Investigation of factors influencing the incidence and prognosis of acute myocardial infarction

PhD thesis

by

Péter Kupó MD

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University of Pécs, Medical School, Heart Institute

Supervisor: András Komócsi MD, PhD, DSc

Head of Doctoral School: Lajos Bogár MD, PhD, DSc

Program leader: István Szokodi MD, PhD, DSc

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1. INTRODUCTION

Coronary heart disease (CHD) is the leading cause of death and disability and has a major impact on both developing and developed nations. The acute manifestation of CHD is defined as an acute coronary syndrome (ACS). The two main cornerstones of the treatment of this condition are the immediate administration of antiplatelet agents after diagnosis and the reperfusion therapy, most commonly percutaneous coronary intervention (PCI), during which the vascular segment responsible for the development of acute myocardial infarction (AMI) is identified and treated by mechanical reperfusion and implantation of stents in the coronary artery stenoses. Although the therapeutic options and strategy for ACS have developed fast in the last decades, there are still unresolved questions in need of further clarification.

Regarding the administration of antiplatelet drugs immediately after diagnosis (being most commonly clopidogrel and aspirin in Hungary), previous studies demonstrated large inter-individual differences in response to clopidogrel. The term "clopidogrel resistance" was created and widely applied to refer to patients with an inappropriate response, which raised important questions regarding the treatment of AMI. Another major issue regarding the treatment of ACS is the type of stents implanted during PCI in different patient populations since nowadays not only bare-metal stents (BMS) but also stents delivering antiproliferative drugs (drug-eluting stent, DES) are available.

In recent years several new anticoagulants (direct oral anticoagulant, DOAC) have been introduced for various indications. Since the use of these drugs concerns large patient populations it brings up important questions regarding their cardiovascular safety.

2. AIMS

The main aims of our studies were the following:

- to compare the safety and efficacy outcomes and to determine the prognostic significance of BMS and DES in elderly patients with an AMI undergoing PCI
- to evaluate the clinical impact of platelet function testing (PFT) guidance among patients with AMI
- to compare the risk of MI among DOAC-treated patients

3. BACKGROUND

3.1. Use of drug-eluting stents in elderly patients with AMI

The superior clinical performance of DES compared to BMS has been widely documented. However, the time required for the development of the endothelial coverage is longer, thus the necessary dual antiplatelet therapy (DAPT) should be prolonged to prevent stent thrombosis. Elderly patients have a higher bleeding risk which might give reason to implant the BMS during PCI. However, in a recent SENIOR trial, the use of DES with a short duration of DAPT proved to be beneficial compared to BMS with a similar duration of DAPT. This trial - by examining elderly patients undergoing acute or elective PCI - demonstrated benefits regarding the composite endpoint of all-cause mortality, MI, stroke, and ischemia-driven target lesion revascularization (TLR), while no difference was detected in bleeding risk between the groups.

3.2. Comparison of platelet function guided versus unguided treatment with $P2Y_{12}$ inhibitors in patients with AMI

Among platelet $P2Y_{12}$ inhibitors, prasugrel and ticagrelor are the preferred choices in the treatment of AMI, however in Hungary, due to the financial and regulatory reasons the earlier generation ADP blocker clopidogrel is used most frequently, despite the well-known phenomenon of clopidogrel resistance. Although the high residual platelet reactivity on clopidogrel (HPRoC) is an independent predictor of stent thrombosis and MI, current guidelines discourage the routine use of platelet function testing (PFT) due to lack of evidence on its ability to improve outcomes. However, local reimbursement regulations in Hungary mandate the use of PFT to identify patients with HPRoC in whom a switch from clopidogrel to prasugrel could be of great importance.

3.3.Direct anticoagulants and the risk of MI

DOACs have been proposed as good alternatives for vitamin K antagonists (VKA). These drugs are widely used since not only they are more convenient (there is no need for laboratory monitoring) but also have been proven to be of similar or higher efficacy in preventing ischemic events and to have a similar or lower risk for bleeding complications. Regarding CV safety, DOACs showed contradictory results. Rivaroxaban in addition to antiplatelet therapy was associated with the prevention of stroke and had a favorable effect on mortality and CV outcomes. In contrast, dabigatran treatment was associated with increased risk for MI. Direct comparative trials are not available to compare the risk of MI among DOAC-treated patients.

4. METHODS

4.1.Use of drug-eluting stents in elderly patients with AMI

The Hungarian Myocardial Infarction Registry (HUMIR) is a prospective registry collecting clinical data on consecutive patients treated for an AMI in Hungary. Patients over the age of 75, undergoing successful PCI for AMI with or without ST-segment elevation were enrolled. Two groups were created according to the type of the implanted stent (DES or BMS). The primary efficacy endpoint was the all-cause mortality within 1 year after the index procedure. Secondary endpoints included the blood transfusion and two composite endpoints: major adverse cardiovascular events (MACE) (composite events of death, recurrent MI and stroke), and repeat revascularization. As the patients were not randomly assigned to DES or BMS treatments, we intended to balance the groups with the help of multiple characteristics that may potentially influence both device selection and outcomes. For this aim, we built a propensity score (PS)-matched cohort using a logistic regression model for DES vs BMS groups, to compute the probability of each treatments.

4.2.Comparison of platelet function guided versus unguided treatment with $P2Y_{12}$ inhibitors in patients with AMI

Patients from HUMIR with the same enrollment criteria without age restriction described in Section 4.1. were included. It was left to the discretion of the treating physicians whether to perform the PFT or not. The primary efficacy endpoint was all-cause mortality within one year after the index procedure. Secondary endpoints included the composite of CV death, recurrent MI, and stroke as well as transfusion and the individual elements of the composite endpoint. PS matching was applied as described in Section 4.1.

4.3.Direct anticoagulants and the risk of MI

A manual search of medical literature was performed for articles reporting randomized clinical trials with DOACs, using the following search terms: “pulmonary embolism,” “atrial fibrillation,” “thromboprophylaxis,” “anticoagulation,” “prevention,” “rivaroxaban OR apixaban OR dabigatran OR edoxaban”. Trials were included if the following criteria were fulfilled: (1) randomized clinical trials (RCTs) that assessed the clinical efficacy and/or safety of an anticoagulant protocol comprising ≥1 DOACs (dabigatran, rivaroxaban, apixaban, or edoxaban) (2) having one or more control group with oral anticoagulation, antiplatelet treatment, or placebo (3) reporting on the frequency of MI or the rate of ACS during the follow-up compliant with intention-to-treat analysis. The primary endpoint of the analysis was the

frequency of MI. The secondary endpoint was overall mortality. As a safety measure, the frequency of major bleeding complications was evaluated. The risk of MI was analyzed in a hierarchical Bayesian mixed-treatment comparison meta-analysis. Treatment effects are reported as a risk ratio with 95% associated credible interval (CrI).

5. RESULTS

5.1.Use of drug-eluting stents in elderly patients with AMI

7383 patients were included. In 4117 (55.8%) cases BMS, in 3266 (44.2%) cases DES was implanted. PS matching was performed which resulted in a matched population of 5780 patients with balanced characteristics. The 1-year all-cause mortality rate was 27.8%. DES-treated subjects had a highly significant, 34% lower hazard for all-cause mortality compared with the BMS group (HR: 0.66, [0.60-0.73], $p<0.001$). Rates of MACE, repeated revascularization and blood transfusion were higher in the BMS group and these differences reached high levels of significance even after PS matching except for transfusion (Figure 1 and Table 1).

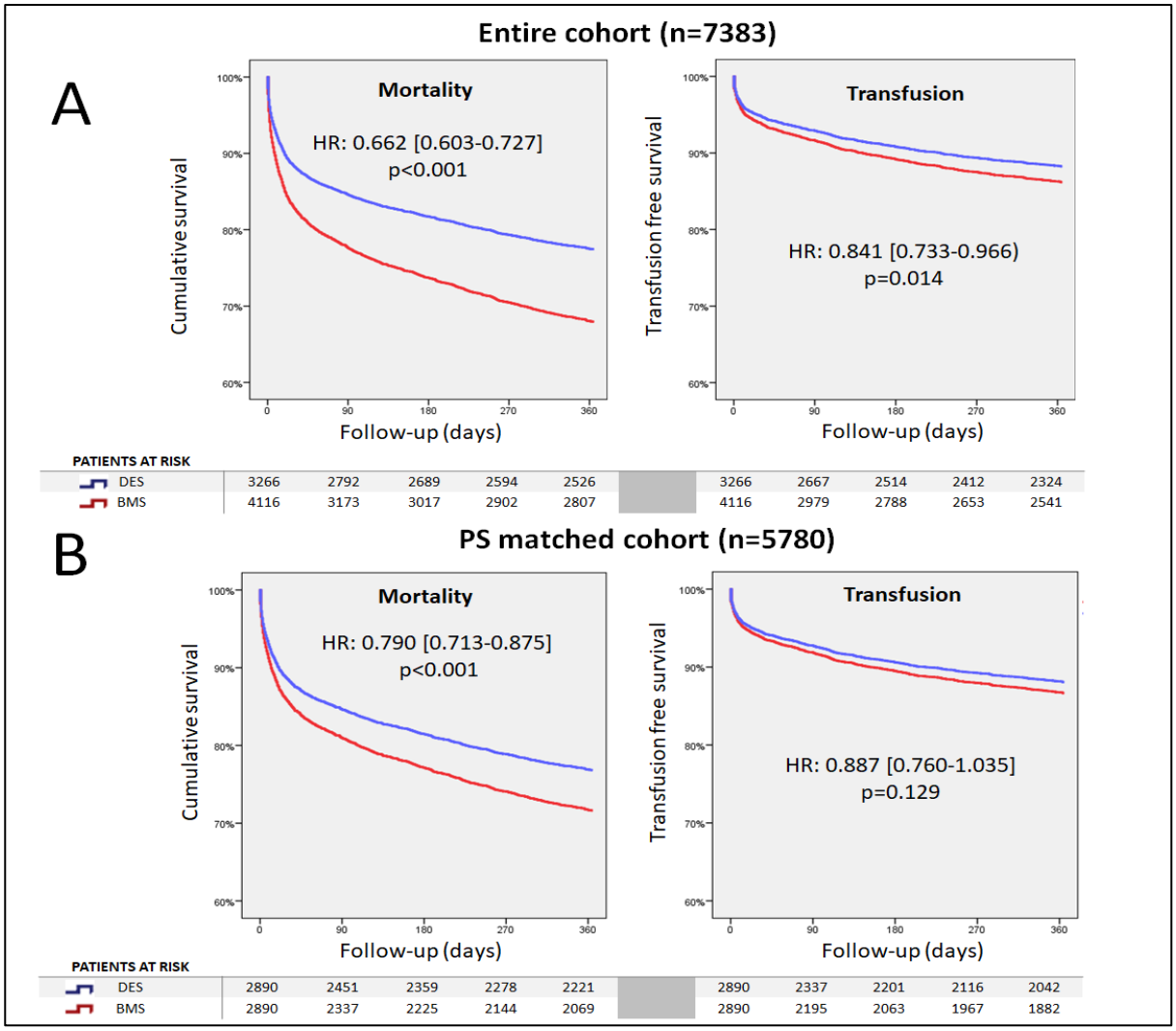

Figure 1. Kaplan-Meier curves of overall survival and blood transfusion-free survival comparing drug-eluting (DES) or bare-metal stent (BMS) implanted patients. Panel A shows the survival differences seen in the overall cohort, while data from the propensity score (PS) are depicted in panel B. Abbreviations: BMS: bare-metal stent; DES: drug-eluting stent; HR: hazard ratio; PS: propensity score

Independent predictors of outcome	Mortality (HR)	95% CI	p-value	Bleeding (HR)	95% CI	p-value
DES	0.75	0.67-0.83	<0.001	0.88	0.76-1.03	0.112
Resuscitation	2.32	1.88-2.88	<0.001	2.32	1.59-3.37	<0.001
Shock	1.87	1.43-2.44	<0.001	-		
Killip status	1.33	1.22-1.45	<0.001	-		
Heart rate (beat/min)	1.01	1.01-1.01	<0.001	1.01	1.003-1.01	0.001
Systolic pressure (mmHg)	0.99	0.98-0.99	<0.001	1.00	0.99-1.00	0.057
Diastolic pressure (mmHg)	-			0.99	0.98-0.99	<0.001
Creatinine level (µmol/l)	1.01	1.004-1.01	<0.001	1.005	1.004-1.006	<0.001
STEMI	0.75	0.67-0.83	<0.001	1.27	1.07-1.50	0.006
Prior MI	-			0.83	0.69-1.003	0.054
Prior stroke	1.46	1.27-1.69	<0.001	-		
Prior heart failure	1.55	1.36-1.75	<0.001	1.44	1.19-1.76	<0.001
Diabetes mellitus	1.21	1.09-1.34	<0.001	1.40	1.20-1.64	<0.001
PAD	1.35	1.18-1.54	<0.001	-		
Hyperlipidemia	0.87	0.77-0.98	0.018	-		
Prior PCI	0.84	0.74-0.96	0.008	-		
Male sex	-			0.80	0.66-0.96	0.020
Height (cm)	-			1.01	1.001-1.03	0.042
Bodyweight (kg)	0.99	0.99-0.99	<0.001	0.99	0.98-1.0	0.009

Table 1. Results of the multivariable Cox regression analysis for the identification of the independent predictors of mortality and bleeding. Abbreviations: CI: confidence interval; DES: drug-eluting stent; HR: hazard ratio; MI: myocardial infarction; PAD: Peripheral arterial disease; STEMI: ST-segment elevation myocardial infarction, PCI: percutaneous coronary intervention.

5.2.Comparison of platelet function guided versus unguided treatment with $P2Y_{12}$ inhibitors in patients with AMI

3974 patients were included. Among the 2901 subjects of the PFT-guided group, 554 (19%) had HPRoC. 70% percent of them were switched to prasugrel, while 30% continued clopidogrel (14% high-dose and 16% standard-dose clopidogrel). In patients without HPRoC, the use of prasugrel was low (2%). Among unguided patients, prasugrel was prescribed only in 4%, while standard-dose clopidogrel was applied in 74%.

In this high-risk cohort, the one-year all-cause mortality rate was 9.5%. PFT-guided subjects had a highly significant, 43% lower hazard for all-cause mortality compared to the unguided group (HR: 0.57, [0.43-0.77], p<0.001, Figure 2). CV mortality was also reduced by 39%. (HR:0.61, [0.45-0.83], p<0.01). In the unmatched total cohort, similar results were observed for all-cause and CV mortality, without a significant difference in the risk of stroke or repeat MI. Since the use of prasugrel was higher in the PFT-guided than in the unguided group (16% vs. 4%, p<0.001), its potential impact on survival was calculated in the overall analysis populations. Prasugrel treatment, however, was not associated with a lower risk of mortality in the PS-matched (HR:0.65 [0.38-1.11]], p=0.116) or in the unmatched cohorts (HR: 0.75 [0.51-1.11], p=0.145).

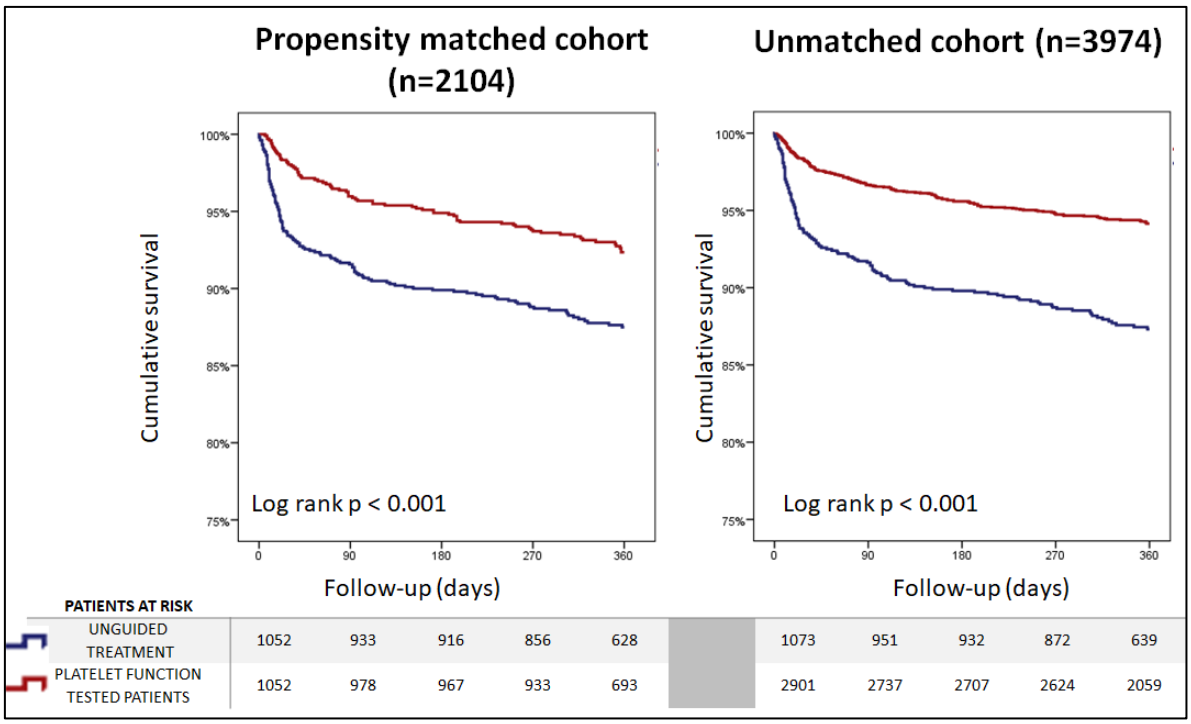

Figure 2. Kaplan Meier curves of survival comparing platelet function test guided versus unguided treated myocardial infarction cases assessed in the propensity score-adjusted sample and the whole cohort.

5.3.Direct anticoagulants and the risk of MI

Twenty-eight RCTs involving 196,761 (range: 1280-27 395) patients were analyzed. According to the applied anticoagulants, study arms were divided into 8 groups. In the included trials, 3554 MIs occurred in the VKA arm with the lowest rate (1.25%) and in the placebo arms with the highest rate (4.55%; Figure 7B). Heterogeneity analysis showed consistent results within treatment groups (dabigatran I^2: 26%, χ^2: p=0.23 and I^2: 0%, χ^2: p ≥0.53 for all other DOACs). Rivaroxaban was associated with a relative risk (RR) reduction of 21% regarding MI when compared to placebo (RR: 0.79 [0.65-0.94]) and a 31% reduction (RR: 0.70 [0.53-0.89]) when compared to dabigatran. Apixaban resulted in 24% (RR: 0.76 [0.58-0.99], and VKA resulted in 19% (RR: 0.81 [0.65-0.98]) risk reduction compared with dabigatran. (Figure 3).

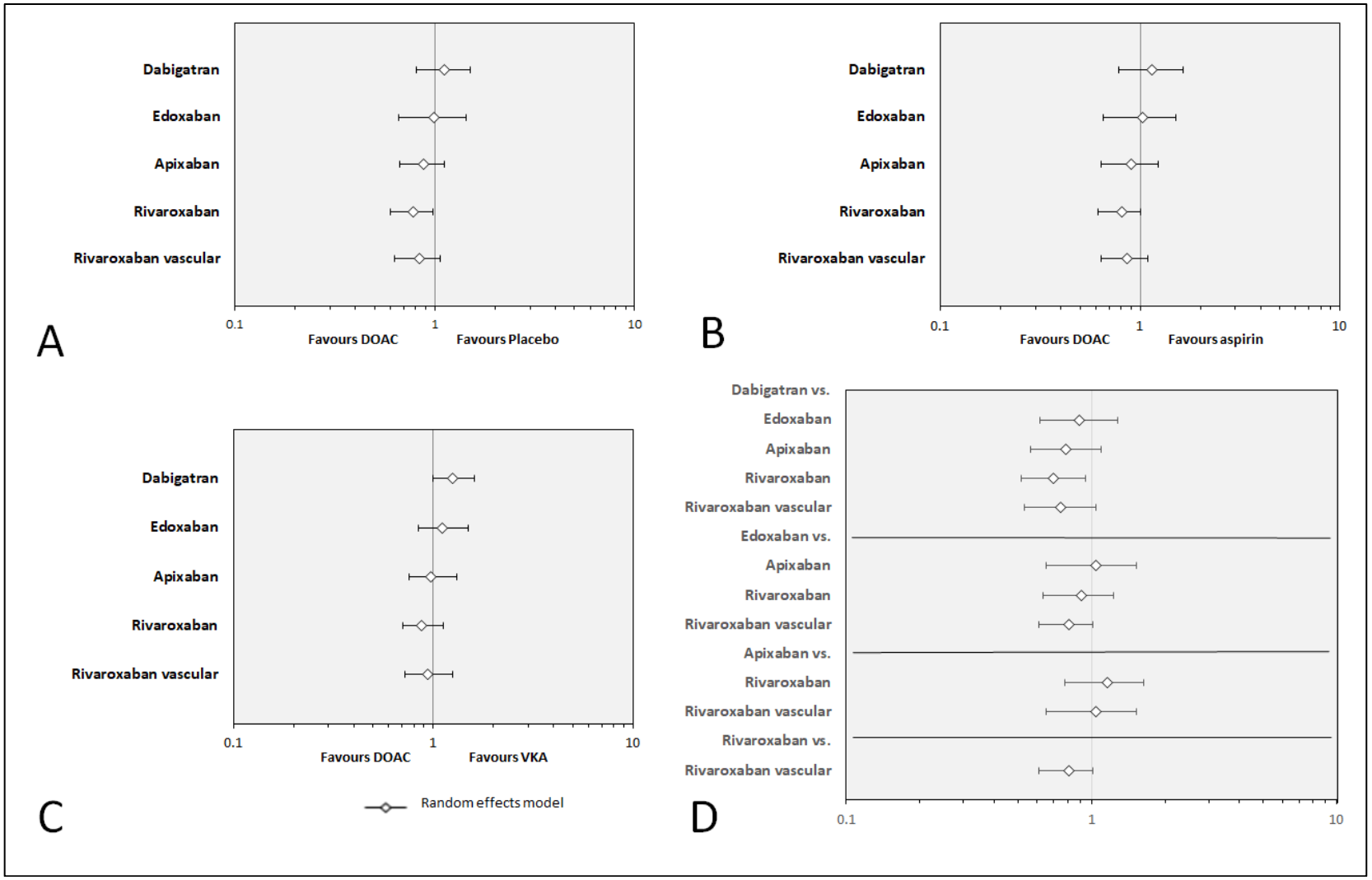

Figure 3. Forest plot of the relative risk of myocardial infarction. A, B, and C, The relation of the myocardial infarction risk of the DOAC treatments compared to the placebo and aspirin of vitamin K antagonist controls, respectively. D, Comparisons among the different DOAC groups. DOAC indicates direct oral anticoagulant; VKA, vitamin K antagonists.

6. DISCUSSION

6.1.Use of drug-eluting stents in elderly patients with AMI

The 2018 European guidelines on myocardial revascularization recommend DES over BMS in case of any PCI procedure, regardless of age. New-generation DES has higher efficacy and safety in comparison with both early-generation DES and BMS. In our study, we have found that DES is still underused in the elderly. The decision for the implantation of BMS rather than DES in this population is driven principally by concerns about higher bleeding risk and DAPT compliance, however, we have found no excess of severe, blood transfusion requiring events in the DES cohort. Similarly to the conclusion of the SENIOR trial – in which patients over 75 years undergoing acute or elective PCI were analyzed - our data also clearly refute the assumption of the higher safety of BMS in a frail and elderly population with AMI.

6.2.Comparison of platelet function guided versus unguided treatment with $P2Y_{12}$ inhibitors in patients with AMI

Our analysis showed improved survival in patients with PFT-guided antiplatelet treatment compared to the unguided strategy. Explorative analyses demonstrated that the results of PFT had an important impact on the selected $P2Y_{12}$ inhibitor therapy as patients without PFT guidance were more frequently kept on clopidogrel, while those in the PFT-guided group harboring HPRoC were mostly switched over to prasugrel. Importantly, prasugrel therapy was not a predictor of lower mortality in the overall cohort, but it was associated with a reduction in all-cause death only in patients with HPRoC. Our data are in line with the results of the GRAVITAS trial as we did not detect a significant clinical difference between high-dose and standard-dose clopidogrel in the case of HPRoC. Our results correspond to those of the TROPICAL ACS study which was the first to support that a PFT-guided strategy is equally safe and effective as the guideline-recommended strategy.

6.3.Direct anticoagulants and the risk of MI

Our analysis assessed the preventive potential of DOACs. The results of our analysis are consistent with the large body of evidence documenting the ability of anticoagulants to reduce ischemic events in patients with or without established CHD, including ACS. We found evidence that the choice of anticoagulant influences the risk of MI in anticoagulated patients. When the risk of MI is taken into consideration, the probability of being the best choice of treatment is the highest for rivaroxaban administered in an antithrombotic or vascular

prevention dose regimen, while the lowest is for VKAs and the direct thrombin inhibitor, dabigatran.

7. NOVEL FINDINGS

Based on the results of the cited experiments and studies, our major novel findings can be summarized as follows:

- Our analysis of a real-life, high-risk elderly population with AMI, demonstrated that DES implantation is an advantageous strategy for elderly patients. The observed benefits may be enhanced by the treatment selection, but even after propensity matching of the treatment groups our data still support the ischemic benefit and revealed no signal of higher bleeding risk. These data support that DES is underused in the aged population and endorse the guideline-recommended use of DES even in high-risk elderly patients with AMI.
- According to the results from an all-comer, high-risk cohort of the HUMIR registry cases with PFT-guided selection of $P2Y_{12}$ inhibitor therapy had lower mortality in contrast to lack of PFT guidance and clinical decision making. Although the PFT-guided group showed a higher frequency of switch-over to prasugrel, allocation to prasugrel versus clopidogrel did not reduce mortality in the overall cohort. In contrast, prasugrel treatment significantly improved survival in patients with HPRoC, compared to standard and high-dose clopidogrel.
- Results of our comprehensive meta-analysis involving 28 RCTs and 196 761 patients showed significant differences in CV safety among oral anticoagulants. The risk of MI is lowest with rivaroxaban, followed by apixaban and edoxaban, while it is the highest for VKA and dabigatran. Differences in risk of MI may influence the choice of treatment and may be considered in the development of personalized antithrombotic regimens.

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IMPACT FACTOR: 7.87

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