Prognostic importance of coronary anatomy and left ventricular ejection fraction despite optimal therapy: Assessment of residual risk in the Clinical Outcomes Utilizing Revascularization and Aggressive DruG Evaluation Trial

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Background It is unknown if baseline angiographic findings can be used to estimate residual risk of patients with chronic stable angina treated with both optimal medical therapy (OMT) and protocol-assigned or symptom-driven percutaneous coronary intervention (PCI).

Methods Death, myocardial infarction (MI), and hospitalization for non–ST-segment elevation acute coronary syndrome were adjudicated in 2,275 COURAGE patients. The number of vessels diseased (VD) was defined as the number of major coronary arteries with ≥50% diameter stenosis. Proximal left anterior descending, either isolated or in combination with other disease, was also evaluated. Depressed left ventricular ejection fraction (LVEF) was defined as ≤50%. Cox regression analyses included these anatomical factors as well as interaction terms for initial treatment assignment (OMT or OMT + PCI).

Results Percutaneous coronary intervention and proximal left anterior descending did not influence any outcome. Death was predicted by low LVEF (hazard ratio [HR] 1.86, CI 1.34-2.59, $P < .001$) and VD (HR 1.45, CI 1.20-1.75, $P < .001$). Myocardial infarction and non–ST-segment elevation acute coronary syndrome were predicted only by VD (HR 1.53, CI 1.30-1.81 and HR 1.24, CI 1.06-1.44, $P = .007$, respectively).

Conclusions In spite of OMT and irrespective of protocol-assigned or clinically driven PCI, LVEF and angiographic burden of disease at baseline retain prognostic power and reflect residual risk for secondary ischemic events. (Am Heart J 2013;166:481-7.)

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Clinical Trial Registration: www.clinicaltrials.gov no. NCT00007657.

Submitted April 28, 2013; accepted July 1, 2013.

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0002-8703/$ - see front matter

http://dx.doi.org/10.1016/j.ahj.2013.07.007

Coronary artery disease (CAD) burden and left ventricular ejection fraction (LVEF) have long been shown to have prognostic significance.[1,2] Early studies showing this prognostic importance were performed before the current era of optimal medical therapy (OMT) and percutaneous coronary intervention (PCI). More recently, observational cardiac computed tomographic angiography studies have also shown that coronary angiography has prognostic utility.[3,4] The latter more modern studies still have lack of uniform utilization of OMT after imaging; absence of event adjudication; low rates of death, myocardial infarction (MI), and hospitalization for non–ST-segment elevation acute coronary syndromes (NSTE-ACS); and a preponderance of PCI events, many of which may have been the result of patient and/or physician bias. Accordingly, it is unknown whether the prognostic value inherent in anatomical coronary assessment by either

angiography or other means is negated by OMT and PCI. If not, then coronary anatomical findings despite the best therapeutic effort may remain useful as measures of residual risk for secondary ischemic events.[5] The COURAGE trial showed noninferiority between a strategy of initial PCI + OMT and OMT alone, with provisions in either strategy for symptom-driven PCI during follow-up. This study population provides a unique and well-characterized cohort to determine whether the influence of aggressive and uniform OMT and either elective or clinically driven revascularization alters the relationships between anatomical patterns of CAD as assessed by angiography or LVEF and residual risk.[6,7]

Methods

The methods and main results of the COURAGE trial have been previously published.[6] Patients with visually assessed significant left main (LM) disease were excluded from the trial. Using previously described quantitative coronary angiography from a core laboratory, 2,275 patients were categorized based on angiographic burden of disease and LVEF.[8,9] The number of vessels diseased (VD) was determined based on lesions ≥50% diameter stenosis (DS) in the main coronary segments of the right (RCA), left anterior descending (LAD), and left circumflex (LCX) arteries and their main branches (first or largest diagonal of the LAD, first or largest obtuse marginal branch of the LCX, and posterior descending and posterolateral segments of a dominant RCA or LCX), LM, or in bypass grafts supplying any of these perfusion territories. Patients were categorized based on the presence of single, double, and triple VD; presence of disease in the RCA, LAD, or LCX (including all combinations); and presence or absence of proximal LAD disease (pLAD). Because patients were enrolled based on angina symptoms, fulfillment of ischemia entry criteria, and visually assessed stenosis, some patients had lesions that fell just above or below the 50% quantitative angiography threshold. This explains our designation "0/1VD" used below which includes 14 patients with subthreshold single-vessel disease in the OMT arm and 11 in the OMT + PCI arm. Left ventricular ejection fraction was obtained either from contrast, nuclear, or echocardiographic studies as for the main report.[6] By study design, patients with LVEF <30% were excluded. Thus, normal LVEF and low LVEF were defined as >50% and ≤50%, respectively.

We analyzed individual, independently adjudicated end points of death, MI (excluding periprocedural MI), and NSTE-ACS, as previously defined.[6] The aggregate end points of death or MI and death or MI or NSTE-ACS were also analyzed. Cox regression analysis was undertaken with variables including treatment assignment (OMT and OMT + PCI), low LVEF (>30%, ≤50%), VD, and clinical characteristics along with interaction terms.[10] Hazard ratios and 95% CIs were calculated. These analyses were repeated using LVEF as a continuous variable. A forest plot was created for the outcomes of interest for the subsets of vessel disease ± low LVEF. The test for homogeneity (interaction) was included as was the interaction term after adjustments (see below). Kaplan-Meier curves were constructed for the composite outcome of death, MI, or NSTE-ACS for subgroups defined by LVEF and angiographic patterns of disease.[11] Log-rank *P* values were calculated. All analyses were adjusted for age, sex, current smoking status, diabetes, prior MI, prior coronary artery bypass graft, presence of clinical heart failure, Canadian Cardiovascular Society angina class, baseline low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol. The only exception was the Kaplan-Meier analysis of patients with 3 VD and low LVEF as the number of events in this group was too small for stable estimates if this many variables were included. Analyses were done using SAS 9.2 and R 2.12.2. $P < .01$ was considered significant as per study policy for subgroup analyses.

Sample size calculations ($\alpha = .05$, $\beta = .80$) were undertaken using observed rates of the composite outcome of death, MI, or NSTE-ACS in patients with 3 VD and low LVEF to demonstrate theoretically the size of a trial required to impart statistical significance to the observed risk reduction by adding PCI to OMT. This was done assuming that the distribution of events was binomial, and then 15% was added for the effect of loss to follow-up.[12]

Funding was provided by the Cooperative Studies Program of the US Department of Veterans Affairs Office of Research and Development, in collaboration with the Canadian Institutes of Health Research, and by unrestricted research grants from Merck, Pfizer, Bristol- Myers Squibb, Fujisawa, Kos Pharmaceuticals, Datascope, AstraZeneca, Key Pharmaceutical, Sanofi-Aventis, First Horizon, and GE Healthcare, including in-kind support with Food and Drug Administration–approved drugs used by study participants. All industrial funding in support of the trial was directed through the US Department of Veterans Affairs. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Results

Table summarizes the Cox regression analyses using treatment assignment to OMT + PCI, VD, and low LVEF variables. Death was predicted by both low LVEF (hazard ratio [HR] 1.86, CI 1.34-2.59, $P < .001$) and VD (HR 1.45, CI 1.20-1.75, $P < 001$). Myocardial infarction was predicted by VD (HR 1.53, CI 1.30-1.81, $P < 001$) as was NSTE-ACS (HR 1.24, CI 1.06-1.44, $P = .007$). The composite of death or MI was predicted by both low LVEF (HR 1.50, CI 1.18-1.91, $P < .001$) and VD (HR 1.43, CI 1.26-1.63, $P < .001$). The composite outcome of death, MI, or NSTE-ACS was also predicted by both low LVEF (HR 1.34, CI 1.10-1.64, $P = .004$) and VD (HR 1.36, CI 1.23-1.51, $P < 001$). No interactions with treatment randomization were significant; pLAD was not predictive of outcome. Reassessment of these relationships using LVEF as a continuous variable confirmed that LVEF was a significant and independent predictor of death ($P < .001$), death or MI ($P < .001$), and death or MI or NSTE-ACS ($P < .001$) but not of MI ($P = .05$) or NSTE-ACS ($P = .14$). Figure 1 shows a forest plot comparing OMT and OMT + PCI for all outcomes. There were no significant differences in outcomes based on randomization, even when adjusted as described above. The highest event rates were seen for the composite end point of death,

Table. Adjusted Cox regression analyses for randomized treatment assignment (OMT or OMT + PCI), stenotic vessels (1, 2, 3 VD), low LVEF, and interactions

Outcome	Variable	HR	95% CI	P
Death (179 events overall)	Initial assignment to OMT + PCI	0.85	0.62, 1.16	.31
	No. of stenotic vessels	1.45	1.20, 1.75	<.001
	Low LVEF	1.86	1.34, 2.59	<.001
	Interaction of treatment and vessels	1.12		.54
	Interaction of treatment and low LVEF	0.70		.29
MI (230 events overall)	Initial assignment to OMT + PCI	0.87	0.67, 1.15	.33
	No. of stenotic vessels	1.53	1.30, 1.81	<.001
	Low LVEF	1.19	0.86, 1.65	.28
	Interaction of treatment and vessels	0.95		.75
	Interaction of treatment and low LVEF	1.16		.65
NSTE-ACS (259 events overall)	Initial assignment to OMT + PCI	1.08	0.84, 1.38	.56
	No. of stenotic vessels	1.24	1.06, 1.44	.007
	Low LVEF	1.09	0.79, 1.49	.61
	Interaction of treatment and vessels	1.01		.94
	Interaction of treatment and Low LVEF	1.08		.81
Death/MI (373 events overall)	Initial assignment to OMT + PCI	0.88	0.71, 1.09	.23
	No. of stenotic vessels	1.43	1.26, 1.63	<.001
	Low LVEF	1.50	1.18, 1.91	<.001
	Interaction of treatment and vessels	0.97		.84
	Interaction of treatment and low LVEF	0.87		.55
Death/MI/NSTE-ACS (574 events overall)	Initial assignment to OMT + PCI	0.93	0.79, 1.10	.39
	No. of stenotic vessels	1.36	1.23, 1.51	<.001
	Low LVEF	1.34	1.10, 1.64	.004
	Interaction of treatment and vessels	1.02		.84
	Interaction of treatment and low LVEF	0.92		.68

MI, or NSTE-ACS in patients with 3 VD and low LVEF (48.8% vs 40.8% per 4.6 years for the OMT and OMT + PCI groups, respectively) indicating a potential 16% risk reduction in the OMT + PCI group.

Figure 2 shows Kaplan-Meier curves of freedom from death, MI, or NSTE-ACS in angiographic subsets determined by VD and LVEF. Prognosis progressively worsened with more severe VD and low LVEF (P = .003). Figure 3 shows the Kaplan-Meier curves for freedom from death, MI, or NSTE-ACS in patients with 3 VD and low LVEF, stratified by initial randomization to OMT + PCI and OMT alone. The curves overlap for the first 2 to 3 years and subsequently separate, suggestive of a more favorable, long-term outcome in the OMT + PCI arm but not statistically significant (P = .59).

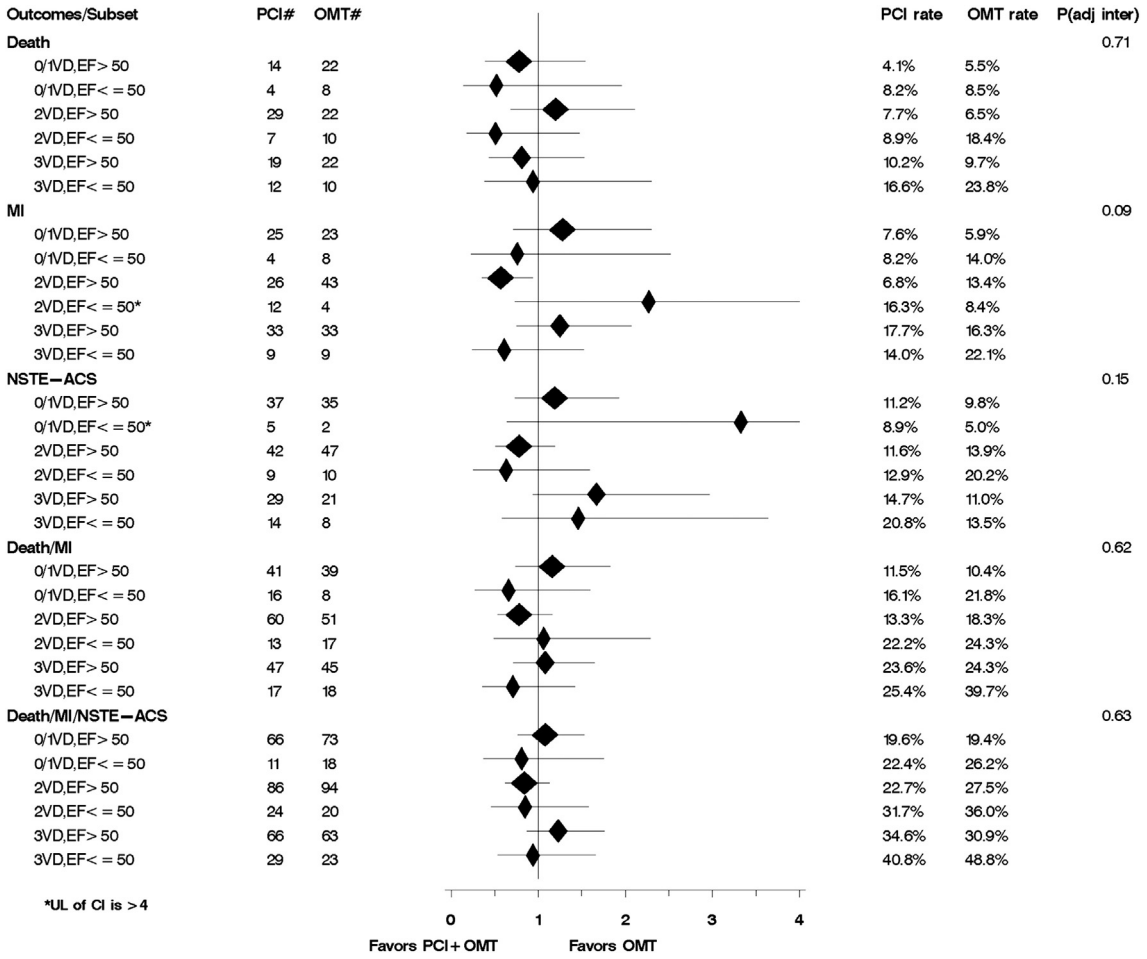
More detailed analyses of the possible impact of pLAD were undertaken. Kaplan-Meier analyses of freedom from death, MI, or NSTE-ACS in angiographic subsets determined by presence or absence of pLAD disease, including presence or absence of low LVEF, showed no significant difference (P = .50). Figure 4 is a Kaplan-Meier plot showing that the extent of VD is a more consistent determinant of death, MI, or NSTE-ACS, irrespective of presence or absence of pLAD (P = .002). The group with the highest proportion free from death, MI, or NSTE-ACS was unexpectedly the group with single-vessel pLAD. There was no subgroup of patients based on percent DS severity of pLAD that showed a preferential outcome with either treatment strategies (Figure 5, P = .79). This figure shows, however, that the worst outcome occurred in the subgroup with pLAD ≥90% DS treated with OMT + PCI.

Discussion

Anatomical assessment of coronary disease and left ventricular systolic function retains prognostic power in spite of OMT and the provision of either initial or symptom-driven PCI. Because this analysis does not include a placebo group, the observed risk for secondary ischemic events during follow-up is a measure of residual risk in spite of modern management. Although traditionally felt to impart residual risk, pLAD was not shown to be predictive of any outcome in the context of modern, evidence-based therapy. These findings are not confounded by periprocedural MIs or PCI events, are based on adjudicated end points, and are adjusted for nonangiographic determinants of risk.

We found no subgroup in which initial PCI improved patient prognosis, thereby confirming the overall COURAGE results.[6] However, the current analysis also underscores, for example, that a patient with single- or double-vessel disease does not "shift" to a lower risk of zero or single-vessel disease merely by successful relief of an obstruction (Figures 1, 3, and 5). Based on the most frequent end point in this analysis (death, MI, or NSTE-ACS as shown in Figure 1), a general bedside assessment of residual risk, showing the interplay and relative

Figure 1



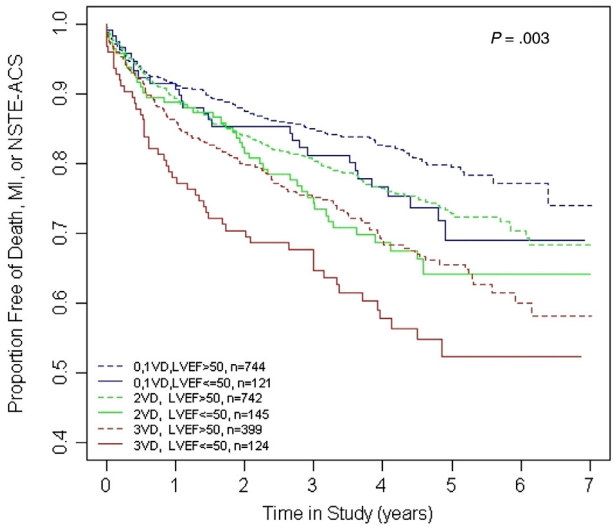
Forest plots showing relative risk of events in angiographic subsets based on initial treatment arm. Rates are expressed as percentages per 4.6 years. Adjustments were made for age, female sex, current smoker, diabetes, prior MI, prior coronary artery bypass graft, heart failure, CCS class, baseline low-density lipoprotein and baseline high-density lipoprotein. #, number of patients; adj inter, adjusted test of interaction; UL, upper limit.

importance of both LVEF and coronary burden at baseline, is shown in Figure 6.

There was, however, a nonsignificant trend toward a lower event rate emerging after >2 years of follow-up in patients with the combination of 3 VD and low LVEF treated with OMT + PCI compared with those treated with OMT alone (Figure 3). A conservative sample size calculation (see "Methods" section) based on rates of death, MI, or NSTE-ACS and the observed risk reduction of 16% (Figure 1) suggests that a trial of 7,008 patients would be required to show this degree of risk reduction with OMT + PCI to be significant. To our knowledge, there are no ongoing trials specifically targeting this highest risk anatomical subgroup of stable CAD patients. Of relevance is the ongoing ISCHEMIA trial, which has an enrollment goal similar to our calculations, but the target population is patients with stable CAD, LVEF ≥35%, and at least moderate ischemia with stress imaging.[13] Randomization to conservative or invasive strategies in that trial occurs before catheterization and is not based on coronary burden of disease.

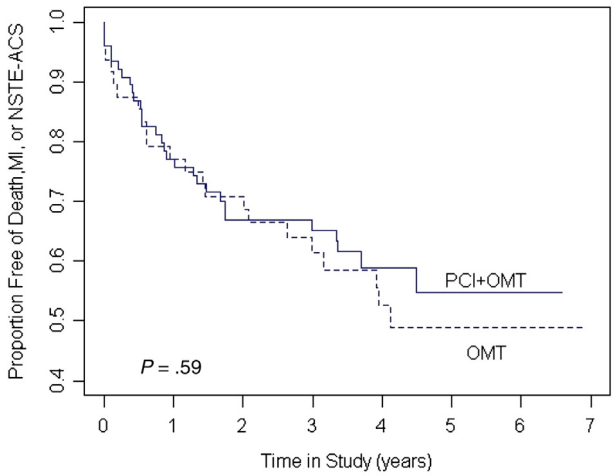
The presence of pLAD as a rationale for favoring OMT + PCI was not borne out by any of our analyses, a finding that is both provocative and perhaps instructive. Whether this is a function of OMT or lack of power or both is unclear. However, unlike all the other angiographic features that appear to confer risk in both untreated patients and in this aggressively treated population, it may well be that this is the only feature of high risk in an untreated population that is effectively abrogated by OMT. Figures 4 and 5 show that pLAD needs to be considered mainly with respect to LVEF and concomitant

Figure 2



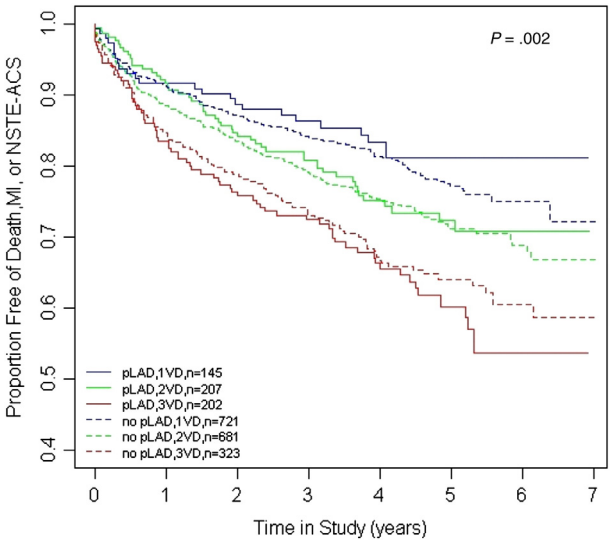
Kaplan-Meier curves showing freedom from the composite end point of death, MI, or NSTE-ACS based on coronary VD and LVEF.

Figure 3



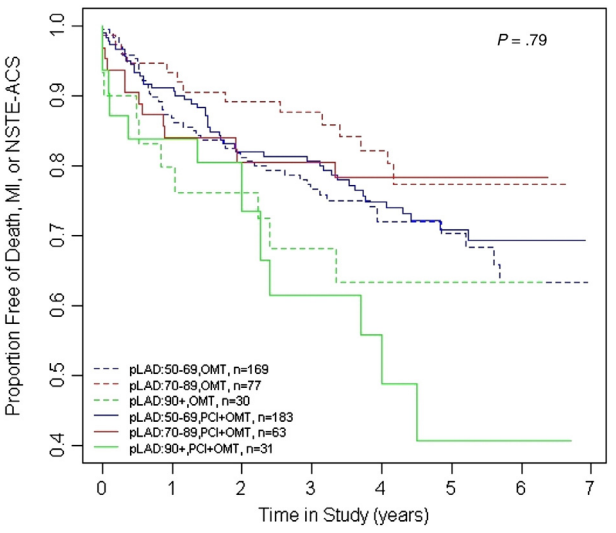
Kaplan-Meier curves showing freedom from outcome of death, MI, or NSTE-ACS in patients with 3-vessel disease and low LVEF, stratified by initial randomization to PCI + OMT or OMT alone (*P* value is unadjusted. See "Methods" section).

Figure 4



Kaplan-Meier curves showing freedom from death/MI/NSTE-ACS according to presence or absence of pLAD and in the presence of significant disease in other vessels.

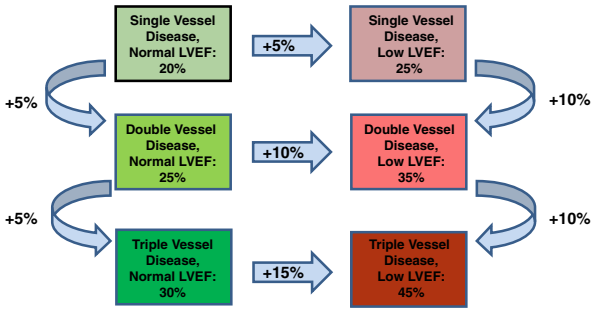
Figure 5



Analysis of patients with increasing severity of proximal left anterior descending stenosis and with respect to randomization to OMT or OMT + PCI.

angiographic burden of disease, compatible with the concept that further MI in patients with already compromised LVEF would be particularly deleterious if caused by pLAD. Current perceptions, practice patterns, and existing guidelines are not conducive to execution of adequately powered clinical trials focusing solely on this particular anatomical subset but may, nevertheless, be warranted, particularly if refined by the additional assessment of the functional significance of the pLAD lesion. This type of patient will be enrolled in the

Figure 6



COURAGE "Rule of Thumb" for estimating residual risk on OMT and either elective or symptom-driven PCI. Rates are for death, MI, or NSTE-ACS expressed as percentages per 4.6 years of follow-up and adjusted as described in "Methods" section.

ISCHEMIA trial.[13] The dominant importance of baseline low LVEF as a predictor of mortality in our population of aggressively treated, stable CAD patients is concordant with a recent analysis of patients with ST-segment elevation MI treated in a large scale, contemporary international study of patients who underwent primary PCI with contemporary antithrombotic regimens.[14]

This study has several limitations. It is a post hoc analysis, and some of the subgroup analyses are impacted by small sample sizes and relatively few events. Results may have been different if a ≥70% DS threshold had been used. However, our detailed analysis of the severity of pLAD lesions failed to show any reason to expect highly disparate conclusions using a higher cutoff in the entire cohort. Moreover, it is hard to predict the effect of the interplay between using a higher threshold that might be associated with a higher risk, counterbalanced by smaller cohort sizes and reduced power. The COURAGE study protocol did not include more detailed angiographic analyses such as Syntax scoring, detailed lesion description, or assessment of angiograms and collateralization at the time of secondary events. By design, the study cannot address LM disease or the additional impact of LVEF <30%. Even so, the current descriptors based on simple measures of angiographic disease burden and LVEF remain applicable and of relevance to general cardiology practice. It is highly likely that many of the lesions used to define VD in this study may not have been physiologically significant if assessed by fractional flow reserve, although all patients had clinically accepted documentation of ischemia by exercise electrocardiography or stress imaging or had convincing symptoms of ongoing ischemia. Thus, the results might be considered to be "diluted" by inclusion of physiologically nonsignificant lesions. In consideration of this possibility, it is even more remarkable that the simple parameters of LVEF and coronary disease burden retain prognostic impact. Finally, PCI during the COURAGE trial was predominantly performed using bare-metal stents with a higher restenosis rate than seen with more current stents. Even so, the end points analyzed in this study (death, MI, NSTE-ACS) have not been shown to be altered by restenosis rates.

In conclusion, angiographic burden of coronary disease and LVEF retain prognostic importance even during contemporary therapy and reflect residual risk for secondary ischemic events. These simple variables help identify patients most in need of newer therapeutic approaches.

Individual disclosures

G. B. John Mancini: Honoraria from Merck Canada, AstraZeneca; Consulting fees from Sanofi-Aventis, GlaxoSmithKline, Amgen
Pamela Hartigan: None
Eric Bates: None
Bernard R. Chaitman: None
Steven P. Sedlis: None
David J. Maron: None
William J. Kostuk: None
John A. Spertus: Grants from Lilly, Genentech, EvaHeart, Gilead; Consulting Fees from Genentech, Amgen, St Jude Medical
Koon K. Teo: None
Marcin Dada: None
Merril Knudtson: None
Daniel S. Berman: None
David C. Booth: None
William E. Boden: None
William S. Weintraub: None

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