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Feasibility and safety of cangrelor in patients with suboptimal $P2Y_{12}$ inhibition undergoing percutaneous coronary intervention: the Dutch Cangrelor registry

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Introduction

Oral dual antiplatelet therapy is the cornerstone of pharmacological treatment in patients with an acute coronary syndromeor stable coronary artery disease (CAD) who undergo (primary) percutaneous coronary intervention (PCI) in order to prevent adverse ischaemic events.[1] Despite the advances of potent $P2Y_{12}$-inhibitors, all oral $P2Y_{12}$-inhibitors pose a relatively slow onset of inhibition and only provide sufficient platelet inhibition 4–6 h after intake of standard loading dose in stable coronary syndrome patients.[2] Therefore, intravenous (iv) administration of a $P2Y_{12}$-inhibitor with rapid on- and offset might be beneficial to overcome the limitations of oral $P2Y_{12}$-inhibitors and might bridge the gap to optimal platelet inhibition that exists with oral $P2Y_{12}$-inhibitors.

Cangrelor is a potent iv $P2Y_{12}$-inhibitor with a potential beneficial profile in reducing ischaemic events without increasing relevant bleeding in patients undergoing PCI.[3] This nationwide registry aims to observe the feasibility and safety of cangrelor in patients with suboptimal $P2Y_{12}$-inhibition who undergo *ad hoc* or primary PCI (pPCI) in daily clinical practice.

Methods

Cangrelor was administered pre-PCI in: (i) $P2Y_{12}$-inhibitor naive patients undergoing *ad hoc* PCI, (ii) ST-elevation myocardial infarction (STEMI)/non-STEMI (NSTEMI) patients undergoing pPCI with suboptimal $P2Y_{12}$-inhibition (vomited after loading dose or pPCI within 2 hours after oral loading dose of $P2Y_{12}$-inhibitor), (iii) stable resuscitated/defibrillated patients with out-of-hospital cardiac arrest (OHCA) due to acute ischaemia who are not able to take an oral loading dose of $P2Y_{12}$-inhibitor, and (iv) STEMI/NSTEMI patients with a high thrombotic burden, identified at the time of angiography.

The main exclusion criteria were: (i) current/chronic treatment with $P2Y_{12}$-inhibitors, (ii) treatment with glycoprotein IIb/IIIa inhibitors, (iii) recent major bleeding complications, (iv) contraindication or known hypersensitivity to aspirin, $P2Y_{12}$-inhibitor or cangrelor, (v) dialysis,

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(vi) pregnant or lactating female, and (vii) currently participating in another investigational drug or drug-coated device study. The study design has been reported previously.[4]

Acute coronary syndrome patients received concomitant medication according to European Society of Cardiology (ESC) guidelines: an oral loading dose of 180 mg ticagrelor, or 600 mg clopidogrel or 60 mg of prasugrel in the ambulance for STEMI patients and at the emergency department for NSTEMI patients. Acute coronary syndrome patients who vomited after the oral loading medication, received a re-loading dose with $P2Y_{12}$-inhibitors after PCI if ticagrelor, or after discontinuation of the cangrelor infusion if clopidogrel or prasugrel. Aspirin was administered to all patients before coronary angiography [500 mg iv in STEMI/NSTEMI/OHCA patients or treatment was started at least 5 days before elective angiography (80 mg orally) in patients undergoing *ad hoc* PCI] according to national ambulance protocol and according to working group guidelines of The Netherlands Society of Cardiology (NVVC). Patients naive for $P2Y_{12}$-inhibition with indication for *ad hoc* PCI, received the oral $P2Y_{12}$ loading dose after PCI, if ticagrelor during or after discontinuation of infusion, or if clopidogrel or prasugrel instantly after discontinuation of the cangrelor infusion. Cangrelor was administered as a bolus of 30 µg/kg, followed by a 2–4 h infusion of 4 µg/kg/min. The timing of administration of cangrelor during the procedure was pre-specified.

The primary endpoint was a composite of all-cause mortality, (recurrent) myocardial infarction (MI), target vessel revascularization, stroke, probable or definite stent thrombosis (ST), and bleeding [according to Bleeding Academic Research Consortium (BARC) grade 2, 3, or 5] at 48 h after PCI.

Descriptive statistics were performed for the primary endpoint. All analyses were performed with SPSS version 26.

Results

Two hundred and fifty patients were enrolled across eight centres in the Netherlands. The indication of cangrelor were $P2Y_{12}$-inhibitor naive patients who underwent *ad hoc* PCI (59%), STEMI/NSTEMI patients with suboptimal $P2Y_{12}$-inhibition (28%), OHCA patients (8%), and STEMI/NSTEMI patients with high thrombus burden (3% and 2%, respectively).

The primary endpoint at 48 h occurred in 21 (8.4%) patients. One (0.4%) patient died because of post-anoxic encephalopathy after OHCA. Target vessel revascularization occurred in one patient (0.4%) due to coronary perforation. No recurrent MI, stroke, or ST occurred. The incidence of bleeding was 7.6% [7.2% BARC 2, 0.4% BARC 3, and 0% BARC 5 bleeding, respectively (*Table 1*)].

Table 1 Peri-procedural characteristics and primary efficacy and safety endpoint

	Cangrelor ($n = 250$)
Indication for cangrelor, *n* (%)	
Naive for P2Y12 inhibition undergoing *ad hoc* PCI	147 (58.8)
STEMI/NSTEMI with suboptimal P2Y12 inhibition	70 (28.0)
OHCA	20 (8.0)
STEMI/NSTEMI with high thrombus burden	13 (5.2)
Pre-PCI loading of $P2Y_{12}$ inhibitor	
Ad hoc PCI	
No loading dose	147 (100)
Ticagrelor	0 (0)
Clopidogrel	0 (0)
ACS	
No loading dose	27 (26.2)
Ticagrelor	72 (69.9)
Clopidogrel	4 (3.9)
Duration of cangrelor infusion, h	
Median	2.4
IQR	2.0–6.0
Access site, *n* (%)	
Radial	224 (89.6)
Femoral	26 (10.4)
Primary endpoint, *n* (%): all-cause death [including cardiac death), recurrent MI, TVR, stroke, definite or probable ST, and bleeding (BARC type 2–5)]	21 (8.4)
Specification of endpoint, *n* (%)	
Death	1 (0.4)
ST	0 (0)
Recurrent MI	0 (0)
TVR	1 (0.4)
Ischaemic CVA	0 (0)
Bleeding	19 (7.6)
BARC 2	18 (7.2)
BARC 3	1 (0.4)
BARC 5	0 (0)

Values are numbers (percent).
BARC, Bleeding Academic Research Consortium; CVA, cerebral vascular accident; MI, myocardial infarction; ST, stent thrombosis.
[a]One patient lost to follow-up.

Discussion

The current guideline-recommended indication of cangrelor is for $P2Y_{12}$-inhibitor naive patients with stable CAD or ACS, who have not been pre-treated with a $P2Y_{12}$-inhibitor at the time of PCI or in those who are considered unable to absorb oral agents. Numerous studies have formed the basis for the currently approved cangrelor regimen.[3] Yet, not many of them included patients with high thrombotic burden, such as OHCA. These categories of patients with often higher platelet reactivity require fast and adequate antiplatelet therapy.

The Dutch Cangrelor registry is the first prospective study that evaluated the feasibility and safety of cangrelor in a wide range of high-risk categories of patients with suboptimal $P2Y_{12}$-inhibition during *ad hoc* and pPCI in daily clinical practice. The low incidence of ischaemic events in the first 48 h after PCI emerged as a principal finding of this study, as well as the acceptable rate of bleeding. The primary endpoint was mainly driven by minor bleeding. These observations confirm and are in line with the findings of the CHAMPION trials.[3]

Some limitations need to be acknowledged, as it is an open label trial with a small cohort of patients without control group. Finally,

our findings may not be applicable in all countries due to differences in healthcare systems.

Lead author biography

Abi Selvarajah MD, is currently working as a resident at the Department of Cardiology, and doing her PhD in optimizing antiplatelet therapy in patients with acute and chronic coronary syndrome under the supervision of dr. R.S. Hermanides, MD PhD and dr. M.A.H. van Leeuwen, MD PhD at Isala Hospital in the Netherlands. Her research interests include acute coronary syndrome, and preventive cardiology. She has authored the design paper of Dutch Cangrelor Registry published in BMC Cardiovascular Disorders. She is currently the sub-investigator for the Dutch CCS Rivaroxaban Registry and Celebrate trial.

Conclusion

Cangrelor showed to have an acceptable safety profile with a low rate of short-term ischaemic outcome in patients with ACS and stable CAD undergoing PCI in daily clinical practice.

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Conflict of interest: none declared.

References

1. Valgimigli M, Bueno H, Byrne RA, Collet J-P, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann F-J, Petricevic M, Roffi M, Gabriel Steg P, Windecker S, Zamorano JL. 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* 2017;**39**:213–260.
2. 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 prasugrel antiplatelet effects in patients with ST-segment-elevation myocardial infarction. *Circ Cardiovasc Interv* 2012;**5**:797–804.
3. Steg PG, Bhatt DL, Hamm CW, Stone GW, Gibson CM, Mahaffey KW, Leonardi S, Liu T, Skerjanec S, Day JR, Iwaoka RS, Stuckey TD, Gogia HS, Gruberg L, French WJ, White HD, Harrington RA. Effect of cangrelor on periprocedural outcomes in percutaneous coronary interventions: a pooled analysis of patient-level data. *Lancet* 2013;**382**:1981–1992.
4. Selvarajah A, Tavenier AH, Bor WL, Houben V, Rasoul S, Kaplan E, Teeuwen K, Hofma SH, Lipsic E, Amoroso G, van Leeuwen MAH, Berg J. M T, van 'T Hof AWJ, Hermanides RS. Feasibility and safety of cangrelor in patients with suboptimal P2Y(12) inhibition undergoing percutaneous coronary intervention: rationale of the Dutch Cangrelor Registry. *BMC Cardiovasc Disord* 2021; **21**:292.