Investigation of the efficacy and safety issues of antithrombotic treatment in cardiovascular medicine

Ph.D. thesis

by

Alexandra Bálint MD

Pécs

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LIST OF ABBREVIATIONS

ACS: acute coronary syndrome

ADP: adenosine diphosphate

AF: atrial fibrillation

AMI: acute myocardial infarction

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 ACS 2–Thrombolysis In Myocardial Infarction 51 trial

AUGUSTUS: A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart

BARC bleeding definition: Bleeding Academic Research Consortium

BMI: Body Mass Index

CABG: Coronary Artery Bypass Graft

CAD: Coronary Artery Disease

CHD: Coronary Heart Disease

CI: Confidence Interval

CIF: Cumulative Incidence Function

CNMA: Component Network Meta-Analysis

COMPASS: Cardiovascular OutcoMes for People Using Anticoagulation StrategieS

CVE: CardioVascular Event

DALYs: Disability Adjusted Life Years

DAPT: Dual Antiplatelet Therapy

DES: Drug Eluting Stent

DOAC: Direct Oral AntiCoagulant

EMBASE: Excerpta Medica database

GUSTO bleeding definition: Global Strategies for Opening Occluded Coronary Arteries

HPR: High Platelet Reactivity

HR: Hazard Ratio

HUMIR: Hungarian Myocardial Infarction Registry

IPA: Inhibition of Platelet Aggregation

ISTH bleeding definition: International Society for Thrombosis and Hemostasis

LD: Loading Dose

LPR: Low Platelet Reactivity

MACE: Major Adverse Cardiovascular Event

MACCE: myocardial infarction, major cerebral or cardiovascular event

MEDLINE: Medical Literature Analysis and Retrieval System Online, National Library of Medical Publications

MD: Maintenance Dose

MD: Mean Difference

MI: Myocardial Infarction

NMA: Network Meta-Analysis

DOAC: Direct Oral AntiCoagulant

NPR: Normal Platelet Reactivity

NVAF: non-valvular atrial fibrillation

OAC: Oral AntiCoagulation

PAD: peripheral artery disease

PCI: percutaneous coronary intervention

PIONEER-AF PCI: Prevention of bleeding in patients with AF undergoing PCI trial

PLATO bleeding definition: Platelet Inhibition and Patient Outcomes

PRI: Platelet Reactivity Index

PROBAST: Prediction model Risk Of Bias Assessment Tool

PROSPERO: International Prospective Register of Systematic Reviews

PRU: Platelet Reactivity Unit

PS: Propensity Score

RCT: Randomized Controlled Trial

REACH: REduction of Atherothrombosis for Continued Health registry

RE-DUAL PCI: Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation trial

RR: Relative Risk, Risk Ratio

SCAD: stable coronary artery disease

ST: stent thrombosis

SOCRATES: Acute Stroke Or Transient IsChaemic Attack TReated With Aspirin or Ticagrelor and Patient OutcomES

SUCRA: Surface Under the Cumulative RAnking curve

TASS: Ticlopidine Aspirin Stroke Study

TAVI: Transcatheter Aortic Valve Implantation

TAT: Triple Antithrombotic Therapy

THALES trial: The Acute Stroke or Transient Ischaemic Attack Treated with Ticagrelor and ASA for Prevention of Stroke and Death

TIA: Transient Ischemic Attack

TIMI bleeding definition: Thrombolysis In Myocardial Infarction

TRIOLOGY ACS: Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome Subjects trial

TRITON TIMI-38: Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction

VASP-P: VAsodilator-Stimulated Phospho Protein

VKA: Vitamin-K Antagonist

WOEST trial: What is the Optimal antiplatElet & Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary StenTing trial

1. PROLOGUE

1.1. Coronary artery disease

Heart disease is a major cause of death and disability in developed countries. One common type of the heart disease is called coronary heart disease (CHD), sometimes referred to as coronary artery disease (CAD). CAD is the foremost single cause of mortality and loss of Disability Adjusted Life Years (DALYs) globally[1]. A large number of this burden falls on low- and middle-income countries accounting for nearly 7 million deaths and 129 million DALYs annually. The coronary arteries supply blood flow to the heart muscle. Plaque damages the coronary arteries, and blood platelets can accumulate to these damaged areas, causing blockage of blood flow. This can lead to ischemia or acute coronary syndrome (ACS). ACS is a life-threatening, disabling medical condition that affects more than 22.000 patients over the age of 20 years in Hungary.[2] Rupture of an atherosclerotic plaque that results in partial or complete occlusion of an epicardial coronary artery causing imbalance between the oxygen supply and demand, is the most common mechanism responsible for ACS. Plaque disruption exposes subendothelial collagen, which results in activation of platelets and the coagulation cascade, leading to thrombus formation and myocardial infarction (MI). Therefore, platelet inhibition therapy plays a key role in the treatment and secondary prevention of acute myocardial infarction (AMI).[3]

1.2. Effect on clinical endpoints achieved by platelet aggregation inhibitors

Antiplatelet therapy represents the cornerstone treatment and secondary prevention of CAD. Compared with placebo, antiplatelet therapy has been shown to reduce recurrent major adverse cardiovascular events (MACE) among patients with stable CAD or ACS.[4] Patients with ACS undergoing percutaneous coronary intervention (PCI) with drug-eluting stents (DES) are currently recommended dual antiplatelet therapy (DAPT), consisting of aspirin (acetylsalicylic acid, ASA) with a P2Y12 receptor (also known as adenosine diphosphate (ADP)-receptor) inhibitor for at least 12 months.[5–8] The pharmacological mechanism of action of platelet aggregation inhibitors is the inhibition of thrombocyte activation and/or impeding aggregation. The treatment goal is preventing thrombotic complications such as stent thrombosis.[9] However, this strategy increases bleeding risk even in patients with a high thrombotic risk of ACS.[10–12]

Furthermore, the degree of the achieved platelet inhibition, as adjudged based on the on-treatment residual platelet reactivity may be variable. Specifically, important inter-individual variability in the response to ADP antagonist therapy has been observed with a potential impact on the clinical outcomes. Patients with a low response to clopidogrel i.e. with high-on clopidogrel platelet reactivity have a higher risk of ischemic adverse events.[13–15] Some reports found another tendency in patients with low-on clopidogrel platelet reactivity toward propensity for bleeding events, however, this was not invariable in all reports.[16–18] Lines of evidence support that the risk represented by the degree of platelet inhibition is more expressed in high-risk individuals, like those who experienced a recent MI.[19,20] The choice of optimal DAPT regimen and duration for patients with CAD requires a tailored approach based on the patient clinical presentation, baseline risk profile and management strategy.

1.3. Aspects of combined treatment of anticoagulation and platelet aggregation inhibitor therapy

Non-valvular atrial fibrillation (NVAF) is the most commonly diagnosed heart rhythm abnormality. In Hungary, it is estimated that approximately 200,000 adults over the age of 65 have NVAF and it occurs in every 10th person over the age of 70.[21] NVAF is also an independent risk factor for ischemic stroke severity, recurrence, and mortality.[22,23] Anticoagulation is required for the prevention of thrombo-embolic complications related to NVAF.[23] Over the past decade, novel direct oral anticoagulants (DOACs), dabigatran, rivaroxaban, apixaban and edoxaban have become the treatment of choice in patients with NVAF over warfarin.[24]

However, estimates suggest that about 30% of patients with NVAF may have simultaneously CAD and 15% will require PCI with stent placement to treat obstructive coronary artery disease during their lifetimes.[25]

Furthermore, the optimal antithrombotic regimen after PCI in patients with NVAF is still unclear. Oral anticoagulation (OAC) is indicated for stroke prevention whereas DAPT is given for the prevention of stent thrombosis. On the other hand, the combination of OAC and DAPT, also known as triple antithrombotic therapy (TAT), comes with a price of a considerably increased risk of major bleeding and mortality.[26] Identifying an optimal antithrombotic regimen to prevent bleeding and ischemic events presents an unmet challenge to physicians treating patients with NVAF.

2. AIMS

The main aims of our studies were the following:

- to evaluate the significance of low platelet reactivity on adverse cardiovascular events
- to investigate the safety and efficacy outcomes of oral anticoagulation and dual antiplatelet therapy after percutaneous coronary intervention
- to compare the safety and efficacy outcomes of ticagrelor with other P2Y12 receptor inhibitors and/or aspirin in the treatment of high-risk patients in secondary stroke prevention

This PhD thesis is based on 3 studies. The first study is a meta-analysis of observational and randomized controlled trials (RCT). The second study is a propensity score matched survival analysis of the prospective Hungarian Myocardial Infarction Registry (HUMIR) collecting clinical data on consecutive patients treated for AMI in Hungary. The third study is based on a network meta-analysis (NMA) of RCTs.

3. BACKGROUND

3.1. Risk of adverse events associated with low platelet reactivity in patients with percutaneous coronary intervention

Clopidogrel used to be the gold standard antiplatelet agent before the introduction of new more potent P2Y12 inhibitors, such as ticagrelor and prasugrel, which demonstrated their clinical advantage in large randomized controlled trials involving ACS patients. Both prasugrel and ticagrelor provide more effective inhibition of platelet function than aspirin, however, their use was followed by an increased bleeding risk. [7,27]

Platelet function testing provides information on individual response to antiplatelet drugs and platelet reactivity that has been associated with a strong correlation to clinical outcomes after ACS.[28,29] Several studies have found a strong relationship between high platelet reactivity (HPR) and increased risk of thrombotic events.[30,31]

With the use of more effective agents the prevalence of HPR has decreased and an increasing proportion of patients have low on-treatment ADP reactivity. However, the clinical significance of low platelet reactivity (LPR) is less well established and it is not measured routinely.

This study demonstrated increased risk of major and minor bleeding events with LPR while patients with LPR had lower risk of non-fatal MI and the composite endpoint of serious vascular events while mortality remained insignificant between the two groups.[32]

3.2. Oral anticoagulation and outcomes in patients with acute myocardial infarction

In patients with NVAF and ACS in addition to antiplatelet therapy anticoagulation is required. The possible drawbacks of this combination have been well studied in patients with AF. [33,34] Specific considerations regarding patients with AF undergoing PCI include the fact that DAPT is essential to prevent stent thrombosis, but insufficient for stroke prevention.[35] Besides that, OAC treatment is necessary for stroke prevention; however, it is unable to provide adequate prevention for new coronary events.[34–36]

Antiplatelets on top of OAC significantly increases the risk of bleeding complications, therefore long-term triple therapy should be avoided.[37,38]

Recently, several trials attempting to optimize the adjunctive pharmacotherapy with direct OACs based protocols were published showing a reduction of bleeding complications.[39,40] Most of these trials were underpowered for ischemic endpoints, and the addition of a P2Y12 inhibitor or aspirin to an OAC showed no significant impact on efficacy. Due to the lack of data on high-risk ACS patients the generalizability of AMI treatment remains unclear. [41]

This study showed that the seemingly higher risk of all-cause mortality and MACE, in patients with AMI who have undergone PCI and treated with concomitant DAPT and were on oral anticoagulation therapy, may be attributable to inherently higher risk of these cases.[41]

3.3. Comparison of ticagrelor treatment with platelet aggregation inhibitors in high-risk patients in secondary stroke prevention

Stroke is ranked as the second leading cause of death worldwide with a mortality rate of 5.5 million per year. For patients who have suffered an ischemic stroke, antiplatelet therapy is also important for secondary prevention.[42] Platelet aggregation plays an important role in the mechanisms of stroke; therefore, antiplatelet therapy interferes with the evolution of these events exerting important preventive capability. According to some recent data ticagrelor might show favorable outcomes in stroke prevention in high-risk patient population.[43] Most recently the The Acute Stroke or Transient Ischaemic Attack Treated with Ticagrelor and ASA for Prevention of Stroke and Death (THALES) trial further supported the potential of ticagrelor and aspirin in stroke prevention. In this trial, combined antiplatelet therapy with ticagrelor resulted in a significant, 17% relative reduction of stroke in patients with mild-to-moderate acute non-cardioembolic ischemic stroke.[44]

Importantly, evidence supports that the intensified or combined antiplatelet therapy is also associated with an increased risk of bleeding that may have an important impact on the risk-benefit relations of these therapies.[45]

This NMA demonstrated benefits of ticagrelor plus aspirin treatment on secondary prevention in patients with vascular risk factors with the significant reduction of ischemic stroke by 20%. While the risk of bleeding, including intracranial bleeding increased. There was no considerable difference in the risk of mortality with ticagrelor on top of aspirin.[46]

4. METHODS

4.1. Risk of adverse events associated with low platelet reactivity in patients with percutaneous coronary intervention

A manual search of medical literature was performed in the National Library of Medical Publications (MEDLINE), Excerpta Medica Database (EMBASE) and Cochrane Library for relevant articles on LPR until Nov 2020. No language restriction was used. Our PICO format included the following terms: (P) patients with ACS and/or undergoing PCI and receiving DAPT consisting of aspirin and clopidogrel, prasugrel or ticagrelor, (I) LPR (C) non-LPR or HPR based on measurement of on-treatment platelet reactivity defined by an ADP-specific platelet function assay and (O) major adverse cardiac events (MACE) and bleeding.

The non-LPR group consisted of HPR or HPR plus normal platelet reactivity (NPR) where data was given for NPR. The clinical outcomes of interest, evaluated at the longest available follow-up of ADP-receptor inhibitor treatment were (a) major bleeding events (defined using the trials internal definitions using Bleeding Academic Research Consortium (BARC 3-5) or Thrombolysis In Myocardial Infarction (TIMI) major criteria), and (b) minor bleeding events (BARC 1-2 or TIMI minor) (16), (c) definite/probable stent thrombosis (ST), (d) non-fatal MI (type 1, 4a, 4b), (e) a composite endpoint of the reported serious vascular events that included cardiovascular death, non-fatal MI or non-fatal stroke, (f) repeated target vessel revascularization, and (g) all-cause mortality.

Studies that assessed responsiveness to clopidogrel, that is a difference between baseline and posttreatment PR (inhibition of platelet aggregation [IPA]), were disregarded. The review protocol was registered in the PROSPERO (International Prospective Register of Systematic Reviews) database a priori under the registration number of CRD42019136393.

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 relevant full texts systematically for eligibility. Disagreements between reviewers were solved by consensus. Unpublished data and meeting abstracts were not considered for the present analysis because results could not be considered as certain and definitive.

The primary endpoint of the analysis was the frequency of major bleeding. All-cause mortality, cardiovascular death, non-fatal MI, stent thrombosis, non-fatal stroke, major plus minor bleeding and repeated target vessel revascularization were defined as secondary endpoints. Both MI and major bleeding were defined according to the internal definitions of the studies. If multiple major bleeding definitions were used, we extracted TIMI major bleeding[47] and BARC[48] major bleeding if available.

Statistical computations were performed using R (v 4.0.03) package 'dmetar' designed for the evaluation of meta-analyses and OpenMeta[Analyst] open source statistical software.[49,50] A random-effect model was applied at all the analyses with DerSimonian-Laird estimation to derive risk ratios (RR) on dichotomous outcomes and weighted mean difference on continuous data with 95% confidence interval. Heterogeneity was tested with chi^2 heterogeneity statistic for which a p-value <0.1 was considered potentially heterogenous. Consistency was assessed using I^2 statistics.[51] Sensitivity analyses were carried out omitting one study at a time and calculating the effect size with the 95% CI to investigate the influence a single study has on the final estimation regarding LPR with increased bleeding risk.

The methodological qualities of the studies were assessed using PROBAST (Prediction model Risk Of Bias Assessment Tool) for assessing the quality of cohorts and the Newcastle-Ottawa Scale with reference to observational studies.[52,53] Publication bias was estimated using funnel plots. Visual evaluation and Egger's regression intercept were used to the check for asymmetry.

4.2. Oral anticoagulation and outcomes in patients with acute myocardial infarction

Data were analyzed from the HUMIR to identify and follow patients after an index event of PCI during the treatment of an AMI. The HUMIR is a prospective registry collecting clinical data on consecutive patients treated for an AMI in Hungary. The data of the patients are collected prospectively according to the statute of CCXLVI./2013 of Hungary via a national internet-based registry.[2,54,55] Data capture covers 178 structured categories including those regarding the performed coronary interventions. Data capture covers 178 structured categories including those regarding the performed coronary interventions. 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 study protocol was approved and the need for informed consent was waived by the Scientific Council for Health, Scientific and Research Ethics Committee, Budapest, Hungary (ETT TUKEB 34858-3/2019/EKU). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

With the intention of analysis, AMI patients (both with or without ST-segment elevation) receiving coronary stent were eligible for enrolment between 1st Jan 2014 and 31st Dec 2017. We created two treatment groups were based on the discharge medication; forming a patient group of anticoagulated cases (OAC group) and a control group of cases without anticoagulation.

The primary efficacy endpoint was all-cause mortality within one year after the index procedure. Secondary endpoints included the transfusion and the composite endpoints of major adverse events (MACE) defined as mortality, non-fatal myocardial infarction (MI) type 1 according to the fourth universal definition of MI,

or stroke.[56] 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.

A propensity score (PS) matched cohort with comparable risk profiles by adjusting for differences in baseline characteristics was built in order to provide an unbiased comparison. For comparisons across different treatment regimens, we applied a PS-adjusted approach.[57] PS was computed by using a logistic regression model for OAC versus control groups where besides age (scale) and gender (category), history of congestive heart failure, hypertension, stroke, diabetes, and vascular disease (e.g. MI, stroke, or peripheral artery disease (PAD)) was entered as categorical variables and were used as predictors. The majority of cases with OAC had AF. As in our aims, PS should reflect the probability of being treated with anticoagulation, the parameters were selected to provide an analogy to the elements of the CHA_2DS_2-VASc score. To isolate the effect of comorbidities from that of arrhythmia, sensitivity analyses with creating an alternative control group (Control B) using the PS score but excluding non-anticoagulated AF patients from pairing as well as a subgroup analysis of AF patients were performed. Cox regression models were used to calculate hazard ratios. To control the potential influence of competing risk, transfusion outcome analyses were supplemented by computing cumulative incidence function (CIF) to show the probability of each event and Gray's test to estimate the difference in the CIF between groups. P-values of <0.05 were considered to indicate statistical significance. The analyses were conducted using the IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA) statistical package and with the 'cmprsk' package in R.[58]

4.3. Comparison of ticagrelor treatment with platelet aggregation inhibitors in high-risk patients in secondary stroke prevention

We performed a systematic review of the available literature in accordance with the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions and the review protocol was registered with PROSPERO under the number of CRD42020170746. Data were collected from MEDLINE®, Cochrane Collaboration of Clinical Trials®, and EMBASE® until 1st Aug 2020 from articles reporting randomized clinical trials with ticagrelor antiplatelet therapy. No language restriction was applied. The query included the following search terms: 'ticagrelor', 'AZD 6140' and 'stroke' using the 'AND' Boolean operator.

In the analysis studies were included that fulfilled the following criteria: (1) RCTs, (2) assessing the clinical efficacy and/or safety of an antiplatelet regime including ticagrelor alone or as part of a DAPT strategy with ticagrelor plus aspirin, and (3) reported on the occurrence of stroke in minimum duration of 30 days (4) in patients with cerebrovascular, coronary or peripheral artery disease. Studies were excluded if any of the following criteria were applied: (1) non-randomized studies, (2) single-arm studies, (3) outcomes of interest were not reported or were impossible to extract or calculate from published results, (4) comparing merely the biological efficacy of the antiplatelet treatment, or (5) duplicate publications. 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. 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.

For definitions of stroke, the internal definitions of the included trials were used if compliant with focal loss of neurologic function caused by an ischemic or hemorrhagic event, with residual symptoms lasting at least 24 hours or leading to death.

The primary efficacy outcome of our analysis was the occurrence or recurrence of stroke including ischemic or hemorrhagic forms. Major bleeding and all-cause mortality were assessed as main safety endpoints. Secondary outcomes included the individual endpoints of ischemic stroke, hemorrhagic stroke, and TIA, MI, major cerebral or cardiovascular event (MACCE) defined as the composite of death, MI and stroke, and cardiovascular death. Additionally, data of disabling stroke (defined as death or Rankin scale >1) were also collected. Furthermore, safety outcomes as the frequency of major and minor bleeding complications and intracranial bleeding were also evaluated. In the case of the availability of multiple major bleeding definitions, we extracted TIMI major bleeding. The data from the intention to treat analyses were extracted and the endpoints of interest were collected until the longest follow-up available.

The methodological qualities of the studies were also assessed using the Cochrane Collaboration tool for assessing the quality of RCTs. Considering that different control groups were used by the trials for comparing outcomes of ticagrelor-medicated patients and that the study arms included combinations as well as monotherapy with different antiplatelets we prespecified the use of multiple treatment NMA supplemented with component NMA (CNMA) modeling.

At the first level, each potential antiplatelet combination was entered as an individual study arm, and data were pooled in a multiple treatment NMA that allows integration of direct and indirect comparisons. We calculated the risk ratio (RR) and its standard error using a frequentist approach to construct an NMA model accounting for the correlated treatment effects.[59] A random-effects model was applied by adding the estimated heterogeneity to the variance of each comparison using an adaptation of the DerSimonian-Laird estimator. The choice of the random-effects model was made based on the consideration that the true preventive effect of antithrombotic treatment may vary from study to study influenced by the heterogeneity of the included trials.

Values of I^2 representing the amount of inconsistency and Cochran's Q statistics and its corresponding p-value measuring the heterogeneity in the network were also calculated. A special case encountered in our network was that treatment arms may be combinations of other treatments or have common components. Therefore, the influence of individual components was intended to be evaluated in an additive model assuming that the effect of treatment combinations is the sum of the effects of its components.[59]

For easier interpretation, effect sizes are depicted in the forms of forest plots with aspirin set as reference. Furthermore, a comparative ranking of the treatments according to the P-scores method (a frequentist analog of SUCRA was conducted.[60]

The assumption of consistency that the direct evidence in a network for the effect size between two treatments does not differ from the indirect evidence was assessed by net heat plots as well as by net-splitting. The latter method splits our network estimates into the contribution of direct and indirect evidence, which allows controlling for inconsistency in specific comparisons.

To assess publication bias, a comparison-adjusted funnel plot, an extension of the common funnel plot in cases of multiple treatment comparisons was used displaying Eggers' test results in support[61] with the additional use of the Cochrane Collaborations assessment tool.

The clustering of the treatment arms was assessed using the estimated RR compared to aspirin in the nearest neighbor analysis. An explorative analysis was performed to assess the potential impact of background risk on the estimated treatment effect. Within this risk of stroke of the study population using clopidogrel plus aspirin therapy was calculated and this continuous variable was used to construct regressor in a Bayesian meta-regression analysis. Additional analyses exploratory analyses included stratification and subgrouping based on the included patient population, multilevel meta-analysis as well as multivariate meta-analysis of direct comparisons using structural equation modeling.

All calculations were performed with the R statistical software package version 3.6.3 (R Development Core Team, 2010) software using the packages ‘meta 4.11-0’, 'netmeta 1.2-0', and ‘gemtc 0.8-4. A p-value < 0.05 was considered to represent statistical significance.

5. RESULTS

5.1. Risk of adverse events associated with low platelet reactivity in patients with percutaneous coronary intervention

Twenty studies involving 19 076 (range: 107-6 267) patients were analyzed. There were 18 observational and 2 RCTs investigating the effect of LPR on clinical outcomes in patients with PCI intervention. The main characteristics of the included studies are shown in Table 1. Most of the patients had ACS[62,63,72,73,64–71], in 4 studies patients with stable CAD[16,30,74,75] were included and in 4 studies both stable CAD and ACS[76–79] patients were followed. Dose of the antiplatelet medication was different as follows: 600 mg loading dose (LD) and 75 mg maintenance dose (MD) up to 150 mg MD; and 300 mg LD plus 75 mg MD for clopidogrel; 60 mg LD or 10 mg MD for prasugrel in one case 20 mg LD and 3.75 mg MD was used[79]; ticagrelor was reported in 1 study[71] with 180 mg LD and 90 mg MD. Study definitions of bleeding were discrepant (Table 1).

Study name/ First author (Publication year)	Follow-up (months)	Patient number	Antiplatelet (LD/ MD, mg)	Clinical setting	Clinical endpoint	Platelet function test	Selected cutoff for LPR	LPR N (%)	Definition of bleeding
Kabbani (2003)	12	112	clopidogrel (300/75)	sCAD	MI UREV RREV	flow cytometry	pGP IIb/IIIa act ≤ 24.9%	56 (50)	NR
ARMYDA-PRO/ Patti (2008)	1	160	clopidogrel (600/75)	ACS	MACE MI, TVR	Verify Now	lowest quartile	40 (25)	BARC
ISAR/Sibbing (2010)	1	2533	clopidogrel (600/75)	CAD	bleeding	MEA	188 AU x min	975 (38.5)	TIMI
Tsukahara (2010)	16	184	clopidogrel (300/75)	ACS	ST bleeding	WBA-neo	PATI >28 µmol/L	46 (25)	BARC
Huczek (2011)	1	374	clopidogrel (600/75)	ACS	bleeding D, MI	Verify Now	PRU≤150	124 (33)	TIMI
ARMYDA-BLEEDS/Patti (2011)	1	310	clopidogrel (600/75)	SA NSTEMI MI	major bleeding	Verify Now	lowest quartile	77 (24.8)	BARC
Bonello (2012)	12	301	clopidogrel (60 LD)	ACS	ST bleeding	VASP-P	PRI<16%	84 (27.9)	TIMI
Cuisset (2012)	1	107	clopidogrel (600/75) prasugrel (10 MD)	ACS	ST MI TVR bleeding	VASP-P	PRI<20%	23 (21.5)	BARC
ARMYDA-PROVE/Mangiacapra (2012)	1	732	clopidogrel (600/75)	SA	D, MI, TVR, bleeding	Verify Now	PRU≤178	248 (33.9)	TIMI
POBA/Cuisset (2013)	6	1542	clopidogrel (600/75, 600/150, 60 LD) prasugrel (10 MD)	NSTEMIS TEMI	ST bleeding	VASP-P	PRI≤10%	69 (4.5)	BARC
Mangiacapra (2014)	1	800	clopidogrel (600/75)	sCAD NSTEMI	ST bleeding ST, TVR, D	Verify Now	PRU≤ 178	272 (34.0)	TIMI
APACHE/ Alfredsson (2015)	6	113	clopidogrel (600/75)	NSTEMI STEMI	D, MI, stroke bleeding	MEA	AUC*min≤ 468	93 (82.3)	TIMI

Li (2016)	12	512	clopidogrel (600/75, 300/75)	ACS	bleeding	Verify Now	PRU≤ 85	46 (8.9)	BARC
Jin (2017)	6	278	clopidogrel (300/75)	ACS	bleeding, entry-site complicatio n	LTA	lowest quartile	61 (21.94)	TIMI
TOPIC/Deharo (2017)	11.9	646	clopidogrel (75 MD) prasugrel (60/10) ticagrelor (180/90)	ACS	bleeding stroke D UREV	VASP-P	PRI< 20%	305 (47.2)	BARC
Mangiacapra (2018)	60	500	clopidogrel (600/75)	sCAD	MI, ST, RREV bleeding	Verify Now	PRU< 178	160 (32.0)	TIMI
Lee (2019)	48	814	clopidogrel (600/75)	SA, ACS	all-cause death	Verify Now	PRU< 85	71 (8.7)	BARC
TROPICAL- ACS/ Aradi (2019)	12	2527	clopidogrel (600/75)	ACS	D, MI, TVR, bleeding	MEA	ADP≤18U	484 (19.2)	BARC
Mshelbwala (2020)	12	252	clopidogrel (600/75)	ACS	MACE	Verify Now	PRU ≤208	144 (57.1)	BARC
PENDULUM/ Nakamura (2020)	12	6267	clopidogrel (300/75) prasugrel (20/3.75)	ACS non-ACS		Verify Now	PRU ≤85	677 (10.8)	BARC

Table 1. Characteristics of the studies included.

Abbreviations: ACS acute coronary syndrome; AUC area under the curve; BARC Bleeding Academic Research Consortium Criteria; D death; LD loading dose; LTA light transmission aggregometry; MD maintenance dose; MEA multiplate electrode aggregometry; MACE major adverse cardiac events; MI myocardial infarct; NR not reported; NSTEMI non ST elevation myocardial infarct; PRI platelet reactivity index, PRU platelet reaction units; RREV repeated revascularization; SA stable angina; sCAD stable coronary artery disease; ST stent thrombosis; STEMI ST elevation myocardial infarct; TIMI Thrombolysis In Myocardial Infarction[47]; TVR target vessel revascularization; UREV urgent revascularization; VASP-P vasodilator-stimulated phosphoprotein.

Analysis of bias showed high quality of source information with low probability of possible bias. No obvious publication bias was found. The mean prevalence of LPR was 27% (95% CI for mean 20-35%, range 4.5-82%). Overall heterogeneity of major and minor bleeding events was considerable (I^2= 80%, $p<0.01$). To find possible determinant of the observed heterogeneity, we analyzed the prevalence of LPR and bleeding events according to type of platelet function device, definition of bleeding events and amount of clopidogrel loading dose.

Based on the sensitivity analysis all types of ADP-specific assays were able to predict the occurrence of bleeding events and the higher risk of patients with LPR was consistent regardless of the clinical presentation. It should be mentioned that considerable heterogeneity was found in the results between vasodilator-stimulated phosphoprotein (VASP-P) and Verify Now assays. However, the Multiplate assay was associated with more homogenous outcomes (Figure 1/A). Subgroup analysis was also performed to assess the potential influence of different clopidogrel LD regimes. Despite the different types of clopidogrel LD, heterogeneity remained high (Figure 1/B). When bleeding outcomes were divided into major and minor events separately the heterogeneity was reduced significantly for major bleeding (I^2=34%) while heterogeneity remained high for minor bleeding (I^2=82%) (Figure 2).

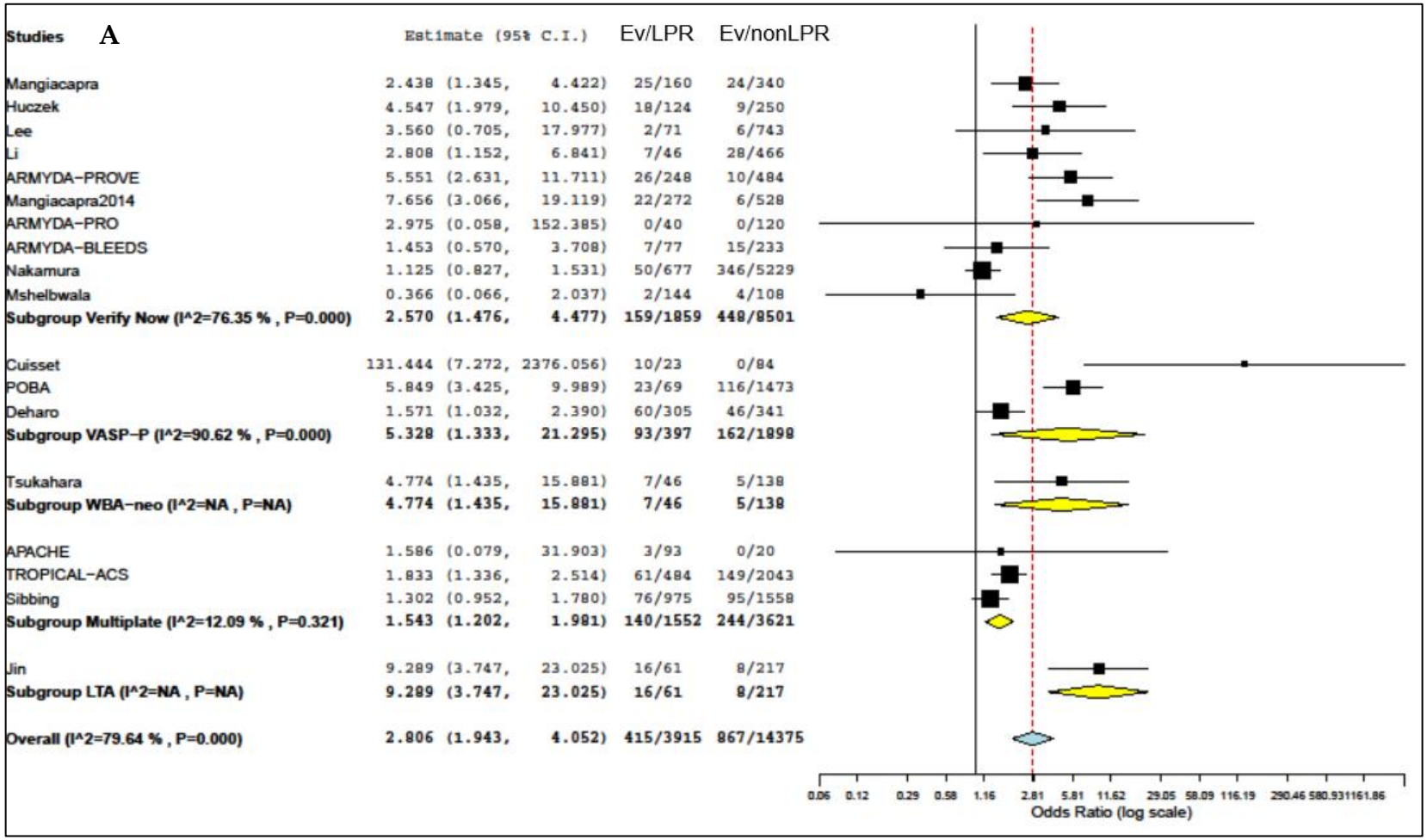

Figure 1. Subgroup analyses.

Panel A Subgroup analysis on bleeding events according to platelet reactivity measuring device.

Subgroup analysis showed considerable heterogeneity in the Verify Now (I2= 76.35%) and VASP-P assay group (I2= 90.62%). The Multiplate device group showed more homogeneous findings (I2=12.09%). Abbreviations: RR risk ratio; CI confidence interval. The diamond represents the cumulative RR and CI of all patient groups. *Mean difference (95% CI)

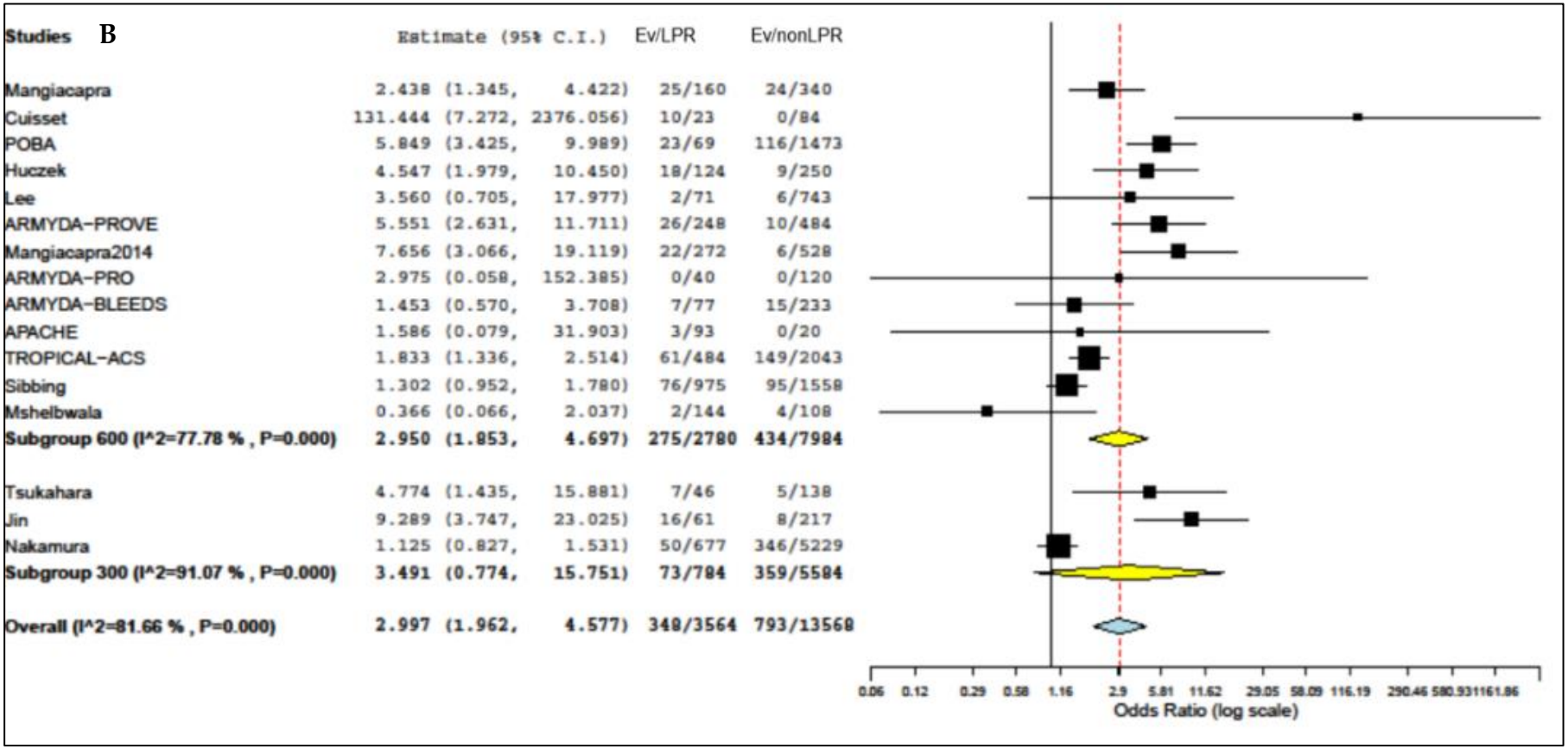

Figure 2. Subgroup analyses

Panel B Subgroup analysis on LPR event rate according to clopidogrel loading dose (LD).

The subgroup analysis shows that different loading dose of Clopidogrel did not decrease the level of heterogeneity. Abbreviations: RR risk ratio, CI confidence interval. The diamond represents the cumulative RR and CI of all patient groups. *Mean difference (95% CI)

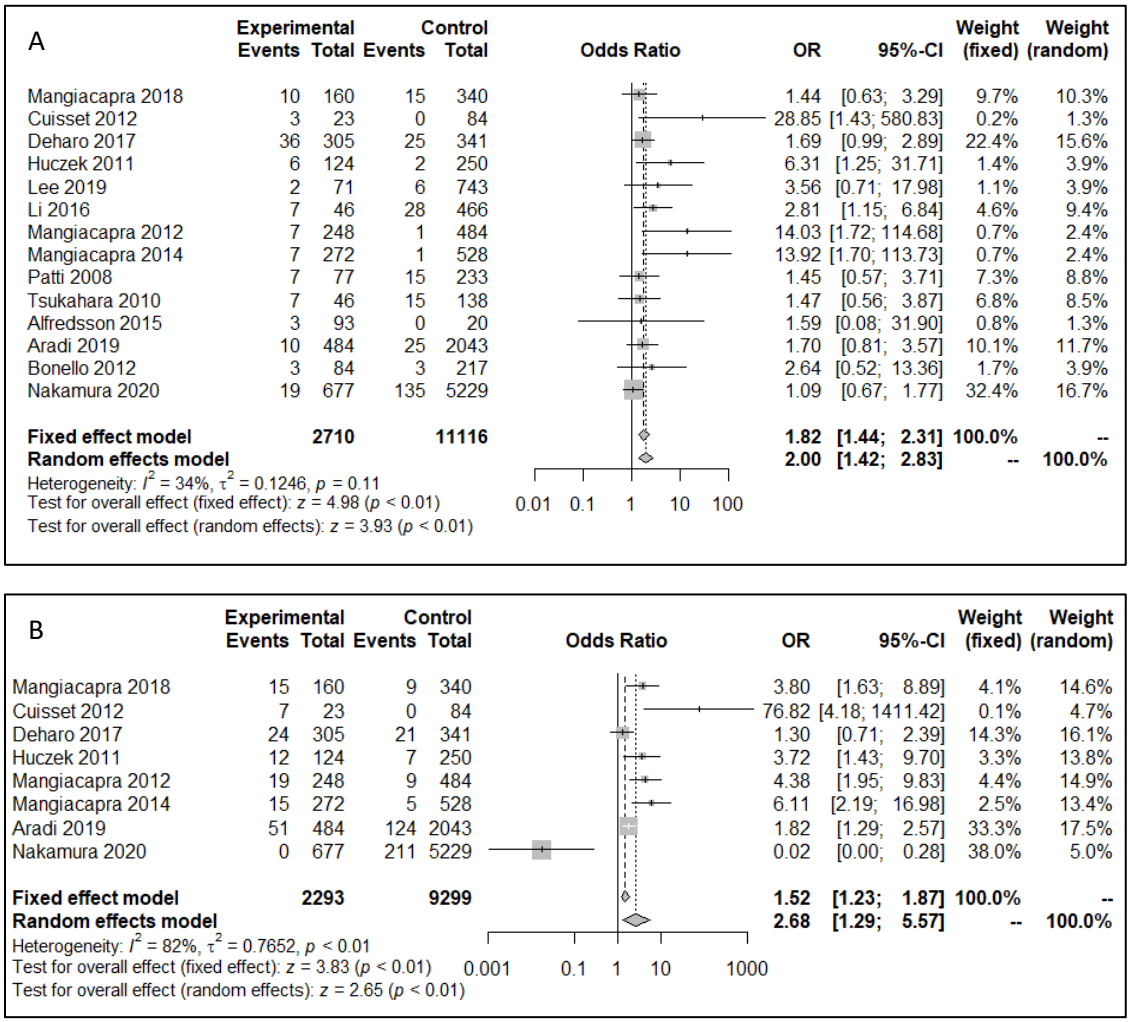

Figure 3. Forest plots of major and minor bleeding events.

Panel A Forest plots of major bleeding events.
Forest plots show increased risk of major bleeding events associated with LPR (RR=2.00, 95% CI: 1.42-2.83, p<0.01).
Abbreviations: OR odds ratio, CI confidence interval. The diamond represents the cumulative OR and CI of all patient groups. *Mean difference (95% CI).

Panel B Forest plots for minor bleeding events.
Forest plots show increased risk of minor bleeding events associated with LPR (RR=2.68, 95% CI: 1.29-5.57, p<0.01).
Abbreviations: RR risk ratio, CI confidence interval. The diamond represents the cumulative OR and CI of all patient groups. *Mean difference (95% CI).

The pooled results of the random-effects model meta-analysis demonstrated a significant increase in major and minor bleeding events with LPR (RR=2.80, 95% CI: 1.95-4.02, p<0.01) (Figure 3).

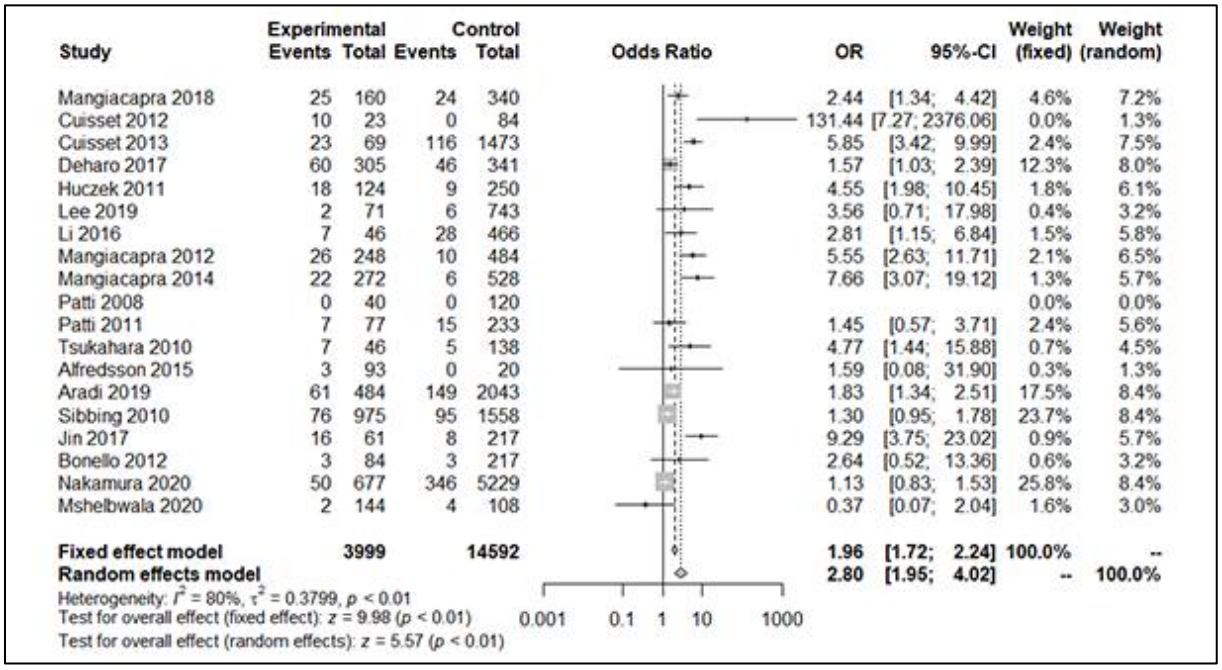

Figure 4. Principal pooled analysis.
Forest plots of major and minor bleeding risk in studies following PCI with LPR versus without LPR. The grey rectangles are proportional with the study weight. The diamond represents the cumulative OR and CI. Abbreviations: LPR low platelet reactivity, OR odds ratio, CI confidence interval.

Patients with LPR had significantly lower risk of non-fatal MI and of serious vascular events (RR=0.59, 95% CI: 0.38-0.91, p<0.05) and (RR=0.50, 95% CI: 0.30- 0.84, p<0.01) respectively (Figure 4).

The risk for ST was 45% lower in the case of LPR, however, this difference did not reach the level of statistical significance (RR=0.55, 95% CI: 0.27-1.11, p=0.10) (Figure 4). Even though the mortality of LPR patients was numerically higher the difference between the two groups remained insignificant (RR=1.57, 95% CI: 0.69-3.57, p=0.28) (Figure 4). No considerable difference was found regarding repeated revascularization (RR=0.96, 95% CI: 0.57-1.60, p=0.84) (Figure 4). Body mass index (BMI) was significantly lower in the LPR group (SMD=-0,18, 95% CI: -0.32 - -0.05, p<0.01) (Figure 5.).

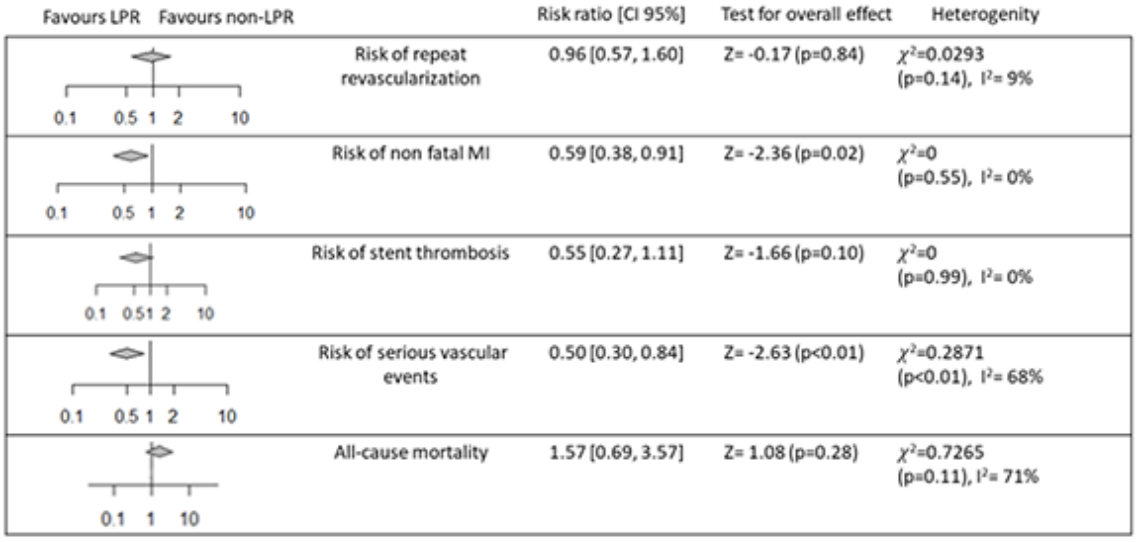

Figure 5. Summary of the outcomes of the secondary endpoints.
The diamond represents the cumulative RR and CI of all patient groups. *Mean difference (95% CI). Abbreviations: MI myocardial infarction, LPR low platelet reactivity, RR risk ratio, CI confidence interval.

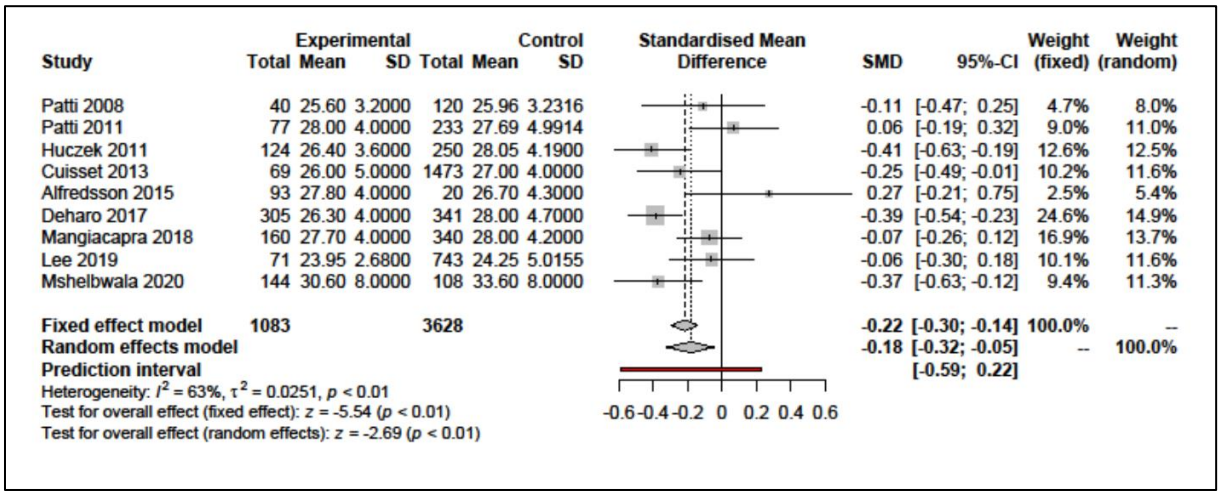

Figure 6. Forest plots showing the association of body mass index (BMI) with LPR.
BMI was significantly lower in the LPR group (WMD=-0,64, 95% CI: -1.24 - -0.04, p=0.037) Abbreviations: SD standard deviation; SMD standard mean deviation; WMD weighted mean difference; CI confidence interval. The diamond represents the cumulative WMD and CI of all patient groups. *Mean difference (95% CI).

5.2. Oral anticoagulation and outcomes in patients with acute myocardial infarction

A study population of 30 681 patients was identified that of 6.51% (n=1875) received OAC (OAC group). The majority of the OAC group was treated with vitamin-K antagonists (VKA) (86%), while direct oral anticoagulants (DOACs) were used in 14% of the cases (2.9% dabigatran, 5.8% rivaroxaban, and 5.2% apixaban). Among 1875 patients of the OAC group in 1646 cases anticoagulation was indicated due to AF Of these cases, 733 patients had AF verified during the hospitalization and in 229 cases (12.2%) had no AF but different indications for anticoagulation. These included deep vein thrombosis (3.4%) or pulmonary embolism (2.7%), an intracardiac thrombus (2.2%), and left ventricular aneurysm (1.9%), mechanical heart valves (1.3%), and miscellaneous thrombotic or embolic reasons altogether less than 1%. Patients treated with OAC were older and were more frequently man. The PS-matching resulted in a matched population of 3750 patients with balanced characteristics leaving only some statistically significant but clinically less relevant differences in continuous parameters like the heart rate (mean difference (*MD*): 6.22 beats/min), systolic blood pressure (*MD*: 2.22 mmHg), weight (*MD*: 2.23 kg), and height (*MD*: 1.06 cm)

In the overall cohort, OAC-treated subjects had a significant, 25% higher hazard for all-cause mortality (13.17% vs. 10.52%, hazard ratio (HR): 1.25, 95% CI 1.01-1.42, p=0.001). Similarly, rates of MACE and transfusion were higher (14.51% vs. 11.70%, HR: 1.24, [1.01-1.40], p=0.001 and 9.97% vs. 6.88%, HR: 1.47 [1.26-1.70], p<0.001 (Figure 6).

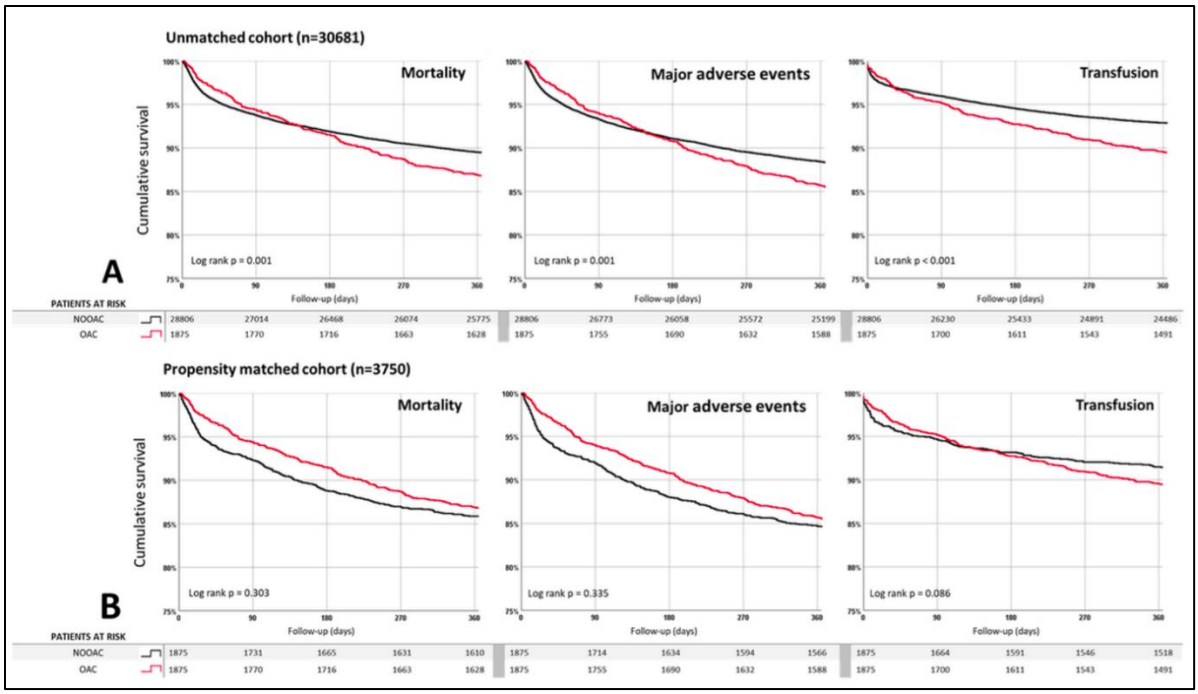

Figure 7. Kaplan-Meier curves of overall mortality, major adverse events and transfusion-free survival comparing patients with or without oral-anticoagulant treatment.

Abbreviations: NOOAC patient group treated without oral anticoagulant therapy, OAC patient population treated with oral anticoagulant therapy.

A tendency of anticoagulated cases for higher rate transfusion prevailed in the PS-matched cohort. (9.97% vs. 8.16% HR: 1.21, [0.97-1.49], p=0.086). Rate of mortality and MACE, however, were less frequent in the OAC-group compared to the PS-matched control group without OAC (13.17% vs. 14.1%, HR: 0.91 [0.77-1.09], p=0.303 and 14.5% vs. 15.36%, HR: 0.92 [0.78-1.09], p=0.335). Importantly, none of these reached the level of significance (Figure 7).

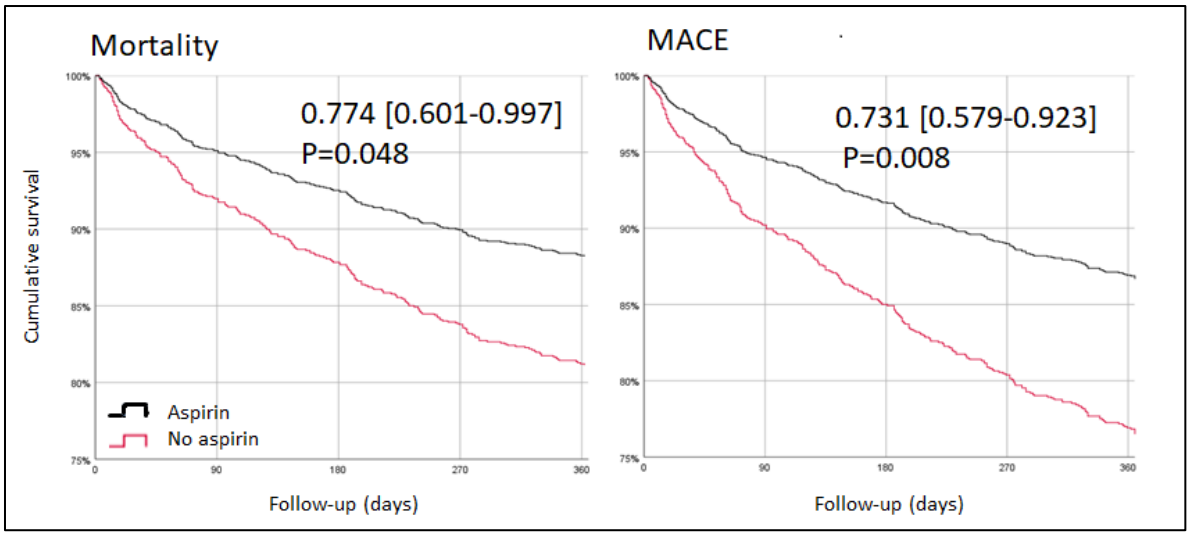

Figure 8. Curves plotting the risk of mortality and major adverse cardiac events among oral anticoagulation treated patients compared between cases receiving or not receiving aspirin.

Importantly, unadjusted subgroup analyses showed a higher risk of ischemic endpoints with VKA or DOAC treatment. MACE and bleeding were significantly higher with VKA but not with DOAC. Among DOACs, rivaroxaban-treated cases had higher rates of transfusion. Regarding the different antiplatelet strategies, compared to the unmatched control higher rate of ischemic and bleeding endpoints were found among the anticoagulated cases unconstrained if they received or not received aspirin or received single or double antiplatelet therapies. All these endpoints were more frequent among cases treated with old P2Y12 inhibitors but not among those receiving newer ADP antagonists. Furthermore, after PS adjustment all but the differences regarding aspirin therapy disappeared.

Similarly, PS-balanced comparisons within the OAC-group showed no differences in mortality, MACE, or bleeding with the only exception of the lower mortality (HR: 0.77, [0.60-0.997], p=0.048) and MACE risk (HR: 0.73 [0.58-0.92], p=0.008) of the aspirin-treated cases compared to the counterparts not receiving aspirin (Figure 7).

5.3. Comparison of ticagrelor treatment with platelet aggregation inhibitors in high-risk patients in secondary stroke prevention

Twenty-six RCTs involving 124 495 (range: 48-21162) patients were analyzed. The main characteristics of these trials are shown in Table 2. Patients were recruited to the trials due to non-severe ischemic stroke or transient ischemic attack (TIA)[80–82], ACS[10,27,91–95,83–90], high risk for ACS[96,97], PAD[98] , coronary artery bypass graft surgery (CABG)[99], known CAD[100,101] or transcatheter aortic valve implantation (TAVI)[102]. According to the applied antiplatelet medication (aspirin or clopidogrel, prasugrel or ticagrelor in monotherapy or combined with aspirin), study groups were divided into 6 groups. The 6 antiplatelet treatment arms allowed 15 possible pairwise comparisons that of 7 was implemented in the included trials. The geometry of the network is depicted in Figure 7A-C. The dose of the long-term P2Y12 inhibitor treatment was different in the trials using 90 mg bid or 60 mg bid for ticagrelor, 75 mg od for clopidogrel, and 10 mg od for prasugrel. Aspirin was administered in a low dose (75 mg-150 mg). Study definitions of bleeding were incosistent[47,48] (Table 2).

Study name/ First author (Publication year)	Follow-up (months)	Treatment (total daily dose, mg)	No. sample size/ T/C	Clinical setting	Exclusion criteria	Clinical endpoint	Definition of bleeding
DISPERSE-2/ Cannon (2007)	3	ticagrelor (2x90) + aspirin (75-100) vs. ticagrelor (2x180) + aspirin (75-100) vs. clopidogrel (75) + aspirin (75-100)	990: 334/323/327	NSTE-ACS	HR for bleeding	bleeding MACCE	TIMI
PLATO/Wallentin (2009)	12	ticagrelor (2x90) + aspirin (75-100) vs. clopidogrel (75) + aspirin (75-100)	18624: 9333/9291	ACS	CI against clopidogrel, need for OAC, HR for bradycardia	bleeding MACCE	TIMI
PEGASUS-TIMI 54/ Bonaca (2015)	33	ticagrelor (2x90) + aspirin (75-150) vs. ticagrelor (2x60) + aspirin (75-150) vs. placebo + aspirin (75-150)	21162: 7050/7045/7067	1-year post-ACS	recent bleeding, prior stroke, need for OAC	MACCE	TIMI
Bonello (2015)	1	ticagrelor (180) + aspirin (150) vs. prasugrel (10) + aspirin(150)	213: 106/107	NSTE-ACS high risk	selection for surgery or medical therapy	rate of periprocedural myonecrosis MACCE bleeding	BARC
PHILO/ Goto (2015)	12	ticagrelor (2x90) + aspirin (75-100) vs. clopidogrel (75) + aspirin (75-100)	801: 401/400	ACS	active or history of bleeding, HR for bradycardia	bleeding MACCE	PLATO
EUCLID/ Hiatt (2016)	30	ticagrelor (2x90) vs. clopidogrel (75)	13855: 6930/6955	PAD	HR for bleeding	bleeding MACCE	TIMI
SOCRATES/ Johnston (2016)	3	ticagrelor (2x90) vs. aspirin (100)	13199: 6589/6610	AIS, TIA	TIA or stroke	MACCE	PLATO
PRAGUE-18/ Motovska (2018)	12	ticagrelor (2x90) + aspirin (100) vs. prasugrel (10) + aspirin (100)	1230: 596/634	ACS	history of stroke, serious bleeding in 6 months	bleeding MACCE	BARC TIMI

Tang (2016)	6	ticagrelor (2x90) + aspirin (100) vs. clopidogrel (75) + aspirin (100)	400: 200/200	STEMI	OAC, CABG	bleeding MACCE	TIMI
Wang (2016)	12	ticagrelor (2x90) + aspirin (100) vs. clopidogrel (75) + aspirin (100)	200: 100/100	ACS	active or history of bleeding	bleeding MACCE	PLATO
Zhang (2016)	6	ticagrelor (2x90) + aspirin (100) vs. clopidogrel (75) + aspirin (100)	181: 91/90	ACS	malignant with HR bleeding	MACCE stent thrombosis	PLATO
Dehghani (2017)	1	ticagrelor (2x90) + aspirin (100) vs. clopidogrel (75) + aspirin (100)	144: 76/68	STEMI	OAC, active or HR bleeding, PCI or CABG previous 3 months	bleeding MACCE	BARC
ExcelsiorLOAD2/ *Hocholczer (2017)*	1	ticagrelor (180) + aspirin (100) vs. clopidogrel (75) + aspirin (100) vs. prasugrel (60) + aspirin (100)	110/45/20/45	stable CAD	AMI OAC acute bleeding	PRU	BARC TIMI
Wu (2018)	12	ticagrelor (2x90) + aspirin (100) vs. clopidogrel (75) + aspirin (100)	257/129/128	ACS	active bleeding history of ICH	MACCE	NA
Zhao (2018)	12	ticagrelor (2x90) + aspirin (100) vs. ticagrelor(2x90) vs. aspirin (100)	500/168/166/166	CABG	HR for bleeding, history of ICH	vein graft patency, bleeding	TIMI
TREAT/Berwanger (2019)	12	ticagrelor (2x90) + aspirin (75-100) vs. clopidogrel (75) + aspirin (75-100)	3799/1913/1886	STEMI-ACS	OAC ischemic stroke within 3 months	MACCE bleeding	BARC TIMI PLATO
THEMIS-PCI/ Bhatt (2019)	40	ticagrelor (2x90), (2x60) + aspirin (75-100) vs.	19220/9619/9601	stable CAD	previous MI or stroke	MACCE	BARC TIMI PLATO

		placebo + aspirin (75-100)					
REAC-TAVI/ Jimenez Diaz (2019)	4	ticagrelor (2x90) + aspirin (100) vs. clopidogrel (75) + aspirin (100)	68/24/24/20	TAVI	OAC bleeding diathesis recent stroke	PRU	NA
TWILIGHT/ Mehran (2019)	12	ticagrelor (2x90) + aspirin (81-100) vs. ticagrelor (2x90) + placebo	7119/3555/3564	high risk*	STEMI OAC	MACCE bleeding	BARC GUSTO ISTH TIMI
TICAKOREA/ Park (2019)	12	ticagrelor (2x90) + aspirin (100) vs. clopidogrel (75) + aspirin (100)	800/400/400	ACS	OAC active bleeding history of bleeding	bleeding	BARC TIMI PLATO
TiCAB/ Schunkert (2019)	12	ticagrelor (2x90) vs. aspirin (100)	1859/931/928	CABG	OAC	MACCE	BARC
ISAR REACT-5/ Schüpke (2019)	12	ticagrelor (2x90) + aspirin (≤100) vs. prasugrel (10) + aspirin (≤100)	4018/2012/2006	ACS	OAC history of stroke or TIA	MACCE bleeding	BARC
PRINCE/ Wang (2019)	3	ticagrelor (2x90) + aspirin (100) vs. clopidogrel (75) + aspirin (100)	675/336/339	TIA ACS	ICH ischemic stroke ACS	HPR stroke	PLATO
POPular AGE/ Gimbel (2020)	12	ticagrelor (2x90) + aspirin (100) or prasugrel (10) vs. clopidogrel (75) + aspirin (100)	1002/502/500	NSTE-ACS	recent major surgery	bleeding all-cause death MI stroke	BARC PLATO TIMI
TICO/ Byeong-Keuk (2020)	12	ticagrelor (2x90) or ticagrelor (2x90) + aspirin (100)	1527/1529	ACS	HR for bleeding prior ICH OAC	net adverse clinical event (death, MI, ST, stroke, TVR)	TIMI
THALES/ Johnston (2020)	1	ticagrelor (2x90) + aspirin (75-100) vs. placebo + aspirin	11016/5523/5493	ACS, stroke	history of ICH, stroke or TIA	composite of stroke or death	GUSTO

Table 2. Characteristics of the included trials.

Abbreviations: ACS acute coronary syndrome; AMI acute myocardial infarction; BARC Bleeding Academic Research Consortium; CABG coronary artery bypast graft; CAD coronary artery disease; CI: contra indication; C clopidogrel; GUSTO Global Strategies for Opening Occluded Coronary Arteries; HPR high platelet reactivity; HR high risk; ICH intracranial hemorrhage; ISTH International Society for Thrombosis and Hemostasis; MACCE major adverse cardiac and cerebrovascular events; MI myocardial infarction; NA not applicable; NSTE-ACS non ST segment elevation ACS; PAD peripheral artery disease; PLATO Platelet Inhibition and Patient Outcomes; PRU platelet reactivity unit; sec secondary; ST stent thrombosis; STEMI ST-segment elevation myocardial infarction; T ticagrelor; TAVI transcatheter aortic valve implantation; TIMI Thrombolysis in Myocardial Infarction; TVR target vessel revascularization; OAC oral anticoagulation; vs versus; *only loading dose was given preprocedural.

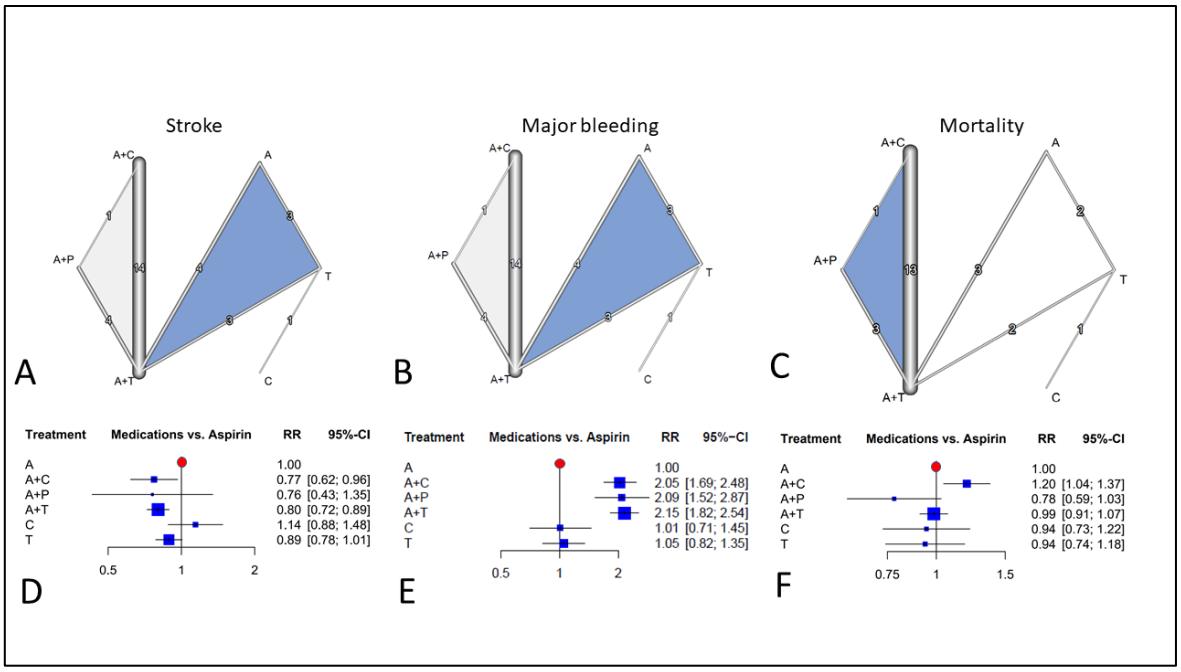

Figure 9. Network layout and the results of the primary endpoints.
Network graphs depict the overall structure of comparisons of primary endpoints in our network. The numbers and the thickness of the edges correspond to the number of studies a specific comparison was tested within. The blue triangles mark the multiarm trials of the network. (Panel A-C) Forest plots show the results of the random-effects network meta-analyses as comparisons with aspirin monotherapy set as reference. (Panel D-E) Abbreviations: A aspirin; C clopidogrel; P prasugrel; T ticagrelor; RR risk ratio; CI confidence interval.

Analysis of bias showed high quality of the source information with a low probability of bias. No obvious publication bias was found. In the included trials 3035 (2.43%) stroke events occurred. Compared to aspirin monotherapy stroke risk was significantly (23%) lower with aspirin plus clopidogrel and 20% lower with aspirin plus ticagrelor combinations. With ticagrelor alone and with the combination of aspirin and prasugrel stroke risk was also lower (11% and 24%) but 14% higher with clopidogrel monotherapy, however, these latter results did not reach the level of statistical significance (Figure 8 A, D). The data were consistent (I^2=0% [0.0%; 34.2%]) and without significant heterogeneity neither within designs nor between designs (p=0.6828 and p=0.8351, respectively).

The risk of ischemic stroke was significantly reduced with ticagrelor plus aspirin (RR: 0.80 [0.71-0.89]). Ticagrelor monotherapy also resulted in a decreasing trend in the risk of ischemic stroke (RR: 0.88 [0.77-1.00], p=0.05). In the case of hemorrhagic stroke, none of the treatments influenced the risk significantly. Combination

ticagrelor to aspirin increased the risk of intracranial bleeding with 53% (RR: 1.53 [1.16-2.03], p=0.05). Data of ischemic stroke were consistent and homogenous while in the case of hemorrhagic stroke moderate heterogeneity was seen (I^2=47%) (Table 3).

Mortality events (5194) were reported in 23 trials. Compared with aspirin, mortality was 20% higher with aspirin plus clopidogrel and showed a decreasing trend with aspirin plus prasugrel (RR: 0.78 [0.59-1.03]). With the other treatments, the difference remained less than 10% and did not reach the level of statistical significance (Figure 8). Low degree of heterogeneity was noted in mortality data (I^2=12.3% [0.0%; 47.1%]). Twenty-one trials reported 2811 major bleeding events classified by the individual trial definitions. Compared with aspirin alone major bleeding was in similar ranges with antiplatelet monotherapies while the relative risk was twice higher with combined antiplatelet therapies (Figure 8/B,E). Low degree inconsistency was noted for major bleeding data (I^2 = 10.2% [0.0%; 45.9%]). Analyses of the clinical outcomes suggested clustering of treatment arms with antiplatelet monotherapies separating from combination therapies (Figure 9). Subgroup analyses stratified according to the inclusion conditions showed data consistent in all strata with more effective stroke reduction of the ticagrelor plus aspirin combination as well as the higher risk of bleeding. Net adverse clinical events data showed a higher level of inconsistency and variances with non-significant relations except for the benefit of ticagrelor plus aspirin in ACS trials. Clopidogrel plus aspirin and ticagrelor plus aspirin were ranked as the most effective strategy for the prevention of stroke (P-score, 0.79 and 0.73). For the prevention of ischemic stroke, the ranking for aspirin plus ticagrelor (A+T) was higher (P-score, 0.72, and 0.81). Ranking with regards to the major bleeding or stroke prevention showed opposite tendencies (R=-0.879, p=0.021) (Figure 9). Regarding major bleeding aspirin was ranked as the safest strategy (P-score, 0.82) (Table 4).

The component analysis reflected that the use of each antiplatelet agent conveyed the reduction of stroke risk, but this effect reached the level of statistical significance only

in the case of ticagrelor. An important increase in bleeding risk was characteristic for all drugs, however, no important change in mortality risk was detected (Table 5).

Secondary outcomes	**A+T**	**A+C**	**A+P**	**C**	**T**
Ischemic stroke	0.80 (0.71; 0.89)*	0.81 (0.63; 1.05)	0.88 (0.6; 1.741)	1.15 (0.89; 1.50)	0.90 (0.79; 1.02)
Hemorrhagic stroke	0.94 (0.62; 1.42)	0.70 (0.36; 1.35)	0.37 (0.084; 1.68)		0.64 (0.27; 1.53)
MACCE	0.89 (0.76; 1.06)	0.95 (0.76; 1.19)	0.92 (0.57; 1.50)	0.83 (0.60; 1.15)	0.85 (0.70; 1.03)
Myocardial infarction	0.84 (0.69; 1.02)	0.96 (0.74; 1.25)	0.62 (0.41; 0.94)*	0.78 (0.52; 1.19)	0.82 (0.61; 1.11)
CV Mortality	0.99 (0.82; 1.18)	1.08 (0.85; 1.38)	0.93 (0.60; 1.43)		1.01 (0.77; 1.33)
Major and minor bleeding	2.58 (2.04; 3.27)*	2.09 (1.56; 2.82)*	1.95 (0.95; 3.99)	1.21 (0.73; 2.02)	1.36 (1.03; 1.79)*
Minor bleeding	4.17 (2.90; 6.00)*	3.27 (2.17; 4.92)*	1.85 (0.19; 17.88)	2.45 (1.14; 5.22)*	3.08 (1.61; 5.88)*
Intracranial hemorrhage	1.53 (1.16; 2.03)*	0.96 (0.55; 1.67)	1.26 (0.04; 40.49)	0.66 (0.28; 1.56)	0.67 (0.33; 1.35)

Table 3. Network meta-analysis results of the secondary outcomes.
Results are risk ratios (95% confidence intervals) from the network meta-analysis between the column defining intervention versus aspirin monotherapy. Here RR > 1 means that the column defined treatment is worse compared to aspirin. Significant results are marked with asterisks. Abbreviations: A aspirin; C clopidogrel; CV cardiovascular; MACCE: major adverse cardiac and cerebrovascular events;, P prasugrel; T ticagrelor.

Intervention	A+C	A+T	A+P	T	A	C
Stroke	0.7936	0.7330	0.7043	0.4992	0.2120	0.0578
Ischemic stroke	0.7273	0.8147	0.5307	0.5758	0.2534	0.0981
Hemorrhagic stroke	0.5156	0.2965	0.7941	0.4849	0.4089	-
Intracranial hemorrhage	0.4989	0.0192	-	0.7832	0.4342	0.7644
Any bleeding	0.2877	0.0440	0.3405	0.6288	0.9441	0.7549
Major bleeding	0.2904	0.0965	0.2181	0.7591	0.8242	0.8117
Minor bleeding	0.3851	0.0870	0.6025	0.3821	0.9382	0.6052
Mortality	0.0175	0.4772	0.9209	0.6106	0.4029	0.5709
Cardiovascular mortality	0.2399	0.5903	0.6643	0.4865	0.5190	-
Myocardial infarction	0.2117	0.5486	0.9173	0.5571	0.1324	0.6329
MACCE	0.3521	0.5785	0.4734	0.7066	0.1946	0.6948

Table 4. The P-score probabilities of antiplatelet treatments on clinical outcomes.

P-score provides likelihood of an intervention to be the most beneficial. The P-score ranking system is a frequentist analog of SUCRA (SUrface Under the Cumulative Ranking curve) that measures the certainty that one treatment is better than another treatment, averaged over all competing treatments. The higher number indicates better treatment rank. Abbreviations: A aspirin, C clopidogrel, MACCE major adverse cerebro- and cardiovascular events, P prasugrel, T ticagrelor.

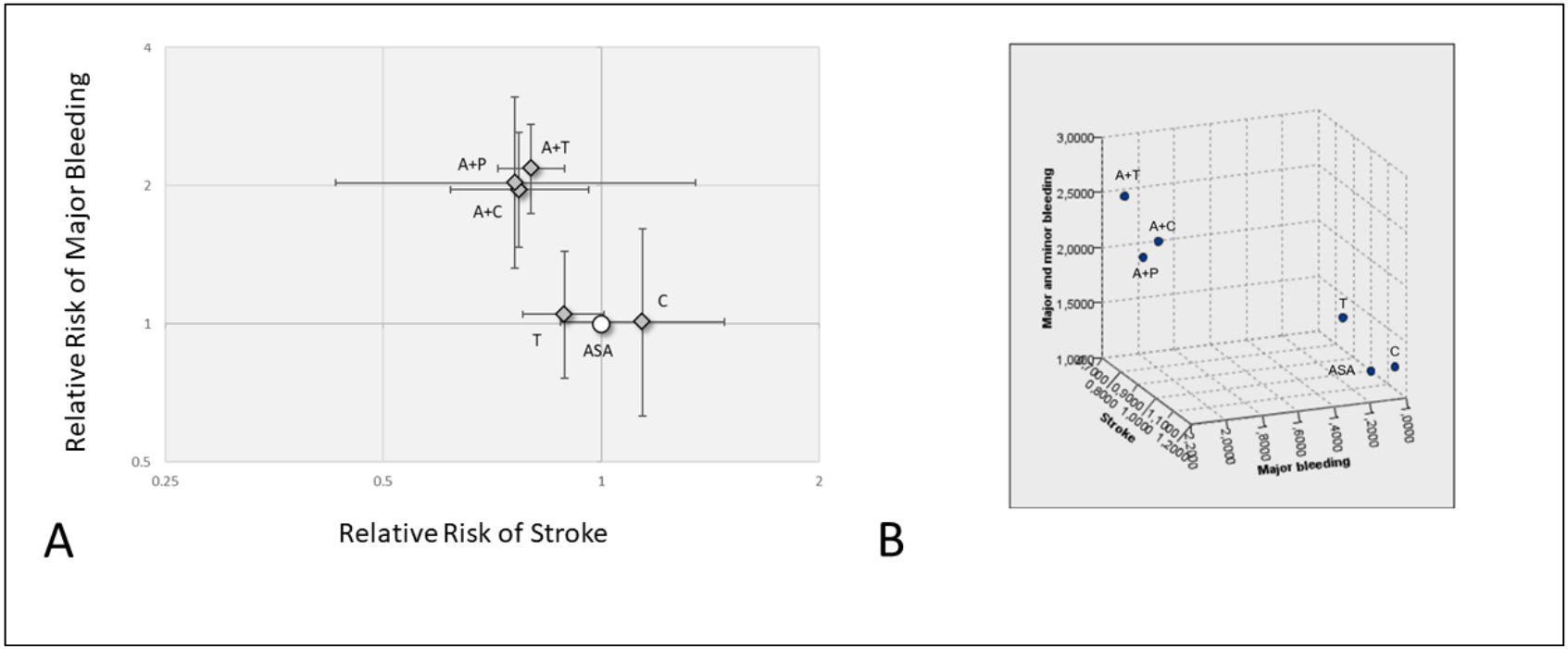

Figure 10. Cluster analysis of the included treatment arms.
Panel A depicts the relative risk of stroke and major bleeding with their respective confidence intervals related to aspirin monotherapy. Both the risk ratio values and the P-score values showed a strong negative correlation between stroke and major bleeding risk. (R=-0.871, p=0.024, and R=-0.899, p=0.015, respectively) Panel B shows the three-dimensional projection of the predictor space of the nearest neighbor analysis derived from the analysis of the 11 analyzed predictors. The plot shows discernible clustering of combined and monotherapies.

	Stroke	p-value	Major bleeding	p-value	Mortality	p-value
Aspirin	-0.10 [0.26;0.06]	0.2094	0.73 [0.41; 1.05]	<0.0001	0.07 [-0.18; 0.31]	0.6043
Clopidogrel	-0.13 [0.32;0.05]	0.1462	0.70 [0.46; 0.94]	<0.0001	0.10 [-0.05; 0.26]	0.1821
Prasugrel	-0.27 [0.84;0.30]	0.3488	0.71 [0.32; 1.09]	0.0003	-0.23 [-0.54; 0.07]	0.1282
Ticagrelor	-0.22 [0.32;0.12]	<0.0001	0.77 [0.57; 0.97]	<0.0001	0.00 [-0.11; 0.11]	0.9809
Inconsistency (I^2)	0% [0.0%;34.2%]		10.2% [0.0%;45.9%]		12.3% [0.0%;47.1%]	
Heterogeneity						
Additive model		0.6707		0.3305		0.2991
Standard model		0.8165		0.2724		0.5929

Table 5. Effect of the individual antiplatelet drugs in the supplementary component network meta-analysis models. Risk difference [95%-Confidence interval].

6. DISCUSSION

6.1. Risk of adverse events associated with low platelet reactivity in patients with percutaneous coronary intervention

In the present meta-analysis involving 19.064 patients, we found evidence that patients with LPR after PCI are at a higher risk of bleeding. LPR response to antiplatelet therapy is also associated with a lower risk of non-fatal myocardial infarction. The composite endpoint of serious vascular events demonstrated lower risk with LPR. The risk of all-cause mortality did not differ significantly between LPR and non-LPR patient groups. Importantly, despite the differences in the methodology, patient selection and cut-off definition among studies, the increased risk of bleeding was homogenously reflected.

In a large population study prospectively reporting on the impact of enhanced response to clopidogrel treatment including 2.533 patients with CAD undergoing planned PCI, LPR was found to be associated with a two-fold higher risk for in-hospital major bleeding events.[103] Further reports supported this concept that LPR is a marker for a higher risk for bleeding also among prasugrel-treated patients.[65,66] However, according to some recent studies optimal platelet reactivity does not denote the same range in every patient population. In the "Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome Subjects" trial (TRIOLOGY ACS) involving ACS patients without PCI found no relationship between LPR and major bleeding risk. Among medically managed non-ST-segment elevation ACS patients receiving prolonged DAPT, platelet reactivity unit (PRU) values were not significantly associated with the long-term risk of major bleeding events, suggesting that LPR does not independently predict serious bleeding risk.[104]

To assess the potential influence of different clopidogrel LD regimes, we performed a subgroup analysis. Our results showed no association between different LDs of clopidogrel and the rate of bleeding events. Our findings are in line with a recent meta-analysis that compared the use of different LDs of clopidogrel and found that these are not associated with an increased risk for major bleeding in 30 days.

However, it also suggested that the administration of 600 mg LD of clopidogrel is associated with a lower risk of MACE.[105] This observation is further supported by a retrospective study of patients with stable coronary artery disease (SCAD) which shows no difference between different LD groups in terms of major bleeding and hemoglobin drop post PCI.[106]

When interpreting data from different platelet function studies the complex mechanisms of bleeding should be considered. Besides the potential impact of platelet inhibition, several clinical factors may affect the risk of these events. Residual PR as an independent risk factor also has several associations with patient characteristics and these may also influence the expressed risk. HPR is more frequently seen in obese and diabetics, while LPR may more likely arise in patients with advanced age and lower body weight.[107,108] Our analysis demonstrated a significant association between LPR and lower BMI. These characteristics may also influence the prognosis and when analyzed in multivariate models the magnitude of risk, like in case of ischemic risk with HPR is considerably reduced.[109]

Importantly, the periprocedural bleeding risk is substantially influenced by the access site selection being significantly higher with transfemoral interventions. Bleeding avoidance strategies like the routine use of the transradial approach may interfere with this risk by reducing bleeding and improving outcomes among high-risk ACS patients.[110]

In our analysis, the rate of transradial approach was 59% (reported in 8 studies including 8.667 patients (45%). However, since this data was not presented in a considerable proportion of studies this impedes the further analysis of potential impact of access site selection.

Our findings are partly in line with the results of a previous meta-analysis published in 2015 including 17 trials with a total of 20.839 patients validating standardized cut-off points for platelet function testing. In that study thienopyridine-treated patients with HPR were associated with a 2.73- fold higher risk for ST ($p<0.00001$) and a 1.5-fold higher risk for mortality ($p<0.05$) compared with those with optimal PR

following PCI meanwhile patients with LPR were associated with a 2-fold increased risk for major bleeding complications without any further reduction in the risk of ST.[105] In our study, there was no considerable difference between LPR and non-LPR groups regarding mortality, ST or repeated revascularization. However, the risk of serious vascular events resulted in significant difference favoring the LPR group. Regarding the risk of non-fatal MI, the event rate was significantly lower in the LPR group.

Some limitations of our analysis should be discussed. Observational studies were included that are usually unbalanced regarding baseline clinical characteristics of the patients. These studies could reflect the real-world practice better, meanwhile due to lack of monitoring drug compliance, underreporting negative results and incomplete follow-up their interpretation may be more difficult and might carry ascertainment biases. To balance possible confounding factors data were pooled with logarithmic transformation according to the random-effect model via generic inverse weighting with the intent of methodical compensation of these factors.

Furthermore, patients were not treated uniformly regarding the LDs of clopidogrel and that platelet function assessments were performed at different time points after PCI with different devices and cut-offs for LPR that may contribute to heterogeneity.

Moreover, there are multiple tests on the field without a real-gold standard. Considering the plethora of the available platelet functions tests we aimed to restrict our analyses to those that implement a method based on ADP-dependent in vitro platelet activation in order to best assess the efficacy of ADP receptor dependent activation pathway. From this aspect we did not restrict the acceptable methodologies based on the final readout of the method. The use of different P2Y12 inhibitors may have also influenced residual platelet reactivity. Due to the lack of patient-level data subgroup analyses were not done to identify drug-related efficacy. It is also important to note that different definitions of bleeding may also contribute to heterogeneity. We aimed to collect data according to the two most widely used standardized definitions the TIMI bleeding and BARC criteria.

6.2 Oral anticoagulation and outcomes in patients with acute myocardial infarction

Our analysis of a large, prospective, unselected database of patients treated with PCI due to an event of AMI showed that AMI patients receiving OAC were older and had a more severe risk profile than patients in the control group and thus anticoagulation was associated with a higher rate of mortality, MACE and transfusion. However, after performing PS-matching these differences were balanced off, and in the PS-matched sample, no difference regarding mortality or MACE persisted. Transfusion remained more frequent in the OAC group; however, this difference did not reach the level of statistical significance. PS-adjusted analyses of the risks within the OAC-treated groups did not explore major differences except for the higher mortality and MACE rates were seen among patients not receiving aspirin.

Conditions requiring long-term anticoagulation including AF, ventricular thrombi, or pulmonary embolism are markers associated with poor prognosis among patients who underwent PCI.[111–113] AF is associated with increased risk for heart failure, dementia, and stroke. Besides other less common causes like ventricular thrombus and deep vein thrombosis or pulmonary embolism, this arrhythmia is the most common cause of anticoagulation among MI patients.

The importance of comorbidities is, however, reflected variably in earlier studies. Patients included in the "REduction of Atherothrombosis for Continued Health" (REACH) registry had a higher risk of major adverse events after a 4-year follow-up if they also suffered from AF. This difference - contrasting our analyses - remained important even after balancing for clinical parameters (24.3% vs 13.3% unadjusted and 18.9% and 9.4% adjusted event rates, respectively). Beyond differences in the inclusion criteria of the REACH registry, some other disparities should be noted that may explain the partially discordant results. Importantly, in the REACH register, a set of clinical factors were used for regression adjustment. Regression adjustment is used frequently in observational studies and it attempts to characterize the effect

estimate at the mean of the factor levels entered the model. But importantly it keeps the sample untouched even if the treatment groups differ considerably in their risk profile. We found that the characteristics of OAC-treated patients consist of a minority of the MI population with major differences from the control cases. Moreover, the PS-based stratification showed that the risk of ischemic and bleeding endpoints was neither homogenous nor linear concerning the PS. Thus, to achieve balance in the measured confounders PS matching was used instead. Furthermore, we used PS as a balancing score to adjust for potential remaining differences within the OAC group analyses.[114] The unfavorable results of patients with AF in the REACH registry can also be explained by the undertreatment of these cases, as the rate of anticoagulation reached only 52% in the 4th year. This is in line with our data where AF, but not anticoagulation was associated with unfavorable results regarding both ischemic and bleeding in regression adjustment analyses.

In our registry, a different approach was conducted to analyze the outcomes of patients after the event of AMI based on their intended OAC treatment status. Earlier experience with warfarin suggested an incremental ischemic benefit when anticoagulant therapy was used in combination with aspirin.[115] These results set the scene for studies using DOACs as an adjunct option to antiplatelet therapy in ACS. With the only exception of rivaroxaban, ACS trials among patients without AF failed to support this concept.[116] However, in the "Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome ACS 2–Thrombolysis In Myocardial Infarction 51" (ATLAS ACS-2–TIMI-51) trial low dose rivaroxaban reduced the risk of major adverse events with a significant mortality reduction.[117] Meta-analysis of these trials found a homogenous effect of DOAC anticoagulation in reducing ischemic endpoints, however, this benefit was counterbalanced with the higher risk of bleeding compared to placebo.[118] Low-dose rivaroxaban also resulted in higher rates of major bleeding but better cardiovascular outcomes in patients with aspirin-treated stable atherosclerotic vascular disease in the Cardiovascular OutcoMes for People Using

Anticoagulation StrategieS (COMPASS) trial.[119] Comorbidity adjusted analyses regarding the agent used for anticoagulation found comparable outcomes of DOAC treated cases to VKA, with an unexpected trend for higher mortality in the case of rivaroxaban. When considering the results of the analysis it is important to note that the use of DOAC represented a minority of our OAC group and that low-dose rivaroxaban was not used in our cohort that makes the importance of this statistically non-significant difference questionable.

Interaction between anticoagulation and antiplatelets has been most extensively examined in cases with AF receiving antiplatelet therapy because of a coronary event or intervention.[120] Recently data from multiple randomized trials were published.[121–124] Pooled meta-analysis of these trials found that anticoagulation applied with single antiplatelet treatment reduces bleeding risk, however, a trend for a higher rate of MI and ST was observed compared to dual-antiplatelet combined anticoagulation.[125] This observation contrasted the What is the Optimal antiplatElet & Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary StenTing (WOEST) trial that found a significant reduction of major adverse events and a decreasing trend of the elements of the composite endpoint if aspirin was withheld in anticoagulated patients. However, in line with the DOAC trials, our results reflected a worse prognosis of anticoagulated patients without aspirin.

6.3. Comparison of ticagrelor treatment with platelet aggregation inhibitors in high-risk patients in secondary stroke prevention

In this multiple treatment network meta-analysis of 26 trials involving 124.495 patients, we found evidence that the choice of antiplatelet strategy influences the risk of stroke in patients with high thrombotic risk. Within this comprehensive analysis of randomized trials testing ticagrelor in a wide range of clinical scenarios we found that ticagrelor plus aspirin, as compared to aspirin alone, was associated with a significant risk reduction of stroke (20%). Data of this analysis showed an important trade-off between stroke prevention and bleeding risk. However, when the risk of major bleeding was taken into consideration, the probability of being the best choice of treatment was the highest for aspirin monotherapy while the lowest for aspirin plus ticagrelor. Additionally, this combination significantly increased the risk of intracranial bleeding. We found important clustering of clinical endpoints among antiplatelet monotherapies and combinations while in models considering the components of the combinations the highest stroke prevention potential and the highest bleeding risk was attributable to ticagrelor.

Platelet-driven thrombotic events play a pivotal role in the development of ischemic vascular events. Earlier analyses found favorable results for aspirin as initial therapy in the prevention of ischemic stroke. [126] However, aspirin monotherapy is not capable of preventing ischemic events in patients at high risk of recurrences like in cases with recent minor stroke or TIA or in patients with acute coronary syndrome.[127] Later development in antiplatelet therapy aimed at the inhibition of alternative pathways including the P2Y12 receptor-mediated activation and in combination with aspirin providing a greater reduction of thromboembolic complications. In the Ticlopidine Aspirin Stroke Study (TASS) ticlopidine alone was superior to aspirin with a 21% risk reduction of fatal and nonfatal stroke. However, due to its unfavorable side-effects and with the availability of more tolerable ADP inhibitors ticlopidine is used scarcely in the clinical praxis. Consequently, as no study was performed comparing ticlopidine to ticagrelor, data of ticlopidine studies were not included in our network

meta-analysis.[128] Moreover, with reassuring results on the reduction in ischemic events seen in ACS, the question was raised whether the intensification of antiplatelet therapy could be similarly beneficial in the prevention of ischemic stroke. Our findings are partly in line with previous meta-analyses indicating that ticagrelor was more effective in reducing combined ischemic and hemorrhagic stroke compared with other antiplatelet regimens in patients with CAD, cerebrovascular disease or PAD and extended these with the observation that stroke prevention potential is consistently reflected in trials with ticagrelor treatment regardless the inclusion condition. Importantly, prevention and bleeding trade-off show clustering at the level of antiplatelet monotherapies and combinations. P2Y12 inhibitor and aspirin combination show more effective stroke prevention, but its use is associated with an increase in the risk of bleeding. This risk includes intracranial bleeding that is significantly higher with ticagrelor and aspirin. The analysis did not show important benefits of ticagrelor based combination when compared to clopidogrel. Net adverse clinical events showed only benefit among studies with ACS patients.[129]

Our network analysis included some trials that also applied prasugrel, another effective but irreversible P2Y12 blocking agent in combination with aspirin. It is important to note that in the fundamental TRITON TIMI-38 trial increasing the risk of bleeding events including fatal bleeding was found in patients with a history of TIA or stroke.[7] Although TRITON-TIMI-38 was not powered for poststroke/TIA events, and only a limited percentage of patients had a history of cerebrovascular disease, prasugrel is contraindicated for them.[7] As all included trials were performed after the TRITON TIMI-38 thus TIA or stroke was a contraindication for prasugrel treatment while ticagrelor was applied even amongst the highest risk for intracranial bleeding like those with recent stroke. We believe that the clinical applicability of prasugrel among patients with earlier cerebrovascular events remains to be studied in greater detail. The magnitude of its treatment effect is, however, at the range of the other P2Y12 inhibitors when applied in patients without a cerebrovascular history.

It remains unclear if the preventive effect of ticagrelor is explainable with its more effective inhibition of P2Y12 dependent platelet activation or with additional effects like increase in adenosine levels due to an additional blockage via ENT-1 leading to platelet inhibition, inflammatory milieu modulation, vasodilation and protection from ischemia and reperfusion injury.[130] With the integration of these data, ticagrelor may have additional protective effects on cerebral ischemia-reperfusion. Additionally, to the potentially lower bleeding risk due to the reversible P2Y12 inhibition, animal studies indicated neuroprotective effects of ticagrelor through endothelial nitric oxide synthase modulation resulting in increased blood flow and reducing infarct volume.[131]

Both the THALES trial and the subgroup analysis of the SOCRATES trial support these findings indicating a risk reduction of 32% with ticagrelor and 27% with aspirin plus ticagrelor over aspirin in patients with minor ischemic stroke or high-risk TIA. [45,80] However, it is important to note that these trials also found an important increase of bleeding complications that may reduce or cancel out the ischemic benefit. Functional health status such as disabling stroke outcome (defined as death or Rankin scale >1) was reported only in the THALES and SOCRATES trials. The analysis of this endpoint did not explore important differences.

7. NOVEL FINDINGS

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

- our meta-analysis supports that LPR is associated with an increased bleeding risk of patients who underwent coronary stent implantation. The possible benefit of this marker in risk stratification or improvement of risk prediction if combining with other factors in prediction models remains to be established by further studies.
- our analysis of a real-life, coronary intervention treated acute myocardial infarction population found that the apparent higher rate of all-cause mortality, and MACE, among OAC-treated patients compared to the patients without OAC treatment may be attributable to the inherently higher risk of these cases. The data from risk-adjusted analyses found a signal for a worse prognosis of anticoagulated cases if aspirin was withheld.
- our analysis of clinical trials supports that the use of ticagrelor as mono- or aspirin combined therapy resulted in more effective stroke prevention in a high-risk patient population. Highlighting the trade-off between bleeding risk and stroke prevention the data show that besides ischemic risk also bleeding risk should be assessed and considered. This lower risk of ischemic stroke with ticagrelor was counterbalanced with a higher risk of major bleeding including an importantly increased risk of intracranial bleeding. The decision regarding the choice of antiplatelet agent and its duration should be individualized according to the risks and benefits of the chosen treatment.

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9. REFERENCES

1. Moran, A. E. *et al.* Assessing the global burden of ischemic heart disease: Part 1: Methods for a systematic review of the global epidemiology of ischemic heart disease in 1990 and 2010. *Glob. Heart* **7**, 315–329 (2012).
2. Jánosi, A. *et al.* Clinical characteristics, hospital care, and prognosis of patients with ST elevation myocardial infarction: Hungarian Myocardial Infarction Registry. *Eur. Hear. J. Suppl.* **16**, A12–A15 (2014).
3. M, N. *et al.* From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. *Circulation* **108**, 1664–1672 (2003).
4. C, B. *et al.* Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet (London, England)* **373**, 1849–1860 (2009).
5. GN, L. *et al.* 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J. Am. Coll. Cardiol.* **68**, 1082–1115 (2016).
6. Valgimigli, M. *et al.* 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur. Heart J.* **39**, 213–260 (2018).
7. Wiviott, S. D. *et al.* Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes. *N. Engl. J. Med.* **357**, 2001–2015 (2007).
8. Wallentin, L. *et al.* Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. *N. Engl. J. Med.* **361**, 1045–1057 (2009).
9. Neumann, F.-J. *et al.* 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur. Heart J.* (2018) doi:10.1093/eurheartj/ehy394.
10. Park, D. W. *et al.* Clinically Significant Bleeding with Ticagrelor Versus Clopidogrel in Korean Patients with Acute Coronary Syndromes Intended for Invasive Management: A Randomized Clinical Trial. *Circulation* **140**, 1865–1877 (2019).
11. EM, A. *et al.* Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction) analysis. *J. Am. Coll. Cardiol.* **51**, 2028–2033 (2008).
12. RC, B. *et al.* Bleeding complications with the P2Y12 receptor antagonists clopidogrel and ticagrelor in the PLATelet inhibition and patient Outcomes

(PLATO) trial. *Eur. Heart J.* **32**, 2933–2944 (2011).

13. Aradi, D. *et al.* Prognostic significance of high on-clopidogrel platelet reactivity after percutaneous coronary intervention: Systematic review and meta-analysis. *Am. Heart J.* **160**, (2010).

14. Fiolaki, A. *et al.* High on treatment platelet reactivity to aspirin and clopidogrel in ischemic stroke: A systematic review and meta-analysis. *J. Neurol. Sci.* **376**, 112–116 (2017).

15. Taglieri, N. *et al.* Risk of Stroke in Patients With High On-Clopidogrel Platelet Reactivity to Adenosine Diphosphate After Percutaneous Coronary Intervention. *Am. J. Cardiol.* **113**, 1807–1814 (2014).

16. Mangiacapra, F. *et al.* Impact of platelet reactivity on 5-year clinical outcomes following percutaneous coronary intervention: a landmark analysis. *J. Thromb. Thrombolysis* **45**, 496–503 (2018).

17. Aradi, D. *et al.* 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.* **36**, 1762–1771 (2015).

18. Cornel, J. H. *et al.* Relationship of Platelet Reactivity With Bleeding Outcomes During Long-Term Treatment With Dual Antiplatelet Therapy For Medically Managed Patients With Non-St-Segment Elevation Acute Coronary Syndromes. *J. Am. Heart Assoc.* **5**, (2016).

19. Sorrentino, S. *et al.* Dual Antiplatelet Therapy Cessation and Adverse Events After Drug-Eluting Stent Implantation in Patients at High Risk for Atherothrombosis (from the PARIS Registry). *Am. J. Cardiol.* **122**, 1638–1646 (2018).

20. Mardikar, H. M. *et al.* Optimal platelet inhibition in patients undergoing PCI: Data from the Multicenter Registry of High-Risk Percutaneous Coronary Intervention and Adequate Platelet Inhibition (MR PCI) study. *Am. Heart J.* **154**, 344.e1-344.e5 (2007).

21. J, T., B, B., G, R., Z, A.-T. & L, K. [The prevalence of atrial fibrillation in Hungary]. *Orv. Hetil.* **153**, 339–342 (2012).

22. HJ, L. *et al.* Stroke severity in atrial fibrillation. The Framingham Study. *Stroke* **27**, 1760–1764 (1996).

23. RH, D. & JI, S. Secondary Stroke Prevention in Nonvalvular Atrial Fibrillation. *South. Med. J.* **109**, 721–729 (2016).

24. Powers, W. J. *et al.* Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke a guideline for healthcare professionals from the

American Heart Association/American Stroke Association. *Stroke* vol. 50 E344–E418 (2019).

25. D, C. *et al.* Management of Antithrombotic Therapy in Atrial Fibrillation Patients Undergoing PCI: JACC State-of-the-Art Review. *J. Am. Coll. Cardiol.* **74**, 83–99 (2019).

26. N, van R. *et al.* Major Bleeding Rates in Atrial Fibrillation Patients on Single, Dual, or Triple Antithrombotic Therapy. *Circulation* **139**, 775–786 (2019).

27. Wallentin, L. *et al.* Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N. Engl. J. Med.* **361**, 1045–1057 (2009).

28. Buonamici, P. *et al.* Impact of Platelet Reactivity After Clopidogrel Administration on Drug-Eluting Stent Thrombosis. *J. Am. Coll. Cardiol.* **49**, 2312–2317 (2007).

29. Cuisset, T. *et al.* Predictive value of post-treatment platelet reactivity for occurrence of post-discharge bleeding after non-ST elevation acute coronary syndrome. Shifting from antiplatelet resistance to bleeding risk assessment? *EuroIntervention* **5**, 325–9 (2009).

30. SIBBING, D. *et al.* Antiplatelet effects of clopidogrel and bleeding in patients undergoing coronary stent placement. *J. Thromb. Haemost.* **8**, 250–256 (2010).

31. Spiliopoulos, S. *et al.* Platelet Responsiveness to Clopidogrel Treatment After Peripheral Endovascular Procedures. *J. Am. Coll. Cardiol.* **61**, 2428–2434 (2013).

32. Bálint, A. *et al.* Increased risk of adverse events in patients with low-on clopidogrel platelet reactivity after percutaneous coronary intervention: A systematic review and meta-analysis. *Cardiol. J.* (2021) doi:10.5603/CJ.A2021.0084.

33. Conen, D. Epidemiology of atrial fibrillation. 1323–1324 (2018) doi:10.1093/eurheartj/ehy171.

34. Kirchhof, P. *et al.* 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS The Task Force for theTask, A., Members, F., Kirchhof, P., Uk, C., Uk, D. K., Uk, B. C., … Germany, G. H. (2016). 2016 ESC Guidelines for the management of. 2893–2962 (2016) doi:10.1093/eurheartj/ehw210.

35. The ACTIVE Writing Group on behalf of the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fi brillation in the Atrial fi brillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* **367**, 1903–12 (2006).

36. Steffel, J. *et al.* The 2018 European Heart Rhythm Association Practical Guide on the use of non-Vitamin K antagonist oral anticoagulants in patients with

atrial fibrillation: Executive summary. *Europace* (2018) doi:10.1093/europace/euy054.

37. Dewilde, W. J. M. *et al.* Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: An open-label, randomised, controlled trial. *Lancet* **381**, 1107–1115 (2013).

38. Connolly, S. J. *et al.* Dabigatran versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* **361**, 1139–51 (2009).

39. Gibson, C. M. *et al.* Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. *N. Engl. J. Med.* **375**, 2423–2434 (2016).

40. Lopes, R. D. *et al.* Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation. *N. Engl. J. Med.* **380**, 1509–1524 (2019).

41. Bálint, A. *et al.* Oral anticoagulation and outcomes in patients with acute myocardial infarction: Insights from the Hungarian Myocardial Infarction Registry. *Int. J. Clin. Pract.* (2021) doi:10.1111/ijcp.14179.

42. Donkor, E. S. Stroke in the 21st Century: A Snapshot of the Burden, Epidemiology, and Quality of Life. *Stroke Research and Treatment* vol. 2018 (2018).

43. Amarenco, P. *et al.* Efficacy and safety of ticagrelor versus aspirin in acute stroke or transient ischaemic attack of atherosclerotic origin: a subgroup analysis of SOCRATES, a randomised, double-blind, controlled trial. *Lancet Neurol.* **16**, 301–310 (2017).

44. SC, J. *et al.* Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA. *N. Engl. J. Med.* **383**, 207–217 (2020).

45. Bhatt, D. L. *et al.* Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events. *N. Engl. J. Med.* **354**, 1706–1717 (2006).

46. A, B., D, T., O, E. A. E. A., P, K. & A, K. Network Meta-Analysis of Ticagrelor for Stroke Prevention in Patients at High Risk for Cardiovascular or Cerebrovascular Events. *Stroke* **52**, 2809–2816 (2021).

47. Thygesen, K. *et al.* Third Universal Definition of Myocardial Infarction. *Circulation* **126**, 2020–2035 (2012).

48. Ndrepepa, G. *et al.* Validation of the Bleeding Academic Research Consortium Definition of Bleeding in Patients With Coronary Artery Disease Undergoing Percutaneous Coronary Intervention. *Circulation* **125**, 1424–1431 (2012).

49. Harrer, M., Cuijpers, P., Furukawa, T. A. & Ebert, D. D. Doing Meta-Analysis With R: A Hands-On Guide. (2021).

50. OpenMeta-Analyst: open-source, cross-platform software for advanced meta-analysis | Colloquium Abstracts. https://abstracts.cochrane.org/2010-keystone/openmeta-analyst-open-source-cross-platform-software-advanced-meta-analysis.

51. 9.5.2 Identifying and measuring heterogeneity. https://handbook-5-1.cochrane.org/chapter_9/9_5_2_identifying_and_measuring_heterogeneity.htm.

52. Wolff, R. F. *et al.* PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies. *Ann. Intern. Med.* **170**, 51 (2019).

53. Wells G. A., Shea B., O'Connell D., Peterson J., Welch V., Losos M., et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-analyses. Available online. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (2000).

54. Jánosi, A. *et al.* Short and long term prognosis of patients with myocardial infarction. Hungarian Myocardial Infarction Registry. *Orv. Hetil.* **154**, 1297–1302 (2013).

55. Komócsi, A. *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.* **214**, 485–90 (2016).

56. Thygesen, K. *et al.* Fourth universal definition of myocardial infarction (2018). *Eur. Heart J.* **40**, 237–269 (2019).

57. Morgan, S. L. & Todd, J. J. A diagnostic routine for the detection of consequential heterogeneity of causal effects with a demonstration from school effects research. *Sociol. Methodol.* **38**, 231–281 (2008).

58. Fine, J. P. & Gray, R. J. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *J. Am. Stat. Assoc.* **94**, 496–509 (1999).

59. Rücker, G. Network meta-analysis, electrical networks and graph theory. *Res. Synth. Methods* **3**, 312–324 (2012).

60. Rücker, G. & Schwarzer, G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med. Res. Methodol.* **15**, 58 (2015).

61. Chaimani, A., Higgins, J. P. T., Mavridis, D., Spyridonos, P. & Salanti, G. Graphical Tools for Network Meta-Analysis in STATA. *PLoS One* **8**, e76654 (2013).

62. Patti, G. *et al.* Point-of-care measurement of clopidogrel responsiveness predicts clinical outcome in patients undergoing percutaneous coronary

intervention results of the ARMYDA-PRO (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty-Platelet Reactivity Predicts Outcome) study. *J. Am. Coll. Cardiol.* **52**, 1128–33 (2008).

63. Tsukahara, K. *et al.* Impact of high-responsiveness to dual antiplatelet therapy on bleeding complications in patients receiving drug-eluting stents. *Circ. J.* **74**, 679–85 (2010).

64. Huczek, Z. *et al.* Medium on-treatment platelet reactivity to ADP is favorable in patients with acute coronary syndromes undergoing coronary stenting. *Platelets* **22**, 521–9 (2011).

65. BONELLO, L. *et al.* Relationship between post-treatment platelet reactivity and ischemic and bleeding events at 1-year follow-up in patients receiving prasugrel. *J. Thromb. Haemost.* **10**, 1999–2005 (2012).

66. Cuisset, T. *et al.* Platelet reactivity in diabetic patients undergoing coronary stenting for acute coronary syndrome treated with clopidogrel loading dose followed by prasugrel maintenance therapy. *Int. J. Cardiol.* **168**, 523–528 (2013).

67. Cuisset, T. *et al.* Clinical Implications of Very Low On-Treatment Platelet Reactivity in Patients Treated With Thienopyridine: The POBA Study (Predictor of Bleedings With Antiplatelet Drugs). *JACC Cardiovasc. Interv.* **6**, 854–863 (2013).

68. Alfredsson, J. *et al.* Large early variation of residual platelet reactivity in Acute Coronary Syndrome patients treated with clopidogrel. *Thromb. Res.* **136**, 335–340 (2015).

69. Li, S., Liu, H. & Liu, J. Predictive performance of adding platelet reactivity on top of CRUSADE score for 1-year bleeding risk in patients with acute coronary syndrome. *J. Thromb. Thrombolysis* **42**, 360–368 (2016).

70. Jin, L. *et al.* The Prognostic Value of ADP-Induced Platelet Aggregation for Bleeding Complications in Low – Intermediate Risk Patients with Acute Coronary Syndrome Taking Clopidogrel After Percutaneous Coronary Intervention. *Hear. Lung Circ.* **26**, 49–57 (2017).

71. Deharo, P. *et al.* Benefit of Switching Dual Antiplatelet Therapy After Acute Coronary Syndrome According to On-Treatment Platelet Reactivity. *JACC Cardiovasc. Interv.* **10**, 2560–2570 (2017).

72. Aradi, D. *et al.* Platelet reactivity and clinical outcomes in acute coronary syndrome patients treated with prasugrel and clopidogrel: a pre-specified exploratory analysis from the TROPICAL-ACS trial. *Eur. Heart J.* **40**, 1942–1951 (2019).

73. Mshelbwala, F. S., Hugenberg, D. W. & Kreutz, R. P. Intensified P2Y12

inhibition for high-on treatment platelet reactivity. *J. Thromb. Thrombolysis* **50**, 619–627 (2020).

74. Kabbani, S. S. *et al.* Usefulness of platelet reactivity before percutaneous coronary intervention in determining cardiac risk one year later. *Am. J. Cardiol.* **91**, 876–878 (2003).

75. Mangiacapra, F. *et al.* A therapeutic window for platelet reactivity for patients undergoing elective percutaneous coronary intervention: Results of the ARMYDA-PROVE (Antiplatelet therapy for Reduction of MYocardial Damage during AngioplastyPlatelet Reactivity for Outcome Valida. *JACC Cardiovasc. Interv.* **5**, 281–289 (2012).

76. Patti, G., Pasceri, V., Vizzi, V., Ricottini, E. & Di Sciascio, G. Usefulness of Platelet Response to Clopidogrel by Point-of-Care Testing to Predict Bleeding Outcomes in Patients Undergoing Percutaneous Coronary Intervention (from the Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty-Bleeding Study). *Am. J. Cardiol.* **107**, 995–1000 (2011).

77. Mangiacapra, F. *et al.* Impact of chronic kidney disease on platelet reactivity and outcomes of patients receiving clopidogrel and undergoing percutaneous coronary intervention. *Am. J. Cardiol.* **113**, 1124–9 (2014).

78. S.N., L., D., M., M.K., S., K.-W., M. & K.-D., Y. Impact of platelet reactivity on long-term prognosis in Korean patients receiving percutaneous coronary intervention. *Platelets* (2019) doi:10.1080/09537104.2018.1562172.

79. Nakamura, M. *et al.* Relationship Between Platelet Reactivity and Ischemic and Bleeding Events After Percutaneous Coronary Intervention in East Asian Patients: 1-Year Results of the PENDULUM Registry. *J. Am. Heart Assoc.* **9**, e015439 (2020).

80. Johnston, S. C. *et al.* Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA. *N. Engl. J. Med.* **383**, 207–217 (2020).

81. Johnston, S. C. *et al.* Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack. *N. Engl. J. Med.* **375**, 35–43 (2016).

82. Wang, Y. *et al.* Ticagrelor plus aspirin versus clopidogrel plus aspirin for platelet reactivity in patients with minor stroke or transient ischaemic attack: Open label, blinded endpoint, randomised controlled phase II trial. *BMJ* **365**, l2211 (2019).

83. Cannon, C. P. *et al.* Safety, Tolerability, and Initial Efficacy of AZD6140, the First Reversible Oral Adenosine Diphosphate Receptor Antagonist, Compared With Clopidogrel, in Patients With Non-ST-Segment Elevation Acute Coronary Syndrome. Primary Results of the DISPERSE-2 Trial. *J. Am. Coll. Cardiol.* **50**, 1844–1851 (2007).

84. Berwanger, O. *et al.* Ticagrelor Versus Clopidogrel in Patients With STEMI Treated With Fibrinolysis: TREAT Trial. *J. Am. Coll. Cardiol.* **73**, 2819–2828 (2019).

85. Schüpke, S. *et al.* Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes. *N. Engl. J. Med.* NEJMoa1908973 (2019) doi:10.1056/NEJMoa1908973.

86. Gimbel, M. *et al.* Clopidogrel versus ticagrelor or prasugrel in patients aged 70 years or older with non-ST-elevation acute coronary syndrome (POPular AGE): the randomised, open-label, non-inferiority trial. *Lancet* **395**, 1374–1381 (2020).

87. Kim, B. K. *et al.* Effect of Ticagrelor Monotherapy vs Ticagrelor with Aspirin on Major Bleeding and Cardiovascular Events in Patients with Acute Coronary Syndrome: The TICO Randomized Clinical Trial. *JAMA - J. Am. Med. Assoc.* **323**, 2407–2416 (2020).

88. Bonaca, M. P. *et al.* Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction. *N. Engl. J. Med.* **372**, 1791–1800 (2015).

89. Goto, S., Huang, C. H., Park, S. J., Emanuelsson, H. & Kimura, T. Ticagrelor vs. Clopidogrel in Japanese, Korean and Taiwanese patients with acute coronary syndrome – Randomized, double-blind, phase III PHILO study. *Circ. J.* **79**, 2452–2460 (2015).

90. Motovska, Z. *et al.* 1-Year Outcomes of Patients Undergoing Primary Angioplasty for Myocardial Infarction Treated With Prasugrel Versus Ticagrelor. *J. Am. Coll. Cardiol.* **71**, 371–381 (2018).

91. Tang, X. *et al.* Assessment of Ticagrelor Versus Clopidogrel Treatment in Patients With ST-elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. *J. Cardiovasc. Pharmacol.* **68**, 115–120 (2016).

92. Wang, H. & Wang, X. Efficacy and safety outcomes of ticagrelor compared with clopidogrel in elderly Chinese patients with acute coronary syndrome. *Ther. Clin. Risk Manag.* **12**, 1101–1105 (2016).

93. Zhang, Y. *et al.* High-dose clopidogrel versus ticagrelor for treatment of acute coronary syndromes after percutaneous coronary intervention in CYP2C19 intermediate or poor metabolizers: a prospective, randomized, open-label, single-centre trial. *Acta Cardiol.* **71**, 309–316 (2016).

94. Dehghani, P. *et al.* Effects of ticagrelor versus clopidogrel on platelet function in fibrinolytic-treated STEMI patients undergoing early PCI. *Am. Heart J.* **192**, 105–112 (2017).

95. Wu, H. B. *et al.* Clinical efficacy of ticagrelor in patients undergoing emergency

intervention for acute myocardial infarction and its impact on platelet aggregation rate. *Am. J. Transl. Res.* **10**, 2175–2183 (2018).

96. Mehran, R. *et al.* Ticagrelor with or without aspirin in high-risk patients after PCI. *N. Engl. J. Med.* **381**, 2032–2042 (2019).

97. Bonello, L. *et al.* Comparison of Ticagrelor Versus Prasugrel to Prevent Periprocedural Myonecrosis in Acute Coronary Syndromes. *Am. J. Cardiol.* **116**, 339–343 (2015).

98. Hiatt, W. R. *et al.* Ticagrelor versus Clopidogrel in Symptomatic Peripheral Artery Disease. *N. Engl. J. Med.* **376**, 32–40 (2017).

99. Zhao, Q. *et al.* Effect of ticagrelor plus aspirin, ticagrelor alone, OR aspirin alone on saphenous vein graft patency 1 year after coronary artery bypass grafting: A Randomized clinical trial. *JAMA - J. Am. Med. Assoc.* **319**, 1677–1686 (2018).

100. Hochholzer, W. *et al.* Randomized Comparison of Oral P2Y12-Receptor Inhibitor Loading Strategies for Transitioning From Cangrelor: The ExcelsiorLOAD2 Trial. *JACC Cardiovasc. Interv.* **10**, 121–129 (2017).

101. Bhatt, D. L. *et al.* Ticagrelor in patients with diabetes and stable coronary artery disease with a history of previous percutaneous coronary intervention (THEMIS-PCI): a phase 3, placebo-controlled, randomised trial. *Lancet* **394**, 1169–1180 (2019).

102. Jimenez Diaz, V. A. *et al.* Assessment of Platelet REACtivity After Transcatheter Aortic Valve Replacement: The REAC-TAVI Trial. *JACC Cardiovasc. Interv.* **12**, 22–32 (2019).

103. SIBBING, D. *et al.* Antiplatelet effects of clopidogrel and bleeding in patients undergoing coronary stent placement. *J. Thromb. Haemost.* **8**, 250–256 (2010).

104. Cornel, J. H. *et al.* Relationship of Platelet Reactivity With Bleeding Outcomes During Long-Term Treatment With Dual Antiplatelet Therapy for Medically Managed Patients With Non-ST-Segment Elevation Acute Coronary Syndromes. *J. Am. Heart Assoc.* **5**, (2016).

105. Aradi, D. *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.* **36**, 1762–71 (2015).

106. Piqueras-Flores, J. *et al.* Efficacy and Safety of Loading Doses With P2Y12-Receptor Antagonists in Patients Without Dual Antiplatelet Therapy Undergoing Elective Coronary Intervention. *J. Cardiovasc. Pharmacol.* **73**, 56–59 (2019).

107. Tekkesin, A. I. *et al.* The first six-month clinical outcomes and risk factors

associated with high on-treatment platelet reactivity of clopidogrel in patients undergoing coronary interventions. *Anatol. J. Cardiol.* **16**, 967–973 (2016).

108. Wakabayashi, S. *et al.* Efficacy of 2.5-mg prasugrel in elderly or low-body-weight patients. *Circ. J.* **82**, 2326–2331 (2018).

109. Droppa, M. *et al.* Evaluation of Clinical Risk Factors to Predict High On-Treatment Platelet Reactivity and Outcome in Patients with Stable Coronary Artery Disease (PREDICT-STABLE). *PLoS One* **10**, e0121620 (2015).

110. Komócsi, A. *et al.* Meta-analysis of randomized trials on access site selection for percutaneous coronary intervention in ST-segment elevation myocardial infarction. *Arch. Med. Sci.* **10**, (2014).

111. Ruff, C. T. *et al.* Long-term cardiovascular outcomes in patients with atrial fibrillation and atherothrombosis in the REACH Registry. *Int. J. Cardiol.* (2014) doi:10.1016/j.ijcard.2013.11.030.

112. Chwan Ng, A. C. *et al.* Long-term cardiovascular and noncardiovascular mortality of 1023 patients with confirmed acute pulmonary embolism. *Circ. Cardiovasc. Qual. Outcomes* **4**, 122–128 (2011).

113. Velangi, P. S. *et al.* Long-Term Embolic Outcomes After Detection of Left Ventricular Thrombus by Late Gadolinium Enhancement Cardiovascular Magnetic Resonance Imaging: A Matched Cohort Study. *Circ. Cardiovasc. Imaging* **12**, e009723 (2019).

114. Austin, P. C. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav. Res.* **46**, 399–424 (2011).

115. Andreotti, F., Testa, L., Biondi-Zoccai, G. G. L. & Crea, F. Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes: an updated and comprehensive meta-analysis of 25,307 patients. *Eur. Heart J.* **27**, 519–26 (2006).

116. 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.* **172**, (2012).

117. Mega, J. L. *et al.* Rivaroxaban in patients with a recent acute coronary syndrome. *N. Engl. J. Med.* (2012) doi:10.1056/NEJMoa1112277.

118. Komócsi, A., Vorobcsuk, A. & Aradi, D. New oral anticoagulants in acute coronary syndromes: What does a meta-analysis tell us? Reply. *JAMA Intern. Med.* **173**, (2013).

119. Eikelboom, J. W. *et al.* Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. *N. Engl. J. Med.* **377**, 1319–1330 (2017).

120. Lopes, R. D. *et al.* Safety and Efficacy of Antithrombotic Strategies in Patients with Atrial Fibrillation Undergoing Percutaneous Coronary Intervention: A Network Meta-analysis of Randomized Controlled Trials. *JAMA Cardiol.* **27701**, 1–9 (2019).

121. Gibson, C. M. *et al.* Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. *N. Engl. J. Med.* **375**, 2423–2434 (2016).

122. Lopes, R. D. *et al.* Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N. Engl. J. Med.* **380**, 1509–1524 (2019).

123. Cannon, C. P. *et al.* Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. *N. Engl. J. Med.* **377**, 1513–1524 (2017).

124. Vranckx, P. *et al.* Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. *Lancet* (2019) doi:10.1016/s0140-6736(19)31872-0.

125. TS, P. *et al.* Revisiting the effects of omitting aspirin in combined antithrombotic therapies for atrial fibrillation and acute coronary syndromes or percutaneous coronary interventions: meta-analysis of pooled data from the PIONEER AF-PCI, RE-DUAL PCI, and AUGUSTUS trials. *Europace* **22**, 33–46 (2020).

126. Rothwell, P. M. *et al.* Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. *Lancet* **388**, 365–375 (2016).

127. Bornstein, N. M. *et al.* Failure of aspirin treatment after stroke. *Stroke* **25**, 275–277 (1994).

128. Hass, W. K. *et al.* A Randomized Trial Comparing Ticlopidine Hydrochloride with Aspirin for the Prevention of Stroke in High-Risk Patients. *N. Engl. J. Med.* **321**, 501–507 (1989).

129. Malhotra, K. *et al.* Ticagrelor for stroke prevention in patients with vascular risk factors: A systematic review and meta-analysis. *J. Neurol. Sci.* **390**, 212–218 (2018).

130. Cattaneo, M., Schulz, R. & Nylander, S. Adenosine-mediated effects of ticagrelor: Evidence and potential clinical relevance. *Journal of the American College of Cardiology* vol. 63 2503–2509 (2014).

131. Yamauchi, K., Imai, T., Shimazawa, M., Iwama, T. & Hara, H. Effects of ticagrelor in a mouse model of ischemic strokearticle. *Sci. Rep.* **7**, 1–10 (2017).

10. SCIENTOMETRICS

Scientific papers:

- Total: **11**
- English language papers: **11**

Impact factor (up to Jan 2022):

- First author: **13.154**
- Cumulative: **29.444**

Citations (up to Jan 2022 based on MTMT2):

- Independent: **36**
- Cumulative: **38**

10.1. Topic-related scientific articles

A Bálint, L Hanák, P Hegyi, Zs Szakács, Sz Eitmann, A Garami, M Solymár, K Márta, Z Rumbus, A Komócsi: Increased risk of adverse events in patients with low-on clopidogrel platelet reactivity after percutaneous coronary intervention: A systematic review and meta-analysis; DOI: https://doi.org/10.5603/CJ.a2021.0084 **Cardiology Journal** (2021) **IF=2.737 (2020) Q2**

A Bálint, P Kupó, D Tornyos, O Abdallaoui, A Jánosi, A Komócsi: Oral anticoagulation and outcomes in patients with acute myocardial infarction: Insights from the Hungarian Myocardial Infarction Registry; DOI: 10.1111/ijcp.14179 **International Journal of Clinical Practice** (2021) **IF=2.503 (2020) Q1**

A Bálint, D Tornyos, O Abdallaoui, P Kupó, A Komócsi: Network Meta-Analysis of Ticagrelor for Stroke Prevention in Patients at High Risk for Cardiovascular or Cerebrovascular Events; DOI: https://doi.org/10.1161/STROKEAHA.120.032670 **Stroke** 2021 **IF=7.914 (2020) Q1**

CUMULATIVE IMPACT FACTOR: **13.154**

10.2. Non-topic-related scientific articles

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; DOI: 10.1007/s10840-019-00683-z.
Journal of Interventional Cardiac Electrophysiology (2019);

IF=1.277 Q2

D Tornyos, **A Bálint**, O Abdallaoui, P Kupó, A Komócsi: Antithrombotic Therapy for Secondary Prevention in Patients with Non-Cardioembolic Stroke or Transient Ischemic Attack: A Systematic Review; DOI: 10.3390/life11050447.
Life (2021) **IF= 3.817 (2020) 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; DOI: 10.1177/0003319719874255.
Angiology (2020) **IF=3.619 Q1**

P Kupó, D Tornyos, **A Bálint**, R Lukács, A Jánosi, A Komócsi: Use of drug-eluting stents in elderly patients with acute myocardial infarction; DOI: 10.1111/ijcp.13652.
International Journal of Clinical Practice (2020) **IF=2.444 Q2**

T Kocsis, B Molnár, D Németh, P Hegyi, Zs Szakács, **A Bálint**, András Garami, A Soós, K Márta , M Solymár: Probiotics have beneficial metabolic effects in patients with type 2 diabetes mellitus: a meta-analysis of randomized clinical trials; DOI: 10.1038/s41598-020-68440-1.
Sci Rep 10**,** 11787 (2020) **IF= 5.133 Q1**

10.3. Topic-related abstracts published in scientific journals

A Bálint, P Kupó, D Tornyos, O Abdallaoui, A Jánosi, A Komócsi: Oral anticoagulation and outcomes in patients with acute myocardial infarction: Insights from the Hungarian Myocardial Infarction Registry.
Medical Conference for PhD Students and Experts of Clinical Sciences 2021: Book of Abstracts pp 41-41 ISBN: 9789634296539

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**

A Bálint, A Komócsi, D Tornyos, P Kupó, E Jánosa , A Jánosi MD VIII. Interdiszciplináris Doktorandusz Konferencia 2019. Absztraktkötet; **8th Interdisciplinary Doctoral Conference 2019. Book of Abstracts**. Pécs, Magyarország: Pécsi Tudományegyetem Doktorandusz Önkormányzat (2019), 118 p. ISBN: 9789634293743

10.4. Non-topic-related abstracts published in scientific journals

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**

Bálint A, Kósa D, Gasz B, Komócsi A:
X. Interdiszciplináris Doktorandusz Konferencia 2021 Absztraktkötet: **10th Interdisciplinary Doctoral Conference 2021 Book of Abstracts. Pécs, Hungary**: Pécsi Tudományegyetem Doktorandusz Önkormányzat (2021), 23 p. ISBN: 978-963-429-820-5

10.5. Oral and poster presentations

2014.04. **Bálint A**, Balogh P: A szív mikroérhálózatának vizsgálata. Házi TDK konferencia szóbeli előadás Pécs,

2017.02.16. **Bálint A**, Pintér T: Új lehetőségek az aortabillentyű sebészetben. Házi TDK konferencia szóbeli előadás, Pécs

2017.03.29. **Bálint A**, Pintér T: Új lehetőségek az aortabillentyű sebészetben. Grastyán konferencia előadás, Pécs

2017.08.25-26. **Bálint A**, Pintér T: Új lehetőségek az aortabillentyű sebészetben. HMAA Balatonfüred konferencia szóbeli előadás

2018.03.09. **Bálint A**, Pintér T: Új lehetőségek az aortabillentyű sebészetben. Korányi konferencia poszter prezentáció, Budapest

2018.03.23. **Bálint A**, Pintér T: Új lehetőségek az aortabillentyű sebészetben. Marosvásárhely OTDK konferencia szóbeli előadás

2019.05.03-05. **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, szóbeli előadás

2019.05.25. **A Bálint**, D Tornyos, E Jánosa, P Kupó, A Jánosi, A Komócsi: Residual platelet reactivity and mortality after myocardial infarction in a platelet function based P2Y12 inhibitor escalation system. Interdisciplinary Doctoral Conference Pécs, 25th May 2019, oral presentation

2021.10.17. **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, 17th Oct 2020, oral presentation

2021.04.18. **A Bálint**, Zs Wlasitsch-Nagy, A Kőnig-Péter, P Varga, J Varga, Á Schlégl, A Komócsi, E Várady, P Bogner, B Gasz: New 3D morphological and functional assessment-based method for surgical education of vascular anastomosis. Vascular Access Society Congress Berlin, online conference, 8th April, 2021, oral presentation

2021.05.15. **A Bálint**, D Kósa, B Gasz, A Komócsi: New, non-invasive computational fluid dynamic methods in the prediction of coronary artery disease progression. Medical Conference for PhD Students and Experts of Clinical Sciences, Pécs, 15th May 2021, poster presentation

2021.05.15. **A Bálint**, P Kupó, D Tornyos, O Abdallaoui, A Jánosi, A Komócsi: Oral anticoagulation and outcomes in patients with acute myocardial infarction: Insights from the Hungarian Myocardial Infarction Registry. Medical Conference for PhD Students and Experts of Clinical Sciences, Pécs, oral presentation, 15th May 2021, oral presentation

2021.10.14. **A Bálint**, P Kupó, D Tornyos, O Abdallaoui, A Komócsi: Ticagrelor alkalmazhatósága stroke prevencióban a kardio- vagy cerebrovaszkuláris események fokozott kockázatának kitett betegeknél: hálózat metaanalízis. A Magyar Kardiológusok Társasága 2021. évi Tudományos Kongresszusa, Balatonfüred 2021.10. 13-16, szóbeli előadás

2021.11.12. **A Bálint**, D Kósa, B Gasz, A Komócsi: New, non-invasive computational fluid dynamic methods in the prediction of coronary artery disease progression. Interdisciplinary Doctoral Conference Pécs, 12th Nov 2021, oral presentation

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12. APPENDIX

Articles related to the thesis

VIA MEDICA

ORIGINAL ARTICLE

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Increased risk of adverse events in patients with low-on clopidogrel platelet reactivity after percutaneous coronary intervention: A systematic review and meta-analysis

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Abstract

Background: *Clinical evidence has been controversial regarding the influence of low platelet reactivity (LPR), ischemic and bleeding outcomes among patients receiving coronary stent implantation. Hence, the present study performed a meta-analysis to systematically evaluate the significance of LPR on adverse cardiovascular events.*

Methods: *MEDLINE, EMBASE and CENTRAL databases were searched up to November 2020 for relevant studies including patients with acute coronary syndrome undergoing percutaneous coronary intervention. LPR was the exposed arm while the non-LPR group represented the control. The primary outcome of interest was bleeding risk including major and minor bleeding events. Secondary outcomes included all-cause mortality, repeated revascularization, nonfatal myocardial infarction, and stent thrombosis. Study-level outcomes were evaluated in random-effect models.*

Results: *A total of 20 studies with 19,064 patients were included. Pooled analysis showed that LPR was associated with an increased bleeding risk (relative risk [RR] 2.80, 95% confidence interval [CI] 1.95–4.02, $p < 0.01$). Patients with LPR had a lower risk of non-fatal myocardial infarction (RR 0.59, 95% CI 0.38–0.91, $p < 0.05$) and of serious vascular events (RR 0.50, 95% CI 0.30–0.84, $p < 0.01$).*

Conclusions: *Low platelet reactivity is associated with an increased bleeding risk of patients who underwent coronary stent implantation. The results suggest possible benefits of this marker in risk stratification, with potential improvement in risk prediction. There are potential advantages using combinations with other factors in prediction models, however, they require further study. PROSPERO registration number: CRD42019136393).* (Cardiol J)

Key words: low platelet reactivity, acute coronary syndrome, percutaneous coronary intervention, bleeding risk, clopidogrel

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Introduction

Dual antiplatelet therapy consisting of acetylsalicylic acid and adenosine diphosphate (ADP) receptor antagonist is essential for patients undergoing percutaneous coronary intervention (PCI) [1]. Clopidogrel used to be the gold standard therapy before the introduction of new P2Y12 inhibitors, such as prasugrel and ticagrelor, which have demonstrated their clinical advantages in large randomized controlled trials (RCTs) involving acute coronary syndrome (ACS) patients [2, 3]. Both prasugrel and ticagrelor provide more effective inhibition of platelet function than acetylsalicylic acid, however, their use was followed by an increased bleeding risk [2, 3].

Platelet function testing assesses individual response to antiplatelet drugs and platelet reactivity (PR) strongly relates to clinical outcomes after ACS [4–6]. Numerous studies have shown a relationship between high platelet reactivity (HPR) and thrombotic events [7–9]. Recent studies have also found that platelet function testing and/or genetic testing may provide important information guiding antiplatelet therapy [10, 11].

With the use of more effective agents, the prevalence of HPR has decreased and an increasing proportion of patients have very low on-treatment ADP reactivity. However, the clinical significance of low platelet ractivity (LPR) is less well established and it is not routinely measured. The effect of LPR was investigated in some studies raising a signal of increased bleeding risk which remains debated, partly due to contradictory results [12–14]. The objective herein, was to perform a systematic review and meta-analysis aimed at assessing the impact of LPR on efficacy and safety outcomes after PCI.

Methods

Search strategy

A systematic review and meta-analysis were performed with reference to the PRISMA guideline [15]. The National Library of Medical Publications (MEDLINE); including its subset, PubMed, the Excerpta Medica Database (EMBASE) and Cochrane Library databases were searched for relevant articles with no restriction of time in November 2020 by using a search strategy that combined the following: Medical Subject Headings and free-text search terms: "acute coronary syndrome" OR "ACS" AND "PCI" OR "percutaneous coronary intervention" AND "platelet reactivity" OR "thrombocyte reactivity". No language restriction was used. The PICO format was adapted to set the inclusion criteria. The PICO items selected were the following: (P) patients with ACS and/or undergoing PCI and receiving dual antiplatelet therapy consisting of acetylsalicylic acid and clopidogrel, prasugrel or ticagrelor, (I) LPR (C) non-LPR or HPR based on the measurement of on-treatment PR defined by an ADP-specific platelet function assay and (O) major adverse cardiac events (MACE) and bleeding. The non-LPR group consisted of HPR or HPR plus normal platelet reactivity (NPR) where data was given for NPR. The clinical outcomes of interest evaluated at the longest available follow-up of ADP-receptor inhibitor treatment were (a) major bleeding events (defined using the trials internal definitions using Bleeding Academic Research Consortium [BARC] 3–5 or Thrombolysis in Myocardial Infarction [TIMI] major criteria), and (b) minor bleeding events (BARC 1–2 or TIMI minor) [16], (c) definite/probable stent thrombosis, (d) non-fatal myocardial infarction (MI) (type 1, 4a, 4b), (e) a composite endpoint of the reported serious vascular events that included cardiovascular death, non-fatal MI or non-fatal stroke, (f) repeated target vessel revascularization, and (g) all-cause mortality.

Studies that assessed responsiveness to clopidogrel, which was the difference between baseline and posttreatment PR (inhibition of platelet aggregation), were excluded from the analysis. The reference lists in the articles were also checked to capture all relevant articles published within the topic of interest.

Data extraction

Observational studies and cohorts — regardless of their prospective/retrospective design — were identified. Two investigators (A.B. and A.K.) independently screened the retrieved titles, abstracts and studies for eligibility and relevant full texts were systematically retrieved for further assessment. Disagreements between reviewers were solved by consensus. The retrieved studies were examined to exclude duplicate or overlapping data. Unpublished data and meeting abstracts were not considered for the present analysis because results could not be considered as certain and definitive.

Risk of bias

The methodological qualities of the studies were assessed using the Prediction model Risk Of Bias Assessment Toll (PROBAST) for assessing the quality of cohorts and the Newcastle-Ottawa Scale with reference to observational studies [17, 18].

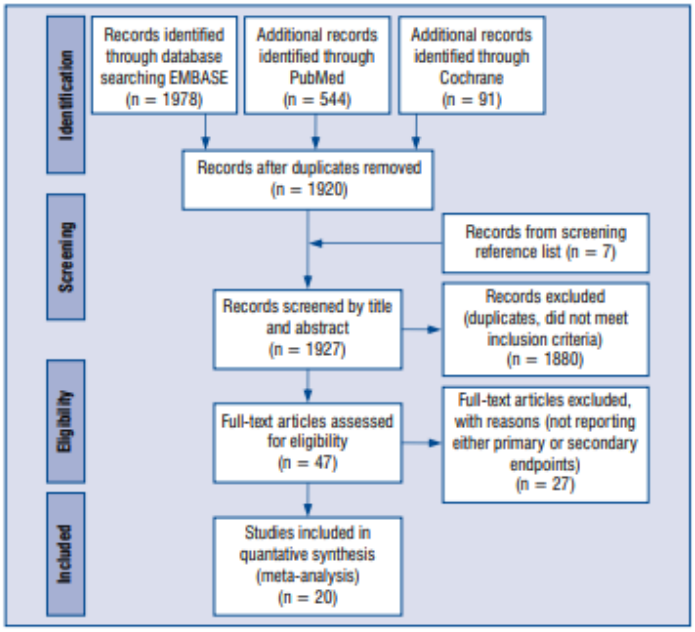

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Publication bias was estimated using funnel plots. Visual evaluation and Egger's regression intercept were used to the check for asymmetry.

Statistical analysis

Statistical computations were performed using R (v 4.0.03) package 'dmetar' designed for the evaluation of meta-analyses and OpenMeta [Analyst] open source statistical softwares. A random-effect model was applied at all the analyses with DerSimonian-Laird estimation to derive risk ratios (RR) on dichotomous outcomes and weighted mean difference on continuous data with a 95% confidence interval [CI]. Heterogeneity was tested with the χ^2 heterogeneity statistic for which a p-value < 0.1 was considered potentially heterogenous. Consistency was assessed using I^2 statistics [19]. Sensitivity analyses were carried out omitting one study at a time and calculating the effect size with the 95% CI to investigate the influence that a single study has on the final estimation regarding LPR with increased bleeding risk.

Ethical approval

Ethical or board review approval was not required for this meta-analysis.

Results

Search results and effect of LPR on the clinical outcomes

Twenty studies, involving 19,064 patients met the inclusion criteria. The process of the literature search and bias assessment is summarized in Figure 1 and for online **Supplementary Figure S4.**

Table 1 describes the main characteristics of the included studies [7, 13, 20–36]. Based on pooled results of the random-effects model meta-analysis, LPR was associated with a significantly increased risk for major and minor bleeding events compared to non-LPR (RR 2.80, 95% CI 1.95–4.02, $p < 0.01$) (Fig. 2).

Patients with LPR had significantly lower risk of non-fatal MI and of serious vascular events (RR 0.59, 95% CI 0.38–0.91, $p < 0.05$ and RR 0.50, 95% CI 0.30–0.84, $p < 0.01$, respectively; Fig. 3). The risk for stent trombosis was 45% lower in the case of LPR, however, this difference did not reach the level of statistical significance (RR 0.55, 95% CI 0.27–1.11, $p = 0.10$; Fig. 3). Even though the mortality of LPR patients was numerically higher the difference between the two groups remained insignificant (RR 1.57, 95% CI 0.69–3.57, $p = 0.28$;

Table 1. Detailed characteristics of studies included in the meta-analysis.

First author	Kabbani [20]	Patti [21]	Sibbing [7]	Tsukahara [22]	Huczek [23]	Patti [24]	Bonello [25]	Cuisset [26]	Mangiacapra [27]	Cuisset [13]
Publication year	2003	2008	2010	2010	2011	2011	2012	2012	2012	2013
Acronym	–	ARMYDA--PRO	ISAR	–	–	ARMYDA-BLEEDS	–	–	ARMYDA--PROVE	POBA
Design	P, O, single center	P, O, single center	P, O, single center	R, O, single center	P, O, single center	P, O, single center	P, O, multicenter	P, O, single center	P, O, multicenter	P, O, single center
Clinical setting	SCAD	ACS, DES	CAD	DES, ACS	ACS	SA, NSTEMI, MI	ACS	ACS	SA	NSTEMI, STEMI
Number of patients	112	160	2533	184	374	310	301	107	732	1542
Platelet function test	Flow cytometry	VerifyNow	MEA	WBA-neo	VerifyNow	VerifyNow	VASP	VASP	VerifyNow	VASP
Selected cut-off for LPR	pGP IIb/IIIa act ≤ 24.9%	lowest quartile	188 AU × min	PATI > 28 μmol/L	PRU ≤ 150	Lowest quartile	PRI < 16%	PRI < 20%	PRU ≤ 178	PRI ≤ 10%
LPR, n (%)	56 (50)	40 (25)	975 (38.5)	46 (25)	124 (33)	77 (24.8)	84 (27.9)	23 (21.5)	248 (33.9)	69 (4.5)
Clopidogrel (LD/MD, mg)	300/75	600/75	600/75	300/75	600/75	600/75	–	600/75	600/75	600/75, 600/150, 60 LD
Prasugrel (LD/MD, mg)	–	–	–	–	–	–	60 LD	10 MD	–	10 MD
Definition of bleeding	NR	BARC	TIMI	BARC	TIMI	BARC	TIMI	BARC	TIMI	BARC
End point	MI, UREV, RREV	MACE, MI, TVR	Bleeding	ST, bleeding	Bleeding, D, MI	Major bleeding	ST, bleeding	ST, MI, TVR, bleeding	D, MI, TVR, bleeding	Bleeding, ST
Follow-up, months	12	1	1	16	1	1	12	1	1	6
Age (mean ± SD)	62.5	66 ± 9	67.5 ± 10.5	68 ± 9	66.6 ± 11.3	66.5	58.1	60.5 ± 10	66 ± 10	64 ± 12.5
Female, n (%)	47 (41.9)	31 (19)	599 (23.6)	52 (28.3)	144 (38.5)	67 (21.6)	34 (11.3)	16 (14.9)	196 (26.8)	70 (4.5)
Diabetes mellitus, n (%)	29 (25.9)	55 (34)	725 (28.6)	88 (47.8)	74 (19.8)	115 (37)	70 (23.3)	107 (100)	216 (29.5)	462 (30.0)
Smoking, n (%)	NR	NR	334 (13.2)	77 (42)	180 (48.1)	NR	154 (51.2)	40 (37.4)	145 (19.8)	NR
Hypertension, n (%)	NR	NR	2295 (90.6)	140 (76.0)	251 (67.1)	NR	122 (40.5)	63 (58.9)	570 (77.8)	886 (57.4)
DES, n (%)	NR	41 (26)	2533 (100)	184 (100)	16 (4.3)	95 (30.6)	NR	NR	201 (27.5)	894 (58.0)
PCI approach (%)	NR	NR	NR	Femoral: 18	Radial: 88 Femoral: 12	Femoral: 100	NR	NR	Femoral: 96 Radial: 4	Radial: 91 Femoral: 9

→

Table 1 (cont.). Characteristics of the studies included in the meta-analysis.

First author	Mangiacapra [28]	Alfredsson [29]	Li [30]	Jin [31]	Deharo [32]	Mangiacapra [14]	Su Nam [33]	Aradi [34]	Mshelbwala [35]	Nakamura [36]
Publication year	2014	2015	2016	2017	2017	2018	2019	2019	2020	2020
Acronym	–	APACHE	–	–	TOPIC	–	–	TROPICAL-ACS	–	PENDULUM
Design	P, O, multicenter	O, single center	R, O, single center	O, single center	RCT, single center	P, O, single center	R, O, single center	RCT, multicenter	R, O, single center	P, O, multicenter
Clinical setting	SCAD,	NSTEMI,	ACS	ACS	ACS	SCAD	SA, ACS	ACS	ACS	ACS,

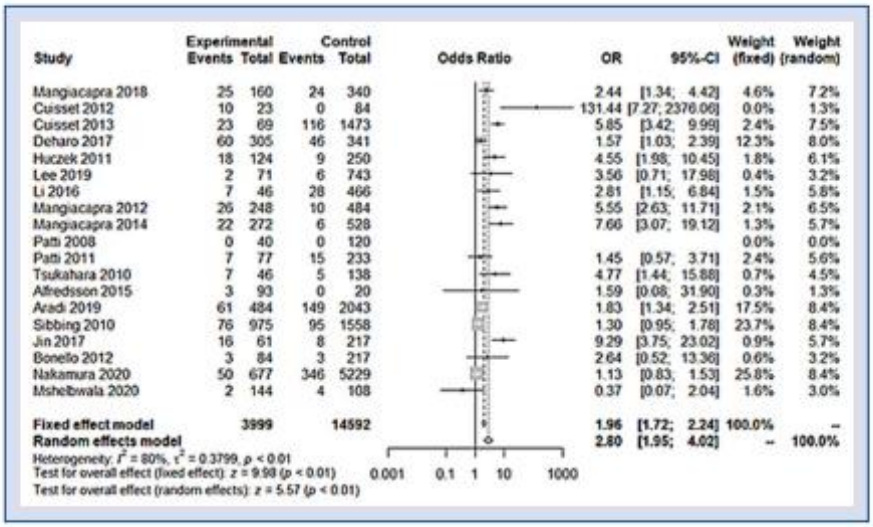

Figure 2. Principal pooled analysis. Forest plots of major and minor bleeding risk in studies following percutaneous coronary intervention with low platelet reactivity (LPR) versus without LPR. The grey rectangles are proportional with the study weight. The diamond represents the cumulative odds ratio (OR) and confidence interval (CI).

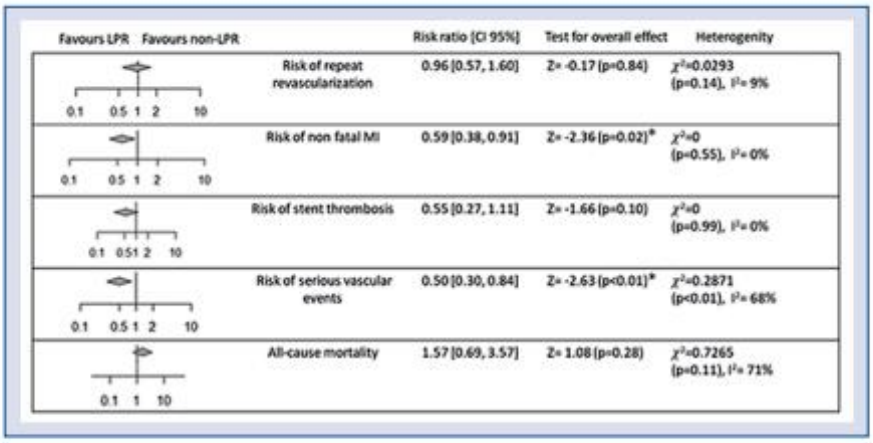

Figure 3. Summary of the outcomes of the secondary endpoints. The diamond represents the cumulative risk ratio and confidence interval (CI) of all patient groups. *Mean difference (95% CI); LPR — low platelet reactivity; MI — myocardial infarction.

Fig. 3). No significant difference was found regarding repeated revascularization (RR 0.96, 95% CI 0.57–1.60, p = 0.84; Fig. 3). Body mass index was significantly lower in the LPR group (standardized mean difference –0.18, 95% CI –0.32 to –0.05, p < 0.01; **Suppl. Fig. S1**).

Heterogeneity and subgroup analyses

The rate of LPR demonstrated a mean prevalence of 27% (95% CI for mean 20–35%, range 4.5–82%). Overall heterogeneity concerning major and minor bleeding events was considerable (I^2 = 80%, p < 0.01). To find possible determinants of the

observed heterogeneity, the prevalence of LPR and bleeding events was analyzed according to the following grouping factors: type of platelet function device, definition of bleeding events and amount of clopidogrel loading dose (LD).

The analysis confirmed that all the selected ADP-specific assays were able to predict the occurrence of bleeding events and the higher risk of patients with LPR was consistent regardless of the clinical presentation. Noticeably, considerable heterogeneity was observed in the results between studies using VASP-P and Verify Now assays; however, the Multiplate assay showed more homogenous findings (**Suppl. Fig. S2**). Subgroup analysis was also performed to assess the potential influence of different clopidogrel LD regimes. Despite the different types of clopidogrel loading dose, heterogeneity remained high (**Suppl. Fig. S2**).

When bleeding events were divided into major and minor events separately the heterogeneity was reduced considerably for major bleeding ($I^2 = 34\%$) while heterogeneity remained high for minor bleeding ($I^2 = 82\%$; **Suppl. Fig. S3**).

Publication bias

Based on visual estimation of the funnel plot for bleeding events, no major asymmetry suggestive for publication bias was found. Furthermore, Egger's regression test confirms no small-study effect (**Suppl. Fig. S4**). Analysis of bias showed high quality of the source information with low probability of possible bias (**Suppl. Fig. S4**).

Discussion

The key finding of this meta-analysis is that patients with LPR after PCI are at a higher risk of bleeding. LPR detected by an ADP-specific laboratory assay is also associated with a lower risk of non-fatal MI. The composite endpoint of serious vascular events demonstrated lower risk with LPR. All-cause mortality did not differ significantly between LPR and non-LPR patient groups. Importantly, despite the differences in the methodology, patient selection and cut-off definition among studies, the increased risk of bleeding was homogenously reflected.

To date, this is the first meta-analysis of studies testing the role of LPR on bleeding and ischemic events in patients who underwent PCI.

In the first study reporting on the impact of enhanced response to clopidogrel treatment including 2,533 patients with coronary artery disease undergoing planned PCI, LPR was found to be associated with a two-fold higher risk for in-hospital major bleeding events [7]. Further reports suggested that LPR is a marker for a higher risk of bleeding events also among prasugrel-treated patients [25, 26].

Some recent studies, however, do not necessarily support that optimal PR does denote the same range in every patient population. In the TRILOGY ACS trial involving ACS patients without PCI, the relationship between LPR and risks of major bleeding was missing. Among medically managed non-ST-segment elevation ACS patients receiving prolonged dual antiplatelet therapy, platelet reactivity unit values were not significantly associated with the long-term risk of major bleeding events, suggesting that LPR does not independently predict serious bleeding risk [37].

Aimed at assessing the potential influence of different clopidogrel LD regimes, a subgroup analysis was performed. The results showed no association between different LDs of clopidogrel and rate of bleeding events. These findings are in line with a recent meta-analysis that compared the use of different LDs of clopidogrel and found that these are not associated with an increased risk for major bleeding within 30 days. However, it also suggested that the administration of 600 mg LD of clopidogrel is associated with a lower risk of MACE [38]. This observation is further supported by a retrospective study of patients with stable coronary artery disease which shows no difference between different LD groups in terms of major bleeding and hemoglobin drop post PCI [39].

When interpreting data from platelet function studies, the complex mechanisms of bleeding should be considered. Besides the potential impact of platelet inhibition, several clinical factors also influence the risk of these events. Residual PR, as an independent risk factor also has several associations with patient characteristics and these may also influence the expressed risk. HPR is more frequently encountered in obese and diabetics, while LPR may more likely arise in patients with advanced age and lower body weight [40, 41]. A significant association of LPR was revealed with lower body mass index in the current analysis. These characteristics may also impact the prognosis and when analyzed in multivariate models, the magnitude of risk, as in cases of ischemic risk with HPR, this risk is considerably reduced [42].

Importantly, periprocedural bleeding risk is substantially influenced by the access site selection, being significantly higher with transfemoral interventions. Bleeding avoidance strategies like

routine use of the transradial approach may interfere with this risk by reducing bleeding and improving outcomes among high-risk ACS patient [43]. In the present analysis, the rate of transradial approach reached 59% (reported in 8 studies including 8,667 [45%] patients). However, since this data was not presented in a considerable proportion of studies this impedes the further analysis of potential impact of access site selection.

The findings herein, are partly in line with the results of a previous meta-analysis published in 2015 including 17 trials with a total of 20,839 patients validating standardized cut-off points for platelet function testing. In that study thienopyridine-treated patients with HPR were associated with 2.73-fold higher risk for stent thrombosis ($p < 0.00001$) and a 1.5-fold higher risk for mortality ($p < 0.05$) compared with those with optimal PR following PCI, meanwhile patients with LPR were associated with a 2-fold increased risk for major bleeding complications without any further reduction in the risk of stent thrombosis [38]. In the present study, there was no significant difference between LPR and non-LPR groups in case of mortality, stent thrombosis or repeated revascularization. However, the risk of serious vascular events resulted in a significant difference favoring the LPR group. Regarding risk of non-fatal MI, the event rate was significantly lower in the LPR group.

However, there are some limitations that may impact the interpretation of the current results. Observational studies were included that are usually unbalanced regarding baseline clinical characteristics of the patients. These studies could reflect the real-world practice better, meanwhile due to a lack of monitoring drug compliance, underreporting negative results and incomplete follow-up, their interpretation may be more difficult and might carry ascertainment biases. To balance possible confounding factors, data were pooled with logarithmic transformation according to the random-effect model via generic inverse weighting with the intent of methodical compensation of these factors.

It should be mentioned that the patients were not treated uniformly regarding the LDs of clopidogrel and that platelet function assessments were performed at different time points after PCI with different devices and cut-offs for LPR that may have contributed to heterogeneity. There are multiple tests in the field with a real-gold standard evidently missing. Considering the plethora of available platelet function tests, the aim to restrict the analyses to those that implement a method based on ADP dependent in vitro platelet activation was used in order to best assess the efficacy of ADP receptor dependent activation pathway. From this perspective, acceptable methodologies were not restricted based on the final readout of the method. The use of different P2Y12 inhibitors may also have influenced residual platelet reactivity. Due to a lack of patient-level data, subgroup analyses were not done to identify drug related efficacy. It is also important to note that different definitions of bleeding may have contributed to heterogeneity. The aim to collect data according to the two most widely used and standardized definitions, the TIMI bleeding and BARC criteria were used.

Conclusions

In conclusion, this meta-analysis supports that LPR is associated with important clinical outcomes of patients who underwent coronary stent implantation. The possible benefit of this marker in risk stratification or improvement of risk prediction, if combined with other factors in prediction models remains to be established by further studies.

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Conflict of interest: Dr. András Komócsi reports personal fees from Bayer Pharma AG, Pfizer, Krka, d. d., Merck & Co., and Servier, outside of the submitted work. The other authors report no conflicts of interest.

References

1. Montalescot G, Sechtem U, Achenbach S, et al. Task Force Members, ESC Committee for Practice Guidelines, Document Reviewers. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013; 34(38): 2949–3003, doi: 10.1093/eurheartj/eht296, indexed in Pubmed: 23996286.
2. Wiviott SD, Braunwald E, McCabe CH, et al. TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007; 357(20): 2001–2015, doi: 10.1056/NEJMoa0706482, indexed in Pubmed: 17982182.
3. Wallentin L, Becker RC, Budaj A, et al. PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009; 361(11): 1045–1057, doi: 10.1056/NEJMoa0904327, indexed in Pubmed: 19717846.

4. Buonamici P, Marcucci R, Migliorini A, et al. Impact of platelet reactivity after clopidogrel administration on drug-eluting stent thrombosis. J Am Coll Cardiol. 2007; 49(24): 2312–2317, doi: 10.1016/j.jacc.2007.01.094, indexed in Pubmed: 17572245.
5. Cuisset T, Cayla G, Frere C, et al. Predictive value of post-treatment platelet reactivity for occurrence of post-discharge bleeding after non-ST elevation acute coronary syndrome. Shifting from antiplatelet resistance to bleeding risk assessment? EuroIntervention. 2009; 5(3): 325–329, doi: 10.4244/51, indexed in Pubmed: 19736156.
6. Matetzky S, Shenkman B, Guetta V, et al. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. Circulation. 2004; 109(25): 3171–3175, doi: 10.1161/01.CIR.0000130846.46168.03, indexed in Pubmed: 15184279.
7. Sibbing D, Schulz S, Braun S, et al. Antiplatelet effects of clopidogrel and bleeding in patients undergoing coronary stent placement. J Thromb Haemost. 2010; 8(2): 250–256, doi: 10.1111/j.1538-7836.2009.03709.x, indexed in Pubmed: 19943882.
8. Geisler T, Langer H, Wydymus M, et al. Low response to clopidogrel is associated with cardiovascular outcome after coronary stent implantation. Eur Heart J. 2006; 27(20): 2420–2425, doi: 10.1093/eurheartj/ehl275, indexed in Pubmed: 17005534.
9. Spiliopoulos S, Pastromas G, Katsanos K, et al. Platelet responsiveness to clopidogrel treatment after peripheral endovascular procedures. J Am Coll Cardiol. 2013; 61(24): 2428–2434, doi: 10.1016/j.jacc.2013.03.036.
10. Sibbing D, Aradi D, Jacobshagen C, et al. 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(10104): 1747–1757, doi: 10.1016/S0140-6736(17)32155-4, indexed in Pubmed: 28855078.
11. Claassens DMF, Vos GJA, Bergmeijer TO, et al. A genotype-guided strategy for oral P2Y inhibitors in primary PCI. N Engl J Med. 2019; 381(17): 1621–1631, doi: 10.1056/NEJMoa1907096, indexed in Pubmed: 31479209.
12. Sibbing D, Schulz S, Braun S, et al. Antiplatelet effects of clopidogrel and bleeding in patients undergoing coronary stent placement. J Thromb Haemost. 2010; 8(2): 250–256, doi: 10.1111/j.1538-7836.2009.03709.x, indexed in Pubmed: 19943882.
13. Cuisset T, Grosdidier C, Loundou AD, et al. Clinical implications of very low on-treatment platelet reactivity in patients treated with thienopyridine: the POBA study (predictor of bleedings with antiplatelet drugs). JACC Cardiovasc Interv. 2013; 6(8): 854–863, doi: 10.1016/j.jcin.2013.04.009, indexed in Pubmed: 23968703.
14. Mangiacapra F, Colaiori I, Ricottini E, et al. Impact of platelet reactivity on 5-year clinical outcomes following percutaneous coronary intervention: a landmark analysis. J Thromb Thrombolysis. 2018; 45(4): 496–503, doi: 10.1007/s11239-018-1630-5, indexed in Pubmed: 29450765.
15. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015; 162(11): 777–784, doi: 10.7326/M14-2385, indexed in Pubmed: 26030634.
16. Mehran R, Rao S, Bhatt D, et al. Standardized bleeding definitions for cardiovascular clinical trials. Circulation. 2011; 123(23): 2736–2747, doi: 10.1161/circulationaha.110.009449.
17. Wolff RF, Moons KGM, Riley RD, et al. PROBAST Group. PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies. Ann Intern Med. 2019; 170(1): 51–58, doi: 10.7326/M18-1376, indexed in Pubmed: 30596875.
18. Wells G. A., Shea B., O'Connell D., Peterson J., Welch V., Losos M. et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-analyses. 2000. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
19. 9.5.2 Identifying and measuring heterogeneity. https://handbook-5-1.cochrane.org/chapter_9/9_5_2_identifying_and_measuring_heterogeneity.htm.
20. Kabbani SS, Watkins MW, Ashikaga T, et al. Usefulness of platelet reactivity before percutaneous coronary intervention in determining cardiac risk one year later. Am J Cardiol. 2003; 91(7): 876–878, doi: 10.1016/s0002-9149(03)00025-0, indexed in Pubmed: 12667577.
21. Patti G, Nusca A, Mangiacapra F, et al. Point-of-care measurement of clopidogrel responsiveness predicts clinical outcome in patients undergoing percutaneous coronary intervention results of the ARMYDA-PRO (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty-Platelet Reactivity Predicts Outcome) study. J Am Coll Cardiol. 2008; 52(14): 1128–1133, doi: 10.1016/j.jacc.2008.06.038, indexed in Pubmed: 18804738.
22. Tsukahara K, Kimura K, Morita S, et al. Impact of high-responsiveness to dual antiplatelet therapy on bleeding complications in patients receiving drug-eluting stents. Circ J. 2010; 74(4): 679–685, doi: 10.1253/circj.cj-09-0601, indexed in Pubmed: 20173303.
23. Huczek Z, Filipiak KJ, Kochman J, et al. Medium on-treatment platelet reactivity to ADP is favorable in patients with acute coronary syndromes undergoing coronary stenting. Platelets. 2011; 22(7): 521–529, doi: 10.3109/09537104.2011.568075, indexed in Pubmed: 21443410.
24. Patti G, Pasceri V, Vizzi V, et al. Usefulness of platelet response to clopidogrel by point-of-care testing to predict bleeding outcomes in patients undergoing percutaneous coronary intervention (from the Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty-Bleeding Study). Am J Cardiol. 2011; 107(7): 995–1000, doi: 10.1016/j.amjcard.2010.11.025, indexed in Pubmed: 21256470.
25. Bonello L, Mancini J, Pansieri M, et al. Relationship between post-treatment platelet reactivity and ischemic and bleeding events at 1-year follow-up in patients receiving prasugrel. J Thromb Haemost. 2012; 10(10): 1999–2005, doi: 10.1111/j.1538-7836.2012.04875.x, indexed in Pubmed: 22863374.
26. Cuisset T, Gaborit B, Dubois N, et al. Platelet reactivity in diabetic patients undergoing coronary stenting for acute coronary syndrome treated with clopidogrel loading dose followed by prasugrel maintenance therapy. Int J Cardiol. 2013; 168(1): 523–528, doi: 10.1016/j.ijcard.2012.09.214, indexed in Pubmed: 23084816.
27. Mangiacapra F, Patti G, Barbato E, et al. A therapeutic window for platelet reactivity for patients undergoing elective percutaneous coronary intervention: results of the ARMYDA-PROVE (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty-Platelet Reactivity for Outcome Validation Effort) study. JACC Cardiovasc Interv. 2012; 5(3): 281–289, doi: 10.1016/j.jcin.2012.01.009, indexed in Pubmed: 22440493.
28. Mangiacapra F, Cavallari I, Barbato E, et al. Impact of chronic kidney disease on platelet reactivity and outcomes of patients re-

ceiving clopidogrel and undergoing percutaneous coronary intervention. Am J Cardiol. 2014; 113(7): 1124–1129, doi: 10.1016/j.amjcard.2013.12.018, indexed in Pubmed: 24507863.
29. Alfredsson J, Lindahl TL, Gustafsson KM, et al. Large early variation of residual platelet reactivity in Acute Coronary Syndrome patients treated with clopidogrel: results from Assessing Platelet Activity in Coronary Heart Disease (APACHE). Thromb Res. 2015; 136(2): 335–340, doi: 10.1016/j.thromres.2015.05.021, indexed in Pubmed: 26033398.
30. Li S, Liu H, Liu J. Predictive performance of adding platelet reactivity on top of CRUSADE score for 1-year bleeding risk in patients with acute coronary syndrome. J Thromb Thrombolysis. 2016; 42(3): 360–368, doi: 10.1007/s11239-016-1366-z, indexed in Pubmed: 27113341.
31. Jin L, Yu H, Dong T, et al. The prognostic value of ADP-induced platelet aggregation for bleeding complications in low- intermediate risk patients with acute coronary syndrome taking clopidogrel after percutaneous coronary intervention. Heart Lung Circ. 2017; 26(1): 49–57, doi: 10.1016/j.hlc.2016.05.113, indexed in Pubmed: 27451349.
32. Deharo P, Quilici J, Camoin-Jau L, et al. Benefit of switching dual antiplatelet therapy after acute coronary syndrome according to on-treatment platelet reactivity: the TOPIC-VASP pre-specified analysis of the topic randomized study. JACC Cardiovasc Interv. 2017; 10(24): 2560–2570, doi: 10.1016/j.jcin.2017.08.044, indexed in Pubmed: 29268886.
33. Su Nam L, Moon D, Sung MK, et al. Impact of platelet reactivity on long-term prognosis in Korean patients receiving percutaneous coronary intervention. Platelets. 2019; 30(8): 1030–1035, doi: 10.1080/09537104.2018.1562172, indexed in Pubmed: 30601072.
34. Aradi D, Gross L, Trenk D, et al. Platelet reactivity and clinical outcomes in acute coronary syndrome patients treated with prasugrel and clopidogrel: a pre-specified exploratory analysis from the TROPICAL-ACS trial. Eur Heart J. 2019; 40(24): 1942–1951, doi: 10.1093/eurheartj/ehz202, indexed in Pubmed: 31226213.
35. Mshelbwala FS, Hugenberg DW, Kreutz RP. Intensified P2Y12 inhibition for high-on treatment platelet reactivity. J Thromb Thrombolysis. 2020; 50(3): 619–627, doi: 10.1007/s11239-020-02075-x, indexed in Pubmed: 32152791.
36. Nakamura M, Kadota K, Takahashi A, et al. PENDULUM Registry Investigators*. Relationship Between Platelet Reactivity and Ischemic and Bleeding Events After Percutaneous Coronary Intervention in East Asian Patients: 1-Year Results of the PENDULUM Registry. J Am Heart Assoc. 2020; 9(10): e015439, doi: 10.1161/JAHA.119.015439, indexed in Pubmed: 32394794.
37. Cornel JH, Ohman EM, Neely B, et al. Relationship of platelet reactivity with bleeding outcomes during long-term treatment with dual antiplatelet therapy for medically managed patients with non-ST-segment elevation acute coronary syndromes. J Am Heart Assoc. 2016; 5(11), doi: 10.1161/JAHA.116.003977, indexed in Pubmed: 27815268.
38. 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(27): 1762–1771, doi: 10.1093/eurheartj/ehv104, indexed in Pubmed: 25896078.
39. Piqueras-Flores J, Jurado-Román A, López-Lluva MT, et al. Efficacy and safety of loading doses with P2Y12-receptor antagonists in patients without dual antiplatelet therapy undergoing elective coronary intervention. J Cardiovasc Pharmacol. 2019; 73(1): 56–59, doi: 10.1097/FJC.0000000000000632, indexed in Pubmed: 30383607.
40. Tekkeşin Aİ, Kaya A, Çakıllı Y, et al. The first six-month clinical outcomes and risk factors associated with high on-treatment platelet reactivity of clopidogrel in patients undergoing coronary interventions. Anatol J Cardiol. 2016; 16(12): 967–973, doi: 10.14744/AnatolJCardiol.2016.6855, indexed in Pubmed: 27271476.
41. Wakabayashi S, Ariyoshi N, Kitahara H, et al. Efficacy of 2.5-mg prasugrel in elderly or low-body-weight patients. Circ J. 2018; 82(9): 2326–2331, doi: 10.1253/circj.CJ-18-0337, indexed in Pubmed: 29962391.
42. Droppa M, Tschernow D, Müller KAL, et al. Evaluation of clinical risk factors to predict high on-treatment platelet reactivity and outcome in patients with stable coronary artery disease (PREDICT-STABLE). PLoS One. 2015; 10(3): e0121620, doi: 10.1371/journal.pone.0121620, indexed in Pubmed: 25799149.
43. Komócsi A, Aradi D, Kehl D, et al. Meta-analysis of randomized trials on access site selection for percutaneous coronary intervention in ST-segment elevation myocardial infarction. Arch Med Sci. 2014; 10(2): 203–212, doi: 10.5114/aoms.2014.42570, indexed in Pubmed: 24904651.

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Oral anticoagulation and outcomes in patients with acute myocardial infarction: Insights from the Hungarian Myocardial Infarction Registry

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Abstract

Introduction: Anticoagulation reduces the risk of stroke and embolization and is recommended in most patients with atrial fibrillation. Patients after coronary intervention and acute coronary syndromes require antiplatelet treatment. Although oral anticoagulation (OAC) therapy may interfere with the outcome of patients after coronary intervention, its exact impact remains unclear. Importantly, risk-benefit relations may be considerably different after myocardial infarction.

Material and Methods: Data of patients registered from the Hungarian Myocardial Infarction Registry, a mandatory nationwide program for hospitals treating patients with myocardial infarction, were processed. Patients registered between 01.2014. and 12.2017 were included. All-cause mortality, the composite of cardiac events (MACE), and transfusion were compared between patients receiving OAC treatment and a propensity score (PS) matched control group. Subgroup analyses of different anticoagulation and antiplatelet strategies were performed with propensity weighted Cox proportional hazards' models to estimate risk during the first year after the index event.

Results: From 30 681 patients 1875 cases received OAC treatment and had apparently worse prognosis. After PS-matching, however, we found no difference regarding mortality (hazard ratio [HR]: 0.91 95% CI 0.77-1.09, $P = .303$), MACE (HR: 0.92 95% CI 0.78-1.09, $P = .335$) or transfusion (HR: 1.21, 95% CI 0.97-1.49, $P = .086$). In PS-adjusted analyses for the OAC group, patients who received aspirin were associated with lower mortality (HR: 0.77, 95% CI: 0.60-0.997, $P = .048$) and MACE (HR:0.73, 95% CI 0.58-0.92, $P = .008$) compared to those without aspirin.

Conclusions: In patients with acute myocardial infarction, the prognosis of OAC-treated patients was comparable to the PS matched control; however, the omission of aspirin therapy was associated with unfavorable outcomes.

What's known

Anticoagulation (OAC) may interfere with the prognosis of patients after coronary intervention and acute coronary syndromes. A higher rate of bleeding and different, sometimes nonsignificant impact on the recurrent ischemic events were reported. Data on the exact impact of OAC therapy in patients after myocardial infarction are lacking.

What's new

Analysis of a real-life, high-risk population with myocardial infarction found a higher rate of all-cause mortality, major adverse cardiovascular events, and transfusion among anticoagulation (OAC) users compared to the patients without OAC treatment. These differences were, however, balanced if comorbidities, age, and gender-matched analyses were performed. Our analysis found a signal that in a mainly Vitamin K antagonist-treated population withheld aspirin was associated with higher ischemic risk.

1 | INTRODUCTION

Coronary heart disease is the leading cause of death and disability.[1] The coagulation, including platelets and the thrombotic cascade, plays an important role in the evolution of acute coronary syndrome (ACS).[2] For patients undergoing percutaneous coronary intervention (PCI) with stent implantation, dual antiplatelet treatment (DAPT) is recommended to prevent recurrent ischemic events. The recommended duration is the longest in patients receiving stent implantation during an event of acute myocardial infarction (AMI).[3]

In a proportion of ACS patients, in addition to the antiplatelet therapy, anticoagulation is required. The potential pitfalls of this combination have been most extensively studied in patients with atrial fibrillation (AF).[4,5] Specific considerations regarding patients with AF undergoing PCI include the fact that DAPT is essential to prevent stent thrombosis but insufficient for stroke prevention.[6] Besides that, oral anticoagulant (OAC) treatment is necessary for stroke prevention; however, it is unable to provide adequate prevention for new coronary events.[5-7] Added antiplatelets and OAC significantly increase the risk of bleeding complications; thus, long-term triple therapy is preferably avoided.[8-10] Recently, several trials attempting to optimize the adjunctive pharmacotherapy with direct OACs-based protocols were published showing a reduction of bleeding complications.[11-14] In most of these trials—although being not powered to compare ischemic endpoints—the practice of adding a P2Y12 inhibitor or aspirin to an OAC, referred to as "dual therapy" was tested and showed no significant impact regarding efficacy. Due to the paucity of data specific to high-risk ACS patients, however, it remains unclear how far results of these trials may be generalized to patient populations treated because of AMI.[15]

This study aimed to compare the outcomes of patients who underwent coronary intervention and were treated with/without OAC in a large unrestricted AMI registry.

2 | METHODS

We used the Hungarian Myocardial Infarction Registry to identify and follow patients after an index event of PCI during the treatment of an AMI. The data capture and follow-up procedures of the registry have already been published in detail previously.[16-19] 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. The study protocol was approved, and the need for informed consent was waived by the Scientific Council for Health, Scientific and Research Ethics Committee, Budapest, Hungary (ETT TUKEB 34858-3/2019/EKU). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Between January 1 2014 and December 31 2017, all AMI patients (both with ST-segment elevation and without) receiving coronary stent were eligible for enrolment. Treatment groups were identified based on the discharge medication, forming a patient group of anticoagulated cases (OAC group) and a control group of cases without anticoagulation.

The primary efficacy endpoint was all-cause mortality within 1 year after the index procedure. Secondary endpoints included the transfusion and the composite endpoints of major adverse events (MACE) defined as mortality, nonfatal myocardial infarction (MI) type 1 according to the fourth universal definition of MI or stroke.[20]

2.1 | Statistical analysis

To facilitate an unbiased comparison, we built a propensity score (PS) matched cohort with comparable risk profiles by adjusting for differences in baseline characteristics. For comparisons across different treatment regimens, we applied a PS-adjusted approach.[21] PS was computed by using a logistic regression model for OAC

versus control groups where besides age (scale) and gender (category), history of congestive heart failure, hypertension, stroke, diabetes, and vascular disease (eg, MI, stroke, or peripheral artery disease) was entered as categorical variables and were used as predictors. The majority of cases with OAC have AF. As in our aims, PS should reflect the probability of being treated with anticoagulation, the parameters were selected to provide an analogy to the elements of the CHA_2DS_2-VASc score. To isolate the effect of comorbidities from that of arrhythmia, sensitivity exercises with creating an alternative control group (Control B) using the PS score but excluding nonanticoagulated AF patients from pairing as well as a subgroup analysis of AF patients were performed. Cox regression models were used to calculate hazard ratios. To tackle the potential influence of competing risk, transfusion outcome analyses were supplemented by computing cumulative incidence function (CIF) to show the probability of each event and Gray's test to estimate the difference in the CIF between groups. *P*-values of <.05 were considered to indicate statistical significance. The analyses were conducted using the SPSS 26 statistical package and with the "cmprsk" package in R.

3 | RESULTS

We identified 40 968 records with an in-hospital treatment of an AMI event. After exclusion of cases with multiple hospitalizations, without PCI or stent implantation, or with missing data, a study population of 30 681 patients was identified that of 6.51% (n = 1875) received oral anticoagulation (Figure S1).

3.1 | Demographic and AF-related characteristics

The OAC population was mainly treated with vitamin-K antagonists (VKA) 86%, while direct oral anticoagulants (DOACs) were used in 14% of the cases (2.9% dabigatran, 5.8% rivaroxaban, and 5.2% apixaban) (Table S1).

Of the 1875 cases in the OAC group 87.8%, 1646 cases had AF as an indication for anticoagulation. Of these cases, 733 patients had AF verified during the hospitalization while 48.7% presented with sinus rhythm. Further 229 cases (12.2%) had no AF but different indications for anticoagulation. These included deep vein thrombosis (3.4%) or pulmonary embolism (2.7%), an intracardiac thrombus (2.2%), left ventricular aneurysm (1.9%), mechanical heart valves (1.3%), and miscellaneous thrombotic or embolic reasons altogether less than 1%. Patients treated with OAC had a higher age and were more frequently man. Furthermore, the presentation was more frequently non-ST-segment elevation ACS with a more severe Killip profile. Prevalence of prior MI, stroke, PCI, and coronary artery bypass graft surgery was higher. The OAC users had more comorbidities such as hypertension, diabetes mellitus, heart failure, and presence of vascular diseases but were less frequently smokers. PS matching resulted in a matched population of 3750 patients with balanced characteristics leaving only some statistically significant but clinically less relevant differences in continuous parameters like the heart rate (mean difference (MD): 6.22 beats/min), systolic blood pressure (MD: 2.22 mmHg), weight (MD: 2.23 kg), and height (MD: 1.06 cm) (Table 1).

The proportion of patients having ECG verified AF during the hospitalization was higher in the OAC group (733 (39.1%)) than in the control or in the matched control (1230 (4.3%) and 104 (5.5.%), respectively, $P < .001$, both) (Table 1). Procedural and treatment characteristics were also well balanced, except for the antiplatelet regimen with a higher rate of clopidogrel and a lower rate of prasugrel and aspirin use in the OAC group (Table S1).

Regarding the overall cohort, OAC-treated subjects had a significant, 25% higher hazard for all-cause mortality (13.17% vs 10.52%, hazard ratio (HR): 1.25, 95% CI 1.01-1.42, $P = .001$). Similarly, rates of MACE and transfusion were higher (14.51% vs 11.70%, HR: 1.24, 95% CI 1.01-1.40, $P = .001$ and 9.97% vs 6.88%, HR: 1.47, 95% CI 1.26-1.70, $P < .001$, respectively). (Figure 1 and Table S2.)

3.2 | Outcomes with propensity-matched groups

A tendency of anticoagulated cases for higher rate transfusion prevailed in the propensity-matched cohort (9.97% vs 8.16%, hazard ratio (HR): 1.21, 95% CI 0.97-1.49, $P = .086$). Rate of mortality and MACE, however, was less frequent in the OAC group compared to the PS-matched control group without oral anticoagulation (13.17% vs 14.1%, HR: 0.91 95% CI 0.77-1.09, $P = .303$ and 14.5% vs 15.36%, HR: 0.92 95% CI 0.78-1.09, $P = .335$, respectively). Importantly, none of these reached the level of significance (Figure 2 and Table S2).

Unadjusted subgroup analyses showed a higher risk of ischemic endpoints with VKA or DOAC treatment. MACE and bleeding were significantly higher with VKA but not with DOAC. Among DOACs, rivaroxaban-treated cases had higher rates of transfusion. Regarding the different antiplatelet strategies, compared to the unmatched control higher rate of ischemic and bleeding endpoints were found among the anticoagulated cases unconstrained if they received or not received aspirin or received single or double antiplatelet therapies. All these endpoints were more frequent among cases treated with old P2Y12 inhibitors but not among those receiving newer ADP antagonists. Importantly, after PS adjustment all but the differences regarding aspirin therapy disappeared (Tables S3 and S4).

Similarly, PS balanced comparisons within the OAC group showed no differences in mortality, MACE, or bleeding with the only exception of the lower mortality (HR: 0.77, 95% CI: 0.60-0.997, $P = .048$) and MACE risk (HR: 0.73 95% CI: 0.58-0.92, $P = .008$) of the aspirin-treated cases compared to the counterparts not receiving aspirin (Table 2, Figure 2, and Table S3).

Analyses of competing risk showed no signal for a major influence of immortal time bias. Analyses with Control B as well as the subgroup analysis of the AF cohort showed data coherent to the main analysis (Figures S4 and S5 and Table S5).

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

Clinical characteristics	OAC group (n = 1875)	Control group (n = 28 806)	*P*-value	PS matched control group (n = 1875)	*P*-value
Age, (years)	68.4 (60.5-75.9)	63.5 (55.5-72.5)	<.001	68.2 (60.4-76.0)	.398
Men	1245 (66.4%)	18 466 (64.1%)	.044	1227 (65.4%)	.535
Presentation					
ST segment elevation myocardial infarction	907 (48.4%)	15 457 (53.7%)	<.001	896 (47.8%)	.719
Shock	22 (1.2%)	236 (0.8%)	.104	15 (0.8%)	.247
Reanimation	56 (3.0%)	902 (3.1%)	.727	45 (2.4%)	.267
Prehospital thrombolysis	6 (0.3%)	74 (0.3%)	.604	4 (0.2%)	.527
Killip class			<.001		.084
I	1636 (87.3%)	26 279 (91.2%)		1681 (89.7%)	
II	193 (10.3%)	1908 (6.6%)		148 (7.9%)	
III	40 (2.1%)	464 (1.6%)		39 (2.1%)	
IV	6 (0.3%)	155 (0.5%)		7 (0.4%)	
Heart rate (bpm)	81 (70-99)	78 (69-89)	<.001	78 (69-89)	<.001
Systolic blood pressure (mmHg)	132 (118-150)	135 (120-150)	<.001	135 (120-150)	.005
Diastolic blood pressure (mmHg)	80 (70-91)	80 (70-90)	.755	80 (70-90)	.053
Weight (kg)	80 (70-91)	80 (70-90)	<.001	80 (70-90)	<.001
Height (cm)	170 (165-175)	170 (164-175)	.209	170 (162-175)	.002
Serum creatinine (μmol/L)	90 (76-110)	81 (68-98)	<.001	86 (71-104)	.387
Medical history					
Hypertension	1530 (81.6%)	21 882 (76.0%)	<.001	1530 (81.6%)	1.000
Diabetes mellitus	664 (35.4%)	8669 (30.1%)	<.001	675 (36.0%)	.708
Hyperlipidaemia	574 (30.6%)	8287 (28.8%)	.088	548 (29.2%)	.354
Peripheral artery disease	260 (13.9%)	2877 (10.0%)	<.001	238 (12.7%)	.290
Smoking	389 (20.7%)	8946 (31.1%)	<.001	427 (22.8%)	.133
History of heart failure	367 (19.6%)	2404 (8.3%)	<.001	354 (18.9%)	.590
Prior myocardial infarction	461 (24.6%)	4915 (17.1%)	<.001	427 (22.8%)	.192
Prior stroke	195 (10.4%)	1981 (6.9%)	<.001	187 (10.0%)	.666
Prior coronary intervention	476 (25.4%)	4721 (16.4%)	<.001	469 (25.0%)	.792
Prior coronary bypass operation	169 (9.0%)	1172 (4.1%)	<.001	144 (7.7%)	.140

Abbreviations: Control group, patients without oral anticoagulant treatment; OAC, patients with oral anticoagulant treatment; PS, propensity score.

4 | DISCUSSION

Our data showed that AMI patients receiving OAC were older and had a more severe risk profile than patients in the control group, and thus, anticoagulation was associated with a higher rate of mortality, MACE, and transfusion. However, after performing PS matching, these differences were balanced off, and in the PS-matched sample, no difference regarding mortality or MACE persisted. Transfusion remained more frequent in the OAC group; however, this difference did not reach the level of statistical significance. PS-adjusted analyses of the risks within the OAC-treated groups did not explore major differences except for the higher mortality and MACE rates that were seen among patients not receiving aspirin.

Conditions requiring long-term anticoagulation including AF, ventricular thrombi, or pulmonary embolism are markers associated with poor prognosis among patients who underwent PCI.[22-24] AF—the most common sustained arrhythmia in clinical practice—is associated with increased risk for heart failure, dementia, and stroke. Besides other less common causes like ventricular thrombus and deep vein thrombosis or pulmonary embolism, this arrhythmia is the most common cause of anticoagulation among MI patients.

The importance of comorbidities is, however, reflected variably in earlier studies. Patients included in the REACH registry had a higher risk of major adverse events after a 4-year follow-up if they also suffered from AF. This difference—contrasting our analyses—remained important even after balancing for clinical parameters (24.3% vs 13.3% unadjusted and 18.9% and 9.4% adjusted event rates, respectively). Beyond differences in the inclusion criteria of the REACH registry, some other disparities should be noted that may explain the partially discordant results. Importantly, in the REACH

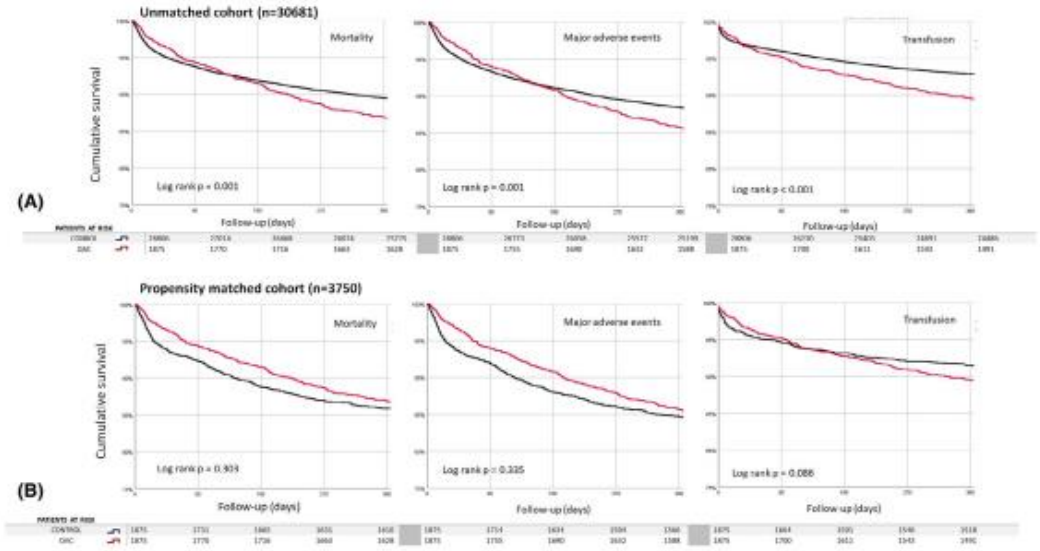
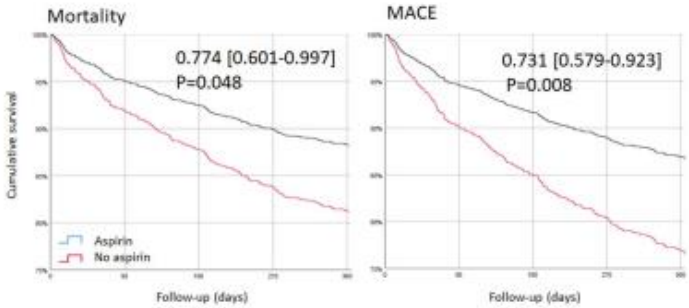


FIGURE 1 Kaplan–Meier curves of overall mortality, major adverse events, and transfusion-free survival comparing patients with or without oral anticoagulant treatment. Panel A shows the survival differences seen in the overall cohort, while data from the propensity score (PS) are depicted in panel B. Abbreviations: control, patients without oral anticoagulant treatment; HR, hazard ratio; OAC, patients receiving oral anticoagulant

FIGURE 2 plotting the risk of mortality and major adverse cardiac events among oral anticoagulation treated patients compared between cases receiving or not receiving aspirin



register, a set of clinical factors were used for regression adjustment. Regression adjustment is used frequently in observational studies, and it attempts to characterize the effect estimate at the mean of the factor levels that entered the model. But importantly, it keeps the sample untouched even if the treatment groups differ considerably in their risk profile. We found that the characteristics of OAC treated patients consist of a minority of the MI population with major differences from the control cases. Moreover, the PS-based stratification showed that the risk of ischemic and bleeding endpoints was neither homogenous nor linear concerning the PS (for further details refer to the Supporting Information Figure S3). Thus, to achieve balance in the measured confounders, PS matching was used instead. Furthermore, we used PS as a balancing score to adjust for potential remaining differences within OAC group analyses.[25]

The unfavorable results of patients with AF in the REACH registry were also explicable with the undertreatment of these cases, as the rate of anticoagulation reached only 52% in the fourth year. This is in line with our data where AF but not anticoagulation was associated with unfavorable results regarding both ischemic and bleeding in regression adjustment analyses (Supporting Information Table S6).

In our registry, a different approach was conducted to analyze the outcomes of patients after the event of AMI based on their intended OAC treatment status. Earlier experience with warfarin suggested an incremental ischemic benefit when anticoagulant therapy was used in combination with aspirin.[26] These results set the stage for studies using DOACs as an adjunct to antiplatelet therapy in ACS. With the only exception of rivaroxaban, ACS trials among patients without AF failed to support this concept.[27] In the ATLAS ACS-2

TABLE 2 Results of the propensity score-adjusted analysis of the oral anticoagulant treated cohort

Treatment	Mortality	MACE	Transfusion
DOAC versus VKA	1.037 [0.873-1.233], $P = .678$	1.010 [0.854-1.195], $P = .906$	0.988 [0.803-1.215], $P = .907$
Apixaban	0.990 [0.566-1.734], $P = .973$	1.167 [0.713-1.910], $P = .539$	1.005 [0.531-1.904], $P = .988$
Dabigatran	0.895 [0.421-1.902], $P = .773$	0.696 [0.309-1.565], $P = .380$	0.343 [0.085-1.384], $P = .133$
Rivaroxaban versus VKA	1.252 [0.774-2.027], $P = .360$	1.062 [0.649-1.737], $P = .812$	1.287 [0.746-2.223], $P = .365$
	df: 3, $P = .773$	df: 3, $P = .741$	df: 3, $P = .366$
ASA versus No ASA	0.774 [0.601-0.997], $P = .048$	0.731 [0.579-0.923], $P = .008$	0.792 [0.584-1.074], $P = .134$
DAPT	0.667 [0.339-1.313], $P = .242$	0.684 [0.349-1.342], $P = .270$	0.649 [0.326-1.291], $P = .218$
SAPT versus Single anticoagulant therapy	0.949 [0.460-1.958], $P = .887$	1.056 [0.517-2.158], $P = .881$	0.820 [0.385-1.748], $P = .608$
	df: 2, $P = .251$	df: 2, $P = .128$	df: 2, $P = .427$
New P2Y12	0.717 [0.345-1.492], $P = .374$	0.901 [0.481-1.689], $P = .746$	0.925 [0.460-1.859], $P = .826$
No P2Y12 versus Old P2Y12	1.175 [0.566-2.443], $P = .665$	0.986 [0.486-1.999], $P = .968$	0.987 [0.439-2.220], $P = .975$
	df: 2, $P = .610$	df: 2, $P = .840$	df: 2, $P = .919$

Abbreviations: ASA, aspirin; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulants; MACE; major adverse cardiovascular events; New P2Y12, prasugrel or ticagrelor; No-ADP, patients not receiving a P2Y12 inhibitor; No-ASA, patients not receiving aspirin; old P2Y12, clopidogrel or ticlopidine); SAPT, single antiplatelet therapy (aspirin or a P2Y12 inhibitor; VKA, Vitamin-K antagonist.

TIMI-51 trial, however, low dose rivaroxaban reduced the risk of major adverse events with a significant mortality reduction.[9] Meta-analysis of these trials found a homogenous effect of DOAC anticoagulation in reducing ischemic endpoints; however, this benefit was counterbalanced with the higher risk of bleeding compared to placebo.[28] The low-dose rivaroxaban also resulted in higher rates of major bleeding but better cardiovascular outcomes in aspirin-treated stable atherosclerotic vascular disease patients in the COMPASS trial.[29]

Comorbidity adjusted analyses regarding the agent used for anticoagulation found comparable outcomes of DOAC-treated cases to VKA, with an unexpected trend for higher mortality in the case of rivaroxaban. When considering the results of the analysis, it is important to note that the use of DOAC represented a minority of our OAC group and that low-dose rivaroxaban was not used in our cohort that makes the importance of this statistically nonsignificant difference questionable.

Interaction between anticoagulation and antiplatelets has been most extensively examined in cases with AF receiving antiplatelet therapy because of a coronary event or intervention.[30] Recently, data from multiple randomized trials were published.[11-14] Pooled meta-analysis of these trials found that anticoagulation applied with single antiplatelet treatment reduces bleeding risk; however, a trend for a higher rate of MI and stent thrombosis was observed compared to dual-antiplatelet combined anticoagulation.[31] This observation contrasted the WOEST trial that found a significant reduction of major adverse events and a decreasing trend of the elements of the composite endpoint if aspirin was withheld in anticoagulated patients. However, in line with the DOAC trials, our results reflected a worse prognosis of anticoagulated patients without aspirin.

It is essential to note that the RCTs assessing DOACs in patients with AF who underwent PCI were underpowered to robustly assess for thrombotic events. Also, the overall prevalence of ACS varied from 37.3% to 52% in these studies.[11-14] These limit the generalizability of findings, and it remains unclear how dual therapy may affect the outcomes compared to triple therapy in this population of characteristically high thrombotic risk.

Keeping in mind that observational analyses do not mean to confute results of randomized trials, we consider that these discrepancies may be secondary to the inherently different populations. While the RCTs included a substantially lower risk PCI population, the risk profile and thus results of different treatment strategies may be greatly different. We consider, however, that results of these trials cannot be generalized to the overall PCI population and strongly believe that specific trials designed and performed in the high-risk MI cohorts required before a firm conclusion can be drawn regarding the safety of the direct anticoagulants or the double therapy in patients treated with PCI during an MI event.

5 | LIMITATIONS

Regarding our study, some limitations may have to be carefully considered. First, this is not a randomized trial capable of providing a completely unbiased assessment of treatment effect. There was substantial heterogeneity in baseline characteristics between the groups. Matching of the PS balanced the significant differences observed between the OAC and control groups in the entire cohort. However, the influence of potentially uncontrolled variables may also not be entirely excluded. Second, we have no information about either the factors of selection or the quality of the OAC treatment. Third, we collected data on transfusion from our national registry which may not correspond entirely with the standard definition of a major bleeding complication used in clinical trials or health insurance databases. As endpoint events were collected using the payer's database, the registry did not schedule patient follow-up visits collecting data that could be used for per-protocol analyses. In the paucity of medication compliance data, we constrained our analyses to intention-to-treat analyses based on the discharge medication defined by the invasive center. However, at the time of the inclusion international and national guidelines supported life-long anticoagulation of AF patients and double antiplatelet treatment for the duration of 12 months after MI. Considering this, we analyzed events in the first year after MI assuming stable treatment in this period.

6 | CONCLUSIONS

In conclusion, our analysis of a real-life, coronary intervention treated AMI population found that the apparent higher rate of all-cause mortality, and MACE, among OAC users compared to the patients without OAC treatment may be attributable to the inherently higher risk of these cases. Thus, no difference regarding mortality or MACE was detected in the propensity-matched sample. The data from risk-adjusted analyses found a signal for a worse prognosis of anticoagulated cases if aspirin was withheld.

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DISCLOSURES

The authors report no relationships that could be construed as a conflict of interest.

AUTHOR CONTRIBUTIONS

All authors have contributed significantly, and all authors agree with the manuscript content. Conception/Design: Alexandra Bálint, András Komócsi; Provision of study materials: András Jánosi; Collection and/or assembly of data: all authors; Data analysis interpretation: all authors; Manuscript writing: all authors; Final approval of the manuscript: all authors.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the Supporting Information of this article.

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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. Authors/Task Force members, Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2014;35:2541-2619.
3. Valgimigli M, Bueno H, Byrne AR, 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.
4. Conen D. Epidemiology of atrial fibrillation. *Eur Heart J*. 2018;39(16):1323-1324. https://doi.org/10.1093/eurheartj/ehy171.
5. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893-2962.
6. The ACTIVE Writing Group on behalf of the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fi brillation in the Atrial fi brillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet*. 2006;367:1903-1912.
7. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-Vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: executive summary. *Europace*. 2018;20:1231-1242. https://doi.org/10.1093/europace/euy054.
8. Dewilde WJM, Oirbans T, Verheugt FWA, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet*. 2013;381:1107-1115.
9. 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. https://doi.org/10.1056/NEJMoa1112277.
10. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139-1151.
11. 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.
12. 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.
13. 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.
14. Vranckx P, Valgimigli M, Eckardt L, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. *Lancet*. 2019;394:1335-1343. https://doi.org/10.1016/s0140-6736(19)31872-0.
15. 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*. 2017;39(3):213-260. https://doi.org/10.1093/eurheartj/ehx419
16. 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.
17. Janosi A, Ofner P, Forster T, et al. 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.
18. 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.
19. 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.
20. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *Eur Heart J*. 2019;40:237-269.
21. Morgan SL, Todd JJ. A diagnostic routine for the detection of consequential heterogeneity of causal effects with a demonstration from school effects research. *Sociol Methodol*. 2008;38:231-281.
22. Ruff CT, Bhatt DL, Steg PG, et al. Long-term cardiovascular outcomes in patients with atrial fibrillation and atherothrombosis in the REACH Registry. *Int J Cardiol*. 2014;170:413-418. https://doi.org/10.1016/j.ijcard.2013.11.030.
23. Chwan Ng AC, Chung T, Sze Chiang Yong A, et al. Long-term cardiovascular and noncardiovascular mortality of 1023 patients with confirmed acute pulmonary embolism. *Circ Cardiovasc Qual Outcomes*. 2011;4:122-128.
24. Velangi PS, Choo C, Chen K-H, et al. Long-term embolic outcomes after detection of left ventricular thrombus by late gadolinium enhancement cardiovascular magnetic resonance imaging: a matched cohort study. *Circ Cardiovasc Imaging*. 2019;12:e009723.
25. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav. Res*. 2011;46:399-424.
26. Andreotti F, Testa L, Biondi-Zoccai GGL, Crea F. Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes: an updated and comprehensive meta-analysis of 25,307 patients. *Eur. Heart J*. 2006;27:519-526.
27. 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):1537-1545.
28. Komócsi A, Vorobcsuk A, Aradi D. New oral anticoagulants in acute coronary syndromes: what does a meta-analysis tell us? Reply. *JAMA Intern Med*. 2013;173(9):835-836.
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. Lopes RD, Hong H, Harskamp RE, et al. Safety and efficacy of antithrombotic strategies in patients with atrial fibrillation undergoing percutaneous coronary intervention: a network meta-analysis of randomized controlled trials. *JAMA Cardiol*. 2019;27701:1-9.
31. Luo C-F, Mo P, Li G-Q, Liu S-M. Aspirin-omitted dual antithrombotic therapy in non-valvular atrial fibrillation patients presenting with acute coronary syndrome or undergoing percutaneous coronary intervention: results of a meta-analysis. *Eur Hear J - Cardiovasc Pharmacother*. 2020. https://doi.org/10.1093/ehjcvp/pvaa016.

SUPPORTING INFORMATION

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

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Network Meta-Analysis of Ticagrelor for Stroke Prevention in Patients at High Risk for Cardiovascular or Cerebrovascular Events

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BACKGROUND AND PURPOSE: Preventive antiplatelet therapy is recommended for patients with cardiac or cerebrovascular atherosclerosis. Ticagrelor has an improved safety and efficacy profile in patients with acute coronary syndrome; however, data regarding stroke prevention remain controversial. We conducted a network meta-analysis to compare ticagrelor with other receptor antagonists (P2Y12) inhibitors and aspirin in monotherapy or combination in the treatment of patients with high risk for cardiovascular or cerebrovascular disease, defined as coronary artery disease, acute coronary syndrome, stroke or transient ischemic attack, or peripheral artery disease.

METHODS: Systematic searches of MEDLINE, EMBASE, and the Cochrane Library were conducted until August 1, 2020. Search terms included ticagrelor, AZD 6140, and stroke. The risk of bias was assessed using the Cochrane Collaboration assessment tool. Random-effects model was used to combine risk estimates across trials and risk ratio with 95% CIs served as summary statistics. The influence of individual components was evaluated in an additive network meta-analysis model. The primary efficacy end point was the occurrence of stroke. The safety end points included bleeding and all-cause mortality.

RESULTS: Twenty-six randomized clinical trials comprising 124 495 patients were analyzed. When compared with controls, ticagrelor plus aspirin significantly reduced the risk of ischemic stroke by 20% (risk ratio, 0.80 [95% CI, 0.71–0.89]). Treatment with ticagrelor monotherapy did not significantly affect ischemic stroke (risk ratio, 0.88 [95% CI, 0.77–1.00]; P=0.05). Compared with aspirin alone, major bleeding was in similar ranges with antiplatelet monotherapies while the relative risk was twice higher with combined antiplatelet therapies. There was no considerable difference in the risk of mortality with ticagrelor plus aspirin (risk ratio, 0.99 [95% CI, 0.91–1.07]).

CONCLUSIONS: Ticagrelor on top of aspirin may provide more favorable outcomes on secondary stroke prevention in patients with vascular risk factors; however, this benefit may come with the price of increased bleeding risk including intracranial bleeding.

GRAPHIC ABSTRACT: An online graphic abstract is available for this article.

Key Words: acute coronary syndrome ■ odds ratio ■ secondary prevention ■ stroke ■ ticagrelor

Stroke is an important cause of morbidity and mortality worldwide.[1] Platelet aggregation contributes to the mechanisms of stroke; therefore, antiplatelet therapy interferes with the evolution of these events exerting important preventive capability. Antiplatelets use different mechanisms to block platelet activation and aggregation, and their use in forms of monotherapy or combination is supported by an important body of evidence.[2,3] Currently, 4 antiplatelet agents and 1 combination are approved by the US Food and Drug Administration for secondary stroke prevention: aspirin, dipyridamole, ticlopidine, clopidogrel, and aspirin combined with clopidogrel.[4] Aspirin acts as

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For Sources of Funding and Disclosures, see page 2815.

Stroke is available at www.ahajournals.org/journal/str

Nonstandard Abbreviations and Acronyms

A+T	aspirin plus ticagrelor
NMA	network meta-analysis
RR	risk ratio
TASS	Ticlopidine Aspirin Stroke Study
TIA	transient ischemic attack
TIMI	Thrombolysis in Myocardial Infarction

an irreversible cyclooxygenase inhibitor suppressing the production of prostaglandins and thromboxanes while dipyridamole blocks the related intracellular cAMP signaling. The latter two drugs, however, act on the interplatelet adenosine diphosphate (ADP) signaling by blocking the surface receptor antagonist (P2Y12) ADP receptor. ADP receptor antagonists show synergistic effects on platelet aggregation when used together with aspirin.[5]

The newer generation of P2Y12 receptor inhibitors achieves more efficient platelet inhibition compared with clopidogrel.[6,7] Clopidogrel and prasugrel share the same active metabolite but with more effective bioactivation of the latter while ticagrelor is a direct-acting reversible P2Y12 receptor antagonist inhibiting ADP-mediated P2Y12-dependent platelet aggregation.[8]

Some recent data suggest the potential benefits of ticagrelor with regard to stroke prevention in high-risk populations.[9] Most recently, the THALES trial (Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA) further supported the potential of ticagrelor and aspirin in stroke prevention. In this trial, combined antiplatelet therapy with ticagrelor resulted in a significant, 17% relative reduction of stroke in patients with mild-to-moderate acute noncardioembolic ischemic stroke.[10]

Importantly, evidence supports that the intensified or combined antiplatelet therapy is also associated with an increased risk of bleeding that may have an important impact on the risk-benefit relations of these therapies.[11]

Based on the previous findings, there is growing interest in comparing ticagrelor mono- and dual antiplatelet therapies for preventing ischemic stroke or transient ischemic attack (TIA). For this purpose, we performed a multiple-treatment network meta-analysis (NMA) of randomized controlled trials to compare the relative efficacy of ticagrelor in preventing stroke in high-risk populations.

METHODS

This systematic review was performed per the standards outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension Statement for Reporting of Systematic Reviews Incorporating NMAs of Health Care Interventions[12] and registered with the International Prospective Register of Systematic Reviews under number CRD42020170746. The data that support the findings of this analysis are available from the corresponding author upon reasonable request.

The authors collected data from 3 online databases: MEDLINE (PubMed), Cochrane Collaboration of Clinical Trials, and EMBASE until August 1, 2020, from articles reporting randomized clinical trials with ticagrelor antiplatelet therapy. No language restriction was used. Broad search terms (ticagrelor, AZD 6140, and stroke) were used and combined using the boolean operator AND.

Studies were included if the following criteria were fulfilled: (1) randomized controlled trials, (2) assessing the clinical efficacy or safety of an antiplatelet regime including ticagrelor alone or as part of a dual antiplatelet therapy strategy with ticagrelor plus aspirin, and (3) reported on the occurrence of stroke in minimum duration of 30 days (4) in patients with cerebrovascular, coronary, or peripheral artery disease.

We excluded studies if any of the following criteria were applied: (1) nonrandomized studies, (2) single-arm studies, (3) outcomes of interest were not reported or were impossible to extract or calculate from published results, (4) comparing merely the biological efficacy of the antiplatelet treatment, or (5) duplicate publications.

Two investigators (A.B. and D.T.) independently evaluated record titles and abstracts of all citations in line with the PICO criteria (patient/population, intervention, comparison and outcomes); any discrepancies were resolved by a third investigator (A.K.).

For definitions of stroke, the internal definitions of the included trials were used if compliant with focal loss of neurological function caused by an ischemic or hemorrhagic event, with residual symptoms lasting at least 24 hours or leading to death.

The primary efficacy outcome of our analysis was the occurrence or recurrence of stroke including ischemic or hemorrhagic forms. Major bleeding and all-cause mortality were assessed as main safety end points. Secondary outcomes included the individual end points of ischemic stroke, hemorrhagic stroke, and TIA, myocardial infarction, major cerebral or cardiovascular event defined as the composite of death, MI, and stroke, and cardiovascular death. Additionally, data of disabling stroke (defined as death or modified Rankin Scale score >1) were also collected. Furthermore, safety outcomes as the frequency of major and minor bleeding complications and intracranial bleeding were also evaluated. In the case of the availability of multiple major bleeding definitions, we extracted the Thrombolysis in Myocardial Infarction (TIMI) major bleeding. The data from the intention-to-treat analyses were extracted, and the end points of interest were collected until the longest follow-up available.

The methodological qualities of the studies were also assessed using the Cochrane Collaboration tool for assessing the quality of randomized controlled trials.

NMA Modeling

Considering that the trials used different control groups for comparing outcomes of ticagrelor-medicated patients and that the study arms included combination as well as monotherapy with different antiplatelets, we prespecified the use of multiple-treatment NMA supplemented with component NMA modeling.

At the first level, each potential antiplatelet combination was entered as an individual study arm, and data were pooled in a multiple-treatment NMA that allows integration of direct and indirect comparisons. We calculated the risk ratio (RR)

and its SE using a frequentist approach to construct an NMA model accounting for the correlated treatment effects.[13] A random-effects model was applied by adding the estimated heterogeneity to the variance of each comparison using an adaptation of the DerSimonian-Laird estimator. The choice of the random-effects model was made based on the consideration that the true preventive effect of antithrombotic treatment may vary from study to study influenced by the heterogeneity of the included trials.

Values of I^2 representing the amount of inconsistency and Cochran Q statistics and its corresponding *P* measuring the heterogeneity in the network were also calculated.[13,14]

A special case encountered in our network was that treatment arms may be combinations of other treatments or have common components. Therefore, the influence of individual components was intended to be evaluated in an additive model assuming that the effect of treatment combinations is the sum of the effects of its components.[15]

For easier interpretation, effect sizes are depicted in the form of forest plots with aspirin set as reference. Furthermore, a comparative ranking of the treatments according to the P-scores method (a frequentist analog of the surface under the cumulative ranking curve) was performed.[16]

The assumption of consistency that the direct evidence in a network for the effect size between two treatments does not differ from the indirect evidence was assessed by net heat plots and by net splitting. The latter method splits our network estimates into the contribution of direct and indirect evidence, which allows controlling for inconsistency in specific comparisons.

To assess publication bias, a comparison-adjusted funnel plot—an extension of the common funnel plot in cases of multiple-treatment comparison—was used displaying Egger test results in support[17] with the additional use of the Cochrane Collaboration assessment tool.

The clustering of the treatment arms was assessed using the estimated relative risk compared with aspirin in the nearest neighbor analysis. An explorative analysis was performed to assess the potential impact of background risk on the estimated treatment effect. Within this, risk of stroke of the study population using clopidogrel plus aspirin therapy was calculated, and this continuous variable was used to construct regressor in a Bayesian metaregression analysis. Additional exploratory analyses included stratification and subgrouping based on the included patient population, multilevel meta-analysis, and multivariate meta-analysis of direct comparisons using structural equation modeling.

All calculations were performed with the R statistical software package, version 3.6.3 (R Development Core Team, 2010), software using the packages meta 4.11-0, netmeta 1.2-0, and gemtc 0.8-4.[18] $P<0.05$ was considered to represent statistical significance.

RESULTS

The literature search resulted in 1335 citations of which 26 were compliant with the inclusion criteria (Figure I in the Data Supplement). Twenty-six randomized controlled trials involving 124 495 patients (range, 48–21 162) were included in the analysis. Clinical characteristics of the populations and procedural data are shown in Table I in the Data Supplement. Table II in the Data Supplement presents the main characteristics of the involved trials.

Patients were recruited to the trials due to nonsevere ischemic stroke or TIA,[10,19,20] acute coronary syndrome,[7,21–34] high risk for acute coronary syndrome,[35,36] peripheral artery disease,[37] coronary artery bypass graft surgery,[38,39] known coronary artery disease,[40,41] or transcatheter aortic valve implantation.[42] Six treatment arms were identified using aspirin or the P2Y12 inhibitors clopidogrel, prasugrel, or ticagrelor in monotherapy or combined with aspirin. The 6 antiplatelet treatment arms allowed 15 possible pairwise comparisons of which 7 were implemented in the included trials (Figure 1).

The dose of the long-term P2Y12 inhibitor treatment was different in the trials using 90 mg BID or 60 mg BID for ticagrelor, 75 mg OD for clopidogrel, and 10 mg OD for prasugrel. Aspirin was administered in a low dose (75–150 mg).

Analysis of bias showed high quality of the source information with a low probability of bias. No obvious publication bias was found in Figures II and III in the Data Supplement. Neither net heat plots nor net-splitting analyses revealed major inconsistencies between direct and indirect evidence (Figures IV and V in the Data Supplement).

Association Between Ticagrelor Treatment and Clinical Outcomes

In the 26 trials, 3035 (2.43%) stroke events were reported. Compared with aspirin monotherapy, stroke risk was significantly 23% lower with aspirin plus clopidogrel and 20% lower with aspirin plus ticagrelor (A+T) combinations. With ticagrelor alone and with the combination of aspirin and prasugrel, stroke risk was also lower (11% and 24%, respectively) but 14% higher with clopidogrel monotherapy; however, these latter results did not reach the level of significance (Figure 1; Table III in the Data Supplement). The data were consistent (I^2, 0% [0.0%–34.2%]) and without significant heterogeneity neither within designs nor between designs ($P=0.6828$ and $P=0.8351$, respectively).

The risk of ischemic stroke was significantly reduced with ticagrelor plus aspirin (RR, 0.80 [95% CI, 0.71–0.89]). Ticagrelor monotherapy also resulted in a decreasing trend in the risk of ischemic stroke (RR, 0.88 [95% CI, 0.77–1.00]; $P=0.05$). In the case of hemorrhagic stroke, none of the treatments influenced the risk significantly. Combination ticagrelor to aspirin increased the risk of intracranial bleeding with 53% (RR, 1.53 [95% CI, 1.16–2.03]; $P=0.05$). Data of ischemic stroke were consistent and homogenous, while in the case of hemorrhagic stroke, moderate heterogeneity was seen (I^2, 47%; Table 1).

Twenty-three trials reported 5194 (4.20 %) mortality events. Compared with aspirin, mortality was 20%

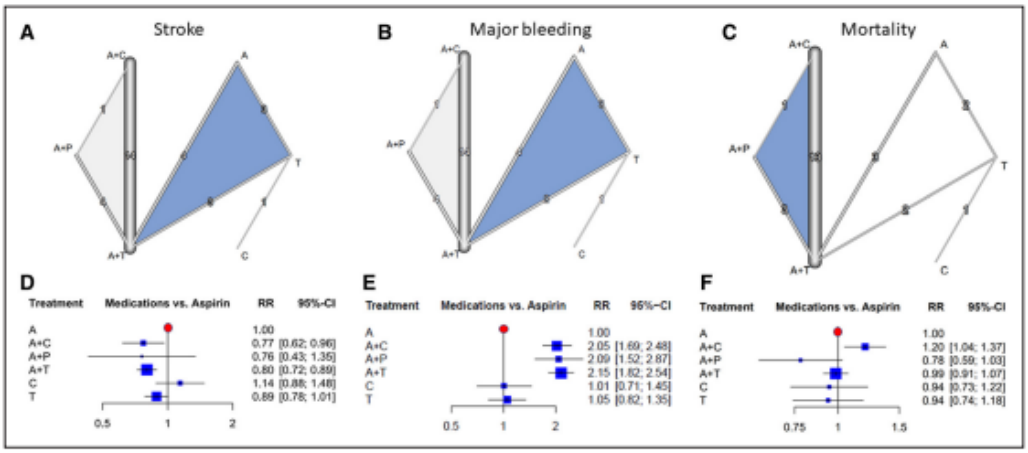

Figure 1. Network layout and the results of the primary end points.
Network graphs depict the overall structure of comparisons of primary end points in our network. The numbers and the thickness of the edges correspond to the number of studies a specific comparison was tested within. The blue triangles mark the multiarm trials of the network. **A**–**C**, Forest plots show the results of the random-effects network meta-analyses as comparisons with aspirin (A) monotherapy set as reference (**D**–**F**). C indicates clopidogrel; P, prasugrel; RR, risk ratio; and T, ticagrelor.

higher with aspirin plus clopidogrel and showed a decreasing trend with aspirin plus prasugrel (RR, 0.78 [95% CI, 0.59–1.03]). With the other treatments, the difference remained <10% and did not reach the level of statistical significance (Figure 1). Low degree of heterogeneity was noted in mortality data (I^2, 12.3% [0.0%–47.1%]).

Twenty-one trials reported 2811 (2.5%) major bleeding events classified by the individual trial definitions. Compared with aspirin alone, major bleeding was in similar ranges with antiplatelet monotherapies while the relative risk was twice higher with combined antiplatelet therapies (Figure 1). Low-degree inconsistency was noted for major bleeding data (I^2, 10.2% [0.0%–45.9%]).

Analyses of the clinical outcomes suggested clustering of treatment arms with antiplatelet monotherapies separating from combination therapies (Figure 2). Metaregression analyses did not find a signal for an important interaction between the background risk of the included population and the risk of stroke or major bleeding using the different antiplatelet regimes (Figure VI in the Data Supplement). Subgroup analyses stratified according to the inclusion conditions showed data consistent in all strata with more effective stroke reduction of the ticagrelor-plus-aspirin combination, as well as the higher risk of bleeding. Net adverse clinical event data showed a higher level of inconsistency and variances with nonsignificant relations except for the benefit of ticagrelor plus aspirin in acute coronary syndrome trials (Table V in the Data Supplement). In accordance with the metaregression analysis, subgrouping, and multilevel analysis reflected consistent results (Figure VII in the Data Supplement). Further exploratory

Table 1. NMA Results of the Secondary Outcomes

Secondary outcomes	A+T	A+C	A+P	C	T
Ischemic stroke	0.80 (0.71–0.89)*	0.81 (0.63–1.05)	0.88 (0.6–1.741)	1.15 (0.89–1.50)	0.90 (0.79–1.02)
Hemorrhagic stroke	0.94 (0.62–1.42)	0.70 (0.36–1.35)	0.37 (0.084–1.68)		0.64 (0.27–1.53)
MACCE	0.89 (0.76–1.06)	0.95 (0.76–1.19)	0.92 (0.57–1.50)	0.83 (0.60–1.15)	0.85 (0.70–1.03)
Myocardial infarction	0.84 (0.69–1.02)	0.96 (0.74–1.25)	0.62 (0.41–0.94)*	0.78 (0.52–1.19)	0.82 (0.61–1.11)
CV mortality	0.99 (0.82–1.18)	1.08 (0.85–1.38)	0.93 (0.60–1.43)		1.01 (0.77–1.33)
Major and minor bleeding	2.58 (2.04–3.27)*	2.09 (1.56–2.82)*	1.95 (0.95–3.99)	1.21 (0.73–2.02)	1.36 (1.03–1.79)*
Minor bleeding	4.17 (2.90–6.00)*	3.27 (2.17–4.92)*	1.85 (0.19–17.88)	2.45 (1.14–5.22)*	3.08 (1.61–5.88)*
Intracranial hemorrhage	1.53 (1.16–2.03)*	0.96 (0.55–1.67)	1.26 (0.04–40.49)	0.66 (0.28–1.56)	0.67 (0.33–1.35)

Results are RRs (95% CIs) from the NMA between the column defining intervention vs aspirin monotherapy. Here, RR >1 means that the column-defined treatment is worse compared with aspirin. A indicates aspirin; CV, cardiovascular; MACCE, major adverse cardiac and cerebrovascular events; NMA, network meta-analysis; P, prasugrel; RR, risk ratio; and T, ticagrelor.
*Significant results.

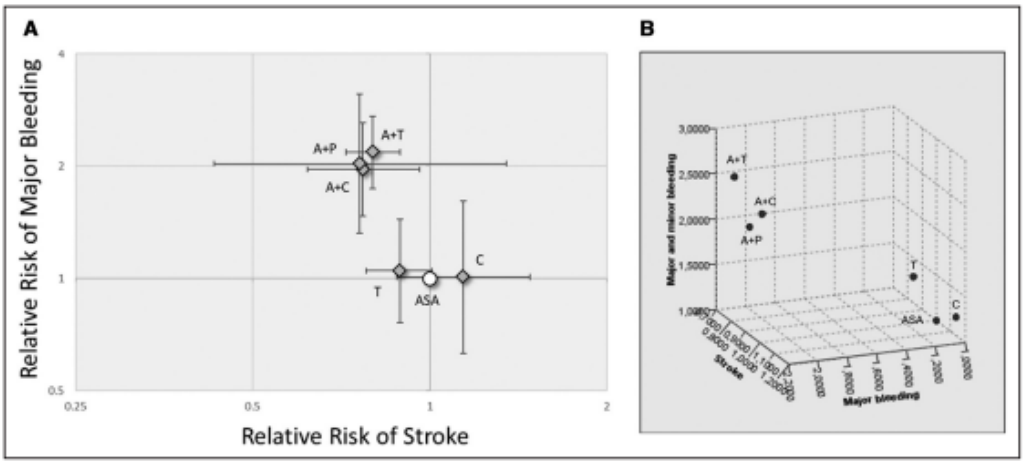

Figure 2. Cluster analysis of the included treatment arms.
A depicts the relative risk of stroke and major bleeding with their respective CIs related to aspirin monotherapy. Both the risk ratio values and the P score values showed a strong negative correlation between stroke and major bleeding risk (R, −0.871; *P*=0.024 and R, −0.899; *P*=0.015, respectively). **B** shows the 3-dimensional projection of the predictor space of the nearest neighbor analysis derived from the analysis of the 11 analyzed predictors. The plot shows discernible clustering of combined therapies and monotherapies. A indicates aspirin; ASA, aspirin alone; C, clopidogrel; P, prasugrel; and T, ticagrelor.

analyses attempting aggregate analyses of prevention and bleeding trade-off neither at the level of disabling conditions nor with multivariate analysis of direct comparisons explored significant differences (Figure VIII in the Data Supplement).

Ranking of Treatment Strategies

Clopidogrel plus aspirin and ticagrelor plus aspirin were ranked as the most effective strategies for the prevention of stroke (P score, 0.79 and 0.73, respectively). For the prevention of ischemic stroke, the ranking for A+T was higher (P score, 0.72 and 0.81, respectively; Table IV in the Data Supplement). Ranking with regard to the major bleeding or stroke prevention showed opposite tendencies (R, −0.879; *P*=0.021; Figure 2). Regarding major bleeding, aspirin was ranked as the safest strategy (P score, 0.82; Table IV in the Data Supplement).

Effect of the Individual Antiplatelets in the Component NMA Models

The component analysis reflected that the use of each antiplatelet agent conveyed the reduction of stroke risk, but this effect reached the level of statistical significance only in the case of ticagrelor. An important increase in bleeding risk was characteristic for all drugs; however, no important change in mortality risk was detected (Table 2).

DISCUSSION

In a multiple-treatment NMA of 26 trials including 124 495 patients, we found further evidence that the choice of antiplatelet strategy influences the risk of stroke in patients with high thrombotic risk. Within this comprehensive analysis of randomized trials testing ticagrelor in a wide range of clinical scenarios, we found that ticagrelor plus aspirin, as

Table 2. Effect of the Individual Antiplatelet Drugs in the Supplementary Component Network Meta-Analysis Models

	Stroke	*P* value	Major bleeding	*P* value	Mortality	*P* value
Aspirin	−0.10 (−0.26 to 0.06)	0.2094	0.73 (0.41 to 1.05)	<0.0001	0.07 (−0.18 to 0.31)	0.6043
Clopidogrel	−0.13 (−0.32 to 0.05)	0.1462	0.70 (0.46 to 0.94)	<0.0001	0.10 (−0.05 to 0.26)	0.1821
Prasugrel	−0.27 (−0.84 to 0.30)	0.3488	0.71 (0.32 to 1.09)	0.0003	−0.23 (−0.54 to 0.07)	0.1282
Ticagrelor	−0.22 (−0.32 to −0.12)	<0.0001	0.77 (0.57 to 0.97)	<0.0001	0.00 (−0.11 to 0.11)	0.9809
Inconsistency (I^2)	0% (0.0% to 34.2%)		10.2% (0.0% to 45.9%)		12.3% (0.0% to 47.1%)	
Heterogeneity						
Additive model		0.6707		0.3305		0.2991
Standard model		0.8165		0.2724		0.5929

Risk difference (95% CI).

compared with aspirin alone, was associated with a significant risk reduction of stroke (20%). Data of this analysis showed an important trade-off between stroke prevention and bleeding risk. Thus, when the risk of major bleeding was taken into consideration, the probability of being the best choice of treatment was the highest for aspirin monotherapy, whereas it was the lowest for A+T. Additionally, this combination significantly increased the risk of intracranial bleeding. We found important clustering of clinical end points among antiplatelet monotherapies and combinations, while in models considering the components of the combinations, the highest stroke prevention potential and the highest bleeding risk were attributable to ticagrelor.

Platelet-driven thrombotic events play a pivotal role in the development of ischemic vascular events. Earlier analyses found favorable results for aspirin as initial therapy in the prevention of ischemic stroke.[43] However, aspirin alone fails to prevent ischemic events in patients at higher risk of recurrences like in cases with recent minor stroke or TIA or in patients with acute coronary syndrome.[44] Later development in antiplatelet therapy aimed at inhibition of alternative pathways including the P2Y12 receptor–mediated activation and in combination with aspirin offering a greater reduction of thromboembolic complications. In TASS (Ticlopidine Aspirin Stroke Study), ticlopidine alone was superior to aspirin with a 21% risk reduction of fatal and nonfatal stroke. However, due to its unfavorable side effects and with the availability of more tolerable ADP inhibitors, ticlopidine is used scarcely in the clinical praxis. Consequently, as no study was performed comparing ticlopidine to ticagrelor, data of ticlopidine studies were not included in our NMA.[45] Moreover, with reassuring data on the reduction in ischemic events seen in acute coronary syndrome, the question was raised whether the intensification of antiplatelet therapy could be similarly beneficial in the prevention of ischemic stroke.

Our findings are partly in line with previous meta-analyses indicating that ticagrelor was more effective in reducing combined ischemic and hemorrhagic stroke compared with other antiplatelet regimens in patients with coronary artery disease, cerebrovascular disease, or peripheral artery disease and extended these with the observation that stroke prevention potential is consistently reflected in trials with ticagrelor treatment regardless of the inclusion condition. Importantly, prevention and bleeding trade-off show clustering at the level of antiplatelet monotherapies and combinations. P2Y12 inhibitor and aspirin combination show more effective stroke prevention, but its use is associated with an increase in the risk of bleeding. This risk includes intracranial bleeding that is significantly higher with ticagrelor and aspirin. The analysis did not show important benefits of ticagrelor-based combination when compared with clopidogrel. Net adverse clinical events showed only benefit among studies with acute coronary syndrome patients.[46]

Our network analysis included some trials that also applied prasugrel—another effective but irreversible P2Y12 blocking agent in combination with aspirin. It is important to note that in the fundamental TRITON-TIMI 38 trial (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction), increasing the risk of bleeding events including fatal bleeding was found in patients with a history of TIA or stroke.[6] Although TRITON-TIMI was not powered for poststroke/TIA events, and only a limited percentage of patients had a history of cerebrovascular disease, prasugrel is contraindicated for them.[6] As all included trials were performed after TRITON-TIMI 38, TIA or stroke was a contraindication for prasugrel treatment while ticagrelor was applied even among the highest risk for intracranial bleeding like those with recent stroke. We believe that the clinical applicability of prasugrel among patients with earlier cerebrovascular events remains to be studied in greater detail. The magnitude of its treatment effect is, however, at the range of the other P2Y12 inhibitors when applied in patients without a cerebrovascular history.

It remains unclear whether the preventive effect of ticagrelor is explainable with its more effective inhibition of P2Y12-dependent platelet activation or with additional effects like increase in adenosine levels due to an additional blockage via ENT-1 (equilibrative nucleoside transporter 1) leading to platelet inhibition, inflammatory milieu modulation, vasodilation, and protection from ischemia and reperfusion injury.[47] Orchestrated by these, ticagrelor may have additional protective effects on cerebral ischemia-reperfusion. Additionally, to the potentially lower bleeding risk due to the reversible P2Y12 inhibition, animal studies indicated neuroprotective effects of ticagrelor through endothelial NO synthase modulation, resulting in increased blood flow and reducing infarct volume.[48]

Both the THALES trial and the subgroup analysis of the SOCRATES trial (Ticagrelor Versus Aspirin in Acute Stroke or Transient Ischemic Attack) support these findings indicating a risk reduction of 32% with ticagrelor and 27% with A+T over aspirin in patients with minor ischemic stroke or high-risk TIA.[11,12] However, it is important to note that these trials also found an important increase of bleeding complications that may reduce or cancel out the ischemic benefit. Functional health status such as disabling stroke outcome (defined as death or modified Rankin Scale score >1) was reported only in the THALES and SOCRATES trials. The analysis of this end point did not explore important differences. The RR was 0.99 (0.93–1.06) in A+T versus aspirin, 0.91 (0.77–1.06) in ticagrelor versus aspirin comparisons, and estimated to be 1.10 (0.92–1.30) in A+T versus ticagrelor (Figure IX in the Data Supplement).

Limitations

The present analysis should be interpreted considering some limitations. It is important to note that multiple mechanisms may lead to the development of stroke and

an important minority of these cases have a cardioembolic origin. Oral anticoagulation remains the treatment of choice of these patients and due to interactions between anticoagulant and antiplatelet therapies cases requiring oral anticoagulation were excluded from these trials.

All analyses were performed by pooling of the active drug arms with various dosages; therefore, it limits our ability to assess how the differential effects of the dosage of these drugs affect the outcomes. Furthermore, the included studies reflected the problems of capturing bleeding events and the lack of one overall accepted bleeding definition system. In 14 trials, the TIMI criteria were used while in 10 other systems like the PLATO (Ticagrelor Compared With Clopidogrel in Patients With Acute Coronary Syndromes trial), BARC (Bleeding Academic Research Consortium), or GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) were applied often in combinations.

The absence of patient-level data precludes adjustments important confounders that might have remained sources of heterogeneity between trials. This is also true of the aspirin dose since potential ticagrelor-aspirin interaction has been documented. The study-level analysis allows limited insight into the time relations of treatment benefit. Moreover, the optimal time frame may differ among pharmacological treatments and combinations.

Conclusions

Comprehensive analysis of clinical trials supports that the use of ticagrelor as mono- or aspirin combined therapy resulted in more effective stroke prevention in a high-risk patient population. Our analyses also underscore the importance of bleeding associated with intensified antiplatelet therapy. Highlighting the trade-off between bleeding risk and stroke prevention, the data show that besides ischemic risk, bleeding risk should be assessed and considered. This lower risk of ischemic stroke with ticagrelor was counterbalanced with a higher risk of major bleeding including an importantly increased risk of intracranial bleeding. Signal of benefit supporting the use of ticagrelor was neither present in the mortality nor in the combined analyses of ischemic and bleeding events. The decision regarding the choice of antiplatelet agent and its duration should be individualized according to the risks and benefits of the chosen treatment. We believe that the development of scoring tools stratifying patients according to their bleeding risk is essential to improve clinical outcomes in conjunction with intensified antiplatelet stroke prevention.

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Disclosures

None.

Supplemental Materials

Online Tables I–V
Online Figures I–IX

REFERENCES

1. Donkor ES. Stroke in the 21st century: a snapshot of the Burden, epidemiology, and quality of life. *Stroke Res Treat*. 2018;2018:3238165. doi: 10.1155/2018/3238165
2. Kornfeld M, Munsayac JR. Antiplatelet medications. In: *Inpatient Anticoagulation*. John Wiley and Sons; 2011:47–65.
3. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, Meade T, et al; Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet*. 2009;373:1849–1860.
4. Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, Gorelick P, Halperin J, Harbaugh R, et al; American Heart Association/American Stroke Association Council on Stroke; Council on Cardiovascular Radiology and Intervention; American Academy of Neurology. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Circulation*. 2006;113:e409–e449.
5. Takahashi Y, Nishida Y, Nakayama T, Asai S. Comparative effect of clopidogrel and aspirin versus aspirin alone on laboratory parameters: a retrospective, observational, cohort study. *Cardiovasc Diabetol*. 2013;12:87. doi: 10.1186/1475-2840-12-87
6. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, et al; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001–2015. doi: 10.1056/NEJMoa0706482
7. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, et al; PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045–1057. doi: 10.1056/NEJMoa0904327
8. Husted S, van Giezen JJ. Ticagrelor: the first reversibly binding oral P2Y12 receptor antagonist. *Cardiovasc Ther*. 2009;27:259–274. doi: 10.1111/j.1755-5922.2009.00096.x
9. Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, Held P, Hill MD, Jonasson J, Kasner SE, Ladenvall P, et al; SOCRATES Steering Committee and Investigators. Efficacy and safety of ticagrelor versus aspirin in acute stroke or transient ischaemic attack of atherosclerotic origin: a subgroup analysis of SOCRATES, a randomised, double-blind, controlled trial. *Lancet Neurol*. 2017;16:301–310. doi: 10.1016/S1474-4422(17)30038-8
10. Johnston SC, Amarenco P, Denison H, Evans SR, Himmelmann A, James S, Knutsson M, Ladenvall P, Molina CA, Wang Y; THALES Investigators. Ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA. *N Engl J Med*. 2020;383:207–217. doi: 10.1056/NEJMoa1916870
11. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, et al; CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med*. 2006;354:1706–1717. doi: 10.1056/NEJMoa060989
12. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Straus S, Thorlund K, Jansen JP, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med*. 2015;162:777–784. doi: 10.7326/M14-2385

13. Rücker G. Network meta-analysis, electrical networks and graph theory. *Res Synth Methods*. 2012;3:312–324. doi: 10.1002/jrsm.1058
14. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539–1558. doi: 10.1002/sim.1186
15. Rücker G, Petropoulou M, Schwarzer G. Network meta-analysis of multicomponent interventions. *Biometrical J*. 2020;62:808–821.
16. Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol*. 2015;15:58. doi: 10.1186/s12874-015-0060-8
17. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoS One*. 2013;8:e76654. doi: 10.1371/journal.pone.0076654
18. Schwarzer G, Carpenter JR, Rücker G. *Meta-Analysis With R:Version 4.0-1*. R Package; 2014.
19. Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, Held P, Jonasson J, Minematsu K, Molina CA, et al; SOCRATES Steering Committee and Investigators. Ticagrelor versus aspirin in acute stroke or transient ischemic attack. *N Engl J Med*. 2016;375:35–43. doi: 10.1056/NEJMoa1603060
20. Wang Y, Chen W, Lin Y, Meng X, Chen G, Wang Z, Wu J, Wang D, Li J, Cao Y, et al; PRINCE Protocol Steering Group. Ticagrelor plus aspirin versus clopidogrel plus aspirin for platelet reactivity in patients with minor stroke or transient ischaemic attack: open label, blinded endpoint, randomised controlled phase II trial. *BMJ*. 2019;365:l2211. doi: 10.1136/bmj.l2211
21. Cannon CP, Husted S, Harrington RA, Scirica BM, Emanuelsson H, Peters G, Storey RF; DISPERSE-2 Investigators. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. *J Am Coll Cardiol*. 2007;50:1844–1851. doi: 10.1016/j.jacc.2007.07.053
22. Berwanger O, Lopes RD, Moia DDF, Fonseca FA, Jiang L, Goodman SG, Nicholls SJ, Parkhomenko A, Averkov O, Tajer C, et al. Ticagrelor versus clopidogrel in patients with STEMI treated with fibrinolysis: TREAT trial. *J Am Coll Cardiol*. 2019;73:2819–2828. doi: 10.1016/j.jacc.2019.03.011
23. Park DW, Kwon O, Jang JS, Yun SC, Park H, Kang DY, Ahn JM, Lee PH, Lee SW, Park SW, et al; TICAKOREA Investigators. Clinically significant bleeding with ticagrelor versus clopidogrel in Korean patients with acute coronary syndromes intended for invasive management: a randomized clinical trial. *Circulation*. 2019;140:1865–1877. doi: 10.1161/CIRCULATIONAHA.119.041766
24. Schüpke S, Neumann FJ, Menichelli M, Mayer K, Bernlochner I, Wöhrle J, Richardt G, Liebetrau C, Witzenbichler B, Antoniucci D, et al; ISAR-REACT 5 Trial Investigators. Ticagrelor or prasugrel in patients with acute coronary syndromes. *N Engl J Med*. 2019;381:1524–1534. doi: 10.1056/NEJMoa1908973
25. Gimbel M, Qaderdan K, Willemsen L, Hermanides R, Bergmeijer T, de Vrey E, Heestermans T, Tjon Joe Gin M, Waalewijn R, Hofma S, et al. Clopidogrel versus ticagrelor or prasugrel in patients aged 70 years or older with non-ST-elevation acute coronary syndrome (POPular AGE): the randomised, open-label, non-inferiority trial. *Lancet*. 2020;395:1374–1381. doi: 10.1016/S0140-6736(20)30325-1
26. Kim BK, Hong SJ, Cho YH, Yun KH, Kim YH, Suh Y, Cho JY, Her AY, Cho S, Jeon DW, et al; TICO Investigators. Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome: the TICO randomized clinical trial. *JAMA*. 2020;323:2407–2416. doi: 10.1001/jama.2020.7580
27. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, et al; PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015;372:1791–1800. doi: 10.1056/NEJMoa1500857
28. Goto S, Huang CH, Park SJ, Emanuelsson H, Kimura T. Ticagrelor vs. clopidogrel in Japanese, Korean and Taiwanese patients with acute coronary syndrome – randomized, double-blind, phase III PHILO study. *Circ J*. 2015;79:2452–2460. doi: 10.1253/circj.CJ-15-0112
29. Motovska Z, Hlinomaz O, Kala P, Hromadka M, Knot J, Varvarovsky I, Dusek J, Jarkovsky J, Miklik R, Rokyta R, et al; PRAGUE-18 Study Group. 1-year outcomes of patients undergoing primary angioplasty for myocardial infarction treated with prasugrel versus ticagrelor. *J Am Coll Cardiol*. 2018;71:371–381. doi: 10.1016/j.jacc.2017.11.008
30. Tang X, Li R, Jing Q, Wang Q, Liu P, Zhang P, Liu Y. Assessment of ticagrelor versus clopidogrel treatment in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *J Cardiovasc Pharmacol*. 2016;68:115–120. doi: 10.1097/FJC.0000000000000390
31. Wang H, Wang X. Efficacy and safety outcomes of ticagrelor compared with clopidogrel in elderly Chinese patients with acute coronary syndrome. *Ther Clin Risk Manag*. 2016;12:1101–1105. doi: 10.2147/TCRM.S108965
32. Zhang Y, Zhao Y, Pang M, Wu Y, Zhuang K, Zhang H, Bhat A. High-dose clopidogrel versus ticagrelor for treatment of acute coronary syndromes after percutaneous coronary intervention in CYP2C19 intermediate or poor metabolizers: a prospective, randomized, open-label, single-centre trial. *Acta Cardiol*. 2016;71:309–316. doi: 10.2143/AC.71.3.3152091
33. Dehghani P, Lavoie A, Lavi S, Crawford JJ, Harenberg S, Zimmermann RH, Booker J, Kelly S, Cantor WJ, Mehta SR, et al. Effects of ticagrelor versus clopidogrel on platelet function in fibrinolytic-treated STEMI patients undergoing early PCI. *Am Heart J*. 2017;192:105–112. doi: 10.1016/j.ahj.2017.07.013
34. Wu HB, Tian HP, Wang XC, Bai SR, Li XN, Zhang LN, Du RP. Clinical efficacy of ticagrelor in patients undergoing emergency intervention for acute myocardial infarction and its impact on platelet aggregation rate. *Am J Transl Res*. 2018;10:2175–2183.
35. Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briguori C, Cha JY, Collier T, Dangas G, Dudek D, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. *N Engl J Med*. 2019;381:2032–2042. doi: 10.1056/NEJMoa1908419
36. Bonello L, Laine M, Cluzel M, Frere C, Mancini J, Hasan A, Thuny F, Gaubert M, Guieu R, Dignat-George F, et al. Comparison of ticagrelor versus prasugrel to prevent periprocedural myonecrosis in acute coronary syndromes. *Am J Cardiol*. 2015;116:339–343. doi: 10.1016/j.amjcard.2015.04.050
37. Hiatt WR, Fowkes FG, Heizer G, Berger JS, Baumgartner I, Held P, Katona BG, Mahaffey KW, Norgren L, Jones WS, et al; EUCLID Trial Steering Committee and Investigators. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. *N Engl J Med*. 2017;376:32–40. doi: 10.1056/NEJMoa1611688
38. Zhao Q, Zhu Y, Xu Z, Cheng Z, Mei J, Chen X, Wang X. Effect of ticagrelor plus aspirin, ticagrelor alone, or aspirin alone on saphenous vein graft patency 1 year after coronary artery bypass grafting: a randomized clinical trial. *JAMA*. 2018;319:1677–1686. doi: 10.1001/jama.2018.3197
39. Schunkert H, Boening A, von Scheidt M, Lanig C, Gusmini F, de Waha A, Kuna C, Fach A, Grothusen C, Oberhoffer M, et al. Randomized trial of ticagrelor vs. aspirin in patients after coronary artery bypass grafting: the TiCAB trial. *Eur Heart J*. 2019;40:2432–2440. doi: 10.1093/eurheartj/ehz185
40. Hochholzer W, Kleiner P, Younas I, Valina CM, Löffelhardt N, Amann M, Bömicke T, Ferenc M, Hauschke D, Trenk D, et al. Randomized comparison of oral P2Y12-receptor inhibitor loading strategies for transitioning from cangrelor: the ExcelsiorLOAD2 trial. *JACC Cardiovasc Interv*. 2017;10:121–129. doi: 10.1016/j.jcin.2016.10.004
41. Bhatt DL, Steg PG, Mehta SR, Leiter LA, Simon T, Fox K, Held C, Andersson M, Himmelmann A, Ridderstråle W, et al; THEMIS Steering Committee and Investigators. Ticagrelor in patients with diabetes and stable coronary artery disease with a history of previous percutaneous coronary intervention (THEMIS-PCI): a phase 3, placebo-controlled, randomised trial. *Lancet*. 2019;394:1169–1180. doi: 10.1016/S0140-6736(19)31887-2
42. Jimenez Diaz VA, Tello-Montoliu A, Moreno R, Cruz Gonzalez I, Baz Alonso JA, Romaguera R, Molina Navarro E, Juan Salvadores P, Paredes Galan E, De Miguel Castro A, et al. Assessment of platelet REACtivity after transcatheter aortic valve replacement: the REAC-TAVI trial. *JACC Cardiovasc Interv*. 2019;12:22–32. doi: 10.1016/j.jcin.2018.10.005
43. Rothwell PM, Algra A, Chen Z, Diener HC, Norrving B, Mehta Z. Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. *Lancet*. 2016;388:365–375. doi: 10.1016/S0140-6736(16)30468-8
44. Bornstein NM, Karepov VG, Aronovich BD, Gorbulev AY, Treves TA, Korczyn AD. Failure of aspirin treatment after stroke. *Stroke*. 1994;25:275–277. doi: 10.1161/01.str.25.2.275
45. Hass WK, Easton JD, Adams HP Jr, Pryse-Phillips W, Molony BA, Anderson S, Kamm B. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. Ticlopidine Aspirin Stroke Study Group. *N Engl J Med*. 1989;321:501–507. doi: 10.1056/NEJM198908243210804
46. Malhotra K, Goyal N, Kasunich AS, Sheth SA, Katsanos AH, Alexandrov AV, Tsivgoulis G. Ticagrelor for stroke prevention in patients with vascular risk factors: a systematic review and meta-analysis. *J Neurol Sci*. 2018;390:212–218. doi: 10.1016/j.jns.2018.05.001
47. Cattaneo M, Schulz R, Nylander S. Adenosine-mediated effects of ticagrelor: evidence and potential clinical relevance. *J Am Coll Cardiol*. 2014;63:2503–2509. doi: 10.1016/j.jacc.2014.03.031
48. Yamauchi K, Imai T, Shimazawa M, Iwama T, Hara H. Effects of ticagrelor in a mouse model of ischemic stroke. *Sci Rep*. 2017;7:12088. doi: 10.1038/s41598-017-12205-w