Title

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Journal

Circulation Cardiovascular Interventions, 14(8)

ISSN

1941-7640

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Publication Date

2021-08-01

DOI

10.1161/circinterventions.120.010323

Peer reviewed

HHS Public Access

Author manuscript

Circ Cardiovasc Interv. Author manuscript; available in PMC 2022 August 10.

Published in final edited form as:

Circ Cardiovasc Interv. 2021 August ; 14(8): e010323. doi:10.1161/CIRCINTERVENTIONS.120.010323.

Comparative Outcomes of PCI for ST-Segment Elevation Myocardial Infarction among Medicare Beneficiaries with Multivessel Coronary Artery Disease: An NCDR R2P Project

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Supplemental Material:
Supplemental Figures I-IV
Supplemental Tables I-VIII

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Abstract

Background: Prior studies on the use of multivessel percutaneous coronary intervention (MV PCI) for patients with STEMI and multivessel coronary artery disease have yielded heterogeneous results. The recent COMPLETE trial demonstrated that MV PCI was superior to culprit-only PCI among patients with STEMI. It is unclear how these trial results apply to clinical decisions encountered in routine practice.

Methods: We studied STEMI admissions among patients >65 years with multivessel disease and CMS-linked data in the NCDR CathPCI Registry® from 7/1/2009–12/31/2017. MV PCI was defined as PCI to a non-culprit lesion ≤45 days of the index procedure. The primary outcome was the composite of death, myocardial infarction, and revascularization from 45 days through 1 year. To account for unmeasured confounders, an instrumental variable analysis (IVA) was used to compare treatment strategies. The instrument was institutional rates of MV PCI. A falsification endpoint of post-discharge major bleeding was utilized to assess for residual confounding.

Results: Of 56,332 admissions from 1,102 institutions, 37.7% received MV PCI ≤45 days of index STEMI PCI. Of those undergoing MV PCI, 74.8% received complete revascularization. In unadjusted analysis, MV PCI was associated with a lower cumulative incidence of the composite outcome between 45 days and 1 year (13.9% vs 18.2% for non-MV PCI, p<0.01). In the IVA, there was no association between MV PCI and the composite outcome (adjusted risk difference [RD] −0.97%; 95%CI −3.52%, 1.59%; p=0.46). An association between MV PCI and the falsification endpoint of major bleeding was not observed (RD −2.54%; 95%CI −5.30%, 0.22%; p=0.07).

Conclusions: In this large, nationwide analysis, we did not find benefit of MV PCI by 1 year among older STEMI patients. The clinical benefit of MV PCI may not extend equally outside of trials to include all patients, including those with more extreme ages and more complex decision making.

Keywords

multivessel coronary artery disease; multivessel percutaneous coronary intervention; death; elderly

Subject Terms

Catheter-Based Coronary and Valvular Interventions; Mortality/Survival

Introduction

Among patients presenting with ST-segment myocardial infarction (STEMI), over half have multivessel disease.[1] As the mortality rate is higher in these patients, there has been an ongoing debate about the use of multivessel percutaneous coronary intervention (MV PCI), a procedure in which severe non-infarct related arteries (IRAs) are intervened upon during the index procedure or in a staged fashion. Advocates of complete revascularization argue

that non-IRA lesions may also be biologically active,[2] and if not intervened upon, leave the patient vulnerable to a subsequent event. Opponents argue that these lesions are more likely "innocent bystanders" and should be treated similarly to those seen in stable ischemic heart disease.[3]

Prior evidence supporting the use of MV PCI in STEMI has been mixed.[4–6] While some earlier studies showed higher mortality with MV PCI compared to IRA only revascularization, others showed a reduction in composite long-term outcomes, though this was driven largely by a reduction in repeat revascularization.[7–12] More recently, the COMPLETE trial involving 4,041 patients found that complete revascularization of all severe non-IRA lesions within 45 days of presentation was superior to culprit-lesion-only PCI in reducing the risk of the composite of cardiovascular death, ischemia-driven revascularization, or myocardial infarction (MI).[13]

The relevance of the COMPLETE trial and previous RCTs to clinical decisions encountered in routine practice is unclear. For instance, most studies excluded patients with complex non-IRA disease, such as chronic total occlusions, left main disease, and disease meeting surgical bypass criteria,[7–10] which is common among those with multivessel disease.[1, 14] In addition, elderly patients, which make up a large portion of the STEMI population, are often not enrolled in RCTs[15]. Although the COMPLETE trial did include patients over the age of 65, this only consisted of 1,613 patients, less than half of the trial's population.[13]

Contemporary registries can assist with applying RCT results in real-world clinical practice.[16–18] As a part of the ACC R2P (Research to Practice) Initiative,[19] we used data from the National Cardiovascular Data Registry (NCDR) CathPCI Registry® to evaluate the comparative effectiveness of MV PCI at 1 year in a broad, unselected population of Medicare patients using an instrumental variable analysis.

Methods

The authors declare that all supporting data are available within the article and its online supplementary files.

Study population

We analyzed data from 7/1/2009 through 12/31/2017 in the NCDR CathPCI Registry® linked to data from the Centers for Medicare and Medicaid Services (CMS).[17, 20] The NCDR CathPCI Registry is a national quality improvement program that collects in-hospital data on patients undergoing PCI.[21] We included all admissions of patients >65 years in which patients received primary PCI for the indication of STEMI ≤12 hours of presentation or PCI ≤24 hours of thrombolysis, and had multivessel disease. Patients were allowed to contribute multiple STEMI admissions as long as each event was ≥1 year from any prior event. Multivessel disease was defined as ≥1 non-IRA lesion in a major epicardial vessel ≥2.5mm in diameter that was distinct from the culprit vessel with ≥50% diameter stenosis by visual estimation for the left main coronary artery or ≥70% diameter stenosis by visual estimation for all other major epicardial vessels. We excluded admissions from hospitals that only performed STEMI PCI or with <10 eligible admissions throughout the study

period, admissions of patients with planned surgical revascularization or prior coronary artery bypass grafting, and admissions associated with cardiogenic shock at the start of PCI. We additionally excluded patients who did not survive to 45 days from the index PCI to allow for staged out-of-hospital procedures, while avoiding immortal time bias.[22, 23]

Exposure

The primary exposure was MV PCI, defined as the placement of coronary stents to ≥2 major epicardial vessels during the index procedure, or the staged placement of a coronary stent to a major epicardial vessel distinct from the index culprit vessel within 45 days of the index PCI. Post-discharge PCI characteristics were ascertained from CathPCI Registry® data.

Variables

All patient, procedural and hospital characteristics, and in-hospital outcomes were evaluated among the total population from CathPCI Registry® version 4.4 (eTable I).[24]

Outcomes

The primary outcome was a composite of death, readmission for MI, or readmission for revascularization between 45 days and 1 year. Secondary outcomes included the individual components of the coprimary outcome, as well as rehospitalization between 45 days and 1 year for unstable angina or HF. Validated claims-based coding algorithms used to define these endpoints can be found in eTable II.[25] As an evaluation of residual unmeasured confounding, we included a falsification endpoint of readmission for major bleeding between 45 days to 1 year.[26, 27] This was chosen as major bleeding would unlikely differ as a consequence of the MV PCI, particularly as all patients had an indication for 1 year of dual antiplatelet therapy due to STEMI PCI, and bleeding was not significantly different between treatment groups in the COMPLETE trial.[13] All endpoints were landmarked at 45 days to allow the inclusion of staged procedures in the MV PCI group without introducing immortal time bias.[22, 23] As such, during the 45 day window, patients could only accrue an exposure to MV PCI. If a death occurred in either group, these patients were not included in the outcome analysis. Furthermore, if an endpoint occurred, this was censored and did not contribute to the outcome analysis.

Statistical Analysis

We compared baseline characteristics among patients who received MV PCI versus those who did not receive MV PCI. Categorical variables were reported as counts and percentages and continuous variables as means and standard deviations. Given the large sample size, standardized differences (SDs) were reported, with a threshold of ≥10% to define a clinically meaningful difference.[28]

We then evaluated the association of MV PCI on long-term outcomes. We performed an instrumental variable analysis with each institution's proportional use of MV PCI as the instrument. When the proper assumptions are met, the instrumental variable categorizes patients into treatment groups independent of patient characteristics.[29] The instrumental variable analysis compares patients and outcomes according to the likelihood of receiving the treatment of interest (i.e. MV PCI) rather than the actual treatment received. It therefore

estimates the treatment effect on the "marginal" population, defined as patients who would receive MV PCI if presenting at institutions with higher MV PCI rates, but would receive culprit-only PCI if presenting at institutions with lower MV PCI rates.[30] The marginal population does not include the group of individuals who would likely receive MV PCI at all institutions, as well as those patients who would never receive MV PCI at any institution. The effect estimate therefore is applicable to those individuals who could be considered to have clinical equipoise based on prevailing practice patterns. We *a priori* designated this as the primary analytic approach due to the non-randomized treatment assignment and concern that patients who were healthier, less frail, and without complex coronary disease would preferentially undergo MV PCI, thus confounding an analysis using traditional regression-based methods.

For the instrument, we used each hospital's proportion use of MV PCI for the entire study period among all patients presenting with STEMI and with multivessel disease. We chose not to account for time as a function of the instrument, as institutions that used either high or low MV PCI were consistent in their practice throughout the study period (eFigure I). We used the 2-stage least squares methodology, which involves the construction of 2 sequential linear regression models.[31] The first stage model generated predicted probabilities of an individual patient's likelihood of receiving MV PCI based on the institution's proportional use of MV PCI, while adjusting for all clinical, procedural, and institutional characteristics as listed in eTable I. The 2nd stage model used the predicted probabilities of MV PCI use from the 1st stage model as the primary predictor and the endpoints of the study as outcomes, again adjusted by the same covariates. The coefficient for the instrumental variable represents the absolute adjusted risk difference of the primary outcome, and is used to summarize the treatment effect. We did not model MV PCI as a time-dependent variable to minimize complexity of the IV analysis, and instead chose to use a landmark analysis to account for the potential impact of immortal time bias[22].

To assess the strength of the instrument, we used the F-test, with a value <10 suggestive of a weak instrument.[29] To assess the exogeneity of the instrument (i.e. the ability of the instrument to predict treatment irrespective of patient characteristics), we compared patient and procedural characteristics, in-hospital outcomes, and discharge prescriptions of guideline-recommended therapies among quintiles of institutions with increasing use of MV PCI. We also examined temporal changes in MV PCI use among the highest and lowest hospital quintiles to assure that any changes in MV PCI use over time were equally distributed across institutions. Finally, to evaluate our hypothesis using more traditional statistical approaches, we created multivariable-adjusted cumulative incidence regression models to examine the association between MV PCI and outcomes (including the falsification endpoint), adjusted for all patient, procedural and institutional characteristics (eTable I). Fine and Gray competing risk regression models were constructed for all outcomes except for death, for which we used a traditional multivariable-adjusted Cox regression model.

Sensitivity Analyses

We performed multiple sensitivity analyses of the instrumental variable analysis. First, we evaluated the influence of complete revascularization of all diseased vessels on the study endpoints. In this analysis, the instrument was institutional use of complete revascularization by 45 days. Complete revascularization was defined as treatment of every major epicardial vessel ≥2.5mm in diameter with ≥50% diameter stenosis by visual estimation for the left main coronary artery or ≥70% diameter stenosis by visual estimation for all other major epicardial vessels. The same instrumental variable approach was used as performed in the primary analysis. Second, we evaluated a shorter landmark period of 15 days in place of 45 days. Finally, we evaluated the IVA results after exclusion of procedures in which the non-culprit artery was treated at the same time as the culprit artery.

A two-sided p-value <0.05 was considered statistically significant without adjustment for multiple comparisons. All analyses were performed using SAS 9.4 (Cary, NC, USA). This study was approved by the Advarra Institutional Review Board. Dr. Secemsky and Dr. Yeh had full access to all the data in the study and take responsibility for its integrity and the data analysis.

Results

Patient and Procedural Characteristics

Among the study population, 56,332 admissions at 1,102 hospitals were included in the analysis (eFigure II). MV PCI was performed in 37.7% (N=21,254) within 45 days after index STEMI PCI. Of those receiving MV PCI, 27.4% (N=5,829) were performed during the index procedure, 30.7% (N=6,528) were performed as a staged procedure during the index hospitalization but after the index procedure, and 41.9% (N=8,897) were performed after discharge from the index procedure within 45 days. Of those undergoing MV PCI, 74.8% received complete revascularization.

The average age of the population was 74.8±7.5 years, with a range from 65 to 104 years and a 99th percentile of 94 years. Baseline characteristics were overall similar between admissions of patients who received MV PCI and those who did not, except those who did not receive MV PCI were slightly older (75.2±7.7 years vs 74.2±7.2 years for MV PCI, SD 12.3) (Table 1). Procedural characteristics were also balanced between groups, with the exception of the IRA (right coronary artery less likely in MV PCI), stent type (drug-eluting stent more likely in MV PCI), and number of diseased vessels (≥2 vessels more likely in MV PCI). There were no significant differences of in-hospital outcomes between groups, or discharge medical therapy from the index admission. Procedural characteristics of the staged PCI were overall similar to the index PCI (eTable III).

Variation in Characteristics by Institutional Use of MV PCI

Hospital use of MV PCI varied widely (eFigure III). The median hospital use of MV PCI was 36.8%, with an interquartile range of 27.6% - 46.4% and a full range of 0% - 92.3%. When hospitals were stratified by quintiles of increasing use of MV PCI, the median use in the lowest quintile was 18.8%, and in the highest quintile was 56.8%. Despite the

wide variation in hospital use of MV PCI, baseline demographic, clinical, and procedural characteristics were largely balanced between quintiles (eTable IV). The prescription of guideline-recommended therapy at discharge from the index PCI and in-hospital outcomes did not differ between hospital quintiles of MV PCI use, suggesting no major differences in the quality of institutions. Hospitals with greater use of MV PCI had expectedly greater annual PCI volumes, but annual STEMI volumes were comparable between hospitals in the lowest and highest quintiles of MV PCI use (eTable V). High MV PCI institutions were more often located in the Midwest and rural settings, and were more often affiliated with teaching institutions.

Unadjusted Outcomes

In unadjusted analysis, MV PCI was associated with a lower cumulative incidence of the composite endpoint of death, MI, or repeat revascularization between 45 days and 1 year (13.9% vs 18.2% for non-MV PCI; hazard ratio [HR] 0.74, 95% confidence interval [CI] 0.71–0.78, p<0.01) (Table 2; Figure 1). Additionally, MV PCI was associated with a lower cumulative incidence of death (5.1% vs 7.3% for non-MV PCI; HR 0.70, 95%CI 0.65–0.75, p<0.01), repeat revascularization (4.8% vs 7.6% for non-MV PCI; HR 0.63, 95%CI 0.58–0.68, p<0.01), and heart failure (11.7% vs 14.2% for non-MV PCI; HR 0.82, 95%CI 0.78–0.86, p<0.01), but not MI (5.0% vs 5.3% for non-MV PCI; HR 0.93, 95%CI 0.86–1.01, p=0.08) or unstable angina (0.4% vs 0.5% for non-MV PCI; HR 0.89, 95%CI 0.69–1.15, p=0.37) (Figures 1 & 2). MV PCI was also associated with a lower incidence of the falsification endpoint, major bleeding (17.5% vs 21.2% for non-MV PCI; HR 0.81, 95%CI 0.78–0.84, p<0.01), suggesting confounding.

Instrumental Variable Outcomes

The stage one F-statistic for evaluating the strength of the IV was 3,475, suggesting that hospital proportion of MV PCI use was a strong instrument for predicting patient treatment with MV PCI. In the instrumental variables analysis, MV PCI was not associated with a difference in the rate of the composite endpoint of death, MI, or repeat revascularization between 45 days and 1 year (adjusted risk difference [RD] −0.97%; 95%CI −3.52%, 1.59%; p=0.46) (Table 2). Additionally, MV PCI use was not associated with death (RD −0.21%; 95%CI −1.96%, 1.55%; p=0.82), MI (RD 0.47%; 95%CI −1.11%, 2.04%; p=0.56), repeat revascularization (RD −1.12%; 95%CI −2.88%, 0.64%; p=0.21), unstable angina (RD 0.08%; 95%CI −0.42%, 0.58%; p=0.74), or HF (95%CI −4.43%, 0.23%; p=0.08). The falsification endpoint of major bleeding was not associated with receipt of MV PCI (RD −2.54%; 95%CI −5.30%, 0.22%; p=0.07), suggesting that the impact of residual confounding was negligible.

Multivariable-Adjusted Regression Outcomes

The associations between MV PCI and the primary and secondary endpoints observed in unadjusted analyses persisted in the multivariable-adjusted cumulative incidence regression models, which adjusted for all patient, procedural and institutional characteristics (Table 2; eTable I). Multivessel PCI remained associated with a lower incidence of the falsification endpoint of major bleeding in the multivariable-adjusted analysis (HR 0.88, 95%CI 0.85–0.93, p<0.01), indicative of residual confounding.

Sensitivity Analyses

Similar to MV PCI, hospital use of complete revascularization varied widely across institutions, with a median use of 27.7%, an interquartile range of 20.0% - 36.5%, and a full range of 0% - 100% (eFigure IV). Baseline characteristics for the cohort were again well-balanced across hospitals with increasing use of complete revascularization (eTables VI–VII). The stage one F-statistic for evaluating the strength of the IV was 2,884, again suggesting that hospital proportion of complete revascularization use was a strong instrument.

Among patients that received complete revascularization, similar outcomes were found as compared with the primary analysis (eTable VIII). In the instrumental variable analysis, there was again no evidence of reduction of any of the endpoints with complete revascularization, apart from a lower rate of heart failure admissions (RD −3.03%; 95%CI −5.52%, −0.54%; p=0.02). Consistent with the primary analysis, the falsification endpoint of major bleeding was non-significantly different in the instrumental variable analysis, yet significant in the unadjusted and multivariate-adjusted regression analyses.

In additional sensitivity analyses, when the landmark period was reduced to 15 days, there remained no association between MV PCI and death or MI (RD 0.40%, 95%CI −2.52, 3.32; p=0.79). Furthermore, after excluding procedures in which the non-culprit lesion was treated at the same time as the culprit lesion, there remained no relationship between MV PCI and death, MI, or repeat revascularization (RD 4.03%, 95%CI −10.18, 2.13; p=0.20).

Discussion

In this large observational analysis of Medicare beneficiaries with multivessel disease and STEMI without cardiogenic shock between 2009 and 2017, we did not find an association between MV PCI and the composite of death, MI, or repeat revascularization between 45 days and 1 year in the primary instrumental variable analysis. Although we did see a signal for these endpoints in the unadjusted and multivariable-adjusted analyses, these results were likely confounded, as suggested by an association between MV PCI and the falsification endpoint (major bleeding). Additionally, unadjusted and multivariable-adjusted analyses showed a dramatic reduction in all-cause death without a significant reduction in MI, again suggestive of confounding given the lack of a clear mechanism by which MV PCI could influence all-cause mortality. The primary study results remained robust in sensitivity analyses, including examining the use of complete revascularization of all diseased vessels.

The COMPLETE trial demonstrated a consistent signal of benefit with MV PCI among a subgroup of patients >65 years, although the risk reduction associated with MV PCI was attenuated, in particular for the coprimary endpoint of death and MI[13].One reason why the results of our analysis differ from that of the COMPLETE trial may be due to the unselected population of older STEMI patients included in this study (mean age 75 years, upper age range 104 years). These older patients represent a large portion of the STEMI population, yet those rarely enrolled in randomized clinical trials[15]. For instance, in the COMPLETE trial, the average age of the randomized population was 62 years, with just under 40% of patients above the age of 65 years[13]. Patients were of similar age in other smaller

randomized trials, such as the Randomized Trial of Preventive Angioplasty in Myocardial Infarction (PRAMI)[7] and Complete revascularization versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI) trial.[9] This is of critical importance when applying trial results to clinical practice, as these elderly patients often present with more complex clinical scenarios where the benefits of non-culprit artery revascularization may not clearly outweigh associated risks. For instance, in an analysis examining in-hospital MV PCI alone among a cohort of elderly STEMI patients, there was evidence of harm associated with MV PCI by 30 days[12]. An ongoing randomized clinical trial of MV PCI among stable STEMI patients ≥65 years (SAFARI STEMI Trial; NCT02939976) will be critical in providing further evidence of the optimal treatment strategy for this patient population.

Although we did find an association between these endpoints and MV PCI in the unadjusted and multivariable adjusted analyses, these results were likely confounded, as suggested by an unexpected association between MV PCI and the falsification endpoint (major bleeding). Furthermore, unadjusted and multivariable analyses showed a reduction in all-cause mortality without a significant reduction in MI, again suggestive of confounding given the lack of clear mechanism by which MV PCI could influence all-cause mortality. We theorize that the differences between the multivariable adjusted and instrumental variable analyses are secondary to patients who carried risk factors not captured in the CathPCI registry that reduced their likelihood of undergoing additional PCI. For instance, frailty is closely linked with both a worse prognosis after acute myocardial infarction and adverse outcomes like bleeding[32, 33]. Traditional methods of adjustment are not able to account for differences in unmeasured variables like frailty; however, instrumental variable methods are in theory able to balance these characteristics between groups via the randomness of treatment assignment resulting from varying PCI practices across operators.

Another explanation of these seemingly discordant results from that of the COMPLETE trial may stem from differences in the types of estimates generated from randomized controlled trials relative to comparative effectiveness studies using instrumental variable analyses among unselected patient populations. The results of the COMPLETE trial represent the effect of MV PCI on the average person across the selected trial population (i.e. the average treatment effect). In contrast, instrumental variable analyses estimate the “local average treatment effect,” or the effect of MV PCI on the group of patients with STEMI and multivessel disease who could receive either culprit-only or MV PCI depending on the prevailing practice patterns at the treating institution.[34] Patients who would likely receive MV PCI regardless of the institution they presented to (for example, a patient with an acute right coronary artery occlusion along with a 95% proximal left anterior descending stenosis) would not contribute to the estimation of the local average treatment effect in an instrumental variable analysis. However, this patient would influence the average treatment effect if randomized in a clinical trial.

This concept is highlighted in a recent sub-analysis of the COMPLETE trial examining non-culprit lesion severity of 3,851 patients by quantitative coronary angiography (QCA)[35]. Patents with non-culprit lesions of <60% stenosis by QCA experienced no reduction in cardiovascular death or MI with MV PCI, whereas those with non-culprit lesions of ≥60%

stenosis by QCA did. The instrumental variable analysis presented in this manuscript provides treatment effect estimates for those patients for whom there might be clinical equipoise, with some physicians choosing to pursue further revascularization and others opting for medical therapy. This may be representative of patients in COMPLETE with less severe lesions by QCA. On the other hand, the average treatment effect of the COMPLETE trial includes all non-culprit lesions, irrespective of QCA severity, and represents the main trial results that found a benefit associated with MV PCI. If the types of patients who most benefited from MV PCI in the COMPLETE trial (i.e. lesions with QCA ≥60% severity) already receive MV PCI at the vast majority of centers in contemporary US practice, then further increases in MV PCI use may provide less benefit than might otherwise be expected based on the positive results of the COMPLETE trial.

Our analysis should be interpreted in the context of its limitations. First, the analysis of outcomes was landmarked at 45 days in order to allow for staged PCIs and avoid the introduction of immortal time bias.[22, 23] However, in doing so, the study may have selected for a healthier elderly population. Although there are alternative methods to account for immortal time bias besides landmark analyses, such as time-varying covariates, these methods are challenging to apply in an IVA. Importantly, when the landmark period was reduced to 15 days, similar findings were observed in the IVA for death and MI. Second, we examined outcomes through 1 year, whereas the COMPLETE trial had follow-up that extended to a median of 3 years. As such, the benefit of MV PCI in our study may emerge with longer follow-up. Third, our data include PCIs from as early as 2009, and it is possible that different generations of drug-eluting stents were used and could have influenced outcomes. Fourth, our analysis included patients who underwent MV PCI during the index procedure, which was not allowed in the COMPLETE trial.[13] Nonetheless, similar to the COMPLETE trial, the majority of patients underwent MV PCI during the index admission. Finally, despite the use of an instrumental variable analysis, the possibility of residual confounding still exists due to the observational nature of our study, particularly if there were unmeasured differences between institutions performing higher versus lower rates of MV PCI. However, institutional characteristics were adjusted for in the instrumental variable analysis, and in-hospital outcomes did not differ between institutional quintiles of MV PCI use, suggesting similar PCI quality across institutions. Furthermore, the falsification endpoint was null in the instrumental variable analysis, which supports the validity of the key assumptions underlying the instrumental variable analysis.[27]

In conclusion, in this large, nationwide analysis, we did not find a benefit of MV PCI by 1 year among older STEMI patients without cardiogenic shock encountered in routine practice. These findings remained robust in sensitivity analyses, including among those who underwent complete revascularization of all diseased vessels. The clinical benefit of MV PCI may not extend equally outside of randomized controlled trials to include patients with more extreme ages and more complex decision making.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Sources of Funding:

This study was funded by the National Cardiovascular Data Registry (NCDR). Dr. Secemsky is funded in part by NIH/NHLBI K23HL150290.

Disclosures:

ES: Consulting/Speakers Bureau/Advisory Board: Bard, Cook, CSI, Janssen, Medtronic, Philips; Grants to Institution: AstraZeneca, Bard, Boston Scientific, Cook, CSI, Medtronic, Philips.

NB: Consulting: Hilabs, Ownership interest: Hilabs

AR: None

RK: None

YW: None

JPC: Dr. Curtis has a contract with the American College of Cardiology for his role as Senior Medical Officer, NCDR; receives salary support from the American College of Cardiology, NCDR; receives funding from the Centers for Medicare & Medicaid Services to develop and maintain performance measures that are used for public reporting; holds equity interest in Medtronic.

TM: Dr. Maddox discloses current grant funding from the NIH NCATS (1U24TR002306-01: A National Center for Digital Health Informatics Innovation), current consulting for Creative Educational Concepts, Inc. and Atheneum Partners, and honoraria and/or expense reimbursement in the past 3 years from the University of Utah (May 2017), New York Presbyterian (Sept 2017), Westchester Medical Center (Oct 2017), Sentara Heart Hospital (Dec 2018), the Henry Ford health system (March 2019), and the University of California San Diego (Jan 2020). He is currently employed as a cardiologist and the executive director of the Healthcare Innovation Lab at BJC HealthCare/Washington University School of Medicine. In this capacity, he is advising Myia Labs, for which his employer is receiving equity compensation in the company. He is receiving no individual compensation from the company. He is also a compensated director for a New Mexico-based foundation, the J.F Maddox Foundation.

SV: Research support: Department of Veterans Affairs, World Heart Federation, Tahir and Jooma Family. Honorarium: American College of Cardiology (Associate Editor for Innovations, acc.org). Steering Committee member: Patient and Provider Assessment of Lipid Management (PALM) registry at the Duke Clinical Research Institute (no financial remuneration).

EA: Dr. Armstrong disclosures consultant/advisory board for Abbott Vascular, Boston Scientific, Cardiovascular Systems, Gore, Intact Vascular, Medtronic, and Philips

KS: Dr. Shunk discloses institutional research support from Siemens Medical Systems, Medinol Ltd, Svelte Medical Systems, Cardiovascular Systems Inc, Boston Scientific and Regeneron Pharmaceuticals, Inc; consulting for Terumo, PercAssist and TransAortic Medical Inc.; and equity options in TransAortic Medical and PercAssist.

RB: Dr. Brindis has a contract with the American College of Cardiology for his role as Senior Medical Officer, NCDR

DB: Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, Medscape Cardiology, PhaseBio, PLx Pharma, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/

Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, Lexicon, Lilly, Medtronic, Pfizer, PhaseBio, PLx Pharma, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, Takeda.

RWH: Consulting/Scientific Advisory Board/Research Grants: Abbott Vascular, AstraZeneca, Boston Scientific, Medtronic. Research Grants: Bard, Cook, Philips

Non-standard Abbreviations and Acronyms:

CMS	Centers for Medicare and Medicaid Services
HR	Hazard Ratio
IRA	Infarct Related Artery
IVA	Instrumental Variable Analysis
MI	Myocardial Infarction
MV PCI	Multivessel Percutaneous Coronary Intervention
NCDR	National Cardiovascular Data Registry
QCA	Quantitative Coronary Angiography
R2P	Research to Practice
RD	Adjusted Risk Difference
SDs	Standardized Differences
STEMI	ST-Segment Elevation Myocardial Infarction

References

1. Park DW, Clare RM, Schulte PJ, Pieper KS, Shaw LK, Califf RM, Ohman EM, Van de Werf F, Hirji S, Harrington RA, et al.Extent, location, and clinical significance of non-infarct-related coronary artery disease among patients with ST-elevation myocardial infarction. Jama. 2014;312:2019–27. [PubMed: 25399277]
2. Goldstein JA, Demetriou D, Grines CL, Pica M, Shoukfeh M and O'Neill WW. Multiple complex coronary plaques in patients with acute myocardial infarction. N Engl J Med. 2000;343:915–22. [PubMed: 11006367]
3. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, et al.Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med. 2007;356:1503–16. [PubMed: 17387127]
4. Vlaar PJ, Mahmoud KD, Holmes DR Jr., van Valkenhoef, Hillege, van der Horst IC, Zijlstra F and de Smet BJ. Culprit vessel only versus multivessel and staged percutaneous coronary intervention for multivessel disease in patients presenting with ST-segment elevation myocardial infarction: a pairwise and network meta-analysis. J Am Coll Cardiol. 2011;58:692–703. [PubMed: 21816304]
5. Toma M, Buller CE, Westerhout CM, Fu Y, O'Neill WW, Holmes DR Jr., Hamm CW, Granger CB and Armstrong PW. Non-culprit coronary artery percutaneous coronary intervention during

acute ST-segment elevation myocardial infarction: insights from the APEX-AMI trial. Eur Heart J. 2010;31:1701–7. [PubMed: 20530505]

6. Hannan EL, Samadashvili Z, Walford G, Holmes DR Jr., Jacobs AK, Stamato NJ, Venditti FJ, Sharma S and King SB 3rd. Culprit vessel percutaneous coronary intervention versus multivessel and staged percutaneous coronary intervention for ST-segment elevation myocardial infarction patients with multivessel disease. JACC Cardiovasc Interv. 2010;3:22–31. [PubMed: 20129564]
7. Wald DS, Morris JK, Wald NJ, Chase AJ, Edwards RJ, Hughes LO, Berry C and Oldroyd KG. Randomized trial of preventive angioplasty in myocardial infarction. N Engl J Med. 2013;369:1115–23. [PubMed: 23991625]
8. Gershlick AH, Khan JN, Kelly DJ, Greenwood JP, Sasikaran T, Curzen N, Blackman DJ, Dalby M, Fairbrother KL, Banya W, et al.Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. J Am Coll Cardiol. 2015;65:963–72. [PubMed: 25766941]
9. Engstrom T, Kelbaek H, Helqvist S, Hofsten DE, Klovgaard L, Holmvang L, Jorgensen E, Pedersen F, Saunamaki K, Clemmensen P, et al.Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3-PRIMULTI): an open-label, randomised controlled trial. Lancet. 2015;386:665–71. [PubMed: 26347918]
10. Smits PC, Abdel-Wahab M, Neumann F-J, Boxma-de Klerk BM, Lunde K, Schotborgh CE, Piroth Z, Horak D, Wlodarczak A, Ong PJ, et al.Fractional Flow Reserve–Guided Multivessel Angioplasty in Myocardial Infarction. N Engl J Med. 2017;376:1234–1244. [PubMed: 28317428]
11. Cavender MA, Milford-Beland S, Roe MT, Peterson ED, Weintraub WS and Rao SV. Prevalence, Predictors, and In-Hospital Outcomes of Non-Infarct Artery Intervention During Primary Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction (from the National Cardiovascular Data Registry). Am J Cardiol. 2009;104:507–513. [PubMed: 19660603]
12. Wang TY, McCoy LA, Bhatt DL, Rao SV, Roe MT, Resnic FS, Cavender MA, Messenger JC and Peterson ED. Multivessel vs culprit-only percutaneous coronary intervention among patients 65 years or older with acute myocardial infarction. Am Heart J. 2016;172:9–18. [PubMed: 26856210]
13. Mehta SR, Wood DA, Storey RF, Mehran R, Bainey KR, Nguyen H, Meeks B, Di Pasquale G, Lopez-Sendon J, Faxon DP, et al.Complete Revascularization with Multivessel PCI for Myocardial Infarction. N Engl J Med. 2019;381:1411–1421. [PubMed: 31475795]
14. Claessen BE, van der Schaaf RJ, Verouden NJ, Stegenga NK, Engstrom AE, Sjauw KD, Kikkert WJ, Vis MM, Baan J Jr., Koch KT, et al.Evaluation of the effect of a concurrent chronic total occlusion on long-term mortality and left ventricular function in patients after primary percutaneous coronary intervention. JACC Cardiovasc Interv. 2009;2:1128–34. [PubMed: 19926056]
15. Nanna MG, Chen ST, Nelson AJ, Navar AM and Peterson ED. Representation of Older Adults in Cardiovascular Disease Trials Since the Inclusion Across the Lifespan Policy. JAMA Intern Med. 2020;180:1531–3. [PubMed: 32897289]
16. Secemsky EA, Butala N, Raja A, Khera R, Wang Y, Curtis JP, Maddox TM, Virani SS, Armstrong EJ, Shunk KA, et al.Temporal Changes and Institutional Variation in Use of Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction With Multivessel Coronary Artery Disease in the United States: An NCDR Research to Practice Project. JAMA Cardiol. 2020;6:574–580.
17. Secemsky EA, Ferro EG, Rao SV, Kirtane A, Tamez H, Zakroysky P, Wojdyla D, Bradley SM, Cohen DJ and Yeh RW. Association of Physician Variation in Use of Manual Aspiration Thrombectomy With Outcomes Following Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction: The National Cardiovascular Data Registry CathPCI Registry. JAMA Cardiol. 2019;4:110–118. [PubMed: 30624549]
18. Secemsky EA, Kirtane A, Bangalore S, Jovin IS, Shah RM, Ferro EG, Wimmer NJ, Roe M, Dai D, Mauri L and Yeh RW. Use and Effectiveness of Bivalirudin Versus Unfractionated Heparin for Percutaneous Coronary Intervention Among Patients With ST-Segment Elevation Myocardial Infarction in the United States. JACC Cardiovasc Interv. 2016;9:2376–2386. [PubMed: 27838271]

19. Maddox TM, Masoudi FA, Oetgen WJ and Rumsfeld JS. The Capacity of Evidence to Inform Practice: The Rapid Registry Response (RRR) Initiative. J Am Coll Cardiol. 2015;65:2252–3. [PubMed: 25998670]
20. Brennan JM, Peterson ED, Messenger JC, Rumsfeld JS, Weintraub WS, Anstrom KJ, Eisenstein EL, Milford-Beland S, Grau-Sepulveda MV, Booth ME, et al.Linking the National Cardiovascular Data Registry CathPCI Registry with Medicare claims data: validation of a longitudinal cohort of elderly patients undergoing cardiac catheterization. Circ Cardiovasc Qual Outcomes. 2012;5:134–40. [PubMed: 22253370]
21. Brindis RG, Fitzgerald S, Anderson HV, Shaw RE, Weintraub WS and Williams JF. The American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR): building a national clinical data repository. J Am Coll Cardiol. 2001;37:2240–5. [PubMed: 11419906]
22. Mi X, Hammill BG, Curtis LH, Lai EC and Setoguchi S. Use of the landmark method to address immortal person-time bias in comparative effectiveness research: a simulation study. Stat Med. 2016;35:4824–4836. [PubMed: 27350312]
23. Suissa SImmortal time bias in pharmaco-epidemiology. Am J Epidemiol. 2008;167:492–9. [PubMed: 18056625]
24. National Cardiovascular Data Registry. Data Elements & Definitions, Technology Downloads and Risk Adjustment. Available at: http://cvquality.acc.org/~/media/QII/NCDR/Data%20Collection%20Forms/CathPCI%20Registry_DataCollectionForm.ashx.Access Date:December 10, 2014.
25. Faridi KF, Tamez H, Butala NM, Song Y, Shen C, Secemsky EA, Mauri L, Curtis JP, Strom JB and Yeh RW. Comparability of Event Adjudication Versus Administrative Billing Claims for Outcome Ascertainment in the DAPT Study: Findings From the EXTEND-DAPT Study. Circ Cardiovasc Qual Outcomes. 2021;14:e006589. [PubMed: 33435731]
26. Wimmer NJ, Resnic FS, Mauri L, Matheny ME and Yeh RW. Comparison of transradial versus transfemoral percutaneous coronary intervention in routine practice: evidence for the importance of “falsification hypotheses” in observational studies of comparative effectiveness. J Am Coll Cardiol. 2013;62:2147–8. [PubMed: 23954334]
27. Pizer SD. Falsification Testing of Instrumental Variables Methods for Comparative Effectiveness Research. Health Serv Res. 2016;51:790–811. [PubMed: 26293167]
28. Austin PC. Using the Standardized Difference to Compare the Prevalence of a Binary Variable Between Two Groups in Observational Research. Communications in Statistics - Simulation and Computation. 2009;38:1228–1234.
29. Staiger DO and Stock JH. Instrumental variables regression with weak instruments. Econometrica. 1997;65:557–586.
30. Harris KM and Remler DK. Who is the marginal patient? Understanding instrumental variables estimates of treatment effects. Health Serv Res. 1998;33:1337–1360. [PubMed: 9865223]
31. Brookhart MA, Rassen JA and Schneeweiss S. Instrumental variable methods in comparative safety and effectiveness research. Pharmacoepidemiol Drug Saf. 2010;19:537–54. [PubMed: 20354968]
32. Damluji AA, Huang J, Bandeen-Roche K, Forman DE, Gerstenblith G, Moscucci M, Resar JR, Varadhan R, Walston JD and Segal JB. Frailty Among Older Adults With Acute Myocardial Infarction and Outcomes From Percutaneous Coronary Interventions. J Am Heart Assoc. 2019;8:e013686. [PubMed: 31475601]
33. Dodson JA, Hochman JS, Roe MT, Chen AY, Chaudhry SI, Katz S, Zhong H, Radford MJ, Udell JA, Bagai A, et al.The Association of Frailty With In-Hospital Bleeding Among Older Adults With Acute Myocardial Infarction. JACC Cardiovas Interv. 2018;11:2287–2296.
34. Imbens GW and Angrist JD. Identification and Estimation of Local Average Treatment Effects. Econometrica. 1994;62:467–475.
35. Sheth T, Pinilla-Echeverri N, Moreno R, Wang J, Wood DA, Storey RF, Mehran R, Bainey KR, Bossard M, Bangalore S, et al.Nonculprit Lesion Severity and Outcome of Revascularization in Patients With STEMI and Multivessel Coronary Disease. J Am Coll Cardiol. 2020;76:1277–1286. [PubMed: 32912441]

What is Known:

- Multivessel percutaneous coronary intervention among patients with ST-segment elevation myocardial infarction (STEMI) has been associated with improved outcomes, including reduced myocardial infarction and repeat revascularization.
- What is not known is how these results translate into clinical practice for an older population of patients with STEMI.

What the Study Adds:

- This analysis demonstrated that among older patients with STEMI in clinical practice, multivessel percutaneous coronary intervention was not associated with reduced death, myocardial infarction or repeat revascularization through one year of follow-up.
- This may be due to a different risk-benefit profile of this population, as well as more complex decision making for operators when indeterminate non-culprit lesions are considered for staged intervention.

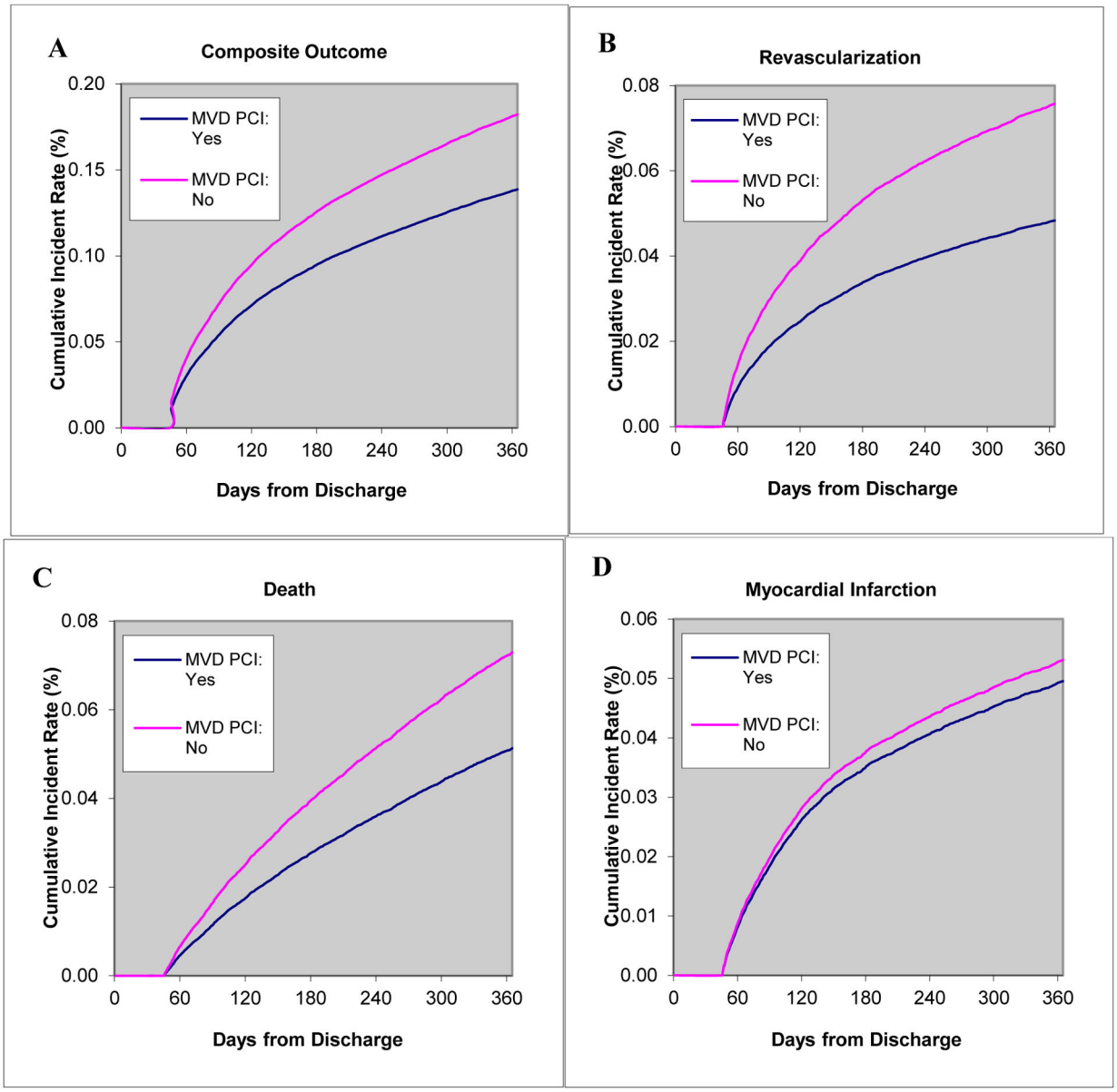

Figure 1.

Unadjusted Cumulative Incidences of the Primary Endpoint and the Individual Components Between 45 to 365 Days among Patients Undergoing Multivessel versus Culprit-Only PCI for STEMI.

Displayed are Kaplan-Meier curves comparing the cumulative incidence of the primary composite endpoint and the individual components, stratified by treatment with multivessel percutaneous coronary intervention (MV PCI). In unadjusted analysis, MV PCI was associated with a reduction in the composite endpoint of repeat revascularization, myocardial infarction or death (A), as well as the individual endpoints of repeat revascularization (B) and death (C). MV PCI was not associated with a reduction in the cumulative incidence of myocardial infarction (D) (p=0.08). *Abbreviations: MV PCI, multivessel percutaneous coronary intervention*

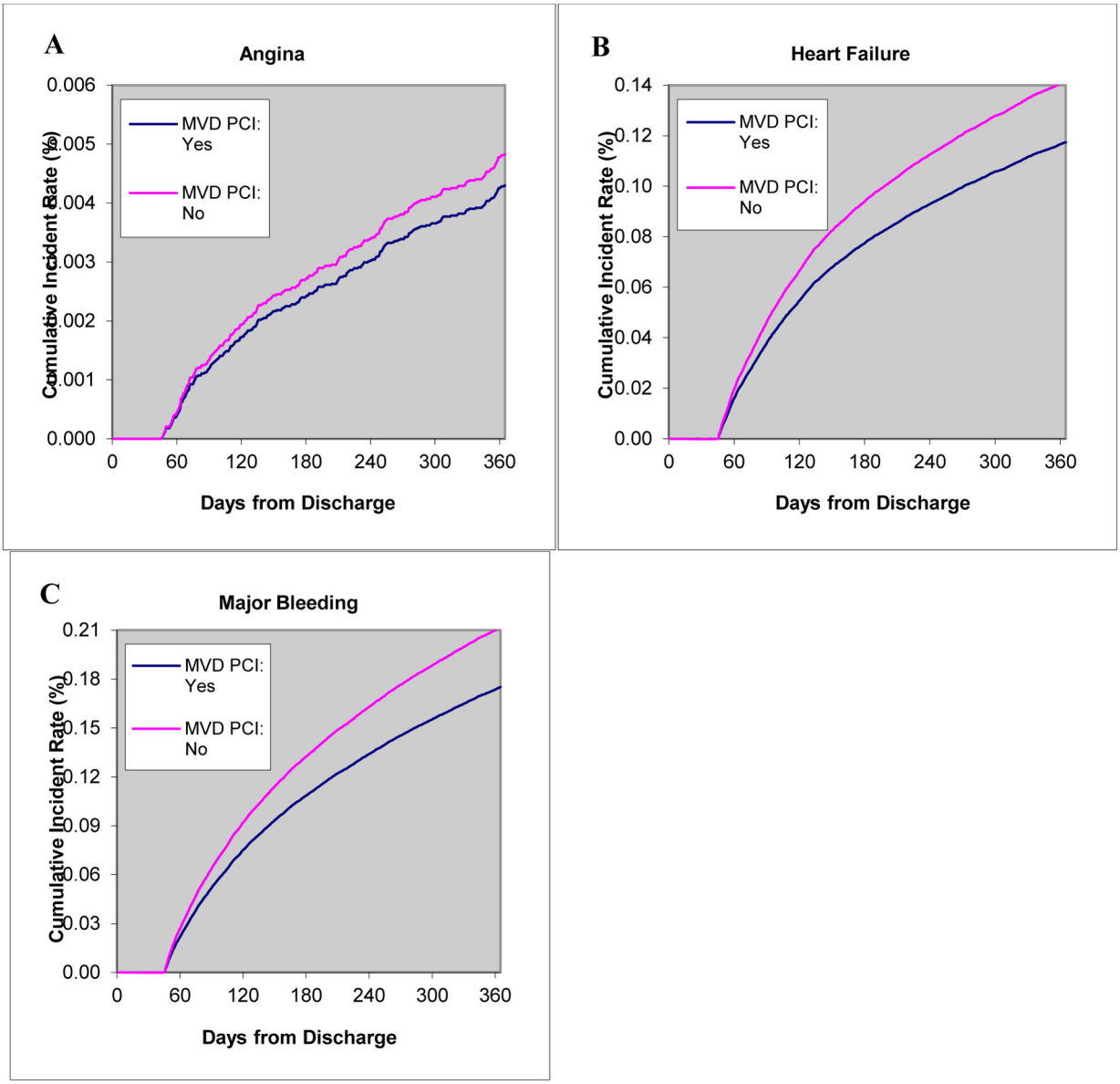

Figure 2.

Unadjusted Cumulative Incidences of the Secondary Endpoints and the Falsification Endpoint (Major Bleeding) Between 45 to 365 Days among Patients Undergoing Multivessel versus Culprit-Only PCI for STEMI.

Displayed are Kaplan-Meier curves comparing the cumulative incidence of the secondary endpoints and the falsification endpoint (major bleeding), stratified by treatment with multivessel percutaneous coronary intervention (MV PCI). In unadjusted analysis, MV PCI was not associated with a reduction in the cumulative incidence of hospitalization for unstable angina (A) ($p=0.37$), but was associated with a reduction in the cumulative incidence of hospitalization for heart failure (B) ($p<0.01$). Notably, MV PCI was also associated with a reduction in the falsification endpoint of major bleeding (C) ($p<0.01$),

suggestive of confounding. *Abbreviations: MV PCI, multivessel percutaneous coronary intervention*

Table 1.

Patient and Procedural Characteristics of the Study Population, Stratified by Treatment with Multivessel Percutaneous Coronary Intervention

Description	Total N=56,332	Non-MV PCI N=35,078	MV PCI N=21,254	SD
Age (mean, STD)	74.8 (7.5)	75.2 (7.7)	74.2 (7.2)	12.3
Male (n, %)	36273 (64.4)	22551 (64.3)	13722 (64.6)	−0.6
White race (n, %)	51503 (91.4)	31966 (91.1)	19357 (91.9)	−2.8
BMI (kg/m^2) (mean, STD)	28.1 (7.7)	28.0 (7.4)	28.3 (8.1)	−4.2
Current smoking (n, %)	10941 (19.4)	7000 (20.0)	3941 (18.5)	3.6
Hypertension (n, %)	42801 (76.0)	26919 (76.7)	15882 (74.7)	4.7
Dyslipidemia (n, %)	36081 (64.1)	22537 (64.3)	13544 (63.7)	1.1
Family history of coronary artery disease (n, %)	7215 (12.8)	4417 (12.6)	2798 (13.2)	−1.7
Prior myocardial infarction (n, %)	10716 (19.0)	6963 (19.9)	3753 (17.7)	5.6
Prior PCI (n, %)	12597 (22.4)	8255 (23.5)	4342 (20.4)	7.5
eGFR (n, %)				
0–29	3832 (6.8)	2620 (7.5)	1212 (5.7)	7.0
30–59	18444 (32.7)	11602 (33.1)	6842 (32.2)	1.9
60+	34056 (60.5)	20856 (59.5)	13200 (62.1)	−5.4
Prior cerebrovascular disease (n, %)	6403 (11.4)	4167 (11.9)	2236 (10.5)	4.3
Prior peripheral artery disease (n, %)	4556 (8.1)	3048 (8.7)	1508 (7.1)	5.9
Chronic lung disease (n, %)	6594 (11.7)	4269 (12.2)	2325 (10.9)	5.9
Diabetes (n, %)	16033 (28.5)	10214 (29.1)	5819 (27.4)	3.9
Prior heart failure (n, %)	3368 (6.0)	2211 (6.3)	1157 (5.4)	3.6
Cardiomyopathy or left ventricular systolic dysfunction (n, %)	3597 (6.4)	2238 (6.4)	1359 (6.4)	−0.1
CCS class (within 2 weeks) (n, %)				
No symptoms	3531 (6.3)	2432 (6.9)	1099 (5.2)	7.3
I	493 (0.9)	325 (0.9)	168 (0.8)	1.5
II	1543 (2.7)	954 (2.7)	589 (2.8)	−0.3
III	7549 (13.4)	4671 (13.3)	2878 (13.5)	−0.7
IV	43216 (76.7)	26696 (76.1)	16520 (77.7)	−3.8
NYHA class (n, %)				
No heart failure in 2 weeks	51852 (92.1)	32275 (92.0)	19577 (92.1)	−0.4
I	524 (0.9)	333 (1.0)	191 (0.9)	0.5
II	1135 (2.0)	697 (2.0)	438 (2.1)	−0.5
III	1380 (2.5)	885 (2.5)	495 (2.3)	1.3
IV	1441 (2.6)	888 (2.5)	553 (4.2)	−0.5
Cardiac arrest within 24 hours (n, %)	2295 (4.1)	1406 (4.0)	889 (4.2)	−0.9
Procedure medication (n, %)				
UFH	40916 (72.6)	25487 (72.7)	15249 (72.6)	0.2

Description	Total N=56,332	Non-MV PCI N=35,078	MV PCI N=21,254	SD
Bivalirudin	25264 (44.9)	15794 (45.0)	9470 (44.6)	0.9
Glycoprotein IIb/IIIa inhibitor	24707 (43.9)	15308 (43.6)	9399 (44.2)	−1.2
Aspirin	51287 (91.0)	31950 (91.1)	19337 (91.0)	0.4
Clopidogrel	32390 (57.5)	20431 (58.2)	11959 (56.3)	4.0
Ticlopidine	103 (0.2)	67 (0.2)	36 (0.2)	0.5
Prasugrel	6326 (11.2)	3773 (10.8)	2553 (12.0)	−4.0
Ticagrelor	11689 (20.8)	6977 (19.9)	4712 (22.2)	−5.6
Radial access	8791 (15.6)	5308 (15.1)	3483 (16.4)	−3.5
Femoral/brachial access	47518 (84.4)	29756 (85.8)	17762 (83.6)	3.5
Infarct-related artery (n, %)				
LMCA	257 (0.5)	63 (0.2)	194 (0.9)	−10.9
LAD	20121 (35.7)	12420 (35.4)	7701 (36.2)	−1.7
LCX	8345 (14.8)	4604 (13.1)	3741 (17.6)	−12.6
RAM	477 (0.9)	220 (0.6)	257 (1.2)	−6.5
RCA	27132 (48.2)	17771 (50.7)	9361 (44.0)	13.3
Facilitated PCI or failed thrombolysis (n, %)	2780 (4.9)	620 (4.6)	1160 (5.5)	−3.9
DES placed (n, %)	38226 (67.9)	21499 (61.3)	16727 (78.7)	−37.9
BMS placed (n, %)	15231 (27.0)	10378 (29.6)	4853 (22.8)	15.2
IABP (n, %)	2691 (4.8)	1662 (4.7)	1029 (4.8)	−0.5
Other mechanical support (n, %)	262 (0.5)	135 (0.4)	127 (0.6)	−37.9
Number of diseased vessels (n, %)				
2	37500 (66.6)	23954 (68.3)	13546 (63.7)	9.7
3+	18832 (33.4)	11124 (31.7)	7708 (36.3)	−9.7
Number of vessels intervened upon (n, %)				
1	43134 (76.6)	35078 (100.0)	8056 (37.9)	208.4
2	11582 (20.6)	---	11582 (54.5)	−178.2
3+	1616 (2.9)	---	1616 (7.6)	−46.7
Total number of stents placed (n, %)				
0	4186 (7.4)	3510 (10.0)	676 (3.2)	26.2
1	25564 (45.4)	19778 (56.4)	5786 (27.2)	61.1
2	16162 (28.7)	8693 (24.8)	7469 (35.1)	−23.1
3	6547 (11.6)	2369 (6.8)	4178 (19.7)	−41.1
4+	3873 (6.9)	728 (2.1)	3145 (14.8)	−51.8
Total stent length (millimeters) (mean, STD)	36.7 (22.6)	30.9 (16.7)	46.3 (27.4)	−72.4
Smallest stent diameter (millimeters) (mean, STD)	2.9 (0.5)	2.9 (0.5)	2.8 (0.4)	34.7
Fluoroscopy time (minutes) (mean, STD)	14.2 (10.30	14.0 (10.1)	14.5 (9.9)	−5.5
Contrast volume (milliliters) (mean, STD)	190.9 (80.2)	185.7 (76.9)	199.6 (84.7)	−17.3
In-hospital outcomes (n, %)				
Myocardial infarction	1272 (2.3)	783 (2.2)	489 (2.3)	−0.5

Description	Total N=56,332	Non-MV PCI N=35,078	MV PCI N=21,254	SD
Heart failure	2252 (4.0)	1407 (4.0)	845 (4.0)	0.2
Bleeding or vascular complication or transfusion	4269 (7.6)	3514 (8.1)	1420 (6.7)	5.5
Acute kidney injury or new need for dialysis	5298 (9.4)	3514 (10.0)	1784 (8.4)	5.6
Length of stay (days) (mean, STD)	4.2 (7.9)	4.1 (6.5)	4.2 (9.7)	−1.2
Discharge medications (n, %)				
ACE inhibitor (any)	32366 (57.5)	19869 (56.6)	12497 (58.8)	−4.4
Angiotensin II receptor blocker (any)	6955 (12.4)	4286 (12.2)	2669 (12.6)	−1.0
Aspirin (any)	53547 (95.1)	33128 (94.4)	20419 (96.1)	−7.5
Beta blocker (any)	50933 (90.4)	31510 (89.8)	19423 (91.4)	−5.3
Statin (any)	52065 (92.4)	32254 (92.0)	19811 (93.2)	−4.8
Non-statin (any)	3585 (6.4)	2186 (6.2)	1399 (6.6)	−1.4
Clopidogrel	36815 (65.4)	23312 (66.5)	13503 (63.5)	6.2
Ticlopidine	102 (0.2)	68 (0.2)	34 (0.2)	0.8
Prasugrel	6678 (11.9)	3854 (11.0)	2824 (13.3)	−7.1
Ticagrelor	10207 (18.1)	5911 (16.9)	4296 (20.2)	−8.7

Abbreviations: BMI, body mass index; BMS, bare metal stent; CCS, Canadian Cardiovascular Society; DES, drug-eluting stent; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; LAD, left anterior descending; LCX› left circumflex artery; LMCA, left main coronary artery; MV, multivessel; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RAM, ramus artery; RCA, right coronary artery; SD, standardized difference; STD, standard deviation; UFH, unfractionated heparin

*Standardized differences were calculated between MV and non-MV cohorts

Table 2.

Outcomes (between 45 days to 1 year) associated with Multivessel Percutaneous Coronary Intervention in Unadjusted, Multivariate Adjusted, and Instrumental Variable Analyses

Outcome	Unadjusted HR (95%CI)	P-value	Adjusted HR (95%CI)	P-value	Adjusted RD (95%CI)	P-value
Death, MI, or repeat revascularization	0.74 (0.71–0.78)	<0.001	0.79 (0.75–0.83)	<0.001	−0.97% (−3.52, 1.59)	0.46
Death	0.70 (0.65–0.75)	<0.001	0.83 (0.77–0.89)	<0.001	−0.21% (−1.96, 1.55)	0.82
MI	0.93 (0.86–1.01)	0.08	0.93 (0.86–1.01)	0.11	0.47% (−1.11, 2.04)	0.56
Repeat revascularization	0.63 (0.58–0.68)	<0.001	0.63 (0.58–0.68)	<0.001	−1.12% (−2.88, 0.64)	0.21
Unstable angina	0.89 (0.69–1.15)	0.37	0.90 (0.69–1.18)	0.45	0.08% (−0.42, 0.58)	0.74
HF	0.82 (0.78–0.86)	<0.001	0.90 (0.86–0.95)	<0.001	−2.10% (−4.43, 0.23)	0.08
Major bleeding (Falsification endpoint)	0.81 (0.78–0.84)	<0.001	0.88 (0.85–0.93)	<0.001	−2.54% (−5.30, 0.22)	0.07

Abbreviations: CI, confidence interval; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; RD, risk difference