A randomized, double-blind, placebo-controlled trial to assess the efficAcy and safety of Trimetazidine in patients with angina pectoris having been treated by percutaneous coronary intervention (ATPCI study): Rationale, design, and baseline characteristics

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Background About 30% of angina patients have persisting symptoms despite successful revascularization and antianginal therapy. Moreover, in stable patients, percutaneous coronary intervention (PCI) does not improve survival as compared with medical therapy alone. Trimetazidine, an antianginal agent devoid of hemodynamic effect, may help reducing symptoms and improving outcomes after PCI. The ATPCI study is investigating the efficacy and safety of adding trimetazidine to standard-of-care in angina patients who had a recent PCI.

Methods ATPCI is a randomized, double-blind, parallel-group, placebo-controlled, event-driven study in patients with coronary artery disease having undergone PCI because of stable angina (elective PCI) or unstable angina/NSTEMI (urgent PCI). After PCI, patients were randomized to trimetazidine (35 mg bid) or placebo on top of standard-of-care including event prevention drugs and antianginal treatment. Patients will be followed for 2 to 4 years. The primary efficacy endpoint is a composite of cardiac death, hospitalization for a cardiac event and recurrence or persistence of angina. Safety events related to trimetazidine use will be monitored.

Results Recruitment lasted from September 2014 to June 2016. A total of 6007 patients were enrolled (58% and 42% after elective and urgent PCI, respectively). Mean age was 61 years, 77% were males, and median durations of coronary artery disease were 1 and 5 months (if urgent or elective PCI, respectively). Almost all patients received drugs for event prevention and antianginal therapy at baseline.

Conclusion The ATPCI study will shed further light on the management of contemporary angina patients after PCI. Results are expected in 2019. (Am Heart J 2019;210:98-107.)

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The goals of management of angina are 2-fold, namely symptoms relief and improvement of prognosis.[1] Medical therapy has been used for many years to achieve these aims, mainly using antianginal drugs such as β-blockers and calcium channel blockers for the reduction of symptoms, and antiplatelet and lipid-lowering agents to improve outcome. Lately, the introduction and refinement of coronary angioplasty techniques have profoundly modified the management of angina. In addition to medical treatment, percutaneous coronary intervention (PCI) is largely used to alleviate symptoms in stable patients, and to improve prognosis in patients with acute coronary syndromes.[2,3] However, in a number of patients, angina may reoccur despite successful revascularization and evidence-based medical therapy.[4] Moreover, recent trials and meta-analyses have shown controversial results on the prognosis benefit of PCI over optimal medical therapy in stable patients.[5-7] Consequently, there is an unmet need for additional strategies to alleviate symptoms and improve outcomes in angina patients after revascularization.

The metabolic agent trimetazidine, a drug which acts directly at the level of myocardial cells, is devoid of hemodynamic effect and is effective in reducing angina symptoms.[8] Trimetazidine shifts cardiac metabolism from β oxidation of free fatty acids to glucose oxidation, which provides more efficient utilization of oxygen in ischemic conditions. The aim of the ongoing "efficAcy and safety of Trimetazidine in Patients with angina pectoris having been treated by percutaneous Coronary Intervention (ATPCI) study" is to investigate the long-term efficacy and safety of adding trimetazidine to evidence-based therapy in angina patients who had a recent PCI. Here, we present the rationale and design of the ATPCI study, and describe the characteristics of the population at baseline.

Rationale

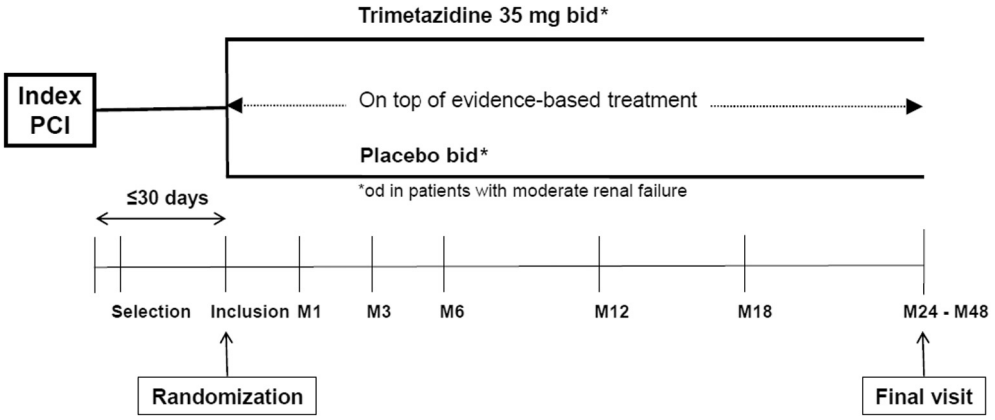
While the benefits of PCI have been demonstrated in acute coronary syndrome, its impact on the prognosis in chronic stable angina patients remains unclear.[9] Results from the landmark Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial showed that PCI does not further reduce mortality or myocardial infarction in stable angina patients as compared with medical therapy alone.[10,11] Similar findings were reported in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) study in which patients with coronary artery disease and type 2 diabetes receiving medical therapy showed similar survival irrespective of revascularization.[12] However, a non-negligible proportion of patients in the medical treatment arm required PCI during follow-up, which is a limitation of those studies. The absence of superiority of PCI over medical therapy in terms of prognosis was, nevertheless, confirmed by a meta-analysis including 7182 stable coronary artery disease patients.[6] In addition, a recent meta-analysis of 5 large studies comparing the 2 strategies in stable angina patients found no superiority of PCI in terms of prognosis over a 5-year period of time.[7]

PCI has been shown to provide angina relief, but despite this improvement, a significant proportion of patients remain symptomatic after the procedure. In the COURAGE trial, 34% of patients reported angina within the first year after PCI.[10] Similar observations can be made in contemporary real-world cohorts. In a retrospective cohort including 8804 patients who underwent PCI, the proportion of symptomatic patients within the first year was 32%.[13] In another cohort of 51,710 patients, this proportion reached 40% three years after PCI.[14] In addition, it seems that the rapid evolution of stenting techniques has substantially reduced the risk of restenosis and reintervention, but did not eliminate the problem of recurrent angina after PCI. In the DUTCH PEERS trial with the last generation drug-eluting stents, 20% of patients were still experiencing chest pain at 1 year and 2 years after PCI.[15]

The causes for recurrent angina after PCI are diverse and include incomplete revascularization, restenosis, and progression of disease in other vessels.[1,16] In addition, myocardial ischemia is a multi-faceted pathology not exclusively related to macrovascular coronary lesions. Inflammation, spasm, and coronary microvascular dysfunction are also important factors contributing to the recurrence of angina despite successful PCI, independently from concomitant obstructive coronary artery disease.[17-20] The treatment of angina after PCI is based on conventional antianginal drugs, typically β-blockers, calcium channel blockers, and long-acting nitrates. These drugs increase coronary flow and/or reduce myocardial oxygen demand through vasodilation and/or decrease in heart rate and myocardial contractility. However, it is not known whether they are effective in other causes of angina such as coronary microvascular dysfunction.[21]

Trimetazidine is devoid of such hemodynamic effects, and acts by modulating cardiac metabolism at the cellular level. Trimetazidine inhibits β oxidation of free fatty acids and indirectly stimulates the activity of pyruvate dehydrogenase, thus directing pyruvate into the mitochondria, avoiding lactic acid formation and preventing intracellular acidosis. By correcting the uncoupling between glycolysis and glucose oxidation, trimetazidine action results in an optimized aerobic and anaerobic energy production during ischemia.[22] A network meta-analysis suggested that trimetazidine is as efficient as other antianginal agents.[23] Moreover, thanks to its complementary mode of action, trimetazidine has been shown to reduce angina symptoms when used in patients uncontrolled by conventional hemodynamic agents.[24] The efficacy of trimetazidine was recently confirmed by EMA which concluded to a positive benefit–risk ratio in patients with angina pectoris.[25]

Figure



Design of ATPCI study.

Several lines of evidence support a possible beneficial effect of trimetazidine in angina patients after PCI. A post-hoc analysis of the TRIMetazidine in POLand (TRIMPOL II) study reports a reduction of angina by trimetazidine in patients experiencing recurrent angina after coronary revascularization despite being treated by metoprolol.[26] In a single-center randomized trial of 700 elderly diabetic patients with multivessel coronary heart disease who underwent drug-eluting stent implantation, treatment with trimetazidine for 2 years after PCI on top of conventional treatment significantly reduced the incidence of angina (28.2% versus 37.6%) and silent ischemia (34.5% versus 45.9%) compared with placebo.[27]

Trimetazidine has not been evaluated in large long-term outcome studies in coronary artery disease patients.[1] Some data indicate that it may improve prognosis in angina patients after myocardial infarction (MI).[28] Other studies suggest that trimetazidine may improve left ventricular function in coronary artery disease patients with reduced ejection fraction.[29]

The ATPCI study will test the hypothesis that chronic treatment with trimetazidine added to guideline-recommended therapy—including drugs for the secondary prevention of coronary artery disease events—is superior to recommended therapy plus placebo in a large population of ischemic patients whose symptoms led to PCI. Patients with stable angina or unstable angina/non-ST elevation myocardial infarction (NSTEMI) leading to PCI were enrolled. Patients with ST elevation myocardial infarction (STEMI) leading to PCI, who have a different pathophysiological and clinical profile, were not enrolled. The efficacy of trimetazidine will be evaluated in terms of symptom reduction and improvement of prognosis, which are the major goals of treatment as outlined by the guidelines.[1] Quality of life is significantly impacted in angina, and its improvement is also an important goal of treatment.[30] Therefore, the ATPCI study will also include the evaluation of patient-reported outcomes in addition to clinical endpoints.

Further to the benefit–risk re-evaluation by EMA in 2012, the assessment of the long-term safety of trimetazidine will also constitute one of the objectives of the trial. To this end, adverse events of interest related to trimetazidine use, including Parkinsonian-related symptoms, will be documented during the ATPCI study, allowing evaluation of the long-term safety of trimetazidine versus placebo in a rigorous setting.

Methods

Study design

The ATPCI trial is an international, multicenter, double-blind, placebo-controlled, event-driven study in angina patients who have undergone recent PCI. Patients are randomized in two parallel groups (trimetazidine 35 mg bid or placebo) on top of guideline-recommended treatment including secondary prevention and antianginal therapy, if required. The design of the study is summarized in Figure. The selection visit has to be performed as soon as possible after successful PCI (index PCI), during the hospitalization or shortly after discharge. The inclusion visit has to be performed as soon as the patient's antianginal treatment (if any) is stabilized, and no later than 30 days after the index PCI. Upon verification of eligibility criteria, patients are randomized to trimetazidine modified-release 35 mg twice daily (dose reduced to once daily for patients with moderate renal failure) or matching placebo. Five to nine visits are to take place during the study (at 1, 3, and 6 months after randomization, and every 6 months afterwards). In addition, a final examination is to take place at the end of the follow-up period, 2 to 4 years after randomization. The following parameters are to be recorded at each follow-up visit: occurrence of prespecified efficacy

Table I. Main inclusion/exclusion criteria of the ATPCI study

Inclusion criteria
Men or women ≥21 years and< 85 years
Evidence of single or multivessel coronary artery disease
Had undergone successful PCI as planned by the operator, and indicated because of angina pectoris in a context of:
- stable angina (elective PCI);
- or acute presentation for unstable angina or NSTEMI (urgent PCI)
With no further revascularization planned
Stable antianginal treatment (if applicable)
Informed consent obtained
Exclusion criteria
Index PCI carried out in the absence of prior chest pain
Index PCI carried out as part of the management of STEMI or within 4 weeks after a STEMI
Procedure-related Q-wave MI or procedural acute myocardial injury
Further revascularization planned during the study
Severe heart failure (NYHA class IV), severe valve disease, severe uncontrolled rhythm disturbance, uncontrolled arterial hypertension, or severe renal failure
Acute MI, repeat revascularization, or hospitalization/prolonged hospitalization due to a cardiovascular event between the index PCI and inclusion
Current or previous movement disorders such as Parkinsonian symptoms, restless leg syndrome, tremors, and gait instability of central origin
Ongoing treatment with trimetazidine, or known hypersensitivity to trimetazidine
Ongoing treatment with perhexiline or ranolazine

MI: myocardial infarction; *NYHA*: New York Heart Association; *PCI*: percutaneous coronary intervention; *STEMI*: ST-segment elevation myocardial infarction.

events (as defined in Appendix C), adverse events including safety events of interest related to trimetazidine use (as defined in Appendix D), Canadian Cardiovascular Society (CCS) classification of angina, number of angina episodes and number of short-acting nitrates taken per week during the 4 weeks preceding the visit, vital signs (heart rate and blood pressure), weight, laboratory examination, and electrocardiogram. In addition, patient-reported outcomes are to be collected by means of the Seattle Angina Questionnaire (in countries where a validated translation is available) and the EQ-5D-3 L questionnaire at all visits up to 1 year of follow-up.

Five supervisory committees have been set up for the study. The Executive Committee is responsible for the development of the study protocol and its amendments in collaboration with the sponsor, and supervises the study progress. The Steering Committee is the representative body of the study investigators. The Cardiovascular Endpoints Adjudication Committee and Safety Endpoints Adjudication Committee are responsible for adjudicating prespecified efficacy events and safety events of interest, respectively, in an independent and blinded manner. Definitions of the endpoints used by the adjudicators are provided in Appendix C and D. The Data Monitoring Committee is responsible for ensuring the safety of participants by reviewing unblinded safety data during the study. It may recommend the early termination of the trial in case of safety concerns. The composition of the five committees is detailed in Appendix A.

The study is ongoing in 365 centers in 27 countries worldwide. The study is performed according to the Declaration of Helsinki (1964 and revisions), and approval from ethic committees has been obtained in all countries. The ATPCI study is registered on www.clinicaltrialsregister.eu (EudraCT Number: 2010–022134-89).

Inclusion and exclusion criteria

The main inclusion and exclusion criteria are listed in Table I. Enrolled participants were between 21 and 85 years old, with documented single or multivessel coronary artery disease, and had undergone a successful PCI indicated because of angina pectoris, occurring either in the context of stable angina (elective PCI), or in the context of an acute presentation such as unstable angina/NSTEMI (urgent PCI). The index PCI had to be completed as initially planned by the operator, with no complications or further planned revascularization. Because they have a different profile requiring a specific management, patients who underwent a PCI due to STEMI were not eligible for the study. Patients could be selected regardless of the presence or absence of angina symptoms after the index PCI. All participants had to give written informed consent to participate in the study.

Background therapy

The study drug (trimetazidine or placebo) is to be administered in addition to routine post-PCI treatment which includes secondary prevention therapy recommended by current guidelines. In addition, the investigator can decide to prescribe background antianginal therapy according to normal practice, local guidelines, and the patient's clinical condition. All antianginal drugs can be used during the study, with the exception of perhexiline, ranolazine, and open-label trimetazidine. Following the index PCI and before inclusion, the initial background antianginal therapy may be withdrawn or

Table II. Primary and secondary endpoints for efficacy and safety

Efficacy

Primary endpoint (time-to-first event)§
- Occurrence of an event in the composite of:
  - cardiac death,
  - hospitalization for a cardiac event*,
  - recurrent or persistent angina† leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies,
  - recurrent or persistent angina† leading to performing a coronary angiography.

Secondary endpoints (time-to-first event)§
- Occurrence of an event in the composite of:
  - cardiac death,
  - hospitalization for a cardiac event*,
  - recurrent or persistent angina† leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies,
  - recurrent or persistent angina† leading to performing a coronary angiography,
  - evidence of ischemia (documented by stress imaging) leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies,
  - evidence of ischemia (documented by stress imaging) leading to performing a coronary angiography.
- Occurrence of an event, either taken individually or as a composite, among the components of the primary and secondary composite endpoints, hospitalization for MI, hospitalization for non-fatal MI, hospitalization for ischemic chest pain, hospitalization for heart failure, any coronary revascularization, and repeat coronary revascularization in response to angina†.
- All-cause mortality

Safety

Primary endpoint
- Incidence of serious emergent adverse events

Secondary endpoints
- Emergent adverse events, including clinically significant abnormalities observed from the electrocardiographic recordings and from laboratory examinations;
- Events of interest‡: neurological symptoms (including Parkinson's syndrome, disorientation, hallucination, and convulsion), coagulation disorders including non-traumatic hemorrhages, thrombocytopenia, agranulocytosis, falls, arterial hypotension, serious skin disorders, and hepatic disorders;
- Blood pressure and heart rate;
- Weight;
- Biochemical and hematological parameters.

MI, myocardial infarction.
*Cardiac event is defined as one of the following: resuscitated cardiac arrest, acute coronary syndrome (unstable angina, STEMI or NSTEMI), heart failure, coronary revascularization, sustained ventricular tachycardia.
† Angina pectoris is defined as an exertional or resting chest discomfort of characteristic quality and duration.
§ As adjudicated by the Cardiovascular Endpoints Adjudication Committee.
‡ As adjudicated by the Safety Endpoints Adjudication Committee.

modified at the discretion of the investigator. In patients prescribed antianginal therapy, the treatment should be stable at the time of inclusion (ie, not modified in terms of doses or drugs). Any intensification of the background antianginal therapy after inclusion (ie, addition, switch, or increase of the dose of antianginal drugs excluding short-acting nitrates) should be clinically justified, and the reasons of change should be fully documented in the patient's record.

Efficacy/safety endpoints

The primary and secondary efficacy and safety endpoints are detailed in Table II. Other efficacy endpoints include CCS class of angina symptoms, number of angina episodes and of short acting nitrates taken per week, and Seattle Angina Questionnaire and EQ-5D-3 L questionnaires scores. The primary and secondary efficacy endpoints will be analyzed on the intent-to-treat basis and a time-to-first event analysis will be used. The primary objective of the study is to demonstrate the superiority of trimetazidine over placebo in reducing the primary composite endpoint (namely cardiac death, hospitalization for a cardiac event and recurrent or persistent angina leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapy or to performing a coronary angiography), and to document the safety of trimetazidine in terms of serious adverse events. During the study, all relevant information regarding prespecified events is to be collected for blinded and independent adjudication by the Cardiovascular Endpoints Adjudication Committee and the Safety Endpoints Adjudication Committee, respectively.

Sample size determination

Assuming an annual incidence rate of the primary efficacy endpoint of 10% in the placebo group, a treatment effect of trimetazidine of 15% relative risk reduction, leading to an expected global annual incidence rate for the primary efficacy endpoint of 9.28%, and considering a 5% type I error rate and a power of

Table III. Baseline characteristics of ATPCI patients

	All patients N = 6007	
	N observed	Mean ± SD or n (%)*
Demography		
Age (years)	6007	60.9 ± 9.7
Male	6007	4624 (77)
Ethnic origin	6007	
Caucasian		5124 (85)
Asian		483 (8)
Other		400 (7)
Vital signs		
Body mass index (kg/m^2)	6001	28.6 ± 4.3
Systolic blood pressure (mmHg)	6004	128 ± 14
Diastolic blood pressure (mmHg)	6004	76 ± 9
Resting heart rate (bpm)	5999	66.4 ± 9.6
Risk factors		
History of hypertension	6007	4965 (83)
History of diabetes mellitus	6007	1668 (28)
Diabetes treated with insulin	6007	468 (8)
History of dyslipidemia	6007	3895 (65)
Smoker (current and former)	6007	3586 (60)
Medical history		
Previous myocardial infarction	6007	2875 (48)
Previous coronary revascularization†	6007	2020 (34)
Peripheral artery disease	6007	414 (7)
Stroke	6007	236 (4)
Characteristics of coronary artery disease		
Duration (months)	6007	
Mean ± SD		33.6 ± 61.3
Median (Q1-Q3)		
Patients with urgent index PCI		1 (0–28)
Patients with elective index PCI		5 (1–45)
CCS class‡	6005	
I		432 (7)
II		2391 (40)
III + IV		3182 (53)
Left ventricular ejection fraction (%)	5175	57.8 ± 8.8
Coronary profile§	6002	
1-vessel disease		3306 (55)
2-vessel disease		1870 (31)
3-vessel disease		826 (14)
Nature of index PCI	6007	
Elective		3490 (58)
Urgent		2517 (42)
Concomitant treatment at inclusion	6007	
β-Blockers		5074 (84)
Dihydropyridine calcium-channel blockers		1539 (26)
Diltiazem or verapamil		132 (2)
Long-acting nitrates		739 (12)
Other anti-anginal therapies		267 (4)
Anti-platelets agents		5996 (100)
Aspirin		5927 (99)
Clopidogrel		4839 (81)
Ticagrelor		990 (16)
Anti-coagulants		331 (6)
Lipid-lowering agents		5870 (98)
Statins		5850 (97)
Angiotensin-converting enzyme inhibitors		3698 (62)

(continued on next page)

Table III (*continued*)

	All patients N = 6007	
	N observed	Mean ± SD or n (%)*
Angiotensin receptor blockers		1307 (22)
Diuretics (excluding aldosterone)		1465 (24)
Aldosterone antagonists		382 (6)

CCS, Canadian Cardiovascular Society; *PCI*, percutaneous coronary intervention.
* Unless stated otherwise.
† Before index PCI.
‡ Worst class within 4 weeks before index PCI.
§ Last coronary angiography before index PCI (patients with stenosis ≥50%).

85%, 1363 first events are necessary. With an expected mean follow-up duration of 3 years and an annual study withdrawal rate of 2% in all groups, 5800 patients are required.

The duration of follow-up (2 to 4 years) may be prolonged in order to achieve the planned number of events.

Description of the randomization process

Patients were allocated to trimetazidine or placebo at the inclusion visit through an interactive web response system using a centralized, balanced, non-adaptive permuted-block randomization process. The randomization was stratified by both country and type of index PCI (elective or urgent).

Statistical methods

Baseline characteristics are summarized as mean (standard deviation) or median for continuous variables and count (percentage) for categorical variables.

The superiority of trimetazidine versus placebo will be tested on the primary adjudicated 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). The type I error rate will be set at 5% (2 sided) for all statistical tests, and estimates of hazard ratios with associated 95% confidence interval will be provided. The treatment effect will be estimated within the subgroups (nature of index PCI). Similar analyses will be performed for secondary efficacy endpoints. For other efficacy endpoints, descriptive statistics will be provided by treatment group at each visit and on the change from baseline. Changes from baseline will be compared between treatment groups using 95% confidence intervals and superiority tests.

Safety analysis will be carried out on all patients who have taken at least one dose of study drug. Global and annual incidence of serious emergent adverse events will be provided for each treatment group. Descriptive statistics will be provided by treatment group for emergent adverse events, vital signs, weight, and laboratory parameters.

During the study, the safety will be reviewed periodically by the Data Monitoring Committee.

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Baseline characteristics

The recruitment of ATPCI study took place between September 17, 2014 and June 15, 2016. The baseline characteristics of the 6007 randomized and included patients are presented in Table III. Mean age of the population is 60.9 ± 9.7 years, and three quarters (77%) are male. The median duration of coronary artery disease at inclusion is 1 month for patients enrolled following an urgent PCI and 5 months for patients enrolled following an elective PCI. Nearly all patients (93%) had a CCS class II to IV in the month preceding the index PCI. More than half of the patients (55%) had a one-vessel disease. Almost half of patients (48%) had a previous myocardial infarction, and one-third (34%) had a previous coronary revascularization before the index PCI. The great majority of patients (83%) had a history of hypertension. Regarding other risk factors, 65% had a history of dyslipidemia, and 60% were either current or past smokers. Diabetes mellitus was present in 28% of patients. The majority of patients (86%) with available measurement of ejection fraction did not show evidence of left ventricular dysfunction (mean left ventricular ejection fraction 57.8 ± 8.8%). A slightly higher proportion of patients (58%) were included following an elective PCI than following an urgent PCI (42%). With regards to antianginal background therapy after index PCI, the majority of patients (84%) were prescribed a β-blocker, and a quarter (28%) calcium channel blockers. Nearly all patients were receiving anti-platelet and lipid-lowering therapy, consisting mostly of aspirin/P2Y12 inhibitor and a statin. Most patients were prescribed a renin-angiotensin-aldosterone system blocker, mostly angiotensin-converting enzyme inhibitor (62%).

Discussion

The ATPCI study enrolled a large population of single (55%) or multivessel (45%) coronary artery disease

patients having been treated by PCI for angina pectoris (in a context of stable or unstable angina/NSTEMI). Most of the patients had been recently diagnosed (median coronary artery disease duration 1 month if urgent index PCI and 5 months if elective index PCI). The prevalence of risk factors and concomitant diseases is in line with what was expected for this type of population, in particular for hypertension (83%), diabetes (28%), dyslipidemia (65%) and history of myocardial infarction (48%). There was no evidence of left ventricular dysfunction. A slightly greater proportion of patients were enrolled following an elective PCI (58%), versus 42% of patients enrolled following unstable angina or NSTEMI. The treatment of patients at baseline was consistent with the current recommendations for event prevention therapy in coronary artery disease patients.[1] Almost all patients were prescribed antianginal therapy, particularly a β-blocker (84%). The characteristics of the ATPCI study population are broadly similar to those of recent interventional trials[31-34] or registries[35,36] of angina patients undergoing elective or urgent PCI, even if our patients were slightly younger.

The ATPCI study will assess if trimetazidine is a useful strategy in the post-PCI setting.

The ATPCI study will give important information on the outcome and management of patients with stable or unstable/NSTEMI who have undergone successful revascularization with PCI. We will assess whether long-term trimetazidine treatment can improve the prognosis of angina patients. This is particularly relevant in view of the paucity of data or disappointing outcome trials with other antianginal drugs in this population. Indeed, despite their established use for controlling symptoms, no antianginal drugs have demonstrated a clear improvement of clinical events in angina patients. Contemporary studies evaluating the effect of β-blockers on outcomes in angina patients are lacking, and results from recent prospective registries suggest they may not reduce cardiovascular events in stable coronary artery disease patients or in the long-term following acute myocardial infarction.[37-39] The calcium channel blocker amlodipine reduced the rate of repeat coronary revascularizations and hospitalizations for angina in coronary artery disease patients, while nifedipine, in a population of stable angina patients, did not have any effect on mortality or MI incidence.[40,41] Recent randomized trials with new antianginal drugs also proved to be disappointing.[42,43] In particular, the RIVER-PCI trial failed to demonstrate the superiority of ranolazine over placebo in improving the prognosis of patients with chronic angina and incomplete revascularization after PCI.[43]

The ATPCI study will also evaluate the effect of trimetazidine on the recurrence and persistence of symptoms leading to the intensification of background angina therapy or to repeat coronary angiography. We hypothesize that the complementary mode of action of trimetazidine, which acts through a metabolic effect at the cellular level, will provide additional angina relief independently from the underlying physiopathology. This is particularly relevant for the patients enrolled in the ATPCI study as coronary obstruction may no longer be the major driver of symptoms, as these patients have been revascularized by PCI. Interestingly, a majority of patients (83%) presented a history of hypertension at baseline, known to be associated with microvascular dysfunction, which may lead to microvascular angina.[44] Angina symptoms caused by microvascular dysfunction are indistinguishable from those caused by epicardial coronary narrowing. However, despite a similar clinical picture, conventional agents have only limited efficacy in microvascular angina, and treatment remains mostly empirical. By acting directly at the cellular level, trimetazidine may prove beneficial in this particular condition, and may help in reducing the occurrence of symptoms after PCI.

In addition to testing the effect of trimetazidine, the ATPCI study will also provide an up-to-date picture of the rate of clinical events up to 2 to 4 years after PCI, in a large population of angina patients with both stable and acute presentation at inclusion, receiving evidence-based therapy. The enrolment phase is now completed, and results are expected in 2019.

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Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2018.12.015.

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