Indian Heart Journal 70 (2018) S323–S328

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Original Article

Open-labeled randomized controlled trial to evaluate the 1-year clinical outcomes of polymer-free sirolimus-eluting coronary stents as compared with biodegradable polymer-based sirolimus-eluting coronary stents

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ARTICLE INFO

Article history:
Received 9 January 2018
Accepted 13 August 2018
Available online 7 September 2018

Keywords:
Polymer-free
Biodegradable polymer
Stent thrombosis
Sirolimus
Randomised controlled trial

ABSTRACT

Background: Head to head trials of clinical outcomes of sirolimus eluting polymer free vs. biodegradable polymer stents are lacking.

Methods: Single centre prospective open labeled randomised controlled clinical trial. Basis for sample size calculation was the rate of MACE from the ISAR TEST 3 trial in which the absolute difference was 10.25% with a standard deviation of 0.24. Assuming null hypothesis, 80% power and 5% alpha error, to detect a 10% difference, adjusting for 10% loss of follow up, *sample size was 204*. Inclusion criteria: Patients with stable coronary artery disease or recent acute coronary syndrome (>1 week from the date of STEMI), being taken up for elective angioplasty. End points: Primary end point was MACE at 1 year and secondary end points at the end of 1 year were cardiac death, urgent target lesion revascularization, acute coronary syndrome, stroke and in-stent re-stenosis.

Results: 204 patients were enrolled between January 2013 to July 2014, 91 in the polymer-free group and 113 in the biodegradable polymer group. Baseline characteristics were comparable between both groups. 21 patients (10.29%), were lost to follow up. MACE at 1 year were comparable in both the groups 3 of 85(3.52%) in the polymer-free group and 3 of 98(3.06%) in the biodegradable polymer group, $p = 0.859$. The secondary end points were also comparable between the two groups- Death- 1 of 85(1.17%) vs. 2 of 98(2.04%), $p = 0.646$, Stroke 0 of 85 vs. 2 of 98(2.04%), $p = 0.185$ and acute coronary syndrome − 2 of 85(2.35%) vs. 1 of 98(1.02%), $p = 0.204$. There were no instances of urgent target lesion re-vascularisation or definite stent thrombosis in either groups. In stent re-stenosis was found in 7 of 85(8.2%) in the polymer-free group vs. 6 of 98(6.12%) in the biodegradable polymer group.

Conclusion: The 1 year MACE rates are comparable in patients who underwent elective coronary revascularization using sirolimus eluting polymer-free and biodegradable polymer stents.

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1. Introduction

Polymer-free stents have been in use for over a decade but head-to-head clinical trials comparing their efficacy to biodegradable polymer stents are lacking.

2. Background

Drug-eluting stents (DES) are metallic platforms coated with antiproliferative agents, which reduce restenosis after coronary angioplasty procedures by inhibiting neointimal hyperplasia.[1,2] This, however, comes at the cost of higher rates of late-stent thrombosis as the uncovered stent struts act as a nidus for thrombus formation.[3,4] Stent platforms are either stainless steel, cobalt chromium, or platinum chromium. It is onto these platforms that anti-neoproliferative drugs are coated on, so that the drug can be released in a controlled fashion over a period of time. Polymers

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https://doi.org/10.1016/j.ihj.2018.08.015
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can be classified as permanent or biodegradable based on whether they persist or degrade. Initial polymers were permanent and used to remain even after the drug was eluted. Being a foreign body, polymers used to cause chronic inflammation and delay endothelial healing.[5–7] The stent struts were thus exposed to blood and would act as a nidus for thrombus formation. Biodegradable polymers (BPs) were developed so as to degrade over a period of time and allow better endothelialization of stent struts and decrease the chance of stent thrombosis.

Nonpolymer stents, also known as polymer-free (PF) stents, were developed in an attempt to do away with the ill effects of polymer-like impaired biocompatibility, inflammation during polymer degradation, and surface coating durability while preserving the benefit of the antiproliferative agent. Numerous designs—titanium-nitric oxide alloy, microporous stainless steel stent, nanoporous hydroxyapatite coating, and magnetic nanoparticles—were developed. The available platforms are Amazon Pax (5 μm abluminal coating of paclitaxel on a crimped cobalt-chromium platform), BioMatrix (modified microstructured abluminal stainless steel stent surface with biolimus A9), Optima (integrated turbostratic coating with multiple grooves on the external surface containing tacrolimus), VESTAsync (microporous hydroxyapatite coating of sirolimus on stainless steel stent surface), and Yukon Choice (modified microporous stainless steel stent surface containing sirolimus).

A number of trials have been carried out comparing stents with permanent polymer against PF stents, and the results have been compiled in a meta-analysis performed by Wu et al in 2015.[8] This meta-analysis shows that PF DES showed a benefit in reducing all-cause death and long-term late lumen loss, but no superiority was found in reducing short-term late lumen loss, myocardial infarction (MI), target vessel revascularization (TVR), and late-stent thrombosis.

The Limus Eluted From a Durable Versus Erodable Stent Coating trial was an "all-comers" randomized controlled clinical trial comparing BioMatrix against CYPHER.[9] The 5-year follow-up showed similar composite major adverse cardiac events (MACEs—cardiac death, MI, and TVR) to be comparable in the first 2 years and BioMatrix to have a statistically significant lower incidence of MACEs from the third year onwards, and the lines on the graph continued to diverge at 5 years. The main cause of the divergence was clinically indicated TVR.

However, trials comparing BP-based stents vs. PF stents are lacking. The only trial comparing stents with BP and the PF stents was the Intracoronary Stenting and Angiographic Results (ISAR) TEST 3 trial, which compared the PF stent Yukon Choice against BP Yukon Choice PC and permanent polymer (PP) CYPHER, all stents being sirolimus eluting.[10] The study was powered to analyze only late loss and not the clinical outcomes. The mean late loss at 6–8 months was found to be thrice as much in the PF group as compared with the BP group and twice as much in the PF group as compared with the BP group. The target lesion revascularization (TLR) at 1 year was 14.4% in the PF group as compared with 6.4% in the BP group. The acute coronary syndrome (ACS) at 1 year was 2% in the PF group as compared with 1.5% in the BP group and stent thrombosis at 1 year was 1.5% in the PF group as compared with 1% in the BP group. In summary, MACE was 9% higher in the PF group as compared with the BP group, but this was only a trend as the study was not powered to look into these clinical end points.

To clear this clinical equipoise, the present study has been designed to study two stents, with the only difference between the two groups being the type of polymer.

3. Research question

Are sirolimus-eluting PF stents associated with a higher, comparable, or lower incidence of MACEs at 1 year when compared with sirolimus-eluting stents with BP?

4. Methods

4.1. Study design

This is a prospective, open-labeled, single-center randomized controlled clinical trial. Inclusion criteria were patients between 18 and 80 years of age, with stable coronary artery disease or recent ACS [excluding those patients who were within 1 week of a ST-elevation myocardial infarction (STEMI)], who were being taken up for elective percutaneous coronary intervention Exclusion criteria were patients with chronic renal failure, questionable drug compliance, expected survival of less than 1 year, significant peripheral vascular disease, those who refused informed consent, concomitant significant valvular heart disease, previous coronary revascularization procedure, previous cerebrovascular accident, known allergies or intolerance to antiplatelet agents, and patients requiring anticoagulation with vitamin K antagonists for any indication.

4.2. Randomization

Randomization protocol chosen was block randomization into groups of four. Based on the permutations, there would be 16 different recurring combinations. Fifty-one random blocks were chosen by a script written in python programming language.

4.3. Hardware

The stents chosen were Yukon Choice (PF) and Yukon Choice PC (BP). The hardware details are compared in Table 1.

4.4. Sample size calculation

Baseline values taken were from the ISAR TEST 3 trial as the trial was performed with the same two stents. The difference in MACE events in the aforementioned trial at 1 year was 9.5%, and the standard deviation was 0.24. Assuming null hypothesis, 80% power and 5% alpha error, to detect a difference of 10% between the two groups, the sample size was calculated to be 92 in each arm. To

Table 1
Hardware characteristics of stents used in the study.

Characteristic	Unit	Polymer free (PF)	Biodegradable polymer (BP)
Polymer		Nil	PDLLA (poly (d,l) lactic acid)
Micropores	2 microns	Both sides	Luminal
Drug		Sirolimus	Sirolimus
Drug concentration	$\mu g/cm^2$	479	180
Platform		316 stainless steel L	316 stainless steel L
Crossing profile	mm	0.89	0.89
No. of pores	million/cm^2	1	1
Strut thickness	microns	87	87

allow for 10% loss to follow-up, the sample size was calculated to be 204.

4.5. Primary and secondary end points

The primary end point MACE was a composite of cardiac death, urgent TVR, and both fatal and nonfatal ACS at the end of 1 year. The secondary end points at the end of 1 year were cardiac death, urgent TVR, ACS, and stroke.

4.6. Antiplatelet strategy

The antiplatelet strategy was a loading dose of clopidogrel 300 or 600 mg, 12 h before the procedure, depending on the operator preference. After the procedure, for 2 weeks, enteric-coated aspirin was to be continued at a dose of 150–325 mg once daily and clopidogrel at the dose of 75 mg twice daily. Following this, dual antiplatelets were to be given for 1 year.

4.7. Follow-up

Direct follow-up at the center 1 year after the procedure was the follow-up of choice. If this was not possible, a telephonic follow-up was performed. Symptomatic patients were to undergo a coronary angiogram. Asymptomatic patients were to undergo treadmill exercise stress testing, and if the test was positive for inducible ischemia, they should undergo a coronary angiogram.

4.8. Ethical considerations

The study design was cleared by the institutional review board, and the trial was registered with the Clinical Trials Registry of India (CTRI) under CTRI/2013/03/004512. All patients were included in the study after obtaining an informed written consent.

4.9. Statistical analysis

Difference in the primary end point was evaluated using the chi-square test with values less than 0.05 taken as significant.

5. Results

Two hundred five patients were enrolled into the study between January 2013 and July 2014. There was one protocol violation in which the patient received a different stent. Ninety-one patients were randomized into the PF group, of which 6 were lost to follow-up, and the rest 85 were analyzed. One hundred thirteen patients were randomized into the BP group, of which 15 were lost to follow-up, and 98 patients were analyzed (Fig. 1).

5.1. Baseline characteristics

The baseline characteristics are given in Table 2. There was no significant difference in the baseline characteristics between the two study groups. The indication for angioplasty is given in Table 3. The most common indication was recent STEMI in both groups.

5.2. Procedural details

The procedural details are summarized in Table 4. The procedural characteristics are comparable between both the study groups. The type of angiographic disease is shown in Fig. 2. Roughly

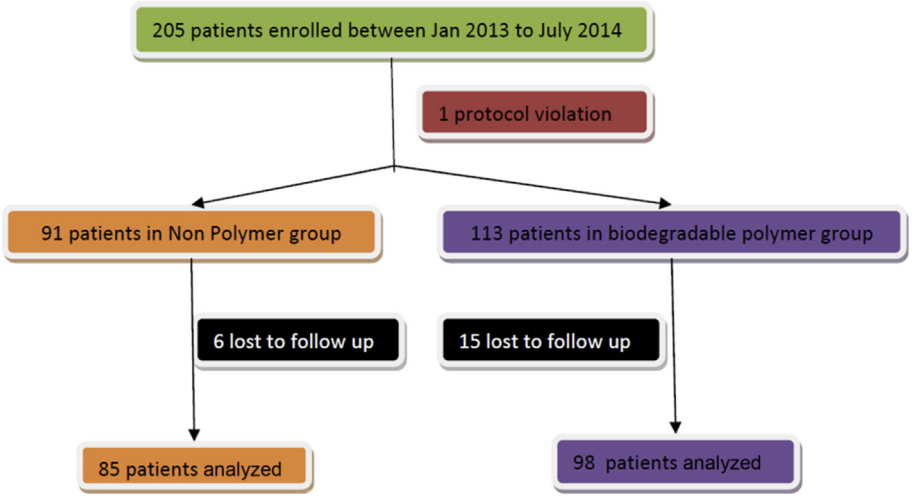

Fig. 1. Flowchart showing flow of patients in the study protocol. Protocol violation was the use of a different stent.

Table 2
Baseline characteristics of patients enrolled in the study.

Characteristic	Subgroup/unit	Polymer free, $n = 91$	Biodegradable polymer, $n = 113$	p Value
Gender	Males	80 (87.91%)	83 (73.45%)	0.64
Diabetic		45 (49.45%)	50 (44.24%)	0.45
	Diabetic on insulin	6 (6.59%)	9 (7.96%)	0.53
Hypertensives		45 (49.45%)	58 (51.33%)	0.79
Peripheral arterial disease		1 (1.09%)	3 (2.65%)	0.43
Mean age		55.8 ± 8.4	56.9 ± 9.8	0.39
Mean ejection fraction	%	57.3 ± 13.9	58.7 ± 12.3	0.43
Mean creatinine	mg/dl	1.0 ± 0.23	1.0 ± 0.75	0.43

Table 3
Indication for angioplasty in patients enrolled in the study.

	Polymer free, $n = 91$	Biodegradable Polymer, $n = 113$	p Value
Recent STEMI	38 (41.76%)	52 (46.02%)	0.76
NSTEMI	19 (20.87%)	31 (27.43%)	0.32
Chronic stable angina	22 (24.17%)	18 (15.93%)	0.09
Unstable angina	12 (13.18%)	9 (7.96%)	0.16
Atypical chest pain	0	3 (2.65%)	NA

NA, not applicable; STEMI, ST-elevation myocardial infarction; NSTEMI, non–ST-elevation myocardial infarction.

60% of patients in both groups had single-vessel disease, 33% had two-vessel disease, and 7% had triple-vessel disease.

5.3. Outcomes at the end of 1 year

Direct follow-up was possible in 144 patients (70.5%). Telephonic follow-up was done in the rest 39 patients (19.2%). Twenty-one patients (10.23%) were lost to follow-up.

The primary end point—MACE (composite of death, ACS and urgent TVR)—was found in 3 of 85 (3.52%) patients in the PF group as compared with 3 of 98 (3.06%) patients in the BP group, p = 0.859. For the secondary end points, there was one death in the PF group (1.17%) and two deaths (2.04%) in the BP groups (p = 0.646). There were two incidences of ischemic stroke in the BP group, and none in the PF group (p = 0.185). There were two instances of unstable angina in the PF group (2.35%) and one instance of non-ST elevation MI in the BP group (1.02%) p = 0.204. There were no instances of stent thrombosis and urgent TVR in both the groups (Table 5).

Fig. 3 shows the flow diagram of events during the study and after follow-up. In the PF group, 18 of 85 (21.17%) patients were symptomatic, and in the BP group, 19 of 98 (19.4%) patients were symptomatic. Only one-third of the symptomatic patients in both the groups were willing to undergo a check angiogram and subsequent revascularization if necessary. Of the asymptomatic patients, 33% of patients in the PF group and roughly 50% of patients in the BP group did not consent for exercise stress testing. TVR at 1

Table 4
Procedural details in patients enrolled in the study.

		Polymer free, $n = 91$	Biodegradable Polymer, $n = 113$	p Value
No. of stents per patient		1.42 ± 0.7	1.42 ± 0.74	0.98
Mean stented diameter	mm	3.18 ± 0.48	2.97 ± 0.673	0.08
Total stented length	mm	28.21 ± 17.10	29.69 ± 21.73	0.27
Predilatation		82/119 (68.9%)	108/159 (67.92%)	0.42
Postdilatation		31/119 (26.05%)	61/159 (38.3%)	0.64
Overlap stenting		5 (5.4%)	6 (5.3%)	0.86
Chronic total occlusions		4 (4.4%)	5 (4.42%)	0.73
Bifurcation lesions		2 (2.19%)	0	NA

NA, not applicable.

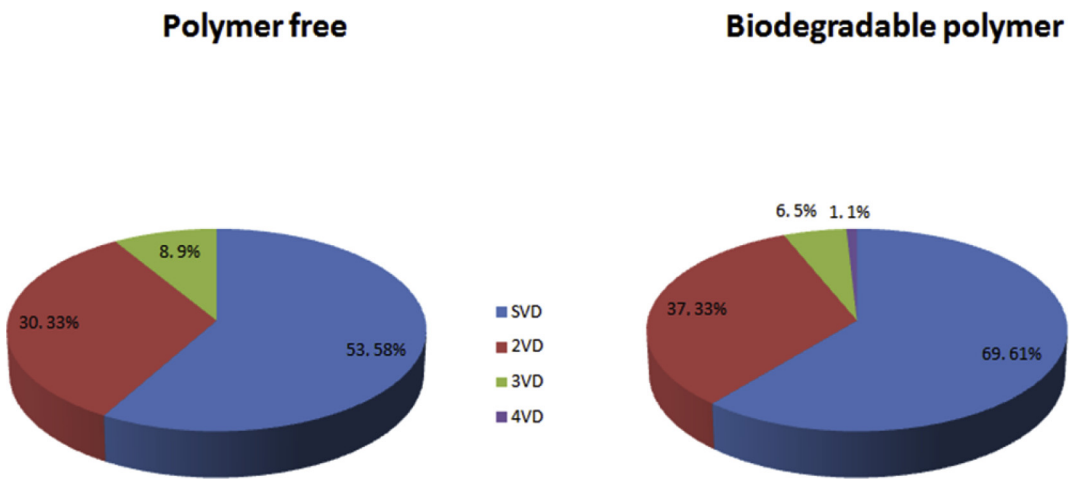

Fig. 2. Pie chart showing the number of diseased coronary arteries in the patients enrolled in the study. SVD, single-vessel disease; 2VD, two-vessel disease; 3VD, three-vessel disease; 4VD, four-vessel disease.

Table 5
Primary and secondary end points in both the study groups.

	Polymer free, $n = 85$	Bio-degradable polymer, $n = 98$	p Value
Composite end point of death, urgent TVR, and MI	3 (3.52%)	3 (3.06%)	0.86
Death	1 (1.17%)	2 (2.04%)	0.65
Ischemic stroke	0	2 (2.04%)	0.19
Acute coronary syndrome	2 (2.35%) (unstable angina)	1 (1.02%) (NSTEMI)	0.20
Urgent target vessel revascularization	0	0	NA
Stent thrombosis	0	0	NA

MI, myocardial infarction; NSTEMI, non–ST-elevation myocardial infarction; NA, not applicable; TVR, target vessel revascularization.

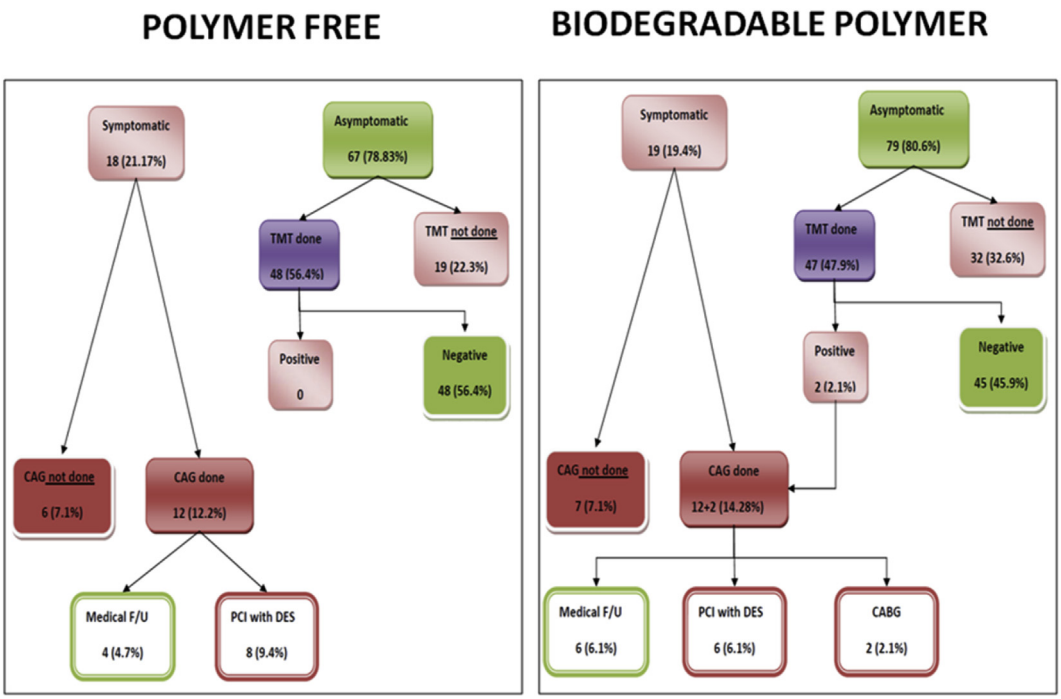

Fig. 3. Flow diagram showing sequence of events in patients during the follow-up period CABG, coronary artery bypass graft; CAG, coronary angiogram; DES, drug-eluting stent; F/U, follow-up; PCI, percutaneous coronary intervention; TMT, treadmill testing.

Table 6
Findings of follow-up angiogram in symptomatic patients.

	Polymer free, $n = 85$	Biodegradable polymer, $n = 98$
In-stent restenosis	7 (8.2%)	6 (6.12%)
Target lesion revascularization	5 (5.88%)	4 (4.08%)
Target vessel revascularization	6 (7.05%)	5 (5.10%)
New lesion in check angiogram	8 (9.41%)	5 (5.10%)
Progression of other lesions	3 (3.53%)	4 (4.08%)

Statistical comparison was not attempted as one-third of symptomatic patients in both groups did not consent for a check coronary angiogram.

year was performed in 9.4% of patients in the PF group and 8.4% of patients in the BP group.

In-stent restenosis (ISR) was found in 8.2% of patients in the PF group and 6.12% of patients in the BP group. The result of TVR, TLR, and new lesions are shown in Table 6.

6. Discussion

This single-center open-labeled randomized clinical trial aimed at clearing the clinical equipoise raised by the results of the ISAR TEST 3 trial which showed a trend to higher MACEs at the end of 1 year in the PF group.[10] The difference was mainly because of the higher TLR in the PF group, and the decision to perform an angiogram was not based on clinical end points. The PF and BP stents used in the present trial were similar in almost all aspects except the presence of polymer. The only other difference was a higher concentration of sirolimus in the PF stents.

The baseline characteristics (Table 2) were comparable between the PF and BP groups. A point worth mentioning in the baseline characteristics was that 40–50% of patients were diabetic in both the groups.

The indication for procedure was recent STEMI in 40–45% of patients in both groups. The mean number of stents, stented diameter, total stented length, and complex lesions were similar in both the groups (Table 4). Sixty percent of patients had single-vessel disease. The mean number of stents deployed being 1.42 in both the groups, the mean stented diameter being approximately 3 mm in both the groups, and the low percentage of chronic total occlusions, bifurcation lesions, and overlap stenting all show that this cohort was at a relatively low risk for ISR. This selection bias for the low-risk cohort is explained by the operators subconsciously excluding patients with a higher number of lesions and complex lesions. The inclusion of such patients would have increased the probability of using a nontrial stent because of nonavailability of adequate sizes of trial stents during the procedure, which would amount to a protocol violation.

The primary end point was comparable in both groups: 3 of 85 (3.52%) patients in the PF group as compared with 3 of 98 (3.06%) patients in the BP group, $p = 0.859$. The secondary end points of cardiac death at 1 year, stroke, urgent TVR, and ACS were not statistically different in both the groups. There were no instances of definite stent thrombosis at 1 year, but the three deaths will have to be considered as probable stent thrombosis.

No meaningful deduction can be made by comparing the ISR, TLR, TVR, and new lesions in a different vessel as a one-third of the symptomatic patients did not undergo check angiogram, and one-third of the asymptomatic patients did not undergo exercise treadmill testing.

The clinical outcomes of PF and BP stents are comparable at 1 year. This study does not show the trend of higher MACEs seen in the ISAR TEST-3 because of the difference in the composite end point. The ISAR TEST-3 used TLR at 1 year, while the present study took urgent TVR as one of the composites for MACE. The TLR at 1 year is 5.88% in this study, and the TLR is 14.4% in the ISAR-TEST 3. No attempt has been made to compare these values as one-third of symptomatic patients in the present study did not consent for check angiogram.

7. Limitations of the study

The study is open labeled and is, therefore, prone to all the biases of an open-labeled design, but the primary end point being a composite of hard end points, makes the effect of biases negligible. One-third of asymptomatic patients were not willing for treadmill testing, and one-third of symptomatic patients chose to be on medical follow-up rather than undergo a check angiogram.

8. Conclusion

There is no difference in the incidence of death, ACS, and urgent TVR, at the end of 1 year between PF and BP sirolimus-eluting stents. Longer follow-up will be required to identify differences in the rates of very late-stent thrombosis between the groups.

Funding

No funding was required for the study as the study involved patients who required angioplasty and the study involved only the selection of stents. This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Conflicts of interest

All authors have none to declare.

Acknowledgments

The authors thank Dr K Sivaprasad, Dr Mathew Iype, Dr Anil Balachandran, Dr Siju Pillai, Dr Sudheer MD, Dr Manu Bhaskar, Dr Faeez Ali, Dr Vijayalekshmi, Dr Rajesh Kumar, Dr Praveen S, Dr Supriya Nambiar, Dr Raji, Dr Suryanth, Prajeesh Joseph, Anju K, and Gracious George for their contribution toward the study.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ihj.2018.08.015.

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