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Cangrelor versus crushed ticagrelor in patients with acute myocardial infarction and cardiogenic shock: rationale and design of the randomised, double-blind DAPT-SHOCK-AMI trial

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ABSTRACT

Cardiogenic shock (CS) is a devastating and fatal complication of acute myocardial infarction (AMI). CS can affect the pharmacokinetics and pharmacodynamics of medications. The unique properties of cangrelor make it the optimal $P2Y_{12}$ inhibitor for CS-AMI, in terms of both efficacy and safety. The DAPT-SHOCK-AMI trial (ClinicalTrials.gov: NCT03551964; EudraCT: 2018-002161-19) will assess the benefits of cangrelor in patients with an initial CS-AMI undergoing primary angioplasty. This randomised, multicentre, placebo-controlled trial of approximately 550 patients (with an allowed 10% increase) in 5 countries using a double-blind design will compare initial $P2Y_{12}$ inhibitor treatment strategies in patients with CS-AMI of (A) intravenous cangrelor and (B) ticagrelor administered as crushed tablets at a loading dose of 180 mg. The primary clinical endpoint is a composite of all-cause death, myocardial infarction (MI), or stroke within 30 days. The main secondary endpoints are (1) the net clinical endpoint, defined as death, MI, urgent revascularisation of the infarct-related artery, stroke, or major bleeding as defined by the Bleeding Academic Research Consortium criteria; (2) cardiovascular-related death, MI, urgent revascularisation, or heart failure; (3) heart failure; and (4) cardiovascular-related death, all (1-4) within 1 year after study enrolment. A platelet reactivity study that tests the laboratory antiplatelet benefits of cangrelor, when given in addition to standard antiplatelet therapy, will be conducted using vasodilator-stimulated phosphoprotein phosphorylation. The primary laboratory endpoints are the periprocedural rate of onset and the proportion of patients who achieve effective $P2Y_{12}$ inhibition. The DAPT-SHOCK-AMI study is the first randomised trial to evaluate the benefits of cangrelor in patients with CS-AMI.

KEYWORDS: adjunctive pharmacotherapy; cardiogenic shock; clinical trials; STEMI

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Introduction

MAGNITUDE OF THE ISSUE

The estimated global annual incidence of acute myocardial infarction (AMI) exceeds 7 million[1]. The average incidence of cardiogenic shock (CS) in patients hospitalised for AMI (CS-AMI) is approximately 7.5%[2]. Most CS-AMI cases have ST-segment elevation MI (STEMI)[3]. An analysis based on extensive US population data (from 1,000 hospitals) documented 44 CS-AMI cases per 100,000 hospitalisations in 2004 and 103 per 100,000 hospitalisations in 2018[3].

The incidence of CS developing during hospitalisation has been decreasing (currently 3.5%), whereas the incidence of initial (primary) shock has been stable or increasing (currently 4.6%)[4,5]. Furthermore, there has been an upward trend in preadmission cardiac arrests in patients with CS-AMI[6].

PHARMACOTHERAPY-RELATED SPECIFICS

CS can affect all aspects of drug pharmacokinetics and pharmacodynamics[7,8]. The splanchnic circulation is hypoperfused because of reflexive vasoconstriction, which is further potentiated during treatment with vasopressor agents – the consequent ischaemia results in liver and kidney dysfunction. The preferred mode of drug administration is parenteral, and drugs that do not undergo metabolism are favoured.

In patients with CS-AMI, metabolism becomes less predictable, which can result in potentially serious adverse events due to overexposure or underexposure to active ingredients[9]. Antithrombotic medications are associated with a risk of bleeding; therefore, drugs with a rapid offset of action and antidotes are particularly beneficial.

EVIDENCE FOR SURVIVAL BENEFIT

Despite advances in medical treatment, reperfusion using primary percutaneous coronary intervention (PCI) remains the only intervention that improves the prognosis of patients with CS-AMI[2,10,11]. An essential component of mechanical reperfusion in AMI is adjuvant antithrombotic pharmacotherapy, which is critical in preventing local thrombus progression and distant embolisation.

ANTIPLATELET THERAPY

Dual antiplatelet therapy using the newer oral $P2Y_{12}$ receptor inhibitors ($iP2Y_{12}$), i.e., ticagrelor or prasugrel, in combination with aspirin, is recommended in patients with AMI undergoing PCI based on the results of the TRITON-TIMI 38 (A Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome Subjects Who Are to Undergo Percutaneous Coronary Intervention)[12] and PLATO (A Comparison of Ticagrelor and Clopidogrel in Patients With Acute Coronary Syndrome)[13] randomised trials. However, CS was an exclusion criterion in the TRITON study, and in the ticagrelor arm of the PLATO study, only 25 patients (0.7%) suffered from CS.

STUDY JUSTIFICATION

CS is the most common cause of death in patients with AMI who survive until hospital admission[2]. The in-hospital mortality rate of patients suffering from primary CS at admission is 44.4%[5], and 20% of the deaths occur during the initial PCI procedure[14]. Characteristics including older age, multivessel coronary artery disease, increased time between symptom onset and reperfusion, and postprocedural Thrombolysis in Myocardial Infarction (TIMI) flow <3 were identified as independent predictors of death in patients with CS-AMI[15]. Rapid and effective platelet inhibition can modify two of the prognosis predictors in CS patients with the highest thrombotic risk, i.e., time until reperfusion and angioplasty outcomes **(Figure 1)**.

The efficient inhibition of platelet aggregation is essential for preventing ischaemic events. The short-term risk of reinfarction is 3-4 times higher (9-12%)[5] in patients with CS. Additionally, CS is the strongest independent predictor of stent thrombosis[16]. Ischaemic stroke occurs in 2.4% of patients with CS; this number rises for more invasive circulatory stabilisation methods[17].

Patients with CS-AMI are also at risk of severe bleeding. Typically, bleeding occurs in 1 out of 5 CS-AMI cases during early hospitalisation[18].

Cangrelor is the best studied $iP2Y_{12}$ with a parenteral mode of application **(Table 1)**. The effective inhibition of adenosine diphosphate (ADP)-induced platelet aggregation occurs 2 minutes after initiating treatment, and the antiplatelet effect is maintained throughout the infusion period[19]. Cangrelor metabolism is independent of splanchnic organ function and does not affect liver enzyme-metabolised drugs. Platelet aggregation is restored approximately 60 minutes after stopping the administration of the drug[19].

Cangrelor therapy initiated concomitantly with crushed ticagrelor tablets in patients with STEMI undergoing primary PCI results in prompt and potent platelet inhibition during the intervention; additionally, cangrelor therapy bridges the gap until the full antiplatelet efficacy of ticagrelor is achieved[20].

The unique pharmacokinetic and pharmacodynamic properties of cangrelor make it the optimal $iP2Y_{12}$ for CS-AMI in terms of efficacy and safety. The degree to which $iP2Y_{12}$ suppresses ADP-mediated platelet function depends on the potency of the antiplatelet drug and the baseline (before treatment) prothrombotic condition; this is most pronounced in STEMI patients. A better understanding of the relationship between study medication-related platelet reactivity inhibition (through quantification of the rate of onset and intensity of inhibition during the peri-PCI period) and clinical outcomes in one trial may contribute to developing more effective and safer treatment strategies[21].

Abbreviations

AMI	acute myocardial infarction	**$iP2Y_{12}$**	$P2Y_{12}$ receptor inhibitors
CS	cardiogenic shock	**PCI**	percutaneous coronary intervention
DAPT-SHOCK-AMI	Dual Antiplatelet Therapy For Shock Patients With Acute Myocardial Infarction	**VASP**	vasodilator-stimulated phosphoprotein

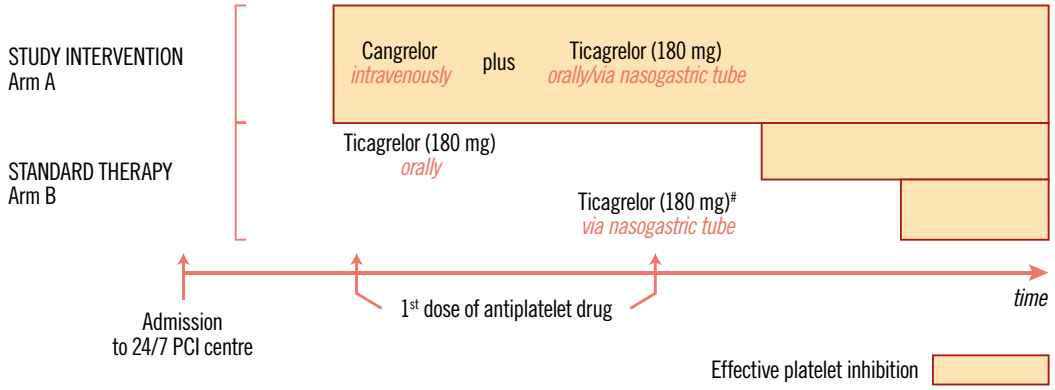

Figure 1. *Benefits of the tested study therapy (study rationale). The first arrow indicates CS-AMI patients' admission to a 24/7 PCI centre, usually directly to the catheterisation laboratory. The upper part of the figure shows patients randomised to cangrelor IV (arm A) achieving effective platelet inhibition immediately after initiation of therapy (large orange bar), irrespective of conscious state and oral intake ability. The lower part shows patients assigned to arm B and treated with ticagrelor. Patients who are able to take ticagrelor orally (second arrow) achieve effective platelet inhibition after hours (medium orange bar). Patients with impaired consciousness cannot receive ticagrelor until after introducing the nasogastric tube (often after arriving at the catheterisation laboratory; third arrow), which represents a further delay in the onset of ticagrelor antiplatelet efficacy (small orange bar). The onset of effective inhibition of platelet reactivity (expressed by colour fill) depends on the antiplatelet drug administered. #Patients with impaired consciousness. CS-AMI: cardiogenic shock complicated acute myocardial infarction; IV: intravenous; PCI: percutaneous coronary intervention*

Table 1. $P2Y_{12}$ receptor inhibitors.

Drug	Structure	Effect	Reversibility	Method of use	Frequency of use
Ticlopidine	Thienopyridine	Indirect	No	Oral	BID
Clopidogrel	Thienopyridine	Indirect	No	Oral	QD
Prasugrel	Thienopyridine	Indirect	No	Oral	QD
Ticagrelor	ATP analogue	Direct	Yes (half-life 6-12 hr)	Oral	BID
Cangrelor	ATP analogue	Direct	Yes (half-life 3 min)	Parenteral	Continuous infusion

ATP: adenosine triphosphate; BID: twice a day; QD: once a day

Study design

STUDY OBJECTIVES

The Dual Antiplatelet Therapy For Shock Patients With Acute Myocardial Infarction trial (DAPT-SHOCK-AMI; ClinicalTrials.gov: NCT03551964, Protocol numbers: 13062017-23-1, EudraCT: 2018-002161-19) is a double-blind, multicentre, international, placebo-controlled trial testing the hypothesis that intravenous cangrelor is (a) more effective in terms of its rate of onset and the proportion of patients achieving effective periprocedural inhibition of ADP-induced platelet aggregation and (b) at least as effective as the recommended treatment of oral (crushed) ticagrelor in reducing major cardiovascular events in patients with initial CS-AMI indicated for primary PCI strategy.

STUDY POPULATION

The study population will be comprised of patients who meet the inclusion criteria, defined as follows: (1) over 18 years of age; (2) AMI according to the ESC/ACC/AHA definition[22] with an indication for emergency PCI (primary PCI strategy); (3) CS due to an AMI present upon admission meeting at least 2 of the following criteria[23]: (a) systolic blood pressure <90 mmHg in the absence of hypovolaemia, (b) need for vasopressor and/or inotropic therapy, and (c) signs of organ hypoperfusion (cyanosis, cold extremities, disorders of consciousness, or heart failure); (4) signed informed consent form as per the applicable legal regulations and regulatory authority requirements; and (5) women with childbearing potential should avoid pregnancy and use a highly effective method of contraception throughout the study period (relevant for long-term use of ticagrelor).

The exclusion criteria are presented in **Supplementary Table 1**.

RANDOMISATION

The patients are randomised in a 1:1 ratio using random permuted blocks, stratified by study centre. Randomisation is performed using an interactive web-response system developed by the Institute of Biostatistics and Analyses, Faculty of Medicine, Masaryk University, Czech Republic on the base of the TrialDB system.

STUDY MEDICATION

The patients are randomised into one of two treatment arms **(Figure 2)** according to the study intervention: arm A: cangrelor versus arm B: ticagrelor.

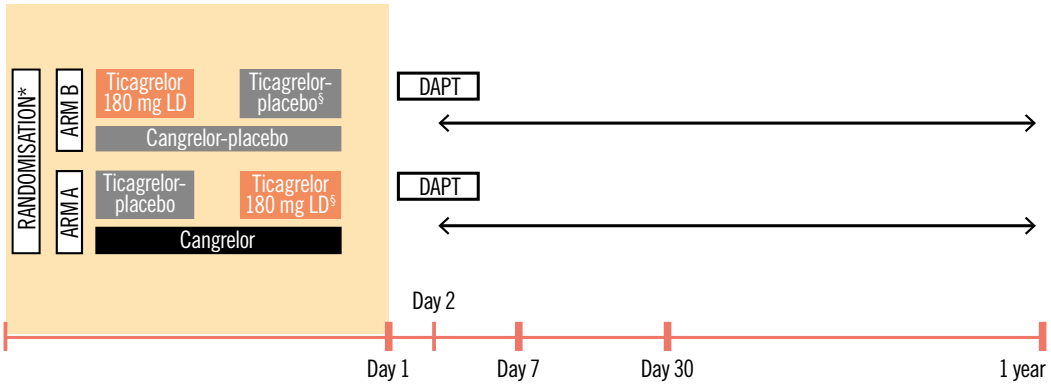

Figure 2. *Study design. Study initiation should be as soon as possible after admission to the hospital. *Study medication administered in addition to initial aspirin IV; §administered 30 minutes before the end of the infusion. Visits: day 7 after randomisation, day 30±5 days, 1 year±14 days. Ticagrelor was in crushed form. DAPT consists of a $P2Y_{12}$ inhibitor plus aspirin. DAPT: dual antiplatelet therapy; IV: intravenous; LD: loading dose*

Patients in arm A will receive the active study medication, cangrelor, as an intravenous (IV) bolus of 30 µg/kg (application <1 min) followed immediately by a continuous infusion at 4 µg/kg. Thirty minutes before the end of the cangrelor infusion, 180 mg of ticagrelor (crushed tablets) will be administered, followed by a maintenance dose of 90 mg every 12 hours **(Supplementary Figure 1)**[24,25].

In arm B of the study, the patients will receive 180 mg of crushed ticagrelor tablets orally as the loading dose, and thereafter a maintenance dose of 90 mg twice daily, as per the guidelines. The placebo dosage, forms, and methods of administration (cangrelor-placebo and ticagrelor-placebo) are identical to those of their respective active substance (cangrelor and ticagrelor). Thus, the cangrelor- and ticagrelor-placebo treatments will be administered in the same way as the IV cangrelor and oral ticagrelor (as crushed tablets), respectively.

Randomisation and initiation of the study medication administration of both compared study arms should be performed immediately (at the earliest possible time) after the patient's admission to the 24/7 PCI centre, which is usually the catheterisation laboratory.

CONCOMITANT THERAPY

The antiplatelet therapy used in this study is $iP2Y_{12}$, which will be administered in addition to an initial aspirin dose of 500 mg IV, followed by 100 mg of aspirin as a daily oral dose. Proton pump inhibitors are recommended to prevent gastrointestinal bleeding. The administration of other standard-care therapies, including additional adjuvant antithrombotic therapy (e.g., a bailout glycoprotein [GP] IIb/IIIa inhibitor and parenteral antithrombin drugs) and mechanical circulatory support, will be left to the discretion of the attending physician.

STUDY FOLLOW-UP

Patients enrolled in the study will be followed for 12 months. A summary of the timing of the visits and examinations that will be performed is presented in **Table 2**. Recommendations regarding treatment during the follow-up period, including dual antiplatelet therapy, will adhere to the appropriate guidelines.

CLINICAL ENDPOINTS

The primary endpoint is defined as a composite of death, myocardial infarction, or stroke 30 days after enrolment into the study. The secondary endpoints are summarised in **Supplementary Table 2**. Other goals include conducting a cost-effectiveness analysis and a magnetic resonance imaging substudy of the predefined endpoints.

PLATELET REACTIVITY STUDY

Patients who meet the enrolment criteria and are randomised at the 5 selected centres will be eligible for the platelet reactivity study. The laboratory antiplatelet effectiveness of the cangrelor and ticagrelor loading dose-based initial $iP2Y_{12}$ strategies will be determined by vasodilator-stimulated phosphoprotein (VASP) phosphorylation using flow cytometry, which is the most specific method for verifying and quantifying the effectiveness of $iP2Y_{12}$ and is associated with clinical outcomes. The determinations will be performed by an accredited facility using standardised sampling kits and protocols specified by the manufacturer. The design of the laboratory study is illustrated in **Figure 3**. The tests will be carried out as follows: before initiating treatment with the antiplatelet study drugs, upon completion of the coronary intervention procedure, 1 hr after PCI, 2 hrs after PCI, at the end of the cangrelor infusion, 1 hr after the end of the infusion, and 2 hrs after the end of the infusion. The primary laboratory endpoint will be assessed at the second and third VASP examinations. Monitoring platelet function dynamics after the intervention will provide important insights into the study – testing a strategy of combined intravenous and oral treatment with $P2Y_{12}$ inhibitors.

SAMPLE SIZE

This study was initially designed to include 304 patients. However, since the beginning of the study, there has been

Table 2. Scheduled visits during the 1-year study follow-up.

	Randomisation Visit 1	Day 7 Visit 2	Day 30±5 days Visit 3	Year 1±14 days Visit 4
Clinical condition	X	X	X	X
ECG	X	X	X	X
Echocardiography	X	X	X	X
#MRI[32]	-	X	X	X
§¶Laboratory sampling	§¶X	¶X	¶X	¶X
Questionnaire on quality of life (EuroQol 5D)[33]	-	-	X	X

#MRI substudy – in selected centres. Laboratory examination involves the following: §examination of the effectiveness of antiplatelet therapy by the determination of VASP phosphorylation via flow cytometry – in selected centres; ¶haematological and biochemical blood tests.
ECG: electrocardiogram; MRI: magnetic resonance imaging; VASP: vasodilator-stimulated phosphoprotein

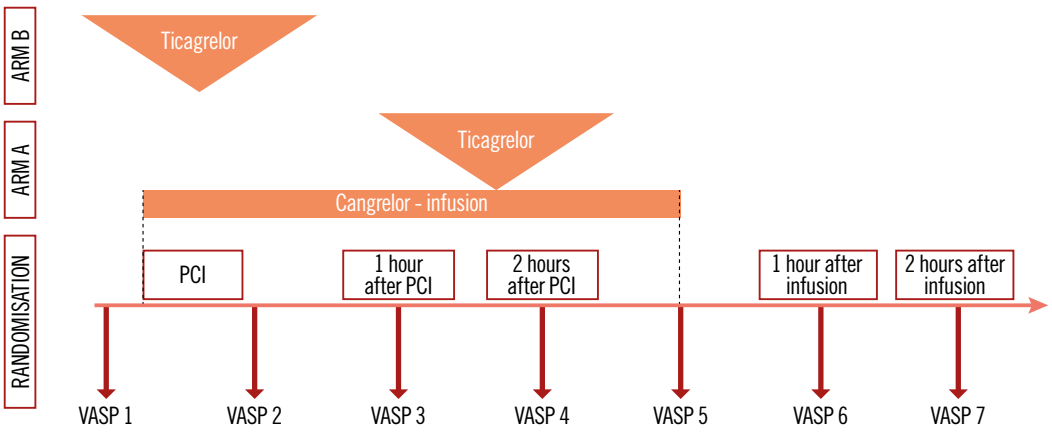

Figure 3. *Platelet reactivity study design. Timing of VASP evaluations: VASP 1 – baseline (before study treatment administration), VASP 2 – at the end of the PCI procedure, VASP 3 – 1 hour after PCI, VASP 4 – 2 hours after PCI, VASP 5 – at the end of the cangrelor infusion, VASP 6 – 1 hour after the end of the infusion, and VASP 7 – 2 hours after the end of the infusion.*
PCI: percutaneous coronary intervention; VASP: vasodilator-stimulated phosphoprotein

a substantial amount of new evidence to consider when calculating study population sizes. The power analysis was computed for the superiority and non-inferiority scenarios under the assumption of primary endpoint occurrences in previous studies and registries, as presented in **Supplementary Table 3**.

The null hypothesis for the primary clinical endpoint was the equality of event rates, and the alternative hypothesis was the inequality of event rates between the analysed groups. Based on an expected event rate of 50% in the control group versus 38% in the cangrelor group, a required power of 80%, and a 2-sided statistical significance level of 5%, 536 patients would be needed to detect a 12% difference between groups and reject the null hypothesis. Allowing for a 3% dropout rate, 550 patients should be enrolled in the study (with a permitted 10% increase). The dropout rate is based on several clinical studies.

Based on an expected event rate of 50% in the control group versus 40% in the cangrelor group (difference 10%), a non-inferiority margin of 1%, a required power of 80%, and a 2-sided statistical significance level of 5%, 506 patients would be required to accept the additional non-inferiority hypothesis.

A power analysis for the platelet reactivity study, with the endpoint of effective inhibition of the platelet VASP <50%, was computed for superiority, requiring a power of 80% and a 2-sided statistical significance level of 5%. The null hypothesis for this endpoint was the equality of event rates, whereas, for the alternative hypothesis, it was the inequality of event rates between the analysed groups. Based on an expected event rate of 70% in the control group versus 90% in the cangrelor group, 124 patients will be required to detect a 20% difference between groups and reject the null hypothesis. The required sample size falls within the practical limits of VASP measurements, which is approximately 150.

The power analysis was computed using the PASS 13 software (2014 [NCSS, LLC]).

STATISTICAL ANALYSES

Statistical analyses will be performed using the SPSS Statistics software, version 28.0.1.1 (IBM). The analyses will be performed using an intention-to-treat principle supplemented by a modified intention-to-treat principle, which only includes patients who receive a dose of the study drug. A sensitivity analysis according to the per-protocol population will also be performed.

Standard descriptive statistics will be calculated in the analysis, i.e., absolute and relative frequencies for categorical variables, and medians supplemented with 5th-95th percentiles or means supplemented with standard deviations for continuous variables. The chi-square test will be used to test the statistical significance of differences in the primary endpoint and all other categorical variables, and the Mann-Whitney U test will be used for continuous variables.

Univariate and multivariate logistic regression or Cox proportional hazards models will be used as additional analyses of the influence of patient characteristics on the endpoint occurrence, and the Kaplan-Meier methodology will be adopted to visualise time-to-event data.

The level of statistical significance will be set at p=0.05. All the statistical analyses will be performed according to the U.S. Food and Drug Administration Guidance Document "E9 Statistical Principles for Clinical Trials" (FDA-1997-D-0508).

STUDY ORGANISATION

This study is a non-commercial, investigator-initiated study, and it is an international project that will be implemented by teams of investigators in 5 countries (the Czech Republic, France, Germany, Poland, and the Slovak Republic). It adheres to the ethical principles of the Declaration of Helsinki, the International Conference on Harmonization of Good Clinical Practice (R2), and all other applicable legal and regulatory requirements, including the General Data Protection Regulation. The study's organisational structure includes executive, steering, and endpoint adjudication committees, and a data safety monitoring board. External clinical research associate organisations will monitor all entries in the electronic case report forms and the completeness of the source documentation.

The institutions' ethics committees will conduct yearly audits of trial protocols and progress during the study. The auditing process is independent of both trial investigators and trial sponsors.

The records of the procedural findings, coronary angiograms, and PCIs will be submitted to the coordinating centre, where they will be evaluated by an independent panel of experts blinded to how medication was allocated within the study.

The assessment of VASP phosphorylation, as part of the platelet reactivity study, will be performed by an external laboratory and personnel blinded to the allocation of the study medication. The laboratory will enter the results directly into a database that will be inaccessible to the investigators.

Discussion

The increasing average age of the global population and the rising incidence of coronary heart disease indicate that the number of people at risk of CS-AMI is growing. However, conducting randomised studies to assess treatments in patients with CS is challenging. Circulatory instability is usually an exclusion criterion for participation in clinical trials attempting to verify the benefits of antithrombotic pharmacotherapies[12]. The currently available evidence is limited to that from small studies and registry data **(Supplementary Table 3)**.

Minimising thrombotic risk and restoring coronary blood flow at the microcirculatory level is critical for reperfusion and a better prognosis for CS-AMI[26]. The safety and efficacy of adjuvant combination antiplatelet therapy is mainly determined by the selection of the optimal inhibitor for ADP-induced platelet activation to be used alongside aspirin. Adding a third antiplatelet drug, such as a GP IIb/IIIa inhibitor, to the combination with aspirin and especially the highly effective iP2Y$_{12}$, ticagrelor, increases the risk of significant bleeding, thereby nullifying any potential benefits in terms of patient outcomes[27]. Cangrelor, in addition to all the other advantages already mentioned for patients with CS-AMI, reduces the periprocedural need for bailout rescue GP IIb/IIIa inhibitors[28].

The initial P2Y$_{12}$ inhibitor treatment strategy with intravenous cangrelor is compared to the crushed tablet form of ticagrelor. This form of ticagrelor loading dose

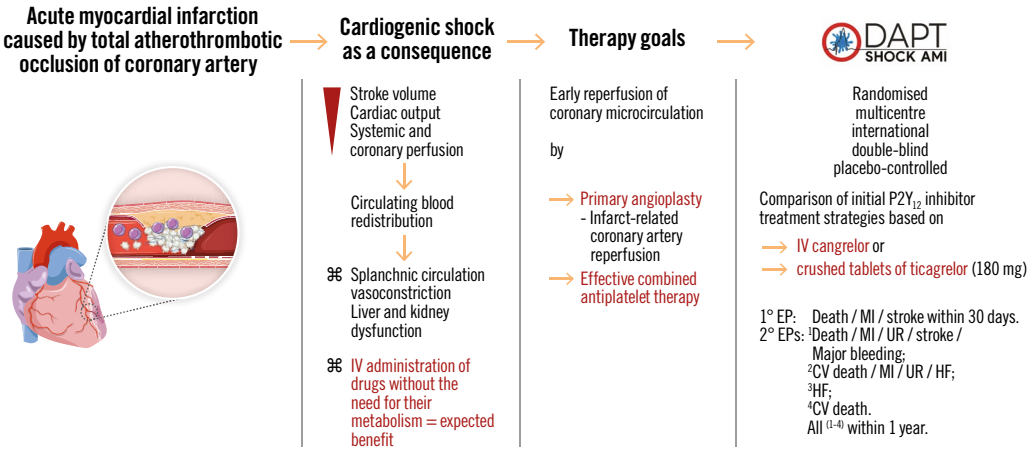

Figure 4. *Study endpoints. The figure summarises the factual basis for conducting the study and outlines the study outcome endpoints. ⌘ refers to the associated data. CV: cardiovascular; EP: endpoint; HF: heart failure; IV: intravenous; MI: myocardial infarction; UR: urgent revascularisation*

demonstrated a faster onset of effective platelet inhibition than the oral dose (whole tablet)[29]. Therefore, despite the lack of evidence of the benefit on patient prognosis, crushed ticagrelor is recommended as the preferred mode of administration in patients with CS[26,30].

The VASP method was selected to monitor the rate of onset and extent of inhibition of $P2Y_{12}$ platelet receptors by the compared drugs. This choice was based on the unique specificity of the VASP assay for the $P2Y_{12}$ signalling pathway, which makes it the only method for monitoring $P2Y_{12}$ inhibitor efficacy that is not influenced by the $P2Y_1$ receptor functional status[31]. Moreover, unlike other assays, such as the widely used point-of-care VerifyNow (Werfen), VASP phosphorylation measurements are not affected by the co-administration of a GP IIb/IIIa inhibitor[31], which is frequently used during primary angioplasty for CS-AMI.

Conclusions

The DAPT-SHOCK-AMI study aims to provide clinical evidence for selecting the appropriate antiplatelet therapies in patients with AMI complicated by initial CS undergoing primary PCI and, thus, potentially improve the prognosis of this often fatal condition **(Figure 4)**.

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Supplementary data

Supplementary Table 1. Study exclusion criteria.
Supplementary Table 2. Secondary endpoints.
Supplementary Table 3. Outcomes of patients with CS-AMI in registries and clinical trials.
Supplementary Figure 1. Study medication.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00203

Supplementary data

Supplementary Table 1. Study exclusion criteria.

EXCLUSION CRITERIA	
1.	Contraindications for antiplatelet therapy with ticagrelor or cangrelor, that is, recent (< 6 months) major bleeding, recent (< 1 month) major surgery or injury, history of intracranial hemorrhage, history of stroke or transient ischemic attack, known ticagrelor or cangrelor intolerance, hypersensitivity to any of the excipients in the investigational medicinal products and placebos, severe hepatic impairment, or co-administration of potent CYP3A4 inhibitors.
2.	Received administration of a loading dose of oral $iP2Y_{12}$ prior to admission (clopidogrel ≥ 300 mg, ticagrelor 180 mg, prasugrel 60 mg).
3.	The need for concomitant chronic anticoagulant treatment.

Supplementary Table 2. Secondary endpoints.

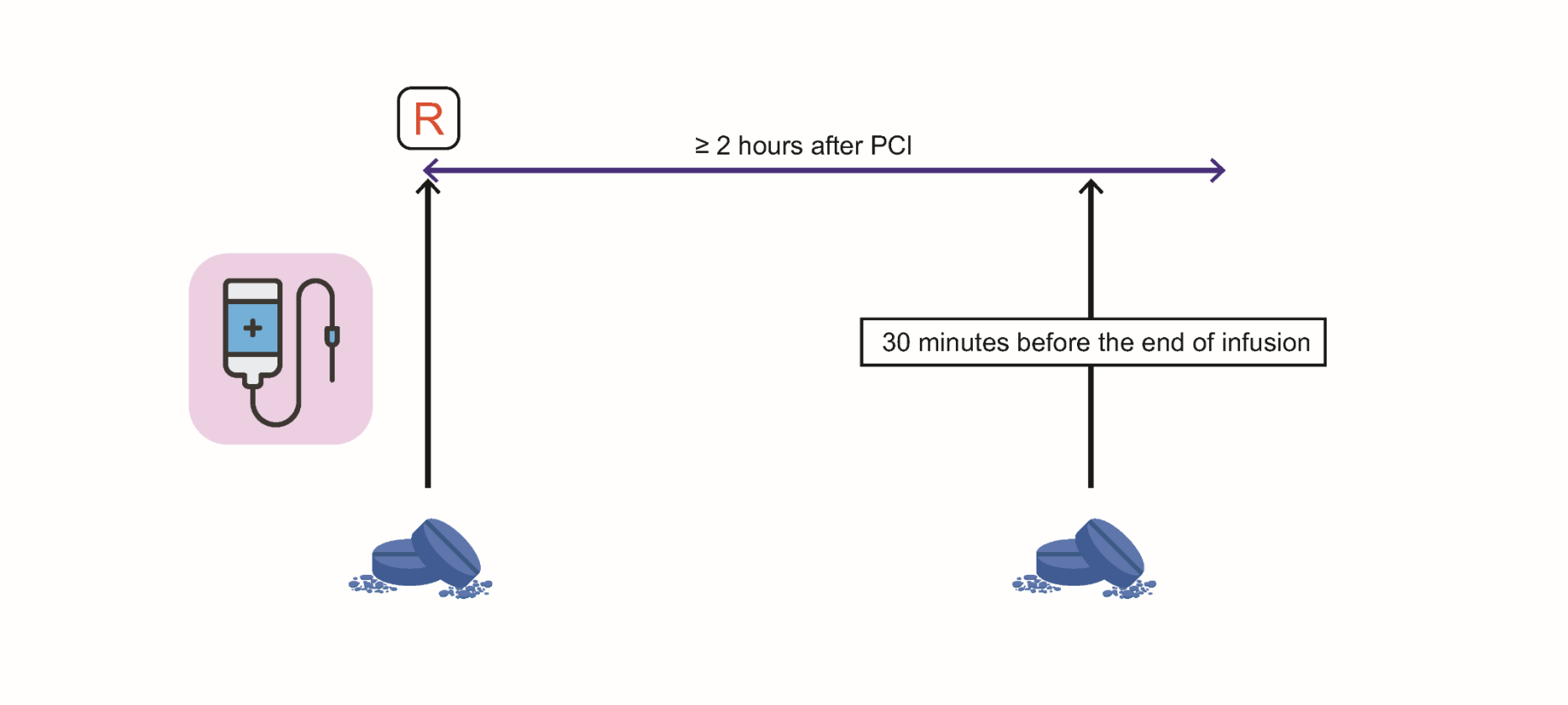
MAIN SECONDARY ENDPOINTS
(1) Net clinical endpoint defined as death, myocardial infarction, urgent revascularization of the infarct-related artery, stroke, or major bleeding as defined by the BARC (Bleeding Academic Research Consortium) criteria. (2) Cardiovascular-related death, myocardial infarction, urgent revascularization, or heart failure. (3) Heart failure. (4) Cardiovascular-related death. *all (1–4) within 30 days and one year after study enrollment.* (5) Bleeding complications as defined by BARC. (6) Stent thrombosis. *(5) and (6) within 30 days after study enrollment.*
THE FOLLOWING ENDPOINTS
(1) Delayed surgery due to a risk of bleeding. (2) Duration of vasoactive pharmacotherapy and mechanical circulatory support. (3) Duration of hospitalization. (4) Maximum values of high-sensitivity cardiac troponin I.

Supplementary Table 3. Outcomes of patients with CS-AMI in registries and clinical trials.

Registry - Country	Occurrence of Endpoints
German Registry {4}	In-hospital mortality 56%.
AMIS PLUS (Switzerland) {5}	In-hospital death from CS at admission 44.4%; Re-infarction 3%.
TRACE registry (Denmark) {34}	30-day mortality 45%, combined MACE (identical population to the DAPT SHOCK) study 53.5%.
FAST MI (France) {35}	In-hospital mortality in CS (primary and secondary) 51.4%, and in primary CS 37.8%.
Danish Registry {36}	30-day mortality 50%.
The United States Database {17}	Ischemic stroke 2.4%.
Study	Occurrence of Endpoints
IABP-SHOCK 2 trial {37}	30-day mortality 39.7%; MI 3%, stroke 1% in the IABP arm and 41.3% in the control arm.
TRIUMPH {38}	30-day mortality 48% in the tilarginin arm and 42% in the placebo arm.
CULPRIT-SHOCK {11}	30-day mortality 55.4% in the multi-vessel PCI- and 45.9% in the culprit-vessel only PCI study arms.
Orban M et al. {39}	30-day mortality 42.1%, MI 1%, and stroke 2% in ticagrelor-treated patients with CS-AMI (N=171).
Droppa M et al. {40}	30-day mortality 29.4% in cangrelor-treated patients with CS or after cardiopulmonary resuscitation (N=136).

Fiore M. et al. {41}	Periprocedural antiplatelet efficacy (defined by VASP index < 50%) post OHCA in ticagrelor-treated patients 11% (N=9), and 85% (N=13) in cangrelor-treated patients.
Droppa M. et al. {42}	Periprocedural antiplatelet efficacy (defined by MEA < 46 U) in cangrelor-treated CS patients (N=8) - 100% responders.
Kordis P. et al. {43}	HPR (defined by PRU > 208) in cangrelor-treated (periprocedural bolus followed by a 4-hour infusion) comatose OHCA patients (N=15 vs. 15 control) at 1 hour (0% vs. 39%) and 3 hours (0% vs. 33%), no difference at 5 and 8 hours.

CS - cardiogenic shock; MACE - major adverse cardiovascular events; MI - myocardial infarction; IABP - intra-aortic balloon pump; PCI - percutaneous coronary intervention; VASP - vasodilator stimulated phosphoprotein; MEA - multiple electrode aggregometry; OHCA - out-of-hospital cardiac arrest; HPR - high on-treatment platelet reactivity; PRU - platelet reactivity unit.



Supplementary Figure 1. Study medication.

A patient enrolled in the study will be treated with study medication consisting of cangrelor or cangrelor-placebo administered intravenously (as a bolus and continuous infusion) and two ticagrelor tablets (á 80 mg) or two ticagrelor-placebo tablets, depending on the arm to which the patient is randomly assigned. The ticagrelor tablets are crushed prior to administration to the patient. The tablet crusher is included in the study medication kit. R – randomisation, PCI – percutaneous coronary intervention.