

# Revascularization Strategies in Patients Presenting With ST-Elevation Myocardial Infarction and Multivessel Coronary Disease

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**The optimal revascularization strategy for residual coronary stenosis following primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction (STEMI) and multivessel disease (MVD) remains controversial. This is a retrospective single-centre study including patients with STEMI and MVD. Based on the revascularization strategy, 3 groups were identified: (1) culprit only (CO), (2) ad hoc multivessel revascularization (MVR), and (3) staged MVR. Clinical outcomes were compared in terms of major adverse cardiac events (MACE), a composite of cardiac death, any myocardial infarction, and any unplanned revascularization at a long-term follow-up. A total of 958 patients were evaluated, 489 in the CO, 254 in the ad hoc, and 215 in the staged group. In the staged group, 65.6% of the patients received planned percutaneous coronary intervention, 9.7% coronary artery bypass grafting, 8.4% no further intervention after lesion reassessment, and in 16.3% an event occurred before the planned procedure. At 1,095 days, MACE was 36.1%, 16.7%, and 31% for CO, ad hoc, and staged groups, respectively. A MVR strategy was associated with lower rate of all-cause death compared with CO (HR 0.50; 95% CI [0.31 to 0.80];  $p = 0.004$ ). Complete revascularization reduced the rate of MACE (HR 0.30 [0.21 to 0.43]  $p < 0.001$ ) compared with incomplete revascularization. Ad hoc MVR had lower rate of MACE compared with staged MVR (HR 0.61 [0.39 to 0.96]  $p = 0.032$ ) mainly driven by less unplanned revascularizations. In conclusion, in patients with STEMI and MVD, complete revascularization reduced the risk of MACE. Ad hoc MVR appeared a reasonable strategy with lower contrast and stent usage and costs. © 2020 Elsevier Inc. All rights reserved. (Am J Cardiol 2020;00:1–6)**

Primary percutaneous coronary intervention (PCI) is the gold standard for the treatment of patients with an acute ST-segment elevation myocardial infarction (STEMI),<sup>1–3</sup> and up to 52% of those cases present with multivessel disease (MVD) increasing the risk of future cardiovascular events.<sup>4</sup> The management of the nonculprit lesions, however, remains controversial.<sup>5</sup> Recent randomized trials showed improved clinical outcomes in patients who underwent complete revascularization. PCI of noninfarct related arteries (non-IRA) was performed either during the index procedure,<sup>6,7</sup> in a staged procedure during hospital admission,<sup>8,9</sup> or mixing the 2 strategies.<sup>10</sup> Based on these data, the current European Guidelines report that revascularization of non-IRA lesions should be considered in STEMI patients with MVD.<sup>11</sup> However, the optimal timing of

revascularization (i.e., immediate vs staged) has not been adequately investigated. Therefore, the purpose of the present study is to evaluate the impact of the different revascularization strategies on clinical outcome in patients presenting with STEMI and MVD.

## Methods

All consecutive patients with MVD (defined as significant stenosis (>50%) in at least 1 nonculprit epicardial coronary artery (>2 mm) as assessed by visual estimation), who underwent primary PCI between January 2010 and March 2017 were eligible for the present study. Out of hospital cardiac arrest, cardiogenic shock, presence of chronic total occlusions, previous coronary artery bypass grafting (CABG), ambiguity about the culprit lesion and unknown final revascularization status (no information regarding the staged procedure) were excluded.

According to the revascularization strategy adopted by the operator at the index PCI, the population was divided into 3 groups: (1) Culprit only (CO): defined as PCI of the culprit artery only followed by medical treatment. (2) Ad hoc multivessel revascularization (MVR): defined as PCI of the IRA and at least one non-IRA at the index procedure followed by

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medical treatment with no further planned revascularization. (3) Staged MVR: defined as the treatment of the IRA  $\pm$  non-IRA at the index procedure followed by planned revascularization of the remaining lesions within 6 weeks. Based on approach and completeness of revascularization 3 specific comparisons were predefined: CO revascularization vs MVR, complete vs incomplete revascularization, and ad hoc vs staged MVR. Major adverse cardiac events (MACE) were defined as a composite of cardiac death, any myocardial infarction (MI) (Q- or non-Q-wave) and any unplanned revascularization (either PCI or CABG).

Overall death was defined as all-cause mortality. All deaths were considered cardiac unless an undisputed noncardiac cause was identified.<sup>12</sup> MI was defined as the increased and/or decreased of cardiac-specific troponin values with at least 1 value above the 99th percentile of the upper reference limit and with the presence of ischemic symptoms, new ischemic electrocardiographic changes, development of pathological Q waves, wall motion abnormalities in a pattern consistent with an ischemic aetiology, and/or presence of intracoronary thrombus.<sup>13</sup> Any unplanned revascularization was defined as any PCI or CABG procedure performed during the follow-up in target and/or nontarget vessels, outside of the initial intended revascularization strategy; this definition included any unplanned revascularization occurring after the index PCI and before the staged revascularization date for the staged cohort. Significant coronary lesions were defined as a lumen diameter stenosis  $\geq 50\%$  as assessed by visual estimation or quantitative coronary analysis. Complete revascularization was considered when all significant coronary lesions suitable for revascularization as per operator's discretion were treated as planned and had a final Thrombolysis in myocardial infarction (TIMI) flow grade 2 or 3 with residual stenosis  $< 30\%$ , otherwise it was considered as incomplete.

Survival data for all patients were obtained from municipal civil registries. A health questionnaire was subsequently sent to all living patients with specific questions on re-admission and major adverse cardiac events. For patients who had an adverse event at another center, general practitioners, referring cardiologists, and patients were contacted as necessary for additional information.

Categorical data are presented as counts and percent, and the differences between groups were tested by the chi-square test or Fisher's exact test when appropriate. Continuous data are presented as median and interquartile range (IQR; 25th to 75th percentile), and the differences between groups tested by the Kruskal-Wallis test. Pairwise comparisons were performed to identify significant differences among groups. The Kaplan-Meier method was used to plot event-free survival curves. Differences were evaluated by the log-rank test. Variables associated with clinical outcomes were identified using univariate Cox proportional-hazards models. Variables with a  $p$  value  $< 0.05$  were introduced into a multivariate Cox proportional-hazards model to adjust for the effect of potential confounders. Proportional hazards assumptions were tested by log-minus-log survival probability plots and by fitting time-dependent covariates. Extended Cox regression including the interaction between group treatment and time was performed when proportional hazards assumptions were not met. Data are presented as hazard ratios (HRs) with 95%

confidence intervals [95%CI]. Overall, tests were 2-tailed and a  $p$  value  $< 0.05$  was considered statistically significant and the Bonferroni correction was applied in cases where pairwise comparisons were performed. SPSS software version 24.0 for Windows (SPSS, Inc., Chicago) was used to perform all analyses.

## Results

From January 2010 to March 2017 a total of 1,473 STEMI patients with MVD were identified. Out of the total population, 958 patients met the inclusion and none of the exclusion criteria. CO revascularization was performed in 489 cases and 469 patients underwent MVR. Ad hoc revascularization of non-IRA arteries was performed in 254 patients and a planned staged revascularization of non-IRA arteries was scheduled for 215 patients. [Supplementary material Figure 1](#). Median follow-up was 1116 days (IQR 226 to 2151 days).

Overall, the staged cohort was younger compared with the other 2 revascularization strategies. Other baseline demographics were well balanced among groups. Baseline characteristics are summarized in [Table 1](#).

The staged group had more frequently 3 vessel disease and or left main disease. The right coronary artery was more often the IRA (46.9% of the cases) with a significantly greater proportion in the CO group, and the newer P2Y12 inhibitors (Prasugrel or Ticagrelor) were more often prescribed to patients who underwent MVR. Although no differences were found in IRA complications, a significantly higher rate of non-IRA complications (dissections, distal embolization, slow flow and/or no-reflow, perforation, sudden thrombosis), was found in the ad hoc MVR strategy. In contrast, the staged group received more number of stents and overall (index + staged procedure) a larger amount of contrast medium. Complete revascularization was achieved in 420 patients. Procedural characteristics are tabulated in [Table 2](#).

Of 215 patients with a planned staged procedure, the staged revascularization was performed in 162 patients (PCI in 141 cases and CABG in 21 cases) at a median of 10.5 days (IQR 4 to 29 days) postindex PCI; in 18 patients (8.4% of the cohort) the non-IRA treatment was aborted after FFR-reassessment of lesion severity, and 35 patients (16.3% of the cohort) required premature revascularization for new STEMI (2 cases), non-ST segment elevation acute coronary syndromes (20 cases), residual angina (11 cases), and decompensated acute heart failure (2 cases); these 35 patients were considered as incomplete revascularization within the staged cohort, and the premature revascularization as an event.

The cumulative incidence of MACE at 1,095 days was 36.1%, 31%, and 16.7% in the CO, staged and ad hoc cohorts, (log-rank test for CO vs ad hoc  $p < 0.001$ , CO vs staged  $p = 0.343$ , and ad hoc vs staged  $p = 0.002$ . [Figure 1](#); [Supplementary material Table 1](#)).

[Table 3](#) shows the risk of outcomes among revascularization strategies. When comparing MVR versus CO no significant difference was found in MACE (HR 0.81; 95%CI [0.59 to 1.10];  $p = 0.184$  [Supplementary material Figure 2-A](#)) or any of the individual components of MACE; however, a significantly lower risk of overall

Table 1  
Baseline characteristics

Variable	Culprit only (n = 489)	Ad hoc multivessel revascularization (n = 254)	Staged multivessel revascularization (n = 215)	p value
Age (Years)	66 (56-76)	66 (55-74)	62 (54-71)	0.012
Men	343/488 (70.1%)	181/254 (71.3%)	167/215 (77.7%)	0.093
Dyslipidemia	161/488 (32.9%)	84/254 (33.1%)	67/215 (31.2%)	0.87
Hypertension	218/488 (44.7%)	101/254 (39.8%)	87/215 (40.5%)	0.35
Diabetes mellitus	82/488 (16.8%)	32/254 (12.6%)	25/215 (11.6%)	0.11
Family history of cardiovascular disease	120/488 (24.6%)	82/254 (32.3%)	85/215 (39.5%)	<0.001
Chronic obstructive pulmonary disease	20/488 (4.1%)	11/254 (4.3%)	6/215 (2.8%)	0.64
Peripheral vascular disease	23/488 (4.7%)	6/254 (2.4%)	4/215 (1.9%)	0.08
Previous myocardial infarction	47/488 (9.6%)	20/254 (7.9%)	14/215 (6.5%)	0.36
Previous percutaneous coronary intervention	56/488 (11.5%)	27/254 (10.6%)	12/215 (5.6%)	0.05
Previous cerebrovascular accident/ischemic transitory attack	31/488 (6.4%)	8/254 (3.1%)	12/215 (5.5%)	0.18
Current smoking	190/488 (39.1%)	100/254 (39.4%)	82/215 (37.8%)	0.96
Basal creatinine ( $\mu\text{mol/L}$ )	81 (69-94)	81.5 (69-96)	81 (69-94)	0.88
Anterior myocardial infarction at presentation	167/489 (34.2%)	91/254 (35.8%)	62/215 (28.8%)	0.24

Dyslipidemia was defined as total cholesterol  $>5.2$  mmol/L, LDL-C  $\geq 3.4$  mmol/L or triglycerides  $\geq 1.7$  mmol/L. Hypertension was defined as blood pressure  $\geq 140/90$  mm Hg (millimeters of mercury). Categorical data are presented as counts and % and tested by chi-square test. Continuous data are presented as median and interquartile range (IQR; 25th to 75th percentile) and tested by Kruskal-Wallis test when appropriate.

Table 2  
Procedural characteristics

Variable	Culprit only (n = 489)	Ad hoc multivessel revascularization (n = 254)	Staged multivessel revascularization (n = 215)	p value
Three vessel coronary disease	133/489 (27.2%)	55/254 (21.7%)	85/215 (39.5%)	<0.001
Left main disease	17/489 (3.5%)	21/254 (8.3%)	23/215 (10.7%)	0.001
Infarct-related artery				
Left main	2/489 (0.4%)	3/254 (1.2%)	0/215 (0%)	0.232
Left anterior descending	161/489 (32.9%)	88/254 (34.6%)	61/215 (28.4%)	0.32
Left circumflex	79/489 (16.2%)	61/254 (24%)	54/215 (25.1%)	0.005
Right	247/489 (50.5%)	102/254 (40.2%)	100/215 (46.5%)	0.027
Infarct-related artery Thrombolysis in myocardial infarction pre 0-1	299/489 (61.1%)	142/254 (55.9%)	142/215 (66%)	0.08
Infarct-related artery Thrombolysis in myocardial infarction post 2-3	483/489 (98.8%)	253/254 (99.6%)	215/215 (100%)	0.16
Infarct-related artery treatment type				0.068
Stenting	474/489 (96.9%)	254/254 (100%)	211/215 (98.1%)	
Plain old balloon angioplasty	13/489 (2.7%)	0/254 (0%)	4/215 (1.9%)	
Thromboaspiration only	2/489 (0.4%)	0/254 (0%)	0/215 (0%)	
Infarct-related artery complications	34/489 (7%)	11/254 (4.3%)	11/215 (5.1%)	0.30
Noninfarct-related artery complications	0/489 (0%)	12/254 (4.7%)	3/215 (1.4%)	<0.001
Glycoprotein IIb/IIIa inhibitor	150/489 (30.7%)	70/254 (27.6%)	66/215 (30.7%)	0.64
Thromboaspiration	281/489 (57.5%)	94/254 (37%)	126/215 (58.6%)	<0.001
Index intracoronary imaging	67/489 (13.7%)	33/254 (13%)	37/215 (17.2%)	0.37
Index fractional flow reserve assessment	11/489 (2.2%)	12/254 (4.7%)	6/215 (2.8%)	0.17
Index drug-eluting stent	461/474 (97.3%)	253/254 (99.6%)	210/212 (96.7%)	0.06
Index stent number	1 (1-2)	2 (2-3)	1 (1.2-2)	<0.001
Index stent length (mm)	28 (18-40)	48.5 (36-66.2)	26 (18-36)	<0.001
Total stent number (index+/-staged)	1 (1-2)	2 (2-3)	2 (1.2-4)	<0.001
Total stent length (mm) (index+/-staged)	28 (18-40)	48.5 (36-66.2)	50 (30-76)	<0.001
Index contrast (ml)	150 (110-200)	170 (140-220)	150 (120-200)	<0.001
Total contrast (ml) (index+/-staged)	150 (110-200)	170 (140-220)	260 (200-340)	<0.001
Complete revascularization	0/489 (0)	243/254 (95.7)	177/215 (82.3)	<0.001
Aspirin prescribed	488/488 (99.8%)	253/254 (99.6%)	215/215 (100%)	0.64
P2Y12 Inhibitor prescribed				
Clopidogrel	214/488 (43.9%)	58/254 (22.8%)	79/215 (36.7%)	<0.001
Ticagrelor	122/488 (25%)	140/254 (55.1%)	70/215 (32.6%)	<0.001
Prasugrel	150/488 (30.7%)	54/254 (21.3%)	66/215 (30.7%)	0.016

Categorical data are presented as counts and % and tested by chi-square test or Fisher's exact test when appropriate. Continuous data are presented as median and Inter-Quartile Range (IQR; 25th to 75th) and tested by Kruskal-Wallis test when appropriate.

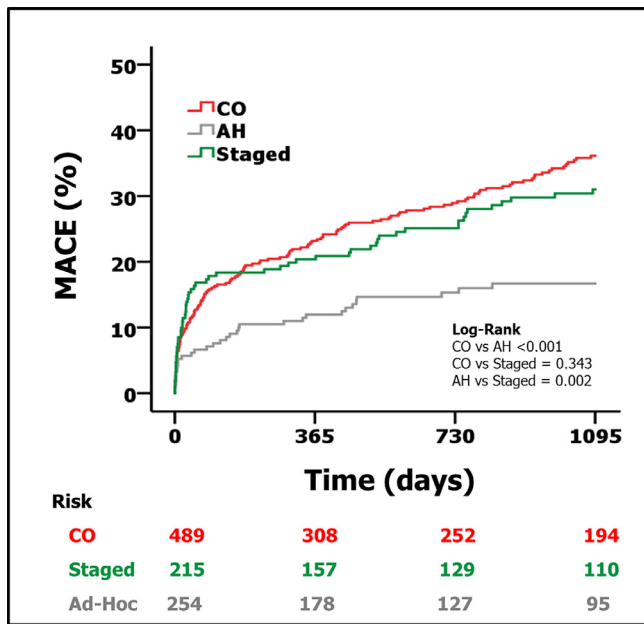


Figure 1. Cumulative incidence of major adverse cardiac events (MACE) at 1095 days. Ad hoc multivessel revascularization (AH). Culprit only (CO); Major Adverse Cardiac Events (MACE); Multivessel revascularization (MVR).

death was present in patients receiving MVR (HR 0.50; 95%CI [0.31 to 0.80]; p = 0.004). Complete revascularization appeared protective for MACE (HR 0.30; 95%CI [0.21 to 0.43]; p < 0.001) mainly driven by a significant reduction in MI (HR 0.47; 95%CI [0.26 to 0.86]; p = 0.014) and unplanned revascularizations (HR 0.15; 95%CI [0.08 to 0.27]; p < 0.001).

In a sub-analysis comparing both MVR strategies, the ad hoc cohort showed a significant lower risk of MACE (HR 0.61; 95%CI [0.39 to 0.96]; p = 0.032) and unplanned revascularizations (HR 0.39; 95%CI [0.22 to 0.67]; p < 0.001. No strategy impacted significantly the risk of future overall death, cardiac death or MI. [Supplementary material Figure 2-B.](#)

**Discussion**

Our main findings are: (1) Ad hoc MVR was associated with lower MACE compared with CO or staged strategies. (2) Less unplanned revascularizations occurred in the ad hoc MVR compared with staged MVR. (3) Complete revascularization was associated with lower MACE compared with incomplete revascularization. (4) Intracoronary imaging assessment or coronary physiology redefines the significance of non-IRA. In line with previous RCTs, our study confirmed a higher incidence of adverse events in patients receiving culprit only revascularization compared with patients treated with a MVR approach.<sup>6-10</sup>

Among the MVR strategies, ad hoc MVR appeared to be strongly related to a reduced early risk of unplanned revascularizations; of note, 16.3% of the staged cohort required unplanned revascularization before the staged intervention. A similar trend was found in the population who underwent complete revascularization at the index procedure as compared with those having a staged procedure

Table 3  
 Comparison between revascularization strategies at 1095 days

EVENT	Multivessel revascularization vs Culprit only (reference)		Complete revascularization vs Incomplete revascularization (reference)		Ad hoc multivessel revascularization vs Staged multivessel revascularization (reference)	
	Univariate HR [95%CI] p value	Adjusted HR [95%CI] p value	Univariate HR [95%CI] p value	Adjusted HR [95%CI] p value	Univariate HR [95%CI] p value	Adjusted HR [95%CI] p value
Major adverse cardiac events	0.65 [0.50-0.84] 0.001	0.81 [0.59-1.10] 0.18	0.32 [0.23-0.43] <0.001	0.30 [0.21-0.43] <0.001	0.51 [0.33-0.78] 0.002	0.61 [0.39-0.96] 0.032
Overall death	0.42 [0.28-0.62] <0.001	0.50 [0.31-0.80] 0.004	0.47 [0.31-0.72] <0.001	0.62 [0.38-1.02] 0.06	2.07 [1.00-4.28] 0.048	1.44 [0.68-3.06] 0.33
Cardiac death	0.56 [0.34-0.93] 0.027	0.62 [0.37-1.05] 0.08	0.61 [0.37-1.03] 0.06	0.70 [0.41-1.19] 0.18	2.05 [0.88-4.81] 0.09	1.30 [0.53-3.14] 0.55
Myocardial infarction	0.55 [0.32-0.96] 0.038	0.57 [0.33-1.00] 0.05	0.45 [0.24-0.81] 0.009	0.47 [0.26-0.86] 0.014	1.08 [0.45-2.61] 0.85	1.05 [0.43-2.54] 0.90
Any unplanned revascularization	0.65 [0.48-0.88] 0.006	0.87 [0.61-1.24] 0.44	0.16* [0.09-0.28] <0.001	0.15* [0.08-0.27] <0.001	0.36 [0.22-0.61] <0.001	0.39 [0.22-0.67] <0.001

Data are presented as Hazard ratio (HR) [95% Confidence Interval (CI)] p value.

\* Proportional Hazard assumptions were not met for this comparison. Extended Cox regression with time-dependent covariate modelling was performed.

in the CvLPRIT trial.<sup>10</sup> Lee et al, additionally reported deferred nonculprit lesions treatment resulting in a higher rate of events, in particular, ischemia-driven revascularisation<sup>14</sup> and, Fukutomi et al, showed a lower overall mortality and MACE when the staged procedure was performed within the first 2 weeks after the index PCI instead of more than 2 weeks. This may reflect the clinical translation of the generalized coronary inflammation during Acute coronary syndrome (ACS), suggesting multiple unstable plaques in different coronary territories.<sup>15–17</sup> Achieving prompt anatomical revascularization of nonculprit significant lesions might be responsible for the reduction in the hazard in a long-term follow-up.

In contrast with previous RCT,<sup>6–10,18,19</sup> we found a significant reduction in the risk of all-cause mortality when MVR was performed. It is important to highlight that RCT have strict inclusion and exclusion criteria along with prespecified treatment protocols and follow-up that might not fully represent the real world clinical practice. Of note, one of the main inclusion criteria shared by those RCT was the clear indication and feasibility for a complete revascularization through a percutaneous approach at the operator's discretion, in addition, only patients with successful PCI of the culprit artery were included, possibly selecting a less high-risk or complex population and excluding CABG as part of the MVR treatment strategy. Moreover, none of the RCT were powered to detect statistically significant differences on mortality but did show numerically lower incidence of death from any cause in the groups receiving MVR.

In line with previous reports,<sup>20–23</sup> we observed a numerically higher mortality rate within the ad hoc group compared with the staged group. In our study, the reduction in mortality risk in the staged population might be due to a selection bias, with this group of patients representing those who survive enough time until the planned procedure was performed. Furthermore, patients who underwent ad hoc MVR might represent a sicker population; in our study, the ad hoc group was older, had more frequently history of previous MI and PCI, presented more frequently with a left coronary artery as the culprit and had a higher incidence of non-IRA complications.

Recent advances in PCI techniques and pharmacotherapy might overshadow the previous advantages found with a staged strategy on mortality, with further unplanned revascularizations being the shifting parameter in the current era. Moreover, a staged strategy was associated with a highest overall amount of contrast and number of stents, which could translate into different levels of contrast-induced nephropathy and long-term restenosis rate.<sup>24</sup> In addition, performing a staged procedure would reasonably be associated with higher health-care costs as compared with an ad hoc strategy.

In line with previous randomized trials,<sup>8–10</sup> our results show that complete revascularization irrespectively of the MVR strategy is associated with a lower rate of MACE, in particular, less MI and unplanned revascularizations. Finally, coronary physiology or intracoronary imaging may further address the clinical significance of nonculprit lesions. In 8.4% of staged procedures, the planned revascularization was not performed due to invasive re-evaluation of the lesions, preventing unnecessary PCI and corroborating the results of the FAME trial.<sup>25</sup> Coronary physiology assessment

of nonculprit arteries during primary PCI is feasible and safe,<sup>6</sup> and might change the angiographic-based strategy in up to 40% of the cases.<sup>26</sup>

The present investigation highlights the importance of complete revascularization in patients presenting with acute MI and MVD and although the optimal timing to perform non-IRA revascularization remains unclear, our data suggest an ad hoc strategy as the most appropriate when feasible, also considering the possible differences in terms of contrast delivered, stents usage and costs. Prospective RCT should shed further light on whether staged or ad hoc MVR should be the default strategy. The ongoing BIOVASC trial (NCT03621501) aims to randomize 1525 patients with ACS and MVD to ad hoc or staged MVR.

This is a single-center retrospective observational study. There was no independent or external monitoring of data entry. Possible case-selection bias is the main limitation of our study; non-IRA treatment strategy was at the operator's discretion, with lesion severity, suitability, and urgency for revascularization being determined by the operator at the index PCI or at the staged procedure, and so was the definition of complete revascularization. A potential Hawthorne effect could have been present in the staged cohort, accounting for some of the unplanned revascularizations occurring before the planned stage date. Our data are hypothesis-generating and require confirmation in large randomized trials because unadjusted variables may have confounded the results.

In conclusion, in patients presenting with STEMI and MVD, complete revascularization reduced the risk of MACE and ad hoc MVR appeared a reasonable strategy.

## Disclosures

The authors have no conflict of interest to declare.

## Author's contribution

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## Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.amjcard.2020.01.050>.



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