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Incremental Prognostic Value of Stress Echocardiography With Carotid Ultrasound for Suspected CAD

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ABSTRACT

OBJECTIVES This study hypothesized that ischemia and atherosclerosis assessment by ultrasound (US) may provide incremental prognostic information in patients with new-onset chest pain who do not have coronary artery disease (CAD).

BACKGROUND The clinical significance of atherosclerosis assessment by carotid US in patients undergoing stress echocardiography (SE) in such patients is unknown.

METHODS Consecutive patients with suspected angina but no history of CAD underwent simultaneous SE and US prospectively to assess myocardial ischemia and carotid plaque burden (CPB), respectively. Patients were followed up for major adverse events (MAEs)—all-cause mortality, nonfatal myocardial infarction, and unplanned coronary revascularization.

RESULTS Of 591 recruited patients, 580 (men, 46%; mean age 59 ± 11 years) patients were available for follow-up. SE demonstrated myocardial ischemia in 12%, but prevalence of carotid plaques was 59%. During a mean follow-up of 1,117 ± 361 days, 40 first MAEs occurred. In the multivariable regression model, pre-test probability (PTP) of CAD ($p = 0.001$), abnormal SE ($p < 0.0001$), and CPB ($p < 0.0001$) predicted MAEs. MAE rates per year increased from 0.9% versus 1.97% versus 4.3% versus 9.7% in patients with no carotid plaque and normal SE versus patients who had plaque and normal SE versus those with no plaque and abnormal SE versus patients with plaque and abnormal SE, respectively ($p < 0.0001$). In hierarchical analysis, plaque burden provided incremental prognostic value over PTP of CAD and SE; likewise, SE was incremental to PTP-CAD and CPB ($p < 0.0001$ for both).

CONCLUSIONS In patients with suspected stable angina without known CAD, simultaneous SE (for ischemia) and US (for atherosclerosis) provided incremental prognostic value. (J Am Coll Cardiol Img 2018;11:173–80)

When patients without a history of coronary artery disease (CAD) present with recent onset suspected angina, they may undergo functional noninvasive tests for detection of myocardial ischemia, both for diagnostic and risk stratification purposes. Although a negative test for ischemia reduces the probability of obstructive CAD, it does not exclude the presence of nonobstructive CAD, which can adversely affect prognosis (1). Preventative pharmacological measures such as aspirin and statins in these patients may improve outcome, despite the absence of ischemia. Conversely, presence of ischemia may occur in the absence of epicardial CAD (e.g., microvascular dysfunction, endothelial dysfunction, and coronary spasm) and may portend better outcomes compared with those with obstructive atherosclerotic disease. A combination of single-photon emission computed tomography (SPECT) or positron emission tomography (PET), and coronary computed tomography

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ABBREVIATIONS AND ACRONYMS

AMI = acute myocardial infarction

CA = coronary angiography

CAD = coronary artery disease

CIMT = carotid intima-media thickness

CP = carotid plaque

CPB = carotid plaque burden

CTA = computed tomography angiography

MAEs = major adverse events

MACEs = major adverse cardiac events

PET = positron emission tomography

PTP = pre-test probability

SPECT = single-photon emission computed tomography

SE = stress echocardiography

US = ultrasound

angiography (CTA) has been proposed for the detection of myocardial ischemia and atherosclerotic disease, respectively, for optimal management of such patients (2,3). However, high ionizing radiation burden, limited availability, and the prohibitive cost of these tests limit their combined use.

Stress echocardiography (SE) is widely used for the diagnosis and risk stratification of patients with recent onset chest pain. Similarly, carotid ultrasound (US), which can detect atherosclerosis and is closely associated with CAD, has also been shown to predict cardiac mortality and acute myocardial infarction (AMI) beyond clinical risk factors in asymptomatic patients (4). SE and US can be performed at the bedside simultaneously without ionizing radiation and are relatively inexpensive. We hypothesized that combined SE and US in patients with recent onset suspected stable angina but without history of CAD may provide incremental prognostic information beyond clinical risk factors. If shown to do so, this would have clinical implications for daily clinical practice. Accordingly, we conducted a large prospective study in such patients referred for SE who also underwent US.

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METHODS

A complete description of the patient selection, SE, US, clinical risk stratification, and coronary angiography (CA) was previously described (5). In summary, consecutive patients investigated because of new-onset stable chest pain, but who did not have a history of CAD or coronary intervention and who were referred for SE on clinical grounds, were enrolled in the study and provided written consent. Ethical and institutional review board approvals were obtained to perform this study.

STRESS ECHOCARDIOGRAPHY. Exercise treadmill testing was the preferred testing method; subjects who were unable to undertake a treadmill test underwent dobutamine stress as per conventional guideline-based protocols. Whenever the left ventricular endocardium was not well delineated in at least 2 consecutive segments, an intravenous microbubble (Sonovue, Bracco, Milan, Italy) was administered. Pre-defined endpoints for test termination were significant chest pain or arrhythmia, achievement of 85% of age-predicted target heart rate (220 − age) or peak doses of dobutamine/atropine, development of wall thickening abnormality, or intolerable side effects. Base and peak images were stored digitally and reported offline by a single expert reader (R.S.) who was blinded to patient characteristics. SE was reported as abnormal in the presence of a wall thickening abnormality in at least 2 consecutive segments. The results were communicated to the referring physicians.

CAROTID ULTRASONOGRAPHY. Carotid arteries were systematically interrogated in long- and short-axis views, including the proximal, mid, distal, and bifurcation of the common carotid artery and the proximal portion of the internal and external carotid arteries. Carotid plaque (CP) ("plaque") was defined per Mannheim consensus as a focal structure encroaching into the arterial lumen by ≥0.5 mm, a distinct area of carotid intima-media thickness (CIMT) ≥50% greater than the adjacent wall, or >1.5 mm in thickness (6). CIMT measurements were taken at the far wall of common carotid artery and bifurcation at end-diastole using a semi-automated edge detection algorithm (QLAB version 8, Philips Medical Systems, Best, the Netherlands). Images were stored digitally and reported offline by a single trained reader (SA) who was blinded to both patient characteristics and SE data. The results were not communicated to the physicians; however, flow-limiting stenosis (≥70%) was reported to the referring physicians. Intraobserver agreement was $k = 0.82$ ($p < 0.0001$).

CA AND REVASCULARIZATION. The decision to proceed to CA and revascularization was made by the referring cardiologist. CAD was defined qualitatively as ≥50% luminal narrowing in ≥1 epicardial arteries or their major branches.

PRE-TEST PROBABILITY OF CAD. This was calculated based on the U.K. National Institute for Health and Clinical Excellence guideline (7), which incorporates chest pain characteristics, age, sex, and risk factors (diabetes, smoking, and hyperlipidemia). Patients were then divided into low, intermediate, and high pre-test probability (PTP) (<10%, 10% to 90%, >90%, respectively) groups.

ASCERTAINMENT OF EVENTS. Primary outcome measures were combined major adverse events (MAEs), defined as all-cause mortality, nonfatal AMI, and unplanned coronary revascularization. The latter was performed on clinical grounds by the attending physician in the context of ongoing angina, despite optimal medical therapy or presentation with unstable angina/AMI, and was not as a direct consequence of the SE result. Secondary outcome measures were combined major cardiovascular adverse events

(MACEs), defined as cardiac mortality, nonfatal AMI, and unplanned coronary revascularization. Combined hard cardiac events (cardiac mortality and AMI) were also assessed. Mortality was determined using the U.K. National Health Service database; a copy of the death certificate was obtained for all deceased patients. Subjects were contacted directly, and incidence of events, including definite or probable AMI, indicated by abnormal electrocardiogram and positive blood markers, as well as CA and revascularization were evaluated by obtaining their medical records.

STATISTICAL ANALYSIS. Baseline patient characteristics, US, and SE results were compared across various outcomes using chi-square and Student *t* tests, as appropriate. The predictors of a first MAE were studied by Cox proportional-hazard regression to evaluate the independent relationship between each parameter and the respective outcome after identification of univariable predictors, with $p \leq 0.05$. This is known as univariable screening, which was pre-specified in the protocol to ensure avoidance of a low event per variable ratio. Plaque was tested as both a categorical (present vs. absent) and a continuous variable as carotid plaque burden (CPB), based on the number of plaques identified, in separate models. Kaplan-Meier survival curves were constructed to plot time-to-event outcomes, which were compared using the log-rank test. Values of $p < 0.05$ were considered statistically significant. Statistical analysis was performed with SPSS version 22.0 (IBM, Armonk, New York).

RESULTS

Of 591 patients recruited, 580 (98%) were available for follow-up. Their demographic characteristics, SE, and carotid data are listed in Table 1. An abnormal SE was reported in 12%, whereas 59% had plaque. Prevalence of plaque was seen in 34% and 64% in patients with low (n = 114) and intermediate PTP (n = 428), respectively. Seven patients had flow-limiting carotid disease (5 in the common carotid artery and 3 in the internal carotid artery), none of whom had an abnormal SE. Of 513 patients with normal SE, 299 (58%) patients had plaque, 164 (55%) of whom were not on statins, which constituted 28% of the whole population.

FOLLOW-UP. During follow-up (1,117 ± 361 days), there were a total of 40 MAEs (12 all-cause mortalities, 9 nonfatal AMIs, and 19 unplanned revascularizations), 32 MACEs (4 cardiovascular mortalities, 9 nonfatal AMI, and 19 unplanned revascularizations), and 13 hard cardiac events (4 cardiovascular mortalities and 9 nonfatal AMIs).

TABLE 1 Baseline Patient Characteristics, SE, and Carotid Ultrasound Findings of the Follow-Up Cohort (n = 580)

Age, yrs	60 ± 11
Male	264 (46)
Body mass index, kg/m^2	28 ± 5
Cardiac risk factors	
Hypertension	315 (54)
Diabetes mellitus	138 (24)
Hypercholesterolemia	336 (58)
Smoker (current or within last year)	67 (12)
FH of premature CAD	195 (34)
Drug history	
Aspirin	164 (28)
Beta-blocker	73 (13)
ACEi/ARB	205 (35)
Statins	233 (40)
PTP of CAD, %	40 ± 30
Prevalence of low PTP	114 (20)
Prevalence of intermediate PTP	428 (74)
Prevalence of high PTP	38 (6)
Exercise SE	356 (61)
Contrast for opacification	285 (49)
Abnormal SE	67 (12)
Carotid plaque	343 (59)
Common carotid artery	110 (32)
Bifurcation	307 (90)
Internal carotid artery	92 (27)
CIMT (mm)	0.68 ± 0.13

Values are mean ± SD or n (%).

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CIMT = carotid intima-media thickness; FH = family history; PTP = pre-test probability; SE = stress echocardiography.

Time to first unplanned revascularization ranged between 346 and 1,684 days; therefore, it was unlikely to be affected by SE result. The annual hard event rate in this population was 2.3%/year, which reflected a high prevalence of intermediate PTP of CAD. No event was reported in patients with significant (>70%) carotid disease.

COX REGRESSION ANALYSIS. Because PTP incorporated chest pain characteristics, age, sex, diabetes mellitus, and smoking status, these components were used collectively. Systemic hypertension, stain therapy, peak rate–pressure product, early revascularization, SE result, and CPB were included. In the multivariable model, PTP, abnormal SE, and CPB predicted MAEs ($p = 0.001$, $p < 0.0001$, $p < 0.0001$, respectively) (Table 2) and MACEs ($p = 0.004$, $p < 0.0001$, $p < 0.0001$, respectively) (Table 2). However, only CPB retained significance in multivariable analysis for the prediction of hard cardiac events ($p < 0.0001$), with SE retaining borderline significance ($p = 0.06$) (Table 2).

When only the intermediate PTP group (74% of patients) was considered, in whom investigation

TABLE 2 Cox Regression Analysis for the Prediction of MAEs, MACEs, and Hard Cardiac Events: Cardiac Mortality + AMI

	Univariable Analysis* p Value	Multivariable Analysis† p Value	HR	95% CI
MAEs				
Statin	**0.028**	0.072		
PTP	**<0.0001**	**0.001**	3.13	1.57-6.27
SE result	**<0.0001**	**<0.0001**	4.41	2.31-8.43
CPB	**<0.0001**	**<0.0001**	1.26	1.13-1.40
MACEs				
Statin	**0.028**	0.12		
PTP	**<0.0001**	**0.004**	3.17	1.44-6.89
SE result	**<0.0001**	**<0.0001**	6.71	3.30-13.64
CPB	**<0.0001**	**<0.0001**	1.32	1.17-1.49
Hard cardiac events: cardiac mortality + AMI				
Hypertension	**0.021**	0.23		
PTP	**0.017**	0.22		
SE result	**0.028**	0.06		
CPB	**<0.0001**	**<0.0001**	1.53	1.27-1.84

*Values in **bold** indicate $p \leq 0.10$. †Values in **bold** indicate $p < 0.05$.

AMI = acute myocardial infarction; CI = confidence interval; CPB = carotid plaque burden; HR = hazard ratio; MACEs = major adverse cardiac events; MAEs = major adverse events; other abbreviations as in Table 1.

was deemed most appropriate, SE and CPB retained their significance in Cox regression analysis for the prediction of MAEs (SE: $p < 0.0001$; CPB: $p < 0.0001$), MACEs (SE: $p < 0.0001$; CPB: $p < 0.0001$), and hard cardiac events (SE: $p = 0.033$; CPB: $p < 0.0001$) (Online Table 1).

SURVIVAL ANALYSIS. Events in SE subgroups based on Kaplan-Meier survival curves. Patients with an abnormal SE had significantly higher rates of MAEs, MACEs, and hard cardiac events compared with normal SE (Table 3). In patients with normal SE, combined hard cardiac event rates were 0.57% per year versus 1.95% per year with an abnormal SE (Online Figures 1A to 1C).

Events in carotid plaque subgroups based on Kaplan-Meier survival curves. Patients with CP, had significantly higher rates of MAEs, MACEs, and hard cardiac events compared with those with no CP (Table 3). In patients with no CP, combined hard cardiac event rates were 0.13% per year versus 1.14% per year in those with CP (Online Figures 2A to 2B).

Combined SE and plaque outcome based on Kaplan-Meier survival curves. Kaplan-Meier survival curves for the predictions of MAEs, MACEs, and hard cardiac events demonstrated a significant stepwise increase in events across all combinations in patients with no plaque and normal SE versus those with plaque and normal SE versus patients with no plaque and abnormal SE versus those with plaque and abnormal SE, respectively (Figures 1A to 1C).

TABLE 3 Incidence of Adverse Events Based on Kaplan-Meier Survival Curve

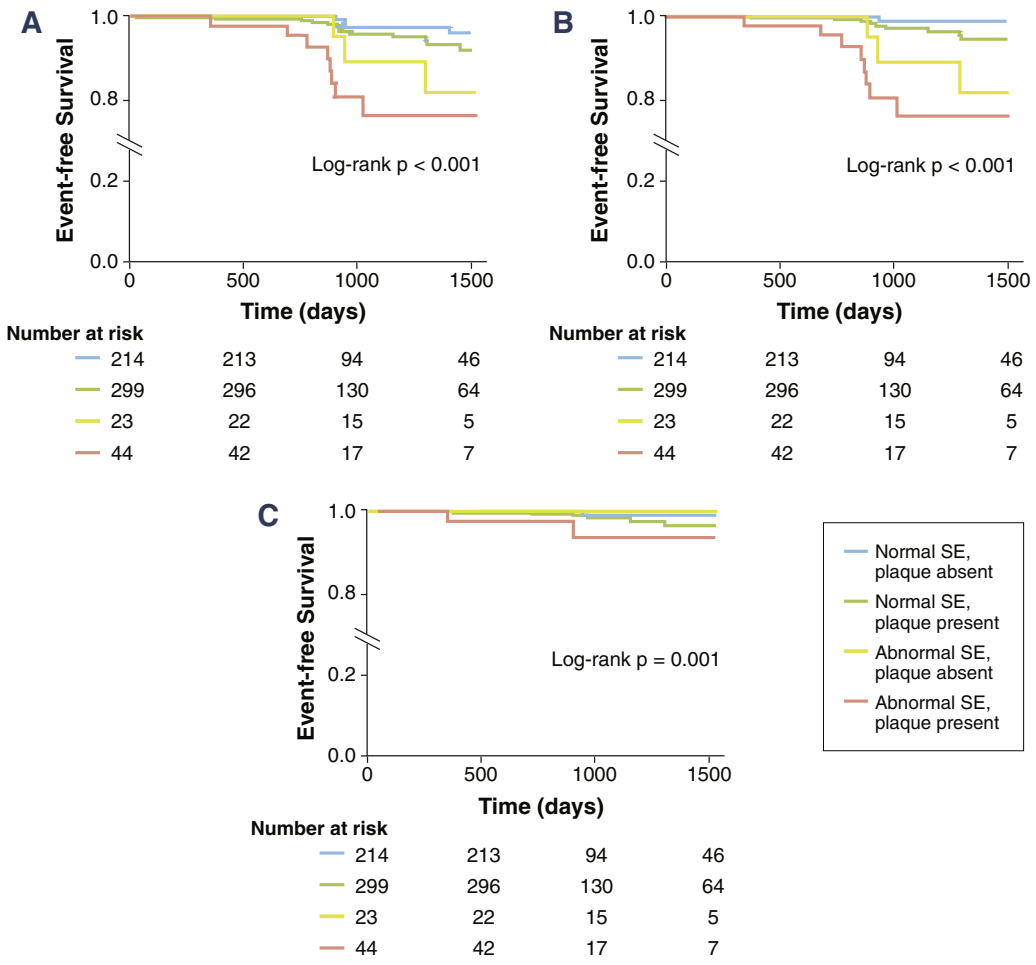
	Normal SE (n = 513)	Abnormal SE (n = 67)	p Value
Normal vs. Abnormal SE			
MAEs	24 (4.7)	16 (24)	<0.0001
MACEs	16 (3.1)	16 (24)	<0.0001
Hard cardiac events	9 (1.75)	4 (6)	0.022
Presence vs. Absence of Carotid Plaque			
	Plaque Absent (n = 237)	**Plaque Present (n = 343)**	**p Value**
MAE	9 (3.7)	31 (9)	0.009
MACE	6 (2.5)	26 (7.6)	0.005
Hard cardiac events	1 (0.4)	12 (3.5)	0.010

Combined SE and CP Results	Normal SE, Plaque Absent	Normal SE, Plaque Present	Abnormal SE, Plaque Absent	Abnormal SE, Plaque Present	p Value
MAEs	6/214 (2.8)	18/299 (6.0)	3/23 (13)	13/44 (29.5)	<0.0001
Annualized MAEs	0.9	1.97	4.3	9.7	
MACEs	3/214 (1.4)	13/299 (4.3)	3/23 (13)	13/44 (29.5)	<0.0001
Annualized MACEs	0.46	1.42	4.3	9.7	
Hard cardiac events	1/214 (0.5)	8/299 (2.7)	0/23(0)	4/44 (9)	0.022
Annualized hard cardiac events	0.15	0.88	0	2.97	

Values are n (%), n/N (%), or %.

CP = carotid plaque; other abbreviations as in Tables 1 and 2.

FIGURE 1 Kaplan-Meier Curves Based on SE and Carotid Plaque Results



(A) Kaplan-Meier survival curves for the predictions of major adverse events, **(B)** major adverse cardiac events, and **(C)** hard cardiac events demonstrate a significant stepwise increase in events across all combinations in patients with no plaque and normal stress echocardiography (SE) versus plaque and normal SE versus no plaque and abnormal SE versus plaque and abnormal SE, respectively.

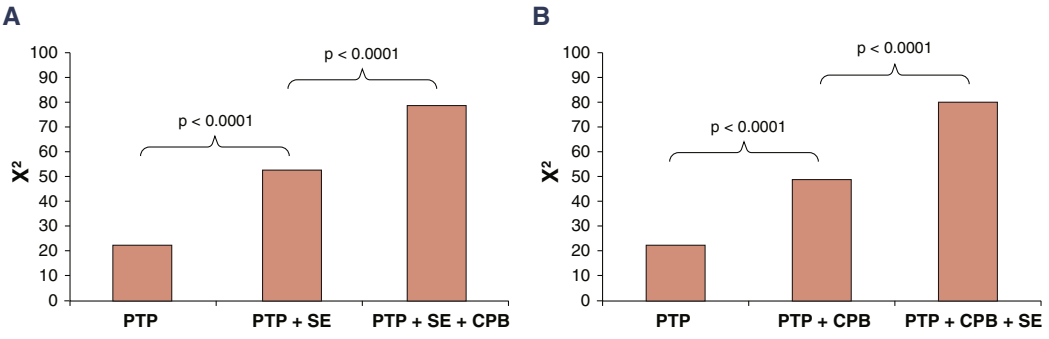
MAE rates per year increased from 0.9% versus 1.97% versus 4.3% versus 9.7% in patients with no plaque and normal SE versus those with plaque and normal SE versus those with no plaque and abnormal SE versus those with plaque and abnormal SE, respectively (**Table 3**). Similar incremental effects were seen with MACEs. Hard cardiac events were 0.15% versus 0.88% versus zero versus 2.97%, respectively.

When prognosis was assessed in a hierarchical manner as done clinically (PTP followed by SE and CPB), it showed a significant increment in the global chi-square for the prediction of MAEs (**Figure 2A**), MACEs, and hard cardiac events (Online Figures 3A and 4A). Similar increments in global chi-square were observed when CPB was assessed after PTP followed by SE for MAEs (**Figure 2B**), MACEs, and hard cardiac events (Online Figures 3B and 4B).

DISCUSSION

This large prospective study was the first to demonstrate the incremental value of myocardial ischemia and atherosclerosis assessment using US (SE and carotid US, respectively), for the prediction of MAEs in patients presenting with recent onset suspected stable angina, but who did not have a history of CAD. The study demonstrated that abnormal SE and CPB were powerful independent predictors of outcome. When clinical and imaging information for ischemia

FIGURE 2 Incremental Value of PTP-CAD, SE, and CPB



(A) When prognosis was assessed in a hierarchical manner as done clinically (pre-test probability [PTP] followed by stress echocardiography [SE] and carotid plaque burden [CPB]), it showed significant increment in the global chi-square for the prediction of a major adverse event. **(B)** Similar increments in the global chi-square were observed when CPB was assessed after PTP followed by SE.

(SE) and atherosclerosis (US) were used in a hierarchical manner as performed clinically (clinical + SE + US), it provided stepwise incremental prognostic information. US followed by SE showed similar results confirming the incremental prognostic value of the 2 tests. The results were also replicated in the intermediate PTP group, in which testing was most warranted. In the whole cohort, MAE rates per year was 0.92% versus 1.97% versus 4.3% versus 9.7% in patients with no plaque and normal SE versus those with plaque and normal SE versus patients with no plaque and abnormal SE versus those with plaque and abnormal SE, respectively. A similar trend was observed when MACEs and hard cardiac events were assessed.

Atherosclerotic disease precedes development of flow-limiting lesions that give rise to ischemic symptoms. However, severe atherosclerotic lesions may be present without manifest disease due to positive arterial remodeling (8), and the first event could thus be death or an acute ischemic event (9). This was clearly shown in our study, that although a normal SE predicted a low annual hard cardiac event rate of approximately 0.57%, the presence of CP increased the event rate by 1.5 times, and the absence of plaque in patients with normal SE reduced it 4 times. Furthermore, because myocardial ischemia on stress testing can occur due to causes other than flow-limiting CAD, the presence of carotid atherosclerosis indicated a high likelihood of CAD compared with those without plaque but who had ischemic SE. This study supported this concept because the presence of plaques more than doubled the cardiac event rate in patients with ischemic SE compared with those without plaques and ischemic SE.

Carotid disease, especially plaque, has been shown to predict future adverse cardiovascular events in large epidemiological studies of asymptomatic individuals (4,10–12), and has also been shown to reflect the presence and severity of CAD (13). The present study extended these findings by demonstrating, for the first time in a cohort of symptomatic patients, that CPB is a powerful predictor of MAEs. Although as a group, it is the plaque burden rather than mere presence of plaque that is the strongest predictor of outcome, on a per patient basis, the mere presence of plaque appeared to define risk. For example, in this study, the hard cardiac event rate was only 0.4% in patients without plaques, but the presence of any plaque increased risk 8-fold.

The studied population was late middle-aged with no history of CAD, but this is typical in routine clinical practice. In a previous publication on the same population, we showed a strong association between the presence of CP and CAD, independent of all known risk factors (5). In a similar population evaluated with coronary CTA, the authors showed the prevalence of coronary atherosclerosis in 70% of patients; a finding that was similar to the present study in terms of carotid atherosclerosis (14). This study also showed that presence of noncalcified plaque in ≤2 coronary segments was an independent predictor of outcome.

The present study demonstrated the prognostic value of myocardial ischemia detected by SE. The annualized hard cardiac event rate in patients with normal SE was 0.57%, which conferred a low risk, in keeping with a recent meta-analysis (15). Presence of ischemia increased the hard cardiac event rate nearly 4-fold to approximately 2%, placing patients in the intermediate risk group, which warrants medical

intervention. SE predicts spontaneous cardiac events such as death and AMI through rupture of plaques that are not necessarily at the site of coronary artery subtending the ischemic myocardium, but that are also subtending nonischemic segments (16). However, as discussed previously, coronary plaque disease may be present without the presence of myocardial ischemia, and these plaques may be unstable. Hence, even in the absence of ischemia, the cardiac event rate increased 1.5 times when CP was present and decreased 4-fold when it was absent.

Similar data were obtained in an identical patient population using coronary CTA for atherosclerosis assessment and SPECT for myocardial ischemia (14). This study also showed that atherosclerosis was more prevalent than myocardial ischemia. The presence of noncalcified coronary plaque improved prediction of outcome beyond clinical data, myocardial ischemia, and even beyond presence of flow-limiting CAD (>50% luminal narrowing on coronary CTA). Furthermore, similar to our study, they showed an incremental prognostic effect when atherosclerosis data were incorporated with myocardial ischemia assessment in the symptomatic population. In another study that combined coronary CTA with SPECT in a predominantly asymptomatic population, in whom stress SPECT was carried out appropriately, the authors demonstrated superior prognostication by atherosclerosis assessment over perfusion (17).

CLINICAL IMPLICATIONS. Both the present study and previously published data (5) suggest that simultaneous assessment of myocardial ischemia and atherosclerosis in patients presenting with suspected stable angina provide incremental prognostic information. Detection of CP is likely to have therapeutic implications. For example, if the test for myocardial ischemia is negative, but the patient has evidence of atherosclerosis, then it could be hypothesized that such patients might benefit from aspirin and statin therapy (18,19), although a randomized prospective study to examine this theory in such patients is required. In our cohort, 28% of patients who had no myocardial ischemia on SE did have carotid atherosclerosis and were not on any primary preventative therapy.

The data on atherosclerosis and myocardial ischemia that provide incremental prognostic benefit have, hitherto, been confined to patients undergoing computed tomography (CT)/SPECT or CT/PET. However, both combination modalities are costly, with a prohibitive ionizing radiation dose, and both modalities are not widely available. This was the first study to show that contemporary SE (harmonic imaging with contrast use where required) and simultaneous US can not only provide similar prognostic information as radiation-based techniques, but was feasible in all patients, free of any ionizing radiation, significantly less costly, and ubiquitously available. Furthermore, unlike CT/SPECT or PET, the data of atherosclerosis and myocardial ischemia could be provided instantly at the bedside.

STUDY LIMITATIONS. This was a single center study in which both SE and carotid images were analyzed by a single (but different) reader. Although SE was reported qualitatively by an expert, US data were analyzed by a recently trained operator, and the excellent interobserver variability supported its translational outlook. The study did not assess the effects of primary prevention therapy in patients with normal SE but who had CPs. Hence, no firm conclusions could be drawn regarding the outcome of primary preventative therapy in this group of patients. The number of hard events was low (although they consisted of 50% of the primary events on which the power calculation was based). Because of relatively low mortality, this endpoint could not be individually assessed. Although 20% of patients belonged to the low PTP group, excluding this group did not alter the data. The strength of the study was that it was large, prospective, and performed in patients who were clinically referred for SE. Carotid US was performed simultaneously. SE data were available for clinical decision making but not the carotid US result, because the latter was analyzed several months later by a separate reader who did not read SE.

CONCLUSIONS

In patients with suspected stable angina but without known CAD, simultaneous SE (for ischemia) and carotid US (for atherosclerosis) provided incremental prognostic value. This study supported performance of carotid US in such patients referred for SE for assessment of myocardial ischemia because it has both prognostic importance and implications for primary prevention.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: SE is commonly used to assess patients with new-onset suspected stable angina.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Although a negative SE is reassuring, it does not exclude the presence of nonflow-limiting CAD, which has been shown to adversely affect prognosis. Carotid US, which can be performed simultaneously, can assess atherosclerotic burden, and in this study, it provided incremental prognostic value beyond SE information.

TRANSLATIONAL OUTLOOK 1: Comprehensive assessment of patients with suspected stable angina without known CAD should include evaluation by SE for myocardial ischemia and carotid US for atherosclerosis.

TRANSLATIONAL OUTLOOK 2: To achieve this, echo laboratories need to invest in staff training, equipment, and software for carotid US, although cost and infrastructural change implications will be minimal.

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KEY WORDS carotid plaque, coronary artery disease, stress echocardiography

APPENDIX For supplemental figures and a table, please see the online version of this paper.