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

Ph.D. Thesis Summary

by

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1. PROLOGUE

Coronary artery disease (CAD) is the foremost single cause of mortality and loss of Disability Adjusted Life Years (DALYs) globally. A large number of this burden falls on low- and middle-income countries accounting for nearly 7 million deaths and 129 million DALYs annually. 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. Patients with ACS undergoing percutaneous coronary intervention (PCI) with drug-eluting stents (DES) are currently recommended dual antiplatelet therapy (DAPT), consisting of aspirin with a P2Y12 receptor inhibitor for at least 12 months. The treatment goal is preventing thrombotic complications such as stent thrombosis. However, this strategy increases bleeding risk even in patients with a high thrombotic risk of ACS. Therefore, unresolved questions still remain in need of clarification.

Non-valvular atrial fibrillation (NVAF) is the most commonly diagnosed heart rhythm abnormality. Anticoagulation is required for the prevention of thrombo-embolic complications related to NVAF. 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. However, estimates suggest that about 30% of patients with NVAF may have simultaneously CAD and 15% will require PCI with stent placement. The optimal antithrombotic regimen after PCI in patients with NVAF is still unclear. 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

3. BACKGROUND

3.1. Risk of adverse events associated with LPR in patients with PCI

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. With the use of more effective agents the prevalence of high platelet reactivity (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.

3.2. Oral anticoagulation and outcomes in patients with AMI

In patients with NVAF and ACS in addition to antiplatelet therapy anticoagulation is required. Specific considerations regarding patients with AF undergoing PCI include the fact that DAPT is essential to prevent stent thrombosis, but insufficient for stroke prevention. Antiplatelets on top of oral anticoagulant (OAC) therapy significantly increases the risk of bleeding complications, therefore long-term triple therapy should be avoided. 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 OAC therapy, may be attributable to inherently higher risk of these cases.

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

For patients who have suffered an ischemic stroke, antiplatelet therapy is also important for secondary prevention. Most recently the THALES trial further supported the potential of ticagrelor and aspirin in stroke prevention. This network meta-analysis (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.

4. METHODS

4.1. Risk of adverse events associated with LPR in patients with PCI

A manual search of medical literature was performed for articles reporting patients with LPR and ACS and/or undergoing PCI receiving DAPT. The clinical outcomes of interest were bleeding events, stent thrombosis, non-fatal myocardial infarction (MI) and the composite endpoint of the reported serious vascular events. 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. 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.

4.2. Oral anticoagulation and outcomes in patients with AMI

The Hungarian Myocardial Infarction Registry (HUMIR) is a prospective registry collecting clinical data on consecutive patients treated for an AMI in Hungary. Patients undergoing successful PCI for AMI with or without ST-segment elevation were enrolled. Two groups were created according to the anticoagulation treatment. 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 MACE defined as mortality, non-fatal MI or stroke. 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. To isolate the effect of comorbidities from that of arrhythmia, sensitivity analyses with creating an alternative control group 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.

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

A manual search of medical literature was performed for articles reporting randomized clinical trials (RCT) with ticagrelor, using the following search terms 'ticagrelor', 'AZD 6140' and 'stroke'. 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 (4) in patients with cerebrovascular, coronary or peripheral artery disease. The primary efficacy outcome of our analysis was the occurrence or recurrence of stroke. Major bleeding and all-cause mortality were assessed as main safety endpoints. Secondary outcomes included ischemic stroke, hemorrhagic stroke, and transient ischemic attack (TIA), MI, major cerebral or cardiovascular event (MACCE). 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 multiple treatment NMA was used. Furthermore, a comparative ranking of the treatments according to the P-scores method was conducted.

5. RESULTS

5.1. Risk of adverse events associated with LPR in patients with PCI

Twenty studies involving 19 076 patients were analyzed. 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 1). 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, $p<0.01$) (Figure 2). 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 2). 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 in subgroup analyses. 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%).

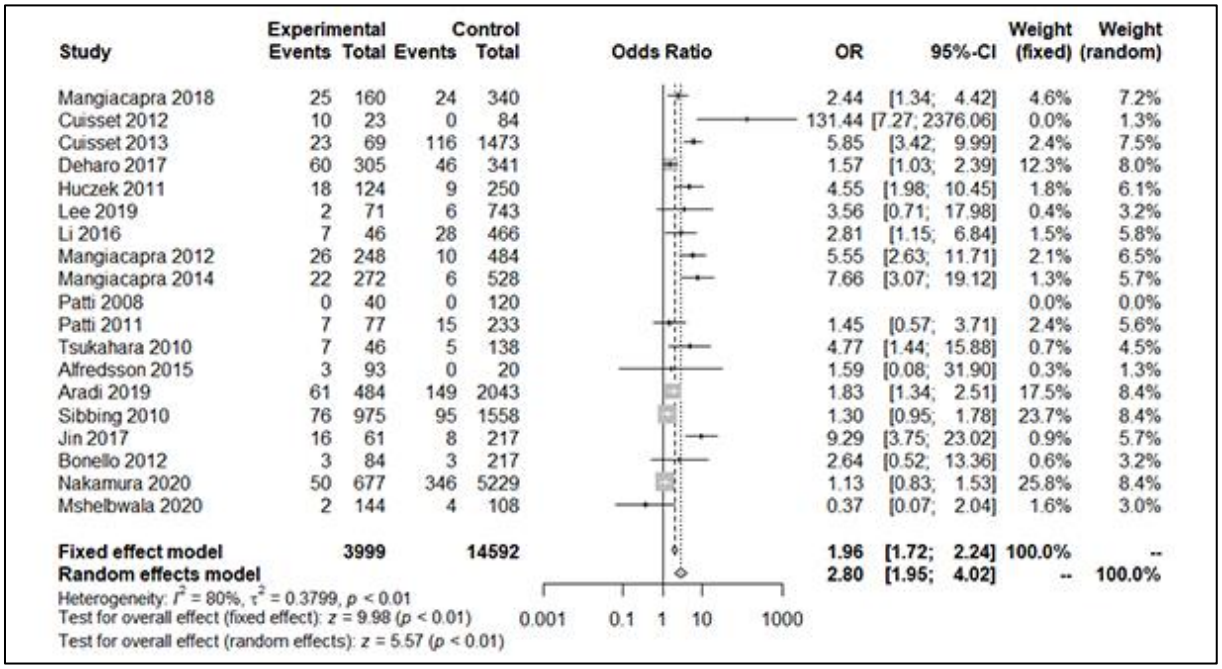

Figure 1. Principal pooled analysis.
Forest plots of major and minor bleeding risk in studies following percutaneous coronary intervention with LPR versus without LPR. The grey rectangles are proportional with the study weight. The diamond represents the cumulative OR and CI. Abbreviations: LPR low platelet reactivity; OR odds ratio; CI confidence interval

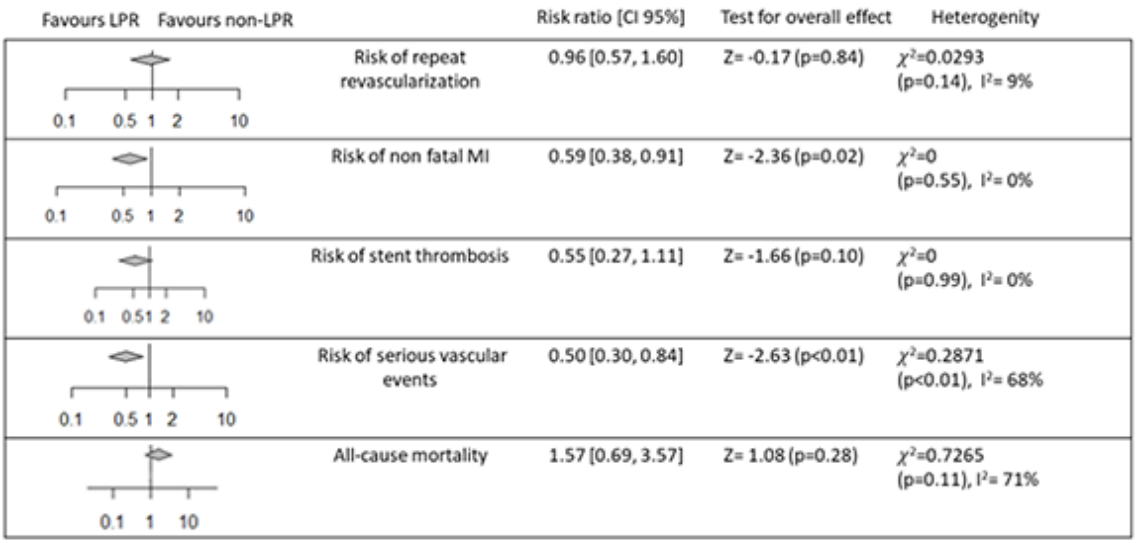

Figure 2. Summary of the outcomes of the secondary endpoints.
The diamond represents the cumulative RR and CI of all patient groups. *Mean difference (95% CI)
Abbreviations: MI myocardial infarction; LPR low platelet reactivity; RR risk ratio; CI confidence interval

5.2. Oral anticoagulation and outcomes in patients with AMI

A study population of 30 681 patients was identified that of 6.51% (n=1875) received oral anticoagulation (OAC group). Among 1875 patients of the OAC group in 1646 cases anticoagulation was indicated due to atrial fibrillation (AF). 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. The propensity score (PS) matching resulted in a matched population of 3750 patients. 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 3).

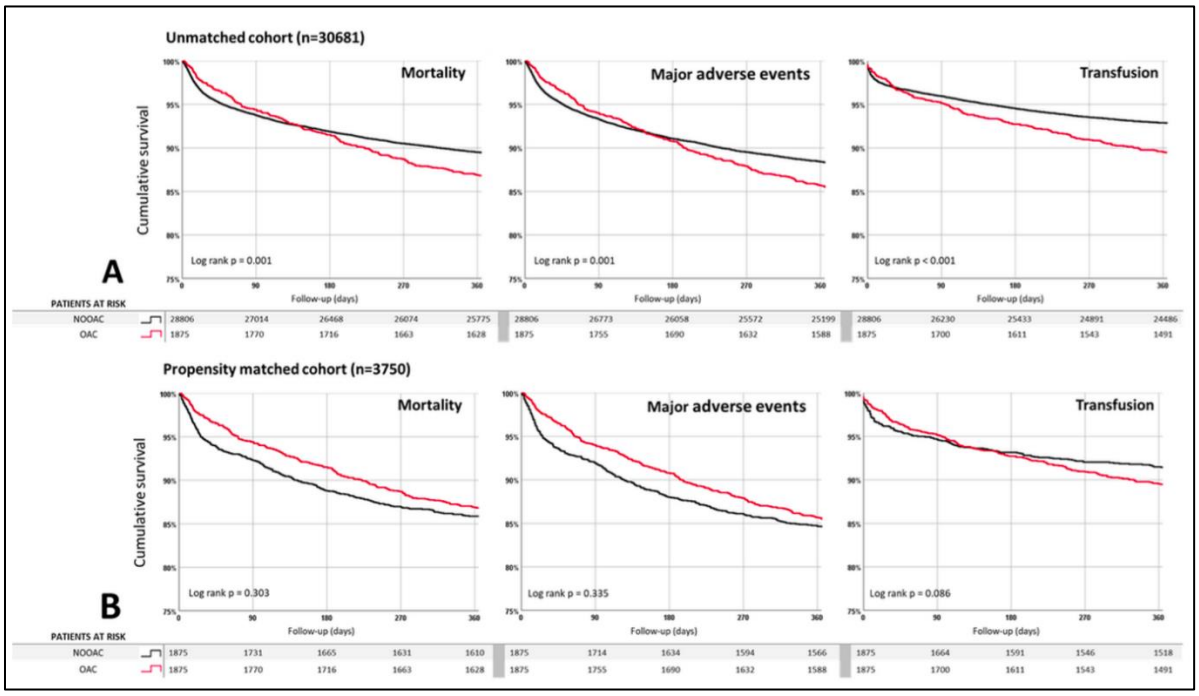

Figure 3. Kaplan-Meier curves of overall mortality, major adverse events and transfusion-free survival comparing patients with or without oral-anticoagulant treatment.
Abbreviations: NOOAC patient group treated without oral anticoagulant therapy; OAC patient population treated with oral anticoagulant 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 4). 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 (Figure 4.)

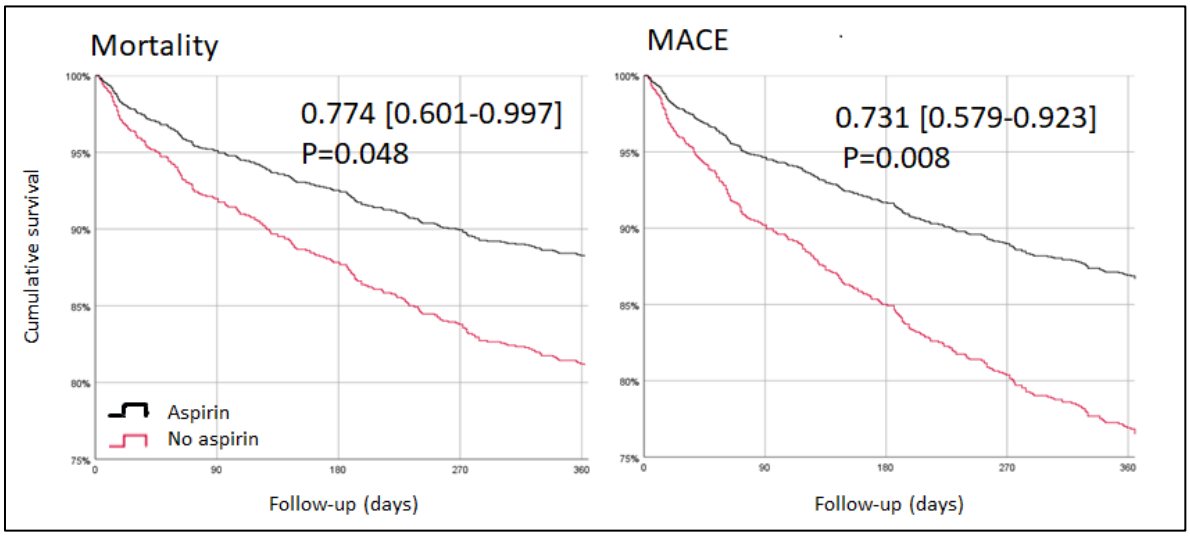

Figure 4. Curves plotting the risk of mortality and major adverse cardiac events among oral anticoagulation treated patients compared between cases receiving or not receiving aspirin.

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. According to the applied antiplatelet medication study groups were divided into 6 groups. 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 5). 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 1). 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 5). 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 5/B,E).

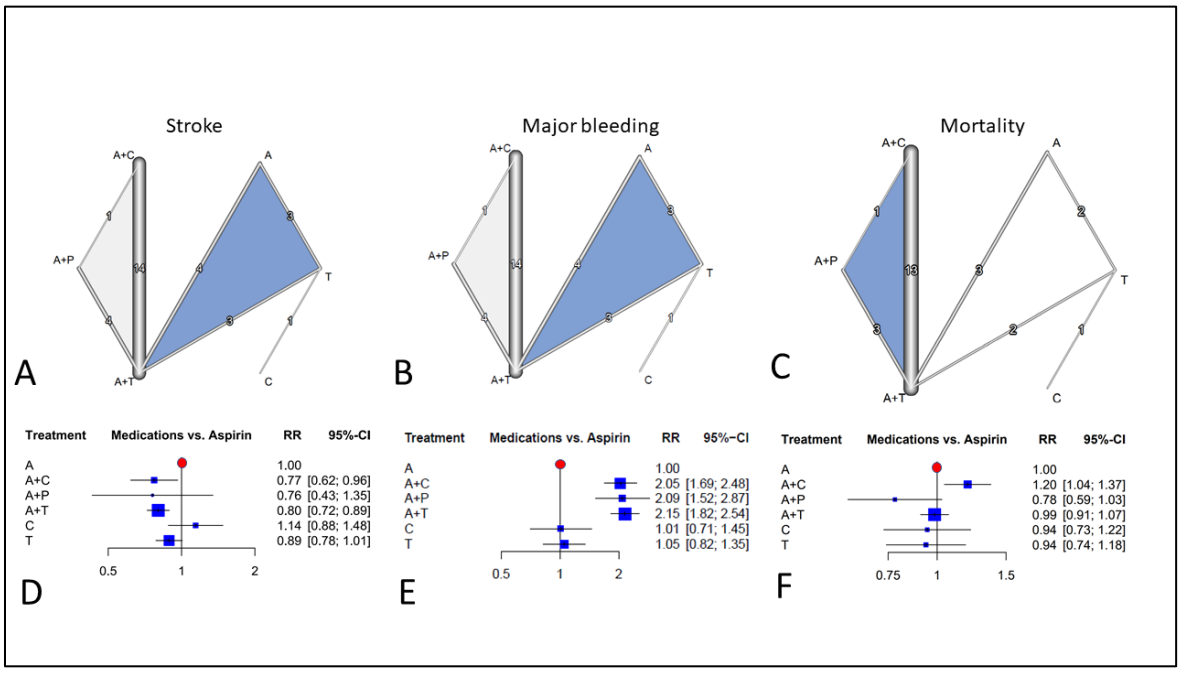

Figure 5. Network layout and the results of the primary endpoints.
Network graphs depict the overall structure of comparisons of primary endpoints in our network. The numbers and the thickness of the edges correspond to the number of studies a specific comparison was tested within. The blue triangles 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

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 1. 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 cerebro- and cardiovascular events, P prasugrel, T ticagrelor

6. DISCUSSION

6.1. Risk of adverse events associated with LPR in patients with PCI

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. Further reports supported this concept that LPR is a marker for a higher risk for bleeding also among prasugrel-treated patients. However, according to some recent studies optimal platelet reactivity does not denote the same range in every patient population. In the TRIOLOGY ACS trial involving ACS patients without PCI found no relationship between LPR and major bleeding risk. 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.

6.2 Oral anticoagulation and outcomes in patients with AMI

Our analysis of a large, prospective, unselected database of patients treated with PCI due to an event of AMI showed that 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 propensity score (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. The WOEST trial showed a significant reduction of MACE 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.

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 MI 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.

8. SCIENTIOMETRICS

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**

8.1. 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 (2021) 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 (2021) Q1**

CUMULATIVE IMPACT FACTOR: **13.154**

8.2. 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**

8.3. 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

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

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

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**

8.5. 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

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. szóbeli előadás

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

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

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

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

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

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

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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