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Outcomes after Multivessel or Culprit-Vessel Intervention for ST-Elevation Myocardial Infarction in Patients With Multivessel Coronary Disease: A Bayesian Cross-Design Meta-Analysis

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Introduction: During primary percutaneous coronary intervention (PCI), patients with ST-elevation myocardial infarction (STEMI) and multivessel coronary disease can undergo either multivessel intervention (MVI) or culprit-vessel intervention (CVI) only. Background: Randomized controlled trials (RCTs) support the use of MVI, but cohort studies support the use of CVI. Methods: We developed Bayesian models that incorporated parameters for study type and study outcome after MVI or CVI. Results: A total of 18 studies (4 RCTs, 3 matched cohort studies, and 11 unmatched observational studies) enrolled 48,398 patients with STEMI and multivessel CAD and reported outcomes after MVI or CVI-only at the time of primary PCI. Using a Bayesian hierarchical model, we found that the point estimates replicated previously reported trends, but the wide Bayesian credible intervals (BCI) excluded any plausible mortality difference between MVI versus CVI in all three study types: RCTs (odds ratio [OR] 0.60, 95% BCI 0.31–1.20), matched cohort studies (OR 1.37, 95% BCI 0.86–2.24), or unmatched cohort studies (OR 1.16, 95% BCI 0.70–1.89). Both the global summary (OR 1.10, 95% BCI 0.74–1.51) and a sensitivity analysis that weighted the RCTs 1–5 times as much as observational studies revealed no credible advantage of one PCI strategy over the other (OR 1.05, 95% BCI 0.64–1.48). Conclusions: Bayesian approaches contextualize the comparison of different strategies by study type and suggest that neither MVI nor CVI emerges as a preferred strategy in an analysis that accounts mortality differences.

Key words: myocardial infarction; randomized trials; percutaneous coronary intervention

INTRODUCTION

Primary percutaneous coronary intervention (PCI) has been a major advance for the treatment of patients with ST-elevation myocardial infarction (STEMI), but the approach to PCI in patients with STEMI and multivessel coronary artery disease (CAD) remains uncertain. It is not clear whether such patients should have all severe stenoses treated during the initial procedure with multivessel intervention (MVI), or whether they should have culprit-vessel intervention (CVI) only. The current knowledge base provides no clear answer, because randomized clinical trials (RCTs) tend to

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The project was conceived while Yulei He was at Harvard Medical School. The findings and conclusions in this paper are those of the author and do not necessarily represent the official position of the National Center for Health Statistics.

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support MVI, whereas observational studies tend to support CVI. As a result, the guidelines from the major cardiac societies vary [1,2], as do the conclusions of several meta-analyses [3,4].

Achieving consensus about PCI strategies for STEMI is challenging because evidence comes from different sources. RCTs are commonly accepted as the "gold standard" for clinical investigation, whereas observational data help to measure the true effectiveness of a treatment within a broader population. Although traditional statistical methods using a stratified meta-analysis can allow studies of different designs to be analyzed separately, a Bayesian cross-design synthesis may compensate for seeming weaknesses of some types of studies and generalize the results for the broader population by pooling evidence from different sources to identify the true treatment effect, which is conditional on both study outcome and study design [5]. The current analysis created a Bayesian hierarchical model to incorporate prior judgments about the relative strengths of different sources of evidence in order to study the relative merits of MVI versus CVI-only for STEMI.

METHODS

Studies

We identified 18 studies [6–23] that met criteria for review. Studies were included if they were: (1) either a RCT of any size, or an observational study containing more than 25 patients per treatment arm, (2) were published in a peer reviewed journal, and (3) reported mortality rates for patients undergoing either MVI or CVI-only at the time of primary PCI. Studies were excluded if they did not separate primary MVI from staged MVI. Two investigators (JAB and JETH) independently abstracted mortality data from study publications. Study outcomes were analyzed according to study type: RCT, matched cohort study, or unmatched retrospective observational study.

Traditional Meta-analysis

To illustrate the effect of MVI and CVI on mortality rates, we used conventional statistical methods to create forest plots. We preferred a random-effects model, because it acknowledges the existence of between-study variation that may arise from heterogeneity in study design.

Bayesian Models

To emulate the random-effects model with a Bayesian approach (Supporting Information Appendix), we used hierarchical meta-analysis and non-informative (i.e., vague) priors so that the posterior inference would be dominated by the likelihood of the data [5,24].

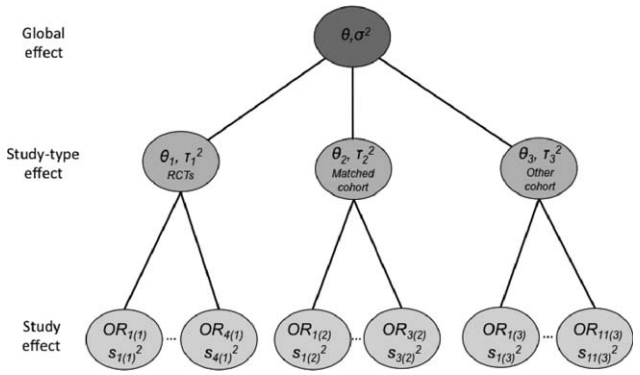

Fig. 1. Hierarchical Model. The parameters include $OR_{i(k)}$ and variances s^2 from each study *i*, the mean study-type effects θ_i and variances τ^2 from each study type *k*, and the global treatment effect θ and its variance σ^2. Abbreviation: RCT indicates randomized controlled trial.

To incorporate prior beliefs about the qualitative differences among the various sources of study heterogeneity, we made the assumption of exchangeability [5,25]. This was based on the reasonable postulation that the trials had fundamental similarities and that the "true" treatment effect θ_i for the ith trial was a random quantity drawn from a population distribution [5]. A three-level hierarchical structure (Fig. 1) modeled the global treatment effect θ according to study outcome and study type (i.e., RCT vs. matched cohort vs. unmatched observational study). We let i refer to the study and k refer to the study type (i is nested within k), for which we assigned $k=1$ for RCTs, $k=2$ for matched cohort studies, and $k=3$ for other unmatched observational studies [24].

Sensitivity Analysis

Many clinical investigators value the results of RCTs more than the results of non-randomized or retrospective studies. Using a Bayesian model, we were able to arbitrarily attach greater weight to the precision of the RCTs than to the precision of the observational studies. The approach involves using a new parameter called the "evidence ratio" (i.e., relative weight) to attach a smaller σ_1^2 and thus a larger weight to the study effect θ_1 from the RCTs than to the study effects θ_2 or θ_3 from the observational studies. If we define the weighting factor for RCTs compared with matched cohort studies as $\alpha_2 = \sigma_2^2/\sigma_1^2$ and the weighting factor for RCTs compared with unmatched observational studies as $\alpha_3 = \sigma_3^2/\sigma_1^2$, we can impose prior distributions on α_2 and α_3 to artificially affect the evidence ratio across different study types. For example, if $\alpha_2 \sim$ Half-Normal[2, 0.5^2],* it implies that evidence

*The half-normal distribution arises from folding a normal distribution around 0 [5].

TABLE I. Mortality After Multivessel or Culprit-Vessel Percutaneous Coronary Intervention (PCI) Performed at the Time of ST-Elevation Myocardial Infarction in the Presence of Multivessel Disease

			Number enrolled		Number with events		
Study	Year of report	Follow-up (days)	Multivessel	Culprit	Multivessel	Culprit	Study type
Randomized controlled trials							
Di Mario et al. [6]	2004	365	52	17	1	0	1
Politi et al. [7]	2010	900	65	84	6	13	1
Wald et al. [8]	2013	700	234	231	12	16	1
Gershlick et al. [9]	2015	365	150	146	4	10	1
Total			**501**	**478**	**23**	**39**	
Matched cohort studies							
Roe et al. [10]	2001	180	79	79	19	13	2
Hannan et al. [11]	2010	1260	503	503	59	54	2
Iqbal et al. [12]	2014	365	403	2,418	41	164	2
Total			**985**	**3,000**	**119**	**231**	
Other observational studies							
Corpus et al. [13]	2004	365	26	354	5	42	3
Qarawani et al. [14]	2008	365	95	25	9	2	3
Varani et al. [15]	2008	In-hospital	147	156	12	8	3
Cavender et al. [16]	2009	In-hospital	3,134	25,802	246	1,321	3
Dziewerz et al. [17]	2010	365	70	707	11	57	3
Toma et al. [18]	2010	90	217	1,984	27	111	3
Bauer et al. [19]	2013	In-hospital	419	2,118	6	72	3
Jaguszewski et al. [20]	2013	In-hospital	1,108	3,833	81	168	3
Jeger et al. [21]	2014	365	442	1,467	12	40	3
Santos et al. [22]	2014	in-hospital	77	180	2	14	3
Manari et al. [23]	2014	730	367	706	26	127	3
Total observational studies			**6,102**	**37,322**	**437**	**1,962**	
TOTAL			**7,588**	**40,810**	**579**	**2,232**	

Study types, 1 = randomized controlled trial, 2 = matched cohort study, 3 = other type of observational study.

from randomized studies is likely to be valued two times as highly as that of matched cohort studies, but they could be valued as much as 3 ($2 + 0.5 \times 2$) times more or just equally valued at 1 ($2 - 2 \times 0.5$). Similarly if $\alpha_3 \sim$ Half-Normal[1,3], it implies that evidence from RCTs is likely to be valued three times as highly as that of unmatched cohort studies, but they could be as much as 5 ($3 + 1 \times 2$) times more or just equally valued at 1 ($5 - 2 \times 2$).

Statistical Methods

All analyses were performed with [R] 3.0.2 [26], using the library package "BRugs" [27], and Markov chain Monte Carlo methods based on Bayesian Inference Using Gibbs Sampling [5,28,29]. Standard meta-analysis was performed in [R] using the library package "meta" 3.8-0 [30]. Sample codes for all analyses are attached (Supporting Information Appendix).

RESULTS

Studies

The evidence base comparing MVI with CVI for patients with STEMI and multivessel CAD arose from 18 studies of different designs: 4 RCTs, 3 matched cohort studies, and 11 general cohort studies, enrolling a total of 48,398 patients (Table I).

RCTs. A pooled analysis of results from four RCTs (Table I) suggested that the mortality rate at longest follow-up was nominally lower after MVI (23/501 [4.6%]) than it was after CVI (39/478 [8.2%]). Judged from both the traditional random-effects model (odds ratio [OR] 0.59, 95% confidence interval [CI] 0.35–1.02) and the Bayesian hierarchical meta-analysis using a non-informative prior distribution (posterior median OR 0.60, 95% Bayesian credible interval [BCI] 0.31–1.20), patients treated with MVI in RCTs had mortality rates no different from those treated with CVI alone (Fig. 2).

Retrospective matched cohort studies. A pooled analysis of results from three matched cohort studies (Table I) suggested that the mortality rate at longest follow-up after MVI (119/985 [12.1%]) was higher than it was after CVI (221/3000 [7.7%]). The traditional statistical approach (OR 1.36, 95% CI 1.06–1.74) suggested that patients treated with MVI had higher mortality rates than those treated with CVI (Fig. 2). On the other hand, the Bayesian model suggested that patients with MVI in matched cohort studies had mortality rates no different from those treated with CVI (OR 1.37, 95% BCI 0.86–2.24).

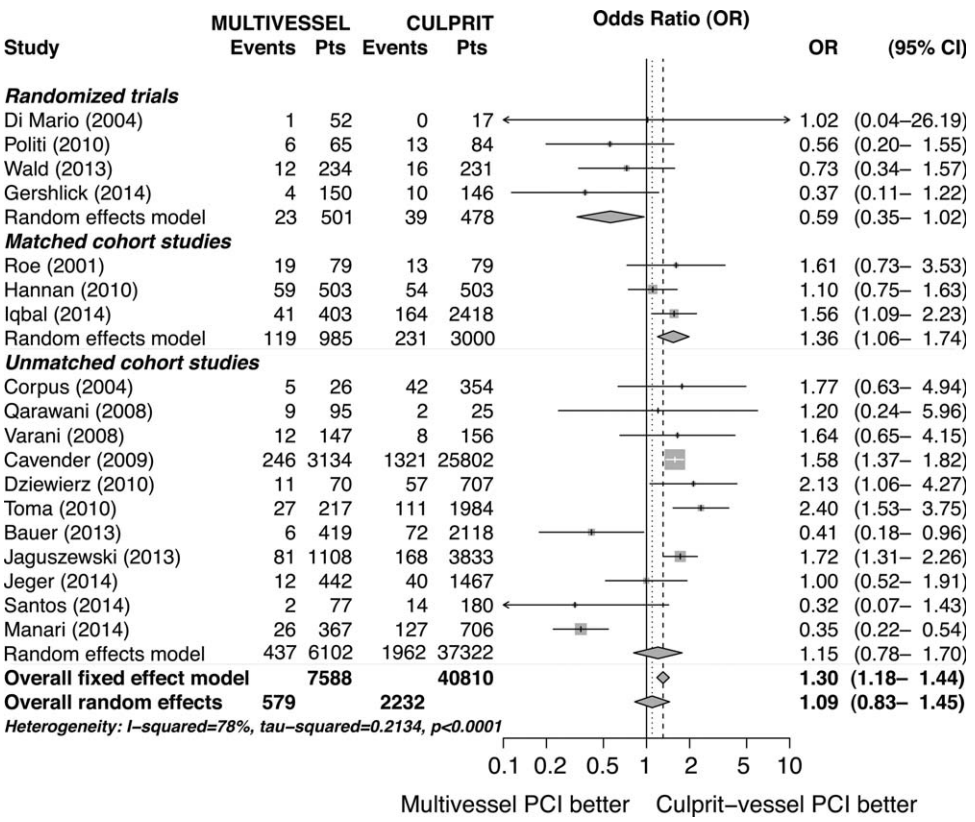

Fig. 2. Forest Plot comparing mortality rates at longest follow-up after treatment with multivessel or culprit-vessel percutaneous coronary intervention performed at the time of the index procedure in the presence of multivessel coronary artery disease. Abbreviations: CI indicates confidence interval; PCI, percutaneous coronary intervention; and Pts, patients.

Other retrospective observational studies. A pooled analysis of results from 11 unmatched observational studies (Table I) showed that the mortality rate after MVI (437/6102 [7.2%]) was nominally higher than that after CVI (1962/37322 [5.3%]). Both the classical (OR 1.15, 95% CI 0.78–1.70) and the Bayesian (OR 1.16, 95% BCI 0.70–1.89) analyses suggested that patients with MVI in unmatched observational studies had mortality rates no different from those treated with CVI (Fig. 2).

Bayesian cross-design analysis. Using a Bayesian cross-design model that incorporated parameters corresponding to study outcome and study type (Fig. 3), we obtained a global summary finding with no difference in mortality rates after MVI or CVI (OR 1.10, 95% BCI 0.74–1.51). In other words, an analysis that accounted for both study result and study type found no plausible treatment difference between MVI and CVI in the entire evidence base of 18 studies.

Sensitivity analyses. An attractive feature of the cross-design model was that it included explicit parameters at the study level, which permitted incorporation of prior judgments about study type through algebraic constraints. Weighting RCTs over observational studies by a factor that ranged from 1 to 5 (Fig. 4) produced an estimate for the posterior median OR closer to 1.00 (1.05, 95% BCI 0.64–1.48) and thus attenuated the nominal advantage favoring the strategy of CVI-only seen in the unadjusted model (OR = 1.10).

DISCUSSION

Several reports have evaluated the role of MVI in patients with STEMI and multivessel CAD. The studies have generated variable conclusions, with some showing a benefit for MVI and others suggesting harm. The variable conclusions of the various studies have posed challenges for the writing committees of the major cardiac societies to use deductive reasoning and intuitive thinking and create clinical practice guidelines [31]. The writing committee for the American College of Cardiology Foundation and American Heart Association (ACCF/AHA) concluded that, "PCI should not be

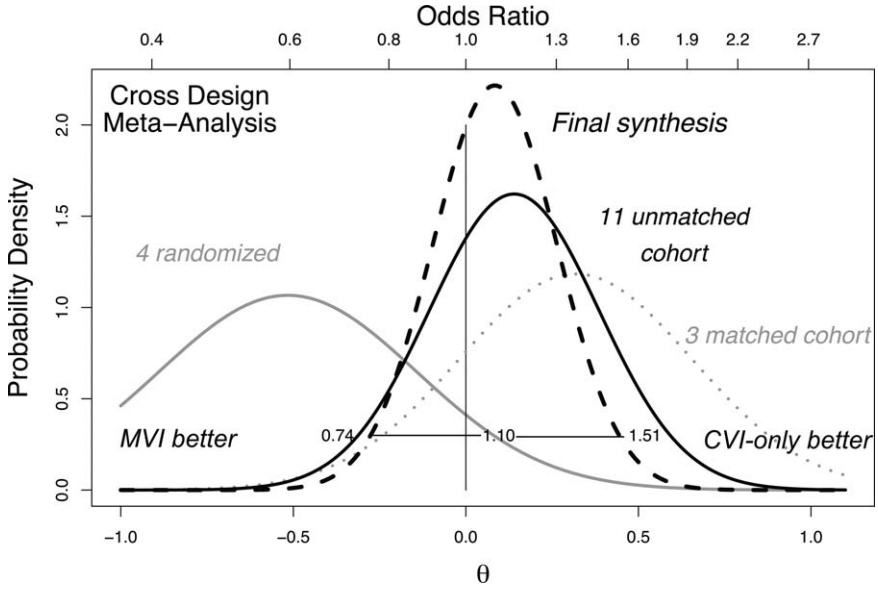

Fig. 3. Bayesian cross-design meta-analysis of study results and study types. In this illustration, information sources segregated by study type are plotted on the familiar OR scale as well on the θ scale, which is equivalent to $\log_e$(OR). The strength of the information from each source is indicated by the narrowness of its curve, with narrower curves excluding more parameter values than wider curves and thus representing stronger sources of information. Data from randomized control trials (gray), which are represented by a bell-shaped curve to show the distribution of all possible ORs based on evidence from four trials, provide weak evidence favoring the strategy of MVI. Data from the three matched cohort studies (dotted gray) favor the strategy of CVI, whereas data from the 11 general unmatched observational studies (black) provide weak evidence favoring the strategy of CVI-only. The final synthesis (dotted black), which combines the data from all 18 studies and generates the posterior median odds ratio and 95% BCI (data labels), suggests no plausible difference in mortality rates after a strategy of MVI or CVI-only at the time of primary intervention. The final synthesis is not three times the height of the other curves, because precision is additive, not curve height. All curves are normalized to 1.

performed in a non-infarct artery at the time of primary PCI in patients without hemodynamic compromise (class III Harm, Level of Evidence: B)" [32], largely based on the results of observational studies demonstrating a worse outcome after MVI than after CVI. However, observational studies are confounded and cannot control for the natural inclination of clinicians to treat sicker patients more intensively.

The writing committee for the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery (ESC/EACTS) concluded that, "Immediate revascularization of significant non-culprit lesions during the same procedure as primary PCI of the culprit vessel may be considered in selected patients (class IIb, Level of Evidence: B)" [2]. This recommendation followed the report of a small RCT demonstrating more favorable outcomes with MVI [9].

The current analysis, which incorporates an approach for analyzing evidence by study type and study result, affirmed several established findings and made new observations. First, a traditional frequentist meta-analysis stratified by study type confirmed the observation that RCTs tended to favor the use of MVI, and that retrospective or observational studies tended to favor the use of CVI-only at the time of primary PCI for STEMI in the presence of multivessel CAD. Second, the use of a Bayesian approach, which related the underlying treatment effect both to the study design and study result, generated a global summary suggesting no credible difference in mortality rates at longest follow-up after MVI or CVI. This implies that the decision between MVI and CVI in patients with STEMI and multivessel CAD should be individualized. Some patients may benefit from MVI while others would do just as well (or better) with CVI. The possible benefits or risks of MVI will depend on several circumstances at the time of the primary PCI, and will vary among patients.

A potential benefit of MVI includes stabilization of all potentially unstable plaques. Angiographic studies indicate that ~40% of patients with myocardial infarction have multiple complex plaques [33,34]. In an autopsy series of 100 patients, Davies and Thomas [35] observed 115 separate thrombi in 74 patients and concluded that the majority of patients who die within 6 hr of MI have "one or more rapidly developing arterial lesions." Thus, in patients with more than one culprit

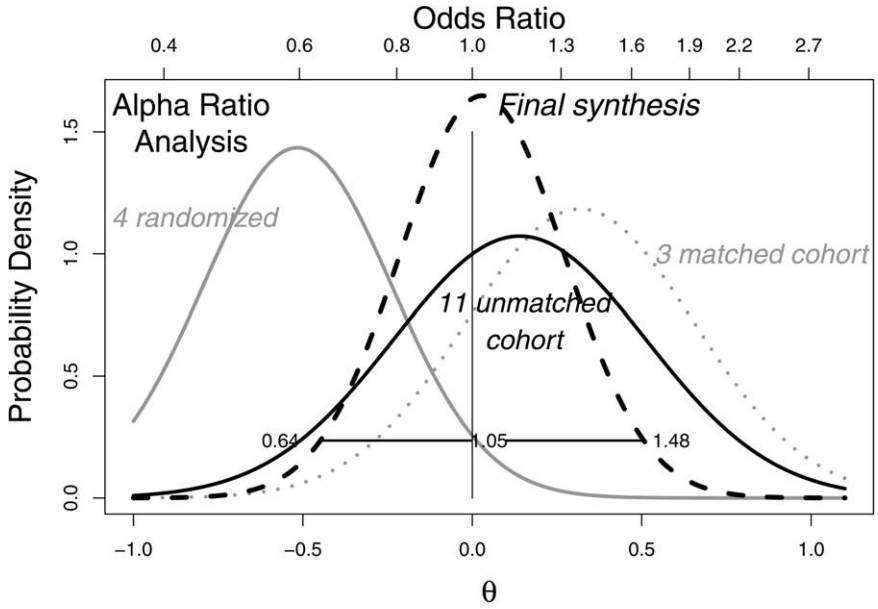

Fig. 4. Triplot of study type, with evidence from RCTs weighted 1- to 5-fold. The evidence from four RCTs (gray) has been weighted 1–5 times more than the evidence from other sources. Data from the 3 matched cohort studies (dotted gray) and data from the 11 general unmatched observational studies (black) remain unweighted. The final synthesis (dotted black), which combines the data from all sources and generates the posterior median odds ratio and 95% BCI (data labels), suggests no credible difference in mortality rates after MVI or CVI only.

lesion, a strategy of MVI may result in a more complete revascularization of unstable plaques and decrease the risk for recurrent ischemic events.

Another theoretical benefit of MVI includes improvement in non-infarct zone regional wall motion. Studies have shown that patients with STEMI have enhanced regional wall motion in the non-infarct zone, but this is attenuated in the presence of multivessel CAD and associated with an increased mortality [36]. The ability of MVI to improve wall motion in the non-infarct zone might be especially important in those patients with severely compromised LV function or ongoing congestive heart failure.

In the setting of an acute myocardial infarction, angiographic studies have reported diminished coronary blood flow in the non-culprit vessel as compared with the flow seen in the same vessel at a time remote from the infarction [37]. PCI of these vessels improve flow to the non-culprit vessel and to the culprit vessel as well [37]. Lastly, as a logistic advantage, MVI offers a convenient single-setting approach to PCI to decrease the likelihood of future visits to the catheterization laboratory. This would likely be the preferred option for the majority of patients.

As a counterargument, MVI may not be the ideal choice for all patients. Concerns about MVI include the potential for severe hemodynamic impairment from a complication of non-culprit vessel PCI. Such complications would be poorly tolerated in a patient during the acute phase of STEMI. Although the strategy of MVI is associated with an increased use of contrast dye and increased rates of contrast-induced nephropathy, this was apparently not seen in RCTs [8,9] but remains a concern in patients with chronic kidney disease.

Another argument against MVI entails the potential risk of over-utilization. The severity of a stenosis in the non-infarct artery is often over-estimated during infarct angiography. About 20% of patients with lesions felt to be "significant" at the time of the initial infarct angiogram are found to have non-significant disease in the non-infarct artery on a follow-up elective angiogram [38]. If MVI is performed at the time of the index infarction, some patients will have had PCI of a lesion that would have been deemed to be insignificant on follow-up angiography.

Overall, the results of the current analysis support a position of equipoise and suggest that the decision between MVI and CVI must be individualized. A tailored approach already seems to have adopted in contemporary practice. Despite guidelines that have discouraged its use, the strategy of MVI has been used in a significant proportion of patients undergoing primary PCI. In HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction), 18.5% of patients underwent multivessel PCI but only 1.5% had cardiogenic shock [39]. In the

New York State Registry, 12.5% underwent multivessel PCI, but only 4.4% met the definitions of hemodynamic compromise [11]. This implies that many clinicians are choosing to perform MVI based on individual circumstances. In making the choice to proceed with MVI, the physician must weigh the risk of procedure-related complications versus the risk recurrent ischemia or hemodynamic compromise, based on such considerations as lesion complexity in non-culprit vessels, contrast load, procedural time, and fatigue among the cardiac catheterization laboratory staff.

Limitations

One must be cautious in interpreting the results of a cross-design analysis, balancing the desire to make use of all available evidence with the acknowledgment of potential weaknesses [5]. Careful sensitivity analyses are vital, and perhaps one reason for the limited uptake of cross-design meta-analyses is that they are not seen as "clean" methods, with each analysis being context-specific [5].

However, Bayesian inference is similar to the diagnostic process. Good clinicians know that an elevated troponin does not always equate with myocardial infarction. Clinical investigators recognize that a study result, given as an OR from comparing treatment *A* with treatment *B*, does not automatically reflect the true underlying treatment difference. Bayesian cross-design methods integrate study results to provide a coherent synthesis of evidence across study types.

CONCLUSIONS

In the current context, neither MVI nor CVI has emerged as a preferred strategy in an analysis that accounts for study type and mortality differences. Bayesian approaches have advantages over traditional statistical approaches and suggest that the choice between MVI and CVI in patients with STEMI and multivessel CAD should be individualized. This conclusion requires validation in prospective clinical trials.

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