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Triple therapy with aspirin, prasugrel and vitamin K antagonists in patients with drug eluting stent implantation and an indication for oral anticoagulation

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Brief Title: Triple therapy with aspirin, prasugrel and vitamin K antagonists

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ABSTRACT

Objectives: The aim of our study was to evaluate whether prasugrel may serve as an alternative to clopidogrel in patients with triple therapy.

Background: About 10% of patients who receive dual antiplatelet therapy after PCI have an indication for oral anticoagulation (OAC) and are thus treated with triple therapy. The standard ADP-receptor blocker in this setting is clopidogrel. Data regarding prasugrel as part of triple therapy is not available.

Methods: We analyzed a consecutive series of 377 patients who underwent DES implantation and have an indication for oral anticoagulation between 2/2009 and 12/2011 and were treated with a six month regimen of aspirin and OAC with either prasugrel or clopidogrel. The primary endpoint was a composite of TIMI major and minor bleeding at 6 months. The secondary endpoint was a composite of death, MI, ischemic stroke or definite stent thrombosis.

Results: 21 patients (5.6%) received prasugrel instead of clopidogrel. These patients had a higher risk profile at baseline and the majority had high platelet reactivity to clopidogrel. TIMI major and minor bleeding occurred significantly more often in the prasugrel as compared to the clopidogrel group (6 (28.6%) vs. 24 (6.7%); unadjusted HR 4.6, 95% CI [1.9-11.4], p<0.001; adjusted HR 3.2, 95% CI [1.1-9.1], p=0.03). There was no significant difference regarding the combined ischemic secondary endpoint (2 (9.5%) vs. 25 (7.0%); unadjusted HR 1.4, 95% CI [0.3-6.1], p=0.61).

Conclusions: These findings suggest that substitution of prasugrel for clopidogrel in patients needing triple therapy increases the risk of bleeding. However, specific randomized trials are needed to define the role of newer ADP receptor antagonists in this setting.

Key words:

Aspirin, prasugrel, clopidogrel, vitamin K antagonist, drug-eluting stent, high platelet reactivity

Abbreviations list

ACS	= Acute coronary syndrome
DES	= Drug-eluting stent
HPR	= High platelet reactivity
INR	= International Normalized Ratio
MEA	= Multiple electrode aggregation
OAC	= Oral Anticoagulation
PCI	= Percutaneous coronary intervention

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INTRODUCTION

Approximately 5-10% of patients undergoing coronary stenting have an additional indication for oral anticoagulation (OAC) (1) and will thus require a so called "triple therapy" consisting of aspirin, OAC and an ADP-receptor antagonist. The most common combination currently consists of aspirin, clopidogrel and a vitamin K antagonist.

Data from retrospective studies has revealed that there is a 3-5 fold increase in bleeding rates associated with this triple therapy as compared to various combinations of dual therapy (2-8). When it comes to ischemic outcomes however, a meta-analysis of non-randomized studies suggested, that triple therapy is more efficacious than dual antiplatelet therapy in the prevention of major adverse cardiovascular events and that there is a significant reduction in all-cause mortality (9). Current guidelines therefore advocate triple therapy in patients on OAC undergoing coronary stent implantation (10,11).

Clopidogrel has been for years the standard antiplatelet agent after coronary stent implantation because of its good safety and efficacy profile(12,13). Its downside however is its non-uniform and rather slow transformation to its active metabolite, leading to a substantial number of patients who display high on treatment platelet reactivity (HPR), a condition associated with a significant increase in ischemic events (14). Newer antiplatelet drugs such as prasugrel (15,16) have therefore been developed to overcome clopidogrels' limitations and recent PCI guidelines suggest, that prasugrel might be considered as an alternative agent in patients treated with clopidogrel with HPR (12). However, data regarding prasugrel as part of triple therapy is not available.

The purpose of our study is therefore to evaluate whether prasugrel may serve as an alternative to clopidogrel in patients with an indication for OAC and DES implantation.

METHODS

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Study Population

This is an analysis of prospectively collected data of patients who presented at Deutsches Herzzentrum and 1. Medizinische Klinik, Klinikum rechts der Isar both in Munich Germany between February 2009, when prasugrel was approved in Europe, and December 2011. All patients who underwent drug eluting stent placement and were discharged with a six month regimen of aspirin, oral anticoagulation with phenprocoumon and an ADP antagonist were included. In stable patients on OAC who underwent PCI, the procedure was postponed until INR values were ≤2.0. In general, bridging therapy was not performed unless patients had a high thrombembolic risk such as a mechanical valve or a recent thrombembolic event.

Antiplatelet therapy

In our center, the standard antiplatelet agent for patients with an indication for OAC who undergo stent implantation is clopidogrel, given with a 600mg loading dose prior to the procedure and a 75mg clopidogrel maintenance dose (17). There were several reasons however why patients on triple therapy were either switched from clopidogrel to prasugrel or primarily received prasugrel: (i) Patients with HPR deemed at particularly increased risk for stent thrombosis (comorbidities, complexity of the intervention, etc.). (ii) When patients with ACS had already received a 60mg prasugrel loading dose, patients were continued on prasugrel maintenance therapy and clopidogrel was not given. (iii) Patients with clopidogrel allergy. (iv) Patients with previous stent thrombosis while being on clopidogrel.

Patients in the prasugrel group received a 10 mg maintenance dose per day (or 5mg in patients ≥75 years and < 60kg body weight). Patients with prior stroke or TIA did not receive prasugrel.

During the procedure, patients were given intravenous aspirin and heparin or bivalirudin.

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Patients were further prescribed aspirin, OAC with a recommendation for lower INR levels (2.5-3.0 in patients with mechanical valves and 2.0-2.5 in other indications) and other cardiac medications according to the judgment of patient's physician..

Assessment of platelet function and tailoring antiplatelet therapy

The ADP-induced platelet aggregation was assessed with multiple electrode aggregation (MEA) using an impedance aggregometer (Multiplate analyzer). Details of this method have been reported previously (18). High platelet reactivity (HPR) to clopidogrel treatment was defined by setting a cut-off point at 468 AU x min (19).

Whole blood was obtained for initial testing from the arterial sheath and placed into lepirudin-containing plastic tubes directly after diagnostic angiography and before administration of any intravenous PCI-related antithrombotic agents. Patients from this study cohort who displayed ADP values ≥468 AU x min were tested again after a sufficient delay from initial loading. Blood for subsequent testing was obtained from an antecubical vein. Those who remained over ≥468 AU x min received another 600mg clopidogrel loading dose and were tested again. If, after the additional loading dose, patients still remained over ≥468 AU x min they received a 60mg prasugrel loading dose. Another platelet function test was performed >2h later to quantify the antiplatelet action of prasugrel.

Study end points and definitions.

The primary clinical end point of this study was the composite of TIMI major and minor bleeding (20) during a 6 month follow-up period. The secondary study end point was a composite of major adverse cardiac and cerebrovascular ischemic events (MACCE) consisting of death, myocardial infarction, ischemic stroke or definite stent thrombosis (ST). The criteria for the diagnosis of major bleeding included intracranial (confirmed by computed tomography or magnetic resonance imaging of head) or clinically significant overt signs of haemorrhage associated with >50g/L decrease in haemoglobin level. Minor bleeding was

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considered observed blood loss and a decrease in haemoglobin level of 30-50 g/L or a decrease in haemoglobin level ≥40 g/L if no bleeding site was identifiable (20). Definite ST was defined according to the Academic Research Consortium criteria (21). All events were adjudicated by an event adjudication committee blinded to the antithrombotic regimen of patients and not involved in the follow-up process.

Follow-up.

Detailed information regarding the occurrence of adverse events was obtained in this population during routine follow-up at 30 days and 6 months for all patients. .

Relevant data were collected from source documents and prospectively entered into a computerized database by specialized personnel of the data coordinating Intracoronary Stenting and Antithrombotic Research (ISAR) center.

Statistical methods. A comparison of discrete variables, expressed as counts (percentages), was performed using the Fisher exact or the χ^2 test, as appropriate. Continuous variables were expressed as means (±SD) and compared with the unpaired, 2-tailed Student t test if normally distributed; otherwise, they were expressed as medians [25th-75th percentile] and statistically analyzed by means of the Wilcoxon rank sum test. Both, unadjusted and adjusted risk estimates were calculated by Cox analysis. In multivariate analysis the independent variables were prasugrel therapy as well as clinical presentation, atrial fibrillation, LV Thrombus and pulmonary embolism/DVT. Those variables were chosen because they were different between the clopidogrel and prasugrel group with a p value < 0.1 at baseline. Kaplan-Meier method was used for building the event curves.

A 2-sided P value < 0.05 was considered to indicate statistical significance. All statistical analyses were performed with the software R (version 2.15.0; The R Foundation for Statistical Computing).

RESULTS

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Patient population

In total, we included 377 patients who underwent DES implantation and were discharged with a triple therapy recommendation for 6 months or longer consisting of aspirin, OAC and an ADP antagonist. Of these patients 21 (5.6%) received prasugrel and 356 (94.4%) received clopidogrel. Indication for prasugrel was HPR in 18 (85.7%) patients, previous stent thrombosis in 1 (4.8%) patient, STEMI in 1 (4.8%) patient and clopidogrel allergy in 1 (4.8%) patient. In the prasugrel group 16 patients were initially loaded with clopidogrel and then switched to prasugrel.

Patients' baseline characteristics differed between groups. In the prasugrel group more patients presented with unstable disease as compared to the clopidogrel group. Indication for OAC was significantly more often the presence of a LV thrombus and less often atrial fibrillation. (Table 1). INR values during follow up were not significantly different between both groups (prasugrel: 2.1±0.7 vs. clopidogrel: 2.2±0.7, p=0.64).

Clinical outcome

TIMI major and minor bleeding occurred significantly more often in the prasugrel as compared to the clopidogrel group (6 (28.6%) vs. 24 (6.7%); HR 4.6, 95% CI [1.9-11.4], p<0.001 (Figure 1). There was no significant difference regarding MACCE (2 (9.5%) vs. 25 (7.0%); HR 1.4, 95% CI [0.3-6.1], p=0.61) (Figure 2, Table 2).

The results of the multivariable Cox proportional hazards model demonstrated that prasugrel therapy was independently associated with 6 month TIMI major and minor bleeding (adjusted HR 3.2, 95% CI [1.1 to 9.1]; p =0.03). In adjusted analysis there was no difference regarding MACCE at 6 months (adjusted HR 1.1, 95% CI [0.2-5.1], p=0.91).

Platelet function testing

Peri-interventional on clopidogrel treatment ADP-induced platelet aggregation values (median [IQR]) assessed with MEA was 812 [778-923] AU x min in the 16 patients that were

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switched over to prasugrel. After a 60 mg prasugrel loading dose, ADP-induced platelet aggregation was 148 [109-198] AU x min ($p<0.001$) (Figure 3). In the clopidogrel patients without a switch of treatment, the ADP-induced platelet aggregation was 229 [152-327] AU x min.

DISCUSSION

In this study we investigated bleeding and ischemic outcomes in patients on triple therapy with prasugrel as compared to clopidogrel. Our study suggests that prasugrel therapy is associated with an increased rate of TIMI major and minor bleeding as compared to clopidogrel in patients who require OAC after DES. There was no significant difference regarding the composite ischemic endpoint between both groups.

As it is known that the second generation thienopyridine prasugrel as compared to clopidogrel is associated with higher bleeding rates (15), it is felt, that its routine use in patients with triple therapy is not recommended. There were some clinical situations however where clopidogrel was assumed not to be the best option and we have identified 21 patients (18 patients with HPR) in our center which have received prasugrel instead of clopidogrel as part of triple therapy. Reasons for a low response to clopidogrel are manifold and include several genetic as well as non-genetic factors such as patients' co-morbidities and co-medications (14). One known agent is the vitamin K antagonist phenprocoumon which shares the same hepatic metabolization pathway as clopidogrel and when both agents are taken concomitantly this was shown to lead to higher ADP-induced platelet aggregation values (22). There are numerous observational studies which have clearly linked HPR to a significant increase in ischemic clinical events (14) while at the same moment an increased response to clopidogrel measured by a low platelet function is linked to increased bleeding rates (23) (24). One may therefore hypothesize, that patients who do not have an adequate response to clopidogrel have a lower bleeding risk as compared to normal responders and

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therefore a more potent ADP antagonist such as prasugrel may be given in order to overcome the low responsiveness and reduce the ischemic risk. The question remains however whether this has an impact on bleeding outcomes especially in those with concomitant OAC therapy. Since 2009 we routinely measure the periprocedural level of P2Y12 inhibition in our center. We have adopted the practice to tailor and individualize antiplatelet therapy according to the results obtained from platelet function testing and the patients risk profile. In the present study we could show that prasugrel may overcome HPR on clopidogrel in patients concomitantly treated with OAC however there was a significant increase in TIMI major and minor bleeding rates in univariable und multivariable analysis. This may be attributed to the fact that in our population, after prasugrel loading, mean aggregation values were 148 AU x min, a value that is below the postulated therapeutic window of optimal platelet response (189 - 467 AU x min) and is associated with increased bleeding rates (25). Furthermore we could show that although baseline characteristics such as clinical presentation and indication for OAC differed, patients with prasugrel therapy showed no difference regarding ischemic events as compared to those on clopidogrel. Results of this study have to be read with caution however because number of patients and therefore also of events were low. An accurate assessment of the antiischemic properties of prasugrel as part of triple therapy in patients with a low response to clopidogrel would need larger cohorts of patients. One may argue however that the additional OAC therapy in a triple therapy patient population may counterbalance for the reduced antiischemic properties of a clopidogrel low response.

Currently there is a lot of discussion in the medical community whether adjusting therapy based on platelet function testing produces a tangible clinical benefit. So far several studies in patients on dual antiplatelet therapy have recently addressed this issue by intensification of clopidogrel therapy and have found conflicting results. On the one side intensification of clopidogrel therapy in patients with ACS undergoing PCI has shown to reduce the incidence

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of ischemic complications (26). On the other side, several recent trials failed to show a clinical benefit from an intensified clopidogrel treatment in stable patients with HPR after PCI (27-29). In our opinion based on the overwhelmingly evidence of observational studies, in general HPR shall be regarded as a modifiable risk factor for ischemic events and current PCI guidelines suggest, that prasugrel might be considered as an alternate agent in patients with a low responsiveness to clopidogrel (12). Our study suggests however that in patients with triple therapy, switching to prasugrel is associated with an increased bleeding risk and therefore assessment of patients' bleeding and thrombotic risk is of upmost importance. Factors that have shown to minimize bleeding complications in such a patient population include to lower the target INR value to 2.0-2.5 (30,31) and to co-prescribe a proton pump inhibitor (32). When prasugrel as part of triple therapy is given, it may be advisable to omit concomitant aspirin therapy, as it has been recently shown that a therapy with OAC and clopidogrel alone significantly reduces bleeding as well as ischemic events as compared to those on triple therapy including aspirin (33). Another important issue is the length of triple therapy which is currently under investigation in the ISAR TRIPLE trial(34). Current guidelines recommend at least 3 month triple therapy after DES and 1 month after BMS implantation (10,35).

We acknowledge two major limitations of the study: First, prasugrel and clopidogrel therapy was not assigned in a randomized manner. Therefore, our observational study could not prevent significant imbalances in baseline characteristics, with prasugrel patients presenting a higher risk profile than their clopidogrel counterpart. Second, because of the specific setting of the study, the number of patients who received prasugrel was very low. This small size of the prasugrel group limits the ability to adjust for potential confounding factors and attenuates the strength of the results. Furthermore the prasugrel group consists of a mixed population of patients most of whom have shown HPR after clopidogrel loading. For this

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reason our findings cannot be extrapolated to patients in whom prasugrel is given as fist line ADP receptor antagonist therapy.

In conclusion we could show that prasugrel is able to overcome HPR to clopidogrel in patients treated concomitantly with OAC after DES. However our study suggests that substitution of prasugrel for clopidogrel in patients needing triple therapy increases the risk of bleeding. Specific randomized trials are needed to define the role of newer ADP receptor antagonists in this setting.

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Reference List

1. Schomig A, Sarafoff N, Seyfarth M. Triple antithrombotic management after stent implantation: when and how? Heart 2009;95:1280-5.

2. Hansen ML, Sorensen R, Clausen MT, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. Arch Intern Med 2010;170:1433-41.

3. Holmes DR, Jr., Kereiakes DJ, Kleiman NS, Moliterno DJ, Patti G, Grines CL. Combining antiplatelet and anticoagulant therapies. J Am Coll Cardiol 2009;54:95-109.

4. Karjalainen PP, Porela P, Ylitalo A, et al. Safety and efficacy of combined antiplatelet-warfarin therapy after coronary stenting. Eur.Heart J. 2007.

5. Nguyen MC, Lim YL, Walton A, et al. Combining warfarin and antiplatelet therapy after coronary stenting in the Global Registry of Acute Coronary Events: is it safe and effective to use just one antiplatelet agent? Eur Heart J 2007;28:1717-22.

6. Ruiz-Nodar JM, Marin F, Hurtado JA, et al. Anticoagulant and antiplatelet therapy use in 426 patients with atrial fibrillation undergoing percutaneous coronary intervention and stent implantation implications for bleeding risk and prognosis. J Am Coll Cardiol 2008;51:818-25.

7. Sorensen R, Hansen ML, Abildstrom SZ, et al. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. Lancet 2009;374:1967-74.

8. Lip GY, Huber K, Andreotti F, et al. Antithrombotic management of atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing coronary

ACCEPTED MANUSCRIPT

stenting: executive summary--a Consensus Document of the European Society of Cardiology Working Group on Thrombosis, endorsed by the European Heart Rhythm Association (EHRA) and the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2010;31:1311-8.

9. Zhao HJ, Zheng ZT, Wang ZH, et al. "Triple therapy" rather than "triple threat": a meta-analysis of the two antithrombotic regimens after stent implantation in patients receiving long-term oral anticoagulant treatment. Chest 2011;139:260-70.

10. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010;31:2369-429.

11. Faxon DP, Eikelboom JW, Berger PB, et al. Consensus Document: Antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting. A North-American perspective. Thromb Haemost 2011;106.

12. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol 2011;58:e44-122.

13. Sarafoff N, Byrne RA, Sibbing D. Clinical use of clopidogrel. Curr Pharm Des 2012.

14. Sibbing D, Byrne RA, Bernlochner I, Kastrati A. High platelet reactivity and clinical outcome - fact and fiction. Thromb Haemost 2011;106:191-202.

15. 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.

16. Wiviott SD, Trenk D, Frelinger AL, et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary

ACCEPTED MANUSCRIPT

intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. Circulation 2007;116:2923-32.

17. Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. Eur Heart J 2010;31:2501-55.
18. Sibbing D, Braun S, Morath T, et al. Platelet reactivity after clopidogrel treatment assessed with point-of-care analysis and early drug-eluting stent thrombosis. J Am Coll Cardiol 2009;53:849-56.
19. Bonello L, Tantry US, Marcucci R, et al. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. J Am Coll Cardiol 2010;56:919-33.
20. The TIMI Study Group, Definitions Used In TIMI Trials. Accessed at www. timi.org in November 2007.
21. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344-51.
22. Sibbing D, von Beckerath N, Morath T, et al. Oral anticoagulation with coumarin derivatives and antiplatelet effects of clopidogrel. Eur Heart J 2010;31:1205-11.
23. Cuisset T, Cayla G, Frere C, et al. Predictive value of post-treatment platelet reactivity for occurrence of post-discharge bleeding after non-ST elevation acute coronary syndrome. Shifting from antiplatelet resistance to bleeding risk assessment? EuroIntervention 2009;5:325-9.
24. Sibbing D, Schulz S, Braun S, et al. Antiplatelet effects of clopidogrel and bleeding in patients undergoing coronary stent placement. J Thromb Haemost 2010;8:250-6.
25. Sibbing D, Steinhubl SR, Schulz S, Schomig A, Kastrati A. Platelet aggregation and its association with stent thrombosis and bleeding in clopidogrel-treated patients:

ACCEPTED MANUSCRIPT

initial evidence of a therapeutic window. J Am Coll Cardiol 2010;56:317-8.

26. Mehta SR, Bassand JP, Chrolavicius S, et al. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. N Engl J Med 2010;363:930-42.

27. Price MJ, Berger PB, Teirstein PS, et al. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. JAMA 2011;305:1097-105.

28. Trenk D, Stone GW, Gawaz M, et al. 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.

29. Collet JP, Cuisset T, Range G, et al. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. N Engl J Med 2012;367:2100-9.

30. Rossini R, Musumeci G, Lettieri C, et al. Long-term outcomes in patients undergoing coronary stenting on dual oral antiplatelet treatment requiring oral anticoagulant therapy. Am J Cardiol 2008;102:1618-23.

31. Sarafoff N, Ndrepepa G, Mehilli J, et al. Aspirin and clopidogrel with or without phenprocoumon after drug eluting coronary stent placement in patients on chronic oral anticoagulation. J Intern Med 2008;264:472-80.

32. Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. N Engl J Med 2010;363:1909-17.

33. Willem Dewilde TO, Freek Verheugt, Johannes Kelder, Bart De Smet, Jean-Paul Herrman, Tom Adriaenssens, Mathias Vrolix, Antonius Heestermans, Marije Vis, Saman Rasoul, Kaioum Sheikjoesoef, Tom Vandendriessche, Carlos Van Mieghem,

ACCEPTED MANUSCRIPT

Kristoff Cornelis, Jeroen Vos, Guus Brueren, Nicolien Breet and Jurriën ten Berg The WOEST Trial: First randomised trial comparing two regimens with and without aspirin in patients on oral anticoagulant therapy undergoing coronary stenting. ESC Congress. Munich, 2012.

34. Kastrati A. Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation (ISAR-TRIPLE), (NCT00776633). 2008.

35. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e531S-75S.

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Figure Legend

Figure 1: Composite of TIMI Major and Minor Bleeding

Kaplan Meier analysis for the primary endpoint (cumulative incidence of TIMI major bleeding and TIMI minor bleeding) at 6 months.

Figure 2: Composite of Death, MI, Ischemic Stroke or Stent Thrombosis

Kaplan Meier analysis for the secondary endpoint (MACCE: cumulative incidence of death, MI, ischemic stroke or stent thrombosis) at 6 months. MI = myocardial infarction; MACCE = major adverse cardiovascular and cerebral events

Figure 3: Periinterventional platelet aggregation values and after prasugrel reloading.

Dot density plot analyses of multiple electrode platelet aggregometry (MEA) measurements for adenosine diphosphate (ADP)-induced platelet aggregation in the prasugrel group. Periprocedural values after initial clopidogrel loading (red) and values after final prasugrel loading (blue) in the patients (n=16) who were switched from clopidogrel to prasugrel. Dots = Individual values; Line = Median

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Table 1: Baseline characteristics of the study population

Characteristics	Prasugrel n = 21 (%)	Clopidogrel n = 356 (%)	p value
Age, years	71±11	72.6 ± 9	0.48
Women	5 (23.8)	70 (19.7)	0.58
Body mass index (kg/m^2)	28.6±4	27.7±5	0.35
Glomerular filtration rate (ml/min/1.73m^2)	76.8±32	72.3±33	0.54
Arterial hypertension	12 (57.1)	209 (58.7)	0.89
Diabetes	7 (33.3)	104 (29.2)	0.68
Current smoker	1 (4.8)	33 (9.3)	0.71
Hypercholesterolemia	16 (76.2)	248 (69.6)	0.53
Clinical presentation			<0.001
Stable angina	7 (33.3)	231 (64.9)	
NSTEMI / UA	6 (28.6)	102 (28.6)	
STEMI	8 (38.1)	23 (6.5)	
Previous myocardial infarction	4 (19.0)	109 (30.6)	0.33
Previous bypass surgery	2 (9.5)	72 (20.2)	0.39
Ejection fraction	41 ± 13	46 ±15	0.10
Indication for OAC			
Atrial Fibrillation	6 (28.6)	286 (80.3)	<0.001
LV Thrombus	7 (33.3)	22 (6.2)	<0.001
Mechanical Valve	2 (9.5)	17 (4.8)	0.29
Pulmonary Embolism/DVT	4 (19.0)	26 (7.3)	0.07
Other	2 (9.5)	5 (1.4)	0.10

Data are numbers of patients (%) or mean ± standard deviation.

UA: Unstable Angina

OAC: Oral anticoagulation

DVT: Deep vein thrombosis

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Table 2: Adverse events at 6 months

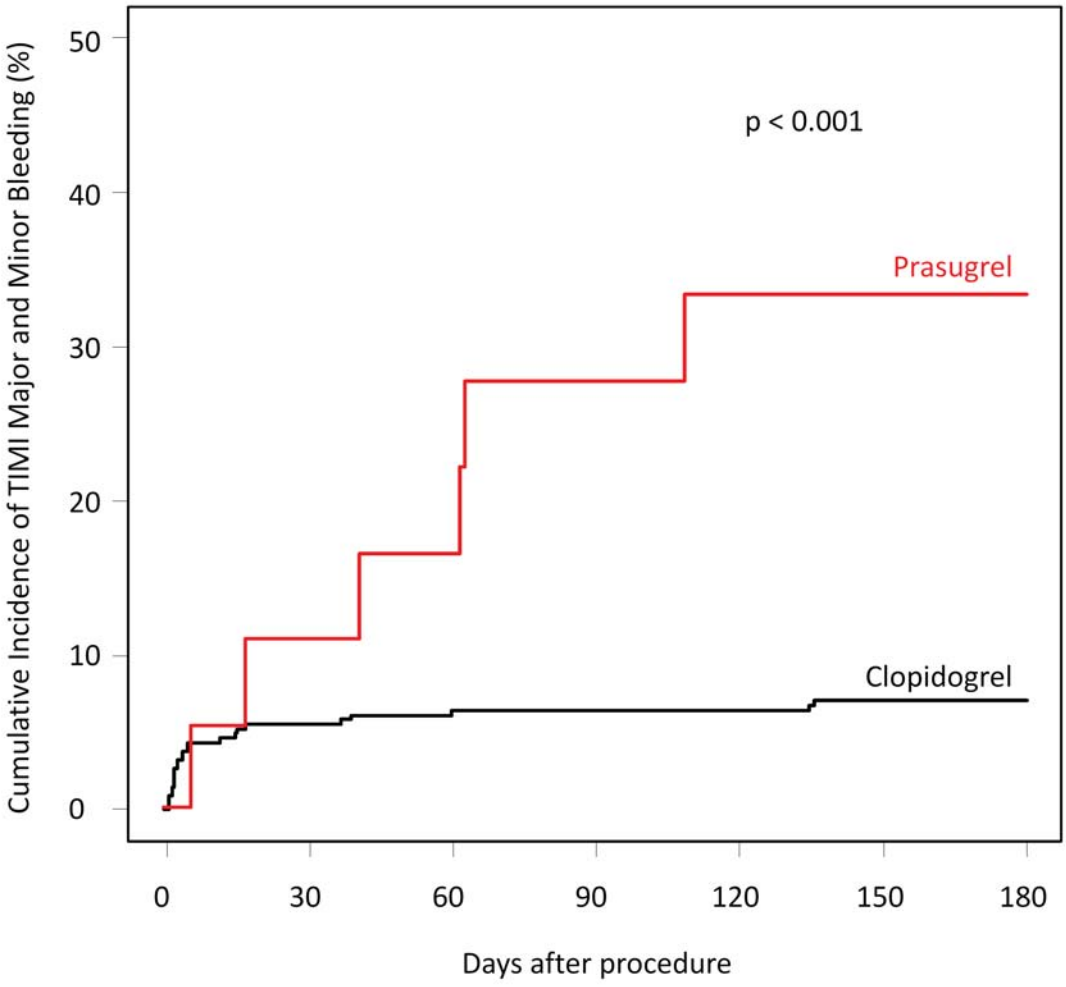
	Prasugrel n = 21 (%)	Clopidogrel n = 356 (%)	unadjusted HR [95% CI]	p value
TIMI Major and Minor	6 (28.6)	24 (6.7)	4.6 [1.9 -11.4]	< 0.001
TIMI Major	3 (14.3)	10 (2.8)	6.1 [1.6-22.1]	0.006
TIMI Minor	3 (14.3)	14 (3.9)	3.8 [1.1-13.1]	0.04
MACCE	2 (9.5)	25 (7.0)	1.4 [0.3-6.1]	0.61
Death	2 (9.5)	14 (3.9)	2.6 [0.6-11.5]	0.20
Myocardial infarction	0	7 (2.0)	-	0.99
Stent thrombosis	0	2 (0.6)	-	0.99
Stroke	1 (4.8)	6 (1.7)	3.1 [0.4-25.4]	0.30
Ischemic	0	5 (1.4)		0.99
Hemorrhagic	1 (4.8)	1 (0.3)	18 [1.1-292]	0.04

Data are number of patients (percentages)

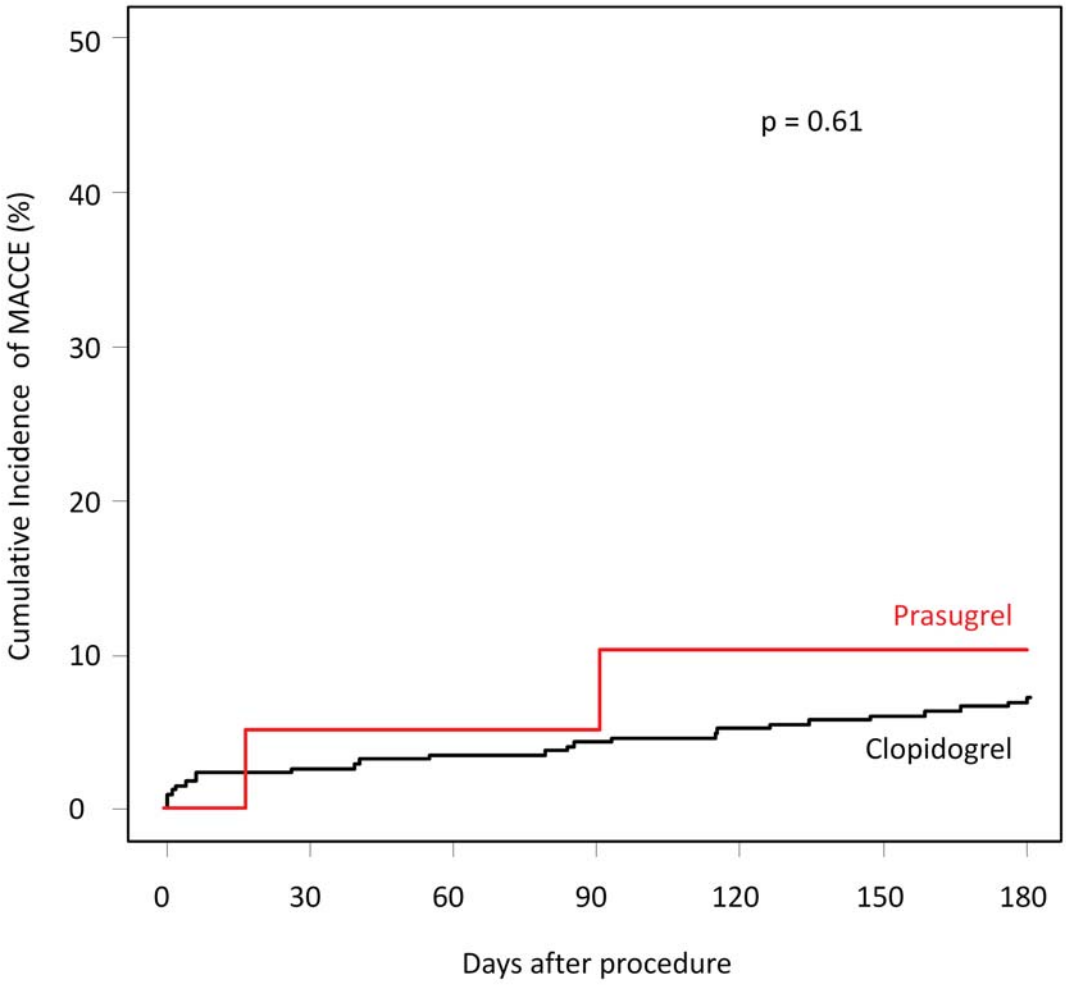
HR: Hazard ratio

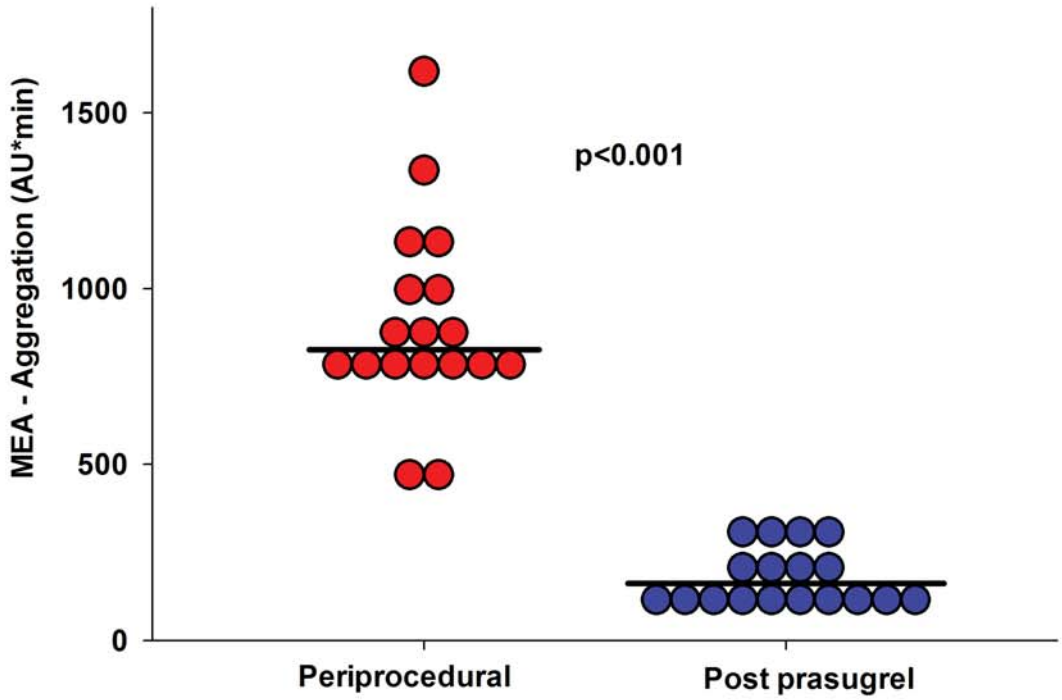
MACCE: Composite of major cardiac and cerebral events: Death, myocardial infarction, stent thrombosis or ischemic stroke

ACCEPTED MANUSCRIPT



ACCEPTED MANUSCRIPT




MEA - Aggregation (AU*min)
1500
1000
500
0
p<0.001
Periprocedural
Post prasugrel