Ticagrelor versus clopidogrel in elective percutaneous coronary intervention (ALPHEUS): a randomised, open-label, phase 3b trial

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Summary

Background Percutaneous coronary intervention (PCI)-related myonecrosis is frequent and can affect the long-term prognosis of patients. To our knowledge, ticagrelor has not been evaluated in elective PCI and could reduce periprocedural ischaemic complications compared with clopidogrel, the currently recommended treatment. The aim of the ALPHEUS study was to examine if ticagrelor was superior to clopidogrel in reducing periprocedural myocardial necrosis in stable coronary patients undergoing high-risk elective PCI.

Methods The ALPHEUS study, a phase 3b, randomised, open-label trial, was done at 49 hospitals in France and Czech Republic. Patients with stable coronary artery disease were eligible for the study if they had an indication for PCI and at least one high-risk characteristic. Eligible patients were randomly assigned (1:1) to either ticagrelor (180 mg loading dose, 90 mg twice daily thereafter for 30 days) or clopidogrel (300–600 mg loading dose, 75 mg daily thereafter for 30 days) by use of an interactive web response system, and stratified by centre. The primary outcome was a composite of PCI-related type 4 (a or b) myocardial infarction or major myocardial injury and the primary safety outcome was major bleeding, both of which were evaluated within 48 h of PCI (or at hospital discharge if earlier). The primary analysis was based on all events that occurred in the intention-to-treat population. The trial was registered with ClinicalTrials.gov, NCT02617290.

Findings Between Jan 9, 2017, and May 28, 2020, 1910 patients were randomly assigned at 49 sites, 956 to the ticagrelor group and 954 to the clopidogrel group. 15 patients were excluded from the ticagrelor group and 12 from the clopidogrel group. At 48 h, the primary outcome was observed in 334 (35%) of 941 patients in the ticagrelor group and 341 (36%) of 942 patients in the clopidogrel group (odds ratio [OR] 0·97, 95% CI 0·80–1·17; p=0·75). The primary safety outcome did not differ between the two groups, but minor bleeding events were more frequently observed with ticagrelor than clopidogrel at 30 days (105 [11%] of 941 patients in the ticagrelor group *vs* 71 [8%] of 942 patients in the clopidogrel group; OR 1·54, 95% CI 1·12–2·11; p=0·0070).

Interpretation Ticagrelor was not superior to clopidogrel in reducing periprocedural myocardial necrosis after elective PCI and did not cause an increase in major bleeding, but did increase the rate of minor bleeding at 30 days. These results support the use of clopidogrel as the standard of care for elective PCI.

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*A complete list of the ALPHEUS investigators is provided in the appendix

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Introduction

Percutaneous coronary intervention (PCI) is widely used in patients with stable coronary artery disease and is considered a safe procedure. Over the past decade, the rates of associated stent thrombosis, Q-wave myocardial infarction, stroke, and death have substantially decreased, and they are now considered rare periprocedural complications. However, development of highly sensitive cardiac troponin assays has led to the documentation of frequent periprocedural myonecrosis. Although often asymptomatic, these periprocedural complications can delay hospital discharge, and have been associated with an increased risk of future major cardiac adverse events, including death.[1–4] Side branch occlusion, slow coronary flow, and embolisation are potential mechanisms of atherothrombotic complications and could be reduced by more effective antiplatelet therapy than the recommended combination of aspirin and clopidogrel. Intravenous cangrelor has shown benefit over clopidogrel in PCI, reducing ischaemic complications at the expense of increased bleeding.[5–7] Despite a higher risk of bleeding, prasugrel and ticagrelor, with a more potent and rapid onset of action compared with clopidogrel, are now the standard of care for PCI in patients with acute coronary syndrome, but have not been well investigated in elective PCI.[8,9] The

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See Online for appendix

Research in context

Evidence before this study

The $P2Y_{12}$ inhibitors prasugrel and ticagrelor provide a higher level of platelet inhibition than clopidogrel, with a faster onset of action and improved clinical outcomes in patients with acute coronary syndrome. These two drugs have not been well investigated in elective percutaneous coronary intervention (PCI) for stable coronary patients and clopidogrel remains the standard of care. Nevertheless, in 2018, European guidelines on revascularisation gave a IIb recommendation to prasugrel and ticagrelor in elective PCI for high-risk situations but without supporting evidence (level of evidence C), resulting in increasing use of these drugs in clinical practice. Hard clinical events are rare after elective PCI but peri-procedural myocardial infarction (type 4a) and myocardial injury are frequent, especially in high-risk situations, and have been associated with a poorer prognosis. Whether ticagrelor could reduce periprocedural myonecrosis in high-risk elective PCI is unknown. To our knowledge, no oral $P2Y_{12}$ inhibitor other than clopidogrel has been appropriately tested in combination with aspirin in elective PCI before this study was undertaken.

Added value of this study

We showed that the higher level of platelet inhibition obtained with ticagrelor compared with clopidogrel did not translate into a reduction of periprocedural myocardial infarction or myocardial injury within 48 h of high-risk PCI in stable coronary patients. None of the clinical outcomes differed between groups at 30-day follow-up, whereas there was an excess of minor bleeding but not of major bleeding in patients treated with ticagrelor.

Implications of all the available evidence

During the conduct of the ALPHEUS study, prasugrel was also compared with clopidogrel in another elective PCI study (the SASSICAIA study). However, this study was ended prematurely after inclusion of 781 patients because of slow enrolment and insufficient funding. We did a pooled analysis of the global data available, representing 2664 stable coronary patients undergoing elective PCI with clopidogrel or stronger $P2Y_{12}$ inhibition using ticagrelor or prasugrel. None of the studies reported an excess of major bleeding with more potent $P2Y_{12}$ inhibitors, but the results were consistent in showing an absence of improved efficacy. Overall, our findings suggest that clopidogrel should remain the recommended standard of care in stable coronary patients undergoing PCI.

assessment of loading with the $P2Y_{12}$ inhibitor ticagrelor or clopidogrel to halt ischaemic events in patients undergoing elective coronary stenting (ALPHEUS) study examined the effect of ticagrelor compared with clopidogrel to reduce periprocedural myocardial necrosis in stable coronary patients undergoing high-risk elective PCI.

Methods

Study design and participants

The ALPHEUS study, a phase 3b, randomised, open-label trial, was done at 49 hospitals in France and Czech Republic. The participating centres, investigators, and study committee members are listed in the appendix (pp 3–13). The study design and protocol have been previously published[10] and approved by the national regulatory authorities and ethics committees or institutional review boards as needed in the participating countries.

Patients with stable coronary artery disease, defined as having a baseline cardiac troponin below the upper limit of the normal or a decreasing level in case of modestly positive cardiac troponin (within the grey zone specific to each high sensitivty troponin assay or below three times the upper limit of the local laboratory normal values), were eligible for the study if they had an indication for PCI and at least one high-risk characteristic (list provided in appendix p 16). Exclusion criteria have been described previously.[10] Patients who were on chronic clopidogrel treatment (maintenance dose for more than 5 days) were eligible for the study. All patients provided written informed consent.

Randomisation and masking

Eligible patients were randomly assigned (1:1) to either ticagrelor or clopidogrel by use of an interactive web response system available via the electronic case report form, and stratified by centre. The study was open label, as a full double-blind design was not possible because of budget constraints across the two European countries. However, the primary endpoint was based on the measurement of post-PCI troponin, which is not subject to interpretation or bias, and the clinical endpoints were all adjudicated in a masked fashion, in addition to reading of PCI videos at a central core laboratory and statistical analyses. Administration of the loading dose of the study drug took place after the angiogram and before PCI, which could be staged (deferred PCI within 24 h of administration of the loading dose of study drug) or immediately after randomisation (ad-hoc PCI was defined as within 3 h after the angiogram). Random assignment could not occur before the coronary status was known.

Procedures

Patients received a loading dose of ticagrelor 180 mg before PCI and 90 mg twice daily thereafter for 30 days or a loading dose of clopidogrel 300–600 mg (dose at the discretion of the physician) and 75 mg daily thereafter for

30 days. Investigators could administer the loading dose as whole or crushed tablets. The duration of study treatment was 30 days after PCI. Beyond 30 days, the choice of treatment was left at the discretion of the treating physician. A pharmacodynamic substudy (the Bio-ALPHEUS study) was done at five participating centres and analysed the level of $P2Y_{12}$ inhibition in a masked fashion at the ACTION central core laboratory (Paris, France). Samples were drawn at baseline, 4 h after the loading dose, and the day after PCI and platelet inhibition was evaluated using the vasodilator-stimulated phosphoprotein platelet reactivity index measured by ELISA, as previously described.[11]

Outcomes

The primary outcome was PCI-related myocardial infarction (type 4a or 4b) or major myocardial injury within 48 h of the procedure (or at hospital discharge if earlier). The definitions[10] have been previously published and are reported in the appendix (p 15). The definition of the primary outcome of the ALPHEUS trial corresponded to the third universal definition of myocardial infarction that was effective at the time of the study design.[12] The fourth universal definition of myocardial infarction was published while the study was ongoing, and the protocol was amended to include the new definition of myocardial injury in the main secondary outcome, combining PCI-related myocardial infarction (type 4a or 4b) and any type of myocardial injury (major or minor).[13]

Other secondary outcomes included the composite of death, myocardial infarction (all type), or stroke or transient ischaemic attack; the composite of death or myocardial infarction (type 1, 4, and 5); and the composite of death, myocardial infarction (type 1, 4, and 5), major myocardial injury, urgent revascularisation, or recurrent ischaemia requiring catheterisation.

The primary safety outcome was major bleeding, evaluated by the Bleeding Academic Research Consortium (BARC) criteria (BARC 3 or 5). Secondary safety outcomes included minor or nuisance bleeding (BARC 1 or 2) and any bleeding (BARC 1 to 5). A net clinical benefit outcome comprising death, myocardial infarction, stroke, or major bleeding was also evaluated.

Bleeding risk was evaluated with the Dual Antiplatelet Therapy (DAPT) score and the PARIS bleeding score.[14,15] In addition to the baseline level, cardiac troponin was measured 6 h and 24 h after PCI or at discharge if this occurred earlier, and the peak values were considered for outcome assessment. Clinical outcomes were evaluated at 48 h and 30 days. All angiographic or PCI videos were analysed by at least two masked independent experts (who did not otherwise participate in the study) of the ACTION central core laboratory. An independent clinical event committee whose members were unaware of the treatment assignments reviewed all outcomes, except death.

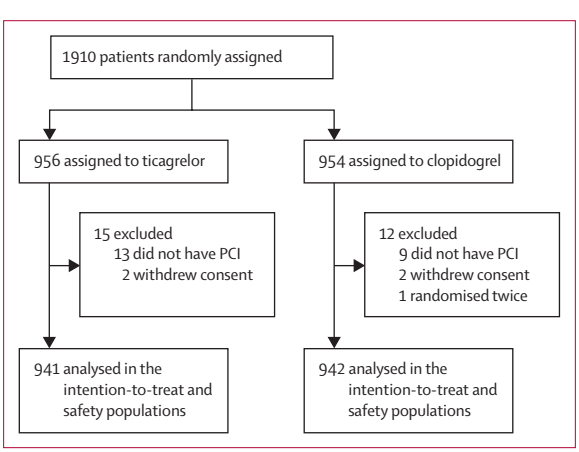

Figure 1: **Trial profile**
PCI=percutaneous coronary intervention.

	Ticagrelor (n=941)	Clopidogrel (n=942)
Age, years	66·0 (9·2)	66·6 (9·7)
Sex		
Female	177 (19%)	207 (22%)
Male	764 (81%)	735 (78%)
Body-mass index, kg/m²	27·8 (4·5)	27·6 (4·9)
Current smoker	166 (18%)	171 (18%)
Hypertension	594 (63%)	607 (64%)
Diabetes	328 (35%)	352 (37%)
Dyslipidaemia	581 (62%)	570 (61%)
Renal insufficiency (creatinine clearance <60 mL/min)	89 (9%)	98 (10%)
Medical history*		
History of acute coronary syndrome (in the past 12 months)	51 (5%)	50 (5%)
Previous coronary artery bypass grafting	62 (7%)	60 (6%)
Previous PCI	339 (36%)	362 (38%)
Peripheral vascular disease	121 (13%)	115 (12%)
Previous stroke or transient ischaemic attack	43 (5%)	49 (5%)
Left ventricular ejection fraction <40% or previous episode of heart failure	46 (5%)	49 (5%)
Treatment on admission		
Proton pump inhibitors†	338 (36%)	347 (37%)
Aspirin	814 (87%)	804 (85%)
Clopidogrel*	388 (41%)	417 (44%)
Procedural characteristics		
Number of high-risk features for PCI	3·2 (1·4)	3·2 (1·5)
Radial or ulnar approach†	891 (95%)	895 (95%)
Multivessel disease	575 (61%)	586 (62%)
Number of stents implanted per patient	1·8 (1·0)	1·8 (1·0)
Total stent length per patient, mm	38·4 (24·5)	38·9 (24·8)

Data are mean (SD) or n (%). PCI=percutaneous coronary intervention. *Data missing for one patient in the ticagrelor group. †Data missing for two patients in the ticagrelor group.

Table 1: **Baseline characteristics**

Statistical analysis

Assuming a total event rate (for the primary outcome) of 30% at 48 h in the clopidogrel group, we calculated that 856 patients per group (1712 total patients) were required for 80% power to detect a difference of six percentage points (20% relative difference) in the primary outcome at a two-sided α level of 5%. Assuming a dropout rate of around 10%, 950 patients per group (1900 total patients) needed to be randomly assigned. A masked sample size reassessment was done on the primary outcome after 50% of patients were included for sample size reassessment (Addplan Software release 4) and we concluded that no sample size adjustment was necessary. The primary analysis was based on all events that occurred in the intention-to-treat population, defined as all patients who underwent randomisation and PCI and who provided written informed consent. In cases of withdrawal of consent, only data recorded before the withdrawal were considered. The safety analysis included all patients who received at least one dose of study drug. The primary outcome was analysed by χ^2 test. Prespecified subgroup analyses to evaluate variations in treatment effect were done by logistic regression models, with terms for treatment, subgroup, and interaction of treatment with subgroup. All reported subgroup analyses were prespecified. Sensitivity analyses were done for primary and secondary endpoints using multivariate mixed logistic models, including centre as a random effect and with or without a priori known risk factors as covariables (diabetes, renal insufficiency, left ventricular ejection fraction <40% or previous episode of heart failure, multivessel disease, number of stents implanted, and total stent length per patient). Secondary outcomes were examined with analyses identical to those described for the primary outcome. Kaplan-Meier estimates of clinical outcomes were also calculated for 30 days after the first dose.

Data were collected and analysed according to the predefined statistical analysis plan by academic statisticians of the ACTION Study Group. A steering committee oversaw the conduct of the trial, in collaboration with representatives of the study sponsor. The trial was monitored by an independent data and safety monitoring board.

All statistical analyses were done using SAS version 9.4 software. The trial was registered with ClinicalTrials.gov, NCT02617290.

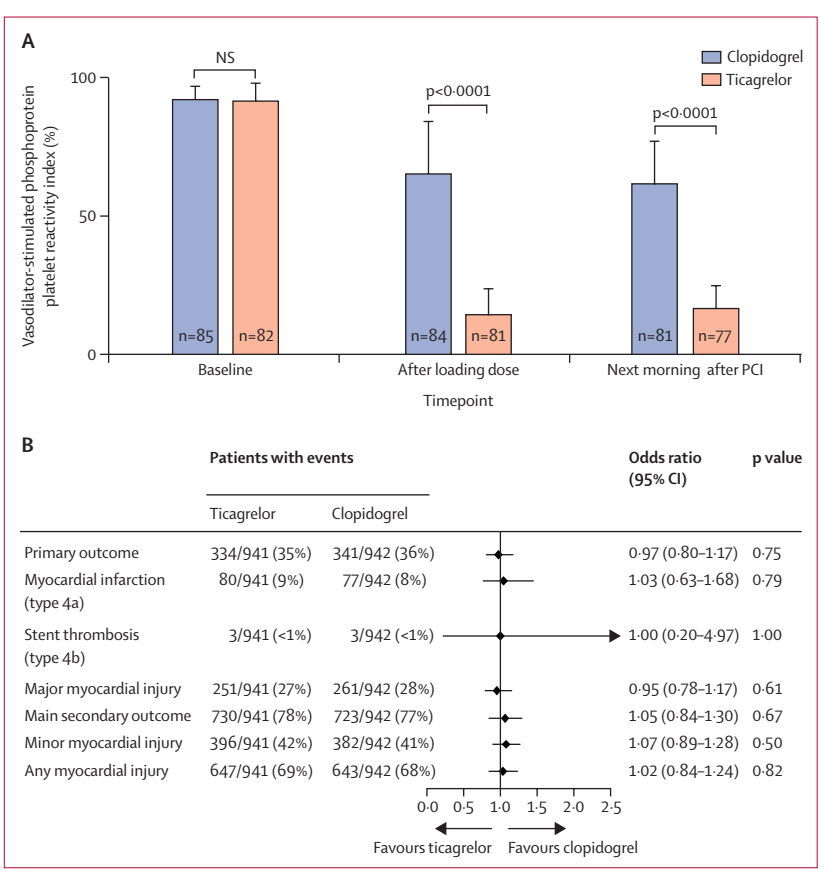

Figure 2: **P2Y$_{12}$-mediated platelet reactivity measured by the vasodilator-stimulated phosphoprotein in the ticagrelor group and clopidogrel group (A) and primary and secondary outcomes at 48 h (B)**
NS=not significant. PCI=percutaneous coronary intervention.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 9, 2017, and May 28, 2020, 1910 patients were randomly assigned at 49 sites, 956 to the ticagrelor group and 954 to the clopidogrel group (figure 1). 15 patients were excluded from the ticagrelor group and 12 from the clopidogrel group. Trial enrolment ended because the number of planned subjects was reached. Patient baseline characteristics were similar between the study groups, and representative of a population of patients with stable coronary disease (table 1). On admission, the electrocardiogram was normal in 1310 (70%) of 1883 patients and baseline cardiac troponin was negative in 1736 (93%) of 1883 patients. Patients with three or more high-risk features represented 1246 (66%) of 1883 PCI procedures (appendix p 19). The bleeding risk was similar in both study groups when evaluated with the DAPT score, but slightly different, with more patients with low bleeding risk in the ticagrelor group when evaluated with the PARIS score (appendix p 20).[14,15]

A radial approach was used in 1786 (95%) of 1883 cases and 3202 (>99%) of 3207 stents implanted were drug-eluting stents. The loading dose of clopidogrel of 600 mg or more was chosen in 635 (67%) of 942 patients and crushed pills were used more frequently in the ticagrelor

group than in the clopidogrel group (178 [19%] of 941 *vs* 62 [6·7%] of 942; p<0·0001). PCI was done in an ad-hoc setting in 998 (53%) of 1883 patients, with no difference between the ticagrelor and clopidogrel groups (p=0·47), and deferred PCI was done in a median of 1·9 days (IQR 0·9–7·0), with no difference between the ticagrelor and clopidogrel groups (p=0·27). The median delay from random assignment to PCI was 2·0 h (IQR 0·3–5·0) in the ticagrelor group and 2·1 h (0·3–4·8) in the clopidogrel group. The median delay from loading dose to PCI was 1·7 h (0·3–4·1) in the ticagrelor group and 1·8 h (0·3–4·2) in the clopidogrel group.

The main results of the masked prespecified platelet substudy in 167 patients showed that $P2Y_{12}$-mediated platelet reactivity was significantly lower with ticagrelor than with clopidogrel when measured a mean of 4·1 h (SD 1·0) after the loading dose and the next day after PCI, a mean of 21·6 h (2·5) after the loading dose (figure 2A).

At 48 h, the primary composite efficacy outcome of periprocedural myocardial infarction and major myocardial injury was observed in 334 (35%) of 941 patients in the ticagrelor group and 341 (36%) of 942 patients in the clopidogrel group (odds ratio 0·97, 95% CI 0·80–1·17; p=0·75; figure 2B). Results were consistent across the individual components of the primary outcome (figure 2B) and across most prespecified subgroups for the primary outcome (appendix p 18). We also adjusted these results on established risk factors for periprocedural events (diabetes, renal insufficiency, left ventricular ejection fraction <40% or previous episode of heart failure, multivessel disease, the number of stents implanted, and the total stent length per patient) and the findings were unchanged (data not shown). The main secondary outcome, comprising periprocedural myocardial infarction and any form of myocardial injury, was similar between the two groups (figure 2B). We observed no significant difference between the study groups for all secondary efficacy outcomes at 30-day follow-up (table 2; figure 3A). Results for the primary and main secondary outcome were similar in sensitivity analyses using mixed logistic regression models (p=0·77 and p=0·81, for the primary outcome and main secondary outcome, respectively). The rates of major complications were low for the hard clinical endpoint with nine stent thromboses, three strokes or transient ischaemic attacks, two deaths, and seven major bleeding episodes at 30 days, over the entire population of 1883 patients.

The primary safety outcome (major bleeding) occurred in only one patient at 48 h and was infrequent and similar in both groups at 30 days (table 3). The rate of minor bleeding was not different at 48 h but was more frequent in the ticagrelor group compared with the clopidogrel group at 30 days, as was the rate of any bleeding (table 3; figure 3B). The net clinical benefit outcome did not differ between the study groups (table 2). Non-bleeding adverse events, especially dyspnoea, were more frequent in the

	Ticagrelor (n=941)	Clopidogrel (n=942)	Odds ratio (95% CI)	p value
At 48 h				
Death, myocardial infarction (type 1, 4, and 5), or stroke or transient ischaemia attack	85 (9%)	80 (8%)	1·07 (0·77–1·47)	0·68
Death or myocardial infarction (type 1, 4 and 5)	84 (9%)	80 (8%)	1·06 (0·77–1·45)	0·74
Death (any cause)	1 (<1%)	0	..	0·50*
Myocardial infarction (type 1, 4, and 5)	83 (9%)	80 (8%)	1·03 (0·63–1·68)	0·90
Stroke or transient ischaemic attack (any)	1 (<1%)	1 (<1%)	1·00 (0·06–16·0)	1·00*
Death (any), myocardial infarction, major myocardial injury, urgent revascularisation, or recurrent ischaemia requiring catheterisation	337 (36%)	342 (36%)	0·98 (0·81–1·18)	0·83
Urgent revascularisation	1 (<1%)	1 (<1%)	1·00 (0·03–39·1)	1·00
Recurrent ischaemia requiring catheterisation	2 (<1%)	3 (<1%)	0·67 (0·08–4·49)	1·00*
Death, myocardial infarction, stroke or transient ischaemic attack, or major bleeding	86 (9%)	80 (8%)	1·08 (0·79–1·49)	0·62
At 30 days				
Death, myocardial infarction (type 1, 4 and 5), or stroke or transient ischaemic attack	90 (10%)	84 (9%)	1·08 (0·69–1·70)	0·73
Death or myocardial infarction (type 1, 4, and 5)	88 (9%)	84 (9%)	1·06 (0·67–1·67)	0·81
Death (any cause)	2 (<1%)	0	..	0·25*
Myocardial infarction (type 1, 4, and 5)	86 (9%)	84 (9%)	1·00 (0·63–1·59)	1·00
Spontaneous myocardial infarction (type 1)	0	5 (1%)	0·0 (0·0–1·09)	0·062*
Stent thrombosis (myocardial infarction type 4b)	6 (1%)	3 (<1%)	2·01 (0·50–8·05)	0·34
Stroke or transient ischaemic attack (any)	2 (<1%)	1 (<1%)	2·00 (0·18–22·14)	0·62
Death (any), myocardial infarction, major myocardial injury, urgent revascularisation, or recurrent ischaemia requiring catheterisation	342 (36%)	350 (37%)	0·96 (0·80–1·17)	0·71
Urgent revascularisation	3 (<1%)	7 (1%)	0·43 (0·11–1·66)	0·34*
Recurrent ischaemia requiring catheterisation	6 (1%)	9 (1%)	0·67 (0·24–1·88)	0·44
Death, myocardial infarction, stroke or transient ischaemic attack, or major bleeding	95 (10%)	85 (9%)	1·19 (0·77–1·84)	0·43

Data are n (%) unless otherwise indicated. Patients could have multiple events. *Exact mid-p value.

Table 2: **Secondary outcomes at 48 h and 30 days**

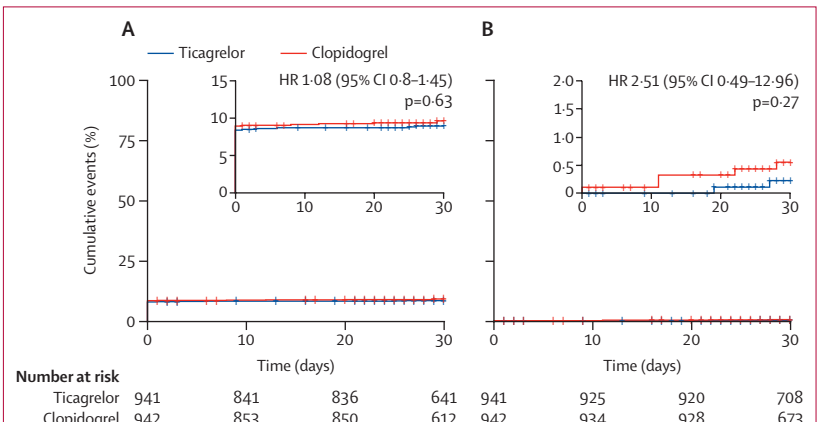

Figure 3: **Kaplan-Meier curves for death, myocardial infarction, or stroke or transient ischaemic attack (A) and major bleeding (Bleeding Academic Research Consortium 3 to 5; B) at 30 days for ticagrelor versus and clopidogrel**
HR=hazard ratio.

ticagrelor group (105 [11%] of 956 patients) compared with the clopidogrel group (five [<1%] of 954 patients) and led to more frequent discontinuation of study drug (21 [2%] of 956 patients in the ticagrelor group *vs* four [<1%] of 954 patients in the clopidogrel group).

Discussion

Despite a higher level of platelet inhibition, ticagrelor was not superior to clopidogrel in reducing periprocedural myocardial infarction or myocardial injury within 48 h of high-risk PCI in stable coronary patients. Moreover, none of our clinical outcomes differed between the study groups at 30-day follow-up. The more potent platelet inhibitory effect of ticagrelor translated to increased minor bleeding.

Our study supports the safety of elective percutaneous revascularisation, with low rates of complications. By contrast, periprocedural myonecrosis was frequent in this study, with a similar level to other studies during the past decade that have used sensitive definitions of myocadial injury and infarction and troponin as a biomarker, but could be more related to mechanical rather than thrombotic causes.[16] Our primary outcome included myocardial infarction type 4a (157 [8%] events), type 4b (six [<1%] events), and myocardial injury as defined in the third universal definitions of myocardial infarction, which were available when the study was designed (512 [27%] events).[11] Our main secondary outcome, which included all degrees of myocardial injury, is aligned with the recent fourth universal definition of myocardial infarction,[12] which appears to be very sensitive, as 1453 (77%) of 1883 patients in our study had some degree of myocardial injury or infarction. Irrespective of the definition and severity of post-procedural myonecrosis, we found no difference between the two study treatments. There is continuing debate over the best definition and clinical impact of these biologically driven events after revascularisation, and PCI in particular. However, several studies and metanalyses have reported that periprocedural myonecrosis, even of limited magnitude, is associated with adverse cardiac events and all-cause mortality.[1–4,17]

Failure of ticagrelor to prevent myonecrosis caused by PCI in stable patients with high-risk features contrasts with the effect of this drug in patients with acute coronary syndrome,[18] which is a different situation with a more thrombotic physiopathology at the time of PCI. In the present study, drug treatment was initiated before PCI in all patients and the results were consistent whatever the delay in administration before PCI. Our results are aligned with other studies in elective PCI,[19–21] and we provide results of a pooled analysis of available global randomised data (ALPHEUS and SASSICAIA trials), representing 2664 stable coronary patients undergoing elective PCI and showing no benefit of stronger $P2Y_{12}$ inhibition using ticagrelor or prasugrel compared with clopidogrel to decrease periprocedural complications (figure 4). Our results are also aligned with studies of PCI in patients with non-ST elevation acute coronary syndrome,[22–24] showing that oral antiplatelet pretreatment might cause more harm than benefit in patients treated with PCI. Our pharmacodynamic data show that ticagrelor was more potent than clopidogrel 4 h after the loading dose, with more than half of patients having high levels of $P2Y_{12}$-mediated platelet reactivity in the clopidogrel group, as well as the next day after PCI, in line with previous pharmacodynamic studies in elective PCI.[25,26] The disconnect between pharmacodynamics and

	Ticagrelor (n=941)	Clopidogrel (n=942)	Odds ratio (95% CI)	p value
At 48 h				
Major bleeding events (BARC 3 or 5)	1 (<1%)	0	..	0·50*
Nuisance or minor bleeding (BARC 1 or 2)	63 (7%)	50 (5%)	1·28 (0·87–1·88)	0·20
Any bleeding (BARC 1 to 5)	64 (7%)	50 (5%)	1·30 (0·89–1·91)	0·17
At 30 days				
Major bleeding events (BARC 3 or 5)	5 (1%)	2 (<1%)	2·51 (0·49–13·0)	0·29*
Nuisance or minor bleeding (BARC 1 or 2)	105 (11%)	71 (8%)	1·54 (1·12–2·11)	0·0070
Any bleeding (BARC 1 to 5)	110 (12%)	73 (8%)	1·58 (1·15–2·15)	0·0039

Data are n (%) unless otherwise indicated. BARC=Bleeding Academic Research Consortium. *Exact mid-p value.

Table 3: **Safety outcomes at 48 h and 30 days**

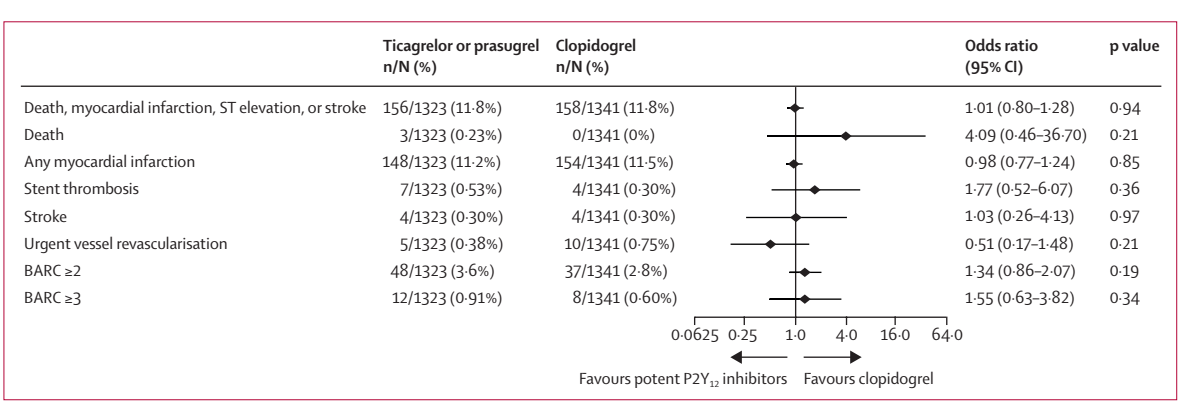

Figure 4: **Pooled analysis of the results of the ALPHEUS and SASSICAIA trials comparing clopidogrel with more potent $P2Y_{12}$ inhibitors (ticagrelor and prasugrel)**
BARC=Bleeding Academic Research Consortium.

clinical outcomes in the ALPHEUS trial has also been observed in other clinical situations.[27] Whether stronger and more rapid platelet inhibition is needed to reduce periprocedural myonecrosis is a relevant question. Previous trials have shown a reduction in cardiac marker release and periprocedural events when using intravenous drugs such as glycoprotein IIb/IIIa inhibitors or cangrelor.[28–30] These drugs immediately provide a more potent effect than that obtained with oral $P2Y_{12}$ inhibitors.

Regarding safety and adverse events, procedures were done almost exclusively with radial access, therefore limiting the risk of access site major bleeding, with little non-access site bleeding (eg, ecchymosis or epistaxis) showing the safety of 30-day dual antiplatelet therapy with both drugs. Beyond 30 days, de-escalation studies have suggested improved safety with single antiplatelet therapy (*vs* dual antiplatelet therapy) in elective PCI.[31]

This trial has limitations related to its design. First, this was an open-label trial with inherent biases that were controlled by the use of the prospective, randomised, open-label, blinded endpoint design, which comprised masked adjudication of all outcomes, masked measurement of troponin after PCI, and an independent masked review of all PCI videos by core laboratory expert readers. Second, the trial does not provide reliable information on hard clinical outcomes, which are rare in elective PCI. Third, all types of troponin assays were authorised in this trial to reflect real-life PCI centres but might have brought heterogeneity, as prognosis thresholds might be dependent on the type of assay used. Fourth, our study included patients on chronic clopidogrel therapy, which represented almost half the study population and could potentially have blunted the differential effect compared with ticagrelor. However, our prespecified subgroup analysis of clopidogrel-naive patients does not support this hypothesis. Finally, whether a similar strategy would have resulted in a different outcome in a population of patients with poor response to clopidogrel with high platelet reactivity is unknown.

In conclusion, in patients undergoing elective high-risk PCI, treatment with ticagrelor showed no difference compared with clopidogrel in reduction of periprocedural myocardial necrosis. Treatment with ticagrelor did not cause an increase in major bleeding but increased the rate of minor bleeding at 30 days. The results of the ALPHEUS trial support the use of clopidogrel as the standard of care for elective PCI in addition to aspirin and pave the way for the evaluation of other strategies to lower periprocedural myonecrosis after elective PCI.

Contributors

JS and GM designed the study, analysed and interpreted the data, and wrote the first draft of the paper. EV analysed the data. All authors were involved with data interpretation, reviewed and revised the draft of the manuscript, and approved the final version for submission. J-PC and GC have verified the underlying data.

Declaration of interests

JS reports receiving consulting and lecture or travel support from AstraZeneca, Bayer HealthCare SAS, Biotronik, BPI France, Boehringer Ingelheim France, CSL Behring SA, Gilead Science, Sanofi-Aventis France, Terumo France SAS, Abbott Medical France SAS, and Zoll. JS is a stockholder of Pharmaseeds. BL has received research grants from Biotronik, Boston Scientific, Daiichi-Sankyo, Fédération Française de Cardiologie, and Institute of CardioMetabolism and Nutrition, consultant fees from Daiichi-Sankyo and Eli Lilly, and lecture fees from AstraZeneca, Medtronic, and Novartis. FBe reports receiving consulting and lecture fees from AstraZeneca, Bristol-Myers Squibb, Medtronic, Biosensors, and Boston Scientific, and institutional research grants from Medtronic, Biosensors, Acist, and Boston Scientific. GR reports receiving speaker or consulting fees from Abbott. ZM reports receiving consulting or speaker fees from AstraZeneca. J-GD reports receiving consulting and lecture fees from AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb/Pfizer, and Sanofi, and grants from Bayer, Bristol-Myers Squibb/Pfizer, and Biosensors. ZB reports institutional research grants from Medtronic and Microport, and lecture or travel support from Abbott Vascular, Microport, Boston Scientific, and Biotronik. TL reports consulting or speaker fees from AstraZeneca, Boston Scientific, and Abbott, and a research grant from AstraZeneca. CP reports consulting or speaker fees from Abbott Vascular. FBo reports consulting or speaker fees from Amgen, Gilead, ViiV Healthcare, Amgen, Sanofi, MSD, and Servier, outside the submitted work. ML reports fellowship grants from Medtronic, Biotronik, and Boston Scientific. GD reports consulting or speaker fees Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Janssen, Sanofi, and Terumo, consulting fees from Boston Scientific and Novo Nordisk, and travel fees from, AstraZeneca, Bayer, and Bristol-Myers Squibb. J-PC reports receiving consulting and lecture fees from AstraZeneca, Bayer, Bristol-Myers Squibb, Fédération Française de Cardiologie, Lead-Up, and WebMD. GC reports receiving research grants, consultant fees, or lectures fees from Amgen, AstraZeneca, Abbott, Bayer, Biotronik, Bristol-Myers Squibb, Pfizer, and Sanofi-Aventis. KB reports speaker or congress fees from Abbott, Medtronic, Novartis, and Teleflex. PK reports consulting or speaker fees from Boston Scientific, Medtronic, Bayer, AstraZeneca, Pfizer, Edwards Sciences, and Boehringer Ingelheim, and research support from Novartis, Zoll, and Amgen. EV reports consulting or speaker fees from Abbott, Bristol-Myers Squibb, Celgene, Edwards, Pfizer, Sanofi, and Novartis. GM reports consulting or speaker fees from Abbott, AIM Group, Amgen, Actelion, American College of Cardiology Foundation, AstraZeneca, Axis-Santé, Bayer, Boston Scientific, Bristol-Myers Squibb, Beth Israel Deaconess Medical, Brigham Women's Hospital, Fréquence Médicale, ICOM, Idorsia, Elsevier, Fédération Française de Cardiologie, Fréquence Médicale, ICAN, Lead-Up, Menarini, Medtronic, MSD, Novo Nordisk, Pfizer, Quantum Genomics, Sanofi Aventis, SCOR Global Life, Servier, and WebMD. All other authors report no competing interests.

Data sharing

Data collected for the study, including individual participant data and a data dictionary defining each field in the set, can be made available to others under the following restrictions: with investigator support, after approval of a proposal by the Allies in Cardiovascular Trials Initiatives and Organized Networks (ACTION) study group and the sponsor of the study, with a signed data access agreement, and with specific funding to access the database. Requests should be sent to johanne.silvain@aphp.fr.

For more on the **ACTION Study Group** see www.action-coeur.org

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