

## Clinical paper

# Antiplatelet effect of clopidogrel is reduced in patients treated with therapeutic hypothermia after cardiac arrest<sup>☆</sup>

Thor Wilhelm Bjelland<sup>a,\*</sup>, Øyvind Hjertner<sup>b,c</sup>, Pål Klepstad<sup>a,d</sup>, Kjell Kaisen<sup>e</sup>, Ola Dale<sup>a,d</sup>, Bjørn Olav Haugen<sup>a,f</sup>

<sup>a</sup> Department of Circulation and Medical Imaging, Medical Faculty, Norwegian University of Science and Technology, 7006 Trondheim, Norway

<sup>b</sup> Department of Cancer Research and Molecular Medicine, Medical Faculty, Norwegian University of Science and Technology, 7006 Trondheim, Norway

<sup>c</sup> Department of Medicine, Trondheim University Hospital, 7006 Trondheim, Norway

<sup>d</sup> Department of Anaesthesiology and Emergency Medicine, Trondheim University Hospital, 7006 Trondheim, Norway

<sup>e</sup> Department of Anaesthesia and Intensive care, Stavanger University Hospital, 4011 Stavanger, Norway

<sup>f</sup> Department of Cardiology, Trondheim University Hospital, 7006 Trondheim, Norway

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## ABSTRACT

**Background:** The platelet inhibitor clopidogrel is administered to patients treated with therapeutic hypothermia following cardiac arrest due to acute coronary syndromes. Interactions with proton pump inhibitors and genetics are factors with a known potential to attenuate the platelet inhibition of clopidogrel. In patients treated with therapeutic hypothermia, reduced gastrointestinal function and hypothermia may also reduce the effect of clopidogrel. To investigate the net platelet inhibition of clopidogrel, we have measured the platelet reactivity index in patients treated with therapeutic hypothermia. **Methods and results:** Twenty-five Caucasian patients treated with clopidogrel and therapeutic hypothermia were prospectively included. Therapeutic hypothermia was defined as 33–34 °C and delivered for 24 h. Clopidogrel loading doses (300–600 mg) were administered enterally the day of admission and followed by 75 mg daily. Blood samples were collected on day 1 ( $n = 25$ ) and day 3 ( $n = 16$ ). The samples were analysed for inhibition by clopidogrel with a vasodilator stimulated phosphoprotein phosphorylation kit. On day 1 and day 3, platelet reactivity index was  $0.77 \pm 0.09$  and  $0.57 \pm 0.16$ , respectively. The number of patients with a satisfactory antiplatelet effect (defined as platelet reactivity index  $< 0.5$ ) were 0 (0%) and 5 (31%), respectively.

**Conclusion:** In patients treated with therapeutic hypothermia after cardiac arrest, the effect of clopidogrel on platelets was virtually nonexistent on day 1 after administration, with some improvement on day 3.

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## 1. Introduction

According to recent guidelines, therapeutic hypothermia (TH) is indicated in comatose patients following successful cardiopulmonary resuscitation (CPR).<sup>1</sup> Of these patients, 37–63% have a myocardial infarction, and should according to treatment guidelines receive clopidogrel, a P2Y<sub>12</sub> inhibitor.<sup>2–5</sup>

Clopidogrel is administered orally. Its effect is dependent on absorption from the gut to systemic circulation, and on metabolic

activation by CYP2C19 and other CYP-P450 enzymes. Approximately 30% of the Caucasian population carries at least one CYP2C19 reduced function allele, reducing the platelet inhibiting effect of clopidogrel and increasing the risk of cardiovascular events.<sup>6–9</sup> Moreover, proton pump inhibitors (PPIs) have been shown to interact with clopidogrel reducing its platelet inhibiting effect, probably by competitive effects on CYP2C19.<sup>10,11</sup>

During TH, several physiological factors may further attenuate the effectiveness of clopidogrel. First, hypothermia, opioids, and acute critical illness reduce gastrointestinal motility.<sup>12,13</sup> This may reduce the uptake of drugs to systemic circulation.<sup>14</sup> Second, hypothermia reduces metabolism in general, which may reduce the metabolic activation of a prodrug such as clopidogrel.<sup>15</sup> Third, in vitro experiments with blood sampled from healthy blood donors have shown that platelet reactivity in some situations is increased during mild hypothermia and that the inhibitory effect of clopidogrel is attenuated.<sup>16</sup>

The combined effect of these conditions on the efficacy of clopidogrel platelet inhibition is unknown. Therefore, the aim of this

**Abbreviations:** TH, therapeutic hypothermia; PPIs, proton pump inhibitors; CPC, cerebral performance category; ACS, acute coronary syndrome; VASP-P, vasodilator stimulated phosphoprotein-phosphorylated; PRI, platelet reactivity index; SAPS II, simplified acute physiology score II; GRVs, gastric residual volumes.

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\* Corresponding author. Abels gate 20D, 7030 Trondheim, Norway.

Tel.: +47 92804463; fax: +47 72826028.

E-mail address: [thorwilh@stud.ntnu.no](mailto:thorwilh@stud.ntnu.no) (T.W. Bjelland).

study was to explore the platelet inhibitory effect of clopidogrel in patients treated with TH.

## 2. Methods

After approval from the ethics committee, patients were included from April 2008 to May 2009. Next of kin were informed, and no patients were included unless their next of kin approved. Deferred consent was sought from patients with a successful recovery, defined as cerebral performance category (CPC) 1 or 2.<sup>17</sup> Patients were treated at the Intensive Care Units (ICU) and Coronary Care Unit (CCU) of two Norwegian study centres, Trondheim University Hospital and Stavanger University Hospital. Patients were recruited through screening for participation in a randomized controlled trial comparing two different protocols for sedation-analgesia in patients treated with TH.<sup>18</sup>

This was a prospective patient series. Inclusion criteria were patients receiving TH following cardiac arrest, and clopidogrel as part of treatment for suspected acute coronary syndrome (ACS). Patients receiving treatment with clopidogrel prior to admittance were excluded. The assay employed requires analysis to be performed within 48 h. Patients were excluded in cases where analysis of the first sample would be impossible due to transport times or lack of competent personnel to perform the analyses (weekends, holidays). Second samples were not collected if time to analysis would be more than 48 h.

Patients received sedatives and analgesics (midazolam and fentanyl, or propofol and remifentanyl), and were mechanically ventilated from the time of admission. Standard TH protocol was 33–34 °C for 24 h, and patients received intensive care as required. TH was induced by external cooling or an intravascular cooling catheter (Allon® and CritiCool™, MTRE Advanced Technologies Ltd., Israel. Arctic Sun, Medivance, USA. CoolGard 3000™, Alsius Corporation, USA). Neuromuscular blocking agents (atracurium or cisatracurium) were administered at the physicians' discretion ( $n = 14$ ). Enteral nutrition was postponed until the patients became normothermic.

Clopidogrel (Plavix, Bristol-Myers Squibb Norway Ltd., Norway) was administered as an enteral loading dose of 300 mg (600 mg if urgent coronary angiography was planned) on the day of admission, and followed by daily maintenance doses of 75 mg. The tablets were crushed and administered through a nasogastric tube.

Whole blood samples (3.5 ml) were collected to citrate-tubes day 1 and day 3 with median [interquartile range] intervals of 21 h [17.5–27.5] and 68 h [63–72] after the first administration of clopidogrel, respectively. The effect of clopidogrel on platelets was analysed using a commercially available dual colour flow cytometer assay (PLT VASP/P2Y<sub>12</sub>, BioCytex, France), which is specific for P2Y<sub>12</sub> inhibitors. Blood samples were first incubated with prostaglandin E<sub>1</sub> (PGE<sub>1</sub>) alone or PGE<sub>1</sub> + adenosine diphosphate. After cellular permeabilization, phosphorylated vasodilator stimulated phosphoprotein (VASP-P) was analysed using a monoclonal anti-VASP-P antibody. VASP phosphorylation correlates with the P2Y<sub>12</sub>-receptor inhibition, whereas its non-phosphorylated state correlates with the active form of P2Y<sub>12</sub>-receptor. The ratios between phosphorylated and non-phosphorylated VASP were used to calculate the platelet reactivity index (PRI), which reflects the effect of clopidogrel. According to previous studies, a PRI <0.5 was regarded as a satisfactory effect of clopidogrel, a PRI ≥0.5 was regarded as an unsatisfactory effect of clopidogrel, and PRI ≥0.7 was considered a normal value for untreated patients.<sup>19–22</sup>

Age, sex, medical history, current treatment for ACS, time from cardiac arrest to hypothermia, time to established enteral nutrition, laboratory results (creatinine, alanine aminotransferase (ALAT),

international normalized ratio of prothrombin time (PT-INR), and albumin), and medications administered between admission and day 3 sample, were obtained from patient records. Core temperature (measured in bladder or vena cava inferior) was recorded at the time of blood sampling. Simplified acute physiology score II (SAPS II) was calculated for the first 24 h according to Le Gall et al.<sup>23</sup>

Data and results following the normal distribution are reported as mean ± SD, other variables are presented as median (range) or median [interquartile range].

## 3. Results

Twenty-five patients were prospectively included in this study. Mean age was 59.7 ± 14.6 years and mean SAPS II the first 24 h was 59 ± 16. One patient had a prior history of hepatic disease, one patient had a history of renal disease, and two patients had a history of diabetes (Table 1). All patients had elevation of troponin T, median (range) 1.35 µg L<sup>-1</sup> (0.18–19.63). The causes of cardiac arrest were as reviewed retrospectively: ST-segment elevation myocardial infarction (STEMI) ( $n = 10$ ), non-ST-segment elevation myocardial infarction (NSTEMI) ( $n = 4$ ), coronary heart disease (CHD) with heart failure ( $n = 2$ ), CHD ( $n = 2$ ), pulmonary embolism ( $n = 1$ ), ventricular tachycardia ( $n = 1$ ) or unknown ( $n = 5$ ). Clopidogrel loading doses were 600 mg in 16 patients, and 300 mg in 9. Details on the treatment of ACS, other medications and results from clinical chemistry analyses are reported in Table 1.

Twenty-five day 1 samples, and sixteen day 3 samples were successfully collected. Nine day 3 samples were not taken for various reasons: Cessation of clopidogrel after day 1 sample ( $n = 1$ ), analysis impossible within 48 h ( $n = 5$ ), death before day 3 ( $n = 2$ ), or transfer to other hospital before day 3 ( $n = 1$ ). At day 1 and day 3 sampling, median core body temperature was 33.2 (32.7–37.4), and 37.5 °C

**Table 1**  
Patient characteristics.

	Value
Age (years)	59.7 ± 14.6
Sex (males/females)	19/6
Coronary angiography	15 (60%)
Percutaneous coronary intervention	13 (52%)
Thrombolytic treatment	3 (12%)
Laboratory results on day of inclusion	
Creatinine (µmol L <sup>-1</sup> )	89 (45–434)
ALAT <sup>a</sup> (U L <sup>-1</sup> )	171 (31–711)
PT-INR <sup>b</sup>	1.1 (0.9–3.8)
Albumin (g L <sup>-1</sup> )	37.3 ± 31
SAPS II 24 h <sup>c</sup>	59 ± 16
Time after cardiac arrest to confirmed temperature <34 °C (h)	5.3 (2.2–32.6)
Time to established enteral nutrition (days)	3.3 ± 0.9
Medications before day 3 sample	
Metoclopramide	9 (36%)
Lactulose	2 (8%)
PPIs <sup>d</sup>	16 (64%)
Omeprazole	1 (4%)
Pantoprazole	9 (36%)
Esomeprazole	6 (24%)
Platelet inhibition before day 3 sample	
ASA <sup>e</sup>	22 (88%)
Abciximab	5 (20%)
Eptifibatide	3 (12%)

Values as mean ± standard deviation, median (range) or number (%) of observations.

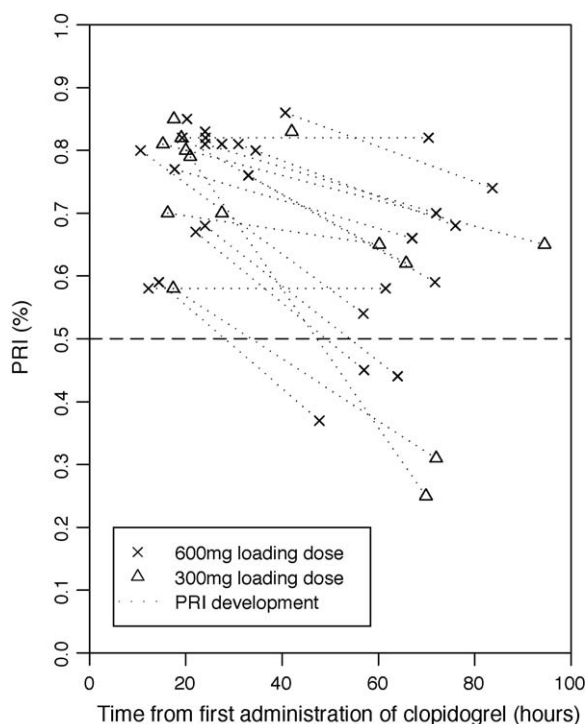
<sup>a</sup> Alanine aminotransferase.

<sup>b</sup> International normalized ratio of prothrombin time.

<sup>c</sup> Simplified acute physiology score II.

<sup>d</sup> Proton pump inhibitors.

<sup>e</sup> Acetylsalicylic acid.



**Fig. 1.** Scatter plot of platelet reactivity index (PRI) values. Loading doses of 300 mg are marked with triangles, 600 mg with crosses. Lines are drawn between day 1 sample and day 3 sample where both exist. A horizontal line has been drawn at PRI 50% for clarity.

**Table 2**  
Sample collection and results.

	Sample results	
	Day 1 (n = 25)	Day 3 (n = 16)
PRI <sup>a</sup>	0.77 ± 0.09	0.57 ± 0.16
Number of samples with satisfactory effect (PRI <50)	0 (0%)	5 (31%)
Number of samples below normal value (PRI <70)	5 (20%)	13 (81%)
Time from first administration to sample (h)	21 [17.5–27.5]	68 [63–72]
Core body temperature at sampling (°C)	33.2 (32.7–37.4)	37.5 (34.7–38.6)

Values as mean ± standard deviation, median (range), median [interquartile range] or number of patients with given score (%).

<sup>a</sup> Platelet reactivity index.

(34.7–38.6), respectively. Zero day 1 samples, and five day 3 samples had PRI <0.5, which is a clopidogrel resistance of 100 and 70%, respectively (Fig. 1). Mean PRI was 0.77 ± 0.09 and 0.57 ± 0.16 on day 1 and day 3, respectively (Table 2).

#### 4. Discussion

The main finding of this study was that the antiplatelet effect of clopidogrel was unsatisfactory in patients treated with TH.

Treatment with clopidogrel is indicated in all patients with ACS, and is particularly important when a percutaneous coronary intervention is performed to avoid stent thrombosis.<sup>4,5</sup> In a recent review on variability in platelet response to aspirin and clopidogrel, Ben-Dor et al. made reference to 11 papers describing significant associations between low response to clopidogrel and adverse clinical outcomes, and concluded that “there is a clear and concerning

relation between low response to clopidogrel and cardiovascular events”.<sup>24</sup> Furthermore, two recent studies by Bonello et al. randomised patients with a low clopidogrel responsiveness to either tailored clopidogrel therapy or control, and showed that clinical outcome in patients with low clopidogrel responsiveness (VASP index <50%) can be improved by adequate platelet therapy.<sup>25,26</sup> In light of these studies, the lack of antiplatelet effect of clopidogrel treatment in the acute phase of TH treated patients in this study is a matter of concern.

There is no uniform definition of low response to clopidogrel using a biological test. The prevalence of clopidogrel resistance depends on definition, type of assay employed, use of PPIs, genetics, clopidogrel dose, and concomitant disease.<sup>7,8,24</sup> According to Ben-Dor et al., clopidogrel resistance has been described in 4–30% of patients.<sup>24</sup> Bonello et al. used the same method to analyse VASP phosphorylation as in our study and reported clopidogrel resistance up to 52%.<sup>25,26</sup> The observed prevalences of clopidogrel resistance in this study, 100 and 70% on day 1 and day 3, respectively, is much higher than expected.

In this study, PPIs were administered to sixteen patients (nine pantoprazole, six esomeprazole, and one omeprazole). Clopidogrel interactions with PPIs reducing clopidogrel platelet inhibition have been described. Gilard et al. employed the same kit as used in this study, and showed that mean PRI in patients treated with both clopidogrel and PPIs, compared to patients treated with clopidogrel alone, was significantly higher.<sup>10</sup> Ho et al. described an increased risk for death or re-hospitalisation when PPIs were used concomitantly with clopidogrel.<sup>11</sup> However, both studies were mainly in patients treated with omeprazole. Interaction between PPIs and clopidogrel was not shown in two studies on patients treated with esomeprazole and pantoprazol.<sup>27,28</sup> Cuisset et al. showed that clopidogrel response in patients receiving pantoprazole is significantly better than in patients receiving omeprazole.<sup>29</sup> Thus, the current literature does not sufficiently support a significant interaction between clopidogrel and the PPIs used in our study.

We did not genotype our patients. Genetic variance with clinical consequences has been described for clopidogrel efficacy.<sup>6,8,9</sup> According to Mega et al., 30% of the Caucasian population carries at least one CYP2C19 reduced function allele. Compared to noncarriers, these individuals have a 32% reduction in plasma exposure to the active metabolite of clopidogrel, 9% lower platelet response, and 53% increased risk for death, myocardial infarction, or stroke.<sup>6</sup> However, if genetic variation should explain our observations solely, virtually all patients would have to carry loss of function alleles. With a prevalence of 30%, this seems unlikely. Therefore, in this study population, factors other than genetic variability are likely to play an important role in the observed nonresponsiveness of clopidogrel.

Two such factors may be reduced uptake, and reduced metabolic conversion of clopidogrel to its active metabolite. Hypothermia, opioids, and acute critical illness are all able to reduce gastrointestinal motility.<sup>12,13</sup> Gastric residual volumes (GRVs) are commonly used to assess gastrointestinal motility.<sup>14</sup> Following enteral administration of acetaminophen to intensive care patients, Landzinski et al. demonstrated significantly greater maximum concentrations, area under curve, and reduced time to maximum concentration in patients with small GRVs.<sup>14</sup> Our patients are hypothermic, receive opioids, and have acute critical illness, resulting in a high risk of reduced gastrointestinal motility, and subsequently a risk of reduced uptake of an enterally administered drug such as clopidogrel.

The second possible factor is reduced activation. Since clopidogrel itself has no platelet inhibiting effect, metabolic conversion to its active metabolite is required. Central core temperature affects the rate of metabolism, described by Q10 ratios. A 10 °C reduction in

temperature will usually cause a 50% reduction in enzyme activity, which equals a  $Q_{10}$  ratio of two.<sup>30</sup> Reduced metabolism or increased serum concentrations has been shown for several drugs in relation to hypothermia.<sup>31</sup> Hypothermia is likely to reduce the enzymatic metabolism of clopidogrel, which potentially may reduce the conversion of a prodrug such as clopidogrel to its active substance.<sup>15</sup> Furthermore, in an in vitro study, mild hypothermia was shown to increase platelet aggregation on blood collected from humans after a loading dose of clopidogrel.<sup>16</sup>

This study has some limitations. First, only 25 patients were studied. Second, because the VASP-P kit employed measures net platelet inhibition by clopidogrel, our study design cannot provide a causal explanation for a lack of inhibition. We did not measure serum concentrations of clopidogrel and its active metabolite. Pharmacokinetic analysis could have helped us determine whether the lack of efficacy is caused by decreased function of the gastrointestinal tract, reduced metabolism to the active metabolite, or both. A combined effect from more than one potential cause is likely, which makes a suitable control group difficult to identify. Third, different loading doses due to administration according to international guidelines may have introduced heterogeneity in our population. However, PRI measurements were uniformly too high on day 1, with few exceptions on day 3. Fourth, we did not measure PRI before induction of hypothermia. However, this study was designed to investigate whether clopidogrel appears to work as intended in patients treated with TH. Despite the limited number of patients we believe the observation of a 100% failure to achieve adequate platelet inhibition at day 1 indicate a significant failure rate of clopidogrel treatment in the acute phase of TH treated patients. In the light of recent studies showing a clear relation between low responsiveness and cardiovascular events, this is a matter of concern, and warrants further studies on antiplatelet therapy in patients treated with TH.

## 5. Conclusions

In patients treated with TH after cardiac arrest, the effect of clopidogrel on platelets was virtually nonexistent on day 1 after administration, with some improvement on day 3.

## Conflict of interest

None.

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