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Inhibition of delta-protein kinase C by delcasertib as an adjunct to primary percutaneous coronary intervention for acute anterior ST-segment elevation myocardial infarction: results of the PROTECTION AMI Randomized Controlled Trial

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Aims Delcasertib is a selective inhibitor of delta-protein kinase C (delta-PKC), which reduced infarct size during ischaemia/reperfusion in animal models and diminished myocardial necrosis and improved reperfusion in a pilot study during primary percutaneous coronary intervention (PCI) for ST elevation myocardial infarction (STEMI).

Methods and results A multicentre, double-blind trial was performed in patients presenting within 6 h and undergoing primary PCI for anterior (the primary analysis cohort, $n = 1010$ patients) or inferior (an exploratory cohort, capped at 166 patients) STEMI. Patients with anterior STEMI were randomized to placebo or one of three doses of delcasertib (50, 150, or 450 mg/h) by intravenous infusion initiated before PCI and continued for ~2.5 h. There were no differences between treatment groups in the primary efficacy endpoint of infarct size measured by creatine kinase MB fraction area under the curve (AUC) (median 5156, 5043, 4419, and 5253 ng h/mL in the placebo, delcasertib 50, 150, and 450 mg/mL groups, respectively) in the anterior STEMI cohort. No treatment-related differences were seen in secondary endpoints of infarct size, electrocardiographic ST-segment recovery AUC or time to stable ST recovery, or left ventricular ejection fraction at 3 months. No differences in rates of adjudicated clinical endpoints (death, heart failure, or serious ventricular arrhythmias) were observed.

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Conclusions Selective inhibition of delta-PKC with intravenous infusion of delcasertib during PCI for acute STEMI in a population of patients treated according to contemporary standard of care did not reduce biomarkers of myocardial injury.

Clinical trial registration ClinicalTrials.gov Identifier: NCT00785954.

Keywords Reperfusion • Myocardial infarction • Stunning • Myocardial • Stents • Pharmacology

Introduction

Coronary artery reperfusion reduces mortality and morbidity among patients with acute myocardial infarction.[1,2] Nevertheless, an important proportion of patients die or develop left ventricular dysfunction and heart failure in the weeks to months after myocardial infarction.[3–6] Reperfusion injury due to tissue inflammation, free radical generation, endothelial dysfunction, and microvascular obstruction may limit infarct salvage in this setting.[7]

Delcasertib is a 23-amino acid peptide inhibitor of the delta isoform of protein kinase C (PKC), which selectively disrupts binding of activated delta-PKC with its receptor for activated C-kinase and does not affect activation or localization of other PKC isozymes. It reaches steady state within 5–30 min after the start of intravenous infusion, with a terminal half life of 2–5 min. In animal models of ischaemia–reperfusion injury, delcasertib reduced infarct size and myocyte and endothelial cellular damage, enhanced recovery of regional ventricular function, and improved infarct zone microvascular flow.[8,9] In a phase I dose-escalation study of 154 patients with acute anterior ST elevation myocardial infarction (STEMI), trends towards improvements in myocardial enzyme release, recovery of electrocardiographic (ECG) ST-segment elevation, and infarct size were observed with intracoronary administration of delcasertib.[10] The Inhibition of delta-PROTEin kinase C for the reducTION of infarct size in Acute Myocardial Infarction (PROTECTION AMI) trial therefore tested the hypothesis that intravenous administration of delcasertib reduces infarct size in patients with anterior STEMI undergoing primary percutaneous coronary intervention (PCI).

Methods

Study design and organization

PROTECTION AMI was phase II, multicentre, dose-ranging, placebo-controlled, double-blind randomized trial. Patients with anterior STEMI served as the primary cohort and were randomized to placebo or one of three doses of delcasertib. An exploratory cohort of patients with high-risk inferior STEMI was randomized to placebo or the highest dose of delcasertib. The trial was sponsored by KAI Pharmaceuticals (South San Francisco, CA, USA) and Bristol-Myers Squibb (New York, NY, USA) and was coordinated by the Cleveland Clinic Coordinating Center for Clinical Research (C5Research) (Cleveland, OH, USA). Medpace (Cincinnati, OH, USA) served as the contract research organization and provided data and site management. An independent Data and Safety Monitoring Board monitored the safety of the study and had access to unblinded data. The steering committee, consisting of academic members and non-voting representatives from the sponsoring companies, designed the trial and were responsible for its scientific conduct. The final study database was provided to C5Research, where the statistical analyses for this article were independently performed. The study chairman drafted this article, with input by all of the steering committee members, and had full access to the data.

Patient population and enrolment

Patients were enrolled at 114 hospitals in 18 countries (see Supplementary material online, Appendix) between December 2008 and June 2010. Patients were eligible for inclusion if they were 18 years of age or older, had at least 30 min of ischaemic symptoms consistent with acute STEMI, and arrived at a facility capable of performing or transferring for PCI within 6 h of symptom onset. Electrocardiographic criteria were $\geq$2 mm of ST segment elevation in at least two contiguous precordial leads (V1–V4) in the anterior STEMI cohort or $\geq$2 mm ST elevation in two inferior leads (II, III, aVF) with ST depression in two other contiguous leads in the large inferior STEMI cohort. Exclusion criteria included prior coronary bypass surgery, left bundle branch block or paced rhythm, persistent hypotension or shock, or fibrinolytic therapy within the prior 72 h. The protocol was approved at the institutional review board of each participating hospital, and all patients gave written informed consent.

Treatment and follow-up

Patients with anterior STEMI were randomized by interactive telephone system to intravenous infusion of placebo or delcasertib 50, 150, or 450 mg/h. Patients in the exploratory inferior STEMI group were randomized to placebo or delcasertib 450 mg/h. Intravenous infusion of study drug was begun as soon as possible after randomization, before the first contrast injection during PCI, and continued until all study drug had been administered (~2.5 h). Cardiac catheterization and PCI were performed according to local standards prior to completion of the study drug infusion. Concomitant medications were administered according to investigator preference.

Endpoints

The primary efficacy endpoint was infarct size measured by cardiac enzymes creatine kinase MB fraction (CK-MB) area under the curve (AUC) using curve fitting techniques.[11] Creatine kinase, CK-MB, and troponin I were measured at enrolment (baseline), 2–4, 6–9, 16–24, 30–40, and 70–80 h after PCI. Secondary measures of infarct size included CK-MB, troponin I, and total CK AUC and peaks.

A 24 h continuous digital 12-lead ECG monitor (NEMON 180+, Northeast Monitoring, Natick, MA, USA) was applied to subjects as soon as possible after randomization and before angiography. Electrocardiographic endpoints were analysed in a blinded core laboratory (eECG Core Laboratory, Duke Clinical Research Institute, Durham, NC, USA) and included ST recovery time-trend curve area and time from drug initiation to stable ST recovery. At 3 months after randomization, N-terminal B-type natriuretic peptide (NT-pro-BNP) levels were measured in all patients and left ventricular ejection fraction was measured by multigated acquisition scan (MUGA) in the anterior MI cohort.

Protocol-defined clinical endpoints (death, cardiogenic shock during the index hospitalization, post-hospitalization heart failure, or serious arrhythmia requiring treatment) were collected through 3 months follow-up and adjudicated by an independent clinical events committee blinded to treatment allocation.

Statistical analysis

The primary analysis and sample size calculations were based upon the anterior MI cohort; the inferior MI cohort was exploratory and sample size was not statistically based. A target sample size of 908 patients (227 per treatment arm) in the anterior MI cohort was calculated based upon an 80% power to detect a 20% reduction in CK-MB AUC with a two-sided *P*-value of <0.05. A sample size of $\sim$150 subjects was chosen for the inferior MI cohort (75 per treatment arm). The 'efficacy population' was all subjects who were randomized, received study drug, and underwent PCI. Safety analyses and assessment of clinical endpoints were performed in the 'treated population' of all subjects who received study drug.

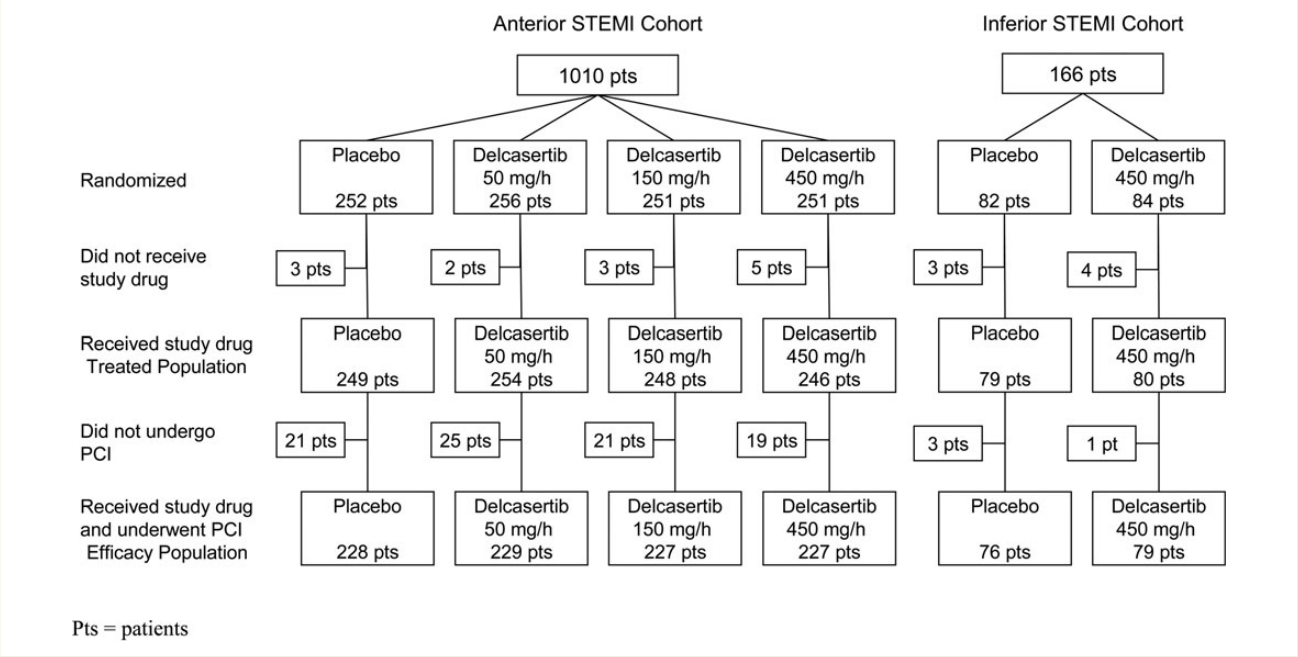

Figure 1 Patient flow through the trial. Treated and efficacy populations. Pts, patients.

Table 1 Baseline characteristics

	Anterior cohort				Inferior cohort	
	Placebo ($n = 249$)	Delcasertib 50 mg/h ($n = 254$)	Delcasertib 150 mg/h ($n = 248$)	Delcasertib 450 mg/h ($n = 246$)	Placebo ($n = 79$)	Delcasertib 450 mg/h ($n = 80$)
Age (years—median, IQR)	61 (52–70)	60 (53–69)	61 (53–70)	59 (52–70)	61 (54–70)	61 (53–70)
Male (%)	79.5	78.3	81.0	79.3	78.5	80
Geographic region (%)						
North America	7.2	7.5	8.5	8.1	15.2	10.0
Australia/New Zealand	8.8	9.8	9.7	8.9	15.2	17.5
Eastern Europe	35.7	37.4	37.5	36.2	27.8	28.8
Western Europe/Israel	48.2	45.3	44.4	46.7	41.8	43.8
Killip Class (%)						
I	91.2	91.3	91.1	91.1	94.9	92.5
II or III	8.8	8.7	8.9	8.9	5.1	7.5
Type 2 diabetes mellitus (%)	15.7	18.1	14.9	16.3	12.7	18.8
Body mass index (kg/m^2—median, IQR)	27 (24–30)	27 (24–30)	27 (25–30)	27 (25–30)	28 (25–31)	26 (24–29)
Prior MI (%)	11.6	11.0	10.9	11.0	16.5	11.3

Treated population. IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 2 Procedural characteristics

	Anterior cohort				Inferior cohort	
	Placebo (*n* = 249)	Delcasertib 50 mg/h (*n* = 254)	Delcasertib 150 mg/h (*n* = 248)	Delcasertib 450 mg/h (*n* = 246)	Placebo (*n* = 79)	Delcasertib 450 mg/h (*n* = 80)
Time (min—median, IQR)						
Symptom onset to hospital	120 (77–188)	120 (63–175)	115 (73–185)	120 (77–181)	115 (60–142)	101 (60–177)
Symptom onset to PCI	193 (148–272)	191 (143–255)	190 (140–275)	185 (143–251)	192 (147–231)	182 (140–298)
Study drug prior to PCI	17 (10–25)	15 (9–27)	17 (10–29)	14 (9–24)	19 (12–30)	20 (9–30)
Hospital presentation to PCI	62 (45–89)	67 (47–102)	65 (42–94)	59 (39–80)	81 (57–110)	82 (54–115)
Initial infarct vessel flow (%)						
TIMI 0	51.8	47.6	46.0	52.8	58.2	62.5
TIMI 1	8.8	10.2	11.7	11.8	12.7	6.3
TIMI 2	15.7	18.9	18.1	15.0	16.5	16.3
TIMI 3	21.7	19.7	22.2	18.7	11.4	15.0
Procedural antithrombotics (%)						
Heparin	90.4	90.4	88.1	93.0	92.1	100
Bivalirudin	7.5	10.9	11.0	5.3	5.3	0
Glycoprotein IIb/IIIa inhibitor	54.8	49.3	49.7	56.3	51.3	56.9
Clopidogrel	75.4	79.0	77.1	78.4	73.7	72.2
Prasugrel	2.2	1.7	0.9	0.9	0	0

Treated population. IQR, interquartile range; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

Table 3 Infarct size and electrocardiographic endpoints

Median (IQR)	Anterior cohort					Inferior cohort		
	Placebo (n = 228)	Delcasertib 50 mg/h (n = 229)	Delcasertib 150 mg/h (n = 227)	Delcasertib 450 mg/h (n = 227)	P-value	Placebo (n = 76)	Delcasertib 450 mg/h (n = 79)	P-value
CK-MB AUC (ng h/mL)	5156 (2581–8567)	5043 (2589–8302)	4419 (1731–9024)	5253 (2504–8317)	0.43	4362 (2316–6828)	3811 (1933–7484)	0.71
CK-MB peak (ng/mL)	299 (148–519)	288 (139–509)	235 (83–540)	256 (152–526)	0.47	210 (100–390)	205 (105–352)	0.77
CK AUC (U h/L)	50 032 (35 008–85 433)	55 694 (25 729–81 842)	49 329 (14 942–87 028)	47 714 (24 494–93 136)	0.67	36 634 (17 501–62 838)	36 069 (17 597–74 448)	0.84
CK peak (U/L)	2158 (1035–3919)	2383 (1087–3656)	2017 (639–3887)	1897 (1023–4052)	0.59	1416 (655–2520)	1457 (828–2727)	0.74
Troponin I AUC (μg h/L)	1441 (593–3034)	1582 (553–2968)	1298 (345–3138)	1383 (489–3493)	0.46	1012 (474–2128)	954 (454–2206)	0.87
Troponin I peak (μg/L)	67 (25–141)	77 (27–145)	66 (15–142)	70 (21–167)	0.38	46 (18–95)	45 (20–99)	0.95
ECG ST AUC (μV-min)	7147 (4800–10 705)	6618 (5060–8901)	6762 (4793–9067)	6705 (4852–10 113)	0.39	5732 (3930–8420)	5633 (4156–8477)	0.66
Time to stable ST recovery (min)	52 (19–88)	48 (18–88)	44 (15–76)	46 (17–92)	0.63	34 (17–53)	29 (13–48)	0.45

Efficacy population. All values are median and interquartile range.
AUC, area under the curve; ECG, electrocardiographic; CK, creatine kinase; CK-MB, creatine kinase MB fraction.

A step-down approach (i.e. 450 mg/h vs. placebo, then 150 mg/h vs. placebo, then 50 mg/h vs. placebo) was used for the comparisons of delcasertib doses vs. placebo. All tests were two-sided and conducted at significance level of 5%. For continuous endpoints, the treatment difference was assessed using the ANOVA model or the corresponding non-parametric tests. For categorical endpoints, the Cochran Mantel–Haenszel test was used to compare delcasertib doses with placebo. A subgroup analysis of efficacy was pre-specified to be based upon infarct vessel flow (TIMI grade 0 or 1 vs. TIMI grade 2 or 3) determined by the site investigator by angiography prior to primary PCI.

Results

A total of 1176 patients were enrolled: 1010 in the anterior MI cohort and 166 in the inferior MI cohort (*Figure 1*). Baseline demographic characteristics were similar among randomized groups within the two cohorts (*Table 1*). Elapsed time between symptom onset and hospital presentation was a median of ~2 h (*Table 2*). Across all treatment groups, a total of 90 patients did not undergo PCI, due most commonly to no significant atherosclerotic stenosis (49 patients), anatomy unsuitable for revascularization (18), or referral for coronary bypass surgery (11). Hospital presentation to PCI ('door-to-balloon') time was 65 min. Study drug was initiated a median of 16 min prior to PCI and administered without interruption to 95% of patients. Discharge medications reflected contemporary evidence-based standard of care, including aspirin in 97% of patients, clopidogrel in 95%, prasugrel in 3%, statins in 98%, beta adrenergic blockers in 89%, and angiotensin converting enzyme inhibitors in 85%.

The primary efficacy endpoint, CK-MB AUC, did not differ significantly among treatment groups within either the anterior or exploratory inferior STEMI cohorts (*Table 3*). No dose effect was observed (*Figure 2*). Similarly, no differences were seen in secondary endpoints of infarct size. There were no differences among treatment groups in the ST segment recovery AUC or time to stable ST recovery by continuous 24 h 12-lead ECG monitoring.

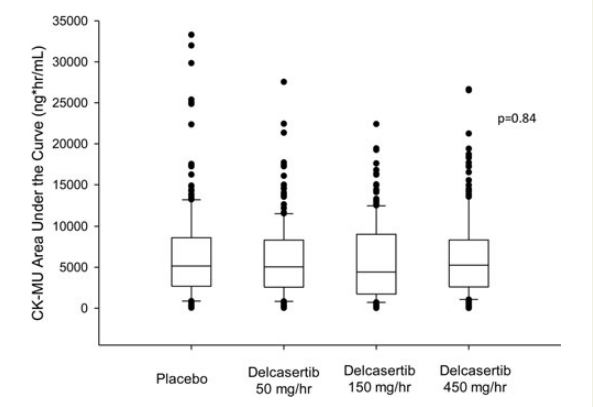

Figure 2 Primary endpoint—median infarct size assessed by CK-MB AUC in the anterior STEMI population. Box-and-whisker plot. The box spans the interquartile range (25th to 75th percentiles), while the line within the box denotes the median. Whiskers extend from the 10th to the 90th percentiles. Dots denote outliers.

Clinical events, left ventricular function, and laboratory measurements by 3-month follow-up are summarized in *Table 4*. There were no differences among treatment groups in the composite or individual clinical endpoints. Similarly, there were no differences in left ventricular ejection fraction as measured by MUGA in the anterior cohort or NT-pro-BNP levels. Patients presenting with TIMI 0/1 flow (63% of patients) had evidence of larger infarctions and worse clinical outcome compared with patients who initially had patent (TIMI 2/3) infarct vessels (*Table 5*). No treatment-related differences in outcomes were observed, however, in either subgroup of patient defined by their initial infarct-vessel patency.

Discussion

The PROTECTION AMI trial tested the effect of selective delta-PKC inhibition with delcasertib on biomarkers of reperfusion injury among patients with acute anterior STEMI undergoing primary PCI. In this phase II dose-ranging study, delcasertib, administered intravenously before and during PCI did not reduce biomarker measures of myocardial infarct size, improve ECG markers of reperfusion, or enhance left ventricular function at 3 months. Although not powered to assess clinical outcome, no differences in ischaemic endpoints were observed.

Reperfusion injury has been defined as 'myocardial injury caused by the restoration of coronary blood flow after an ischemic episode' which '... culminates in the death of cardiac myocytes that were viable immediately before myocardial reperfusion'.[12] A variety of pathologic processes occurring during the ischaemia–reperfusion cycle have been implicated, including intracellular and myocardial calcium overload, rapid restoration of physiologic pH, and neutrophil infiltration and inflammation.[7] These mechanisms may converge on a common pathway of mitochondrial injury and dysfunction, with uncoupling of oxidative phosphorylation, mitochondrial swelling, and hypercontracture.[13,14]

While reperfusion injury in animal models of ischaemia–reperfusion may account for up to half of the eventual infarct size, the existence of reperfusion injury in humans is controversial as it is difficult to differentiate the extent to which myocardial tissue has become irreversibly injured prior to reperfusion vs. injury and additional necrosis induced by reperfusion *per se*.[15] Uncertainty regarding whether reperfusion injury is an important process in humans has been sustained by an almost uniform lack of success of different investigations aimed at improving infarct salvage. Approaches which have failed to reduce reperfusion injury and improve clinical outcome in clinical trials include antioxidants,[16] inhibitors of calcium overload,[5] anti-inflammatory agents (including antibodies to CD18, CD11, or C5 complement),[3] or glucose-insulin-potassium,[6] magnesium,[4,17] or adenosine.[18]

Protein kinase C is a family of isoenzymes which transduce extracellular signals by translocating to unique subcellular sites upon activation.[9,19,20] During reperfusion, activated delta-PKC translocates to the mitochondria and mediates necrosis and apoptosis. Delta-PKC knockout mice exhibit reduced myocardial damage following coronary ischaemia and reduced infarct size after stroke.[8,9,21] In a porcine model of coronary occlusion and myocardial infarction, brief intracoronary administration of an inhibitor to delta-PKC reduced infarct size and troponin release by 80–85% and improved left

Table 4 Outcome at 3 months

	Anterior cohort					Inferior cohort				
	Placebo (*n* = 249)	Delcasertib 50 mg/h (*n* = 254)	Delcasertib 150 mg/h (*n* = 248)	Delcasertib 450 mg/h (*n* = 246)	*P*-value	Placebo (*n* = 79)	Delcasertib 450 mg/h (*n* = 80)	*P*-value
Death, shock, CHF, or ventricular arrhythmia (%)	8.8	8.7	8.9	7.3	0.91	3.8	3.8	1.0
Death (%)	3.2	3.9	4.0	2.4	0.74	2.5	2.5	1.0
Cardiogenic shock (%)	3.5	2.4	3.2	0.8	0.20	1.3	1.3	1.0
Congestive heart failure (%)	4.4	3.9	2.8	4.5	0.76	1.3	1.3	1.0
Ventricular arrhythmia (%)	1.2	0.8	0.4	1.6	0.52	1.3	0	0.50
N-terminal B-type natriuretic peptide (pmol/L), median (IQR)	41 (18–111)	53 (21–112)	50 (20–106)	44 (20–120)	0.84	27 (14–62)	25 (15–55)	0.67
Left ventricular ejection fraction (%) median (IQR)	52 (41–62)	52 (41–61)	49 (39–60)	51 (39–60)	0.50	Not measured	Not measured	–

Treated population for clinical endpoints, efficacy population for N-terminal B-type peptide and left ventricular ejection fraction.

Table 5 Outcome according to pre-percutaneous coronary intervention infarct vessel patency

TIMI 0/1	Anterior cohort					Inferior cohort		
	Placebo ($n = 151$)	**Delcasertib 50 mg/h ($n = 147$)**	**Delcasertib 150 mg/h ($n = 143$)**	**Delcasertib 450 mg/h ($n = 159$)**	***P*-value**	**Placebo ($n = 56$)**	**Delcasertib 450 mg/h ($n = 55$)**	***P*-value**
CK-MB AUC (ng h/mL), median (IQR)	6634 (4298–9940)	6325 (3831–9280)	6275 (3036–10 274)	5998 (3233–8708)	0.33	4647 (2778–8274)	4819 (2420–8128)	0.80
ECG ST AUC (μV-min), median (IQR)	7977 (5672–11 182)	6892 (5192–9032)	6994 (5111–10 074)	7002 (5210–11 494)	0.15	6118 (4549–9194)	5886 (4471–8656)	0.82
Death, shock, CHF, or ventricular arrhythmia at 3 months (%)	11.3	10.2	9.1	10.1	0.94	3.6	3.6	1.0
LV ejection fraction by MUGA at 3 months (%), median (IQR)	49 (40–57)	47 (39–56)	47 (36–55)	49 (38–58)	0.65	NA	NA	–
TIMI 2/3	Placebo ($n = 93$)	Delcasertib 50 mg/h ($n = 98$)	Delcasertib 150 mg/h ($n = 100$)	Delcasertib 450 mg/h ($n = 83$)		Placebo ($n = 22$)	Delcasertib 450 mg/h ($n = 25$)	
CK-MB AUC (ng h/mL), median (IQR)	2684 (868–4770)	2272 (908–5310)	2151 (941–4458)	3811 (1405–7242)	0.11	2309 (818–5845)	2294 (1302–5196)	0.96
ECG ST AUC (μV-min), median (IQR)	5983 (4348–9130)	6195 (4475–8770)	6242 (4639–8289)	6427 (4434–9358)	0.95	4007 (3229–6225)	5502 (3789–8008)	0.12
Death, shock, CHF, or ventricular arrhythmia at 3 months (%)	4.3	7.1	9.0	2.4	0.23	4.5	4.0	1.0
LV ejection fraction by MUGA at 3 months (%), median (IQR)	58 (47–65)	58 (51–67)	56 (43–65)	55 (43–64)	0.33	NA	NA	–

LV, left ventricle.
Efficacy population for ECG, CK-MB, and LV ejection fraction endpoints, treated population for clinical events. Other abbreviations as in previous tables.

ventricular function; myocardial salvage was accompanied by marked reductions in markers of apoptosis.[9] Moreover, evidence in murine and porcine models supports a salutary effect of delta-PKC inhibition on microvascular function and myocardial perfusion.[9]

Various members of the PKC family modulate a diverse spectrum of cellular activities; activation of the epsilon-PKC isoform by ischaemia, for example, is protective and enhances myocardial salvage during reperfusion in animal models.[8] Specificity is therefore an essential characteristic of any pharmacologic inhibitor of PKC to avoid off-target effects which may attenuate benefit or lead to unexpected toxicity. Rather than binding to the catalytic site, which is structurally similar across the PKC family, delcasertib binds to the intracellular isozyme-specific anchor receptor of delta-PKC and selectively prevents the translocation that is necessary for the enzymatic action of delta-PKC.[22,23] No adverse effects of delcasertib have been observed in human studies at doses up to those investigated in the current trial.

An initial dose-escalation study, the Direct Inhibition of delta-Protein Kinase C Enzyme to Limit Total Infarct Size in Acute Myocardial Infarction (DELTA-MI) trial, suggested that intracoronary administration of delcasertib prior to primary PCI might reduce myocardial reperfusion injury during anterior STEMI.[10] Patients were randomized once an occluded infarct vessel (TIMI 0 or 1 flow) was documented by angiography, and delcasertib was administered as two 1 min intracoronary injections through the guide catheter and balloon angioplasty catheter prior to and immediately after reperfusion. Although not powered to show significant reductions in enzyme release in the individual dosing groups, consistent trends of 18–25% reductions in CK-MB AUC were observed among the 154 patients enrolled in that trial. Moreover, continuous ECG monitoring suggested improvement in microvascular perfusion, with an overall 31% reduction in ST-segment recovery AUC and a 63% reduction in the incidence of ECG recurrent ischaemia.

The current phase II PROTECTION AMI trial was designed to extend the findings of DELTA-MI with more definitive measurements of the effects of delcasertib on myocardial salvage and microvascular reperfusion and to a larger and broader population of patients with STEMI. Delcasertib was administered by intravenous infusion prior to cardiac catheterization, rather than by intracoronary route used in DELTA-MI, in order to simplify administration, permit any beneficial effect of delcasertib through collateral flow or intermittent patency prior to reperfusion by PCI, prolong tissue exposure to the drug, and improve the generalizability of the therapy to a diverse population of patients. Although circulating levels of delcasertib were not measured in PROTECTION AMI, the doses had been calculated to provide steady-state blood concentrations that would meet or exceed levels required to prevent reperfusion injury in animal models and to deliver cardiac tissue doses similar to those with intracoronary administration in the DELTA-MI trial. Explanations for the failure of delcasertib to reduce reperfusion injury in PROTECTION AMI are speculative. The favourable trends in the earlier DELTA-MI may merely have been due to the play of chance in a small trial with multiple dosing arms, and delta-PKC may not be a useful target for prevention of reperfusion injury despite the mechanistic evidence. Alternatively, differences in designs of the two studies may have been relevant, particularly with regard to inclusion of patients regardless of baseline infarct vessel occlusion and intravenous rather than intracoronary administration. Patients in PROTECTION AMI were randomized and study drug initiated prior to angiography and definition of infarct vessel patency. As a consequence, approximately one-third of patients in the trial had spontaneously reperfused prior to PCI, a group who had smaller infarcts and better clinical outcome overall and in whom reperfusion injury may have commenced prior to administration of study drug. Nevertheless, benefit of delcasertib could not be shown in patients with either patent or occluded infarct vessels on initial angiography (*Table 5*). It is also possible that even the highest dose of delcasertib used in this study was insufficient by intravenous administration, and the lack of observed toxicity leaves unanswered the question of whether higher doses may have been feasible and effective. It is unlikely that adverse drug–drug interactions with other evidence-based therapies for STEMI (e.g. anticoagulants) could have attenuated a benefit of delcasertib, as this small peptide is rapidly degraded by serum proteases, does not displace other serum protein-bound drugs, and does not activate or inhibit cytochrome P450 enzymes.

In summary, selective inhibition of delta-PKC during PCI for acute anterior STEMI did not reduce biomarkers of myocardial injury. This finding, in the context of previous unsuccessful investigations aimed at diminishing reperfusion injury, highlights the inability to extrapolate promising findings from animal models to humans, the pragmatic difficulties in prospectively identifying patients at greatest risk for reperfusion injury at the time of acute intervention, and the limitations of surrogate measures of outcome that may be insensitive to important mechanistic effects in studies underpowered to show true clinical benefit. Future clinical investigations in this field might best focus on agents which inhibit necrotic or apoptotic pathways and utilize several angiographic and/or ECG biomarkers of potential infarct size and spontaneous infarct vessel reperfusion to best target those patients at highest risk for ischaemia–reperfusion injury.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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