European Heart Journal (2011) **32**, 2135–2142
doi:10.1093/eurheartj/ehr066

Plasma renin activity predicts cardiovascular mortality in the Heart Outcomes Prevention Evaluation (HOPE) study

Subodh Verma[1,2]*, Milan Gupta[1,2,3], Daniel T. Holmes[4], Liqin Xu[5], Hwee Teoh[1,2], Sunayna Gupta[1], Salim Yusuf[3,5], and Eva M. Lonn[3,5]*

[1]Division of Cardiac Surgery, Keenan Research Centre in the Li Ka Shing Knowledge Institute of St Michael's, University of Toronto, Toronto, ON, Canada; [2]Canadian Cardiovascular Research Network, Brampton, ON, Canada; [3]Department of Medicine, McMaster University, Hamilton Health Sciences, Hamilton, ON, Canada; [4]Department of Pathology and Laboratory Medicine, University of British Columbia, St Paul's Hospital, Vancouver, BC, Canada; and [5]Population Health Research Institute, McMaster University, Hamilton Health Sciences, Hamilton, ON, Canada

Received 27 June 2010; revised 29 November 2010; accepted 5 January 2011; online publish-ahead-of-print 17 March 2011

See page 2096 for the editorial comment on this article (doi:10.1093/eurheartj/ehr074)

Aims Plasma renin activity (PRA) has been proposed as an independent predictor of cardiovascular (CV) risk, but there are limited data from large prospective studies, particularly in patients with stable vascular disease and/or diabetes, without heart failure.

Methods and results We evaluated the predictive value of PRA as a marker of CV events and mortality in a large population of patients with stable chronic vascular disease and/or diabetes and one CV risk factor. Baseline PRA was measured in 2913 patients enrolled in the Heart Outcomes Prevention Evaluation (HOPE) study. Subjects were followed for a median of 4.5 years. Compared with the referent lowest fifth, subjects in the highest fifth of the PRA distribution had a hazard ratio (HR) of 1.38 (95% confidence interval, 1.03–1.86; $P = 0.03$) for the composite of major vascular events, with an HR of 1.89 for CV death. These associations remained statistically significant after full adjustment for clinical characteristics, background use of β-blockers, diuretics, allocation to ramipril, in addition to inflammatory biomarkers, high-sensitivity C-reactive protein, and N-terminal pro-brain natriuretic peptide.

Conclusion High PRA is an independent predictor of major vascular events and mortality in a stable population of high-risk patients with atherosclerosis and/or diabetes. Although an increase in PRA could be a marker of more intense antihypertensive therapy, our results suggest that PRA may represent a risk marker and potential target for therapy in high-risk patients with atherosclerosis and/or diabetes.

Keywords Renin • Cardiovascular diseases • Mortality • Risk factors • Renin–angiotensin system • Direct renin inhibitors

Introduction

Inhibition of the renin–angiotensin system (RAS) with angiotensin-converting enzyme-inhibitors or angiotensin receptor blockers has emerged as a cornerstone of contemporary cardiovascular (CV) risk reduction. These therapies offer robust reductions in heart failure,[1,2] in CV mortality post-myocardial infarction (MI),[3–5] and in CV events in high-risk patients with atherosclerosis or diabetes,[3,6,7] although a substantial residual risk remains.

Activation of the RAS results in a series of complex enzymatic reactions that culminate in the generation of angiotensin (Ang) II, the main effector molecule of the system, central to multiple causal pathways in hypertension, heart failure, and atherosclerosis.[8] Plasma renin activity (PRA) has been suggested as a surrogate of RAS activation and a marker of increased CV risk.[9–13] Studies in chronic heart failure generally reported associations between increased PRA and poor prognosis, although such associations did not always retain statistical significance in models adjusted for other markers of risk.[14–18] Moreover, to date, there are

*Corresponding author. Tel: +1 416 864 5997, Fax: +1 416 864 5881, Email: subodh.verma@sympatico.ca (S.V.); Tel: +1 905 525 9140 ext. 40331, Fax: +1 905 297 3782, Email: eva.lonn@phri.ca (E.M.L.)

limited data evaluating the prognostic relevance of PRA in patients *without* heart failure, who may be expected to have less profound RAS activation and the available data are further confounded by methodological differences in measuring PRA vs. concentration in previous reports.[12,19–26] To this aim, we assessed the associations of baseline PRA concentrations with CV events and mortality in 2913 patients with stable vascular disease and/or diabetes enrolled in the Heart Outcomes Prevention Evaluation (HOPE) study.[6]

Methods

Study population

The HOPE study was a multicentre, randomized, clinical trial of ramipril, vitamin E, both, or neither for the prevention of CV events among 9541 patients aged 55 or older with stable vascular disease, or diabetes with additional risk factors. Patients were excluded if they had heart failure or if they were known to have a low ejection fraction (<40%), uncontrolled hypertension, or overt nephropathy or to have had an MI or stroke in the 4 weeks before enrolment. A detailed study description has been previously published.[6] Baseline blood samples were available from the 3199 Canadian HOPE study patients.[27] As the available thawed blood sample volumes from 286 patients were too small for adequate analysis, we report on 2913 patients in this cohort. Blood samples were processed immediately upon collection, separated into multiple aliquots, and shipped on dry ice to the core laboratory where they were stored at −80°C. The HOPE central laboratory was located in Hamilton, Canada.

Clinical events

The primary HOPE study endpoint was the composite of MI, stroke, or CV death, referred to as major vascular events in this report. Among the additional prospectively defined and collected HOPE study outcomes, we a priori defined as outcomes of interest for the evaluation of associations with baseline PRA, the following: MI, stroke, CV death, total mortality, and heart failure (defined as heart failure hospitalizations and non-hospitalized heart failure diagnosed clinically at the 6 monthly visits). Events were centrally adjudicated by a committee blinded to treatment allocation in the trial. Detailed information about the follow-up procedures is published elsewhere.[6] The median follow-up was 4.5 years, inter-quartile range (IQR), 4.1–4.8 years.

Laboratory analysis

Plasma renin activity was determined using the Diasorin (Stillwater, MN, USA) GammaCoat® Plasma Renin Activity ^{125}I Radioimmunoassay kit (details are provided in the Supplementary material online, Appendix). Observed within-run and between-run coefficients of variations were 7 and 8% at 1.60 ng/mL/h, 7 and 7% at 4.15 ng/mL/h, and 8 and 8% at 15.30 ng/mL/h. C-reactive protein was measured with a high-sensitivity, automated-rate nephelometric immunoassay (Dade Behring high-sensitivity CRP, BNII Nephelometer System, Marburg, Germany). N-terminal pro-brain natriuretic peptide (NT-proBNP) was determined with an electrochemiluminescent sandwich immunoassay (Roche Diagnostics, Mannheim, Germany) on an Elecsys System 2010. Intra- and inter-assay precision was 0.8–3.0% and 2.2–5.8%, respectively, as reported previously. The linear range of detection of this assay was 5–35 000 pg/mL. Additional laboratory assays used routine methods as described previously.

Statistical analysis

Plasma renin activity values were log-transformed to improve the normality of distribution and the Student's *t*-test was used to compare log(PRA) between patients with and those without events. We prespecified a priori to evaluate the relationship between PRA and outcomes based on quintiles of the PRA distribution. Accordingly, the Kaplan–Meier curves for cumulative CV events were plotted by quintiles of PRA and the upper vs. the lowest fifth were compared with the log-rank test. The association of PRA by quintiles with events was further evaluated by Cox's multivariable regression analysis and stratified by ramipril and vitamin E allocation in the trial. We checked the assumption of proportionality of hazard with the log[−log(survival)] plot and by the time-dependent covariate test. The proportional hazard assumption was satisfied for all outcomes evaluated. The Wald χ^2 test was used to indicate differences across quintiles. Age- and sex-adjusted and fully multivariable adjusted hazard ratios (HRs) were estimated. Full adjustment was performed using both clinical variables (age, gender, smoking, hypertension, diabetes, CV disease, systolic blood pressure, and creatinine) and the HOPE risk score, which was derived from the HOPE study, and shown to reliably discriminate risk in the HOPE study population. The HOPE risk score considers age, gender, smoking status, hypertension, left ventricular hypertrophy, diabetes, prior stroke, peripheral vascular, coronary artery disease, and microalbuminuria (HOPE risk score = 0.03883 × age + 0.33281 × male + 0.42740 × current smoker + 0.11243 × hypertension + 0.12071 × left ventricular hypertrophy + 0.30451 × diabetes + 0.32957 × history of stroke + 0.34318 × peripheral arterial disease + 0.53028 × coronary artery disease + 0.43560 × microalbuminuria).[7,28] Additional adjustments were conducted for baseline high-sensitivity C-reactive protein and NT-proBNP levels and for treatment allocation to ramipril and baseline use of β-blockers and diuretics. All tests were made at a two-sided, 5% significance level. Statistical analyses were performed using the SAS package version 9.1.3 (SAS Institute, Inc., Cary, NC, USA).

Results

Table 1 shows the baseline characteristics of the study participants. The mean age was 65 years, 22% were women, 94% had vascular disease (coronary, peripheral, or cerebrovascular disease), 41% had hypertension, 34% had diabetes, 32% were using lipid-lowering therapies, 42% were receiving β-blockers, and 12% were receiving diuretics. We have previously reported that baseline characteristics of the Canadian HOPE population, in whom PRA was determined, were similar to the overall HOPE study population.[3] The median PRA was 0.82 (IQR, 0.41–1.53) ng/mL/h, median NT-proBNP was 18.09 (IQR, 17.39–18.81) pmol/L, and median high-sensitivity C-reactive protein level was 2.64 (IQR, 2.54–2.74) mg/L. Baseline characteristics associated with higher PRA included history of diabetes or known CV disease, and those on diuretics, whereas individuals on β-blockers had lower PRA (*Table 1*).

During follow-up, 437 patients (15%) experienced a primary HOPE endpoint (MI, stroke, or CV death), 321 (11.02%) sustained an MI, 95 (3.26%) a stroke, 211 (7.24%) had heart failure, 178 (6.11%) died of CV causes, and 131 (4.5%) of non-CV causes. Patients who died of CV causes and those who died of any cause had higher median PRA than those who did not, 0.90 (IQR, 0.50–1.85) vs. 0.81 (IQR, 0.40–1.51) ng/mL/h, $P = 0.04$, and 0.93 (IQR, 0.50–1.91) vs. 0.81 (IQR, 0.40–1.49) ng/mL/h,

Table 1 Baseline characteristics of the study population

	All participants (n = 2913)	Quintile of plasma renin activity (ng/mL/h)					P-value for trend
		1 <0.35 (n = 602)	2 0.35–0.63 (n = 568)	3 0.63–1.03 (n = 584)	4 1.03–1.79 (n = 581)	5 >1.79 (n = 578)	
Age (years)	65.4 ± 6.6	65.9 ± 6.6	66.2 ± 6.5	65.1 ± 6.5	64.8 ± 6.3	64.8 ± 6.8	0.5369
Male	2265 (77.8)	450 (74.8)	435 (76.6)	479 (82)	460 (79.2)	441 (76.3)	0.084
Body mass index (kg/m^2)	27.8 ± 4.3	28.1 ± 4.2	27.6 ± 4.2	27.8 ± 4.1	27.7 ± 4.3	28.1 ± 4.7	0.1384
Systolic blood pressure (mmHg)	135.6 ± 18.40	138.5 ± 18.4	136.1 ± 18.4	134.9 ± 19.0	133.6 ± 17.8	134.7 ± 18.2	0.0034
Diastolic blood pressure (mmHg)	77.2 ± 9.7	78.5 ± 9.4	76.9 ± 9.9	76.6 ± 9.4	76.8 ± 9.4	77.3 ± 10.0	0.8198
History of hypertension	1198 (41.1)	281 (46.7)	254 (44.7)	208 (35.6)	210 (36.1)	245 (42.4)	0.2442
History of diabetes mellitus	985 (33.8)	186 (30.9)	189 (33.3)	203 (34.8)	201 (34.6)	206 (35.6)	0.032
Smoking status							
Never	672 (23.1)	167 (27.7)	143 (25.2)	120 (20.5)	113 (19.4)	129 (22.3)	0.0473
Former	1836 (63.0)	354 (58.8)	356 (62.7)	390 (66.8)	389 (67)	347 (60)	0.9104
Current	404 (13.9)	81 (13.5)	68 (12)	74 (12.7)	79 (13.6)	102 (17.6)	0.7223
Coronary artery disease	2490 (85.5)	517 (85.9)	484 (85.2)	507 (86.8)	500 (86.1)	482 (83.4)	0.0748
Peripheral vascular disease	1197 (41.1)	224 (37.2)	222 (39.1)	239 (40.9)	248 (42.7)	264 (45.7)	0.6685
Cardiovascular disease	2731 (93.8)	554 (92)	534 (94)	555 (95)	541 (93.1)	547 (94.6)	<0.0001
Medications							
Lipid-lowering agent	929 (31.9)	195 (32.4)	161 (28.3)	195 (33.4)	189 (32.5)	189 (32.7)	0.236
β-Blocker	1236 (42.4)	377 (62.6)	282 (49.6)	218 (37.3)	191 (32.9)	168 (29.1)	0.0481
Diuretics	352 (12.1)	41 (6.8)	55 (9.7)	48 (8.2)	63 (10.8)	145 (25.1)	0.016
Total cholesterol (mmol/L)	5.39 (5.36–5.43)	5.39 (5.31–5.47)	5.33 (5.25–5.41)	5.35 (5.27–5.43)	5.42 (5.35–5.5)	5.48 (5.4–5.57)	0.1483
LDL cholesterol (mmol/L)	3.12 (2.88–3.38)	3.22 (3.10–3.34)	3.23 (3.09–3.39)	3.38 (3.23–3.54)	3.33 (3.13–3.55)	3.34 (3.15–3.54)	0.132
HDL cholesterol (mmol/L)	1.01 (1.00–1.02)	1.01 (0.99–1.03)	1.02 (1.00–1.04)	0.99 (0.97–1.01)	1.01 (0.99–1.03)	1.02 (1.00–1.05)	0.4573
Creatinine, (μmol/L)	98.56 ± 21.12	97.68 ± 21.12	97.68 ± 21.12	98.56 ± 19.36	99.44 ± 20.24	101.2 ± 22.88	0.1322
Plasma renin activity, (ng/mL/h)	0.82 (0.41–1.53)	0.17 (0.16–0.18)	0.49 (0.48–0.49)	0.81 (0.81–0.82)	1.34 (1.32–1.36)	3.48 (3.31–3.66)	<0.0001
NT-proBNP (pmol/L)	18.09 (17.39–18.81)	22.47 (20.74–24.34)	20.4 (18.73–22.21)	17.32 (15.89–18.88)	15.33 (14.02–16.77)	15.79 (14.38–17.35)	<0.0001
High-sensitivity C-reactive protein (mg/L)	2.64 (2.54–2.74)	2.48 (2.28–2.69)	2.39 (2.2–2.59)	2.45 (2.25–2.68)	2.63 (2.42–2.86)	3.38 (3.1–3.68)	<0.0001

Values are mean ± SD, n (%), or median (IQR). Categorical variables were compared using the χ^2 test. Continuous variables were compared using either the ANOVA F-test (age, BMI, SBP, DBP, and creatinine) or the Wilcoxon test (total cholesterol, LDL, HDL, and PRA).

$P = 0.02$, respectively. Plasma renin activity was not significantly different in patients who did vs. those who did not have a major vascular event, MI, stroke, or heart failure (data not shown).

For patients in the highest compared with the lowest fifth of the baseline PRA distribution, the unadjusted HR for the composite of major vascular events, which included MI, stroke, and CV death, was 1.38 [95% confidence interval (CI), 1.03–1.86; $P = 0.03$] (*Table 2*). This was driven by an increase in the risk for CV death in individuals in the top vs. the lowest quintile (HR, 1.89; 95% CI, 1.17–3.05; $P = 0.01$). Similarly, subjects in the highest compared with the lowest fifth of the PRA distribution had an increased risk for total mortality and a trend towards an increased risk for heart failure, but baseline PRA did not predict incident MI, stroke, or non-CV death (*Table 2*).

The adjusted HRs for major vascular events, CV death, and total mortality according to baseline levels of PRA are shown in *Tables 3–5*, respectively. Patients in the highest compared with the lowest PRA fifth had an increased risk of major vascular events after adjustment for either (i) age and gender, (ii) clinical variables (age, gender, smoking, hypertension, diabetes, CV disease, systolic blood pressure, and creatinine) plus treatment allocation to ramipril, and background use of β blockers and diuretics, and (iii) HOPE risk score plus ramipril, β-blockers, diuretics, high-sensitivity C-reactive protein, and NT-proBNP. This was driven primarily by an increased risk of CV death (*Table 4*), but not all-cause mortality (*Table 5*), or heart failure (see Supplementary material online, Appendix, *Table S1*) in fully adjusted models.

The Kaplan–Meier rates of CV death according to quintiles of PRA are displayed in *Figure 1*.

In an exploratory *post hoc* analysis, we evaluated the associations between tertiles of baseline PRA and outcomes. Results were similar (data not shown, available upon request).

Table 2 Hazard ratios for major cardiovascular events according to baseline plasma renin activity

Cardiovascular event	Total number of events	Quintile of plasma renin activity (ng/mL/h)					*P*-value for trend
		1 <0.35	2 0.35–0.63	3 0.63–1.03	4 1.03–1.79	5 >1.79	
Major vascular events							
Number of events	437	75	92	92	77	101	0.15
HR (95% CI)		1	1.26 (0.93–1.71)	1.23 (0.91–1.66)	1.02 (0.75–1.40)	1.38 (1.03–1.86)	
P-value			0.13	0.19	0.9	0.03	
Myocardial infarction							
Number of events	321	57	70	64	61	69	0.65
HR (95% CI)		1	1.27 (0.90–1.79)	1.11 (0.78–1.59)	1.07 (0.75–1.53)	1.23 (0.87–1.74)	
P-value			0.18	0.55	0.71	0.24	
Stroke							
Number of events	95	17	19	23	12	24	0.26
RR (95% CI)		1	1.12 (0.59–2.14)	1.34 (0.72–2.48)	0.69 (0.33–1.44)	1.43 (0.78–2.64)	
P-value			0.72	0.36	0.32	0.25	
Cardiovascular death							
Number of events	178	24	36	38	34	46	0.14
HR (95% CI)		1	1.48 (0.89–2.44)	1.5 (0.91–2.48)	1.36 (0.81–2.26)	1.89 (1.17–3.05)	
P-value			0.13	0.11	0.24	0.01	
Non-cardiovascular death							
Number of events	131	34	18	20	19	40	0.005
RR (95% CI)		1	0.57 (0.32–1.00)	0.61 (0.35–1.05)	0.58 (0.33–1.02)	1.26 (0.80–1.99)	
P-value			0.05	0.07	0.06	0.33	
Total mortality							
Number of events	309	58	54	58	53	86	0.01
HR (95% CI)		1	0.96 (0.67–1.39)	0.99 (0.69–1.43)	0.92 (0.63–1.33)	1.53 (1.10–2.13)	
P-value			0.83	0.97	0.64	0.01	
Heart failure							
Number of events	211	36	41	51	37	46	0.12
HR (95% CI)		1	1.3 (0.87–1.95)	1.67 (1.14–2.46)	1.34 (0.90–2.01)	1.43 (0.96–2.14)	
P-value			0.21	0.01	0.15	0.08	

HR, hazard ratio; CI, confidence interval.

Table 3 Adjusted hazard ratios for major cardiovascular events according to baseline plasma renin activity

Adjustment	Quintile of plasma renin activity (ng/mL/h)					*P*-value for trend
	1 <0.35	2 0.35–0.63	3 0.63–1.03	4 1.03–1.79	5 >1.79	
Age + male						
Adjusted HR (95% CI)	1	1.30 (0.95–1.78)	1.23 (0.90–1.70)	1.07 (0.77–1.49)	1.48 (1.09–2.02)	0.09
P-value		0.1	0.19	0.67	0.01	
Clinical variables[a] + ramipril + β-blocker use + diuretics						
Adjusted HR (95% CI)	1	1.29 (0.94–1.76)	1.23 (0.89–1.70)	1.09 (0.78–1.52)	1.38 (0.99–1.90)	0.28
P-value		0.12	0.21	0.64	0.05	
HOPE score[b] + ramipril + β-blocker use + diuretics + log C-reactive protein + log NT-proBNP						
Adjusted HR (95% CI)	1	1.18 (0.84–1.66)	1.21 (0.86–1.70)	1.02 (0.72–1.46)	1.42 (1.01–1.99)	0.23
P-value		0.34	0.27	0.91	0.04	

[a]Adjusted for age + male + current smoker + hypertension + diabetes + cardiovascular vascular disease + systolic blood pressure + creatinine.
[b]HOPE score = 0.03883 × age + 0.33281 × male + 0.42740 × current smoker + 0.11243 × hypertension + 0.12071 × left ventricular hypertrophy + 0.30451 × diabetes + 0.32957 × history of stroke + 0.34318 × peripheral arterial disease + 0.53028 × coronary artery disease + 0.43560 × microalbuminuria; derived from the HOPE study based on observed events and considering all baseline variables.

Table 4 Adjusted hazard ratios for cardiovascular death according to baseline plasma renin activity

Adjustment	Quintile of plasma renin activity (ng/mL/h)					*P*-value for trend
	1 <0.35	2 0.35–0.63	3 0.63–1.03	4 1.03–1.79	5 >1.79	
Age + male						
Adjusted HR (95% CI)	1	1.58 (0.94–2.65)	1.60 (0.95–2.68)	1.49 (0.88–2.53)	1.99 (1.30–3.29)	0.13
P-value		0.08	0.08	0.14	0.008	
Clinical variables[a] + ramipril + β-blocker use + diuretics						
Adjusted HR (95% CI)	1	1.56 (0.93–2.63)	1.59 (0.94–2.69)	1.55 (0.90–2.65)	1.76 (1.04–2.98)	0.31
P-value		0.09	0.09	0.11	0.04	
HOPE score[b] + ramipril + β-blocker use + Diuretics + log C-reactive protein + log NT-proBNP						
Adjusted HR (95% CI)	1	1.29 (0.72–2.31)	1.48 (0.84–2.62)	1.38 (0.76–2.49)	1.68 (0.96–2.96)	0.48
P-value		0.4	0.017	0.29	0.07	

[a]Adjusted for age + male + current smoker + hypertension + diabetes + cardiovascular vascular disease + systolic blood pressure + creatinine.
[b]HOPE score = 0.03883 × age + 0.33281 × male + 0.42740 × current smoker + 0.11243 × hypertension + 0.12071 × left ventricular hypertrophy + 0.30451 × diabetes + 0.32957 × history of stroke + 0.34318 × peripheral arterial disease + 0.53028 × coronary artery disease + 0.43560 × microalbuminuria; derived from the HOPE study based on observed events and considering all baseline variables.

Discussion

The major finding of our study is that PRA was a predictor of major vascular events in a large cohort of patients with stable atherosclerotic vascular disease and/or diabetes. The strength of the association was greatest for CV death, such that individuals in the upper fifth of the PRA distribution (>1.79 ng/mL/h; median 3.48, IQR = 3.31–3.66) had an increase in CV death compared with those individuals in the referent lowest fifth (<0.35 ng/mL/h; median 0.17, IQR = 0.16–0.18). The predictive value of elevated PRA was observed after multivariable analyses, after adjusting for traditional CV risk factors in addition to the background use of therapies known to modulate RAS and PRA, namely diuretics, β-blockers, and treatment allocation to ramipril in the trial. Furthermore, the strength of these associations was maintained after robust adjustment using the HOPE risk score model, background medication use, inflammatory biomarkers, high-sensitivity C-reactive protein, and NT-proBNP.

The increased CV risk associated with elevated PRA in our study was not attenuated by the adjustment for treatment allocation to ramipril, background use of β-blockers (known to lower PRA), and diuretics (known to increase PRA). These data argue that the predictive value of high vs. low PRA is not altered by therapies known to modulate the RAS or PRA *per se*.

Table 5 Adjusted hazard ratios for total mortality according to baseline plasma renin activity

Adjustment	Quintile of plasma renin activity (ng/mL/h)					*P*-value for trend
	1 <0.35	2 0.35–0.63	3 0.63–1.03	4 1.03–1.79	5 >1.79	
Age + male						
Adjusted HR (95% CI)	1	0.99 (0.68–1.44)	1.02 (0.70–1.48)	0.99 (0.68–1.45)	1.56 (1.11–2.20)	0.03
P-value		0.96	0.91	0.97	0.01	
Clinical variables[a] + ramipril + β-blocker use + diuretics						
Adjusted HR (95% CI)	1	0.94 (0.65–1.37)	0.94 (0.64–1.38)	0.92 (0.62–1.35)	1.25 (0.87–1.80)	0.37
P-value		0.76	0.75	0.66	0.22	
HOPE score[b] + ramipril + β-blocker use + diuretics + log C-reactive protein + log NT-proBNP						
Adjusted HR (95% CI)	1	0.77 (0.51–1.16)	0.87 (0.58–1.30)	0.84 (0.55–1.26)	1.18 (0.80–1.72)	0.21
P-value		0.21	0.5	0.39	0.41	

[a]Adjusted for Age + male + current smoker + hypertension + diabetes + cardiovascular vascular disease + systolic blood pressure + creatinine.
[b]HOPE score = 0.03883 × age + 0.33281 × male + 0.42740 × current smoker + 0.11243 × hypertension + 0.12071 × left ventricular hypertrophy + 0.30451 × diabetes + 0.32957 × history of stroke + 0.34318 × peripheral arterial disease + 0.53028 × coronary artery disease + 0.43560 × microalbuminuria; derived from the HOPE study based on observed events and considering all baseline variables.

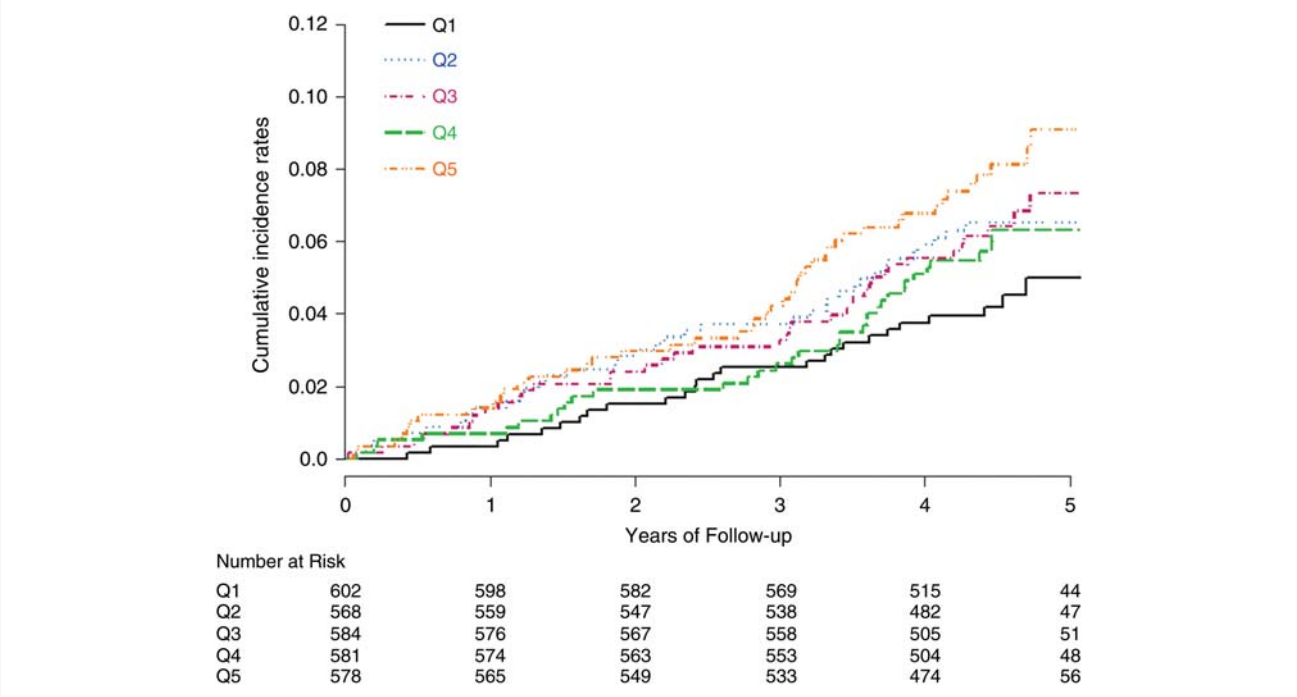

Figure 1 The Kaplan–Meier plot for cumulative outcome of cardiovascular death by fifths of plasma renin activity. Patients in the upper vs. the lowest plasma renin activity fifth had increased rates of cardiovascular death (*P* log-rank = 0.006).

In our analyses, PRA emerged as an independent predictor of CV death, but not with MI or stroke. The mechanistic basis for this finding remains unclear. It may be hypothesized that PRA may identify a population of patients at risk of increased mortality, in part via either transition to heart failure or sudden cardiac death. Alternately, these findings may be related to the known difficulty in establishing the precise cause of death in CV patients and it is possible that some CV deaths classified as sudden, arrhythmic, etc. may have been in fact related to fatal MI or stroke.

The present analyses provide an important translational framework for various experimental studies, implicating PRA in the pathogenesis of CV disease. Indeed, renin is the initial and rate-limiting step of the RAS and many experimental and clinical

studies which provide evidence that the RAS is capable of stimulating atherosclerosis by triggering basic reactions ultimately lead to growth, instability, and rupture of atherosclerotic plaques and facilitation of thrombosis. In addition, it is now widely held that renin and prorenin may exert direct (receptor-mediated, Ang II-independent) effects augmenting pro-inflammatory and pro-fibrotic pathways.[29] Furthermore, prorenin activation of the pro(-renin) receptor promotes cell surface Ang II production via non-proteolytic activation, which may contribute to local tissue damage.[30] Additionally, as reported by Nguyen *et al.*, renin bound to the (pro)renin receptor gains markedly enhanced catalytic activity and, in this fashion, can dramatically magnify Ang II signalling.[31] This has led to the hypothesis that renin may play a causal or permissive role in the development of organ damage and that pharmacological targeting of PRA may be a unique approach to limit disease progression. Currently, completed trials suggest that pharmacological interruption of the RAS system by limiting PRA may protect against cardio-renal injury.[31–33].

Relatively, few previous studies have evaluated the role of PRA as a biomarker of vascular disease and most of these observations have been made in either primary prevention cohorts with or without hypertension and in patients with chronic heart failure or left ventricular dysfunction post-MI. Overall, previous data evaluating PRA to CV outcomes is limited and, in many instances, cannot be readily extrapolated, given earlier concerns over assay characteristics and the varying reporting of PRA vs. renin concentration in the literature. Studies evaluating the role of renin as a predictor of events in primary prevention have yielded mixed results. Although earlier studies demonstrated an association between plasma renin concentration or PRA to an increased risk of MI, CV death, and all cause mortality in hypertensive subjects,[12,19,20] other studies in hypertension and a prospective community-based studies did not find such an association.[23,24] However, more recent analyses of data from the Framingham Study suggest an association between plasma renin concentration and total mortality risk in both hypertensive and normotensive subjects, with no association with MI or major coronary events.[25,26] Furthermore, in elderly patients with hypertension, elevated PRA levels were associated with left ventricular hypertrophy[21] and a nested case-controlled study of patients with prior stroke reported a positive association between increasing renin concentrations and risk of MI.[22] More robust data are available in patients with heart failure, and/or left ventricular dysfunction post-MI, where PRA was significantly associated with mortality and transition to severe heart failure.[14–18] Our study is the largest report, to date, in which the relationship of PRA with events has been examined in a well-characterized population of patients with stable atherosclerosis and/or diabetes.

Limitations of this study are noted. Firstly, patients in the HOPE study prior to randomization were on open-label ramipril during a run-in period. However, once tolerability was established, patients received a 2-week washout prior to randomization occurring. Secondly, the observed associations of baseline PRA with CV events were noted in the highest vs. lowest PRA distribution, without a significant trend across increasing quintiles. The lack of trend may be related to the overall low levels of PRA in this population of patients without heart failure. A potential threshold effect cannot be excluded, so that only patients with highest PRA levels in this population had increased RAS activation and were at increased CV risk. Thirdly, an increase in PRA could be a marker of more intense antihypertensive therapy since it stands to reason that patients with worse hypertensive CV disease are likely to have the highest complication rates and would need more antihypertensive therapy.

In conclusion, our analyses indicate that baseline PRA predicts the risk of future major vascular events, notably CV death in a population of high-risk patients with atherosclerosis or diabetes. Individuals in the top PRA quintile have a nearly two-fold increased risk of CV death, and the strength of these associations was independent of clinical characteristics, background use of β-blockers and diuretics, treatment allocation to ramipril, and inflammatory biomarkers. Plasma renin activity may thus represent a novel risk marker in this population.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Funding

This work was supported in part by grant-in-aid awards from the Heart and Stroke Foundation of Ontario and the Canadian Institutes of Health Research to S.V. Novartis Canada provided an unrestricted research grant to partially defray the costs for PRA measurements but had no role in the collection, management, analysis, or interpretation of the data; in the preparation, review, or approval of the manuscript; in the decision to submit the manuscript for publication or the target journal. S.V. is the Canada Research Chair in Atherosclerosis. S.Y. is the Heart and Stroke Foundation of Ontario Research Chair.

Conflict of interest: S.V. has received speaking honoraria and/or research grants from AstraZeneca, Merck, Novartis, and Pfizer. M.G. has received speaking honoraria and research grants from Novartis. E.M.L. has received speaking honoraria and/or research grants from Astra Zeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Roche, Servier, and Solvay.

References

1. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, Yusuf S, Pocock S. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 2003;**362**:759–766.
2. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991; **325**:293–302.
3. Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. *Lancet* 2006;**368**:581–588.
4. Pfeffer MA, Braunwald E, Moyé LA, Basta L, Brown EJ Jr, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, Klein M, Lamas GA, Packer M, Rouleau J, Rouleau JL, Rutherford J, Wertheimer JH, Hawkins CM, on behalf of the SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992;**327**: 669–677.
5. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP, Solomon SD, Swedberg K, Van de Werf F, White H, Leimberger JD, Henis M, Edwards S, Zelenkofske S, Sellers MA, Califf RM. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;**349**:1893–1906.

6. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;**342**:145–153.
7. Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P, Anderson C. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;**358**:1547–1559.
8. Schmieder RE, Hilgers KF, Schlaich MP, Schmidt BM. Renin–angiotensin system and cardiovascular risk. *Lancet* 2007;**369**:1208–1219.
9. Laragh JH. The renin system and future trends in management of high blood pressure. *Clin Exp Hypertens* 1980;**2**:525–552.
10. Laragh JH, Sealey JE. Abnormal sodium metabolism and plasma renin activity (renal renin secretion) and the vasoconstriction volume hypothesis: implications for pathogenesis and treatment of hypertension and its vascular consequences (heart attack, stroke). *Clin Chem* 1991;**37**:1820–1827.
11. Brunner HR, Gavras H, Laragh JH. Specific inhibition of the renin–angiotensin system: a key to understanding blood pressure regulation. *Prog Cardiovasc Dis* 1974;**17**:87–98.
12. Brunner HR, Laragh JH, Baer L, Newton MA, Goodwin FT, Krakoff LR, Bard RH, Buhler FR. Essential hypertension: renin and aldosterone, heart attack and stroke. *N Engl J Med* 1972;**286**:441–449.
13. Brunner HR, Sealey JE, Laragh JH. Renin as a risk factor in essential hypertension: more evidence. *Am J Med* 1973;**55**:295–302.
14. Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS, Simon AB, Rector T. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med* 1984;**311**:819–823.
15. Francis GS, Cohn JN, Johnson G, Rector TS, Goldman S, Simon A. Plasma norepinephrine, plasma renin activity, and congestive heart failure. Relations to survival and the effects of therapy in V-HeFT II. The V-HeFT VA Cooperative Studies Group. *Circulation* 1993;**87**:VI40–VI48.
16. Latini R, Masson S, Anand I, Salio M, Hester A, Judd D, Barlera S, Maggioni AP, Tognoni G, Cohn JN. The comparative prognostic value of plasma neurohormones at baseline in patients with heart failure enrolled in Val-HeFT. *Eur Heart J* 2004;**25**:292–299.
17. Rouleau JL, Packer M, Moyé L, de Champlain J, Bichet D, Klein M, Rouleau JR, Sussex B, Arnold JM, Sestier F, Parker JO, McEwan P, Bernstein V, Cuddy TE, Lamas G, Gottlieb SS, McCans J, Nadeau C, Delage F, Wun C-C C, Pfeffer MA. Prognostic value of neurohumoral activation in patients with an acute myocardial infarction: effect of captopril. *J Am Coll Cardiol* 1994;**24**:583–591.
18. Tsutamoto T, Sakai H, Tanaka T, Fujii M, Yamamoto T, Wada A, Ohnishi M, Horie M. Comparison of active renin concentration and plasma renin activity as a prognostic predictor in patients with heart failure. *Circ J* 2007;**71**:915–921.
19. Alderman MH, Madhavan S, Ooi WL, Cohen H, Sealey JE, Laragh JH. Association of the renin-sodium profile with the risk of myocardial infarction in patients with hypertension. *N Engl J Med* 1991;**324**:1098–1104.
20. Alderman MH, Ooi WL, Cohen H, Madhavan S, Sealey JE, Laragh JH. Plasma renin activity: a risk factor for myocardial infarction in hypertensive patients. *Am J Hypertens* 1997;**10**:1–8.
21. Aronow WS, Ahn C, Kronzon I, Gutstein H. Association of plasma renin activity and echocardiographic left ventricular hypertrophy with frequency of new coronary events and new atherothrombotic brain infarction in older persons with systemic hypertension. *Am J Cardiol* 1997;**79**:1543–1545.
22. Campbell DJ, Woodward M, Chalmers JP, Colman SA, Jenkins AJ, Kemp BE, Neal BC, Patel A, MacMahon SW. Prediction of myocardial infarction by N--terminal-pro-B-type natriuretic peptide, C-reactive protein, and renin in subjects with cerebrovascular disease. *Circulation* 2005;**112**:110–116.
23. Doyle AE, Jerums G, Johnston CI, Louis WJ. Plasma renin levels and vascular complications in hypertension. *Br Med J* 1973;**2**:206–207.
24. Meade TW, Cooper JA, Peart WS. Plasma renin activity and ischemic heart disease. *N Engl J Med* 1993;**329**:616–619.
25. Parikh NI, Gona P, Larson MG, Wang TJ, Newton-Cheh C, Levy D, Benjamin EJ, Kannel WB, Vasan RS. Plasma renin and risk of cardiovascular disease and mortality: the Framingham Heart Study. *Eur Heart J* 2007;**28**:2644–2652.
26. Wang TJ, Gona P, Larson MG, Tofler GH, Levy D, Newton-Cheh C, Jacques PF, Rifai N, Selhub J, Robins SJ, Benjamin EJ, D'Agostino RB, Vasan RS. Multiple biomarkers for the prediction of first major cardiovascular events and death. *N Engl J Med* 2006;**355**:2631–2639.
27. Blankenberg S, McQueen MJ, Smieja M, Pogue J, Balion C, Lonn E, Rupprecht HJ, Bickel C, Tiret L, Cambien F, Gerstein H, Munzel T, Yusuf S. Comparative impact of multiple biomarkers and N-Terminal pro-brain natriuretic peptide in the context of conventional risk factors for the prediction of recurrent cardiovascular events in the Heart Outcomes Prevention Evaluation (HOPE) Study. *Circulation* 2006;**114**:201–208.
28. Yusuf S, Pogue J. ACE inhibition in stable coronary artery disease. *N Engl J Med* 2005;**352**:937–939; author reply 937–939.
29. Campbell DJ. Critical review of prorenin and (pro)renin receptor research. *Hypertension* 2008;**51**:1259–1264.
30. Nguyen G, Delarue F, Burckle C, Bouzhir L, Giller T, Sraer JD. Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin. *J Clin Invest* 2002;**109**:1417–1427.
31. McMurray JJV, Pitt B, Latini R, Maggioni AP, Solomon SD, Keefe DL, Ford J, Verma A, Lewsey J. Effects of the oral direct renin inhibitor aliskiren in patients with symptomatic heart failure. *Circ Heart Fail* 2008;**1**:17–24.
32. Parving HH, Persson F, Lewis JB, Lewis EJ, Hollenberg NK. Aliskiren combined with losartan in type 2 diabetes and nephropathy. *N Engl J Med* 2008;**358**:2433–2446.
33. Solomon SD, Appelbaum E, Manning WJ, Verma A, Berglund T, Lukashevich V, Cherif Papst C, Smith BA, Dahlof B. Effect of the direct renin inhibitor aliskiren, the angiotensin receptor blocker losartan, or both on left ventricular mass in patients with hypertension and left ventricular hypertrophy. *Circulation* 2009;**119**:530–537.