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Variability in eGFR and the risk of major clinical outcomes in diabetes: post-hoc analysis from the ADVANCE trial

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ABSTRACT

There are limited data on whether estimated glomerular filtration rate (eGFR) variability modifies the risk of future clinical outcomes in type 2 diabetes mellitus (T2DM). We assessed the association between 20-month eGFR variability and the risk of major clinical outcomes in T2DM amongst 8241 participants in the ADVANCE trial. Variability in eGFR (coefficient of variation;CV_{eGFR}) was calculated from 3 serum creatinine measurements over 20 months. Participants were classified into 3 groups by thirds of CV_{eGFR}: low (≤6.4;reference), moderate (>6.4 to ≤12.1) and high (>12.1). The primary outcome was the composite of major macrovascular events, new or worsening nephropathy and all-cause mortality. Cox regression models were used to estimate hazard ratios (HRs). Over a median follow-up of 2.9 years following the 20-month period, 932(11.3%) primary outcomes were recorded. Compared with low variability, greater 20-month eGFR variability was independently associated with higher risk of the primary outcome (HR for moderate and high variability:1.07, 95%CI:0.91-1.27 and 1.22, 95%CI:1.03-1.45, respectively) with evidence of a positive linear trend(p=0.015). These data indicate that eGFR variability predict changes in the risk of major clinical outcomes in T2DM.

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INTRODUCTION

Diabetes is the leading cause of chronic kidney disease (CKD).[1] People with diabetic kidney disease are at increased risk of poor outcomes including end-stage kidney disease and cardiovascular disease.[2] Monitoring disease progression and the possibility of future adverse events is thus a cornerstone of the management of this high-risk group.[3] Routine assessments of estimated glomerular filtration rate (eGFR) is an important component of this management strategy.

One frequently observed occurrence in such routine outpatient assessments is within-person fluctuations in eGFR. However, whether this variation modifies the risk of clinical outcomes and death, or is non-consequential physiological variation, in people with type 2 diabetes mellitus (T2DM) remain uncertain. A small number of studies to date have reported higher risk of adverse kidney outcomes and all-cause death associated with greater eGFR variability[4,5]. However, these have been limited by narrow inclusion criteria: studying mostly men[4] and/or people with lower eGFR (<60 ml/min/1.73m^2). An assessment of the clinical significance of eGFR variability in broader high-risk groups including T2DM is needed.

Using data from the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE), a randomised controlled trial (RCT) in patients with T2DM[6-8], we assessed the relationships between 20-month variability in eGFR and major macrovascular events, new or worsening nephropathy events, and all-cause mortality.

Research Design and Methods

Study design and population

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ADVANCE was a 2x2 factorial RCT evaluating the effects of blood pressure lowering (perindopril-indapamide combination vs. placebo) and intensive blood glucose lowering (HbA1c ≤6.5% vs. standard glucose control) treatment on vascular outcomes in 11,140 individuals with T2DM aged ≥55 years at high risk of cardiovascular events recruited in 20 countries.[6] All participants provided written informed consent.

Study outcomes and follow-up

The primary outcome for this study was the composite of major macrovascular events (myocardial infarction, stroke or other cardiovascular death), new or worsening nephropathy (defined as new-onset macroalbuminuria, end-stage kidney disease, renal death and doubling of creatinine to >200 μmol/l) and all-cause mortality. Secondary outcomes were the individual components. Participants were followed from their two-year visit until the earliest of the first study event, death or the end of follow-up (median 5 years; Supplementary figure 1).

Statistical methods

Participants with serum creatinine measurements at 4, 12 and 24 months after randomisation were eligible for inclusion into the current study. Patients with study outcomes during the first two years; those with missing serum creatinine or covariate information, were excluded.

To account for known acute increases in serum creatinine following initiation of angiotensin-converting enzyme (ACE) inhibitors[9-10], we excluded the serum creatinine measurement obtained during the first 4 months. We therefore assessed eGFR[11] variability over a 20-month period based on serum creatinine measurements obtained at 4, 12 and 24 months after randomisation. Variability in eGFR was assessed using the coefficient of variation (CV_{eGFR}). Participants were then grouped by thirds of CV_{eGFR} (presented as a percentage) defined as: low

(≤6.4; reference group), moderate (>6.4 to ≤12.1) and high (>12.1) variability. We also assessed variability as a continuous variable using restricted cubic spline regression models.

Log-linear trends across CV_{eGFR} categories at baseline were tested by linear regression analysis and logistic regression analysis, as appropriate. Cox regression models were used to estimate hazard ratios (HRs), and their corresponding 95% confidence intervals (CIs), for eGFR variability adjusting for baseline participant characteristics (see Figure 1 for full list).

We conducted sensitivity analysis in which we repeated analyses: 1) adjusting Cox models for eGFR slope at 24 months after randomisation (estimated based on the same three eGFR measurements over the 20-month period using linear mixed models) and both baseline eGFR and eGFR slope, and 2) using two alternative indices of eGFR variability: standard deviation (SD; SD_{eGFR}) and range ($range_{eGFR}$).

Statistical analyses were performed with Stata software (release 16.1, StataCorp, College Station, TX, USA). A two-sided p-value <0.05 was considered statistically significant.

Data availability

Restrictions apply to the availability of these data, which were used by agreement of the ADVANCE steering committee for the current study, and so are not publicly available.

Results

Of the 11,140 participants in the ADVANCE trial, 8241 participants (73.9%) were eligible for inclusion in the current study (Supplementary figure 1). The mean age of the cohort was 68.1

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years (SD 6.3), 43% were female and the mean duration of diabetes was 8.2 years at baseline (interquartile interval [IQI]:5.0-13.1) (Table 1).

Variability in eGFR in the first 20 months

Among patients with eGFR ≥60 ml/min/1.73m^2 at the time of the first eGFR measurement (n=6239), 35.7% (n=2229), 34.3% (n=2142) and 29.9% (n=1868) experienced low, moderate and high variability over the following 20 months, respectively. Conversely, in those with eGFR <60 ml/min/1.73m^2 at the time of the first eGFR measurement (n=2002), corresponding figures were 25.9% (n=518), 30.2% (n=605) and 43.9% (n=879), respectively. The overall median CV_{eGFR}, SD_{eGFR} and $range_{eGFR}$ were 8.9 (IQI:5.1-14.6), 6.2 ml/min/1.73m^2 (IQI:3.5-10.0 ml/min/1.73m^2), and 11.6 ml/min/1.73m^2 (IQI:6.6-19.2 ml/min/1.73m^2), respectively (Supplementary figure 2). The proportions of people with eGFR <60 ml/min/1.73m^2 (n=2002) were higher in the high (43.9%) and moderate (30.2%) CV_{eGFR} variability groups compared with the low variability group (25.9%). However, similar patterns were not observed when participants were grouped according to tertiles of SD_{eGFR} (29.3%, 31.4% and 39.3%, respectively) and $range_{eGFR}$ (29.2%, 31.8%, 39.0%, respectively; Supplementary table 1).

Clinical events during further follow-up

During a median 2.9 years (IQI:2.5-3.0) following the 20-month period in which eGFR variability was measured, 932 patients (11.3%) developed the primary composite outcome. There were 466 major macrovascular events (5.6%), 296 new or worsening nephropathy events (3.5%) and 418 deaths (5.0%). Overall, greater eGFR variability, assessed by the CV_{eGFR}, over 20 months was independently associated with higher risk of the primary outcome (HR for moderate and high variability compared with low variability: 1.07, 95% CI:0.91-1.27 and 1.22,

95% CI:1.03-1.45, respectively; Figure 1) with evidence of a positive log-linear trend (p=0.015).

Results for new or worsening nephropathy were consistent with those for the primary outcome (HR for moderate and high variability compared with low variability: 1.07, 95% CI:0.77-1.48 and 1.45, 95% CI:1.07-1.97, respectively; Figure 1). We did not observe statistically significant associations between greater eGFR variability and the risk of major macrovascular events or all-cause mortality. However, the overall direction of the associations was similar compared to those observed for the primary outcome and new or worsening nephropathy.

An evaluation of the relationship between continuous CV_{eGFR} and the risk of study outcomes showed similar associations for the primary and secondary outcomes (Supplementary figure 3).

Additional sensitivity analysis in which 1) models were adjusted for eGFR slope (HR for primary outcome for moderate and high variability vs. low variability: 1.14, 95% CI:0.96-1.34 and 1.36, 95% CI:1.16-1.61, respectively; Supplementary figure 4), 2) models were adjusted for both baseline eGFR and eGFR slope (HR 1.07, 95% CI:0.91-1.27 and 1.23, 95% CI:1.04-1.45, respectively; Supplementary figure 5) and 3) eGFR variability was defined using SD_{eGFR} (HR 1.11, 95% CI:0.95-1.31 and 1.22, 95% CI:1.04-1.44, respectively; Supplementary figure 6) and $range_{eGFR}$ (HR 1.13, 95% CI:0.96-1.32 and 1.22, 95% CI:1.03-1.44, respectively; Supplementary figure 7) showed similar results.

Discussion

In this analysis of 8241 patients with T2DM, greater variability in eGFR over 20 months predicted higher risk of major clinical outcomes with evidence of a positive linear trend. Much

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of the association was driven by a higher risk of new or worsening nephropathy among those who experienced greater magnitudes of eGFR variability. Similar statistically significant associations were not observed for the major macrovascular events and all-cause death, although the direction of the association remained consistent. Overall findings were consistently observed when eGFR variability was defined using alternative measures including standard deviation and range, or when models were adjusted for baseline eGFR and eGFR slope. Our results suggest that greater eGFR variability may increase the future risk of clinically important outcomes in people with T2DM.

Few studies have assessed the relationships between eGFR variability and clinical outcomes. The study by Al-Aly et al.[4] reported a significantly increased risk of death associated with high eGFR variability in a cohort of 51,304 US veterans with reduced eGFR (HR 1.34, 95% CI:1.28-1.40). In another smaller study of 2869 patients with CKD in Japan, greater eGFR variability was associated with a higher risk of cardiovascular events (HR for highest vs. lowest tertile of eGFR variability: 1.90, 95% CI:1.03-3.71).[12] Our results further expand on these studies by showing a positive linear association between eGFR variability and a range of clinically relevant outcomes in people with T2DM.

Greater within-person eGFR variability observed in the outpatient setting (i.e. variability not related to acute insults in kidney function) may be attributable to 1) deteriorating capacity to maintain renal homeostasis induced by progressive kidney function loss (i.e. an indicator of eGFR decline) and/or 2) external factors (e.g. medication use) that contribute to more random fluctuations that may not necessarily be associated with any discernible trends in eGFR trajectory. Our results showed that even after accounting for both baseline eGFR and eGFR slope (i.e. potential causative factors that may explain greater eGFR variability), greater eGFR

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variability predicted increased risk of major clinical outcomes in T2DM – i.e. greater eGFR variability in people with T2DM may have meaningful prognostic utility independent of baseline eGFR, including those in whom progressive eGFR decline is absent. Indeed, it has been postulated that loss of physiological homeostasis contributes to variability in a number of other measures such as blood pressure,[13-15] which in turn drives the increased risk of poor outcomes including cardiovascular disease and microvascular complications. Of note, while the mechanism through which this increased risk is driven may be similar to that postulated for the relationship between blood pressure variability and outcomes, our analyses accounted for blood pressure variability, suggesting that eGFR variability predicts changes in risk independent of blood pressure variability.

The strengths of our study include the assessment of the relationship between eGFR variability and clinically important outcomes based on multiple approaches and the large and diverse participant population derived from an international, multicentre RCT. Our study, however, has limitations. We used eGFR (instead of direct GFR measurement) which itself is subject to variation due to analytical error associated with creatinine measurement. It is possible that this may have led to some misclassification of eGFR variability. New or worsening nephropathy consisted mostly of new-onset macroalbuminuria (81%) and thus we were limited in our ability to assess the impact of eGFR variability on longer-term kidney outcomes. We assessed eGFR variability within the setting of a RCT and therefore the results may have limited generalisability to broader populations in more routine clinical settings.

In conclusion, greater variability in eGFR over 20 months predicted higher risk of major clinical outcomes. Our results suggest that greater variability in eGFR, over and above single

values of eGFR, may increase the future risk of clinically important outcomes in people with T2DM and that it may be an important prognostic marker in this population.

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Conflict of interest

MJ reports receiving grant support from the NHMRC and unrestricted grant support from VentureWise (a wholly owned commercial subsidiary of NPS MedicineWise) to conduct a commissioned project funded by AstraZeneca, outside the submitted work. SVB has received speaker honoraria from Amgen, Bayer and Pfizer and served on the advisory boards of Bayer and AstraZeneca. MW reports consultancy fees from Amgen, Kirin and Freeline outside the submitted work and grants from the NHMRC. JC received research grants from NHMRC and from Servier for the ADVANCE trial, and honoraria for speaking about these studies at scientific meetings.

Author contributions

MJ, JC, VP and MW contributed to the concept and rationale for the study and interpretation of the results. MJ conducted statistical analysis and drafted the manuscript with advice from MW. All authors contributed to discussion and reviewed and edited the manuscript. MJ and MW are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Table 1: Characteristics of study participants by eGFR variability (thirds of eGFR coefficient of variation [CV]; CV_{eGFR})

	Thirds of CV_{eGFR} (ml/min/1.73m^2)			
Variable	Low variability (≤6.4)	Moderate variability (>6.4 to ≤12.1)	High variability (>12.1)	*P* for trend
Number of participants	2,747	2,747	2,747	
Demographic factors				
Age (years)	67.9 (6.4)	68.3 (6.2)	67.9 (6.2)	0.758
Female (%)	1,042 (38)	1,107 (40)	1,426 (52)	<0.001
Residence in Asia (%)	970 (35)	943 (34)	1,419 (52)	<0.001
Medical and Lifestyle history				
Duration of diabetes mellitus (years)	8.1 (4.2-13.1)	9.1 (5.1-13.2)	9.1 (5.1-13.2)	0.001
History of macrovascular disease at baseline (%)	809 (29)	860 (31)	887 (32)	0.023
Current smoking (%)	354 (13)	256 (9)	200 (7)	<0.001
Current alcohol drinking (%)	868 (32)	802 (29)	528 (19)	<0.001
ACE inhibitor use (%)	1,449 (53)	1,421 (52)	1,368 (50)	0.029
ADVANCE randomisation: perindopril-indapamide	1,281 (47)	1,405 (51)	1,430 (52)	<0.001
ADVANCE randomisation: intensive blood glucose control	1,424 (52)	1,367 (50)	1,434 (52)	0.787
Risk factors				
SBP (mmHg)	138 (18)	137 (18)	136 (18)	0.077
DBP (mmHg)	77 (10)	77 (10)	76 (10)	0.001
Body mass index (kg/m^2)	28.2 (5.2)	28.4 (5.1)	27.9 (5.1)	0.011
Haemoglobin A_{1c} (%)	6.9 (1.2)	6.9 (1.1)	6.9 (1.3)	0.300
Total cholesterol (mmol/l)	4.8 (1.0)	4.8 (1.1)	5.0 (1.1)	<0.001
Triglycerides (mmol/l)	1.5 (1.1-2.1)	1.6 (1.1-2.2)	1.6 (1.2-2.3)	<0.001
UACR (µg/mg)	13.3 (6.5-32)	14 (6.8-33)	15.7 (7.8-42.4)	0.001
CV_{SBP} (mmHg)	29.9 (4.7)	30.1 (4.8)	30.1 (4.8)	0.033
First eGFR (ml/min/1.73m^2) measurement^	76.7 (16.6)	71.7 (15.3)	69.5 (17.7)	<0.001
Last eGFR (ml/min/1.73m^2) measurement^	76.3 (16.5)	71.1 (15.8)	67.6 (18.8)	<0.001
Mean rate of eGFR change (ml/min/1.73m^2) over 20 months (SD)	-0.19 (2.2)	-0.33 (4.9)	-0.97 (10.7)	<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; ^assessed during the 24-month eGFR variability assessment period

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Figure legend

Figure 1: The association between levels of eGFR variability (coefficient of variation [CV]; CV_{eGFR}) and clinical outcomes

Variability defined as: 1) low variability: CVeGFR ≤6.4 (reference); 2) moderate variability: CVeGFR >6.4 to ≤12.1; and 3) high variability: CVeGFR >12.1; Models were adjusted for age*, sex, randomised blood pressure-lowering intervention, randomised glucose control intervention, region of residence, duration of diabetes*, history of macrovascular diseases*, smoking habit*, drinking habit*, body mass index*, angiotensin-converting enzyme (ACE) inhibitor use*, HbA1c*, total cholesterol*, low-density lipoprotein (LDL) cholesterol*, high-density lipoprotein (HDL) cholesterol*, log-transformed triglyceride*, estimated glomerular filtration rate* (eGFR), systolic blood pressure* (BP), log-transformed urine albumin-to-creatinine ratio* (UACR) and variability of systolic BP; participant characteristics were assessed at the 24-month study visit, where available (*indicate characteristics assessed at the 24 months visit). Models were adjusted for participant characteristics assessed at the 24-month study visit (after randomisation), where available (including eGFR); otherwise, values assessed at study registration were used.

Table legend

Table 1: Characteristics of study participants by eGFR variability (thirds of eGFR coefficient of variation; CV_{eGFR})

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Figure 1: The association between levels of eGFR variability (coefficient of variation [CV]; CVeGFR) and clinical outcomes