JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 7, NO. 2, 2014

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcin.2013.10.017

CORONARY
Clinical Research

Predicting Outcome in the COURAGE Trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation)

Coronary Anatomy Versus Ischemia

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Objectives The aim of this study was to determine the relative utility of anatomic and ischemic burden of coronary artery disease for predicting outcomes.

Background Both anatomic burden and ischemic burden of coronary artery disease determine patient prognosis and influence myocardial revascularization decisions. When both measures are available, their relative utility for prognostication and management choice is controversial.

Methods A total of 621 patients enrolled in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial with baseline quantitative nuclear single-photon emission computed tomography (SPECT) and quantitative coronary angiography were studied. Several multiple regression models were constructed to determine independent predictors of the endpoint of death, myocardial infarction (MI) (excluding periprocedural MI) and non–ST-segment elevation acute coronary syndromes (NSTE-ACS). Ischemic burden during stress SPECT, anatomic burden derived from angiography, left ventricular ejection fraction, and assignment to either optimal medical therapy (OMT) + percutaneous coronary intervention (PCI) or OMT alone were analyzed.

Results In nonadjusted and adjusted regression models, anatomic burden and left ventricular ejection fraction were consistent predictors of death, MI, and NSTE-ACS, whereas ischemic burden and treatment assignment were not. There was a marginal ($p = 0.03$) effect of the interaction term of anatomic and ischemic burden for the prediction of clinical outcome, but separately or in combination, neither anatomy nor ischemia interacted with therapeutic strategy to predict outcome.

Conclusions In a cohort of patients treated with OMT, anatomic burden was a consistent predictor of death, MI, and NSTE-ACS, whereas ischemic burden was not. Importantly, neither determination, even in combination, identified a patient profile benefiting preferentially from an invasive therapeutic strategy. (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation [COURAGE]; NCT00007657) (J Am Coll Cardiol Intv 2014;7:195–201) © 2014 by the American College of Cardiology Foundation

Measures of either anatomic or ischemic burden are routinely used clinically to assess prognosis and select treatment strategies (1). The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial showed noninferiority between a strategy of initial optimal medical therapy (OMT) + percutaneous coronary intervention (PCI) and OMT alone for prevention of death or myocardial infarction (MI) (2). A substudy of 314 patients with baseline and follow-up nuclear studies showed that OMT + PCI was associated with a greater decrease in ischemia as measured by quantitative stress single-photon emission computed tomography (SPECT) and that the presence of at least a moderate degree of baseline ischemia might be a predictor of benefit from an initial strategy of OMT + PCI (3). A subsequent analysis of all patients for whom pre-randomization SPECT information was available reported no decrease in death or MI among patients with moderate to severe ischemia who were randomized to OMT + PCI (4). Although several quantitative angiographic analyses of the COURAGE trial have demonstrated the prognostic importance of baseline angiographic characteristics and left ventricular function status, none have clearly identified an anatomic subset favoring an initial OMT + PCI strategy (5–7) and no direct comparison with ischemic burden has been conducted. The purpose of the current analysis was 2-fold: 1) to explore the relative and potentially synergistic prognostic importance of quantitative assessment of angiographic anatomic burden and stress-induced ischemic burden for the prediction of death, MI, or non–ST-segment elevation acute coronary syndrome (NSTE-ACS) while on OMT; and 2) to determine whether a combination of anatomic and ischemic burden would identify patients who would benefit from an initial PCI management strategy.

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Abbreviations and Acronyms

CABG = coronary artery bypass graft

LVEF = left ventricular ejection fraction

MI = myocardial infarction

NSTE-ACS = non–ST-segment elevation acute coronary syndromes

OMT = optimal medical therapy

PCI = percutaneous coronary intervention

SPECT = single-photon emission computed tomography

Methods

The main trial results, assessment methods for quantitative nuclear ischemic burden, methods for quantitative coronary angiography, and definitions of clinical endpoints have been previously published (2). The clinical endpoint for this analysis was a composite of death, MI, and NSTE-ACS. Periprocedural MIs were excluded from all analyses. SPECT and coronary angiography studies were analyzed in core laboratories. SPECT myocardial perfusion studies were analyzed quantitatively using the measurement of the total perfusion defect, combining perfusion defect extent and severity on a continuous pixel-by-pixel basis and expressed as a percent of the total left ventricular myocardium (QPS, Cedars-Sinai Medical Center, Los Angeles, California) (8). The percent of ischemic myocardium was calculated by subtracting the rest from the stress total perfusion defect and used as a continuous variable. Contrast coronary angiograms were assessed for the presence of stenoses ≥50% in the major epicardial vessels and primary branches (5). Patients who failed to meet the 50% diameter stenosis threshold by quantitative coronary angiography were designated as having "no" vessel disease. By distinguishing between proximal and nonproximal left anterior descending and circumflex artery disease, different gradations of single-, double-, and triple-vessel disease could be described anatomically, thereby creating an anatomic burden score suitable for use as a continuous variable (0 to 17 scoring scale; see Table 1). By design of

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Manuscript received August 21, 2013; revised manuscript received October 12, 2013, accepted October 24, 2013.

Table 1. Grading Scale for Anatomic Burden of Disease on the Basis of Location of ≥50% Diameter Stenoses

Anatomic Burden Score	Location of Stenoses ≥50%	Traditional Vessel Disease Designation
0	None	0
1	RCA	1
2	LCX (not proximal LCX)	1
3	Proximal LCX	1
4	LAD (not proximal LAD)	1
5	Proximal LAD	1
6	LCX (not proximal LCX) + RCA	2
7	Proximal LCX + RCA	2
8	LAD (not proximal LAD) + RCA	2
9	Proximal LAD + RCA	2
10	LAD (not proximal LAD) + LCX (not proximal LCX)	2
11	Proximal LAD + LCX (not proximal LCX)	2
12	LAD (not proximal LAD) + proximal LCX	2
13	Proximal LAD + proximal LCX	2
14	LAD (not proximal LAD) + LCX (not proximal LCX) + RCA	3
15	LAD (not proximal LAD) + proximal LCX + RCA	3
16	Proximal LAD + LCX (not proximal LCX) + RCA	3
17	Proximal LAD + proximal LCX + RCA	3

LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery.

the COURAGE trial, there were no patients with left main coronary artery disease.

Multiple logistic survival analysis was used to determine independent predictors of death, MI, and NSTE-ACS. Left ventricular ejection fraction (LVEF) was included a priori in all logistic regression analyses to account for the effects of irreversible ventricular damage and irreversible ischemia that would otherwise confound the interpretation of the nuclear and angiographic assessments. Other factors that might affect generalizability were identified by comparison of the patients in this analysis with the remaining patients enrolled in the trial. Between-group comparisons were undertaken using the *t*, chi-square, or Fisher exact test where appropriate. Logistic regression analyses were repeated to adjust for differences in this cohort compared with the overall COURAGE trial cohort. Results with $p < 0.01$ were considered statistically significant.

Results

There were 621 patients with quantitative angiographic and nuclear data. The mean follow-up was 4.69 ± 1.68 years. There were 185 events (death/MI/NSTE-ACS) in the 621 patients, yielding a raw rate of events of 29.8% and an overall event rate of 30.2%/4.69 years taking into account individual follow-up time and censoring of recurrent events. Table 2 shows the characteristics of this study group by randomization to OMT + PCI or OMT; no differences were detected. Table 3 shows a comparison of this group with the remaining patients enrolled in the trial. The current study cohort, compared with the overall COURAGE trial population, had significantly fewer white, more hypertensive, more diabetic, more previous coronary artery bypass graft (CABG) surgery, fewer patients with Canadian Cardiovascular Society class II and III, and more triple-vessel disease patients. Additionally, angina duration was shorter and high-density lipoprotein levels were lower. These factors were used to adjust results.

Table 2. Characteristics of Patients With Both Quantitative Nuclear and Coronary Angiography Studies Assigned to OMT + PCI or OMT Alone

Characteristic	OMT + PCI (n = 313)	OMT (n = 308)	p Value
Female	36 (12)	42 (14)	0.42
White	244 (78)	251 (81)	0.31
Hypertension	233 (75)	227 (74)	0.73
Diabetes	115 (37)	121 (40)	0.55
Family history of Coronary Artery Disease	155 (56)	145 (54)	0.63
Current smoker	85 (27)	80 (26)	0.74
Heart failure	20 (6)	11 (4)	0.11
Previous MI	116 (38)	110 (36)	0.78
Previous PCI	54 (17)	47 (15)	0.51
Previous CABG	52 (17)	37 (12)	0.11
CCS			
0	39 (12)	38 (37)	0.98
I	118 (38)	114 (37)	
II	96 (31)	99 (32)	
III	60 (19)	57 (19)	
Age, yrs	62.1 ± 10.3	62.6 ± 10.1	0.56
BMI, kg/m^2	29.5 ± 4.9	30.1 ± 5.5	0.71
Perfusion defect, %	7.7 ± 5.7	7.8 ± 6.2	0.79
LVEF, %	60.1 ± 11.8	60.7 ± 10.0	0.46
Anatomic burden score (0–17)	7.8 ± 4.9	7.4 ± 4.8	0.24
Angina frequency, episodes/week	3 (1–5)	2 (1–5)	0.68
Angina duration, yrs	3 (1–12)	3 (1–8)	0.33
LDL, mg/dl	99 (78–123)	100 (81–121)	0.76
HDL, mg/dl	37 (32–46)	39 (33–45)	0.09
Triglycerides, mg/dl	154 (103–217)	152 (102–213)	0.81

Values are mean (%), mean ± SD, or median (interquartile range).

BMI = body mass index; CABG = coronary artery bypass graft; CCS = Canadian Cardiovascular Society; HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; OMT = optimal medical therapy; PCI = percutaneous coronary intervention.

Table 4 shows the results of 3 different multiple logistic regression analyses with model 1 containing only the primary factors of interest and models 2 and 3 including interaction terms. Treatment assignment to OMT + PCI or OMT did not predict outcome in any model; similarly, nor did ischemic burden (Fig. 1). Consistent predictors were LVEF and anatomic burden of disease (Fig. 2). These

Table 3. Characteristics of Patients in the Current Study Compared With the Other Patients Enrolled in the COURAGE Trial

Characteristic	Study Group (N = 621)	Nonstudy Group (N = 1,666)	p Value
Female	78 (13)	260 (16)	0.07
White	495 (80)	1,468 (89)	<0.001
Hypertension	460 (75)	1,061 (65)	<0.001
Diabetes	236 (38)	530 (32)	0.008
Family history of Coronary Artery Disease	300 (55)	793 (53)	0.43
Current smoker	165 (27)	488 (29)	0.19
Heart failure	31 (5)	77 (5)	0.70
Previous MI	226 (37)	650 (40)	0.24
Previous PCI	101 (16)	258 (16)	0.64
Previous CABG	89 (14)	159 (10)	0.001
CCS			
0	77 (12)	206 (12)	<0.001
I	232 (37)	449 (27)	
II	195 (31)	639 (38)	
III	117 (19)	365 (22)	
Age, yrs	62.4 ± 10.2	62.0 ± 9.8	0.42
BMI, kg/m^2	29.8 ± 5.2	29.5 ± 5.0	0.25
Angina frequency, episodes/week	3 (1–5)	3 (1–6)	0.43
Angina duration, yrs	3 (1–9)	6 (2–21)	<0.001
LDL, mg/dl	99 (80–122)	101 (82–124)	0.27
HDL, mg/dl	38 (33–45)	40 (33–47)	<0.001
Triglycerides, mg/dl	152 (102–214)	145 (104–210)	0.08

Values are mean (%), mean ± SD, or median (interquartile range).
Abbreviations as in Table 2.

results were not materially changed after adjusting for the confounders listed in the preceding text. Of the multiple confounders, a history of hypertension and CABG surgery were additional consistent and independent predictors of death, MI, or NSTE-ACS (data not shown).

Model 2 (Table 4) shows the absence of any interaction between treatment and LVEF, anatomic burden, ischemic burden, or the combination of anatomic and ischemic burden. The only interaction approaching statistical significance was between anatomic and ischemic burden ($p = 0.03$) (model 3 in Table 4). Figure 3 explores this interaction further. The basis of the borderline positive interaction term appears in Figure 3 to emerge predominantly from the progressively higher event rates within the higher atherosclerotic burden group. The event rate was progressively higher with increasing ischemic burden only in patients with high atherosclerotic burden. In contrast, event rates were generally progressively higher on the basis of the degree of anatomic burden, irrespective of amount of ischemic myocardium.

Discussion

Anatomic burden assessed by coronary angiography and ischemic burden assessed by stress SPECT myocardial perfusion imaging are commonly used to assess prognosis, and both influence therapy in patients with stable ischemic heart disease. Accordingly, this analysis was designed to directly compare these 2 risk stratification methods and to explore whether they could also identify patients with greater benefits from an initial intervention strategy. Our analyses indicate that when both anatomic burden and ischemic burden of disease at baseline are considered concomitantly, ischemic burden was not an independent predictor of death, MI, or NSTE-ACS. In contrast, anatomic burden and

Table 4. Multiple Logistic Survival Analyses to Determine Predictors of Death, MI, or NSTE-ACS

Model 1 (No Interactions)			Model 2 (Interactions With Treatment)			Model 3 (Interactions With Each Other)		
Variables	OR (95% CL)	p Value	Variables	OR (95% CL)	p Value	Variables	OR (95% CL)	p Value
Treatment assignment*	1.00 (0.75–1.34)	1.00	Treatment assignment	1.03 (0.76–1.39)	0.84	Treatment assignment	1.01 (0.76–1.36)	0.93
Ischemic burden	1.01 (0.98–1.03)	0.54	Ischemic burden	1.01 (0.99–1.03)	0.46	Ischemic burden	1.01 (0.98–1.04)	0.54
LVEF†	0.98 (0.97–1.00)	0.0095	LVEF	0.98 (0.97–1.00)	0.006	LVEF	0.98 (0.97–0.99)	0.003
Atherosclerotic burden	1.05 (1.02–1.08)	0.002	Atherosclerotic burden	1.05 (1.02–1.08)	0.003	Atherosclerotic burden	1.05 (1.02–1.09)	<0.001
			Interaction of treatment and ischemic burden		0.07	Interaction of ischemic burden and LVEF		0.50
			Interaction of treatment and LVEF		0.51	Interaction of ischemic burden and atherosclerotic burden		0.03
			Interaction of treatment and atherosclerotic burden		0.07	Interaction of LVEF and atherosclerotic burden		0.19
			Interaction of treatment, ischemic burden, and atherosclerotic burden		0.24	Interaction of ischemic burden, LVEF, and atherosclerotic burden		0.50

*Optimal medical therapy or optimal medical therapy + percutaneous coronary intervention. †LVEF.
CL = confidence limits; NSTE-ACS = non–ST-segment elevation acute coronary syndrome; OR = odds ratio; other abbreviations as in Table 2.

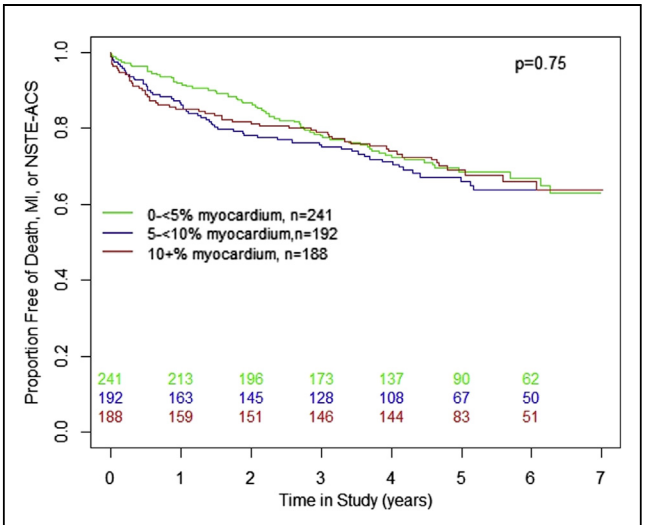

Figure 1. Freedom From Death, MI, or NSTE-ACS by Percent of Ischemic Myocardium

The number of patients pertaining to each colored curve are shown per year of follow-up. The percent of ischemic myocardium is calculated as described in the text and represents the burden of reversible ischemia at baseline. No significant relationship with the outcome of death/myocardial infarction (MI)/non–ST-segment elevation acute coronary syndromes (NSTE-ACS) was detected (p = 0.75).

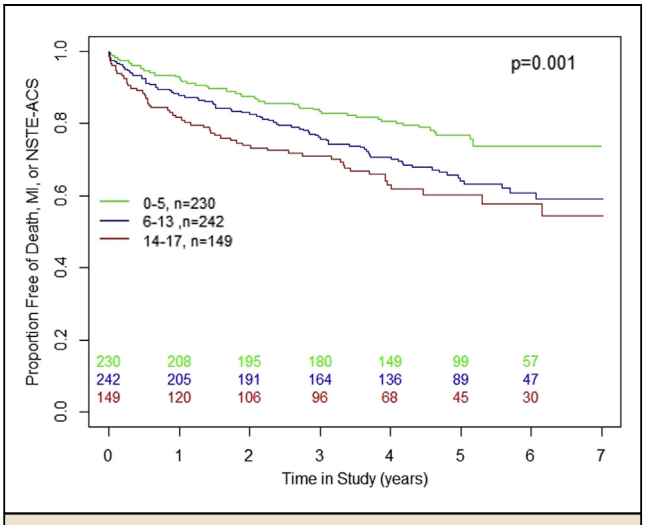

Figure 2. Freedom From Death, Myocardial Infarction, or Non–ST-Segment Elevation Acute Coronary Syndrome by Anatomic Burden

The number of patients pertaining to each colored curve are shown per year of follow-up. The atherosclerotic burden of disease was determined using the graduated scale shown in Table 1. The clusters of 0-5, 6-13, and 14-17 correspond to traditional vessel disease designations of 0/1, 2, and 3 vessel disease, respectively. Angiographic burden of disease was significantly predictive of death/MI/NSTE-ACS (p = 0.001). Abbreviations as in Figure 1.

LVEF were consistently seen to be independent predictors of death, MI, or NSTE-ACS. The interaction term of ischemic burden and anatomic burden at baseline was of only borderline significance as a predictor of death, MI, or NSTE-ACS, where it was primarily of benefit in risk-stratifying the outcomes of those with the most severe anatomic burden. More importantly, none of these factors identified patients who would benefit from an initial invasive strategy.

These results are concordant with a recent analysis of nearly 1,400 patients in the COURAGE trial showing that the extent of site-defined ischemia did not predict adverse events and did not alter treatment effectiveness (4). These results are also concordant with a recent analysis of the STICH (Comparison of Surgical and Medical Treatment of Congestive Heart Failure and Coronary artery Disease) trial in patients with severely reduced LVEF, which concluded that inducible ischemia did not identify patients with worse prognosis or those with greater benefit from revascularization with CABG surgery over OMT (9). Similarly, a nuclear substudy of the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial showed that LVEF, but not the percent of ischemic myocardium, predicted event rates (10). Our results allow extension of this concept to nondiabetic patients, LVEF >35%, and revascularization with PCI.

Our data suggesting that ischemia may be most important in those with more severe atherosclerotic burden (Fig. 3) provide an important justification for the ongoing ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA). The ISCHEMIA trial uses coronary computed tomography to exclude patients with significant left main coronary artery or minimal atherosclerotic disease and will randomize 8,000 patients with at least moderate ischemia to an initial invasive strategy of catheterization followed by revascularization (PCI or CABG) as warranted + OMT versus an initial conservative strategy of OMT alone with catheterization and revascularization reserved for patients in whom OMT failed. It will be possible to determine whether ischemic burden at baseline retains prognostic power while receiving OMT. The size of this study will overcome any sample size limitations in the current analysis and will define the incremental contribution of ischemia to atherosclerotic burden for prognostication and selection of an optimal management strategy.

Our current findings are discordant with observational cohort studies implying that the severity of ischemic burden can identify patients who would benefit from an invasive revascularization strategy (11–17). This may be explained by the strict adherence to protocol-driven OMT in the current cohort, which cannot be mandated in observational studies. In addition, the difficulties of fully assessing and adjusting for confounders in observational studies are well known.

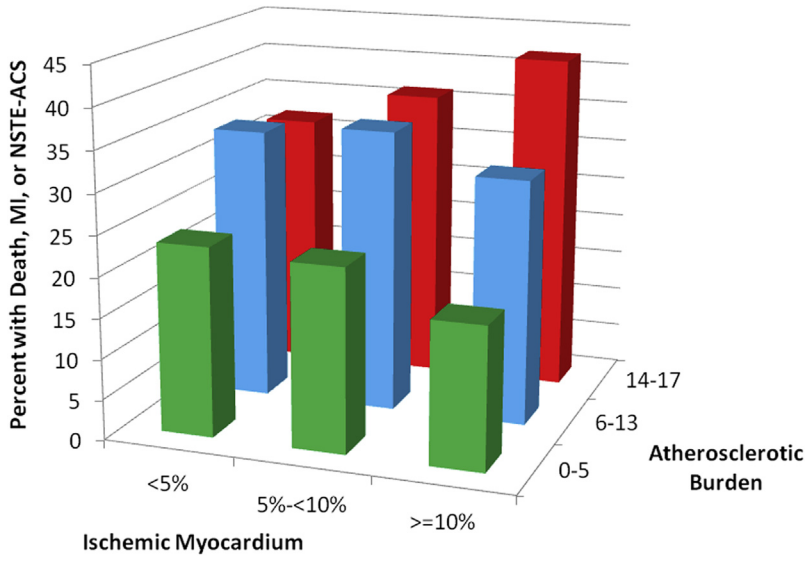

Figure 3. Proportion of Patients With Death, Myocardial Infarction or Non–ST-Segment Elevation Acute Coronary Syndrome by Ischemic Myocardium and Atherosclerotic Burden of Disease

The borderline interaction between ischemic and angiographic burden of disease for prediction of outcome is explored further in this plot showing the relationship of these parameters to the outcomes of death/MI/NSTE-ACS when considered concomitantly. Outcome worsens in a generally consistent fashion with increasing atherosclerotic burden of disease. Outcome does not worsen consistently with increasing ischemic burden except in the subset of patients with the highest degree of atherosclerotic burden. $p = 0.03$ and not significant for COURAGE post-hoc analyses. See Methods and Table 4, model 3. Abbreviations as in Figure 1.

There may, however, also be important physiological reasons for the findings. It is apparent that OMT has the ability to reduce ischemic burden, but not as rapidly or extensively as PCI in the short term (3,18,19). OMT may achieve a sizable reduction in ischemia and comparable reduction in angina-free status over the long term (2). Thus, the overlapping anti-ischemic nature of both strategies may contribute over the long term to the abrogation of the prognostic importance of baseline, pre-treatment inducible ischemia. The vasculoprotective effect of OMT, with respect to plaque stabilization and progression, may also partially explain the inability to identify an advantage over the long term of OMT + PCI versus OMT alone. However, neither sufficiently reverses the burden of atherosclerosis, and neither completely suppresses progression or plaque disruption throughout the entire coronary tree (6). Because increasing burden of significant anatomic stenoses is likely to also be associated with more subclinical atherosclerotic lesions (i.e., nonobstructing plaques that may be "vulnerable"), adverse clinical outcomes that occur may be greatly influenced by their disruption more so than by the flow-limiting nature of obstructive plaques. Thus, baseline anatomic disease retains value as an index or surrogate measure of the extent of fertile soil for future cardiac events.

Study limitations. This analysis has limitations derived from its post hoc nature, the relatively small sample size ($n = 621$), the potential for residual confounding despite the adjustments undertaken, the lack of serial assessments of inducible ischemia after implementation of OMT with or without PCI, the inability to retrospectively calculate more detailed angiographic indexes such as SYNTAX score, the absence of lesion-specific fractional flow reserve measurements, and execution during the bare metal stent era. Despite these limitations, the findings are concordant with the emerging concepts identified in other similar analyses (4,9) and extend the implications to include a very demographically broad group of patients (diabetic and nondiabetic, normal or only mildly depressed LVEF, revascularization with stents or CABG) in the context of modern evidence-based medical therapy complemented by either elective or urgent PCI. The findings further challenge the existing paradigm regarding the role of inducible ischemia in choosing a revascularization strategy, thereby also underscoring the critical need to re-evaluate this concept through the ongoing ISCHEMIA trial.

Conclusions

In patients treated with OMT with or without elective or symptom-warranted PCI, anatomic burden of coronary disease, but not ischemic burden, predicted the risk of death, MI, and NSTE-ACS, but neither coronary anatomy nor ischemia, even in combination, identified a patient profile

benefiting preferentially from an initial invasive therapeutic strategy.

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Key Words: angiographic burden ■ coronary angiography ■ ischemia ■ ischemic burden ■ nuclear perfusion imaging ■ stable ischemic heart disease.