Prehospital administration of P2Y12 inhibitors and early coronary reperfusion in primary PCI: a non-randomized comparative study

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Summary

The newer oral P2Y12 inhibitors prasugrel and ticagrelor have been reported to be more potent and faster-acting antiplatelet agents than clopidogrel. This study aimed to investigate whether prehospital loading with prasugrel or ticagrelor improves early coronary reperfusion as compared to prehospital loading with clopidogrel in a real-world ST-elevation myocardial infarction (STEMI) setting. Over a 70-month period, 3497 patients with on-going STEMI of less than 6 hours and without cardiac arrest or cardiogenic shock underwent primary percutaneous coronary intervention (PPCI) at our centre. The primary endpoint of this study was the proportion of patients who did not meet the criteria for TIMI (Thrombolysis In Myocardial Infarction) flow grade 3 in the infarct-related artery at initial angiography before PPCI. Prehospital loading with prasugrel (n = 883) or ticagrelor (n = 491) did not significantly improve coronary reperfusion as compared to prehospital loading with clopidogrel (n = 1,532) – a TIMI-flow 3 at initial angiography was absent in 71.7 %, 69.0 % and 71.5 % of patients, respectively. Major adverse cardiac event (MACE) rates were low at 30 days (3.4 % to 4.0 %) and did not significantly differ between the different P2Y12 inhibitor regimens. In conclusion, this large observational, non-randomised study is the first to show that prehospital loading with the newer P2Y12 inhibitors does not improve early coronary reperfusion as compared to prehospital loading with clopidogrel in a PPCI cohort excluding cardiac arrest and cardiogenic shock.

Keywords

ST-elevation myocardial infarction, antiplatelet therapy, pretreatment, coronary reperfusion

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Received: January 10, 2015
Accepted after major revision: April 3, 2015
Epub ahead of print: May 21, 2015

http://dx.doi.org/10.1160/TH15-01-0026
Thromb Haemost 2015; 114: ■■■

Introduction

Effective antiplatelet therapy is of critical importance in patients with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI). Both European and American guidelines recommend that patients undergoing PPCI should receive a combination of double antiplatelet therapy (DAPT) with aspirin and an oral P2Y12 inhibitor as early as possible before angiography, in combination with a parenteral anticoagulant (1, 2).

The superiority of the newer P2Y12 inhibitors – over clopidogrel – in the prevention of ischemic events has been reported in the large, randomized controlled TRITON-TIMI 38 (prasugrel) and PLATO (ticagrelor) trials – however, in both trials, these drugs were administered in-hospital (3, 4). No clinical trials to date have compared the different P2Y12 inhibitors in a real-world STEMI setting of DAPT commencement prior to hospital admission.

Although a number of pharmacokinetic/dynamic studies have demonstrated that loading with the newer P2Y12 inhibitors results in a faster and more effective antiplatelet effect than with clopidogrel (5–8), there are no studies available comparing the effect of the different P2Y12 inhibitors on early (pre-PCI) coronary reperfusion when administered in the prehospital setting. Recently, the ATLANTIC study reported that prehospital ticagrelor did not improve early coronary reperfusion as compared to in-hospital ticagrelor; however, the median time difference between both treatment regimens was only 0.5 hours (h) (9).

The aim of this observational, non-randomized study was to investigate whether prehospital loading with one of the newer P2Y12 inhibitors improves early coronary reperfusion as compared to prehospital loading with clopidogrel in a real-world STEMI setting.

Materials and methods

Study population

Between January 2009 and October 2014, a total of 4,742 STEMI patients underwent PPCI at Rigshospitalet, Copenhagen (Denmark). Patients with chest pain >6 h, presenting with cardiac arrest or in cardiogenic shock, or those randomised in the EUROMAX trial (10) were excluded from this study. The main focus of

this study was on those patients receiving a single prehospital loading dose (LD1) of clopidogrel (600 mg), prasugrel (60 mg) or ticagrelor (180 mg). Data on patients receiving a double loading dose of clopidogrel (prehospital, LD1) + prasugrel or ticagrelor (at arrival in cath-lab, LD2) can be found in the Supplementary Material (available online at www.thrombosis-online.com). All clinical and procedural data were stored in a digital database and were retrospectively analysed for the purpose of this study. The study complies with the declaration of Helsinki on ethical principles for medical research involving human subjects and patients gave written informed consent for analysis and anonymous publication of their data.

Study endpoints

The primary endpoint of this study was the proportion of patients who did not meet the criteria for TIMI (Thrombolysis In Myocardial Infarction) flow grade 3 in the infarct-related artery at initial angiography before PCI. The secondary endpoints included the composite of death, recurrent myocardial infarction (MI), and urgent revascularisation at 30 days; definite stent thrombosis at 24 h and 30 days, major bleeding at 30 days, and TIMI flow grade 3 at the end of the procedure. MI was defined in accordance with the universal definition proposed in 2007 (11); routine measurements of CK-MB were performed within the first 24 h post-PPCI. Definite stent thrombosis was defined in accordance with the Academic Research Consortium criteria (12). Major bleeding was defined according to the PLATO criteria (4). TIMI flow was assessed by the PCI operator, no core-lab was used. Based on the East Denmark STEMI Registry, we had a 100% follow-up for all events reported in this study; but there was no event adjudication.

Statistical analysis

Categorical variables are reported as absolute values (n) and percentages (%), and were compared using the Chi-square or Fisher exact test. Continuous variables are presented as means ± standard deviation (SD) or medians [interquartile range, IQR], and were compared using the Student's t-test or Wilcoxon rank-sum test. Angiographic and clinical outcomes for the different P2Y12 inhibitor regimens were compared using a multivariate logistic regression analysis, adjusted for those variables with a $p < 0.10$ on univariate analysis. For this regression analysis, some variables were pooled: abciximab and eptifibatide were pooled into the variable glycoprotein IIb/IIIa inhibitor (GPI), and old and new-generation drug-eluting stent (DES) were pooled into the variable DES; regarding the time variables, only the variable LD1-to-angiography was used. All statistical analyses were performed with SPSS version 20 (SPSS Inc, Chicago, IL, USA) and statistical significance was defined as $p < 0.05$.

Results

P2Y12 inhibitor subgroups

Of all PPCI patients treated between January 2009 and October 2014, 3497 patients had symptom duration of less than 6 h and did not present with cardiac arrest or in cardiogenic shock – this was our study population (►Figure 1). Based on the different loading regimens with P2Y12 inhibitors, the study population was divided into five subgroups: i) clopidogrel-LD1 (n = 1532); ii) clopidogrel-LD1 + prasugrel-LD2 (n = 445); iii) prasugrel-LD1 (n = 883); iv) clopidogrel-LD1 + ticagrelor-LD2 (n = 77); and v) ticagrelor-LD1 (n = 491) (►Figure 2). Baseline characteristics of patients who were administered a single LD1 of clopidogrel, prasugrel or ticagrelor can be found in ►Table 1. All data of patients with clopidogrel-LD1 and an additional LD2 with prasugrel or ticagrelor can be found in Suppl. Tables 1–2 (available online at www.thrombosis-online.com).

Prehospital pharmacological treatment

As shown in ►Figure 2A, pretreatment with acetylsalicylic acid (ASA, 300 mg) and unfractionated heparin (UFH, 10,000 IU) has been standard-of-care for STEMI patients over the past six years. In the period 2009–2011, the majority of patients were administered a loading dose of clopidogrel (600 mg) in the ambulance (LD1). In the period 2013–2014, the newer P2Y12 inhibitors prasugrel (60 mg, loading dose) and ticagrelor (180 mg, loading dose) have become the drugs of choice for adenosine diphosphate (ADP) receptor inhibition in the prehospital setting (LD1).

In-hospital pharmacological treatment

Several changes in the in-hospital pharmacological regimens have occurred over the past six years. Administration of the oral P2Y12 inhibitors prasugrel (LD2, 60 mg) or ticagrelor (LD2, 180 mg) – on top of a prehospital loading dose of clopidogrel (LD1, 600 mg) – has been common practice in the transition period 2011–2012. GPI were routinely used during PPCI in the period 2009–2011; nowadays these intravenous antiplatelet agents are only used as bailout therapy in the event of angiographic evidence of large thrombus, slow or no-reflow and other thrombotic complications (< 10% of cases). Bivalirudin has been increasingly used since 2011, with approximately 80% of STEMI patients receiving this drug within the last two years (►Figure 2B).

Angiographic endpoints

Prehospital loading with the newer P2Y12 inhibitors did not result in a higher rate of coronary reperfusion before (►Figure 2C) and after PPCI (►Figure 2D). As shown in ►Table 2, a TIMI-flow grade 3 at initial angiography was absent in 71.5%, 71.7% and 69.0% of STEMI patients preloaded with clopidogrel-LD1, prasugrel-LD1, or ticagrelor-LD1, respectively. In addition, a TIMI-flow grade 3 after PPCI was absent in 7.8%, 7.4% and 6.2% of STEMI

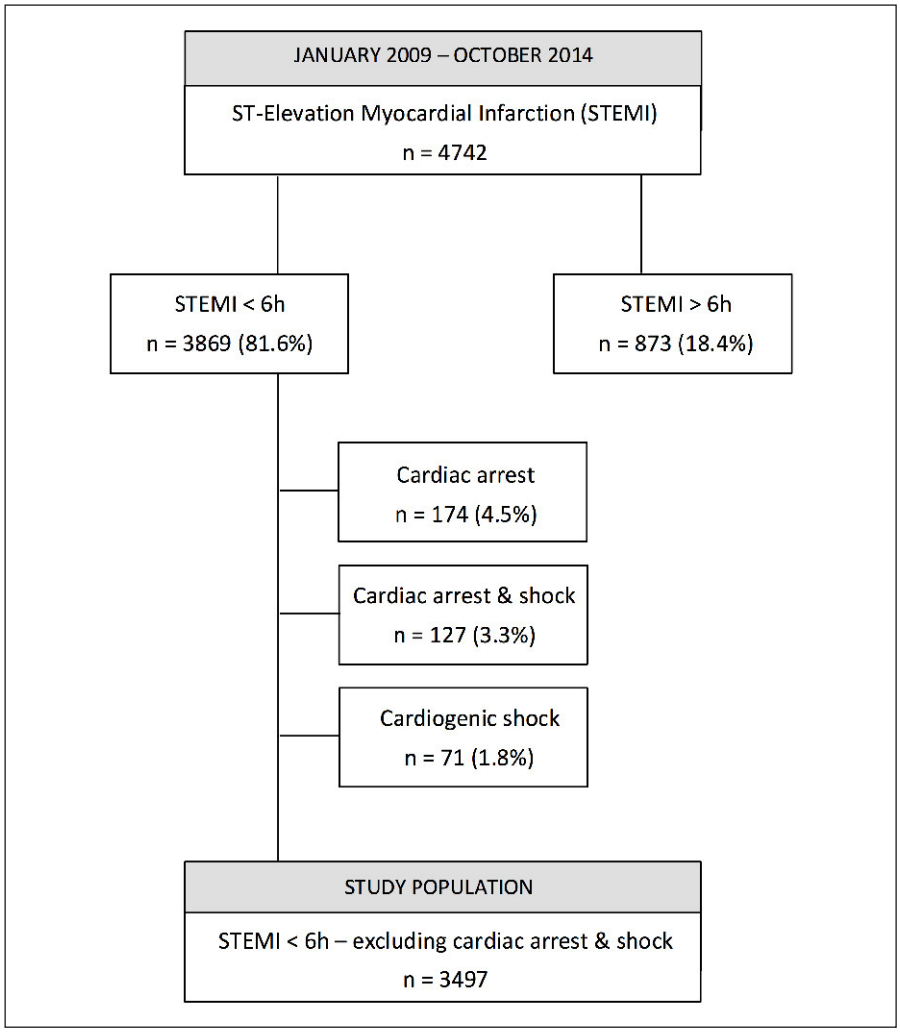


Figure 1: Flow diagram of study population selection.

patients pretreated with clopidogrel-LD1, prasugrel-LD1, or ticagrelor-LD1, respectively.

Clinical endpoints

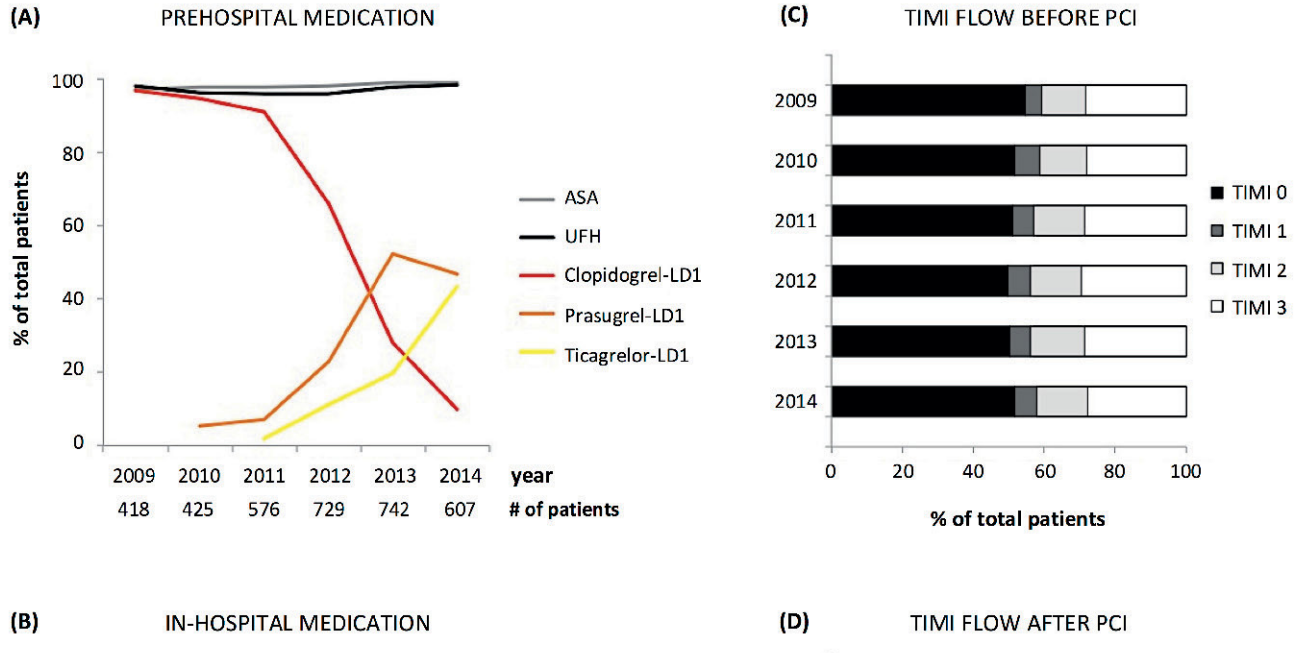
At 30-days follow-up, no differences were evident among the different subgroups in terms of the clinical endpoints death from any cause, recurrent MI, and urgent revascularisation as well as the composite endpoint MACE (►Table 2, ►Figure 3). Nor was there a statistical difference for definite stent thrombosis at 24 h and 30 days and for the safety endpoint major bleeding at 30 days (►Table 2). Similar results were obtained when the clopidogrel-LD1 subgroup was compared with a pooled prasugrel-LD1/ticagrelor-LD1 subgroup (Suppl. Table 3, available online at www.thrombosis-online.com).

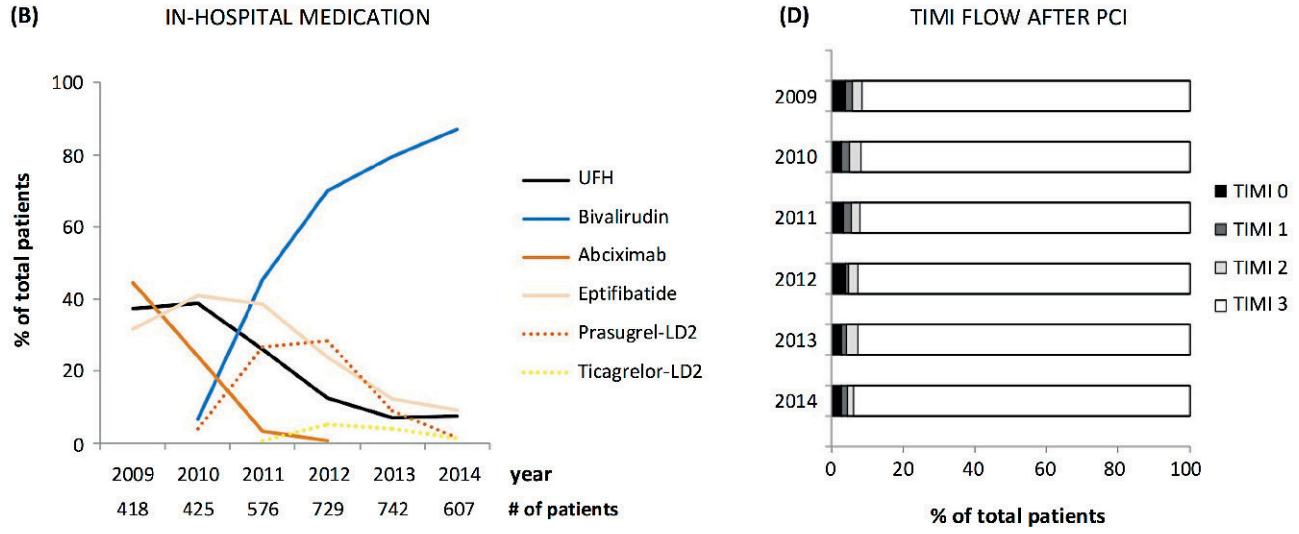
Discussion

In this study, we demonstrate that implementation of the latest ESC-STEMI guidelines recommendation on pre-hospital antiplatelet treatment – which prompted a shift from clopidogrel to the newer P2Y12 inhibitors – did not result in a higher rate of early coronary reperfusion in our STEMI population. Neither prasugrel nor ticagrelor were associated with a lower rate of MACE at 30-days follow-up, whereas major bleeding rates were similar among all different P2Y12 inhibitor regimens.

Early coronary reperfusion

Prehospital treatment of ongoing STEMI with fibrinolytic agents or GPI has been associated with improved coronary reperfusion and outcomes. However, this more aggressive pretreatment has also been associated with an increased bleeding risk (13, 14). The European STEMI guidelines do not recommend routine use of GPI "in the era of potent DAPT" and states that the value of starting GPI upstream of the catheterisation laboratory is, at best, un-





	2009	2010	2011	2012	2013	2014	Total
Clopidogrel-LD1	410	378	359	232	110	43	1532
Clopidogrel-LD1 + Prasugrel-LD2	0	17	151	203	65	9	445
Prasugrel-LD1	0	22	41	163	380	277	883
Clopidogrel-LD1 + Ticagrelor-LD2	0	0	4	37	28	8	77
Ticagrelor-LD1	0	0	10	79	144	258	491

Figure 2: Pharmacological regimens and angiographic outcomes. A-B) Overview of the different prehospital and in-hospital medical regimens used in patients with on-going STEMI of less than 6 hours and without cardiac arrest or cardiogenic shock, referred to our centre for primary PCI (PPCI) between January 2009 and October 2014 – due to a centralisation operation, the number of PPCI significantly increased from July 2011 on. C-D) Bar charts showing the proportion of patients (% of total patients per year) with TIMI-flow grades 0 to 3 at initial angiography before PCI (upper right panel) and at completion of PPCI (middle right panel). E) The bottom panel gives the number of patients in the five different subgroups as divided per year and the total number of patients per subgroup. ASA = acetylsalicylic acid; LD1 = prehospital loading dose; LD2 = in-hospital loading dose; PCI = percutaneous coronary intervention; TIMI = thrombolysis in myocardial infarction; UFH = unfractionated heparin.

Table 1: Baseline characteristics.

	Clopidogrel-LD1	Prasugrel-LD1		Ticagrelor-LD1	
	(n = 1532)	(n = 883)	P-value	(n = 491)	P-value
Patient characteristics					
Age, years	63.9 ± 12.9	63.4 ± 11.1	0.254	63.2 ± 12.5	0.283
Male	1133 (74.0)	658 (74.5)	0.858	356 (72.5)	0.550
Hypertension	545 (35.6)	307 (34.8)	0.821	178 (36.3)	0.827
Hypercholesterolaemia	367 (24.0)	216 (24.5)	0.852	125 (25.5)	0.539
Body mass index, kg/m^2	26.8 ± 5.1	27.3 ± 12.5	0.323	27.1 ± 4.9	0.353
Diabetes mellitus	202 (13.2)	109 (12.3)	0.626	62 (12.6)	0.808
Current smoker	660 (43.1)	383 (43.4)	0.640	194 (39.5)	0.180
Family history	455 (29.7)	270 (30.6)	0.775	137 (27.9)	0.481
Previous AMI	130 (8.5)	80 (9.1)	0.683	37 (7.5)	0.568
Previous PCI	166 (10.8)	88 (10.0)	0.584	54 (11.0)	0.986
Previous CABG	18 (1.2)	15 (1.7)	0.371	9 (1.8)	0.379
Atrial fibrillation	90 (5.9)	42 (4.8)	0.305	24 (4.9)	0.476
Peripheral artery disease	61 (4.0)	27 (3.1)	0.288	14 (2.9)	0.309
Previous CVA	103 (6.7)	26 (2.9)	< 0.001	24 (4.9)	0.176
Chronic obstructive lung disease	48 (3.1)	27 (3.1)	1.000	20 (4.1)	0.389
Chronic kidney disease	30 (2.0)	17 (1.9)	1.000	14 (2.9)	0.316
Angiographic findings					
One-vessel disease	937 (61.2)	555 (62.9)	0.650	318 (64.8)	0.168
Multi-vessel disease	595 (38.8)	328 (37.1)	0.650	173 (35.2)	0.168
Involvement of LAD-1/2	574 (37.5)	317 (35.9)	0.657	173 (35.2)	0.402
Therapeutic management					
Pre-hospital					
Acetylsalicylic acid	1502 (98.0)	871 (98.6)	0.345	485 (98.8)	0.380
Heparin	1467 (95.8)	839 (95.0)	0.503	472 (96.1)	0.818
In-hospital					
Heparin	151 (9.9)	16 (1.8)	< 0.001	17 (3.5)	< 0.001
Bivalirudin	421 (27.5)	702 (79.5)	< 0.001	389 (79.2)	< 0.001
Abciximab	292 (19.1)	5 (0.6)	< 0.001	1 (0.2)	< 0.001
Eptifibatide	504 (32.9)	130 (14.7)	< 0.001	64 (13.0)	< 0.001
Thrombusaspiration	798 (52.1)	474 (53.7)	0.511	216 (44.0)	0.002
Stent implantation	1447 (94.5)	824 (93.3)	0.327	459 (93.5)	0.491
BMS	232 (15.1)	54 (6.1)	< 0.001	14 (2.9)	< 0.001
DES, old-generation	191 (12.5)	16 (1.8)	< 0.001	2 (0.4)	< 0.001
DES, new-generation	1109 (72.4)	813 (92.1)	< 0.001	475 (96.7)	< 0.001
Time line					
Chest pain-to-ECG, min	69 [35–140]	60 [34–118]	0.017	71 [31–146]	0.793
ECG-to-arrival at cathlab, min	69 [46–98]	57 [44–75]	< 0.001	66 [50–88]	0.096
LD1-to-angiography, min	77 [53–108]	64 [53–84]	< 0.001	74 [56–95]	0.131
LD1-to-PCI (first wire), min	100 [66–119]	77 [65–98]	< 0.001	86 [69–106]	0.158

Values are mean ± SD, n (%), or median [IQR]. Statistical analysis as compared to clopidogrel-LD1 subgroup. AMI = acute myocardial infarction; BMS = bare metal stent; CABG = coronary artery bypass graft surgery; CVA = cerebrovascular accident; DES = drug-eluting stent; LAD = left anterior descending artery; LD1 = prehospital loading dose; PCI = percutaneous coronary intervention.

Table 2: Outcome.

	Clopidogrel-LD1	Prasugrel-LD1	Prasugrel-LD1 vs Clopidogrel-LD1	
	(n = 1532)	(n = 883)	Adjusted OR* (95% CI)	P-value
Angiographic endpoint				
Absence of TIMI-flow 3 before PCI	1095 (71.5)	633 (71.7)	1.01 (0.84–1.22)	0.889
Absence of TIMI-flow 3 after PCI	106 (7.8)	60 (7.4)	0.83 (0.60–1.14)	0.345
Clinical endpoints at 30 days				
MACE	62 (4.0)	30 (3.4)	0.80 (0.49–1.30)	0.373
Death from any cause	46 (3.0)	23 (2.6)	0.82 (0.48–1.37)	0.440
Recurrent MI	10 (0.7)	5 (0.6)	0.87 (0.30–2.54)	0.795
Urgent revascularization	14 (0.9)	7 (0.8)	0.87 (0.35–2.16)	0.758
In-hospital MACE	49 (3.2)	22 (2.5)	0.73 (0.43–1.23)	0.233
Definite stent thrombosis				
< 24 hours after PPCI	6 (0.4)	1 (0.1)	0.29 (0.04–2.40)	0.250
< 30 days after PPCI	13 (0.8)	3 (0.3)	0.40 (0.11–1.40)	0.152
Major bleeding	63 (4.1)	25 (2.8)	0.86 (0.53–1.43)	0.580
	Clopidogrel-LD1	**Ticagrelor-LD1**	**Ticagrelor-LD1 vs Clopidogrel-LD1**	
	(n = 1532)	**(n = 491)**	**Adjusted OR* (95% CI)**	**P-value**
Angiographic endpoint				
Absence of TIMI-flow 3 before PCI	1095 (71.5)	339 (69.0)	0.89 (0.71–1.11)	0.302
Absence of TIMI-flow 3 after PCI	106 (7.8)	29 (6.2)	0.76 (0.51–1.35)	0.270
Clinical endpoints at 30 days				
MACE	62 (4.0)	17 (3.5)	0.82 (0.44–1.49)	0.541
Death from any cause	46 (3.0)	14 (2.9)	0.87 (0.45–1.71)	0.640
Recurrent MI	10 (0.7)	2 (0.4)	0.62 (0.14–2.85)	0.541
Urgent revascularization	14 (0.9)	3 (0.6)	0.67 (0.19–2.33)	0.525
In-hospital MACE	49 (3.2)	11 (2.2)	0.66 (0.32–1.33)	0.209
Definite stent thrombosis				
< 24 hours after PPCI	6 (0.4)	1 (0.2)	0.52 (0.06–4.32)	0.544
< 30 days after PPCI	13 (0.8)	2 (0.4)	0.48 (0.11–2.13)	0.332
Major bleeding	63 (4.1)	13 (2.6)	0.83 (0.31–2.21)	0.703

* Adjusted for those variables with $p < 0.10$ on univariate analysis. No adjustment was made for clinical endpoints with an event rate < 1%. The primary endpoint did not need adjustment for in-hospital therapeutic management. CI = confidence interval; LD1 = prehospital loading dose; MACE = major adverse cardiovascular event; MI = myocardial infarction; OR = odds ratio; PPCI = primary percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

certain (1). In accordance, the American STEMI guidelines state "it may be reasonable" to administer GPI in the pre-cathlab setting when PPCI is intended – however, this is only a Class IIB recommendation (2).

In the recent ATLANTIC study – comparing prehospital vs in-hospital ticagrelor in STEMI patients – it was shown that prehospital administration of this direct P2Y12 inhibitor did not improve reperfusion of the culprit artery before PCI (9). In the correspondence following this study, it was discussed that this negative result was not unexpected, since pharmacodynamic studies have shown that at least some hours are required to achieve effective platelet inhibition in STEMI patients who receive a standard loading dose of ticagrelor (15, 16). In the ATLANTIC study, there was a median time difference of only 45 minutes (min) from LD1 to angiography and a median time difference of only 31 min between LD1 (i.e. prehospital loading) and LD2 (i.e. in-hospital loading) (9). In our study, the time interval between LD1 and angiography was approximately 65–75 min (▶Table 1). However, despite these longer time intervals, we did not measure a higher rate of early coronary reperfusion after prehospital loading with the newer P2Y12 inhibitors as compared to clopidogrel. Based on these data, we can conclude that pretreatment with the most potent oral P2Y12 in-

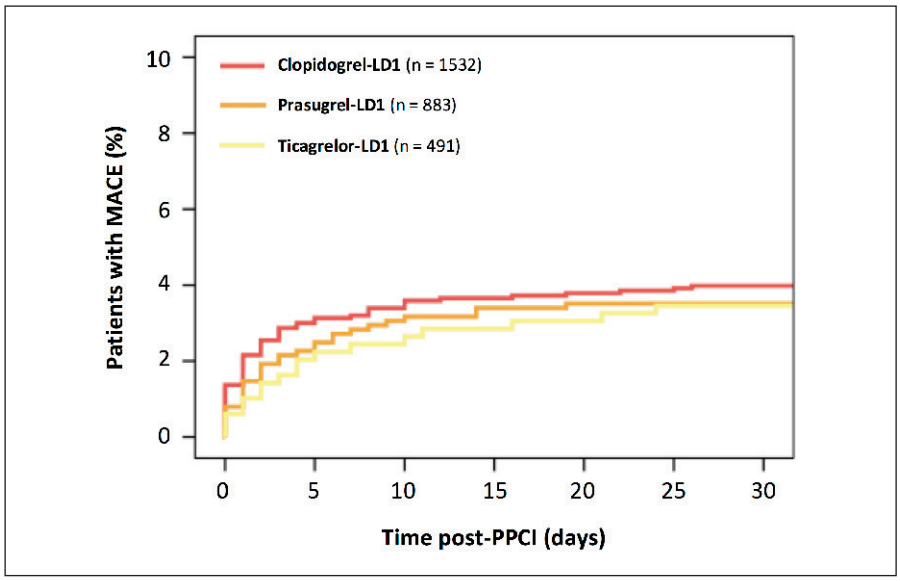


Figure 3: Kaplan-Meier curves for major adverse cardiac events (MACE). Cumulative event rates of MACE up to 30 days for the different subgroups: Clopidogrel-LD1 (red line); Prasugrel-LD1 (orange line); and Ticagrelor-LD1 (yellow line).

hibitors was not associated with improved coronary reperfusion at the time of angiography.

Parental drug administration will be the option to take if a higher rate of early coronary reperfusion is aimed for; however, a main concern is the risk of major bleeding. A clever and "titrated" combination of intravenous (IV) and peroral (PO) anti-thrombotic drugs could be a solution to this problem. In this regard, we refer to the FABOLUS PRO trial, in which different IV/PO antithrombotic drug combinations were studied. Interestingly, the concomitant administration of a GPI bolus-only regimen and prasugrel allowed immediate and sustained inhibition of platelet activation (17). Similar IV/PO combinations, including the intravenous P2Y12 inhibitor cangrelor, need further testing in prospective randomised clinical trials.

Early stent thrombosis

Stent thrombosis remains a major concern in STEMI patients with an excess three- to four-fold increased risk compared with PCI in an elective setting (18). In the TRITON-TIMI 38 and PLATO STEMI cohorts, treatment with prasugrel or ticagrelor was associated with a reduced rate of stent thrombosis (clopidogrel 2.7% vs prasugrel 1.5% at 15 months; clopidogrel 2.4% vs ticagrelor 1.6% at 12 months); however, in both trials, the P2Y12 inhibitors were only administered in-hospital (19, 20). Whether prehospital administration of these drugs can further reduce the risk of stent thrombosis is unknown.

In the recent ATLANTIC study, the rate of definite stent thrombosis at 24 h was significantly lower in the prehospital ticagrelor group as compared to the in-hospital ticagrelor group. As a result, the authors concluded that prehospital administration of ticagrelor may prevent stent thrombosis in the very early phase after PPCI (9). However, this result has to be interpreted with caution as 1) there was only 31 min difference between the prehospital and in-hospital administration of ticagrelor, with no statistical difference in measured platelet-reactivity between the two treatment strategies; 2) the rate of definite stent thrombosis at 24 h was unusually high (0.8%) in the in-hospital ticagrelor group; and 3) besides effective antiplatelet therapy, other important angiographic factors predispose to stent thrombosis such as coronary stent undersizing and stent edge plaque burden.

In this study, the rate of definite stent thrombosis was very low across all subgroups including patients receiving the slower-acting drug clopidogrel. Although the rate of definite stent thrombosis at 24 h and 30 days was double in the clopidogrel-LD1 subgroup as compared to prasugrel-LD1 and ticagrelor-LD1 subgroups, there was no statistical difference (▶Table 2). Importantly, also these results have to be interpreted with caution, as this observational study was not properly designed and powered to detect a statistical difference for this particular event (with a low incidence) and in-hospital pharmacological regimens were also different for the compared subgroups. Clearly, further studies with better statistical power will be needed to clarify this topic.

Clinical outcomes

The rate of the combined primary endpoint (cardiovascular death, recurrent MI, stroke) was reduced with prasugrel and ticagrelor in the STEMI cohorts in the pivotal trials comparing these agents with clopidogrel. The difference between prasugrel and clopidogrel in the TRITION-TIMI 38 trial could be ascribed to a reduction of early events (<30 days) in the prasugrel group, whereas the curves ran parallel throughout further follow-up (19). In contrast, in the PLATO trial, the curves for ticagrelor and clopidogrel ran parallel during the first 30 days and only diverged in the later follow-up period (20).

In this observational study with prehospital loading of the P2Y12 inhibitors, no difference was observed between the differ-

What is known about this topic?

- The newer P2Y12 inhibitors prasugrel and ticagrelor have been reported to be more potent and faster-acting antiplatelet agents than clopidogrel.
- The European STEMI guidelines recommend that patients undergoing PPCI should receive one of the newer P2Y12 inhibitors as early as possible before angiography.

What does this paper add?

- This study demonstrates that prehospital loading with the newer P2Y12 inhibitors does not improve early coronary reperfusion as compared to prehospital loading with clopidogrel.
- Cardiovascular event rates at 30 days were low in our PPCI cohort excluding cardiac arrest and cardiogenic shock and did not differ between the different prehospital P2Y12 inhibitor regimens.

ent P2Y12 inhibitors with regards to the clinical endpoints death, recurrent MI, and urgent revascularisation; nor was there a difference in the rate of major bleeding events at 30 days. Although several possible confounding factors should be taken into account when interpreting these results, we can state that cardiovascular event rates were in general low in our all-comers STEMI population – excluding cardiac arrest and cardiogenic shock – and in the same range as those reported in the ATLANTIC study. In this latter study, prehospital administration of ticagrelor was reported to be safe (similar number of bleeding events) and did not result in a reduction of major adverse cardiac events (MACE) as compared to in-hospital ticagrelor administration (9).

Based on pharmacodynamic studies, it makes completely sense to recommend administration of the more potent P2Y12 inhibitors as early as possible in order to achieve early efficacy. However, so far, there is no evidence available supporting the need for prehospital loading with one of the newer P2Y12 inhibitors instead of clopidogrel. Moreover, 10–20 % of patients triaged to emergency coronary angiography – due to suspected STEMI – will not proceed to PPCI (9, 21). Whether pre-hospital treatment with any kind of P2Y12 inhibitor will influence further treatment of these patients negatively (i.e. in case of need for acute cardiac surgery) needs to be further investigated.

Abbreviations

ADP = adenosine diphosphate; ASA = acetylsalicylic acid; CABG = coronary artery bypass graft surgery; DAPT = double antiplatelet therapy; GPI = glycoprotein IIb/IIIa inhibitor; LD1 = prehospital loading dose; LD2 = in-hospital loading dose; MACE = major adverse cardiovascular event; PPCI = primary percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction; TIMI = thrombolysis in myocardial infarction; UFH = unfractionated heparin.

Limitations

The main limitation of this study was its design, resulting in non-standardised in-hospital treatment regimens. However, concerning the impact of the different P2Y12 inhibitors on the primary endpoint of this study, this issue should not be considered a confounding factor – as the two other prehospital medications (ASA, heparin) remained unchanged for all subgroups. The decision to use either prasugrel or ticagrelor was mainly based on catchment area for the emergency medical services in our region; this also explains the shorter LD1-to-arrival in cathlab time interval in the prasugrel-LD1 subgroup as this drug is mainly used by paramedics in Copenhagen city (and less so in the more peripheral regions). Late in our study period, where all three drugs were available, clopidogrel and ticagrelor administration could be related to selection bias due to fewer restrictions for these drugs as compared to prasugrel (i.e. history of stroke/ischaemic attack, age ≥ 75 years and/or weight < 60 kg). Clopidogrel might have also been the drug of choice for patients already on oral anticoagulant therapy, which are often patients with more risk factors and/or of higher age. Baseline characteristics presented in this study do not support these speculations but, as an observational non-randomised study, the possibility of selection bias must be taken into consideration.

Conclusions

In this large observational, non-randomised study, we demonstrate as the first that prehospital loading with the newer, faster-acting P2Y12 inhibitors does not improve early coronary reperfusion as compared to prehospital loading with clopidogrel in a real-world PPCI population.

Acknowledgments

We would like to acknowledge Mrs. Anne-Cathrine Preis and Mr. Sybe De Backer for their help in data acquisition and data analysis.

Conflicts of interest

T.E. has received grants from and is a member of the advisory board of Eli Lilly, Novo Nordisk and Zealand Pharma. L.B. is supported by a grant from EAPCI. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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