Risk for Cardiovascular Outcomes among Subjects with Atherosclerotic Cardiovascular Disease and Greater-than-Normal Estimated Glomerular Filtration Rate

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Background and objectives: Estimating equations for calculating glomerular filtration rate (eGFR) occasionally identify patients with elevated eGFR, yet the prognostic significance remains to be determined. This study sought to define the association of an elevated eGFR on the risk for death and cardiovascular outcomes among subjects with atherosclerotic cardiovascular disease.

Design, setting, participants, & measurements: Data from 8941 subjects who had a history of atherosclerotic vascular disease and were enrolled in the Blockade of the Glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion trial were analyzed. Time to the composite end point of death, congestive heart failure, myocardial infarction, or stroke was modeled using Cox proportion hazards regression. Glomerular filtration rate was estimated using the Modification of Diet in Renal Disease and Cockcroft-Gault formulas.

Results: Compared with subjects with eGFR of 100 to 125 ml/min per 1.73 m^2, subjects with eGFR ≥125 (n = 462) were younger, female, and nonwhite. In addition, subjects with an elevated eGFR were more likely to have diabetes and congestive heart failure. In adjusted analyses, every 10-ml/min per 1.73 m^2 decrease in eGFR <100 was associated with a 13% increased hazard for the composite end point. In addition, every 10-ml/min per 1.73 m^2 increase in eGFR ≥100 was associated with a 9% increased hazard for the composite end point.

Conclusions: In individuals with a history of vascular disease, the relationship between eGFR and cardiovascular outcomes may be parabolic, with increased risk among patients with both reduced and elevated eGFR.

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The number of adults in the United States with chronic kidney disease (CKD) is approximately 19 million and growing rapidly (1,2). Patients with CKD have higher cardiovascular risk than the general population, resulting in a tremendous burden of morbidity and mortality (3). An estimated GFR (eGFR) of <60 ml/min per 1.73 m^2 is recognized as a major cardiovascular risk factor in several national guidelines (4,5); however, the clinical impact of an above-normal eGFR remains to be determined.

Because CKD may be "clinically silent," identification often relies on laboratory measurements to estimate GFR as an index of kidney function. Although the best method to determine renal function is a measured GFR, time and expense limitations have led to the routine use of estimating equations for determining renal function (*e.g.*, Cockcroft-Gault and Modification of Diet in Renal Disease [MDRD] equations) (6–8). Although these equations have been used to identify patients with CKD, they also occasionally identify individuals with eGFR that are greater than normal. Although increased eGFR has been identified in patients with diabetes and more recently in patients with metabolic syndrome (9), the clinical impact of an above-normal eGFR has yet to be elucidated.

Although an estimated 55% of patients with significant atherosclerotic cardiovascular disease have some degree of renal insufficiency (10), patients with CKD are often excluded from large cardiovascular trials. When renal function is examined in patients who undergo cardiovascular diagnostic and therapeutic procedures, attention is focused on patients with lower GFR. Given that kidney function is associated with clinical outcomes and the relationship between renal function at the higher end of the spectrum has not been explored, we undertook this analysis to elucidate the association of increased GFR on the rate of death and progression of cardiovascular events.

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Concise Methods

The Blockade of the Glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion (BRAVO) trial has previously been described in detail (11,12). In summary, BRAVO was a double-blind, multicenter trial in which patients with vascular disease were randomly assigned to lotrafiban (an oral glycoprotein IIb/IIIa inhibitor) or matching placebo daily plus aspirin once daily. Subjects ($n = 9190$) were treated with either 30 or 50 mg of lotrafiban/placebo twice daily, depending on their age and renal function. All subjects received concomitant aspirin therapy at a dosage determined by the investigator's usual practice but no less than 75 mg/d and no more than 325 mg/d.

The primary efficacy end point of the BRAVO study was the time to first occurrence of the composite of death by any cause, myocardial infarction (MI), stroke, recurrent ischemia requiring hospitalization, or urgent ischemia-driven revascularizations. Patients qualified for the study when they had (*1*) an MI within 14 d of the baseline evaluation; (*2*) the diagnosis of unstable angina within 14 d of the baseline evaluation; (*3*) an ischemic stroke confirmed by history, physical examination, and computed tomographic or magnetic resonance imaging scan to be entered into the study no sooner than 5 d and no later than 30 d after the acute event; (*4*) a transient ischemic attack within 30 d of the baseline evaluation confirmed through positive history and/or physical examination in the absence of any significant findings on the computed tomography or magnetic resonance imaging scan; or (*5*) had evidence of peripheral vascular disease combined with evidence of either cardiovascular or cerebrovascular disease. Patients were enrolled into the trial during their initial hospitalization with an acute event or at their first clinic visit. Patients with severe CKD (creatinine clearance [CrCl] <30 ml/min by Cockcroft-Gault formula) and patients with concomitant severe disease, such as neoplasm that was likely to limit life expectancy or study participation to <2 yr, were excluded.

Measurement of Kidney Function

Although it has not yet been validated across all patient populations, the MDRD equation is the currently accepted tool used to estimate GFR and advocated in Clinical Practice Guidelines of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) (13). For this analysis, eGFR was calculated using the abbreviated MDRD equation (6,8):

$$\text{eGFR (ml/min per 1.73 m}^2) = [186 \times S_{Cr}^{-1.154} \times \text{age}^{-0.203} \times 0.742 \text{ (if female)} \times 1.210 \text{ (black)}]$$

where S_{Cr} is serum creatinine. In additional sensitivity analyses, CrCl was calculated using the Cockcroft-Gault equation (7) using ideal body weight (14–16):

$$\text{CrCl (ml/min)} = [(140 - \text{age}) \times \text{body weight (kg)}/72 \times S_{Cr}] \times 0.85 \text{ (if female)}$$

eGFR was analyzed as a continuous variable whenever possible. Subjects had S_{Cr} measured at baseline; at 72 h or hospital discharge; at 7, 10, 14 and d and 3 mo; and every 3 mo subsequently until completion of the trial.

Primary Outcome

The primary outcome for this analysis was time to the composite end point of death, congestive heart failure (CHF) hospitalization, MI, or stroke.

Statistical Analyses

Demographic and clinical factors were summarized and compared between groups of subjects stratified on renal function. Continuous and categorical variables were compared using the Spearman correlation test and the Kruskal-Wallis test, respectively.

Time to the first occurrence of one of the events in the composite end point was compared across groups characterized by baseline eGFR. Univariate survival probabilities were compared among groups of subjects on the basis of category of baseline eGFR using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazards regression was used to model the association between time-varying eGFR and the hazard for the composite end point controlled for other predictors. Proportional hazards assumptions and linearity assumptions for continuous variables were assessed. The assumption of linearity was checked in the model for the continuous variable by restricted cubic splines. When the relationship was found to be nonlinear, appropriate transformations were applied. Because of a nonlinear association between eGFR and log hazards ratio, a two-piece-wise linear spline was used to represent the associations of GFR. eGFR and the occurrence of percutaneous transluminal coronary angioplasty (PTCA) during follow-up were treated as time-dependent covariates in the model. The following baseline variables were tested for inclusion in the final model: Age; race; gender; tobacco use; body mass index (BMI); heart rate; aspirin dosage of ≥162 mg/d; history of diabetes, hypertension, CHF, or previous PTCA; and history of unstable angina, MI, peripheral vascular disease, stroke, or transient ischemic attack as qualifying event for enrollment into BRAVO. Randomization arm (lotrafiban *versus* placebo) was forced into all models. The risk factors that were finally retained in the model for adjustment were chosen using $P = 0.10$ as inclusion criterion. An adjusted comparison of the hazard associated with time-varying eGFR was plotted using a smoothed curve generated through SAS (SAS Institute, Cary, NC).

Sensitivity analyses were performed replacing eGFR estimated by the MDRD equation with CrCl estimated by Cockcroft-Gault equation. Further sensitivity analyses included multivariable analyses that censored on the occurrence of coronary artery bypass graft surgery during follow-up.

All *P* values reported are two-sided, and all confidence intervals (CI) reported are 95% intervals. All analyses were performed using SAS 8.2. The study was approved by an institutional review committee, and the subjects gave informed consent.

Results

Clinical and Demographic Characteristics of Subjects

A total of 8941 subjects who were enrolled in BRAVO and had baseline S_{Cr} measurements were included in this analysis (Table 1). In general, subjects with lower baseline eGFR were more likely to be older, female, and white and to have a history of diabetes, hypertension, and CHF. Subjects with lower eGFR were also more likely to have unstable angina or peripheral vascular disease as compared with a stroke as the qualifying diagnosis for enrollment into the BRAVO trial. Subjects with lower eGFR were less likely to have smoked tobacco and to have a history of undergoing PTCA before enrollment and were less likely to be taking aspirin ≥162 mg at baseline.

A total of 360 (4.0%) subjects had an eGFR from 125 to 150 ml/min per 1.73 m^2, and 102 (1.1%) subjects had an eGFR ≥150 ml/min/1.73m^2. Comparing subjects in these two categories with subjects with eGFR from 100 to 125 ml/min per 1.73 m^2, subjects with greater eGFR were more likely to be younger, female, and nonwhite. Subjects with eGFR ≥125 also had a higher heart rate and were more likely to have diabetes and CHF compared with subjects with eGFR from 100 to 125.

Table 1. Subject characteristics stratified by baseline eGFR (ml/min per 1.73 m^2)[a]

Characteristic	Entire Cohort	eGFR <45	eGFR ≥45 and <60	eGFR ≥60 and <75	eGFR ≥75 and <100	eGFR ≥100 and <125	eGFR ≥125 and <150	eGFR ≥150	*P*
n (%)	8941 (100)	409 (4.6)	1089 (12.2)	2091 (23.4)	3502 (39.2)	1388 (15.5)	360 (4.0)	102 (1.1)	
Age (yr; mean ± SD)	62.2 ± 11.1	69.0 ± 9.3	68.0 ± 9.7	64.7 ± 10.5	60.7 ± 10.7	58.1 ± 11.1	55.3 ± 10.5	57.0 ± 11.1	<0.0001
Male (%)	70.7	56.2	60.8	69.4	74.9	74.5	68.6	71.6	<0.0001
White race (%)	94.0	94.9	95.8	94.8	94.1	93.2	88.9	83.3	<0.0001
BMI (mean ± SD)[b]	27.8 ± 5.2	28.7 ± 8.7	27.7 ± 4.5	27.7 ± 4.6	27.8 ± 4.8	27.9 ± 6.3	28.1 ± 5.8	28.1 ± 6.1	0.3
Heart rate (bpm; mean ± SD[c]	69.8 ± 10.8	70.5 ± 11.1	69.2 ± 10.6	69.6 ± 10.9	67.6 ± 10.8	70.2 ± 10.6	71.2 ± 11.0	73.4 ± 10.3	0.02
Diabetes (%)	22.6	31.3	27.8	21.5	19.8	23.6	25.8	26.5	0.001
Hypertension (%)	66.9	80.9	77.8	69.9	63.3	61.6	59.4	58.8	<0.0001
CHF (%)	9.0	23.0	14.3	9.9	6.8	5.8	5.6	9.8	<0.0001
MI (%)[d]	25.2	25.9	24.3	24.4	25.8	25.4	25.0	25.5	0.2
Unstable angina (%)[d]	26.6	31.8	26.6	29.2	26.5	22.7	22.5	27.5	<0.0001
Peripheral vascular disease (%)[d]	16.2	22.7	19.7	16.1	15.1	14.8	15.6	15.7	<0.0001
Stroke (%)[d]	24.4	22.0	24.4	21.5	25.1	26.9	28.3	22.5	0.0001
Tobacco abuse (%)	26.6	16.4	18.0	21.2	28.3	36.3	40.0	33.3	<0.0001
Previous or baseline PTCA (%)	29.5	22.2	24.4	28.8	31.8	30.1	31.4	30.4	<0.0001
Baseline aspirin dosage ≥162 mg	47.7	40.1	43.6	44.1	48.4	52.4	61.1	66.7	<0.0001

[a]*P* values for continuous variable obtained by Spearman correlation coefficients, *P* values for categorical variables obtained by Wilcoxon rank-sum tests. BMI, body mass index; BPM, beats per minute; CHF, congestive heart failure; eGFR, estimated GFR; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.

[b]*n* = 8813 (data for 128 subjects are missing).

[c]*n* = 8829 (data for 112 subjects are missing).

[d]Qualifying event for enrollment into BRAVO.

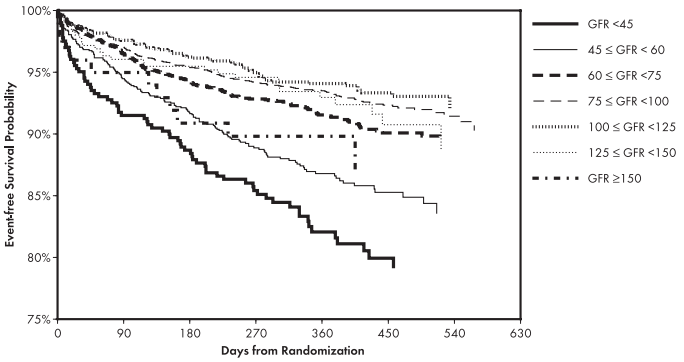

Figure 1. Kaplan-Meier Survival curves for time to first event of death, congestive heart failure (CHF), myocardial infarction (MI), or stroke among subjects grouped by baseline estimated GFR (eGFR).

Time to Death, CHF, MI, or Stroke

Time to death, CHF, MI, or stroke was different among subjects grouped by baseline eGFR (log-rank statistic = 100.7, $P < 0.0001$; Figure 1). In general, survival decreased among categories of subjects with lower eGFR at baseline. Subjects with the lowest baseline eGFR had the poorest survival of the entire cohort. Subjects with the most elevated eGFR (≥150 ml/min per 1.73 m^2) similarly had poor overall survival rates.

Unadjusted clinical event rates by baseline eGFR are summarized in Table 2. In general, for subjects with eGFR <100 ml/min per 1.73 m^2, the clinical event rates increased with decreasing eGFR. This trend, however, did not continue among subjects with eGFR ≥125 ml/min per 1.73 m^2. Among subjects with eGFR ≥125 ml/min per 1.73 m^2 at baseline, the number of composite events increased relative to subjects with eGFR from 100 to 125, mostly as a result of an increase in MI and stroke.

In a multivariable model, a nonmonotonic relationship was observed when the association between time-dependent eGFR and time to the composite end point of death, CHF, MI, or stroke was examined (Table 3, Figure 2). Among subjects with an eGFR <100 ml/min per 1.73 m^2, each 10-ml/min per 1.73 m^2 decrease in eGFR was associated with a 13% increase in the hazard for the composite end point (hazard ratio [HR] 1.13; $P < 0.0001$); however, among subjects with an eGFR ≥100 ml/min per 1.73 m^2, each 10-ml/min per 1.73 m^2 increase in eGFR was associated with a 9% increase in the hazard for the composite end point (HR 1.09; $P = 0.003$). Other significant predictors of the composite outcome included history of CHF at baseline ($P < 0.0001$), increasing age ($P < 0.0001$), the presence of diabetes ($P < 0.0001$), MI as the qualifying event for enrollment ($P = 0.001$), the occurrence of PTCA during the observation period ($P = 0.009$), tobacco abuse ($P = 0.03$), and increasing heart rate ($P = 0.05$). Peripheral vascular disease as the qualifying event for enrollment into BRAVO was associated with a decreased risk for the composite end point ($P = 0.007$).

There was a significant interaction between age and decreasing eGFR <100 ml/min per 1.73 m^2 ($P = 0.002$) as predictors of the composite end point, but there was no significant interaction between age and increasing eGFR ≥100, suggesting that age did not confound the relationship between elevated eGFR and detrimental cardiovascular outcomes. Among subjects who were ≥55 yr of age, every 10-ml/min per 1.73 m^2 decrease in eGFR <100 was associated with an increased risk for the composite end point (HR 1.19; 95% CI 1.14 to 1.25), which was nonsignificant among subjects who were younger than 55 yr (HR 0.93; 95% CI 0.81 to 1.07). There were no significant interactions between the presence of diabetes and increasing eGFR ≥100 ($P = 0.15$) or decreasing eGFR <100 ($P = 0.87$).

Sensitivity Analyses

To test whether the increased risk associated with elevated eGFR was associated only with the use of the MDRD as an estimating equation, we performed sensitivity analyses in which kidney function was estimated with the Cockcroft-Gault equation to determine the association between elevated CrCl and clinical outcomes. Unadjusted comparisons of the rates of the composite end point among subjects who were categorized by CrCl as measured by Cockcroft-Gault are summarized in Table 4.

In adjusted analysis that included CrCl estimated by the Cockcroft-Gault equation as a time-varying covariate, there

Table 2. Number of subjects who experienced each event, grouped by baseline eGFR (ml/min per 1.73 m^2)[a]

Parameter (*n* [%])	Entire Cohort	eGFR <45	eGFR ≥45 and <60	eGFR ≥60 and <75	eGFR ≥75 and <100	eGFR ≥100 and <125	eGFR ≥125 and <150	eGFR ≥150
n (%)	8941 (100)	409 (4.6)	1089 (12.2)	2091 (23.4)	3502 (39.2)	1388 (15.5)	360 (4.0)	102 (1.1)
Composite end point[b]	750 (8.4)	72 (17.6)	141 (12.9)	179 (8.6)	239 (6.8)	81 (5.8)	27 (7.5)	11 (10.8)
Death as first event	164 (1.8)	16 (3.9)	32 (2.9)	47 (2.2)	46 (1.3)	15 (1.1)	7 (1.9)	1 (1.0)
CHF as first event	239 (2.7)	34 (8.3)	49 (4.5)	60 (2.9)	78 (2.2)	14 (1.0)	3 (0.8)	1 (1.0)
MI as first event	163 (1.8)	21 (5.1)	28 (2.6)	32 (1.5)	52 (1.5)	22 (1.6)	3 (0.8)	5 (4.9)
Stroke as first event	194 (2.2)	5 (1.2)	34 (3.1)	41 (2.0)	66 (1.9)	30 (2.2)	14 (3.9)	4 (3.9)

[a]This table lists each patient only once on the basis of the first event.
[b]Composite end point of death, CHF, MI, and stroke.

Table 3. Multivariable model of predictors of death, CHF, MI, or stroke[a]

Variable	HR (95% CI)	*P*
eGFR <100 (per 10 ml/min per 1.73 m^2 decrease)[b]	1.13 (1.08 to 1.18)	<0.0001
eGFR ≥100 (per 10 ml/min per 1.73 m^2 increase)[b]	1.09 (1.03 to 1.16)	0.003
History of CHF	2.30 (1.92 to 2.75)	<0.0001
Age (per increase of 10 yr)	1.32 (1.22 to 1.43)	<0.0001
History of diabetes	1.69 (1.45 to 2.00)	<0.0001
MI[c]	1.36 (1.16 to 1.59)	0.0001
PTCA during period of observation[b]	1.49 (1.10 to 2.00)	0.009
Tobacco abuse	1.21 (1.02 to 1.45)	0.03
Heart rate (per increase of 1 bpm)	1.01 (1.00 to 1.01)	0.05
Peripheral vascular disease[c]	0.77 (0.63 to 0.93)	0.007
White race	0.77 (0.59 to 1.01)	0.06
Treatment arm (lotrafiban *versus* placebo)	1.12 (0.98 to 1.30)	0.1

[a]The following baseline variables were tested for inclusion in the final model and removed with a $P > 0.10$: BMI; male gender; history of hypertension or history of PTCA; unstable angina, TIA, or stroke as qualifying event for enrollment into BRAVO; and aspirin dosage ≥162 mg. CI, confidence interval; HR, hazard ratio.
[b]Treated as a time-varying covariate.
[c]Qualifying event for enrollment into BRAVO.

was a nonlinear association between CrCl and the log HR of the primary outcome. In multivariable models, every 10-ml/min decrease in CrCl below 90 ml/min was associated with a 19% increase hazard for the composite end point (HR 1.19; 95% CI 1.13 to 1.25; $P < 0.001$; Table 5; however, every-10 ml/min increase in CrCl above 90 ml/min was also associated with a 10% increased hazard for the composite end point (HR 1.10; 95% CI 1.03 to 1.17; $P = 0.006$). We also performed analyses that censored on the occurrence of coronary artery bypass graft and found similar results (data not shown).

Discussion

Whereas a decreased GFR is clearly associated with increased mortality among patients with atherosclerotic cardiovascular disease (17), the prognostic impact of increased GFR is not known. Among a cohort of subjects with atherosclerotic cardiovascular disease, this study demonstrates that an eGFR above the "normal" range may be associated with increased adverse outcomes, including MI, CHF, stroke, and all-cause mortality.

Although no previous study has demonstrated detrimental outcomes associated with higher GFR among patients with atherosclerotic cardiovascular disease, previous investigations have suggested that an elevated GFR is associated with other target organ damage (18,19). For example, among 111 hypertensive subjects with normal renal function, glomerular hyperfiltration was associated with the presence of left ventricular hypertrophy, after adjustment for age, BMI, body surface area, and arterial pressure (19). The presence of cardiac hypertrophy, glomerular hyperfiltration, and sodium retention has particularly been noted among black subjects with hypertension (18). In addition, studies have suggested that the presence of glomerular hyperfiltration in subjects with hypertension and diabetes increases a patient's risk for progressive renal dysfunction (20–24). Finally, a recent study of 1572 young healthy men identified metabolic risk factors such as obesity and high BP to be risk factors for the presence of glomerular hyperfiltration (9). Thus, our study is consistent with previous research that implicates elevated GFR to be an early marker of an "at risk" patient population.

The relationships identified in this study may be supported by two different hypotheses. The relationship between hyperfiltration and the development of overt proteinuria and progression of kidney disease among patients with diabetes is widely known (23). Arguably, although this may be a mechanism through which this relationship is mediated among patients with diabetes, a detrimental association with elevated eGFR is demonstrated here among subjects without diabetes, in whom hyperfiltration has not been shown to be part of the pathology of their renal disease. Thus, the difference in clinical

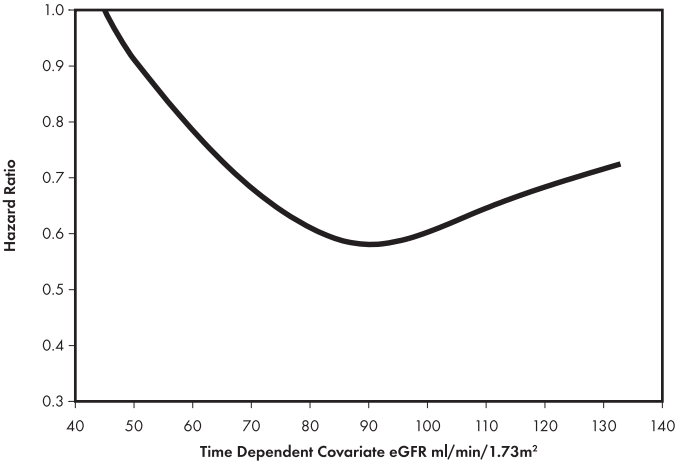

Figure 2. Adjusted hazard ratio by time-dependent covariate eGFR on composite end point of death, CHF, MI, or stroke. The reference group is subjects with the poorest kidney function, eGFR <45 ml/min per 1.73 m^2.

outcomes among subjects with elevated eGFR may be due to hyperfiltration or alternatively may be identifying a subgroup of subjects in whom kidney function is falsely overestimated.

Furthermore, a degree of variability is introduced into the estimation given that eGFR and CrCl rely on demographic and anthropometric variables as surrogates for muscle mass. A full discussion of the validity and utility of these equations is reviewed extensively elsewhere (25–28). In short, recognized limitations to using the Cockcroft-Gault equation include its inherent overestimation of GFR because creatinine is secreted by proximal tubular cells, as well as its failure to account for body surface area, which may be influenced by nutritional state. Conversely, the MDRD equation does factor in body surface area, as well as race, because black individuals generally have higher S_{Cr} levels as a result in part of increased muscle mass. In one recent study (29), the MDRD equation was found to outperform the Cockcroft-Gault equation in subjects with CKD and GFR <60 ml/min per 1.73 m^2 and those with diabetic nephropathy; however, this study also demonstrated that both equations greatly overestimate the relationship between S_{Cr} and GFR in kidney donors. Another study identified the MDRD equation compared with Cockcroft-Gault equation to be more precise and more accurate for predicting GFR in healthy adults; however, MDRD consistently underestimated GFR (27). Thus, the application of these estimating equations may be somewhat problematic in subjects with GFR closer to normal ranges (27,29). The limitations of estimating equations further underscores the need for other markers of kidney damage that may also predict cardiovascular outcomes, such as cystatin C.

Whereas overestimation of renal function is more frequently seen among subjects who are older or have a disparity between greater body weight and lean body mass, little or no significant differences were seen among the groups of subjects with elevated eGFR compared with those in the category of eGFR from

Table 4. Number of subjects who experienced each event, grouped by baseline CrCl (ml/min)[a]

Parameter (*n* [%])	Entire Cohort	CrCl <45	CrCl ≥45 and <60	CrCl ≥60 and <75	CrCl ≥75 and <100	CrCl ≥100 and <125	CrCl ≥125 and <150	CrCl ≥ 150
n (%)	8813 (100)	1111 (12.6)	1870 (21.2)	2028 (23.0)	2607 (29.6)	922 (10.5)	214 (2.4)	61 (0.7)
Composite end point[b]	737 (8.4)	176 (15.8)	186 (9.9)	143 (7.1)	160 (6.1)	50 (5.4)	18 (8.4)	4 (6.6)
Death as first event	162 (1.8)	45 (4.1)	47 (2.5)	32 (1.6)	26 (1.0)	9 (1.0)	2 (0.9)	1 (1.6)
CHF as first event	236 (2.7)	71 (6.4)	70 (3.7)	36 (1.8)	51 (2.0)	5 (0.5)	2 (0.9)	1 (1.6)
MI as first event	160 (1.8)	39 (3.5)	30 (1.6)	33 (1.6)	38 (1.5)	11 (1.2)	7 (3.3)	2 (3.3)
Stroke as first event	189 (2.1)	26 (2.3)	42 (2.2)	43 (2.1)	46 (1.8)	25 (2.7)	7 (3.3)	0 (0.0)

[a]This table lists each patient only once on the basis of the first event.
[b]Composite end point of death, CHF, MI, and stroke.

Table 5. Multivariable model of predictors of death, CHF, MI, or stroke[a]

Variable	HR (95% CI)	*P*
CrCl <90 (per 10-ml/min decrease)[b]	1.19 (1.13 to 1.25)	<0.0001
CrCl ≥90 (per 10-ml/min increase)[b]	1.10 (1.03 to 1.17)	0.006
History of CHF	2.29 (1.91 to 2.73)	<0.0001
Presence of diabetes	1.73 (1.49 to 2.01)	<0.0001
Age, per 10-yr increase	1.21 (1.10 to 1.32)	<0.0001
MI[c]	1.34 (1.14 to 1.57)	0.0003
Male gender	1.28 (1.08 to 1.51)	0.005
PTCA during period of observation[b]	1.48 (1.10 to 2.00)	0.01
Heart rate (per increase of 1 bpm)	1.01 (1.00 to 1.01)	0.05
Tobacco abuse	1.20 (1.01 to 1.43)	0.05
Peripheral vascular disease[c]	0.75 (0.62 to 0.91)	0.003
Treatment arm (lotrafiban *versus* placebo)	1.12 (0.97 to 0.29)	0.1

[a]The following baseline variables were tested for inclusion in the final model and removed with a $P > 0.10$: BMI; race; history of hypertension or PTCA; unstable angina, TIA, or stroke as qualifying event for enrollment into BRAVO; and aspirin dosage ≥162 mg.
[b]Treated as a time-varying covariate.
[c]Qualifying event for enrollment into BRAVO.

100 to 125 ml/min per 1.73 m^2. Despite observing similar BMI across the groups, one limitation to note is that we did not have information about body composition. The poorer outcomes in the most elevated eGFR groups may in fact be related to a higher degree of cachexia, with a decreased muscle mass resulting in a decreased S_{Cr} (and therefore an apparent higher eGFR). Nonetheless, BMI were similar in all subgroups within this study. Although it is not possible to discern which mechanism contributes more among the cohort overall or among specific subjects, practically this association may define a population of subjects who are at higher risk for poor outcomes.

The finding that subjects with elevated eGFR have poorer outcomes creates a problem in characterizing what is usually referred to as the "normal" group. Patients with eGFR ≥90 ml/min per 1.73 m^2 are thought to have normal kidney function, relative to those with eGFR <90 ml/min per 1.73 m^2; however, this study has identified a subset of subjects (specifically those with eGFR ≥125 ml/min per 1.73 m^2) within that normal group who in fact have a worse cardiovascular risk profile. When comparing subjects with and without kidney disease using the accepted cutoff of an eGFR of 90, one may erroneously find no apparent difference between the two because the normal kidney group actually includes a potentially sicker cohort of subjects: Those with eGFR elevated ≥125 ml/min per 1.73 m^2.

Although this study demonstrates that subjects with eGFR at higher-than-normal range are at greater risk for adverse outcomes, these findings should be interpreted in the setting of several limitations. This cohort was recruited for a trial and is therefore not population-based. Selection biases for patient inclusion may affect these results and should be considered in generalizing these results to all subjects with CKD, particularly with respect to race. In addition, the study did not collect information on certain cardioprotective medications (*e.g.*, angiotensin-converting enzyme inhibitors, β blockers) or metabolic risk factors (*e.g.*, impaired fasting glucose), which may confound the relationship between elevated eGFR and detrimental cardiovascular outcomes. "Prediabetes" was not characterized in our analysis and has been associated with glomerular hyperfiltration (30) and increased cardiovascular risk (31); therefore, our investigation cannot fully explain whether elevated eGFR is independently associated with cardiovascular outcomes or whether it is a marker of subjects with high metabolic risk profiles and poorer outcomes. Furthermore, information on external factors that may decrease S_{Cr} (and therefore increase eGFR), such as excessive hydration or a low-protein diet, and information on proteinuria were not available.

Despite limitations in the accuracy of assessing renal function with estimating equations, subjects in this study who were found to have elevated eGFR had a higher risk for adverse cardiovascular outcomes. This finding is particularly important because subjects with increased eGFR have not previously been characterized as being at higher risk when compared with those with other levels of eGFR. If confirmed in additional studies, then such prognostic information could be used clinically to identify subjects who have a greater need for effective treatments that minimize their cardiovascular risk.

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Disclosures

J.D.E. serves as a consultant to and on the advisory board for Sanofi-Aventis and Boehringer-Ingelheim.

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