

Research Article

Usefulness of Stress Myocardial Perfusion Imaging and Baseline Clinical Factors to Predict Cardiovascular Events in Patients with Peripheral Artery Disease

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Abstract

Introduction: Peripheral Artery Disease (PAD) is a well-established risk factor for poor cardiovascular prognosis. Stress Myocardial Perfusion Imaging (MPI) is a widely used diagnostic and prognostic tool for Coronary Artery Disease (CAD). Normal stress MPI generally correlates with excellent cardiovascular prognosis. We assessed the usefulness of stress MPI and baseline clinical factors as independent predictors of cardiovascular events in patients with PAD and suspected or known CAD.

Methods: Stress MPI was performed in 97 PAD patients. The mean follow-up period was 30 months. PAD was defined as an ankle-brachial index of <0.9 or a history of revascularisation for PAD. Advanced Chronic Kidney Disease (CKD) was defined as Stage IV to V CKD or CKD requiring haemodialysis. Cardiovascular events included cardiac death, nonfatal myocardial infarction and Braunwald class III unstable angina requiring hospitalisation.

Results: Cardiovascular events were observed in 28 patients (29%). Multivariate Cox regression analysis revealed that advanced CKD (hazard ratio = 4.03; $P < 0.001$); left ventricular ejection fraction (hazard ratio = 0.96; $P = 0.008$); and, summed stress scores on stress MPI (hazard ratio = 1.15; $P = 0.013$) were independent and significant predictors of cardiovascular events.

Conclusion: In PAD patients, advanced CKD, impaired left ventricular systolic function and abnormal summed stress scores on stress MPI can be significant and independent predictors of cardiovascular events. In patients who have these risk factors, aggressive management strategies (strengthened suboptimal therapies and careful observation) should be implemented as early as possible.

Keywords: Chronic Kidney Disease; Coronary Artery Disease; Myocardial Perfusion Defect; Prognosis

Abbreviations

ABI: Ankle-Brachial Index; CAD: Coronary Artery Disease; CKD: Chronic Kidney Disease; eGFR: Estimated Glomerular Filtration Rate; LVEF: Left Ventricular Ejection Fraction; MI: Myocardial Infarction; MPI: Myocardial Perfusion Imaging; PAD: Peripheral Artery Disease; QGS: Quantitative Gated SPECT; SSS: Summed Stress Score; SRS: Summed Rest Score; SDS: Summed Difference Score; SPECT: Single-Photon Emission Computed Tomography

Introduction

PAD is well established as a risk factor for cardiovascular disease, and previous angiographic studies have shown that 33–55% of patients with asymptomatic PAD have significant coronary stenosis [1-6]. CKD is also a major cardiovascular risk factor [7-10], and poor cardiovascular prognosis is characteristic of CKD patients treated with haemodialysis. Previous studies have established the usefulness of stress MPI to diagnose CAD and to assess cardiovascular prognosis [11-19]. Normal stress MPI results correlate with excellent cardiovascular prognosis, as evidenced by the annual cardiovascular

event rate of <1% [20]. On the other hand, in CKD patients treated with haemodialysis, normal stress MPI results are not necessarily associated with good cardiovascular prognosis; of haemodialysis patients with normal stress MRI results, 4–9% per year experience cardiovascular events, with poor prognosis [21,22]. Here, we assess the usefulness of baseline clinical factors and stress MPI to predict cardiovascular events in patients with PAD and suspected or known CAD.

Methods

Patients and study protocol

This was a retrospective study of patients who had undergone stress MPI. In total, 1015 consecutive patients with a suspected or confirmed history of CAD underwent thallium-201 stress MPI between 2008 and 2010. The following patients were excluded: 154 with no prognostic data following stress MPI; 760 with no evidence of PAD; and 4 with significant ischaemia (SDS of ≥ 2 on stress MPI) who achieved revascularization within 2 months of subsequent percutaneous coronary intervention [14]. In total, 97 patients with

PAD were included in the study. PAD was defined on the basis of a previous medical history of angioplasty of peripheral arteries or an ABI of <0.9 [1-3].

The study protocol was approved by the Committee on Human Investigation of the Toho University Ohashi Medical Center (approval No. 12-62), and the study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki (as revised in Tokyo in 2004) and subsequent revisions. All included patients provided informed consent.

Information on the history of PAD was obtained from clinical records or patient interviews. In addition, data on age, sex, medication usage, past medical history and other coronary risk factors were routinely collected during stress MPI. The following were considered possible cardiovascular risk factors: cigarette smoking (current and past), history of hypertension, diabetes, hyperlipidaemia, or CKD; or a history of CAD in a first-degree relative (aged <55 years for men and <65 years for women). Hypertension was defined as systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg or current treatment with antihypertensive medications. Diabetes was defined as fasting blood glucose >126 mg/dL, glycosylated haemoglobin >6.5% (based on the National Glycohemoglobin Standardization Program definition) or current treatment with insulin or oral anti-diabetic medications. Hyperlipidaemia was defined as the presence of hypercholesterolaemia (total cholesterol >220 mg/dL), hypertriglyceridaemia (serum triglyceride >150 mg/dL) or current lipid-lowering therapy. CKD was defined according to the National Kidney Foundation criteria [23] as an eGFR of < 60 mL/min/1.73 m² or persistent proteinuria for at least 3 months. Advanced CKD was defined as confirmed (2 consecutive measurements ≥3 months apart) eGFR ≤ 30 mL/min/1.73 m² (Stage IV to V of CKD) and haemodialysis for ≥1 month. The LVEF was measured by motion-mode echocardiography within 1 month of stress MPI.

Stress MPI

Exercise or pharmacological stress tests were performed. Cardiac medications and caffeine ingestion were stopped for 1 day before the examination. All exercise tests were performed using a treadmill; no patient underwent ergometer exercise stress testing. The treadmill exercise test (Bruce protocol) was considered adequate if patients achieved 85% of the maximum predicted heart rate or developed chest pain. Patients with limited exercise capacity (who failed to achieve 85% of the predicted heart rate during the treadmill test) underwent a pharmacological stress test using intravenous adenosine infusion. Adenosine and thallium-201 were administered in different arms. An automated infusion pump was used to deliver intravenous adenosine (0.120 mg/kg/min) over 6 min. Thallium-201 (111 MBq; Fujifilm RI Pharma Co., Ltd., Tokyo, Japan) was injected into a peripheral vein either 1 min before cessation of the treadmill stress test or 3 min after initiation of adenosine infusion.

All myocardial perfusion SPECT data were acquired using a 3-headed gamma camera (MS-3; Siemens, Chicago, IL, USA) equipped with a low-energy cardiofocal collimator and a computer interface (ICON; Siemens, Chicago, IL, USA). Stress SPECT was performed 10 after stress testing, and resting SPECT was performed 4 after MPI. In total, 90 projections were obtained for 20 s each in 4/360° intervals and stored on 64 × 64 matrices. A 15% symmetrical energy window

centred on the 70 keV peak was used. Tomographic reconstruction was performed by the standard filtered back-projection technique using a Butterworth filter with a cut-off frequency of 0.5 cycles/pixel, and an order of 5. No correction was made for attenuation or scatter.

SPECT images were reoriented along the short horizontal and vertical long axes for analysis. SPECT data analysis was performed on the basis of agreement between at least two experienced nuclear medicine physicians (T.F. and M.M). Defects were classified as reversible (including partially reversible) or fixed (irreversible). SPECT images were assessed to determine the presence, location and severity of any perfusion defect. Observers assessed SPECT images visually and did not use software applications. The left ventricle was divided into 17 segments, each of which was assigned a score using a 5-point scoring system (0 = normal, 1 = mildly reduced, 2 = moderately reduced, 3 = severely reduced and 4 = uptake absent). The following scores were calculated: the Summed Score at Stress (SSS) which showed myocardial ischaemia and MI; the summed score at rest Summed Rest Score (SRS) which showed MI and prolonged myocardial ischaemia [24] and the difference between the Stress and rest Scores (SDS), which showed myocardial ischaemia. As demonstrated in previous studies, based on an excellent cardiovascular prognosis, an SSS of <4 was considered to be normal [12,25,26].

Endpoints and follow-up

Follow-up commenced after the assessment of clinical information and stress MPI. Cardiovascular events considered as endpoints were cardiac death, nonfatal MI and Braunwald class III unstable angina requiring hospitalisation. Cardiac deaths included sudden death, fatal MI and death due to heart failure or death due to arrhythmia. Sudden death was defined as witnessed cardiac arrest, death within 1 h of onset of acute symptoms or unexpected death in people who had been considered well for the previous 24 h. Braunwald class III unstable angina was defined as acute angina at rest within 48 h of onset. Patients were regularly followed up for a mean duration of 31 ± 21 months (range, 1–65 months).

Statistical analysis

Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as observed number of patients (percentage). To compare patient characteristics between groups, the Mann-Whitney *U* test was used for continuous variables, and Fisher's exact test was used for categorical variables. Cox regression hazard analysis was used to assess the possible risk factors. Kaplan-Meier event-free curves were generated, and the risks of endpoints were compared between patient groups using log-rank tests. Statistical analyses were performed using SPSS statistical software (SPSS Incorporated, Chicago, Illinois, USA). A *P* value <0.05 was considered statistically significant.

Results and Discussion

Patient characteristics

Table 1 summarizes patient characteristics and compares the results of patients who developed cardiovascular events with those of patients who did not. The frequency of advanced CKD, a familial history of CAD and a history of CAD were significantly higher in patients who developed cardiovascular events. Patients who developed cardiovascular events had lower LVEFs on echocardiography.

Table 1: Patients' characteristics.

	Overall	Events +	Events -	P
	(n = 97)	(n = 28)	(n = 69)	
Age, years	75 ± 11	74 ± 10	75 ± 11	0.49
Male	66 (68%)	22 (79%)	44 (64%)	0.23
Hypertension	85 (88%)	26 (93%)	59 (86%)	0.5
Diabetes	56 (58%)	17 (61%)	39 (57%)	0.82
Hyperlipidaemia	62 (64%)	17 (61%)	45 (65%)	0.82
CKD	71 (73%)	22 (79%)	49 (71%)	0.61
Advanced CKD	42 (43%)	17 (61%)	25 (36%)	0.04
Haemodialysis	28 (29%)	12 (43%)	16 (23%)	0.08
Smoking history	66 (68%)	21 (75%)	45 (65%)	0.47
Current smoking status	14 (14%)	6 (21%)	8 (12%)	0.22
Familial history of CAD	13 (13%)	7 (25%)	6 (9%)	0.05
Cerebral vascular disease	30 (31%)	9 (32%)	21 (30%)	>0.99
History of revascularisation for PAD	39 (40%)	11 (39%)	28 (41%)	>0.99
History of CAD	45 (46%)	18 (64%)	27 (39%)	0.03
History of MI	19 (20%)	8 (29%)	11 (16%)	0.17
Laboratory data				
Haemoglobin	11.7 ± 2.0	11.7 ± 1.8	11.6 ± 0.4	0.81
Albumin	3.9 ± 0.5	4.0 ± 0.5	3.9 ± 0.5	0.49
HbA1c	6.1 ± 1.0	6.2 ± 1.1	6.0 ± 1.0	0.55
LDL cholesterol	98 ± 28	95 ± 28	99 ± 29	0.68
HDL cholesterol	51 ± 16	49 ± 15	52 ± 16	0.32
LDL/HDL	2.1 ± 0.8	2.1 ± 0.8	2.1 ± 0.8	0.98
Echocardiography				
LVEF	61 ± 14	54 ± 16	64 ± 13	0
Adenosine stress test	90 (93%)	25 (89%)	65 (94%)	0.41
MPI				
SSS	2.5 ± 3.4	4.6 ± 4.8	1.6 ± 2.1	0.01
SRS	1.2 ± 2.6	2.6 ± 3.9	0.7 ± 1.5	0.02
SDS	1.2 ± 2.2	2.0 ± 3.1	0.9 ± 1.6	0.16
Medication				
Antiplatelet	77 (79%)	22 (79%)	55 (80%)	>0.99
Aspirin	58 (60%)	18 (64%)	40 (58%)	0.65
Clopidogrel	22 (23%)	6 (21%)	16 (23%)	>0.99
Cilostazol	11 (11%)	5 (18%)	23 (27%)	0.29
ACE-I/ARB	68 (70%)	17 (61%)	51 (74%)	0.23
Beta-blocker	33 (34%)	10 (36%)	23 (33%)	0.82
Ca channel blocker	49 (51%)	14 (50%)	35 (51%)	>0.99
Diuretics	44 (45%)	15 (54%)	29 (42%)	0.37
Statin	45 (46%)	13 (46%)	32 (46%)	>0.99

CKD: Chronic Kidney Disease; CAD: Coronary Artery Disease; MI: Myocardial Infarction; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; LVEF: Left Ventricular Ejection Fraction; MPI: Myocardial Perfusion Imaging; SSS: Summed Stress Score; SRS: Summed Rest Score; SDS: Summed Difference Score; ACE-I: Angiotensin-Converting Enzyme Inhibitor; ARB: Angiotensin II Receptor Blocker.

Table 2: Univariate Cox Regression Analysis.

	Hazard ratio	95% CI	P
Male	1.76	0.71–4.35	0.22
Age	1	0.97–1.06	0.99
Cerebral vascular disease	1.08	0.48–2.35	0.88
History of revascularisation for PAD	0.88	0.41–1.89	0.75
Hypertension	2.29	0.54–9.62	0.26
Diabetes	1.19	0.56–2.54	0.66
CKD	1.65	0.67–4.08	0.28
Advanced CKD	2.75	1.28–5.92	0.01
Haemodialysis	2.12	1.01–4.48	0.049
Hyperlipidaemia	1.41	0.66–3.03	0.37
Current smoking status	1.81	0.73–4.46	0.2
Smoking history	1.39	0.59–3.27	0.45
Familial history of CAD	2.55	0.99–6.02	0.05
History of CAD	2.37	0.99–5.24	0.05
History of MI	1.64	0.72–3.72	0.24
Laboratory data			
Haemoglobin	0.97	0.80–1.17	0.73
Albumin	1.21	0.51–2.90	0.66
LDL	0.99	0.98–1.01	0.88
HDL	0.98	0.96–1.01	0.28
LDL/HDL	1.12	0.70–1.80	0.65
Echocardiography			
LVEF	0.95	0.93–0.98	<0.001
Stress test			
Adenosine stress test	0.6	0.18–2.00	0.41
Stress MPI			
SSS	1.21	1.11–1.33	<0.001
SRS	1.18	1.07–1.31	0.001
SDS	1.19	1.03–1.37	0.017

CI: Confidence Interval; PAD: Peripheral Arterial Disease; CKD: Chronic Kidney Disease; CAD: Coronary Artery Disease; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; LVEF: Left Ventricular Ejection Fraction; MPI: Myocardial Perfusion Imaging; SSS: Summed Stress Score; SRS: Summed Rest Score; SDS: Summed Difference Score.

Regarding stress MPI results, SSS and SRS were significantly higher in patients who developed cardiovascular events.

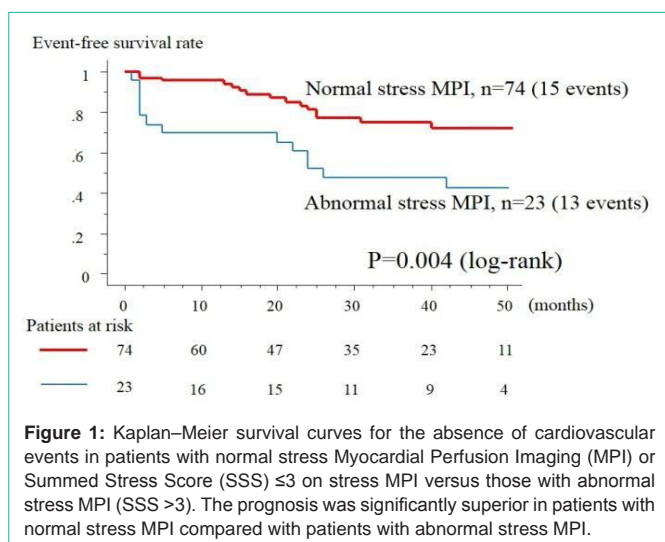
Outcomes

Cardiovascular events occurred in 28 patients with PAD (cardiac death in 12 patients, nonfatal MI in 11 patients and Braunwald III unstable angina in five patients). Univariate Cox regression hazard analysis (Table 2) revealed that advanced CKD, haemodialysis, reduced LVEF on echocardiography and abnormal parameters of stress MPI (SSS, SRS and SDS) were significant predictors of cardiovascular events. As previously reported, the minimum number of variables that should be entered into a multivariable model is a function of the number of events that occur during the study. In general, 1 variable for every 10 events is strongly recommended [27]. From the Cox univariate regression analysis, the relative risk

Table 3: Multivariate Cox regression analysis.

	Hazard ratio	95% CI	P
Advanced CKD	4.03	1.77–9.17	<0.001
LVEF	0.96	0.93–0.99	0.008
SSS	1.15	1.03–1.28	0.013

CI: Confidence Interval; CKD: Chronic Kidney Disease; LVEF: Left Ventricular Ejection Fraction; SSS: Summed Stress score.



level was calculated by multivariate Cox regression hazard analysis for cardiovascular events associated with advanced CKD, LVEF on echocardiography and SSS on stress MPI. Advanced CKD (hazard ratio = 4.03, $P < 0.001$), reduced LVEF on echocardiography (hazard ratio = 0.96, $P = 0.008$) and abnormal SSS on stress MPI (hazard ratio = 1.15, $P = 0.013$) were independent and significant risk factors for cardiovascular events (Table 3).

The Kaplan-Meier survival curves shown in Figure 1 reveal a superior prognosis (concerning cardiovascular events) in patients with normal stress MPI (SSS ≤3) compared with patients with abnormal stress MPI (SSS >3). However, as shown in Figure 1, even patients with normal stress MPI did not have a very good prognosis for cardiovascular events (3 events; 4% in the first year), although their cardiovascular prognosis was better than that of patients with abnormal stress MPI. Although 74 of 97 (76%) patients had normal stress MPI results, we also assessed the prognosis of patients with abnormal stress MPI (SSS >3 and <7 versus SSS ≥7). The difference was not significant in our relatively small sample, but the prognosis tended to be better in patients with SSS >3 and <7 than in patients with SSS ≥7 [3 events in 9 patients (33%) versus 10 events in 14 patients (71%), $P = 0.08$].

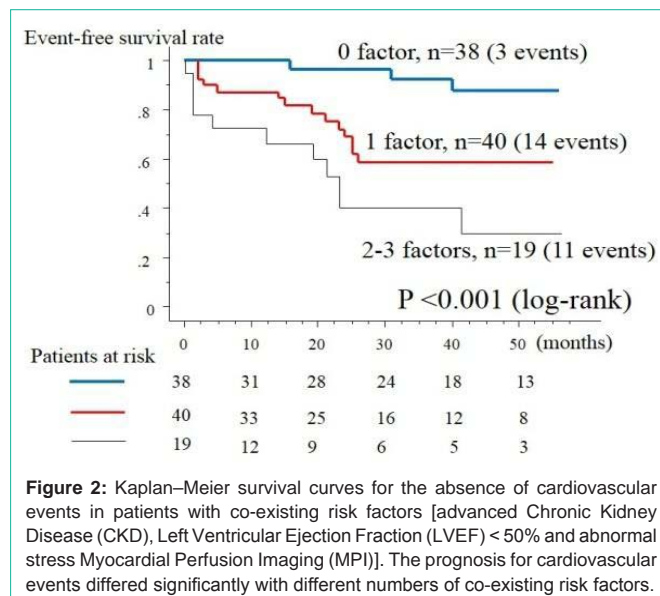
This study also examined the predictive value of the number of risk factors (abnormal stress MPI, advanced CKD and LVEF <50%) that indicated poor cardiovascular prognosis. The number of risk factors identified by multivariate Cox regression analysis was then determined as follows: 0 risk factor, $n = 38$, 3 events (8%); 1 risk factor, $n = 40$, 14 events (35%); 2 risk factors, $n = 15$, 8 events (53%); and 3 risk factors, $n = 4$, 3 events (75%). In univariate Cox regression analysis, the number of risk factors was identified as a predictor of cardiovascular events (hazard ratio = 2.32, $P < 0.001$).

Figure 2 compares the Kaplan-Meier survival curves for patients with different numbers of risk factors (0, 1 and 2-3 factors). The prognosis of cardiovascular events was significantly different with different numbers of co-existing risk factors.

Discussion

Atherosclerosis is a systemic degenerative inflammatory vascular disease and is the primary underlying cause of CAD. About half of all patients who die from CAD have no previous diagnosis or symptoms of cardiac disease [28]. Previous studies have shown that PAD is a risk factor for cardiovascular disease [1-3]. In fact, previous angiographic studies have shown that 33–55% of asymptomatic patients with PAD have significant coronary stenosis [4-6]. The present study demonstrated that advanced CKD, reduced LVEF and the grade of defects in the stress phase assessed by stress MPI results were significant and independent predictors of cardiovascular events in patients with PAD. In addition, previous studies at our institution have shown that PAD is a key factor among patients with normal stress MPI [29], and abnormal stress MPI and PAD are independent and significant predictors of cardiovascular events in haemodialysis patients [30]. Even in patients who have normal stress MPI, PAD is a significant predictor of poor cardiovascular outcomes.

The relationship between CKD and adverse cardiovascular prognosis has been established by large community-based studies [7-10], and in patients who undergo stress MPI, lower eGFR is an independent and significant predictor of cardiovascular events [31-33]. In univariate Cox regression analysis, the present study showed that advanced CKD (including haemodialysis in 28 patients) was a stronger predictor of adverse outcomes than CKD and haemodialysis. However, CKD itself is not a useful predictor of cardiovascular events. Interestingly, 71 patients (73%) in our study had CKD, but cardiovascular events were not frequent in these CKD patients. Seven of 26 (27%) non-CKD patients had abnormal stress MPI. However, no cardiovascular events occurred in this group during the first year, while 2 of 19 (11%) non-CKD patients with normal stress MPI experienced cardiovascular events. The cardiovascular prognosis was not particularly good in non-CKD patients with normal stress MPI.



In this analysis, 74 of 97 patients presented with normal stress MPI. We could not adequately assess the prognosis of the 23 patients with abnormal stress MPI. We conclude that patients with a SSS >3 and <7 showed a tendency toward better outcomes than patients with a SSS \geq 7, but these observations await statistical confirmation in larger studies.

LVEF has been widely used to assess prognosis in cardiovascular disease [34-37], and the values of LVEF measured by echocardiography, electrocardiogram-gated SPECT and left ventriculography are closely correlated [38]. The present study showed that reduced LVEF, assessed by echocardiography, could be a predictor of cardiovascular events.

Aggressive management strategies (careful observation, strengthening of so-called suboptimal therapies and coronary revascularisation when myocardial ischaemia is observed) are needed as early as possible to prevent adverse cardiac events in patients with PAD, particularly in those with co-existing advanced CKD, reduced left ventricular systolic function and high SSS on stress MPI, regardless of the presence or absence of typical angina symptoms.

Study limitations

An important limitation of this study is that, because it was a single-centre retrospective trial, selection bias could be included. Baseline patient characteristics such as clinical data related to symptoms or history may not be completely accurate. Electrocardiogram-gated SPECT was only performed in 28 patients, in 9 of whom cardiovascular events were observed. During the period when stress MPI was assessed (2008–2010), the technique was not performed regularly at our institution because of the limited information-processing ability of the available instruments. Moreover, we believed that decreased myocardial thallium washout was suitable to detect myocardial ischaemia, particularly in patients with multiple-vessel disease and balanced ischaemia. Compared with technetium, thallium was not suitable for QGS and increased radiation exposure. We could not assess the predictive value of cardiac function measured by QGS, including the LV end-diastolic and end-systolic volumes, LVEF and peak filling rate because we did not use QGS in all patients. The periods between stress MPI and gathering of laboratory data (i.e. examination of ABI or echocardiography) varied, but all these data were obtained within a 3-month period before and after stress MPI. Finally, we cannot exclude the possibility that cardiovascular events were missed because of insufficient follow-up.

Conclusion

In conclusion, although the present study has several limitations, we believe our findings provide valuable insights into the usefulness of both background risk factors and stress MPI as predictors of cardiovascular risk in patients with PAD. In patients with PAD, baseline clinical factors (such as advanced CKD), cardiac functions and stress MPI can be powerful predictors of cardiovascular events.

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