponin, and N-terminal pro–brain natriuretic peptide. 8-oxo-2′-dG indicates 8-OH-deoxyguanosine; CI, confidence interval; HR, hazard ratio.
*Allowing for the competing risk of death.

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nonfatal CVD events, and potentially points to the different pathogenic forces in total CVD events when compared with CVD death, with a potentially important role for oxidative stress in the latter. Notably, similar to EMPA-REG outcomes, both death from HF and hospitalization for HF were associated with 8-oxo-2′-dG. However, this association was attenuated after adjusting for other risk factors, although the small number of HF events means there is a low power to explore this outcome in any detail.

Study Strengths and Limitations

The strengths of this study include the large cohort of well-characterized patients, with few dropouts (only 17 of 11 140 in the original study), outcome verification by an independent review committee, and the high level of diabetes mellitus care, typical of a clinical trial. A limitation is that oxidative stress was quantified by means of a single measure, which is clearly inadequate for a dynamic process. We also used an ELISA to assess 8-oxo-2′-dG in plasma samples, as conventional chromatographic methods do not have the sensitivity to measure plasma levels. Although the circulating levels of 8-oxo-2′-dG detailed in this study are similar to those reported in cross-sectional studies using ELISA-based assays in patients with diabetes mellitus[25–27] and other settings,[28–32] it is understood that ELISA overestimates 8-oxo-2′-dG when compared with high-sensitivity mass spectroscopy.[33] This is partly because of the former method including DNA fragments containing 8-oxo-2′-dG, in addition to free 8-oxo-2′-dG, as well as the presence of interfering compounds in plasma. Nonetheless, the clear correlation of 8-oxo-2′-dG with mortality is consistent with prior data on other markers of oxidative stress.

Finally, observational studies only demonstrate association and not causality. Although there is a strong scientific rationale, the mechanics (causality) behind these observations are beyond the scope of the current investigation. We have undertaken detailed analyses to control for possible confounders, eg, in multivariate regression, and competing risk analysis. We have clearly shown that after adjusting for conventional risk factors associated with CVD death, an independent association between 8-oxo-2′-dG was maintained. This suggests that 8-oxo-2′-dG is not just an epiphenomenon. However, it is not possible to account for unmeasured confounders, such as microbiome and diet composition, mental health, or exposure to atmospheric pollution, all of which may influence markers of oxidative stress and CVD mortality.

Conclusions

8-Oxo-2′-dG is independently associated with CVD death and all-cause mortality in patients with type 2 diabetes mellitus, consistent with the role of oxidative damage in the development and progression of cardiovascular decompensation in diabetes mellitus. This observation supports the call for better-targeted antioxidant therapies[34] and well-designed appropriately powered human studies, especially in those with elevated CVD risk, in whom oxidative stress is usually particularly high and remains untreated.

Author Contributions

Thomas drafted the article, which was redrafted by Woodward and Chalmers. Thomas and Pickering performed the laboratory tests on 8-oxo-2′-dG. Woodward and Li were responsible for the statistics. All other authors contributed to the acquisition of data and gave comments on the original draft. Professor Mark Woodward is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Disclosures

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References

1. Forbes JM, Cooper ME. Mechanisms of diabetic complications. *Physiol Rev*. 2013;93:137–188.
2. Ames BN. Endogenous oxidative DNA damage, aging, and cancer. *Free Radic Res Commun*. 1989;7:121–128.
3. Valavanidis A, Vlachogianni T, Fiotakis C. 8-hydroxy-2′-deoxyguanosine (8-OHdG): a critical biomarker of oxidative stress and carcinogenesis. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev*. 2009;27:120–139.
4. Kroese LJ, Scheffer PG. 8-hydroxy-2′-deoxyguanosine and cardiovascular disease: a systematic review. *Curr Atheroscler Rep*. 2014;16:452.
5. Di Minno A, Turnu L, Porro B, Squellerio I, Cavalca V, Tremoli E, Di Minno MN. 8-hydroxy-2-deoxyguanosine levels and cardiovascular disease: a systematic review and meta-analysis of the literature. *Antioxid Redox Signal*. 2016;24:548–555.
6. Di Minno A, Turnu L, Porro B, Squellerio I, Cavalca V, Tremoli E, Di Minno MN. 8-hydroxy-2-deoxyguanosine levels and heart failure: a systematic review and meta-analysis of the literature. *Nutr Metab Cardiovasc Dis*. 2017;27:201–208.
7. Machowska A, Sun J, Qureshi AR, Isoyama N, Leurs P, Anderstam B, Heimburger O, Barany P, Stenvinkel P, Lindholm B. Plasma pentosidine and its association with mortality in patients with chronic kidney disease. *PLoS One*. 2016;11:e0163826.
8. Suzuki S, Shishido T, Ishino M, Katoh S, Sasaki T, Nishiyama S, Miyashita T, Miyamoto T, Nitobe J, Watanabe T, Takeishi Y, Kubota I. 8-hydroxy-2′-deoxyguanosine is a prognostic mediator for cardiac event. *Eur J Clin Invest*. 2011;41:759–766.
9. Susa T, Kobayashi S, Tanaka T, Murakami W, Akashi S, Kunitsugu I, Okuda S, Doi M, Wada Y, Nao T, Yamada J, Ueyama T, Okamura T, Yano M, Matsuzaki M. Urinary 8-hydroxy-2′-deoxyguanosine as a novel biomarker for predicting cardiac events and evaluating the effectiveness of carvedilol treatment in patients with chronic systolic heart failure. *Circ J*. 2012;76:117–126.
10. Broedbaek K, Siersma V, Henriksen T, Weimann A, Petersen M, Andersen JT, Jimenez-Solem E, Stovgaard ES, Hansen LJ, Henriksen JE, Bonnema SJ, Olivarius Nde F, Poulsen HE. Urinary markers of nucleic acid oxidation and long-term mortality of newly diagnosed type 2 diabetic patients. *Diabetes Care*. 2011;34:2594–2596.
11. Broedbaek K, Siersma V, Henriksen T, Weimann A, Petersen M, Andersen JT, Jimenez-Solem E, Hansen LJ, Henriksen JE, Bonnema SJ, de Fine Olivarius N, Friis S, Poulsen HE. Urinary markers of nucleic acid oxidation and cancer in type 2 diabetes. *Redox Biol*. 2015;4:34–39.
12. Group AC, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358:2560–2572.
13. Patel A, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, Harrap S, Poulter N, Marre M, Cooper M, Glasziou P, Grobbee DE, Hamet P, Heller S, Liu LS, Mancia G, Mogensen CE, Pan CY, Rodgers A, Williams B. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet*. 2007;370:829–840.
14. Study rationale and design of ADVANCE: action in diabetes and vascular disease—preterax and diamicron MR controlled evaluation. *Diabetologia*. 2001;44:1118–1120.
15. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF III, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
16. Hillis GS, Welsh P, Chalmers J, Perkovic V, Chow CK, Li Q, Jun M, Neal B, Zoungas S, Poulter N, Mancia G, Williams B, Sattar N, Woodward M. The relative and combined ability of high-sensitivity cardiac troponin T and N-terminal pro-B-type natriuretic peptide to predict cardiovascular events and death in patients with type 2 diabetes. *Diabetes Care*. 2014;37:295–303.
17. Welsh P, Woodward M, Hillis GS, Li Q, Marre M, Williams B, Poulter N, Ryan L, Harrap S, Patel A, Chalmers J, Sattar N. Do cardiac biomarkers NT-proBNP and hsTnT predict microvascular events in patients with type 2 diabetes? Results from the ADVANCE trial. *Diabetes Care*. 2014;37:2202–2210.
18. Lowe G, Woodward M, Hillis G, Rumley A, Li Q, Harrap S, Marre M, Hamet P, Patel A, Poulter N, Chalmers J. Circulating inflammatory markers and the risk of vascular complications and mortality in people with type 2 diabetes and cardiovascular disease or risk factors: the ADVANCE study. *Diabetes*. 2014;63:1115–1123.
19. Schottker B, Brenner H, Jansen EH, Gardiner J, Peasey A, Kubinova R, Pajak A, Topor-Madry R, Tamosiunas A, Saum KU, Holleczek B, Pikhart H, Bobak M. Evidence for the free radical/oxidative stress theory of ageing from the CHANCES consortium: a meta-analysis of individual participant data. *BMC Med*. 2015;13:300.
20. Mohammedi K, Bellili-Munoz N, Marklund SL, Driss F, Le Nagard H, Patente TA, Fumeron F, Roussel R, Hadjadj S, Marre M, Velho G. Plasma extracellular superoxide dismutase concentration, allelic variations in the SOD3 gene and risk of myocardial infarction and all-cause mortality in people with type 1 and type 2 diabetes. *Cardiovasc Diabetol*. 2015;14:845.

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21. Poulsen HE, Nadal LL, Broedbaek K, Nielsen PE, Weimann A. Detection and interpretation of 8-oxodG and 8-oxoGua in urine, plasma and cerebrospinal fluid. *Biochem Biophys Acta*. 2014;1840:801–808.
22. Il'yasova D, Scarbrough P, Spasojevic I. Urinary biomarkers of oxidative status. *Clin Chim Acta*. 2012;413:1446–1453.
23. Masugata H, Senda S, Inukai M, Himoto T, Imachi H, Murao K, Hosomi N, Okada H, Goda F. Association between oxidative stress assessed by urinary 8-hydroxydeoxyguanosine and the cardiac function in hypertensive patients without overt heart disease. *Clin Exp Hypertens*. 2013;35:308–312.
24. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128.
25. Pan HZ, Zhang H, Chang D, Li H, Sui H. The change of oxidative stress products in diabetes mellitus and diabetic retinopathy. *Br J Ophthalmol*. 2008;92:548–551.
26. Pan HZ, Chang D, Feng LG, Xu FJ, Kuang HY, Lu MJ. Oxidative damage to DNA and its relationship with diabetic complications. *Biomed Environ Sci*. 2007;20:160–163.
27. Ma D, Zhu W, Hu S, Yu X, Yang Y. Association between oxidative stress and telomere length in Type 1 and Type 2 diabetic patients. *J Endocrinol Invest*. 2013;36:1032–1037.
28. Matzi V, Greilberger JF, Lindenmann J, Neuboeck N, Nuhsbaumer S, Zelzer S, Tafeit E, Maier A, Smolle-Juettner MF. Application of hyperbaric oxygen reduce oxidative damage of plasmatic carbonyl proteins and 8-OHdG by activating glutathion peroxidase. *Clin Lab*. 2015;61:587–593.
29. Xu H, Watanabe M, Qureshi AR, Heimburger O, Barany P, Anderstam B, Eriksson M, Stenvinkel P, Lindholm B. Oxidative DNA damage and mortality in hemodialysis and peritoneal dialysis patients. *Perit Dial Int*. 2015;35:206–215.
30. Yeniova AO, Uzman M, Kefeli A, Basyigit S, Ata N, Dal K, Guresci S, Nazligul Y. Serum 8 hydroxydeoxyguanosine and cytotoxin associated gene a as markers for *Helicobacter pylori* infection. *Asian Pac J Cancer Prev*. 2015;16:5199–5203.
31. Loffredo L, Marcoccia A, Pignatelli P, Andreozzi P, Borgia MC, Cangemi R, Chiarotti F, Violi F. Oxidative-stress-mediated arterial dysfunction in patients with peripheral arterial disease. *Eur Heart J*. 2007;28:608–612.
32. Xiang F, Shuanglun X, Jingfeng W, Ruqiong N, Yuan Z, Yongqing L, Jun Z. Association of serum 8-hydroxy-2′-deoxyguanosine levels with the presence and severity of coronary artery disease. *Coron Artery Dis*. 2011;22:223–227.
33. Hu CW, Huang YJ, Li YJ, Chao MR. Correlation between concentrations of 8-oxo-7,8-dihydro-2′-deoxyguanosine in urine, plasma and saliva measured by on-line solid-phase extraction LC-MS/MS. *Clin Chim Acta*. 2010;411:1218–1222.
34. Di Marco E, Jha JC, Sharma A, Wilkinson-Berka JL, Jandeleit-Dahm KA, de Haan JB. Are reactive oxygen species still the basis for diabetic complications? *Clin Sci*. 2015;129:199–216.

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SUPPLEMENTAL MATERIAL

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Germany (2 centers, 327 participants) – B Matschke**,** M Hanefeld, E Henkel, C Kohler, D Lehmann, P Ott, A Pahner, U Stier, T Temelkova-Kurktschiev (Centre for Clinical Studies GWT, TU Dresden), B Andratschke-Gentsch, G Bueschges, P Markhof, G Meier, M Nischwitz, S Schmid, C Von Schacky (Preventive Cardiology Med.Klinik, Munich).
Hungary (12 centers, 434 participants) – L Koranyi, National Advisor (Heart Centre Foundation-DRC Ltd, Balatonfüred)**,** G Jermendy, J Nadas (Bajcsy Zsilinszky Kórház), C Csongradi, G Kasa, T Kozma, Z Matyus, M Tarko (BAZ Megyei Kórház), L Koranyi, B Kovacs, E Kulcsar, (DRC Kft.), L Deak, Z Kovacs, G Rumi (Kaposi Mór Megyei Kórház), M Dudas, A Gyimesi, R Varga (Pándy Kálmán Megyei Kórház), I Csapo, J Fovenyi, I Hermanyi, G Kolev (Peterfy S.u. Kórház-Rendelointezet), T Hidvegi, C Mate, I Nemeth, B Szeri (Petz Aladár Megyei Kórház), M Herold, B Sarman, A Somogyi (Sote II. Számú Belgyógyászati Klinika), M Balsay, Z Bencsik, E Eory, T Korodi, M Sereg (Szent György Kórház), Z Hohmann, Z Lengyel, P Voros (Szent István Kórház), E Domotor, T Fuleki, Z Munster (Vasutegeszsegugyi KHT.) Z Bujtor, T Oroszlan, F Tarnok (Zala Megyei Önkormányzat Kórháza).
India (4 centers, 471 participants) – R Anand, S Das, G Karthikeyan, R Lakshmy, N Naik, D Prabhakaran, KS Reddy, S Sen, N Tandon (All India Institute of Medical Sciences, Delhi), M Ahmed, M Ali, A Anjaneyulu, K Naidu, K Raju, L Rao, N Reddy, P Reddy, B Sethi, (Care Hospital, Hyderabad), P Joshi, S Kumbhalmar, K Lokhande, P Rathod, S Sable (Government Medical College, Nagpur), K Karkuzhali, S Mariyam, V Mohan, S Poongothai, G Premalatha, J Salomi, V Selvi, R Srinivasan, R Visalatchi (Madras Diabetic Research Foundation).
Ireland (5 centers, 441 participants) – M Ashraf, J Barton, J Chong, M Courcy, M Elfadil, C Kelly (Ballinasloe Hospital, Co. Galway), B Aloul, C Collier, E Dolan, C Foley, B Gallagher, B Gusau, L Hacke, E Ho, B Maguire, A Stanton, C Thompson, M Twohill (Beaumont Hospital, Dublin), R Firth, A Gribben, S Hoashi, M Joyce, H O'Loughlin, S Rizvi, B Wade (Mater Hospital, Dublin), A Brennan, D Byrne, M Cullen, A Khamis, M Murphy, M Ryan (St James Hospital, Dublin), M Bell, C Bramhill, C Campbell, N Corredia, L Cullen, J Gibney, T Kyaw Tun, K Mullan, D Owens, N Phelan, C Tan, G Tomkin

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(Tallaght Hospital, Dublin).
Italy (1 center, 21 participants) – P Galli, G Mancia, F Paleari, V Vilei, C Whisstock (Ospedale San Gerardo, U.O. Diabetologia, Milan).
Lithuania (3 centers, 118 participants) – R Babarskienie, I Milvidaite (Institute of Cardiology, Kaunas), A Gintautaite, R Sirvyte, G Varoneckas (Palanga Institute of Psychophysiology and Rehabilitation), V Grizas, J Marcinkeviciene, V Tumyniene, D Vasiliauskas, G Vytautas (Private Cardiological Clinic, Kaunas).
Malaysia (5 centers, 236 participants) – K Hla, A Kalairajah, S Nayar, L Ramanathan, (Hospital Ipoh), R Abdullah, W Bakar, T Ismail, N Kamaruddin, A Loganathan, F Majid, N Mansor, Z Mohamed, N Mustafa, H Nawawi, N Nor, K Subramaniam, K Yusoff (Hospital Putrajaya), N Aziz, G Eng Leong, C Gaik Kin, H Jeremiah, A Khir, S Lim, M Mumtaz (Penang Medical College), A Abdul Rashid, R Alias, S Bahari Ismail, W bt Wan Mohamad, R bt Zainal-Abidin, K Daud, R Doud, A-A Ismail, H Masandid, M Mohamed, M Mumtaz, S Wahab, W Wan Bebakar (Universiti Sains Malaysia, Kota Bharu), SP Chan, FL Hew, MH Lim, Rokiah P, KH Yeoh (University of Malaya Medical Centre, Kuala Lumpur).
Netherlands (10 centers, 630 participants) – M Alhakim, A Amin, K Asten, J vd Berg Putten, B Bierman, H Boer, R Bredemeijer, F Durian, A Jansen, P Muilwijk, J Muilwijk6 Vermeer, W Opstelten, S Ponteyn-Rose, C Sluijters, C Sumajow, J Swart, D Tavenier, L van Oort, J van Vliet, I van Welson (ANDROMED Baarn), P Blokzyl-Mol, H Bulk, D Faber-Mollema, T Leutscher, D Mulder, R Ottema, C Prins, E Soer, J Tiebesl (ANDROMED Groningen), M Fierkens, P Jaspers, Y Koster (ANDROMED Oost), T Bell, C Geerts, C Gieskes, H Jalloh-Vos , G Pegt , D Ramautarsing , W Schenk , W van Kempen , A van Kempen , J van Meurs, C Vink (ANDROMED Rotterdam), W Venekamp (Atrium Brunssum), L Bie, D Hollander-Bosboom, J Keyzer, A Lieverse, B Lokhorst, A Rompen, S Sanders, G ten Berge-Lammens, A van Foreest-Bruggink, M Vrugt (Diagnostisch Centrum Eindhoven / Justus Medical Research), I Boerema-Zikkenheiner, S de Haan-Zwart, R Timmerman, P Viergever (Gemini Ziekenhuis, Den Helder), W Bossen, B Elzinga, W Janssen, M Knot, A Prins (Martini Ziekenhuis, Groningen), L Boonman-de Winter, J Bosser-van Rijckevorsel, M de Zwaan-Herfst, E Erdtsieck-Ernste, M Froger-Nuyten, E Jonk-Smulders, A Offringa, A van der Smissen-van Meel, M van Veen (Stichting Huisartsen Laboratorium, Etten Leur), J Arendhorst, C Bonekamp, N Jans, P Meeuwese, M Scholten, B Tjaden, S van der Meer, R van Kuppevelt (Tollenslaan/Zeist).
New Zealand (8 centers, 504 participants) – C Florkowski, R McEwan, P McGregor, R Scott, C Strey (Christchurch Hospital), S Brown, J Kenyon, R Leikis, R Luke (Hawkes Bay), J Baker, W Chiu, R Clarke, A Dissanayake, M Elston, S Gunatilaka,G Kerr, J Leary, J Moffat, I Rosen, M Te Whiu (Middlemore Hospital, Auckland), S Austin, J Singh, G Ward (North Shore Hospital, Auckland), G Carswell, S Cruz, P Dixon, D Nesdale, H Snell (Palmerston North Hospital), C Barker, A Burton, J Doran, F Gale, M Hammond, M Hills (Timaru Hospital), F Bartley, P Dunn, A Johnstone, D McLeod, E Reda, A Waterman (Waikato Hospital), T Clarke, P Cresswell, C Eagleton, A Ferguson, A-M Gallen, L Kent, J Krebs, I Rosemergy, C Ross, R Smith (Wellington Hospital).
Philippines (4 centers, 136 participants) – G Capulong, P de la Pena, C Fabros, M Galan, S Pascual, M Que (East Avenue Medical Centre, Quezon City), J Agra, C Alcantara, G Avila, L Delos Santos, L Guzman, M Licaros, A Panelo, C Solfelix (Institute for Studies in Diabetes Foundation, Marikina City), J Aragon, M Capuli-Isidro, A Daria, L Del Rosario, C Derpo, C Gonzales, E Lim, A Litonjua, C Narvacan-Montano, T Obrero, J Oreal, R Pallera, E Pipo, C Pollisco, S Trinidad (Makati Medical Center, Manila), C Jimeno, M Lim-Abrahan, A Manansala, N Nicodemus (Philippine General Hospital, Manila).
Poland (17 centers, 604 particiapnts) – A Januszewicz, National Advisor (Instytut Kardiologii,Warsaw), J Sieradzki National Advisor (Katedra i Klinika Chorob

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Czubek, P Latacz, B Nessler, W Piwowarska (Klinika Choroby Wiencowej, Krakow), L Czupryniak, J Loba, M Pawlowski, M Saryusz-Wolska (Klinika Diabetologii, Lodz), J Kadziela, B Norwa-Otto, W Ruzyllo (Klinika Kardiologii Ogolnej / Intytyt Kardiologii, Warsaw), A Boruczkowska, J Gluszek, T Kosicka, B Krasinska, A Tykarski, A Wichrowska (Klinika Nadcisnienia Tetniczego i Chorob Naczyn AM, Poznan), S Czekalski, A Simachowicz, A Wasik-Olejnik (Klinika Nefrologii AM, Poznan), B Brzezicki, M Ciesielska, A Ganska, B Gornikiewicz-Brzezicka (NZOZ Poradnia Endokrynologii i Nadcisnienia Tetniczego, Elblag), E Bandurska-Stankiewicz, U Tarasiewicz (Osrodek Diabetologii I Zaburzen Metabolizmu WSZ, Olsztyn), M Chlebus, A Najwa, E Trzepla, B Zapecka-Dubno (Poliklinika SPCSK,Warsaw), M Steuer, E Steuer (PULS MED,Katowice), W Dworzanski, K Michalczyk, J Pikula, E Tylec (Wojewodzki Szpital Specjalistyczny, Radom).

Russia (7 centers, 164 participants) – R Bogieva, I Chazova, D Duishvili, V Gornostaev, K **Mamyrbaeva,** V Moiseev, V Mychka (Cardiology Research Complex, Moscow), A Aleksandrov, T Kravchenko, I Martyanova, V Vilkov (Endocrinology Research Centre, Cardiology, Moscow), N Galitsyna, M Shestakova, N Zaytseva (Endocrinology Research Centre, Nephrology, Moscow), A Babenko, A Volkova, A Zalevskaya (Pavlov's Medical University, St Petersburg), Z Kaverzina, I Martyanova, D Nebieridze, R Oganov, S Tolpygina (Research Centre, Moscow), V Dorofeikov, F Gugova, A Konrady, A Kurbanovna, E Shlyakhto, N Zvartau (Research Institute, St Petersburg), T Dmitrova, A Fremovceva, I Kobalava, A Sirotkina (Russian People's Friendship University, Moscow).

Slovakia (12 centers, 458 participants) –I Balažovjech, National Advisor (Fakultná Nemocnica, Bratislava) H Horvathova, B Krahulec, R Lahitova, R Lamitova, L Strbova, J Sukeova (Fakultná Nemocnica, Bratislava), M Mokan, D Pridavkova, S Smatanova, L Sutarik (Fakultná Nemocnica, Martin), E Simkova, V Spisak, D Stranankova (Interne oddelenie A - NsP, Zilina), J Morsky, L Ruffini, E Tataiova (Kardiologicka Ambulancia, Rimavska Sobota), S Krcmery, Z Mikes, (Klinika Geriatrie LFUK, Bratislava), L Hricova, A Jurcina, , M Marcinova, M Sedlakova P Sefara, P Spurny, E Szokeova (Klinika gerontologie a geriatrie, Košice), M Snincak (Letecka Vojenska Nemocnica, Košice), A Banikova, M Gaziova, K Micko, J Nociar, M Pivkova, B Rajtukova (Nemocnica s Poliklinikou, Lucenec), V Ambrovicova, J Antolik, A Cibulkova, L Ondrusova, G Sojka (Nemocnica s poliklinikou, Levice), M Hranai, M Korpasova, P Minarik, O Moravcikova, M Porubska, J Sirotiakova, M Rac, (Nemocnica s poliklinikou, Nitra), J Mazur, M Moravcova, P Sulej (NsP-JIS, Dolny Kubin), L Beles, K Belesova, G Jakabova, M Zelinska (Poliklinika Vychod, Košice).

United Kingdom (22 centers, 1324 participants) – M Bruce, A De Vries, J Furnace, C Jamieson, M Macleod, P McDonald, S Ross (Aberdeen Royal Infirmary), J Bright, D Darko, D Hopkins (Central Middlesex Hospital), G Beevers, R Haynes, V Karthikeyan, HS Lim, GYH Lip, J Partridge, (City Hospital, Birmingham), M Appleby, R Donnelly, A-M Dwyer, T Gibson, A Scott (Derbyshire Royal Infirmary), B Fisher, J Gray, J McKenzie, G Paice

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(Glasgow Royal Infirmary), A Baksi, J Bartlett, D Hogan, S Moody, Z Thomas, E Whittingstall, P Wilson (St Mary's Hospital, Isle of Wight), S Jackson, L Meakin, L Walwyn (Leicester Royal Infirmary), S Chandran, S Heslop, A Joshi, J Vora, F Westwell, H White (Royal Liverpool University Hospital), M Banerjee, J Collins, K Cruickshank, J Dunkerley, C Harrison, K Hart, M Holland, M Luckson, S Shaw, T Wood (Manchester Royal Infirmary), F Forbes, K Gallagher, A Harrower, D Matthews, E McIntyre, G McKay, J McMahon (Monklands Hospital, Airdrie), L Dudgeon, C Fox, K Hall, M Hollway, L James, S Marsh, D Morgan, G Nayani, V Richards, C Staff, J Stockman (Northampton General Hospital), D James, V Patel, C Randall (George Elliot Hospital, Nuneaton), A Begg, R Grogan, J Hinnie, M McIntyre (Royal Alexandra Hospital, Paisley), F Coates, P Davies, A George, S Golding-Cook, C Hamon, M Jefferies, E Kolinsky, C Meachin, A Millward, K Neeves, M Soler-Lopez, J Stokes (Clinical Research Unit, Plymouth Postgraduate Medical School), B Cunningham, D Ghosh, M Mukhtar, E Simpson, H Simpson (The Diabetes Centre, Reading), R Howard, J Inglis, R Mukhtar, J Reckless, A Robinson, C Shute, C Stirling, A Ward(Royal United Hospital, Bath), J Day, C Green, P Jackson, A Roberts, E Wallis (Sheffield Hallamshire Hospital), M Cunningham, S Heller, S Hudson (Sheffield Northern Hospital), B Ariff, J Bunker, W Callister, C Coghlan, R Elkeles, R Fernandez, V Gordon, J Harman, N Jugnee, L Knisley, J Macduff, J Mackay, K McFadden-Lewis, A McKerracher, P Mistry, S Mitchell, S Murphy, A Strain, S Thom, O Trainor, S Whitehouse, A Zambanni (St. Marys Hospital, London), S Boardman, C Reid, V Reid (Warwick General Hospital), C Coddington, A Ellis, C Holliday, C Slater (West Byfleet Health Care Research), D Brown, V Dawson, H Gibson, P Jennings, J Thow, S Whitwell (York District Hospital).

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Relationship Between Plasma 8–OH–Deoxyguanosine and Cardiovascular Disease and Survival in Type 2 Diabetes Mellitus: Results From the ADVANCE Trial

Merlin C. Thomas, Mark Woodward, Qiang Li, Raelene Pickering, Christos Tikellis, Neil Poulter, Mark E. Cooper, Michel Marre, Sophia Zoungas, John Chalmers and the ADVANCE Collaborative Group

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