TITOLO DELLA TESI:

Pharmacodynamic of antithrombotic therapies in high cardiovascular risk patients

Dottorato di Ricerca in Scienze Cliniche

XXX ciclo

Tesi di Dottorato

Dott.ssa Benedetta Bellandi

The Thesis (summary)

This thesis addresses different aspects of antithrombotic strategies in patients with acute coronary syndrome, mainly in ST elevation acute myocardial infarction (STEMI) patients treated with percutaneous coronary intervention (PCI), regarding their efficacy and safety during the acute phase as well as their appropriateness and impact on long-term outcomes.

Part 2 focused on pharmacodynamic evaluation of ticagrelor and prasugrel, new potent P2Y12 inhibitor that are recommendend in addition to aspirin in STEMI patients. Previous studies showed that in STEMI patients these drugs are fast acting but they take at least 2-3 hours to reach their antiplatelet effect. Therefore in the clinical scenario of STEMI patients in which a potent and fast antiplatelet effect is pivotal, several studies and strategies have been investigated in order to improve this aspect. In **Chapter 2** were described the effects of crushed ticagrelor tablet administration in STEMI patients compared with standard integral tablets in providing earlier platelet inhibition and confirming its feasibility. On the other side, **Chapter 3** and **4** discussed the potential role of morphine administration in delaying antiplatelet effect of prasugrel and ticagrelor in order to find potential strategies to improve pharmacodynamics effect of these drugs.

Part 3 is centered on safety aspects of antithrombotic strategies. In particular **Chapter 5** regards the effect of bivalurin as compared to unfractionated heparin in reducing nonaccess site bleedings in acute coronary syndrome patients treated with PCI. **Chapter 6** evaluates bleeding and ischaemic events using different doses of prasugrel 1 month after acute coronary syndrome.

Part 4 is dedicated to antithrombotic streategies used in clinical daily practice in acute coronary syndrome (ACS) patients and in long-term outcomes. In particular

Chapter 7 describes the differences from real life data to guidelines recommendation and **Chapter 8** evaluates long term clinical events in ACS patients and the role of different risk factors in predicting high ischemic risk at follow-up.

Part 1: Introduction

Cardiovascular diseases are the principal cause of death in the western countries (1). In the last decades several therapeutic strategies were progressively introduced in our clinical practice to improve survival and clinical outcomes in patients with cardiovascular disease (2). Antithrombotic therapies are the pivotal part of the mainstay treatment of patients with cardiovascular disease especially in patients with acute coronary syndrome (ACS) in addiction to reperfusion therapies (3). In particular platelets and coagulative cascade play a fundamental role in the pathogenesis of ACS, moreover they are involved in potential thrombotic events after percutaneous coronary implantation. Therefore in this clinical scenario the reduction of the thrombotic burden is fundamental; a rapid, potent and effective platelet inhibition represent the basis of pharmachological strategies. Several efforts have been established in order to improve antiplatelet therapies, to search for potential strategies to achieve fast and grat platelet inhibition and to recognize patients at high ischemic risk, especially regarding long-term antiplatelet therapies (4). In particular, patients with advanced age, diabetes mellitus, previous myocardial infarction, previous stroke or patients with chronic kidney disease have been classified as patients at high cardiovascular risk. These patients present high ischemic risk in the initial phase of ACS but also a high risk of long term disease progression, indicating a need for prolonged surveillance and aggressive secondary preventive measures, including prolonged dual antiplatelet therapies (5,6).

Antithrombotic pharmacological strategies

Dual antiplatelet therapy with aspirin and ADP receptor antagonist represent the fundamental therapy of ACS patients. This evidence derives from the results of the CURE trial that showed the superiority of 1 year versus 1 month administration of

dual antiplatelet therapy with aspirin and clopidogrel in reducing the risk of major ischemic events (7).

Current guidelines recommend the use of prasugrel or ticagrelor in association with aspirin in acute coronary syndrome patients (8). This recommendation derives from the results of the randomized clinical trial TRITON-TIMI 38 and PLATO that have compared respectively prasugrel and ticagrelor versus clopidogrel in patients with acute coronary syndrome at intermediate-elevate risk. These trials showed the superiority of prasugrel and ticagrelor versus clopidogrel in reducing ischemic end-points (9, 10). The study results were related mainly to the different metabolic activation of the new drugs, reaching a faster and more efficient platelet activation as compared with the one of clopidogrel that comprehend a complex metabolic activation by two hepatic steps, in which genetic variants of hepatic cytochrome and isoenzimes play an important role in reducing the percentage of active drug. Pharmacodymanic studies on healthy volunteers showed a fast onset of action of prasugrel and ticagrelor. Randomized pharmacodynamic studies on STEMI patients showed that al least 3-4 hours are needed to reach effective platelet activation either with prasugrel or with ticagrelor administration (11). Therefore several strategies are currently under investigation in order to achieve a faster platelet inhibition in particular in the first hours of STEMI occurrence, in which effective platelet inhibition plays a fundamental role. In particular the potential role of cangrelor, endovenous direct P2Y12 inhibitor, that showed in ACS patients the superiority versus clopidogrel in reducing ischemic events including stent thrombosis rate, is expected to be intriguing (12-14). Glicoprotein IIbIIIa (GPI) inhibitors are fast acting and potent drugs that clearly demonstrate advantages in the acute phase of acute myocardial infarction, currently they are used only in bailout situation due to their

high risk of bleeding complication, raising concerns about the correct balance between ischemic prevention and haemorragic risk (15). Moreover during ACS is essential the blockage of coagulative cascade, in particular the inhibition of thrombin generation, pivotal juncyion point of the coagulative cascade and platelet activation. Heparin, anthitrombin III inhibitor, represents the standard anticoagulation of acute myocardial infarction patients. Bivalirudin, direct thrombin inhibitor, can represent an alternative to heparin use. Despite the results of previous studies that showed lower bleeding risk using bivalirudin as compared with heparin plus GPI, recent trials showed no benefit in outcomes but an increased risk of stent thrombosis using bivalirudin versus heparin (16, 17). Finally, the length of dual antiplatelet therapy is still a matter of debate. Currently dual antiplatelet therapy is recommended for 12 months after ACS. The presence of several studies, trials and registries regarding shorter or prolonged dual antiplatelet therapy strategies resulted in several scores, as the PARIS , DAPT, PRECISE related to clinical characteristics of patients that help physician to tailor the length of antiplatelet therapies for each single patients (18).

References

1. Mitka M. Heart disease a global health threat. JAMA. 2004;291:2533.
2. Davi G, Patrono C. Platelet activation and atherothrombosis. N Engl J Med. 2007;357:2482-94.
3. De Luca G, Cassetti E, Marino P. Percutaneous coronary intervention-related time delay, patient's risk profile, and survival benefits of primary angio- plasty vs lytic therapy in ST-segment elevation myocardial infarction. Am J Emerg Med 2009;27:712e9.
4. Tomas Jernberg, Pa˚l Hasvold, Martin Henriksson, Hans Hjelm, Marcus Thuresson, and Magnus Janzon. Cardiovascular risk in post-myocardial infarction patients:

nationwide real world data demonstrate the importance of a long-term perspective. European Heart Journal (2015) 36, 1163–1170.

5. Bortnick AE, Epps KC, Selzer F, Anwaruddin S, Marroquin OC, Srinivas V, Holper EM, Wilensky RL. Five-year follow-up of patients treated for coronary artery disease in the face of an increasing burden of co-morbidity and disease complexity. Am J Cardiol 2014; 113: 573-9.

6. Klempfner R, Elis A, Matezky S, Keren G, Roth A, Finkelstein A, Banai S, Goldenberg I, Fisman EZ, Tenenbaum A, Arbel Y. Temporal trends in management and outcome of diabetic and non-diabetic patients with acute coronary syndrome (ACS): residual risk of long-term mortality persists: Insights from the ACS Israeli Survey (ACSIS) 2000-2010. Int J Cardiol. 2015 Jan 20;179:546-51.

7. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, Bengtsson O, Oude Ophuis T, Budaj A, Theroux P, Ruda M, Hamm C, Goto S, Spinar J, Nicolau JC, Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E, Sabatine MS; PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med. 2015;372:1791-800.

8. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators Effects of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Elevation. N Engl J Med 2001; 345:494-502August 16, 2001DOI: 10.1056/NEJMoa010746

9. Borja Ibanez, Stefan James, Stefan Agewall, Manuel J Antunes, Chiara Bucciarelli-Ducci, Héctor Bueno, Alida L P Caforio, Filippo Crea, John A Goudevenos, Sigrun Halvorsen, Gerhard Hindricks, Adnan Kastrati, Mattie J Lenzen, Eva Prescott, Marco Roffi, Marco Valgimigli, Christoph Varenhorst, Pascal Vranckx, Petr Widimský, ESC Scientific Document Group ; 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC), European Heart Journal, , ehx393,

https://doi.org/10.1093/eurheartj/ehx393

10. Michelson AD, Frelinger AL 3rd, Braunwald E, et al., for the TRITON-TIMI 38 Investigators. Pharmacodynamic assessment of platelet inhibition by prasugrel vs. clopidogrel in the TRITON-TIMI 38 trial. Eur Heart J 2009;30:1753–63.

11. Lars Wallentin, M.D., Ph.D., Richard C. Becker, M.D., Andrzej Budaj, M.D., Ph.D., Christopher P. Cannon, M.D., Håkan Emanuelsson, M.D., Ph.D., Claes Held, M.D., Ph.D., Jay Horrow, M.D., Steen Husted, M.D., D.Sc., Stefan James, M.D., Ph.D., Hugo Katus, M.D., Kenneth W. Mahaffey, M.D., Benjamin M. Scirica, M.D., M.P.H., Allan Skene, Ph.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., D.M., and Robert A. Harrington, M.D., for the PLATO Investigators. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. N Engl J Med 2009; 361:1045-1057.

12. Parodi, R. Marcucci, R. Valenti, et al., High residual platelet reactivity after clopidogrel loading and long-term cardiovascular events among patients with acute coronary syndromes undergoing PCI, JAMA 306 (2011) 1215–1223.

13. Parodi G, Valenti R, Bellandi B, et al. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. J Am Coll Cardiol 2013;61:1601-6.

14. Marcucci R, Gori AM, Paniccia R, et al. Cardiovascular death and nonfatal myocardial infarction in acute coronary syndrome patients receiving coronary stenting are predicted by residual platelet reactivity to ADP detected by a point-of-care assay: a 12-month follow-up. Circulation 2009;119:237-42.

15. Deepak L. Bhatt, M.D., M.P.H., Gregg W. Stone, M.D., Kenneth W. Mahaffey, M.D., C. Michael Gibson, M.D., P. Gabriel Steg, M.D., Christian W. Hamm, M.D., Matthew J. Price, M.D., Sergio Leonardi, M.D., Dianne Gallup, M.S., Ezio Bramucci, M.D., Peter W. Radke, M.D., Petr Widimský, M.D., D.Sc., Frantisek Tousek, M.D., Jeffrey Tauth, M.D., Douglas Spriggs, M.D., Brent T. McLaurin, M.D., Dominick J. Angiolillo, M.D., Ph.D., Philippe Généreux, M.D., Tiepu Liu, M.D., Ph.D., Jayne Prats, Ph.D., Meredith Todd, B.Sc., Simona Skerjanec, Pharm.D., Harvey D. White, D.Sc., and Robert A. Harrington, M.D., for the CHAMPION PHOENIX Investigators. Effect of Platelet Inhibition with Cangrelor during PCI on Ischemic Events. N Engl J Med

2013; 368:1303-1313

16. De Luca G1, Gibson CM, Bellandi F, Murphy S, Maioli M, Noc M, Zeymer U, Dudek D, Arntz HR, Zorman S, Gabriel HM, Emre A, Cutlip D, Biondi-Zoccai G, Rakowski T, Gyongyosi M, Marino P, Huber K, van't Hof AW. Early glycoprotein IIb-IIIa inhibitors in primary angioplasty (EGYPT) cooperation: an individual patient data meta-analysis. Heart. 2008 Dec;94(12):1548-58. doi: 10.1136/hrt.2008.141648. Epub 2008 May 12

17. Gregg W. Stone, M.D., Bernhard Witzenbichler, M.D., Giulio Guagliumi, M.D., Jan Z. Peruga, M.D., Bruce R. Brodie, M.D., Dariusz Dudek, M.D., Ran Kornowski, M.D., Franz Hartmann, M.D., Bernard J. Gersh, M.B., Ch.B., D.Phil., Stuart J. Pocock, Ph.D., George Dangas, M.D., Ph.D., S. Chiu Wong, M.D., Ajay J. Kirtane, M.D., Helen Parise, Sc.D., and Roxana Mehran, M.D., for the HORIZONS-AMI Trial Investigators. Bivalirudin during Primary PCI in Acute Myocardial Infarction. N Engl J Med 2008; 358:2218-2230

18. Adeel Shahzad, Ian Kemp, Christine Mars, Keith Wilson, Claire Roome, Rob Cooper, Mohammed Andron, Clare Appleby, Mike Fisher, Aleem Khand, Babu Kunadian, Joseph D Mills, John L Morris, William L Morrison, Shahzad Munir, Nick D Palmer, Raphael A Perry, David R Ramsdale, Periaswamy Velavan, Rod H Stables, for the HEAT-PPCI trial investigators . Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial . Lancet 2014; 384: 1849–58

19. Marco Valgimigli, Héctor Bueno, Robert A Byrne, Jean-Philippe Collet, Francesco Costa, Anders Jeppsson, Peter Jüni, Adnan Kastrati, Philippe Kolh, Laura Mauri, Gilles Montalescot, Franz-Josef Neumann, Mate Petricevic, Marco Roffi, Philippe Gabriel Steg, Stephan Windecker, Jose Luis Zamorano, Glenn N Levine, ESC Scientific Document Group , ESC Committee for Practice Guidelines (CPG) , ESC National Cardiac Societies ; 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS), European Heart Journal, , ehx419, https://doi.org/10.1093/eurheartj/ehx419

Part 2: The pharmacodynamic effects of new P2Y12 inhibitors in STEMI patients and drugs interaction.

Chapter 2:

Ticagrelor crushed tablets administration in STEMI patients: the MOJITO study.

Guido Parodi, MD, PhD,[a, b] Ioanna Xanthopoulou, MD,[c] Benedetta Bellandi, MD,[a] Vassilios Gkizas, MD,[c] Renato Valenti, MD, [a] Stavros Karanikas, MD,[d] Angela Migliorini, MD,[a] Christos Angelidis, MD,[e] Rosanna Abbate, MD,[a, b] Sotirios Patsilinakos, MD, [c] Giorgio J Baldereschi, MD,[a] Rossella Marcucci, MD, PhD,[a, b] Gian Franco Gensini,[a, b, f] MD, David Antoniucci, MD,[a] Dimitrios Alexopoulos, MD,[c]

a, Department of Heart and Vessels, Careggi Hospital, Florence, Italy; b, Post-graduate School in Cardiology, University of Florence, Italy; c, Department of Cardiology, Patras University Hospital, Rion, Patras, Greece; d, Department of Cardiology, Konstantopoulio General Hospital, Athens, Greece; e, Department of Cardiology, Athens General Hospital "G. Gennimatas", Athens, Greece; f, Don Carlo Gnocchi Foundation, Centro S. Maria agli Ulivi, Onlus IRCCS, Florence, Italy.

J Am Coll Cardiol. 2015 Feb 10;65(5):511-2.

To the Editor: In healthy volunteers, 300 mg clopidogrel administered crushed via a nasogastric tube results in faster and greater bioavailability of the drug compared to orally given whole tablets (1). Recently, Crean at al. reported that ticagrelor tablets could be easily crushed and prepared for oral and nasogastric tube administration, delivering the full dose of the original tablet (2).

The Mashed Or Just Integral pill of TicagrelOr (MOJITO) study was a prospective, four-centre, international, randomized active-controlled study with the aim to evaluate the superiority of ticagrelor crushed pills versus integral tables of equal dose in decreasing platelet reactivity in P2Y12-naive, ST-elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention (PPCI). The study was approved by the local ethical committee and registered (ClinicalTrials.gov Identifier: NCT01992523). All patients gave informed consent. Following exclusions (Figure S1), 82 patients were randomized to either ticagrelor 180 mg loading dose (LD) crushed or oral integral tables of equal dose before PPCI. Crushed tablets were prepared placing 2 ticagrelor pills in a mortar and mashing for 60 seconds using a pestle (2). The total contents of the mortar was transferred to the dosing cup, 50 mL of purify water was added, and the suspension mixed up before drinking. Platelet function testing was performed with VerifyNow at baseline and at 1, 2, 4 and 8 hours and results are reported in P2Y12 reaction units (PRU) (3). High platelet reactivity (HPR) was defined as a PRU ≥ 208. The primary end point was PRU 1 hour after LD.

Forward stepwise binary logistic regression analysis was used to evaluate the independent contribution of clinical characteristics to HPR at 1 hour with variables entered into the model being age (years), body mass index, diabetes mellitus, morphine use, baseline PRU value, ticagrelor crushed pills. A significance of .05 was required for a variable to be included in the multivariate model, whereas .10 was the cut-off value for exclusion. Odds

ratios (OR) and 95% CI were calculated. A P value < .05 was considered statistically significant.

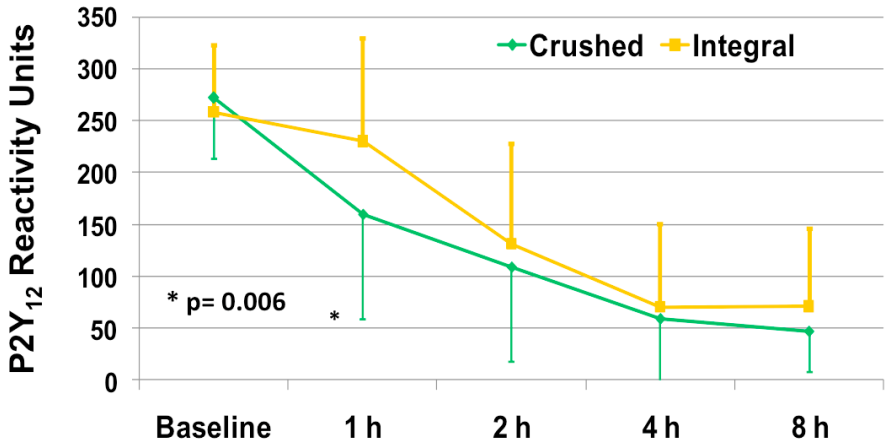
Baseline characteristics did not significantly differ between groups (Table S1). PRU 1 hour after the LD was 168 (61-251) and 252 (167-301) in crushed and integral groups, respectively (p=0.006), with no differences observed at 2, 4 and 8 hours (Figure 1). HPR was found in 14 (35%) and 26 (63%) patients (p=0.011) at 1 hour and in 8 (20%) and 11 (28%) patients (p=0.431) at 2 hours, respectively. Independent predictors of HPR 1 hour after LD were morphine use (increased HPR) and crushed ticagrelor tablet administration (decreased HPR) (Table S2). Morphine treated patients showed higher 1–hour PRU values also in the crushed ticagrelor group (p=0.001). Adverse events were not increased by the administration of crushed ticagrelor (Table S3).

Our study shows, for the first time, that ticagrelor crushed tablets administration in STEMI patients is feasible and provides earlier platelet inhibition as compared with standard integral tablets. If this effect may translate in fewer acute stent thrombosis and in better myocardial reperfusion should be assessed in broader studies. All P2Y12 receptor antagonists used at the present time in STEMI treatment are only available in the oral form. This is an important limitation in patients with difficulties with swallowing such as elderly, previous stroke, dysphagia and sedated or intubated patients. Our study might also support the use of crushed ticagrelor in patients unable to swallow.

Our results must be evaluated in light of some limitations. First, the small sample size is certainly the most important limitation. However, we were able to enroll a prospective homogenous population of STEMI patients that mirrors other similar studies, and clinical outcome data were reported only as indicative. The safety profile and patient's tolerance of crushed ticagrelor tablets should be definitively tested in broader studies. Second, to

confirm enhanced drug absorption a pharmacokinetic analysis could also have been performed. Higher plasma levels of ticagrelor and its active metabolite with crushed tablets as compared with integral tablets have been recently reported in healthy subjects (4). Finally, unmeasured confounder and overfitting risks cannot be excluded in our multivariable model. These limitations notwithstanding, the present study provides unique and potentially important insights in the treatment of STEMI patients.

Figure 1. Platelet Inhibition over time. Platelet reactivity was assessed at baseline and 1, 2, 4, 8 hours after a 180mg ticagrelor loading dose in patients treated by crushed (◊) or integral tablets (□). Data are expressed as means ± SD.



REFERENCES

1. Zafar MU, Farkouh ME, Fuster V, et al. Crushed clopidogrel administered via nasogastric tube has faster and greater absorption than oral whole tablets. J Interv Cardiol 2009;22:385-9

2. Crean B, Finnie C, Crosby A. Evaluation of crushed ticagrelor tablet doses: recovery following crushing and naso-gastric tube passage ex vivo. Drugs 2013;13:153-7.

3. Parodi G, Valenti R, Bellandi B, et al. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. J Am Coll Cardiol 2013; 61:1601-6.

4. Teng R, Carlson G, Hsia J. Crushing ticagrelor tablets accelerates exposure compared with intact tablets. J Am Coll Cardiol. 2014;63

Chapter 3:

Morphine is associated with a delayed activity of oral antiplatelet agents in patients with ST-elevation acute myocardial infarction undergoing primary percutaneous coronary intervention.

Guido Parodi, MD, PhD; Benedetta Bellandi, MD; Ioanna Xanthopoulou, MD; Piera Capranzano, MD; Davide Capodanno, MD, PhD; Renato Valenti, MD; Katerina Stavrou, MD; Angela Migliorini, MD; David Antoniucci, MD; Corrado Tamburino, MD; Dimitrios Alexopoulos, MD

Circ Cardiovasc Interv. 2014 Dec 31;8(1).

ABSTRACT

Background—Morphine is recommended in patients with ST-segment–elevation myocardial infarction, including those undergoing primary percutaneous coronary intervention. Suboptimal antiplatelet effect during and after primary percutaneous coronary intervention is associated with increased thrombotic complications. It was hypothesized a potential drug–drug interaction between morphine and antiplatelet agents. We sought to assess platelet inhibition after a loading dose of the currently recommended antiplatelet agents in ST-segment–elevation myocardial infarction patients according to morphine use.

Methods and Results—Three hundred patients undergoing primary percutaneous coronary intervention receiving either prasugrel (n=95) or ticagrelor (n=205) loading dose had platelet reactivity assessed by VerifyNow 1, 2, and 4 hours after loading dose. Patients treated with morphine (n=95; 32%) had a higher incidence of vomit (15% versus 2%; *P*=0.001). P2Y12 reactivity units 2 hours after the loading dose was 187 (153–221) and 133 (102–165) in patient with and without morphine (*P*<0.001); the difference persisted after excluding patients with vomit (*P*<0.0001). High residual platelet reactivity (P2Y12 reactivity units ≥208) at 2 hours was found in 53% and 29% patients with and without morphine (*P*<0.001) and without difference between prasugrel and ticagrelor patients. The independent predictors of high residual platelet reactivity at 2 hours were morphine use (odds ratio, 2.91 [1.71–4.97]; *P*<0.0001) and age (odds ratio, 1.03 [1.01– 1.05]; *P*=0.010). Morphine remained associated with high residual platelet reactivity after propensity score adjustment (c-statistic, 0.68; 95% con dence interval, 0.66–0.70; *P*=0.879 for Hosmer–Lemeshow test).

Conclusions—In patients with ST-segment–elevation myocardial infarction, morphine use is associated with a delayed onset of action of the oral antiplatelet agents. This association persisted after adjusting for the propensity to receive morphine and after excluding patients with vomit.

Introduction

Despite the lack of rigorous studies designed to assess the effect of morphine administration in patient with acute myocardial infarction, clinical practice guidelines for the management of patients with ST-segment–elevation myocar- dial infarction (STEMI) strongly recommend morphine for analgesia.1,2 This recommendation derives only from expert opinion.

In patients with STEMI undergoing primary percutaneous coronary intervention (PPCI), a signi cant number of drugs are usually administered, thereby raising the potential risk for drug-to-drug interaction. Antiplatelet agents are the mainstay of pharmacological treatment in patients presenting with an acute coronary syndrome, including STEMI. In a recent small randomized study aimed to investigate the onset time of the novel P2Y12 receptor inhibitors (ie, prasugrel and ticagrelor) in STEMI, a delayed antiplatelet effect caused by morphine use in the rst hours of STEMI has been hypothesized.3

There may be a biologically plausible cause–effect rela- tion in this association, given that morphine inhibits gastric emptying, thereby delaying absorption and possibly result- ing in decreased peak plasma levels of orally administered drugs.4 To corroborate this hypothesis, the present multicenter study sought to assess platelet inhibition after a loading dose (LD) of prasugrel and ticagrelor, after strati cation by use of morphine.

Methods

Study Design

This study was a patient-level integrated analysis exploring the effect of morphine on platelet reactivity in STEMI patients undergoing PPCI treated with ticagrelor or prasugrel from 5 studies in which residual platelet reactivity was assessed by VerifyNow after LD. This study in- cluded published trials by Parodi et al3,5 and Alexopoulos et al6,7 and an unpublished study from Catania University. The studies were approved by the local ethical committees. All patients gave informed consent. We asked the study principal investigators to stratify each enrolled patient according to morphine use before antiplatelet agent LD and to look for occurrence of vomit (de ned as forceful expulsion of gastric content by the mouth within 2 hours from prasugrel or ticagrelor LD).

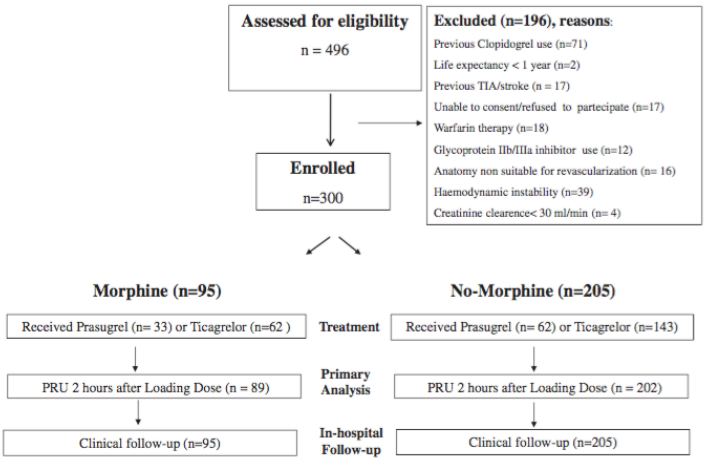


Figure 1. Study flow-chart. Number of patients screened and finally enrolled. PRU indicates $P2Y_{12}$ reactivity units; and TIA, transient ischemic attack.

Patient Population

A diagnosis of STEMI within 12 hours of symptoms onset was re- quired for study entry. Exclusion criteria were (1) age <18 year, (2) ac- tive bleeding or bleeding diathesis, (3) any previous transient ischemic attack or stroke, (4) administration of

ticlopidine, clopidogrel, prasug- rel, ticagrelor, or glycoprotein IIb/IIIa inhibitors in the week before the index event, (5) need for chronic anticoagulant therapy, (6) known rele- vant hematologic deviations, (7) life expectancy <1 year, (8) known se- vere liver or renal disease, and (9) hemodynamic instability. The study ow chart is reported in Figure 1. At 3 participating institutions, out of 496 STEMI patients, we analyzed 300 subjects who were P2Y12 in- hibitor naïve and received prasugrel 60 mg (n= 95) or ticagrelor 180 or 360 mg LD (n= 205) before PPCI. Patients who received an increased ticagrelor LD were included in 2 randomized studies approved by the local Ethic Committees.5,7 The LD was given as soon as possible in the emergency room or in the Cath-Laboratory. Dual antiplatelet therapy (aspirin 100 mg OD in combination with prasugrel 5–10 mg OD or ticagrelor 90 mg BID) was recommended for 12 months.

Concomitant Antithrombotic Medications

The following antithrombotic agents were given on top of prasug- rel or ticagrelor at the time of PPCI: (a) aspirin 300 to 500 mg LD

End Points

The primary study end-point was residual platelet reactivity by PRU VerifyNow 2 hours after LD. Secondary end-points were (1) the per- centage of patients with HRPR at 2 hours from administration of the LD and (2) incidence of vomit.

Statistical Analysis

Categorical data are presented as frequencies and group percentages. Continuous data with normal and skewed distribution are presented as means±SD and medians (first to third quartile), respectively. The Kolmogorov–Smirnov test was used to examine data distribution nor- mality. For the purpose of the current analysis, patients' characteris- tics are presented by morphine use.

The multivariable analysis used to evaluate the independent contri- bution of clinical characteristics to HRPR at 2 hours was performed by forward stepwise binary logistic regression. A signi cance level of 0.05 was required for a variable to be included in the multivariate model, whereas 0.20 was the cut-off value for exclusion. Moreover, variables known to affect platelet reactivity were forced into the nal model. Candidate variables entered into the model were age (years), body mass index, diabetes mellitus, systolic blood pressure, bivali- rudin administration, ticagrelor use, and morphine use. Odds ratios and 95% con dence intervals (CI) were calculated. A propensity score analysis was also performed with a logistic regression mod- el from which the probability for morphine use was calculated for each patient to compensate for the nonrandomized administration of morphine. Variables that were signi cantly different between the 2 groups and those that are known to affect platelet reactivity were incorporated in the model: age (years), sex, body mass index, dia- betes mellitus, smoking, killip class, systolic blood pressure, heart rate, anterior infarct location, and bivalirudin.9,10 Model discrimina- tion was assessed with the c-statistic and goodness of t with the Hosmer–Lemeshow test. Thereafter, a logistic regression analysis was performed to adjust HRPR for the propensity score used as a con- tinuous covariate. PRU differences between groups were analyzed via a mixed linear model with time and morphine use as xed effects, propensity score as covariate, patient and study as random effects to account for within-study correlation. To account for within-study cor- relation of participants, we also modeled the study as a random in- tercept.11 Adjusted estimates for HRPR (presented as risk ratios with corresponding *P* values) were derived from a generalized estimating equations model using log-Poisson function with robust variance esti- mator, with time as within-subject effect, morphine treatment as xed

effect, and propensity score as a covariate, using an autoregressive correlation matrix. All tests were 2-tailed, and statistical signi cance was considered for *P* values <0.05. All statistical analyses were per- formed using SPSS for Windows (version 16.0, SPSS Inc, Chicago, IL) and NCSS 8 (NCSS, Kaysville, Utah).

Results

Baseline and Procedural Characteristics

Overall, we analyzed 95 and 205 STEMI patients treated with or without morphine, respectively, according to the deci- sion of the attending physicians in the ambulance or in the emergency room. Median total morphine dose per patient was 4 (2–6) mg with a range of 2 to 12 mg. Demographic and clini- cal characteristics of patients by morphine use are presented in Table 1. Prasugrel or ticagrelor LD was given in 24% patients in the emergency room and in 76% patients in the Cath Lab- oratory, without differences between the 2 groups. During PPCI, bivalirudin was used in 204 (68%) patients; the remain- ing subjects received unfractionated heparin. There were no signi cant difference in the baseline characteristics between patients with and without morphine, but a lower body mass index, a more prevalent bivalirudin use, and a trend toward a higher systolic blood pressure in morphine-treated patients (Table 1). As expected, patients treated with morphine had a higher incidence of vomit (15% versus 2%; *P*=0.001) as com- pared with those without.

Table 1. Demographic and Clinical Characteristics of Study Patients

	Overall Population N=300	No Morphine Use N=205	Morphine Use N=95	*P* Value
Male sex	232 (77.3)	162 (79.0)	70 (73.3)	0.30
Age, y	61.4±12.7	61.1±12.6	62.0±13.0	0.50
BMI, kg/m^2	27.7±4.7	28.1±5.0	26.8±3.9	0.025
Hyperlipidemia	106 (35.3)	77 (37.6)	29 (30.5)	0.23
Hypertension	157 (52.3)	111 (54.1)	46 (48.4)	0.36
Diabetes mellitus	37 (12.3)	23 (11.2)	14 (14.7)	0.39
Smoking	162 (54.0)	108 (52.7)	54 (56.8)	0.50
Familiar history of CAD	87 (29.0)	56 (27.3)	31 (32.6)	0.34
Prior myocardial infarction	22 (7.3)	14 (6.8)	8 (8.4)	0.62
Prior CABG	3 (1.0)	2 (1.0)	1 (1.1)	0.95
Prior PCI	18 (6.0)	11 (5.4)	7 (7.4)	0.50
Systolic blood pressure (mm Hg)	135.7±26.9	133.9±26.2	139.9±28.2	0.08
Heart rate, bpm	79.1±17.6	78.9±16.9	79.5±19.1	0.78
Killip class >2	6 (2.0)	3 (1.5)	3 (3.1)	0.80
Hemodynamic instability	7 (2.3)	4 (2.0)	3 (3.2)	0.52
Vomiting	19 (6.3)	5 (2.4)	14 (14.7)	<0.001
Anterior infarction location	133 (44.3)	86 (41.9)	47 (49.5)	0.22
Bivalirudin	204 (68.0)	131 (63.9)	73 (76.8)	0.025
P2Y12 inhibitor				0.44
Prasugrel 60 mg	95 (31.7)	62 (30.2)	33 (34.7)	
Ticagrelor 180 mg	134 (44.7)	94 (45.9)	40 (42.1)	
Ticagrelor 360 mg	71 (23.7)	49 (23.9)	22 (23.2)	
Radial access site	32 (10.7)	24 (11.7)	8 (8.4)	0.39
Coronary artery disease				0.87
1 vessel	164 (54.7)	110 (53.7)	54 (56.8)	
2 vessels	87 (29.0)	61 (29.8)	26 (27.4)	
3 vessels	49 (16.3)	34 (16.6)	15 (15.8)	
Creatinine clearance, mL/min	99 (74–122)	96 (73–125)	100 (75–122)	0.89
Creatinine clearance <60 mL/min	42 (14.0)	27 (13.2)	15 (15.8)	0.60
Hemoglobin, mg/dL	14.1±1.8	14.2±1.5	14.0±1.9	0.49
LVEF, %	47.3±8.7	47.7±8.7	46.3±8.8	0.20
Study				0.11
Rapid 1[3]	50 (16.7)	29 (14.1)	21 (22.1)	
Rapid 2[5]	50 (16.7)	29 (14.1)	21 (22.1)	
Alexopoulos et al[6]	56 (18.7)	42 (20.5)	14 (14.7)	
Alexopoulos et al[7]	82 (27.3)	60 (29.3)	22 (23.2)	
Catania study (unpublished)	62 (20.7)	45 (22.0)	17 (17.9)	

Data are expressed as means±SD, medians (first to third quartiles) or n (%). Creatinine clearance was calculated using the Cockcroft-Gault equation. BMI indicates body mass index; CABG, coronary-artery bypass grafting; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; and PRU indicates P2Y12 reaction units.

Residual Platelet Reactivity

Patients who received morphine had higher PRU during study measurements as compared with those who did not: 182.3 PRU (95% CI, 164.2–200.3) versus 140.3 PRU (95% CI, 128.2– 152.4), with a mean difference of 42.0 PRU (95% CI, 19.8–

64.1), *P*<0.001 (Figure 2). The PRU values at 2 hours (primary end-point) were 187.3 (153.4–221.2) and 133.7 (102.3–165.0) in patients with and without morphine (*P*<0.001); the difference between the 2 study groups persisted after excluding patients with vomit (222.0 [89.0–282.0] versus 107.0 [29.5– 225.5]; *P*<0.0001). The PRU difference was still present at 4 hours (*P*=0.04). In ticagrelor-treated patients (excluding patients who received prasugrel), PRU 2 hours after LD was 231 (114–287) and 110 (33–226) in patients with and without morphine (*P*<0.001). Overall, HRPR at 2 hours was found in 53% and 29% patients with and without morphine (*P*<0.001; Table 2), without differences between prasugrel and ticagrelor patients (39% versus 37%; *P*=0.72). Generalized estimating equations modeling revealed that morphine use was overall associated with an increased risk of HRPR using either the 208 or the 230 threshold: risk ratio=1.55 (95% CI, 1.28–1.87), *P*<0.001 and risk ratio=1.44 (95% CI: 1.20–1.86), *P*<0.001 respectively. The independent predictors of HRPR at 2 hours were morphine use (odds ratio, 2.91 [1.71–4.97]; *P*<0.0001) and age (odds ratio, 1.03 [1.01–1.05]; *P*=0.010). Morphine remained signi cantly associated with HRPR (odds ratio, 1.89 [1.40– 2.56]; *P*<0.001) after propensity score adjustment (c-statistic, 0.68; 95% CI, 0.66–0.70; *P*=0.879 for Hosmer–Lemeshow test).

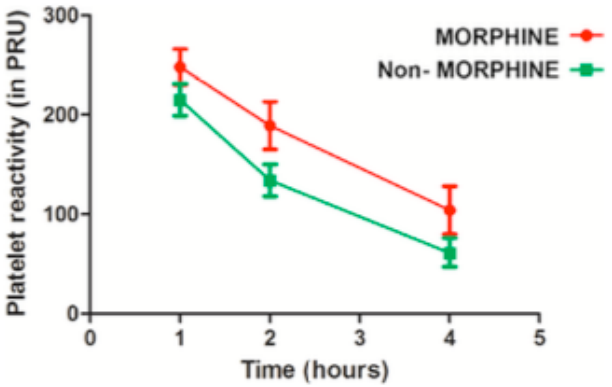


Figure 2. Platelet reactivity over time of patients who received morphine or non-morphine. PRU was significantly higher in the morphine group than in the non-morphine group (P<0.001). There was also a significant effect in platelet reactivity over time (P<0.001). No significant morphine-by-time interaction was observed. Means and 95% confidence intervals are displayed. PRU indicates $P2Y_{12}$ reactivity units.

Table 2. High Residual Platelet Reactivity Rates at Study Time Points

	No Morphine Use (n=205)	Morphine Use (n=95)	Adjusted RR (95% CI)	*P* Value
Hour 1	(N=154)	(N=67)		
≥208 PRU	92 (59.7)	53 (79.1)	1.32 (1.10–1.59)	0.003
≥230 PRU	84 (54.5)	44 (65.7)	1.17 (0.93–1.49)	0.23
Hour 2	(N=202)	(N=89)		
≥208 PRU	59 (29.2)	47 (52.8)	1.89 (1.40–2.56)	<0.001
≥230 PRU	49 (24.3)	42 (47.2)	2.06 (1.46–2.89)	<0.001
Hour 4	(N=126)	(N=70)		
≥208 PRU	12 (9.5)	17 (24.3)	2.11 (1.06–4.21)	0.03
≥230 PRU	7 (5.6)	13 (18.6)	2.77 (1.14–6.73)	0.03

Data are expressed as n (%). CI indicates confidence interval; PRU, P2Y12 reaction units; and RR, risk ratio.

In-Hospital Outcome

Clinical events observed during the hospital stay are reported in Table 3. Possibly reflecting the small sample size and the limited time of observation, there was no significant difference in event rates between the 2 study groups.

Discussion

The study results can be summarized as follow: 1. In patients with STEMI, morphine use is associated with a

delayed onset of action of the oral antiplatelet agents. 2. The drug-to-drug interaction persisted after adjusting for the probability to receive morphine and after excluding patients

with vomit. 3. The effect of morphine on platelet inhibition was consistent in

prasugrel and ticagrelor patients. In the present multicenter pharmacodynamic study, morphine use was associated with a delayed onset activity of the new oral antiplatelet agents, prasugrel and ticagrelor. In fact, morphine-treated patients showed higher residual platelet reactivity values 1, 2, and 4 hours after drug LD. Of note, morphine has a half live of ≈2 hours, and 3 half- lives are needed to decrease by ≈90% the plasma concentra- tion. Thus, >6 hours are needed to spontaneously reverse morphine effect. Naloxone (morphine synthetic reversal agent) was not used in our study patients. The negative effect of morphine on platelet inhibition is not only con- ned when vomit occurs as a side effect of its use because after excluding patients with vomit, morphine-treated sub- jects still clearly have higher residual platelet reactivity as compared with subjects who did not receive morphine. The effect was consistent with the P2Y12 receptor irreversible inhibitor prasugrel and the nonthienopyridine reversible antiplatelet agent ticagrelor. Given the well-known delayed onset of action and effect variability of clopidogrel as com- pared with prasugrel and ticagrelor,12,13 it is easy to antici- pate a similar and even more clinically evident interaction between morphine and clopidogrel. However, the use of the more effective new oral antiplatelet agents is strongly recommended and

increasing in the setting of STEMI. The morphine–antiplatelet agent interaction is likely a non drug-speci c phenomena and related to the inhibition of the

normal muscular activity of the stomach and the intestines, which may lead to vomit or delayed gastric emptying, which in turn delays absorption and decreases peak plasma levels of orally administered drugs.

Along with morphine, age was confirmed to be a strong predictor of HRPR.14,15 On the other hand, the type of antiplatelet agent did not result as an independent predictor of HRPR. Thus, ticagrelor, even if it is adsorbed as an active compound without the need for a metabolic activation at the liver level,

showed a similar delayed of action, suggesting a similar delayed adsorption as compared with prasugrel. This fact is also reinforced by the fact that some patients enrolled in this study received an increased ticagrelor LD. As a matter of fact, in the administration of ticagrelor in the cath laboratory or in the ambulance for new ST-elevation myocardial infarction to open the coronary artery (ATLANTIC) Trial, patients who did not receive morphine had a significant improvement in the ECG-based primary end point, with a significant *P* value for interaction between morphine use and time of ticagrelor administration.16

We may also hypothesize that patients who received morphine might be subjects at higher risk. However, after adjusting for the baseline clinical characteristics, morphine use remained associated with HRPR 2 hours after drug LD. This association was confirmed after the calculation of the probability for each patient to receive morphine and using the obtained propensity score in the multivariable model. However, it is not possible to rule out that in sicker patients, hemodynamic disarrangement, adrenergic activation, systemic vasoconstriction with the reduction of blood volume to the abdomen may contribute to the delayed drug adsorption and

to the reduced platelet inhibition. Recent data suggest that suboptimal platelet inhibition early after PPCI may be associated with thrombotic complications, including stent thrombosis.17 Given the key importance of platelet inhibition in patients treated by PPCI for STEMI and the absence of data that may support a potential clinical benefit of morphine in patients with acute myocardial infarction, more caution should be used regarding morphine administration in STEMI patients and a restricted morphine use seems to be reasonably recommended. Other strategies beside morphine may reduce chest pain levels in STEMI patients. It has been documented since a long time that β-blockers18 and nitrates19 are able to reduce acute myocardial infarction– related chest pain. Aspirin itself has relevant analgesic proper- ties, and alternative analgesics might be considered in STEMI patients. Finally, myocardial ischemia relief (ie, reperfusion) is the definitive chest pain control strategy.

Our study must be evaluated in light of some limitations. First, this was not a randomized comparison, and a further randomized study is needed to con rm the potential effect of morphine use in STEMI patients undergoing PPCI. Second, this is a pharmacodynamic study and the small sample size does not allow to assess the potential effect of morphine on clinical end-points. HRPR is not precisely equivalent to reduced antiplatelet effect: pretreatment aggregability may also be important. Moreover, to confirmed impaired drug absorption, a pharmacokinetic analysis should have been per- formed. However, a small recent study, obtained in 24 healthy volunteers, documented that morphine delays clopidogrel absorption and decreases plasma levels of clopidogrel active metabolite.20 Finally, unmeasured residual bias and the risk of overfitting cannot be excluded even in our parsimonious multivariable model. These limitations notwithstanding the present study provides

several unique and potentially important insights in the treatment of STEMI patients by PPCI and newer antiplatelet agents.

References

1.O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso JE, Tracy CM, Woo YJ, Zhao DX; CF/AHA Task Force. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:529–555. doi: 10.1161/CIR.0b013e3182742c84.

2.Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van 't Hof A, Widimsky P, Zahger D. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012;33:2569–2619.

3.Parodi G, Valenti R, Bellandi B, Migliorini A, Marcucci R, Comito V, Carrabba N, Santini A, Gensini GF, Abbate R, Antoniucci D. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myo- cardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. *J Am Coll Cardiol*. 2013;61:1601–1606. doi: 10.1016/j.jacc.2013.01.024.

4.Nimmo WS, Heading RC, Wilson J, Tothill P, Prescott LF. Inhibition of gastric emptying and drug absorption by narcotic analgesics. *Br J Clin Pharmacol*. 1975;2:509–513.

5.Parodi G, Bellandi B, Valenti R, Migliorini A, Marcucci R, Carrabba N, Giurlani L, Gensini GF, Abbate R, Antoniucci D. Comparison of double (360 mg) ticagrelor loading dose with standard (60 mg) prasugrel load- ing dose in ST-elevation myocardial infarction patients: the Rapid Activity of Platelet Inhibitor Drugs (RAPID) primary PCI 2 study. *Am Heart J*. 2014;167:909–914. doi: 10.1016/j.ahj.2014.03.011. 6.Alexopoulos D, Xanthopoulou I, Gkizas V, Kassimis G, Theodoropoulos KC, Makris G, Koutsogiannis N, Damelou A, Tsigkas G, Davlouros P, Hahalis G. Randomized assessment

of ticagrelor versus prasug- rel antiplatelet effects in patients with ST-segment-elevation myocar- dial infarction. *Circ Cardiovasc Interv*. 2012;5:797–804. doi: 10.1161/ CIRCINTERVENTIONS.112.972323.

7.Alexopoulos D, Gkizas V, Patsilinakos S, Xanthopoulou I, Angelidis C, Anthopoulos P, Makris G, Perperis A, Karanikas S, Koutsogiannis N, Davlouros P, Deftereos S, Chiladakis J, Hahalis G. Double versus stan- dard loading dose of ticagrelor: onset of antiplatelet action in patients with STEMI undergoing primary PCI. *J Am Coll Cardiol*. 2013;62:940–941. doi: 10.1016/j.jacc.2013.05.021.

8.Tantry US, Bonello L, Aradi D, Price MJ, Jeong YH, Angiolillo DJ, Stone GW, Curzen N, Geisler T, Ten Berg J, Kirtane A, Siller-Matula J, Mahla E, Becker RC, Bhatt DL, Waksman R, Rao SV, Alexopoulos D,

9.Marcucci R, Reny JL, Trenk D, Sibbing D, Gurbel PA; Working Group on On-Treatment Platelet Reactivity. Consensus and update on the de nition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. *J Am Coll Cardiol*. 2013;62:2261–2273. doi: 10.1016/j.jacc.2013.07.101.

10. Pirracchio R, Resche-Rigon M, Chevret S. Evaluation of the propensity score methods for estimating marginal odds ratios in case of small sample size. *BMC Med Res Methodol*. 2012;12:70. doi: 10.1186/1471-2288-12-70.

11. Broookhart MA, Wang PS, Solomon DH, Schneeweiss S. Variable selec- tion for propensity score models. *Am J Epidemiol*. 2006;163:1149–1156.

12. Riley RD, Kauser I, Bland M, Thijs L, Staessen JA, Wang J, Gueyf er F, Deeks JJ. Meta-analysis of randomised trials with a continuous outcome according to baseline imbalance and availability of individual participant data. *Stat Med*. 2013;32:2747–2766. doi: 10.1002/sim.5726.

12. Michelson AD, Frelinger AL, III, Braunwald E, Downey WE, Angiolillo DJ, Xenopoulos NP, Jakubowski JA, Li Y, Murphy SA, Qin J, McCabe CH, Antman EM, Wiviott SD; TRITON-TIMI 38 Investigators. Pharmacodynamic assessment of platelet inhibition by prasugrel vs. clopi- dogrel in the TRITON-TIMI 38 trial. *Eur Heart J*. 2009;30:1753–1763. doi: 10.1093/eurheartj/ehp159.

14. Storey RF, Angiolillo DJ, Patil SB, Desai B, Ecob R, Husted S, Emanuelsson H, Cannon CP, Becker RC, Wallentin L. Inhibitory effects of ticagrelor compared with clopidogrel on platelet function in patients with acute coronary syndromes: the PLATO (PLATelet inhibition and pa- tient Outcomes) PLATELET substudy. *J Am Coll Cardiol*. 2010;56:1456– 1462. doi: 10.1016/j.jacc.2010.03.100.

15. Parodi G, Marcucci R, Valenti R, Gori AM, Migliorini A, Giusti B, Buonamici P, Gensini GF, Abbate R, Antoniucci D. High residual platelet reactivity after clopidogrel loading and long-term cardiovascular

events among patients with acute coronary syndromes undergoing PCI. *JAMA*. 2011;306:1215–1223. doi: 10.1001/jama.2011.1332.

15. Silvain J, Cayla G, Hulot JS, Finzi J, Kerneis M, O'Connor SA, Bellemain-Appaix A, Barthélémy O, Beygui F, Collet JP, Montalescot G. High on-thienopyridine platelet reactivity in elderly coronary patients: the SENIOR-PLATELET study. *Eur Heart J*. 2012;33:1241–1249. doi: 10.1093/eurheartj/ehr407.

16. Montalescot G, van 't Hof AW, Lapostolle F, Silvain J, Lassen JF, Bolognese L, Cantor WJ, Cequier A, Chettibi M, Goodman SG, Hammett CJ, Huber K, Janzon M, Merkely B, Storey RF, Zeymer U, Stibbe O, Ecollan P, Heutz WM, Swahn E, Collet JP, Willems FF, Baradat C, Licour M, Tsatsaris A, Vicaut E, Hamm CW; ATLANTIC Investigators. Prehospital ticagrelor in ST-segment elevation myocardial infarction. *N Engl J Med*. 2014;371:1016–1027. doi: 10.1056/NEJMoa1407024.

17. Steg PG, van 't Hof A, Hamm CW, Clemmensen P, Lapostolle F, Coste P, Ten Berg J, Van Grunsven P, Eggink GJ, Nibbe L, Zeymer U, Campo dell' Orto M, Nef H, Steinmetz J, Soulat L, Huber K, Deliargyris EN, Bernstein D, Schuette D, Prats J, Clayton T, Pocock S, Hamon M, Goldstein P; EUROMAX Investigators. Bivalirudin started during emergency trans- port for primary PCI. *N Engl J Med*. 2013;369:2207–2217. doi: 10.1056/ NEJMoa1311096.

18. Yusuf S, Sleight P, Rossi P, Ramsdale D, Peto R, Furze L, Sterry H, Pearson M, Motwani R, Parish S, Gray R, Bennett D, Bray C. Reduction in infarct size, arrhythmias and chest pain by early intravenous beta block- ade in suspected acute myocardial infarction. *Circulation*. 1983;67(6 pt 2):I32–I41.

19. Kim YI, Williams JF Jr. Large dose sublingual nitroglycerin in acute myo- cardial infarction: relief of chest pain and reduction of Q wave evolution. *Am J Cardiol*. 1982;49:842–848.

20. Hobl EL, Stimp T, Ebner J, Schoergenhofer C, Derhaschnig U, Sunder- Plassmann R, Jilma-Stohlawetz P, Mannhalter C, Posch M, Jilma B. Morphine decreases clopidogrel concentrations and effects: a random- ized, double-blind, placebo-controlled trial. *J Am Coll Cardiol*. 2014;63: 630–635. doi: 10.1016/j.jacc.2013.10.068.

Chapter 4:

Morphine use and myocardial reperfusion in patients with acute myocardial infarction treated with primary PCI.

Benedetta Bellandi, MD,[a] Chiara Zocchi, MD,[a] Ioanna Xanthopoulou, MD,[b] Fernando Scudiero, MD,[a,c] Renato Valenti, MD,[a] Angela Migliorini, MD,[a] David Antoniucci, MD,[a] Niccolò Marchionni, MD,[a] Dimitrios Alexopoulos, MD,[b] Guido Parodi, MD, PhD.[a, c]

a, Cardiovascular and Thoracic Department, Careggi Hospital, Florence, Italy; b, Department of Cardiology, Patras University Hospital, Rion, Patras, Greece; c, Post-graduate School in Cardiology, University of Florence, Italy.

This study was supported by the "A.R. CARD" Foundation, Florence, Italy

Authorship: all authors had access to data and a role in writing the article.

Int J Cardiol. 2016 Oct 15;221:567-71.

ABSTRACT

Background: Antiplatelet therapy is the mainstay of pharmacological treatment for patients with ST-segment elevation myocardial infarction (STEMI) in order to prevent recurrences and improve clinical outcomes. Morphine is frequently used in STEMI patients, even if recently it has been associated with a delayed onset of action of the oral antiplatelet agents. There are no data regarding the impact of morphine on myocardial reperfusion after primary percutaneous coronary intervention (PPCI).

Objective: This study sought to assess myocardial reperfusion by early ST-segment resolution (≥ 50% at 30 minutes) according to morphine use in STEMI patients undergoing PPCI.

Methods: 182 STEMI patients undergoing PPCI and receiving either prasugrel (n=51) or ticagrelor (n=131) LD who were antiplatelet and anticoagulant therapies naïve were included in the study. All patients had serial ST-segment elevation evaluations by ECG and residual platelet reactivity assessments by VerifyNow P2Y12 Reactivity Units (PRU).

Results: Overall, 74 (41%) patients received morphine according to the attending physician preference and showed lower ST-segment resolution rate as compared with patients without morphine (76% vs 87%, p=0.047). Higher baseline TIMI flow < 2 rate (79% vs 64%, p= 0.036) and peak CPK values (1821 [924-3283] U/L vs 1483 [718-2327] U/L, p= 0.034) were observed in morphine patients. Moreover a delayed response to oral antiplatelet LD (PRU area under the curve [AOU0-8]: 1448±448 vs 686±292, p= 0.001, Figure 1) was documented in patients with morphine as compared with those without. The independent predictors of early ST-segment elevation resolution failure were PRU ≥ 208 after antiplatelet LD (OR 2.78 95% CI 1.08-7.14, p=0.034) and TIMI flow grade <3 after PPCI (OR 5.89 95% CI 1.64-21.12; p=0.009), but not morphine use.

Conclusions: In STEMI patients undergoing PPCI, morphine use is associated with a more frequent high residual platelet reactivity and a poorer myocardial reperfusion evaluated with ST-segment elevation analysis. Independent predictors of impaired myocardial reperfusion were: high residual platelet reactivity and TIMI flow grade after PPCI but not morphine use, questioning the direct relationship between morphine and worse myocardial reperfusion.

Introduction

Optimal myocardial reperfusion represents the goal of ST-segment elevation myocardial infarction (STEMI) therapy, since early and effective myocardial reperfusion is related to better clinical outcomes at short and long-term follow-up [1]. Effective antiplatelet therapy is required in patients with STEMI patients undergoing primary percutaneous coronary intervention (PPCI) in order to reduce ischemic complications and improve clinical outcomes [2]. Current guidelines strongly recommend the use of prasugrel or ticagrelor over clopidogrel in addition to aspirin as early as possible for their rapid onset of action and greater potency [3,4]. In addition, in this clinical setting, guidelines recommend morphine administration to reduce patients' pain and anxiety. Recent pharmacodynamic and pharmacokynetic studies showed that morphine use is associated with a delayed onset of action of oral $P2Y_{12}$ antiplatelet agents [5-10]. However, data on myocardial reperfusion evaluation according to morphine use in STEMI patients are scant and conflicting [11,12].

Methods

From January 2012 to January 2014, 251 STEMI patients undergoing PPCI at 2 centers (Florence and Patras) receiving either prasugrel (60 mg) or ticagrelor (180 mg) were screened for eligibility in the present study. Of these, 182 who were antiplatelet and anticoagulant therapies naïve and did not meet any of other pre-defined exclusion criteria (Figure 1) underwent serial residual platelet reactivity evaluations after $P2Y_{12}$ inhibitor loading dose (LD) and were included in the present analysis. The $P2Y_{12}$ inhibitor LD was administered as soon as possible in the Emergency Room or in the Catheterization Laboratory, in all cases before PPCI. The following antithrombotic agents were given on top of $P2Y_{12}$ platelet receptor inhibitors at the time of PPCI: a) aspirin 300-500 mg LD followed by 100 mg od; b) bivalirudin: 0.75 mg/kg bolus followed by 1.75 mg/kg/h

infusion during PPCI or unfractionated heparin 70 UI/kg bolus followed by additional boluses to achieve an activated clotting time of 250 to 300 seconds during PPCI. Patients were stratified according to morphine use, which was prescribed at attending physician's discretion. A 12-lead electrocardiogram was recorded before the procedure and 30 minutes after infarct-related artery (IRA) recanalization, with an error time-wise of 30 ± 5 minutes. The ST-segment changes were evaluated in the single lead with the most prominent ST-segment elevation before mechanical intervention. The ST-segment elevation was measured to the nearest 0.5 mm at 60 milliseconds after the J point with the aid of handheld calipers. According to a previous report, early ST-segment elevation resolution was defined as ≥ 50% decrease in ST-segment elevation after IRA recanalization [13]. ST-segment evaluation was blinded to morphine administration. Ischemia time was defined as pain-to-balloon time (minutes). Blood sampling for platelet function test was performed at baseline (hour 0) and at 1, 2, 4 and 8 hours from $P2Y_{12}$ inhibitor LD. In all cases, peripheral venous blood was drawn with a loose tourniquet through a short venous catheter inserted into a forearm vein. The first 2 to 4 mL of blood were discarded to avoid spontaneous platelet activation and blood was collected in 3.2% citrate (1.8 mL draw plastic Vacuette tubes; Greiner, Monroe, NC). Platelet function testing was performed with the VerifyNow (Accumetrics Inc, San Diego, CA) point-of-care $P2Y_{12}$ function assay, with results reported in $P2Y_{12}$ reaction units (PRU). High residual platelet reactivity (HRPR) was defined as a PRU ≥ 208. Coronary blood flow was evaluated at initial angiography and at the end of PPCI with the TIMI flow grade method [14]. Collateral circulation and thrombus burden of IRA were evaluated at initial angiography respectively with the Rentrop Classification [15] and with the Thrombus Burden Classification [16], respectively. The TIMI risk score was calculated for each patients [17]. Bleeding events were defined according to TIMI classification [14]. The

primary end point was early ST-segment resolution 30 minutes after IRA recanalization. Secondary endpoints were: HRPR at 1, 2, 4 and 8 hours from $P2Y_{12}$ inhibitor LD and the area under the curve (AUC) of PRU values, calculated with the Riemann Sum method [18]. Informed consent was obtained from each patient and the study protocol conforms to the Declaration of Helsinki.

Continuous data were expressed as mean ± standard deviation or medians (quartiles) as appropriate, and categorical data as proportions (%). Data were compared by the χ^2 test or Fisher exact test for categorical variables and unpaired *t* test or Mann-Whitney U-test for continuous variables, as appropriate. A multivariable model with forward stepwise binary logistic regression analysis was calculated to identify the independent predictors of early ST-segment resolution. The variables entered into the model were: age (years), diabetes mellitus, Killip class, morphine use, PRU value ≥ 208 2 hours after LD, and TIMI flow post-PCI. The consistence of PRU effect on ST-segment resolution according to morphine use was explored by the interaction test. A further multivariable model was calculated to evaluate the independent predictors of morphine administration, using the forward stepwise binary logistic regression analysis. The variables entered into this model were: age (years), diabetes mellitus, Killip class, TIMI flow at initial angiography, Rentrop coronary collateral grade, chest pain type, ischemia time, systolic blood pressure, heart rate. A significance of .05 was required for a variable to be included in the multivariate models, whereas .10 was the cut-off value for exclusion. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. A P value < .05 was considered statistically significant. All tests were two-sided. Analyses were performed with SPSS 19 (IBM Corporation, Somers, NY). Interobserver and intraobserver variability of ST segment resolution by ECG measurements were tested using intraclass correlation and a value >0.9 was defined as excellent correlation.

Results

Of 182 patients enrolled, 74 (41%) were treated with morphine with a mean dose of 6±3 mg. Baseline clinical characteristics were similar in patients who were, or were not treated with morphine (Table 1). No significant differences were reported regarding the proportion of patients treated with morphine across the two different centers (44% in Florence and 27% in Patras, p= 0.062). Fifty-one (28%) patients received prasugrel and 131 (82%) ticagrelor LD. As expected, patients treated with morphine had a higher incidence of vomiting (11% vs. 6%; p=0.034). Procedure-related data showed significantly higher rate of TIMI flow grade < 2 at initial angiography (79% vs. 64%, p= 0.036) and a trend for higher thrombotic burden (thrombus burden≥4: 85% vs. 74%, p= 0.094; Table 2) in morphine treated patients. A lower ST-segment resolution rate at 30 minutes after IRA recanalization (76% vs. 87%, p=0.047) was observed in morphine patients (Table 3). Moreover, morphine treated patients had higher CPK peak [1821 (924-3283) U/L vs. 1483 (718-2327 U/L), p= 0.034] and a trend for a lower left ventricular ejection fraction at discharge (46±9%vs 48±9%, p= 0.079) (Table 3). Patients treated with morphine presented significantly higher PRU values up to 8 hours (area under the curve AOU_{0-8} 1448±448 vs. 686±292, p= 0.001; Figure 2). This association persisted after excluding patients with vomiting and was independent of oral $P2Y_{12}$ inhibitor type (data not showed). In-hospital outcomes are reported in Table 4. PRU ≥ 208 after $P2Y_{12}$ antiplatelet inhibitor LD (OR 2.78 95% CI 1.08-7.14, p=0.034) and TIMI flow grade <3 after PPCI (OR 5.89 95% CI 1.64-21.12; p=0.009), but not morphine use, were independent predictors of early ST-segment elevation resolution failure. PRU effect on ST-segment resolution was independent of morphine use (p for interaction = 0.151). No clinical, electrocardiographic or angiographic characteristic emerged as independent predictor of morphine administration. Interobserver and intraobserver variability showed

excellent correlation for ST-segment resolution analysis (intraclass correlation; inter=0.910, intra=0.958).

Table 1: Baseline characteristics of study patients treated with or without morphine

Variable	All (n=182)	No Morphine (n=108)	Morphine (n=74)	P Value
Age (years)	64 ± 13	64 ± 13	64 ± 13	0.925
Male gender	136 (75%)	82 (76%)	54 (73%)	0.653
Body Mass Index	27 ± 5	27 ± 5	27 ± 5	0.397
Smokers	85 (47%)	49 (45%)	36 (49%)	0.663
Hypertension	106 (58%)	65 (60%)	41 (55%)	0.521
Dyslipidemia	50 (27%)	32 (30%)	18 (24%)	0.431
Diabetes Mellitus	37 (20%)	25 (23%)	12 (16%)	0.254
Familiar history of CAD	32 (18%)	19 (18%)	13 (18%)	0.997
Previous myocardial infarction	18 (10%)	9 (8%)	6 (8%)	0.952
Previous PCI	13 (7%)	9 (8%)	4 (6%)	0.451
Previous CABG	2 (1%)	1 (1%)	1 (1%)	0.787
Hystory of renal failure	10 (5%)	8 (7%)	2 (3%)	0.171
Systolic blood pressure (mmHg)	142 ± 29	142 ± 27	142 ± 31	0.997
Systolic blood pressure <90mmHg	5 (3%)	4 (4%)	1 (2%)	0.340
Heart rate (bpm)	79 ± 21	80 ± 19	76 ± 23	0.334
Heart rate ≥ 90 bpm	124 (68%)	72 (78%)	52 (70%)	0.315
Typical chest pain	174 (95%)	104 (96%)	70 (94%)	0.582
Pressure rate product	10950 ± 4407	11523 ± 3499	11252 ± 5396	0.716
Vomit	16 (9%)	5 (6%)	11 (17%)	0.034
Cardiogenic shock	9 (5%)	5 (5%)	4 (5%)	0.941
Killip class ≥ 2	27 (15%)	14 (13%)	13 (17%)	0.390

TIMI risk score> 4	58 (32%)	32 (30%)	26 (35%)	0.329
Anterior myocardial infarction	83 (46%)	49 (45%)	34 (46%)	0.848
Pain to balloon time (minutes)	104 ± 77	111 ± 86	95 ± 61	0.178

Table 2: Angiographic and procedural related characteristics of study patients treated with or without morphine

Variable	**All (n=182)**	**No Morphine (n=108)**	**Morphine (n=74)**	**P Value**
P2Y12 inhibitor administration				0.624
Emergency room	42 (23%)	26 (24%)	16 (22%)	
Cath lab	140 (77%)	82 (75%)	58 (78%)	
P2Y12 inhibitor type				0.273
Prasugrel	51 (28%)	27 (25%)	24 (32%)	
Ticagrelor	131 (72%)	81 (75%)	50 (68%)	
Culprit lesion location				0.570
Left main	5 (3%)	4 (5%)	1 (1%)	
Left anterior descending	62 (42%)	33 (40%)	29 (45%)	
Circumflex artery	27 (18%)	17 (20%)	10 (15%)	
Right coronary artery	54 (36%)	29 (35%)	25 (38%)	
Coronary artery disease extension				0.567
1 vessel disease	93 (51%)	56 (52%)	37 (50%)	
2 vessel disease	57 (31%)	31 (29%)	26 (35%)	
3 vessel disease	32 (18%)	21 (19%)	11 (15%)	
Number of treated vessel				0.607
1 treated vessel	168 (92%)	101 (95%)	67 (94%)	

2 treated vessel	8 (5%)	4 (4%)	4 (6%)	
Access site				0.124
Femoral	173 (95%)	99 (92%)	74 (100%)	
Radial	3 (2%)	3 (4%)	0	
Bivalirudin	161 (88%)	94 (87%)	67 (90%)	0.467
TIMI flow grade pre PCI < 2	127 (70%)	69 (64%)	58 (79%)	0.036
TIMI flow grade post PCI ≥ 3	165 (91%)	100 (93%)	65 (88%)	0.278
Rentrop collateral grade ≥2	17 (9%)	10 (9%)	7 (10%)	0.755
Thrombus burden ≥4	132 (72%)	75 (74%)	57 (85%)	0.094
Thrombectomy	102 (57%)	53 (64%)	49 (72%)	0.422
Intra aortic balloon pump	6 (3%)	3 (4%)	3 (5%)	0.759

Table 3: Reperfusion and pharmacodymanic data of study patients treated with or without morphine

Variable	**All (n=182)**	**No Morphine (n=108)**	**Morphine (n=74)**	**P Value**
Basal ST-segment elevation (mm)	3.1 ± 1.8	2.9 ± 1.8	3.4 ± 1.8	0.117
ST-segment at 30 minutes (mm)	1.1 ± 1.1	0.8 ± 0.9	1.4 ± 1.2	0.009
ST-segment resolution at 30 minutes (≥50%)	150 (82%)	94 (87%)	56 (76%)	0.047
CPK peak (U/L)	1613 (773-2732)	1483 (718-2327)	1821 (924-3283)	0.034
CPK time (hours)	6 (5-12)	6 (6-12)	6 (3-12)	0.160
LV EF at discharge (%)	47 ± 9	48 ± 9	46 ± 9	0.079
Basal PRU	292 ± 66	287±70	298±58	0.304

PRU 1h	200 ± 109	176±120	235±79	0.002
PRU 2h	120 ± 118	119±118	182±109	0.000
PRU 4h	84 ± 98	62±86	113±109	0.001
PRU 8h	65 ± 70	60±68	71±73	0.457
AUC (0-8)	1072 ± 557	1448 ± 488	686 ± 292	0.001

PRU: platelet reactivity units; AUC: area under the curve; CPK: creatine phoshokinase; LVEF: left ventricular ejection fraction

Table 4: In-hospital outcomes of study patients treated with or without morphine

Variable	**All (n=182)**	**No Morphine (n=108)**	**Morphine (n=74)**	**p Value**
Death	5 (2.8%)	3 (2.8%)	2 (2.7%)	0.976
Reinfarction	2 (1%)	1 (0.9%)	1 (1.4%)	0.787
Stroke	0	0	0	-
Heart failure	15 (8.2%)	7 (6.4%)	8 (12.9%)	0.396
Dyspnoea	6 (3.3%)	4 (3.7%)	2 (2.8%)	0.726
Contrast induced nefropathy	16 (8.8%)	10 (9.6%)	6 (7.9%)	0.721
Vascular complications	5 (2.7%)	4 (4.9%)	1 (1.6%)	0.289
TIMI Major bleeding	6 (3.3%)	4 (3.7%)	2 (2.7%)	0.702
TIMI Minor bleeding	8 (4.4%)	3 (3.7%)	5 (7.7%)	0.402
TIMI Minimal bleeding	5 (2.7%)	3 (2.5%)	2 (3.3%)	0.792
Hospitalization lenght (days)	3.8 ± 3.2	3.6 ± 2.7	4.1 ± 3.9	0.471

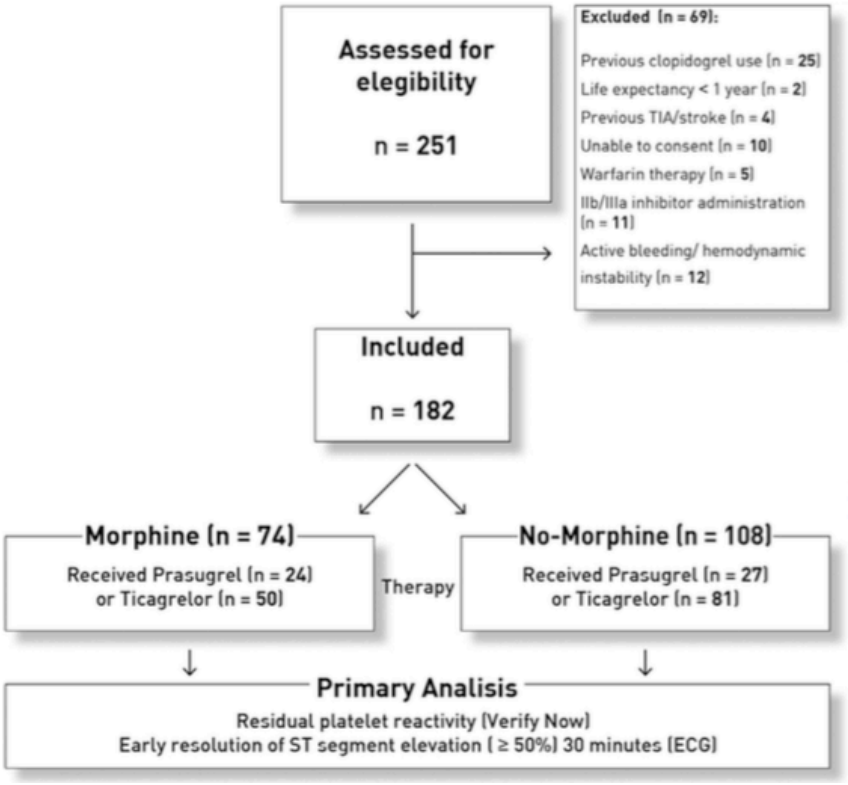


Figure 1: Study flow-chart

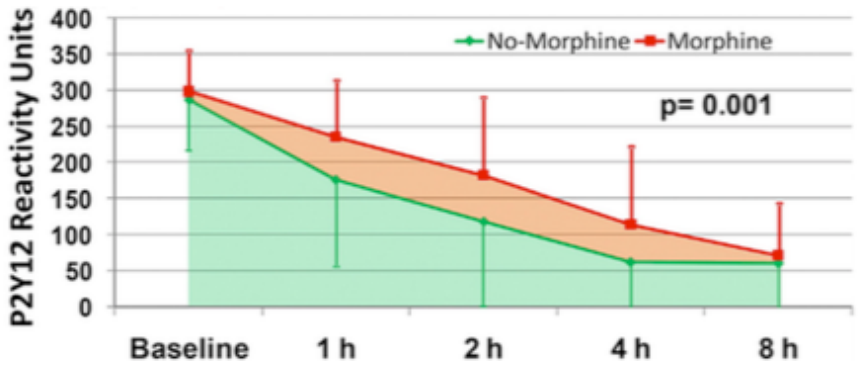


Figure 2: Area under the curve of residual platelet reactivity over time (from baseline to 8 hours from $P2Y_{12}$ inhibitor loading dose) in patients treated (red area) or not (green area) with morphine.

Discussion

The main results of the present study can be summarized as follows:

1) Platelet residual reactivity and TIMI flow grade<3 after PPCI, but not morphine use, were independent predictors of early ST-segment resolution failure;
2) Morphine use was associated with HRPR, higher rate of vomiting, poor early ST-segment resolution, larger infarct-size and a trend towards greater left ventricular dysfunction at discharge;
3) No clinical, electrocardiographic or angiographic parameters predicted the use of morphine in STEMI patients.

ST-segment resolution is a tool used to assess the efficacy, and the potential clinical benefit, of myocardial reperfusion. In our analysis of STEMI patients undergoing PPCI and treated as early as possible with P2Y12 antiplatelet inhibitors, sub-optimal platelet inhibition and epicardial vessel recanalization at the end of the procedure were more likely to induce poor myocardial reperfusion. The relation between final TIMI blood flow after PPCI and myocardial salvage was previously described and was found to predict in-hospital complications and long-term outcome [24, 25]. Our study confirms this association, and further strengthens the concept that adequate platelet inhibition should be pursued at the time of PPCI, not only to reduce the risk of recurring ischemic events, but also to achieve optimal myocardial reperfusion. Our data also confirm the results of previous studies demonstrating that aggressive platelet inhibition with intravenous abciximab is associated with improved ST-segment resolution and reduced infarct size [22]. We can hypothesize several theoretical mechanisms through which HRPR during and early after PPCI may negatively influence myocardial reperfusion by: increasing the likelihood of 1) coronary distal embolization, 2) side vessel occlusion, 3) treated vessel

reocclusion/restenosis, or 4) reducing the pleiotropic/ off-target effects of antiplatelet drugs [23]. Morphine is used in STEMI patients to relief pain and anxiety and has recently been associated with higher rates of HRPR early after $P2Y_{12}$ platelet inhibitor LD. In our study, residual platelet reactivity 1, 2 and 4 hours from antiplatelet agent LD was greater in patients treated than in those untreated with morphine. This drug-to-drug interaction was limited in time, since after only 8 hours from $P2Y_{12}$ inhibitor LD, a time interval compatible with morphine clearance, residual platelet reactivity became similar in the two groups. The morphine-antiplatelet agent interaction is likely mediated by inhibition of gastrointestinal motility, which may lead to vomiting or delayed gastric emptying that, in turns, delays or reduces the absorption of orally administered drugs, thereby deferring or reducing their peak plasma levels [25]. Beyond this, we can also hypothesize that the impact of morphine on myocardial reperfusion may be due to collateral drug effects such as bradycardia, hypotension or respiratory depression that might contribute to myocardial hypoxia. Moreover, morphine itself might positively influence reperfusion with other mechanisms including the possible role of opioid receptor-mediated pre- and post-conditioning [26-28]. In our study, patients treated with morphine had lower early ST-segment resolution rate, greater infarct size as assessed by peak enzymes and poorer left ventricular function at discharge, confirming the results of the ATLANTIC trial, in which patients co-treated with ticagrelor and morphine before hospitalizations presented a worse ST-segment resolution than those not receiving morphine [29]. Main at al. reported higher mortality rate in acute coronary syndrome patients treated with morphine but no data were reported regarding myocardial reperfusion and morphine administration in this population of NSTEMI patients, and the relationship between morphine use and mortality remained unexplored [30]. Despite these assumptions, our analysis showed that HRPR and TIMI flow<3 at final

angiography, but not morphine, were independent predictors of worse myocardial reperfusion. This evidence underline that, while morphine is an important factor contributing to HRPR, a direct morphine impact on reperfusion is unlikely. Thus, the observed association between morphine use and worse myocardial reperfusion is likely mediated by the pharmacodynamic interaction between opioids and oral antiplatelet agents.

An initial hypothesis of the present analysis was that clinical, electrocardiographic and angiographic features could have increased in STEMI patients undergoing PPCI the probability of morphine administration that, in turn, might influence their outcome. In contrast with this hypothesis, we failed to identify any clinical predictor of morphine use, such as chest pain characteristics, baseline ST-segment elevation degree, a completely occluded vessel at initial angiography and/or the absence of collateral circulation. Probably, morphine administration was driven by several factors: the experience and the symptom perception of health-care personnel, the subjectivity of patient's symptom and its relation with anxiety. Pulmonary edema was not a driver of morphine use, since Killip class was similar in the 2 study groups. This is in agreement with current debate regarding morphine use in acutely decompensated heart failure, which has been associated with a greater need for mechanical ventilation, prolonged hospitalization and higher mortality [31].

Some limitations of our study must be acknowledged. First, the lack of an assessment of pain intensity with a standardized scale is certainly the most important one. However, we have to admit that, due to the subjective and highly dynamic nature of this parameter, a standardized scale providing a reliable evaluation of intensity of chest pain secondary to myocardial ischemia is not yet available; moreover, also the critical phase of acute

STEMI makes the clinical use of a formally validated questionnaire difficult and impractical.

The second limitation consists in the fact that the study end-point was not clinical, but a surrogate marker of myocardial reperfusion (early ST-segment resolution). However, this parameter has been associated with a hard outcome such as survival in several STEMI trials [22]. Furthermore, we have to consider that magnetic resonance imaging (MRI) data were not available in our study. Due to possible hemodynamic instability and the high prevalence of renal failure or claustrophobia, MRI evaluation is quite often unfeasible during the first days after STEMI. The small sample size represents a third study limitation. However, our patients have the uniqueness of serial evaluation of platelet reactivity from the first hours after myocardial revascularization. Finally, the non-randomized nature of the study cannot allow to exclude possible unmeasured confounders. Consequently, the present study results should only be considered as hypothesis generating.

Conclusions:

In STEMI patients undergoing PPCI, morphine use is associated with a more frequent HRPR and a poorer myocardial reperfusion evaluated with ST-segment elevation analysis. Independent predictors of impaired myocardial reperfusion were: HRPR and TIMI flow grade after PPCI but not morphine use, questioning the direct relationship between morphine and worse myocardial reperfusion.

References:

1. Busk M, Kaltoft A, Nielsen SS, et al. Infarct size and myocardial salvage after primary angioplasty in patients presenting with symptoms for <12 h vs 12-72 h. Eur Heart J 2009;**30**:1322-30.
2. Parodi G, Marcucci R, Valenti R, et al. High residual platelet reactivity after clopidogrel loading and long-term cardiovascular events among patients with acute coronary syndromes undergoing PCI. JAMA 2011; **306**;1215-1223.

3. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Am Coll Cardiol. 2013;**61**:e78-e140.
4. Steg G, James SK, Atar D, et al. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012**;33**:2569–619.
5. Parodi G, Valenti R, Bellandi B, et al. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. J Am Coll Cardiol. 2013;**61**:1601–6.
6. Parodi G, Bellandi B, Xanthopoulou I, et al. Morphine is associated with a delayed activity of oral antiplatelet agents in patients with ST-elevation acute myocardial infarction undergoing primary percutaneous coronary intervention.Circ Cardiovasc Interv. 2014; **8**: 1.
7. Hobl EL, Stimpfl T, Ebner J, et al. Morphine decreases clopidogrel concentrations and effects: A randomized, double blind, placebo-controlled trial. J Am Coll Cardiol 2014;**63**:630–5.
8. Kubica J, Adamski P, Ostrowska M, et al. Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial. Eur Heart J 2016; **37**: 245-52.
9. Silvain J, Storey R, Cayla G, et al, ACTION Coeur Research Group, Paris, France. P2y12 Receptor Inhibition According to Prehospital Administration of Ticagrelor in Primary PCI for St Elevation Myocardial Infarction: The Private-Atlantic Study. JACC 2015,**65**, 108.
10. Parodi G. Chest pain relief in patients with acute myocardial infarction. Eur Heart J Acute Cardiovasc Care 2015; **22**: pii: 2048872615584078.
11. Iakobishvili Z, Porter A, Battler A, et al. Effect of narcotic treatment on outcomes of acute coronary syndromes. Am J Cardiol 2010;**105**:912–916.
12. Gross ER, Hsu AK, Gross GJ. Acute methadone treatment reduces myocardial infarct size via the delta-opioid receptor in rats during reperfusion. AnesthAnalg2009;**109**:1395–1402.

13. Santoro GM, Antoniucci D, Valenti R, et al. Rapid Reduction of ST-Segment Elevation After Successful Direct Angioplasty in Acute Myocardial Infarction. Am J Cardiol 1997;**80**:685–9.

14. The TIMI Study Group. The Thrombolysis in Miocardial Infarction (TIMI) trial. N Engl Med. 1985; **312**:932.

15. Rentrop KP, Cohen M, Blanke H, Phillips RA. Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. J Am Coll Cardiol, 1985;**5**:587-92 .

16. Sianos G, Papafakilis MI, Serruys PW. Angiographic thrombus burden classification in patients with ST-segment elevation myocardial infarction treated with percutaneous coronary intervention. J Invasive Cardiol 2010;**22**:6B-14B.

17. Morrow DA, Antman EM, Charlesworth A, et al. TIMI Risk Score for ST-Elevation Myocardial Infarction: A convenient, bedside, clinical score for risk assessment at presentation: An intravenous nPA for treatment of infracting myocardium early II Trial Substudy. Circulation 2000;**102**:2031-7.

18. Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation 2006;**114**:774–782.

19. Thomas GB Jr; Finney RL. Calculus and Analytic Geometry (9th ed.), Addison Wesley, 1996, ISBN 0-201-53174-7

20. Mehta RH, Harjai KJ, Cox D, et al, on behalf of the Primary Angioplasty in Myocardial Infarction (PAMI) Investigators. Clinical and angiographic correlates and outcomes of suboptimal coronary flow in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention. J Am Coll Cardiol 2003;**42**:1739–46.

21. Parodi G, Valenti R, Carrabba N, et al. Long-term prognostic implications of non-optimal primary angioplasty for acute myocardial infarction. Cath Cardiovasc Interv 2006; **68**:50-55.

22. Antoniucci D, Rodriguez A, Hempel A, et al. Randomized trial comparing primary infarct artery stenting with or without abciximab in acute myocardial infarction. J Am Coll Cardiol, 2003; **42**:1879-85.

23. Cattaneo M, Schulz R, Nylander S. Adenosine-Mediated Effects of Ticagrelor Evidence and Potential Clinical Relevance. J Am Coll Cardiol. 2014;**63**:2503–9.

24. Nimmo WS, Heading RC, Wilson J, Tothill P, Pescott LF. Inhibition of gastric emptying and drug absorption by narcotic analgesics. Br J Clin Pharmacol 1975;**2**:509-13.

25. De Luca A and Coupar IM. Insights into opioid action in the intestinal tract. PharmacolTher1996; **2**: 103–115.

26. He SF, Zhu HJ, Yi Han Z. MicroRNA-133b-5p Is Involved in Cardioprotection of Morphine Preconditioning in Rat Cardiomyocytes by Targeting *Fas*. Canadian Journal 2015; in press.

27. Headrick JP, Hoe LES, Du Toit EF et al. Opioid receptors and cardioprotection- 'opioidergic conditioning' of the heart. British Journal of Pharmacology 2015; 172: 2026-2050.

28. Lu Y, Hu J, Dong C. Morphine may enhance the cardioprotection induced by remote ischemic preconditioning. Int J Cardiol 2015; 6;187:443-4.

29. Montalescot G, van 't Hof AW, Lapostolle F, et al; ATLANTIC Investigators. Prehospital ticagrelor in ST-segment elevation myocardial infarction. N Engl J Med 2014; **371**: 2338-9.

30. Meine TJ, Roe MT, Chen AY, et al; CRUSADE Investigators.Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. Am Heart J 2005;**149**:1043-9.

31. Peacock WF, Hollander JE, Diercks DB, Lopatin M, Fonarow G, Emerman CL. Morphine and outcomes in acute decompensated heart failure: an ADHERE analysis. Emerg med J 2008;**25**:205-209.

Part 3: Safety of antithrombotic strategies in STEMI patients

Chapter 5:

Impact of anticoagulation strategy with bivalirudin or heparin on nonaccess site bleeding in percutaneous coronary interventions: A meta-analysis of randomized trials.

Monica Verdoia,1 MD , Lucia Barbieri,1,2 MD, Guido Parodi,3 MD, Benedetta Bellandi,3 MD, Alon Schaffer,1 MD, Harry Suryapranata,4 MD, PhD, and Giuseppe De Luca,1* MD, PhD

1Division of Cardiology, Azienda Ospedaliera-Universitaria "Maggiore della Carita ", Eastern Piedmont University, Novara, Italy 2Division of Cardiology, Ospedale S. Andrea, Vercelli, Italy 3Division of Cardiology, Ospedale Careggi, Firenze, Italy 4Department of Cardiology, UMC St Radboud, Nijmegen, The Netherlands

Disclosure: The authors declare no conflict of interest or funding support.

*Correspondence to: Giuseppe De Luca; Associate Professor of Cardiology, Chief Interventional Cardiology, Ospedale "Maggiore della Carit a", Eastern Piedmont

Catheter Cardiovasc Interv. 2017 Oct 1;90(4):553-565.

ABSTRACT

Background: Transradial approach has significantly decreased the rate of access site bleeding in patients undergoing percutaneous coronary interventions (PCI), therefore potentially mitigating the benefits offered by bivalirudin in lowering major bleeding compli- cations as compared to heparin. However, nonaccess site bleeding, that represent the majority of hemorrhagic complications, still carry negative prognostic consequences for these patients and no study has so far defined the exact impact of bivalirudin on nonaccess site bleeding, that was therefore the aim of present meta-analysis. Methods and study outcomes: Literature archives (Pubmed, EMBASE, Cochrane) and main scientific sessions were scanned comparing bivalirudin vs. heparin in patients undergoing PCI. Pri- mary endpoint was the occurrence of nonaccess site bleeding within 30 days. Secondary endpoints were 30 days mortality and the occurrence of access-site bleeding. Results: A total of nine randomized clinical trials were finally included, involving 32,587 patients, 55.8% randomized to bivalirudin. Bivalirudin significantly reduced the rate of nonaccess site bleeding (2.6 vs. 3.8%, OR [95% CI] 5 0.68 [0.60–0.77], P < 0.00001, Phet 5 0.10). However, the reduction of hemorrhagic events was more pronounced when bivalirudin was com- pared to heparin plus glycoprotein IIbIIIa inhibitors than when it was compared to heparin alone (r520.01 (20.02; 20.001), P50.02). Similar results were observed for access-site bleeding (OR [95% CI]50.67 [0.57–0.79], P<0.000001, Phet50.10), with a significant role of glycoprotein IIbIIIa inhibitors use (r520.02 (20.04; 20.004), P50.017). Moreover, the observed benefits in hemorrhagic complications did not translate into mortality benefits (OR [95% CI] 5 0.89 [0.76–1.05], P 5 0.18; Phet 5 0.12; r 5 0.21 (21.12; 1.53), P 5 0.76). Conclusions: The present meta-analysis shows that bivalirudin can provide a significant reduction of

both access and nonaccess site bleeding in patients undergoing PCI. Howev- er, these hemorrhagic benefits did not impact on survival, and moreover, were significantly conditioned by the association of heparin with potent antithrombotic strategies, such as glycoprotein IIbIIIa inhibitors, rather than by heparin or bivalirudin alone. Therefore, we could not provide any clinical evidence for the routine use of bivalirudin as preferred anti- coagulation strategy for PCI.

BACKGROUND

Advances in antithrombotic therapies have improved the outcomes of patients with acute coronary syndromes (ACS) undergoing percutaneous coronary revascularization, although carrying an intrinsic risk of enhancing bleeding complications [1–3].

Radial approach has dramatically reduced the rate of access-site hemorrhagic complications, thus being indicated nowadays as the most preferred strategy for performing percutaneous coronary interventions (PCI) [4–6].

However, nonaccess site bleeding still represents a challenging issue in patients undergoing PCI. In fact, they account for up to two-thirds of all major bleeding events, whose occurrence has demonstrated negative prognostic implications, being associated with a 2 to 4- fold increase in mortality [7].

Bivalirudin has been proposed as an anticoagulation strategy alternative to heparin during PCI, offering theoretical benefits in bleeding [8], whose real extent has not been clearly defined by previous randomized trials, as consequence of the potential interaction with access-site hemorrhagic complications [9]. In fact, while the reduction of bleeding with bivalirudin was more evident with the preferential use of transfemoral PCI, most recent evidence has emerged that the use of radial access could vanish the expected safety benefits of bivalirudin, thus raising concerns on the exact role of this anticoagulation strategy on the occurrence of major bleeding complications in the era of transradial PCI [10, 11].

Therefore, the present study aimed to provide a meta-analytic overview of randomized trials evaluating the impact of bivalirudin vs. heparin on the occurrence of nonaccess site bleeding in patients undergoing PCI.

METHODS Eligibility and Search Strategy

The literature was scanned by formal searches of electronic databases (MEDLINE, Cochrane, and EMBASE) for clinical studies and furthermore the scientific session abstracts, searched on the TCT (www.tctmd.com), EuroPCR (www.europcr.com), ACC (www.acc.org), AHA (www.aha.org), and ESC (www.escardio.org) websites, for oral presentations and/or expert slide presentations from January 1990 to September 2015. Studies were included when comparing bivalirudin vs. heparin in patients under- going percutaneous coronary interventions. The following key words were used: “bivalirudin and acute coronary syndrome” or “bivalirudin versus heparin” or “bivalirudin and trial”. No language restrictions were enforced.

Data Extraction and Validity Assessment

Data were independently abstracted by two investigators. In case of incomplete or unclear data, authors, where possible, were contacted. Disagreements were resolved by consensus. Data were managed according to the intention-to-treat principle.

Outcome Measures

Primary endpoint was the rate of non access-site bleeding at 30 days follow-up. Secondary endpoints were over- all mortality at 30 days and the occurrence of access-site bleeding within the first 30 days from randomization.

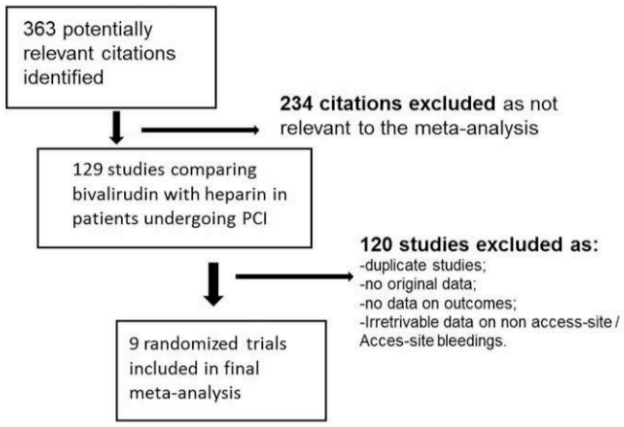


Fig. 1. Flow diagram of the systematic overview process.

DATA ANALYSIS

Statistical analysis was performed using the Review Manager 5.23 freeware package, SPSS 17.0 statistical package. Odds ratio (OR) and 95% confidence intervals (95% CI) were used as summary statistics. The pooled odds ratio was calculated using a fixed effect model. The Breslow–Day test was used to examine the statistical evidence of heterogeneity across the studies ($P < 0.1$). The study quality was evaluated by the same two investigators according to a score, that, as previously described [12], was expressed on a ordinal scale, allocating 1 point for the presence of each of the following: 1) statement of objectives; 2) explicit inclusion and exclusion criteria; 3) description of intervention; 4) objective means of follow- up; 5) availability of data on endpoint events; 6) power analysis; 7) description of statistical methods; 8) multi- center design; 9) discussion of withdrawals; 10) details on medical therapy. A meta-regression analysis was carried out to evaluate: the relationship between the reduction of access and nonaccess site bleeding with bivalirudin and patients' risk profile (as log of the odds for bleeding in the control group) or the rate of transradial PCI and the differential use of glycoprotein IIbIIIa inhibitors (as the percentage of adjunctive use of GPII- bIIIa inhibitors in control vs. bivalirudin arm). Moreover, the relationship between the benefits in mortality from bivalirudin vs. heparin and the reduction in non access- site bleeding complications with bivalirudin (as log of the odds ratio for bleeding in bivalirudin vs. control group) was also evaluated. The study was performed in compliance with the Quality of Reporting of Meta- Analyses (PRISMA) guidelines [13].

RESULTS Eligible Studies

A total of nine randomized clinical trials [14–22] were finally included, for a total population of 32,587 patients (Fig. 1). Among them, 18,212 patients (55.8%) were randomized to bivalirudin, while 14,375 patients (44.2%) to unfractionated heparin (UFH) with or without planned GPIIb/IIIa inhibitors. Detailed characteristics of included trials are shown in Table I. As displayed in Table II, mean age was 65.1.1 6 5.8 years, with 24.7% of diabetics, and 18.1% with renal failure. Use of GPIIbIIIa inhibitors was 11.1% in the bivalirudin group (excluded in 1 trials [20]) and 63% in the UFH group (planned 100% in 3 trials [14, 19, 20]). Three trials were con- ducted on STEMI patients [16, 18, 19], while 3 trials focused on patients with ACS (UA/NSTEMI) [14, 20, 21], and 3 on elective patients [15, 17, 22]. Follow-up data were collected at 30 days in all studies.

TABLE I. Characteristics of Included Studies

Study name	Enrolment year	Type	Study population	Inclusion	Exclusion	Bleeding definition (nonaccess)	Quality score
ACUITY	2003–2005	Multicentre RCT	ACS	1) >18 years; 2) symptoms of unstable angina for >10 min within the preceding 24 h and at least one among i) new ST-segment depression or transient elevation of 1 mm or more; ii) raised troponin I, T, or creatine kinase MB isozyme; iii) known coronary artery disease.	1) acute ST-segment elevation myocardial infarction; 2) shock; 3) bleeding diathesis or major bleeding episode <2 weeks; 4) thrombocytopenia; 5) creatinine clearance <30 mL/min; 6) recent administration of abciximab, warfarin, fondaparinux, fibrinolytic agents, bivalirudin, or two or more doses of low molecular mass heparin; 7) allergy to study drugs or iodinated contrast that could not be adequately premedicated	All major bleedings (study definition)—access site bleedings	10
ARNO	2006–2008	Single center, RCT	Elective	1) Written, informed consent.	1) acute ST-segment elevation myocardial infarction; 2) PCI for chronic total occlusion; 3) creatinine clearance <30 ml/min or serum creatinine> 3 mg/dl or dialysis; 4) life expectancy of <1 year; 5) active bleeding, bleeding diathesis, or recent major surgery; 6) gastrointestinal or genitourinary bleeding <6 weeks; 7) pretreatment with UFH or LMWH or bivalirudin before PCI; 8) uncontrolled hypertension; 9) relevant hematologic abnormalities; 10) allergy to the study medications; 11) history of heparin-induced thrombocytopenia; 12) age <18 years	Nonaccess site Major bleedings (REPLACE 2 trial criteria)	9
CACHET	1998–2000	Single center, RCT	Elective	1) Elective coronary exam; 2) >21 years of age	1) planned atherectomy; 2) acute myocardial infarction (MI) <24 h; 3) coronary intervention <6 months; 4) warfarin therapy; 5) stroke <2 years or with residual neurologic deficit; 6) intracranial neoplasm, aneurysm, or arteriovenous malformation; 7) active bleeding or recent surgery or trauma; 8) blood pressure > 180/100 mm Hg	Nonaccess site Major bleedings (study definition)	9
EUROMAX	NA	Multicentre RCT	STEMI	1) men and nonpregnant women; 2) 18 years or older; 3) symptoms with a presumed diagnosis of STEMI <12 h; 4) any of the following conditions: ST-segment elevation	1) bleeding diathesis or hematological disease or history of intracerebral mass, aneurysm, arteriovenous malformation, hemorrhagic stroke, intracranial hemorrhage or bleeding <t 2 weeks; 2) surgery <2 weeks;	All Major bleedings (study definition)- Access site bleedings	10

Published on behalf of The Society for Cardiovascular Angiography and Interventions (SCAI). Catheterization and Cardiovascular Interventions DOI 10.1002/ccd.

TABLE I. *Continued*

Study name	Enrolment year	Type	Study population	Inclusion	Exclusion	Bleeding definition (nonaccess)	Quality score
				of at least 1 mm in two contiguous leads on ECG, presumed new left bundle–branch block, or ST-segment depression of at least 1 mm in at least two leads in V1–V3 with a positive terminal T wave.; scheduled for angiography with the intention of performing primary PCI <2 h after the first medical contact.	3) warfarin (not if international normalized ratio known to be <1.5); 4) unfractionated heparin, low-molecular-weight heparin or bivalirudin before randomization; 5) Thrombolytic therapy <48 h; 6) Absolute contraindications or allergy that cannot be premedicated to iodinated contrast or to any of the study medications; 7) Contraindications to angiography, 8) pregnant or nursing mothers; 9) creatinine clearance <30 mL/min or dialysis; 10) Previous enrollment in this or other studies; 11) not available primary PCI-capable hospital; 12) Estimated body weight of >120 kg.		
HORIZON-AMI	2005–2008	Multicentre RCT	STEMI	1) 18 years or older; 2) symptom duration of 20–720 min; 3) ST-segment elevation of 1 mm or more in two or more contiguous leads, new left bundle branch block, or true posterior myocardial infarction	1) contraindications to study drugs; 2) previous administration of thrombolytic therapy, bivalirudin, GPI, low-molecular-weight heparin, or fondaparinux for the present admission; 3) use of warfarin; 4) history of bleeding diathesis, coagulopathy, heparin-induced thrombo cytopenia, intracerebral mass,aneurysm, arteriovenous malformation, or previous haemorrhagic stroke; 5) stroke or transient ischaemic attack <6 months or any permanent neurological deficit; 6) refusal to receive blood transfusions;7) gastrointestinal or genitourinary bleeding <2 months; 8) major surgery <6 weeks; 9) known platelet count of fewer than 100,000 cells per mm^3 or hemoglobin of lower than 100 g/L; 10) planned elective surgical procedure; 11) coronary stent implantation <30 days; 12) life expectancy <1 year	All Major bleedings (study definition)- Access site bleedings	**11**

TABLE I. *Continued*

Study name	Enrolment year	Type	Study population	Inclusion	Exclusion	Bleeding definition (nonaccess)	Quality score
ISAR -REACT 4	NA	Multicentre RCT	Angina or unstable angina with positive cardiac markers	1) Angina >20 min or recurrent episodes within 48 h; 2) increase of cardiac biomarkers; 3) coronary stenoses requiring PCI.	1) acute myocardial infarction <48 h; 2) cardiogenic shock; 3) pericarditis; 4) malignancy or other comorbid conditions with life expectancy <one year; 5) active bleeding or a bleeding diathesis or history; 6) any history of intracranial bleeding or structural intracranial abnormalities; 7) refusal to receive a transfusion;8) blood pressure >180/110 mm Hg despite therapy;9) planned staged PCI procedure within 30 days or PCI within the prior 30 days;10) hemoglobin <100 g/L, platelet count < 100 × 109 cells/L or >600 × 109 cells/L; 11) GFR <30 ml/min or serum creatinine >30 mg/L; 12) allergy or intolerance to any study drug or to stainless steel or to contrast media; 13) pregnancy; 14) coumarin within 7 days; 15) glycoprotein IIb/IIIa inhibitor <14 days, unfractionated heparin within 4 h, LMWH <8 h, and bivalirudin <24 h	All Major bleedings (study definition)- Access site bleedings	**10**
NAPLES III	NA	Single center, RCT	Elective PCI in biomarker negative patients at high risk of bleeding (risk score ≥10)	1) Age >18 years; 2) Bleeding risk score ≥10; 3) Procedure planned through the femoral approach; 4) angiographic evidence of de novo or restenotic lesions requiring revascularization; 5) Stable or unstable angina or documented silent ischemia; 6) Negative biomarkers of myocardial injury; 8) Double antiplatelet therapy; 7) Stable hemodynamic conditions	1) Bleeding risk score <10; 2) Pregnancy; 3) Ongoing or recent (<48 h) episode of STEMI or NSTEMI; 4) Negative biomarkers of myocardial injury; 5) Chronic dialysis and/or history or previous dialysis; 6) Hemodynamic instability requiring inotropic support or IABP; 7) Ongoing or recent (<7 days) treatment with glycoprotein IIb/IIIa inhibitors; 8) Ongoing or recent (6 months) bleeding or bleeding diathesis; 9) Recent (within 6 months) stroke; 10) History of heparin-induced thrombocitopenia; 11) Platelet count <100.000/mm3	All Major bleedings (study definition)- Access site bleedings	**9**
BRIGHT	2012–2013	Multicentre RCT	STEMI/NSTEMI patients with planned emergency PCI	1) 18 to 80 years old; 2) STEMI within 12 h of symptom onset, or within 12–24 h if ongoing chest pain, continuous ST elevation or new	1) Thrombolysis within 72 h; 2) Cardiogenic shock; 3) Any anticoagulant agents used within 48 h before randomization; 4) Active bleeding or bleeding diathesis; 5)	Nonaccess site Major bleedings (BARC 2,3-5 definition)	**9**

TABLE I. *Continued*

Study name	Enrolment year	Type	Study population	Inclusion	Exclusion	Bleeding definition (nonaccess)	Quality score
				LBBB; 3) NSTEMI within 72 h of symptom onset; 4) Planned emergency PCI; 5) Written informed consent before catheterization	Hemoglobin <100 g/L or platelet count <100 ×109/L; 6) Creatinine clearance <30 mL/min; 7) Known allergy to the study drugs or devices (including heparin induced thrombocytopenia)		
MATRIX-	Oct 2011–Nov 2014	Multicentre RCT	ACS or STEMI	For ACS all the three: 1) History consistent with new, or worsening ischemia, occurring at rest or with minimal activity; 2) Enrolment within 7 days of the most recent symptoms; 3) Planned coronary angiography with indication to PCI; At least 2 of the following: 1) ≥60 years old; 2) Troponin T or I or CK-MB above the upper limit of normal; 3) ECG changes compatible with ischemia, i.e., ST depression of ≥1 mm in two contiguous leads, T-wave inversion >3 mm, or any dynamic ST shifts For STEMI both: 1) Chest pain for >20 min with an ST-segment elevation ≥ 1 mm or greater in two or more contiguous leads, or with a new left bundle-branch block or with ST-segment depression of ≥1 mm in two or more of leads V1–3 with a positive terminal T wave; 2) Admission either within 12 h of symptom onset or between 12 and 24 h after onset with continuing ischemia or previous fibrinolytic treatment.	1) Patients who cannot give informed consent or have a life expectancy of less than 30 days; 2) Allergy or intolerance to bivalirudin or unfractionated heparin; 3) Treatment with low-molecular-weight heparin within the past 6 h; 4) Treatment with any glycoprotein inhibitor in the previous 3 days; 5) Absolute contraindications or allergy, that cannot be premedicated, to iodinated contrast or to any of the study medications, including both aspirin and clopidogrel; 6) Contraindications to angiography, including but not limited to severe peripheral vascular disease; 7) If it is known, a creatinine clearance less than 30 ml per minute or dialysis dependent; 8)Previous enrolment in this study PCI in the previous 30 days	Nonaccess site Major bleedings (BARC 2,3-5 definition)	**10**

TABLE II. *Continued*

Study	Study drug design	Dose Biva	Dose UFH	Biva N°	UFH N°	Follow-up max (days)	Biva mean age	UFH mean age	Biva male gender (%)	UFH male gender (%)	Biva DM (%)	UFH DM (%)	Biva GPIs (%)	UFH GPIs (%)	Biva radial (%)	UFH radial (%)
	IIbIIIa inhibitors)	infusion of 1.75 mg/kg per hour for the duration of the procedure														
BRIGHT	Periprocedural bivalirudin vs. UFH (bailout Gp IIbIIIa inhibitors)	0.75 mg/kg bolus + 1.75 mg/kg/h infusion	Heparin 100 U/kg bolus + additional dose if ACT <200 s	735	1459	365	57.3	58.2	82.7	81.9	22.9	21.4	4.4	52.8	78	79.9
MATRIX	Periprocedural bivalirudin vs. UFH (provisional Gp IIbIIIa inhibitors—bailout only in bivalirudin group)	0.75 mg per kg body weight bolus of bivaliruding, followed by infusion of 1.75 mg/kg per hour until completion of the PCI, then either stopped or prolonged (full dose for up to 4 h of at a reduced dose of 0.25 mg per kg per hour for >6 h) according to assignment	70–100 U/kg (or 50–70 U/kg in patients receiving glycoprotein IIbIIIa inhibitors)	3610	3603	30	65.4	65.4	75.7	75.7	22.6	21.8	4.6	25.8	49.8	49.9

TABLE II. Clinical Features of Patients in Included Studies

Study	Study drug design	Dose Biva	Dose UFH	Biva N°	UFH N°	Follow-up max (days)	Biva mean age	UFH mean age	Biva male gender (%)	UFH male gender (%)	Biva DM (%)	UFH DM (%)	Biva GPIs (%)	UFH GPIs (%)	Biva radial (%)	UFH radial (%)
ACUITY	Periprocedural bivalirudin or periprocedural bivalirudin + - planned Gp IIb-IIIa inhibitors for 12–18 h	0.75 mg/kg bolus infusion of 1.75 mg/kg per hour for the procedure duration	bolus of 60 IU/kg plus infusion of 12 IU/kg per hour	5228	2561	365	63	63	74	73	28	28	53	97	6.1	6.5
ARNO	Periprocedural bivalirudin vs. UFH + postprocedural protamine (provisional Gp IIbIIIa inhibitors)	0.75 mg/kg, followed by infusion of 1.75 mg/kg/h for the duration of the procedure	bolus of 100 IU/kg body weight; additional boluses for activated clotting 250 to 300	425	425	30	68.7	69.1	77	75	21	22	15	28	0	0
CACHET	Bivalirudin + provisional abciximab vs. UFH + planned abciximab	0.75 mg/kg bolus, infusion of 1.75 mg/kg/h for the procedure duration	70 U/kg bolus (maximum,7000 U), to achieve ACT 200 s	59	94	7	65	62	73	77	n.d.	n.d.	31	100	–	–
EUROMAX	Periprocedural bivalirudin vs. heparin (provisional Gp IIbIIIa inhibitors)	0·75 mg/kg and infusion of 1·75 mg/kg per h continuedfor at least 4 h after PCI	100 IU per kilogram or 60 IU per with a glycoprotein IIb/IIIa inhibitor or enoxaparin	1089	1109	30	61	62	73.7	77.6	11.7	15.3	11.5	69.1	46.8	45.2
HORIZON-AMI	Periprocedural Bivalirudin vs. UFH + planned Gp IIb-IIIa inhibitors	0·75 mg/kg and infusion of 1·75 mg/kg per h.	bolus of 60 IU/kg to an activated clotting time of 200–250 s	1800	1802	1095	59.8	60.7	77.1	76.1	16.5	17.3	7.2	94.5	6.2	5.9
ISAR - REACT 4	Bivalirudin vs. UFH + planned abciximab	0.75 mg/kg of bivalirudin, followed by an infusion of 1.75 mg/kg/hr for the duration of the procedure	bolus of 70 U/kg of unfractionated heparin	860	861	365	67.5	67.5	76.9	76.8	28.3	29.8	0	100	0.5	0.2
NAPLES III	Periprocedural bivalirudin vs. UFH (provisional Gp	Bolus of 0.75 mg/kg i.v. prior to the start of the procedure, followed by	70 U/kg i.v. prior to start the procedure	418	419	365	78	78	49.5	45.5	45.2	43	0.5	1.3	0.5	0.5

Published on behalf of The Society for Cardiovascular Angiography and Interventions (SCAI). Catheterization and Cardiovascular Interventions DOI 10.1002/ccd.

CLINICAL OUTCOME Nonaccess-Site Bleeding

Data on nonaccess site bleeding were available in 32,470 patients (99.6%). A nonaccess site bleeding occurred in 1005 (3.1%) of patients, with a significant lower rate of events in patients treated with bivalirudin (2.6% (466/18135) vs. 3.8% (539/14335), OR [95% CI] 5 0.68 [0.60–0.77], P < 0.00001, Phet 5 0.10), as shown in Fig. 2.

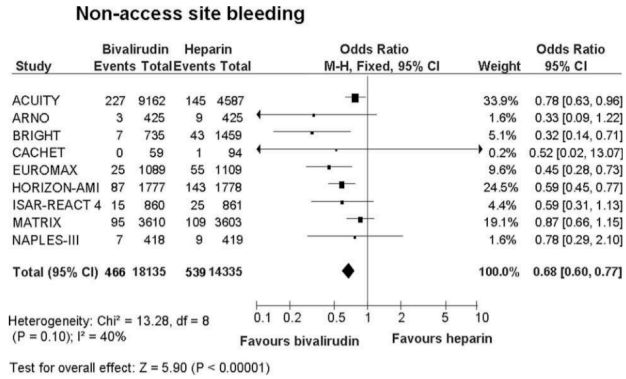


Fig. 2. Bivalirudin versus UFH on nonaccess site bleeding (within 30 days) with odds ratios and 95% confidence intervals (CI). The size of the data markers (squares) is approximately proportional to the statistical weight of each trial.

However, the benefits of bivalirudin on nonaccess site bleeding were mostly observed in patients with acute coronary syndromes (2.6% (456/ 17233) vs. 3.8% (520/13397), OR [95% CI] 5 OR [95% CI] 5 0.68 [0.60–0.78], P < 0.00001, Phet 5 0.04), whereas the difference did not reach a statistical significance among elective patients (1.1% (10 (902) vs. 2% (19/938), OR [95% CI] 50.55 [0.26–1.17], P50.12,Phet 5 0.59, P interaction 5 0.58).

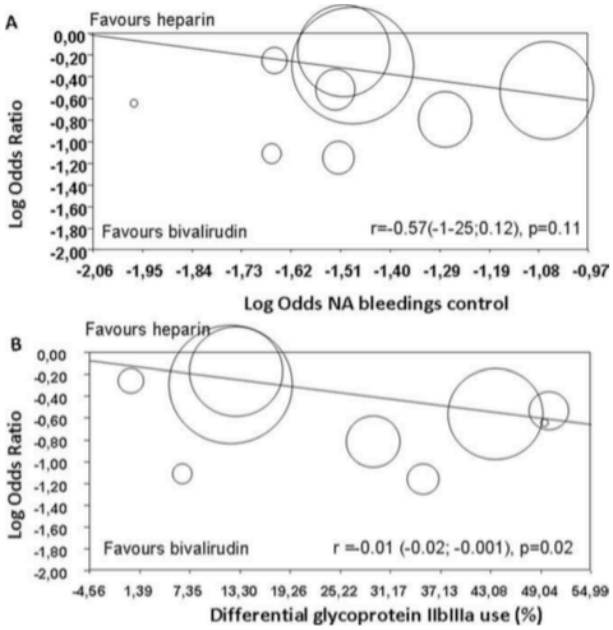


Fig. 3. Fixed-effect meta-regression analyses for the risk (OR) of nonaccess site bleeding between bivalirudin and UFH according to patients' risk profile (as log of the odds for bleeding in the control group; A—upper graph) or the differential use of glycoprotein IIbIIIa inhibitors in the two arms (B—lower graph). The size of the circle corresponds to the statistical weight of each study.

In fact, as shown in Fig. 3A, the reduction in non access-site bleeding with bivalirudin was not related with patients' risk profile [r520.57 (21–25; 0.12), P50.11]. However, the benefits of bivalirudin were more marked in those studies with larger use of glycoprotein IIb/IIIa inhibitors in association to heparin [r 5 20.01 (20.02; 20.001), P 5 0.02], Fig. 3B.

SECONDARY ENDPOINTS Access-Site Bleeding

Data on access site bleeding were available in 32,470 patients (99.6%). An access site bleeding occurred in 593 (1.8%) of patients, with a significantly lower rate of events in patients treated with bivalirudin (1.6% (282/18135) vs. 2.2% (311/14335), OR [95% CI] 5 0.67 [0.57–0.79], P < 0.000001, Phet 5 0.10).

These benefits, however, were restricted to the ACS population (1.6% (274/17233) vs. 2.2% (302/13397), OR [95% CI] 5 0.66 [0.56–0.78], P < 0.00001, Phet 5 0.16), and not confirmed among the elective subgroup (0.88% (8/902) vs. 0.85% (8/938), OR [95% CI] 5 1.02 [0.39–2.63], P 5 0.97, Phet 5 0.09, P inter- action 5 0.38). The reduction in access-site bleeding with bivalirudin was related neither with patients' risk profile (r 5 0.56 (20.39; 1.51), P 5 0.24) nor with the rate of transradial approach in control group (r5 20.88 (22.37; 0.97), P 5 0.35). However, the benefits of bivalirudin were more relevant in those studies with larger use of glycoprotein IIbIIIa inhibitors in association to heparin (r 5 20.02 (20.04; 20.004), P 5 0.017).

Overall Mortality

Data on overall mortality were available in 32,517 patients (99.8%). Death occurred in 597 (1.8%) of patients. As shown in Fig. 4, no difference in mortality was observed between bivalirudin and UFH (1.7% (310/18158) vs. 2% (287/14359), OR [95% CI]50.89 [0.76–1.05], P 5 0.18; Phet 5 0.12). No impact was observed either in ACS (1.7% (299/17256) vs. 2% (275/13421), OR [95% CI] 5 0.89 [0.75–1.06], P50.18, Phet50.18) or elective patients (1.2% (11/ 902) vs. 1.2% (12/938), OR [95% CI]50.92 [0.40– 2.09], P 5 0.84, Phet 5 0.05, P interaction 5 0.95).

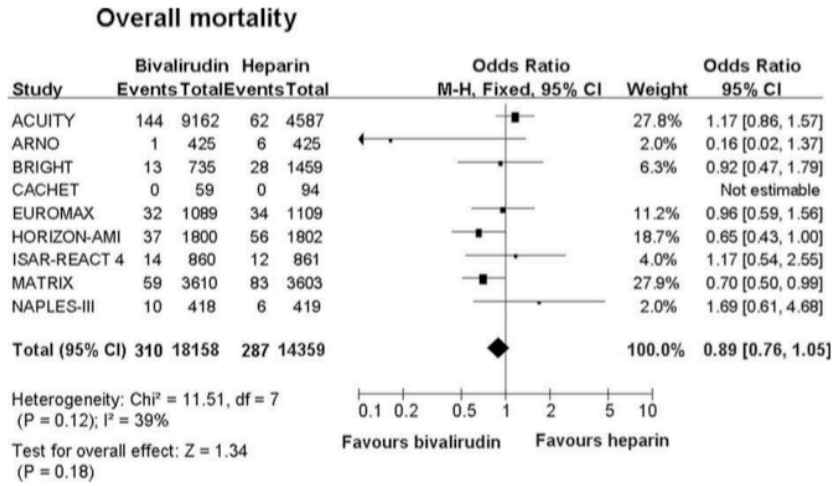


Fig. 4. Bivalirudin versus UFH on overall mortality (within 30 days), with odds ratios and 95% confidence intervals (CI). The size of the data markers (squares) is approximately proportional to the statistical weight of each trial.

By meta-regression analysis, the reduction in mortal- ity with bivalirudin was not related with the differential risk in nonaccess site bleeding (r50.21 (21,12; 1.53), P50.76, Fig. 5A), or access-site bleeding (r50.33 (20.35;1.02), P50.34, Fig. 5B) and neither with the differential rate of GPIIbIIIa inhibitors use (r50.007 (20.009; 0.01), P 5 0.88, Fig. 5C).

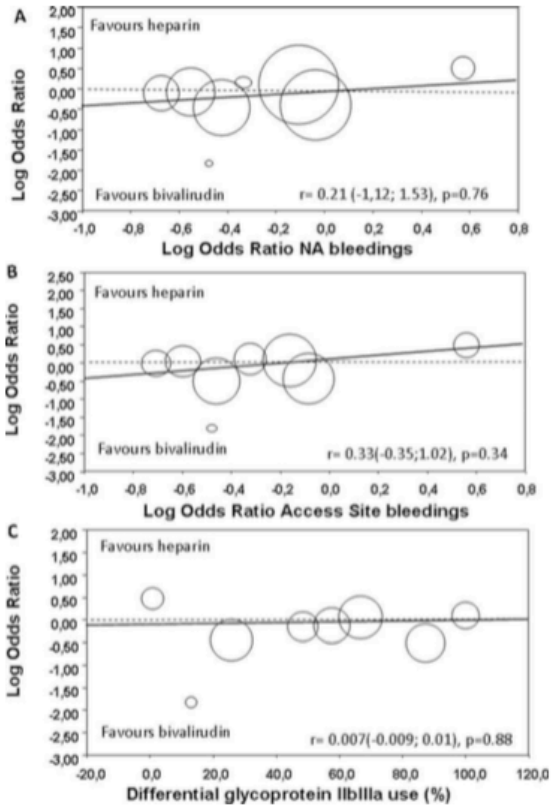


Fig. 5. Fixed-effect meta-regression analyses for the risk (OR) of mortality between bivalirudin and UFH according to the difference in nonaccess site bleeding (A; upper graph) or access-site of bleeding (B; mid graph) or use of GP IIbIIIa inhibitors (C, lower graph). The size of the circle corresponds to the statistical weight of each study.

DISCUSSION

This is the most comprehensive meta-analysis evaluating the impact of bivalirudin, as compared to heparin on non access-site bleeding in patients undergoing per-cutaneous coronary interventions. Our main finding is that bivalirudin provides a significant reduction in access and nonaccess site bleeding, that however did not translate into mortality benefits. Moreover, these findings were largely dependent on the use of GPII- bIIIa inhibitors in association to heparin rather than bivalirudin.

Bivalirudin has emerged in the last years as an anti- coagulation strategy alternative to heparin during PCI. In the first randomized trial (HAS [Hirulog Angioplas- ty Study]) [23] comparing bivalirudin with heparin in over 4000 patients undergoing

PCI for a recent acute coronary syndrome, bivalirudin was at least as effec- tive as UFH in preventing ischemic events, providing, nonetheless, a lower risk of bleeding.

However, the beneficial effects of bivalirudin on hemorrhagic complications have been questioned by the most recent BRAVE-4 and HEAT–PPCI trials [24, 25], and also in real-life registries. In particular, MacHaalany et al. [26], have reported that bivalirudin reduced both ischemic and bleeding events as com- pared to UFH in patients undergoing PCI through a femoral route, but not in the radial-treated patients, suggesting a potential interaction of access-site bleeding in conditioning the results of bivalirudin.

A similar hypothesis has also been confirmed in the recent MATRIX trial [21] that has included more than 7000 patients with ACS in a double randomized strategy comparing bivalirudin to heparin and transradial to transfemoral PCI. Valgimigli et al. showed that bivalirudin was comparable to heparin in terms of net clinical benefit, including major bleeding or major adverse cardiovascular event, additionally displaying a higher- than-expected rate of MI and stent thrombosis. However, independently from the anticoagulation strategy used for PCI, radial approach significantly lowered the occurrence of vascular bleeding thus suggesting that access-site complications could play only a marginal role in an era when transradial PCI is preferred also in more complex patients. A similar conclusion was reached by Perdoncin et al. [10] in a propensity score- matched population.

Nevertheless, nonaccess site bleeding represents the majority of hemorrhagic complications for patients undergoing PCI. In a previous patient-level analysis of three randomized trials, Verheugt et al. [7] concluded that nonaccess site bleeding, mainly with a genitouri- nary and gastrointestinal localization, could account for approximately two-thirds of all bleeding events after PCI, and this was associated

with a fourfold increase in 1-year mortality. Use of bivalirudin rather than hep- arin plus a glycoprotein IIb/IIIa inhibitor significantly decreased these events of up to 40%. A similar conclu- sion has been recently reached in a subgroup analysis of the ACUITY trial [27], where bivalirudin could pre- vent both access and nonaccess-site bleeding only in patients treated with transfemoral PCI, whilst not reaching statistical significance, in transradial group, also for nonaccess site bleeding. However, the small sample size might have conditioned these findings. Moreover, also in the larger transfemoral cohort, the rate of nonaccess hemorrhagic complications was markedly increased in the arm receiving bivaliru- din 1 GPIIbIIIa rather than bivalirudin alone (3.8 vs. 2.7%), thus suggesting that these findings could be related to the use of more potent antithrombotic thera- pies rather than to bivalirudin vs. heparin. However, no study has ever explored this topic.

This is the largest meta-analysis conducted so far evaluating the impact of these two different anticoagu- lation strategies for PCI on the occurrence of nonac- cess site bleeding. We found a significant lower rate of both access and nonaccess site hemorrhagic complications with bivalir- udin as compared to heparin. However, the benefits of bivalirudin were greatly influenced by the larger use of glycoprotein IIbIIIa inhibitors only in the heparin arm. In fact, such benefits were restricted to the patients admitted for acute coronary syndromes, where the larg- er use of antiplatelet agents, and especially in the hepa- rin arm, might have played a relevant role in these findings. Moreover, bivalirudin did not provide any benefit in terms of overall mortality, and neither the survival was influenced by the reduction in access or nonaccess bleeding with bivalirudin.

Similar results have recently been reached in a meta- analysis by Cavender et al. [28], that has clearly shown that the positive effects of bivalirudin on overall major

bleeding could be observed only when glycoprotein IIb/ IIIa inhibitors were used predominantly in the UFH arm only, otherwise displaying no significant impact on bleeding.

Therefore, considering the uncertain benefits of bivalirudin vs. heparin in preventing bleeding complications, mainly driven by the differential use of concomitant antithrombotic therapies, and accounting for the lack of improvement in outcomes associated with this strategy, there is no evidence for supporting a routine use of bivalirudin as the most cost-effective strategy.

LIMITATIONS

A first limitation to our study can be considered the synthesis of heterogeneous trials, including a population of lower risk stable patients, but also patients with acute coronary syndromes or STEMI. Moreover, different definitions of major bleeding events were used in the included studies. However, no significant heterogeneity was observed in the results for all our study outcomes.

Another limitation can be considered the use of differential durations of bivalirudin administration, with or without extended post-PCI infusion and variations in the dosage of heparin in the control group However, in the majority of the included studies UFH was administered at similar dosages, ranging from 60 to 75 U/kg.

Finally, the lack of individual patients' data did not allow a subgroup analysis, and therefore we could not fully address the role of GPIIbIIIa inhibitors administration or other patients' clinical and demographic characteristics, such as age or renal failure, that are known to potentially condition the risk of hemorrhagic complications [29].

CONCLUSIONS

The present meta-analysis shows that bivalirudin can provide a significant reduction of both access and nonaccess site bleeding in patients undergoing PCI. However, these hemorrhagic benefits did not impact on survival, and moreover, were significantly conditioned by the association of heparin with potent antithrombotic strategies, such as glycoprotein IIbIIIa inhibitors, rather than by heparin or bivalirudin alone. Therefore, we could not provide any clinical evidence for the routine use of bivalirudin as preferred anticoagulation strategy for PCI.

REFERENCES

1. Navarese EP, De Luca G, Castriota F, et al. Low-molecular- weight heparins vs. unfractionated heparin in the setting of percu- taneous coronary intervention for ST-elevation myocardial infarction: a meta-analysis. J Thromb Haemost 2011;9:1902–1915.

2. De Luca G, Navarese EP, Cassetti E, et al. Meta-analysis of randomized trials of glycoprotein IIb/IIIa inhibitors in high-risk acute coronary syndromes patients undergoing invasive strategy. Am J Cardiol 2011;107:198–203.

3. Verdoia M, Schaffer A, Barbieri L, et al. Optimal duration of dual antiplatelet therapy after DES implantation: A meta- analysis of 11 randomized trials. Angiology 2016;67:224–238.

4. Valgimigli M, Gagnor A, Calabr o P, et al. Radial versus femo- ral access in patients with acute coronary syndromes undergoing invasive management: A randomized multicentre trial. Lancet 2015;385:2465–2476.

5. De Luca G, Schaffer A, Wirianta J, et al. Comprehensive meta- analysis of radial vs femoral approach in primary angioplasty for STEMI. Int J Cardiol 2013;168:2070–2081.

6. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients present- ing without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:2129–2200.

7. Verheugt FW, Steinhubl SR, Hamon M, et al. Incidence, prog- nostic impact, and influence of antithrombotic therapy on access and nonaccess site bleeding in percutaneous coronary interven- tion. JACC Cardiovasc Interv 2011;4:191–197.

8. Manoukian SV, Feit F, Mehran R, et al. Impact of major bleed- ing on 30-day mortality and clinical outcomes in patients with acute coronary syndromes. An Analysis from the ACUITY Tri- al. J Am Coll Cardiol 2007;49:1362–1368.

9. Hamon M, Coste P, Van't Hof A, et al. Impact of arterial access site on outcomes after primary percutaneous coronary interven- tion: Prespecified subgroup analysis from the EUROMAX trial. Circ Cardiovasc Interv 2015;8:e002049.

10. Perdoncin E, Seth M, Dixon S, et al. The comparative efficacy of bivalirudin is markedly attenuated by use of radial access: Insights from Blue Cross Blue Shield of Michigan Cardiovascu- lar Consortium. Eur Heart J 2015. [Epub ahead of print]

11. Baklanov DV, Kim S, Marso SP, et al. Comparison of bivaliru- din and radial access across a spectrum of preprocedural risk of bleeding in percutaneous coronary intervention: Analysis from the national cardiovascular data registry. Circ Cardiovasc Interv 2013;6:347–353.

12. Biondi-Zoccai GG, Abbate A, Agostoni P, et al. Stenting versus surgical bypass grafting for coronary artery disease: Systematic overview and meta-analysis of randomized trials. Ital Heart J 2003;4:271–280.

13.Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA state- ment for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. Ann Intern Med 2009;151:W65–W94.

14. Stone GW, White HD, Ohman EM, et al. Bivalirudin in patients with acute coronary syndromes undergoing percutaneous coro- nary intervention: A subgroup analysis from the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial. Lancet 2007;369:907–919.

15.Parodi G, Migliorini A, Valenti R, et al. Comparison of bivalir-udin and unfractionated heparin plus protamine in patients with coronary heart disease undergoing percutaneous coronary inter- vention (from the Antithrombotic Regimens aNd Outcome [ARNO] trial). Am J Cardiol 2010;105:1053–1059.

16.Han Y, Guo J, Zheng Y, et al. Bivalirudin vs heparin with or without tirofiban during primary percutaneous coronary inter- vention in acute myocardial infarction: The BRIGHT random- ized clinical trial. JAMA 2015;313:1336–1346.

17.Lincoff AM, Kleiman NS, Kottke-Marchant K, et al. Bivalirudin with planned or provisional abciximab versus low-dose heparin and abciximab during percutaneous coronary revascularization: Results of the Comparison of Abciximab Complications with Hirulog for Ischemic Events Trial (CACHET). Am Heart J 2002;143:847–853.

18.Steg PG, van 't Hof A, Hamm CW, et al. Bivalirudin started during emergency transport for primary PCI. N Engl J Med 2013;369:2207–2217.

19.Stone GW, Witzenbichler B, Guagliumi G, et al. Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): Final 3-year results from a multicentre, randomised controlled trial. Lancet 2011; 25377:2193–2204.

20.Shulz S, Kastrati A, Ferenc M, et al. One-year outcomes with abciximab and unfractionated heparin versus bivalirudin during percutaneous coronary interventions in patients with non-ST- segment elevation myocardial infarction: Updated results from the ISAR-REACT 4 trial. EuroIntervention 2013;9:430–436.21. 21.Valgimigli M, Frigoli E, Leonardi S, et al. Bivalirudin or unfractionated heparin in acute coronary syndromes. N Engl J Med 2015;373:997–1009.22.

22.Briguori C, Visconti G, Focaccio A, et al. Novel approaches for preventing or limiting events (Naples) III trial: Randomized comparison of bivalirudin versus unfractionated heparin in patients at increased risk of bleeding undergoing transfemoral elective coronary stenting. JACC Cardiovasc Interv 2015;8:414–

23.Bittl JA, Chaitman BR, Feit F, et al. Bivalirudin versus heparin during coronary angioplasty for unstable or postinfarction angi- na: Final report reanalysis of the Hirulog Angioplasty Study. Am Heart J 2001;142:952–959.

24.Schulz S, Richardt G, Laugwitz KL, et al. Prasugrel plus bivaliru- din vs. clopidogrel plus heparin in patients with ST-segment elevation myocardial infarction. Eur Heart J 2014;35:2285–2294.

25.Shahzad A, Kemp I, Mars C, et al. Unfractionated heparin ver- sus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): An open-label, single centre, randomised con- trolled trial. Lancet 2014;384:1849–1858.

26.MacHaalany J, Abdelaal E, Bataille Y, et al. Benefit of bivaliru- din versus heparin after transradial and transfemoral percutane- ous coronary intervention. Am J Cardiol 2012;110:1742–1748.

27.Hamon M, Rasmussen LH, Manoukian SV, et al. Choice of arterial access site and outcomes in patients with acute coronary syndromes managed with an early invasive strategy: The ACU- ITY trial. EuroIntervention 2009;5:115–120.

28.Cavender MA, Sabatine MS. Bivalirudin versus heparin in patients planned for percutaneous coronary intervention: A meta-analysis of randomised controlled trials. Lancet 2014; 384: 599–606.

29.De Luca L, Tomai F, Verdoia M, et al. Evaluation and management of special subgroups after primary percutaneous coronary intervention. Am Heart J 2010;160: S22–S27.

Chapter 6:

Bleeding events and maintenance dose of prasugrel:

BLESS pilot study.

Nazario Carrabba, MD, Guido Parodi, MD, Rossella Marcucci, MD $, Renato Valenti, MD, Anna Maria Gori, BD $*, Angela Migliorini, MD, Vincenzo Comito, MD, Benedetta Bellandi, MD, Rosanna Abbate, MD§, Gian Franco Gensini, MD$*, David Antoniucci, MD.

From Department of Cardiology, Careggi Hospital, Florence Italy

$ Department of Experimental and Clinical Medicine, University of Florence Italy

*Don Gnocchi Foundation, Florence Italy

Open Heart. 2016 Oct 31;3(2)

ABSTRACT

Aims The optimal level of residual platelet reactivity (RPR) with prasugrel may change over time after an acute coronary syndrome (ACS). To evaluate changes in RPR over time, and bleeding and ischemic events rate using 5 vs. 10 mg maintenance dose (MD) regimens of prasugrel in ACS patients 1 month after drug eluting stent (DES) implantation.

Methods and results: After 60 mg loading dose of prasugrel (T0) followed by 10 mg/day for 1 month, patients were randomized to receive prasugrel 10 mg/day (n=95, group A) or 5 mg/day MD (n=98, group B) up to 1 year. RPR was assessed by light transmittance aggregometry at T0, 37 (T1) and 180 days (T2) in 152 patients. The primary endpoint was BARC bleeding events ≥2 between 1 and 12 months, and the secondary composite exploratory endpoint was cardiac death, myocardial infarction, stroke, and definite/probable stent thrombosis (ClinicalTrial.gov identifier: NCT1790854). The trial was prematurely stopped after enrolling 193 of 450 planned patients due to lower than expected event rates. Baseline clinical characteristics of two arms were well matched as well as RPR (T0). From T0 to T1, RPR significantly increased in both group A and B and the increase was higher for group B (delta ADP 10 μmol: 13.8%±14.7% vs. 23.5%±19.2%, p=0.001). At T2 a lower rate of high RPR patients were found in group A (2.6% vs.13.3%; p=0.014). The BARC type ≥2 bleeding occurred in 12.6% of group A vs. 4.1% of group B (OR: 0.29, 95% CI 0.09-0.94) and the secondary endpoint in 2.1% vs. 1.0% (p=0.542), respectively. No definite/probable stent thrombosis occurred.

Conclusions: RPR increases from T0 to T1 with a further increase of RPR reducing prasugrel MD to 5 mg compared to 10 mg/day 1 month after ACS. This strategy might be able to optimize the risk/benefit profile of prasugrel MD, being it associated with a 71%

risk reduction in BARC type ≥2 bleedings without any apparent increase in thrombotic events.

INTRODUCTION

The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI-38) study showed that in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) the use of prasugrel translated into reduced ischemic event rate but it was also associated with increased major bleeding rate compared with clopidogrel (1). Furthermore, the FDA review of TRITON study (2) highlighted that the risk-benefit appears to be greatest early in therapy with prasugrel, with fewer end points prevented per bleed as therapy is continued. In addition, the increase of residual platelet reactivity (RPR) after early period of ACS (3,4) and the association between bleeding events and low RPR are well known (5). Thus, the optimal level of platelet inhibition with prasugrel may change over time after an ACS. Therefore, switching from prasugrel 10 mg/day maintenance dose (MD) to 5 mg/day MD 1 month after the index event may be considered as able to reduce bleeding events. We sought to evaluate RPR change over time and the occurrence of bleeding and ischemic events using reduced MD of prasugrel (5 vs. 10 mg) in ACS patients 1 month after drug eluting stents (DES) implantation.

METHODS

Study design and population

The BLESS (Bleeding Events and Maintenance Dose of Prasugrel) trial was an open label, randomized, single centre study, designed to evaluate whether 1-month after PCI for ACS the shifting of prasugrel MD from 10 mg to 5 mg/day may reduce bleeding events. A detailed description of the study design (Figure S1) and methods (purpose, inclusion and exclusion criteria, end points, and sample size) is provided

in the supplementary appendix. Briefly, all ACS patients (≤ 75 years) underwent 2nd or 3th generation DES implantation and received 60 mg loading dose (T0) of prasugrel followed by 10 mg/day for 1 month. Thereafter, patients confirmed to be adherent to prasugrel therapy were randomized to receive prasugrel 10 mg/day (group A) or 5 mg/day MD (group B) up to 1 year. All patients received 325 mg of aspirin followed by 100 mg/day for at least 1 year. RPR was assessed by light transmittance aggregometry at T0, 37 (T1) and 180 days (T2) (6). The study was supported by the investigators (ClinicalTrial.gov identifier: NCT1790854). The protocol was approved by local investigational review boards and performed in compliance with good clinical practice and the Declaration of Helsinki. All patients provided signed informed consent prior to any study procedure.

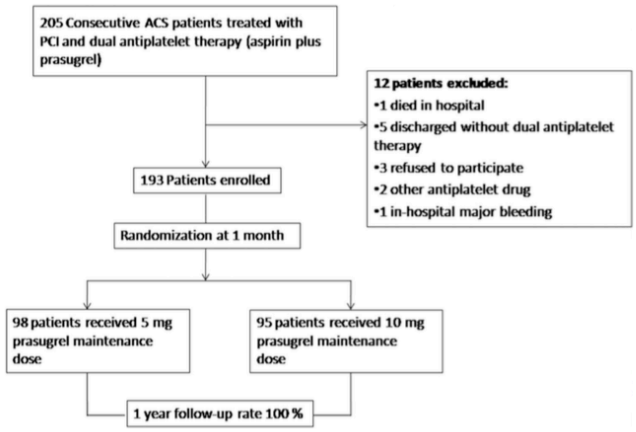


Figure 1 BLESS trial flow chart. ACS, acute coronary syndrome; BLESS, Bleeding Events and Maintenance Dose of Prasugrel; PCI, percutaneous coronary intervention.

Study endpoints. The safety primary endpoint was the occurrence of bleeding type ≥2 events according to the Bleeding Academic Research Consortium (BARC) criteria (7), during the randomized treatment period (from month 1 to month 12). The secondary

composite exploratory endpoint was cardiac death, myocardial infarction (MI), or stroke (6). Other secondary end points of the study were: 1) the occurrence of definite or probable stent thrombosis from 1 to 12 months (8); 2) the pharmacodynamic response in patients with MD prasugrel 10 mg/day compared with those who were randomized to MD prasugrel 5 mg/day; 3) the incidence of high RPR patients defined as ADP 10 μmol ≥70%. More detailed definitions of the end points are provided in the supplementary appendix.

Data management. In-hospital adverse events were recorded before discharge. One-month, 6-month and 12-month clinical follow-up data were obtained in outpatient consultation. Adverse clinical events were independently adjudicated by an external clinical event committee whose members were unaware of the group assignments. All source documents concerning events were provided to the clinical event committee, for accuracy and completeness.

Statistical analysis. Discrete data were summarized as frequencies, whereas continuous data as mean ± SD or median. The Chi-square test or Fisher's exact test were used for comparison of categorical variables, and the unpaired 2-tailed Student's *t*- test or Kolmogorov-Smirnov nonparametric test were used to test differences among continuous variables for the end point. Odds risk (OR) and 95% confidence interval (CI) were calculated. The time course of changes of RPR between and within groups was made by ANOVA analysis. BARC bleeding event-free survival was estimated by the Kaplan-Meier method. The log-rank test was used to compare BARC type ≥2 bleeding between patients treated with prasugrel 5mg/day MD and patients treated with prasugrel 10 mg/day MD. All tests were 2-sided and a $P< 0.05$ was considered significant. All analyses were performed using the software package SPSS 19.0 (SPSS Inc., Chicago, Il).

RESULTS

Due to fewer than expected events, the trial was prematurely stopped after enrolling 193 of 450 planned patients. Thus, between November 2012 and April 2014 a total of 193 patients were enrolled in the BLESS study (study flow, figure 1): 95 patients randomized to prasugrel MD 10 mg/day (group A) and 98 to prasugrel MD 5 mg/day (group B). Baseline clinical characteristics of two arm's patients were well matched (see Table 1). The incidence of diabetes, female gender, chronic renal failure, previous PCI and CABG, and reduced left ventricular ejection fraction were not different between two group patients. Overall, 29% presented with acute myocardial infarction. Moreover, 61% of patients showed multivessel coronary artery disease and 15% left main disease (Table 2). All patients underwent PCI using 2nd and 3th generation DES, with a mean of 1.5± 0.7 vessel treated, and with a mean stent length of 31±21 mm. At hospital discharge, the medical therapy prescribed was similar between groups.

Table 1 Baseline characteristics and clinical presentation at hospital admission of study population

Variables	Group A (10/10) (n=95)	Group B (10/5) (n=98)	All (n=193)	p Value
Age, years	62.2±10.0	62.2±10.2	62.2±10.1	0.992
Female gender	13 (13.7)	14 (14.3)	27 (14.0)	0.904
Body mass index, kg/m^2	27.5±3.3	27.2±3.6	27.3±3.4	0.505
Body mass index ≥30	26 (27.4)	20 (20.4)	46 (23.8)	0.311
Diabetes mellitus	29 (30.5)	21 (21.4)	50 (25.9)	0.149
Hyperlipidaemia	48 (50.5)	43 (43.9)	91 (47.2)	0.355
Smoker	29 (30.5)	39 (39.8)	68 (35.2)	0.178
Hypertension	55 (57.9)	56 (57.1)	111 (57.5)	0.916
Previous MI	24 (25.3)	17 (17.3)	41 (21.2)	0.179
Previous PCI	32 (33.7)	28 (28.6)	60 (31.1)	0.443
Previous CABG	5 (5.3)	3 (3.1)	8 (4.1)	0.443
Chronic renal failure	8 (8.6)	4 (4.1)	12 (6.3)	0.205
LV ejection fraction (%)	51.8±9.0	52.8±9.4	52.3±9.2	0.429
LV ejection fraction ≤40%	12 (12.6)	12 (12.2)	24 (12.4)	0.935
STEMI	29 (30.5)	27 (27.6)	56 (29.0)	0.649

Values are expressed as mean±SD or n (%).
MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LV, left ventricular; STEMI, ST-elevation myocardial infarction.

Table 2 Angiographic, procedural characteristics and discharge therapy of study population

Variables	Group A (10/10) (n=95)	Group B (10/5) (n=98)	All (n=193)	p Value
Angiographic characteristics				
Multivessel coronary disease	61 (64.2)	57 (58.2)	118 (61.1)	0.389
Three-vessel coronary disease	30 (31.6)	25 (25.5)	55 (28.5)	0.350
Left main disease	14 (14.7)	15 (15.3)	29 (15.0)	0.912
Procedural characteristics				
Number of treated vessels	1.5±0.7	1.5±0.7	1.5±0.7	0.798
Total stent length, mm	49.0±35.7	41.4±29.7	45.2±33.0	0.107
Stent length per culprit vessel, mm	33.4±23.6	28.7±18.0	31.0±21.0	0.118
Number of stents per patient	2.3±1.3	2.0±1.2	2.2±1.3	0.145
Number of stents per culprit vessel	1.6±0.8	1.4±0.7	1.5±0.8	0.179
Multivessel PCI	39 (41.1)	38 (38.8)	77 (39.9)	0.747
DES	95 (100)	98 (100)	193 (100)	–
Second-generation DES	72 (75.8)	70 (71.4)	142 (73.5)	0.492
Everolimus Eluting Stent (Xience)	65 (90.3)	59 (85.5)	124 (87.9)	0.233
Everolimus Eluting Platinum Chromium Stent (Promus Element Plus)	6 (8.3)	9 (13.0)	15 (10.6)	0.365
Zotarolimus Eluting Stent (Resolute Integrity)	1 (1.4)	2 (2.9)	3 (2.1)	0.535
Third-generation DES	23 (24.2)	28 (28.6)	51 (26.4)	0.492
Biodegradable polymer biolimus-eluting stent (Nobori)	10 (43.5)	9 (32.1)	19 (37.3)	0.405
BioFreedom Polymer-Free (Cre8)	13 (56.5)	19 (67.9)	32 (62.7)	0.405
GP inhibitors IIb/IIIa	18 (18.9)	23(23.5)	41 (21%)	0.442
Discharge therapy				
Aspirin	95 (100)	98 (100)	193 (100)	–
Statins	92 (96.8)	92 (93.9)	184 (95.3)	0.329
ACE inhibitors or ARBs	67 (70.5)	78 (79.6)	145 (75.1)	0.145
β-blockers	70 (73.7)	60 (61.2)	130 (67.4)	0.065
Proton pump inhibitors	78 (82.1)	71 (72.4)	149 (77.2)	0.110
Hospital length of stay, day	3.4±2.0	3.7±5.9	3.5±4.4	0.544

Values are expressed as mean±SD or n (%).
ARBs, angiotensin receptor blockers; DES, drug-eluting stent; GP, glycoprotein; PCI, percutaneous coronary intervention.

Pharmacodynamic findings. Out of 193 patients, RPR was assessed in 152, since 41 patients receiving IIb/IIIa inhibitors during the PCI procedures were excluded. The RPR at T0 were similar between group A and group B (ADP 10 µmol: 34.5±16.2 vs. 31.5±17.2; p=0.697, respectively). Out of 152, 2 (1.3%) high RPR patients were found. From T0 to T1, the RPR significantly increased in group A as well as in group B and the increase was higher for group B (delta ADP 10 µmol: 13.8%±14.7% vs. 23.5%±19.2%, p=0.005), but from T1 to T2 no further increase of RPR was found in both groups (see ANOVA analysis in Figure 2). At T2 a lower rate of high RPR patients were found in group A compared with the group B (2.6% vs.13.3%; p=0.014).

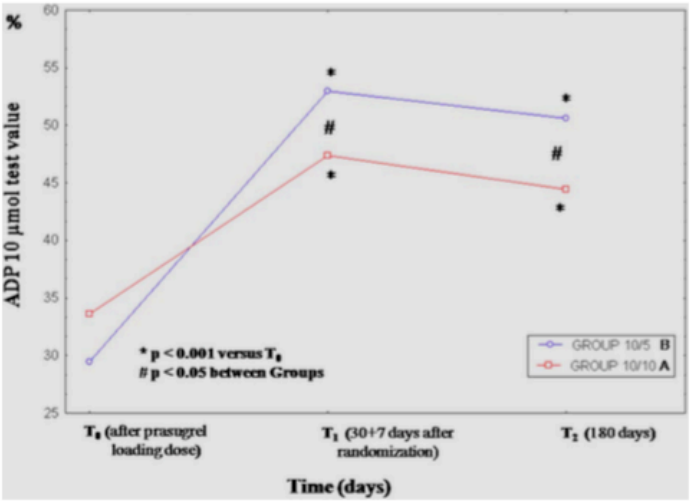


Figure 2 Time course and magnitude of changes of RPR within group B prasugrel 10/5 mg/day (—○—) and group A prasugrel 10/10 mg/day (—□—) and between groups. RPR, residual platelet reactivity.

Safety primary end points. Any BARC bleedings were observed in 47.3% and 31.6% of group A and B, (p= 0.025); the BARC type 1 or 2 bleeding occurred in 45.3% vs. 29.6% (p =0.024), the BARC type 2 in 10.5% and 2% (p= 0.014), the BARC type 3a in 2.1% vs. 2.0% (p=0.974), and the BARC type 2 or 3a in 12.6% and 4.1% (OR: 0.29, 95% CI 0.09-0.94; p= 0.031), respectively (see Table 3). No BARC type 4 or 5 occurred. Event-free survival from BARC type ≥2 bleeding during randomization period is shown in Figure 3. Freedom from BARC type ≥2 bleeding events was higher in 5 mg/day prasugrel MD arm in comparison with 10 mg/day prasugrel MD arm (log-rank test, p=0.030).

Table 3 Clinical outcomes during randomisation period (from 1 to 12 months)

Variables	Group A 10/10 (n=95)	Group B 10/5 (n=98)	All (n=193)	OR	95% CI	p Value
Primary safety end points						
BARC						
Any bleeding	45 (47.3)	31 (31.6)	76 (39)	0.51	0.28 to 0.92	0.025
Type 1	33 (34.7)	27 (27.5)	60 (31.0)	0.71	0.39 to 1.31	0.280
Type 2	10 (10.5)	2 (2.0)	12 (6.2)	0.17	0.03 to 0.83	0.014
Type 1 and 2	43 (45.3)	29 (29.6)	72 (37.3)	0.51	0.28 to 0.91	0.024
Type 3						
Type 3a	2 (2.1)	2 (2.0)	4 (2.0)	0.96	0.13 to 7.02	0.974
Type 3b	0 (0)	0 (0)	0 (0)	–	–	–
Type 3c	0 (0)	0 (0)	0 (0)	–	–	–
Type 2 and 3	12 (12.6)	4 (4.1)	16 (8.2)	0.29	0.09 to 0.94	0.031
Type 4	0 (0)	0 (0)	0 (0)	–	–	–
Type 5						
Type 5a	0 (0)	0 (0)	0 (0)	–	–	–
Type 5b	0 (0)	0 (0)	0 (0)	–	–	–
Secondary efficacy composite end points						
MACE	2 (2.1)	1 (1.0)	3 (1.6)			0.542
Cardiac death	0 (0)	0 (0)	0 (0)			–
Myocardial infarction	1 (1.1)	1 (1.0)	2 (1.0)			0.982
TIA or stroke	1 (1.1)	0 (0)	1 (0.5)			0.309
Other secondary end points						
Definite/probable stent thrombosis	0 (0)	0 (0)	0 (0)	–	–	–
Prasugrel discontinuation*	2 (2.1)	0 (0)	2 (1.0)			0.149
Non cardiac death†	1 (1.1)	0 (0)	1 (0.5)			0.309
Urgent TVR	1 (1.1)	0 (0)	1 (0.5)			0.309
Angiographic sixth month follow-up	83 (87.4)	79 (80.6)	162 (83.9)			0.201
Definite stent thrombosis	0 (0)	0 (0)	0 (0)	–	–	–
Restenosis	13 (15.7)	8 (10.1)	21 (13.0)			0.294

Values are expressed as mean±SD or n (%).
*Gastric bleeding at 6 months and haemorrhagic stroke at 7 months.
†Creutzfeldt-Jakob disease.
BARC, Bleeding Academic Research Consortium; MACE, major adverse cardiovascular event; TIA, transient ischaemic attack; TVR, target vessel revascularisation.

Efficacy secondary end points. The secondary composite endpoint occurred in 2.1% of group A (1 MI, 1 stroke) vs. 1.0% of group B (1 MI), p= 0.542 (see Table 3). Considering the balance of safety and efficacy end point, the net clinical benefit was in favor of group B: 14.7 vs. 5.1%; (OR:0.31, 95% CI 0.10-0.90, p= 0.024). Urgent target vessel revascularization rate were very low in both groups: 1 (1.1%) in group A vs. 0 (0%) in group B (p= 0.309). No definite or probable stent thrombosis occurred in both groups [clinical follow-up rate 100%, 6-month angiographic follow-up rate 83.9% (162/193)]. During the randomization period, two patients, both in group A, discontinued prasugrel: a gastric bleeding occurred at 6 month in the first patient and a hemorrhagic stroke occurred at 7 months in the second.

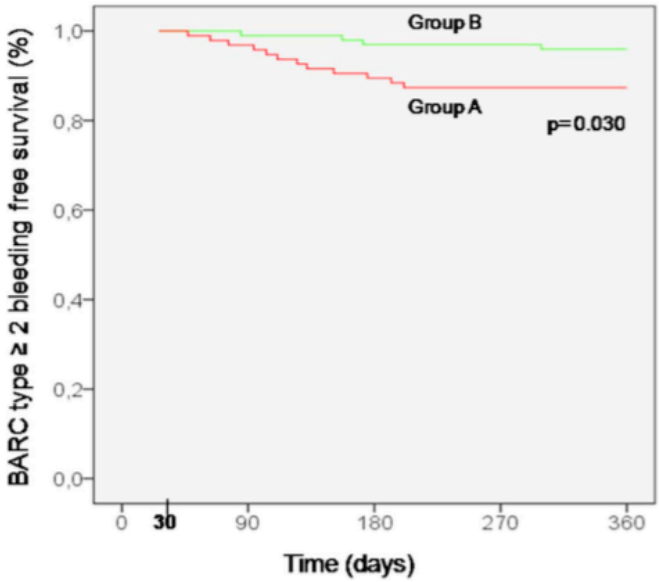


Figure 3 BARC type ≥2 bleeding-free survival according to the treatment with 5 mg/day prasugrel MD group B (—), or 10 mg/day prasugrel MD group A (—). Event rates were compared by log-rank test. BARC, Bleeding Academic Research Consortium; MD, maintenance dose.

DISCUSSION

This study is, to our knowledge, the first randomized comparison of prasugrel 5 mg MD and 10 mg MD, 1 month after an ACS event. The main findings of the study are the following: 1) in aspirin ACS patients at steady state for MD prasugrel 10 mg, values of RPR significantly increase in comparison with those obtained soon after 60 mg prasugrel LD; 2) 1 month after an ACS event switching prasugrel MD from 10 to 5 mg/day is associated with further increase in RPR, resulting in a higher rate of high RPR patients; 3) this strategy is associated with a 71% risk reduction in BARC type ≥2 bleeding without any apparent increase in thrombotic events.

Pharmacodynamic findings. A 5 mg/day prasugrel MD was used in the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute

Coronary Syndromes (TRILOGY ACS) trial (9) to reduce bleeding complications in the vulnerable groups of elderly (>75 years) patients and younger, low-body-weight patients (<60 Kg). RPR values of patients less than 60 Kg and 75 years or older with stable coronary artery disease, close to 2-weeks of prasugrel MD 5 mg/day therapy was non-inferior to prasugrel MD 10 mg/day used in younger, heavier patients, as determined by conventional platelet aggregometry (10,11). The antiplatelet effects of the prasugrel MD 5 mg/day were greater than the effects with clopidogrel among both the elderly and younger patients with low body weight. These pharmacodynamic findings were confirmed in the larger TRILOGY platelet function substudy using the VerifyNow P2Y12 assay (12). Direct pharmacodynamic data to support the potential use of prasugrel MD 5 mg/day to reduce bleeding risk without an increase in the ischemic risk in ACS patients (≤75 years old) 1 month after 60 mg prasugrel LD for PCI are lacking. In the present study, we reported that the RPR increases between loading dose and 1 month, and an excess of RPR was found after shifting prasugrel MD from 10 to 5 mg/day. Whether, 1 month after index PCI for ACS, this level of RPR may represent the optimal platelet inhibition, where efficacy is maintained but bleeding risk is lower is not proven. High on treatment RPR is well defined for clopidogrel and has been clearly identified as a risk marker for ischemic events (13). High on treatment RPR can also exist with prasugrel in ACS after a LD of 60 mg and to a lower extent (<6% of treated patient) on the MD of 10 mg (14). Recent randomized trials as well as registry designed to evaluate whether more intensive antiplatelet therapy in acute phase, using high dose clopidogrel (15,6) or prasugrel (16,17), might improve clinical outcome failed to show the benefit of this strategy. Differently, the present study was designed to evaluate the possibility to optimize level of platelet inhibition obtained with prasugrel after the acute phase of

ACS, focusing the concept that the optimal level of platelet inhibition may change over time.

Safety primary end points. The adoption of the strategy reducing MD of prasugrel from 10 to 5 mg/day might be able to optimize the risk/benefit profile of prasugrel in ACS patients 1 month after 2nd or 3th generation DES implantation. In fact, a 49% risk reduction in any BARC bleedings is associated with this strategy. Specifically, in the present study the most common bleedings are BARC type 1. However, nuisance-bleeding type 1 occurrence seems to be not significantly influenced by a reduced prasugrel MD strategy. On the contrary, an 83% risk reduction in BARC type 2 bleedings and, yet, a 71% risk reduction in BARC ≥2 were associated with reduced prasugrel MD strategy. These findings are not negligible, since the occurrence of BARC type 2 bleedings, even minor, may be clinically relevant hurting patient day life and potentially reducing patient adherence to treatment with new antiplatelet agents such as prasugrel, favouring its disruption with potential consequences on ischemic events (18). Moreover, in the present study no discontinuation of prasugrel MD 5 mg was observed. Conversely, two patients taking 10 mg MD discontinued prasugrel, without occurrence of ischemic event, confirming that the association between discontinuation of dual anti-platelet therapy, due to bleeding, and increased thrombotic risk is very strong within 30 days (18). Finally, in the BLESS study the BARC ≥ 2 bleeding event curves begin to separate soon after randomization period and continue to diverge throughout the follow-up favouring prasugrel MD 5 mg/day (Figure 3), in keeping with previous and recent observations (19,20).

Efficacy secondary end points. Regarding the secondary exploratory efficacy end points, it is important to note that the efficacy of the strategy using reduced MD of prasugrel seems preserved in our study. In fact, limited by the small number of

patients included, we did not observe any increase in thrombotic events using prasugrel MD 5 mg/day. Surprisingly, we observed an impressive "0" rate of definite or probable stent thromboses in the BLESS study population. Compared with bare metal stent and first generation DES, the risk of definite or probable stent thrombosis is an average 50% lower with new generation DES (21,22). A significant reduction of stent thrombosis was observed in the TRITON (1) and in the Platelet Inhibition and Patient Outcomes (PLATO) (23) studies using first generation DES in only 40% and 19% of cases, respectively. It is conceivable that our study benefited from the use of 2nd and 3th generation DES. These devices were recently shown to be superior to the first-generation DES for both revascularization and clinical outcomes (24). This may be due to the fact that new generation DES with thin stent struts, advanced/absent polymers and improved anti-proliferation agents along with better implantation techniques available, promote an early healing of stent struts favouring a near "0" stent thrombosis. On this regard, it is important to note that the thrombotic risk of our study population was not low, taking into account that the BLESS study enrolled only ACS patients, including patients with STEMI. Finally, one should realize that in the early phase of an ACS, it is important to obtain and maintain an effective level of platelet inhibition. One month after an ACS, the optimal level of platelet inhibition may change and the adoption of a tailored strategy, using a reduced MD of prasugrel, might optimize the risk/benefit profile of prasugrel providing slightly less, but still consistent, platelet inhibition that translate into reducing bleeding risk without increasing the risk of thrombotic events related to the stent as well as occurring in other vascular location, as suggested by the net clinical benefit from our study. Whether the prolongation of dual antiplatelet therapy with aspirin plus reduced prasugrel MD may be beneficial beyond 1 year in

ACS patients remains to be investigated (20). Of course, we recognize that no definitive conclusions can be drawn from the BLESS study, however these findings can add some insights to the body of evidence of the dual antiplatelet therapy in ACS patient and may help us to customize the dual antiplatelet therapy according to the type of stent implanted in ACS patient (20,25).

Study limitations Due to the low events rate, the BLESS study was prematurely interrupted resulting in the enrolment in a population underpowered for clinical events. However, the observed 71% risk reduction of BARC Type ≥2 bleeding without any apparent increase of thrombotic events may be considered as a hypothesis-generating finding. Moreover, the pharmacodynamic data associated with this strategy in current PCI patients have never been described and may be clinically relevant. Importantly, one should realize that the BLESS results are obtained on aspirin ACS patients. Finally, whether the treatment benefit observed may be generalizable to non-thienopyridine P2Y12 inhibitor or other stent types (23,26-27) is unknown.

CONCLUSIONS

The BLESS trial shows that in ACS patients the RPR increases shifting from 60 mg loading dose to 10 mg/day prasugrel MD. A further increase in RPR and a higher rate of high RPR patients was observed shifting from 10 mg/day to 5 mg/day prasugrel MD after 1 month. This strategy might be able to optimize the risk/benefit profile of prasugrel MD in ACS after 2nd or 3th generation DES implantation, being it associated with a 71% risk reduction in BARC type ≥2 bleedings without any apparent increase in thrombotic events. The modulation of platelet inhibition over

time after an ACS appears to be an attractive strategy and should be tested in larger clinical trials.

REFERENCES

1) Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;**357**:2001-15.
2) U.S. Food and Drug Administration. Cardiovascular and Renal Drug Advisory Committee briefing document on prasugrel for ACS. February 3, 2009. Available at: http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4412b1-01-FDA.pdf. Accessed April 24, 2009.
3) Campo G, Parrinello G, Ferraresi P, Lunghi B, Tebaldi M, Miccoli M, Marchesini J, Bernardi F, Ferrari R, Valgimigli M. Prospective evaluation of on-clopidogrel platelet reactivity over time in patients treated with percutaneous coronary intervention relationship with gene polymorphisms and clinical outcome. *J Am Coll Cardiol* 2011;**57**:2474-83.
4) Althoff TF, Fischer M, Langer E, Ziemer S & Baumann, G. 'Sustained enhancement of residual platelet reactivity after coronary stenting in patients with myocardial infarction compared to elective patients. *Thromb Res* 2010;**125**:e190-e196.
5) Parodi G, Bellandi B, Venditti F, Carrabba N, Valenti R, Migliorini A, Grassellini S, Ramazzotti E, Antoniucci D. Residual Platelet Reactivity, Bleedings, and Adherence to Treatment in Patients Having Coronary Stent Implantation Treated With Prasugrel. *Am J Cardiol*, 2012;**63**:1061-70.
6) Parodi G, Marcucci R, Valenti R, Gori AM, Migliorini A, Giusti B, Buonamici P, Gensini GF, Abbate R, Antoniucci D. High Residual Platelet Reactivity After Clopidogrel Loading and Long-term Cardiovascular Events Among Patients With Acute Coronary Syndromes Undergoing PCI. *JAMA* 2011;**306**:1215-23.
7) Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D,Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized Bleeding Definitions for Cardiovascular

Clinical Trials A Consensus Report From the Bleeding Academic Research Consortium. Circulation 2011;123:2736-74.

8) Mauri L, Hsieh W, Massaro JM, Ho KKL, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med* 2007;**356**:1020-29.

9) Roe MT, Armstrong PW, Fox KA, White HD, Prabhakaran D, Goodman SG, Cornel JH, Bhatt DL, Clemmensen P, Martinez F, Ardissino D, Nicolau JC, Boden WE, Gurbel PA, Ruzyllo W, Dalby AJ, McGuire DK, Leiva-Pons JL, Parkhomenko A, Gottlieb S, Topacio GO, Hamm C, Pavlides G, Goudev AR, Oto A, Tseng CD,Merkely B, Gasparovic V, Corbalan R, Cinteză M, McLendon RC, Winters KJ, Brown EB, Lokhnygina Y, Aylward PE, Huber K, Hochman JS, Ohman EM;TRILOGY ACS Investigators. Prasugrel versus Clopidogrel for Acute Coronary Syndromes without Revascularization. *N Engl J Med* 2012;**367**:1297-1309.

10) Erlinge D, Gurbel PA, James S, Lindahl TL, Svensson P, Ten Berg JM, Foley DP, Wagner H, Brown PB, Luo J, Zhou C, Moser BA, Jakubowski JA, Small DS,Winters KJ, Angiolillo DJ. Prasugrel 5 mg in the very elderly attenuates platelet inhibition but maintains non-inferiority to prasugrel 10 mg in nonelderly patients: the GENERATION trial, a pharmacodynamic and pharmakinetic study in stable coronary artery disease patients. *J Am Coll Cardiol* 2013;**62**:577-83.

11) Erlinge D, Ten Berg J, Foley D, Angiolillo DJ, Wagner H, Brown PB, Zhou C, Luo J, Jakubowski JA, Moser B, Small DS, Bergmeijer T, James S, Winters KJ. Reduction in platelet reactivity with prasugrel 5 mg in low-body-eight patients is noniferior to prasugrel 10 mg in higher-body-weight patients: results from the FEATHER trial. *J Am Coll Cardiol* 2012;**59**:E341-E341

12) Gurbel PA, Erlinge D, Ohman EM, Neely B, Neely M, Goodman SG, Huber K, Chan MY, Cornel JH, Brown E, Zhou C, Jakubowski JA, White HD, Fox KA, Prabhakaran D, Armstrong PW, Tantry US, Roe T; TRILOGY ACS Platelet Function Substudy Investigators. Platelet Function During Extended Prasugrel and Clopidogrel Therapy for Patients With ACS Treated Without Revascularization The TRILOGY ACS Platelet Function Substudy. *JAMA* 2012;**308**:1785-94

13) Gurbel PA. The relationship of platelet reactivity to the occurrence of post-stenting ischemic events: emergence of a new cardiovascular risk factor. *Rev Cardiovasc Med*. 2006;**7** Suppl 4:S20-8.

14) Bonello L, Pansieri M, Mancini J, Bonello R, Maillard L, Barnay P, Rossi P, Ait-Mokhtar O, Jouve B, Collet F, Peyre JP, Wittenberg O, de Labriolle A, Camilleri E,Cheneau E, Cabassome E, Dignat-George F, Camoin-Jau L, Paganelli F. High On-Treatment Platelet Reactivity After Prasugrel Loading Dose and Cardiovascular Events After Percutaneous Coronary Intervention in Acute Coronary Syndromes. *J Am Coll Cardiol* 2011;**58**:467-73.

15) Price MJ, Berger PB, Teirstein PS, Tanguay JF, Angiolillo DJ, Spriggs D, Puri S, Robbins M, Garratt KN, Bertrand OF, Stillabower ME, Aragon JR, Kandzari DE,Stinis CT, Lee MS, Manoukian SV, Cannon CP, Schork NJ, Topol EJ; GRAVITAS Investigators. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *JAMA* 2011;**305**:1097-105.

16) Collet JP, Cuisset T, Rangé G, Cayla G, Elhadad S, Pouillot C, Henry P, Motreff P, Carrié D, Boueri Z, Belle L, Van Belle E, Rousseau H, Aubry P, Monségu J, Sabouret P, O'Connor SA, Abtan J, Kerneis M, Saint-Etienne C, Barthélémy O, Beygui F, Silvain J, Vicaut E, Montalescot G; ARCTICInvestigators. Bedside Monitoring to Adjust Antiplatelet Therapy for Coronary Stenting. *N Engl J Med* 2012;**367**:2100-09.

17) Trenk D, Stone GW, Gawaz M, Kastrati A, Angiolillo DJ, Müller U, Richardt G, Jakubowski JA, Neumann FJ.A Randomized Trial of Prasugrel Versus Clopidogrel in Patients With High Platelet Reactivity on Clopidogrel After Elective Percutaneous Coronary Intervention With Implantation of Drug-Eluting Stents. Results of the TRIGGER-PCI (Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) Study. *J Am Coll Cardiol* 2012;**59**:2159-64.

18) Mehran R, Baber U, Steg PG, Ariti C, Weisz G, Witzenbichler B, Henry TD, Kini AS, Stuckey T, Cohen DJ, Berger PB, Iakovou I, Dangas G, Waksman R,Antoniucci D, Sartori S, Krucoff MW, Hermiller JB, Shawl F, Gibson CM, Chieffo A, Alu M, Moliterno DJ, Colombo A, Pocock S. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. Lancet 2013;382:1714-22.

19) Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, Castriota F, Colombo F, Tebaldi M, Fucà G, Kubbajeh M, Cangiano E, Minarelli M, Scalone A, Cavazza C, Frangione A, Borghesi M, Marchesini J, Parrinello G, Ferrari R; Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study

(PRODIGY) Investigators.Short- versus long-term duration of dual antiplatelet therapy after coronary stenting: A randomized multicenter trial. *Circulation* 2012;**125**:2015-26.

20) Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR Jr, Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM; DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 2014; **371**:2155-66.

21) Stefanini GG, Byrne RA, Serruys PW, de Waha A, Meier B, Massberg S, Jüni P, Schömig A, Windecker S, Kastrati A. Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISARTEST 4, and LEADERS randomized trials. *Eur Heart J* 2012;**33**:1214-22.

22) Palmerini T, Biondi-Zoccai G, Della Riva D, Stettler C, Sangiorgi D, D'Ascenzo F, Kimura T, Briguori C, Sabatè M, Kim HS, De Waha A, Kedhi E, Smits PC, Kaiser C, Sardella G, Marullo A, Kirtane AJ, Leon MB, Stone GW. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet* 2012;**379**:1393-1402.

23) Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG,Storey RF, Harrington RA; PLATO Investigators, Freij A, Thorsén M. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. *N Engl J Med* 2009; **361**:1045-57.

24) Gilard M, Barragan P, Noryani AA, Noor HA, Majwal T, Hovasse T, Castellant P, Schneeberger M, Maillard L, Bressolette E, Wojcik J, Delarche N, Blanchard D, Jouve B, Ormezzano O, Paganelli F, Levy G, Sainsous J, Carrie D, Furber A, Berland J, Darremont O, Le Breton H,Lyuycx-Bore A, Gommeaux A, Cassat C, Kermarrec A, Cazaux P, Druelles P, Dauphin R, Armengaud J, Dupouy P, Champagnac D,Ohlmann P, Endresen K, Benamer H, Kiss RG, Ungi I, Boschat J, Morice MC. Six-month versus 24-month dual antiplatelet therapy after implantation of drug eluting stents in patients non-resistant to aspirin: ITALIC, a randomized multicenter trial. *J Am Coll Cardiol*. 2014, doi: 10.1016/j.jacc.2014.11.008.

25) Garratt KN, Weaver WD, Jenkins RJ, et al. Prasugrel Plus Aspirin Beyond 12 Months Is Associated With Improved Outcomes After Taxus Liberté Paclitaxel-Eluting Coronary Stent Placement. Circulation 2015;131: 62-73.

26) Windecker S, Remondino A, Eberli FR, Jüni P, Räber L, Wenaweser P, Togni M, Billinger M, Tüller D, Seiler C, Roffi M, Corti R, Sütsch G, Maier W, Lüscher T,Hess OM, Egger M, Meier B. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. *N Engl J Med* 2005;**353**: 653-62.

27) Morice MC, Colombo A, Meier B, Serruys P, Tamburino C, Guagliumi G, Sousa E, Stoll HP; REALITY Trial Investigators. Sirolimus- vs paclitaxel-eluting stents in de-novo coronary artery lesions: the REALITY trial: a randomized controlled trial. *JAMA* 2006;**295**: 895-904.

Part 4: Antiplatelet drugs in acute coronary syndrome patients: from acute phase to long-term therapies

Chapter 7:

APpropriateness Assessment in Antiplatelet THerapY (APATHY) registry: Insight from current clinical practice.

Nazario Carrabba, MD; Benedetta Bellandi, MD; Parodi Guido, MD; Emanuele Cecchi, MD; Giorgio Baldereschi, MD; Cristina Giglioli, MD; Serafina Valente, MD; Rossella Marcucci, MD; Niccolò Marchionni, MD; David Antoniucci, MD.

From the Cardiovascular and Thoracic Department of Careggi Hospital, Florence, Italy

Int J Cardiol. 2017 Oct 1;244:13-16.

ABSTRACT

Background: Third generation and more potent P2Y12 inhibitors have now recommended for the treatment of acute coronary syndrome (ACS). We sought to evaluate contemporary antithrombotic strategies employed in patients admitted for an ACS to a tertiary center, Careggi Hospital.

Methods and Results: From January to June 2014, 430 consecutive ACS patients were treated with percutaneous coronary intervention (PCI) and stent by 3 groups of interventional cardiologists available 24 h, 7 days/week: 23.5% with ST-elevation myocardial infarction (STEMI) and 76.5% with non-STEMI/unstable angina (UA). Aspirin and clopidogrel (52%) were the most commonly used antithrombotic therapies, being prasugrel associated with aspirin in 110 (26%) and ticagrelor in 97 (23%) of ACS. Inappropriate use of prasugrel (Tia/Ictus) was found in 2 (1.8%) patients and not recommended use (> 75 years, without diabetes or previous myocardial infarction) in 11 (10%). Not recommended use of ticagrelor and concomitant use of warfarin was found in 4 patients (4.4%). An upgrade switching from clopidogrel to prasugrel occurred in 29% [32/110 patients: 28 showing high residual platelet reactivity (HRPR: ADP 10 μmol<70%), and 4 receiving left main stenting], while an upgrade from clopidogrel to ticagrelor occurred in 13.4% (13/97 patients, all showing HRPR, but 1 affected by clopidogrel allergic reaction). The most powerful predictor for prescription of third generation P2Y12 inhibitors was the presence of HRPR (OR 5.473, 95% CI 2.41-12.43, P<.0001) and the behavior of attending cardiologist (HR 0.674, 95% CI 0.573-0.847, P=.001), whereas the older age reduced the probability of receiving it (OR 0.963, 95%CI 0.943-0.984, P=.001).

Conclusions: The clopidogrel remained the most common P2Y12 inhibitor employed for PCI in ACS, despite current recommendation. The rate of inappropriate/not recommended prescription of third generation P2Y12 inhibitors was low and the switching was largely based on HRPR associated with clopidogrel. These findings suggest the need to improve evidence-based third generation prescription of P2Y12 inhibitors

Introduction

Prasugrel and Ticagrelor significantly decreased cardiovascular death, myocardial infarction (MI), and stroke compared with clopidogrel in TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis in Myocardial Infarction 38) and in PLATO respectively (1,2). However, prasugrel use was associated with increased bleeding in patients with a history of previous stroke or transient ischemic attack (TIA) and was not associated with favorable net clinical benefit in those >75 years of age and in low-body weight patients. The prasugrel package insert (3) includes a black box warning for patients with previous stroke/TIA and also discourage its use in patients aged >75 years due to an increased risk of fatal intracranial bleeding and uncertain benefit, except in high-risk situations (age >75 years with history of diabetes or a previous MI). On the other hand, the most common adverse reactions associated with the use of ticagrelor in PLATO included bleeding and dyspnea. Moreover, in an Holter substudy of PLATO, more patients had ventricular pauses with ticagrelor than with clopidogrel in the acute phase. The ticagrelor package insert reports to avoid ticagrelor in patients with severe hepatic impairment, and caution is needed in patients with dyspnea and in patients with sick sinus syndrome, 2nd or 3rd degree AV block, or bradycardic-related syncope and not protected with a pacemaker. The current European guidelines for ACS patients undergoing PCI (4) assign a Class I recommendation for prasugrel and ticagrelor use in patients without contraindications. In the present registry we examined the antithrombotic strategies employed in patients admitted for an acute coronary syndrome (ACS) in the Cardiovascular and Thoracic Department of Careggi Hospital, Florence Italy.

Methods

This registry is a single centre, retrospective, quality improvement registry aimed to evaluate in-hospital use of antithrombotic therapies in consecutive ACS patients admitted to our high volume PCI center. Three groups of interventional cardiologists were available 24 h, 7 days/week. Briefly, inclusion criteria for the Registry were: patients≥18 years old admitted to a CCU with a diagnosis of ACS were eligible if they had cardiac ischemia-related symptoms of ≥10 min duration and concurrent biomarker evidence of ACS and/or concurrent electrocardiographic changes. The study was approved by the local ethical committee. All patients gave informed consent. The antithrombotic treatment strategy for ACS was left at discretion of the attending cardiologist. High and low residual platelet reactivity (HRPR and LRPR) was assessed by light transmittance aggregometry (LTA) and defined as ADP 10 mmol >70% and <19%, respectively (5). Prasugrel use in patients with a documented history of previous stroke or TIA was defined as inappropriate and prasugrel use in patients >75 years of age without diabetes or a previous MI was defined not recommended (6). In addition, we examined prasugrel and ticagrelor use in patients receiving concomitant aspirin and warfarin, since not recommended, because the efficacy and safety of prasugrel or ticagrelor (as a third agent) have not been evaluated in this subgroup. Finally, we examined the determinants of the third generation P2Y12 prescription, both prasugrel and ticagrelor, in comparison to clopidogrel using multivariable regression model.

Statistical analysis

Categorical variables are presented as number and percentages, and compared by the χ 2 test. Continuous variables are presented as mean and standard deviation (SD). Continuous variables were compared by the t-test, If normally distributed, or by the

Mann–Whitney U-test, if not. In the present analysis, we divided the population of interest into three groups: patients receiving second generation P2Y12 inhibitor clopidogrel and patients receiving third generation P2Y12 inhibitors prasugrel and ticagrelor. All the variables which were statistically significant at univariate analysis were included in a multivariable model (logistic regression), to identify the independent predictors of prescribing third generation P2Y12 inhibitors. The variables included in the logistic model were: age, gender, low body weight, groups of interventionists, HRPR, previous MI and diabetes. A P-value <0.05 was considered statistically significant. All tests were two-sided. Analyses were performed with the SPSS system software, version 12.

Results

From January 2014 and June 2014, 430 consecutive ACS patients were treated with PCI and stent: 23.5% with ST-elevation myocardial infarction (STEMI) and 76.5% with unstable angina non-STEMI (UA/NSTEMI**).** During Hospitalization, overall aspirin was administered in 89% of patients and third generation P2Y12 inhibitors in 49%. Specifically, aspirin and clopidogrel (52%) were still the most commonly used antithrombotic therapies, being prasugrel associated with aspirin in 26% (110) and ticagrelor in 23% (97) of ACS. Patients receiving third generation P2Y12 inhibitors were more frequently males and smokers and a strong trend towards a younger age was found in comparison to patients receiving clopidogrel (Table 1). A history of chronic kidney disease was more frequently observed in patients receiving clopidogrel, whereas a trend towards a higher rate of previous TIA/stroke was found in this group. Patients presenting with STEMI were treated more frequently with third generation P2Y12 inhibitors (71%), while UA/NSTEMI patients were largely treated with clopidogrel (59%). The pretreatment strategy (loading dose before angiography) with P2Y12 inhibitors was

adopted in 45% of ACS (Table 2). Specifically, a low rate of pretreatment for STEMI patients was observed, favoring third generation P2Y12 inhibitors, in comparison to a high rate of pretreatment for UA/NSTEMI, largely based on clopidogrel use, 15% vs. 54% ($p<0.001$), respectively. Switching between P2Y12 inhibitors occurred in 15% of ACS patients. Specifically, an upgrade from clopidogrel to prasugrel occurred in 29% (32/110: 28 clopidogrel patients showing HRPR, and 4 patients receiving left main stenting). In addition 2 patients taking ticagrelor and showing advance atrio-ventricular block were shifted to prasugrel (change between the third generation P2Y12 inhibitors). Moreover, in 2 patients taking prasugrel and showing very low residual platelet reactivity at platelet function test the prasugrel maintenance dose was reduced from 10 to 5 mg/day. On the other hand, an upgrade from clopidogrel to ticagrelor occurred in 13.4% (13/97), all patients showing HRPR, but one affected by clopidogrel allergic reaction. The inappropriate use of prasugrel was found in 2 patients (1.8%), the not recommended use in 11 (10%) patients and the concomitant use of warfarin in none; whereas not recommended use of ticagrelor and concomitant use of warfarin was observed in 4 patients (4.4%). Finally, a downgrade from ticagrelor to clopidogrel occurred in 23% (15/223: 1 patients for urgent noncardiovascular surgery, 1 patients affected by ticagrelor allergic reaction, 3 patients receiving warfarin for atrial fibrillation, 1 patients leaving in east European country, 3 patients affected by dyspnea, 1 patients showing advanced AV block or symptomatic bradycardia and 5 patients for unknown reasons. At multivariable analysis, the most powerful predictor for prescription of third generation P2Y12 inhibitors was the presence of HRPR (HR 5.473, 95% CI 2.41-12.43, $p<.0001$) and the behavior attending cardiologists (HR 0.674, 95% CI 0.573-0.847, $P=.001$), whereas the old age reduced the probability of receiving third generation P2Y12 inhibitors (HR 0.963, 95% CI 0.943-0.984, $p=.001$) (Table 3). The low body weight, gender, previous MI and the

diabetes did not emerge in this model. According the antithrombotic strategy, the rate of death, recurrent MI, stroke and congestive heart failure were not different between groups, as well as the rate of TIMI major and TIMI minor bleeding, except the rate of TIMI minimal bleeding occurring less frequently in the clopidogrel group (Table 4).

Table 1: Baseline characteristics of study patients treated with P2Y12 inhibitors

Variable	All n=430	Clopidogrel n=223 (52%)	Prasugrel n= 110 (26%)	Ticagrelor n=97 (23%)	P value
Elderly (> 75 yrs)	166 (39)	98 (44)	35 (32)	33 (34)	0.065
Male gender	310 (73)	148 (66)	90 (84)	72 (76)	0.002
Weight < 60 kg	32 (9)	23 (12)	4 (5)	5 (6)	0.104
Smoking habits					0.002
Current Smokers	100 (25)	38 (17)	28 (31)	34 (38)	
Previous Smokers	114 (29)	67 (31)	22 (25)	25 (28)	0.002
Hypertension	304 (67)	161 (72)	79 (73)	64 (67)	0.661
Dyslipidemia	239 (57)	125 (26)	62 (59)	52 (54)	0.781
Diabetes Mellitus	130 (31)	65 (29)	38 (35)	27 (28)	0.481
Familiarhistory of CAD	82 (24)	37 (19)	23 (29)	22 (30)	0.093
Previous myocardial infarction	138 (34)	74 (35)	38 (36)	26 (29)	0.449
Previous PCI	162 (38)	85 (38)	47 (44)	30 (31)	0.196
Previous CABG	36 (8)	21 (9)	9 (8)	6 (6)	0.639
History of renal failure	52 (13)	33 (15)	15 (15)	4 (4)	0.024
Previous TIA/Stroke	27 (6)	19 (9)	2 (2)	6 (6)	0.069
Peripheral artery disease	77 (21)	41 (20)	22 (25)	14 (17)	0.391
Cardiogenic shock	30 (7)	12 (5)	11 (11)	7 (7)	0.231
Access site					0.0001
Femoral	323 (81)	162 (77)	95 (95)	66 (72)	
Radial	77 (18)	47 (21)	5 (5)	25 (26)	

BMI: body mass index; CAD: coronary artery disease; PCI: percutaneous coronary intervention; CABG: coronary artery by-pass graft; TIMI: thrombolysis and myocardial classification

Table 2. Antiplatelet therapy characteristics

Variable	All	Clopidogrel	Prasugrel	Ticagrelor	P value
	n= 430	n= 223 (52%)	n= 110 (26%)	n= 97 (23%)	
Center					0.0001
1	270 (63)	120 (54)	98 (89)	52 (54)	
2	94 (22)	52 (23)	12 (11)	30 (31)	
3	66 (15)	51 (23)	0 (0)	15 (15)	
STEMI	101 (23.5)	30 (13)	31 (28)	40 (41)	0.0001
UA/NSTEMI	329 (76.5)	193 (86)	79 (71)	57 (59)	0.0001
Pretreatment	192 (45)	117 (52)	51 (46)	24 (25)	0.0001
NSTEMI	177 (41)	111 (50)	46 (42)	20 (21)	0.009
STEMI	15 (3)	6 (3)	5 (4)	4 (4)	0.543
Treatment location					0.0001
Ambulance	12 (3)	3 (1)	3 (3)	6 (6)	
ER	4 (1)	1 (1)	0 (0)	3 (1)	
CCU	147 (34)	70 (31)	33 (30)	44 (45)	
Cath Lab	196 (46)	122 (55)	43 (39)	31 (32)	
Switch	64 (15)	15 (7)	36 (33)	13 (13)	0.0001
Not reccomended	15 (3)	0 (0)	11 (10)	4 (4.4)	
ɔn					
Inappropriate prescription	2 (1)	0 (0)	2 (1)	0 (0)	
Aspirin treatment	382 (89)	202 (91)	93 (84)	87 (90)	0.562

ER: emergency room; CCU: cardiac coronary unit; Cath Lab: catheterization laboratory; STEMI: ST-elevation myocardial infarction; ACS: acute coronary syndrome; UA: unstable angina.

Table 3. Multivariate analysis: predictors of Prasugrel or Ticagrelor use

Variable	Hazard Ratios	95% Confidence Interval	P value
Age	0.963	0.943-0.984	0.001
Male gender	-	-	-
ADP switch	5.473	2.410-12.430	0.0001
Center	0.674	0.537-0.847	0.001
Previous MI	-	-	-
Diabetes	-	-	-
Weight	-	-	-

ADP: adenosin diphosphate; MI: myocardial infarction

Table 4. In-hospital Outcomes

Variable	All n= 430	Clopidogrel n= 223 (52%)	Prasugrel n= 110 (26%)	Ticagrelor n= 97 (23%)	P value
In-hospital death	14 (3.3)	7 (3.2)	4 (3.7)	3 (3.1)	0.958
Re-AMI	3 (0.7)	1 (0.5)	2 (1.9)	0 (0)	0.229
CIN	17 (4.1)	9 (4.1)	5 (4.8)	3 (3.2)	0.861
TIMI Major bleeding	4 (1.0)	4 (1.9)	0 (0)	0 (0)	0.157
TIMI Minor bleeding	15 (3.8)	7 (3.3)	3 (3.1)	5 (5.7)	0.562
TIMI Minimal bleeding	25 (6.3)	6 (2.8)	7 (7.2)	12 (13.5)	0.002
Congestive heart failure	48 (11.5)	24 (11.0)	14 (13.2)	10 (10.9)	0.823
Stroke	2 (0.5)	2 (0.9)	0 (0)	0 (0)	0.406
Vascular complication	17 (14.1)	10 (4.5)	2 (1.9)	5 (5.4)	0.400

Re-AMI: recurrent acute myocardial infarction; CIN: contrast induced nephropathy

Discussion

In the US PINNACLE registry (6), 18.3% of patients were receiving prasugrel for an inappropriate or a not recommended indication. Moreover, registry from Michigan found that among patients receiving prasugrel, 6% to 10% had >1 contraindication to prasugrel (7). They reported higher rates of bleeding and vascular complications in these patients, with no difference in ischemic outcomes. Our registry indicates a 11.8% of inappropriate/not recommended prasugrel prescribed in high volume PCI center, similar to the rate of Michigan study (7). In addition, 4.4% of not recommended ticagrelor use was observed due to concomitant aspirin and warfarin administration. The rate of pretreatment strategy with P2Y12 inhibitors for UA/NSTEMI appears unawares high considering the high volume center for PCI involved. However, in the APATHY registry the data collection started before the publication of the ACCOAST trial findings (8), partially explaining these results. At contrary, a low rate of pretreatment strategy with P2Y12 for STEMI found in our registry deserve some considerations. The time elapsed from symptoms onset to hospital admission by ambulance in Florence district is not so long and, frequently, the door-to-balloon time is very short, determining an optimal logistic situation in the Florence district. It's conceivable that the use of third generation P2Y12 inhibitors in the ambulance for STEMI patients may improve the outcome, although the additional value of this strategy is not completely supported by ATLANTIC trial findings (9). Interestingly, in the present registry the most powerful predictor for prescription of third generation P2Y12 inhibitors at hospital discharge was the assessment of HRPR by platelet function test. However, this strategy is not recommended and previous studies failed to show any advantage of this strategy (10,11). In addition, in this registry, the third generation P2Y12 inhibitors were mainly prescribed among younger patients, thus different antithrombotic strategies might be related to different ischemic and

bleeding risk profiles of ACS populations, or might be related to the tendency of physicians to administer more potent drugs after knowing coronary anatomy, as occurring in 4 patients showing left main disease. Finally, although the use of ticagrelor in ACS patients taking warfarin is not recommended, being yet not demonstrated the efficacy and safety of this association, again the behavior of attending physician play a key role on this not recommended prescription. During the hospital stay, we did not found any increase in ischemic events, in terms of mortality and recurrent MI, neither we observed any increase in TIMI major bleeding and minor bleeding, but only the rate of minimal bleeding significantly increased. However, it's possible that in middle and long term the inappropriate/not recommended use of prasugrel and ticagrelor in ACS patients, may lead to increased rates of major bleeding and offset any anti-ischemic benefit of third generation P2Y12 inhibitors. We recognize several limitations of the present registry. This is a retrospective registry. Previous TIA/stroke and prasugrel use were self-reported. The inappropriate and not recommended prasugrel prescription rate and the rate of not recommended ticagrelor use with warfarin may be higher in non-high PCI volume center. Moreover, data on the contraindications to clopidogrel, reason for choosing prasugrel or ticagrelor instead of clopidogrel, and ischemic and bleeding outcomes are not collected in the APATHY registry, and analyses pertaining to these variables, therefore, could not be performed. Finally, the findings of this study cannot be extended to ACS patients managed conservatively, since not included in the APATHY registry, and, yet, caution is need in result's interpretation.

Conclusions

Our contemporary registry shows that the clopidogrel remained the most common P2Y12 inhibitor employed for PCI in ACS, despite current recommendations. The inapproriate/not recommended prescription of third genrationP2Y12 inhibitors was low and the switching to the third and more potent P2Y12 inhibitors was largely based on HRPR associated with clopidogrel. Our findings suggest the need to improve evidence-based third generation P2Y12 inhibitors prescription.

References

1) Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357: 2001–15.

2) Wallentin L, Becker RC, Buda A, et al. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. N Engl J Med 2009;361: 1045-105.

3) Prasugrel [package insert]. Indianapolis, IN: Eli Lilly and Company, 2013.

4) Windecker S, Kolh P, Alfonso F, et al 2014 ESC/EACTS Guidelines on myocardial Revascularization The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). European Heart Journal doi:10.1093/eurheartj/ehu278

5) Tantry US, Bonello L, Aradi D, et al. Consensus and Update on the Definition of On-Treatment Platelet Reactivity to Adenosine Diphosphate Associated With Ischemia and Bleeding. J Am Coll Cardiol 2013;62:2261–73.

6) Hira RS. Frequency and Practice-Level Variation in Inappropriate and Non recommended Prasugrel Prescribing. Insights From the NCDR PINNACLE Registry. J Am Coll Cardiol 2014;63, No. 25.

7) Sandhu A, Seth M, Dixon S, et al. Contemporary use of prasugrel in clinical practice: insights from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium. Circ Cardiovasc Qual Outcomes 2013;6:293-8.

8) Montalescot G, Collet JP, Ecollan P et al. Effect of Prasugrel Pre-Treatment Strategy in Patients Undergoing Percutaneous Coronary Intervention for NSTEMI. The ACCOAST-PCI Study. J Am Coll Cardiol. 2014;64:2563-2571.

9) Montalescot G, van 't Hof AW, Lapostolle F, et al. Prehospital Ticagrelor in ST-Segment Elevation Myocardial Infarction. N Engl J Med 2014;371:1016-102.

10) Mehta SR, Tanguay JF, Eikelboom JW, Jolly SS. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. Lancet 2010;376:1233-43.

11) Bonello L, Pansieri M, Mancini J, et al. High on-treatment platelet reactivity after prasugrel loading dose and cardiovascular events after percutaneous coronary intervention in acute coronary syndromes. J Am Coll Cardiol 2011;58:467–73.

Chapter 8 :

Clinical events beyond one year after an acute coronary syndrome: insights from the RECLOSE 2-ACS study.

Guido Parodi, MD, PhD[1]; Benedetta Bellandi, MD[1]; Giuseppe Tarantini MD[2]; Fernando Scudiero, MD[1]; Renato Valenti, MD[1]; Rossella Marcucci, MD[1]; Angela Migliorini, MD[1], Niccolò Marchionni, MD[1]; Anna Maria Gori, BS[1]; Chiara Zocchi, MD[1]; and David Antoniucci, MD[1].

From 1 the Cardiovascular and Thoracic Department, Careggi University Hospital, Florence, Italy

and 2 the Cardiovascular and Thoracic Department, Padua University, Padua, Italy (GT).

EuroIntervention. 2017 Mar 20; 12(16):2018-2024.

ABSTRACT

Aims: Optimal duration of dual antiplatelet therapy after an acute coronary syndrome (ACS) is still unknown and debated. We sought to assess the incidence of adverse clinical events beyond 12 months after an ACS in patients treated by percutaneous coronary intervention (PCI) and clopidogrel.

Methods and results: Among 1592 consecutive ACS patients treated by PCI enrolled in the RECLOSE-2 ACS study and without event within 1 year, 1310 (82%) patients presented at least 1 risk factor such as: age ≥ 65 years, diabetes, prior myocardial infarction (MI), chronic kidney disease and multivessel coronary disease. The primary end-point rate (the composite of cardiac death, MI, stroke and any urgent coronary revascularization) was 3.7% per year after the first 12 months. Adverse event rate beyond 12 months was higher in patients with at least 1 risk factor as compared with patients without (8.1% vs 1.8%, p<0.001). Each additional risk factor was associated with a relative risk for long term adverse event of 1.66 (95%CI 1.41-1.96; p=0.0001). Independent predictors of late events were age ≥65 years (OR 2.11; 95%CI 1.38-3.37, p=0.002), insulin-treated diabetes mellitus (OR 2.29; 95%CI 1.41-3.71, p=0.001), chronic kidney disease (OR 1.93; 95%CI 1.21-3.09, p=0.006), prior MI (OR 2.71; 95%CI 1.85-3.97, p=0.0001), and multivessel coronary disease (OR 1.53; 95%CI 1.18-1.97, p=0.01).

Conclusions: Patients at risk of adverse events beyond 12 months after an ACS may be identified by simple clinical and angiographic characteristics such as age, diabetes, chronic kidney disease, prior MI and multivessel CAD. The risk of adverse events progressively increases with the number of these high risk features.

INTRODUCTION

Activated platelets have a key role in the development of atherothrombotic events leading to acute coronary syndromes (ACS),[1] and dual antiplatelet therapy (DAPT) represents a cornerstone in secondary prevention after an acute myocardial infarction. In particular, current practice guidelines recommend the addition to aspirin of a platelet $P2Y_{12}$ receptor inhibitor for 12 months after an ACS.[2,3] Routine 12-month DAPT length recommendation derived largely from the designs of previous trials [4-6] but it has a weak biological basis, and the comparisons of different DAPT lengths are scarce and not rigorous in ACS patients. Moreover, in current clinical practice DAPT is frequently prolonged beyond 1 year in patients considered at high risk of thrombosis.[7] So far, optimal DAPT length after an ACS is a matter of debate.[8-11] The PEGASUS Trial showed that DAPT with aspirin and ticagrelor is able to prevent recurring ischemic events well beyond 12 months after a myocardial infarction, at the price of increased major bleedings.[8] Data on the comparison of 12-month with more prolonged DAPT or, more appropriately, on the clinical impact of DAPT length individually tailored on the basis of ischemic and bleeding risk profile, are completely lacking. Finally, the adverse event rates beyond 12 months in ACS patients treated by percutaneous coronary intervention (PCI) are limited, but likely heterogeneous and dependent on patient's risk profile. Thus, we sought to assess adverse events occurring beyond 12 months in ACS patients receiving invasive management and clopidogrel treatment enrolled in the Responsiveness to Clopidogrel and Stent Thrombosis 2-ACS (RECLOSE 2-ACS) study.[12]

METHODS

Study Design

The RECLOSE 2-ACS study design has previously been described.[12] Briefly, it was an observational, single-center cohort study of consecutive patients with ACS undergoing

invasive treatment. All patients were treated with clopidogrel 600 mg loading dose followed by 75 mg daily dose on top of aspirin. Platelet reactivity after clopidogrel loading was prospectively assessed for every patient with light transmittance aggregometry (LTA), and patients with high platelet reactivity (HRPR; defined as ADP 10 test $\geq$ 70%) received a tailored antiplatelet therapy, generally represented by 150 mg clopidogrel maintenance dose. Long-term DAPT (>12 months) was strongly recommended. The study was approved by the local ethical committee. All patients gave informed consent. The present study is based on a retrospective post-hoc analysis of the RECLOSE 2-ACS study.

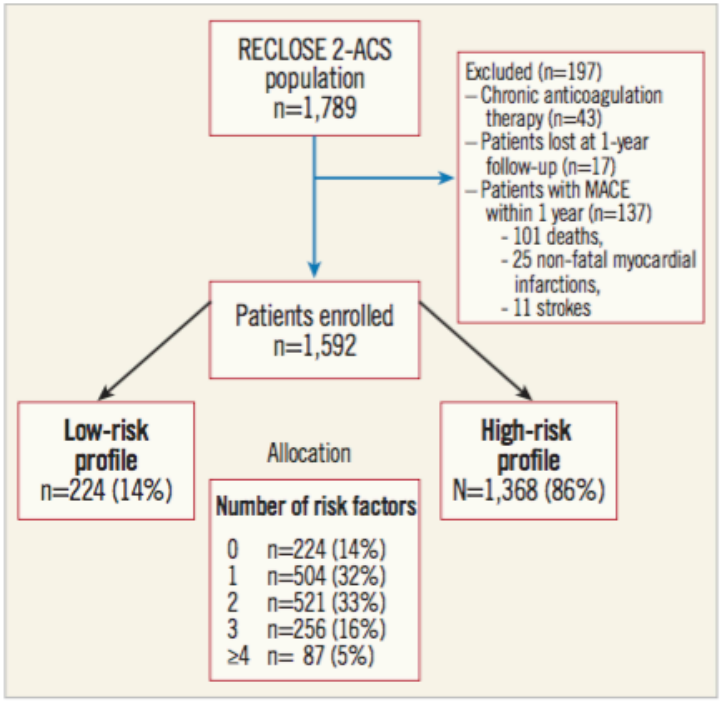
Patient Population

Of 1789 patients enrolled in the RECLOSE 2-ACS, 197 were excluded because they were lost to follow-up within 1 year (n=17), experienced new events within 1 year (n=137), or had an indication to chronic anticoagulant therapy (n= 43). The remaining 1592 patients were included in the present analysis (Figure 1). Almost all patients (97%) were on aspirin. Based on the PEGASUS trial study design,[8] patients were classified as at high-risk in the presence of at least one of the following 5 characteristics: age $\geq$ 65 year, diabetes mellitus, chronic kidney disease (creatinine clearance < 60 mL/min), prior myocardial infarction, and multivessel CAD.

End Points

The primary end point of this study was a composite of major adverse cardiovascular events (MACCE: cardiac death, non fatal myocardial infarction, urgent coronary revascularization, and stroke) beyond one year after the index ACS event. Individual components of the primary end point, stent thrombosis, and TIMI major bleeding were secondary end points with previously defined definitions.[12]

Figure 1. Study Flow-chart



Follow-Up

All patients had scheduled follow-up at 1, 6, and 12 months from ACS and annually thereafter. All other possible information gathered from hospital readmission charts or by referring physicians, relatives, or municipality vital registries, were entered into the prospective data-base.

Statistical Analysis

Discrete data are expressed as frequencies, and continuous data as mean ± SD or median and interquartile range as appropriate. The $\chi 2$ test was used to compare categorical variables, and the unpaired 2-tailed Student *t* test or Mann–Whitney rank sum test was used to test differences between continuous variables. Survival curves were generated with the use of the Kaplan–Meier method, and the difference between groups was

assessed by log-rank test. Multivariable regression analysis to evaluate the independent contribution of clinical, angiographic, procedural, and platelet reactivity variables to the primary end point was performed by the forward stepwise Cox proportional hazards model. The variables entered into the model were as follows: age $\geq$ 65 years, male sex, smoking habits, diabetes mellitus requiring or not insulin treatment, hypertension, prior myocardial infarction, chronic kidney disease, multivessel coronary artery disease (CAD), left ventricular ejection fraction $\leq$ 40%, use of drug-eluting stents (DES), total stent length, HRPR, clopidogrel therapy length (months). The proportional hazard assumption was assesses and satisfied graphically by plotting log (-log) survival curves against log survival time for each predictor category and verifying whether the curves were parallel, and in addition, using time-dependent covariates. We performed sensitivity analysis in order to test how robust the model was relative to the included population by assessing the effect of adding patients excluded due to events within 1 year and looking for recurrent events after the first 12 months according to the number of risk factors. The DAPT score[13] was calculated for each patient enrolled in our study. Moreover, MACCE and bleeding rates at long-term follow-up were calculated with Kaplan Meier method in ($\geq$2) high versus (<2) low DAPT score patients and compared with the log-rank test. Discrimination was assessed by calculating the area under the receiver-operating characteristic curve and expressed as the C statistic. A p value < 0.05 was considered significant. All tests were 2-sided. Analyses were performed with SPSS 19 statistical package (IBM Corporation, Somers, NY).

RESULTS

Patient population, treatment and outcomes

Of 1592 study patients, 1368 (86%) with at least 1 risk factor were included in the high-risk group and 224 (14%) were in the low-risk group (no risk factor). Their baseline clinical and angiographic characteristics are summarized in Table 1. The two study groups showed significant differences in almost all baseline characteristics. In particular, high-risk profile patients presented a higher prevalence of cardiovascular risk factors, NSTEMI as ACS presentation, Killip class 3 or more, HRPR, and had greater CAD severity as well.

Table 1: Baseline characteristics of study patients

Variable	All (n=1592)	Low risk profile pts (n=224)	High risk profile pts (n=1368)	p value
Age (years)	69 (61-78)	57 (51-62)	72 (65-79)	0.0001
Age >65 years	1019 (64)	-	1019 (64)	-
Age >75 years	568 (36)	-	568 (36)	-
Male gender	1274 (80)	198 (88)	1076 (79)	0.001
Body Mass Index	26 (24-28)	26 (24-28)	26 (24-28)	0.951
Familiar history of CAD	113 (7)	32 (14)	81 (6)	0.0001
Smoker	402 (25)	113 (50)	289 (21)	0.0001
Hypertension	905 (57)	81 (36)	824 (60)	0.0001
Dyslipidemia	712 (45)	73 (33)	639 (479	0.0001
Diabetes mellitus	307 (19)	-	307 (19)	-
Non Insulin Treated	178 (11		178 (13)	-
Insulin Treated	129 (8)		129 (9)	-
Previous myocardial infarction	282 (18)	-	282 (18)	-
Multivessel CAD	896 (56)	-	896 (56)	-
3 vessel disease	418 (26)	-	418 (26)	-
Treated vessel				
Left main	102 (6)	2 (1)	100 (6)	0.0001
Left anterior descending artery	835 (52)	103 (6)	732 (46)	0.019
Circumflex coronary artery	526 (33)	49 (3)	477 (30)	0.0001
Right coronary artery	634 (40)	70 (4)	564 (35)	0.099
Other vessel	46 (3)	1 (1)	45 (3)	0.016
Previous PCI	225 (14)	15 (7)	210 (15)	0.001
Previous CABG	74 (5)	1 (1)	73 (6)	0.001

Killip class ≥ 3	74 (5)	1 (1)	73 (6)	0.001
LVEF ≤ 40%	450 (28)	44 (20)	406 (30)	0.002
Renal Failure	160 (10)	-	160 (10)	-
HRPR	212 (13)	17 (8)	195 (14)	0.006
Aspirin Resistance	296 (19)	23 (10)	273 (20)	0.0001
Clopidogrel therapy length (months)	28±13	29±13	28±13	0.413
Clopidogrel therapy >12 months	1406 (88)	203 (91)	1203 (88)	0.190
Clopidogrel therapy >24 months	1010 (63)	141 (63)	869 (64)	0.922
Clopidogrel therapy >36 months	407 (26)	61 (27)	346 (25)	0517
Type of ACS				
STEMI	742 (47)	138 (62)	604 (44)	0.0001
NSTEMI/ UA	850 (53)	86 (38)	764 (56)	0.0001
DES use	829 (52)	92 (41)	737 (54)	0.001
Multivessel PCI	478 (30)	-	478 (35)	-
Total stent length (mm)	24 (16-41)	13 (18-26)	26 (16-44)	0.0001

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CAD, coronary artery disease; DES, drug eluting stent; HRPR, high residual platelet reactivity; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; OAD, orally administered antidiabetic drug; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction ; UA, unstable angina;

Adjusted Kaplan Meier curves for the primary end point in high and low risk profile patients are reported in Figure 2. Table 2 summarizes the clinical outcomes beyond 1 year in low- and high-risk groups. MACCE rates beyond 12 months were higher in patients with as compared with patients without at least 1 risk factor (8.1% vs 1.8%, p=0.001). The difference in MACCE rate was mainly driven by fatal events (cardiac mortality: 0.9% in low-risk patients and 4.3% in those at high-risk; p=0.013), while there was no significant difference in either the other components of the primary end point or in the frequency of stent thrombosis (p=0.104).

Table 2: Outcomes of study population beyond 1 year from ACS

	Low risk profile pts (n=224)	High risk profile pts (n=1368)	p value†
Primary end-point rate estimation (%)*			
2 years	0.9±0.6	3.5±0.5	0.001
3 years	1.4±0.8	8.9±0.9	0.001
4years	2.5±1.3	11.4±1.1	0.001
Adverse Clinical Outcomes Occurred between 1 and 4 years from ACS			
Primary End-point	4 (1.8%)	111 (8.1%)	0.001
Cardiac death	2 (0.9%)	59 (4.3%)	0.013
Non Fatal Myocardial Infarction	3 (1.3%)	33 (2.4%)	0.315
Urgent revascularization	2 (0.9 %)	31 (2.3%)	0.181
Stroke	1 (0.4%)	23 (1.7%)	0.161
Stent Thrombosis	0 (0%)	16 (1.2%)	0.104
TIMI Major Bleeding	2 (0.9%)	22 (1.6%)	0.415

* Estimation rate by Kaplan Meier curves of the primary end-point: the composite of cardiac death, myocardial infarction, stroke, and any urgent coronary revascularization.
† by Log Rank Test

Predictors of adverse events

At Cox multivariable analysis, age ≥65 years (OR 2.11; 95%CI 1.38-3.37, p=0.002), insulin-treated diabetes mellitus (OR 2.29; 95%CI 1.41-3.71, p=0.001), chronic kidney disease (OR 1.93; 95%CI 1.21-3.09, p=0.006), prior MI (OR 2.71; 95%CI 1.85-3.97, p=0.0001), and multivessel coronary disease (OR 1.53; 95%CI 1.18-1.97, p=0.01) were all independent predictors of MACCE (study primary composite end point). Among the RECLOSE 2-ACS study population, the DAPT score showed poor discrimination (*c* statistic: MACCE model, 0.58 [95%CI, 0.52 to 0.63]; major bleeding model, 0.60 [95%CI, 0.49 to 0.71]). The MACCE rates beyond 12 months from the index event were greater, but not significantly different, among the high-DAPT score patients compared

with the low- DAPT score patients (12.9% high-score patients vs 7.8 % low-score patients [OR 1.34, 95%CI 0.93 to 1.94], p =0.115). Rates of major bleedings were significantly different by score (1.8%% in the high-score patients vs 4.2% in the low-score patients [OR 0.34, 95% CI 0.17 to 0.92], p =0.026)

Clinical outcome and number of risk factors

Of 1368 high-risk profile patients, 504 (32%), 521 (33%), 256 (16%) and 87 (5%) had 1, 2, 3 or 4 or more risk factors, respectively. Event rate curves stratified by number of risk factors are reported in Figure 3. The overall estimated long-term MACCE prevalence for patients with 0, 1, 2, 3, ≥4 risk factors was respectively 3.2±1.3, 6.3±1.3, 10.5±1.7, 15.4±3.2, 34.6±7.6 (p=0.001). Primary endpoint rate progressively increased with the number of risk factors and each additional high risk factor was associated with a relative risk for long term MACCE of 1.66 (95% CI 1.41- 1.96; p= 0.0001). In the sensitivity analysis including patients with an event within the first year after the index ACS the results did not significantly differ and each additional risk factor was associated with a relative risk for long term MACCE of 1.50 (95% CI 1.34- 1.68; p< 0.0001). In addition, the association between the number of risk factors and event rates beyond 12 months persisted after the exclusion of patients showing HRPR on clopidogrel (n=248, RR: 1.54[1.27-1.86]; p=0.0001) or those who withdrawn clopidogrel ≤ 12 months (n= 186, RR: 1.62[1.35-1.95]; p=0.0001).

One year after ACS, TIMI major bleeding rates were low and not significantly different between high- and low-risk patients (0.9% vs 1.6%, p= 0.415). Moreover, major bleeding estimation rates did not significantly increase with the number of risk factors (Figure 4).

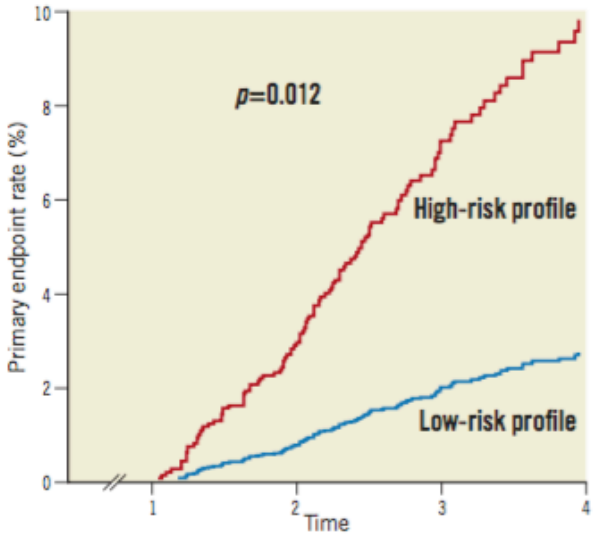
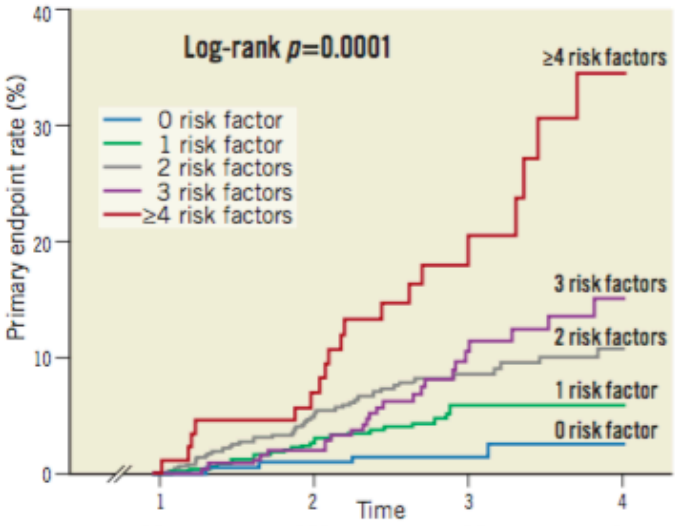


Figure 2. Kaplan-Meier curves depicting adverse event (primary end-point: the composite of cardiac death, myocardial infarction, stroke, and any urgent coronary revascularization) rates beyond 1 after an acute coronary syndrome according to the presence or absence of risk factors adjusted for potential confounders.



No at risk				
0 risk factor	225	208	96	37
1 risk factor	504	472	211	73
2 risk factors	521	477	214	77
3 risk factors	256	239	101	38
≥4 risk factors	87	76	31	9

Figure 3. Kaplan-Meier curves depicting adverse event (primary end-point: the composite of cardiac death, myocardial infarction, stroke, and any urgent coronary revascularization)

ratesbeyond 1 after an acute coronary syndrome according to the number of risk factors (0, 1, 2, 3, ≥4 risk factors).

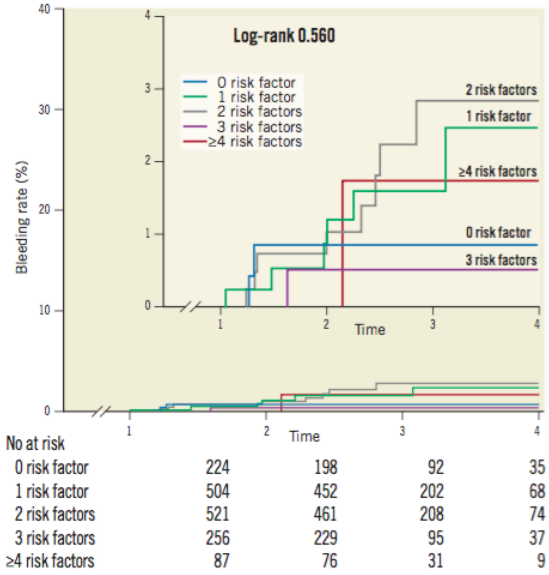


Figure 4. Kaplan-Meier curves depicting major bleeding rates beyond 1 after an acute coronary syndrome according to the number of risk factors (0, 1, 2, 3, ≥4 risk factors).

DISCUSSION

The main findings of the present study may be summarized as follows:

1) Event rates beyond 1 year from the index ACS event are relatively low but not negligible.
2) Patients at risk of adverse events beyond 12 months after an ACS may be identified by simple clinical and angiographic characteristics, such as age, diabetes, prior myocardial infarction, chronic kidney disease and multivessel CAD.
3) The risk of adverse events progressively increases with the number of these high-risk features.

4) The association between adverse events 1 year after ACS and the number of risk factors persists after the exclusion of patients showing HRPR on clopidogrel or of those who withdrawn clopidogrel ≤ 12 months.

Until now, ACS patient outcome have been mainly assessed within the first 12 months from the index event, while information on long-term event rates is limited. Patients with event within 1 year from the index event were excluded from the analysis because, in these cases, DAPT prescription is driven by the recent ACS event. In our large prospective registry of consecutive ACS patients treated with PCI, and event-free during the first year after the index event, adverse event rate was relatively low (around 3.7% per year) but clearly not negligible. Predictors of adverse events beyond 12 months were 5 well know risk factors for patients with ACS including advanced age, insulin-treated diabetes mellitus, prior myocardial infarction, chronic kidney disease and multivessel CAD. Almost identical risk factors have been selected as additional high-risk clinical characteristics for the inclusion in the PEGASUS trial [8] due to the expected association with increased long-term adverse event rates. In the PEGASUS trial, the use of ticagrelor >1 year after an acute myocardial infarction resulted in reduced ischemic event rate, at the price of increased major bleeding events, with a disappointing overall risk/benefit profile. The need for a more accurate stratification of long-term patient's risk emerged from the PEGASUS trial. In fact, at subgroup analyses, no single risk factor alone indicated a category of patients who might benefit from prolonged/resumed ticagrelor therapy.[8]

From our study, emerged that most ACS patients (86%) present at least 1 of the aforementioned risk factor and can be considered at increased risk of event late after the index event. Odd ratios for adverse clinical events after 1 year from the index event were similar and around 2 for each risk factor. Accordingly, the risk of adverse event progressively increased with the number of risk factors, which appeared to impact

synergistically, with each additional risk factor being associated with a 66% relative risk long term increase in MACCE at long term follow-up. As a consequence, patients with 2, 3 and 4 or more risk factors presented a remarkably high event rates beyond 12 months after the ACS. At the same time, bleeding event rates did not result to increase with the number of these risk factors, at least not in similar proportions. The strong association of risk factors with long-term risk of MACCE seems to carry important prognostic information. Thus, the simple number of risk factors in a given patient or the inclusion of these high-risk features in more elaborated and complete risk scores might help to select ACS patients who might profit the most from prolonged DAPT to optimize secondary prevention strategies, assuming the higher bleeding risk associated with prolonged DAPT. Unfortunately, in the DAPT Trial, among patients not sustaining major bleeding or ischemic events 1 year after PCI, a prediction score assessing late ischemic and bleeding risks to inform dual antiplatelet therapy duration showed modest accuracy in derivation and validation cohorts,[13]confirmed by our analysis.

The optimal duration of DAPT has been more extensively assessed in patients undergoing coronary drug eluting stent (DES) implantation. A recent meta-analysis including 3166 patients from 10 randomized trials underlined that the treatment with DAPT beyond 1 year after DES implantation in unselected patients may reduce recurring myocardial infarction and stent thrombosis, but it is associated with increased mortality because of an increase risk of non–cardiovascular mortality not counterbalanced by the reduction in cardiac mortality.[14] Thus, also in the setting of patients undergoing DES implantation an individually tailored approach, carefully considering the individual benefit-risk profile in prescribing prolonged DAPT, seems to be the most appropriate, and convenient, secondary prevention strategy.

Our study must be evaluated in light of some limitations. First, study results are based on a post-hoc analysis of a prospective registry and can be only considered hypothesis generating. Second, we reported no difference in major bleeding rates beyond 1 year from ACS between risk groups; however, this study was likely underpowered for detecting differences in major bleeding rates, and this finding needs to be confirmed in larger cohorts. We have also to consider that bleeding risk may derive from comorbidities and predisposing conditions not included in the key 5 risk factors that we considered (i.e, age, diabetes, prior myocardial infarction, chronic kidney disease and multivessel CAD). In the present study we documented that the relationship of the considered risk factors is strong with adverse ischemic events beyond 1 year, but weak with late bleeding events. Third, our patients did not receive the two new P2Y12 inhibitors (i.e. prasugrel and ticagrelor) which were not available at the time of study enrollment. Thus, we are not able to speculate to which extent these results would be different using the new drugs rather than clopidogrel, and hence our results cannot be generalized to patients receiving prasugrel or ticagrelor. However, prolonged clopidogrel therapy showed to be able to reduce event rates beyond 12 months from a myocardial infarction.[14] Our study findings were obtained in patients treated with prolonged clopidogrel therapy, and the association between adverse events 1 year after ACS and the number of risk factors persisted after the exclusion of patients showing HRPR on clopidogrel (poor responders to the drug) or those who withdrawn clopidogrel ≤12 months (non-adherence to the drug). The favorable effect of prolonged DAPT with ticagrelor in the PEGASUS Trial might derive from a class effect, since ticagrelor has been compared only with placebo.[8] On the other hand, the results obtained with ticagrelor in the PEGASUS Trial should be extended with caution to other $P2Y_{12}$ receptor antagonists, such as clopidogrel or prasugrel, since ticagrelor has several off-target effects able to impact on atherothrombotic events.[16-17] Fourth, all

patients in our study had been treated with PCI, therefore our results are not applicable to patients undergoing coronary artery bypass graft or to medically managed patients.

CONCLUSIONS

Patients at risk of adverse events beyond 12 months after an ACS may be identified by simple clinical and angiographic characteristics such as advanced age, diabetes, chronic kidney disease, prior myocardial infarction and multivessel coronary artery disease. The risk of late adverse events progressively increases with the number of these risk factors. Patients with multiple risk factors are those who might benefit the most from aggressive secondary prevention strategies, including prolonged DAPT, a concept that future trials need to validate.

REFERENCES

1. Davi G, Patrono C. Platelet activation and atherothrombosis. N Engl J Med 2007;357:2482-2494.
2. Amsterdam EA; Wenger NK; Brindis RG; Casey DEJr; Ganiats TG; Holmes DRJr; Jaffe AS; Jneid H; Kelly RF; Kontos MC; Levine GN; Liebson PR; Mukherjee D; Peterson DE; Sabatine MS; Smalling RW; Zieman SJ. AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014; 64:2645-2687
3. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W, Zahger D. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2011; 32: 2999–3054

4. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Fox KK. Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001; 345:494-502
5. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007; 357:2001-2015
6. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA; PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009; 361:1045-1057
7. Bueno H; Pocock S; Danchin N; Annemans L; Medina J; Millegård M; Van de Werf F. EPICOR: An International Study of the Duration of Dual Antiplatelet Therapy in Survivors of Acute Coronary Syndromes. Circulation 2014; 130:A16705
8. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, Bengtsson O, Oude Ophuis T, Budaj A, Theroux P, Ruda M, Hamm C, Goto S, Spinar J, Nicolau JC, Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E, Sabatine MS; PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med. 2015 May 7;372:1791-800
9. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR Jr, Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM; DAPT Study Investigators. DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 2014;371:2155-66.
10. Udell JA, Bonaca MP, Collet JP, Lincoff AM, Kereiakes DJ, Costa F, Lee CW, Mauri L, Valgimigli M, Park SJ, Montalescot G, Sabatine MS, Braunwald E, Bhatt DL. Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials. Eur Heart J. 2016 Jan 21;37:390-9.

11. Yeh RW, Mauri L, Kereiakes DJ. Dual antiplatelet platelet therapy duration following coronary stenting. J Am Coll Cardiol 2015;65:787-90.

12. Parodi G, Marcucci R, Valenti R, Gori AM, Migliorini A, Giusti B, Buonamici P, Gensini GF, Abbate R, Antoniucci D. High residual platelet reactivity after clopidogrel loading and long-term cardiovascular events among patients with acute coronary syndromes undergoing PCI. JAMA 2011;306:1215-23.

13. Yeh RW, Secemsky EA, Kereiakes DJ, Normand SL, Gershlick AH, Cohen DJ, Spertus JA, Steg PG, Cutlip DE, Rinaldi MJ, Camenzind E,Wijns W, Apruzzese PK, Song Y, Massaro JM, Mauri L; DAPT Study Investigators. Development and Validation of a Prediction Rule for Benefit and Harm of Dual Antiplatelet Therapy Beyond 1 Year After Percutaneous Coronary Intervention. JAMA 2016; 315(16):1735-49.

14. Palmerini T, Benedetto U, Bacchi-Reggiani L, Della Riva D, Biondi-Zoccai G, Feres F, Abizaid A, Hong MK, Kim BK, Jang Y, Kim HS, Park KW, Genereux P, Bhatt DL, Orlandi C, De Servi S, Petrou M, Rapezzi C, Stone GW. Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials. Lancet 2015; 385:2371-82.

15. Bhatt DL, Flather MD, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Fabry-Ribaudo L, Hu T, Topol EJ, Fox KA;CHARISMA Investigators. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. J Am Coll Cardiol 2007;49:1982-8.

16. Cattaneo M, Schulz R, Nylander S. Adenosine-mediated effects of ticagrelor: Evidence and potential clinical relevance. J Am Coll Cardiol 2014; 63:2503–9.

17. Teng R, Mitchell PD, Butler KA. Pharmacokinetic interaction studies of co-administration of ticagrelor and atorvastatin or simvastatin in healthy volunteers. Eur J Clin Pharmacol 2013; 69:477-87.

Summary and conclusions

In this thesis we addressed several aspects of antithrombotic strategies in patients with acute coronary syndrome, from P2Y12 inhibitor pharmacodymic evaluation in the acute phase, to safety concerns, and concluding with analysis of real life data as compared to guidelines recommendation and with the recognition of potential clinical risk factors that can be used to guide long-term antithrombotic strategies.

In **Chapter 2** we evaluated the potential role of crushed ticagrelor administration in STEMI patients. All P2Y12 receptor antagonists used at the time of study design in STEMI treatment waere only available in the oral form. This was an important limitation in patients with difficulties with swallowing such as elderly, patients with previous stroke, dysphagia and sedated or intubated patients. Our study stated that ticagrelor crushed tablets administration in STEMI patients is feasible and provides earlier platelet inhibition as compared with standard integral tablets.

Chapter 3 consider the impact of morphine use in STEMI patients in delaying the onset of action of the oral antiplatelet agents. This association persisted after adjusting for the propensity to receive morphine and after excluding patients with vomit.

In **Chapter 4** we evaluated the relation between morphine use, platelet reactivity and myocardial reperfusion. In particular, in STEMI patients undergoing PPCI, morphine use was associated with more frequent rate of high residual platelet reactivity and a poorer myocardial reperfusion evaluated with ST-segment elevation analysis. Independent predictors of impaired myocardial reperfusion were: high residual platelet reactivity and TIMI flow grade after PPCI but not morphine use, questioning the direct relationship between morphine and worse myocardial reperfusion.

Chapter 5 assessed with meta-analysis method, the role of different antithrombotic treatment in reducing non access site bleeding, clinical occurrence related to worst clinical outcomes. The present meta-analysis showed that bivalirudin could provide a significant

reduction of both access and nonaccess site bleeding in patients undergoing PCI. However, these hemorrhagic benefits did not impact on survival, and moreover, were significantly conditioned by the association of heparin with potent antithrombotic strategies, such as glycoprotein IIbIIIa inhibitors, rather than by heparin or bivalirudin alone. Therefore, we could not provide any clinical evidence for the routine use of bivalirudin as preferred anti-coagulation strategy for PCI.

Chapter 6 analysed possible antiplatelet strategies after the acute phase of ACS patients treated with PCI. In particular we evaluated changes of platelet reactivity over time, bleeding and ischemic events using different prasugrel maintenance doses.

Chapter 7 examined the contemporary clinical practice of our Institution. The use of clopidogrel, at the time of analisation still remained the most common P2Y12 inhibitor employed for PCI in ACS patients, despite current recommendations. The inapproriate/not recommended prescription of third genrationP2Y12 inhibitors was low and the switching to the third and more potent P2Y12 inhibitors was largely based on HRPR associated with clopidogrel.

Finally, **Chapter 8** identified patients at risk of adverse events beyond 12 months after an ACS event by simple clinical and angiographic characteristics such as age, diabetes, chronic kidney disease, prior MI and multivessel CAD. The risk of adverse events progressively increases with the number of these high risk features.

Future directions in the management of platelet reactivity and antithrombotic therapies in acute coronary syndrome patients

1 Several strategies have been evaluated in order to bridge the gap of the delayed onset of action of oral antiplatelet agents: clopidogrel, prasugrel, and ticagrelor, such as upstream administration of P2Y12 inhibitors, loading dose modification, crushing pills, use of an intravenous P2Y12 inhibitor or glycoprotein IIb/IIIa inhibitors' (GPI) administration, and avoid or reduce morphine use. Despite all these strategies taken in cosideration, currenlty a gap between P2Y12 adiministration and the pharmacodynamic effect during the acute phase of STEMI still remain and further studies era needed to evaluate this condition.

2 Cangrelor is a new intravenous direct P2Y12 inhibitor. After Cangrelor administration occurs at least 2 minutes to achieve effective platelet inhibition and at least 1 hour to return to basal level of platelet function after its discontinuation. This drug may be used in ACS patients undergoing PCI not already receiving an oral P2Y12 inhibitor or GPI with high thrombotic risk. Cangrelor significantly reduces the rate of ischemic events, including stent thrombosis during PCI, with no significant increase in severe bleeding as compared to clopidogrel in acute coronary sindrome patients undergoing PCI. Despite these interesting outcomes, real life data regarding pharmacodynamic effects and clinical outcomes in STEMI patients are still lacking.

3 In the clinical scenario of ACS patients, antithrombotic treatments aim to reduce the thrombotic burden, especially in the acute phase, the risk of stent thrombosis and of long-term ischemic events occurrence. In addition to the development of new more potent and faster antiplatelet agents, implementation of secondary prevention measures, recognizing clinical characteristics of patients high risk of future events is of pivotal importance to guide long-term antithrombotic treatment is and to improve long term event free survival anf mortality.

4 Great advances in research have been accomplished also in the field of non antiplatelet agents. In particular the pleiotropic role of statins, beyond the reduction of cholesterol level, providing protective effects from procedural myocardial injury, contrast induced nephropathy and anti-inflammatory effects that can positively modulate platelets reactivity is currently evaluated. Moreover the impact of the new antibodies against PCSK9 LDL receptors in reducing LDL plasmatic levels and also cardiovascular mortality could have further clinical implications. Finally, potential role of anti-inflammatory therapy is currently evaluated. Experimental and clinical data suggest that reducing inflammation without affecting lipid levels may reduce the risk of cardiovascular disease. Yet, the inflammatory hypothesis of atherothrombosis has remained unproved.

5 Finally, most randomized trial failed to demonstrate an outcome benefit from tailoring antiplatelet therapy based on aggregation tests. In particular in the era of new and fast antiplatelet agents the role of aggregation tests in daily clinical practice have been reduced. Future trials should investigate the correct management of patients at high bleeding risk or at risk of recurrent clinical ischemic event, in accord or not to platelet function test, in order to guide the following antiplatelet therapies.