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Trial Design

# Rationale and design of the Statins Evaluation in Coronary procedUres and REvascularization: The SECURE-PCI Trial

Otavio Berwanger, MD, PhD *, Pedro G.M. de Barros e Silva, MD, MHS, PhD, Frederico Toledo Campo Dall Orto, MD, Pedro Beraldo de Andrade, MD, Igor Ribeiro de Castro Bienert, MD, Carlos Eduardo Bosso, MD, José Mangione, MD, Carisi Anne Polanczyk, MD, Amanda Sousa, MD, Renato Kalil, MD, Luciano de Moura Santos, MD, Andrei C. Sposito, MD, PhD, Rafael L. Rech, MD, MSc, PhD, Antonio Carlos Sobral Sousa, MD, PhD, Felipe Baldissera, MD, Bruno Ramos Nascimento, MD, MSc, PhD, Isabella de Andrade Jesuíno, BPharm, Eliana Vieira Santucci, BPTh, Lucas Petri Damiani, MSc, Ligia N. Laranjeira, RT, Juliana A. Borges de Oliveira, RN, Roberto R. Giraldez, MD, PhD, Alexandre Biasi Cavalcanti, MD, PhD, Sabrina Bernardez Pereira, MD, PhD, Luiz Alberto Mattos, MD, PhD, Luciana Vidal Armaganijan, MD, MHS, PhD, Hélio Penna Guimarães, MD, MSc, PhD, José Eduardo Sousa, MD, PhD, John H. Alexander, MD, MHS, Christopher B. Granger, MD, Renato D. Lopes, MD, MHS, PhD

*Research Institute–Heart Hospital (HCor), Rua Abílio Soares 250, 12th floor, 04005-000, São Paulo, SP, Brazil*

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ABSTRACT

*Background:* Previous evidence suggests that acute treatment with statins reduce atherosclerotic complications, including periprocedural myocardial infarction, but currently, there are no large, adequately powered studies to define the effects of early, high-dose statins in patients with acute coronary syndrome (ACS) and planned invasive management.

*Objectives:* The main goal of Statins Evaluation in Coronary procedUres and REvascularization (SECURE-PCI) Trial is to determine whether the early use of a loading dose of 80 mg of atorvastatin before an intended percutaneous coronary intervention followed by an additional dose of 80 mg 24 hours after the procedure will be able to reduce the rates of major cardiovascular events at 30 days in patients with an ACS.

*Design:* The SECURE-PCI study is a pragmatic, multicenter, double-blind, placebo-controlled randomized trial planned to enroll around 4,200 patients in 58 different sites in Brazil. The primary outcome is the rate of *major cardiovascular events* at 30 days defined as a composite of all-cause mortality, nonfatal acute myocardial infarction, nonfatal stroke, and coronary revascularization.

*Summary:* The SECURE PCI is a large randomized trial testing a strategy of early, high-dose statin in patients with ACS and will provide important information about the acute treatment of this patient population.



Ischemic heart disease represents the leading cause of death and disability worldwide.[1,2] The acute life-threatening manifestation of ischemic heart disease is acute coronary syndrome (ACS). There are several therapies known to be beneficial for patients with ACS, including percutaneous coronary intervention (PCI).[3,4] However, PCI has been associated with a cumulative incidence of periprocedural myocardial infarction (MI) ranging from less than 1% to greater than 10%.[5-13]

The relevance of preventing periprocedural MI lies on the fact that observational studies have shown an independent association between periprocedural MI and subsequent mortality (both total and cardiovascular).[5-7] The pathogenesis of periprocedural MI is probably related to inflammatory mechanisms and to the extent of vessel disruption and damage caused by the procedure.[5-13]

Statins are a well-known group of drugs that reduce the risk of major cardiovascular events (MACE) in both primary and secondary prevention.[3,4] At the long term, the beneficial effects of statins are

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* Reprint requests: Dr. Otavio Berwanger, MD, PhD, Research Institute–Heart Hospital (HCor), Rua Abílio Soares 250, 12th floor, 04005-000, São Paulo, SP, Brazil.
*E-mail address:* oberwanger@hcor.com.br (O. Berwanger)

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attributable to low-density lipoprotein (LDL)-cholesterol reduction. Conversely, mechanistic studies suggest that statins also possess effects beyond lipid lowering (pleotropic effects) that could act at the short term. Such effects include the possibility of anti-inflammatory mechanism and direct benefits to endothelial function via regulation of nitric oxide synthesis, stabilizing vulnerable plaques by reducing metalloproteinase activity, and enhancing endothelial progenitor cell production.[14-16] These effects may reduce the risk of early events like periprocedural MI in patients undergoing PCI.

Thus, oral administration of loading doses of statins before and after PCI with stenting may contribute to attenuate the inflammatory cascade by reducing reactivity and promoting the stability of the target lesion. This benefit then extends to other stenosis potentially vulnerable to rupture, stabilizing the atherosclerotic burden and potentially reducing the occurrence of cardiovascular events in the short and long terms.

## Evidence from randomized clinical trials and meta-analysis for the use of statins in the peri-PCI setting

Previous trials[17-20] have shown potential benefit of a loading dose of statin in stable coronary disease and non-ST elevation ACS, including also patients on chronic statin therapy (a summary of the ARMYDA trials in 3 different scenarios is presented in Table I).

Regarding ST-elevation myocardial infarction, there is little evidence about the effect of acute statin treatment in this population. Nevertheless, a study with 171 patients has shown an improvement in coronary flow after angioplasty in patients who had received the high dose of atorvastatin.[21]

These interesting and encouraging results in small studies led to the performance of meta-analyses.[8,9] In 2010,[8] a meta-analysis including 21 randomized controlled trials (RCTs) (total of 4,805 patients) assessed the effects of statins in patients undergoing cardiac and noncardiac procedures. Of these trials, 10 studies assessed patients undergoing PCI (total of 1,406 patients) with variable methodological quality (only 3 trials were RCTs encompassing 354 patients). This meta-analysis suggested a reduced risk of postprocedural MI associated with the use of statins (risk ratio = 0.59, 95% CI: 0.47-0.74), in addition to a nonsignificant reduction in total mortality.[8] In 2011, a collaborative patient-level meta-analysis of 13 randomized studies[9] included 3,341 patients undergoing urgent and elective PCI and showed a 44% risk reduction in the rate of major adverse cardiac events at 30 days related to the use of statin. Considering the early use of high-dose statins in cases of ACS, a total of 1,032 patients were included in previous studies, and the relatively low number of MACEs limited a definitive conclusion regarding the benefit of loading dose of statins on clinical end points for the ACS population. The authors of the meta-analyses concluded that larger studies were necessary to define the potential benefit and its magnitude of early and high dose of statin in patients with ACS.

### *Why do we need a new study?*

Early and high dose of statin has shown promising results with an aggregate 44% relative risk reduction in MACE at 30 days considering pooled data from published studies.[9] On the other hand, the available trials included individually a small number of patients and had different inclusion criteria, methodologies, and schemes of statin therapy, which limit the reliability and applicability of these results in clinical practice. Additionally, these studies suggested that the administration of statins before PCI may have a positive effect on the occurrence of periprocedural MI but did not show statistically significant reductions on other clinically relevant outcomes such as mortality. Finally, most patients included in previous trials were patients with stable coronary disease and not with ACS.

**Table I**
Statin strategy and main results of ARMYDA, ARMYDA ACS, and ARMYDA RECAPTURE

| Study | Procedures | Main results |
|---|---|---|
| ARMYDA-2004 | 153 patients: statin naive with stable angina, positive stress test, and PCI indication. Atorvastatin 40 mg vs placebo 7 d before procedure. | Pretreatment with atorvastatin reduced the occurrence of peri-PCI MI |
| ARMYDA ACS 2007 | 171 patients: non-ST-segment elevation acute coronary syndrome (non-ST ACS), statin naive. Intervention was 80 mg of atorvastatin 12 h preprocedure + 40 mg 2 h preprocedure (all patients received 40 mg/d postprocedure). | Patients that used statin had lower rates of the composite cardiovascular outcome (death, MI, or unplanned revascularization) |
| ARMYDA RECAPTURE 2009 | 383 patients: stable angina or non-ST ACS with previous use of statin comparing 80 mg 12 h pre-PCI + 40 mg pre-PCI vs placebo. | Reduced MACE (cardiac death, MI, or unplanned revascularization) in 30 d in the group treated with statin. |

## Methods

### *Study design*

The Statins Evaluation in Coronary procedUres and REvascularization (SECURE-PCI) trial is an academic-led, randomized, double-blind, pragmatic, multicenter trial designed to provide reliable evidence of the risk-benefit ratio of an early strategy with high-dose statin before and after PCI in patients presenting with ACS. The SECURE-PCI Trial aims to randomize around 4,200 patients with ACS invasively managed, with PCI if appropriate, to receive 80 mg of atorvastatin or placebo before an intended PCI followed by 80 mg or matching placebo 24 hours after the procedure with both arms receiving a maintenance dose of atorvastatin 40 mg qd for 30 days.

### *Primary objective*

The primary objective was to determine in patients with ACS and planned invasive management whether the early administration of a high dose of 80 mg of atorvastatin before an intended PCI, followed by an additional dose of 80 mg 24 hours after the procedure, will be able to reduce the rates of MACE. The primary outcome is a composite of all-cause mortality, nonfatal MI, nonfatal stroke, or coronary revascularization at 30 days after the index ACS event.

### *Secondary objectives*

The secondary objectives were to assess the treatment effect of 80 mg atorvastatin before and after PCI on the rates of the composite outcome (all-cause mortality, nonfatal MI, nonfatal stroke, or coronary revascularization) at 6 and 12 months and also on the occurrence of the individual components of MACE and the following clinical outcomes at 30 days, 6 months, and 12 months: cardiovascular death, stent thrombosis, and target vessel revascularization. Landmark analysis will be performed to assess treatment effect at different time points.

### *Safety outcomes*

The occurrence of other safety outcomes will be evaluated at 30 days, such as elevation of aspartate aminotransferase and alanine aminotransferase, and myopathy (assessed by creatine phosphokinase blood dosages). Beyond laboratory results, the following safety outcomes will also be systematically evaluated: bleeding and rhabdomyolysis at 7 days or hospital discharge.

*Inclusion criteria*

Patients of either sex, aged ≥18 years, who have given written informed consent and with ACS with planned invasive management within 7 days from the onset of the ACS (including those with ST-segment elevation MI treated with primary PCI) will be eligible to SECURE-PCI (all the inclusion criteria are described in Table II).

*Exclusion criteria*

Previous use of statins (for any period prior to inclusion in this study) will not be considered an exclusion criterion for the SECURE-PCI Trial (Table II). However, for safety reasons, patients should not have received a maximum dose of statin in the 24 hours before the loading dose to be eligible for the study. Maximum dosage will be considered as atorvastatin 80 mg, rosuvastatin 40 mg, simvastatin 80 mg, pravastatin 40 mg, and fluvastatin 80 mg. Differences in the treatment effects between these 2 groups of patients (naive or not) will be assessed using prespecified subgroup analyses.

*Randomization, allocation concealment, and blinding*

The randomization list will be generated using a validated online software (available at the Clinical Trial System, Sistema de Estudos Clínicos, IEP, HCor, São Paulo–SP, Brazil) and blocks of variable sizes. Randomization will be stratified by center and by type of ACS (ST elevation or non–ST elevation), considering ACS with ST elevation only those patients intending primary PCI. The investigators will access the SECURE-PCI Trial Web site and fill in a simple medical record form to enroll and randomize patients. Our Clinical Trial System (https://servicos.hcor.com.br/iep/estudoclinico) is a central randomization system that ensures allocation concealment. In the SECURE-PCI Trial, patients, investigators, outcome reviewers, and the statistician in charge of data analysis will be blinded for treatment allocation throughout the study period.

*Study procedures*

*Patient recruitment*

Approximately 60 centers will participate in the study. Patients will be enrolled at emergency hospitals and PCI-capable cardiovascular centers.

*Data entry system*

Data will be managed using an Electronic Data Capture system. Case report forms (CRFs) data will be transferred to an electronic record and sent to the Coordinating Center in a validation database. CRFs will be entirely filled and sent online; they also will be signed electronically, and for access, a personal, nontransferable password is used.

*Intervention*

After providing a written informed consent, patients will be allocated at a 1:1 ratio to receive either 80 mg of atorvastatin or matching placebo before and after the intended PCI (Figure). Randomization will be conducted electronically. Once patient data are entered into the system, an identification number will be assigned to that patient; the corresponding treatment kit will already be available at the institution and will be given to the patient (the contents of each unidentified kit will be either atorvastatin or placebo).

For patients with ACS without ST elevation, the pre-PCI dose will be administered between 2 and 12 hours before the procedure. Facilities that perform ad hoc PCI should give the study drug 2 to 12 hours before the coronary procedure. For patients with ACS with ST elevation, the loading dose will be administered as soon as possible before the primary PCI. According to the protocol procedures, the patient will receive a second loading dose of 80 mg atorvastatin or matching placebo 24 hours after the procedure.

**Table II**
Eligibility criteria for SECURE-PCI Trial

| |
|---|
| Inclusion criteria: |
| 1. Age equal or above 18 y |
| 2. Signed informed consent |
| 3. Diagnosis of ACS* intended to be treated with PCI during the same hospitalization and within 7 d |
| Exclusion criteria: |
| 1. Pregnant or breastfeeding women |
| 2. Women aged <45 y not using effective contraceptive methods (regular use of contraceptive pills, IUD, tubal ligation) |
| 3. Previous inclusion in the study |
| 4. Concurrent participation in other RCTs involving the use of hypolipemiant agents |
| 5. Drug hypersensitivity |
| 6. History of advanced liver disease (primary biliary cirrhosis, sclerosing cholangitis, acute hepatitis, persistent elevations of liver transaminases >3 times above the upper limit of normal) |
| 7. Use of any statin at a maximum dose in the last 24 h before the loading dose |
| 8. Use of any fibrate in the last 24 h before the loading dose |

* The diagnosis of ACS for inclusion criteria includes at least 2 of the following: angina-like chest pain or ischemic equivalent chest pain; electrocardiographic abnormalities compatible with angina (ST-segment elevation higher than 2 mm on precordial leads and higher than 1 mm on peripheral leads or new left bundle-branch block, ST-segment depression of at least 0.5 mm or T-wave inversion greater than 0.2 mV) on at least 2 contiguous leads; values above the upper limit reference value for myocardial markers of necrosis (troponin and/or CK-MB).

All patients enrolled in the study (both intervention and control groups) will receive 40 mg of atorvastatin daily after the procedure, starting on the next day after the reloading post-PCI dose was administered until the 30-day follow-up visit. After this period, statin use continues to be recommended, but the agent and dosage are defined by physician's discretion. Beyond the 30-day follow-up visit, a phone call with patients at 6 and 12 months is a part of the protocol procedures to capture the clinical outcomes during the study period.

The CRFs include collection of baseline data, clinical outcomes, cardiac markers, and others serum measurements in all patients included in the trial (Appendix).

*Study co-interventions*

Because of the pragmatic nature of the study, co-interventions will be determined by physician discretion. Nevertheless, early invasive stratification within 48 hours and the use of the agents recommended by evidence-based guidelines will be strongly recommended to all.[3,4]

PCI will be performed according to the clinical practice of each center using either the transfemoral or the transradial access. Stent implantation, as well as stent characteristics, will be defined by the interventional cardiology team in charge of the procedure.

Patients who are randomized but do not undergo PCI will be analyzed according to the intention-to-treat analysis. There are 2 possible situations in this scenario:

1. Patients are randomized and receive the study loading dose, and the PCI is delayed beyond 24 hours: when the PCI is rescheduled, patients will receive another loading dose before the procedure (called *contingence medication*). After PCI, patients will also receive the booster dose after 24 hours from PCI, and the maintenance statin should be started in the next following day according to the protocol.
2. Patients are randomized and receive the study loading dose, and PCI is not performed following the diagnostic coronary angiography, generally because the intervention is not considered clinically indicated based on the coronary anatomy. In this case, patients will receive the second booster of atorvastatin 80 mg according to the investigator decision (recommended by the protocol in the cases that angiography detects coronary artery disease). The site investigator will need to maintain the follow-up until 12 months with the same scheduled visits.

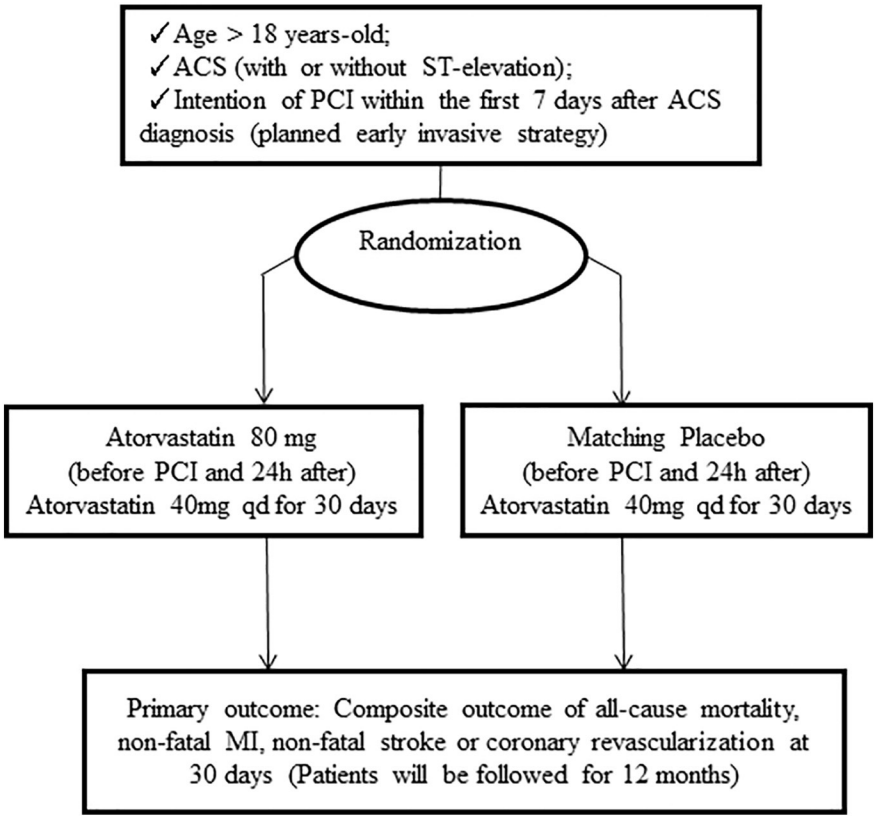


**Figure** SECURE-PCI trial flowchart.

**Table III**
Criteria for periprocedural myocardial infarction

| Baseline cardiac biomarkers | Angiographic evidence; ECG; ischemic symptoms criteria | Post-PCI cardiac biomarkers |
|---|---|---|
| Baseline normal | Not required to qualify MI | CK-MB ≥3× URL or troponin ≥5× URL (if CK-MB not available) |
| Baseline abnormal and decreasing but and no intervening event from elevated sample to PCI reported on eCRF | Not required to qualify MI | Reelevation of CKMB ≥3× ULN or troponin ≥5× ULN (if CK-MB not available) and ≥20% from the NADIR (lowest previous sample prior to the peak) |
| Baseline abnormal and increasing postprocedure or baseline unknown | New ischemic symptoms for at least 20 min and site-reported angiographic procedural complication during PCI or new ischemic ECG changes (per 12-lead ECG tracing) | Continued elevation of CKMB ≥3× ULN and/or troponin ≥5× ULN (if CK-MB not available) |

*Clinical outcomes*

All clinical events included in the primary and secondary outcomes will be reviewed by at least 2 independent members from an independent blinded clinical events classification (CEC) committee. The primary outcome of the SECURE-PCI Trial will be *MACE*, defined as a composite of all-cause mortality, nonfatal MI, nonfatal stroke, or coronary revascularization at 30 days. The secondary outcomes occurring in 12 months and bleeding events will also be adjudicated. All of the definitions were based on criteria used in prior pivotal trials in ACS including the peri-PCI MI definition (Table III).[8-11,17-20] Considering that peri-PCI MI has different definitions, a sensitivity analysis of this outcome according to the universal consensus from 2012[13] and the Society for Cardiovascular Angiography and Interventions[22] criteria will also be performed. The detailed definitions of the primary outcomes of the study protocol are described in the supplementary appendix.

*Statistical analysis plan*

*Sample size calculation*

We used the event rate from the largest available meta-analysis of statin therapy peri-PCI to calculate the sample size.[9] Considering a primary outcome (MACE) rate of 12.3% at 30 days, a relative risk reduction of 25%, a power of 90%, and a 2-tailed alpha of 5%, at least 4,192 patients will be included in the study. The expectation is that around 70% of the patients will undergo PCI, which will assure approximately 80% power for this prespecified analysis.

*Statistical analysis*

To maintain the benefits of randomization, all analyses will follow the intention-to-treat principle. Time until the occurrence of outcomes will be presented using Kaplan-Meier survival curves. The effect of treatment, measured by the hazard ratio, will be obtained using Cox

regression. For all effect parameters, 95% CIs will be reported. All analyses will consider a 2-tailed α of 5% and will be performed on the R statistical software.

Prespecified subgroup analyses include the following: men versus women; age ≥ or <65 years; patients with ACS with or without ST-segment elevation MI; patients with and without previous statin use (>30 days); and diabetic or nondiabetic. We will also compare the outcomes between patients treated with PCI or not and, in the PCI group, patients with drug-eluting stents versus patients with bare metal stents.

*Organizational structure*

The Research Institute HCor of the Heart Hospital of São Paulo (HCor) and the Brazilian Clinical Research Institute (BCRI) are the coordinating centers of this study, being responsible for the study design, operations, conduct, and leadership. Both institutions will be responsible for site management and will provide guidance and support to the participating centers to ensure adherence to the research protocol. Both institutes will be responsible for site monitoring. The BCRI will be responsible for the CEC process during the study. The Research Institute HCor will be responsible for regulatory affairs and data management and will perform the statistical analysis of the study. Beyond key members from BCRI and HCOR, external thought leaders will also be included in the Steering Committee of the trial. The Steering Committee will provide scientific direction and input, address policy issues regarding the protocol, and meet periodically to assess the study progress. A subset of the Steering Committee will constitute the Publications Committee.

*Funding*

The SECURE-PCI trial was designed by Research Institute HCor and BCRI, both academic research institutes based in São Paulo, Brazil, and was funded by the Brazilian Ministry of Health (PROADI-SUS Program). The authors are solely responsible for the design and conduct of this study, all study analyses, and the drafting and editing of the paper.

## Discussion

The use of statins in ACS patients is well established and routinely recommended by evidence-based guidelines.[3,4] These patients should use *high-intensity statin therapy* which is defined as daily dose that lowers LDL-cholesterol by ≥50%.[23] Thus, the current recommendation is the use of atorvastatin 40-80 mg or rosuvastatin 20-40 mg in patients at high risk for cardiovascular events including ACSs.[3,4,23] However, there is still a debate on the benefit of a loading dose in the peri-PCI setting (pre- and postintervention).

In the SECURE-PCI trial, patients with all the types of ACS will be included, and the effect of high-dose statin before and after PCI on major cardiovascular outcomes will be assessed. All the patients, regardless of randomized treatment assignment, will receive atorvastatin 40 mg for at least 30 days, and patients who were treated with nonmaximum dose of statin before enrollment will be included. Thus, all the patients enrolled (control or intervention) will receive high-intensity statin therapy according to the current guideline recomendations.[3,4] The difference between the groups is the use of loading doses before and after PCI.

The potential benefit of the statin intervention in the SECURE-PCI trial will not be directly related to the LDL-cholesterol effect. The long-term benefit of reducing LDL by using statin is well proven and is related to the level of LDL-cholesterol achieved with the therapy. A 1·0-mmol/L reduction in LDL-cholesterol by the use of statin causes a more than 20% reduction in cardiovascular events.[24] This clinical benefit is even higher in a sustained long-term treatment.[24] On the other side, immediate effect of statin therapy and the clinical relevance of the other mechanisms beyond LDL-cholesterol reduction still need confirmation. The pleiotropic effects of statins support the mechanistic plausibility of the approach used in SECURE-PCI. The meta-regression analysis performed in the study by Winchester et al[8] indicated that benefits were observed in patients who received statin both 7 days and hours before the procedure. All previous data reinforce that an early effect of statin has the potential to reduce MACE. More recent meta-analysis published during the enrolment period of SECURE-PCI corroborates with the potential benefit of this strategy in reducing major adverse cardiac events, especially periprocedural MI.[25]

The statin intervention in SECURE-PCI will be performed hours before the PCI. Patients treated with primary PCI for ST-elevation MI will receive the loading dose as soon as possible. In the first ARMYDA trial,[17] patients with stable coronary disease receiving elective PCI initiated statin a week before the procedure. However, in an ACS setting, the timing for statin initiation before PCI is short because current guidelines recommend early invasive strategy.[3,4] Previous studies that tested this strategy in the ACS population[8,9] administered the statin intervention 2 to 12 hours before PCI. In summary, previous data are insufficient to provide reliable evidence about the impact of loading dose of statin on MACE but support the statin regimen that was chosen to be prospectively tested in the SECURE-PCI trial.

Finally, prior studies have suggested that this early effect of statin reduces mainly peri-PCI events, especially type 4a MI. Therefore, the primary outcome in SECURE-PCI will be assessed in 30 days and includes peri-PCI MI that will be systematically evaluated by serial CKMB and troponin pre- (when possible) and after PCI (routinely) with central adjudication. Nevertheless, because some acute interventions may also reflect differences after the acute phase, we will also explore clinical outcomes as secondary objectives after 30 days using landmark analysis. Assuming that around 70% of the patients will undergo PCI, SECURE-PCI will have appropriate statistical power to also evaluate the potential effect of loading dose of statin in this population. Thus, our study will address the uncertainty around loading dose of statin in the overall ACS population and particularly in the subgroup of patients undergoing PCI, who is vulnerable to the occurrence of a periprocedural MI.

## Conclusions

The SECURE-PCI trial will test an early strategy with high-dose statin before and after PCI in patients presenting with ACS, including patients with and without ST-segment elevation and also among naive or previous users of statins. Therefore, SECURE-PCI will include the full spectrum of ACS patients intended to be treated with an invasive strategy and is designed to provide a clear answer about the efficacy of loading doses of atorvastatin pre- and post-PCI in this population.

## Conflict of interests

The authors declare no conflict of interest.

## Organization

*Steering Committee:* Otávio Berwanger (Co-chair), Renato D. Lopes (Co-chair), Pedro Gabriel M. de Barros e Silva, Luiz Alberto Mattos, Alexandre Biasi Cavalcanti, Hélio Penna Guimarães, Amanda G. M. R. Sousa, José Eduardo M. R. Sousa, Roberto Rocha C. V. Giraldez, Christopher B. Granger, John H. Alexander.

*CEC Committee:* Renato D. Lopes (Chair); *CEC reviewers:* Pedro G. M. de Barros e Silva, Luciana Vidal Armaganijan, Thiago Andrade de Macedo, Érique José Farias Peixoto de Miranda, Lucas Colombo Godoy, Marília Harumi Higuchi dos Santos, Marcelo Katz, Adriano Augusto Meirelles Truffa, Roger Oliveira; *CEC staff*: Lilian Mazza Barbosa, Mayara Vioto Valois e Flávia de Mattos Egydio.

*Participating Centers and Site Investigators:* Hospital do Coração de Poços de Caldas: Frederico Toledo Campo Dall Orto; Santa Casa de Marília: Pedro Beraldo de Andrade; Hospital de Clinicas da Faculdade

Estadual de Marilia: Igor Ribeiro De Castro Bienert; Santa Casa/ Instituto do Coração Presidente Prudente: Carlos Eduardo Bosso; Hospital São Francisco: José Mangione; Hospital de Clínicas de Porto Alegre: Carisi Anne Polanczyk, Mariana Furtado; Instituto Dante Pazzanese de Cardiologia: Amanda Sousa; Instituto de Cardiologia (IC FUC): Renato Kalil; Instituto de Cardiologia do Distrito Federal: Luciano De Moura Santos; Hospital de Clinicas da Universidade Estadual de Campinas: Andrei C. Sposito; Hospital de Clínicas Gaspar Vianna: Helder Jose Lima Reis; Hospital Evangélico de Vila Velha: Roberto Ramos Barbosa; Lifecenter: Estevão Lanna Figueiredo; Hospital Regional de Presidente Prudente: Margaret Assad Cavalcante; Instituto de Pesquisa e Estudos Médicos de Itajaí (IPEMI): Felipe Baldissera; Santa Casa de Curitiba: José Ribas Fortes; Hospital das Clinicas FMUSRP: José Antonio Marin-Neto; Hospital Universitário Ulbra / Mãe de Deus Canoas: Rafael L. Rech; São Lucas Médico Hospitalar: Antonio Carlos Sobral Sousa; Hospital de Base Fundação Faculdade de Medicina de São José Do Rio Preto: Lilia Nigro Maia; Pio XII: Raphael Kazuo; Hospital Santa Isabel: Adrian Kormann; Instituto Cardiopulmonar: Luiz Eduardo Fonteles Ritt; Santa Casa de Porto Alegre: Mauro Ricardo Nunes Pontes; PROCAPE - Hospital Universitário Oswaldo Cruz: Dario Sobral Filho; Hospital Totalcor: Antonio Baruzzi; Hospital Universitário Ciências Médicas–BH: Bruno Ramos Nascimento; Policlin: Raphael Kazuo; Hospital das Clínicas da Unesp de Botucatu: João Carlos Hueb; Hospital São Vicente de Paulo: Rogério Tadeu Tumelero, Norberto Toazza Duda; Instituto do Coração (Incor HCFMUSP): Roberto Giraldez; Hospital Bandeirantes: Marcelo José De Carvalho Cantarelli; Hospital Santa Rita: Raul Daurea Mora Junior; Hospital Beneficência Portuguesa: José Mangione; Hospital Santa Marcelina: Jamil Ribeiro Cade; Hospital Tacchini: Ricardo de Gasperi; Hospital Samaritano: Francisco De Paula Stella; Hospital Unimed Rio: Wolney De Andrade Martins; Hospital Dom Pedro de Alcântara: Edval Gomes; Santa Casa de Juiz de Fora: Antônio José Muniz; Hospital Felicio Rocho: Jamil Abdalla Saad; Fundação Bahiana de Cardiologia-FBC: Álvaro Rabelo Jr; Hospital da Bahia: Marianna Deway Andrade Dracoulakis; Hospital Vila Serra: João Carlos Belo Lisboa Dias; Hospital e Maternidade Dr Christóvão da Gama: Rogério Krakauer; HU–Unimar: Ricardo Tofano; São Bernardo Apart Hospital: João Miguel Malta Dantas; Hosp de Messejana: Carlos Alberto S Gomes, Sandra Falcão; Hospital São Jose do Avaí: Antônio Carlos Botelho Da Silva; Hospital Madre Teresa: Dr Roberto Luiz Marino; Hospital Municipal São Francisco de Assis Prefeitura do Municipio de Porto Real: Guilherme Abdalla; Instituto de Moléstias Cardiovasculares: Dr Pedro Garzon; Hospital do Coração: Ieda Maria Liguori; Hospital Vaz Monteiro: Ernesto Lippi; IECAC - Instituto Estadual de Cardiologia Aloysio de Castro: Edgard Quintella; Instituto Do Coração Do Triangulo Mineiro: Roberto Vieira Botelho; Liga Mineira de Ressuscitação Cardiopulmonar–Ligar: Yorghos Michalaros; Santa Casa de São Paulo: Renato Alves Jorge.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2017.12.018.

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