

# Systematic review and meta-analysis of outcomes after coronary revascularization procedures with regard to antiplatelet treatment and bleeding complications

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Ph.D. thesis

by

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## **1 Introduction**

Meta-analysis is a statistical technique for summarising, and reviewing previously published quantitative research. Practitioners, clinicians have to face an informational boom of the modern medicine. There is too much information around for people to keep up to date, on the other hand high quality information is often not easy to find. Elaborating a summary of available literature and performing a critical review of the obtained data is becoming more and more important. Using meta-analysis, a specially developed statistical armamentarium that allows cumulating the available data of independent observation, enables to analyse a wide variety of questions and allows not only a summary but also an integration of the evidences with higher statistical power and more precise effect estimates.

## **2 Background**

Transradial coronary angioplasty (TRPCI) has gained widespread acceptance since its introduction by Kiemeneij and Laarman. Radial access has been proven to be a highly safe and effective technique for both diagnostic- and therapeutic procedures. Advantages of the transradial approach over the transfemoral include safe and easy haemostasis due to compressibility of the artery, and consequent lack of need for post procedural bed rest permitting immediate ambulation, greater comfort, and earlier discharge. These have been shown to reduce the costs of hospitalization and improve quality of life for patients. Although it is technically more challenging, transradial intervention is feasible in the setting of acute coronary syndromes. The major advantage of the TRPCI is the near elimination of clinically significant access site complications, even in patients at high risk (i.e. patients treated with GP IIb/IIIa inhibitors or shortly after systemic thrombolysis). Bleeding events, and the consequent need for transfusion, are independent determinants of survival in acute coronary syndromes. Their relation to short- and long-term mortality has been demonstrated in major randomized trials as well as through the evaluation of registries. Low incidence of vascular access site bleeding complications suggests that the transradial approach may be a safe alternative to the femoral technique employed in acute myocardial infarction with ST segment elevation (STEMI), particularly when an aggressive anticoagulation- and antiplatelet regimen is applied. On the contrary, the possible greater occurrence of procedural failure and longer procedural times occasioned by difficulty in puncturing the radial artery, inability to cannulate the coronaries, or impossibility to perform

the angioplasty, are factors that raise concerns as to whether radial access remains beneficial in the setting where timely reperfusion is critical, in STEMI for instance. The safety of transradial- and transfemoral PCI in AMI were compared in numerous trials; however, most of them included small patient groups. Despite consistent demonstration of lower bleeding rates, only inconclusive results are available regarding recurrent ischemic events; most of these studies were underpowered to evaluate this issue.

Large body of evidence supports the application of dual antiplatelet therapy (DAPT) in patients with acute coronary syndromes (ACS) and after percutaneous coronary interventions. Clopidogrel, an irreversible inhibitor of the platelet P<sub>2</sub>Y<sub>12</sub> ADP-receptor, is the cornerstone of the DAPT. The inhibitory effect of clopidogrel lasts for the whole life-span of the platelet as platelets are not capable for protein synthesis. Due to the slow onset of action, clopidogrel is recommended in an oral bolus before coronary angiography to achieve rapid platelet inhibition in patients with ACS. In the past years, aggressive clopidogrel based antiplatelet protocols have been shown to be effective in reducing recurrent thrombo- ischemic events. This strategy is predominantly important in patients with ACS, in whom the prompt and potent antiplatelet therapy is associated with the greatest clinical benefit. Although most patients with ACS are candidates for percutaneous coronary interventions (PCI), some patients with ACS require surgical revascularization. This proportion is low among those with ST-segment elevation myocardial infarction (MI), but can reach 10% in patients with non-ST segment elevation MI. Similarly, there are also many stable angina patients taking clopidogrel before coronary artery bypass grafting (CABG) procedures due to the prior PCI or acute coronary event. As a result, the administration of clopidogrel is quite common before cardiac surgery. As the impaired platelet function during CABG might be associated with higher rate of bleeding complications, it is recommended to discontinue clopidogrel for at least five days before surgery. However, in certain cases, it is not possible to wait for the wash-out period, and many patients undergo surgical revascularization under the effect of clopidogrel. On the other hand some recent studies support that persisting inhibition of platelet aggregation beside the higher risk for bleeding may have beneficial effect in terms of reduction of perioperative myocardial infarction or graft patency. Several studies intended to clarify the potential harm and benefit associated with clopidogrel therapy prior to CABG. As these studies resulted in heterogeneous and inconclusive results

currently, there is no consensus regarding the impact of clopidogrel treatment on clinical outcome after cardiac surgery.

Numerous reports have found that the antiplatelet efficacy of clopidogrel exhibits considerable inter-individual variability. According to our current understanding, the insufficient and highly unpredictable generation of its active metabolite is largely responsible for the inter-individual differences observed in post-treatment platelet reactivity. As the active metabolite formation is influenced by genetic, clinical and pharmacological factors, the development of high on-clopidogrel platelet reactivity (HPR) is a multifactorial process. As recently evidenced, low compliance is also a remarkable reason for measuring HPR in the patient. Up to now, numerous in vitro or ex vivo laboratory assays have been developed to monitor on-clopidogrel platelet reactivity. Using these assays, accumulating number of observational studies have found that patients with HPR have higher risk for recurrent ischemic events, including myocardial infarction and stent thrombosis (ST). However, routine platelet function testing is not yet recommended. First, this is due to the somewhat arbitrary-used and non-standardized definitions for HPR. Second, the prognostic significance of HPR after PCI is unclear as prospective, adequately-powered clinical trials are lacking. Third, there is no consensus on the ideal platelet function assay to monitor on-clopidogrel platelet reactivity.

### **3 Aims**

The main goal of the thesis to systematically overview and analyze the available medical literature, which reported clinical outcomes after revascularization procedures.

Percutaneous coronary intervention (PCI) is routinely preformed through the femoral approach, which was the gold-standard method. Nevertheless, this access route accompanies higher rate of bleeding complications. Transradial approach has a lower incidence of bleeding complications. However requires longer learning curve and might increase the procedural time and more importantly the time to reperfusion, and the rate of procedural failure. Therefore our aim was to perform a systematic review of the literature comparing the safety and efficacy of the two vascular accesses.

Antiplatelets prevent the recidive ischaemic events after PCI, but among patients, who require urgent surgical revascularization, the antiplatelet regime increases the risk of bleeding complications after operation. The higher rates of blood product transfusion may have an effect on morbidity and mortality. For that reason our aim was to evaluate the impact of preoperative administered clopidogrel on the outcome of patients referred for surgical revascularization.

Several studies reported data about insufficient clopidogrel therapy, inter-individual differences on clopidogrel responsiveness. In case of non-responsiveness the incidence of adverse event corresponds with clopidogrel naive patients. Accordingly our aim was to collect and summarize the available evidence regarding the prognostic significance of high on-clopidogrel platelet reactivity.

## **4 Transradial versus transfemoral percutaneous coronary intervention in acute myocardial infarction**

### **4.1 Methods**

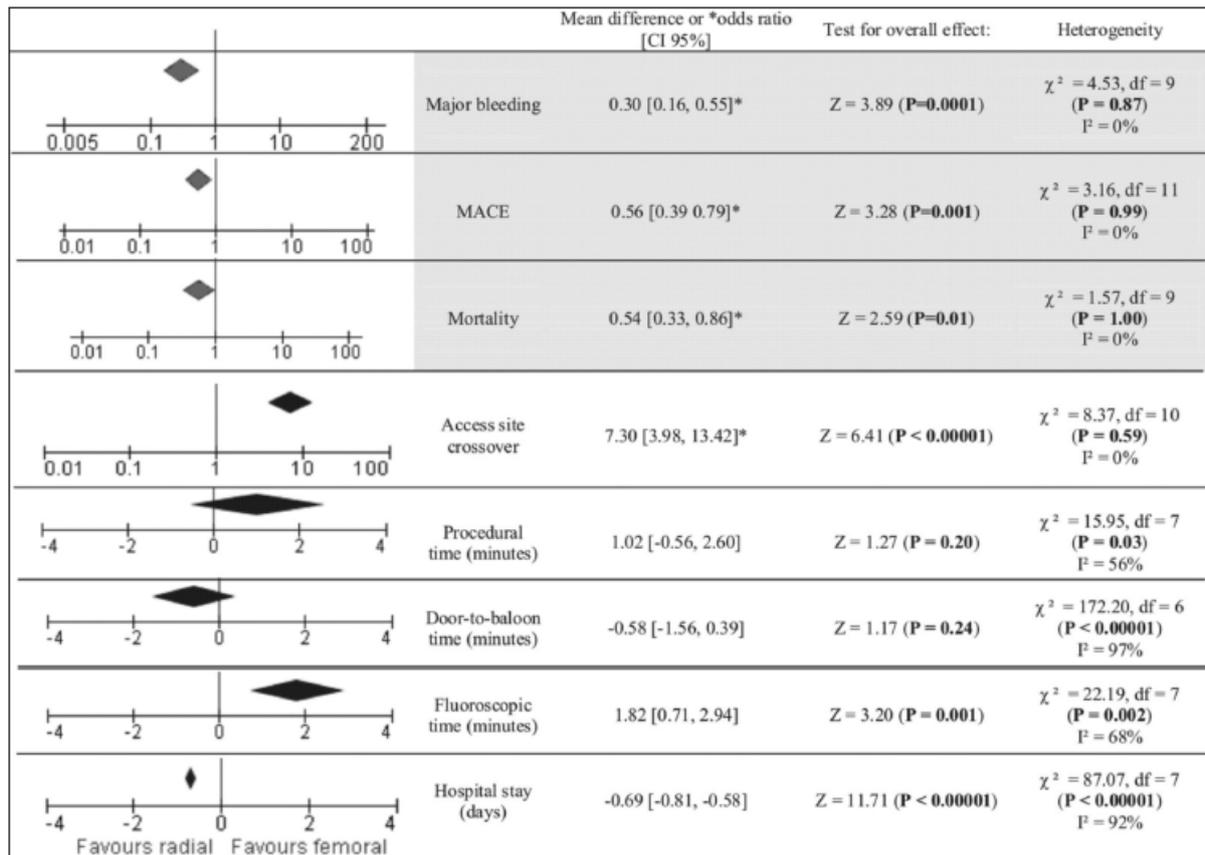
Randomized, case-control, and cohort studies comparing access-related complications were analyzed. Our objective was to determine if radial access reduces major bleeding and thereby reduces death and ischemic events compared to femoral access in this setting. A fixed-effects model was used with random effects for sensitivity analysis.

### **4.2 Results**

The radial approach reduced risk for major bleeding by 70% compared to transfemoral PCI (TFPCI) (0.77% vs 2.61%; Figure 1). Reductions in the composite of death, myocardial infarction, and stroke were also significant (3.65% vs. 6.55%; Figure 1). Pooling the 29 events (2.59%) of 1421 TRPCI and 55 (3.18%) of 1800 TFPCI demonstrated a significant mortality reduction in the case of TRPCI (Figure 1). There were no differences in procedural time and in time to reperfusion between the two access routes. Fluoroscopic times were longer in case of TRPCI; however, there was significant heterogeneity among studies in these parameters. Access site crossover was less frequent in the case of the transfemoral approach while the total hospital charge, assessed in eight studies was lower in the case of the transradial (Figure 1). OR calculations were also performed according to a random effects model, yielding similar results with regard to both the direction and

magnitude of overall effects. Stratification and sensitivity analysis excluding non-randomized studies showed results similar to those of the comprehensive analysis. Findings were also comparable after pre-specified stratification in studies involving high-risk patients (i.e. studies that included >30% of patients with preceding thrombolysis, and with >90% use of GP IIb/IIIa inhibitors) and higher than median versus lower than median quality studies.

1. Figure: Transradial coronary intervention improves clinical outcome in STEMI



Abbreviations: CI: confidence interval, MACE: major adverse cardiovascular events

## 5 Outcomes of patients receiving clopidogrel prior to cardiac surgery

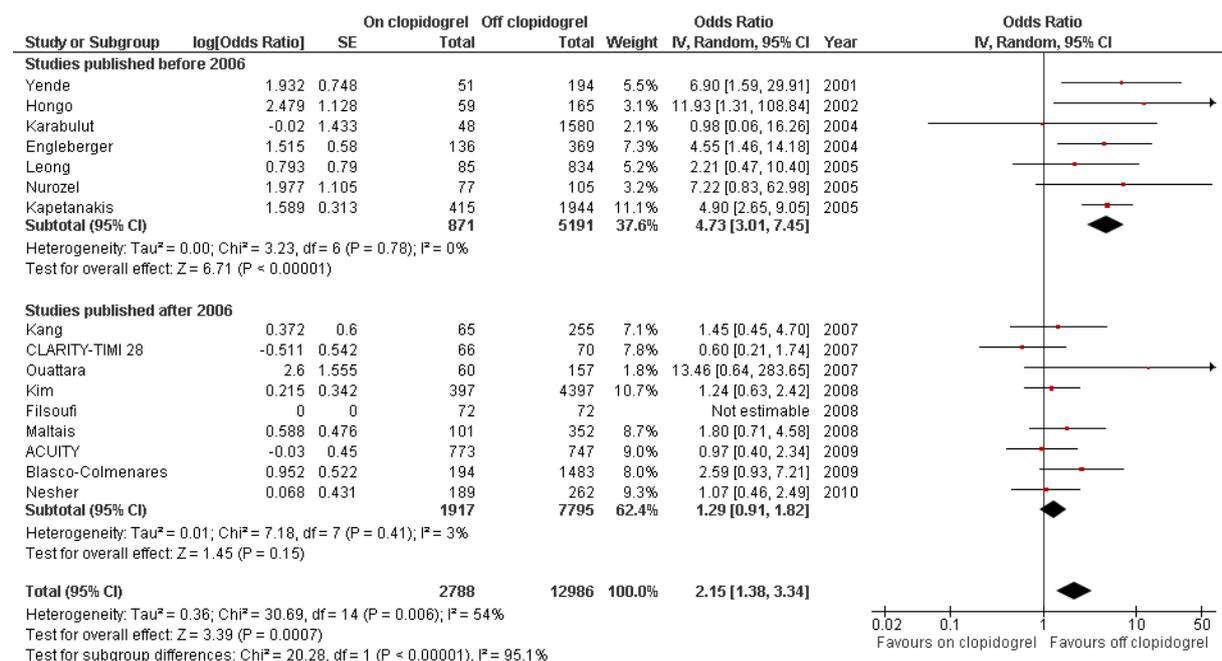
### 5.1 Methods

PubMed and Central databases were searched for relevant studies published between January 2001 and May 2010. The main outcome measures were the rates of red blood cell (RBC) transfusion, reoperation, myocardial infarction and postoperative mortality. The outcome parameters were pooled with the random-effect model via generic-inverse variance-weighting.

## 5.2 Results

We observed an increase in cardiovascular mortality among patients receiving clopidogrel before surgery (OR: 1.24; 95%CI: 1.03-1.49,  $p=0.03$ ) that was not heterogeneous among studies ( $I^2$ : 0%,  $\text{Chi}^2$ : 4.68,  $p=0.99$ ). Clopidogrel administration within 7 days before cardiac surgery was associated with a significant increase in the rates of RBC transfusions (OR: 1.82; 95%CI: 1.40-2.37;  $p<0.00001$ ) and in bleeding-triggered reoperations (OR: 2.15; 95%CI: 1.38-3.34;  $p<0.00001$ ; Figure 2). However, these outcomes showed significant heterogeneity among studies (transfusion:  $I^2$ : 84%,  $\text{Chi}^2$ : 82.52,  $p<0.00001$ , reoperation: Figure 2). According to subgroup analyses, the highest risk for RBC transfusion, major bleeding or reoperation was seen if the discontinuation of clopidogrel was shorter than 3 days prior to surgery. (OR: 7.56 (95%CI: 2.38-23.99); OR: 6.62 (95%CI: 1.69-25.95) and OR: 3.40 (95%CI: 1.51-7.65), respectively). This higher risk for transfusion was less prominent when clopidogrel was discontinued earlier. In studies comparing the discontinuation before and after 5 days only a strong trend for higher rate of transfusion was found (OR: 1.36; 95%CI: 1.00-1.84;  $p=0.05$ ). Notably, Reoperation rates were significantly higher in studies published before 2006 (Figure 2). There were no difference in the incidence of postoperative myocardial infarction between groups; however the pooled results were heterogeneous. (OR: 0.83; 95%CI: 0.44-1.57;  $p=0.57$ ).

2. Figure: Impact of preoperative administered clopidogrel on bleeding triggered reoperation. Subgroup analysis according to publication year



Abbreviations: SE: standard error, CI: confidence interval

## **6 Prognostic significance of high on-clopidogrel platelet reactivity after percutaneous coronary intervention**

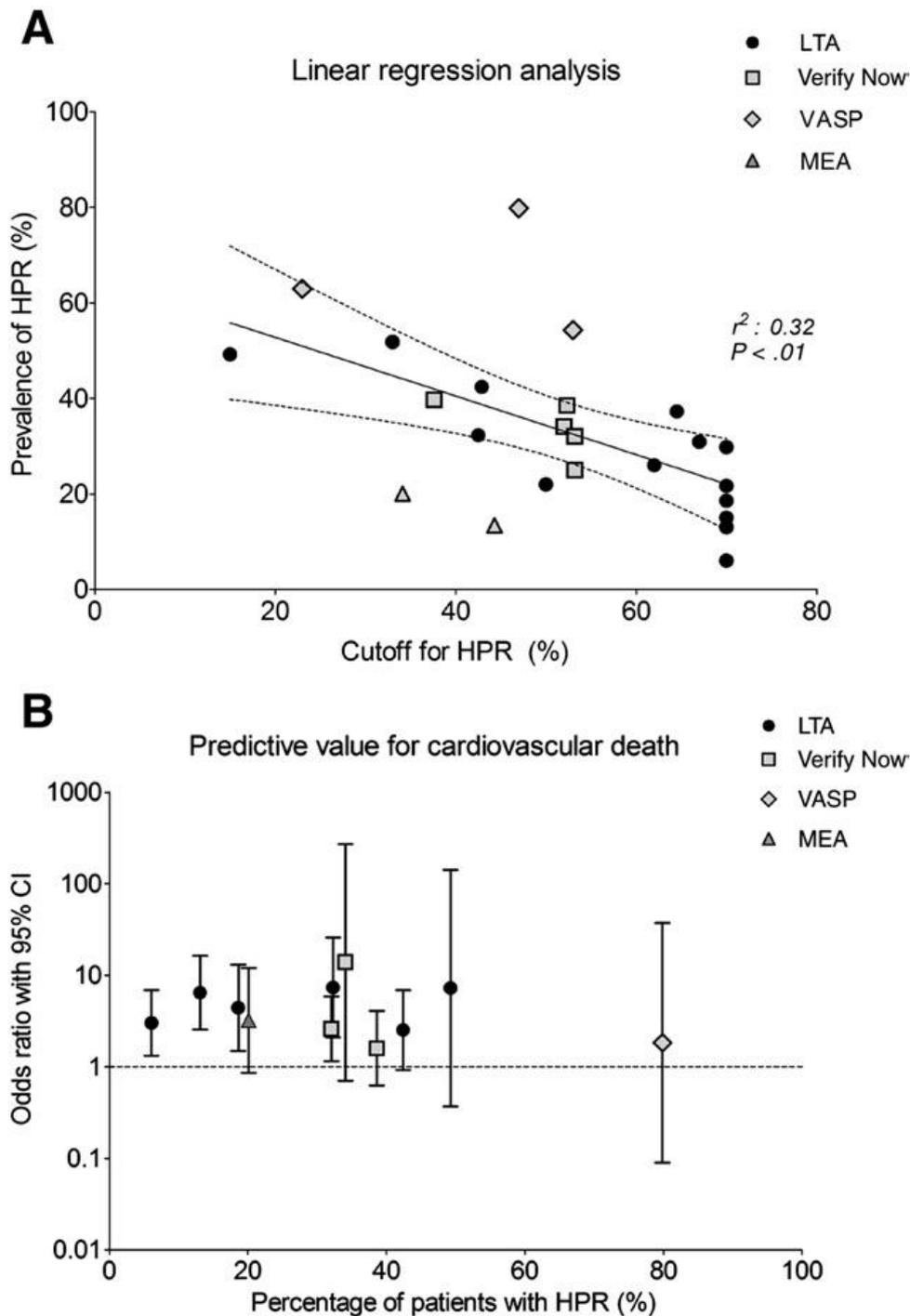
### **6.1 Methods**

Relevant observational studies published between January 2003 and February 2010 were searched that presented intent-to-treat analyses on the clinical relevance of HPR measured with an adenosine diphosphate (ADP)-specific platelet function assay. The main outcome measures were cardiovascular (CV) death, definite/probable stent thrombosis (ST), nonfatal myocardial infarction (MI), and a composite end point of reported ischemic events. The outcome parameters were pooled with the random-effect model via generic inverse variance weighting.

### **6.2 Results**

#### Prevalence of high on-clopidogrel platelet reactivity

In the 20 studies, including 9,187 patients, the rate of HPR showed large heterogeneity with a mean prevalence of 32.3% (95% CI for mean: 25.9–40.5; range: 6.06–79.86). To find possible determinants of the observed heterogeneity, the prevalence of HPR was analyzed according to the following grouping factors: type of platelet function device, the selected platelet reactivity cutoff, the amount of clopidogrel loading dose, time of assessment from loading/last clopidogrel dose, proportion of acute coronary syndrome patients in each group. Among the recruited studies, the selected platelet reactivity cutoff and the type of the platelet function device interacted significantly with the prevalence of HPR. The selected cutoff was in strong, inverse correlation with the rate of HPR. (Figure 3/A) Among the devices, the most P<sub>2</sub>Y<sub>12</sub>-specific assay (VASP) indicated the highest rates of HPR.



Impact of the methodological heterogeneity in platelet aggregation tests. **A**, Linear regression analysis between the selected cutoff and the prevalence rate for high platelet reactivity (HPR). Whereas LTA<sub>ADP</sub> and VASP measure platelet reactivity in a 0% to 100% scale, results might range between 18 and 435 PRU in case of the VerifyNow<sub>P2Y12</sub> and between 0 and 122 U in case of MEA<sub>ADP</sub> assay according to the description of the manufacturer. Thereby, results of the VerifyNow<sub>P2Y12</sub> and MEA<sub>ADP</sub> assays were normalized to a 0 to 100 scale, where the lowest potential value (18 PRU and 0 U) reflects 0% and the highest potential value (435 PRU and 122 U) means 100%. **B**, The impact of the prevalence rate of HPR on the relative risk of CV death.

Based on the pooled results, HPR was associated with a significant, 3-fold increase in non-fatal MI (OR: 3.00; 95%CI: 2.26-3.99;  $p < 0.00001$ ), a 4-fold increase in definite/probable ST (OR: 4.14; 95%CI: 2.74-6.25;  $p < 0.0001$ ) and a 5-fold increase in the rate of composite

ischemic events (OR: 4.95; 95%CI: 3.34-7.34;  $p < 0.00001$ ). Importantly, patients with HPR defined by an ADP-specific platelet function assay had a 3.4-fold increase in cardiovascular mortality compared to those with normal on-clopidogrel ADP-reactivity (OR: 3.35, 95%CI: 2.39-4.70,  $p < 0.00001$ ). When the subgroup of studies using receiver operating characteristic (ROC)-defined cutoffs for HPR was analyzed separately, similar outputs were gained (CV death 2.34 [1.40-3.92], MI 2.89 [2.07-4.04], ST 4.75 [2.13-10.63], and CIE: 3.06 [2.07- 4.51];  $P < 0.001$  in all cases). Although there was large methodical heterogeneity among the platelet function assays as well as in the selected cutoffs for HPR, the predicted risk for CV death, non-fatal MI and ST were not heterogeneous between studies. On the contrary, there was significant heterogeneity in case of the less standardized, composite end point.

When the predictive value of each assay was analyzed separately, only LTA-defined HPR was significantly associated with CV death, MI, and ST (death: 4.18 [2.70-6.46], MI: 2.93 [1.97-4.35], ST: 3.66 [2.32-5.78];  $P < 0.0001$  in all cases). The VerifyNow<sub>P2Y12</sub> predicted CV death and MI (death: 2.28 [1.23-4.25],  $P = 0.009$ ; MI: 2.98 [1.94-4.58],  $P < 0.00001$ ), but only a trend was observed regarding ST (4.17 [0.81-21.63],  $P = 0.09$ ). MEA<sub>ADP</sub> significantly predicted MI and ST (MI: 4.03 [1.16-14.00],  $P = 0.03$ ; ST: 13.89 [2.63-73.45],  $P = 0.002$ ), but only a trend was observed regarding CV death (3.21 [0.86-12.00],  $P = 0.08$ ). Based on the results of 2 small studies, VASP-defined HPR was predictive neither for CV death (1.84 [0.09-37.07],  $P = 0.69$ ) nor for ST (1.48 [0.28-7.77],  $P = 0.64$ ).

## **7 Novel findings of the thesis**

Main findings of the thesis are the followings:

Transradial percutaneous coronary intervention reduces the risk of periprocedural major bleeding and major adverse events in the ST-elevation acute myocardial infarction setting. Difference between two access routes was not represented in procedural time and in time to reperfusion. Nevertheless the mortality significantly decreased in transradial route.

Clopidogrel pre-treatment of patients before cardiac surgery, increases the risk of major bleeding. A trend for improvement can be observed in the frequency of the need for reoperation. However perioperative care and surgical practice seems to adapt the changed medication protocol. Our meta-analysis found statistically significantly increased risk for mortality.

High on-clopidogrel platelet reactivity, measured by an ADP-specific platelet function assay after percutaneous coronary intervention, is a strong predictor of cardiovascular death, myocardial infarction and stent thrombosis in patients after percutaneous coronary intervention. Although there were large differences in the methodology, patient selection and cutoff definition between studies, the predicted risk of cardiovascular death, myocardial infarction and stent thrombosis were not heterogeneous.

## **8 Acknowledgement**

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## 9 List of publication

### 9.1 Topic related articles

- A. Vorobcsuk, A. Kónyi, D. Aradi, I. G. Horváth, I. Ungi, Y. Louvard, A. Komócsi. Transradial versus Transfemoral Percutaneous Coronary Intervention in Acute Myocardial Infarction. Systematic Overview and Meta-Analysis. American Heart Journal. 2009 Nov;158(5):814-21.  
(IF 4.357, 2009) (Independent citation: 11)
- D. Aradi, A. Komócsi, A. Vorobcsuk, O. Rideg, M. Tóké-Füzesi, T. Magyarlaki, I. G. Horváth, V. Serebruany. Prognostic significance of high on-clopidogrel platelet reactivity after percutaneous coronary intervention: systematic review and meta-analysis. American Heart Journal. 2010 Sep;160(3):543-51.  
(IF 4.357, 2009) (Independent citation: 1)
- A. Vorobcsuk, D. Aradi, K. Farkasfalvi, I.G. Horváth, A. Komócsi. Outcomes of patients receiving clopidogrel prior to cardiac surgery. International Journal of Cardiology. 2010 doi:10.1016/j.ijcard.2010.10.034.  
(IF 3.469, 2009)
- A. Komócsi, A. Vorobcsuk, D. Aradi. Transradial Percutaneous Coronary Intervention in Acute Myocardial Infarction. Interventional Medicine and Applied Sciences 2010 2(2) 53-58.

### 9.2 Non-topic related articles

- D. Aradi; A. Vorobcsuk; T. Pintér; Zs Lenkey; I.G. Horváth; A. Komócsi. Low platelet disaggregation predicts poor response to 150 mg clopidogrel in patients with elevated platelet reactivity. Platelets 2010 Feb;21(1):1-10  
(IF 2.271, 2008)
- D. Aradi, T. Magyarlaki, M. Tóké-Füzesi, O. Rideg, A. Vorobcsuk, A. Komócsi. Comparison of conventional aggregometry with VASP for monitoring P<sub>2</sub>Y<sub>12</sub>-specific platelet inhibition. Platelets. 2010;21(7):563-70.  
(IF 2.272, 2009)
- D. Aradi, A. Vorobcsuk, A. Komócsi. Optimizing clopidogrel therapy before stent implantation: should clinical setting be taken into account? J Am Coll Cardiol. 2008 Oct 14;52(16):1349 *letter*  
(IF 11.438, 2008)

**Cumulative impact factor: 16.726 (with including IF of the letter: 28.164)**

### 9.3 International abstracts, posters

2010

#### European Society of Cardiology Congress Stockholm

- Doubling the maintenance dose of clopidogrel in patients with high post-clopidogrel platelet reactivity after elective percutaneous coronary intervention: the DOSER randomized, placebo-controlled trial.  
D. Aradi, O. Rideg, T. Magyarlaki, A. Vorobcsuk, B. Magyar, T. Pintér, A. Kónyi, I.G. Horváth, A. Komócsi. Abstract No. 5340 Eur Heart J (2010) 31 (Abstract supplement), 970

### **EuroPCR, Congress of the European Association of Percutaneous Cardiovascular Interventions Paris**

- Cardiovascular outcomes in patients with high post-clopidogrel platelet reactivity  
D. Aradi, A. Vorobcsuk, I.G. Horváth, V. Serebruany, A. Komócsi

2009

### **European Society of Cardiology Congress Barcelona**

- Monitoring P<sub>2</sub>Y<sub>12</sub> receptor inhibition with light transmission aggregometry: a comparison with vasodilator stimulated phosphoprotein phosphorylation assay.  
D. Aradi, A. Vorobcsuk, M. Tőkés-Füzesi, T. Magyarlaci, I.G. Horváth, A. Komócsi. University of Pécs, Hungary Abstract No. P1317 Eur Heart J (2009) 30 (suppl 1):195
- Transradial percutaneous coronary intervention improves outcome in acute myocardial infarction. A meta-analysis.  
A. Komócsi, A. Vorobcsuk, I. Ungi\*, D. Aradi, I.G. Horváth, A. Kónyi. University of Pécs, Heart Center, Pécs, Hungary,\*2<sup>nd</sup> Dept. of Internal Medicine, Szeged, Hungary Abstract No. P5283 Eur Heart J (2009) 30 (suppl 1):926

2005

### **18th Annual Congress – Amsterdam, Netherlands**

- Hemodynamic measurements after coronary bypass operation and intraaortic balloon pump implantation  
Sz. Czuczor, I. Gyórimolnár, L. Melczer, R. Kiss, A. Vorobcsuk, L. Papp. Intensive Care Unit of Cardiac Surgery, Heart Clinic, University of Pécs, Faculty of Medicine. Intensive Care Medicine 2005 V31-211
- The effect of sterile and non-sterile towels on skin bacterial flora following iodine shower  
Sz. Czuczor, I. Gyórimolnár, I. Bártai\*, A. Vorobcsuk, M. Kerényi\*. Intensive Care Unit of Cardiac Surgery, Heart Clinic, University of Pécs, Faculty of Medicine, Dept. of Anaesthesia, \*Medical Microbiology, University of Pécs, Faculty of Medicine. Intensive Care Medicine 2005 V31-183

## **9.4 Hungarian abstracts, posters**

2010

### **Magyar Szívsebészeti Társaság Tudományos Kongresszusa**

- Preoperatív clopidogrel kezelés hatása a morbiditásra és mortalitásra szívműtött betegekben.  
Vorobcsuk A., Aradi D., Farkasfalvi K., Szabados S. Horváth I.G., Komócsi A.

### **Magyar Kardiológus Társaság Tudományos Kongresszusa**

- A clopidogrel hatékonysága és a klinikai végpontok előfordulása közötti összefüggés stent implantation átesett betegeknél: a témában megjelent tanulmányok szisztematikus áttekintése és meta-analízise.  
Vorobcsuk A., Aradi D., Horváth I.G., Komócsi A.

## **Magyar Aneszteziológiai és Intenzív Terápiás Társaság Tudományos Kongresszusa**

- Preoperatív clopidogrel kezelés hatása a klinikai végkimenetelre és a vérzéses szövődmények előfordulására szívsebészeti beavatkozás során: a témában megjelent tanulmányok szisztematikus áttekintése és meta-analízise.

Vorobcsuk A., Aradi D., Farkasfalvi K., Komócsi A.

2009

### **Magyar Kardiológus Társaság Tudományos Kongresszusa**

- Optikai aggregometria mérési eredményeinek összevetése specifikus P<sub>2</sub>Y<sub>12</sub> receptor gátlás áramlási citometriás meghatározásával.

Aradi D., Vorobcsuk A., Sayour A., Magyarlaci T., Tőkés-Füzesi M., Rideg O., Horváth I.G., Komócsi A. *Cardiologia Hugarica* 2009; 39: A19

- Transzradiális PCI akut myokardiális infarktus ellátása során – szisztematikus irodalmi áttekintés és metaanalízis.

Komócsi A., Vorobcsuk A., Ungi I., Aradi D., Horváth I.G., Kónyi A. *Cardiologia Hugarica* 2009; 39: A1

2008

### **Magyar Kardiológus Társaság Tudományos Kongresszusa**

- Folyamatos cardiac output monitorozás vezérelte bal kamrai elektród pozicionálás.

Czuczor Sz., Melczer L., Kiss R., Vorobcsuk A., Harsányi K., Győrimolnár I., Papp L. *Cardiologia Hugarica* 2008; 38: B51

2007

### **14th Annual Congress of the Hungarian Society of Cardiac Surgery**

- Effect of different type fluid loading on pulmonary permeability after cardiac surgery

I. Győrimolnár, A. Vorobcsuk, K. Farkasfalvi, Zs. Tóth, L. Papp. University of Pécs, Heart Center, Pécs, Hungary, *Cardiologia Hugarica* 2007; 3: D4

2005

### **Magyar Aneszteziológiai és Intenzív Terápiás Társaság 33. Nemzeti Kongresszusa és 5. Duna Kongresszus**

- Haemodinamikai mérőmódszerek alkalmazása coronária műtéten átesett betegeken intraaorticus ballon pumpa támogatás mellett.

Vorobcsuk A., Czuczor Sz., Győrimolnár I., Melczer L., Papp L. PTE ÁOK Szívgyógyászati Klinika E 40

- Povidone-jóddal történő teljes test fürdetés hatása a bőrfloorára a perioperatív szakban.

Czuczor Sz., Győrimolnár I., Bártai I., Kiss R., Vorobcsuk A., Kerényi M. PTE ÁOK Szívgyógyászati Klinika, PTE ÁOK AITI, PTE ÁOK Microbiológiai Intézet E 41