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Clopidogrel Versus Newer P2Y12 Antagonists for Percutaneous Coronary Intervention in Patients with Out-of-Hospital Cardiac Arrest Managed with Therapeutic Hypothermia: A Meta-Analysis

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BRIEF REPORT

Clopidogrel Versus Newer P2Y12 Antagonists for Percutaneous Coronary Intervention in Patients with Out-of-Hospital Cardiac Arrest Managed with Therapeutic Hypothermia: A Meta-Analysis

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ABSTRACT

Introduction: The impact of therapeutic hypothermia (TH) on outcomes of percutaneous coronary intervention (PCI) and the optimal antiplatelet treatment remains debatable.

Methods: Electronic databases were searched for randomized trials and observational studies to evaluate the available clinical evidence comparing the use of clopidogrel versus newer P2Y12 antagonists in cases of TH after PCI. The primary outcome was in-hospital definite stent thrombosis while the secondary outcomes were in-hospital mortality and major bleeding. Fixed-effects risk ratios (RRs) were estimated using Mantel–Haenszel method.

Results: The final analysis included five studies with a total of 290 patients. There was no difference in the incidence of stent thrombosis (RR 0.92; 95% CI 0.35–2.38), in-hospital mortality (RR 1.38; 95% CI 0.72–2.65), and major bleeding (RR 0.89; 95% CI 0.33–2.40) between patients receiving clopidogrel versus those receiving newer agents.

Conclusions: This meta-analysis showed no difference between clopidogrel and newer antiplatelet agents in the incidence of stent thrombosis or in-hospital mortality for PCI in cases of TH. Further randomized studies are needed to explore the optimal dual antiplatelet treatment in TH.

Keywords: Anti-platelets; Percutaneous coronary intervention; Stent thrombosis; Therapeutic hypothermia

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INTRODUCTION

Out of hospital cardiac arrest (OHCA) carries a significant mortality worldwide [1]. Therapeutic hypothermia (TH) as well as early percutaneous coronary intervention (PCI) for patients with OHCA and suspected myocardial injury have

been shown to improve outcomes [2, 3]. The impact of TH on outcomes of PCI remains debatable. Some studies have demonstrated higher incidence of stent thrombosis associating TH after PCI [3, 4]. Experimental studies have raised concerns regarding the efficacy of clopidogrel in cases of hypothermia, possibly by augmenting adenosine diphosphate (ADP)-induced platelet aggregation [5]. Hypothermia also impairs the pharmacokinetic profile of clopidogrel including its absorption, and enzymatic activation to the active metabolites [1, 5]. Some studies showed a better platelet inhibition with ticagrelor and prasugrel compared to clopidogrel in TH [2, 6]. However, the clinical translation of these experimental observations is not clear. We conducted this meta-analysis to evaluate the available clinical evidence comparing the use of clopidogrel versus newer P2Y12 antagonists in cases of TH after PCI.

METHODS

We performed a computerized search of MEDLINE, EMBASE, and COCHRANE databases through December 2017, for studies on survivors of OHCA receiving TH who underwent PCI. A similar search strategy was also done for abstracts of the major scientific sessions (American College of Cardiology, European Society of Cardiology, the American Heart Association and European Association of Cardiothoracic Anesthesiologists) up to December 2017. We further screened the bibliographies of the retrieved studies as well as clinicaltrials.gov for any relevant studies not retrieved by the initial search. Studies were included when clinical outcomes for patients receiving clopidogrel versus one of the newer antiplatelet agents (ticagrelor or prasugrel) were reported. The study designs, intervention strategies and main outcomes were extracted by two investigators (A.H and K.B). Discrepancies among investigators were resolved by consensus. The primary outcome was in-hospital definite stent thrombosis. Identified cases of definite stent thrombosis were established in all studies in accordance with the Academic Research Consortium definition [7]. Secondary outcomes included in-hospital mortality and major bleeding. Fixed-effects and random-effects risk ratios (RRs) were estimated using Mantel–Haenszel method. Heterogeneity was calculated using the I^2 test. Statistical analyses were conducted using RevMan 5.0 software (Cochrane Collaboration, Oxford, UK). The current analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Checklist (Supplemental Table 1). We used the Newcastle–Ottawa score to assess the quality of included studies [8].

This article does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

Our final analysis included five studies with a total of 290 patients. One study was a prospective randomized-controlled trial [2], while two studies were prospective non-randomized [1, 6] and two studies were retrospective studies [3, 4]. In those studies, TH protocols included maintaining a temperature of 32–34 °C for 12–24 h (Table 1). In all studies, patients received periprocedural aspirin and P2Y12 receptor inhibitors via nasogastric tube. Baseline characteristics

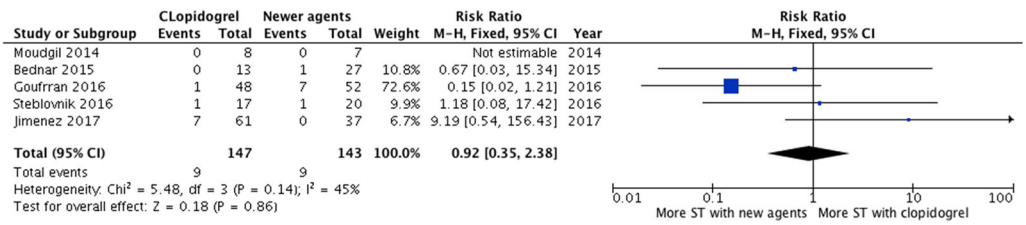

Fig. 1 Forrest plot for definite stent thrombosis for clopidogrel versus newer anti-platelet agents. *ST* stent thrombosis

Table 1 Baseline characteristics of included studies

Studies	Design	Clopidogrel (*n*)	Prasugrel (*n*)	Ticagrelor (*n*)	Hypothermia details
Moudgil et al. (2014)	Prospective non-randomized	8	–	7	Temperature of 33 °C for 24 h
Bednar et al. (2015)	Prospective non-randomized	13	18	9	Temperature 33–34 °C for 12 h
Goufrran et al. (2016)	Retrospective	48	22	30	Temperature 32–34 °C for 24 h
Steblovnik et al. (2016)	Prospective randomized	17	–	20	Temperature 32–34 °C for 24 h
Jimenez et al. (2017)	Retrospective	61	5	32	Temperature 33 °C for 24 h

of included studies are described in Supplemental Table 2. Using Newcastle–Ottawa score all studies were assessed to have good quality, except one study of fair quality [2] (Supplemental Table 3). The incidence of stent thrombosis was not different between patients receiving clopidogrel 9 (6.1%) versus those receiving newer agents 9 (6.3%) (RR 0.92; 95% CI 0.35–2.38; $p = 0.86$) with moderate heterogeneity ($I^2 = 45\%$) (Fig. 1). Sub-group analysis showed no difference between clopidogrel versus newer agents in retrospective studies (RR 0.92; 95% CI 0.31–2.71; $p = 0.88$) compared with prospective studies (RR 0.91; 95% CI 0.12–6.91; $p = 0.93$) ($P_{\text{interaction}} = 0.99$). Further sub-group analysis showed no difference when comparing clopidogrel versus ticagrelor (RR 1.09; 95% CI 0.37–3.24; $p = 0.88$) or clopidogrel versus prasugrel (RR 0.38; 95% CI 0.09–1.51; $p = 0.17$) ($P_{\text{interaction}} = 0.24$). In-hospital all-cause mortality (reported in three studies) was not statistically different between clopidogrel 20 (24.4%) and newer agents 11 (15.5%) (RR 1.38; 95% CI 0.72–2.65; $p = 0.34$; $I^2 = 0\%$) [1, 4, 6]. Similarly, three studies reported major bleeding events [1, 4, 6], and no significant difference was detected between clopidogrel 8 (9.8%) and newer agents 7 (9.9%) (RR 0.89; 95% CI 0.33–2.40; $p = 0.82$; $I^2 = 0\%$). Publication bias could not be assessed due to the few number of studies included in the analysis.

DISCUSSION

This meta-analysis of five clinical studies with a total of 290 patients demonstrated that among patients receiving TH after PCI, no significant difference existed between clopidogrel and newer agents (ticagrelor or prasugrel) regarding in-hospital stent thrombosis, all-cause mortality or major bleeding. Overall, the incidences of stent thrombosis in our analysis (6.1% with clopidogrel and 6.3% with newer agents) was higher than reported incidences of stent thrombosis in non-hypothermia conditions [9].

Little evidence is available regarding the optimal dual antiplatelet regimen in OHCA patients receiving TH after PCI. TH treatment as well as the post-resuscitation syndrome have been both associated with a pro-thrombotic state [5]. In addition, altered absorption and pharmacokinetics of different medications has been reported with TH [1, 5].

The results of our meta-analysis did not show a difference in clinical outcomes between hypothermia patients receiving clopidogrel versus newer agents. The lack of difference in

stent thrombosis is in discordance with the experimental findings of less efficacy of clopidogrel compared with newer agents in TH [1, 2]. This comes in accordance with studies suggesting a poor correlation between platelet testing and clinical outcomes in patients receiving dual antiplatelet therapy [2]. An increase in bleeding events has been reported with TH [4], however; we found no significant difference in major bleeding events among clopidogrel and the newer agents.

To the best of our knowledge, this is the first conducted meta-analysis with the totality of available data comparing clopidogrel to newer antiplatelet agents in cases of TH after PCI. This current analysis has some limitations. The small sample size in our analysis might have not been adequate to detect differences in our study outcomes. However, there are only few available studies on the topic. Unfortunately, many useful clinical data were not available for our analysis, such as generation of drug eluting stents used, shockable versus un-shockable rhythms, laboratory and medications data. While most of the available clinical studies in this topic are observational studies, the only included randomized study did not show a difference between clopidogrel and ticagrelor in clinical outcomes [2]. The potential for unmeasured bias exists due to the observational nature of some of the included studies as well as the diversity and complexity of patients experiencing OHCA. Further randomized studies are needed at a larger scale to better explore the optimal dual antiplatelet treatment in cases of TH.

CONCLUSIONS

This meta-analysis showed no difference between clopidogrel and newer antiplatelet agents in the incidence of stent thrombosis or in-hospital mortality for PCI in cases of TH. Further randomized studies are needed to explore the optimal dual antiplatelet treatment in TH.

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Compliance with ethics guidelines. This article does not contain any studies with human participants or animals performed by any of the authors.

Data availability. All data generated or analyzed during this study are included in this published article/as supplementary information files.

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