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

PhD thesis

by

Péter Kupó MD

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ACS: acute coronary syndrome

AF: atrial fibrillation

AMI: acute myocardial infarction

ANTARCTIC: “Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome” trial

anti-Xa: activated factor X inhibitor

ARCTIC: “Assessment by a Double Randomization of a Conventional Antiplatelet Strategy versus a Monitoring-guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption versus Continuation One Year after Stenting” trial

ASA: acetylsalicylic acid, aspirin

ATLAS ACS 2–TIMI 51: “Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 51” trial

AUGUSTUS: “An Open-label, 2 x 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention” trial

BMS: bare-metal stent

CHD: coronary heart disease

CI: confidence interval

COMPASS: “Cardiovascular Outcomes for People Using Anticoagulation Strategies” trial

CrI: credible interval

CV: cardiovascular

CYP: cytochrome P450 enzyme

DAPT: dual antiplatelet therapy

DES: drug-eluting stent

DOAC: direct oral anticoagulant

DTI: direct thrombin inhibitor

DVT: deep vein thrombosis

ECV: elective cardioversion

ENGAGE AF—TIMI 48: the "Global Study to Assess the Safety and Effectiveness of Edoxaban vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation" trial

ESC: European Society of Cardiology

ESUS: embolic stroke of undetermined source

EXAMINATION: Clinical Evaluation of Everolimus Eluting Coronary Stents in the Treatment of Patients With ST-Segment Elevation Myocardial Infarction trial

GRAVITAS: "Gauging Responsiveness With A VerifyNow Assay-Impact On Thrombosis And Safety" trial

HPR: high residual platelet reactivity

HPRoC: high platelet reactivity on clopidogrel

HR: hazard ratio

HUMIR: Hungarian Myocardial Infarction Registry

ISTH: International Society on Thrombosis and Hemostasis

MACE: major adverse cardiovascular events

MANAGE: "Management of Myocardial Injury After Noncardiac Surgery" trial

MI: myocardial infarction

NMA: network meta-analysis

PCI: percutaneous coronary intervention

PE: pulmonary embolism

PFT: platelet function testing

PS: propensity score

RCT: randomized clinical trial

RE-LY: Randomized Evaluation of Long Term Anticoagulant Therapy with Dabigatran Etexilate trial

RR: relative risk

SENIOR: Short Duration of Dual antiplatElet Therapy With SyNergy II Stent in Patients Older Than 75 Years Undergoing Percutaneous Coronary Revascularization trial

STEMI: ST-segment elevation myocardial infarction

SWAP: "SWitching Anti Platelet" trial

TIMI: thrombolysis in myocardial infarction

TLR: target lesion revascularization

TRIPLET: "Transferring From Clopidogrel Loading Dose to Prasugrel Loading Dose in Acute Coronary Syndrome Patients" trial

TROPICAL ACS: “Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment For Acute Coronary Syndromes Trial” study

U: unit

VKA: vitamin K antagonist

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.[1,2] The acute manifestation of CHD is defined as acute coronary syndrome (ACS). ACS is a life-threatening, high-mortality disease that affects 25-30,000 patients a year in Hungary. ACS evolves as a progressive disbalance of oxygen supply and demand in the heart, caused – in majority of cases – by a ruptured unstable atherosclerotic plaque.[3] One of the important keys to the pathogenesis of myocardial infarction (MI) is the activation of platelets, which can lead to blood clots formation and even causing complete coronary occlusion. Inhibition of platelet aggregation belongs to the main therapeutic targets in patients with an acute myocardial infarction (AMI) and antiplatelets are also crucial for secondary prevention.[4–6] Reperfusion therapy serves as the main cornerstone for the treatment of ACS.[4,6] During percutaneous coronary intervention (PCI) the vascular segment responsible for the development of ACS is identified and treated by mechanical reperfusion and implanting stents in the coronary artery stenoses.

Stents delivering anti-proliferative drugs (drug-eluting stent, DES) became available in the early 2000s providing an effective solution to the frequent restenosis of the earlier generation bare-metal stents (BMS) and replacing the latter gradually.[7] Development of antiplatelet therapy that is required to prevent thrombosis of the implanted stent was one of the most important prerequisite to the widespread of interventional cardiology.[7] Dual antiplatelet therapy (DAPT) defined as the use of a $P2Y_{12}$ receptor (also known as ADP-receptor) inhibitor (clopidogrel, ticagrelor or prasugrel) besides aspirin (acetylsalicylic acid, ASA) has been shown to be an effective therapeutic strategy to prevent recurrent ischemic events. Compared with DES, the time required for the development of the endothelial coverage is shorter, thus the risk of suspension of DAPT may be lower with BMS.[8] Elderly patients have a higher bleeding risk

and this may lead to the use of BMS during coronary interventions despite the fact that due to the more favorable clinical outcome, the European Society of Cardiology (ESC) recommended DES implantation in all PCIs involving stent implantation based on its 2018 recommendation on myocardial revascularization.[7,9] Although the use of BMS is decreasing in the developed countries, it is still applied in the course of approximately 20% of all PCI.[10,11]

Inhibition of platelet aggregation is one of the major therapeutic targets in patients with AMI. Among platelet $P2Y_{12}$ inhibitors, prasugrel and ticagrelor are the preferred choices for patients with AMI.[12,13] Due to contraindications, financial restrictions and regulatory reasons, the availability of prasugrel and ticagrelor is not uniform across countries while the use of clopidogrel and switching between $P2Y_{12}$ inhibitors is frequent.[14–16] For financial reasons, clopidogrel is the most commonly applied $P2Y_{12}$ inhibitor in Hungary. However, clopidogrel treatment has a number of disadvantages, mainly due to its poor bioavailability.[17] Clopidogrel is a pro-drug that is absorbed in the intestine and activated in the liver.[18,19] The conversion of clopidogrel to its active metabolite requires activations via the cytochrome P450 enzyme (CYP) isoform CYP2C19 in the liver. Approximately 80% of the pro-drug is hydrolyzed by esterases in the blood to an inactive carboxylic acid derivative (SR26334). The generating active metabolite (R-130964) binds specifically and irreversibly to the $P2Y_{12}$ receptors of the platelets during hepatic circulation, thus preventing ADP-stimulated activation and aggregation processes during the whole platelet lifespan.[20] The activity of the CYP2C19 isoenzyme is genetically determined and is also affected by drug interactions, resulting in the formation of active metabolites from clopidogrel to become inefficient, vulnerable and unpredictable. Therefore, the level of $P2Y_{12}$ inhibition measured by laboratory methods and thus residual platelet reactivity shows significant variability among clopidogrel-treated individuals.[21] Early studies demonstrated large inter-individual differences in response to a fix-dose of clopidogrel, thus the term “clopidogrel resistance” was created and widely applied to refer to patients with

an inappropriate response.[22,23] In addition to the type of stent implanted, high residual platelet reactivity (HPR) confirmed by laboratory assessments is also an independent predictor of stent thrombosis and recurrent ischemic events.[24–26]

Coagulation cascade plays an important role in the development of AMI.[13] Earlier analyses found that long-term treatment with Vitamin K antagonists (VKA), in monotherapy or in combination with ASA is superior to ASA alone for secondary prevention after AMI.[27] Importantly, direct oral anticoagulants (DOACs) showed dissimilar results regarding cardiovascular (CV) safety. Rivaroxaban showed favorable outcomes when combined with ASA among patients with stable atherosclerotic disease, and it also reduced ischemic risk in ACS.[28,29] In contrast, signals from earlier studies have raised safety concerns regarding MI risk among dabigatran-treated patients, but dabigatran lowered the risk of major vascular complications among patients with myocardial injury after surgery.[30,31]

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 ACS 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

This PhD thesis is based on 3 studies. The first two are propensity score matched survival analyses of a prospective Hungarian Myocardial Infarction Registry collecting clinical data on consecutive patients treated for an AMI in Hungary. The third study is based on a network meta-analysis (NMA) of randomized clinical trials.

3. BACKGROUND

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

DESs are widely used in the treatment of coronary stenosis. The superior clinical performance of DES compared to BMS has been widely documented and confirmed.[7,32] It is well-known, that DES have reduced rates of restenosis and repeat revascularization compared with BMS. However, in addition to its many advantageous properties time required for the development of the endothelial coverage is longer, thus necessary DAPT interval after DES implantation should be prolonged to prevent stent thrombosis.

Elderly patients have a higher bleeding risk and this may lead to the use of BMS during coronary interventions.[11] However, in line with several trials the recent "Short Duration of Dual antiplatElet Therapy With SyNergy II Stent in Patients Older Than 75 Years Undergoing Percutaneous Coronary Revascularization" (SENIOR) trial found that among elderly patients, the use of DES with a short duration of DAPT strategy is beneficial compared with BMS and a similar duration of DAPT. This trial 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.[33]

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

Inhibition of platelet aggregation is one of the main therapeutic cornerstones to treat patients with an AMI. Among platelet $P2Y_{12}$ inhibitors, prasugrel and ticagrelor are the preferred choices for patients with AMI.[12,13] Due the financial and regulatory reasons, the availability of these drugs is not optimal, thus the earlier generation ADP blocker clopidogrel is still frequently used.[15] High platelet reactivity on clopidogrel (HPRoC) is an independent predictor of stent thrombosis and MI.[24,26,34] However, current guidelines discourage the routine use of PFT due to lack of evidence on the ability of PFT based $P2Y_{12}$therapy to improve outcomes.[12,13] Local reimbursement regulations in Hungary mandate PFT on clopidogrel, and prasugrel is reimbursed for patients with HPRoC. This policy resulted in a high penetration of PFT across invasive centers.

3.3.Direct anticoagulants and the risk of MI

More, than ten years have passed since the approval of the first nonvitamin K antagonist oral anticoagulants. DOACs have been proposed as an alternative term for this class of agents including oral direct thrombin inhibitors (DTIs) and activated factor X inhibitors (anti-Xa).[35] In several fields, compared to VKA, DOACs have been proven to have similar or higher efficacy in preventing ischemic events and similar or lower risk for major bleeding, bleeding-related case fatalities, and intracranial bleeding.[36,37] Furthermore, DOACs alleviate several problems associated with VKA use including the need for laboratory monitoring due to the narrow therapeutic window and drug/food interactions.[38] Consequently, DOACs have been widely adopted.[39]

Notably, DOACs showed contradictory results regarding CV safety. Rivaroxaban in addition to antiplatelet therapy was associated with the prevention of stroke and had a favorable effect on mortality and CV outcomes.[28,29,40] In contrast, dabigatran treatment was associated with increased risk for MI.[41] 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. The patients' data are collected prospectively according to the statute of CCXLVI./2013 of Hungary via a national internet-based registry. Data capture covers 178 structured categories including those regarding the performed coronary interventions and included 92% of all AMI cases in 2017. The system is web-based: the records of data, the control, and the necessary data corrections take place on-line. An independent cardiologist validates the recorded data by occasionally checking hospital source documents. At the time of the index event variables are recorded, including social security number, gender, past medical history, time of onset of complaints, time of first medical contact, and that of hospital admission. Information about blood pressure, pulse rate, electrocardiogram, and Killip class observed on hospital admission are also recorded. The way and timing of treatment, complications during in-patient care, and discharge medication were investigated.

Outcome data including vital status and repeated hospitalizations are regularly received from the electronic database of the national healthcare insurance provider. The protocol of the study is in accordance with the Declaration of Helsinki and it was approved by the Hungarian National Committee on Health Research Ethics.[42–44]

For the purpose of the analysis records of patients between 1 January 2014 and 31 December 2017, all patients with AMI were selected for enrolment if a coronary intervention was performed successfully. The patients were eligible over the age of 75, including cases with and without ST-segment elevation if coronary intervention was performed. We created two groups

according to the type of the implanted stent (DES or BMS); cases where stent was not implanted or both DES and BMS were implanted during the intervention were excluded.

DAPT was the intended antiplatelet strategy during the 1st year after the intervention. $P2Y_{12}$ inhibitor treatment before intervention comprised clopidogrel, usually given in a loading dose of 600 mg, but left to the decision of the treating physicians. After the intervention, prasugrel and clopidogrel were available for long-term treatment. Importantly, it was left to the discretion of the treating physicians whether to leave the patients on clopidogrel or switch to prasugrel but in the case of the latter a 5 mg reduced daily dose was proposed over 75 years' age. Ticagrelor was not reimbursed in Hungary at the time of the study, restricting its use to a 0.08% in our dataset. Altogether, prasugrel use was also rare and reached 2.95% in the study population. Thienopyridines were supplemented with low dose ASA —typically 100 mg—with an optional loading dose of 300-500 mg. The intended length of DAPT was 12 months regardless of the stent type. The use of perioperative anticoagulation, as well as the administration of platelet IIb/IIIa inhibitors, were allowed according to the local protocols.

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) and repeat revascularization. MACE included composite events of death, recurrent MI and stroke, while coronary intervention or bypass surgery defined the repeat revascularization.

Events were obtained from the vital status database of the National Health Insurance Fund. Data related to recurrent hospitalization for AMI, stroke, repeat revascularization, as well as for bleeding event leading to blood transfusion were extracted from the database of the National Health Insurance Fund.

Variables are presented as means ± SD, medians with 25th and 75th quartiles or as frequencies and percentages. Unpaired t-tests were used for comparisons of continuous variables between groups. Categorical variables were compared using $\chi 2$ or Fisher's exact tests.

As the patients were not randomly assigned to DES or BMS treatments, we assumed that treatment selection may have an impact on the results potentially biasing towards favoring the DES treatment. Thus, 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 with a comparable chance for either strategy by adjusting for differences in the baseline characteristics. In a logistic regression model for DES vs BMS groups, the probability of both treatment was computed. Clinical factors from the medical history as well as patient characteristics at presentation and with potential influence on the decision were used as predictors in calculating the PS. In the PS-matching procedure randomly selected patients in the DES group were matched with a patient from the BMS group with the closest estimated PS value. A 1-to-1 matched analysis without replacement was performed with the match tolerance set to <0.01.

In Cox-regression analyses, associations between clinical outcomes and stent type were first analyzed in univariable models. We determined hazard ratios (HRs) together with 95% confidence intervals (95% CIs). A multivariable Cox proportional hazards model was used to determine the independent predictors of all-cause mortality and blood transfusion. In this analysis potential, clinically relevant predictors of outcome were also included then were further entered into a multivariable regression model. In the multivariable model, a backward stepwise conditional method was used to find the independent predictors. During this approach, a stepwise removal of the weakest factors without significantly decreasing overall model performance was performed. Aalen's additive regression model analysis was used to evaluate time-dependent changes in the risk of transfusions between the DES vs BMS-group. All

reported p values are two-sided and p values of <0.05 were considered to indicate statistical significance. This analysis was conducted using the SPSS 24 statistical package.

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

Data extracted from HUMIR were also used for this analysis. The infarct registry functioned as described above. However, at the time of the conduction of this study, the registry operated on a voluntary basis capturing 51% of AMI cases treated countrywide.

Between March 1 2013 and March 1 2014 all patients with AMI (both with ST segment elevation and without) were eligible for enrolment if intervention was performed successfully with stent implantation and there was no contraindication to treatment with a $P2Y_{12}$ inhibitor for 1 year. Data of patients treated in 15 centers of invasive cardiology collaborating with providing and monitoring platelet function data were analyzed.

Patients with an indication for chronic oral anticoagulation, history of stroke or transient ischemic attack, aged older than 75 years, weighting less than 60 kg-s or administration of $P2Y_{12}$ inhibitors other than clopidogrel or prasugrel before or during intervention were excluded. Thienopyridines were supplemented with low dose ASA typically 100 mg with an optional loading dose of 300-500 mg. Use of perioperative anticoagulation as well as administration of GPIIb/IIIa inhibitors were allowed based on local protocols and the operator's decision.

Generally, $P2Y_{12}$ inhibitor treatment before intervention comprised clopidogrel, usually given in a loading dose of 600 mg, but left to the decision of the treating physicians. After intervention, both prasugrel and clopidogrel were available for long-term treatment. However, while clopidogrel use was not restricted by any reimbursement rule, prasugrel was reimbursed at 70% only if PFT results confirmed HPRoC. Importantly, it was left to the discretion of the treating physicians whether to perform PFT and make the choice based on PFT (PFT-guided group) or make a clinical decision without PFT (Unguided group).

All participating centers used a homogeneous method for PFT, which was the Multiplate analyzer (Roche Diagnostics GmbH, Rotkreuz, Switzerland). PFT was performed at least 6 hours after the intervention or at least 24 h after platelet IIb/IIIa inhibitor treatment cessation.[45,46] HPRoC was defined as an adenosine diphosphate test level >46 unit (U).[45] The choice of $P2Y_{12}$ inhibitor in patients with HPRoC was also left to the treating physician: either switch to prasugrel or high (150 mg/day), or conventional doses (75 mg) of clopidogrel were allowed.

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. Overall mortality was obtained from the patient vital status in the database of the Hungarian Central Statistical Office and the National Health Insurance Fund including the date and the cause of death. Among patients who died, cause of death was assessed by qualifying deaths related to infection, malignancy, and trauma as non-CV. Data related to recurrent hospitalization for AMI, for stroke, as well as for bleeding event leading to transfusion were extracted from the database of the National Health Insurance Fund.

Variables are presented as means ± SD or as frequencies and percentages. Unpaired t-tests were used for comparisons of continuous variables between groups. Categorical variables were compared using $\chi 2$ or Fisher's exact test as appropriate. As eligible patients were not randomly assigned to PFT-guided or unguided treatments, we intended to balance the groups to reduce potential bias associated with treatment selection. For this aim PS matching was applied as described in Section 4.1. PS was computed by using a logistic regression model for PFT-guided versus unguided groups.

Unadjusted HRs together with 95% CIs were determined in univariate Cox proportional models, and then a multivariable Cox proportional hazards model was used to determine

independent predictors of all-cause mortality. As a sensitivity exercise, PFT-guided and unguided patients were compared also in the PS-unmatched study population with Cox regression analyses. All reported p values are 2-sided, and p values of <0.05 were considered to indicate statistical significance. The analysis was conducted by using the SPSS 22 statistical package.

4.3.Direct anticoagulants and the risk of MI

A manual search of medical literature was performed in PubMed (MEDLINE), EMBASE, and Cochrane Trials from inception until May 31 2019, for articles reporting randomized clinical trials with DOACs. No language restriction was used. The query included the following terms linked with Boolean operators: "pulmonary embolism," "atrial fibrillation," "thromboprophylaxis," "anticoagulation," "prevention," "rivaroxaban OR apixaban OR dabigatran OR edoxaban".

In the analysis, we included trials that fulfilled the following criteria: (1) randomized clinical trials (RCTs) that assessed the clinical efficacy and/or safety of an anticoagulant protocol comprising either ≥1 of the approved and marketed DOACs, that is, dabigatran, rivaroxaban, apixaban, or edoxaban. (2) Having one or more control group with oral anticoagulation, antiplatelet treatment, or placebo. (3) Reporting the frequency of MI or the rate of ACS during the follow-up compliant with intention-to-treat analysis. Studies that aimed to compare merely the biological efficacy of the anticoagulant protocol and trials not reporting the frequency of MI were excluded. Nonrandomized studies, registries, and uncontrolled or cohort studies as well as reviews were disregarded. The review protocol was registered in the PROSPERO database a priori under the registration number of CRD42018103000.

All the relevant articles were combined in a reference manager software (EndNote X8; Clarivate Analytics, PI, USA) to remove duplicates by searching overlaps between titles, abstracts, authors, and publication year. After removing duplicates, we screened the articles by title, abstract, and full texts against our predefined eligibility criteria. Each phase was carried out by 2 independent investigators in duplicate, none of whom were blinded to publication data. Third-party arbitration resolved any discrepancies.

The following details were recorded for each study: study name, first author, year of publication, period of study, the applied doses of oral anticoagulant, number of patients, length

of treatment period, length of follow-up, inclusion and exclusion criteria, protocol definitions of MI as well as patient and procedural characteristics including mean age, sex, and the following risk factors: diabetes, hypercholesterolemia, and hypertension.

The primary end point of the analysis was the frequency of MI. Overall mortality was defined as a secondary end point. As a safety measure, frequency of major bleeding complications was evaluated. Both MI and major bleeding were defined according to the internal definitions of the studies.[47,48] If multiple major bleeding definitions were used, we extracted thrombolysis in myocardial infarction (TIMI) major bleeding and International Society on Thrombosis and Hemostasis (ISTH) major bleeding if available. The data from intention to treat analyses were extracted. The end points of interest were collected until the longest follow-up available.

Analyses of subgroups, heterogeneity, as well as assessment of bias were performed using the Cochrane Review Manager version 5.3. software.[49] Degree of inconsistency among studies was quantified by means of I^2. Cochrane Q heterogeneity test (χ^2) was also performed. These data were reported as percentage of the I^2 together with the p value of the χ^2 test. The likelihood of publication bias was visually assessed by generating a funnel plot for the primary end point. The risk of MI was analyzed in a hierarchical Bayesian mixed-treatment comparison meta-analysis. The Bayesian analysis allows the combination of existing knowledge with new information according to established rules of probability.[50] Substantive prior knowledge can thereby be included in any Bayesian analysis by choice of initial (predata) distribution. We wanted our final (posterior) distribution to reflect the information in our data set only and not to be influenced by our choice of initial (prior) distribution. Therefore, “noninformative” prior distributions were used throughout so that the data from the trials dominated the final inferences. The RCT data were then added via the Bayes rule to produce posterior distributions. Treatment effects are reported as risk ratio with 95% associated credible interval (CrI), which

is a Bayesian analog of the 95% CI from traditional meta-analyses. Inferences were calculated with a Gibbs sampler algorithm as implemented through WinBUGS software (version 1.4.3; MRC Biostatistics Unit, Cambridge, United Kingdom).[51] To ensure convergence, 3 Markov Monte Carlo chains were run. Data input and graphical output were performed using the NetMetaXL interface. [52] Inferences based on random effects models are presented. The choice of random-effects model was made based on the consideration that the true preventive effect of anticoagulant treatment may vary from study to study influenced by heterogeneity of the included trials. Random effects model accounts better for interstudy differences; furthermore, it results in wider CrIs and thus provides more conservative and robust results. In addition, subgroup analyses were performed by building networks of studies performed in the same risk groups as well as according to MI definitions.

5. RESULTS

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

From 1 January 2014 to 31 December 2017 data of 40968 patients hospitalized for an AMI were entered into the registry. 36177 (88.3%) of these patients were treated with coronary intervention, 8532 (23.6%) of them were over the age of 75. After excluding those patients (13.5%) in whom no stent was implanted or both BMS and DES were implanted, an unmatched patient pool of 7383 cases was obtained. In 4117 (55.8%) cases BMS, in 3266 (44.2%) cases DES was implanted (Figure 1). As expected, there were numerous differences in baseline characteristics between the two groups. To adjust for these differences, PS matching was performed that resulted in a matched population of 5780 patients with balanced characteristics (Table 1).

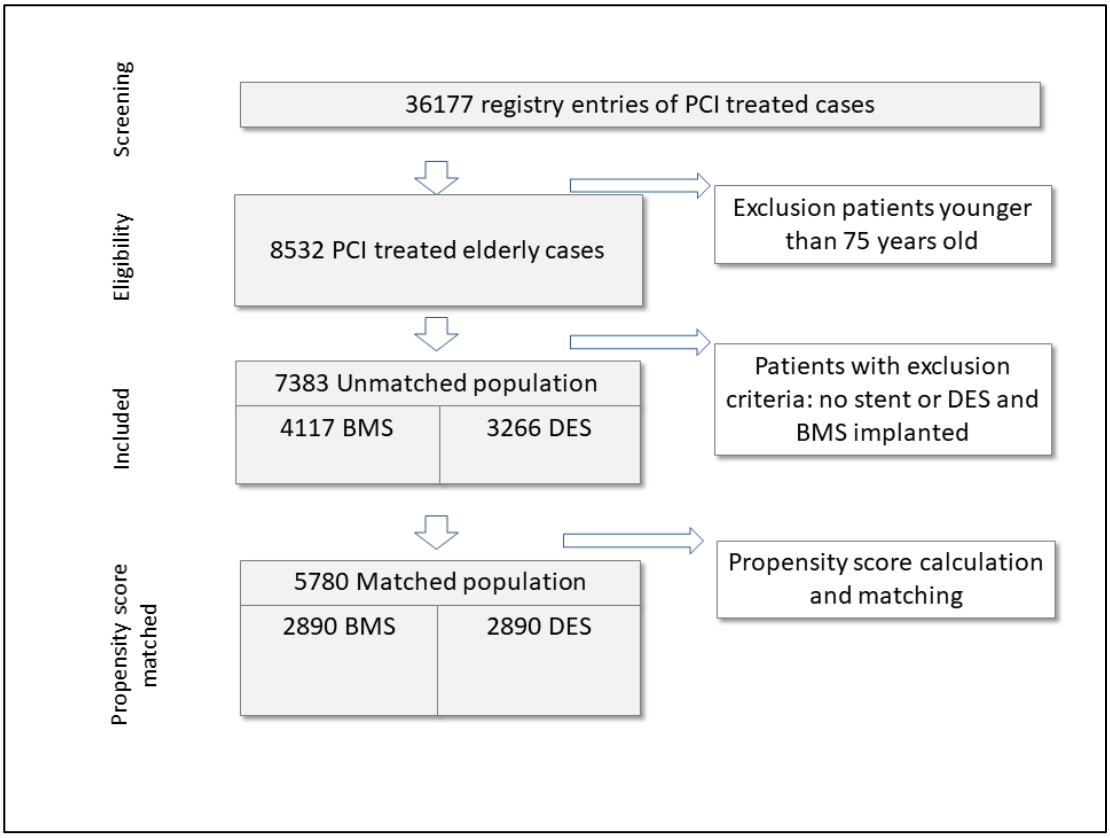

Figure 1. Flowchart of patient selection. Abbreviations: BMS: bare-metal stent, DES: drug-eluting stent, PCI: percutaneous coronary intervention

Clinical characteristics	Entire cohort (n=7383)			Propensity matched cohort (n=5780)		
	DES group (n=3266)	BMS group (n=4117)	p value	DES group (n=2890)	BMS group (n=2890)	p value
Age, (years)	79.8 (77.2-83.2)	80.8 (77.8-84.5)	<0.001	80.0 (77.4-83.5)	80.1 (77.3-83.5)	0.974
Men	1642 (50.3%)	1801 (43.7%)	<0.001	1389 (48.1%)	1391 (48.1%)	0.958
Presentation						
STEMI	1181 (36.2%)	2132 (51.8%)	<0.001	1170 (40.5%)	1200 (41.5%)	0.422
Shock	62 (1.9%)	104 (2.5%)	0.071	57 (2.0%)	58 (2.0 %)	0.925
Reanimation	86 (2.6%)	139 (3.4%)	0.065	78 (2.7%)	80 (2.8%)	0.872
Heart rate (bpm)	77 (68-90)	78 (68-90)	0.100	77 (68-90)	78 (68-90)	0.862
Systolic BP (mmHg)	134 (120-150)	130 (115-150)	<0.001	133 (118-150)	132 (118-150)	0.964
Diastolic BP (mmHg)	78 (68.0-84.0)	76 (67-85)	0.167	78 (69-84)	78 (69-85)	0.531
Weight (kg)	74 (68-81)	74 (65-80)	<0.001	74 (68-80)	74 (66-80)	0.682
Height (cm)	166 (162–170)	166 (160-170)	0.005	166 (160-170)	166 (160-170)	0.689
Medical history						
Hypertension	2896 (88.7%)	3560 (86.5%)	0.005	2547 (88.1%)	2529 (87.5%)	0.469
Diabetes mellitus	1300 (39.8%)	1293 (31.4%)	<0.001	1056 (36.5%)	1052 (36.4%)	0.913
Hyperlipidemia	1093 (33.5%)	1131 (27.5%)	<0.001	916 (31.7%)	893 (30.9%)	0.514
PAD	483 (14.8%)	564 (13.7%)	0.183	420 (14.5%)	435 (15.1%)	0.578
History of heart failure	617 (18.9%)	589 (14.3%)	<0.001	489 (16.9%)	471 (16.3%)	0.525
Prior MI	977 (29.9%)	876 (21.3%)	<0.001	744 (25.7%)	749 (25.9%)	0.881
Prior stroke	363 (11.1%)	491 (11.9%)	0.279	328 (11.3%)	339 (11.7%)	0.651
Prior coronary intervention	976 (29.9%)	722 (17.5%)	<0.001	687 (23.8%)	669 (23.1%)	0.576
Prior CABG	283 (8.7%)	189 (4.6%)	<0.001	184 (6.4%)	180 (6.2%)	0.829

Table 1. Characteristics of the patient population before and after propensity score matching. Abbreviations: BMS: bare-metal stent; BP: blood pressure; CABG: coronary bypass surgery; DES: drug-eluting stent; MI: myocardial infarction; PAD: peripheral arterial disease; STEMI: ST-segment elevation myocardial infarction

During the follow-up period, 2054 patients died, resulting in a 1-year all-cause mortality rate of 27.8%, in this unselected, high-risk elderly cohort. DES-treated subjects had a highly significant, 34% lower hazard for all-cause mortality compared with the BMS group (22.7% vs. 31.9%, p<0.001). Rates of all individual endpoints including ischemic events, revascularization and blood transfusion were higher in the BMS group and these differences reached high levels of significance, except for the low rate endpoints of repeated MI and coronary bypass operations (Figure 2 and Table 2).

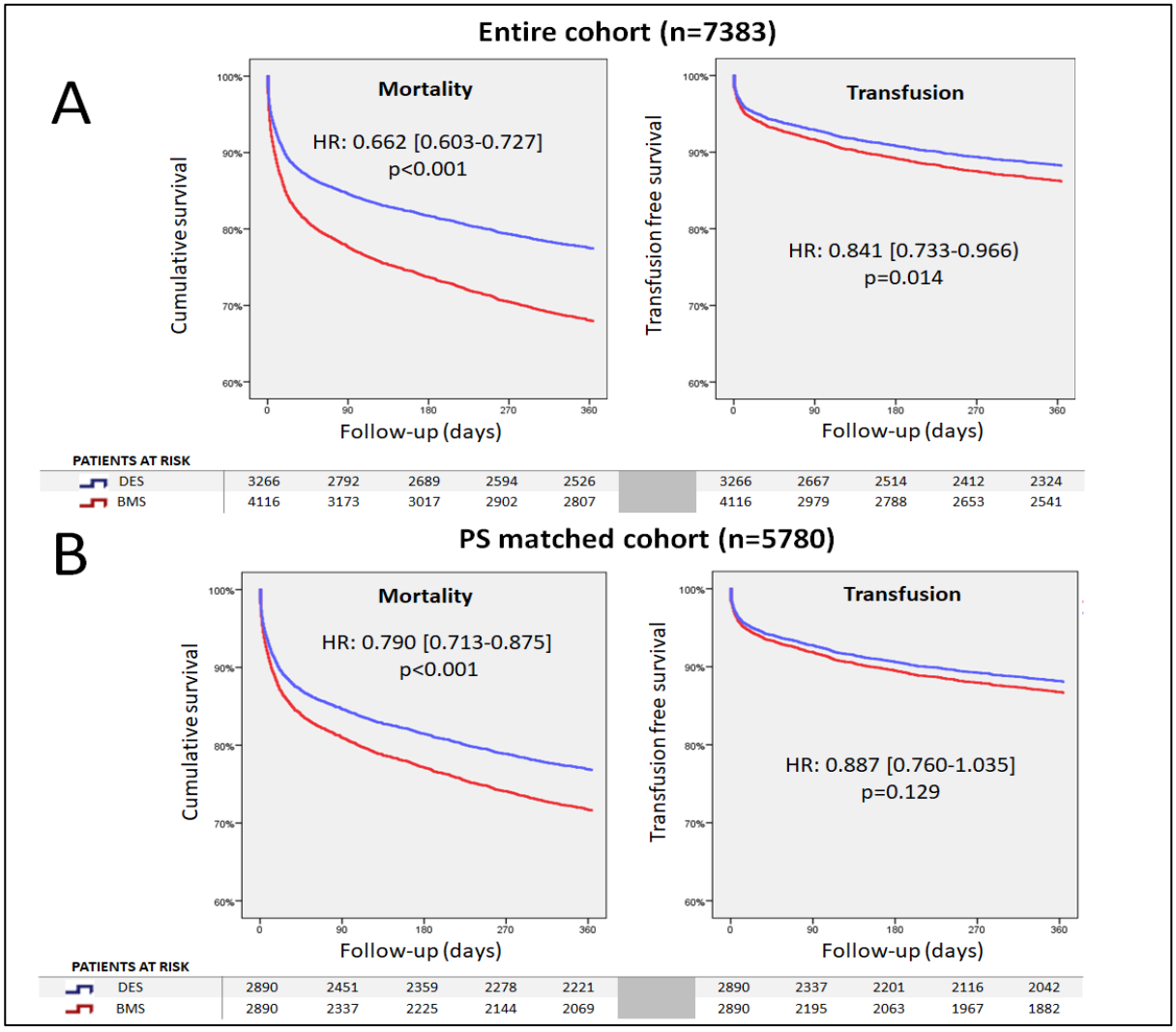

Figure 2. Kaplan-Meier curves of overall survival and blood transfusion-free survival comparing drug-eluting (DES) or bare-metal stent (BMS) implanted patients. Panel A shows the survival differences seen in the overall cohort, while data from the propensity score (PS) are depicted in panel B. Abbreviations: BMS: bare-metal stent; DES: drug-eluting stent; HR: hazard ratio; PS: propensity score

Unmatched cohort (7383)	DES (3266)	BMS (4117)	Hazard ratio (95% CI), p value
Overall mortality	740 (22.7 %)	1314 (31.9 %)	0.66 [0.60-0.73], p<0.001
Transfusion	347 (10.6 %)	479 (11.6 %)	0.84 [0.73-0.97], p=0.014
Major adverse cardiac events	763 (23.4 %)	1351 (32.8 %)	0.66 [0.60-0.72], p<0.001
Myocardial infarction	40 (1.2 %)	64 (1.6 %)	0.69 [0.46-1.03], p=0.068
Stroke	61 (1.9 %)	105 (2.6 %)	0.69 [0.50-0.95], p=0.023
Repeat revascularization	256 (7.8 %)	403 (9.8 %)	0.70 [0.61-0.83], p<0.001
PCI	237 (7.3 %)	372 (9.0 %)	0.72 [0.61-0.84], p<0.001
CABG	23 (0.7 %)	36 (0.9 %)	0.66 [0.39-1.14], p=0.134
PS matched cohort (5780)	**DES (2890)**	**BMS (2890)**	**Hazard ratio (95% CI), p value**
Overall mortality	669 (23.1 %)	821 (28.4 %)	0.79 [0.71-0.88], p<0.001
Transfusion	310 (10.7 %)	336 (11.6 %)	0.89 [0.76-1.04], p=0.129
Major adverse cardiac events	685 (23.7 %)	854 (29.6 %)	0.77 [0.70-0.85], p<0.001
Myocardial infarction	33 (1.1 %)	51 (1.8 %)	0.62 [0.40-0.95], p=0.029
Stroke	48 (1.7 %)	80 (2.8 %)	0.60 [0.42-0.86], p=0.005
Repeat revascularization	213 (7.4 %)	322 (11.1 %)	0.62 [0.52-0.73], p<0.001
PCI	196 (6.8 %)	247 (8.6 %)	0.59 [0.49-0.722], p<0.001
CABG	18 (0.6 %)	28 (1.0 %)	0.54 [0.30-1.01], p=0.052

Table 2. Primary and secondary outcomes in unmatched and propensity-matched cohorts
Abbreviations: BMS: bare-metal stent; CABG: coronary artery bypass grafting; CI: confidence interval; DES: drug-eluting stent; PCI: percutaneous coronary intervention; PS: propensity score.

In the propensity-matched cohort, similar trends were detected. However, the magnitude of reduction was less pronounced for the ischemic endpoints (21% vs 34% reduction of mortality, 34% vs 23% reduction of MACE, in the overall and the PS-matched cohort, respectively). Blood transfusion rate reduction was 11% in the PS-matched cohort and this did not reach the level of significance. Reduction of repeat revascularization was highly significant in the PS-matched cohort (Table 2). The observed 5.3% absolute risk reduction of mortality in the matched cohort corresponds to 19 patients needed to treat, to prevent one death.

Aalen's additive regression model analysis showed no sign of time-dependent changes in the risk of transfusions between the DES- and BMS-treated elderly population (Figure 3). When assessed in multiple regression models, stent type prevailed as an independent predictor of mortality but not of blood transfusion (Table 3).

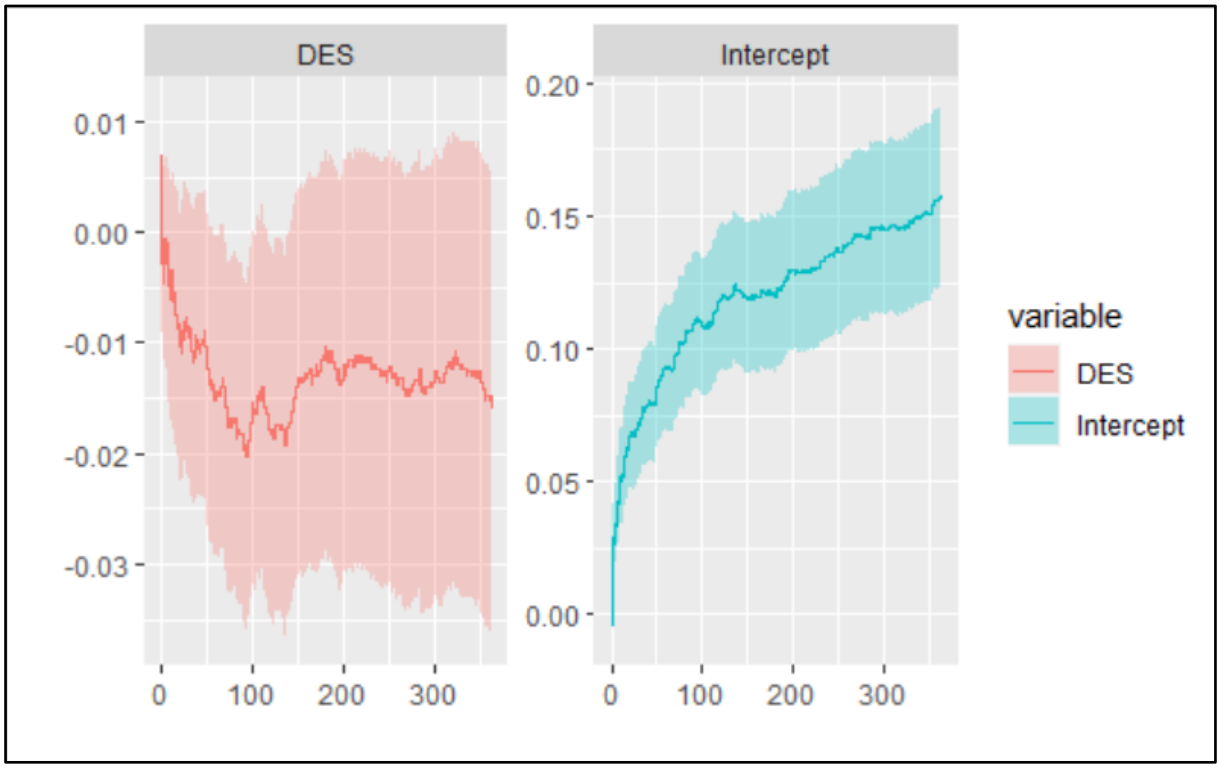

Figure 3. Estimated cumulative regression function for covariate drug-eluting stent (DES). Aalen's additive regression model analysis show no signal of time dependent changes in the risk of transfusions between the DES and bare metal stent (BMS) treated elderly population.

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	-		
Hyperlipidaemia	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 3. 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

From March 1 2013 and March 1 2014 data of 6795 patients hospitalized in the participating centers for an event of AMI were entered in the registry. Of these, 5583 (82.2%) patients were treated with PCI and stenting. In 3715 cases (66.5%), long-term $P2Y_{12}$ inhibitor treatment was chosen based on PFT results (PFT-guided group), while PFT was not performed in 1868 cases (unguided group, 33.5%). After excluding 29% patients with absolute or relative contraindications to prasugrel an unmatched patient pool of 3974 cases was obtained (Figure 4). There were significant differences in baseline characteristics between the groups. To adjust for these differences, PS matching was performed that resulted in a matched population of 2104 patients (Table 4).

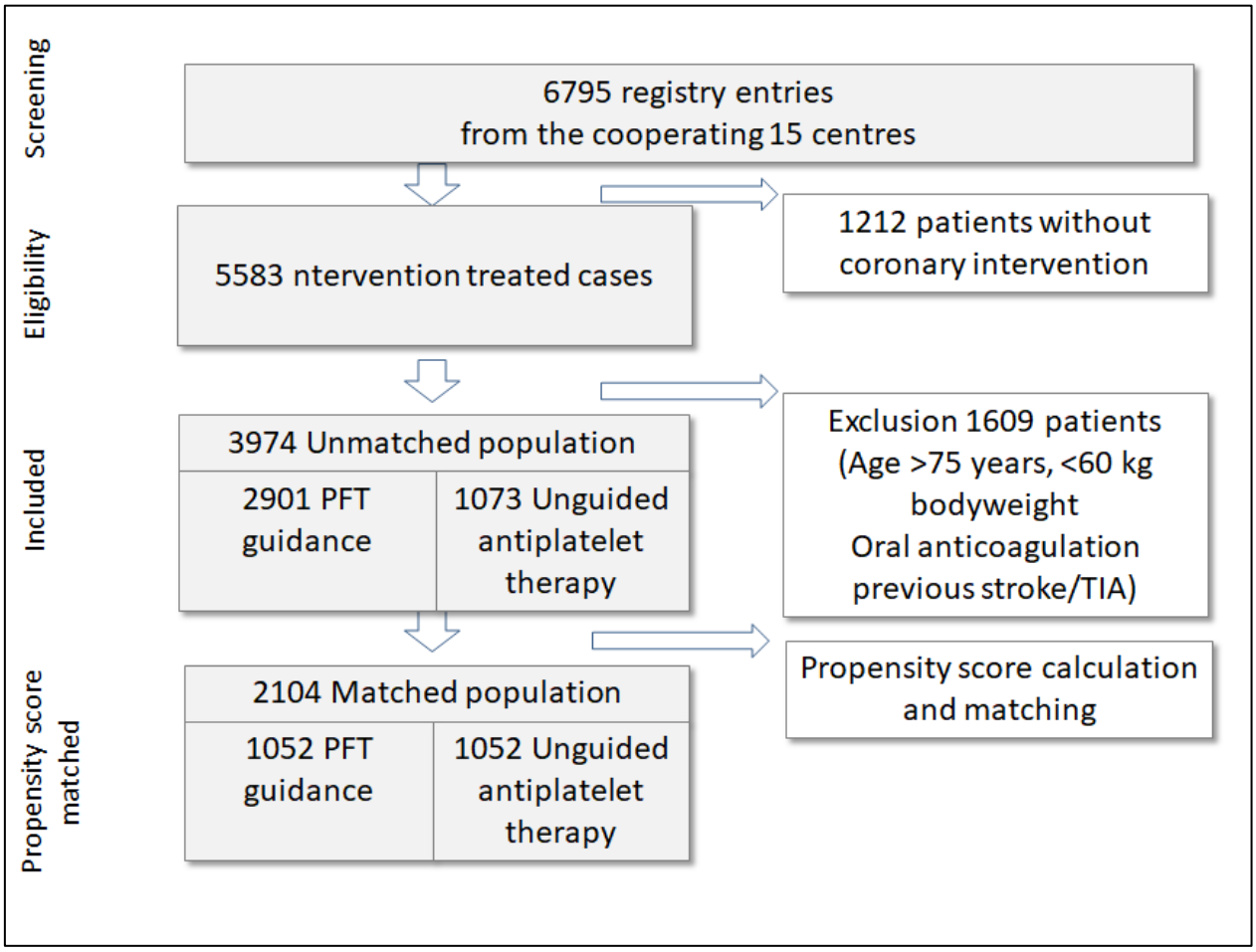

Figure 4. Flowchart of patient selection. Abbreviations: PFT: platelet function testing; TIA: transient ischemic attack

Clinical characteristics	Entire cohort (n=3974)			Propensity matched cohort (n=2104)		
	PFT-guided (n=2901)	Unguided treatment (n=1073)	p value	PFT-guided (n=1052)	Unguided treatment (n=1052)	p value
Age, (years)	58.9 ± 9.6	60.5 ± 9.2	<0.001	60.5 ± 9.0	60.5 ± 9.1	0.926
Men	69.3 %	65.7 %	0.035	65.3 %	66.1 %	0.748
Medical history						
Hypertension	64.6 %	71.2 %	<0.001	68.41 %	70.6 %	0.297
Diabetes mellitus	24.8 %	29.2 %	0.006	27.8 %	28.4 %	0.734
Hyperlipidemia	11.1 %	5.1 %	<0.001	3.7 %	5.2 %	0.113
Prior MI	15.8 %	27.4 %	<0.001	26.6 %	26.0 %	0.771
Prior PCI	4.6 %	7.3 %	0.001	7.1 %	7.4 %	0.867
Prior CABG	1.8 %	1.0 %	0.113	0.8 %	1.0 %	0.646
PAD	5.3 %	11.6 %	<0.001	10.2 %	10.4 %	0.943
Presentation						
STEMI	64.1 %	51.0 %	<0.001	55.1 %	51.7 %	0.126
Heart rate (bpm)	79.8 ± 17.1	80.6 ± 18.1	0.236	81.4 ± 18.0	80.5 ± 18.1	0.250
Systolic BP	137.9 ± 24.2	136.6 ± 25.7	0.191	138.6 ± 24.8	136.5 ± 25.7	0.054
Diastolic BP	70.0 ± 24.7	68.7 ± 25.0	0.168	67.9 ± 26.1	68.8 ± 25.1	0.440
APD reactivity	32.5 ± 19.5	-	NA	32.5 ± 19.9	-	NA
HPR	19.1 %	-	NA	18.6 %	-	NA
Medications						
Clopidogrel 75 mg daily	50.6 %	74.3 %	<0.001	43.6 %	74.2 %	<0.001
Clopidogrel 150 mg daily	34.4 %	21.6 %	<0.001	40.2 %	21.8 %	0.547
Prasugrel	15.0 %	4.1 %	<0.001	16.2 %	4.0 %	<0.001
Aspirin	71.1 %	81.0 %	<0.001	80.9 %	79 %	0.547
ß-blocker	84.1 %	90.6 %	<0.001	88.5 %	90.4 %	0.176
Statin	81.0 %	91.8 %	<0.001	91.6 %	91.7 %	0.579

Table 4. Characteristics of the patient population before and after propensity score matching. Abbreviations: ADP: adenosine diphosphate, BP: blood pressure, CABG: coronary artery bypass surgery; HPR: high residual platelet reactivity, MI: myocardial infarction; PAD: peripheral arterial disease; STEMI: ST-segment elevation myocardial infarction

Among the 2901 subjects of the PFT-guided group, 554 (19%) had HPRoC. Seventy percent of them were switched to prasugrel, while 30% continued clopidogrel (14% high-dose and 16% standard dose clopidogrel). In patients without HPRoC (no HPRoC group), use of prasugrel was low (2%), resulting in an overall high proportion of patients continuing clopidogrel based on PFT-guidance. Among unguided patients, prasugrel was prescribed only in 4%, while low-dose clopidogrel was quite frequent (74%). Treatment allocation patterns in the PS-matched cohort remained similar with 77% switch-over to prasugrel in patients with HPRoC.

During the follow-up period 200 patients died from the PS-matched cohort, resulting in a one-year all-cause mortality rate of 9.5%, in this high-risk cohort. 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 5).

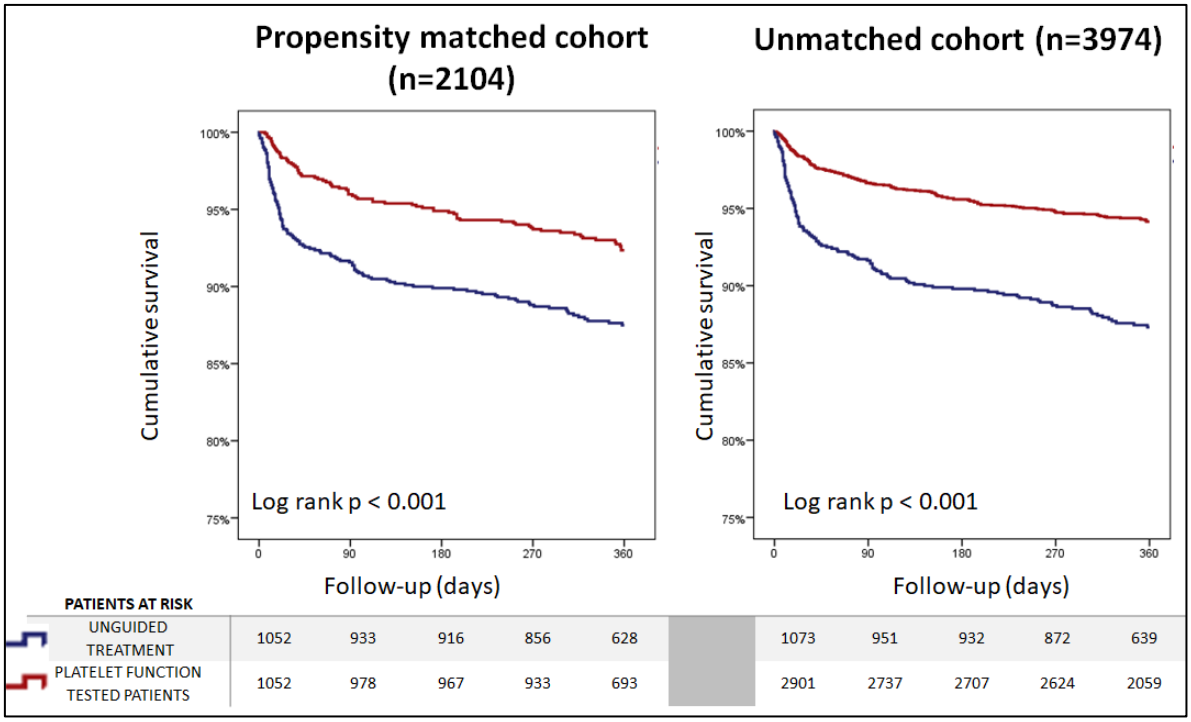

Figure 5. Kaplan Meier curves of survival comparing platelet function test guided versus unguided treated myocardial infarction cases assessed in the propensity score adjusted sample and in the whole cohort.

Similar to this, CV mortality was also reduced by 39%. (HR:0.61, [0.45-0.83], p<0.01, Table 5). In the unmatched total cohort including 3974 patients, similar results were observed for all-cause and CV mortality, without a significant difference in the risk of stroke or repeat MI. (Table 5).

A. **Propensity matched cohort (n=2104)**			
	Nr. of patients (%)		**Hazard Ratio [95% Confidence interval]**
	Platelet function guided treatment (n=1052)	**Unguided treatment (n=1052)**	
Death from any cause	75 (7.1 %)	125 (11.9 %)	0.57 [0.43-0.77]***
Death from cardiovascular causes	66 (6.3 %)	104 (9.9 %)	0.61 [0.45-0.83]**
Repeated myocardial infarction	29 (2.8 %)	20 (1.9 %)	1.38 [0.78-2.44]
Stroke	8 (0.8 %)	8 (0.8 %)	0.95 [0.36-2.54]
Major adverse cardiac events (cardiovascular death, myocardial infarction, or stroke)	97 (9.2 %)	126 (12.0 %)	0.74 [0.57-0.96]*
Transfusion	74 (7.0 %)	67 (6.4 %)	1.01 [0.73-1.41]
B. Unmatched cohort (n=3974)			
	Platelet function guided treatment (n=2901)	Unguided treatment (n=1073)	Hazard Ratio [95% Confidence interval]
Death from any cause	163 (5.6 %)	129 (12.0 %)	0.44 [0.35-0.56]***
Death from cardiovascular causes	139 (4.8 %)	107 (10.0 %)	0.45 [0.35-0.58]***
Repeated myocardial infarction	71 (2.4 %)	20 (1.9 %)	1.22 [0.74-2.01]
Stroke	23 (0.8 %)	8 (0.7 %)	0.99 [0.44-2.21]
Major adverse cardiac events (cardiovascular death, myocardial infarction, or stroke)	218 (7.5 %)	129 (12.0 %)	0.59 [0.47-0.73]***
Transfusion	131 (4.5 %)	70 (6.5 %)	1.03 [0.92-1.64]

Table 5. Clinical outcomes of platelet function test guided versus unguided patients. Data from Cox-regression analyses are presented as hazard ratio [95% Confidence interval], asterisks marks comparisons with p value * <0.05, ** <0.01, and *** <0.001. Patients could have had more than one type of end point.

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 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).

As a pre-specified analysis, the clinical impact of prasugrel and clopidogrel were tested on all-cause mortality within subgroups of PFT-guided and unguided therapy, and across HPRoC groups. Within the PFT-guided group of PS-matched patients, clopidogrel use was associated with significantly worse survival compared to prasugrel in case of HPRoC. Among clopidogrel-treated patients with HPRoC, high dose clopidogrel was associated with a numerically lower risk for mortality than standard-dose clopidogrel (8.7% vs. 21.7%) but this difference did not reach the level of statistical significance (HR: 0.37 [0.07-1.88], p=0.228). In the unguided group and in patients without HPRoC of the guided cohort, prasugrel versus clopidogrel therapy was not a significant predictor of survival (Figure 6).

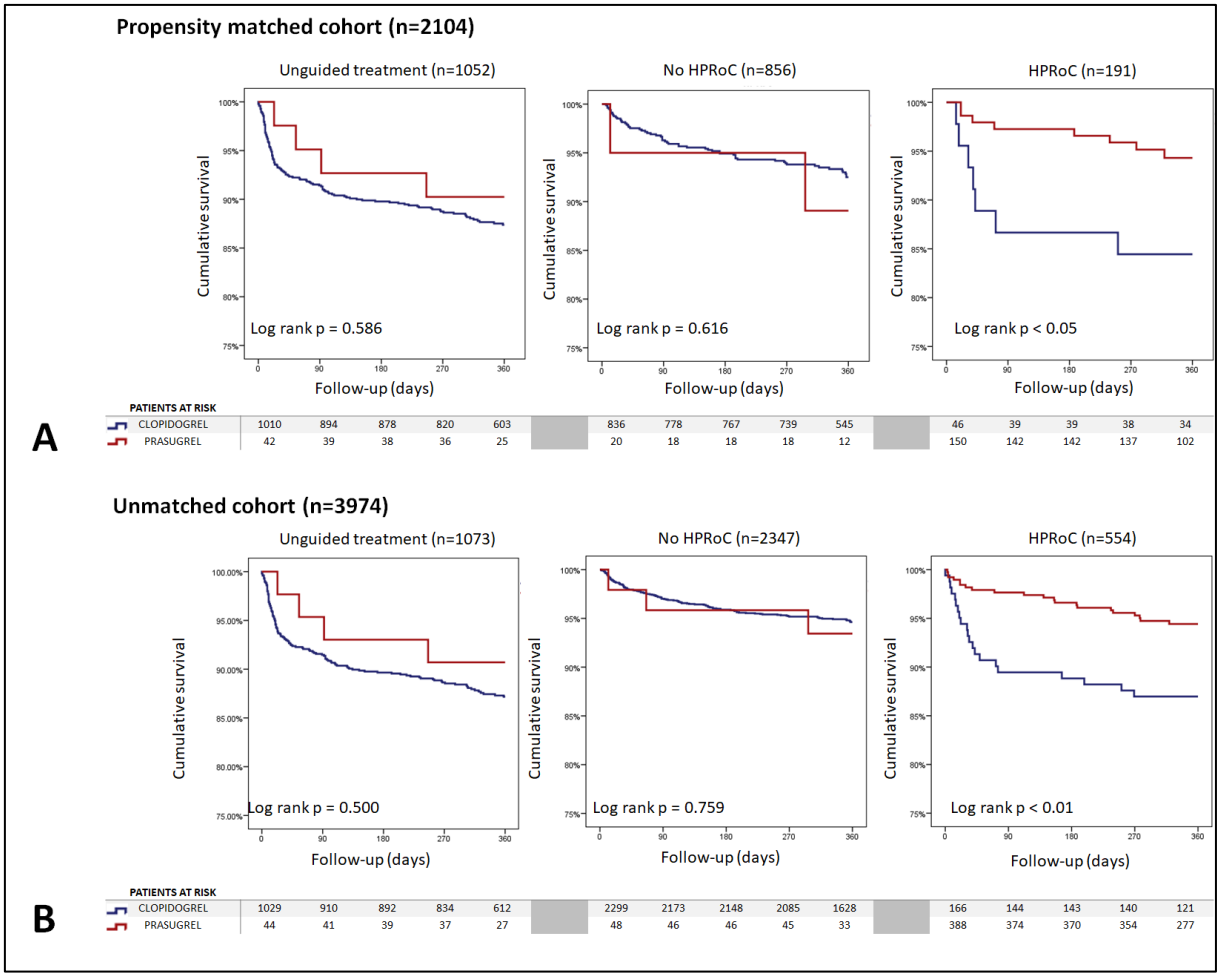

Figure 6. Kaplan-Meier curves depicting the outcome of patients with prasugrel or clopidogrel treatment in the strata of unguided treatment, high platelet reactivity on clopidogrel (HPRoC) or no HPRoC.

5.3.Direct anticoagulants and the risk of MI

Twenty-eight RCTs involving 196 761 (range: 1280-27 395) patients were analyzed. The main characteristics of these trials are shown in Table 6. Patients were recruited to the trials due to nonvalvular atrial fibrillation (AF),[53–60] including those scheduled for elective cardioversion (ECV),[61–63] patients after embolic stroke of undetermined source,[64,65] patients treated for pulmonary embolism (PE) or deep vein thrombosis (DVT),[66–73] as well as cases at high risk for CHD[29,74,75] including ACS. According to the applied anticoagulants, study arms were grouped into 8 groups. The geometry of the network is depicted in Figure 7A. Dose of the anticoagulant was different and as follows: 150 mg twice daily and 110 mg twice daily for dabigatran, 5 mg once daily to 10 mg twice daily for apixaban, 30 mg once daily and 60 mg once daily for edoxaban, while rivaroxaban dose ranged from 10 mg daily (once daily or twice daily) up to 30 mg daily except for 4 studies testing "rivaroxaban vascular" 2.5 mg twice-daily doses.[28,29,57,74] Control treatment arm was ASA in 5, VKA in 18, and placebo in 5 trials. Study definitions of MI were discrepant[47,48] (Table 6).

Study name/ First author (Publication year)	Period of study	Study drug (total daily dose, mg)	Comparator drug	Patients number	Follow-up (months)	Inclusion criteria	MI definition	MB definition
AMPLIFY/G. Agnelli (2013)	2008-2013	apixaban (20 first 7 days, 10)	warfarin	5395	7	confirmed symptomatic proximal DVT or PE	2≥ of the followings: symptoms; ECG abnormalities, elevated cardiac biomarkers	Based on ISTH MB
APPRAISE-2/ J. H. Alexander (2011)	2009-2011	apixaban (10)	placebo	7392	8	ACS within 7 days	2≥ of the followings: symptoms; ECG abnormalities, elevated cardiac biomarkers	Based on TIMI MB
ARISTOTLE/ C.B. Granger (2011)	2006-2011	apixaban (10)	warfarin	18,201	21,6	AF or flutter, ≥1 RF for stroke	IRCE	Based on TIMI MB
ATLAS ACS 2-TIMI 51/ J. L. Mega (2012)	2008-2011	rivaroxaban (5/10)	placebo	15,342	13,1	ASA or DAPT, ACS	IRCE	Based on TIMI MB
AUGUSTUS/ R. D. Lopes (2019)	2015-2018	apixaban (10/5)	warfarin	4614	6	NVAF, stable or unstable CAD treated with PCI	IRCE	Based on ISTH MB
AVERROES/ S. J. Connolly (2011)	2007-2010	apixaban (10/5)	ASA (81-324 mg)	5599	13,2	≥50 years, documented AF within prior 6 months	IRCE	Based on ISTH MB
COMPASS/ J. W. Eikelboom (2017)	2013-2017	rivaroxaban (5) + ASA / rivaroxaban (10)	ASA (100 mg)	27,395	23	CAD or PAD	Compatible with UDMI 2012	Based on ISTH MB
COMMANDER HF/ F. Zannad (2018)	2013-2017	rivaroxaban (5)	placebo	5022	21.1	chronic HF, EF<40% CAD, and elevated plasma concentrations of natriuretic peptide	Compatible with UDMI 2012	Based on ISTH MB

Study name/ First author (Publication year)	Period of study	Study drug (total daily dose, mg)	Comparator drug	Patients number	Follow-up (months)	Inclusion criteria	MI definition	MB definition
EINSTEIN-CHOICE/ J. I. Weitz (2017)	2014-2016	rivaroxaban (20/10)	ASA (100 mg)	3365	12+1	confirmed, symptomatic proximal DVT or PE	Compatible with UDMI 2012	Based on ISTH MB
EINSTEIN-DVT/ R. Bauersachs (2010)	2007-2010	rivaroxaban (30 3 weeks, 20)	warfarin / acenocoumarol	3429	12	symptomatic, recurrent DVT or nonfatal or fatal PE	IRCE	Based on ISTH MB
EINSTEIN-PE/ H. R. Büller (2012)	2007-2011	rivaroxaban (30 3 weeks, 20)	warfarin / acenocoumarol	4832	12	symptomatic PE with or without symptomatic DVT	IRCE	Based on ISTH MB
EMANATE / M. D. Ezekowitz (2018)	2014-2017	apixaban (10/5)	warfarin	1500	1,2/2,4	elective electrical/ pharmacological cardioversion	IRCE	Based on ISTH MB
ENGAGE AF - TIMI 48/ R. P. Giugliano (2013)	2008-2013	edoxaban (60/30)	warfarin	21,105	33,2	AF, a CHADS2 score of ≥2	IRCE	Based on ISTH MB
ENSURE-AF/ A. Goette (2016)	2014-2016	edoxaban (60/30)	warfarin	2199	1/1,63+1	Ongoing AF lasting at least 48 hrs but <= 12 months, elective ECV	IRCE	Based on ISTH MB
Hokusai-VTE/ Hokusai investigators (2013)	2009-2013	edoxaban (60/30)	warfarin	8240	12	confirmed DVT and/or symptomatic PE	Compatible with UDMI 2012	Based on ISTH MB
J-ROCKET AF/ M. Hori (2012)	2007-2009	rivaroxaban (15)	warfarin	1280	30+1	AF; prior ischemic stroke, TIA or non-CNS systemic embolism or ≥2 RF for stroke	2≥ of the followings: symptoms; ECG abnormalities, elevated cardiac biomarkers	Based on ISTH MB

Study name/ First author (Publication year)	Period of study	Study drug (total daily dose, mg)	Comparator drug	Patients number	Follow-up (months)	Inclusion criteria	MI definition	MB definition
MANAGE/ Manage Investigators.(2018)	2013-2018	dabigatran (220)	placebo	1754	16	undergone noncardiac surgery, MINS	IRCE	Based on ISTH MB
NAVIGATE ESUS/ R. G. Hart (2018)	2014-2018	rivaroxaban (15)	ASA (100 mg)	7213	15	ESUS, within 7 days and 6 months before screening	IRCE	Based on ISTH MB
PIONEER AF-PCI/ C.M. Gibson (2016)	2013-2016	rivaroxaban (10-15/5)	warfarin	2214	12	PCI with stent placement, history of AF	IRCE	Based on TIMI MB
RE-COVER II/ S. Schulman (2014)	2008-2011	dabigatran (300)	warfarin	2568	6+1	symptomatic, confirmed proximal DVT of the legs, or PE	IRCE	Based on ISTH MB
RE-COVER/ S. Schulman (2009)	2006-2009	dabigatran (300)	warfarin	2539	6+1	acute, symptomatic, proximal DVT or PE	IRCE	Based on ISTH MB
RE-DUAL/ C. P. Cannon (2017)	2014-2017	dabigatran (300/220)	warfarin	2725	14	NVAF, stable or unstable CAD treated with PCI	Compatible with UDMI 2012	Based on TIMI MB
RE-LY/ S. J. Connolly (2009)	2005-2009	dabigatran (300/220)	warfarin	18,113	24	AF and risk of stroke	IRCE	Based on ISTH MB
RE-MEDY/ S. Schulman (2013)	2006-2011	dabigatran (300)	warfarin	2856	36	symptomatic, proximal DVT or PE, previously treated with AC	IRCE	Based on ISTH MB
RE-SONATE/ S. Schilman (2013)	2007-2011	dabigatran (300)	placebo	1343	12	symptomatic, proximal DVT or PE, previously treated with AC	IRCE	Based on ISTH MB
RE-SPECT ESUS/ H. C. Diener (2019)	2014-2018	dabigatran (300/220)	ASA (100)	5390	19	ESUS within 3 months before screening	IRCE	Based on ISTH MB

Study name/ First author (Publication year)	Period of study	Study drug (total daily dose, mg)	Comparator drug	Patients number	Follow-up (months)	Inclusion criteria	MI definition	MB definition
ROCKET AF/ M. R. Patel (2011)	2006-2010	rivaroxaban (20/15)	warfarin	14,236	23,6	AF; prior ischemic stroke, TIA or non-CNS systemic embolism or ≥2 RF for stroke	2≥ of the followings: symptoms; ECG abnormalities, elevated cardiac biomarkers	Based on ISTH MB
X-VeRT/ R. Cappato (2014)	2012-2014	rivaroxaban (20/15)	warfarin / acenocoumarol	1504	1,5/2,68+1	elective electrical or pharmacological cardioversion	IRCE	Based on ISTH MB

Table 6. Characteristics of the included trials. Abbreviations: AC: anticoagulation; ACS: acute coronary syndrome; AF: atrial fibrillation; ASA: aspirin; CAD: coronary artery disease; CNS: central nervous system; DAPT: dual antiplatelet therapy; DVT: deep vein thrombosis; ECG: electrocardiography; ESUS: embolic stroke of undetermined source; GI: gastrointestinal; HF: heart failure; IRCE: Investigator reported clinical event; ISTH: International Society of Thrombosis and Haemostasis; LA: left atrial; LMWH: low-molecular-weight heparin; MB: major bleeding; MINS: myocardial injury after noncardiac surgery; MS: mitral stenosis; NA: not available; NVAF: nonvalvular atrial fibrillation; NYHA: New York Heart Association; PAD: peripheral arterial disease; PCI: percutaneous coronary intervention; PE: pulmonary embolism; RF: risk factor; STD: ST depression; STE: ST elevation; TIA: transient ischemic attack; TIMI: Thrombolysis in Myocardial Infarction; UDMI: universal definition of myocardial infarction; [47,48] URL: upper rate limit; VKA: vitamin K antagonist.

Low-dose (≤100/≤165 mg daily) ASA treatment was allowed in all studies. Analysis of bias showed high quality of the source information with low probability of possible bias. No obvious publication bias was found. In the included trials, 3554 MIs occurred in the VKA arm with 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. Furthermore, rivaroxaban in vascular dose resulted in 16% (RR: 0.70 [0.70-0.99]) reduction compared with placebo, as well as 27% (RR 0.80 [0.56-0.96] risk reduction compared to dabigatran (Table 7).

Leave-one-out analysis disregarding the data from the Randomized Evaluation of Long Term Anticoagulant Therapy with Dabigatran Etexilate (RE-LY) trial showed similar relations with lower MI risk with rivaroxaban than with placebo (0.78 [0.64-0.94]) and dabigatran as well (RR: 0.66 [0.49-0.89]). The computed probability of being the first best choice of treatment was 61.8% for rivaroxaban, 17.4% for very low-dose rivaroxaban (5 mg daily), 14.2% for apixaban, 2.4% for VKAs, 3.0% for edoxaban, 1.1% for ASA, and <0.1% for placebo and dabigatran in the network. Ranking remained unaffected if data from the RE-LY trial were censored from the analysis. Ranking based on mortality and major bleeding result showed trends of similar ranks with MI and mortality, while trends of major bleeding showed opposite tendencies with lower ranking of bleeding at treatments with higher rankings in MI (Figure 7C). However, neither of these trends were significant at regression analyses of the surface under the cumulative ranking area values (R^2 for MI and mortality: 0.035, p=0.66 and R^2 for MI and major bleeding: 0.30, p=0.16).

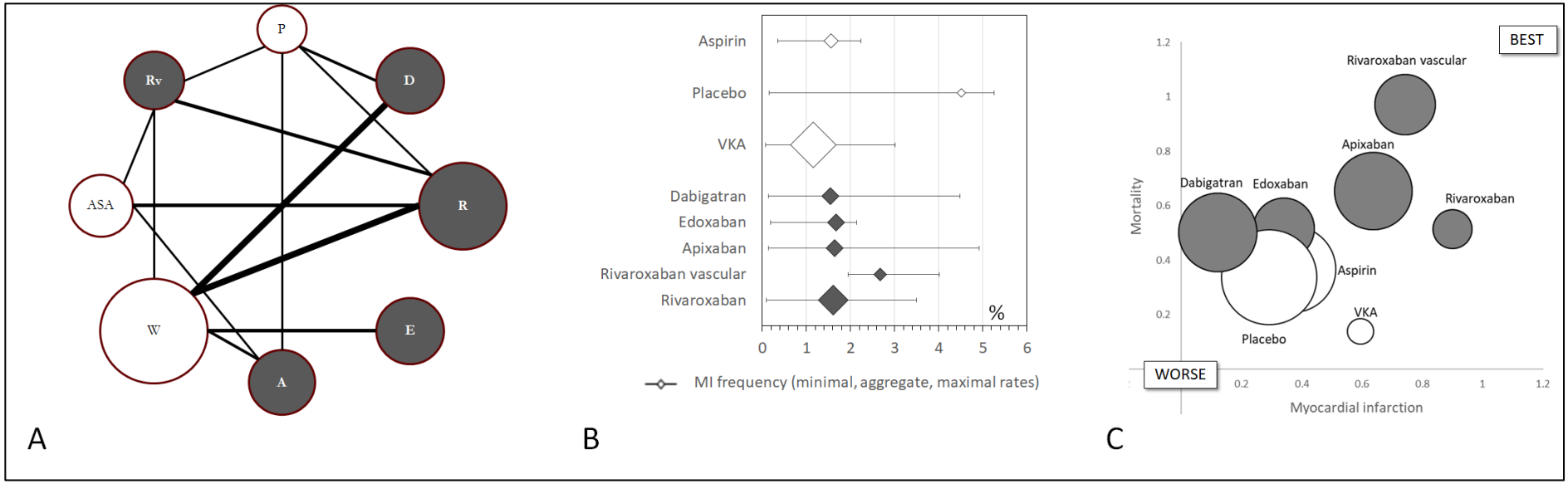

Figure 7. Study network, myocardial infarction frequencies, and ranking. A, Plot of the study network. Nodes show anticoagulation treatments being compared, and edges represent an available direct comparison between pairs of intervention. B, Rate of myocardial infarction according to the treatment groups. Whiskers depict minimal and maximal rates. The diamond depicts the aggregate rate, and its size is proportional to the number of patients treated with the particular intervention. C, Clustered ranking plot of the network. The plot is based on the cluster analysis of SUCRA curves, and the plot shows SUCRA values for the risk of myocardial infarction and mortality. Size of the circles is plotted based on the SUCRA values for major bleeding. AP indicates placebo; D, dabigatran; R, rivaroxaban; E, edoxaban; A, apixaban; W, warfarin; ASA, aspirin; Rv, rivaroxaban vascular dose; SUCRA, surface under the cumulative ranking. Abbreviation: MI: myocardial infarction

Rivaroxaban				Treatment 1			
0.94 (0.76 – 1.15) 1.22 (1.04 – 1.45)* 1.82 (0.79 – 2.17)	Rivaroxaban vascular			Myocardial infarction Mortality Major bleeding	Treatment 2		
0.90 (0.68 – 1.18) 1.03 (0.87 – 1.25) 1.72 (0.97 – 3.13)	0.95 (0.70 – 1.29) 0.85 (0.69 – 1.07) 1.35 (0.66 – 2.70)	Apixaban					
0.88 (0.70 – 1.12) 0.92 (0.79 – 1.07) 0.90 (0.62 – 1.33)	0.93 (0.72 – 1.25) 0.75 (0.61 – 0.92)* 0.71 (0.39 – 1.22)	0.98 (0.76 – 1.31) 0.88 (0.76 – 1.02) 0.52 (0.31 – 0.88)*	VKA				
0.81 (0.61 – 1.01) 0.96 (0.82 – 1.14) 2.08 (0.23 – 3.57)	0.86 (0.64 – 1.09) 0.79 (0.66 – 0.95)* 1.61 (0.85 – 3.03)	0.90 (0.64 – 1.23) 0.93 (0.76 – 1.13) 1.21 (0.63 – 2.27)	0.92 (0.64 – 1.23) 1.05 (0.86 – 1.28) 2.27 (1.28 – 4.16)*	Aspirin			
0.79 (0.55 – 1.13) 1.00 (0.81 – 1.25) 1.28 (0.64 – 2.63)	0.84 (0.57 – 1.24) 0.82 (0.64 – 1.06) 1.00 (0.43 – 2.22)	0.88 (0.60 – 1.30) 0.97 (0.77 – 1.19) 0.74 (0.34 – 1.62)	0.90 (0.67 – 1.17) 1.01 (0.93 – 1.27) 1.41 (0.79 – 2.56)	0.97 (0.66 – 1.53) 1.04 (0.81 – 1.33) 0.62 (0.27 – 1.42)	Edoxaban		
0.78 (0.60 – 0.98)* 0.96 (0.79 – 1.16) 2.77 (1.54 – 5.00)*	0.84 (0.64 – 1.06) 0.78 (0.63 – 0.97)* 2.13 (1.08 – 4.17)*	0.87 (0.67 – 1.11) 0.92 (0.75 – 1.12) 1.59 (0.84 – 3.03)	0.89 (0.66 – 1.14) 1.04 (0.86 – 1.27) 3.03 (1.75 – 6.67)*	0.97 (0.72 – 1.33) 0.99 (0.79 – 1.24) 1.33 (0.64 – 2.70)	1.00 (0.66 – 1.44) 0.96 (0.75 – 1.22) 2.13 (0.95 – 4.76)	Placebo	
0.70 (0.52 – 0.95)* 1.00 (0.82 – 1.21) 1.72 (1.05 – 2.94)*	0.75 (0.53 – 1.04) 0.82 (0.65 – 1.03) 1.35 (0.71 – 2.56)	0.78 (0.56 – 1.09) 0.96 (0.78 – 1.16) 1.01 (0.55 – 1.89)	0.80 (0.62 – 1.00)* 1.09 (0.94 – 1.23) 1.92 (1.32 – 2.86)*	0.87 (0.61 – 1.28) 1.03 (0.82 – 1.30) 0.84 (0.43 – 1.67)	0.89 (0.61 – 1.27) 1.00 (0.81 – 1.22) 1.35 (0.68 – 2.77)	0.90 (0.66 – 1.23) 1.04 (0.85 – 1.28) 0.63 (0.37 – 1.10)	Dabigatran

Table 7. Indirect Comparisons of Different Oral Anticoagulants in a Network Meta-Analysis. Abbreviation: VKA: vitamin K antagonist. League table shows the risk ratios (RR) and the 95% credible interval (CrI) of the different oral anticoagulants in a random effect model with vague prior for myocardial infarction (first line), mortality (second line), and major bleeding (third line). RR < 1 means that the top left treatment (Treatment 1) is better. * marks the comparisons where the CrI did not overlap the line of equivalence.

Regarding the clinical background 14 studies included patients with high risk for cerebrovascular event including 12 trials in AF and 2 trials of ESUS. Nine studies were performed in patients with DVT/PE and 8 studies included patient with coronary disease or with high risk for coronary event (Table 6). The included studies used different definitions for MI. Five studies used biomarker based definitions for MI that is compatible with the universal definition of MI [48] (Definition 1). Four studies defined MI as 2 ≥ of the followings: specific symptoms; ECG abnormalities, elevated cardiac biomarkers (Definition 2) while in 19 studies investigator reported MI events were reported without further definitions (Definition 3). Subgroup analysis of studies of the different setting did show consistent results with the main findings of the full analysis (Table 8). Studies using Definition 1. for MI did not composed a closed network. Both the subgroup analyses of studies using the other two definitions as well as the leave-out analyses of either definition showed consistent results as well. Similarly, ranking of the different treatments were not substantially effected in the subgroup analyses (Figure 8).

	number of studies	*Rivaroxaban vs Dabigatran*	*Rivaroxaban vascular vs Dabigatran*	*Apixaban vs Dabigatran*	*VKA vs Dabigatran*	*Rivaroxaban vs Placebo*	*Rivaroxaban vascular vs Placebo*
Full analysis	28	0.69* (0.53 – 0.89)	0.73 (0.56 – 0.96)	0.76 (0.58 – 0.99)	0.81* (0.65 – 0.98)	0.79* (0.65 – 0.94)	0.84* (0.70 – 0.99)
Clinical setting							
Stroke prevention (ESUS or AF)	14	0.66* (0.45 – 0.96)	0.60 (0.29 – 1.17)	0.71 (0.49 – 1.01)	0.79 (0.60 – 1.02)	NA	NA
AF	12	0.61 (0.29 – 1.26)	0.67 (0.42 – 1.09)	0.71 (0.46 – 1.11)	0.80 (0.58 – 1.07)	NA	NA
Coronary disease (or high risk for coronary event)	8	0.69* (0.53 – 0.89)	0.73* (0.56 – 0.96)	0.76 (0.58 – 0.99)	0.81* (0.65 – 0.98)	0.79* (0.65 – 0.94)	0.84* (0.70 – 0.99)
Deep vein thrombosis / Pulmonary embolism	9	0.40 (0.05 – 4.62)	NA	0.80 (0.04 – 19.04)	0.36 (0.08 – 1.61)	0.40 (0.00 – 45.77)	NA
Myocardial infarction definitions							
Definition 1	5	-	-	-	-	-	-
Definition 2	4	NA	NA	NA	NA	0.46 (0.01 – 13.03)	NA
Definition 3	19	0.73 (0.46 – 1.09)	0.82 (0.47 – 1.26)	0.71 (0.43 – 1.05)	0.79 (0.52 – 1.05)	0.74 (0.49 – 1.03)	0.84 (0.52 – 1.15)
Definition 1&2	9	0.71 (0.16 – 5.92)	0.82 (0.15 – 12.40)	1.01 (0.17 – 14.28)	0.73 (0.22 – 2.56)	0.70 (0.09 – 3.78)	0.79 (0.18 – 3.84)
Definition 2&3	23	0.70* (0.49 – 0.97)	0.78 (0.51 – 1.12)	0.78 (0.55 – 1.08)	0.82 (0.59 – 1.07)	0.77* (0.58 – 0.99)	0.86 (0.61 – 1.12)
Definition 1&3	24	0.74 (0.54 – 1.00)	0.78 (0.57 – 1.07)	0.70* (0.51 – 0.95)	0.78* (0.62 – 0.96)	0.77* (0.61 – 0.95)	0.82* (0.67 – 0.99)

Table 8. Subgroup analysis of studies of the different settings. Abbreviation: AF: atrial fibrillation; ESUS: embolic stroke of undetermined source; VKA, Vitamin K antagonist. * marks the comparisons where the CrI did not overlap the line of equivalence.

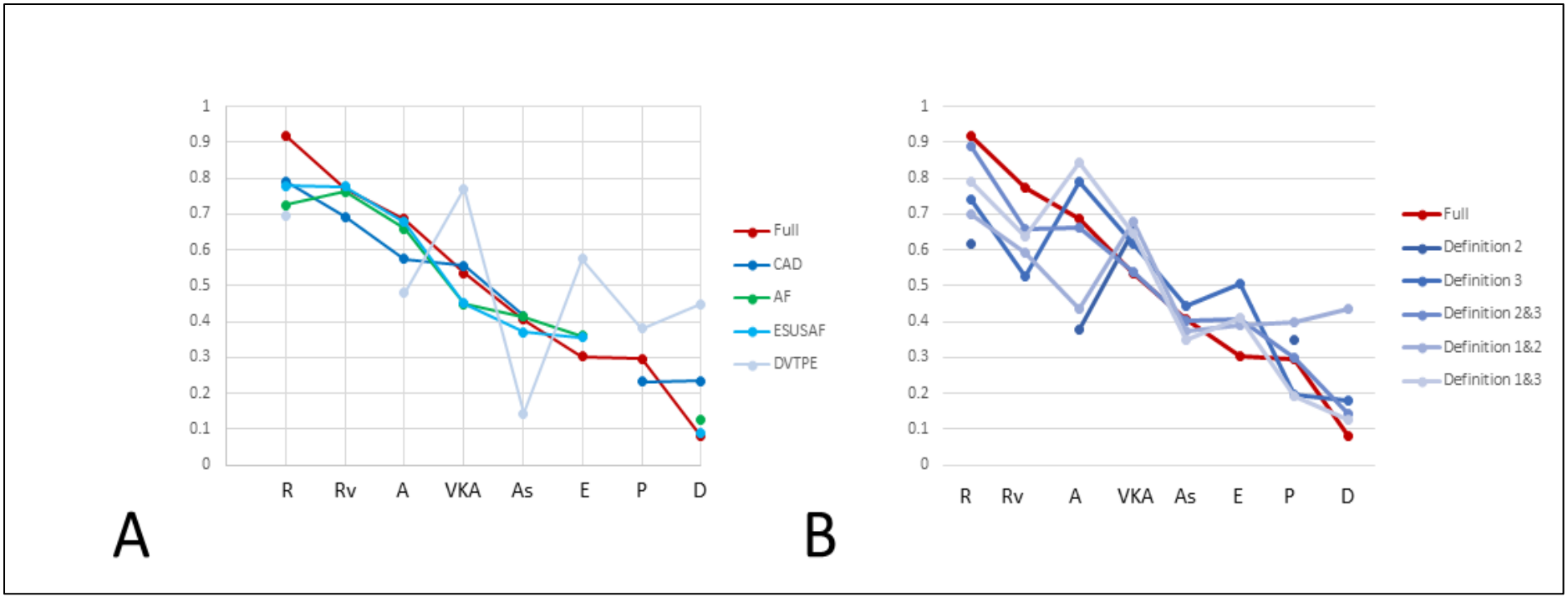

Figure 8. Plots showing the effect of the subgroup analyses on the ranking of the different treatment strategies as reflected by the Surface Under the Cumulative Ranking (SUCRA) values in the different subgroups. Abbreviations: CAD: coronary artery disease, AF: atrial fibrillation, ESUS: embolic stroke of undetermined source, DVT: deep vein thrombosis, PE: pulmonary embolism, R: rivaroxaban, Rv: rivaroxaban vascular, A: apixaban, VKA: vitamin K antagonist, As: aspirin, E: edoxaban, P: placebo, D: dabigatran.

6. DISCUSSION

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

In a large registry of AMI patients undergoing coronary intervention procedure, we have found that the DES was underused in elderly people even though current guidelines clearly specify that DES should be used in AMI regardless of age. Better prognosis was seen among those venerable patients who underwent coronary intervention at the event of AMI and received a DES.

The incidence of AMI is increasing in elderly patients, representing a growing segment of the population with amplified frailty and a higher rate of comorbidities.[76,77] Elderly account for one third of the patients undergoing hospitalization for an ACS however, they are inadequately represented in clinical trials.[78–80] Based on the limited evidence, the management of this population is considerably challenging. Real word data showed that coronary intervention is beneficial among elderly patients in MI.[44] In the last decade some safety concerns with early generation DES have arisen after reports suggesting a higher incidence of late stent thrombosis associated with DES implantation in comparison to BMS.[81] Early generation DES have now been supplanted by new-generation DES with higher efficacy and safety in comparison with both early generation DES and BMS.[7] However, in several countries elderly patients still frequently receive BMS with the intent to shorten the duration of DAPT, to reduce bleeding complications.[9] Though, the 2018 European guidelines on myocardial revascularization recommend DES over BMS for any PCI its use still accounts for approximately 20% of all PCI procedures.[7,10,11] Previous studies demonstrated the short- and long-term efficacy of DES among elderly patients.[82–87] It is of particular importance that none of these analyses found increased bleeding risk associated with DES.

Most recently, the SENIOR trial compared DES to BMS applying a short duration of DAPT in age ≥ 75 patients, who underwent percutaneous coronary revascularization. Antiplatelet strategy consisted DAPT for 1 month in patients with a stable presentation and 6 months for those with an unstable presentation. The rate of patients with ACS was 45%. The primary endpoint (composite of all-cause mortality, MI, stroke or ischemia-driven TLR occurred less frequently in the DES group with BMS-like DAPT regimen, however, this difference was caused by a significantly lower rate of TLR in the DES group. Meanwhile rates of all-cause mortality, CV death, MI and stroke were similar between groups. Similarly to the earlier studies, no difference was found either in bleeding complications or ST at 1-year follow.[33] Most data supported the use of new-generation DES in elderly populations, however, while these trials included different proportions of ACS cases the "Clinical Evaluation of Everolimus Eluting Coronary Stents in the Treatment of Patients With ST-Segment Elevation Myocardial Infarction" (EXAMINATION) trial studied everolimus-eluting stents in ST-Elevation Myocardial Infarction (STEMI). In contrast, to the earlier trials, results of a post hoc analysis of elderly (age ≥ 75) patients found no benefit of DES either in the primary composite endpoint of all-cause death, any MI or any revascularization, or in MI, or in the need for subsequent revascularization.[88] The decision for the implantation of BMS rather than DES is driven principally by concerns about higher bleeding risk and DAPT compliance.[11] Accordingly, prolonged DAPT seems to be the main reason against the use of DES in elderly patients undergoing PCI.[89] In cases with AMI the recommended duration of DAPT is 12 months regardless of the type of the stent implanted, however, in case of bleeding, interruption after 1 month is considered to be less dangerous with BMS compared with DES.[12] Theoretically the possible earlier cessation of DAPT in case of BMS might prevent the development of bleeding complications, however, we found no excess of severe, blood transfusion requiring events in the DES cohort. Using the data capture of a national MI registry we studied an unselected high-

risk patient-group of AMI with a 28% risk of death within 1 year after the stent implantation. Our data clearly refute the assumption of the higher safety of BMS in a frail and elderly population. The analysis of the clinical characteristics in our cohort supported that BMS was preferably implanted in fragile cases with higher age and multiple risks. However, prognostic benefit in terms of mortality, major ischemic events as well as that of the repeat revascularization prevailed in the propensity-matched analyses. Besides the favourable rate of MACE, bleeding events were not more frequent in the DES group even in our matched sample.

Some limitations of our study need to be acknowledged. Most importantly this is not a randomized trial capable of providing a completely unbiased assessment of treatment effect. Data regarding actual duration of antiplatelet use and type of bleeding events are not available. Therefore, blood transfusion has been used as a surrogate in this study. Similarly, repeat revascularization is used instead of target vessel revascularization as specific data are lacking in this regard. In fact, the lower blood transfusion rate of the DES-treated cases, together with the clinical characteristics of the unbalanced cohort support the potential influence of a selection bias with DES implanted in healthier patients with potentially a better outcome. The PS matching balanced the significant differences observed between the DES and BMS groups in the entire cohort. However, the influence of potentially uncontrolled variables may also not be entirely excluded. Keeping this limitation in mind and considering that our data originate from a nation-wide, multi-center registry, together with the statistically robust difference in the propensity-matched cohorts confirms the validity of the results.

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

Our analysis of a large, prospective, unselected database of patients treated with coronary intervention due to an event of AMI showed improved survival in patients with PFT-guided antiplatelet treatment compared to unguided strategy. Explorative analyses demonstrated that the results of PFT had 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. These findings may explain why not prasugrel therapy, but PFT-guided $P2Y_{12}$ inhibitor treatment selection prevailed as an independent predictor of improved survival in multivariate analysis. These results were confirmed both in the overall and in the PS-matched cohorts.

Prasugrel and ticagrelor showed a significant reduction in the risk of ischemic endpoints in AMI patients.[90,91] However, both potent $P2Y_{12}$ inhibitors were associated with a higher risk for major bleeding and in case of prasugrel, no apparent benefit in patients over 75 years of age or with low bodyweight was shown. These together with the higher treatment costs still limit the clinical uptake of newer $P2Y_{12}$ inhibitors in the routine.[14,92,93] Tailoring treatments based on biomarkers and genes is an emerging field in multiple areas of medicine. Studies of genetic testing may identify individuals with characteristics that may affect pharmacodynamic effects of clopidogrel while theoretically, PFT could be useful to measure the achieved platelet inhibition and guide the choice of the $P2Y_{12}$ inhibitor to reach an optimal range of platelet inhibition.[94,95] Genetic polymorphisms targeted by the tests may affect clopidogrel absorption, metabolism that have minor or no influence on new generation $P2Y_{12}$ blockers effects. In contrast, PFT is more subject to methodological difficulties but reflect an actual state of platelet

inhibition.[16,94–96] Importantly, three available randomized controlled trials failed to support the use of PFT to adjust treatment in patients undergoing coronary intervention.[97–99] Consequently the 2017 ESC focused update document on DAPT in CAD do not recommend the routine PFT to adjust antiplatelet therapy before or after elective stenting.[12]

From 2011, Hungarian health insurer reimbursed prasugrel for ACS patients undergoing coronary intervention who had either diabetes or AMI, but only in cases when PFT verified the clopidogrel non-responder status. The reimbursement is independent from the genetic characteristics. This regulation practically acts as a prasugrel prescribing policy due to the high costs of unreimbursed prasugrel for patients and resulted in a high frequency of PFT screening. Our data are in line with the results of the "Gauging Responsiveness With A VerifyNow Assay-Impact On Thrombosis And Safety" (GRAVITAS) trial as we did not detect a significant clinical difference between high-dose and standard dose clopidogrel in case of HPRoC.[97] The "Assessment by a Double Randomization of a Conventional Antiplatelet Strategy versus a Monitoring-guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption versus Continuation One Year after Stenting" (ARCTIC) study randomized patients to PFT-guided and unguided strategies, similar to our design. However, cases with ST segment elevation – similarly to the GRAVITAS trial – were excluded. Importantly, interventions to overcome low responsiveness included complex pharmacological strategies but switching over to prasugrel was rarely used (9%).[98] In the "Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome" (ANTARCTIC) trial acute coronary patients over 75 years to received either 5 mg prasugrel or PFT-guided therapy including 5 or 10 mg prasugrel or 75 mg clopidogrel according to the results of VerifyNow testing. Importantly, the ANTARCTIC study was mostly a step-down trial with 40% of the patients switched back to clopidogrel an only 4% scaled up to 10 mg of prasugrel.[99] Similar to ANTARCTIC, the "Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet

Treatment For Acute Coronary Syndromes Trial" (TROPICAL ACS) trial also used a PFT-guided de-escalation approach based on the Multiplate assay. In the trial, patients with AMI were randomized to universal prasugrel treatment or PFT-guided early de-escalation from prasugrel to clopidogrel, if no HPRoC was detected. The TROPICAL ACS study is the first to support that a PFT-guided strategy is equally safe and effective as the guideline recommended strategy.[100] Our registry recruited, a high-risk, routine AMI cohort with patients including 55% ST segment elevation and 45% AMI without ST segment elevation applying 70% - switch-over rate to prasugrel. In this high-risk registry cohort, we could analyze predictors of mortality, resulting in strong statistical associations.

Although in the trial leading to the approval of prasugrel previous exposure to clopidogrel was an exclusion criterion for study entry, we have increasing amount of data regarding switching between antiplatelets.[14,90,101] In fact, switching occurs frequently in clinical practice for various reasons. Differences in pharmacology due to binding site, half-life, and speed of onset and offset of action differences may incite drug interactions. Studies have not raised any major concerns associated with the clopidogrel-prasugrel switch but consistently showed decreased level of residual platelet reactivity.[101] The most relevant studies were the "SWitching Anti Platelet" (SWAP) and the "Transferring From Clopidogrel Loading Dose to Prasugrel Loading Dose in Acute Coronary Syndrome Patients" (TRIPLET) trials that included acute cases with results raising no concerns regarding prasugrel administration among clopidogrel treated patients.[102,103] The recently published ESC focused update on DAPT in coronary artery disease also provide switching algorithms in case of clinical need.[12]

Our data originate from a nation-wide, multi-center screening system using uniform whole blood impedance aggregometry that strengths the results, however, there remain important limitations to acknowledge. First, we have no information, how the individual decisions based on patient characteristics and logistics were made. Indeed, cases in whom PFT was performed

differed in several features from the unguided patients. Although exclusion of cases with absolute and relative contraindications to prasugrel and PS matching balanced significant differences observed between the PFT-guided and unguided groups, other, potentially uncontrolled variables may also exist that potentially influenced the choice of treatment. Taking this limitation into account, the statistically robust difference ($p<0.001$) in the propensity-matched cohorts confirms validity of results. Second, we collected information regarding the clinical events using a payer's database that may have not used as standardized definitions for bleeding event, stent thrombosis and MI as usual in clinical trials. Furthermore, the fact that ticagrelor was not available at the time of the study it may restrict its generalizability. Third, in our prospective database we lack reliable information regarding the drug-compliance and later changes on medications and we confined our analyses to intention-to-treat groups based on the discharge summaries of the index events.

6.3.Direct anticoagulants and the risk of MI

In this meta-analysis involving 196761 patients, we found evidence that the choice of anticoagulant influences the risk of MI in anticoagulated patients. When risk of MI is taken into consideration, the probability of being the best choice of treatment is the highest for rivaroxaban administered in antithrombotic or vascular prevention dose regimen, while the lowest is for VKAs and the direct thrombin inhibitor, dabigatran.

Coagulation plays pivotal role in the development of CV events; thus, CV safety of these drugs is of paramount interest. Earlier analyses found favorable results for VKAs in the prevention after AMI. [27] However, frequent bleeding complications and the narrow therapeutic window with the need for careful monitoring, in addition to drug and food interactions, limit the benefits. [104] In recent years, VKAs are progressively replaced by the specifically acting oral anticoagulants (DOACs) offering an easier and potentially safer option leading to a high number of patients exposed to these drugs. Moreover, improving safety and convenience of use raised the question as to whether DOACs reopen the field of CV prevention for anticoagulation.

Several recent trials supported this concept including the "Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 51" (ATLAS ACS 2–TIMI 51) trial, where 2.5 mg rivaroxaban twice daily improved the CV outcomes compared to placebo. Despite the higher risk of bleeding, compared to placebo vascular dose rivaroxaban reduced the rate of death of CV origin (2.7% vs. 4.1%, p=0.002) and all other causes (2.9% vs 4.5%, p=0.002).[28] More recently in the "Cardiovascular Outcomes for People Using Anticoagulation Strategies" (COMPASS) trial, low dose rivaroxaban combined with ASA was associated with a reduced risk of ischemic events and mortality among patients with established, stable atherosclerotic disease, compared to those receiving ASA monotherapy. Although bleeding complications were also more common, the combined treatment with low-dose rivaroxaban resulted in

superior net clinical benefit.[29] Furthermore, in the "Management of Myocardial Injury After Noncardiac Surgery" (MANAGE) trial among patients with myocardial injury after noncardiac surgery, twice-daily 110 mg dabigatran was tested against placebo and resulted in fewer major vascular events, while bleeding complications were similar in frequency (p=0.012 and p=0.76, respectively).[31]

Contrasting these recent results, there has been some question ever since the publication of one of the earliest DOAC phase 3 study, the RE-LY trial.[59] In this trial, 2 doses of dabigatran were shown to be either more effective in preventing stroke with a similar bleeding risk or safer than warfarin with similar prevention efficacy. Importantly, this study reflected that patients receiving anticoagulant treatment for AF remain at risk of MI and found an excessive risk of MI with dabigatran. There were numerically more MIs with both doses of dabigatran than with warfarin, and the difference reached statistical significance regarding the higher, 150 mg dose. However, a subsequent post hoc analysis revealed additional events of stroke, bleeding, and MI, and the revised results no longer showed a significant difference in MI.[105]

In the paucity of direct comparison randomized trials, several studies including prospective and retrospective registries attempted verification and characterization of the magnitude of the potential MI risk of dabigatran-treated patients. These studies, though subjected to several methodological shortcomings, especially an uncontrollable selection bias, could neither reliably support nor refute the importance of this signal.[106–108] Our extended review including a broad range of studies found that the data of randomized trials show important differences favoring the Xa inhibitor rivaroxaban and apixaban over dabigatran. This extends the earlier observations supporting that signal persists even after exclusion of the RE-LY data and reaches beyond the field of patients with AF.

Since the 2012 version of the ESC CV disease prevention guideline, the concept of primary and secondary prevention has been discouraged and replaced by the recognition that

atherosclerosis is a continuous process.[109] 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.

Our analysis assessed the preventive potential of DOACs. The inclusion of 5 placebo and 5 ASA-controlled trials enables to relate this potential to established preventive therapy. The RRs of the anticoagulant treatments compared to ASA were independent from both the rate of antiplatelet treatment and background risk. Importantly, the subgroup analyses according to the clinical indications or the treatment length did not show a major influence on the results. These findings suggest that the preventive potential of DOACs is heterogeneous, correlates with that of ASA and VKA, and is independent of the concomitant antiplatelet treatment.

The risk of MI with DOAC treatment has been assessed in earlier systematic reviews and meta-analyses. Besides that, these analyses did not include the results of some pivotal recent trials including the COMPASS, MANAGE, and "An Open-label, 2 x 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention" (AUGUSTUS) studies; they share some common limitations. These comprise inclusion of underpowered, dose-finding, phase 2 trials.[110–113] Only a few of them included trials with the recently approved edoxaban[113–115] but included trials with drugs that stopped development.[110,111,114,115] Some previous works restricted the analysis to trials related only to AF and or DVT/PE.[113–115] Some based their assumptions on the less robust fixed effect model that accounts for interstudy heterogeneity less adequately.[112,113]

Some limitations of our analysis should be discussed. The paucity of randomized trials comparing different DOAC agents was one of the main reasons for the choice of this analysis but represents also a limitation as the presented statistical inferences rely substantially on indirect comparisons. It is improbable that a specific trial with MI as an end point and aiming

to perform a direct comparison of oral anticoagulants will ever be conducted; thus, analysis of the available data set remains the only option to shed light on these relationships.

Furthermore, safety and efficacy profiles of the anticoagulants may be dose dependent, and the variability in drug regimens might be a source of distortion. In fact, in trials testing >1 dose of DOACs, the rate of MI was different in some cases but similar in others. For example, 2.4% and 1.89% with 30 and 60 mg once-daily edoxaban in the "Global Study to Assess the Safety and Effectiveness of Edoxaban vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation" (ENGAGE AF—TIMI 48) trial, or 1.46% and 1.43% with 110 or 150 mg twice-daily dabigatran in the RE-LY trial among patients with AF, respectively.[54] However, in most of the remaining trials, the rather complicated schemes do not permit the study of dose–effect relationships. Thus, we decided to form our analysis groups based on DOAC exposure, with one exception regarding the distinction of the very low-dose rivaroxaban. Earlier studies with warfarin show that ischemic protection requires to reach a threshold of anticoagulation; above this limit, the rate of bleeding complications but not necessarily the preventive potential increases.[116] Acknowledging that this relation may apply to other means of anticoagulation, we handled "vascular dose" rivaroxaban as distinct treatment groups. Regarding VKA treatment, all but 3 included trials used warfarin in their VKA arms. In 3 trials, acenocoumarol was also allowed.[61,69,70] Acknowledging that differences may exist in CV safety of the different VKAs due to the paucity of specific data, we could not differentiate among them. Furthermore, definition of MI slightly differed across studies, and none of them included trials had MI as an end point. Moreover, there are >1 publication regarding the rates of MI in the RE-LY trial.[59,105] This shows that even with meticulously conducted trials, the capture and adjudication of events may be incomplete. As data in the first publication reflected the results of the prospective event adjudication instead of a post hoc analysis, we used these in our analyses.[59] Furthermore, we performed sensitivity analyses that did not show important influence on the result.

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 ACS, 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. 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.

8. REFERENCES

1. Roth GA, Huffman MD, Moran AE, et al.: Global and regional patterns in cardiovascular mortality from 1990 to 2013. Circulation 2015; 132:1667–1678.
2. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M: Cardiovascular disease in Europe: Epidemiological update 2016. Eur. Heart J. 2016,.
3. Neumann F-J, Sousa-Uva M, Ahlsson A, et al.: 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019; 40:87–165.
4. Roffi M, Patrono C, Collet JP, et al.: 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent st-segment elevation: Task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of . Eur. Heart J. 2016; 37:267-315.
5. Piepoli MF, Hoes AW, Agewall S, et al.: 2016 European Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2016; 37:2315–2381.
6. Ibanez B, James S, Agewall S, et al.: 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur. Heart J. 2018; 39:119-177.
7. Neumann FJ, Sousa-Uva M, Ahlsson A, et al.: 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur. Heart J. 2019; 40:87-165.
8. Habib A, Finn A V.: Endothelialization of Drug Eluting Stents and its Impact on Dual Anti-platelet Therapy Duration. Pharmacol Res 2015; 93:22–27.
9. Gerber RT, Satpal F, Mrcp SA, et al.: Age is not a bar to PCI : Insights from the long-term outcomes from off-site PCI in a real-world setting. J Interv Cardiol 2017; 30:347–355.
10. Rymer JA, Harrison RW, Dai D, et al.: Trends in Bare-Metal Stent Use in the United States in Patients Aged ≥65 Years (from the CathPCI Registry). Am J Cardiol Elsevier Inc., 2016; 118:959–966.
11. Morice M-C, Urban P, Greene S, Schuler G, Chevalier B: Why Are We Still Using Coronary Bare-Metal Stents ? J Am Coll Cardiol Elsevier Inc., 2013; 61:1122–1123.
12. Valgimigli M, Bueno H, Byrne RA, et al.: 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. Eur Heart J 2018; 39:213–260.
13. Authors/Task Force members, Windecker S, Kolh P, et al.: 2014 ESC/EACTS

Guidelines on myocardial revascularization. Eur Heart J; 35:2541–2619.

14. Bagai A, Peterson ED, McCoy LA, et al.: Association of measured platelet reactivity with changes in P2Y 12 receptor inhibitor therapy and outcomes after myocardial infarction: Insights into routine clinical practice from the TReatment with ADP receptor iNhibitorS: Longitudinal Assessment of Treatment Patterns and Events after Acute Coronary Syndrome (TRANSLATE-ACS) study. Am Heart J 2017; 187:19-28.
15. Aradi D, Tornyos A, Pintér T, et al.: Optimizing P2Y12 receptor inhibition in patients with acute coronary syndrome on the basis of platelet function testing: Impact of prasugrel and high-dose clopidogrel. J Am Coll Cardiol 2014; 63:1061-70.
16. Angiolillo DJ, Rollini F, Storey RF, et al.: International expert consensus on switching platelet P2Y12 receptor-inhibiting therapies. Circulation 2017; 136:1955–1975.
17. Komócsi A, Rudas L, Kiss RG, Becker D, Keltai M, Aradi D: Konszenzus ajánlás a trombocitaaggregáció-gátlás méréséről koronária stent-implantáción átesett betegek esetén [Recommendation of platelet aggregation measurement after stent implantation]. Cardiol Hung 2011; 41:2-19.
18. Lins R, Broekhuysen J, Necciari J, Deroubaix X: Pharmacokinetic profile of 14C-labeled clopidogrel. Semin Thromb Hemost 1999; 25 Suppl 2:29-33.
19. Savi P, Herbert JM, Pflieger AM, et al.: Importance of hepatic metabolism in the antiaggregating activity of the thienopyridine clopidogrel. Biochem Pharmacol 1992; 44:527-532.
20. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al.: Variability in Individual Responsiveness to Clopidogrel. Clinical Implications, Management, and Future Perspectives. J. Am. Coll. Cardiol. 2007; 49:1505-16.
21. Garabedian T, Alam S: High residual platelet reactivity on clopidogrel: its significance and therapeutic challenges overcoming clopidogrel resistance. Cardiovasc Diagn Ther 2013; 3:23-37.
22. Müller I, Besta F, Schulz C, Massberg S, Schönig A, Gawaz M: Prevalence of clopidogrel non-responders among patients with stable angina pectoris scheduled for elective coronary stent placement. Thromb Haemost 2003; 89:783-787.
23. Wiviott SD, Antman EM: Clopidogrel resistance: a new chapter in a fast-moving story. Circulation. 2004; 109:3063-3067.
24. Aradi D, Komócsi A, Vorobcsuk A, et al.: Prognostic significance of high on-clopidogrel platelet reactivity after percutaneous coronary intervention: Systematic review and meta-analysis. Am Heart J 2010; 160:543-551.

25. Palmerini T, Kirtane AJ, Serruys PW, et al.: Stent thrombosis with everolimus-eluting stents: Meta-analysis of comparative randomized controlled trials. Circ Cardiovasc Interv 2012; 5:357–364.
26. Aradi D, Kirtane A, Bonello L, et al.: Bleeding and stent thrombosis on P2Y12-inhibitors: Collaborative analysis on the role of platelet reactivity for risk stratification after percutaneous coronary intervention. Eur Heart J 2015; 36:1762-1771.
27. Anand SS, Yusuf S: Oral anticoagulants in patients with coronary artery disease. J Am Coll Cardiol 2003; 41:62S-69S.
28. Mega JL, Braunwald E, Wiviott SD, et al.: Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med 2012; 366:9–19.
29. Eikelboom JW, Connolly SJ, Bosch J, et al.: Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med 2017; 377:1319–1330.
30. Uchino K, Hernandez A V.: Dabigatran association with higher risk of acute coronary events: Meta-analysis of noninferiority randomized controlled trials. Arch. Intern. Med. 2012; 172:397-402.
31. Devereaux PJ, Duceppe E, Guyatt G, et al.: Dabigatran in patients with myocardial injury after non-cardiac surgery (MANAGE): an international, randomised, placebo-controlled trial. Lancet 2018; 391:2325–2334.
32. Knuuti J, Wijns W, Saraste A, et al.: 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020; 41:407–477.
33. Varenne O, Cook S, Sideris G, et al.: Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. Lancet 2018; 391:41–50.
34. Stone GW, Witzenbichler B, Weisz G, et al.: Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): A prospective multicentre registry study. Lancet 2013; 382:614-623.
35. Barnes GD, Ageno W, Ansell J, Kaatz S: Recommendation on the nomenclature for oral anticoagulants: communication from the SSC of the ISTH. J Thromb Haemost 2015; 13:1154–1156.
36. Caldeira D, Barra M, Pinto FJ, Ferreira JJ, Costa J: Intracranial hemorrhage risk with the new oral anticoagulants: a systematic review and meta-analysis. J Neurol 2015; 262:516–522.
37. Caldeira D, Rodrigues FB, Barra M, et al.: Non-vitamin K antagonist oral anticoagulants and major bleeding-related fatality in patients with atrial fibrillation and venous

thromboembolism: a systematic review and meta-analysis. Heart 2015; 101:1204–1211.
38. Vranckx P, Valgimigli M, Heidbuchel H: The Significance of Drug–Drug and Drug–Food Interactions of Oral Anticoagulation. Arrhythmia Electrophysiol Rev 2018; 7:55.
39. Huisman M V., Rothman KJ, Paquette M, et al.: The Changing Landscape for Stroke Prevention in AF: Findings From the GLORIA-AF Registry Phase 2. J Am Coll Cardiol 2017; 69:777–785.
40. Khan S, Valavoor S, Khan M, et al.: Meta-analysis of safety and efficacy of low dose rivaroxaban on coronary artery disease. J Am Coll Cardiol 2019; 73: Supplement 1.
41. Douxfils J, Buckinx F, Mullier F, et al.: Dabigatran Etexilate and Risk of Myocardial Infarction, Other Cardiovascular Events, Major Bleeding, and All-Cause Mortality: A Systematic Review and Meta-analysis of Randomized Controlled Trials. J Am Heart Assoc 2014; 3:e000515.
42. Jánosi A, Ofner P: National Myocardial Infarction Registry. Orv Hetil 2014; 155:740–744.
43. Jánosi A, Ofner P, Forster T, Édes I, Tóth K, Merkely B: Clinical characteristics, hospital care, and prognosis of patients with ST elevation myocardial infarction: Hungarian Myocardial Infarction Registry. Eur Hear J Suppl 2014; 16:A12–A15.
44. Komócsi A, Simon M, Merkely B, et al.: Underuse of coronary intervention and its impact on mortality in the elderly with myocardial infarction. A propensity-matched analysis from the Hungarian Myocardial Infarction Registry. Int J Cardiol 2016; 214:485–490.
45. Aradi D, Storey RF, Komócsi A, et al.: Expert position paper on the role of platelet function testing in patients undergoing percutaneous coronary intervention. Eur. Heart J. 2014;35:209-215.
46. Kupó P, Aradi D, Tornyos A, Tokés-Füzesi M, Komócsi A: Assessment of platelet function in patients receiving tirofiban early after primary coronary intervention. Interv Med Appl Sci 2016; 8:135-140.
47. Thygesen K, Alpert JS, White HD, et al.: Universal definition of myocardial infarction. Circulation 2007; 116:2634–2653.
48. Thygesen K, Alpert JS, Jaffe AS, et al.: Third universal definition of myocardial infarction. Circulation 2012; 125:2020–2035.
49. The Nordic Cochrane Centre: Review Manager. Cochrane Collab. 2014
50. Riley RD, Jackson D, Salanti G, et al. Multivariate and network meta-analysis of multiple outcomes and multiple treatments: rationale, concepts, and examples. BMJ

2017; 358:j3932.

51. Lunn DJ, Thomas A, Best N, Spiegelhalter D: WinBUGS - A Bayesian modelling framework: Concepts, structure, and extensibility. Stat Comput 2000; 10:325–337.
52. Brown S, Hutton B, Clifford T, Coyle D, Grima D, Wells G, Cameron C: A microsoft-excel-based tool for running and critically appraising network meta-analyses-an overview and application of NetMetaXL. Syst Rev 2014; 3:110.
53. Granger CB, Alexander JH, McMurray JJ V, et al.: Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011; 15:981–992.
54. Giugliano RP, Ruff CT, Braunwald E, et al.: Edoxaban versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med 2013; 369:2093–2104.
55. Connolly SJ, Eikelboom J, Joyner C, et al.: Apixaban in patients with atrial fibrillation. N Engl J Med 2011; 364:806–17.
56. Hori M, Matsumoto M, Tanahashi N, et al.: Rivaroxaban vs. Warfarin in Japanese Patients With Atrial Fibrillation. Circ J 2012; 76:2104–2111.
57. Gibson CM, Mehran R, Bode C, et al.: Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. N Engl J Med 2016; 375:2423–2434.
58. Cannon CP, Bhatt DL, Oldgren J, et al.: Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. N Engl J Med 2017; 377:1513–1524.
59. Connolly SJ, Ezekowitz MD, Yusuf S, et al.: Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361:1139–1151.
60. Patel MR, Mahaffey KW, Garg J, et al.: Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365:883–891.
61. Cappato R, Ezekowitz MD, Klein AL, et al.: Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. Eur Heart J 2014; 35:3346–3355.
62. Goette A, Merino JL, Ezekowitz MD, et al.: Edoxaban versus enoxaparin–warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. Lancet Elsevier Ltd, 2016; 388:1995–2003.
63. Ezekowitz MD, Pollack C V., Halperin JL, et al.: Apixaban compared to heparin/Vitamin K antagonist in patients with atrial fibrillation scheduled for cardioversion: The EMANATE trial. Eur Heart J 2018; 39:2959–2971.
64. Hart RG, Sharma M, Mundl H, et al.: Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source. N Engl J Med 2018; 378:2191–2201.
65. Diener H-C, Sacco RL, Easton JD, et al.: Dabigatran for Prevention of Stroke after Embolic Stroke of Undetermined Source. N Engl J Med 2019; 380:1906–1917.

66. Agnelli G, Buller HR, Cohen A, et al.: Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013; 369:799–808.
67. Weitz JI, Lensing AWA, Prins MH, et al.: Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism. N Engl J Med 2017; 376:1211–1222.
68. Scott D, Brenner B, Buller HR, et al.: Oral Rivaroxaban for Symptomatic Venous Thromboembolism. N Engl J Med 2010; 363:2499–2510.
69. Büller HR, Prins MH, Lensin AW a, et al.: Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012; 366:1287–1297.
70. Investigators TH-V: Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism. N Engl J Med 2013; 369:1406–1415.
71. Schulman S, Kearon C, Kakkar AK, et al.: Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009; 361:2342–2352.
72. Schulman S, Kakkar AK, Goldhaber SZ, et al.: Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation 2014; 129:764–772.
73. Schulman S, Kearon C, Kakkar AK, et al.: Extended Use of Dabigatran, Warfarin, or Placebo in Venous Thromboembolism. N Engl J Med 2013; 368:709–718.
74. Zannad F, Anker SD, Byra WM, et al.: Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease. N Engl J Med 2018; 379:1332–1342.
75. Lopes RD, Heizer G, Aronson R, et al.: Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation. N Engl J Med 2019; 380:1509–1524.
76. Gerber, Rihal CS, Sundt TM, et al.: Coronary Revascularization in the Community. J Am Coll Cardiol 2007; 50:1223–1229.
77. Masoudi FA, Ponirakis A, Lemos JA De, et al.: Trends in U.S. Cardiovascular Care: 2016 Report from 4 ACC National Cardiovascular Data Registries. J Am Coll Cardiol 2017; 69:1427–1450.
78. Sandhu K, Nadar S: Percutaneous coronary intervention in the elderly. Int J Cardiol 2015; 199:342–355.
79. Graham MM, Ghali WA, Faris PD, et al.: Survival After Coronary Revascularization in the Elderly. Circulation 2002; 105:2378–2384.
80. Kaehler J, Meinertz T, Hamm CW: Coronary interventions in the elderly. Heart 2006; 92:1167–1171.
81. Qasim A, Cosgrave J, Latib A, Colombo A: Long-Term Follow-Up of Drug-Eluting Stents When Inserted for On- and Off-Label Indications. Am J Cardiol 2007; 100:1619–

1624.

82. Forman DE, Cox DA, Ellis SG, Lasala JM, Ormiston JA, Stone GW, Turco MA, Wei JY, Joshi AA, Dawkins KD, Baim DS: Long-Term Paclitaxel-Eluting Stent Outcomes in Elderly Patients. Circ Cardiovasc Interv 2009; 2:178–187.
83. Wang TY, Ms C, Masoudi FA, et al.: Percutaneous coronary intervention and drug-eluting stent use among patients ≥85 years of age in the United States. J Am Coll Cardiol 2012; 59:105–112.
84. Puymirat E, Mangiacapra F, Peace A, et al.: Safety and effectiveness of drug-eluting stents versus bare-metal stents in elderly patients with small coronary vessel disease. Arch Cardiovasc Dis 2013; 106:554–561.
85. Kurz DJ, Bernheim AM, Tüller D, Zbinden R, Jeger R: Improved outcomes of elderly patients treated with drug-eluting versus bare metal stents in large coronary arteries: results from the BAsel Stent Kosten-Effektivitäts Trial PROspective Validation Examination randomized trial. Am Heart J 2015; 170:787–795.
86. Belder A De, De JM, Hernandez T, et al.: A prospective randomized trial of everolimus-eluting stents versus bare-metal stents in octogenarians: the XIMA Trial (Xience or Vision Stents for the Management of Angina in the Elderly). J Am Coll Cardiol 2014; 63:1371–1375.
87. Morice M, Talwar S, Gaemperli O, et al.: Drug-coated versus bare-metal stents for elderly patients: A predefined sub-study of the LEADERS FREE trial. Int J Cardiol 2017; 243:110–115.
88. Ielasi A, Brugaletta S, Silvestro A, et al.: Everolimus-eluting stent versus bare-metal stent in elderly (≥75 years) versus non-elderly (<75 years) patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: insights from the examination trial. Int J Cardiol 2015; 179:73–78.
89. Spertus JA, Kettelkamp R, Vance C, et al.: Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. Circulation 2006; 113:2803–2809.
90. Wiviott SD, Braunwald E, McCabe CH, et al.: Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007; 357:2001–2015.
91. Wallentin L, Becker RC, Budaj A, et al.: Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009; 361:1045-1057.
92. Bueno H, Sinnaeve P, Annemans L, et al.: Opportunities for improvement in anti-thrombotic therapy and other strategies for the management of acute coronary

syndromes: Insights from EPICOR, an international study of current practice patterns. Eur Hear journal Acute Cardiovasc care 2016; 5:3-12.

93. Sherwood MW, Wiviott SD, Peng SA, et al.: Early clopidogrel versus prasugrel use among contemporary STEMI and NSTEMI patients in the US: insights from the National Cardiovascular Data Registry. J Am Heart Assoc 2014; 3: e000849.
94. Angiolillo DJ, Ferreiro JL, Price MJ, Kirtane AJ, Stone GW: Platelet function and genetic testing. J. Am. Coll. Cardiol. 2013; 62(17 Suppl):S21-31.
95. Gajda SN, Kołtowski L, Tomaniak M: Most recent evidence behind aggregometry and genotyping methods as platelet function testing for tailored anti-platelet treatment among PCI patients. Adv. Clin. Exp. Med. 2015; 24:687-93.
96. Rideg O, Komcsi A, Magyarlaki T, et al.: Impact of genetic variants on post-clopidogrel platelet reactivity in patients after elective percutaneous coronary intervention. Pharmacogenomics 2011; 12:1269-80.
97. Price MJ, Endemann S, Gollapudi RR, et al.: Prognostic significance of post-clopidogrel platelet reactivity assessed by a point-of-care assay on thrombotic events after drug-eluting stent implantation. Eur Heart J 2008; 29:992-1000.
98. Collet JP, Cuisset T, Rangé G, et al.: Bedside Monitoring to Adjust Antiplatelet Therapy for Coronary Stenting. N Engl J Med 2012; 367:2100-2109.
99. Cayla G, Cuisset T, Silvain J, et al.: Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial. Lancet 2016; 388:2015-2022.
100. Sibbing D, Aradi D, Jacobshagen C, et al.: Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. Lancet 2017; 14;390:1747-1757.
101. Rollini F, Franchi F, Angiolillo DJ: Switching P2Y12-receptor inhibitors in patients with coronary artery disease. Nat. Rev. Cardiol. 2016; 13:11-27.
102. Angiolillo DJ, Saucedo JF, Deraad R, et al.: Increased platelet inhibition after switching from maintenance clopidogrel to prasugrel in patients with acute coronary syndromes: Results of the SWAP (SWitching Anti Platelet) study. J Am Coll Cardiol 2010; 56:1017-1023.
103. Diodati JG, Saucedo JF, French JK, et al.: Effect on platelet reactivity from a prasugrel loading dose after a clopidogrel loading dose compared with a prasugrel loading dose

alone. Circ Cardiovasc Interv 2013; 6:567–574.

104. Komócsi A, Vorobcsuk A, Kehl D, Aradi D: Use of new-generation oral anticoagulant agents in patients receiving antiplatelet therapy after an acute coronary syndrome: systematic review and meta-analysis of randomized controlled trials. Arch Intern Med 2012; 172:1537–1545.
105. Hohnloser SH, Oldgren J, Yang S, et al.: Myocardial ischemic events in patients with atrial fibrillation treated with dabigatran or warfarin in the RE-LY (Randomized evaluation of long-term anticoagulation therapy) trial. Circulation 2012; 125:669–676.
106. Larsen TB, Rasmussen LH, Skjøth F, et al.: Efficacy and safety of dabigatran etexilate and warfarin in "real-world" patients with atrial fibrillation: A prospective nationwide cohort study. J Am Coll Cardiol 2013; 61:2264–2273.
107. Larsen TB, Rasmussen LH, Gorst-Rasmussen A, et al.: Myocardial ischemic events in "Real world" patients with atrial fibrillation treated with dabigatran or warfarin. Am J Med 2014; 127:329–336.
108. Lee CJ-Y, Gerds TA, Carlson N, et al. Risk of Myocardial Infarction in Anticoagulated Patients With Atrial Fibrillation. J Am Coll Cardiol 2018; 72:17 LP – 26.
109. Perk J, De Backer G, Gohlke H, et al.: European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J 2012; 33:1635–1701.
110. Mak KH: Coronary and mortality risk of novel oral antithrombotic agents: A meta-analysis of large randomised trials. BMJ Open 2012; 2:e001592.
111. Oldgren J, Wallentin L, Alexander JH, et al.: New oral anticoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: A systematic review and meta-analysis. Eur Heart J 2013; 34:1670–1680.
112. Loke YK, Pradhan S, Yeong JK a. Y, Kwok CS: Comparative coronary risks of apixaban, rivaroxaban and dabigatran: a meta-analysis and adjusted indirect comparison. Br J Clin Pharmacol 2014; 78:707–717.
113. López-López JA, Sterne JAC, Thom HHZ, et al.: Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. BMJ 2017; 358:j5058.
114. Morimoto T, Crawford B, Wada K, Ueda S: Comparative efficacy and safety of novel oral anticoagulants in patients with atrial fibrillation: A network meta-analysis with the

adjustment for the possible bias from open label studies. J Cardiol 2015; 66:466–474.

115. Tornyos A, Kehl D, D'Ascenzo F, Komocsi A: Risk of Myocardial Infarction in Patients with Long-Term Non-Vitamin K Antagonist Oral Anticoagulant Treatment. Prog Cardiovasc Dis 2016; 58:483–494.

116. Hylek EM, Go AS, Chang Y, et al.: Effect of Intensity of Oral Anticoagulation on Stroke Severity and Mortality in Atrial Fibrillation. N Engl J Med 2003; 349:1019–1026.

9. PUBLICATION LIST

TOPIC-RELATED SCIENTIFIC ARTICLES

P Kupó, D Tornyos, A Bálint, R Lukács, A Jánosi, A Komócsi: Use of drug-eluting stents in elderly patients with acute myocardial infarction;
International Journal of Clinical Practice (2020) In press. **IF=2.444 Q2**

P Kupó, Zs Szakács, M Solymár, T Habon, L Czopf, L Hategan, B Csányi, J Borbás, A Tringer, G Varga, M Balaskó, R Sepp, P Hegyi, A Bálint, A Komócsi: Direct Anticoagulants and Risk of Myocardial Infarction, a Multiple Treatment Network Meta-Analysis;
Angiology (2020); 71:27-37 **IF=2.255 Q2**

A Komócsi, D Aradi, T Szűk, GG Nagy, E Noori, Z Ruzsa, RG Kiss, P Andrássy, L Nagy, FT Nagy, G Lupkovics, Zs Kőszegi, CA Dézsi, E Papp, Zs Molnár, P Kupó, P Ofner, B Merkely, A Jánosi: Comparison of Platelet Function Guided Versus Unguided Treatment With P2Y12 Inhibitors in Patients With Acute Myocardial Infarction (from the Hungarian Myocardial Infarction Registry);
American Journal of Cardiology (2018); 121:1129-1137 **IF=3.171 Q1**

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NON-TOPIC RELATED SCIENTIFIC ARTICLES

A Tornyos, A Vorobcsuk, P Kupó, D Aradi, D Kehl, A Komócsi: Apixaban and risk of myocardial infarction: meta-analysis of randomized controlled trials;
Journal of Thrombosis and Thrombolysis (2015); 40:1-11 **IF=2.169 Q2**

P Kupó, D Aradi, A Tornyos, M Tőkes-Füzesi, A Komócsi: Assessment of platelet function in patients receiving tirofiban early after primary coronary intervention;
Interventional Medical Applied Sciences (2016); 8:135-140 **Q4**

D Tényi, Cs Gyimesi, P Kupo, R Horváth, B Bóné, P Barsi, N Kovács, T Simor, Zs Siegler, L Környei, A Fogarasi, J Janszky: Ictal asystole: A systematic review;
Epilepsia (2017); 58:356-362 **IF=5.562 Q1**

P Kupó, L Sághy, R Pap: Intracardiac echocardiography from the right ventricular outflow tract confirms an accessory pathway in the aortomitral continuity;
Journal of Cardiovascular Electrophysiology (2019); 30:2117-2118 **IF=2.424 Q1**

P Kupó, R Pap, L Sághy, D Tényi, A Bálint, D Debreceni, I Basu-Ray, A Komócsi: Ultrasound guidance for femoral venous access in electrophysiology procedures-systematic review and meta-analysis;
Journal of Interventional Cardiac Electrophysiology (2019); Online ahead of print
IF=1.277 Q2

Kupó P, Sághy L: Sugárterhelés az invazív kardiológiában

Cardiologia Hungarica (2019); 49:166-169 **Q4**

AA Elnour, A Komócsi, P Kupó, IYE Khidir, S Zachariah, K Gnana, S Asim, A Sadik: The role of Direct Oral Anticoagulant in patients with Acute Coronary Syndrome on single or dual antiplatelet regime: review of opportunities and challenges;
Current Clinical Pharmacology (2020); Online ahead of print **Q2**

Vámos M, Kupó P: A pitvarfibrilláció transzkatéteres kezelése: az újabb vizsgálatok eredményei
Medical Tribune (2020)18:44-46 **Q4**

Schvartz N, Kohári M, Kupó P, Pap R: Wolff–Parkinson–White-szindróma indukálta cardiomyopathia
Cardiologia Hungarica (2020); 50:202-205 **Q4**

TOPIC-RELATED ABSTRACTS PUBLISHED IN SCIENTIFIC JOURNALS

Bálint A, Tornyos D, Jánosa E, Kupó P, Jánosi A, Komócsi A: A vérlemezke reaktivitás és a klinikai kimenetel miokardiális infarktus után a vérlemezke funkció mérésen alapuló P2Y12 inhibitor eszkalációs rendszerben A Magyar Kardiológusok Társasága 2019. évi Tudományos Kongresszusa, Balatonfüred 2019.05.03 - 05.
Cardiologia Hungarica (2019); 49 (Suppl B); B60 **Q4**

Tornyos D, Lukács R, Bálint A, Kupó P, Jánosi A, Komócsi A: Gyógyszer kibocsátó stent alkalmazása idős betegek esetében myokardiális infarktus miatt – elemzés a Nemzeti Szívinfarktus Regiszter adataiból. A Magyar Kardiológusok Társasága 2019. évi Tudományos Kongresszusa, Balatonfüred 2019.05.03 - 05.
Cardiologia Hungarica (2019); 49 (Suppl B); B8 **Q4**

NON-TOPIC RELATED ABSTRACTS PUBLISHED IN SCIENTIFIC JOURNALS

A Komócsi, A Tornyos, P Kupó, M Tőkes-Füzesi, O Rideg, D Aradi.: Impact of platelet volume and platelet reactivity on thrombotic events in ACS patients on clopidogrel or prasugrel after PCI. EuroPCR 2014 Paris, France 2014 May 20-23 Euro14A-OP089
Eurointervention (2014); 10 (Abstract Supplement) 80. **IF=3.769 Q1**

Kupó P., Kombinált trombocita aggregációgátló kezelés hatékonyságának mérése.
Orvosképzés 2015; (90): 490. **Q4**

E Fődi, P Kupó, T Simor: The aid of high resolution electroanatomical mapping in ablation of atrial tachyarrhythmias.
Europace (2017); 9 (Abstract Supplement) iii70 **IF=5.231 Q1**

F Molnár, P Kupó, E Fődi, G Vilmányi, T Simor, R Faludi: Assessment of the subclinical cardiac involvement in patients with myotonic dystrophy.

European Heart Journal – Cardiovascular Imaging (2019); 20 (Abstract Supplement) 170 **IF=4.841 Q1**

I Basu-Ray, D Khanra, B Duggal, A Komócsi, P Kupó, TJ Bunch, P Das, R Kabra, M Saeed: A comparaison of outcomes of catheter ablation (CA) for ventricular arrhythmias (VA) in ischemic cardiomyopathy (ICMP) vs non-ischaemic cardiomyopathy
Heart Rhythm, (2019); 16 (Abstract Supplement) S555 **IF= 5.739 Q1**

E Fődi, D Ruzsa, RJ Van Der Geest, P Kupó, Zs Meiszterics, Z Kőhalmi, B Gaszner, T Simor: Assessment of scar formation after cryoballon pulmonary vein isolation by 3d left atrial late gadolinium enhancement magnetic resonance imaging.
Europace (2019); 21 (Abstract Supplement) 601 **IF= 4.045 Q1**

Kupó P, Pap R, Bencsik G, Sághy L: Különböző terápiás stratégiák rövid- és hosszú távú hatékonyságának vizsgálata perimitrális flutter esetén. A Magyar Kardiológusok Társasága 2019. évi Tudományos Kongresszusa, Balatonfüred 2019.05.03 - 05.
Cardiologia Hungarica (2019); 49 (Suppl B); B85 **Q4**

Fődi E, Ruzsa DM, van der Geest RJ, Kupó P, Meiszterics Zs, Kőhalmi Z, Gaszner B, Simor T: Bal pitvari hegek vizsgálata 3D MR képalkotás segítségével cryoballonnal végzett pulmonális vénaizolációt követően. A Magyar Kardiológusok Társasága 2019. évi Tudományos Kongresszusa, Balatonfüred 2019.05.03 - 05.
Cardiologia Hungarica (2019); 49 (Suppl B); B88 **Q4**

Ruzsa DM, Kupó P, Fődi E, Simor T: Perzisztens pitvarfibrilláló betegek ablációja „CLOSE – Protokoll" szerint, korai eredményeink. A Magyar Kardiológusok Társasága 2019. évi Tudományos Kongresszusa, Balatonfüred 2019.05.03 - 05.
Cardiologia Hungarica (2019); 90 (Suppl B); B88 **Q4**

Debreceni D, Kupó P, Fődi E, Tornyos D, Tényi D, Komócsi A, Simor T: Konvencionálisan végzett, valamint zero-fluoroszkópos katéterablációk összehasonlítása PSVT-k esetén: single-center vizsgálat. A Magyar Kardiológusok Társasága 2019. évi Tudományos Kongresszusa, Balatonfüred 2019.05.03 - 05.
Cardiologia Hungarica (2019); 90 (Suppl B); B88 **Q4**

P Kupó, R Pap, G Bencsik., L Sághy: Short and long term efficiency of different therapeutic approaches to perimitral atrial flutter.
Europace (2020); 22 (Abstract Supplement) 114 **IF= 4.045 Q1**

P Kupó, R Pap, G Bencsik, M Kohári, A Benák, M Miklós, L Sághy: Ultrasound guidance for femoral venous access in patients undergoing pulmonary vein isolation: a quasi-randomized study.
Europace (2020); 22 (Abstract Supplement) 115 **IF= 4.045 Q1**

N Schvartz, M Pribojszki, A Sellei, K Gion, T Kincses, T Riesz, P Kupó, M Miklos, A Benák, M Kohári, A Makai, G Bencsik, R Pap, L Sághy: P564 Silent cerebral ischemic lesions after left-sided ablation for paroxysmal supraventricular tachycardia.
Europace (2020); 22 (Abstract Supplement) 78 **IF= 4.045 Q1**

P Kupó, R Pap, G Bencsik, M Kohári, A Benák, M Miklós, L Sághy: Ultrasound guidance for femoral venous access in patients undergoing pulmonary vein isolation: a quasi-randomized study.
Heart Rhythm, (2020); 17 (Abstract Supplement) S524 **IF= 5.739 Q1**

ORAL AND POSTER PRESENTATIONS

Kupó P: Kombinált trombocita aggregációgátló kezelés hatékonyságának mérése. VI. Nemzetközi XII. Országos Interdiszciplináris Grastyán Konferencia. Pécs, 2014. március 18-20.

Kupó P: Kombinált trombocita aggregációgátló kezelés hatékonyságának mérése. PTE Általános Orvostudományi Kar Tudományos Diákköri Konferencia, Pécs, 2014. április 3-4.

Kupó P: Kombinált trombocita aggregáció gátló kezelés hatékonyságának mérése. II. Minősítő Konferencia. Pécs, 2014. szeptember 18-19.

Kupó P: Mire – is – kell figyelni egy szívinfarktus után? VII. Nemzetközi XII. Országos Interdiszciplináris Grastyán Konferencia. Pécs, 2015. március 19-21.

Kupó P: Egy "sokat tudó" köteg ablációjának rövid története. A Magyar Kardiológusok Társasága 2016. évi Tudományos Kongresszusa, Balatonfüred 2016.05.06 - 05.09.

Kupó P, Fődi E, Simor T: 3. AV-csomó lassú pálya abláció – ionizáló sugárzás használata nélkül. Pécsi Tudományegyetem Általános Orvostudományi Kar Tanulságos Esetek Fóruma. Pécs, 2018. február 5.

Kupó P, Fődi E, Debreceni D, Simor T: Konvencionálisan végzett, valamint elektroanatómiai térképezőrendszer vezérelt katéterablációk összehasonlítása PSVT-k esetén: retrospektív single center vizsgálat. Magyar Kardiológusok Társasága, XI. Aritmia és Pacemaker Napok. Sárvár, 2018. szeptember 27-29.

Kupó P, Fődi E, Simor T: Kihívást jelentő esetünk: thrombus a bal pitvarban járulékos kötegablációt követően. PIKNIK SUMMIT konferencia. Siófok, 2018. október 26-27.

Komócsi A, Kupó P, Kehl D: Risk of myocardial infarction in patients treated with direct oral anticoagulants, network meta-analysis of randomized trials. JCR Joint Meeting on Coronary Revascularization. 2018. 12. 07-08. Busan, South Korea

Kupó P: Szemléletváltás az ablációra kerülő PF betegek anticoagulálásában. Magyar Kardiológusok Társasága, XII. Aritmia és Pacemaker Kongresszus. Budapest, 2019. szeptember 26-28.

Kupó P: Ultrahang-vezérelt vena femoralis punkció elektrofiziológiai vizsgálatok során – metaanalízis. Magyar Kardiológusok Társasága, XII. Aritmia és Pacemaker Kongresszus. Budapest, 2019. szeptember 26-28.

Kupó P: Ultrahang-vezérelt vs. konvencionálisan végzett vena femoralis punkció pulmonalis vénaizoláción áteső betegek esetén: retrospektív, single-center vizsgálat. Magyar

Kardiológusok Társasága, XII. Aritmia és Pacemaker Kongresszus. Budapest, 2019. szeptember 26-28.

Kupó P: Különböző terápiás stratégiák rövid- és hosszú távú hatékonyságának vizsgálata perimitralis flutter esetén. Magyar Kardiológusok Társasága, XII. Aritmia és Pacemaker Kongresszus. Budapest, 2019. szeptember 26-28.

P Kupó: Challenges in SVT ablation: Pseudo V-A-A-V response. Young EP Academy. Hamburg, 2019. november 12-15.

Kupó P: Magas thromboembóliás és vérzéses rizikó egyszerre: hogyan antikoaguláljuk az ablációra kerülő pitvarfibrilláló betegeket? Magyar Kardiológusok Társasága és Magyar Stroke Társaság PIKNIK program 2. webcastja. Szeged, 2020. június 10.

Kupó P: A 2020-as pitvarfibrillációs ESC irányelv újdonságai Szegedi Tudományegyetem Online EKG tanfolyam. 2020. október 2.

A Bálint, D Tornyos, P Kupó, A Komócsi: Ticagrelor for stroke prevention in patients at high risk for cardiovascular or cerebrovascular events: a systematic review and network meta-analysis of randomized controlled trials. Medical Conference for PhD Students and Experts of Clinical Sciences, Pécs, 2020. október 17.

D Debreceni, E Fődi, D Tornyos, A Komócsi, T Simor, P Kupó: Zero-fluoroscopy strategy for catheterablation of paroxysmals supraventricular arrhythmias: single-center study. Medical Conference for PhD Students and Experts of Clinical Sciences, Pécs, 2020. október 17.

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Use of drug-eluting stents in elderly patients with acute myocardial infarction

An analysis of the Hungarian Myocardial Infarction Registry

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Abstract

Background: Bare-metal stents (BMS) are frequently implanted in elderly patients instead of drug-eluting stents (DES). We aimed to compare the prognosis of patients treated for myocardial infarction with the two types of stents over the age of 75.

Methods: Data of patients registered in the Hungarian Myocardial Infarction Registry, a mandatory nationwide programme for hospitals treating patients with myocardial infarction were processed. From patients included between January 2014 and December 2017 we created two groups according to DES and BMS implantation. The outcome measures included all-cause mortality, the composite of cardiac events (MACE), repeated revascularisation and transfusion. Propensity score matching was used to balance the groups and Cox proportional hazards' models to estimate the risk during the 1st year after the index event.

Results: From 7383 patients (age: 81.08 ± 4.38 years) 3266 (44.2%) patients received DES. The PS-matched cohort included 5780 cases with balanced characteristics. In the DES group, the mortality (HR 0.66 [0.60-0.72]), MACE (HR 0.66 [0.60-0.72]) and the rate of transfusion (HR 0.84 [0.73-0.97]) were significantly lower. The PS-matched cohort showed a similar trend but with a lower rate of benefits with a 21% reduction of mortality and 23% of MACE. Difference in transfusion did not reach the level of significance. In multivariate models, stent type prevailed as an independent predictor of mortality and but not of transfusion.

Conclusions: Based on our analysis of a real-life, high-risk population, implantation of DES seems to be an advantageous strategy for elderly patients.

1 | INTRODUCTION

Drug-eluting stents (DES) are widely used in the treatment of coronary stenosis. Compared with DES, the time required for the development of the endothelial coverage is shorter, thus the risk of suspension of double antiplatelet therapy (DAPT) may be lower with bare-metal stents (BMS).[1] Elderly patients have a higher bleeding risk and this may lead to the use of BMS during coronary interventions.[2] In line with several trials the recent "Short Duration of Dual antiplatElet Therapy With SyNergy II Stent in Patients Older Than 75 Years Undergoing Percutaneous Coronary Revascularization" (SENIOR) trial found that among elderly patients, the use of DES with a short duration of DAPT strategy is beneficial compared with BMS and a similar duration of DAPT. This trial demonstrated benefits regarding the composite endpoint of all-cause mortality, myocardial infarction, stroke and ischaemia-driven target

lesion revascularisation, while no difference was detected in bleeding risk between the groups.[3]

However, the recommended DAPT duration is longer and the risk profile of patients may be different in cases with acute myocardial infarction (AMI). Thus, it is unclear how the choice of stent influences the outcomes in a high-risk unselected elderly population with myocardial infarction (MI).

The aim of this study was to compare the outcomes in a large unrestricted MI registry between the two types of stents in elderly patients undergoing coronary intervention.

What's known

- Management of the acute coronary syndrome in elderly people population is challenging.
- Compared with drug-eluting stents, the time required for the development of the endothelial coverage is shorter, thus the risk of suspension of double antiplatelet therapy may be lower with bare-metal stents.
- Bare-metal stents have been frequently implanted in elderly patients so far.

What's new

- Our results show that drug-elusive stents are advantageous in elderly patients.
- We found that stent type prevailed as an independent predictor of mortality.

2 | MATERIALS AND METHODS

The Hungarian Myocardial Infarction Registry (HUMIR) is a prospective, registry collecting clinical data on consecutive patients treated for an AMI in Hungary. The data on capture and follow-up procedures of the HUMIR has already been published in details previously.[4-7] Briefly, the patient's data are collected prospectively according to the statute of CCXLVI./2013 of Hungary via a national internet-based registry. Data capture covers 178 structured categories including those regarding the performed coronary interventions and included 92% of all AMI cases in 2017. An independent ethical board supervises the use of the data and permitted the current analysis of anonymised records.

Outcome data including vital status and repeated hospitalisations are regularly received from the electronic database of the national healthcare insurance provider.[4-7] The protocol of the study is in accordance with the Declaration of Helsinki and it was approved by the Hungarian National Committee on Health Research Ethics.

For the purpose of the current analyses records of patients between 1 January 2014 and 31 December 2017, all patients with AMI were selected for enrolment if a coronary intervention was performed successfully. The patients were eligible over the age of 75, including cases with and without ST-segment elevation if coronary intervention was performed. We created two groups according to the type of the implanted stent (DES or BMS); cases where stent was not implanted or both DES and BMS were implanted during the intervention were excluded.

DAPT was the intended antiplatelet strategy during the 1st year after the intervention. $P2Y_{12}$-inhibitor treatment before intervention comprised clopidogrel, usually given in a loading dose of 600 mg, but left to the decision of the treating physicians. After the intervention, prasugrel and clopidogrel were available for long-term treatment. Importantly, it was left to the discretion of the treating physicians whether to leave the patients on clopidogrel or switch to prasugrel but in the case of the latter a 5 mg reduced daily dose was proposed over 75 years' age. Ticagrelor was not reimbursed in Hungary at the time of the study, restricting its use to a 0.08% in our dataset. Altogether, prasugrel use was also rare and reached 2.95% in the study population. Thienopyridines were supplemented with low dose aspirin—typically 100 mg—with an optional loading dose of 300-500 mg. The intended length of DAPT was 12 months regardless of the stent type. The use of perioperative anticoagulation, as well as the administration of platelet IIb/IIIa inhibitors, were allowed according to the local protocols.

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 events (MACE) and repeat revascularisation. MACE included composite events of death, recurrent MI and stroke, while coronary intervention or bypass surgery defined the repeat revascularisation.

Events were obtained from the vital status database of the National Health Insurance Fund. Data related to recurrent hospitalisation for AMI, stroke, repeat revascularisation, as well as for bleeding event leading to blood transfusion were extracted from the database of the National Health Insurance Fund.

Variables are presented as means ± SD, medians with 25th and 75th quartiles or as frequencies and percentages. Unpaired t-tests were used for comparisons of continuous variables between groups. Categorical variables were compared using χ^2 or Fisher's exact tests.

As the patients were not randomly assigned to DES or BMS treatments, we assumed that treatment selection may have an impact on the results potentially biasing towards favouring the DES treatment. Thus, 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 with a comparable chance for either strategy by adjusting for differences in the baseline characteristics. In a logistic regression model for DES vs BMS groups, the probability of both treatment was computed. Clinical factors from the medical history as well as patient characteristics at presentation and with potential influence on the decision were used as predictors in calculating the PS (Table 1). In the PS-matching procedure randomly selected patients in the DES group were matched with a patient from the BMS group with the closest estimated PS value. A 1-to-1 matched analysis without replacement was performed with the match tolerance set to <0.01.

TABLE 1 Characteristics of the patient population before and after propensity score matching

	Entire cohort (n = 7383)			Propensity-matched cohort (n = 5780)		
Clinical characteristics	DES group (n = 3266)	BMS group (n = 4117)	*P* value	DES group (n = 2890)	BMS group (n = 2890)	*P* value
Age, (years)	79.8 (77.2-83.2)	80.8 (77.8-84.5)	<.001	80.0 (77.4-83.5)	80.1 (77.3-83.5)	.974
Men	1642 (50.3%)	1801 (43.7%)	<.001	1389 (48.1%)	1391 (48.1%)	.958
Presentation						
ST segment elevation myocardial infarction	1181 (36.2%)	2132 (51.8%)	<.001	1170 (40.5%)	1200 (41.5%)	.422
Shock	62 (1.9%)	104 (2.5%)	.071	57 (2.0%)	58 (2.0%)	.925
Reanimation	86 (2.6%)	139 (3.4%)	.065	78 (2.7%)	80 (2.8%)	.872
Prehospital thrombolysis	2 (0.1%)	9 (0.2%)	.127	2 (0.1%)	3 (0.1%)	1.000
Killip Class			<.001			.924
I	2873 (88.0%)	3453 (83.9%)		2522 (87.3%)	2538 (87.8%)	
II	278 (8.5%)	449 (10.9%)		264 (9.1%)	251 (8.7%)	
III	82 (2.5%)	140 (3.4%)		81 (2.8%)	80 (2.8%)	
IV	24 (0.7%)	59 (1.4%)		23 (0.8%)	21 (0.7%)	
Heart rate (bpm)	77 (68-90)	78 (68-90)	.100	77 (68-90)	78 (68-90)	.862
Systolic blood pressure (mm Hg)	134 (120-150)	130 (115-150)	<.001	133 (118-150)	132 (118-150)	.964
Diastolic blood pressure (mm Hg)	78 (68.0-84.0)	76 (67-85)	.167	78 (69-84)	78 (69-85)	.531
Weight (kg)	74 (68-81)	74 (65-80)	<.001	74 (68-80)	74 (66-80)	.682
Height (cm)	166 (162-170)	166 (160-170)	.005	166 (160-170)	166 (160-170)	.689
Medical history						
Hypertension	2896 (88.7%)	3560 (86.5%)	.005	2547 (88.1%)	2529 (87.5%)	.469
Diabetes mellitus	1300 (39.8%)	1293 (31.4%)	<.001	1056 (36.5%)	1052 (36.4%)	.913
Hyperlipidaemia	1093 (33.5%)	1131 (27.5%)	<.001	916 (31.7%)	893 (30.9%)	.514
Peripheral artery disease	483 (14.8%)	564 (13.7%)	.183	420 (14.5%)	435 (15.1%)	.578
Smoker	167 (5.1%)	229 (5.6%)	.395	154 (5.3%)	154 (5.3%)	1.000
History of heart failure	617 (18.9%)	589 (14.3%)	<.001	489 (16.9%)	471 (16.3%)	.525
Prior myocardial infarction	977 (29.9%)	876 (21.3%)	<.001	744 (25.7%)	749 (25.9%)	.881
Prior stroke	363 (11.1%)	491 (11.9%)	.279	328 (11.3%)	339 (11.7%)	.651
Prior coronary intervention	976 (29.9%)	722 (17.5%)	<.001	687 (23.8%)	669 (23.1%)	.576
Prior coronary bypass grafting	283 (8.7%)	189 (4.6%)	<.001	184 (6.4%)	180 (6.2%)	.829
Oral anticoagulation	262 (8.0%)	335 (8.1%)	.864	221 (7.6%)	245 (8.4%)	.267

In Cox-regression analyses, associations between clinical outcomes and stent type were first analysed in univariable models. We determined hazard ratios (HRs) together with 95% confidence intervals (95% CIs). A multivariable Cox proportional hazards model was used to determine the independent predictors of all-cause mortality and blood transfusion. In this analysis potential, clinically relevant predictors of outcome were also included then were further entered into a multivariable regression model. In the multivariable model, a backward stepwise conditional method was used to find the independent predictors. During this approach, a stepwise removal of the weakest factors without significantly decreasing overall model performance was performed. Aalen's additive regression model analysis was used to evaluate time-dependent changes in the risk of transfusions between the DES vs BMS-group. All reported *P* values are two-sided and *P* values of <.05 were considered to indicate statistical significance. This analysis was conducted using the SPSS 24 statistical package.

3 | RESULTS

From 1 January 2014 to 31 December 2017 data of 40 968 patients hospitalised for an AMI were entered into the registry. 36 177 (88.3%) of these patients were treated with coronary intervention,

8532 (23.6%) of them were over the age of 75. After excluding those patients (13.5%) in whom no stent was implanted or both BMS and DES were implanted, an unmatched patient pool of 7383 cases was obtained. In 4117 (55.8%) cases BMS, in 3266 (44.2%) cases DES was implanted (Figure 1).

As expected, there were numerous differences in baseline characteristics between the two groups. To adjust for these differences, PS matching was performed that resulted in a matched population of 5780 patients with balanced characteristics (Table 1).

During the follow-up period, 2054 patients died, resulting in a 1-year all-cause mortality rate of 27.8%, in this unselected, high-risk elderly cohort. DES-treated subjects had a highly significant, 34% lower hazard for all-cause mortality compared with the BMS group (22.7% vs 31.9%, $P < .001$). Rates of all individual endpoints including ischemic events, revascularisation and blood transfusion were lower in the BMS group and these differences reached high levels of significance, except for the low rate endpoints of repeated MI and coronary bypass operations (Figure 2 and Table 2).

In the propensity-matched cohort, similar trends were detected. However, the magnitude of reduction was less pronounced for the ischemic endpoints (21% vs 34% reduction of mortality, 34% vs 23% reduction of MACE, in the overall and the PS-matched cohort, respectively). Blood transfusion rate reduction was 11% in the PS-matched cohort and this did not reach the level of significance. Reduction of repeat revascularisation was highly significant in the PS-matched cohort (Table 2). The observed 5.3% absolute risk reduction of mortality in the matched cohort corresponds to 19 patients needed to treat, to prevent one death.

Aalen's additive regression model analysis showed no sign of time-dependent changes in the risk of transfusions between the DES- and BMS-treated elderly population (Supporting information Figure 1).

When assessed in multiple regression models, stent type prevailed as an independent predictor of mortality but not of blood transfusion (Table 3, Supporting information Table 1).

4 | DISCUSSION

In a large registry of AMI patients undergoing coronary intervention procedure, we have found that the DES was underused in elderly people despite the fact that current guidelines clearly specify that DES should be used in AMI regardless of age. Better prognosis was seen among those venerable patients who underwent coronary intervention at the event of AMI and received a DES.

The incidence of AMI is increasing in elderly patients, representing a growing segment of the population with amplified frailty and a higher rate of comorbidities.[8,9] Elderly account for one third of the patients undergoing hospitalisation for an acute coronary syndrome (ACS),[10] however, they are inadequately represented in clinical trials.[11,12] Based on the limited evidence, the management of this population is considerably challenging. Real word data showed that coronary intervention is beneficial among elderly patients in MI.[7] In the last decade some safety concerns with early generation DES have arisen after reports suggesting a higher incidence of late stent thrombosis (ST) associated with DES implantation in

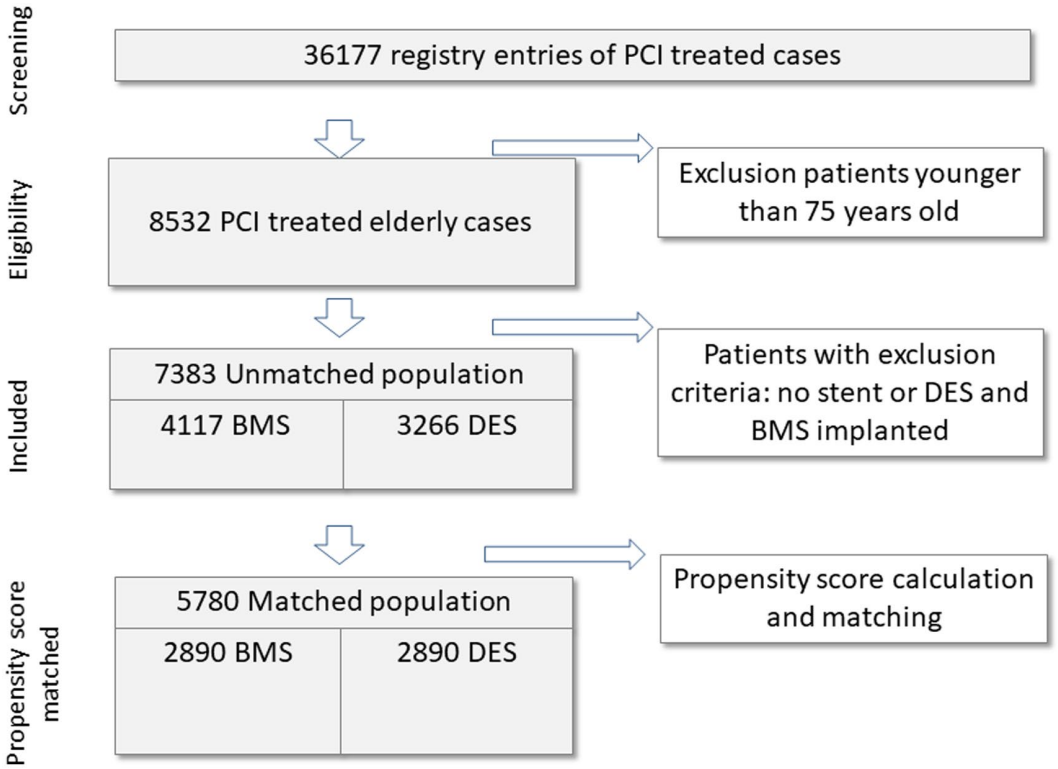

FIGURE 1 Flowchart of patient selection. BMS, bare-metal stent; DES, drug-eluting stent; PCI, percutaneous coronary intervention

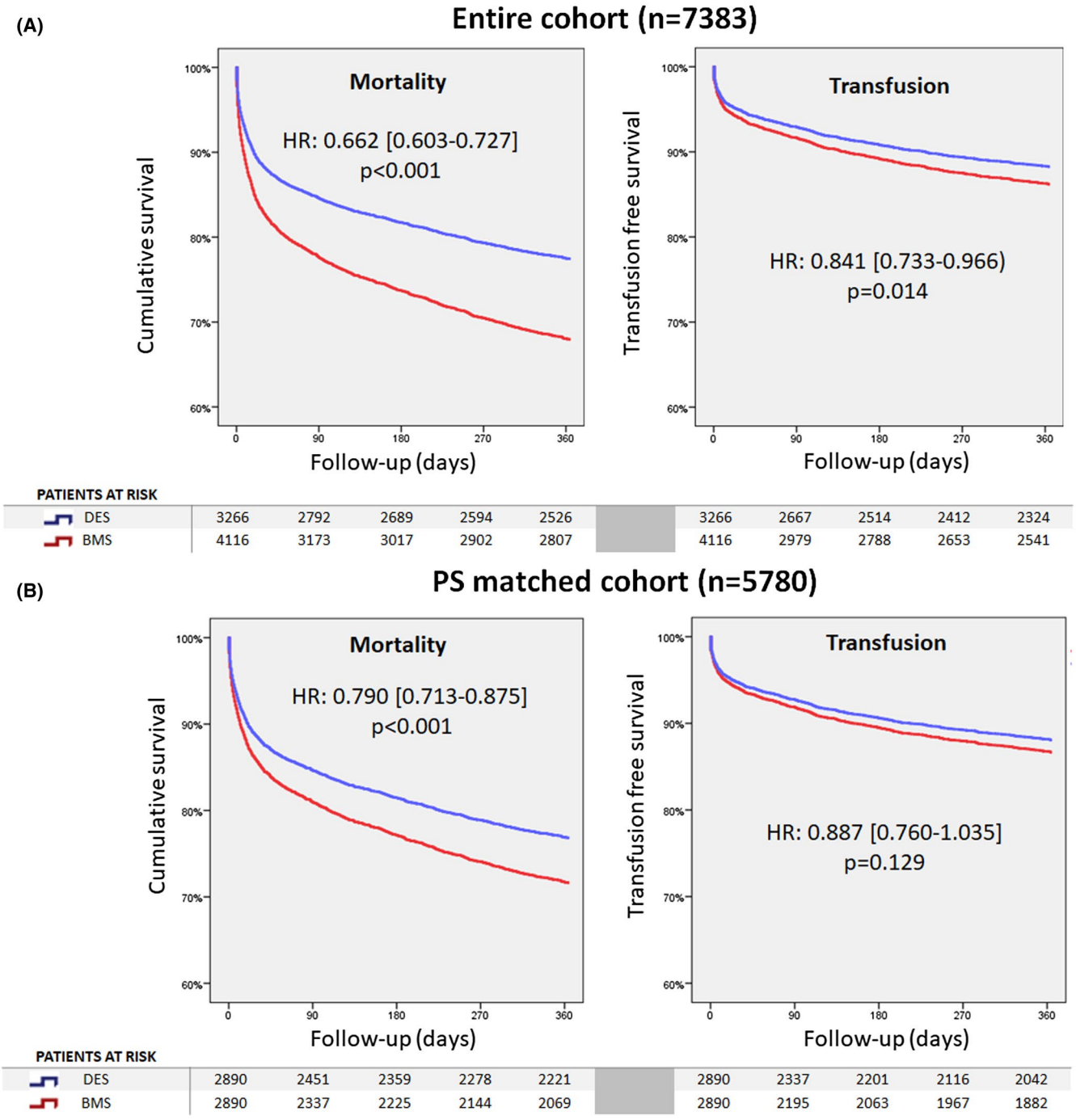

FIGURE 2 Kaplan-Meier curves of overall survival and blood transfusion-free survival comparing drug-eluting (DES) or bare-metal stent (BMS) implanted patients. Panel A shows the survival differences seen in the overall cohort, while data from the propensity score (PS) are depicted in panel B. BMS, bare-metal stent; DES, drug-eluting stent; HR, hazard ratio; PS, propensity score

comparison to BMS.[13] Early generation DES have now been supplanted by new-generation DES with higher efficacy and safety in comparison with both early generation DES and BMS.[14] However, in several countries elderly patients still frequently receive BMS with the intent to shorten the duration of DAPT, to reduce bleeding complications.[2] Though, the 2018 European guidelines on myocardial revascularisation recommend DES over BMS for any percutaneous coronary intervention (PCI) and the use of BMS is decreasing in developed countries, BMS use still accounts for approximately 20% of all PCI procedures in the USA.[14-16] Previous studies demonstrated the short- and long-term efficacy of DES among elderly patients.[17-22] It is of particular importance that none of these analyses found increased bleeding risk associated with DES.

Most recently, the SENIOR trial compared DES to BMS applying a short duration of DAPT in age ≥ 75 patients, who underwent percutaneous coronary revascularisation. Antiplatelet strategy consisted DAPT for 1 month in patients with a stable presentation and 6 months for those with an unstable presentation. The rate of

TABLE 2 Primary and secondary outcomes in unmatched and propensity-matched cohorts

Unmatched cohort (7383)	DES (3266)	BMS (4117)	Hazard ratio (95% confidence interval), *P* value
Overall mortality	740 (22.7%)	1314 (31.9%)	0.66 [0.60-0.73], *P* < .001
Blood transfusion	347 (10.6%)	479 (11.6%)	0.84 [0.73-0.97], *P* = .014
Major adverse cardiovascular events (death, myocardial infarction, stroke)	763 (23.4%)	1351 (32.8%)	0.66 [0.60-0.72], *P* < .001
Major adverse cardiac events + Repeat revascularisation	987 (30.2%)	1692 (41.1%)	0.67 [0.62-0.72], *P* < .001
Myocardial infarction	40 (1.2%)	64 (1.6%)	0.69 [0.46-1.03], *P* = .068
Stroke	61 (1.9%)	105 (2.6%)	0.69 [0.50-0.95], *P* = .023
Repeat revascularisation	256 (7.8%)	403 (9.8%)	0.70 [0.61-0.83], *P* < .001
PCI	237 (7.3%)	372 (9.0%)	0.72 [0.61-0.84], *P* < .001
CABG	23 (0.7%)	36 (0.9%)	0.66 [0.39-1.14], *P* = .134
PS-matched cohort (5780)	**DES (2890)**	**BMS (2890)**	**Hazard ratio (95% confidence interval), *P* value**
Overall mortality	669 (23.1%)	821 (28.4%)	0.79 [0.71-0.88], *P* < .001
Blood transfusion	310 (10.7%)	336 (11.6%)	0.89 [0.76-1.04], *P* = .129
Major adverse cardiovascular events (death, myocardial infarction, stroke)	685 (23.7%)	854 (29.6%)	0.77 [0.70-0.85], *P* < .001
Major adverse cardiac events + Repeat revascularisation	873 (30.2%)	1121 (38.8%)	0.73 [0.67-0.80], *P* < .001
Myocardial infarction	33 (1.1%)	51 (1.8%)	0.62 [0.40-0.95], *P* = .029
Stroke	48 (1.7%)	80 (2.8%)	0.60 [0.42-0.86], *P* = .005
Repeat revascularisation	213 (7.4%)	322 (11.1%)	0.62 [0.52-0.73], *P* < .001
PCI	196 (6.8%)	247 (8.6%)	0.59 [0.49-0.72], *P* < .001
CABG	18 (0.6%)	28 (1.0%)	0.54 [0.30-1.01], *P* = .052

Abbreviations: BMS, bare-metal stent; CABG, coronary artery bypass grafting; DES, drug-eluting stent; PCI, percutaneous coronary intervention; PS, propensity score.

patients with ACS was 45%. The primary endpoint (composite of all-cause mortality, MI, stroke or ischaemia-driven target lesion revascularisation (TLR)) occurred less frequently in the DES group with BMS-like DAPT regimen, however, this difference was caused by a significantly lower rate of TLR in the DES group. Meanwhile rates of all-cause mortality, cardiovascular death, MI and stroke were similar between groups. Similarly to the earlier studies, no difference was found either in bleeding complications or ST at 1-year follow.[3] Most data supported the use of new-generation DES in elderly populations, however, while these trials included different proportions of ACS cases the "Clinical Evaluation of Everolimus Eluting Coronary Stents in the Treatment of Patients With ST-Segment Elevation Myocardial Infarction" (EXAMINATION) trial studied everolimus-eluting stents in ST-segment elevation myocardial infarction (STEMI). In contrast, to the earlier trials, results of a post hoc analysis of elderly (age ≥ 75) patients found no benefit of DES either in the primary composite endpoint of all-cause death, any MI or any revascularisation, or in MI, or in the need for subsequent revascularisation.[23] The decision for the implantation of BMS rather than DES is driven principally by concerns about higher bleeding risk and DAPT compliance.[16] Accordingly, prolonged DAPT seems to be the main reason against the use of DES in elderly patients undergoing PCI.[24] In cases with acute MI the recommended duration of DAPT is 12 months regardless of the type of the stent implanted, however, in case of bleeding, interruption after 1 month is considered to be less dangerous with BMS compared with DES. Theoretically the possible earlier cessation of DAPT in case of BMS might prevent the development of bleeding complications, however, we found no excess of severe, blood transfusion requiring events in the DES cohort.[25] Using the data capture of a national MI registry we studied an unselected high-risk patient-group of AMI with a 28% risk of death within 1 year after the stent implantation. Our data clearly refute the assumption

TABLE 3 Results of the multivariable Cox regression analysis for the identification of the independent predictors of mortality and bleeding

Independent predictors of outcome	Mortality (Hazard ratio)	95% confidence interval	*P* value	Bleeding (Hazard ratio)	95% confidence interval	*P* value
DES	0.75	0.67-0.83	<.001	0.88	0.76-1.03	.112
Resuscitation	2.32	1.88-2.88	<.001	2.32	1.59-3.37	<.001
Shock	1.87	1.43-2.44	<.001	–		
Killip status	1.33	1.22-1.45	<.001	–		
Heart rate (beat/min)	1.01	1.01-1.01	<.001	1.01	1.003-1.01	.001
Systolic pressure (mm Hg)	0.99	0.98-0.99	<.001	1.00	0.99-1.00	.057
Diastolic pressure (mm Hg)	–			0.99	0.98-0.99	<.001
Creatinine level (μmol/L)	1.01	1.004-1.01	<.001	1.005	1.004-1.006	<.001
STEMI	0.75	0.67-0.83	<.001	1.27	1.07-1.50	.006
Prior myocardial infarction	–			0.83	0.69-1.003	.054
Prior stroke	1.46	1.27-1.69	<.001	–		
Prior heart failure	1.55	1.36-1.75	<.001	1.44	1.19-1.76	<.001
Diabetes mellitus	1.21	1.09-1.34	<.001	1.40	1.20-1.64	<.001
Peripheral artery disease	1.35	1.18-1.54	<.001	–		
Hyperlipidaemia	0.87	0.77-0.98	.018	–		
Prior PCI	0.84	0.74-0.96	.008	–		
Ejection fraction[a]	1.68	1.58-1.79	<.001	1.24	1.13-1.37	<.001
Number of revascularised vessels	1.24	1.01-1.54	<.001	1.24	1.01-1.54	.045
Male sex	–			0.80	0.66-0.96	.020
Height (cm)	–			1.01	1.001-1.03	.042
Bodyweight (kg)	0.99	0.99-0.99	<.001	0.99	0.98-0.998	.009

Abbreviations: DES, drug-eluting stent; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.
[a]Ejection fraction was categorically coded as EF > 50%, 40%-49%, 30%-39% or <29%.

of the higher safety of BMS in a frail and elderly population. The analysis of the clinical characteristics in our cohort supported that BMS was preferably implanted in fragile cases with higher age and multiple risks. However, prognostic benefit in terms of mortality, major ischemic events as well as that of the repeat revascularisation prevailed in the propensity-matched analyses. Besides the favourable rate of MACE, bleeding events were not more frequent in the DES group even in our matched sample.

Some limitations of our study need to be acknowledged. Most importantly this is not a randomised trial capable of providing a completely unbiased assessment of treatment effect. Data regarding actual duration of antiplatelet use and type of bleeding events are not available. Therefore, blood transfusion has been used as a surrogate in this study. Similarly, repeat revascularisation is used instead of target vessel revascularisation as specific data are lacking in this regard. In fact, the lower blood transfusion rate of the DES-treated cases, together with the clinical characteristics of the unbalanced cohort support the potential influence of a selection bias with DES implanted in healthier patients with potentially a better outcome. The PS matching balanced the significant differences observed between the DES and BMS groups in the entire cohort. However, the influence of potentially uncontrolled variables may also not be entirely excluded. Keeping this limitation in mind and considering that our data originate from a nation-wide, multi-centre registry, together with the statistically robust difference in the propensity-matched cohorts confirms the validity of the results.

5 | CONCLUSIONS

In conclusion, our analysis of a real-life, high-risk elderly population, 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.

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DISCLOSURES

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REFERENCES

1. Habib A, Finn AV. Endothelialization of drug eluting stents and its impact on dual anti-platelet therapy duration. *Pharmacol Res*. 2015;93:22-27. https://doi.org/10.1016/j.phrs.2014.12.003.
2. Gerber RT, Satpal F, Mrcp SA, et al. Age is not a bar to PCI: insights from the long-term outcomes from off-site PCI in a real-world setting. *J Interv Cardiol*. 2017;30:347-355. https://doi.org/10.1111/joic.12400.
3. Varenne O, Cook S, Sideris G, et al. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. *Lancet*. 2018;391:41-50. https://doi.org/10.1016/S0140-6736(17)32713-7.
4. Jánosi A, Ofner P, Merkely B, et al. Short and long term prognosis of patients with myocardial infarction. Hungarian Myocardial Infarction Registry. *Orv Hetil*. 2013;154:1297-1302. https://doi.org/10.1556/OH.2013.29679.
5. Jánosi A, Ofner P, Forster T, Édes I, Tóth K, Merkely B. Clinical characteristics, hospital care, and prognosis of patients with ST elevation myocardial infarction: Hungarian Myocardial Infarction Registry. *Eur Hear J Suppl*. 2014;16:A12-A15. https://doi.org/10.1093/eurheartj/sut004.
6. Komócsi A, Aradi D, Szűk T, et al. Comparison of platelet function guided versus unguided treatment with P2Y12 inhibitors in patients with acute myocardial infarction (from the Hungarian Myocardial Infarction Registry). *Am J Cardiol*. 2018;121:1129-1137. https://doi.org/10.1016/j.amjcard.2018.01.032.
7. Komócsi A, Simon M, Merkely B, et al. Underuse of coronary intervention and its impact on mortality in the elderly with myocardial infarction. A propensity-matched analysis from the Hungarian Myocardial Infarction Registry. *Int J Cardiol*. 2016;214:485-490. https://doi.org/10.1016/j.ijcard.2016.04.012.
8. Gerber Y, Rihal CS, Sundt TM, et al. Coronary revascularization in the community. *J Am Coll Cardiol*. 2007;50:1223-1229. https://doi.org/10.1016/j.jacc.2007.06.022.
9. Masoudi FA, Ponirakis A, De LJA, et al. Trends in U.S. Cardiovascular Care: 2016 Report from 4 ACC National Cardiovascular Data Registries. *J Am Coll Cardiol*. 2017;69:1427-1450. https://doi.org/10.1016/j.jacc.2016.12.004.
10. Sandhu K, Nadar S. Percutaneous coronary intervention in the elderly. *Int J Cardiol*. 2015;199:342-355. https://doi.org/10.1016/j.ijcard.2015.05.188.
11. Graham MM, Ghali WA, Faris PD, et al. Survival after coronary revascularization in the elderly. *Circulation*. 2002;105:2378-2384. https://doi.org/10.1161/01.CIR.0000016640.99114.3D.
12. Kaehler J, Meinertz T, Hamm CW. Coronary interventions in the elderly. *Heart*. 2006;92:1167-1171. https://doi.org/10.1136/hrt.2005.071266.
13. Qasim A, Cosgrave J, Latib A, Colombo A. Long-term follow-up of drug-eluting stents when inserted for on- and off-label indications. *Am J Cardiol*. 2007;100:1619-1624. https://doi.org/10.1016/j.amjcard.2007.07.013.
14. Neumann F-J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87-165. https://doi.org/10.1093/eurheartj/ehy394.
15. Rymer JA, Harrison RW, Dai D, et al. Trends in bare-metal stent use in the United States in patients aged ≥65 years (from the CathPCI Registry). *Am J Cardiol*. 2016;118:959-966. https://doi.org/10.1016/j.amjcard.2016.06.061.
16. Morice M-C, Urban P, Greene S, Schuler G, Chevalier B. Why are we still using coronary bare-metal stents? *J Am Coll Cardiol*. 2013;61:1122-1123. https://doi.org/10.1016/j.jacc.2012.11.049.
17. Forman DE, Cox DA, Ellis SG, et al. Long-term paclitaxel-eluting stent outcomes in elderly patients. *Circ Cardiovasc Interv*. 2009;2:178-187. https://doi.org/10.1161/CIRCINTERVENTIONS.109.855221.
18. Wang TY, Masoudi FA, Messenger JC, et al. Percutaneous coronary intervention and drug-eluting stent use among patients ≥85 years of age in the United States. *J Am Coll Cardiol*. 2012;59:105-112. https://doi.org/10.1016/j.jacc.2011.10.853.
19. Puymirat E, Mangiacapra F, Peace A, et al. Safety and effectiveness of drug-eluting stents versus bare-metal stents in elderly patients with small coronary vessel disease. *Arch Cardiovasc Dis*. 2013;106:554-561. https://doi.org/10.1016/j.acvd.2013.06.056.
20. Kurz DJ, Bernheim AM, Tüller D, et al. Improved outcomes of elderly patients treated with drug-eluting versus bare metal stents in large coronary arteries: results from the BAsel Stent Kosten-Effektivitäts Trial PROspective Validation Examination randomized trial. *Am Heart J*. 2015;170:787-795. https://doi.org/10.1016/j.ahj.2015.07.009.
21. de Belder A, de la Torre Hernandez JM, Lopez-Palop R, et al. A prospective randomized trial of everolimus-eluting stents versus bare-metal stents in octogenarians: the XIMA Trial (Xience or Vision Stents for the Management of Angina in the Elderly). *J Am Coll Cardiol*. 2014;63:1371-1375. https://doi.org/10.1016/j.jacc.2013.10.053.
22. Morice M-C, Talwar S, Gaemperli O, et al. Drug-coated versus bare-metal stents for elderly patients: A predefined sub-study of the LEADERS FREE trial. *Int J Cardiol*. 2017;243:110-115. https://doi.org/10.1016/j.ijcard.2017.04.079.
23. Ielasi A, Brugaletta S, Silvestro A, et al. Everolimus-eluting stent versus bare-metal stent in elderly (≥75 years) versus non-elderly (<75 years) patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: insights from the examination trial. *Int J Cardiol*. 2015;179:73-78. https://doi.org/10.1016/j.ijcard.2014.10.038.
24. Spertus JA, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. *Circulation*. 2006;113:2803-2809. https://doi.org/10.1161/CIRCULATIONAHA.106.618066.
25. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur Heart J*. 2018;39:213-260. https://doi.org/10.1093/ejcts/ezx334.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Direct Anticoagulants and Risk of Myocardial Infarction, a Multiple Treatment Network Meta-Analysis

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Abstract

We assessed the cardiovascular safety of long-term direct-acting oral anticoagulant (DOAC) treatment. A search of the medical literature was performed from inception until May 31, 2019. Inclusion criteria were (1) randomized trial that assessed the clinical efficacy and/or safety of 1 or more DOAC, (2) control group including oral anticoagulation and/or antiplatelet and/or placebo treatment, and (3) the incidence of acute coronary syndrome during follow-up was reported. Fixed-effect and random-effects models were applied. The analyzed outcomes were myocardial infarction (MI), major bleeding, and mortality. Twenty-eight randomized clinical trials (196 761 patients) were included. Rivaroxaban was associated with a 21% reduction in the relative risk of MI when compared to placebo (relative risk [RR]: 0.79 [95% credible interval, CrI: 0.65-0.94]) and a 31% reduction (RR: 0.70 [95% CrI: 0.53-0.89]) when compared to dabigatran. Apixaban resulted in 24% (RR: 0.76 [95% CrI: 0.58-0.99]) and vitamin K antagonists anticoagulation resulted in 19% (RR: 0.81 [95% CrI: 0.65-0.98]) risk reduction compared to dabigatran. The computed probability of being the first best choice of treatment was 61.8% for rivaroxaban. Cardiovascular safety shows considerable heterogeneity among oral anticoagulants. Treatment with rivaroxaban is associated with reduced rate of MI.

Keywords

myocardial infarction, non-vitamin k antagonist oral anticoagulants, network meta-analysis

Introduction

Ten years have passed since the approval of the first non-vitamin K antagonist oral anticoagulants. Direct oral anticoagulants (DOACs) have been proposed as an alternative term for this class of agents including oral direct thrombin inhibitors (DTIs) and activated factor X inhibitors (anti-Xa).[1] In several fields, compared to vitamin K antagonists (VKA), DOACs have been proven to have similar or higher efficacy in preventing ischemic events and similar or lower risk for major bleeding, bleeding-related case fatalities, and intracranial bleeding.[2,3] Furthermore, DOACs alleviate several problems associated with VKA use including the need for laboratory monitoring due to the narrow therapeutic window and drug/food interactions. [4] Consequently, DOACs have been widely adopted.[5]

Coronary heart disease (CHD) is the leading cause of death and disability having a major impact on both developing and developed nations.[6] The coagulation cascade plays an important role in the evolution of acute coronary syndrome (ACS) events.[7] Earlier analyses found that long-term treatment with VKAs, in monotherapy or in combination with aspirin, is superior to aspirin alone for secondary prevention after acute myocardial infarction (MI).[8]

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Importantly, DOACs showed dissimilar results regarding cardiovascular (CV) safety. Rivaroxaban showed favorable outcomes when combined with aspirin among patients with stable atherosclerotic disease, and it also reduced ischemic risk in ACS.[9,10] In contrast, signals from earlier studies have raised safety concerns regarding MI risk among dabigatran-treated patients, but dabigatran lowered the risk of major vascular complications among patients with myocardial injury after surgery.[11,12]

Direct comparative trials are not available to compare the risk of MI among DOAC-treated patients. Therefore, we performed a Bayesian multiple treatment network meta-analysis (NMA) of randomized clinical trials in order to summarize the data of DOAC trials and gain insight into CV safety.

Methods

A manual search of medical literature was performed in PubMed (MEDLINE), EMBASE, and Cochrane Trials from inception until May 31, 2019, for articles reporting randomized clinical trials with DOACs. No language restriction was used. The query included the following terms linked with Boolean operators: "pulmonary embolism," "atrial fibrillation," "thromboprophylaxis," "anticoagulation," "prevention," "rivaroxaban OR apixaban OR dabigatran OR edoxaban" (for detailed search history, refer to the Online Appendix).

In the analysis, we included trials that fulfilled the following criteria: (1) randomized clinical trials (RCTs) that assessed the clinical efficacy and/or safety of an anticoagulant protocol comprising either $\geq$1 of the approved and marketed DOACs, that is, dabigatran, rivaroxaban, apixaban, or edoxaban. (2) Having one or more control group with oral anticoagulation, antiplatelet treatment, or placebo. (3) Reporting the frequency of MI or the rate of ACS during the follow-up compliant with intention-to-treat analysis. Studies that aimed to compare merely the biological efficacy of the anticoagulant protocol and trials not reporting the frequency of MI were excluded. Nonrandomized studies, registries, and uncontrolled or cohort studies as well as reviews were disregarded. The review protocol was registered in the PROSPERO database a priori under the registration number of CRD42018103000.

All the relevant articles were combined in a reference manager software (EndNote X8; Clarivate Analytics, Philadelphia, PI) to remove duplicates by searching overlaps between titles, abstracts, authors, and publication year. After removing duplicates, we screened the articles by title, abstract, and full texts against our predefined eligibility criteria. Each phase was carried out by 2 independent investigators (P.K. and Z.S.) in duplicate, none of whom were blinded to publication data. Third-party (A.K.) arbitration resolved any discrepancies.

The following details were recorded for each study: study name, first author, year of publication, period of study, the applied doses of oral anticoagulant, number of patients, length of treatment period, length of follow-up, inclusion and exclusion criteria, protocol definitions of MI as well as patient and procedural characteristics including mean age, sex, and the following risk factors: diabetes, hypercholesterolemia, and hypertension.

The primary end point of the analysis was the frequency of MI. Overall mortality was defined as a secondary end point. As a safety measure, frequency of major bleeding complications was evaluated. Both MI and major bleeding were defined according to the internal definitions of the studies. If multiple major bleeding definitions were used, we extracted thrombolysis in myocardial infarction (TIMI) major bleeding and International Society on Thrombosis and Hemostasis major bleeding if available (Table 1). The data from intention to treat analyses were extracted. The end points of interest were collected until the longest follow-up available.

Analyses of subgroups, heterogeneity, as well as assessment of bias were performed using the Cochrane Review Manager version 5.3. software.[15] Degree of inconsistency among studies was quantified by means of I2. Cochrane Q heterogeneity test (χ^2) was also performed. These data were reported as percentage of the I2 together with the P value of the χ^2 test. The likelihood of publication bias was visually assessed by generating a funnel plot for the primary end point. The risk of MI was analyzed in a hierarchical Bayesian mixed-treatment comparison meta-analysis. The Bayesian analysis allows the combination of existing knowledge with new information according to established rules of probability.[16] Substantive prior knowledge can thereby be included in any Bayesian analysis by choice of initial (predata) distribution. We wanted our final (posterior) distribution to reflect the information in our data set only and not to be influenced by our choice of initial (prior) distribution. Therefore, "noninformative" prior distributions were used throughout so that the data from the trials dominated the final inferences. The RCT data were then added via the Bayes rule to produce posterior distributions. Treatment effects are reported as risk ratio with 95% associated credible interval (CrI), which is a Bayesian analog of the 95% confidence interval from traditional meta-analyses. Inferences were calculated with a Gibbs sampler algorithm as implemented through WinBUGS software (version 1.4.3; MRC Biostatistics Unit, Cambridge, United Kingdom).[17] To ensure convergence, 3 Markov Monte Carlo chains were run. Data input and graphical output were performed using the NetMetaXL interface.[18] Inferences based on random effects models are presented. The choice of random-effects model was made based on the consideration that the true preventive effect of anticoagulant treatment may vary from study to study influenced by heterogeneity of the included trials. Random-effects model accounts better for interstudy differences; furthermore, it results in wider credible intervals and thus provides more conservative and robust results. To supplement the information of random-effects modeling, fixed-effects models were also built and analyzed as sensitivity test. Subgroup analyses were performed by building networks of studies performed in the same risk groups as well as according to MI definitions (see Online Appendix). Meta-regression analyses were performed using the Open Meta-analyst software (Brown University, RI).[19]

Table 1. Study Characteristics of the Included Trials.[a]

Study name/First Author (Publication year)	Period of Study	Study Drug (Total Daily Dose, mg)	Comparator Drug	Patients Number	Follow-Up, months	Inclusion Criteria	MI Definition	MB Definition
AMPLIFY/G. Agnelli (2013)	2008-2013	Apixaban (20 first 7 days, 10)	Warfarin	5395	7	Confirmed symptomatic proximal DVT or PE	2≥ of the followings: symptoms; ECG abnormalities, elevated cardiac biomarkers	Based on ISTH MB
APPRAISE-2/J. H. Alexander (2011)	2009-2011	Apixaban (10)	Placebo	7392	8	ACS within 7 days	2≥ of the followings: symptoms; ECG abnormalities, elevated cardiac biomarkers	Based on TIMI MB
ARISTOTLE/C.B. Granger (2011)	2006-2011	Apixaban (10)	Warfarin	18 201	21.6	AF or flutter, ≥1 RF for stroke	IRCE	Based on TIMI MB
ATLAS ACS 2-TIMI 51/J. L. Mega (2012)	2008-2011	Rivaroxaban (5/10)	Placebo	15 342	13.1	ASA or DAPT, ACS	IRCE	Based on TIMI MB
AUGUSTUS/R. D. Lopes (2019)	2015-2018	Apixaban (10/5)	Warfarin	4614	6	NVAF, stable or unstable CAD treated with PCI	IRCE	Based on ISTH MB
AVERROES/S. J. Connolly (2011)	2007-2010	Apixaban (10/5)	ASA(81-324 mg)	5599	13.2	≥50 years, documented AF within prior 6 months	IRCE	Based on ISTH MB
COMPASS/J. W. Eikelboom (2017)	2013-2017	Rivaroxaban (5) + ASA/rivaroxaban (10)	ASA (100 mg)	27 395	23	CAD or PAD	Compatible with UDMI 2012	Based on ISTH MB
COMMANDER HF/F. Zannad (2018)	2013-2017	Rivaroxaban (5)	Placebo	5022	21.1	Chronic HF, EF<40% CAD, and elevated plasma concentrations of natriuretic peptide	Compatible with UDMI 2012	Based on ISTH MB
EINSTEIN-CHOICE/J. I. Weitz (2017)	2014-2016	Rivaroxaban (20/10)	ASA (100 mg)	3365	12+1	Confirmed, symptomatic proximal DVT or PE	Compatible with UDMI 2012	Based on ISTH MB
EINSTEIN-DVT/R. Bauersachs (2010)	2007-2010	Rivaroxaban (30 3 weeks, 20)	Warfarin/ acenocoumarol	3429	12	Symptomatic, recurrent DVT or nonfatal or fatal PE	IRCE	Based on ISTH MB
EINSTEIN-PE/H. R. Büller (2012)	2007-2011	Rivaroxaban (30 3 weeks, 20)	Warfarin/ acenocoumarol	4832	12	Symptomatic PE with or without symptomatic DVT	IRCE	Based on ISTH MB
EMANATE/M. D. Ezekowitz (2018)	2014-2017	Apixaban (10/5)	Warfarin	1500	1.2/2.4	Elective electrical or pharmacological cardioversion	IRCE	Based on ISTH MB
ENGAGE AF—TIMI 48/R. P. Giugliano (2013)	2008-2013	Edoxaban (60/30)	Warfarin	21,105	33.2	AF, a CHADS2 score of ≥2	IRCE	Based on ISTH MB
ENSURE-AF/A. Goette (2016)	2014-2016	Edoxaban (60/30)	Warfarin	2199	1/1.63+1	Ongoing AF lasting at least 48 hours but ≤12 months, elective ECV	IRCE	Based on ISTH MB
Hokusai-VTE/Hokusai investigators (2013)	2009-2013	Edoxaban (60/30)	Warfarin	8240	12	Confirmed DVT and/or symptomatic PE	Compatible with UDMI 2012	Based on ISTH MB
J-ROCKET AF/M. Hori (2012)	2007-2009	Rivaroxaban (15)	Warfarin	1280	30+1	AF; prior ischemic stroke, TIA or non-CNS systemic embolism or ≥2 RF for stroke	2≥ of the followings: symptoms; ECG abnormalities, elevated cardiac biomarkers	Based on ISTH MB

(continued)

Table 1. (continued)

Study name/First Author (Publication year)	Period of Study	Study Drug (Total Daily Dose, mg)	Comparator Drug	Patients Number	Follow-Up, months	Inclusion Criteria	MI Definition	MB Definition
MANAGE/Manage investigators (2018)	2013-2018	Dabigatran (220)	Placebo	1754	16	Undergone noncardiac surgery, MINS	IRCE	Based on ISTH MB
NAVIGATE ESUS/R. G. Hart (2018)	2014-2018	Rivaroxaban (15)	ASA (100 mg)	7213	15	ESUS, within 7 days and 6 months before screening	IRCE	Based on ISTH MB
PIONEER AF-PCI/C.M. Gibson (2016)	2013-2016	Rivaroxaban (10-15/5)	Warfarin	2214	12	PCI with stent placement, history of AF	IRCE	Based on TIMI MB
RE-COVER II/S. Schulman (2014)	2008-2011	Dabigatran (300)	Warfarin	2568	6+1	Symptomatic, confirmed proximal DVT of the legs, or PE	IRCE	Based on ISTH MB
RE-COVER/S. Schulman (2009)	2006-2009	Dabigatran (300)	Warfarin	2539	6+1	Acute, symptomatic, proximal DVT or PE	IRCE	Based on ISTH MB
RE-DUAL/C. P. Cannon (2017)	2014-2017	Dabigatran (300/220)	Warfarin	2725	14	NVAF, stable or unstable CAD treated with PCI	Compatible with UDMI 2012	Based on TIMI MB
RE-LY/S. J. Connolly (2009)	2005-2009	Dabigatran (300/220)	Warfarin	18 113	24	AF and risk of stroke	IRCE	Based on ISTH MB
RE-MEDY/S. Schulman (2013)	2006-2011	Dabigatran (300)	Warfarin	2856	36	Symptomatic, proximal DVT or PE, previously treated with AC	IRCE	Based on ISTH MB
RE-SONATE/S. Schilman (2013)	2007-2011	Dabigatran (300)	Placebo	1343	12	Symptomatic, proximal DVT or PE, previously treated with AC	IRCE	Based on ISTH MB
RE-SPECT ESUS/H. C. Diener (2019)	2014-2018	Dabigatran (300/220)	ASA (100)	5390	19	ESUS within 3 months before screening	IRCE	Based on ISTH MB
ROCKET AF/M. R. Patel (2011)	2006-2010	Rivaroxaban (20/15)	Warfarin	14 236	23.6	AF; prior ischemic stroke, TIA or non-CNS systemic embolism or $\geq$2 RF for stroke	2$\geq$ of the followings: symptoms; ECG abnormalities, elevated cardiac biomarkers	Based on ISTH MB
X-VeRT/R. Cappato (2014)	2012-2014	Rivaroxaban (20/15)	Warfarin/ acenocoumarol	1504	1.5/2.68+1	Elective electrical or pharmacological cardioversion	IRCE	Based on ISTH MB

Abbreviations: AC, anticoagulation; ACS, acute coronary syndrome; AF, atrial fibrillation; ASA, aspirin; ATLAS ACS 2–TIMI 51, Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 51; CAD, coronary artery disease; CNS, central nervous system; COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies; DAPT, dual antiplatelet therapy; DVT, deep vein thrombosis; ECG, Electrocardiography; ESUS, embolic stroke of undetermined source; GI, gastrointestinal; HF, heart failure; IRCE, Investigator reported clinical event; ISTH, International Society of Thrombosis and Haemostasis; LA, left atrial; LMWH, low-molecular-weight heparin; MB, major bleeding; MANAGE, Management of Myocardial Injury After Noncardiac Surgery; MI, myocardial infarction; MINS, myocardial injury after noncardiac surgery; MS, mitral stenosis; NA, not available; NVAF, nonvalvular atrial fibrillation; NYHA, New York Heart Association; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PE, pulmonary embolism; RE-LY, Randomized Evaluation of Long Term Anticoagulant Therapy with Dabigatran Etexilate; RF, risk factor; STD, ST depression; STE, ST elevation; TIA, transient ischemic attack; TIMI, Thrombolysis in Myocardial Infarction; UDMI, universal definition of myocardial infarction;[13,14] URL, upper rate limit; VKA, vitamin K antagonist.

[a] For resolution of study acronyms please refer to the Supplementary data.

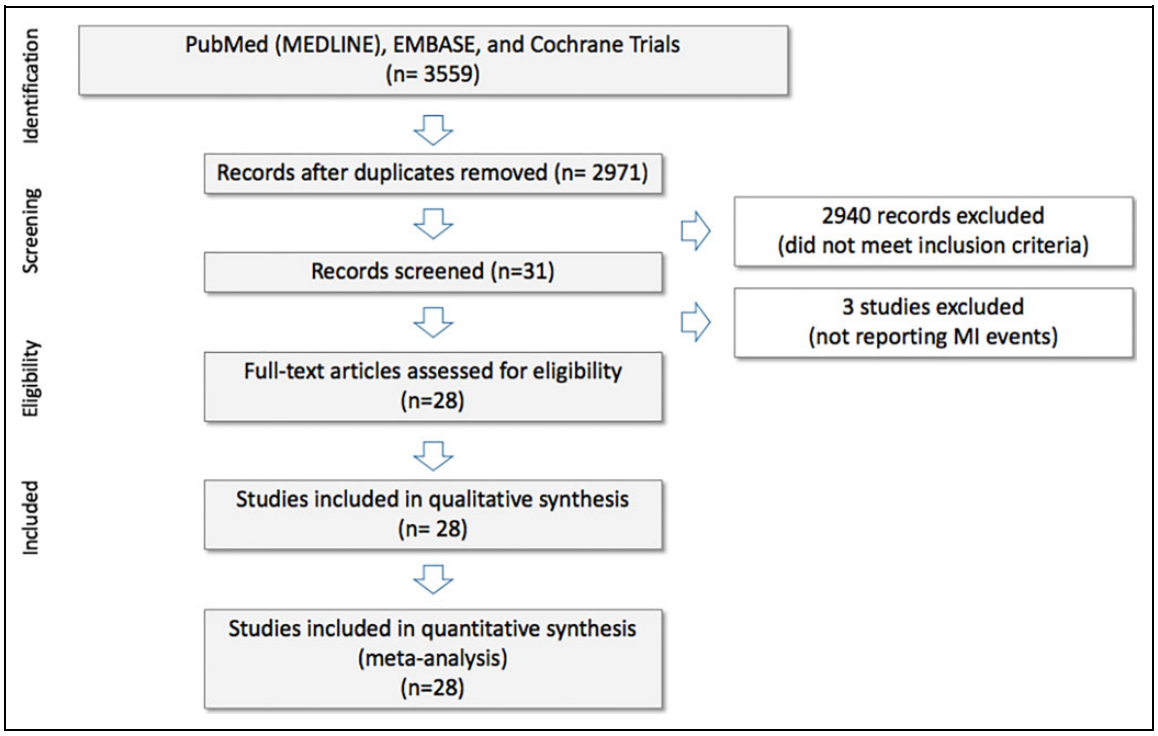

Figure 1. PRISMA flow diagram of the systematic review and source selection.

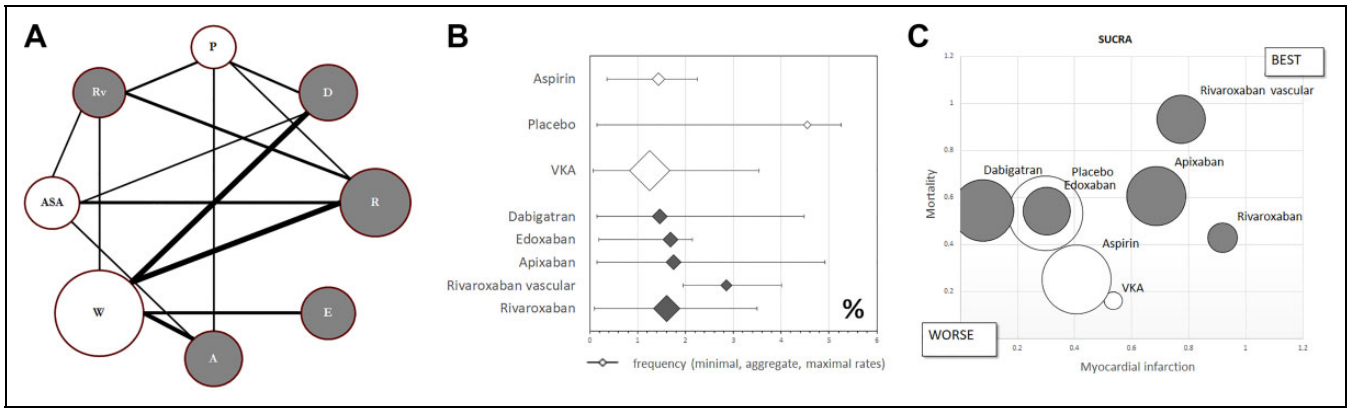

Figure 2. Study network, myocardial infarction frequencies, and ranking. A, Plot of the study network. Nodes show anticoagulation treatments being compared, and edges represent an available direct comparison between pairs of intervention. B, Rate of myocardial infarction according to the treatment groups. Whiskers depict minimal and maximal rates. The diamond depicts the aggregate rate, and its size is proportional to the number of patients treated with the particular intervention. C, Clustered ranking plot of the network. The plot is based on the cluster analysis of SUCRA curves, and the plot shows SUCRA values for the risk of myocardial infarction and mortality. Size of the circles is plotted based on the SUCRA values for major bleeding. AP indicates placebo; D, dabigatran; R, rivaroxaban; E, edoxaban; A, apixaban; W, warfarin; ASA, aspirin; Rv, rivaroxaban vascular dose; SUCRA, surface under the cumulative ranking.

Results

Twenty-eight RCTs involving 196 761 (range: 1280-27 395) patients were analyzed (Figure 1). The main characteristics of these trials are shown in Table 1. Clinical characteristics of the included populations and procedural data of the trials are reported in Supplementary Table 1. Patients were recruited to the trials due to nonvalvular atrial fibrillation,[20-27] including those scheduled for elective cardioversion,[28-30] patients after embolic stroke of undetermined source,[31,32] patients treated for pulmonary embolism or deep vein thrombosis,[33-40] as well as cases at high risk for CHD[10,41,42] including ACS. According to the applied anticoagulants, study arms were grouped into 8 groups. The geometry of the network is depicted in Figure 2A. Dose of the anticoagulant was different and as follows: 150 mg twice daily and 110 mg twice daily for dabigatran, 5 mg once daily to 10 mg twice daily for apixaban, 30 mg once

Table 2. Indirect Comparisons of Different Oral Anticoagulants in a Network Meta-Analysis.[a]

Rivaroxaban				Treatment 1			
0.94 (0.76-1.15) 1.22 (1.04-1.45)[b] 1.82 (0.79-2.17)	Rivaroxaban vascular			Myocardial infarction Mortality Major bleeding	Treatment 2		
0.90 (0.68-1.18) 1.03 (0.87-1.25) 1.72 (0.97-3.13)	0.95 (0.70-1.29) 0.85 (0.69-1.07) 1.35 (0.66-2.70)	Apixaban					
0.88 (0.70-1.12) 0.92 (0.79-1.07) 0.90 (0.62-1.33)	0.93 (0.72-1.25) 0.75 (0.61-0.92)[b] 0.71 (0.39-1.22)	0.98 (0.76-1.31) 0.88 (0.76-1.02) 0.52 (0.31-0.88)[b]	VKA				
0.81 (0.61-1.01) 0.96 (0.82-1.14) 2.08 (0.23-3.57)	0.86 (0.64-1.09) 0.79 (0.66-0.95)[b] 1.61 (0.85-3.03)	0.90 (0.64-1.23) 0.93 (0.76-1.13) 1.21 (0.63-2.27)	0.92 (0.64-1.23) 1.05 (0.86-1.28) 2.27 (1.28-4.16)[b]	Aspirin			
0.79 (0.55-1.13) 1.00 (0.81-1.25) 1.28 (0.64-2.63)	0.84 (0.57-1.24) 0.82 (0.64-1.06) 1.00 (0.43-2.22)	0.88 (0.60-1.30) 0.97 (0.77-1.19) 0.74 (0.34-1.62)	0.90 (0.67-1.17) 1.01 (0.93-1.27) 1.41 (0.79-2.56)	0.97 (0.66-1.53) 1.04 (0.81-1.33) 0.62 (0.27-1.42)	Edoxaban		
0.79 (0.65-0.94)[b] 0.96 (0.79-1.16) 2.77 (1.54-5.00)[b]	0.84 (0.70-0.99) [b] 0.78 (0.63-0.97)[b] 2.13 (1.08-4.17)[b]	0.87 (0.67-1.11) 0.92 (0.75-1.12) 1.59 (0.84-3.03)	0.89 (0.66-1.14) 1.04 (0.86-1.27) 3.03 (1.75-6.67)[b]	0.97 (0.72-1.33) 0.99 (0.79-1.24) 1.33 (0.64-2.70)	1.00 (0.66-1.44) 0.96 (0.75-1.22) 2.13 (0.95-4.76)	Placebo	
0.70 (0.53-0.89)[b] 1.00 (0.82-1.21) 1.72 (1.05-2.94)[b]	0.80 (0.56-0.96)[b] 0.82 (0.65-1.03) 1.35 (0.71-2.56)	0.76 (0.58-0.99)[b] 0.96 (0.78-1.16) 1.01 (0.55-1.89)	0.81 (0.65-0.98)[b] 1.09 (0.94-1.23) 1.92 (1.32-2.86)[b]	0.87 (0.61-1.28) 1.03 (0.82-1.30) 0.84 (0.43-1.67)	0.89 (0.61-1.27) 1.00 (0.81-1.22) 1.35 (0.68-2.77)	0.90 (0.66-1.23) 1.04 (0.85-1.28) 0.63 (0.37-1.10)	Dabigatran

Abbreviation: VKA: vitamin K antagonist.
[a]League table shows the risk ratios (RR) and the 95% credible interval (CrI) of the different oral anticoagulants in a random effect model with vague prior for myocardial infarction (first line), mortality (second line), and major bleeding (third line). RR < 1 means that the top left treatment (Treatment 1) is better.
[b]The comparisons where the CrI did not overlap the line of equivalence.

daily and 60 mg once daily for edoxaban, while rivaroxaban dose ranged from 10 mg daily (once daily or twice daily) up to 30 mg daily except for 4 studies testing "rivaroxaban vascular" 2.5 mg twice-daily doses.[9,10,24,41] Control treatment arm was aspirin in 5, VKA in 18, and placebo in 5 trials. Study definitions of MI were discrepant (Table 1).[13,14]

Low-dose ($\leq$100/$\leq$165 mg daily) aspirin treatment was allowed in all studies. Combined antiplatelet therapy was allowed in 13 studies.[9,12,41,42,43,23-27,29,36,40] Analysis of bias showed high quality of the source information with low probability of possible bias. No obvious publication bias was found (Supplemental Figures 1 and 2).

In the included trials, 3554 MIs occurred in the VKA arm with lowest rate (1.25%) and in the placebo arms with the highest rate (4.55%; Figure 2B). Heterogeneity analysis showed consistent results within treatment groups (dabigatran I2: 26%, χ^2: $P = .23$ and I^2: 0%, χ^2: $P \geq .53$ for all other DOACs), while high heterogeneity was seen among DOAC subgroups (I2: 64.2%, χ^2: $P = .02$; Supplemental Figure 1). Exclusion of the Secondary Prevention of Venous Thrombo Embolism (RE-MEDY) or the Management of Myocardial Injury After Noncardiac Surgery (MANAGE) trial but none of the others corrected the I2 value in the dabigatran subgroup to zero (data not shown).

Rivaroxaban was associated with a relative risk (RR) reduction of 21% regarding MI when compared to placebo (RR: 0.79 [95% CrI: 0.65-0.94]) and a 31% reduction (RR: 0.70 [95% CrI: 0.53-0.89]) when compared to dabigatran. Apixaban resulted in 24% (RR: 0.76 [95% CrI: 0.58-0.99], and VKA resulted in 19% (RR: 0.81 [95% CrI: 0.65-0.98]) risk reduction compared with dabigatran. Furthermore, rivaroxaban in vascular dose resulted in 16% (RR: 0.70 [95% CrI: 0.70-0.99]) reduction compared with placebo, as well as 27% (RR 0.80 [95% CrI: 0.56-0.96] risk reduction compared to dabigatran (Table 2, Figure 3).

Leave-one-out analysis disregarding the data from the Randomized Evaluation of Long Term Anticoagulant Therapy with Dabigatran Etexilate (RE-LY) trial showed similar relations with lower MI risk with rivaroxaban than with placebo (0.78 [0.64-0.94]) and dabigatran as well (RR: 0.66 [0.49-0.89]; Supplemental Table 4).

The computed probability of being the first best choice of treatment was 61.8% for rivaroxaban, 17.4% for very low-dose rivaroxaban (5 mg daily), 14.2% for apixaban, 2.4% for VKAs, 3.0% for edoxaban, 1.1% for aspirin, and <0.1% for placebo and dabigatran in the network.

Ranking remained unaffected if data from the RE-LY trial were censored from the analysis. Ranking based on mortality and major bleeding result showed trends of similar ranks with MI and mortality, while trends of major bleeding showed opposite tendencies with lower ranking of bleeding at treatments with higher rankings in MI (Figure 2C). However, neither of these trends were significant at regression analyses of the surface under the cumulative ranking area values (R^2 for MI and mortality: 0.035, $P = .6577$ and R^2 for MI and major bleeding: 0.2963, $P = .1630$).

In univariate meta-regression analyses, the rate of MI showed positive association with the background risk and to the rate of antiplatelet use but not to the treatment duration. In

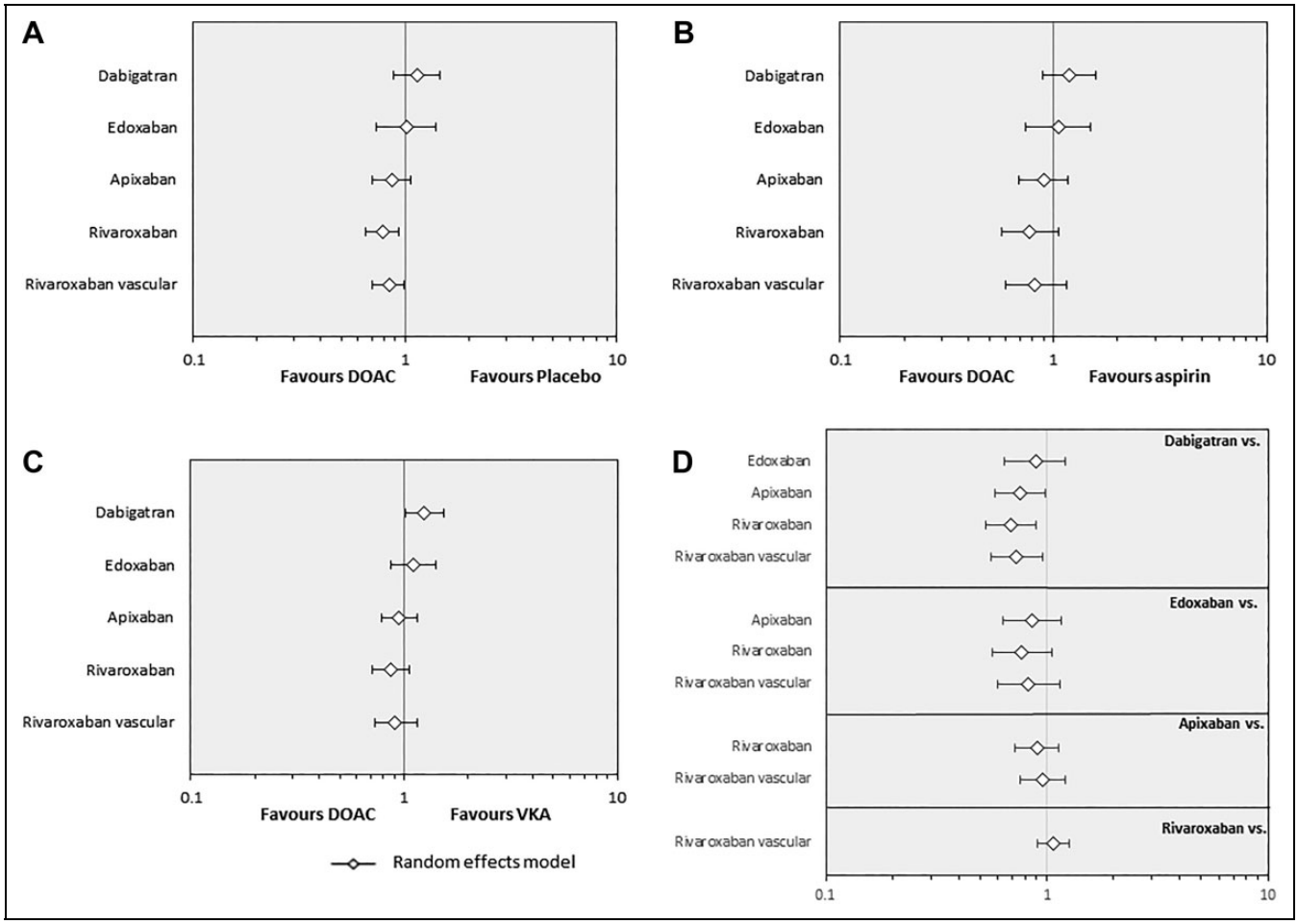

Figure 3. Forest plot of the relative risk of myocardial infarction. A, B, and C, The relation of the myocardial infarction risk of the DOAC treatments compared to the placebo and aspirin of vitamin K antagonist controls, respectively. D, Comparisons among the different DOAC groups. DOAC indicates direct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

multiple analysis background risk, prevailed as a significant determinant of the MI frequency ($P = .871$ for antiplatelet and $P < .001$ for the background risk). However, analyses of the RR against aspirin showed no association either with the antiplatelet use or with the background risk (Figure 4).

Discussion

In this meta-analysis involving 196 761 patients, we found evidence that the choice of anticoagulant influences the risk of MI in anticoagulated patients. When risk of MI is taken into consideration, the probability of being the best choice of treatment is the highest for rivaroxaban administered in antithrombotic or vascular prevention dose regimen, while the lowest is for VKAs and the direct thrombin inhibitor, dabigatran.

Coagulation plays pivotal role in the development of CV events; thus, CV safety of these drugs is of paramount interest. Earlier analyses found favorable results for VKAs in the prevention after acute MI.[8] However, frequent bleeding complications and the narrow therapeutic window with the need for careful monitoring, in addition to drug and food interactions, limit the benefits.[44] In recent years, VKAs are progressively replaced by the specifically acting oral anticoagulants (DOACs) offering an easier and potentially safer option leading to a high number of patients exposed to these drugs. Moreover, improving safety and convenience of use raised the question as to whether DOACs reopen the field of CV prevention for anticoagulation.

Several recent trials supported this concept including the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2–TIMI 51) trial, where 2.5 mg rivaroxaban twice daily improved the CV outcomes compared to placebo. Despite the higher risk of bleeding, compared to placebo vascular dose rivaroxaban reduced the rate of death of CV origin (2.7% vs 4.1%, $P = .002$) and all other causes (2.9% vs 4.5%, $P = .002$).[9] More recently in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, low-dose rivaroxaban combined with aspirin was associated with a reduced risk of ischemic events and mortality among patients with established, stable atherosclerotic disease, compared to those receiving aspirin monotherapy. Although

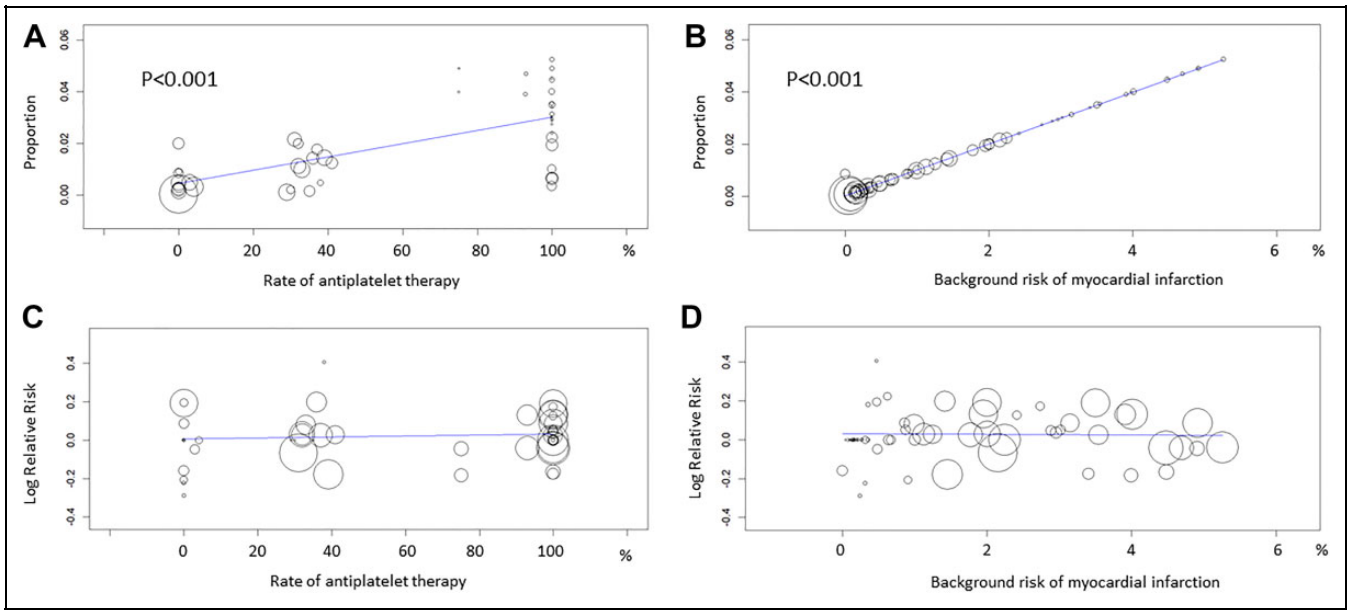

Figure 4. Meta-regression analyses. In univariate meta-regression analyses, the rate of myocardial infarction (MI) showed positive regression to the rate of antiplatelet use as well as to the background risk (A and B). Analyses of the risk ratio against aspirin showed no regression either to the antiplatelet use or to the background risk (C and D).

bleeding complications were also more common, the combined treatment with low-dose rivaroxaban resulted in superior net clinical benefit.[10] Furthermore, in the MANAGE trial among patients with myocardial injury after noncardiac surgery, twice-daily 110 mg dabigatran was tested against placebo and resulted in fewer major vascular events, while bleeding complications were similar in frequency ($P = .0115$ and $P = .76$, respectively).[12]

Contrasting these recent results, there has been some question ever since the publication of one of the earliest DOAC phase 3 study, the RE-LY trial.[26] In this trial, 2 doses of dabigatran were shown to be either more effective in preventing stroke with a similar bleeding risk or safer than warfarin with similar prevention efficacy. Importantly, this study reflected that patients receiving anticoagulant treatment for atrial fibrillation remain at risk of MI and found an excessive risk of MI with dabigatran. There were numerically more MIs with both doses of dabigatran than with warfarin, and the difference reached statistical significance regarding the higher, 150 mg dose. However, a subsequent post hoc analysis revealed additional events of stroke, bleeding, and MI, and the revised results no longer showed a significant difference in MI.[45]

In the paucity of direct comparison randomized trials, several studies including prospective and retrospective registries attempted verification and characterization of the magnitude of the potential MI risk of dabigatran-treated patients. These studies, though subjected to several methodological shortcomings, especially an uncontrollable selection bias, could neither reliably support nor refute the importance of this signal.[46-48] Our extended review including a broad range of studies found that the data of randomized trials show important differences favoring the Xa inhibitor rivaroxaban and apixaban over dabigatran. This extends the earlier observations supporting that signal persists even after exclusion of the RE-LY data and reaches beyond the field of patients with atrial fibrillation.

Since the 2012 version of the European Society of Cardiology CV disease prevention guideline, the concept of primary and secondary prevention has been discouraged and replaced by the recognition that atherosclerosis is a continuous process.[49] 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.

Our analysis assessed the preventive potential of DOACs from 2 approaches. First, the inclusion of 5 placebo and 5 aspirin-controlled trials enables to relate this potential to established preventive therapy. Second, we found that the differences in the rate of MI in the study arms were explainable by the background risk of the included study populations rather than by the differences in the rate of antiplatelet treatment. The relative risks of the anticoagulant treatments compared to aspirin were independent from both the rate of antiplatelet treatment and background risk. Importantly, the subgroup analyses according to the clinical indications or the treatment length did not show a major influence on the results. These findings suggest that the preventive potential of DOACs is heterogeneous, correlates with that of aspirin and VKA, and is independent of the concomitant antiplatelet treatment.

The risk of MI with DOAC treatment has been assessed in earlier systematic reviews and meta-analyses. Besides that, these analyses did not include the results of some pivotal recent trials including the COMPASS, MANAGE, and AUGUSTUS

studies; they share some common limitations. These comprise inclusion of underpowered, dose-finding, phase 2 trials.[50-53] Only a few of them included trials with the recently approved edoxaban[53-55] but included trials with drugs that stopped development.[50,51,54,55] Some previous works restricted the analysis to trials related only to atrial fibrillation and or deep vein thrombosis/pulmonary embolism.[53-55] Some based their assumptions on the less robust fixed effect model that accounts for interstudy heterogeneity less adequately.[52,53]

Some limitations of our analysis should be discussed. The paucity of randomized trials comparing different DOAC agents was one of the main reasons for the choice of this analysis but represents also a limitation as the presented statistical inferences rely substantially on indirect comparisons. It is improbable that a specific trial with MI as an end point and aiming to perform a direct comparison of oral anticoagulants will ever be conducted; thus, analysis of the available data set remains the only option to shed light on these relationships.

Furthermore, safety and efficacy profiles of the anticoagulants may be dose dependent, and the variability in drug regimens might be a source of distortion. In fact, in trials testing >1 dose of DOACs, the rate of MI was different in some cases but similar in others. For example, 2.4% and 1.89% with 30 and 60 mg once-daily edoxaban in the Global Study to Assess the Safety and Effectiveness of Edoxaban vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation (ENGAGE AF—TIMI 48) trial, or 1.46% and 1.43% with 110 or 150 mg twice-daily dabigatran in the RE-LY trial among patients with AF, respectively.[21] However, in most of the remaining trials, the rather complicated schemes do not permit the study of dose–effect relationships. Thus, we decided to form our analysis groups based on DOAC exposure, with one exception regarding the distinction of the very low-dose rivaroxaban. Earlier studies with warfarin show that ischemic protection requires to reach a threshold of anticoagulation; above this limit, the rate of bleeding complications but not necessarily the preventive potential increases.[56] Acknowledging that this relation may apply to other means of anticoagulation, we handled "vascular dose" rivaroxaban as distinct treatment groups. Regarding VKA treatment, all but 3 included trials used warfarin in their VKA arms. In 3 trials, acenocoumarol was also allowed (see Table 1). Acknowledging that differences may exist in CV safety of the different VKAs due to the paucity of specific data, we could not differentiate among them. Furthermore, definition of MI slightly differed across studies, and none of them included trials had MI as an end point. Moreover, there are >1 publication regarding the rates of MI in the RE-LY trial.[26,45] This shows that even with meticulously conducted trials, the capture and adjudication of events may be incomplete. As data in the first publication reflected the results of the prospective event adjudication instead of a post hoc analysis, we used these in our analyses.[26] Furthermore, we performed sensitivity analyses that did not show important influence on the result.

Conclusions

Our comprehensive meta-analysis involving 28 RCTs and 196 761 patients has identified significant differences in CV safety among oral anticoagulants. 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.

Authors' Note

All authors contributed to (1) conception and design, or acquisition of data or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and (3) final approval of the version to be published.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: András Komócsi: Lecture fees from Bayer Healthcare Pharmaceuticals, Eli Lilly, KRKA, MSD, Pfizer, Boehringer-Ingelheim and Abbot Vascular. Tamas Habon: Lecture fees from Bayer, Boehringer-Ingelheim, MSD, Novartis, Pfizer, Roche and Servier. The other authors have no potential conflict of interest.

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Supplemental Material

Supplemental material for this article is available online.

References

1. Barnes GD, Ageno W, Ansell J, Kaatz S. Recommendation on the nomenclature for oral anticoagulants: communication from the SSC of the ISTH. *J Thromb Haemost*. 2015;13(6):1154-56.
2. Caldeira D, Barra M, Pinto FJ, Ferreira JJ, Costa J. Intracranial hemorrhage risk with the new oral anticoagulants: a systematic review and meta-analysis. *J Neurol*. 2015;262(3):516-22.
3. Caldeira D, Rodrigues FB, Barra M, et al. Non-vitamin K antagonist oral anticoagulants and major bleeding-related fatality in patients with atrial fibrillation and venous thromboembolism: a systematic review and meta-analysis. *Heart*. 2015;101(15):1204-11.
4. Vranckx P, Valgimigli M, Heidbuchel H. The significance of drug–drug and drug–food interactions of oral anticoagulation. *Arrhythm Electrophysiol Rev*. 2018;7(1):55-61.
5. Huisman MV, Rothman KJ, Paquette M, et al. The changing landscape for stroke prevention in AF: findings from the

GLORIA-AF registry phase 2. *J Am Coll Cardiol*. 2017;69(7): 777-85.
6. Roth GA, Huffman MD, Moran AE, et al. Global and regional patterns in cardiovascular mortality from 1990 to 2013. *Circulation*. 2015;132(17):1667-78.
7. Members AF, Windecker S, Kolh P, et al. 2014 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2014; 35(37):2541-19.
8. Anand SS, Yusuf S. Oral anticoagulants in patients with coronary artery disease. *J Am Coll Cardiol*. 2003;41(4 Suppl S):62S-9S.
9. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012; 366(1):9-19.
10. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med*. 2017;377(14):1319-30.
11. Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. *Arch Intern Med*. 2012;172(5):397-402.
12. Devereaux PJ, Duceppe E, Guyatt G, et al. Dabigatran in patients with myocardial injury after non-cardiac surgery (MANAGE): an international, randomised, placebo-controlled trial. *Lancet*. 2018; 391(10137):2325-34.
13. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. *Circulation*. 2007;116(22):2634-53.
14. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Circulation*. 2012;126(16):2020-35.
15. The Nordic Cochrane Centre. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration. 2014.
16. Riley RD, Jackson D, Salanti G, et al. Multivariate and network meta-analysis of multiple outcomes and multiple treatments: rationale, concepts, and examples. *BMJ*. 2017;358:j3932.
17. Lunn DJ, Thomas A, Best N, Spiegelhalter D.WinBUGS—A Bayesian modelling framework: concepts, structure, and extensibility. *Stat Comput*. 2000;10(4):325-37.
18. Brown S, Hutton B, Clifford T, et al. A microsoft-excel-based tool for running and critically appraising network meta-analyses-an overview and application of NetMetaXL. *Syst Rev*. 2014;3:110.
19. Wallace BC, Dahabreh IJ, Trikalinos TA, Lau J, Trow P, Schmid CH. Closing the gap between methodologists and end-users: R as a computational back-end. *J Stat Softw*. 2012;49:1-15.
20. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-92.
21. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013; 369(22):2093-104.
22. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011;364(9):806-17.
23. Hori M, Matsumoto M, Tanahashi N, et al. Rivaroxaban vs. warfarin in japanese patients with atrial fibrillation. *Circ J*. 2012; 76(9):2104-11.
24. Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med*. 2016;375:2423-34.
25. Cannon CP, Bhatt DL, Oldgren J, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med*. 2017;377(16):1513-24.
26. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009; 361(12):1139-51.
27. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011; 365(10):883-91.
28. Cappato R, Ezekowitz MD, Klein AL, et al. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. *Eur Heart J*. 2014;35(47):3346-55.
29. Goette A, Merino JL, Ezekowitz MD, et al. Edoxaban versus enoxaparin–warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. *Lancet*. 2016;388(10055):1995-2003.
30. Ezekowitz MD, Pollack C V., Halperin JL, et al. Apixaban compared to heparin/Vitamin K antagonist in patients with atrial fibrillation scheduled for cardioversion: the EMANATE trial. *Eur Heart J*. 2018;39(32):2959-71.
31. Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med*. 2018;378(23):2191-201.
32. Diener H-C, Sacco RL, Easton JD, et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source. *N Engl J Med*. 2019;380(20):1906-17.
33. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369(9):799-808.
34. Weitz JI, Lensing AWA, Prins MH, et al. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. *N Engl J Med*. 2017;376(13):1211-22.
35. Scott D, Brenner B, Buller HR, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363(26): 2499-510.
36. Büller HR, Prins MH, Lensin AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366(14):1287-97.
37. Investigators THV. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013; 369(15):1406-15.
38. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009;361(24):2342-52.
39. Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation*. 2014;129(7):764-72.
40. Schulman S, Kearon C, Kakkar AK, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med*. 2013;368(8):709-18.
41. Zannad F, Anker SD, Byra WM, et al. Rivaroxaban in patients with heart failure, sinus rhythm, and coronary disease. *N Engl J Med*. 2018;379(14):1332-42.
42. Lopes RD, Heizer G, Aronson R, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N Engl J Med*. 2019;380(16):1509-24.

43. Alexander JH, Lopes RD, James S, et al. Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med*. 2011; 365(8):699-708.
44. Komócsi A, Vorobcsuk A, Kehl D, Aradi D. Use of new-generation oral anticoagulant agents in patients receiving antiplatelet therapy after an acute coronary syndrome: systematic review and meta-analysis of randomized controlled trials. *Arch Intern Med*. 2012;172(20):1537-45.
45. Hohnloser SH, Oldgren J, Yang S, et al. Myocardial ischemic events in patients with atrial fibrillation treated with dabigatran or warfarin in the RE-LY (Randomized evaluation of long-term anticoagulation therapy) trial. *Circulation*. 2012;125(5):669-76.
46. Larsen TB, Rasmussen LH, Skjøth F, et al. Efficacy and safety of dabigatran etexilate and warfarin in "real-world" patients with atrial fibrillation: a prospective nationwide cohort study. *J Am Coll Cardiol*. 2013;61(22):2264-73.
47. Larsen TB, Rasmussen LH, Gorst-Rasmussen A, et al. Myocardial ischemic events in "real world" patients with atrial fibrillation treated with dabigatran or warfarin. *Am J Med*. 2014;127(4):329-36.
48. Lee CJ-Y, Gerds TA, Carlson N, et al. Risk of myocardial infarction in anticoagulated patients with atrial fibrillation. *J Am Coll Cardiol*. 2018;72(1):17-26.
49. Perk J, De Backer G, Gohlke H, et al. European guidelines on cardiovascular disease prevention in clinical practice (version 2012): the fifth joint task force of the european society of cardiology and other societies on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2012;33(13):1635-701.
50. Mak KH. Coronary and mortality risk of novel oral antithrombotic agents: a meta-analysis of large randomised trials. *BMJ Open*. 2012;2(5):pii: e001592.
51. Oldgren J, Wallentin L, Alexander JH, et al. New oral anticoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: a systematic review and meta-analysis. *Eur Heart J*. 2013;34(22):1670-80.
52. Loke YK, Pradhan S, Yeong JK, Kwok CS Comparative coronary risks of apixaban, rivaroxaban and dabigatran: a meta-analysis and adjusted indirect comparison. *Br J Clin Pharmacol*. 2014; 78(4):707-17.
53. López-López JA, Sterne JAC, Thom HHZ, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. *BMJ*. 2017;358:j5058.
54. Morimoto T, Crawford B, Wada K, Ueda S.Comparative efficacy and safety of novel oral anticoagulants in patients with atrial fibrillation: a network meta-analysis with the adjustment for the possible bias from open label studies. *J Cardiol*. 2015;66(6): 466-74.
55. Tornyos A, Kehl D, D'Ascenzo F, Komocsi A. Risk of myocardial infarction in patients with long-term non-vitamin k antagonist oral anticoagulant treatment. *Prog Cardiovasc Dis*. 2016;58(5): 483-94.
56. Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med*. 2003;349(11):1019-26.

Comparison of Platelet Function Guided Versus Unguided Treatment With P2Y12 Inhibitors in Patients With Acute Myocardial Infarction (from the Hungarian Myocardial Infarction Registry)

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Evidence is conflicting regarding the clinical benefits of selecting $P2Y_{12}$ inhibitors based on platelet function testing (PFT). Between March 1, 2013 and March 1, 2014, we collected clinical characteristics and platelet function data in a nationwide acute myocardial infarction (AMI) registry from 15 interventional cardiology centers in Hungary. The risk of all-cause mortality at 1 year were compared after propensity score (PS) matching between patients receiving PFT-guided and unguided $P2Y_{12}$-inhibitor therapies. High platelet reactivity on clopidogrel (HPRoC) was uniformly defined with the Multiplate assay. A total of 5,583 patients with AMI and coronary intervention were registered. After exclusion of cases with contraindication to prasugrel, propensity matching resulted in a sample of 2,104 patients with well-adjusted characteristics. Clopidogrel was the dominant $P2Y_{12}$ inhibitor in both groups (unguided: 96% vs PFT guided: 85%, p <0.001). In the PFT-guided group, 19% of patients had HPRoC and 77% of them were switched to prasugrel. According to the adjusted analysis, all-cause mortality at 1 year was significantly lower in the PFT-guided compared with the unguided group (hazard ratio 0.57 [95% confidence interval 0.43 to 0.77], p <0.001). Although prasugrel treatment was not associated with lower all-cause mortality in the overall cohort, patients with HPRoC who switched to prasugrel had significantly lower mortality when compared with those continuing clopidogrel (hazard ratio 0.33 [95% confidence interval 0.12 to 0.92], p <0.05). In conclusion, in patients with AMI, PFT-guided treatment with a high rate of switchover to prasugrel was associated with a lower risk of mortality. Prasugrel was a predictor of lower mortality in patients with HPRoC but not in the overall cohort of AMI. **(Am J Cardiol 2018;121:1129–1137)**

Inhibition of platelet aggregation is one of the major therapeutic targets in patients with an acute myocardial infarction (AMI). Among platelet $P2Y_{12}$-receptor inhibitors, prasugrel and ticagrelor are the preferred choices for patients with AMI.[1,2] Due to contraindications, financial restrictions, and regulatory reasons, the availability of prasugrel and ticagrelor is not uniform across countries, whereas the use of clopidogrel and switching between $P2Y_{12}$ inhibitors is frequent.[3–5] High platelet reactivity on clopidogrel (HPRoC) is an independent predictor of stent thrombosis and myocardial infarction.[6–8] However, current guidelines discourage the routine use of platelet function testing (PFT) due to lack of evidence on the ability

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See page 1136 for disclosure information.

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of PFT-based $P2Y_{12}$ therapy to improve outcomes.[1,2] Local reimbursement regulations in Hungary mandate PFT on clopidogrel, and prasugrel is reimbursed for patients with HPRoC. This policy resulted in a high penetration of PFT across invasive centers. We sought to evaluate the clinical impact of PFT guidance based on a nationwide registry of patients with AMI who were treated with coronary intervention.

Methods

The Hungarian Myocardial Infarction Registry is a prospective, Internet-based registry collecting clinical data on consecutive patients treated for an event of AMI in Hungary, a country with 9.8 million residents. At the time of the conduction of the present study, the registry operated on a voluntary basis, capturing 51% of AMI cases treated countrywide.[9–11] The protocol of the study is in accordance with the Declaration of Helsinki and was reviewed by the ethical board. All patients recorded in the registry gave written informed consent.

Between March 1, 2013 and March 1, 2014, all patients with AMI (both with ST segment elevation and without) were eligible for enrollment if intervention was performed successfully with stent implantation and there was no contraindication to treatment with a $P2Y_{12}$ inhibitor for 1 year. Data of patients treated in 15 centers of invasive cardiology collaborating with providing and monitoring platelet function data were analyzed.

Patients with an indication of chronic oral anticoagulation, with a history of stroke or transient ischemic attack, who are aged older than 75 years, who weigh less than 60 kg, or who have had an administration of $P2Y_{12}$ inhibitors other than clopidogrel or prasugrel before or during intervention were excluded. Thienopyridins were supplemented with low-dose aspirin, typically 100 mg with an optional loading dose of 300 to 500 mg. The use of perioperative anticoagulation and the administration of platelet IIb/IIIa inhibitors were allowed according to the local protocols.

Generally, $P2Y_{12}$-inhibitor treatment before intervention comprised clopidogrel, usually given in a loading dose of 600 mg but left to the decision of the treating physicians. After intervention, both prasugrel and clopidogrel were available for long-term treatment. However, although clopidogrel use was not restricted by any reimbursement rule, prasugrel was reimbursed at 70% only if PFT results confirmed HPRoC. Importantly, it was left to the discretion of the treating physicians whether to perform PFT and make the choice based on PFT (PFT-guided group) or make a clinical decision without PFT (unguided group).

All participating centers used a homogeneous method for PFT, which was the Multiplate analyzer (Roche Diagnostics GmbH, Rotkreuz, Switzerland). PFT was performed at least 6 hours after the intervention or at least 24 hours after platelet IIb/IIIa inhibitor treatment cessation.[12] HPRoC was defined as an adenosine diphosphate test level >46 U.[12] The choice of P2Y12 inhibitor in patients with HPRoC was also left to the treating physician: either switch to prasugrel, or high (150 mg/day) or conventional doses (75 mg) of clopidogrel were allowed.

The primary efficacy end point was all-cause mortality within 1 year after the index procedure. Secondary end points included the composite of cardiovascular death, recurrent myocardial infarction, and stroke as well as transfusion and the individual elements of the composite end point. Overall mortality was obtained from the patient vital status in the database of the Hungarian Central Statistical Office and the National Health Insurance Fund, including the date and the cause of death. In patients who died, the cause of death was assessed by qualifying deaths related to infection, malignancy, and trauma as noncardiovascular. Data related to recurrent hospitalization for AMI, for stroke, as well as for bleeding event leading to transfusion were extracted from the database of the National Health Insurance Fund.

Variables are presented as means ± SD or as frequencies and percentages. Unpaired *t* tests were used for comparisons of continuous variables between groups. Categorical variables were compared using chi-square or Fisher's exact test as appropriate. As eligible patients were not randomly assigned to PFT-guided or unguided treatments, we intended to balance the groups to reduce potential bias associated with treatment selection. For this aim we built a propensity score (PS)–matched cohort with comparable chance for either strategy by adjusting for differences in baseline characteristics. PS was computed by using a logistic regression model for PFT-guided versus unguided groups. Patient characteristics at presentation and clinical factors from the medical history with potential influence on the decision regarding PFT (listed in Table 1) were used as predictors in calculating PS. In the PS-matching procedure, we first randomly selected a patient in the unguided group and matched him or her with a patient from the PFT-guided group with the closest estimated PS value. We performed a 1-to-1 matched analysis without replacement with a match tolerance of <0.01. Unadjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were determined in univariate Cox proportional models, and then a multivariable Cox proportional hazards model was used to determine independent predictors of all-cause mortality. As a sensitivity exercise, PFT-guided and unguided patients were compared also in the PS-unmatched study population with Cox regression analyses. All reported p values are 2-sided, and p values of <0.05 were considered to indicate statistical significance. This analysis was conducted using the SPSS 22 statistical package.

Results

From March 1, 2013 to March 1, 2014, data of 6,795 patients hospitalized in the participating centers for an event of AMI were entered in the registry. Of these, 5,583 patients (82.2%) were treated with coronary intervention and stenting. In 3,715 cases (66.5%), long-term $P2Y_{12}$-inhibitor treatment was chosen based on PFT results (PFT-guided group), whereas PFT was not performed in 1,868 cases (unguided group 33.5%). After excluding 29% of patients with absolute or relative contraindications to prasugrel, an unmatched patient pool of 3,974 cases was obtained (Figure 1). As expected, there were numerous differences in baseline characteristics between the groups. To adjust for these differences, PS matching was performed that resulted in a matched population of 2,104 patients (Table 1).

Among the 2,901 subjects of the PFT-guided group, 554 (19%) had HPRoC. Seventy percent of them were switched

Table 1
Characteristics of the patient population before and after propensity score matching

Clinical characteristics	Entire cohort (n = 3974)			Propensity matched cohort (n = 2104)		
	PFT-guided (n = 2901)	Unguided treatment (n = 1073)	p value	PFT-guided (n = 1052)	Unguided treatment (n = 1052)	p value
Age, (years) *	58.9 ± 9.6	60.5 ± 9.2	<0.001	60.5 ± 9.0	60.5 ± 9.1	0.926
Men *	69.3 %	65.7 %	0.035	65.3 %	66.1 %	0.748
Medical history						
Hypertension	64.6 %	71.2 %	<0.001	68.41 %	70.6 %	0.297
Diabetes mellitus	24.8 %	29.2 %	0.006	27.8 %	28.4 %	0.734
- insulin	1.6 %	1.6 %	1.000	1.0 %	1.5 %	0.324
Hyperlipidemia *	11.1 %	5.1 %	<0.001	3.7 %	5.2 %	0.113
Smoker (current/past/never)	35.2/1.6/63.3 %	36.1/2.1/61.9 %	0.458	36.2/1.8/62.0 %	36.2/1.9/61.8 %	0.950
Prior myocardial infarction	15.8 %	27.4 %	<0.001	26.6 %	26.0 %	0.771
Prior coronary intervention*	4.6 %	7.3 %	0.001	7.1 %	7.4 %	0.867
Prior of coronary bypass operation *	1.8 %	1.0 %	0.113	0.8 %	1.0 %	0.646
Peripheral artery disease *	5.3 %	11.6 %	<0.001	10.2 %	10.4 %	0.943
Presentation						
ST segment elevation myocardial infarction *	64.1 %	51.0 %	<0.001	55.1 %	51.7 %	0.126
Culprit artery (LM/LAD/Cx/RCA/VSG	2.8/46.7/23.0/35.8/1.2 %	3.3/44.1/25.9/35.8/1.1 %	0.3461	2.9/46.7/24.4/34.3/1.2 %	2.9/44.2/25.5/36.0/1.0 %	0.734
Heart rate (bpm)	79.8 ± 17.1	80.6 ± 18.1	0.236	81.4 ± 18.0	80.5 ± 18.1	0.250
Systolic blood pressure (mm Hg)*	137.9 ± 24.2	136.6 ± 25.7	0.191	138.6 ± 24.8	136.5 ± 25.7	0.054
Diastolic blood pressure (mm Hg)*	70.0 ± 24.7	68.7 ± 25.0	0.168	67.9 ± 26.1	68.8 ± 25.1	0.440
Adenosin diphosphate reactivity	32.5 ± 19.5	-	NA	32.5 ± 19.9	-	NA
High platelet reactivity	19.1 %	-	NA	18.6 %	-	NA
Medications						
Clopidogrel 75 mg daily	50.6 %	74.3 %	<0.001	43.6 %	74.2 %	<0.001
Clopidogrel 150 mg daily	34.4 %	21.6 %		40.2 %	21.8 %	
Prasugrel	15.0 %	4.1 %		16.2 %	4.0 %	
Aspirin	71.1 %	81.0 %	<0.001	80.9 %	79 %	0.547
ß-blocker	84.1 %	90.6 %	<0.001	88.5 %	90.4 %	0.176
Statin	81.0 %	91.8 %	<0.001	91.6 %	91.7 %	0.579

Data are presented as percentages or as mean ± standard deviation. Asterisk marks parameters associated to the invasive therapy in binary logistic model. * p value < 0.1.

LM = left main coronary artery; LAD = left anterior descending artery; Cx = left circumflex artery; RCA = right coronary artery; SVG = saphenous vein graft.

to prasugrel, whereas 30% continued clopidogrel (14% high-dose and 16% standard-dose clopidogrel). In patients without HPRoC (no HPRoC group), use of prasugrel was low (2%), resulting in an overall high proportion of patients continuing clopidogrel based on PFT guidance. Among unguided patients, prasugrel was prescribed only in 4%, whereas low-dose clopidogrel was quite frequent (74%). Treatment allocation patterns in the PS-matched cohort remained similar with 77% switchover to prasugrel in patients with HPRoC (Figure 2).

During the follow-up period, 200 patients died from the PS-matched cohort, resulting in a 1-year all-cause mortality rate of 9.5%, in this unselected, high-risk cohort. PFT-guided subjects had a highly significant, 43% lower hazard for all-cause mortality compared with the unguided group. Similar to this, cardiovascular mortality was also reduced by 39% (Figure 3 and Table 2). In the unmatched total cohort including 3,974 patients, similar results were observed for all-cause and cardiovascular mortality without a significant difference in the risk of stroke or repeat myocardial infarction (Table 2). As 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 lower risk of mortality in the PS-matched (HR 0.65 [0.38 to 1.11], p = 0.116) or in the unmatched cohorts (HR 0.75 [0.51 to 1.11], p = 0.145).

As a prespecified analysis, the clinical impact of prasugrel and clopidogrel were tested on all-cause mortality within subgroups of PFT-guided and unguided therapy, and across HPRoC groups. Within the PFT-guided group of PS-matched patients, clopidogrel use was associated with significantly worse survival compared with prasugrel in case of HPRoC. Among clopidogrel-treated patients with HPRoC, high-dose clopidogrel was associated with a numerically lower risk of mortality than standard-dose clopidogrel (8.7% vs 21.7%),

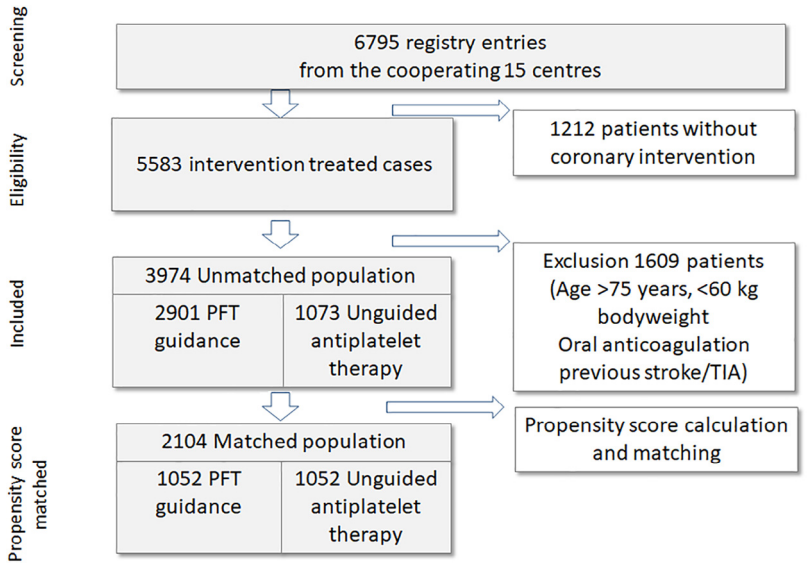


Figure 1. Flowchart of patient selection. TIA = transient ischemic attack.

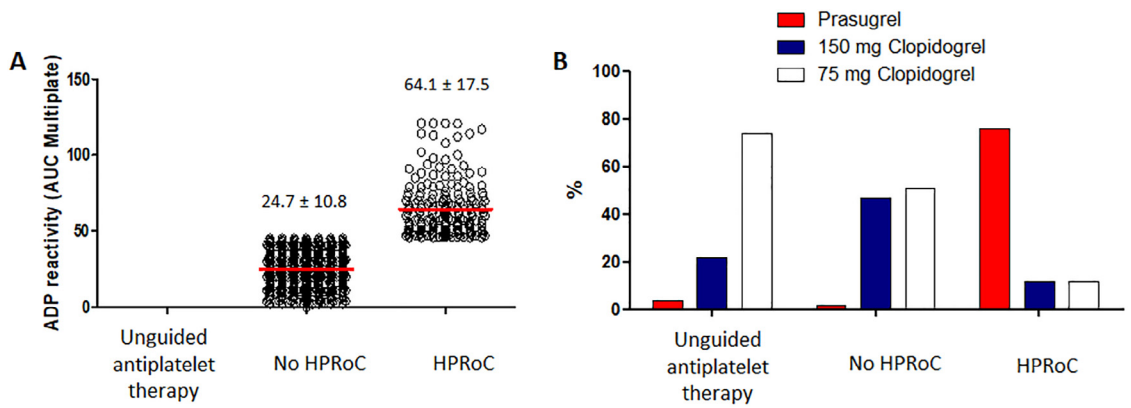


Figure 2. Results of the platelet function tests (*A*) and $P2Y_{12}$ antagonist therapy in the platelet function test results defined groups of the propensity-adjusted sample (*B*). ADP = adenosine diphosphate; AUC = area under the curve.

but this difference did not reach the level of statistical significance (HR 0.37 [95% CI 0.07 to 1.88], p = 0.228). In the unguided group and in patients without HPRoC of the guided cohort, prasugrel versus clopidogrel therapy was not a significant predictor of survival (Figures 4 and 5).

To separate and analyze the potential role of PFT on mortality independently from other potentially relevant determinants, univariate and multivariate models were generated. In the multivariate model, beyond known risk factors including age, smoking, history of peripheral artery disease, hypertension, diabetes, high heart rate or low arterial pressures at presentation, and left main coronary involvement, PFT guidance remained a significant, independent predictor of lower all-cause mortality, whereas prasugrel therapy was not associated with an improved overall survival (Table 3).

Discussion

Our analysis of a large, prospective, unselected database of patients treated with coronary intervention due to an event of AMI showed improved survival in patients with PFT-guided antiplatelet treatment compared with an 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, whereas 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. These findings may explain why PFT-guided $P2Y_{12}$-inhibitor treatment selection, but not prasugrel therapy, prevailed as an independent predictor of improved survival in the multivariate analysis. These results were confirmed both in the overall and in the PS-matched cohorts.

Prasugrel and ticagrelor showed a significant reduction in the risk of ischemic end points in AMI patients.[13,14] However, both potent $P2Y_{12}$ inhibitors were associated with a higher risk of major bleeding, and in case of prasugrel, no apparent benefit in patients over 75 years of age or with low body

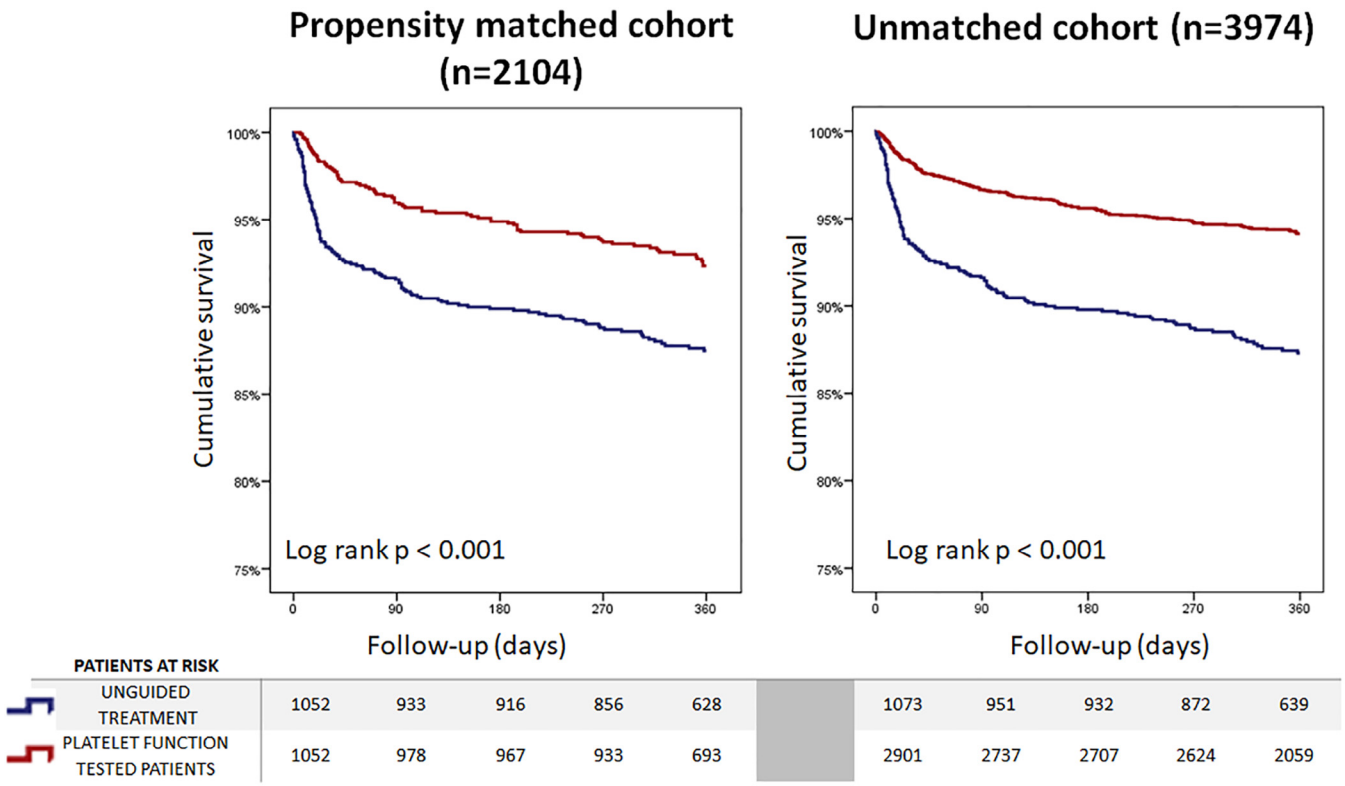


Figure 3. Kaplan–Meier curves of survival comparing platelet function test–guided versus unguided treated myocardial infarction cases assessed in the PS-adjusted sample and in the whole cohort.

Table 2
Clinical outcomes of platelet function test guided versus unguided patients

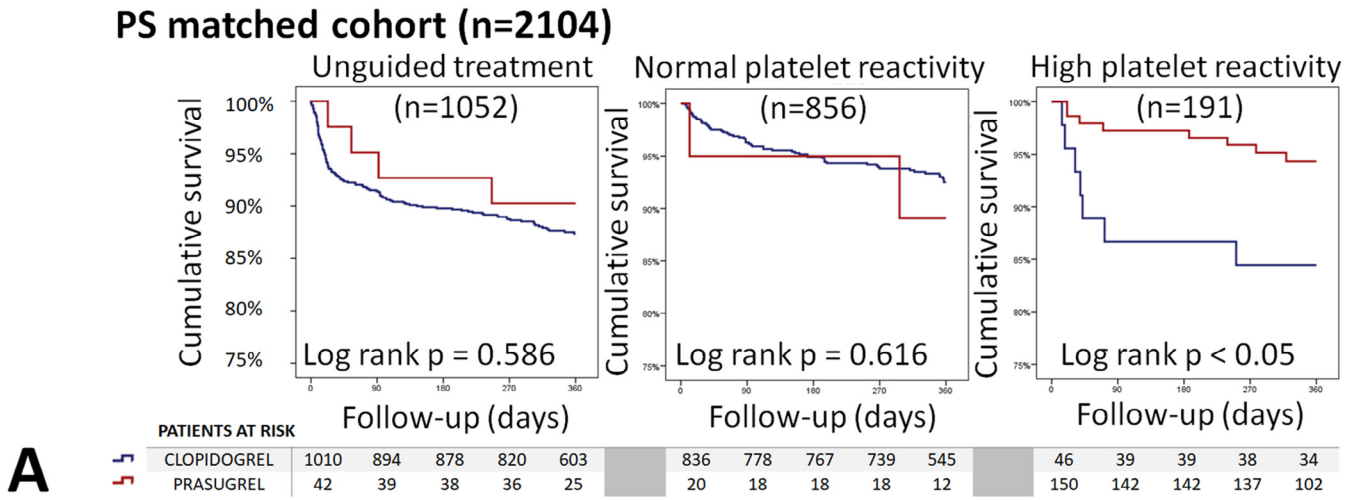
A. Propensity matched cohort (n = 2104)

	Nr. of patients (%)		Hazard Ratio [95% Confidence interval]
	Platelet function guided treatment (n = 1052)	Unguided treatment (n = 1052)	
Death from any cause	75 (7.1 %)	125 (11.9 %)	0.57 [0.43–0.77]***
Death from cardiovascular causes	66 (6.3 %)	104 (9.9 %)	0.61 [0.45–0.83]**
Repeated myocardial infarction	29 (2.8 %)	20 (1.9 %)	1.38 [0.78–2.44]
Stroke	8 (0.8 %)	8 (0.8 %)	0.95 [0.36–2.54]
Major adverse cardiac events (cardiovascular death, myocardial infarction, or stroke)	97 (9.2 %)	126 (12.0 %)	0.74 [0.57–0.96]*
Transfusion	74 (7.0 %)	67 (6.4 %)	1.01 [0.73–1.41]

B. Unmatched cohort (n = 3974)

	Platelet function guided treatment (n = 2901)	Unguided treatment (n = 1073)	Hazard Ratio [95% Confidence interval]
Death from any cause	163 (5.6 %)	129 (12.0 %)	0.44 [0.35–0.56]***
Death from cardiovascular causes	139 (4.8 %)	107 (10.0 %)	0.45 [0.35–0.58]***
Repeated myocardial infarction	71 (2.4 %)	20 (1.9 %)	1.22 [0.74–2.01]
Stroke	23 (0.8 %)	8 (0.7 %)	0.99 [0.44–2.21]
Major adverse cardiac events (cardiovascular death, myocardial infarction, or stroke)	218 (7.5 %)	129 (12.0 %)	0.59 [0.47–0.73]***
Transfusion	131 (4.5 %)	70 (6.5 %)	1.03 [0.92–1.64]

Data from Cox-regression analyses are presented as hazard ratio [95% Confidence interval], asterisks marks comparisons with p value * < 0.05, ** <0.01, and *** <0.001. Patients could have had more than one type of end point.



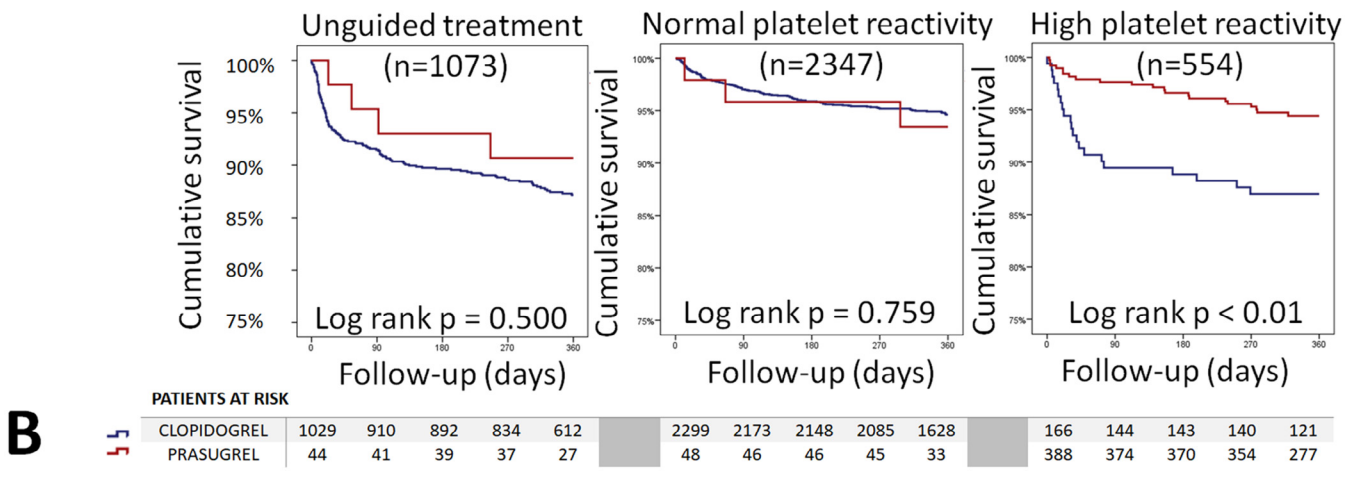


Figure 4. Kaplan–Meier curves depicting the outcome of patients with prasugrel or clopidogrel treatment in the strata of unguided treatment, HPRoC or no HPRoC. (*A*) Propensity-matched cohort (n = 2,104). (*B*) Unmatched cohort (n = 3,974).

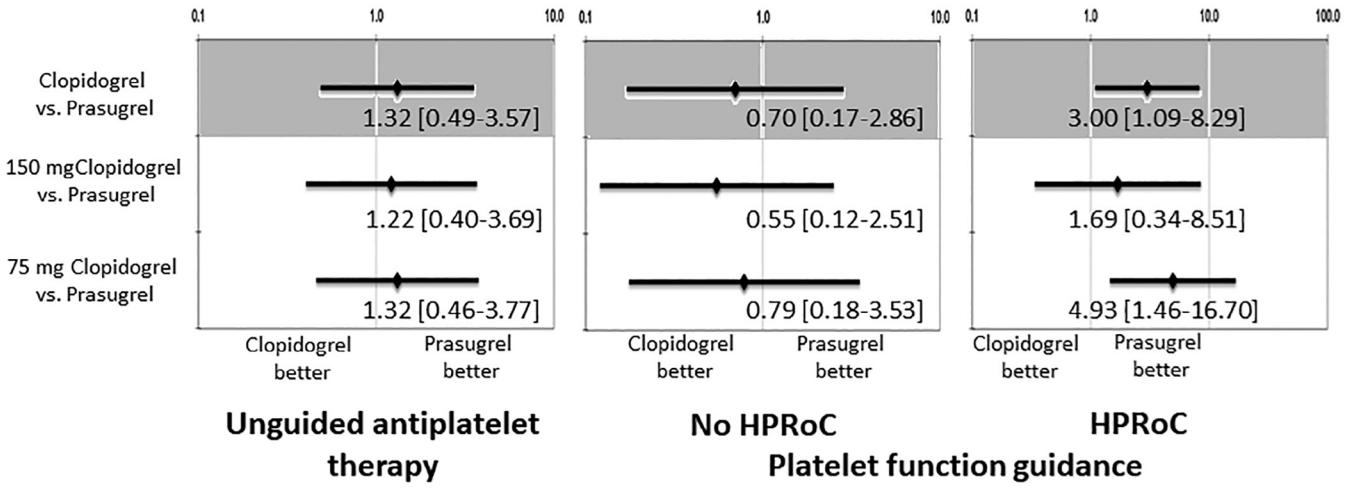


Figure 5. Subgroup analyses within the propensity-matched cohort according to platelet function test results. Forest plots depict HR and 95% CI of 1-year mortality according to the used $P2Y_{12}$ blocker. $P_{interaction} = 0.63$.

Table 3
Clinical, procedural, and pharmacological predictors of all-cause death at one year

Variable	Univariate Cox proportional hazard model	p-value	Multivariate Cox proportional hazard model	p-value
	Hazard Ratio [95% Confidence Interval]		Hazard Ratio [95% Confidence Interval]	
History of peripheral artery disease	2.79 [2.01–3.88]	<0.001	2.97 [2.11–4.18]	0.001
Smoker	1.59 [1.17–2.17]	0.003	1.74 [1.27–2.38]	0.001
Age (per 10 yrs increase)	1.56 [1.34–1.82]	<0.001	1.62 [1.38–1.90]	<0.001
Heart rate (per 10/min increase)	1.26 [1.18–1.34]	<0.001	1.25 [1.17–1.33]	<0.001
Systolic blood pressure (per 10 Hgmm increase)	0.85 [0.80–0.90]	<0.001	0.83 [0.78–0.88]	<0.001
Platelet function test guidance	0.57 [0.43–0.77]	<0.001	0.52 [0.39–0.69]	<0.001
Hypertension	1.24 [0.93–1.66]	0.149	1.56 [1.14–2.10]	0.005
Diabetes	1.57 [1.18–2.08]	0.002	1.55 [1.11–2.03]	0.005
Culprit artery: left main coronary	3.01 [1.80–5.02]	<0.001	2.01 [1.18–3.39]	<0.009
Diastolic blood pressure (per 10 mm Hg increase)	0.98 [0.93–1.03]	0.422	0.94 [0.88–1.00]	0.036
Male gender	0.92 [067-1.22]	0.545		
Hyperlipidaemia	0.83 [0.39–1.76]	0.626		
Prior myocardial infarction	0.98 [0.72–1.35]	0.910		
Prior of coronary bypass operation	1.09 [0.27–4.39]	0.905		
ST segment elevation myocardial infarction	1.27 [0.96–1.68]	0.102		
Prasugrel treatment	0.65 [0.38–1.11]	0.116		

weight was shown. These, together with the higher-treatment costs, still limit the clinical uptake of newer $P2Y_{12}$-receptor inhibitors in the routine.[3,15,16] Tailoring treatments based on biomarkers and genes is an emerging field in multiple areas of medicine. Studies of genetic testing may identify subjects with characteristics that may affect pharmacodynamic effects of clopidogrel, whereas theoretically, PFT could be useful in measuring the achieved platelet inhibition and guide the choice of the $P2Y_{12}$ inhibitor to reach an optimal range of platelet inhibition.[17,18] Genetic polymorphisms targeted by the tests may affect clopidogrel absorption, metabolism that has minor or no influence on new-generation $P2Y_{12}$ blockers' effects. In contrast, PFT is more subject to methodologic difficulties but reflect an actual state of platelet inhibition.[12,17–19] Importantly, 3 available randomized controlled trials failed to support the use of PFT to adjust treatment in patients undergoing coronary intervention.[2,20–22] Consequently the 2017 ESC–focused update document on dual antiplatelet therapy in coronary artery disease does not recommend the routine PFT to adjust antiplatelet therapy before or after elective stenting.[2]

From 2011, Hungarian health insurer reimbursed prasugrel for acute coronary syndrome patients undergoing coronary intervention who had either diabetes or AMI, but only in cases when PFT verified the clopidogrel nonresponder status. The reimbursement is independent from the genetic characteristics. This regulation practically acts as a prasugrel prescribing policy due to the high costs of unreimbursed prasugrel for patients and resulted in a high frequency of PFT screening. 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 case of HPRoC.[20] The ARCTIC study randomized patients to PFT-guided and unguided strategies, similar to our design. However, cases with ST segment elevation—similar to the GRAVITAS trial—were excluded. Importantly, interventions to overcome low responsiveness included complex pharmacologic strategies, but switching over to prasugrel was rarely used (9%).[21] In the ANTARCTIC acute coronary patients over 75 years received either 5 mg of prasugrel or PFT-guided therapy including 5 or 10 mg of prasugrel or 75 mg of clopidogrel according to the results of VerifyNow testing. Importantly, the ANTARCTIC study was mostly a step-down trial with 40% of the patients switched back to clopidogrel and only 4% scaled up to 10 mg of prasugrel.[22] Similar to ANTARCTIC, the recently published TROPICAL ACS trial also used a PFT-guided de-escalation approach based on the Multiplate (Roche Diagnostics GmbH) assay. In the trial, patients with AMI were randomized to universal prasugrel treatment or PFT-guided early de-escalation from prasugrel to clopidogrel if no HPRoC was detected. The TROPICAL ACS study is the first to support that a PFT-guided strategy is equally safe and effective as the guideline-recommended strategy.[23] Our registry recruited a high-risk, routine AMI cohort with patients including 55% ST-segment elevation and 45% AMI without ST-segment elevation applying 70% switchover rate to prasugrel. In this high-risk registry cohort, we could analyze predictors of mortality, resulting in strong statistical associations.

Although in the trial leading to the approval of prasugrel previous exposure to clopidogrel was an exclusion criterion for study entry, we have increasing amount of data regarding switching between antiplatelets.[3,13,24] In fact, switching occurs frequently in clinical practice for various reasons. Differences in pharmacology due to binding site, half-life, and speed of onset and offset of action differences may incite drug interactions. Studies have not raised any major concerns associated with the clopidogrel–prasugrel switch but consistently showed a decreased level of residual platelet reactivity.[24] The most relevant studies were the SWAP and the TRIPLET trials that included acute cases with results raising no concerns regarding prasugrel administration in clopidogrel-treated patients.[25,26] The recently published ESC–focused update on dual antiplatelet therapy in coronary artery disease also provides switching algorithms in case of clinical need.[2]

Our data originate from a nationwide, multicenter screening system using uniform whole-blood impedance aggregometry that strengthens the results; however, there remain important limitations to acknowledge. First, we have no information on how the individual decisions based on patient characteristics and logistics were made. Indeed, patients in whom PFT was performed differed in several features from the unguided patients. Although the exclusion of cases with absolute and relative contraindications to prasugrel and PS matching balanced significant differences observed between the PFT-guided and unguided groups, other, potentially uncontrolled variables may also exist that potentially influenced the choice of treatment. Keeping this limitation in mind, the statistically robust difference ($p < 0.001$) in the propensity-matched cohorts confirms the validity of the results. Second, we collected information regarding the clinical events using a payer's database that may not have been used as standardized definitions for a bleeding event, stent thrombosis, and myocardial infarction as usual in clinical trials. Furthermore, because ticagrelor was not available at the time of the study, it may restrict its generalizability. Third, in our prospective database we lack reliable information regarding the drug-compliance and later changes on medications, and we confined our analyses to intention-to-treat groups based on the discharge summaries of the index events.

Conclusions

Based on the results from an all-comer, high-risk cohort of a nationwide registry of AMI patients, 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 switchover 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 with standard- and high-dose clopidogrel.

Disclosures

Dr. Komócsi reports nonfinancial support from Eli Lilly and Company during the conduct of the study and personal fees from Eli Lilly and Company, Bayer Pharma AG, Pfizer, Krka, d. d., Merck & Co., Inc., and Servier outside of the submitted work.

Dr. Aradi reports personal fees from Roche Diagnostics, DSI/Lilly, AstraZeneca Krka, Bayer, Pfizer, and MSD outside of the submitted work. The other authors report no conflicts of interest.

1. Windecker S, Kolh P, Alfonso F, Collet J-P, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann F-J, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J* 2014;35:2541–2619.
2. Valgimigli M, Bueno H, Byrne RA, Collet J-P, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann F-J, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN, ESC Scientific Document Group, ESC Committee for Practice Guidelines (CPG), ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur Heart J* 2017;doi:10.1093/eurheartj/ehx503. [Epub ahead of print].
3. Bagai A, Peterson ED, McCoy LA, Effron MB, Zettler ME, Stone GW, Henry TD, Cohen DJ, Schulte PJ, Anstrom KJ, Wang TY. Association of measured platelet reactivity with changes in P2Y12 receptor inhibitor therapy and outcomes after myocardial infarction: insights into routine clinical practice from the treatment with ADP receptor inhibitors: longitudinal assessment of treatment patterns and events after acute coronary syndrome (TRANSLATE-ACS) study. *Am Heart J* 2017;187:19–28.
4. Aradi D, Tornyos A, Pintér T, Vorobcsuk A, Kónyi A, Faluközy J, Veress G, Magyari B, Horváth IG, Komócsi A. Optimizing P2Y12 receptor inhibition in patients with acute coronary syndrome on the basis of platelet function testing. *J Am Coll Cardiol* 2014;63:1061–1070.
5. Angiolillo DJ, Rollini F, Storey RF, Bhatt DL, James S, Schneider DJ, Sibbing D, So DYF, Trenk D, Alexopoulos D, Gurbel PA, Hochholzer W, De Luca L, Bonello L, Aradi D, Cuisset T, Tantry US, Wang TY, Valgimigli M, Waksman R, Mehran R, Montalescot G, Franchi F, Price MJ. International expert consensus on switching platelet $P2Y_{12}$ receptor–inhibiting therapies. *Circulation* 2017;136:1955–1975.
6. Stone GW, Witzenbichler B, Weisz G, Rinaldi MJ, Neumann F-J, Metzger DC, Henry TD, Cox DA, Duffy PL, Mazzaferri E, Gurbel PA, Xu K, Parise H, Kirtane AJ, Brodie BR, Mehran R, Stuckey TD, ADAPT-DES Investigators. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. *Lancet* 2013;382:614–623.
7. Aradi D, Komócsi A, Vorobcsuk A, Rideg O, Tőkés-Füzesi M, Magyarlaki T, Horváth IG, Serebruany VL. Prognostic significance of high on-clopidogrel platelet reactivity after percutaneous coronary intervention: systematic review and meta-analysis. *Am Heart J* 2010;160:543–551.
8. Aradi D, Kirtane A, Bonello L, Gurbel PA, Tantry US, Huber K, Freynhofer MK, ten Berg J, Janssen P, Angiolillo DJ, Siller-Matula JM, Marcucci R, Patti G, Mangiacapra F, Valgimigli M, Morel O, Palmerini T, Price MJ, Cuisset T, Kastrati A, Stone GW, Sibbing D. Bleeding and stent thrombosis on $P2Y_{12}$ -inhibitors: collaborative analysis on the role of platelet reactivity for risk stratification after percutaneous coronary intervention. *Eur Heart J* 2015;36:1762–1771.
9. Janosi A, Ofner P, Forster T, Edes I, Toth K, Merkely B. Clinical characteristics, hospital care, and prognosis of patients with ST elevation myocardial infarction: Hungarian myocardial infarction registry. *Eur Hear J Suppl* 2014;16:A12–A15.
10. Jánosi A, Ofner P, Merkely B, Polgár P, Zámolyi K, Kiss RG, Édes I, Csapó K, Nagy L, Lupkovics G, Herceg B, Tomcsányi J, László Z, Vértes A, Simon J, Katona A, Juhász F, Bajkó F, Varjú I, Dinya E. Short and long term prognosis of patients with myocardial infarction. Hungarian Myocardial Infarction Registry. *Orv Hetil* 2013;154:1297–1302.
11. Komócsi A, Simon M, Merkely B, Szűk T, Kiss RG, Aradi D, Ruzsa Z, Andrássy P, Nagy L, Lupkovics G, Kőszegi Z, Ofner P, Jánosi A. Underuse of coronary intervention and its impact on mortality in the elderly with myocardial infarction. A propensity-matched analysis from the Hungarian Myocardial Infarction Registry. *Int J Cardiol* 2016;214:485–490.
12. Aradi D, Storey RF, Komócsi A, Trenk D, Gulba D, Kiss RG, Husted S, Bonello L, Sibbing D, Collet J-P, Huber K, Working Group on Thrombosis of the European Society of Cardiology. Expert position paper on the role of platelet function testing in patients undergoing percutaneous coronary intervention. *Eur Heart J* 2014;35:209–215.
13. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann F-J, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM, TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;357:2001–2015.
14. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, PLATO Investigators, Freij A, Thorsén M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045–1057.
15. Bueno H, Sinnaeve P, Annemans L, Danchin N, Licour M, Medina J, Pocock S, Sánchez-Covisa J, Storey RF, Jukema JW, Zeymer U, Van de Werf F, EPICOR Investigators. Opportunities for improvement in antithrombotic therapy and other strategies for the management of acute coronary syndromes: insights from EPICOR, an international study of current practice patterns. *Eur Heart J Acute Cardiovasc Care* 2016;5:3–12.

16. Sherwood MW, Wiviott SD, Peng SA, Roe MT, Delemos J, Peterson ED, Wang TY. Early clopidogrel versus prasugrel use among contemporary STEMI and NSTEMI patients in the US: insights from the National Cardiovascular Data Registry. *J Am Heart Assoc* 2014;3:e000849.
17. Angiolillo DJ, Ferreiro JL, Price MJ, Kirtane AJ. Platelet function and genetic testing. *J Am Coll Cardiol* 2013;62:S21–S31.
18. Gajda SN, Kołtowski Ł, Tomaniak M. Most recent evidence behind aggregometry and genotyping methods as platelet function testing for tailored anti-platelet treatment among PCI patients. *Adv Clin Exp Med* 2015;24:687–693.
19. Rideg O, Komócsi A, Magyarlaki T, Tőkés-Füzesi M, Miseta A, Kovács GL, Aradi D. Impact of genetic variants on post-clopidogrel platelet reactivity in patients after elective percutaneous coronary intervention. *Pharmacogenomics* 2011;12:1269–1280.
20. Price MJ, Endemann S, Gollapudi RR, Valencia R, Stinis CT, Levisay JP, Ernst A, Sawhney NS, Schatz RA, Teirstein PS. Prognostic significance of post-clopidogrel platelet reactivity assessed by a point-of-care assay on thrombotic events after drug-eluting stent implantation. *Eur Heart J* 2008;29:992–1000.
21. Collet J-P, Cuisset T, Rangé G, Cayla G, Elhadad S, Pouillot C, Henry P, Motreff P, Carrié D, Boueri Z, Belle L, Van Belle E, Rousseau H, Aubry P, Monségu J, Sabouret P, O'Connor SA, Abtan J, Kerneis M, Saint-Etienne C, Barthélémy O, Beygui F, Silvain J, Vicaut E, Montalescot G, ARCTIC Investigators. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. *N Engl J Med* 2012;367:2100–2109.
22. Cayla G, Cuisset T, Silvain J, Leclercq F, Manzo-Silberman S, Saint-Etienne C, Delarche N, Bellemain-Appaix A, Range G, El Mahmoud R, Carrié D, Belle L, Souteyrand G, Aubry P, Sabouret P, du Fretay XH, Beygui F, Bonnet J-L, Lattuca B, Pouillot C, Varenne O, Boueri Z, Van Belle E, Henry P, Motreff P, Elhadad S, Salem J-E, Abtan J, Rousseau H, Collet J-P, Vicaut E, Montalescot G, ANTARCTIC Investigators. Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial. *Lancet* 2016;388:2015–2022.
23. Sibbing D, Aradi D, Jacobshagen C, Gross L, Trenk D, Geisler T, Orban M, Hadamitzky M, Merkely B, Kiss RG, Komócsi A, Dézsi CA, Holdt L, Felix SB, Parma R, Klopotowski M, Schwinger RHG, Rieber J, Huber K, Neumann FJ, Koltowski L, Mehilli J, Huczek Z, Massberg S, TROPICAL-ACS Investigators. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. *Lancet* 2017;390:1747–1757.
24. Rollini F, Franchi F, Angiolillo DJ. Switching P2Y12-receptor inhibitors in patients with coronary artery disease. *Nat Rev Cardiol* 2016;13:11–27.
25. Angiolillo DJ, Saucedo JF, DeRaad R, Frelinger AL, Gurbel PA, Costigan TM, Jakubowski JA, Ojeh CK, Effron MB, SWAP Investigators. Increased platelet inhibition after switching from maintenance clopidogrel to prasugrel in patients with acute coronary syndromes. *J Am Coll Cardiol* 2010;56:1017–1023.
26. Diodati JG, Saucedo JF, French JK, Fung AY, Cardillo TE, Henneges C, Effron MB, Fisher HN, Angiolillo DJ. Effect on platelet reactivity from a prasugrel loading dose after a clopidogrel loading dose compared with a prasugrel loading dose alone: transferring from clopidogrel loading dose to prasugrel loading dose in acute coronary syndrome patients (TRIPLET). *Circ Cardiovasc Interv* 2013;6:567–574.