ORIGINAL RESEARCH

Effect of Coronary Revascularization on the Prognostic Value of Stress Myocardial Contrast Wall Motion and Perfusion Imaging

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***Background*—**The assessment of myocardial perfusion (MP) and wall motion (WM) using contrast dipyridamole echocardiography (cSE-WMP) improves the sensitivity to detect coronary artery disease and the stratification of cardiac events, but its long-term value for fatal and nonfatal ischemic cardiac events, also with respect to patients undergoing revascularization or not, remains to be determined.

***Methods and Results*—**One-thousand three-hundred and twenty-nine patients with suspect or known CAD who underwent cSE-WMP were followed for a median 5.5 years. The independent prognostic value of cSE-WMP regarding cardiac death or nonfatal myocardial infarction was related to stress WM and MP, rest ejection fraction, clinical risk factors, and medications. Patients revascularized after cSE-WMP were separately analyzed to determine whether the procedure influenced outcome and whether this depends on cSE-WMP results. A total of 125 cardiac fatal and nonfatal ischemic events (9.4%) occurred during the follow-up (61 deaths, 64 myocardial infarctions). The 5-year event rate with normal MP and WM was 5.9%, 9.9% with isolated MP defects (normal WM), and 15.5% with both MP and WM abnormalities. In patients not undergoing revascularization (n=1111), reversible MP defects added discrimination value over WM response and clinical factors/medication data (P=0.001), while in the cohort undergoing revascularization (n=218), cSE-WMP results did not influence outcome.

***Conclusions*—**cSE-WMP, with both contrast MP and WM assessments, provides independent, incremental prognostic information regarding ischemic cardiac events at 5 years in patients with known or suspected coronary artery disease. Revascularization reduces cardiac events after an abnormal cSE-WMP, resulting in outcomes not different from those in patients with normal cSE-WMP. **(*J Am Heart Assoc*. 2017;6:e006202. DOI: 10.1161/JAHA.117.006202.)**

Key Words: cardiac events • contrast echocardiography • coronary artery disease • death • dipyridamole • ischemia • myocardial perfusion • prognosis • stress-echocardiography • wall motion

Pharmacologic stress echocardiography using wall motion (WM) assessment is an established technique for the detection and prognostication of coronary artery disease (CAD) using dobutamine[1–6] or vasodilators.[7–9] Contrast stress echocardiography with additional myocardial perfusion assessment (cSE-WMP) has demonstrated further increase in predictive accuracy for hard cardiac events in patients with suspected or known CAD, either during dobutamine[10,11] or vasodilator[12–14] stress. As far as WM assessment is concerned, cSE-WMP also has the advantage of maximizing test feasibility over standard stress echocardiography, with quality of acoustic windows not representing an issue when taking advantage of ultrasound contrast media.[15] Still, the few studies assessing cSE-WMP for prognosis do not address its value specifically in predicting true ischemic events (cardiac death and nonfatal acute myocardial infarction [MI]),[10–20] and it is not known how the use of cSE-WMP as a gatekeeper to coronary angiography and subsequent revascularization does relate to long-term outcome in subsequently revascularized and nonrevascularized patients. Previous cSE-WMP studies reported only on combined end points with prevalence of all-cause deaths, half of them represented by cancer deaths, pneumonia, or other diseases that may not be directly influenced by coronary ischemia at stress testing.[10–14] Cardiac ischemic events are instead clinically relevant end points, currently modifiable by timely aggressive medical or surgical therapy, if highest-risk subjects can be identified.[21]

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Clinical Perspective

What Is New?

- Cardiac ischemic fatal and nonfatal events are predicted *in the long-term* by contrast pharmacologic vasodilator stress-echocardiography, relying either on WM or on myocardial perfusion, *incrementally* to clinical and drug therapy data.
- Such prognostic value is now demonstrated in a truly contemporary population, pharmacologically and interventionally treated according to most recent guidelines.
- Such prognostic value of the index stress-echocardiogram is apparently lost after patients with a positive test undergo revascularization, indirectly indicating a prognostic benefit of revascularization itself in such patients with significant reversible ischemia.
- Such significant and beneficial effect of revascularization was not recorded in patients demonstrating only reversible myocardial perfusion defects, in the absence of WM, generally representing less extensive and less severe reversible ischemia.

What Are the Clinical Implications?

- Our data add to few other retrospective studies suggesting that revascularization is prognostically beneficial only in the presence of a certain amount of demonstrable reversible ischemia at provocative testing, suggesting that revascularization probably should not be considered the primary therapy in patients with suspect or known CAD with only mild reversible ischemia.

In this article, we report long-term follow-up in the largest published cSE-WMP database, comprising 1329 contemporary patients, with an average 5.5 years follow-up, more than double the follow-up of previously published cSE-WMP studies.

The hypotheses of the current study are that both the perfusion and WM analysis during cSE-WMP are able to predict the incidence of cardiac ischemic events at 5 years in patients with known or suspected CAD. Secondly, we hypothesized that aggressive medical and revascularization therapy following an abnormal cSE-WMP would significantly influence outcome.

Methods

Patients

We analyzed the outcome of 1329 consecutive patients with known or suspected CAD who were referred for cSE-WMP using commercially available contrast agents in our laboratory from January 2008 to December 2011. Among them 1252 were already included in a prior prognostic analysis reporting on a significantly shorter follow-up.[12] Reasons for referral were evaluation of chest pain or dyspnea for suspect CAD in 941 (71%), preoperative risk assessment in 128 (10%), evaluation of multiple cardiac risk factors in 59 (4%), or functional assessment of known CAD in 201 (15%). The study was approved by the Institutional Review Board of the Parma Medical Center and all patients gave informed consent. Follow-up was completed in September 2016. The population consisted of 794 men (60%) and mean age in the study population was 66±11 years. Risk factors for CAD (Table 1) were systemic hypertension in 940 (71%), hypercholesterolemia in 760 (57%), cigarette smoking in 314 (24%), and diabetes mellitus in 334 (25%). Two hundred eighty-eight patients (22%) had a history of a previous MI and 372 overall (28%) had a history of at least 1 (primary or elective) percutaneous or surgical coronary revascularization procedure. Four hundred forty-five patients had known CAD, in the form of previous revascularization or MI. Drug therapy was initially recorded for all at the time of testing, in patients who underwent early revascularization within 90 days it was updated to the therapy prescribed after their routine 6-month postrevascularization visit, so that the therapy early revascularized patients were truly on for most of their follow-up period was the only medications considered in statistical analysis. In this context, 798 patients (60%) were on β-blockers, 823 (62%) angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, 830 (62%) were on aspirin, 246 (19%) on clopidogrel, and 749 (56%) were taking statins.

Diabetes mellitus was defined as a fasting plasma glucose level >125 mg/dL or the need for insulin or oral hypoglycemic agents. Hypercholesterolemia was defined as total cholesterol >200 mg/dL or treatment with lipid-lowering medications. Hypertension was defined as blood pressure >140/90 mm Hg or use of antihypertensive medication.

Stress Protocol

Dipyridamole was infused at the total dose of 0.84 mg/kg in all patients. A total of 461 underwent a 10-minute 0.84 mg/kg dipyridamole infusion+atropine administration (up to 1 mg), while the majority of patients (n=868) underwent a 6-minute protocol, consisting of the 0.84 mg/kg dipyridamole infusion, which does not require additional atropine administration. Two-dimensional echocardiography, 12-lead ECGs, and blood pressure monitoring were performed in accordance with established standard protocols.[1] Aminophylline was routinely used to reverse dipyridamole effect. When an obvious new WM abnormality (≥1 akinetic segment) was observed by the physician performing the test, dipyridamole infusion was stopped, and aminophylline was administered.

Table 1. Clinical Characteristics and Echocardiographic Findings

	Overall (n=1329)	No PCI/CABG (n=1111)	PCI/CABG (n=218)	*P* Value
Risk factors and patient history				
Mean age±SD	66±11	66±11	68±9	0.021
Male sex, n (%)	794 (60)	636 (57)	158 (72)	<0.001
Family history of CAD, n (%)	389 (29)	335 (30)	54 (25)	0.110
Current cigarette smoking, n (%)	314 (24)	264 (24)	50 (23)	0.793
Hypercholesterolemia, n (%)†	760 (57)	611 (55)	149 (68)	<0.001
Diabetes mellitus, n (%)	334 (25)	266 (24)	68 (31)	0.024
Hypertension, n (%)*	940 (71)	774 (70)	166 (76)	0.055
Obesity, n (%)	175 (13)	153 (14)	22 (10)	0.142
Known CAD (prior MI or revascularization)	445 (34)	352 (32)	102 (47)	<0.001
Previous MI	288 (22)	217 (20)	71 (33)	<0.001
Previous revascularization	372 (28)	290 (26)	82 (38)	0.001
Medications				
ASA, n (%)	830 (62)	647 (58)	183 (84)	<0.001
Plavix/Ticlop, n (%)	246 (19)	146 (13)	100 (46)	<0.001
β-Blockers, n (%)	798 (60)	620 (56)	178 (82)	<0.001
ACE-I/ARB, n (%)	823 (62)	659 (59)	164 (75)	<0.001
Statins, n (%)	749 (56)	578 (52)	171 (78)	<0.001
Echocardiography				
Reduced rest LVEF (<50%), n (%)	323 (24)	264 (24)	59 (27)	0.299
Fixed WM abnormalities, n (%)	382 (29)	282 (25)	100 (46)	<0.001
Inducible WM abnormalities, n (%)	248 (19)	79 (7)	169 (78)	<0.001
Fixed MP abnormalities, n (%)	330 (25)	245 (22)	85 (39)	<0.001
Inducible MP abnormalities, n (%)	411 (31)	219 (20)	192 (88)	<0.001
No inducible MP abnormalities, n (%)	918 (69)	892 (80)	26 (12)	<0.001
Only inducible MP abnormalities, n (%)	163 (12)	140 (13)	23 (11)	<0.001

Data presented are mean value±SD or n (%) of patients. ACE-I indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; ASA, acetylsalicylic acid; CABG, coronary artery bypass graft; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MP, myocardial perfusion; PCI, percutaneous coronary revascularization; WM, wall motion.

*Blood pressure ≥140/90 mm Hg or treatment of hypertension.

†Total cholesterol >200 mg/dL or treatment of hypercholesterolemia.

cSE-WMP Imaging

The test was performed with a commercially available ultrasound scanner (ie33; Philips Medical Systems) equipped with low mechanical-index real-time pulse sequence schemes that deploy interpulse phase-amplitude modulation.[12] cSE-WMP was performed using the phospholipid-encapsulated microbubble SonoVue® (Bracco Imaging, Milan, Italy), either in repeated slow 0.5-mL boluses (850 patients) or continuous infusion at 0.8 to 1.2 mL/min (479 patients) using a dedicated rotating pump.

Myocardial perfusion (MP) was studied at rest and after dipyridamole infusion by activation of low mechanical-index power-modulation imaging so that cineloops of flash-replenishment sequences (both real-time and end-systolic triggered at every cardiac cycle) were digitally acquired in the apical 4-, 2-, and 3-chamber views. The low-mechanical index setting was activated just before administration of contrast and the time gain compensation and 2-dimensional gain settings were adjusted to suppress any nonlinear signals from tissue at a mechanical index=0.08 to 0.12 and frame rate >30 Hz. In case of bolus contrast administration (SonoVue® 0.5 mL), the ideal timing to start acquiring the MP flash-replenishment sequences was when attenuation from left ventricular cavity contrast had resolved, usually 15 s after peak video intensity was reached, during the initial washout of contrast. WM was

assessed at rest and after dipyridamole infusion by activation of a specific preset for contrast WM analysis (left ventricular opacification, with harmonic imaging, a higher mechanical index=0.27 and frame rate=40 Hz) or with the same preset used for MP assessment depending on which allowed technically better WM imaging in the specific patient, while the standard 2-dimensional preset was only resumed, after complete microbubble clearance, for continuous WM monitoring through the remainder of the stress test.

Image Analysis

The left ventricle was divided into 17 segments according to the recommendations of the American and European Societies of Echocardiography.[1,2]

MP was visually assessed, using the following criteria: normal MP after dipyridamole was assigned if myocardium was fully replenished 1.5 to 2 s after the end of the flash impulse, and stress perfusion was defined as abnormal if myocardium was not fully replenished after this time in ≥1 contiguous segment. Normal myocardial replenishment at rest was defined as complete replenishment within 4 s after the flash impulse. A MP defect was scored as fixed or reversible based on its presence at rest. Left ventricle segments were excluded from MP reading if not clearly visualized, because of shadowing artifacts or low ultrasound penetration, especially in the basal segments. Segmental WM was graded as follows: normal=1; hypokinetic=2; akinetic=3; and dyskinetic=4. Reversible ischemia was defined as the occurrence of a stress-induced new dyssynergy or worsening of rest hypokinesia in ≥1 segment.

Patients were also classified according to the extent of abnormality. They were considered to have single-vessel abnormality when the MP defect or WM abnormality involved only 1 coronary artery territory and multivessel abnormality when the MP defect or WM abnormality involved >1 coronary artery territory. The left ventricular apex, anteroseptal, distal septum, and anterior walls were assigned to the left anterior descending coronary artery, the lateral wall to the left circumflex, and the inferior wall and basal septum to the right coronary artery. The results of both MP and WM analyses were made available to the referring physicians. The interobserver agreement data assessed in 2 previous studies in our lab are between 80% and 87.5% (k=0.60–0.75) for MP and between 90% and 95% (k=0.80–0.83) for WM assessments.[12,20]

Follow-Up

Follow-up was obtained by review of the patient's hospital electronic records, regional health database, national cancer registry, and telephone interview when inconsistencies were found.

The study primary end point was only for *ischemic cardiac events* defined as death from an ischemic cardiac cause+nonfatal MI. If a patient first had a nonfatal MI and also died subsequently in the follow-up, only the first event was recorded. In the current study, we selected cardiac death and not all-cause death[22] to exclude deaths related to cancer, infections, or other causes, which in cardiac studies generally account for half of total mortality, and cannot be attributed directly to CAD although they may have some association, possibly based on shared risk factors.[23] Nonfatal MI was defined by means of a serial increase in cardiac-specific enzymes and development of new ECG changes.

Statistical Analysis

Continuous variables are expressed as mean and SD, categorical variables as number of patients and proportions. Kaplan–Meier event-free survival curves for the prespecified end points across categorical variables were estimated and compared using the Log-rank test. For the analysis of cardiac mortality, patients dying of other causes were censored from follow-up at the time of death.

Univariate and multivariable Cox proportional hazard models were used to estimate the risk of events.

Rest left ventricular ejection fraction (LVEF) was analyzed as a dichotomous variable (<50% or ≥50%); additional clinical variables considered in the analyses were defined according to the Framingham risk score assessment. They included diabetes mellitus, hypercholesterolemia, and hypertension. Clinical variables such as history of prior MI, known CAD, and prior revascularization were also considered. Echocardiographic parameters were rest LVEF, WM, and MP ischemic responses to dipyridamole. Acetylsalicylic acid, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, clopidogrel, and statin therapy *at enrollment* were considered, but in patients who underwent revascularization within 90 days it was updated to the therapy prescribed after their routine 6-month postrevascularization visit. All clinical and cSE-WMP variables with $P<0.1$ at univariate analysis were considered for multivariable models.

A first multivariable *clinical* model was derived, then cSE-WMP variables were added sequentially to the model. The significance of additional variables to previous modeling steps was based on the likelihood ratio test. The usefulness of contrast cSE-WMP variables—MP and WM— over clinical variables was then verified in terms of discrimination power using the Harrell's C index.

All analyses were also repeated after breaking the study population into those who did and did not undergo a revascularization procedure following cSE-WMP.

In the overall population, risk reclassification was evaluated in terms of continuous net reclassification index (NRI) rather

than categorical NRI, because of unclear cutoffs to be used for the definition of low, intermediate, and high-risk groups in a selected population undergoing provocative testing.

For all Cox models, the proportional hazard assumption was assessed using the Schoenfeld test.

Results

There were 1329 patients enrolled, mean age was 66±11 years, 60% were males, 25% were diabetic, and 33% had previously known CAD, in the form of prior MI or prior revascularization. Baseline LVEF was 57±8%, with 323 (25%) having an LVEF at baseline <50% (range 25–49%). During the study period, 218 patients (16%) underwent revascularization procedures, either percutaneous (n=207) or surgical (n=16), while 7 of such patients underwent both types of revascularization. Most of these patients (n=179, 82%) were electively revascularized within 3 months of the cSE-WMP. Of the 218 revascularized patients, 169 (78%) had a cSE-WMP with reversible abnormality for both WM and MP, 23 (10%) only for MP, and 26 (12%) did not demonstrate any WM or MP abnormality. These 26 patients were referred for angiography and revascularization on the basis of persistent symptoms and in some cases (18 out of 26) according to a second provocative test discordant with the negative cSE-WMP.

In the remaining 1111 patients who did not undergo revascularization at any time, the cSE-WMP study was interpreted as normal for both WM and MP in 892 patients (80%), abnormal for MP only in 140 patients (13%), and ischemic for both MP and WM in 79 (7%). In the study cohort, no patient had abnormal WM with normal MP. The distribution of the results of WM and MP analysis in the overall cohort as well as stratified by subsequent revascularization is presented in Table 1, together with baseline characteristics, and drug therapy.

Patients who underwent subsequent revascularization differed from the group of patients who did not regarding more frequent abnormal cSE-WMP results and higher medication use, as expected, while among risk factors they differed for being more frequently male, hypercholesterolemic, and more frequently with a known history of CAD. Association of cSE-WMP results with the subsequent coronary revascularization procedure are graphically depicted in Figure 1.

Outcome

The median follow-up was 2013 days (lower, upper quartiles 1555, 2299 days). During the entire follow-up, ischemic cardiac deaths were 61 (4.6%) and 64 patients had a nonfatal MI (4.8%). During the follow-up period, patients who were not revascularized (n=1111) had 90 ischemic fatal or nonfatal cardiac events, while revascularized patients (n=218) had 35 ischemic fatal or nonfatal cardiac events.

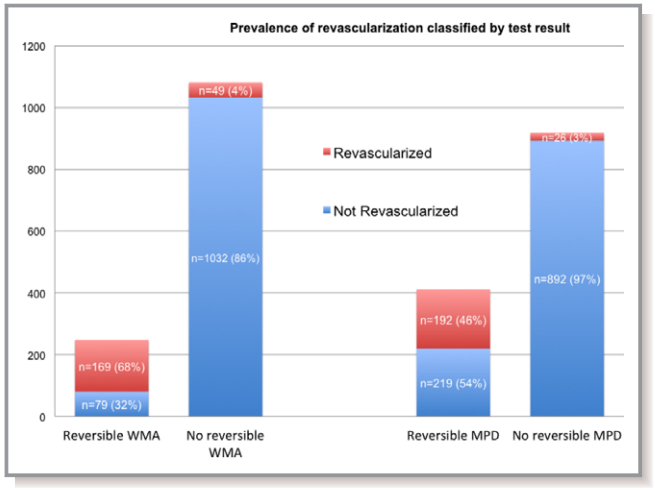

Figure 1. Bar graph demonstrating that, as expected, the percentage of subjects undergoing a revascularization procedure after contrast dipyridamole echocardiography was higher after abnormal tests, compared with the very limited number of subjects who underwent revascularization notwithstanding a normal test. MPD indicates myocardial perfusion defect; WMA, wall motion abnormality.

Outcome According to cSE-WMP Results

The outcome of patients, according to a normal test, presence of isolated reversible MP defect (normal WM), or the presence of both reversible MP and WM abnormalities, is graphically depicted as 5-year event rates in Figure 2, and using Kaplan–Meier event-free survival curves in Figure 3 for the primary end point of cardiac ischemic fatal and nonfatal events, and in Figure 4 separately showing event-free Kaplan–Meier curves for either cardiac death (Figure 4A) or MI (Figure 4B). Depending on cSE-WMP results, patients with reversible WM and perfusion abnormalities demonstrated the worst outcome, patients with isolated reversible MP abnormalities (in the absence of WM abnormality) had an intermediate outcome, while the best outcome was for patients with fully normal cSE-WMP. Event-free survival curves were significantly different for primary cardiac ischemic events (Log-rank $P<0.001$) and also for cardiac death and nonfatal MI as single end points (Log-rank <0.01).

Predictors of Ischemic Cardiac Events

Table 2 shows univariable predictors of the primary end point. Age (HR 1.052, 95% CI 1.032–1.071), known CAD (2.510, 95% CI 1.766–3.569), diabetes mellitus (1.780, 95% CI

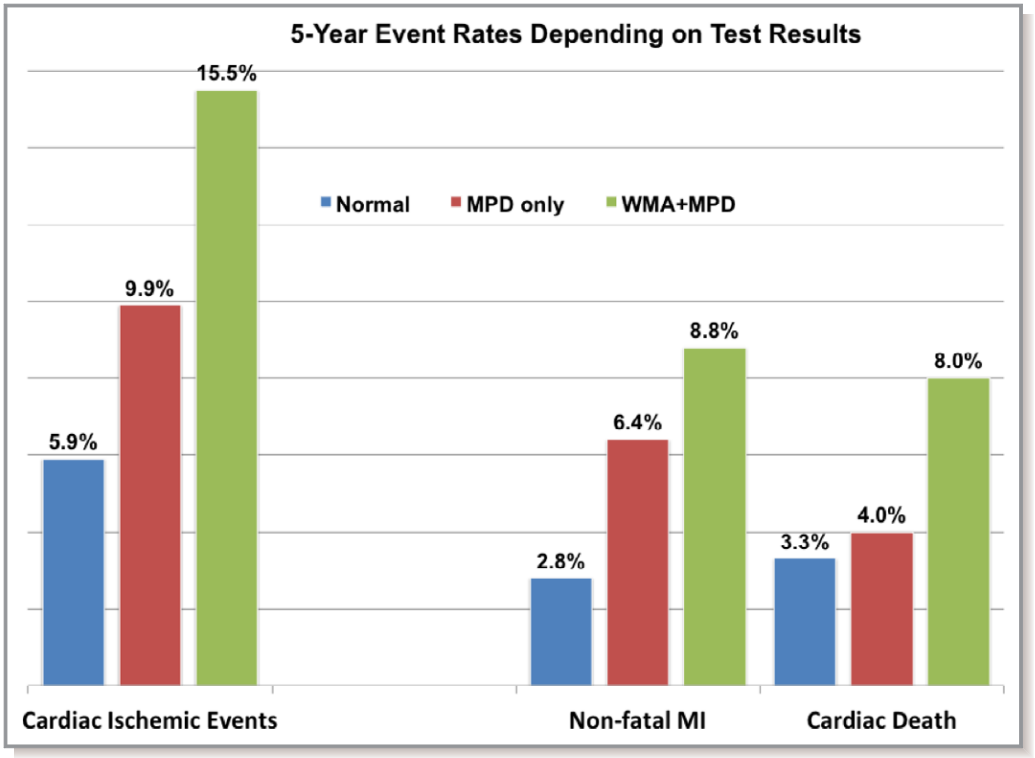

Figure 2. Five-year event rate for primary cardiac ischemic events end point, and its breakdown into cardiac death and nonfatal myocardial infarction based on contrast dipyridamole echocardiography results. MI indicates myocardial infarction; MPD, myocardial perfusion defect; WMA, wall motion abnormality.

1.235–2.565), and undergoing revascularization after cSE-WMP (HR=1.872, 95% CI 1.266–2.767) were the clinically significant univariable predictors. Among the drugs, therapy with acetylsalicylic acid (HR=2.355, 95% CI 1.538–3.606), clopidogrel (HR 2.461, 95% CI 1.705–3.554), angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (HR 1.495, 95% CI 1.021–2.189), or statin (HR 1.895, 95% CI 1.291–2.782) were significant predictors. Rest and stress echocardiography demonstrated the following significant predictors: LVEF <50% (HR 1.701, 95% CI 1.180–2.453), reversible WM abnormality (HR 2.451, 95% CI 1.701–3.534), reversible MP abnormalities (HR 2.337, 95% CI 1.645–3.320), fixed MP abnormalities (HR=2.066, 95% CI 1.443–2.959), and reversible WM or MP abnormalities (HR 2.729, 95% CI 1.856–4.013).

Multivariable Predictors and Incremental Value of cSE-WMP Over Clinical Characteristics

Table 3 shows sequential Cox regression models fit to test the incremental performance of prediction models when cSE-WMP variables were added over clinical variables and drug therapy, reporting χ^2 and Harrell's C index for discrimination for each of them.

The model comprising abnormal stress WM demonstrated a significantly higher χ^2 (P=0.005) and Harrell's C for discrimination (difference [95% CI]=0.019 [0.001–0.038]; P=0.037) compared with the initial reference clinical+drug therapy model and the same was true for the model adding reversible MP data to the baseline model with clinical and drug therapy data, with both higher χ^2 (P=0.001) and Harrell's C for discrimination (difference [95% CI]=0.022 [0.001–0.042]; P=0.039). On the contrary, there was no additional independent value or increase of the model discrimination ability when adding MP and WM sequentially (last model in Table 3).

Similarly for risk reclassification, models in which either WM or MP was added to the model including only clinical+drug therapy data significantly improved risk reclassification (respectively continuous NRI [95% CI]=0.382 [0.209–0.556], P<0.001 and continuous NRI [95% CI]=0.448 [0.265–0.630], P<0.001). When both WM and MP were added to the initial reference clinical+drug therapy model, the ability to reclassify risk was even better as compared with the model with the sole WM (continuous NRI [95% CI]=0.306 [0.134–0.478], P<0.001) but not in comparison with the model including clinical+drug therapy and MP (continuous NRI [95% CI]=−0.105 [−0.279 to 0.069], P=0.238; categorical NRI

[95% CI]=−0.004 [−0.009 to 0], *P*=0.095), showing superiority of MP to risk reclassify patients compared with WM.

Predictors of Ischemic Cardiac Events Stratifying for Revascularization

Table 4 shows univariable predictors of the primary end point after dividing patients into the 1111 who did not have subsequent coronary revascularization and the 218 who did.

In patients who *did not undergo revascularization*, age (HR 1.056, 95% CI 1.034–1.079), known CAD (HR 3.219, 95% CI 2.123–4.881), and diabetes mellitus (HR 1.895, 95% CI 1.231–2.919) were the significant clinical predictors at univariable analysis. Among the drugs, therapy with acetylsalicylic acid (HR 2.984, 95% CI 1.798–4.952), clopidogrel (HR=2.517, 95% CI 1.577–4.018), β-blockers (HR=1.529, 95% CI 0.993–2.354, borderline *P*=0.054), angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (HR=1.567, 95% CI 1.006–2.440), or statin (HR=1.930, 95% CI 1.245–2.991) were significant predictors. Rest and stress echocardiography demonstrated the following predictors: LVEF <50% (HR 1.905, 95% CI 1.243–2.920), reversible WM abnormality (HR 3.585, 95% CI 2.137–6.014), reversible MP abnormalities (HR=2.567, 95% CI 1.676–3.933), fixed MP abnormalities (HR=1.842, 95% CI 1.188–2.856), and reversible WM or MP abnormalities (HR=3.990, 95% CI 2.344–6.793).

In patients who *did undergo revascularization*, apart from age (HR 1.034, 95% CI 0.995–1.074) and β-blockers (HR 0.509, 95% CI=0.245–1.061) resulting only in borderline significance, only a fixed MP abnormality was clearly significant (HR 2.181, 95% CI 1.119–4.247) at univariable analysis.

Table 5 shows sequential Cox regression multivariable models fit to test the incremental performance of prediction models when cSE-WMP variables were added over clinical variables and drug therapy, reporting χ^2 and Harrell's C index for discrimination for each of them. Compared with the results of the multivariable models in the entire population (Table 3), when dividing patients who did not or did undergo revascularization, diverse independent predictors were identified. In patients undergoing revascularization, not only do the models comprising either WM or MP on top of clinical and drug therapy both demonstrate a significant increase in χ^2 and Harrell's C for discrimination compared with clinical and drug therapy variables, but the last model with both reversible WM and MP stress variables demonstrates a significant increase also compared with the model with only WM (χ^2 from 74.82 to 78.42, borderline *P*=0.058, Harrell's C from 0.720 to 0.724, difference [95% CI]=0.004 [0.001–0.023]; *P*=0.044). It demonstrates that MP analysis in patients not undergoing revascularization was useful for better stratification of the primary end point, even when considering WM responses as well as clinical and drug therapy variables. In multivariable

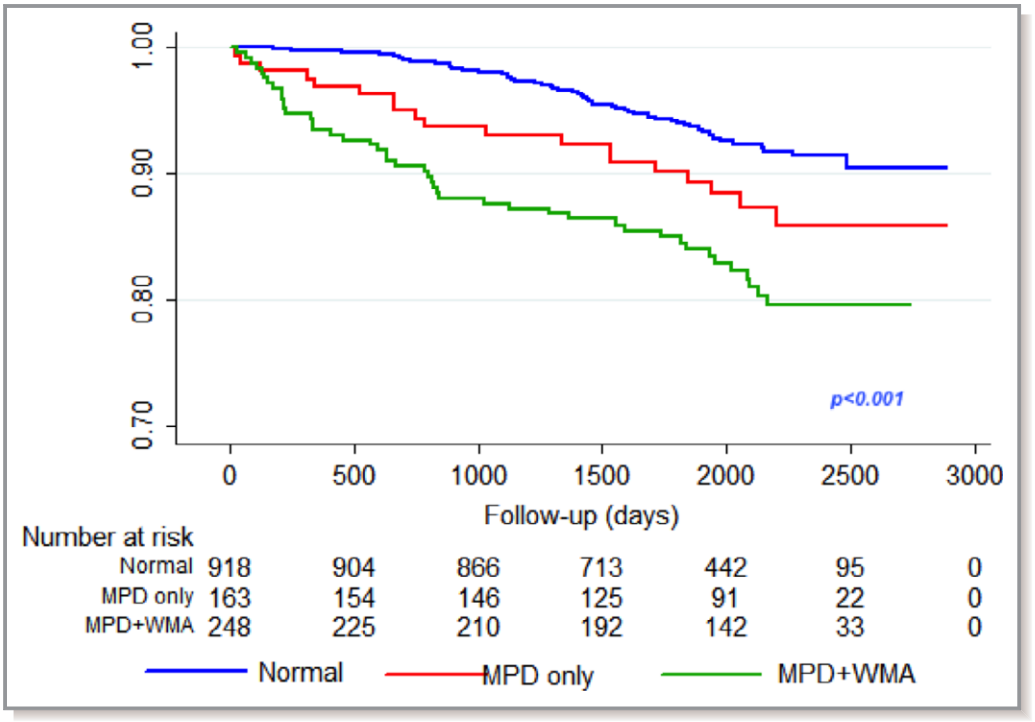

Figure 3. Kaplan–Meier event-free survival curves for cardiac ischemic events based on results of contrast dipyridamole echocardiography. The overall difference among the curves is highly statistically significant (Log-rank <0.001). MPD indicates myocardial perfusion defect; WMA, wall motion abnormality.

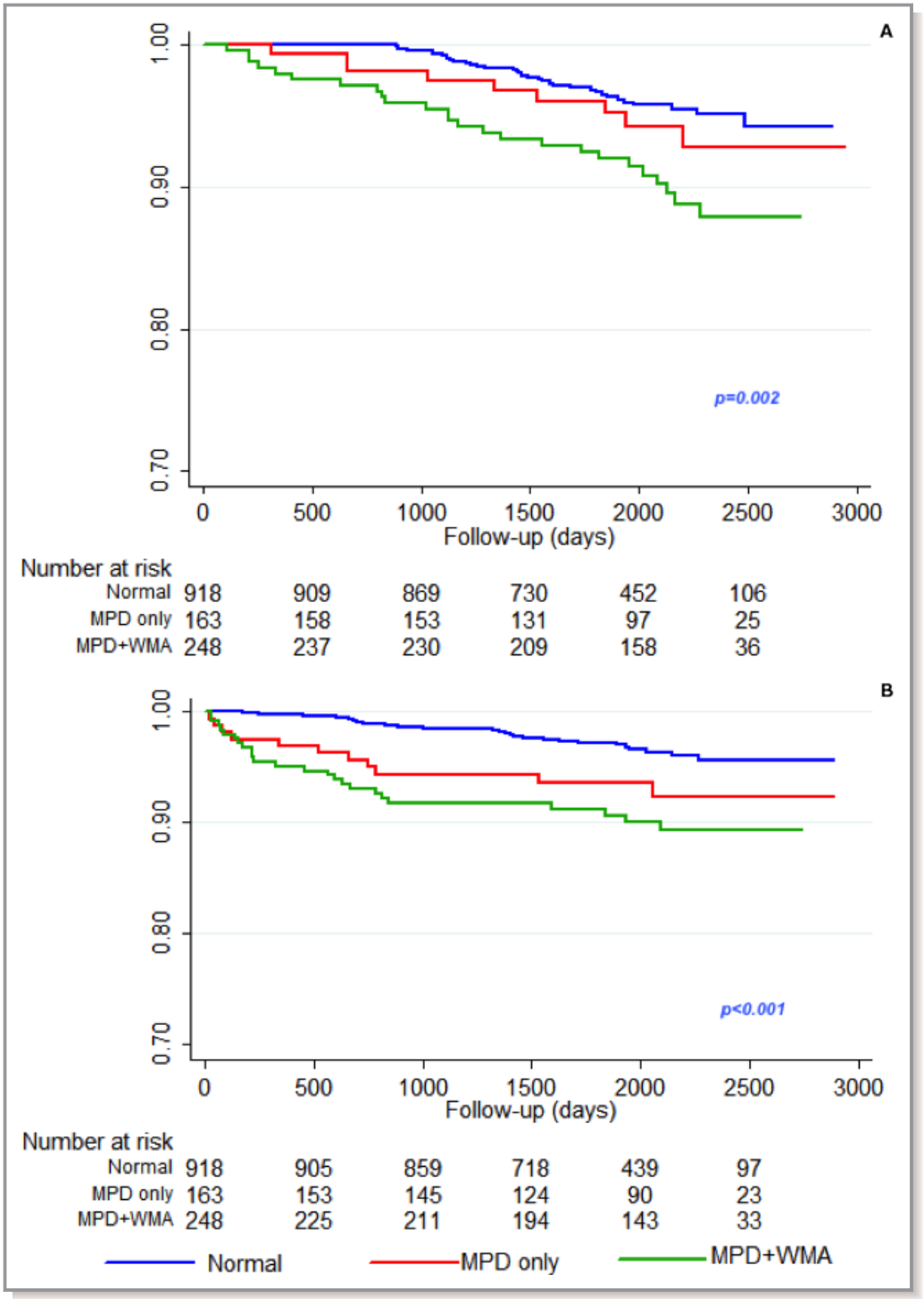

Figure 4. Event-free survival curves for single components of the primary end point, cardiac death (A) and nonfatal MI (B), based on results of contrast dipyridamole echocardiography, The overall difference among the curves is highly statistically significant (Log-rank=0.002 for cardiac death and <0.001 for nonfatal myocardial infarction). MI indicates myocardial infarction; MPD, myocardial perfusion defect; WMA, wall motion abnormality.

models for the 218 patients who underwent revascularization (Table 6), only the addition of fixed MP abnormalities significantly improved the clinical model including age and β-blockers therapy (χ^2 from 6.36 to 11.67, *P*=0.021, Harrell's C from 0.576 to 0.622, difference [95% CI]=0.046 [0.029–0.086]; *P*=0.009).

Table 2. Univariate Analysis of Main Clinical, Medications, and Imaging Parameters as Predictors of Cardiac Ischemic Events

Ischemic Cardiac Events		
Univariate Analysis	HR (95% CI)	*P* Value
Clinical		
Age	1.052 (1.032–1.071)*	0.000*
Male sex	1.282 (0.888–1.850)	0.185
Known CAD (MI/PCI/CABG)	2.510 (1.766–3.569)*	0.000*
Family history of CAD	0.965 (0.651–1.431)	0.860
Smoke	0.763 (0.489–1.191)	0.233
Hypercholesterolemia	1.242 (0.865–1.784)	0.240
Diabetes mellitus	1.780 (1.235–2.565)*	0.002*
Hypertension	1.242 (0.827–1.863)	0.296
Obesity	0.835 (0.479–1.455)	0.524
Revascularization within 90 d after stress echocardiogram	1.872 (1.266–2.767)*	0.002*
Drugs		
ASA	2.355 (1.538–3.606)*	0.000*
Clopidogrel	2.461 (1.705–3.554)*	0.000*
β-Blockers	1.364 (0.941–1.977)	0.101
ACE-I/ARBs	1.495 (1.021–2.189)*	0.039*
Statin	1.895 (1.291–2.782)*	0.001*
Imaging		
Rest LVEF reduction (<50%)	1.701 (1.180–2.453)*	0.004*
Reversible WM abnormality	2.451 (1.701–3.534)*	0.000*
Fixed WM abnormalities	1.367 (0.949–1.970)	0.094
Reversible MP abnormalities	2.337 (1.645–3.320)*	0.000*
Fixed MP abnormalities	2.066 (1.443–2.959)*	0.000*
Reversible WM or MP abnormalities	2.729 (1.856–4.013)*	0.000*

All patients with inducible WM abnormalities also had reversible MP defect. ACE-I indicates angiotensin-converting enzyme inhibitors; ASA, acetylsalicylic acid; ARBs, angiotensin receptor blockers; CAD, coronary artery disease; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MP, myocardial perfusion; PCI/CABG, percutaneous/surgical coronary revascularization; WM, wall motion.
*Statistically significant predictor.

Event Rates and Survival Free From Cardiac Events in Revascularized Versus Not-Revascularized Patients

Figure 5 bar graph shows event rates at 2 different time points (3- and 6-year follow-up) for patients with normal or abnormal stress WM who did or did not undergo revascularization after the cSE-WMP test.

Such data suggest that revascularization improved both 3- and 6-year outcome in patients with an abnormal stress-echo for WM assessment, while on the other hand it apparently negatively affected outcome in patients who underwent revascularization, notwithstanding a normal WM response at prior stress-echo.

Figure 6 shows survival free from cardiac ischemic events in patients who either did not undergo subsequent revascularization (Figure 6A) or who did undergo revascularization (Figure 6B). Survival curves for the 3 types of possible cSE-WMP response (normal, isolated reversible MP abnormality, or both MP+WM abnormality) are shown in the upper panels while mid and lower panels dichotomize response based on WM or MP assessment. While test results appear to have a clear risk-stratifying value in patients who subsequently did not undergo revascularization (Log-rank $P<0.001$), such value is apparently completely lost in patients subsequently revascularized (Log-rank not significant), indirectly indicating that revascularization acts as an outcome-modifier after cSE-WMP.

Figure 7 shows the event-free survival for patients testing abnormal or normal, respectively, at WM assessment (left) or myocardial perfusion assessment. It should be emphasized that only 49 patients were revascularized, notwithstanding normal stress WM and only 26 with normal myocardial perfusion at stress. Either considering WM (Log-rank $P=0.04$) or myocardial perfusion assessment (Log-rank $P=0.027$), the patients with a normal cSE-WMP who were subsequently revascularized fared worse, while the opposite was not true for abnormal cSE-WMP (upper panels).

Discussion

In this study, we evaluated the ability of vasodilator cSE-WMP, based on MP and WM assessments, to predict *long-term* risk of incident fatal and nonfatal cardiac ischemic events, namely, nonfatal MI or cardiac death, in a contemporary group of patients with known or suspected CAD undergoing contrast stress-echocardiography for clinical indications.

The current study is unique in that it studies the largest cohort ever studied with contrast myocardial perfusion and WM assessment stress-echocardiography, reporting on a truly contemporary (enrolled 2008–2012) and hence presumably high-intensity medical therapy cohort, with almost double follow-up compared to existing similar studies. Large sample and long follow-up contributed with achieve sufficient statistical power to aim for the first time at purely cardiac ischemic fatal and nonfatal events and draw robust conclusions regarding the incremental performance of prediction models when cSE-WMP variables were added over clinical and drug therapy data.

Role of MP and WM Imaging in Predicting Events

Both reversible MP abnormalities or reversible WM abnormalities during cSE-WMP were independently predictive of 5-year ischemic events, with an isolated reversible MP defect

Table 3. Multivariable Models to Predict Ischemic Cardiac Events

Multivariable Models	Ischemic Cardiac Events			
	HR (95% CI)	*P* Value	χ^2	Harrell's C (95% CI)
Clinical model				
Age	1.046 (1.03–1.07)	0.000	67.5	0.701 (0.658–0.744)
Diabetes mellitus	1.431 (0.987–2.074)	0.059		
Known CAD	1.733 (1.158–2.593)	0.008		
ASA	1.522 (0.970–2.389)	0.068		
Clopidogrel	1.483 (0.978–2.247)	0.063		
Clinical+stress-echocardiography WM				
Age	1.045 (1.025–1.065)	0.000	73.5*	0.720† (0.678–0.763)
Diabetes mellitus	1.383 (0.953–2.006)	0.088		
Known CAD	1.775 (1.195–2.637)	0.004		
ASA	1.391 (0.881–2.195)	0.157		
Clopidogrel	1.310 (0.862–1.989)	0.206		
Reversible WM abnormality	1.758 (1.196–2.585)	0.004		
Clinical+stress-echocardiography MP				
Age	1.046 (1.026–1.066)	0.000	76.3*	0.723† (0.681–0.764)
Diabetes mellitus	1.409 (0.972–2.041)	0.070		
Known CAD	1.810 (1.217–2.693)	0.003		
ASA	1.339 (0.847–2.118)	0.212		
Clopidogrel	1.299 (0.857–1.969)	0.218		
Reversible MP abnormality	1.839 (1.275–2.652)	0.001		
Clinical+stress-echocardiography WM and MP				
Age	1.45 (1.025–1.066)	0.000	76.7*†	0.725† (0.683–0.766)
Diabetes mellitus	1.395 (0.961–2.024)	0.080		
Known CAD	1.806 (1.215–2.684)	0.003		
ASA	1.335 (0.843–2.111)	0.218		
Clopidogrel	1.281 (0.844–1.944)	0.245		
Reversible MP abnormality	1.633 (0.971–2.747)	0.064		
Reversible WM abnormalities	1.197 (0.695–2.063)	0.517		

All patients with inducible WM abnormalities also had reversible MP defect. The last model (WM and MP) with both WM and MP is not significantly more accurate than the previous models with only WM or MP, while they maintain higher Harrell's C and χ^2 compared with the clinical model. ASA indicates acetylsalicylic acid; CAD, coronary artery disease; HR, hazard ratio; MP, myocardial perfusion; WM, wall motion.

*Means $P<0.01$ all compared with clinical model.

†Means $P<0.05$.

portending an intermediate prognosis between a normal test and a fully ischemic test with both reversible MP and WM abnormality. This is in line with prior studies and pathophysiology, although to date no cSE-WMP study addressed such a 5-year event-rate, but only shorter follow-up periods.

Revascularization Impact

With all limitations of retrospective nonrandomized studies, by keeping patients who were subsequently revascularized, and not censoring them at the time of revascularization, we were allowed to infer that the long-term impact of revascularization may be dependent on the results of the cSE-WMP study. This specific patient population (ie, those revascularized following a normal or abnormal stress echocardiogram) has not been evaluated in terms of long-term impact in the current era of background intensive medical therapy. Importantly, risk stratification operated by MP and WM variables during cSE-WMP was much more robustly demonstrated in multivariable models in patients who did not undergo revascularization after their stress test. cSE-WMP stratification value in fact did not hold in patients undergoing subsequent coronary revascularization; in

Table 4. Univariate Analysis of Main Clinical Variables, Medications, and Imaging Parameters as Predictors of Cardiac Ischemic Events, Once Patients Are Divided Based on Whether They Underwent Revascularization or Not After Their Stress Echocardiogram

Ischemic Cardiac Events				
	Non Revascularized (n=1111)		Revascularized (n=218)	
Univariate Analysis	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Clinical				
Age	1.056 (1.034–1.079)*	0.000*	1.034 (0.995–1.074)*	0.087*
Male sex	1.436 (0.933–2.212)	0.100	0.685 (0.341–1.377)	0.289
Known CAD (MI/PCI/CABG)	3.219 (2.123–4.881)*	0.000*	1.049 (0.541–2.036)	0.887
Family history of CAD	1.118 (0.715–1.747)	0.626	0.673 (0.279–1.623)	0.378
Smoke	0.632 (0.363–1.100)	0.104	1.204 (0.564–2.571)	0.631
Hypercholesterolemia	1.169 (0.768–1.779)	0.467	1.195 (0.574–2.488)	0.635
Diabetes mellitus	1.895 (1.231–2.919)*	0.004*	1.295 (0.652–2.570)	0.460
Hypertension	1.409 (0.864–2.296)	0.169	0.801 (0.385–1.667)	0.553
Obesity	0.877 (0.467–1.648)	0.683	0.798 (0.244–2.607)	0.709
Drugs				
ASA	2.984 (1.798–4.952)*	0.000*	0.601 (0.273–1.323)	0.206
Clopidogrel	2.517 (1.577–4.018)*	0.000*	1.633 (0.836–3.191)	0.151
β-Blockers	1.529 (0.993–2.354)*	0.054*	0.509 (0.245–1.061)*	0.071*
ACE-I/ARBs	1.567 (1.006–2.440)*	0.047*	0.878 (0.411–1.878)	0.738
Statin	1.930 (1.245–2.991)*	0.003*	1.066 (0.466–2.441)	0.879
Imaging				
Rest LVEF reduction (<50%)	1.905 (1.243–2.920)*	0.003*	1.213 (0.594–2.477)	0.597
Reversible WM abnormality	3.585 (2.137–6.014)*	0.000*	1.018 (0.462–2.240)	0.965
Fixed WM abnormality	1.291 (0.826–2.017)	0.262	1.187 (0.611–2.306)	0.612
Reversible MP abnormality	2.567 (1.676–3.933)*	0.000*	0.859 (0.333–2.216)	0.754
Fixed MP abnormality	1.842 (1.188–2.856)*	0.006*	2.181 (1.119–4.247)*	0.022*
Reversible WM/MP abnormality	3.990 (2.344–6.793)*	0.000*	0.880 (0.339–2.287)	0.794

All patients with inducible WM abnormalities also had reversible MP defect. ACE-I indicates angiotensin-converting enzyme inhibitor; ASA, acetylsalicylic acid; ARBs, angiotensin receptor blockers; CAD, coronary artery disease; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MP, myocardial perfusion; PCI/CABG, percutaneous/surgical coronary revascularization; WM, wall motion.
*Statistically significant predictor.

this context, the result of their previous cSE-WMP was apparently not significant for subsequent risk restratification. In other words, our study *suggests* that a revascularization procedure exerted an effect on outcome, which tended to finally equalize subsequent prognosis in all patients. The current study suggests that patients with a positive cSE-WMP, specifically with reversible WM abnormalities, do benefit significantly from revascularization, while the ones with a normal cSE-WMP probably should not undergo revascularization, at least as far as a beneficial effect on cardiac ischemic events is the aim of such procedure. However, the current study was retrospective and not randomized, and the decision to indicate revascularization was based on clinical grounds, heavily influenced by test positivity. Similar findings were found in at least 1 scintigraphic[24] and 1 recent dobutamine echo[25] which were also retrospective and observational studies; they enrolled patients in the 1990s, and their applicability to the current era may be limited; furthermore, they apparently did not correct for significant outcome-modifying therapy, such as statins and antiplatelets, very tightly interacting with revascularization procedures, always upscaled after a revascularization procedure and currently much more intensive than was used 2 decades ago. While in such studies the amount of reversible ischemia needed to make revascularization prognostically useful is moderate to severe, in our study such differentiation appeared to be between milder forms of ischemia being related to isolated MP abnormalities and more severe forms being related to any amount of WM abnormality accompanying MP abnormalities. This may relate to the use of vasodilator stress versus dobutamine or exercise "demand" stressors.

Table 5. Multivariable Models to Predict Ischemic Cardiac Events in the 1111 Patients Who Did Not Undergo Revascularization After cSE-WMP

Multivariable Models	Ischemic Cardiac Events			
	HR (95% CI)	*P* Value	χ^2	Harrell's C (95% CI)
Clinical model				
Age	1.050 (1.027–1.074)	0.000	63.72	0.692 (0.647–0.737)
Known CAD	2.438 (1.578–3.766)	0.000		
Diabetes mellitus	1.587 (1.026–2.454)	0.038		
ASA	1.849 (1.084–3.153)	0.024		
Clinical+echocardiography WM				
Age	1.049 (1.025–1.073)	0.000	74.82*	0.720† (0.678–0.763)
Known CAD	2.384 (1.543–3.684)	0.000		
Diabetes mellitus	1.545 (0.998–2.390)	0.051		
ASA	1.736 (1.015–2.969)	0.044		
Reversible WM abnormalities	2.662 (1.580–4.485)	0.000		
Clinical+echocardiography MP				
Age	1.051 (1.028–1.076)	0.000	76.23*	0.719† (0.677–0.760)
Known CAD	2.456 (1.588–3.798)	0.000		
Diabetes mellitus	1.563 (1.010–2.418)	0.045		
ASA	1.673 (0.977–2.866)	0.061		
Reversible MP abnormalities	2.246 (1.461–3.454)	0.000		
Clinical+echocardiography WM and MP				
Age	1.050 (1.026–1.074)	0.000	78.42‡	0.724‡ (0.683–0.765)
Known CAD	2.415 (1.561–3.735)	0.000		
Diabetes mellitus	1.545 (0.998–2.391)	0.051		
ASA	1.668 (0.973–2.857)	0.063		
Reversible WM abnormalities	1.669 (0.848–3.284)	0.138		
Reversible MP abnormalities	1.771 (1.013–3.097)	0.045		

All patients with inducible WM abnormalities also had reversible MP defect. ASA indicates acetylsalicylic acid; CAD, coronary artery disease; cSE-WMP, contrast stress echocardiography with additional myocardial perfusion assessment; HR, hazard ratio; MP, myocardial perfusion; WM, wall motion.
*Means $P<0.01$ compared with clinical model.
†Means $P<0.05$ compared with previous clinical model.
‡Means $P\leq0.05$ compared with clinical+echocardiography WM model.

Only prospective multicenter studies, such as the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial, for example, will hopefully definitely confirm whether the presence of reversible ischemia, and which amount, is truly a key prerequirement to indicate revascularization in stable CAD on prognostic grounds.

Comparison With Fractional Flow Reserve

cSE-WMP results might be useful for the decision to revascularize or not, similar to what fractional flow reserve (FFR) studies have recently proposed.[26–28] Our findings point in the same direction to what has been observed with invasive FFR; such multicenter studies prospectively demonstrated that FFR is prognostically useful to proceed to revascularization, but in patients already selected to undergo diagnostic coronary angiography, although they fell short of demonstrating a benefit regarding hard events, death and MI, since in the FAME 2 study (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) the FFR-guided percutaneous coronary revascularization arm was favored on comparison of the primary composite end point of death, MI, and target vessel revascularization, but such finding was driven by urgent target vessel revascularization.[28,29] cSE-WMP is a gatekeeper that may be useful at a higher decisional level compared with FFR, when, in the work-up of suspect/known CAD, chest pain needs to be categorized as ischemic or not, and cSE-WMP may in some ways be more useful in identifying those likely to

Table 6. Multivariable Models to Predict Ischemic Cardiac Events in the 218 Patients Who Did Undergo Revascularization After cSE-WMP

Multivariable Models	Ischemic Cardiac Events			
	HR (95% CI)	*P* Value	χ^2	Harrell's C (95% CI)
Clinical model				
Age	1.036 (0.997–1.076)	0.071	6.36	0.576 (0.526–0.626)
β-Blockers	0.487 (0.234–1.015)	0.055		
Clinical+echocardiography MP				
Age	1.036 (0.997–1.076)	0.072	11.67*	0.622† (0.572–0.673)
β-Blockers	0.455 (0.216–0.955)	0.037		
Fixed MP abnormalities	2.200 (1.126–4.299)	0.021		

cSE-WMP indicates contrast stress echocardiography with additional myocardial perfusion assessment; HR, hazard ratio; MP, myocardial perfusion.
*Means $P<0.01$ compared with clinical model.
†Means $P<0.05$ compared with previous clinical model.

benefit from revascularization for truly severe ischemic events, in particular for the possibility to assess myocardial blood flow at tissue level using contrast MP.[30]

Study Limitations

Keeping revascularized patients has pros and cons, and is less typical than censoring patients at the time of revascularization, which is moreover also questionable because of the introduction of the bias of excluding most patients testing as abnormal at cSE-WMP, who are the ones generally undergoing revascularization, also precluding assessing the potential effect of revascularization.

In our study, as in all studies considering drug therapy (in particular if per-protocol updated after revascularization as in the current study), some drugs, such as antiplatelets and statins, were very tightly linked to the revascularization procedure and such drugs and revascularization to abnormal

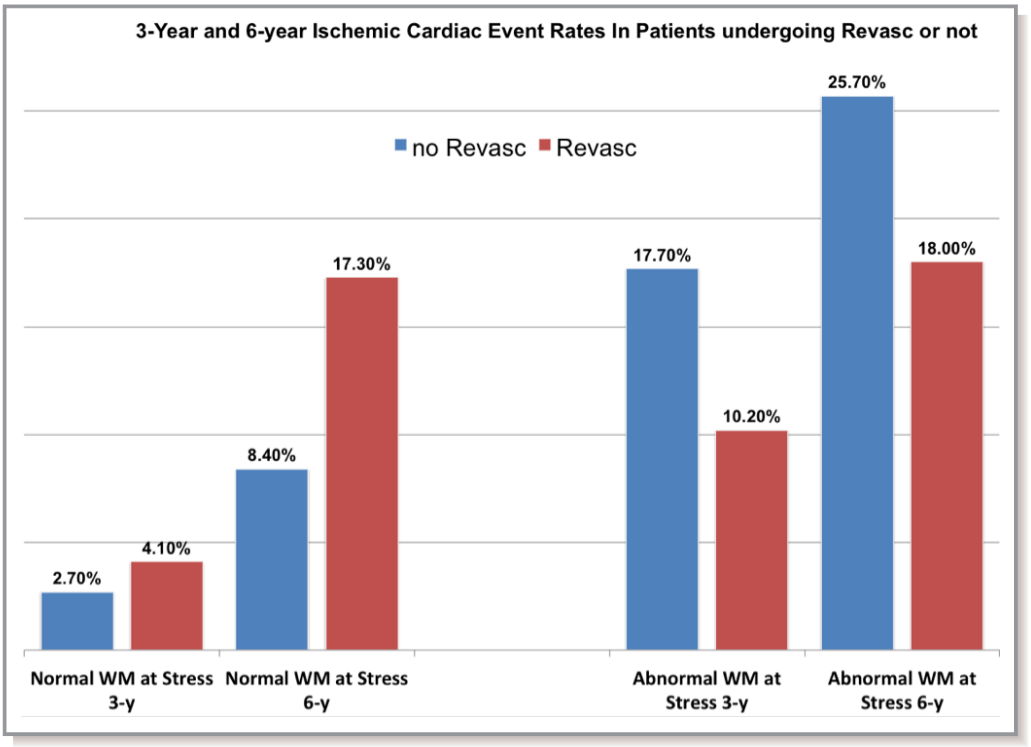

Figure 5. Histograms demonstrate how coronary revascularization was associated with both 3- and 6-year better outcome in patients with a positive stress echocardiogram for wall motion assessment, while on the other hand it apparently negatively affected outcome in patients who underwent revascularization with a normal wall motion response at prior stress echocardiogram. WM indicates wall motion.

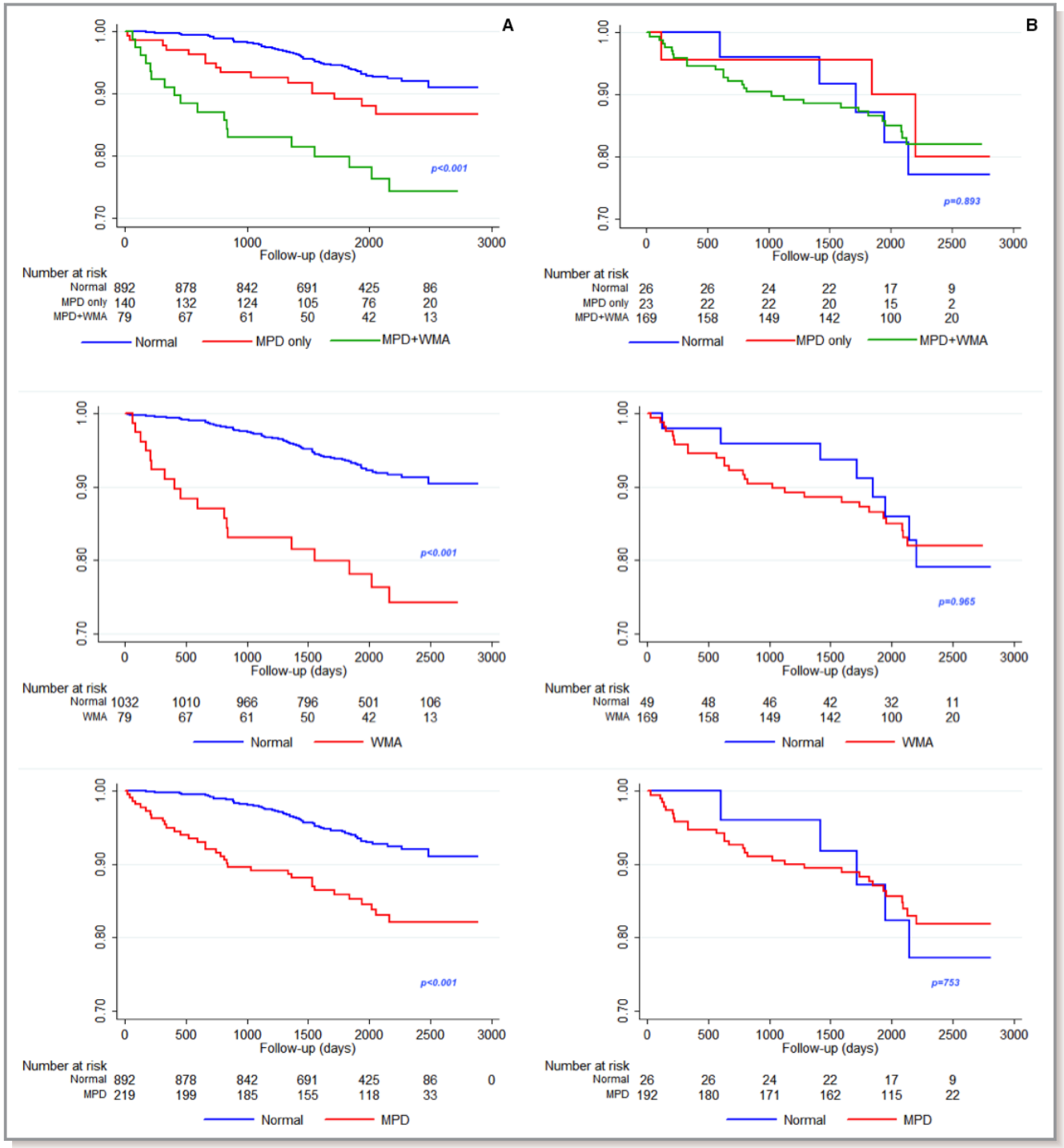

Figure 6. Shows survival free from cardiac ischemic events in patients who either did not undergo subsequent revascularization (A) or who did undergo revascularization (B). Survival curves for the 3 types of possible contrast dipyridamole echocardiography response (normal, isolated reversible myocardial perfusion defect [MPD], or both MPD+wall motion abnormality [WMA]) are shown in the upper panels while mid and lower panels dichotomize response based on wall motion or myocardial perfusion assessment. While test results have a clear prognostic value in patients who subsequently did not undergo revascularization, such value is lost in patients subsequently revascularized, indirectly indicating that revascularization acts as an outcome-modifier.

cSE-WMP. Thus, it was not statistically fair to try to analyze revascularization in a multivariable analysis, because of interaction with the abovementioned parameters. We rather chose to stratify for revascularization, and also present the data separately for patients who did or did not undergo revascularization. However, we acknowledge that only 218 patients were

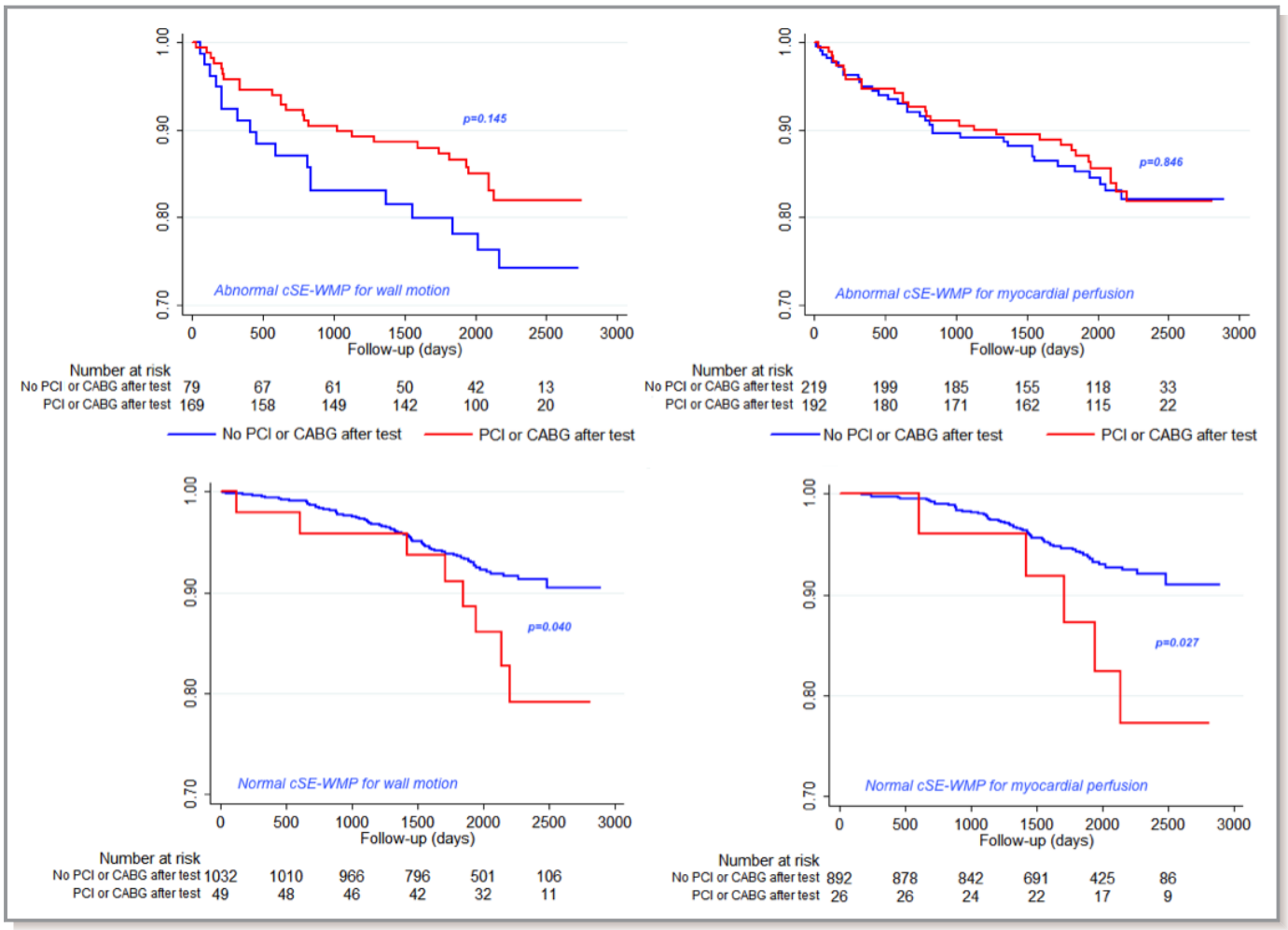

Figure 7. Event-free survival curves for patients testing abnormal or normal, respectively, at wall motion assessment (left) or myocardial perfusion assessment. It should be emphasized that only 49 patients were revascularized notwithstanding normal stress wall motion and only 26 with normal myocardial perfusion at stress. Either for wall motion (Log-rank *P*=0.04) or myocardial perfusion assessment (Log-rank *P*=0.027), patients with a normal contrast dipyridamole echocardiography who are subsequently revascularized anyway fared worse, while the opposite was not true for abnormal contrast dipyridamole echocardiography (upper panels) not showing statistically significant differences, although a trend toward better outcome if a revascularized patient had abnormal stress wall motion was shown. CABG indicates coronary artery bypass graft; cSE-WMP, contrast stress echocardiography with additional myocardial perfusion assessment; PCI, percutaneous coronary revascularization.

finally revascularized and only 35 fatal and nonfatal events recorded during the follow-up in this subgroup of patients, so that the sample size seems too small to make any meaningful inferences in this subset. Among the 1329 patients included in the study, 1252 were already included in a prior prognostic study with significantly shorter follow-up.[12]

Electrocardiographic and hemodynamic changes during stress were not analyzed in our study, but these parameters have never been clearly associated with prognosis during dipyridamole stress echocardiography.[7–9]

Perfusion imaging during echocardiography requires significant specific expertise, not very differently from other advanced ultrasound, nuclear, or other imaging techniques.

Both bolus and continuous-infusion contrast techniques were employed for this study. Although continuous infusion would have been the ideal technique for analyzing contrast replenishment following a high mechanical index impulse, we found that the bolus technique resulted in much lower contrast utilization and produced equivalent results for visual analysis.

Conclusions

cSE-WMP provides independent and incremental information for the prediction of 5-year ischemic cardiac events in addition to clinical and rest imaging variables in current-era patients with known or suspected CAD, after adjustment for clinical and medications data. As expected and previously reported, an isolated reversible MP defect without WM abnormality is in general a more benign finding compared with a reversible MP

defect associated with a reversible WMA. There is also a suggestion that revascularization reduces ischemic cardiac events only after a positive cSE-WMP, more clearly if WM response is considered, while performing revascularization despite the fact that a negative cSE-WMP for MP or WM might be detrimental. This was per se a collateral interesting result of our study, that long-term ischemic cardiac event rate in patients undergoing stress echocardiography may be heavily influenced by subsequent revascularization and by cSE-WMP results before revascularization, which is not a consolidated finding in the literature.

Disclosures

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