Clinical Trial Protocol

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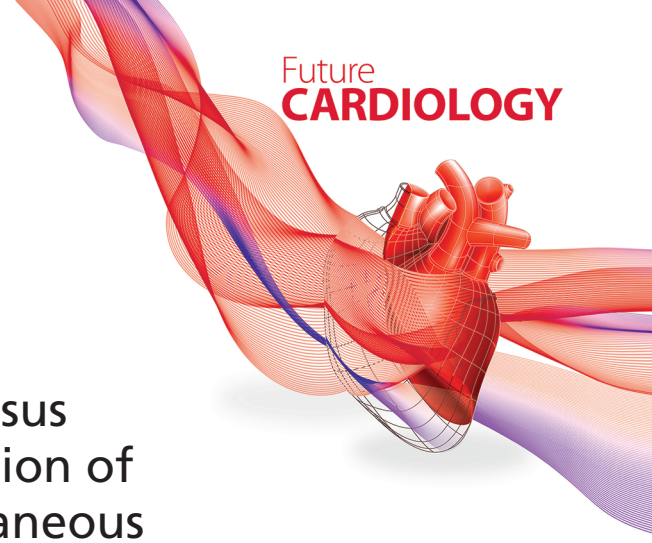

Randomized comparison between bare-metal stent plus colchicine versus drug-eluting stent alone in prevention of clinical adverse events after percutaneous coronary intervention

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The use of colchicine is associated with a significant reduction of cardiac adverse events in patients with coronary artery disease. Past small randomized trials with oral immunosuppressive or anti-inflammatory therapies have demonstrated a reduction of adverse clinical events after bare metal stent implantation. The potential role of adjunctive colchicine after bare-metal stent implantation, compared with drug-eluting stent alone, is unknown. The primary end point of the study will be to compare cost–effectiveness at 1 year of follow-up of coronary intervention with bare-metal stent implantation plus 1 mg of colchicine during 3 months versus percutaneous coronary intervention with drug-eluting stent implantation alone.

ClinicalTrials.gov identifier: NCT04382443

Lay abstract: Colchicine is an anti-inflammatory drug used to reduce the chance of heart attacks in patients with heart disease. The use of stents – small tubes inserted into blood vessels to keep them open – in this group of people is well known, and several small clinical trials have been carried out to investigate this. Our trial aims to assess if there is a role for using colchicine after inserting a stent, compared with using stents that release drugs themselves (drug-eluting stents), to reduce side effects and complications of cardiac procedures. Our primary objective will be to demonstrate that this drug, combined with the old metallic stent designs, will prevent future complications in comparison with the latest generation of drug-eluting stents.

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Keywords: acute coronary syndromes • bare-metal stents • colchicine • coronary artery disease • drug-eluting stents • restenosis

Background

Since the introduction of the second generation of drug-eluting stents (DES2), they have become the default strategy during percutaneous coronary interventions (PCI) in most clinical and angiographic scenarios [1–3]. With the new DES2 designs – polymer-free, biopolymers or biodegradable polymers – the incidence of late and very late stent thrombosis (ST) was almost gone [4,5]. In the past, ST was frequently observed with the first DES designs (DES1); this, together with bleeding risk, was the major limitation of DES1 [6,7]. ST and excess bleeding risk are rarely

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seen in contemporary PCI with DES2 [8,9]. However, despite all these advantages, old bare-metal stents (BMS) technology is still used in certain clinical conditions, including in geographic scenarios where economic constraints exist [10]. The most important differences between DES and BMS are the rate of target vessel revascularization (TVR) and TVR myocardial infarction (TVR-MI) within the first year without any difference in the outcome beyond that [11]. The largest randomized comparison between DES2 and BMS at 6 years of follow-up showed only advantages of DES2 over BMS in the rates of repeat revascularization procedures, without differences in any cause of death, myocardial infarction (MI) or quality of life [12]. Of interest, in a large contemporary registry from the USA [13], in spite of DES being used in more than 83% of PCI procedures, the proportion of patients undergoing in-stent restenosis (ISR) after PCI increased from 10.1 to 10.8% between 2009 and 2017. Of note, DES ISR rose from 5.4% in 2009 to 6.3% in 2017 ($p < 0.001$). Conversely, the proportion of patients with BMS ISR declined from 2.6% in 2009 to 0.9% in 2017 ($p < 0.001$). In this registry, BMS is still used in >16% of patients [13]. Furthermore, in spite of the early advantages of DES2 over BMS, they did not appear to reduce the gap between PCI and coronary artery bypass grafting (CABG) in multiple patient risk scenarios [14].

As was demonstrated by the most recent randomized clinical trials (RCT) comparing DES2 with CABG, significant differences between PCI and CABG were observed in favor of the latter, including large differences in the incidence of spontaneous MI beyond 30 days [15–18]. Despite the problem of ST almost disappearing with the new DES2 designs, neo-atherosclerosis or endothelial dysfunction are still present and could be related to late adverse cardiac events after DES2 implantation [19–22].

Rationale for the trial

The study is designed to test the hypothesis that PCI with oral colchicine (OC) for 3 months after BMS implantation would produce a similar number of major adverse cardiac events (MACEs) at 1 year as in those patients treated with DES, while reducing the costs. Differences in repeat revascularization procedures between BMS and DES are observed only within the first year after PCI. After the first year, need for revascularization procedures is similar between both groups [11,12] or is even less favorable with DES. Large registries have shown attrition of the efficacy of DES over time to an extent not seen with BMS in the past [23]. This trial is expected to be performed in four centers in Argentina and the trial acronym is ORCA, for ORal Colchicine in Argentina.

In recent years, the use of low doses of colchicine was associated with a significant reduction of cardiac adverse events in patients with acute or chronic coronary artery disease, including reduction of angiographic restenosis [24–27]. Results from the COLCOT trial, in which patients with acute myocardial infarction (AMI) who received PCI were treated with colchicine at low doses, showed that it was associated with a significant decrease in combined ischemia cardiovascular events compared with the placebo group. The primary end point was observed in 5.5% of the patients in the colchicine group, as compared with 7.1% of those in the placebo group (hazard ratio: 0.77; 95% CI: 0.61–0.96; $p = 0.02$) [24].

Furthermore, in a small randomized trial in diabetic patients [27] in whom only the use of BMS was allowed, colchicine was associated with a significant reduction of in-stent restenosis compared with placebo (odds ratio: 0.38; 95% CI: 0.18–0.79; $p = 0.007$).

Oral prevention of restenosis and TVR with immunosuppressive or anti-inflammatory agents after BMS implantation has previously been demonstrated in several relatively small investigator-driven RCTs [28–33] and systematic review and meta-analysis [34,35]. In two of these studies, the use of oral rapamycin and prednisone reduced adverse events as also compared with DES1 [30,31].

However, the lack of large controlled studies together with the improvement of DES technology means that definitive conclusions cannot be drawn. The present study is an investigator-driven RCT on the value of low doses of colchicine combined with BMS as compared with DES2 without colchicine.

Study design & methods

Study design

This is a prospective, multicenter, randomized controlled, unblinded trial at up to four sites in the Autonomous City of Buenos Aires and the Province of Buenos Aires to enrol 450 subjects with myocardial ischemia in the native coronary artery. The overall study flowchart is presented in Figure 1. This study has been registered at clinicaltrials.gov (NCT04382443) according to the statement of the International Committee of Medical Journal Editors. The study is performed following the Declaration of Helsinki and International Conference on Harmonization of Good Clinical Practices. The study protocol and informed consent have been reviewed and

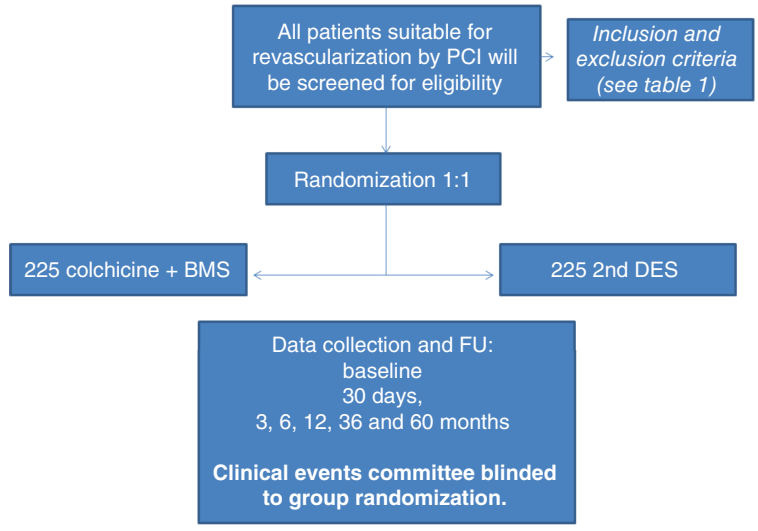

Figure 1. Flow chart from ORCA randomized clinical trial.
BMS: Bare-metal stent; DES2: Second generation drug-eluting stent; FU: Follow-up; PCI: Percutaneous coronary intervention.

Table 1. Eligibility criteria.

Clinical and angiographic inclusion criteria
1. The subject must be ≥18 years old
2. Patient (or legal guardian) indicates an understanding of the trial requirements and the treatment procedures and provides written informed consent before procedures are performed
3. Patient has symptomatic coronary artery disease or silent ischemia with objective evidence of ischemia or acute coronary syndromes
4. Patient has one or more coronary artery stenosis of ≥70% in a coronary artery with a visually estimated reference vessel diameter ≥2.50 mm
5. A PCI procedure is indicated
6. Left ventricular ejection fraction >40% as measured within 60 days before enrollment
7. Patient is willing to comply with all follow-up evaluations required by the protocol
8. No restrictions are placed on the total number of treated lesions, treated vessels, lesion length or the number of stents implanted
Clinical and angiographic exclusion criteria
1. The subject has a known allergy to contrast (that cannot be adequately premedicated) and/or the stent system or colchicine (e.g., cobalt–chromium alloy, stainless steel, all P2Y12 inhibitors, aspirin)
2. Planned surgery within 30 days after index PCI
3. Associated serious medical illnesses (e.g., cancer, congestive heart failure) with estimated life expectancy <36 months
4. Current drug abuse (e.g., alcohol, cocaine, heroin)
5. A planned interventional or surgical procedure that may cause noncompliance with the protocol, or confound data interpretation
6. Patient has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions
7. Patient is participating in another investigational clinical trial that has not reached its primary end point or, in the opinion of the investigator, may cause noncompliance with the protocol or confound data interpretation
8. Patient intends to participate in another investigational drug or device clinical trial within 12 months after the index procedure
9. Patient with known intention to procreate within 12 months after the index procedure (sexually active women of childbearing potential must agree to use a reliable method of contraception from the time of screening through 12 months after the index procedure)
10. Patient is a woman who is pregnant or nursing (a pregnancy test must be performed within 7 days before the index procedure)
11. DES restenosis from previous PCI interventions
12. Previous PCI with DES in the target vessel
13. The subject has an additional clinically significant lesion(s) in the target vessel for which an intervention may be required within 12 months after the index procedure
14. No planned staged procedures are allowed after the index procedure
15. The patient will be unavailable to close follow-up

DES: Drug-eluting stent; PCI: Percutaneous coronary intervention.

approved by an Independent Ethical and Review Board Committee as well by the Institutional Clinical Board at each participating center. Written informed consent for participation in the trial was obtained from all enrolled patients. This Phase IV protocol was presented and informed to Argentina National regulatory authorities for Health, Technology and Medications. Eligibility criteria are shown in Table 1.

Planned sample size & randomization

We scheduled 450 patients for elective PCI with coronary artery disease suitable for stent implantation; they are openly randomized 1:1 to either PCI with BMS plus OC or PCI with DES only. The detailed inclusion and exclusion criteria for the present study are listed in Table 1. The planned enrollment duration is between March 2020 and March 2021, and the enrollment period may be extended if necessary. Enrollment began after the protocol

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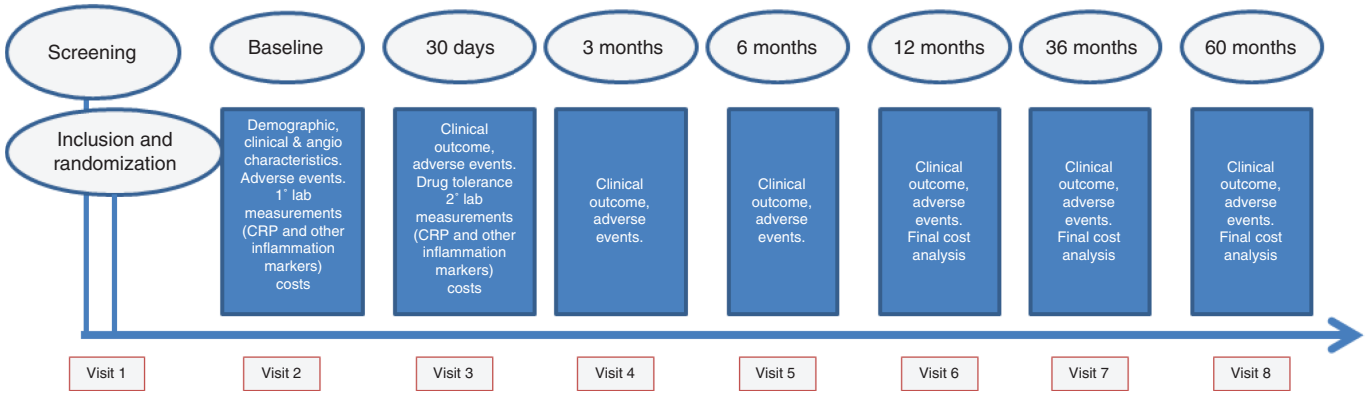

Figure 2. Timeline of ORCA randomized clinical trial.
PCR: Protein-C reactive.

and the informed consent were approved by the Independent Ethical and Review Board Committee. There were 139 patients enrolled until September 2020. The randomization serial numbers for patients and participating centers will be performed by Interactive Web Randomization System. The study will be complete when all patients have undergone 12 months of follow-up.

Planned study period

For the study, clinical end point measurements will be conducted in hospital at 30 days and thereafter twice a year during the 5 years of follow-up, either by telephone or contact with a physician referral (Figure 2). Patients in the OC group will be contacted personally 3 and 7 days after PCI and thereafter twice a month for the duration of the colchicine treatment (3 months).

End points between arms will be compared during all follow-up periods, although the primary end point will be determined at 1 year of follow-up. We expected follow-up compliance of >95% at 1 year.

Before entering the study, patients should give home address, mail address, phone, cellular phone, details of close relatives and /or reference physician contact details. Patients expected to move outside the Buenos Aires City area in the next year were excluded. All baseline clinical, angiographic and procedural data and follow-up events will be filed by electronic case report form. Primary end points will be reported at 1, 3 and 5 years. A timeline of the trial is shown in Figure 2.

Study intervention & medication

The allowed BMS are those of standard of care, approved for clinical use by local regulatory authorities. In the DES group, the DES design should be any DES2 approved by local regulatory authorities for clinical use and with previous RCTs showing noninferiority studies with the gold standard DES2 (durable polymer everolimus-eluting or zotarolimus-eluting stent).

Colchicine

During the last decade, the use of colchicine in the cardiology field has increased, especially after the discovery that the drug has shown better outcomes in terms of cardiovascular events and endothelial dysfunction in patients with Mediterranean fever [37]. In animal models, intimal hyperplasia and leukocyte VEGF expression were inhibited by the use of colchicine, which also demonstrates a synergistic protective effect with atorvastatin, reducing CRP and lipoprotein-associated phospholipase A2 [38–40]. Although usually mild and transient, abdominal pain, diarrhea, nausea and vomiting are the most common adverse reactions (>20%) when prescribed for acute or chronic conditions [40]. Certain drugs increase the potential for colchicine toxicity (primarily eliminated by hepatobiliary excretion) via CYP3A4 activity. In patients with normal creatinine clearance, colchicine excretion is up to 10–20%. There are reports that the concomitant use of colchicine with statins, fenofibrate/gemfibrozil, cyclosporine or digoxin produces transient myopathy and/or rhabdomyolysis in rare cases, but this generally resolves once colchicine is stopped.

Table 2. End point definitions.

Death	Cardiovascular death includes sudden cardiac death, death due to acute MI, arrhythmia, heart failure, stroke, other cardiovascular causes, or bleeding Non-cardiovascular death: any death with known cause not of cardiac or vascular cause
Myocardial infarction (MI)	Increase in cardiac biomarkers (CK-MB or troponin) >5× URL, with one of the following: • Evidence of prolonged chest pain • Ischemic ST-segment changes or new pathological Q waves • Noninvasive evidence of new regional wall motion abnormality
Post-procedure MI	The occurrence of MI within 7 days after PCI. Patients with normal baseline CK-MB: the peak CK-MB measured within 48 h of the procedure rises to ≥5 × URL, with or without new pathologic Q-waves in at least two contiguous leads or new persistent left bundle branch block
Spontaneous MI	The occurrence of MI more than 7 days after PCI
	Each MI will also be classified as ST-segment elevation MI or non-ST-segment elevation MI
Stent thrombosis	Defined per the Academic Research Consortium criteria [48]
Target lesion revascularization	Repeat revascularization (including PCI and coronary artery bypass grafting) for target lesions, in the presence of symptoms or objective signs of ischemia
Target Vessel MI	Spontaneous MI associated with target vessel, identified by electrocardiographic changes or coronary angiography

CK-MB: Creatin-Kinase MB; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; URL: Upper reference limit.

Antiplatelet therapy

Dual antiplatelet therapy (DAPT) is required for all included patients. Aspirin (≥300 mg) will be administered orally at least 1 hour before catheterization and an oral loading dose of either clopidogrel (600 mg), prasugrel (60 mg), or ticagrelor (180 mg).

All patients assigned DES treatment should take clopidogrel, prasugrel or ticagrelor plus 100 mg aspirin daily for 12 months. Despite some DES2 designs, a short period of DAPT was recommended [41] driven by common clinical practice in Argentina [42] and physician preference; most patients continue with DAPT 12 months after initial PCI, independent of clinical status at admission or DES design, hence the recommendation for 12 months of DAPT in all DES2 arm patients [42].

In all patients with acute coronary syndroms (ACS), prasugrel is the preferred drug according to current experiences and recommendations [43–45]. Patients with stable angina in the OC group will receive 30 days of DAPT and thereafter 100 mg of aspirin for 1 year [46,47]. Patients with ACS including MI, ST elevation myocardial infarction (STEMI) and non-STEMI will receive DAPT for 6 months and thereafter 100 mg of aspirin for 1 year.

A maintenance dose of 75 mg once daily for clopidogrel is standard of care, as well as Prasugrel 10 mg once daily (5 mg for patients weighing <60 kg or aged >75 years) and Ticagrelor 90 mg twice a day. In patients with acute coronary syndromes who received colchicine, DAPT is recommended for at least 6 months.

Unfractionated heparin is suggested as per guideline recommendations during PCI. Other drugs such as enoxaparin, bivalirudin or others could be administrated per standard of care.

Colchicine will be administered after randomization in the group of patients with BMS at the time of the index PCI at a dose of 0.5 mg twice daily for 3 months (Figure 1).

Study end points & end points definitions

The primary end point of the study will be to compare cost–effectiveness at 1 year of two revascularization strategies during PCI plus stent implantation. The primary end point will be also reported at 3 and 5 years of follow-up.

Assuming the incidence of MACEs between both arms will be similar, the OC plus BMS group at 1 year of follow-up will have significantly lower overall cost compared with PCI with DES. MACE is defined as incidence of any cause of death, MI (spontaneous or TVR-MI), cerebrovascular accident or ischemic TVR.

Other end points are target lesion failure defined as cardiac death (if the event cannot be determined with certainty, it will be assumed to be cardiac), MI and ischemia-driven target lesion revascularization. TVR refers to an ischemia-driven repeat revascularization in target and nontarget lesions of the treated coronary vessel. Target lesion revascularization is counted as repeat revascularization in the target lesion.

MI will be defined as periprocedural during initial PCI or TVR PCI at follow-up; spontaneous MI will be defined as any MI occurring beyond 7 days of initial PCI to 5 years after randomization. Non-ST-elevation MI at follow-up will be defined when Creatin-Kinase MB (CKMB) rises five-times or more from baseline levels. Other end point definitions are listed in Table 2.

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As a secondary end point, a substudy of the changes in the biological markers of inflammation in some prespecified patients with the acute coronary syndrome will be analyzed. The following biomarkers will be measured in both groups: IL-6, metalloproteinase, adiponectin and CRP. The samples will be taken on the first day of the angioplasty and after 30 days.

Statistical analysis

The sample size for the study was calculated based on a test for trend analysis. According to previous data with colchicine plus BMS and DES, it was predicted that the incidence of TVR would be similar in both revascularization therapies. Therefore sample size estimates were calculated based on differences in cost–effectiveness between the two revascularization strategies, with a statistical power of 90%. Assuming similar effectiveness of the two treatment arms, cost variance will be driven by the price difference between DES and BMS and by the need for a longer DAPT duration in the control DES group.

We analyzed only direct costs and cost differences between the two revascularization strategies (using the microcosting method) because the indirect costs are the same, taking into account that the same procedure is done in both groups. A noninferiority test was selected under the hypothesis of equivalence in clinical efficacy between both strategies. The hypothesis was that the average DES cost minus the average cost of colchicine plus BMS was greater than the prespecified noninferiority threshold level, and as a consequence DES would not be cost-effective compared with OC plus BMS.

Trial organization

The trial was designed by the principal investigator and the steering committee. The steering executive committee members are also responsible for reporting the results and drafting the manuscripts. The steering committee, together with the data and safety monitoring committee and the independent end points adjudication committee, are involved in the present trial. Details of the trial organization are listed in the supplementary material.

Conclusions

In this multicenter randomized study of patients undergoing PCI, we seek to demonstrate that the addition of a low dose of colchicine for 3 months in the BMS arm will be more cost-effective at 1 year of follow-up than DES implantation alone.

We hypothesize that colchicine may have an important role in the prevention of cardiac adverse events after BMS-PCI, as suggested by recent RCTs.

Taking into account that differences between DES and BMS are mostly confined to the first year after PCI, we expect no significant differences in outcome at late and very late follow-up between the two revascularization strategies; thus the initial 1-year cost–effectiveness advantage of BMS plus colchicine will be maintained over 5 years.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

Background & rationale

- Since the introduction of the second generation of drug-eluting stents (DES 2), they have become the default strategy during percutaneous coronary intervention (PCI).
- However, bare-metal stent (BMS) technology is still used in certain clinical conditions, including in geographic scenarios where there are economic constraints. In fact, the largest randomized comparison between DES2 and BMS at 6 years of follow-up showed only advantages of DES2 over BMS in rates of repeat revascularization procedures during the first year, without differences in any cause of death, myocardial infarction or quality of life.
- Recently, the use of low doses of colchicine has been associated with a significant reduction of cardiac adverse events in patients with acute or chronic coronary artery disease in a large randomized clinical trial.
- In the past several small randomized trials with oral immunosuppressive or anti-inflammatory therapies, including colchicine, have demonstrated a reduction in angiographic restenosis and clinical adverse events after BMS implantation.
- The potential role of adjunctive low doses of colchicine after BMS implantation as compared with DES2 implantation alone in reducing cardiac adverse events after PCI is unknown.

Study design & eligibility criteria

- This is a prospective, multicenter, randomized controlled, unblinded trial in four sites in Buenos Aires Argentina. The study has been registered at clinicaltrials.gov according to the statement of the International Committee of Medical Journal Editors. The study protocol and informed consent have been reviewed and approved by an independent ethical and review board committee. Written informed consent for participation in the trial will be obtained from all enrolled patients.

Clinical & angiographic inclusion criteria

- No age limit.
- Angiographically eligible for PCI and stent implantation.
- Patient has symptomatic stable or unstable coronary artery disease or silent ischemia with objective evidence of ischemia.
- Patient has normal or mild compromise of left ventricular ejection fraction.
- Patient has one or more coronary artery stenosis with $\geq$70% suitable for stenting.

Primary end point

- We will compare cost–effectiveness at 1 year of follow-up of PCI with BMS implantation plus 1 mg of colchicine during 3 months versus PCI with DES2 implantation alone.

Conclusions

- In this randomized study we hope to demonstrate that in patients undergoing PCI, the strategy of BMS implantation plus addition of 1 mg of colchicine for 3 months will be cost-effective compared with treatment with DES2 alone.

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