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Clinical use of cangrelor: a real world multicenter experience from South Italy Insights from the M.O.Ca. registry

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ABSTRACT

BACKGROUND: Dual antiplatelet therapy (DAPT) with acetylsalicylic acid and oral $P2Y_{12}$ inhibitor ($P2Y_{12}$-I) represents the standard of care for patients with acute coronary syndromes (ACS) or with chronic coronary syndromes (CCS) treated with percutaneous coronary intervention (PCI). Cangrelor, the first intravenous $P2Y_{12}$-I, is deemed to overcome the drawbacks of the oral administration; nevertheless real world data on this new drug are scanty. We sought to investigate routine clinical use of cangrelor in four interventional centers of Italy.

METHODS: We enrolled 241 consecutive patients (196 ACS, 45 CCS) treated with cangrelor during PCI. Drug administration modalities and in-hospital clinical outcomes were evaluated. A subanalysis in patients selected on the basis of the CHAMPION Phoenix trial inclusion/exclusion criteria (CHAMPION-like subpopulation) was also performed.

RESULTS: Cangrelor was mainly utilized in ACS patients, who presented poorer clinical conditions and higher bleeding risk. Cangrelor was given only in $P2Y_{12}$-I naïve patients; switch to clopidogrel was always done at the end of the infusion, while ticagrelor or prasugrel were prevalently given 30 minutes before. In-hospital mortality was 10.0% and GUSTO moderate/severe bleeding was 2.5%. Bleeding data showed nevertheless to be in line with the CHAMPION Phoenix results in the "CHAMPION-like" subpopulation.

CONCLUSIONS: Cangrelor was predominantly used in ACS with modalities substantially in accord with the label indications. Poor clinical outcomes are due to the prevalent utilization in highly challenging clinical settings, nevertheless the rate of bleeding and stent thrombosis are in line with the randomized trials if analyzed in a subpopulation of comparable risk profile.

KEYWORDS: Cangrelor; DAPT; $P2Y_{12}$ inhibitors.

Introduction

The dual antiplatelet therapy (DAPT), consisting of the association of acetylsalicylic acid and an inhibitor of the $P2Y_{12}$ receptor, represents the standard of care for patients with acute coronary syndromes (ACS) or with chronic coronary syndromes (CCS) undergoing percutaneous coronary intervention (PCI)[1]. Aim of the DAPT is the inhibition of platelet aggregation to prevent thrombus formation which is involved in the pathogenesis of ACS and is a possible complication after stent implantation [2]. As a consequence, an effective platelet inhibition showed to reduce the rate of adverse coronary ischemic events after both the first ACS episode and after PCI with stent [3,4]. To date, clopidogrel, ticagrelor, and prasugrel are the most widely used oral $P2Y_{12}$ inhibitors ($P2Y_{12}$-I) as part of the DAPT [5]. These $P2Y_{12}$-I share nevertheless some common limitations: slow onset of action, slow offset of action, and the impossibility to be administrated or to be fully effective in patients with orotracheal intubation, vomit, and impaired intestinal absorption [6]. Notably, the delay in platelet inhibition represents a relevant weakness in clinical settings requiring rapid antiplatelet effect [7]. Cangrelor is a novel intravenous $P2Y_{12}$-I able to overcome all the above mentioned drawbacks [5]. Cangrelor was approved by the European Medicines Agency (EMA) on the basis of three large randomized clinical trials included in the CHAMPION (Cangrelor versus standard therapy to achieve optimal management of platelet inhibition) program. The CHAMPION studies demonstrated that cangrelor reduces ischemic complications after PCI with no increase of GUSTO (Global Use of Strategies to Open Occluded Coronary Artery) severe/life threatening bleedings [8-11]. However, these randomized trials were followed by only very few real-world data from everyday clinical practice [12,13]. We sought to investigate the real world use of cangrelor in four south-Italy interventional centres. In detail, we focused on the clinical settings of utilization, modality of the switch to oral $P2Y_{12}$-I, and in-hospital ischemic and hemorrhagic outcomes.

Materials and methods

The study enrolled all consecutive patients treated with cangrelor during PCI procedures performed in the Cardiology Divisions of the following hospital: Azienda Ospedaliero Universitaria Consorziale Policlinico of Bari, L. Bellomo Hospital of Andria, Federico II University of Naples, Santissima Annunziata Hospital of Taranto. In each center, from the first availability of the drug and through January 2021, all patients were enrolled; the first

patient was treated in September 2019. The study has an ambispective design since data were both retrospectively and prospectively collected; the ethics committees of all centers approved the study and all patients provided a written informed consent with the exception of those unable for clinical reasons. PCI procedures were performed per standard of care and at the discretion of the treating physicians. The use of cangrelor was decided by the interventional cardiologist on an individual basis, taking into consideration both clinical and procedural features. In all patients cangrelor was administered after the coronary angiography and immediately before PCI with a 30 microg/kg bolus and a 4 microg/kg/min infusion as per label recommendations. The adjunctive pharmacological therapy was at physician's discretion and largely based on contemporary best practice according to the national and European scientific societies. Taking part to the study did not modify in any way patients' diagnostic and therapeutic workup.

The registry was broadly inclusive, since only patients younger than 18 years old or enrolled in a research study were excluded. Information on baseline demographics, clinical characteristics, processes of care, and in-hospital outcomes were collected.

Patients at high bleeding risk (HBR) were identified according to the Academic Research Consortium (ARC) definition [14]. The hemorrhagic risk was also calculated on the basis of the PRECISE DAPT score [15]. Complex PCI was defined as a procedure with at least one of the following angiographic characteristics: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with deployment of 2 stents, total stent length >60mm, chronic total occlusion [16].

Due to the observatory nature of the study no preliminary hypotheses were generated. The clinical endpoints of the study were: bleeding defined according to the BARC, GUSTO, TIMI, and ISHT definitions [17-20], death, definite or probable stent thrombosis (ST) assessed according to the ARC definition [21], acute myocardial infarction (AMI) defined on the basis of its fourth universal definition, [22] and periprocedural myocardial infarction according to the CHAMPION PHOENIX definition [10].

The database was built up by Excel software (Microsoft Corporation, Redmond, Washington, USA); data were analyzed by IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). The study population was divided on the basis of the diagnosis of presentation [CCS, ACS, non-ST-segment elevation acute coronary syndromes (NSTE-ACS), ST-segment acute myocardial infarction (STEMI)]. Baseline

characteristics, procedural features, and follow-up data of the overall population and per group were presented. The clinical endpoints were also analyzed in a specific subpopulation selected on the basis of the CHAMPION Phoenix enrolment criteria. Continuous variables, described as ranges and means ± standard deviations, were compared by student's T test for independent data (parametric). Categorical variables, expressed as numbers with percentages, were compared by Chi-square test or Fisher exact test, when indicated. For all tests significance was set for a two-tailed value of $p<0.05$.

Data availability: the data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

Results

Overall study cohort included 241 patients: 45 in the CCS and 196 in the ACS group. They represented the 17.1% of the patients undergone PCI at the participating centers since the local introduction of cangrelor; in detail cangrelor was used in the 13.5% and 18.3% of PCI respectively executed for CCS and ACS (p=0.044; Figure 1). Baseline characteristics of the overall population and per group are reported in Table I and S1. Demographic features were similar between ACS and CCS patients. Most of the known markers of ischemic risk showed a higher prevalence in the CCS group, but threshold for significance was reached only for diabetes (p=0.042) and prior coronary revascularization (P=0.046). On the other hand, baseline laboratory data (hemoglobin, white blood cells, glycemia, and low-density lipoprotein levels) were at disadvantage of the ACS group. Poor clinical conditions at presentation (Killip class ≥2, cardiogenic shock, left ventricle ejection fraction, orotracheal intubation, and cardiac arrest) were also more prevalent among ACS patients, as expected. Moreover, the ACS group also showed a tendency toward a greater bleeding risk, as suggested by the higher PRECISE DAPT score (p=0.050) and the superior (though not significantly) quote of HBR patients according to the ARC definition.

Angiographic characteristics of the coronary disease and PCI features are reported in Table II. Radial access was prevalent (80.5% of all procedures) but less used in the ACS group (p=0.02). Coronary disease was multivessel in 58.6% of cases, the left anterior descending artery was the treated vessel in 51.9% of PCI, 35.7% of patients received more than one stent with a total medium stent length of 38.28 ± 24.04 mm, while the multivessel PCI rate was 15.8%. Use of GpIIb/IIIa inhibitors was marginal and limited to

three ACS patients. Giustino's criteria for complex PCI were met in 17.8% of CCS and 19.9% of ACS patients. The switch to an oral $P2Y_{12}$-I was always performed with a loading dose: 180 mg for ticagrelor, 60 mg for prasugrel, 600 mg for clopidogrel. Further characteristics of the switching modalities are detailed in the Tables IIIa and IIIb. Briefly, cangrelor infusion lasted two hours in 97.4% of cases; in two patients the infusion was shorter and in four longer. Concerning the timing of the switch, clopidogrel was always given at the end of cangrelor infusion, while ticagrelor and prasugrel 30 minutes before the stop of the infusion in the 73.5% and 91.3% of cases respectively. The choice of the oral $P2Y_{12}$-I was driven by the index event as depicted in Table IIIb and Figure 2; clopidogrel was administrated in 91.1% of CCS, but also in 29.4% of ACS patients. Among the ACS patients switched to a more potent $P2Y_{12}$-I (70.6%), ticagrelor was preferred over prasugrel in 82.6% of cases. Worthy of mention that 13.8% of ACS and 4.4% of CCS patients were discharged on a triple antithrombotic therapy.

Clinical outcome data are shown in Table IV. Duration of hospital stay was 7.21 ± 5.45 days. Seven patients in the ACS group suffered from contrast induced nephropathy. One definite and one probable ST were observed in two ACS patients. One periprocedural AMI was due to a ST and one occurred in a patient with a Factor V Leiden mutation. Hemorrhagic complications happened in 2.9% of the overall population: GUSTO severe/life threatening bleedings were reported in 0.4% of patients, while this percentage rose to 2.5% considering also GUSTO moderate bleeding. Overall mortality rate was 10.0%, with a significant difference between the CCS and ACS group (0% vs 12.2%, p=0.010). As strictly concerns ACS, mortality rate was higher in STEMI (17.4%) as compared to NSTE-ACS patients (4.9%), as depicted in Table S2. However, death rate reassessed after the exclusion of patients who presented with shock, orotracheal intubation, and/or cardiac arrest, resulted downsized to 3% in the overall population, 5.1% in STEMI, and 2.6% in NSTE-ACS patients. Table V shows bleeding and ST data in a subgroup of patients selected on the basis of the CHAMPION Phoenix inclusion/exclusion criteria (the "CHAMPION like" population). Bleedings evaluated by GUSTO and TIMI definitions were in line with those observed in the CHAMPION Phoenix trial. Similarly, ST (definite, probable, and combined) data were also comparable with those of the randomized trial.

Discussion

The main findings of this real-world registry are: 1. Cangrelor was mainly used in ACS patients rather than in CCS patients; 2. Cangrelor administration and switch to oral $P2Y_{12}$-I was in line with label recommendations; 3. Clinical outcomes in terms of mortality and bleeding were only "apparently" disappointing and are widely explained by a biased use of the drug in a cohort of patients at very high clinical risk.

In our registry, 81.3% of patients had an ACS as clinical presentation (47.7% STEMI, 33.6% NSTE-ACS) and the remaining 18.7% a CCS. The prevalent use of cangrelor in the setting of ACS is in line with the recent observational study by Grimfjard, based on the Swedish SCAAR registry [12], which included only STEMI patients because this setting exceeded the 98% of cases in which cangrelor was used in Sweden. Moreover, another registry also showed a prevalent use of cangrelor in ACS patients who represented the 93% of the entire study population [13]. Nevertheless, divergently from the above mentioned observational studies, our cohort appears less dissimilar from the CHAMPION Phoenix trial population in which CCS patients accounted for about the 43%. The enrollment of all consecutive patients regardless of the clinical presentation provides indeed a more comprehensive snapshot of the real world use of the drug. The baseline characteristics of our population might explain why cangrelor was prevalently used in ACS. ACS patients showed indeed a high hemorrhagic risk at presentation since they had a higher rate of previous bleedings, lower hemoglobin levels, and were more often on chronic therapy with anticoagulants. As a confirmation, they presented with a higher PRECISE DAPT score and a larger quote of HBR subjects according to the ACR definition. Moreover, in line with the current recommendations, about 21% of ACS patients were "ideal" patients for cangrelor use since they accessed the cathlab intubated, in state of shock, or resuscitated from cardiac arrest [23]. In summary, the combination of the rapid onset of action, rapid recovery of platelet function in HBR conditions, and avoidance of the oral intake limitations might be the rationale for the prevalent cangrelor use in the setting of ACS.

Another finding of the present registry is the rigorous compliance, in terms of patients selection and switch modality to oral $P2Y_{12}$-I, with the design of the registration studies. Accordingly, all treated patients were naïve per any previous $P2Y_{12}$-I and duration of infusion was 120 minutes in almost all cases. Oral $P2Y_{12}$-I were administrated at different time-points: a loading clopidogrel dose at the end of the cangrelor infusion, while loading doses of prasugrel or ticagrelor were in most cases given 30 minutes before, but never

earlier. Thus, the involved interventional cardiologists showed a strict respect of EMA's indications as reported in the label. This evidence is other than banal since one third of the cangrelor patients included in the SCAAR observational study had been pretreated with ticagrelor and one other third received ticagrelor at the start of the intravenous infusion [12]. The off-label timing of the switch is actually supported by some studies, mainly based on pharmacokinetic data, that claimed the safety of the coadministration [24-26]. Nevertheless, only the full respect of the label indications, as in our study, makes the outcome results comparable with the cangrelor registration studies. In agreement with the current guidelines [1], for CCS patients the use of clopidogrel was roughly mandatory, while patients with ACS were switched to a potent $P2Y_{12}$-I in the 70.6% of cases. Moreover, when a more potent oral $P2Y_{12}$-I was given, ticagrelor was preferred over prasugrel in 82.6% of cases (Fig. 2). This preference might be explained by the more solid evidences on the safe and effective co-administration of cangrelor and ticagrelor, which has also permitted in US the on-label administration of ticagrelor at any point in time of cangrelor infusion [26]. Nevertheless the doubt about a drug-drug interaction between cangrelor and prasugrel, which share the same $P2Y_{12}$ receptor binding site, has been partly dispelled by the pharmacokinetic data from the ExcelsiorLOAD2 trial, [25] which supports a comparable antiplatelet effects of ticagrelor and prasugrel when given at the start of cangrelor infusion. Despite the quote of 29.4% of clopidogrel administration in ACS patients is consistent with other ACS registries [27-29], it is only partly ascribable to the proportion of patients deemed to receive a triple antithrombotic therapy and supports the above mentioned hypothesis of the use of cangrelor in patients who are judged at HBR.

Efficacy and safety endpoints are limited by the cohort size, nevertheless what meets the eye at first glance is the high all-cause mortality (10.0%), which is mainly driven by the subpopulation of STEMI patients (17.4%). Yet, this outcome might have been influenced by the high percentage of patients who accessed the cath-lab in critical conditions as proved by the non negligible quote of orotracheal intubation, cardiac arrest, and cardiogenic shock [30]. All these conditions are, as previously pointed out, ideal settings for cangrelor use. The tendency of the operators to prevalently use cangrelor in clinically challenging situations is supported by the consistency of our data with the SCAAR registry which included only STEMI patients and reported a 30 days death rate of 15.1%. The exclusion of the above mentioned conditions from our registry drops the mortality rate of the STEMI subgroup to 5.1%, which is in line with recent real world data

on non cangrelor-treated STEMI patients [27-29,31]. During hospital stay one case of definite and one of probable ST were registered; the consequent 0.8% rate of combined definite/probable ST is consistent with both the CHAMPION Phoenix (0.8% at 48 hours from the PCI) and the SCAAR registry (0.7% at 30 days).

Another significant finding of this registry regards the bleeding events. We observed that moderate/severe GUSTO bleedings account for 2.5% in our cohort compared to the 0.6% in the CHAMPION Phoenix study. However, several considerations should be done in interpreting these results: first, ACS patients were more represented in our registry than in the randomized trial; second, in the latter the need for a written informed consent tended to exclude intubated and resuscitated patients who present high bleeding risk, [32,33]; third, all those patients with a history of stroke, cancer, recent trauma or major surgery, active bleeding, known bleeding diathesis, and chronic oral anticoagulant therapy were non eligible for the randomized study. The imbalance between the risk profile of the two cohorts is proved by the analysis of the bleeding data, according to multiple currently used definitions, performed in a "CHAMPION like" group, generated by applying to our population the CHAMPION Phoenix enrolment criteria. In this subgroup of patients bleeding events were indeed definitely in line with those observed in the randomized trial.

The present analysis could not avoid certain limitations. The non-randomized nature of the data may result in a selection bias: the use of cangrelor was at the discretion of the physician and was preferred in ACS setting and clinically more challenging presentations. Moreover, the sample size was small, so the reliability of the efficacy and safety endpoints is jeopardized; nevertheless it should be considered that, to the best of authors knowledge, only other two real world reports on this innovative pharmacological approach are available in literature. Finally, no details on cardiopulmonary resuscitation and management of shocked patients were provided.

Conclusions

The present registry reports for the first time on the initial experience of cangrelor use in all coronary syndrome settings. This real world snapshot suggests that cangrelor is prevalently used in patients with ACS, than in those with CCS. This choice might have been driven by the higher bleeding risk at baseline and the preclusion or expected ineffectiveness of the oral administration in extremely challenging clinical settings. The modalities of cangrelor

utilization and switching to oral $P2Y_{12}$-I were respectful of label indications. In hospital clinical endpoints were in line with the results of the randomized trials with cangrelor if the same inclusion/exclusion criteria were applied.

REFERENCES

1. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, *et al*. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019; 40(2): 87–165. doi:10.1093/eurheartj/ehy394.
2. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, *et al*. 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). Eur Heart J 2018; 39(3): 213–260. doi: 10.1093/eurheartj/ehx419.
3. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, 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(7): 494–502. doi: 10.1056/NEJMoa010746.
4. Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK, *et al*. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. N Engl J Med 1998; 339(23): 1665–1671. doi: 10.1056/NEJM199812033392303.
5. Gorog DA, Geisler T. Platelet Inhibition in Acute Coronary Syndrome and Percutaneous Coronary Intervention: Insights from the Past and Present. Thromb Haemost 2020; 120(4): 565–578. doi: 10.1055/s-0040-1702920.
6. Alexopoulos D, Pappas C, Sfantou D, Lekakis J. Cangrelor in Percutaneous Coronary Intervention: Current Status and Perspectives. J Cardiovasc Pharmacol Ther 2018; 23(1): 13–22. doi: 10.1177/1074248417715004.
7. Pepe M, Cafaro A, Paradies V, Signore N, Addabbo F, Bortone AS, *et al*. Time-dependent benefits of pre-treatment with new oral P2Y12 -inhibitors in patients addressed to primary PCI for acute ST-elevation myocardial infarction. Catheter Cardiovasc Interv 2019; 93(4): 592–601. doi: 10.1002/ccd.27863.
8. Harrington RA, Stone GW, McNulty S, White HD, Lincoff AM, Gibson CM, *et al*. Platelet inhibition with cangrelor in patients undergoing PCI. N Engl J Med 2009; 361(24): 2318–2329. doi: 10.1056/NEJMoa0908628.

9. Bhatt DL, Lincoff AM, Gibson CM, Stone GW, McNulty S, Montalescot G, *et al*. Intravenous platelet blockade with cangrelor during PCI. N Engl J Med 2009; 361(24): 2330–2341. doi: 10.1056/NEJMoa0908629.
10. Bhatt DL, Stone GW, Mahaffey KW, Gibson CM, Steg PG, Hamm CW, *et al*. Effect of platelet inhibition with cangrelor during PCI on ischemic events. N Engl J Med 2013; 368(14): 1303–1313. doi: 10.1056/NEJMoa1300815.
11. Stone GW, Généreux P, Harrington RA, White HD, Gibson CM, Steg PG, *et al*. Impact of lesion complexity on peri-procedural adverse events and the benefit of potent intravenous platelet adenosine diphosphate receptor inhibition after percutaneous coronary intervention: core laboratory analysis from 10 854 patients from the CHAMPION PHOENIX trial. Eur Heart J 2018; 39(46): 4112–4121. doi: 10.1093/eurheartj/ehy562.
12. Grimfjärd P, Lagerqvist B, Erlinge D, Varenhorst C, James S. Clinical use of cangrelor: nationwide experience from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). Eur Heart J Cardiovasc Pharmacother 2019; 5(3): 151–157. doi: 10.1093/ehjcvp/pvz002.
13. Hideo-Kajita A, Rogers T, Buchanan K, Iantorno M, Gajanana D, Ozaki Y, *et al*. Effects of Cangrelor as Adjunct Therapy to Percutaneous Coronary Intervention. Am J Cardiol 2019; 123(8): 1228–1238. doi: 10.1016/j.amjcard.2019.01.031.
14. Urban P, Mehran R, Colleran R, Angiolillo DJ, Byrne RA, Capodanno D, *et al*. Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. Eur Heart J 2019; 40(31): 2632–2653. doi: 10.1093/eurheartj/ehz372.
15. Costa F, van Klaveren D, James S, Heg D, Räber L, Feres F, *et al*. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet 2017; 389(10073): 1025–1034. doi: 10.1016/S0140-6736(17)30397-5.
16. Giustino G, Chieffo A, Palmerini T, Valgimigli M, Feres F, Abizaid A, *et al*. Efficacy and Safety of Dual Antiplatelet Therapy After Complex PCI. J Am Coll Cardiol 2016; 68(17): 1851–1864. doi: 10.1016/S0140-6736(17)30397-5.

17. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, *et al*. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011; 123(23): 2736–2747. doi: 10.1161/CIRCULATIONAHA.110.009449.
18. GUSTO investigator. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993; 329(10): 673–682. doi: 10.1056/NEJM199309023291001.
19. Mega JL, Braunwald E, Mohanavelu S, Burton P, Poulter R, Misselwitz F, *et al*. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. Lancet 2009; 374(9683): 29–38. doi: 10.1016/S0140-6736(09)60738-8.
20. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005; 3(4): 692–694. doi: 10.1111/j.1538-7836.2005.01204.x.
21. Pinto Slottow TL, Waksman R. Overview of the 2006 Food and Drug Administration Circulatory System Devices Panel meeting on drug-eluting stent thrombosis. Catheter Cardiovasc Interv 2007; 69(7): 1064–1074. doi: 10.1002/ccd.21179.
22. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, *et al*. Fourth universal definition of myocardial infarction. Eur Heart J 2019; 40: 237-269. doi.org/10.1093/eurheartj/ehy462.
23. Gorog DA, Price S, Sibbing D, Baumbach A, Capodanno D, Gigante B, *et al*. Antithrombotic therapy in patients with acute coronary syndrome complicated by cardiogenic shock or out-of-hospital cardiac arrest: a Joint Position Paper from the European Society of Cardiology (ESC) Working Group on Thrombosis, in association with the Acute Cardiovascular Care Association (ACCA) and European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J Cardiovasc Pharmacother 2020 Feb 12 [e-pub ahead of print], doi: 10.1093/ehjcvp/pvaa009.
24. Hochholzer W, Amann M, Titov A, Younas I, Löffelhardt N, Riede F, *et al*. Randomized Comparison of Different Thienopyridine Loading Strategies in

Patients Undergoing Elective Coronary Intervention: The ExcelsiorLOAD Trial. J Am Coll Cardiol Intv 2016; 9(3): 219–227. doi: 10.1016/j.jcin.2015.10.036.

25. Hochholzer W, Kleiner P, Younas I, Valina CM, Löffelhardt N, Amann M, *et al*. Randomized Comparison of Oral P2Y12-Receptor Inhibitor Loading Strategies for Transitioning From Cangrelor: The ExcelsiorLOAD2 Trial. J Am Coll Cardiol Intv 2017; 10(2): 121–129. doi: 10.1016/j.jcin.2016.10.004.
26. Franchi F, Rollini F, Rivas A, Wali M, Briceno M, Agarwal M, *et al*. Platelet Inhibition With Cangrelor and Crushed Ticagrelor in Patients With ST-Segment-Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. Circulation 2019; 139(14): 1661–1670. doi: 10.1161/CIRCULATIONAHA.118.038317.
27. De Luca L, Leonardi S, Cavallini C, Lucci D, Musumeci G, Caporale R, *et al*. Contemporary antithrombotic strategies in patients with acute coronary syndrome admitted to cardiac care units in Italy: The EYESHOT Study. Eur Heart J Acute Cardiovasc Care 2015; 4(5): 441–452. doi: 10.1177/2048872614560505.
28. De Luca L, D'Ascenzo F, Musumeci G, Saia F, Parodi G, Varbella F, *et al*. Incidence and outcome of switching of oral platelet P2Y12 receptor inhibitors in patients with acute coronary syndromes undergoing percutaneous coronary intervention: the SCOPE registry. EuroIntervention 2017; 13(4): 459–466. doi: 10.4244/EIJ-D-17-00092.
29. Redfors B, Dworeck C, Haraldsson I, Angerås O, Odenstedt J, Ioanes D, *et al*. Pretreatment with P2Y12 receptor antagonists in ST-elevation myocardial infarction: a report from the Swedish Coronary Angiography and Angioplasty Registry. Eur Heart J 2019; 40(15): 1202–1210. doi: 10.1093/eurheartj/ehz069.
30. Pepe M, Bortone AS, Giordano A, Cecere A, Burattini O, Nestola PL, *et al*. Cardiogenic Shock Following Acute Myocardial Infarction: What's New? Cardiogenic Shock Following Acute Myocardial Infarction: What's New?. Shock 2020; 53(4): 391–399. doi: 10.1097/SHK.0000000000001377.
31. Pepe M, Sardella G, Stefanini GG, Corcione N, Nestola PL, Morello A, *et al*. Impact of Insulin-Treated and Noninsulin-Treated Diabetes Mellitus in All-Comer Patients Undergoing Percutaneous Coronary Interventions With Polymer-Free Biolimus-Eluting Stent (from the RUDI-FREE Registry). Am J Cardiol 2019; 124(10): 1518–1527. doi: 10.1016/j.amjcard.2019.08.015.

32. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, *et al*. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. N Engl J Med 1999; 341(9): 625–634. doi: 10.1056/NEJM199908263410901.
33. Thiele H, Akin I, Sandri M, Fuernau G, de Waha S, Meyer-Saraei R, *et al*. PCI Strategies in Patients with Acute Myocardial Infarction and Cardiogenic Shock. N Engl J Med 2017; 377(25): 2419–2432. doi: 10.1056/NEJMoa1710261.

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TABLES

Table I.— Anamnestic data and baseline characteristics

	Overall *(N=241, 100%)*	***CCS*** *(N=45, 18.7%)*	***ACS*** *(N=196, 81.3%)*	***P***
Anamnestic data				
Age, yrs	68.69 ± 10.94	68.76 ± 10.31	68.67± 11.10	0.964
≥75 years old	75 (31.1%)	15 (33.3%)	60 (30.6%)	0.722
Male sex	182 (75.5%)	35 (77.8%)	147 (75.0%)	0.696
Diabetes mellitus	53 (22.0%)	15 (33.3%)	38 (19.4%)	0.042
Arterial hypertension	189 (78.4%)	36 (80.0%)	153 (78.1%)	0.776
Dyslipidaemia	167 (69.3%)	33 (73.3%)	134 (68.4%)	0.515
Current smoker	74 (30.7%)	9 (20.0%)	65 (33.2%)	0.084
Family history of CAD	52 (21.6%)	10 (22.2%)	42 (21.4%)	0.907
Obesity	46 (19.1%)	10 (22.2%)	36 (18.4%)	0.553
Weight (kg)	78.66 ± 14.34	80.82 ± 12.06	78.35 ± 14.65	0.453
<60 Kg	8 (3.3%)	1 (2.2%)	7 (3.6%)	1
Prior percutaneous coronary intervention	38(15.8%)	10 (22.2%)	28(14.3%)	0.188
Prior coronary bypass	15(6.2%)	5 (11.1%)	10 (5.1%)	0.165
Prior coronary revascularization	49(20.3%)	14 (31.1%)	35(17.9%)	0.046
Prior myocardial infarction	27 (11.2%)	6 (13.3%)	21 (10.7%)	0.615
Prior stroke	4 (1.7%)	2 (4.4%)	2 (1.0%)	0.159
Prior haemorrhages	6 (2.5%)	0 (0%)	6 (3.1%)	0.597
Peripheral artery disease	20 (8.3%)	5 (11.1%)	15 (7.7%)	0.547
Recent major trauma or surgery	3 (1.2%)	0 (0%)	3 (1.5%)	1
Chronic kidney disease	56 (23.2%)	10 (22.2%)	46 (23.5%)	0.858
Chronic OAC therapy	18 (7.5%)	1 (2.2%)	17 (8.7%)	0.209
Baseline characteristic				

eGFR	80.07 ± 31.24	76.91 ± 24.85	80.86 ± 32.65	0.454
Creatinine	1.07 ± 0.75	1.02 ± 0.32	1.08 ± 0.83	0.638
Glycemia	130.20 ± 63.20	113.78 ± 33.84	134.32 ± 68.08	0.051
LDL	99.24 ± 37.45	88.03 ± 29.08	101.97 ± 38.81	0.042
Haemoglobin	13.58 ± 1.93	14.04 ± 1.47	13.47 ± 2.02	0.078
Platelets	227.25 ± 84.18	227.98 ± 73.96	227.07 ± 86.66	0.948
White blood cells	9.89 ± 4.00	7.49 ± 1.91	10.55 ± 4.18	<0.005
LVEF at admission (%)	46.97 ± 10.54	49.73 ±11.51	46.28 ± 10.20	0.052
Killip class ≥ 2 at admission	46 (19.1%)	3 (6.7%)	43 (21.9%)	0.020
Orotracheal intubation	23 (9.5%)	0 (0%)	23 (11.7%)	0.010
Cardiocirculatory arrest	26 (10.8%)	1 (2.2%)	25 (12.8%)	0.058
Shock	29 (12.0%)	0 (0%)	29 (14.8%)	0.004
Orotracheal intubation, cardiocirculatory arrest or shock patients	42 (17.4%)	1 (2.2%)	41 (20.9%)	<0.005
High Bleeding Risk patients (ACR definition)	71 (29.5%)	9 (20.0%)	62 (31.6%)	0.123
PRECISE DAPT	23.43± 15.06	19.45± 10.95	24.43 ± 15.80	0.050
PRECISE DAPT ≥25 (%)	87 (36.1%)	14 (31.1%)	73 (37.2%)	0.440

Values are expressed as mean±SD or n (%).

CAD: coronary artery disease, OAC: oral anticoagulation, eGFR= Estimated glomerular filtration rate, LDL: low-density lipoprotein, LVEF: left ventricular ejection fraction

Table II.— Procedural features

	Overall *(N=241, 100%)*	***CCS*** *(N=45, 18.7%)*	***ACS*** *(N=196, 81.3%)*	***P***
Femoral access	47 (19.5%)	3 (6.7%)	44 (22.4%)	0.020
Radial access	194 (80.5%)	42 (93.3%)	152 (77.6%)	0.020
LM disease (/195)	8 (4.1%)	1 (2.8%)	7 (4.4%)	1
Multivessel CAD (/203)	119 (58.6%)	27 (62.8%)	92 (57.9%)	0.560
Treated vessel				
LAD	125 (51.9%)	24 (53.3%)	101 (51.5%)	0.827
LCX	39 (16.2%)	5 (11.1%)	34 (17.3%)	0.375
RCA	73 (30.3%)	13 (28.9%)	60 (30.6%)	0.821
LM	7 (2.9%)	2 (4.4%)	5 (2.6%)	0.618
SVG	2 (0.8%)	0 (0%)	2 (1.0%)	1
Drug eluting stents	234 (97.1%)	44 (97.8%)	190 (96.9%)	1
Stent number/pt.	1.47± 0.83	1.47 ± 0.89	1.47 ± 0.81	0.954
Stent number ≥ 2	86 (35.7%)	15 (33.3%)	71 (36.2%)	0.845
Total stent length	38.28 ± 24.04	38.07 ± 24.23	38.33 ± 24.05	0.947
Multivessel PCI	38 (15.8%)	9 (20.0%)	29 (14.8%)	0.388
Bifurcations	32 (13.3%)	5 (11.1%)	27 (13.8%)	0.809
IIb/IIIa inhibitors infusion	3 (1.2%)	0 (0%)	3 (1.5%)	1
Drug eluting balloon	12 (5.0%)	2 (4.4%)	10 (5.1%)	0.855
Complex PCI*	47 (19.5%)	8 (17.8%)	39 (19.9%)	0.735
≥3 lesions	5 (2.1%)	2 (4.4%)	3 (1.5%)	0.235
≥3 vessels	6 (2.5%)	2 (4.4%)	4 (2.0%)	0.312
≥3 stents	25 (10.4%)	4 (8.9%)	21 (10.7%)	1
≥60 mm total stent length	42 (17.4%)	8 (17.8%)	34 (17.3%)	0.945
2-stents technique bifurcations	8 (3.3%)	0 (0%)	8 (4.1%)	0.358
Chronic total occlusion lesions	0 (0%)	0 (0%)	0 (0%)	
Transferred for surgical	9 (3.7%)	1 (2.2%)	8 (4.1%)	1

revascularization				
No Reflow	6 (2.5%)	0 (0%)	6 (3.1%)	0.597
PCI failure	4 (1.7%)	0 (0%)	4 (2.0%)	1

Values are expressed as mean±SD or n (%)

* According to Giustino'sdefinition (Giustino 2016)

LM: left main, CAD: coronary artery disease, LAD: left anterior discending, LCX: left circumflex artery, RCA: right coronary artery, SVG: simple venous graft, PCI: percutaneous coronary intervention

Table IIIa.— Switch to oral $P2Y_{12}$ inhibitor modalities

	Overall (N=232)#	*Clopidogrel (N=96)*	*Ticagrelor (N=113)*	*Prasugrel (N=23)*
Infusion time				
120 minutes Cangrelor infusion	226 (97.4%)	94 (97.9%)	110 (97.3%)	22 (95.7%)
Less than120 minutes	2 (0.9%)	0 (0%)	1 (0.9%)	1 (4.3%)
More than 120 minutes	4 (1.7%)	2 (2.1%)	2 (1.8%)	0 (0%)
Switch timing				
At the end of Cangrelor infusion	128 (55.2%)	96 (100%)	30 (26.5%)	2 (8.7%)
30 minutes before	104 (44.8%)	0 (0%)	83 (73.5%)	21 (91.3%)
More than 30 minutes before	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table IIIb.— Choice of the oral $P2Y_{12}$ inhibitor according to clinical presentation

	Switch to Clopidogrel	*Switch to Ticagrelor*	*Switch to Prasugrel*
CCS (N=45)	41 (91.1%)	4 (8.9%)	0 (0%)
ACS (N=187)	55 (29.4%)*	109 (58.3%)	23 (12.3%)
STEMI (N=108)	27 (25%)	65 (60.2%)	16 (14.8%)
NSTE-ACS (N=79)	28 (35.4%)	44 (55.7%)	7 (8.9%)
Overall (N=232)#	96 (41.4%)	113 (48.7%)	23 (9.9%)

#Nine patients never switched to an oral $P2Y_{12}$ inhibitor for clinical reasons (e.g.exitus, early haemorrhagic complications).

*28 patients (15%) were on triple antithrombotic therapy and in the remaining 27 (14.4%) Clopidogrel was preferred over a more potent oral $P2Y_{12}$-I based upon clinical judgment.

Table IV.— In-hospital follow-up data

	Overall *(N=241, 100%)*	***CCS*** *(N=45, 18.7%)*	***ACS*** *(N=196, 81.3%)*	***P***
Days of hospitalization	7.21 ± 5.45	5.91 ± 5.03	7.53 ± 5.51	0.080
Triple therapy at discharge	29 (12.0%)	2 (4.4%)	27 (13.8%)	0.124
Staged PCI	38 (15.8%)	3 (6.7%)	35 (17.9%)	0.070
Contrast induced nephropathy	7 (2.9%)	0 (0%)	7 (3.6%)	0.198
Myocardial infarction	3 (1.2%)	0 (0%)	3 (1.5%)	1
Periprocedural myocardial infarction	2 (0.8%)	0 (0%)	2 (1.0%)	1
Definite stent thrombosis	1 (0.4%)	0 (0%)	1 (0.5%)	1
Probable stent thrombosis	1 (0.4%)	0 (0%)	1 (0.5%)	1
BARC bleeding ≥3a	7 (2.9%)	2 (4.4%)	5 (2.6%)	0.618
TIMI major bleeding	3 (1.2%)	1 (2.2%)	2 (1.0%)	0.464
TIMI at least minor bleeding	7 (2.9%)	2 (4.4%)	5 (2.6%)	0.618
ISTH major bleeding	6 (2.5%)	2 (4.4%)	4 (2.0%)	0.312
GUSTO severe bleeding	1 (0.4%)	0 (0%)	1 (0.5%)	1
GUSTO at least moderate bleeding	6 (2.5%)	1 (2.2%)	5 (2.6%)	1
All-cause death	24 (10.0%)	0 (0%)	24 (12.2%)	0.010
Mortality reassessed after exclusion of cardiocirculatory arrest, orotracheal intubation and cardiogenic shock patient				
All-cause death	6/199 (3.0%)	0/44 (0%)	6/155 (3.9%)	0.342

Values are expressed as mean±SD or n (%).

PCI: percutaneous coronary intervention.

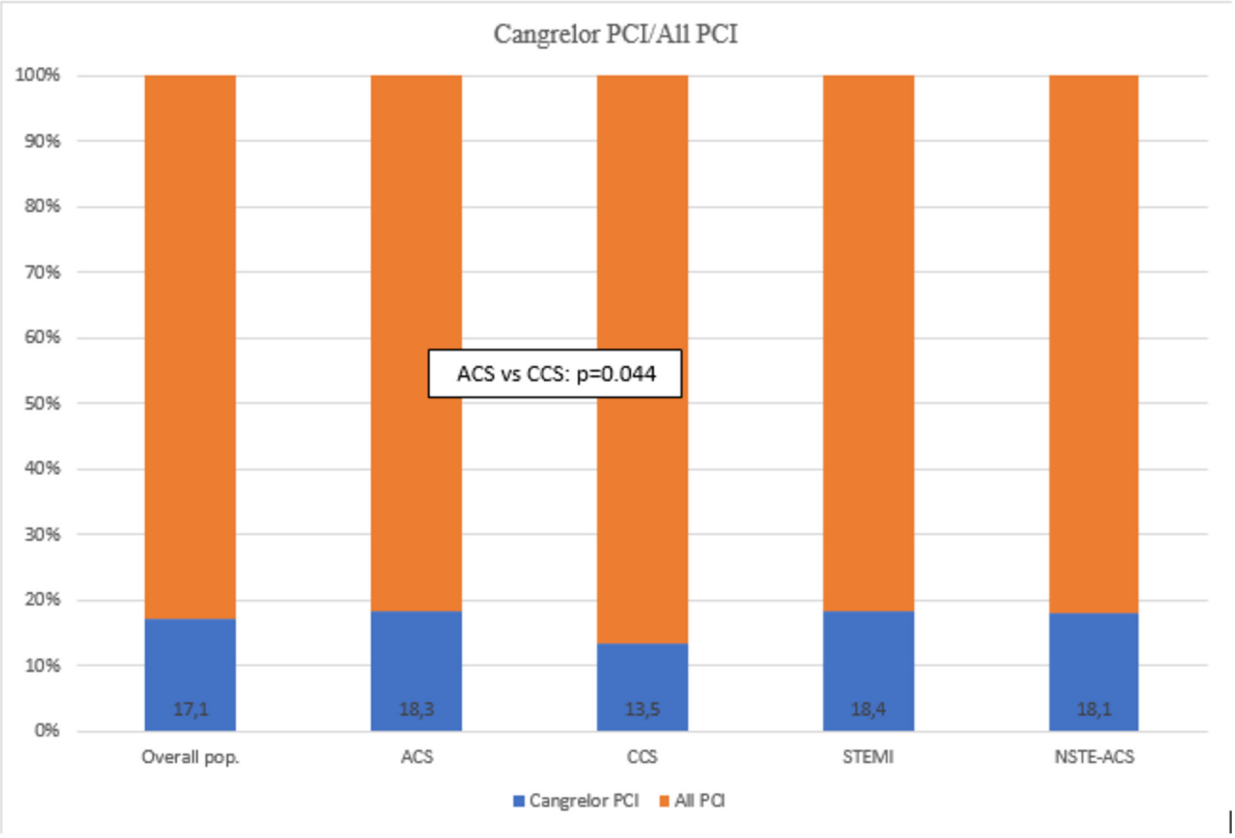
Table V.— Clinical endpoints in "CHAMPION like" population

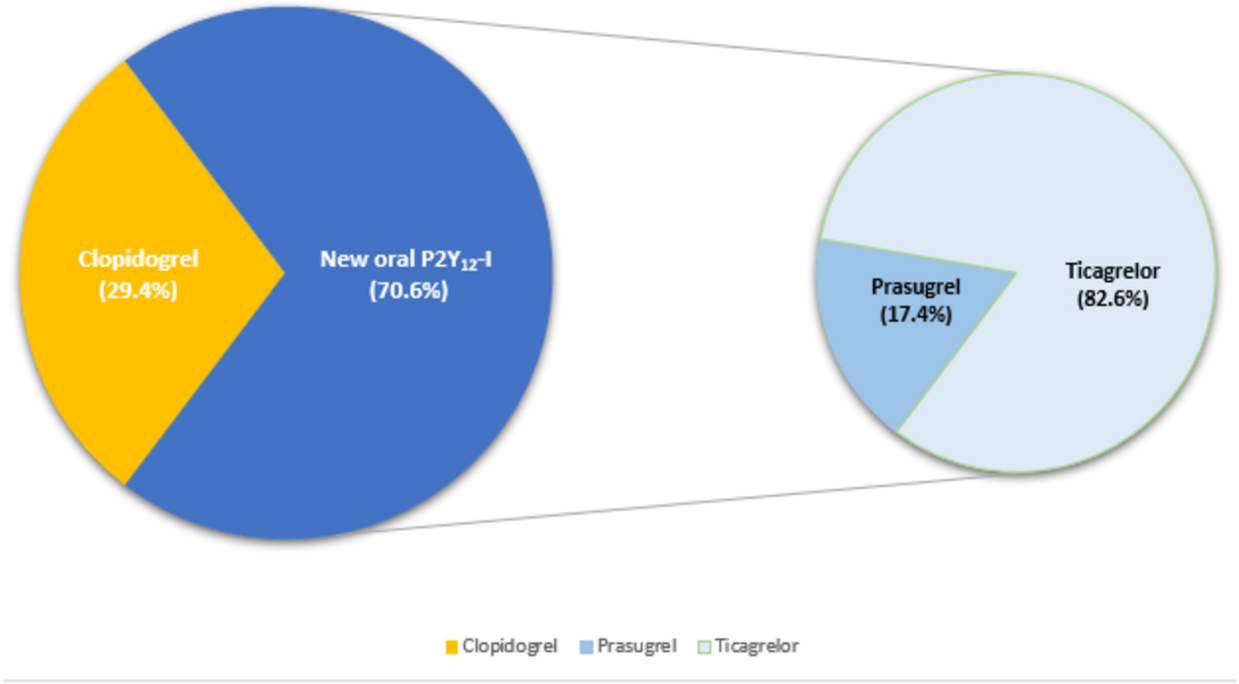
	Overall Population (N=241)	*"CHAMPION like" population* (N=164)*	*CHAMPION PHOENIX*	*CHAMPION Steg et al. meta-analysis*
BARC ≥3a	2.9%	0.6%	0.4%	/
GUSTO severe/life threating	0.4%	0%	0.2%	0.2%
GUSTO moderate	2.1%	0.6%	0.4%	0.6%
GUSTO severe or moderate	2.5%	0.6%	0.6%	0.8%
TIMI major	1.2%	0%	0.1%	0.3%
TIMI minor	1.7%	0.6%	0.2%	0.6%
TIMI major or minor	2.9%	0.6%	0.3%	0.9%
ISTH major	2.5%	0%	/	/
Definite stent thrombosis	0.4%	0%	0.2%	/
Probable stent thrombosis	0.4%	0.6%	0.6%	/
Definite/probable stent thrombosis	0.8%	0.6%	0.8%	0.5%

TITLES OF FIGURES

Figure 1.— Percentage of cangrelor use per clinical presentation. Cangrelor was mainly utilized in ACS rather than CCS patients (p=0.044).

Figure 2. — The choice of the oral P2Y12-I to switch to in ACS patients. Between the two more potent oral P2Y12-I ticagrelor was largely preferred over prasugrel.





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