The efficacy and safety of trimetazidine in patients having been treated by percutaneous coronary intervention (ATPCI): Results of a randomised double-blind placebo-controlled trial.

Roberto Ferrari, MD[a,b], Ian Ford, PhD[c], Kim Fox, MD[d], Jean Pascal Challeton[e], Anne Correges[e], Michal Tendera, MD[f], Petr Widimský, MD[g], Nicolas Danchin, MD[h], on behalf of the ATPCI investigators.

[a] Cardiovascular Centre, University of Ferrara, Via Aldo Moro 8, 44124 Cona, Ferrara, Italy;

[b] Maria Cecilia Hospital, Via Corriera 1, 48033 Cotignola (RA), Italy;

[c] Robertson Centre for Biostatistics, University of Glasgow, Boyd Orr Building University Avenue, G12 8QQ Glasgow, Scotland.

[d] National Heart and Lung Institute- Imperial College, Guy Scadding Building, Dovehouse St, Chelsea, London SW3 6LY, United Kingdom; Royal Brompton Hospital, Sydney St, Chelsea, London SW3 6NP, United Kingdom.

[e] Institut de Recherches Internationales Servier, 50 Rue Carnot, Suresnes Cedex, France

[f] Department of Cardiology and Structural Heart Disease, Medical University of Silesia, Poniatowskiego 15, 40-055 Katowice, Poland.

[g] Cardiocenter, Third Faculty of Medicine, Charles University, Ruská 2411, 100 00 Prague 10-Vinohrady,, Czech Republic.

[h] Assistance Publique-Hôpitaux de Paris (AP-HP) 3 Avenue Victoria, 75004 Paris, Hôpital Européen Georges Pompidou (HEGP), Department of Cardiology, 20 Rue Leblanc, 75015 Paris, France; Université Paris-Descartes, 31 Boulevard Pasteur, 75015 Paris, France; INSERM U-970, Rue de la Chine 4 75020 Paris, France.

Address for correspondence: Roberto Ferrari, MD, Chair of Cardiology, Azienda Ospedaliero-Universitaria di Ferrara, Ospedale di Cona, Via Aldo Moro 8, 44124 (Cona) Ferrara, Italy

Email: fri@unife.it **- Telephone:** +39 0532 239882**.**

Keywords: percutaneous coronary intervention, angina pectoris, trimetazidine, Coronary Artery Disease

Word count (manuscript text): 3143

Abstract: 311

Summary

Background. Angina may persist or reoccur despite successful revascularisation with percutaneous coronary intervention (PCI) and antianginal therapy. Additionally, PCI in stable patients, has not been shown to improve survival compared to optimal medical therapy. Trimetazidine is an antianginal agent which improves energy metabolism of the ischaemic myocardium and may improve outcomes and symptoms of patients who recently had a PCI.

Methods. We conducted a randomised double-blind, placebo-controlled event-driven trial of trimetazidine added to standard background therapy versus placebo in 6007 patients who had undergone successful PCI, either elective for stable angina (n=3490) or urgent for unstable angina or NSTEMI (n=2517). Patients were randomly assigned to trimetazidine 35 mg MR bid (n=2998) or matching placebo (n=3009). The primary efficacy endpoint was a composite of cardiac death, hospitalisation for cardiac event and recurrence or persistence of angina leading to addition, switch or increase of the dose of at least one anti-anginal drug or to the performance of a coronary angiography. The efficacy analyses were performed according to the intention to treat principle. The primary safety endpoint was all reported serious adverse events. The study is registered on www.clinicaltrialsregister.eu (EudraCT Number= 2010-022134-89).

Findings: After a median follow-up of 47·5 months, no statistically significant difference was found in primary endpoint incidence between the trimetazidine group and the placebo group (23·3% and 23·7%, respectively; hazard ratio, 0·98; 95% confidence interval, 0·88—1·09; p=0·727), nor were there statistically significant differences in the incidence of the components of the primary endpoint. Similar results were obtained in the elective and urgent PCI groups. No significant difference was seen in the safety events as compared to placebo.

Interpretation: The ATPCI study results show that the prophylactic use of trimetazidine added with guideline-recommended medical therapy did not improve patient outcome after a successful elective or urgent PCI. No safety issues were identified with trimetazidine in the studied population.

Funding: Servier, France

Research In Context

Evidence before the study

When faced with a patient with angina pectoris, it is recommended to initiate medical therapy to relieve symptoms and to improve the prognosis. Percutaneous Coronary Intervention (PCI) may then be considered to alleviate symptoms in those patients who do not respond to medical therapy as well as to improve prognosis in those with acute coronary syndromes. Unfortunately, angina pectoris may reoccur despite successful PCI. There is paucity of data regarding the prognostic benefits of antianginal drugs in post-PCI patients.

Added value of the study

ATPCI was a large-scale, randomised, double-blind, placebo-controlled study to test the use of trimetazidine added to guideline-recommended therapy in a population of 6007 patients having had a recent PCI for stable angina or unstable angina/non-ST segment elevation myocardial infarction (NSTEMI). Trimetazidine is an antianginal agent devoid of haemodynamic effects that acts by improving the metabolism of the ischaemic myocardium. Trimetazidine, under ischaemic conditions, shifts Free Fatty Acids (FFA) towards glucose utilisation. In so doing, it allows production of anaerobic ATP and reduces acidosis.

We found that, as compared with placebo, trimetazidine did not improve the primary composite efficacy endpoint of cardiac death, hospitalisation for cardiac event, recurrence or persistence of angina during a median follow-up of 47·5 months. Similar results were obtained in the elective and urgent PCI group. Recurrence of angina (CCS class ≥2) after successful PCI occurred in 15·1% of patients in the trimetazidine group after 1 year and 9·8% at the end of the follow-up, with no difference between treatment groups.

ATPCI also showed that long-term use of trimetazidine was not associated with any safety issues.

Implications of all the available evidence

Long-term outcomes of patients undergoing successful angioplasty for angina and NSTE acute coronary syndrome and receiving contemporary optimal medical therapy is good. Routine use of trimetazidine does not improve cardiac events in this population.

INTRODUCTION

The treatment aim for chronic stable angina is to relieve symptoms and improve prognosis through medical therapy and revascularisation [1]. Percutaneous coronary intervention (PCI) is often used to alleviate symptoms in stable patients who do not respond to medical therapy and to improve prognosis in those with acute coronary syndromes [2]. Angina may reoccur despite successful revascularisation and the prognostic benefits of PCI over or on top of optimal medical therapy in stable angina is disputed [3-6]. Management of recurring or residual angina after PCI is an unmet need that now needs to be addressed.
Trimetazidine is an antianginal agent that differs from those most commonly used, as it is devoid of hemodynamic effect and exerts its antianginal action by improving the metabolic efficiency of the ischaemic myocardium [7]. “Trimetazidine improves the activity of pyruvate dehydrogenase, the enzyme that allows the entry of pyruvate from the cytosol into the mitochondria for subsequent oxidation in the Kreb’s cycle. At the same time, trimetazidine inhibits the beta-oxidation of the free fatty acids (FFA). These effects are favourable under ischaemic conditions. By shifting substrate utilisation from FFA to carbohydrates, trimetazidine allows the formation of anaerobic ATP, which, although limited, occurs in absence of oxygen, the limiting factor for energy production under ischaemic condition. By removing

pyruvate from the cytosol, trimetazidine attenuates lactic acid production, thus reducing acidosis that contributes to the occurrence of angina"[7]. Trimetazidine outside the US, UK, and Western Europe is a widely prescribed treatment either at the dose of 20 mg three times a day or 35 mg twice daily in the management of angina and recommended in combination with beta-blockers or calcium antagonists, although the benefits of Trimetazidine on exercise testing have not been consistently evident [8, 9, 10] . The most used and current dose is 35 mg bd, the one used in the trial. Current opinion favours that microvascular dysfunction plays an important role in the pathophysiology of angina following PCI for many patients [8]. Trimetazidine is thought to be particularly effective in managing patients with microvascular dysfunction and consequently is recommended in this context [7, 11, 12].
The efficAcy and safety of Trimetazidine in Patients with angina pectoris having been treated by percutaneous Coronary Intervention (ATPCI) study was designed to assess the long-term potential benefits and safety of trimetazidine added to standard evidence-based medical treatment in patients who had a recent successful PCI.

METHODS

Trial design, participants and study drug

We conducted this randomised, double-blind, placebo-controlled, parallel group, event-driven, international, multicentre study in angina patients who have undergone recent successful PCI in 365 centres in 27 countries [13]. The study protocol, available with full text in the supplementary materials, was approved by the Ethics Committee at each participating institution. All the patients provided written informed consent.

Eligible patients were men or women aged between 21 and 85 years with documented single or multivessel coronary artery disease (CAD), who had undergone a successful PCI less than 30 days before inclusion, occurring in the context of either stable angina (elective PCI), or an acute presentation such as unstable angina or NSTEMI (urgent PCI). PCI was considered successful by the investigators when the procedure was uncomplicated with satisfactory angiographic and symptomatic response. Patients who underwent a PCI due to STEMI were not eligible for the study. The index PCI had to be completed as initially planned, with no complications and no further planned revascularisation. Patients were included regardless of the presence or absence of angina symptoms after the index PCI. However, it is unlikely that patients who continued to complain of angina would have been considered to have had a successful PCI and therefore randomised (Detailed inclusion and exclusion criteria are provided in the supplementary materials, Table S1).

The study drug was administered in addition to routine post-PCI treatment including secondary prevention therapy according to current guidelines. Treating clinicians were free to prescribe background antianginal therapy with the exception of perhexiline, ranolazine, and open-label trimetazidine. Antianginal treatment was required to be stable at the time of inclusion. Treatments were considered stable by the investigators when there was no need to change type or dose of the anti-anginal and/or hypertensive therapy after PCI.

Procedures

Patients were allocated to either trimetazidine or placebo at inclusion by an interactive web response system using a centralised, balanced, non-adaptive permuted-block randomisation process. Randomisation was stratified by both country and type of index PCI (elective or urgent). The allocation sequence was generated at the sponsor level by a statistician through validated in-house application software; access was restricted to people responsible for the study therapeutic units production until database lock. These people had no involvement in the rest of the trial. Study investigators, including all research teams and patients, were masked to treatment allocation.

Up to one month after PCI, patients were randomised to either trimetazidine modified-release (MR) 35 mg twice daily or once daily for patients with moderate renal failure, or matching placebo. Patients were evaluated after randomisation at trial visits at 1, 3, 6 months and thereafter at 6-month intervals.

Endpoints

The primary efficacy endpoint was the composite of cardiac death, or hospitalisation for a cardiac event, or recurrent or persistent angina leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies, or recurrent or persistent angina leading to performing a coronary angiography. The main secondary efficacy endpoint was the composite of cardiac death, or hospitalisation for a cardiac event, or recurrent or persistent angina leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies, or recurrent or persistent angina leading to performing a coronary angiography, or evidence of ischemia (documented by stress imaging) leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies, or evidence of ischemia (documented by stress imaging) leading to performing a coronary angiography. Other secondary endpoints were all-cause mortality, occurrence of an event, either taken individually or as a composite, among the components of the primary and the main secondary composite endpoints, hospitalisation for MI, hospitalisation for non-fatal MI, hospitalisation for ischaemic chest pain, hospitalisation for heart failure, any coronary revascularisation, and repeat coronary revascularisation in response to angina.

All of these outcomes were analysed on a time-to-first-event basis. All outcomes were blindly adjudicated by the members of the Cardiovascular Endpoints Adjudication Committee, according to pre-specified criteria (with definitions and charters listed in the supplementary materials, Table S2). Other efficacy endpoints such as the number of reported angina episodes per week were recorded throughout the study.

The primary safety endpoint was any serious adverse event. Neurological symptoms (including Parkinson's syndrome, disorientation, hallucination, and convulsion), coagulation disorders including non-traumatic haemorrhages, thrombocytopenia, agranulocytosis, falls, arterial hypotension, serious skin disorders, and hepatic disorders were pre-specified events of interest and were adjudicated blindly by a separate Safety Endpoints Adjudication Committee (the charter of the Safety Endpoint Adjudication Committee is available in the supplementary material).

Statistical analyses

We calculated that 1363 primary efficacy outcomes would provide the trial with a power of 85% to detect a hazard ratio of 0.85 for the primary endpoint with trimetazidine compared to placebo, at a significance level of 5% (two-sided). With an expected annual event incidence of 10% in the placebo group, we estimated that the enrolment of approximately 5800 patients would provide the required number of primary events, based on an accrual period of two years, a total study duration of four years, and an annual study withdrawal rate of 2%. However, as the primary efficacy endpoint event rate was lower than expected, the Executive Committee decided to prolong the follow-up by one year. No comparative interim analysis was performed.

Baseline characteristics are shown according to study groups as means (standard deviation) or median for continuous variables and as numbers and percentages for categorical variables.

The superiority of trimetazidine versus placebo has been tested on the adjudicated primary efficacy endpoint according to the intention-to-treat principle using a Cox's proportional hazards model adjusted for country and nature of the index PCI (elective or urgent). Results are presented as hazard ratio (HR) and 95% confidence interval (95% CI) with corresponding p-value. The type I error rate was set at 5% (two-sided). Pre-specified subgroup analyses were performed according to the nature of the index PCI.

Similar analyses were performed for other time-to-event secondary endpoints (no p-value was provided as primary efficacy endpoint is not statistically significant). Other efficacy endpoints were described by visit.

Safety analysis was performed for all patients who had taken at least one dose of study drug. Global and annual incidence of serious emergent adverse events and pre-specified events of interest are provided for each treatment group during the treatment period. The differences between groups in annual incidence rates with associated 95% CI are also provided. Descriptive statistics are provided by treatment group for emergent adverse events.

SAS software, version 9·2 (SAS Institute, North Carolina, USA) was used for all statistical analyses.

Role of the funding source

The trial was sponsored by Servier. The Executive Committee, which included non-voting representatives of the sponsor, was responsible for the study design, the interpretation of the results, the writing of the manuscript, and the decision to submit the manuscript for publication. Members of the medical and scientific department of the sponsor supported the work of the Executive Committee, but did not make any scientific or other contribution independent of this committee. The sponsor was responsible for data management and final statistical analyses.

The safety of the trial was overseen by an independent Data Monitoring Committee (the charter of the Data Monitoring Committee is available in the supplementary material). The Executive Committee had full access to the data and takes full responsibility for the accuracy and completeness of the data and the analysis performed as well as for the fidelity of this report to the trial protocol.

Data sharing

Anonymised patient-level, study-level clinical trial data (including clinical study report) and study protocol, underlying the results reported in this article will be shared in agreement with the Servier data sharing policy available at https://clinicaltrials.servier.com/data-request-portal/ .

Access to data will be granted to researchers identified in the research proposal directed to https://clinicaltrials.servier.com/data-request-portal/ to achieve the aims described in this proposal, and provided its approval by a dedicated committee and signature of data sharing agreement by requestor.

RESULTS

Randomisation and follow-up

Figure 1 shows the trial profile. From September 2014 to June 2016, a total of 6007 patients were randomly assigned to either trimetazidine (n=2998) or placebo (n=3009) at 365 centres in 27 countries. The last visit occurred in December 2019. The median follow-up duration was 47·5 months (interquartile range, 42·3 to 53·3).

Characteristics of the participants

The two groups were well-balanced with respect to baseline characteristics (Table 1). 3490 patients were included following an elective PCI and 2517 following an urgent PCI (supplementary materials, table S3). The mean age was 60·9 (*9·7*) years (18·7% ≥70 years), 77·0% were men and 85·3% were Caucasian. Approximately half (54·6%) of the patients had one-vessel disease. 2065 patients (35%) had incomplete revascularisation, which means that after PCI there was a 50% or more diameter stenosis in one or more major epicardial coronary arteries. . The patients were receiving appropriate guideline-recommended therapy for cardiovascular disease.

Outcomes

Effects of trimetazidine on the primary composite efficacy endpoint are shown in Figure 2. There was no difference in the primary endpoint between trimetazidine and placebo (23·3% and 23·7% respectively, [HR] 0·98; [95% CI] 0·88—1·09; p=0·73), as well as in its components analysed individually (Table 2). Similar results were obtained in the elective and urgent PCI groups (supplementary materials, Figure S1). There was no difference in the major secondary endpoint (23·5% and 24·0% for trimetazidine and placebo, respectively) (Table 2). There were no differences between the two groups in the reasons for hospitalisation for cardiac events (supplementary materials, Table S4). Among other secondary endpoints (Table 3), neither all-cause mortality nor the composite of hospitalisation for MI (fatal or non-fatal) or cardiac death were modified by assigned randomised treatment. Kaplan Meier cumulative event curves for the secondary endpoints of major interest are reported in the online supplement. There was no evidence of interaction between the effects of randomised treatment for different subgroups for the primary endpoint (Figure 3). A total of 3942 (66%) patients had complete revascularisation. The effects of trimetazidine on this subset of patients was not different from placebo. The percentage of patients with CCS class 2 or higher decreased throughout the study similarly in the trimetazidine and placebo groups (supplementary materials, Table S5), with 18·0% CCS class 2 or higher at 1 month, 15·1% at 12 months, and 9.8% at the end of the study in the trimetazidine group (18·2%, 14·1%, and 10·0% respectively in the placebo group). We could not find any regional or national difference in the 27 countries from Europe, South America, and Asia where the study was conducted.

The primary safety endpoint (incidence of serious adverse events) occurred in 40·9% of patients in the trimetazidine group and in 41·1% in the placebo group (table 4). There was no difference between the treatment groups when events were split by System Organ Class (supplementary materials, Table S6). There were 651 (21·8%) study drug withdrawals in patients assigned to trimetazidine and 642 (21·5%) in the placebo group. Study drug withdrawal was due to adverse events in 272 patients (9·1%) in the trimetazidine group and in 267 patients (8·9%) in the placebo group. The adjudicated adverse events of interest were no more frequent in the trimetazidine group as compared to the placebo group (Table 4). Possible association between trimetazidine and Parkinsonism was previously noted although, more recently, this is no longer considered to be an issue. Accordingly, the rate of neurological symptoms was 7·7% in the trimetazidine group versus 7·0% in the placebo group and the rate of Parkinson's syndrome was 0·3% versus 0·2%. There was no difference between groups in the incidence of coagulation disorders (including non-traumatic haemorrhages), thrombocytopenia, agranulocytosis, falls, arterial hypotension, hepatic disorders or serious skin disorders.

DISCUSSION

This study investigated the prophylactic use of trimetazidine, added to background guidelines-based medical treatment in patients with CAD, who underwent a successful PCI because of stable angina or unstable angina/NSTEMI. No benefit was found for trimetazidine in reducing the risk of cardiac events. Successful elective and urgent PCI was associated with a better outcome than had been predicted at the outset, such that the follow-up was prolonged by 12 months to obtain sufficient number of events. Cardiac death occurred in 2·4% and non-fatal MI in 4% over a median follow-up of 4·1 years. In contrast, a recent meta-analysis of 19 PCI trials, involving 25 032 patients, reported a 3·7% cardiac death rate with a second-generation drug-eluting stent (DES) implantation after a median follow-up of 4·1 years, and 5·0% for non-fatal myocardial infarction [14]. This difference probably relates to the study population. The ATPCI study included younger patients with a low atherosclerotic burden (approximately half had single vessel disease), only after the investigator was reassured that the procedure had been successfully completed as planned, without complications. Most patients had preserved ejection fraction. Also, preventive therapy use was excellent in our study: 99% were on dual antiplatelet treatment, 96% on lipid-lowering agents and 81% on renin-angiotensin inhibitors. Moreover, the patients from the various trials included in the meta-analysis were enrolled between 2000 and 2012,

several years before the recruitment in the ATPCI study. Likely, and unsurprisingly, the outcome of the disease has improved over time, in parallel with general life style improvements, particularly for patients with CAD. Adherence to comptemporary guideline-recommended medical therapy has also increased, especially in clinical trials. Additionally, the indications for elective PCI have become more selective, with the growing use of fractional flow reserve to determine actual presence of ischemia [15]. The technology and materials for PCI also have greatly improved over the years. These factors all together probably explain the relatively low event incidence in ATPCI.

Similar results were obtained with ranolazine in the recent RIVER-PCI study [16]. As in ATPCI, the RIVER PCI patients received contemporary therapy but were selected for having incomplete revascularisation after PCI, which is associated with a worse prognosis. However, only patients with a successful PCI were enrolled in ATPCI. This difference in the enrolment criteria might explain the longer follow-up needed in ATPCI to achieve a similar number of events observed in RIVER-PCI. Notably, in RIVER-PCI the addition of ranolazine, a piperazine derivative similar to trimetazidine, although acting through a different mechanism, deprived of negative inotropic, chronotropic and dromotropic effect like trimetazidine, failed to improve outcome.

Anginal type chest pain occurs most frequently in the first four to six weeks following PCI though uncommonly due to restenosis. Although angina may be related to incomplete revascularisation, it is often considered to occur as a consequence of multiple mechanisms, including microvascular dysfunction. It has been suggested that this may become recognised as an important mechanism underlying refractory angina which has been demonstrated to occur in around 20% of patients in the first year after PCI [5, 6, 17, 18]. Treatment is a challenge and metabolic agents such as trimetazidine have been proposed where all other conventional anti-anginal treatments failed [7]. This was the background upon which the ATPCI study has been designed [12].

In our study, we found that recurrence of angina was uncommon with no difference between the two treatment groups. Much of this may be explained by the high routine use of antianginal medications following PCI: 83·9% of patients received beta-blocking agents, and 27·6% calcium channel blockers with an average of 1·3 antianginal agents per patient, not including study treatment. These medications may have been prescribed for reasons other than angina, such as blood pressure control and therefore may have contributed to the lack of benefit seen with trimetazidine. In addition, ischaemia might improve over time as collateral coronary flow develops, or as a consequence of stabilised coronary plaques. Patients might also become accustomed their condition and protect themselves from provoking angina. Equally, the treatment adherence has improved. Likely in the specific ATPCI population, combining successful PCI with optimal preventive and antianginal therapy was sufficient for symptom control in the majority of cases.

Trimetazidine is different from the classical anti-ischaemic/antianginal drugs. Its action is independent of heart rate or blood pressure reduction, but improves cardiac energy metabolism, favouring glucose over free fatty acid utilisation. Thus, trimetazidine does not prevent ischaemia from developing but prevents some of the consequences of ischaemia. The metabolic effects of trimetazidine are most evident when ischaemia is at its peak, during physical effort for example [8, 9, 10]. It allows more anaerobic ATP generation from glycolysis, and less lactate production from the ischaemic myocytes.

Lastly, trimetazidine was not associated with any safety issues. There were no statistically significant differences on the primary safety endpoint. The incidence of adjudicated adverse events was low and well-balanced between treatment groups. In particular, the occurrence of neurological symptoms such as Parkinson's disease, atypical Parkinsonism or drug-induced Parkinsonism, was similar in the placebo and trimetazidine arms.

Study Limitation

Trimetazidine was initially developed as an anti-anginal treatment administered three times a day in the dose of 20 mg. Later on, this regimen was considered inconvenient and was largely supplanted by a twice-daily modified release preparation (35 mg bd); this dose is registered for the treatment of angina. It follows that the results can only be considered in terms of the dose of trimetazidine MR 35 mg bd in this study and not any other regimen or higher dose which may have a different efficacy and safety profile.

Another limitation is that any potential benefit of trimetazidine may have been attenuated because most patients were routinely treated with beta-blockers (84%), long acting nitrates (12%), and calcium blockers (27%), considering that 83% of them were hypertensive. However, it should be remembered that trimetazidine is only indicated as a part of combination therapy for angina. It should be appreciated that patients were only randomised after a successful PCI and, therefore, the findings apply to the development of emergent events including angina occurring following PCI as opposed to managing patients actively complaining of angina. Another limitation is that the presence of angina immediately post-PCI before randomisation was not recorded. However, PCI was considered successful by the investigators and, at four weeks after randomisation, angina was present only in 18% of patients and not modified by treatment.

Another hypothesis was that amelioration/improvement of ischaemic metabolism by trimetazidine may be effective in improving the outcome following PCI, particularly by preventing those events associated with angina.

In conclusion, the long-term outcome of patients undergoing successful PCI for stable angina or NSTE Acute Coronary Syndrome receiving contemporary treatments is better than was predicted at the onset of the study. The ATPCI study shows that the prophylactic use of trimetazidine added to guideline-recommended medical therapy did not improve the outcome in patients after a successful elective or urgent PCI. No safety issues were identified.

Acknowledgement

The authors are indebted to the patients who participated in the trial and to all physicians involved. Special thanks to Anne Corrèges and the statistical team which provided the analyses. Special thanks to Silvia Felloni, secretary to RF for secretarial help.

Contributors

All authors participated in the design of the study, the interpretation of the data, and the writing of the article. All authors have read and approved the final version.

Declaration of interests

RF, IF, KF, MT, PW, ND received fees, honoraria and travel expenses from Servier. RF has also received research grants and personal fees from Novartis, personal fees from Merck Serono, Boehringer Ingelheim, Sunpharma, Lupin, Doc Generici, Pfizer, Spa Prodotti Antibiotici. He is a director of Art Research and Science S.r.l (A.R.S.1). KF has received in addition fees and/or travel expenses from AstraZeneca, Celixir, CellAegis, UCB, and Broadview Ventures. He is a Director of Vesalius trials Ltd. JPC reports salary from Servier during the conduct of the study. AC reports salary from Servier during the conduct of the study. MT received also personal fees from Bayer, Cadila Pharmaceuticals, Janssen-Cilag, Kowa, PERFUSE group, UCB Pharmaceuticals. ND has received in addition grants, personal fees and non-financial support from Amgen, AstraZeneca, Bayer, BMS, Sanofi, personal fees from Boehringer Ingelheim, Intercept, MSD, Novo Nordisk, Pfizer, UCB

Data sharing

Anonymise patient-level, study-level clinical trial data (including clinical study report) and study protocol, underline the results reported in this article will be shared in agreement with the Servier data sharing policy available at Https://clinicaltrials.servier.com/data-request-portal/.

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1 Table 1:· Baseline characteristics in the intent-to-treat analysis population (n= 6007)

	Trimetazidine (n=2998)	**Placebo (n=3009)**
Demography	..	..
Age (years)	61·1 (9·6)	60·7 (9·8)
Age >=70 years old	561 (18·7%)	562 (18·7%)
Male	2311(77·1%)	2313(76·9%)
Ethnic origin	..	..
Caucasian	2546 (84·9%)	2578 (85·7%)
Asian	241 (8·0%)	242 (8·0%)
Other	211 (7·0%)	189 (6·3%)
History of ischaemic heart disease	..	..
Number of stenosed vessels	..	..
1	1621 (54·1%)	1660 (55·2%)
2	951 (31·7%)	936 (31·1%)
3	426 (14·2%)	409 (13·6%)
Modality of revascularisation	..	..
Urgent	1256 (41·9%)	1261 (41·9%)
Elective	1742 (58·1%)	1748 (58·1%)
CCS class*	..	..
I	191 (6·4%)	240 (8·0%)
II	1223 (40·8%)	1168 (38·8%)
III+IV	1583 (52·8%)	1600 (53·2%)
Left ventricular ejection fraction (%)	..	..
<40	54 (2·1%)	65 (2·5%)
40-49	296 (11·3%)	307 (12·0%)
≥50	2262 (86·6%)	2192 (85·5%)
Medical history	..	..
Previous myocardial infarction	1448 (48·3%)	1433 (47·6%)
Previous coronary revascularisation	1002 (33·4%)	1025 (34·1%)
Hypertension	2490 (83·1%)	2482 (82 5%)
Stroke	121 (4·0%)	118 (3·9%)
Peripheral artery disease	212 (7·1%)	209 (6·9%)
Diabetes	831 (27·7%)	839 (27·9%)
Concomitant treatment ongoing at inclusion	..	..
Anti-platelets agents	2988 (99·7%)	3004 (99·8%)
Aspirin	2930 (97·7%)	2963 (98·5%)
Clopidogrel	2402 (80·1%)	2416 (80·3%)
Ticagrelor	494 (16·5%)	484 (16·1%)
Other P2Y12 inhibitors	64 (2·1%)	77 (2·6%)
Anticoagulants	139 (4·6%)	122 (4·1%)
Lipid-lowering agents	2887 (96·3%)	2917 (96·9%)
Statins	2878 (96·0%)	2904 (96·5%)
Other lipid-lowering agents	139 (4·6%)	162 (5·4%)
Angiotensin-converting enzyme inhibitors	1826 (60·9%)	1809 (60·1%)
Angiotensin receptor blockers	636 (21·2%)	655 (21·8%)
Diuretics (excluding aldosterone antagonists)	714 (23·8%)	751 (25·0%)
Antianginal therapy	2778 (92·7%)	2812 (93·5%)
Beta-blockers	2508 (83·7%)	2530 (84·1%)
Long-acting nitrates or molsidomine	371 (12·4 %)	375 (12·5%)
CCB (dihydropiridine or not)	828 (27·6%)	827 (27·5%)
Other antianginal therapy **	665 (22·2%)	695 (23·1%)

2 Data are number of patients (%) or mean (SD). CCS: Canadian Cardiovascular Society. CCB: Calcium channel blocker
3 * Worst class within 4 weeks before index PCI

** short-acting nitrates, ivabradine, nicorandil, ranolazine, perhexiline and open-label trimetazidine in a few patients in violation to the protocol

Table 2: Effects on primary, major and main secondary efficacy endpoints in the intent-to-treat population (n=6007)

Data are number of first events (%), hazard ratio (HR)*, 95% confidence intervals (95% CI), and p-value

	Trimetazidine (n=2998)	**Placebo (n=3009)**	**HR (95% CI)**	**p-value**
Primary endpoint Cardiac death or hospitalisation for cardiac event or angina leading to coronary angiography or angina leading to increase/switch in anti-anginal therapies	700 (23·3%)	714 (23·7%)	0·98 (0.88;1 09)	0·727
Major secondary endpoint Cardiac death or hospitalisation for cardiac event or angina leading to coronary angiography or angina leading to increase/switch in anti-anginal therapies or ischemia leading to coronary angiography or ischemia leading to increase/switch in anti-anginal therapies	706 (23·5%)	723 (24·0%)	0·98 (0·88;1·08)	
Components of the primary endpoint analysed individually **				
Cardiac death	64 (2·1%)	79 (2·6%)	0·81 (0·58;1·13)	
Hospitalisation for cardiac events ***	402 (13.4%)	402 (13·4%)	1·01 (0·88;1·16)	
Angina leading to coronary angiography	508 (16·9%)	499 (16·6%)	1·02 (0·90;1·15)	
Angina leading to increase/switch in anti-anginal therapies	392 (13.1%)	389 (12.9%)	1·01 (0·88;1·17)	

* Estimates (trimetazidine versus placebo) were based on a Cox proportional-hazards model, with adjustment for the country and the nature of index PCI (elective/urgent).

** The endpoints (first events) are analysed independently from Primary Composite Endpoint (PCE)· A patient may be included in the event count for more than one component and thus the sum of events of all those endpoints will be greater than the number of PCE.

*** hospitalisation for the following events: acute myocardial infarction, unstable angina, angina and/or ischaemia leading to coronary revascularisation, heart failure, resuscitated cardiac arrest, sustained ventricular tachycardia.

Table 3: Other secondary efficacy endpoints in the intent-to-treat population (n= 6007)

Data are number of first events (%), hazard ratio (HR)*, 95% confidence intervals (95% CI)

	Trimetazidine (n=2998)	**Placebo (n=3009)**	**HR (95% CI)**
All-cause mortality	141 (4·7%)	151 (5·0%)	0·93 (0·74;1·17)
Cardiac death or hospitalisation for a cardiac event	436 (14·5%)	449 (14·9%)	0·98 (0·86;1·11)
Hospitalisation for fatal or non-fatal MI or cardiac death	176 (5·9%)	194 (6·4%)	0·91 (0·74;1·12)
Hospitalisation for fatal or non-fatal MI	129 (4·3%)	128 (4·3%)	1·02 (0·80;1·30)
Hospitalisation for non-fatal MI	122 (4·1%)	122 (4·1%)	1·01 (0·78;1·30)
Hospitalisation for heart failure	66 (2·2%)	66 (2·2%)	1·01 (0·72;1·42)
Hospitalisation for ischaemic chest pain	538 (17·9%)	514 (17·1%)	1·05 (0·93;1·19)
Any coronary revascularisation	357 (11·9%)	358 (11·9%)	1·00 (0·86;1·16)
Repeat coronary revascularisation in response to angina	332 (11·1%)	322 (10·7%)	1·04 (0·89;1·21)
Angina leading to coronary angiography or increase/switch in anti-anginal therapies	631 (21·0%)	624 (20·7%)	1·01 (0·91;1·13)
Ischemia leading to coronary angiography	15 (0·5%)	18 (0·6%)	0·84 (0·43;1·67)
Ischemia leading to increase/switch in anti-anginal therapies	4 (0·1%)	5 (0·2%)	0·84 (0·23;3·14)

* Estimates (trimetazidine versus placebo) were based on a Cox proportional-hazards model, with adjustment for the country and the nature of index PCI (elective/urgent).

MI: Myocardial infarction

Table 4: Primary Safety Endpoint and Adverse Events of Interest in the safety analysis population (n=5973)

Data are number of patients having experienced at least one event (%), difference *(Trimetazidine minus Placebo)* in annual incidences (E), 95% confidence intervals (95% CI)

	Trimetazidine (n=2983)		**Placebo (n=2990)**		**E (95% CI)**
	n	%	n	%	E (95% CI)
Primary safety endpoint					
Serious treatment emergent Adverse Event	1219	40.9%	1230	41.1%	-0·09 (-0·99;0·81)
Adverse Events of Interest					
Neurological symptoms	230	7.71	209	6.99	0.20 (-0.18;0.58)
Parkinson's syndrome	9	0.30	5	0.17	0·04 (-0.03;0.11)
Parkinson's disease	8	0.27	5	0.17	0.03(-0.04;0.09)
Drug induced Parkinsonism	1	0.03	0	0.00	0.01(-0.01;0.03)*
Disorientation	6	0.20	2	0.07	0.04(-0.01;0.09)
Hallucination	2	0.07	0	0.00	0.02(-0.01;0.04)*
Convulsion	5	0.17	6	0.20	-0.01(-0.07;0.05)
Coagulation disorders and Non-traumatic haemorrhages	198	6.64	198	6.62	0.00(-0.36;0.36)
Major bleeding (grade2)	84	2.82	87	2.91	-0.03(-0.27;0.21)
Coagulation disorders	42	1.41	36	1.20	0.06(-0.10;0.22)
Thrombocytopenia	68	2.28	67	2.24	0.01(-0.20;0.22)
Agranulocytosis	3	0.10	3	0.10	0.00(-0.04;0.04)
Falls	100	3.35	83	2.78	0.16(-0.09;0.41)
Arterial hypotension	107	3.59	116	3.88	-0.08(-0.35;0.19)
Hypotension (supine position)	50	1.68	62	2.07	-0.11(-0.30;0.08)
Orthostatic hypotension	38	1.27	37	1.24	0.01(-0.15;0.17)
Serious skin disorders	45	1.51	31	1.04	0.13(-0.03;0.29)
Hepatic disorders	152	5.10	164	5.48	-0.11(-0.43;0.21)

*Confidence intervals should be interpreted with caution because of the small number of events

NC: Not Calculated

Figure legends

Figure 1: Trial profile

Figure 2: Kaplan-Meier cumulative event curves for the primary efficacy composite endpoint

Figure 3: Forest Plot of the primary efficacy composite endpoint in different subgroups

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ATPCI Committees

Executive Committee

R. Ferrari (Chairman, Ferrara, Italy), N. Danchin (Paris, France), I. Ford (Glasgow, UK), K. Fox (London, UK), M. Marzilli (Pisa, Italy), M. Tendera (Katowice, Poland), P. Widimský (Prague, Czech Republic).

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Data Monitoring Committee

P.G. Steg (Chairman, Paris, France), J. Benichou (Statistician, Bihorel, France), C. Rapezzi (Bologna, Italy), M. Volterrani (Rome, Italy)

ATPCI Investigators

Algeria (60 patients): MT Bouafia, N Hammoudi, N Zaoui.

Argentina: (244 patients): MB Barbieri LR Cartasegna, RMA Colque, DD Grinfeld, LR Grinfeld, MA Hominal, AD Hrabar, H Londero, HA Luquez, SM Macin, G Moises Azize, OR Montaña, AD Prado, JM Sala, RA Sarmiento, M Snitman, FJ Sokn, MS Trivi, NA Vita, CJ Zaidman.

Austria (28 patients): J Auer, D Botegal, I Lang, S Perl, RA Riedlbauer, T Stefenelli, F Weidinger.

Bosnia and Herzegovina (120 patients): T Kovacevic Preradovic, D Markota, E Osmanovic, M Spuzic, I Terzic.

Belarus (114 patients): A Dorogokupetz, AG Mrochek, D Protasevich, A Prystrom, N Soroka.

Brazil (280 patients): PR Avancini Caramori, MCVB Braile Sternieri, F Carvalho Neuenschwander, JBMX De Moraes Junior, MON De Santos, B Garbelini Junior, RE Gomes Sarmento Leite, LHW Gowdak, AH Herdy, JS Issa, LF Leite Tanajura, AP Morales Kormann, J Novaes Cardoso, P Pimentel Filho, DB Precoma, F Rossi Dos Santos, JA Saad, WF Saporito, MH Vidotti.

China (199 patients): X Chen, Y Chen, Y Gong, T Guo, Y Guo, A Li, G Li, W Li, Z Meng, D Peng, J Wang, Z Wang, Z Wu, B Xu, P Yang, Z Yuan, F Zhang, S Zhang.

Columbia (105 patients): JL Accini Mendoza, C Arana Londono, R Botero, D Isaza Restrepo, NI Jaramillo Gomez, CA Martinez, DI Molina De Salazar, G Sanchez Vallejo.

Croatia (214 patients): A Anic, Z Babic, I Hadzibegovic, M Knezevic Pravecek, E Margetic, D Milicic, H Pintaric, D Pocanic, P Samardzic, I Sesto, J Sikic Vagic, K Stambuk, B Starcevic, R Steiner, V Tomulic.

Czech Republic (295 patients): L Ballek, T Budesinsky, M Cepelak, O Cermak, J Danczik, L Groch, I Hornacek, T Kovarnik, H Krejcova, R Kryza, M Mikus, L Nechvatal, M Opocensky, H Skalicka, M Smid, T Velimsky, D Vencour, P Zajicek.

France (60 patients): A Bellemain-Appaix, F Beygui, G Cayla, P Coste, M Elbaz, JN Labeque, G Range, F Schiele.

Georgia (300 patients): G Chapidze, N Emukhvari, G Khabeishvili, Z Lominadze, M Mamatsashvili, Z Pagava, K Paposhvili, L Rigvava, T Shaburishvili, I Sikharulidze.

Greece (40 patients): G Filippatos, I Goudevenos, C Karvounis, P Korantzopoulos, F Parthenakis, D Stakos, P Vardas, V Voudris.

Italy (260 patients): R Antonicelli, C Auguadro, M Balbi, S Berti, N Brunetti, C Campana, C Cuccia, M Di Biase, S Felis, M Gnemmi, G Guardigli, A Liso, F Mascia, E Orsini, F Pelliccia, V Pernice, P Perrone Filardi, F Potere, B Reimers, B Ricciardelli, ML Rossi, F Scalise, P Scuri, G Sinicropi, C Tamburino, L Tavazzi, G Vadala, A Vetrano.

Republic of Korea (203 patients): IH Chae, WC Kang, BK Kim, DI Kim, HS Kim, JS Kim, SH Kim, HL Kim, JH Kim, HM Kwon, SW Lim, HK Park, HS Park, SJ Park, JY Yang.

Montenegro (74 patients): S Dragnic, M Rabrenovic.

Peru (110 patients): J Aguero, ON Aguirre Zurita, HA Anchante Hernandez, LR Cardenas Levano, CN Conde Vela, RM Correa Flores, PD Cruz Colca, J Heredia Landeo, LA Mejia Vargas Machuca, ML Pariona Javier, C Rios Vasquez.

Poland (771 patients): J Adamus, J Baska, W Bebenek, M Biedrzycka, K Cymerman, P Czaja, S Dobrzycki, A Drzewiecka, D Dudek, P Firych, RJ Gil, G Irlik, R Kaliszczak, A Karczmarczyk, P Kolaczyk, J Kolowca, A Kowalisko, M Makowiecka Ciesla, B Mocarska-Gorna, P Napora, M Nartowicz-Sloniewska, K Paschalis-Purtak, J Peruga, Z Pijanowski, L Polonski, T Pusz, R Sciborski, E Straburzynska-Migaj, M Strawczynski, K Styka, A Szyszka, J Tarchalski, R Targonski, P Turek, I Wozniak-Skowerska, B Zieba, E Zielinska, M Zielinski.

Portugal (80 patients): D Brito, P Farto e Abreu, R Fontes-Carvalho, L Gonçalves, C Martins, P Monteiro, L Raposo, R Santos, H Vinhas.

Romania (297 patients): G Aron, C Arsenescu-Georgescu, G Badea, D Bartos, E Bobescu, MCA Constantinescu, D Crisu, DR Dimulescu, V Dobreanu, S Dumitrescu, N Florescu, EF Fulop, CS Literat, C Macarie, I Manitiu, C Militaru, B Minescu, V Miu, MM Opris, CF Pop, MI Popescu, I Radu, L Serban, I Stanca, G Stanciulescu, RV Stanescu-Cioranu, C Statescu, AT Tiron, MC Tomescu, OC Voicu.

Russian federation (773 patients): I Avdeeva, E Baranov, S Boldueva, G Chumakova, D Duplyakov, M Freydlin, A Frolov, L Gapon, I Gordeev, Y Karpov, AA Kastanayan, O Khrustalev, E Kosmacheva, V Kostenko, E Kretov, A Kuimov, YM Lopatin, E Nifontov, V Oleynikov, A Panov, N Pikalova, L Pimenov, N Polezhaeva, E Puntus, A Repin, S Sayganov, S Shalaev, O Soloviev, A Timofeev, L Tsyba, P Yakhontova, SS Yakushin, V Zvereva.

Serbia (322 patients): S Apostolovic, A Arandelovic, B Beleslin, N Cemerlic Adjic, A Davidovic, M Dekleva, S Hinic, R Jung, D Kordic, I Matic, O Micic, V Miloradovic, V Mitov, A Neskovic, S Obradovic, B Pavlovic, Z Perisic, A Ristic, N Stokuca Korac.

Slovakia (150 patients): V Bugan, T Duris, A Dzupina, S Filipova, M Hranai, E Hrbata, V Macek, I Nedelova, D Pella, J Stuchlikova, J Strbova.

Spain (275 patients): JM Alegret Colome, JJ Alonso Martin, P Avanzas Fernandez, JL Blanco Coronado, J Bruguera Cortada, JM Cruz Fernández, R Dalmau Gonzalez-Gallarza, AJ Fernández Romero, S Gomez Moreno, JR Gonzalez Juanatey, R Hidalgo Urbano, E Lopez De Sa Areses, V Lopez Garcia Aranda, C Macaya De Miguel, JJ Munoz Lopez, DA Pascual Figal, A Perez De Prado, J Punti Sala, VM Rodriguez Blanco, P Talavera Calle, M Vida Gutierrez, F Worner Diz, JL Zamorano Gomez.

Turkey (110 patients): A Arat, M Kanadasi, B Mutlu, M Sahin, D Ural, E Yeter.

Ukraine (454 patients): K Amosova, G Dzyak, A Faynyk, S Furkalo, I Karpenko, I Kovalskyi, I Kraiz, M Kushnir, Y Kyyak, O Parkhomenko, M Rishko, A Rudenko, L Rudenko, I Rudyk, D Sebov, Y Sokolov, S Sushkov, I Vakaliuk, A Vasilyeva, O Yepanchintseva, S Zhurba .

Vietnam (69 patients): QH Do, MH Pham, NV Pham, TN Vo, QN Vu.

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