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An Invasive or Conservative Strategy in Patients With Diabetes Mellitus and Non–ST-Segment Elevation Acute Coronary Syndromes

A Collaborative Meta-Analysis of Randomized Trials

Michelle L. O'Donoghue, MD, MPH,* Ajay Vaidya, MD, MPH,† Rizwan Afsal, MSc,‡ Joakim Alfredsson, MD, PhD,§ William E. Boden, MD,‖ Eugene Braunwald, MD,* Christopher P. Cannon, MD,* Tim C. Clayton, MSc,¶ Robbert J. de Winter, MD, PhD,# Keith A. A. Fox, MB ChB,** Bo Lagerqvist, MD, PhD,†† Peter A. McCullough, MD, MPH,‡‡ Sabina A. Murphy, MPH,* Rudolf Spacek, MD, PhD,§§ Eva Swahn, MD, PhD,§ Fons Windhausen, MD,# Marc S. Sabatine, MD, MPH*

Boston, Massachusetts; San Francisco, California; Hamilton, Ontario, Canada; Linköping and Uppsala, Sweden; Albany, New York; London and Edinburgh, United Kingdom; Amsterdam, the Netherlands; Novi, Michigan; and Prague, Czech Republic

Objectives The purpose of this study was to conduct a meta-analysis to examine an invasive or conservative strategy in diabetic versus nondiabetic patients.

Background Diabetic patients are at increased risk of cardiovascular events after an acute coronary syndrome, yet it remains unknown whether they derive enhanced benefit from an invasive strategy.

Methods Randomized trials comparing an invasive versus conservative treatment strategy were identified. The prevalence of cardiovascular events through 12 months was reported for each trial, stratified by diabetes mellitus status and randomized treatment strategy. Relative risk (RR) ratios and absolute risk reductions were combined using random-effects models.

Results Data were combined across 9 trials comprising 9,904 subjects of whom 1,789 (18.1%) had diabetes mellitus. The RRs for death, nonfatal myocardial infarction (MI), or rehospitalization with an acute coronary syndrome for an invasive versus conservative strategy were similar between diabetic patients (RR: 0.87; 95% confidence interval [CI]: 0.73 to 1.03) and nondiabetic patients (RR: 0.86; 95% CI: 0.70 to 1.06; p interaction = 0.83). An invasive strategy reduced nonfatal MI in diabetic patients (RR: 0.71; 95% CI: 0.55 to 0.92), but not in nondiabetic patients (RR: 0.98; 95% CI: 0.74 to 1.29; p interaction = 0.09). The absolute risk reduction in MI with an invasive strategy was greater in diabetic than nondiabetic patients (absolute risk reduction: 3.7% vs. 0.1%; p interaction = 0.02). There were no differences in death or stroke between groups (p interactions 0.68 and 0.20, respectively).

Conclusions An early invasive strategy yielded similar RR reductions in overall cardiovascular events in diabetic and nondiabetic patients. However, an invasive strategy appeared to reduce recurrent nonfatal MI to a greater extent in diabetic patients. These data support the updated guidelines that recommend an invasive strategy for patients with diabetes mellitus and non–ST-segment elevation acute coronary syndromes. (J Am Coll Cardiol 2012;60:106–11)

From the *TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts; †Cardiovascular Division, University of California, San Francisco, San Francisco, California; ‡Department of Medicine, Hamilton Health Sciences, McMaster University, Hamilton, Ontario, Canada; §Department of Cardiology, Department of Medical and Health Sciences, Faculty of Health Sciences, Linköping University, University Hospital, Linköping, Sweden; ‖Department of Medicine, Albany Stratton VA Medical Center, Albany, New York; ¶London School of Hygiene and Tropical Medicine, London, United Kingdom; #Academic Medical Center, Amsterdam, the Netherlands; **University and Royal Infirmary of Edinburgh, Edinburgh, United Kingdom; ††Uppsala University Hospital, Uppsala, Sweden; ‡‡St. John Providence Health System Providence Park Heart Institute, Novi, Michigan; and the §§3rd Medical Faculty Prague, Prague, Czech

Clinical practice guidelines recommend an invasive strategy in patients with non–ST-segment elevation (NSTE) acute coronary syndromes (ACS) who have high-risk features (1,2). Although individuals with diabetes mellitus (DM) are at increased risk of recurrent cardiovascular events, they also have a higher prevalence of concurrent disease states that may place them at increased risk of complications after coronary angiography or revascularization (3,4). As such, the relative benefit of an invasive strategy in this patient population with its associated comorbid conditions remains unknown.

The updated European Society of Cardiology and American College of Cardiology/American Heart Association guidelines have now included DM on the list of characteristics for which an invasive strategy is preferred (1,2). However, the evidence to support this decision is currently restricted to subgroup analyses presented from 2 trials (5,6). Because individual trials have been underpowered to examine subgroups, we conducted a collaborative meta-analysis to examine the benefit of an invasive strategy in diabetic and nondiabetic patients with NSTE-ACS.

Methods

A total of 18 randomized clinical trials were identified through literature review, and 9 were subsequently excluded for prespecified criteria (Online Fig. 1). Nine remaining trials were determined to be eligible and agreed to participate (Table 1).

The incidence of 12-month cardiovascular outcomes was provided from each trial team in tabular format, stratified by DM status. A diagnosis of DM was determined at the baseline visit and captured on the case report forms. Data were further substratified by the presence or absence of biomarker elevation (creatine kinase–myocardial band or troponin) or ST-segment deviation. Biomarker analyses were restricted to those trials that enrolled patients both with and without biomarker elevation.

Statistical analyses. A meta-analysis was performed using random-effects models stratified by DM status, using the method by DerSimonian and Laird (7). Effect modification was assessed by calculating the interaction term between treatment strategy and subgroup for each individual trial, combining these interaction terms in a random-effects model, and then testing the significance of the combined interaction estimate. Heterogeneity across trials was determined using the Cochran Q statistic (Online Appendix). All statistical analyses were performed by using Stata/SE version 9.0 (StataCorp, College Station, Texas). All tests were 2-sided, with $p < 0.05$ considered significant.

Abbreviations and Acronyms

ACS = acute coronary syndrome
CI = confidence interval
DM = diabetes mellitus
NSTE = non–ST-segment elevation
MI = myocardial infarction
OR = odds ratio
RR = relative risk

Results

Across the 9 selected trials, DM status and outcome data were available for a total of 9,904 patients. Of these patients, 1,789 (18.1%) were recorded to have a diagnosis of DM at the time of their baseline visit. Overall, patients with DM tended to be older and were more likely to be female, have hypertension, hyperlipidemia, and a history of MI than non-diabetic patients (Online Table 1). Subjects with DM had more extensive coronary artery disease on angiography, including a higher prevalence of 3-vessel or left main coronary artery disease (48% vs. 31%; $p < 0.001$). In the invasive arm, the frequency of revascularization was similar between groups (67.8% vs. 66.0%; $p = 0.31$); however, diabetic patients were more likely to have undergone coronary artery bypass graft surgery (31.9% vs. 25.9%; $p < 0.001$).

During 12 months of follow-up, the triple composite endpoint of incidence of death, MI, or rehospitalization with ACS was 30.5% in diabetic patients versus 20.3% in nondiabetic patients ($p < 0.001$). Patients with DM had nearly a 3-fold higher rate of death (9.3% vs. 3.2%; $p < 0.001$), and a higher rate of nonfatal MI (11.3% vs. 7.1%;

Table 1 Characteristics of Trials in the Meta-Analysis*

Trial Name	Year of Publication	N	Proportions of Subjects With DM, %	In-Hospital Rate of Angiography in the Conservative Arm, %
TIMI IIIB	1994	782	14.6	57
MATE	1998	201	17.9	60
VANQWISH	1998	919	26.1	23
FRISC II†	1999	2,457	12.2	10
TACTICS–TIMI 18‡	2001	2,220	27.6	51
VINO	2002	131	23.7	12
RITA 3	2002	1,810	13.5	16
ICTUS	2005	1,200	13.8	53
OASIS-5 Substudy	2012	184	25.0	40

*References and full trial names are included in the Online Appendix. †For the FRISC II trial, data on rehospitalization with acute coronary syndromes were available for subjects enrolled in Denmark and Sweden, representing 97% of the study population. ‡For the TACTICS–TIMI 18 trial, data were available through 6 months.
DM = diabetes mellitus.

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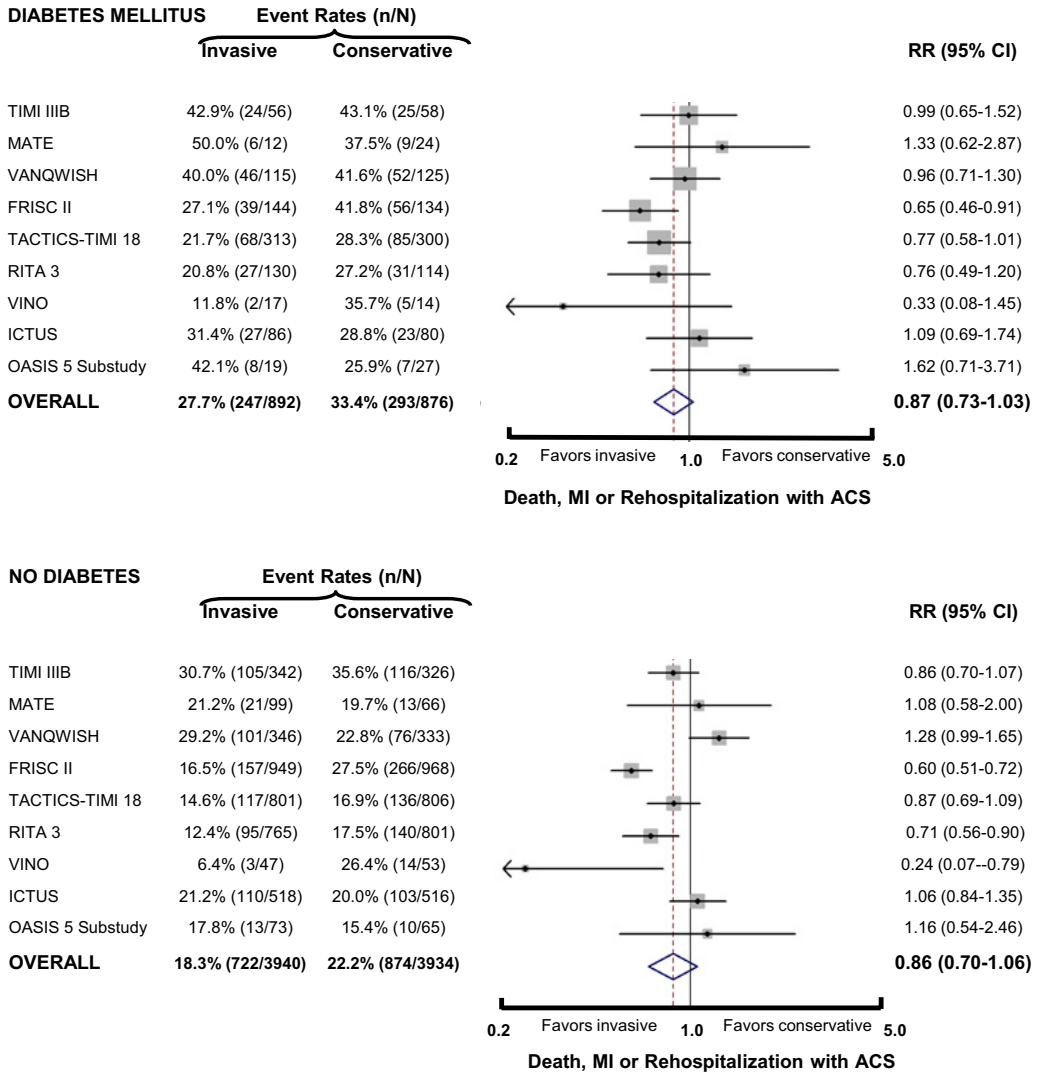

Figure 1 **Benefit of an Invasive Strategy by Diabetes Mellitus Status**

The relative risk (RR) of death, myocardial infarction (MI), or rehospitalization with acute coronary syndrome (ACS) with an invasive versus conservative treatment strategy stratified by the presence **(top)** or absence **(bottom)** of diabetes mellitus. Number of subjects in denominators reflects those with ascertainment for the composite endpoint. CI = confidence interval. References and full trial names are included in the Online Appendix.

$p < 0.001$) and rehospitalization with ACS (18.1% vs. 13.0%; $p < 0.001$) compared with nondiabetic patients.

DM status and clinical outcomes. An invasive strategy was associated with a comparable relative reduction in death, MI, or rehospitalization with ACS in patients with DM (relative risk [RR]: 0.87; 95% confidence interval [CI]: 0.73 to 1.03) or without DM (RR: 0.86; 95% CI: 0.70 to 1.06; p interaction = 0.83) (Fig. 1). In terms of the absolute benefit of an invasive strategy, the absolute risk reduction was 5.1% in diabetic patients compared with 3.2% in nondiabetic patients for the triple composite endpoint (p interaction = 0.24) (Table 2).

There tended to be a greater relative reduction in nonfatal MI in diabetic patients managed with an invasive strategy (RR: 0.71; 95% CI: 0.55 to 0.92) compared with nondiabetic patients (RR: 0.98; 95% CI: 0.74 to 1.29; p interaction = 0.09). Moreover, the absolute reduction in nonfatal MI risk with an invasive strategy was greater in diabetic than nondiabetic patients (absolute risk reduction: 3.7% vs. 0.1%; p interaction = 0.02) (Table 2).

An invasive strategy significantly reduced the risk of rehospitalization with ACS by 25% in patients with and without DM (p interaction = 0.68). By contrast, an invasive strategy did not reduce the RR of death in either diabetic or nondiabetic patients (p interaction = 0.87) (Table 2).

Timing of events. An early hazard of cardiovascular events before hospital discharge was observed for patients randomized to an invasive strategy compared with a conservative

Table 2 Pooled 12-Month Event Numbers, RR (95% CI), and ARR (95% CI) for an Invasive Versus Conservative Treatment Strategy, Stratified by DM Status

Endpoint	DM Status	Invasive Strategy	Conservative Strategy	RR (95% CI)	ARR (95% CI)
Death, MI, or rehospitalization with ACS	DM	247/892	293/876	0.87 (0.73–1.03)	5.1% (0.1% to 10.2%)
	No DM	722/3,940	874/3,934	0.86 (0.70–1.06)	3.2% (−0.9% to 7.4%)
Death or MI	DM	162/903	184/886	0.89 (0.68–1.16)	2.2% (−3.4% to 7.9%)
	No DM	401/4,058	406/4,057	1.04 (0.79–1.37)	0.1% (−3.0% to 2.8%)
Death	DM	85/903	82/886	1.01 (0.70–1.45)	−0.4% (−4.1% to 3.2%)
	No DM	130/4,058	128/4,057	1.00 (0.68–1.48)	−0.1% (−1.4% to 1.3%)
Nonfatal MI	DM	84/903	119/886	0.71 (0.55–0.92)	3.7% (1.1% to 6.3%)
	No DM	280/4,058	294/4,057	0.98 (0.74–1.29)	0.1% (−1.7% to 1.9%)
Rehospitalization with ACS	DM	135/892	185/876	0.75 (0.61–0.92)	5.6% (2.2% to 9.1%)
	No DM	422/3,940	599/3,934	0.75 (0.61–0.93)	3.3% (0.4% to 6.2%)

Values are n/N unless otherwise indicated. Number of subjects in denominators reflects those with ascertainment for the composite endpoint. Interaction testing for the RR between diabetic and nondiabetic patients: death/MI/ACS, p interaction = 0.83; death/MI, p interaction = 0.33; death, p interaction = 0.87; nonfatal MI, p interaction = 0.09; rehospitalization with ACS, p interaction = 0.68). ARR interaction testing: death/MI/ACS, p interaction = 0.24; death/MI, p interaction = 0.27; death, p interaction = 0.77; nonfatal MI, p interaction = 0.02; rehospitalization with ACS, p interaction = 0.20.
ACS = acute coronary syndrome(s); ARR = absolute risk reduction; CI = confidence interval; DM = diabetes mellitus; MI = myocardial infarction; RR = relative risk.

strategy. This early hazard was similar in both diabetic (RR: 1.27; 95% CI: 0.85 to 1.88) and nondiabetic (RR: 1.38; 95% CI: 0.99 to 1.92) patients (p interaction = 0.80). After hospital discharge, a similar trend toward a reduction in death or MI was seen in both diabetic (RR: 0.78; 95% CI: 0.57 to 1.08) and nondiabetic (RR: 0.77; 95% CI: 0.55 to 1.07) patients (p interaction = 0.72).

Biomarkers and additional predictors of risk. Subjects with DM had a comparable reduction in death or MI with an invasive strategy regardless of whether they also had elevated biomarkers (creatine kinase–myocardial band or troponin; p interaction = 0.65). Similarly, the presence or absence of ST-segment deviation did not appear to further identify those patients with DM who derived a greater benefit from an invasive strategy (p interaction = 0.83).

In contrast, among nondiabetic patients, elevated biomarkers identified those individuals with a greater benefit from an invasive strategy (RR: 0.68; 95% CI: 0.55 to 0.84), whereas there was no apparent benefit from an invasive strategy in patients who were nondiabetic and biomarker negative (RR: 1.17; 95% CI: 0.89 to 1.54; p interaction = 0.006). Correspondingly, the absolute risk reduction in death or MI with an invasive strategy was 3.7% in nondiabetic patients with elevated biomarkers compared with an absolute increase in death or MI of 0.8% in patients without biomarker elevation (p interaction = 0.001). The presence or absence of ST-segment deviation did not discriminate those with benefit from an invasive strategy among nondiabetic patients (p interaction = 0.14).

Figure 2 highlights the relative utility of DM status, cardiac biomarkers, and ST-segment deviation for helping to identify those individuals with a greater benefit with an invasive strategy.

Discussion

The findings of this collaborative meta-analysis suggest that a diagnosis of DM helps to identify an important subset of individuals at increased risk of adverse outcomes who may benefit more from an invasive strategy after NSTE-ACS. For nondiabetic individuals, additional high-risk features such as cardiac biomarker elevation are required to help identify those who benefit from an invasive approach. These data provide new evidence to support the updated European Society of Cardiology and American College of Cardiology/American Heart Association guidelines, which now recommend an invasive strategy for high-risk patients with NSTE-ACS, including those with DM (1,2).

Although individuals with DM are at increased risk of adverse outcomes after ACS (8,9), they also have a higher prevalence of comorbid conditions that may place them at greater risk of complications after coronary angiography or revascularization. In particular, patients with DM have a higher prevalence of hypertension, obesity, heart failure, stroke, and impaired renal function (8). To that end, patients with DM have been shown to be at increased risk of short- and long-term complications, including death and major adverse cardiovascular events, after percutaneous coronary intervention (3) and coronary artery bypass graft surgery compared with nondiabetic patients (4).

To date, only 2 substudies of randomized trials have examined the benefit of an invasive strategy in diabetic patients. In the FRISC II (Fragmin and Fast Revascularisation During Instability in Coronary Artery Disease) trial, patients with DM had a comparable reduction in death or MI (odds ratio [OR]: 0.61; 95% CI: 0.36 to 1.04) at 1 year compared with nondiabetic patients (OR: 0.72; 95% CI: 0.54 to 0.95) (6). Similarly, in TACTICS–TIMI 18 (Treat Angina with Aggrastat and Determine Cost of Therapy With an Invasive or Conservative Strategy–Thrombolysis in Myocardial Infarction 18), an invasive strategy reduced the risk of death, MI, or rehospitalization with ACS to a similar extent in diabetic patients (OR: 0.66; 95% CI: 0.46 to 0.96) and nondiabetic patients (OR: 0.84; 95% CI: 0.64 to 1.11), although in both of these trials, there was a trend toward a greater benefit in diabetic individuals (5). In the main ICTUS (Invasive Versus Conservative Treatment in Unstable Coro-

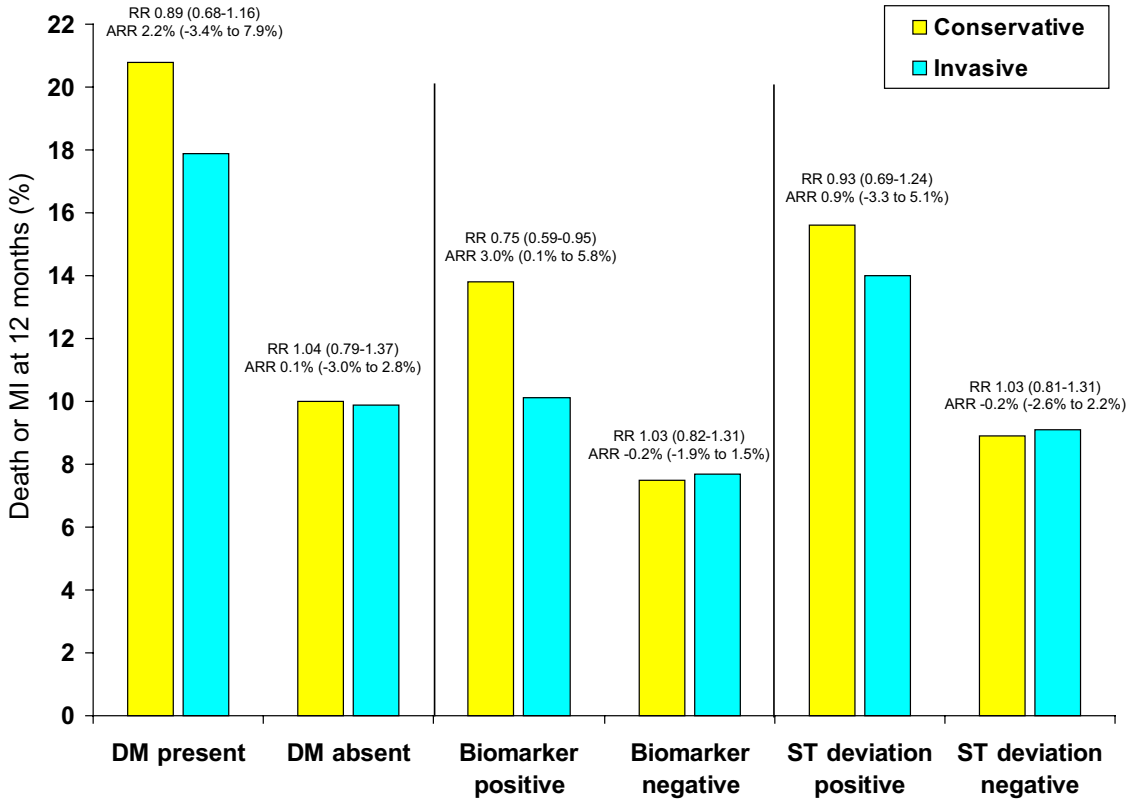

Figure 2 **Benefit of an Invasive Strategy by High-Risk Subgroup**

The relative benefit of an invasive versus conservative strategy in high-risk groups, including patients with diabetes mellitus (DM), elevated biomarkers (creatine kinase-myocardial band or troponin) or ST-segment deviation on electrocardiography. The bar graph displays the overall pooled incidence of death or MI at 12 months by subgroup and treatment arm. Relative risk (RR) (95% confidence interval [CI]) and absolute risk reduction (ARR) (95% CI) are also shown. RR and ARR calculations were derived from random-effects models. Abbreviations as in Figure 1.

nary Syndromes) publication, both diabetic and nondiabetic patients appeared to have a similar trend that favored a conservative (or selective invasive) strategy (10). Although there was no heterogeneity regarding treatment benefit, individual trials have been underpowered to detect an interaction between subgroups.

In the current meta-analysis, we found that patients with DM had a benefit from an invasive strategy at least comparable to that seen in nondiabetic individuals. Importantly, our findings demonstrate that an invasive strategy significantly reduced the risk of nonfatal MI in patients with DM (RR: 0.71; 95% CI: 0.55 to 0.92), whereas there was less apparent benefit in nondiabetic subjects (RR: 0.98; 95% CI: 0.74 to 1.29; p interaction = 0.09). In terms of absolute benefit, the number of nonfatal MIs prevented with an invasive strategy over 1 year per 1,000 diabetic patients was 37 compared with only 1 nonfatal MI prevented per 1,000 patients without DM. Among all nondiabetic patients, an invasive strategy did not reduce the risk of death or MI (RR: 1.04; 95% CI: 0.79 to 1.37) in the absence of high-risk features. However, the presence of elevated biomarkers was highly effective at risk-stratifying those nondiabetic patients who could derive a significant benefit from an invasive approach.

Study limitations. As with any meta-analysis, limitations to the methodology included heterogeneity among trials and the possibility of publication bias. There may have been misclassification of patients regarding their DM status. Other factors correlated with diabetes might partially explain some of the observed differences. However, as recognized by the American College of Cardiology/American Heart Association, DM offers an easily ascertained and validated risk factor. Tests for interactions between subgroups were conservative and may have missed a true interaction when one existed. As well, patient-level data were not available, and therefore it was not possible to explore individual-level covariates. Importantly, effect modification was assessed at the level of each individual trial; therefore, differences across trials should not bias the results. Moreover, the results of the current meta-analysis were qualitatively consistent over time and did not change when the earliest 3 trials were excluded from the analysis.

Conclusions

In summary, this is the first large-scale collaborative meta-analysis to examine the effect of an invasive strategy between diabetic and nondiabetic patients with NSTE-ACS. By examining outcomes for >9,900 patients, we were able to demonstrate that a routine invasive strategy significantly reduced the 1-year incidence of MI and rehospitalization with ACS in diabetic patients. In contrast, in nondiabetic individuals, elevated cardiac biomarkers were an important discriminator to help identify those who derived benefit from a routine invasive approach. These findings suggest that specific high-risk features such as DM and cardiac biomarkers are useful to help identify those individuals who will benefit from an invasive approach in NSTE-ACS.

Reprint requests and correspondence: Dr. Michelle L. O'Donoghue, Cardiovascular Division, Brigham and Women's Hospital, TIMI Study Group, 350 Longwood Avenue, 1st Floor, Boston, Massachusetts 02115. E-mail: modonoghue@partners.org.

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Key Words: conservative strategy ■ diabetes mellitus ■ invasive strategy ■ meta-analysis.

APPENDIX

For supplemental material, please see online version of this article.