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# Complete vs Culprit-Only Revascularization in Older Patients With Myocardial Infarction and High Bleeding Risk
## A Randomized Clinical Trial

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**IMPORTANCE** Patients with high bleeding risk (HBR) have a poor prognosis, and it is not known if they may benefit from complete revascularization after myocardial infarction (MI).

**OBJECTIVE** To investigate the benefit of physiology-guided complete revascularization vs a culprit-only strategy in patients with HBR, MI, and multivessel disease.

**DESIGN, SETTING, AND PARTICIPANTS** This was a prespecified analysis of the Functional Assessment in Elderly MI Patients With Multivessel Disease (FIRE) randomized clinical trial data. FIRE was an investigator-initiated, open-label, multicenter trial. Patients 75 years or older with MI and multivessel disease were enrolled at 34 European centers from July 2019 through October 2021. Physiology treatment was performed either by angiography- or wire-based assessment. Patients were divided into HBR or non-HBR categories in accordance with the Academic Research Consortium HBR document.

**INTERVENTIONS** Patients were randomized to either physiology-guided complete revascularization or culprit-only strategy.

**MAIN OUTCOMES AND MEASURES** The primary outcome comprised a composite of death, MI, stroke, or revascularization at 1 year. Secondary outcomes included a composite of cardiovascular death or MI and Bleeding Academic Research Consortium (BARC) types 3 to 5.

**RESULTS** Among 1445 patients (mean [SD] age, 81 [5] years; 917 male [63%]), 1025 (71%) met HBR criteria. Patients with HBR were at higher risk for the primary end point (hazard ratio [HR], 2.01; 95% CI, 1.47-2.76), cardiovascular death or MI (HR, 1.89; 95% CI, 1.26-2.83), and BARC types 3 to 5 (HR, 3.28; 95% CI, 1.40-7.64). The primary end point was significantly reduced with physiology-guided complete revascularization as compared with culprit-only strategy in patients with HBR (HR, 0.73; 95% CI, 0.55-0.96). No indication of interaction was noted between revascularization strategy and HBR status for primary and secondary end points.

**CONCLUSIONS AND RELEVANCE** HBR status is prevalent among older patients with MI, significantly increasing the likelihood of adverse events. Physiology-guided complete revascularization emerges as an effective strategy, in comparison with culprit-only revascularization, for mitigating ischemic adverse events, including cardiovascular death and MI.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: NCT03772743

Visual Abstract

Supplemental content

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High bleeding risk (HBR) status represents a heterogenous condition that encompasses advanced age and/or severe comorbid conditions (anemia, chronic kidney disease, other hematological disorders, etc) and/or ongoing oral anticoagulant therapy.[1-4] Irrespective of these factors, HBR status unequivocally correlates with an increased risk of bleeding and ischemic complications.[1-4] To date, endeavors to enhance the outcomes of patients with HBR have predominantly centered on prompt identification of HBR status, choice of the radial artery as preferred vascular access for invasive procedures, optimization of antithrombotic regimens (intensity and length modulation), and selection of new-generation drug-eluting platforms.[5-9] To our knowledge, no data are available regarding the best revascularization strategy. Consensus documents suggest following the appropriate criteria and avoiding unnecessary revascularizations.[9] Randomized clinical trials and meta-analyses have clearly shown that complete revascularization in patients with myocardial infarction (MI) and multivessel disease is associated with a better clinical outcome, but whether this can be extrapolated to patients with HBR, MI, and multivessel disease is unclear.[10-13] The Functional Assessment in Elderly MI Patients With Multivessel Disease (FIRE) randomized clinical trial enrolled patients 75 years or older with MI and multivessel disease and showed a benefit in terms of ischemic adverse events in those randomized to physiology-guided complete revascularization.[12,13] As advanced age is one of the determinants of HBR status, including the fact that comorbidities associated with HBR are more frequent in older patients, the FIRE study population represents a unique opportunity to generate evidence regarding the optimal revascularization strategy for patients with HBR.

### Key Points

**Question** Can patients with high bleeding risk (HBR) and myocardial infarction (MI) benefit from complete revascularization as compared with a culprit-only strategy?

**Findings** In this prespecified analysis of the Functional Assessment in Elderly MI Patients With Multivessel Disease (FIRE) randomized clinical trial including 1445 patients, HBR status was common in older patients with MI and correlated with a significant increase in the risk of ischemic and bleeding complications. Physiology-guided complete revascularization effectively improves outcomes and decreases complication rate, irrespective of HBR status.

**Meaning** HBR status alone should not be a deterrent to applying physiology-guided complete revascularization in older patients with MI and multivessel disease.

## Methods

The FIRE study was a multicenter, investigator-initiated, randomized clinical trial comparing the efficacy of physiology-guided complete myocardial revascularization vs a culprit-only strategy in older patients with MI and multivessel disease.[12,13] The design, baseline characteristics, and primary results of the trial have been detailed in previous publications.[12,13] All enrolled patients provided written informed consent, and the trial protocol was approved by the institutional review board at each participating center (Supplement 1 and Supplement 2). The present study is a prespecified analysis of the FIRE trial aiming to (1) describe the frequency and prognostic impact of HBR status and (2) investigate the comparative efficacy and safety outcomes across HBR status of physiology-guided complete revascularization vs culprit-only strategy. For the present study, we followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

### Study Patients

Eligible patients were individuals aged 75 years or older who had been admitted to the hospital with either ST-segment–elevation MI (STEMI) or non–ST-segment–elevation MI (NSTEMI).[9,10] Furthermore, they were required to have undergone successful percutaneous coronary intervention (PCI) of the culprit lesion and needed to present at least 1 nonculprit coronary artery lesion with a minimum diameter of 2.5 mm and a diameter stenosis of 50% to 99%.[12,13] All patients were enrolled in Europe in centers where race and ethnicity heterogeneity is low. The vast majority of patients included in the study were White, therefore, no specific data regarding race and ethnicity were gathered for this study. Exclusion criteria included the inability to distinctly identify a culprit lesion based on clinical history, electrocardiogram, echocardiography, and angiography; presence of the nonculprit lesion in the left main, planned, or prior surgical revascularization; and a life expectancy of less than 1 year.[12,13]

### Study Procedures

Patients were randomized between July 18, 2019, and October 25, 2021. Patients who had been randomly assigned to physiology-guided complete revascularization received physiological assessment of nonculprit lesions using wire-based (hyperemic or nonhyperemic) and/or angiography-based (quantitative flow ratio [Medis Medical Imaging Systems B.V.]) measurements. All nonculprit lesions deemed functionally significant were subjected to PCI with subsequent stent implantation.[12,13] Conversely, patients assigned to culprit-only revascularization did not receive revascularization for nonculprit lesions.[12,13] In both treatment groups, the implantation of sirolimus-eluting biodegradable-polymer ultrathin stents (Supraflex Cruz [Sahajanand Medical Technologies]) was strongly recommended.[12,13] All individuals within both treatment arms received optimal medical therapy in accordance with established guidelines.

### Study End Points

The primary outcome was a composite end point of death, MI, stroke, or ischemia-driven coronary revascularization occurring within 1 year of randomization.[12,13] A key secondary outcome was the 1-year composite end point of cardiovascular death or MI. Other secondary outcomes comprised the individual components of the primary outcome and bleeding defined by the Bleeding Academic Research Consortium (BARC) types 3, 4, or 5. Outcome events were adjudicated according to definitions of the ARC and BARC consensus documents.[14,15]



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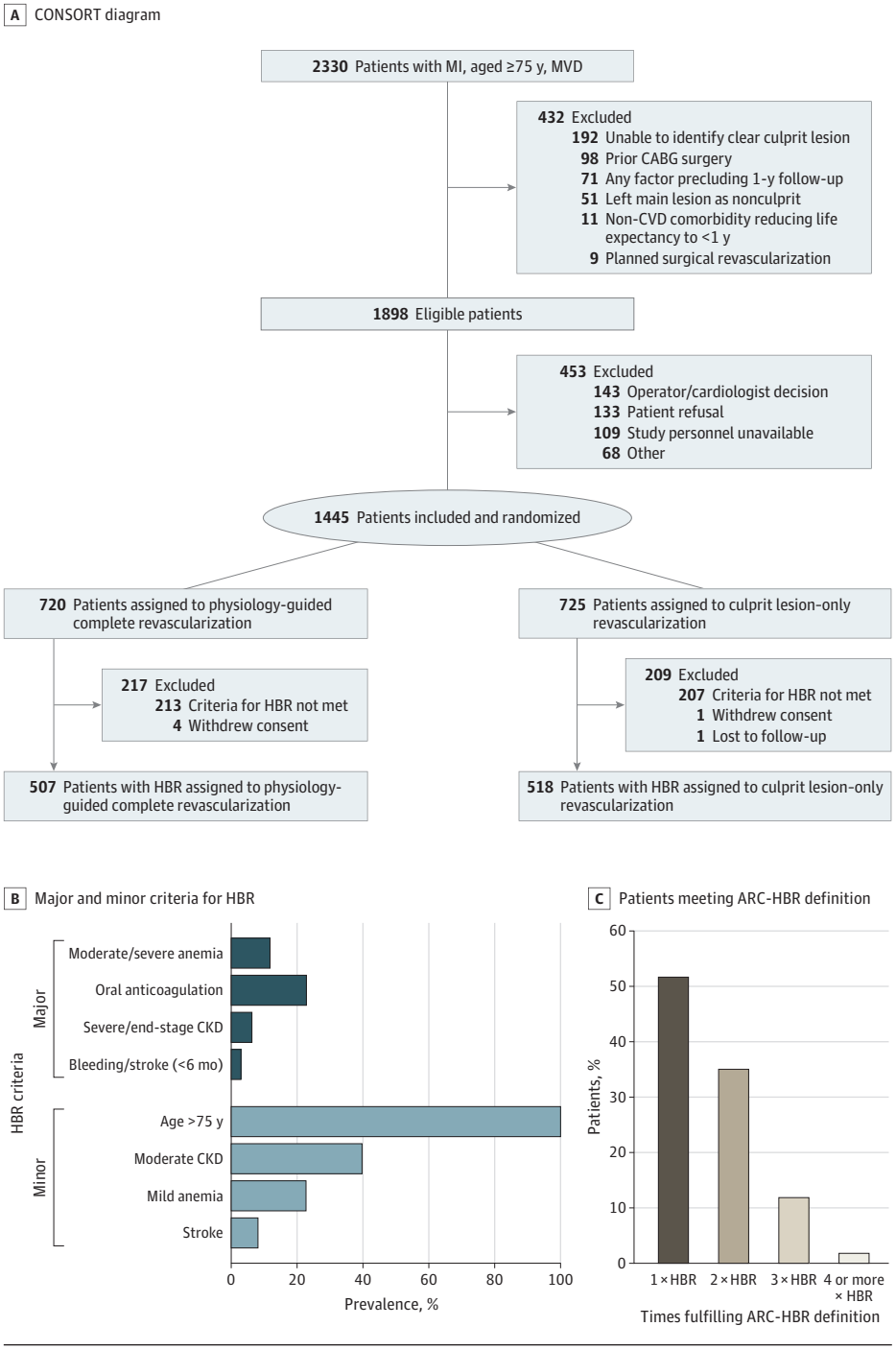
**Figure 1. Patient Flow Diagram, Prevalence of Academic Research Consortium (ARC)–High Bleeding Risk (HBR) Criteria, and ARC-HBR Definition in the HBR Group**




A, Consolidated Standards of Reporting Trials (CONSORT) diagram. B, Prevalence of major and minor ARC-HBR criteria. C, Percentage of patients with HBR meeting 1, 2, 3, or 4 or more times the ARC-HBR definition. CABG indicates coronary artery bypass graft; CKD, chronic kidney disease; CVD, cardiovascular disease; MI, myocardial infarction; MVD, multivessel disease.

All events were reported by investigators and analyzed and adjudicated by an independent clinical evaluation committee, blinded to the randomization arm.

## HBR Definition

The criteria for HBR were established in accordance with the ARC-HBR document, and both major and minor HBR criteria were systematically collected within the electronic case report form by the investigators.[3] Patients were categorized as having HBR if they fulfilled at least 1 major criterion or 2 minor criteria. Conversely, individuals not meeting any ARC-HBR criterion or patients with only 1 minor criterion were considered part of the non-HBR group. The study protocol recommended dual antiplatelet therapy (DAPT) for a minimum of 1 year, except for patients with HBR.[12,13] In patients with HBR, in agreement with available consensus document,[16]



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Table 1. Baseline Characteristics According to High Bleeding Risk (HBR) Status and Randomization Arm

| Characteristic | Non-HBR (n = 420) | HBR (n = 1025) | *P* value | Non-HBR | | | HBR | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Culprit only (n = 207) | Physiology-guided complete (n = 213) | *P* value | Culprit only (n = 518) | Physiology-guided complete (n = 507) | *P* value |
| Age, mean (SD), y | 79.6 (4) | 81.5 (4) | <.001 | 79.3 (4) | 79.8 (4) | .13 | 81.6 (5) | 81.4 (4) | .62 |
| Sex, No. (%) | | | | | | | | | |
| Female | 140 (33) | 388 (38) | .12 | 71 (34) | 69 (32) | .76 | 194 (37) | 194 (38) | .84 |
| Male | 280 (66) | 637 (62) | | 136 (66) | 144 (68) | | 324 (63) | 313 (62) | |
| Medical history, No. (%) | | | | | | | | | |
| Hypertension | 323 (77) | 862 (84) | <.001 | 49 (24) | 48 (22) | .87 | 434 (84) | 428 (84) | .85 |
| Dyslipidemia | 232 (55) | 527 (51) | .21 | 117 (56) | 115 (54) | .67 | 258 (50) | 269 (53) | .33 |
| Diabetes | 120 (28) | 343 (33) | .09 | 56 (27) | 64 (30) | .57 | 177 (34) | 166 (33) | .68 |
| Current smoker | 46 (11) | 77 (8) | .04 | 16 (8) | 30 (14) | .07 | 46 (9) | 31 (6) | .12 |
| Prior MI | 40 (10) | 180 (17) | <.001 | 18 (9) | 22 (10) | .69 | 98 (19) | 82 (16) | .28 |
| Prior PCI | 52 (12) | 205 (20) | <.001 | 26 (12) | 26 (12) | .97 | 110 (21) | 95 (19) | .36 |
| History of AF | 4 (1) | 196 (19) | <.001 | 2 (1) | 2 (1) | .64 | 107 (21) | 89 (17) | .24 |
| eGFR <60[a] | 0 | 662 (65) | <.001 | 207 (100) | 213 (100) | .81 | 332 (64) | 330 (65) | .79 |
| PAD | 49 (12) | 200 (19) | <.001 | 22 (11) | 27 (13) | .62 | 105 (20) | 95 (19) | .59 |
| CVA | 0 | 119 (12) | <.001 | 0 | 0 | .81 | 63 (12) | 56 (11) | .65 |
| Clinical presentation, No. (%) | | | | | | | | | |
| STEMI | 164 (39) | 345 (34) | .07 | 87 (42) | 77 (37) | .26 | 169 (33) | 176 (35) | .52 |
| NSTEMI | 256 (61) | 680 (66) | | 120 (58) | 136 (63) | | 349 (67) | 331 (65) | |
| Killip ≥2 | 75 (18) | 337 (33) | <.001 | 34 (16) | 41 (19) | .80 | 177 (34) | 163 (32) | .80 |
| LVEF, mean (SD), % | 51.1 (10) | 48.4 (11) | <.001 | 51.1 (10) | 50.9 (10) | .79 | 48.2 (11) | 48.7 (10) | .41 |
| Culprit vessel, No. (%) | | | | | | | | | |
| Left main coronary artery | 8 (2) | 68 (7) | <.001 | 4 (2) | 4 (2) | .46 | 37 (7) | 31 (6) | .63 |
| Left anterior descending artery | 186 (44) | 473 (46) | | 86 (41) | 100 (47) | | 244 (47) | 229 (45) | |
| Circumflex artery | 95 (23) | 174 (17) | | 54 (26) | 41 (19) | | 79 (15) | 95 (19) | |
| Right coronary artery | 120 (28) | 293 (28) | | 59 (28) | 61 (29) | | 150 (29) | 143 (28) | |
| Ramus intermedius artery | 11 (3) | 17 (2) | | 4 (2) | 7 (3) | | 8 (2) | 9 (2) | |
| Antithrombotic drugs at discharge, No. (%)[b] | | | | | | | | | |
| Aspirin | 419 (99) | 956 (93) | <.001 | 206 (99) | 213 (100) | .77 | 477 (92) | 479 (94) | .42 |
| Clopidogrel | 103 (25) | 626 (61) | <.001 | 50 (24) | 53 (25) | .59 | 308 (59) | 318 (63) | .64 |
| Ticagrelor | 297 (71) | 366 (36) | | 149 (72) | 148 (69) | | 188 (36) | 178 (35) | |
| Prasugrel | 19 (4.5) | 13 (1) | | 7 (3) | 12 (5) | | 9 (2) | 4 (1) | |
| Vitamin K antagonist | 0 | 63 (6) | <.001 | 0 | 0 | .77 | 36 (7) | 27 (5) | .34 |
| NOAC | 0 | 266 (26) | <.001 | 0 | 0 | .77 | 129 (25) | 137 (27) | .48 |
| Dual antiplatelet therapy | 419 (99) | 676 (66) | <.001 | 206 (99) | 213 (100) | .77 | 341 (66) | 335 (66) | .91 |
| Dual antithrombotic therapy | 0 | 53 (5) | <.001 | 0 | 0 | >.99 | 31 (6) | 22 (4) | .27 |
| Triple antithrombotic therapy | 0 | 276 (27) | <.001 | 0 | 0 | >.99 | 134 (26) | 142 (28) | .55 |

Abbreviations: AF, atrial fibrillation; CVA, cerebrovascular accident; eGFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NOAC, non–vitamin K antagonist oral anticoagulant; NSTEMI, non–ST-segment–elevation myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction.

[a] eGFR measured as milliliters per minute per 1.73 $m^2$ and calculated by Chronic Kidney Disease Epidemiology Collaboration formula.

[b] The analysis considers only patients discharged alive (n = 1009).

DAPT was suggested for 1 month. In the presence of oral anticoagulant therapy, the protocol suggested dual antithrombotic therapy (ie, clopidogrel plus novel oral anticoagulant). If the physician opted for triple antithrombotic therapy (ie, aspirin, clopidogrel, and novel oral anticoagulant), such a regimen was recommended for a maximum period of 30 days.

## Statistical Analysis

In the present analysis, patients were divided according to HBR status and their assigned randomization arm. Statistical analysis was conducted in accordance with the intention-to-treat principle, where all patients were assessed based on their designated treatment group. The normal distribution of continuous



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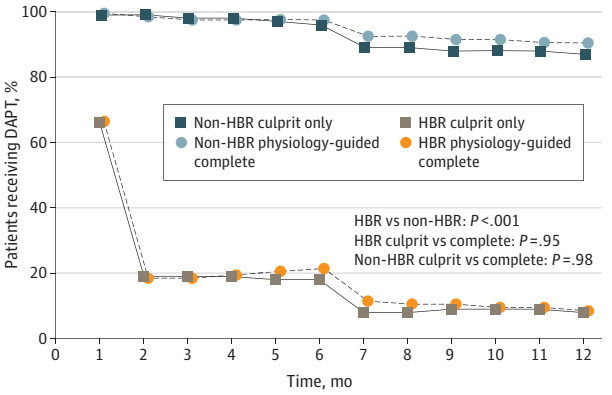
variables was assessed through the Shapiro-Wilk test. Continuous variables were summarized with means (SD) or median (IQR), and comparisons were executed using the *t* test or Wilcoxon test, as appropriate. Categorical variables were presented as frequencies and percentages, and comparative analyses were conducted using either the Pearson $\chi^2$ or Fisher exact test, in alignment with appropriateness. The pattern over time of patients with DAPT between patients with and without HBR (**Figure 1**) was analyzed with the $\chi^2$ Cochran-Armitage test. Time-to-event data were evaluated with the use of Kaplan-Meier estimates and Cox proportional hazards models, dividing the study population according to HBR status and/or randomization arm. The proportionality assumption was tested by Schoenfeld residuals and was met ($P > .05$ for all outcomes). Estimates and CIs for the outcomes that included cardiovascular death were adjusted for the competing risk of noncardiovascular death. Other secondary and safety outcomes were adjusted for the competing risk of death. Subsequently, we conducted a Cox regression analysis with interaction testing to determine whether the effect of revascularization strategy on the prespecified end points was consistent across both patients with and without HBR. The interaction test was carried out with likelihood ratio tests of the null hypothesis that the interaction coefficient was zero. The statistical analyses were performed using R statistical software, version 4.2 (R Foundation for Statistical Computing). All *P* values were 2-sided, and a *P* value <.05 was considered statistically significant.

## Results

Of the total 1445 patients (mean [SD] age, 81 [5] years; 917 male [63%]; 528 female [37%]) enrolled in the FIRE trial, 1025 (71%) fell within the HBR category, as defined by the ARC-HBR criteria (Figure 1A). The prevalence of each major and minor criterion within the HBR group is shown in Figure 1B. Specifically, 511 patients (49.8%) exhibited at least 1 major criterion. Further examination within the HBR group revealed that 528 patients (51.5%) fulfilled the ARC-HBR definition on a singular occasion, 358 (34.9%) met it 2 times, 121 (11.8%) met it 3 times, and 18 (1.8%) met it 4 times or more (Figure 1C). Significant disparities in baseline characteristics emerged between patients with and without HBR (**Table 1**). Compared with patients without HBR, patients in the HBR group were older (mean [SD] age, 81.5 [4] years vs 79.6 [4] years) and had a greater burden of comorbidities (eg, hypertension: 862 of 1025 [84%] vs 323 of 420 [77%]) (Table 1). At hospital admission, Killip class was worse in patients with HBR than those without HBR (337 of 1025 [33%] vs 75 of 420 [18%]) (Table 1). At hospital discharge, patients with HBR had lower left ventricle ejection fraction than those without HBR (mean [SD], 48.4% [11%] vs 51.1% [10%]), with clopidogrel being the most frequently prescribed P2Y12 inhibitor (626 of 1025 [61%] vs 103 of 420 [25%]); conversely, the prescription of DAPT was less common in this group (676 of 1025 [66%] vs 419 of 420 [99%]) (Table 1). DAPT prescription over time was lower in patients with HBR compared with patients in the non-HBR group (*P* for trend < .001) (**Figure 2**). After the first month, fewer than one-fifth of patients with HBR continued taking DAPT (Figure 2). In contrast, the non-HBR and HBR subgroups allocated to physiology-guided complete revascularization vs a culprit-only strategy exhibited a notable alignment in terms of demographics, medical history, clinical presentation, and medications on discharge (Table 1). Analyzing DAPT prescription over time, we observed that it was not associated with randomization arms (Figure 2).

**Figure 2. Percentage of Patients Receiving Dual Antiplatelet Therapy (DAPT) Over Time According to High Bleeding Risk (HBR) Status and Randomization Arm**




### Clinical Outcomes of Patients With and Without HBR

The occurrence of the primary end point was higher in patients with HBR (21% [218 of 1025] vs 11% [47 of 420]; $P < .001$; hazard ratio [HR], 2.01; 95% CI, 1.47-2.76). Similarly, patients with HBR were at increased risk of cardiovascular death or MI (13% [133 of 1025] vs 7% [29 of 420]; $P = .001$; HR, 1.89; 95% CI, 1.26-2.83), death (13% [136 of 1025] vs 5% [23 of 420]; $P < .001$; HR, 2.53; 95% CI, 1.63-3.94), and cardiovascular death (8% [78 of 1025] vs 3% [14 of 420]; $P = .003$; HR, 2.33; 95% CI, 1.32-4.12). As expected, the cumulative occurrence of BARC types 3 to 5 was higher in patients with HBR than in those without HBR (6% [63 of 1025] vs 2% [7 of 420]; $P = .006$; HR, 3.28; 95% CI, 1.40-7.64).

### Clinical Outcomes of Physiology-Guided Complete Revascularization vs Culprit-Only According to HBR Status

In the FIRE trial, physiology-guided revascularization was obtained by either angiography- or wire-based assessment (35% [320 of 909 vessels] vs 65% [589 of 909 vessels]). Angiography-based physiology was used both in patients with STEMI and NSTEMI (34% [86 of 249] vs 66% [163 of 249]). The most frequently interrogated vessels by angiography-based physiology were the left anterior descending and right coronary arteries (32% [103 of 320] and 37% [118 of 320], respectively). No significant interaction was noted between revascularization strategy and HBR status with respect to both primary and secondary end points (**Table 2** and **Figure 3**A). The primary end



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Table 2. Clinical Outcomes According to Randomization Arm and High Bleeding Risk (HBR) Status

| Outcome | Non-HBR (n = 420) | | | HBR (n = 1025) | | | |
|---|---|---|---|---|---|---|---|
| | Culprit only (n = 207) | Physiology-guided complete (n = 213) | *P* value | Culprit only (n = 518) | Physiology-guided complete (n = 507) | *P* value | *P* value for interaction |
| **Primary outcome** | | | | | | | |
| Composite of death, myocardial infarction, stroke, or ischemia-driven revascularization | | | | | | | |
| No. (%) | 29 (14) | 18 (8.5) | .07 | 123 (24) | 95 (19) | .04 | .55 |
| HR (95% CI) | 0.60 (0.33-1.08) | | | 0.73 (0.55-0.96) | | | |
| **Secondary outcomes** | | | | | | | |
| Cardiovascular death, myocardial infarction | | | | | | | |
| No. (%) | 20 (10) | 9 (4) | .03 | 78 (15) | 55 (11) | .047 | .24 |
| HR (95% CI) | 0.42 (0.19-0.93) | | | 0.71 (0.50-0.99) | | | |
| Death | | | | | | | |
| No. (%) | 13 (6) | 10 (5) | .49 | 80 (15) | 56 (11) | .04 | .88 |
| HR (95% CI) | 0.75 (0.33-1.70) | | | 0.70 (0.49-0.98) | | | |
| Cardiovascular death | | | | | | | |
| No. (%) | 8 (4) | 6 (3) | .56 | 48 (9) | 30 (6) | .04 | .72 |
| HR (95% CI) | 0.73 (0.25-2.12) | | | 0.62 (0.40-0.98) | | | |
| Myocardial infarction | | | | | | | |
| No. (%) | 15 (7) | 4 (2) | .01 | 36 (7) | 28 (5.5) | .31 | .07 |
| HR (95% CI) | 0.24 (0.07-0.83) | | | 0.88 (0.51-1.51) | | | |
| Stroke | | | | | | | |
| No. (%) | 2 (1) | 2 (1) | .98 | 5 (1) | 10 (2) | .19 | .40 |
| HR (95% CI) | 0.98 (0.14-6.92) | | | 2.73 (.73-1.31) | | | |
| Ischemia-driven coronary revascularization | | | | | | | |
| No. (%) | 10 (5) | 5 (2) | .16 | 39 (7.5) | 26 (5) | .10 | .76 |
| HR (95% CI) | 0.52 (0.18-1.54) | | | 0.64 (0.37-1.09) | | | |
| Definite stent thrombosis | | | | | | | |
| No. (%) | 0 | 0 | NA | 5 (1) | 6 (1) | NA | NA |
| HR (95% CI) | NA | | | NA | | | |
| Probable stent thrombosis | | | | | | | |
| No. (%) | 0 | 1 (0.5) | NA | 3 (0.5) | 0 | NA | NA |
| HR (95% CI) | NA | | | NA | | | |
| BARC type 3, 4, or 5 bleeding | | | | | | | |
| No. (%) | 2 (1) | 5 (2) | .29 | 34 (6.5) | 29 (6) | .53 | .08 |
| HR (95% CI) | 4.88 (0.57-41.98) | | | 0.69 (0.38-1.25) | | | |

Abbreviations: BARC, Bleeding Academic Research Consortium; HR, hazard ratio; NA, not assessed.

point was significantly reduced with physiology-guided complete revascularization as compared with culprit-only strategy in patients with HBR (19% [95 of 507] vs 24% [123 of 518]; *P* = .04; HR, 0.73; 95% CI, 0.55-0.96), without significant interaction in patients without HBR (8.5% [18 of 213] vs 14% [29 of 207]; *P* = .07; HR, 0.60; 95% CI, 0.33-1.08; *P* for interaction =.55) (Table 2 and Figure 3B). Physiology-guided complete revascularization was consistently associated with lower cardiovascular death or MI in both non-HBR and HBR groups (non-HBR: HR, 0.42; 95% CI, 0.19-0.93; HBR: HR, 0.71; 95% CI, 0.50-0.99; *P* for interaction = .24) (Table 2 and Figure 3A). At further analysis, no indication of interaction was noted between revascularization strategy and HBR status for other secondary end points, including BARC types 3 to 5 (Table 2 and Figure 3A).

## Discussion

The primary findings of this study are summarized as follows. First, HBR status was common within a predominantly unselected group of older patients with MI and multivessel disease, with a notable occurrence of 71% (95% CI, 68%-73%). Second, HBR status substantially amplified the risk of adverse events. This is not limited to bleeding complications, but it includes hard ischemic end points such as death and cardiovascular death or MI. Third, physiology-guided complete revascularization led to a meaningful decrease in both primary end point and occurrence of cardiovascular death or MI, independent of HBR status. This underscores the fact that the ex-



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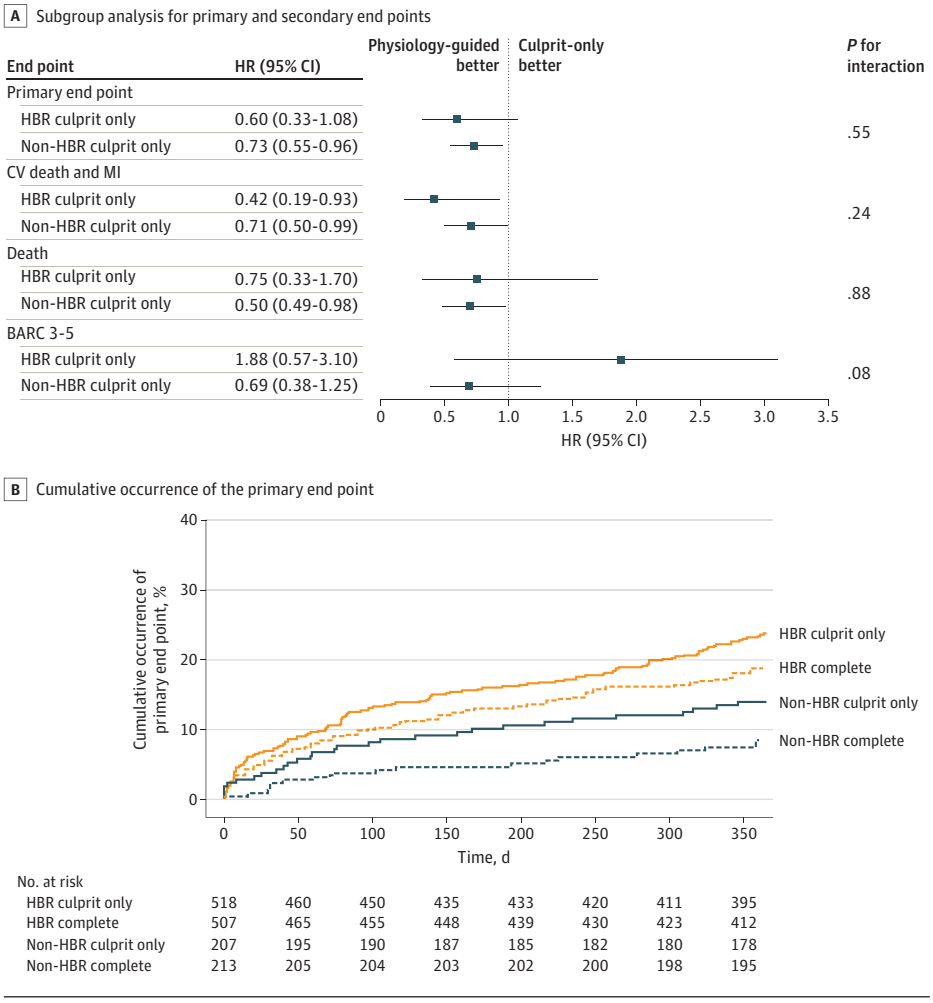
**Figure 3. Subgroup Analysis for the Primary and Secondary End Points Stratifying Patients in High Bleeding Risk (HBR) and Non-HBR Groups and Cumulative Occurrence of the Primary End Point in Patients According to HBR Status and Randomization Arm**




A, Subgroup analysis. B, Kaplan-Meier curve of the cumulative occurrence of the primary end point. BARC indicates Bleeding Academic Research Consortium; CV, cardiovascular; HR, hazard ratio.

pected benefits of complete revascularization remain intact for patients with HBR, despite potential challenges.

PCI stands as the primary approach to address obstructive coronary artery disease, yet clinicians encounter the intricate task of balancing bleeding and ischemia risks. In the past, the focal concern was avoiding periprocedural bleeding complications. Cardiologists commonly used femoral access for PCI, concurrently administering heparin along with glycoprotein IIb/IIIa inhibitors during the procedure. Subsequent studies underscored the fact that radial access and alternative drug protocols, like bivalirudin, notably decreased in-hospital major bleeding incidents.[17,18] This subsequently shifted the spotlight toward averting bleeding after discharge. In 2019, the ARC-HBR established a consensus definition of HBR based on existing evidence.[3] HBR status involves approximately 30% to 40% of the general population of patients undergoing PCI, and it is associated with a significant increase in the risk of bleeding complications and all-cause mortality.[1-4] Trying to generate evidence for the optimization of the outcomes of patients with HBR, many randomized clinical trials have been conducted on vascular access, antithrombotic regimens, and stent platforms.[4-9] Growing evidence supported the benefit of an antithrombotic strategy consisting of antiplatelet monotherapy after a shortened DAPT vs conventional DAPT. Additionally, the safety profile of present stent platforms with shortened DAPT regimen was corroborated.[4-9] However, no investigations have directly tackled the optimal revascularization approach for multivessel disease in patients with HBR presenting with MI.

Available data highlighted that complete revascularization is frequently underused in patients with HBR.[19,20] This observation, although not unexpected, is rooted in clinical practice, where the count of implanted stents and the extensive coronary treatment often dictate prolonged DAPT. In addition, patients with HBR frequently show a more complex coronary anatomy, severe calcifications, 3-vessel disease, all factors that may discourage pursuing complete revascularization due to concerns of periprocedural complications.[21,22] Finally, each procedure carries inherent risks of bleeding that are independent of the revascularization strategy.



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Building on this foundation, the clinical implications of our analysis are transformative. We confirmed that HBR status is a common clinical pattern in older patients with MI, undeniably associated with poor prognoses. Allocating resources to a physiology-guided complete revascularization presents a formidable avenue for enhancing prognostic outcomes by significantly curbing the incidences of death, MI, and revascularization.

However, realizing these promising outcomes necessitated meticulous consideration of several pivotal factors. First, the revascularization of nonculprit lesions was guided by coronary physiology. This strategic approach channels efforts toward ischemia-generating lesions, where the prospect of achieving clinical benefits is higher. Coronary physiology guidance results in fewer unnecessary procedures and stents, simplifies the management of 3-vessel disease, and then minimizes the risk of periprocedural complications.[23] Second, the implantation of last generation drug-eluting stents reduced the risk of stent-related adverse events. Finally, in agreement with current standards, patients with HBR who participated in the FIRE trial were treated with short DAPT regimens. This stands as a noteworthy point because the enrolled patients exhibited substantial ischemic risks due to their advanced age, multiple comorbidities, and multivessel disease. Research has demonstrated that in the presence of HBR status, using a prolonged DAPT regimen is not the most effective approach to reduce ischemic risk.[24] The possible advantages of this approach are overshadowed by a higher chance of bleeding complications and their impact on mortality. In these cases, physicians should identify alternative strategies, and our data indicate that a physiology-guided complete revascularization with latest generation drug-eluting stent and short DAPT regimen could be a more suitable option.

### Limitations

The present prespecified analysis has certain limitations that should be taken into consideration. Although prespecified, to investigate the effect of physiology-guided complete revascularization in patients with HBR was not the primary aim of the FIRE trial. Second, the FIRE trial was powered for the composite end point of death, MI, stroke, and ischemia-driven revascularization. Findings on secondary end points should be considered with caution. Furthermore, it should be noted that complete revascularization was guided by coronary physiology and with the implantation of sirolimus-eluting biodegradable-polymer ultrathin stents. As such, it remains uncertain whether our study's outcomes can be extrapolated to patients managed with different strategies and stent platforms. Lastly, it is essential to recognize that our findings pertain to the specific context of this trial, in which the majority of participating centers possessed extensive expertise in coronary physiology.

## Conclusions

The present prespecified analysis of the FIRE randomized clinical trial suggests that HBR status was common in older patients with MI and was associated with a higher risk of ischemic and bleeding complications, including death. Physiology-guided complete revascularization emerged as an effective method to reduce ischemic complications, including cardiovascular death and MI, and should be considered in the treatment of patients with HBR.

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