Feasibility and safety of cangrelor in patients with suboptimal P2Y12 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 syndrome or 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 P2Y12-inhibitors, all oral P2Y12-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 P2Y12-inhibitor with rapid on- and off-set might be beneficial to overcome the limitations of oral P2Y12-inhibitors and might bridge the gap to optimal platelet inhibition that exists with oral P2Y12-inhibitors.

Cangrelor is a potent iv P2Y12-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 P2Y12-inhibition who undergo ad hoc or primary PCI (pPCI) in daily clinical practice.

Methods

Cangrelor was administered pre-PCI in: (i) P2Y12-inhibitor naive patients undergoing ad hoc PCI, (ii) ST-elevation myocardial infarction (STEMI)/non-STEMI (NSTEMI) patients undergoing pPCI with suboptimal P2Y12 inhibition (vomited after loading dose or pPCI within 2 hours after oral loading dose of P2Y12-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 P2Y12-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 P2Y12-inhibitors, (ii) treatment with glycoprotein IIb/IIIa inhibitors, (iii) recent major bleeding complications, (iv) contraindication or known hypersensitivity to aspirin, P2Y12-inhibitor or cangrelor, (v) dialysis,
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 the cangrelor infusion if clopidogrel or prasugrel. Aspirin was administered as a bolus of 30 mg/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, 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 due to 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)].

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. 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.

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 P2Y12 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) |
| Specifi cation of endpoint, n (%) |
| Death | 1 (0.4) |
| ST | 0 (0) |
| Recurrent MI | 0 (0) |
| TVR | 1 (0.4) |
| Ischaemic CVA | 0 (0) |
| Bleeding |
| BARC 2 | 19 (7.6) |
| 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.

*One patient lost to follow-up.

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. 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.

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