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(REVIEW ARTICLE)

Effectiveness of in-stent restenosis treatment using drug-eluting stents, paclitaxel-coated balloons, and sirolimus-coated balloons in managing complications after PCI in atherosclerosis patients

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Abstract

Introduction: Coronary artery disease (CAD) is one of the leading causes of death worldwide. One of the primary causes of CAD is atherosclerosis. One of the management strategies for atherosclerosis is Percutaneous Coronary Intervention (PCI) using drug-eluting stents (DES). This procedure involves the insertion of a catheter to place a stent that opens narrowed blood vessels due to plaque accumulation. However, this procedure may be repeated due to complications such as in-stent restenosis (ISR), which is the re-narrowing of the arterial lumen after stent placement, caused by intimal hyperplasia. Two endovascular interventions that can be options for treating ISR are re-implantation of a DES or the use of drug-coated balloons (DCB). DCB presents an alternative to re-stenting. There are two DCB treatment options: Paclitaxel Coated Balloon (PCB) and Sirolimus Coated Balloon (SCB), whose effectiveness will be compared.

Methods: This literature review is written as a result of various interrelated literature studies, supported by analytical discussions. Literature search sources used six databases namely PubMed, Web of Science, Scopus, CINAHL, Proquest, and Cochrane with published years 2014-2024. The types of studies included are full text articles, systematic review, meta-analysis, randomized controlled trials, and case-control study.

Summary: Both DCBs showed nearly identical angiographic courses with very low lumen narrowing in this high-risk group in the treatment of DES restenosis after 6 months. This is the first indication that SCB is as effective as the best-in-class PCB.

Keywords: Atherosclerosis; PCI; ISR; Neointimal Hyperplasia; DES; DCB; PCB; SCB

1. Introduction

Nowadays, coronary artery disease (CAD) poses a serious threat as it is one of the leading diseases with high mortality and morbidity rates worldwide, including in Indonesia. CAD is a heart dysfunction primarily caused by the inadequate blood supply to the heart muscle due to the narrowing and blockage of coronary blood vessels in the process of atherosclerosis. The clinical manifestations of CAD include chest pain or discomfort in the chest during activities such as climbing, heavy physical exertion, hurried walking, or long-distance walking.(1)

CAD is one of the leading causes of death worldwide. In 2015, CAD was the leading cause of death, responsible for 8.9 million deaths globally, as well as 164 million Disability Adjusted Life Years (DALY).(2) According to the 2019 Global Burden of Disease study, Indonesia ranked fifth among countries with the highest cardiovascular disease-related

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mortality rates in the world.(3) This disease contributes the most to cardiovascular diseases in both developing and developed countries. As age increases, the likelihood of an individual suffering from coronary artery disease also rises, which can lead to sudden death.(4)

The high prevalence of coronary artery disease has significant impacts on society, both in terms of health and socio-economic factors. The primary cause of heart disease is atherosclerosis, which includes conditions such as aneurysms, peripheral artery disease, stroke, and CAD. Atherosclerosis itself is a condition of large and small arteries characterized by the deposition of lipids, platelets, macrophages, and leukocytes throughout the intimal layer and in the medial layer of the arteries.(5) One of the management strategies for atherosclerosis is percutaneous coronary intervention (PCI) using drug-eluting stents (DES), a procedure that involves the insertion of a catheter to place a stent in order to open narrowed blood vessels due to plaque accumulation. Unfortunately, this procedure may need to be repeated due to complications such as in-stent restenosis (ISR), which is the re-narrowing of the arterial lumen after stent placement, caused by neointimal hyperplasia.(6)

Given the still high prevalence and limited technological advancements in managing recurrent complications after PCI with DES, there is a need for innovative treatments that can help reduce mortality and morbidity caused ISR in PCI procedures with DES. This literature review, conducted through both online and offline searches, aims to explore the potential of two endovascular procedures as treatment options for ISR: re-implantation of DES or the use of drug-coated balloons (DCB). There are two DCB treatment options, namely Paclitaxel Coated Balloon (PCB) and Sirolimus Coated Balloon (SCB), whose effectiveness will be compared.

2. Material and methods

To identify articles for this review, the search way of this literature review was undertaken in multiple databases instance Pubmed, Web of Science, Scopus, CINAHL, Proquest, and Cochrane using Boolean functions AND/OR with some MESH terms keywords, such as ("Atheroscleros*"), ("Percutaneous Coronary Intervention*"), ("Neointima Formation"), ("Drug eluting stent*"), ("Drug coated stent*"), ("Drug coated balloon"), ("Paclitaxel coated balloon"), ("Sirolimus coated balloon), ("Coronary restenos*"), and ("In stent restenos*"). The types of studies are full text articles, systematic review, meta-analysis, randomized controlled trials, case-control study that appraise the effectiveness of DES, PCB, and SCB in treating complication after PCI from 2014 - 2024. This review also focuses on the study that discusses the therapeutic targets of ISR, the mechanism and the advantages & disadvantages of DES, PCB, and SCB as a treatment of PCI complications. Excluded study types were review articles, letters, books, and editorials. The author was last searched on 5th December 2024.

3. Results and discussion

Despite advancements in coronary stent technology, ISR continues to be a common complication of PCI. Percutaneous therapy continues to evolve with various available options such as balloon angioplasty, stenting, and coronary atherectomy. Plain balloon angioplasty and stenting have been used for a long time, but the performance of both procedures is limited by the high prevalence of restenosis or the risk of stent fracture, which typically occurs in long distal lesions. Several breakthroughs in clinical needs and cutting-edge treatments in the field of endovascular therapy include DES and Drug-Coated Balloons (DCB).(7)

3.1. Target Patients for Therapy: Stent Dislodgement

Stent dislodgement is a very rare complication, with an incidence rate exceeding 8% per day for displaced stents. This complication can lead to serious consequences, including distal embolization, vessel occlusion, or the need for emergency interventions to restore blood flow and re-position the stent.(8) In cases of stent dislodgement, complications such as embolism can occur, requiring emergency cardiac surgery and potentially leading to death. However, with advancements in catheterization device design, the incidence of stent dislodgement has significantly decreased, and a wider range of retrieval techniques have been developed. Several stent retrieval techniques have shown high success rates, with some achieving up to 86% success. (9)

Damaged stents have become a particular concern since the era of DES placement, as they are associated with stent thrombosis and ISR. The incidence of stent damage is relatively rare, with an occurrence rate ranging from 1% to 16%.(10) The mechanism of in-stent restenosis in damaged stents is related to the low drug content on the areas of the stent that have been compromised, as well as the high mechanical irritation caused by smooth muscle proliferation and impaired reendothelialization. Damaged stents are also associated with factors such as stent length, stent over-

expansion, stent overlap, and lesion calcification. However, in the era of DES, reports of stent dislodgement have become rare.

3.2. Drug Eluting Stent (DES)

Drug-eluting stents (DES) represent a major revolution in interventional cardiology, widely replacing the use of bare-metal stents (BMS). The introduction of DES has made PCI simpler, safer, and more durable. The use of DES significantly reduces the occurrence of restenosis complications and decreases the frequency of repeat revascularization procedures.(11) In its development, DES have an alternative in the form of bioabsorbable or biodegradable drug-coated stents. One example is sirolimus, an antibiotic with anti-growth and anticancer effects. The materials used to create DES include polylactic acid (PLA) and polyglycolic acid (PGA), which help reduce adhesion during stent placement. However, the use of DES still requires careful attention, as various complications can arise from their use, such as stent dislodgement, stent fracture, spiral dissection, and stent thrombosis.

3.3. Drug Coated Balloon (DCB)

Drug-coated balloon (DCB) was created as a substitute therapy for ISR and coronary artery atherosclerosis. Compared to DES, DCB has the advantage of not requiring an extra stent layer, which lowers lumen impingement, neointimal growth, and mechanical problems such thrombosis, fractures, and malposition. Since the permanent placement of metal stents can raise the risk of thrombosis, DCB can be given to patients who have already had stent implantation.(7)

3.4. Paclitaxel Coated Balloon (PCB)

Paclitaxel is a chemotherapy drug commonly used to treat various types of cancer, including breast cancer, ovarian cancer, lung cancer, and others. It works by stabilizing microtubules, which are structures inside cells that are necessary for cell division. By stabilizing these microtubules, paclitaxel prevents the cells from completing their division process, leading to cell death. This mechanism of action makes it an effective treatment for cancer, although it can also affect normal, rapidly dividing cells, leading to side effects.(12)

According to the 2014 ESC/EACTS Guidelines on Myocardial Revascularization, Paclitaxel coated balloons (PCB) have evolved into a first line treatment option for in-stent restenosis in coronary arteries due to their ability to avoid the need for additional stent layers. Moreover, they have the potential to shorten the duration of dual antiplatelet therapy without increasing the risk of thrombosis.(13) So far, paclitaxel is preferred for use as a drug in balloon coatings due to its ability to permanently adhere to microtubes. Its high lipophilicity and strong adhesion to various cellular constituents enhance its effectiveness and precise targeting at the intended site. The balloon catheter consists of a semi-compliant balloon coated with a low dose of paclitaxel (2 $\mu g/mm^2$), with tri-n-butyl citrate acetate used as an excipient.(14)

3.5. Debate Regarding the Use of Paclitaxel-Coated Balloons (PCB)

Klumb et al. describe in their meta-analysis study, which included 28 randomized trials involving more than 4,600 subjects with peripheral artery disease, that they identified an excess in late mortality rates starting from two years after treatment with PCI using drug-coated devices, compared to those who received treatment without drug-coated devices.(14)

Although it is appropriate to market newer-generation devices based on more comprehensive products, ease of use, or compatibility with smaller diameter catheters, readers should keep in mind that all recent peer-reviewed assessments of long-term data from PCB have not identified a dose-response relationship for mortality or causal mechanisms, whether at low or high doses.(15)

3.6. Sirolimus Coated Balloon (SCB)

Sirolimus (also known as rapamycin) is a macrolide compound originally discovered as a natural product from Streptomyces hygroscopicus. It has potent antiproliferative, immunosuppressive, and anti-inflammatory properties, which make it useful in various clinical applications, particularly in the prevention of organ transplant rejection and the treatment of certain cancers. Sirolimus-coated balloon (SCB) has emerged as a new therapeutic option for the treatment of ISR, particularly in narrow vessels.(16)

So far, sirolimus has dominated the treatment of complex acute coronary syndromes, although paclitaxel remains the only drug in balloon catheters that has been proven to inhibit restenosis. Sirolimus and its analogs reversibly bind to FKBP-12, forming a complex that inhibits the progression of the cell cycle during the G1 and S phases.(17) In the case

of drug delivery via stents, sirolimus is released over a certain period as an effective inhibitor of neointimal proliferation. The gradual release of sirolimus helps prevent the excessive growth of smooth muscle cells in the arterial wall, which can lead to restenosis, thus maintaining the patency of the treated vessel and reducing the need for further interventions.

With a stiff hypotube and a distal tip size of 0.016", the SCB is a novel type of fast exchange monorail balloon. Compared to paclitaxel, sirolimus has a broader therapeutic window. Because sirolimus has a low lipophilicity, it can diffuse and penetrate the artery wall during balloon inflation because it is wrapped in a phospholipid protective package that contains nano-sized drug particles (100–300 nm in diameter). Spray coating is used to evenly distribute the medication carrier unit over the balloon's surface. The most popular balloon sizes are 1.5 mm to 4.0 mm in diameter and 10 mm to 40 mm in length..(16)

3.7. Sirolimus Coated Balloon (SCB) and Its Effects on Blood

In contrast to most medications, sirolimus has a low concentration in plasma and a high concentration in erythrocytes, or red blood cells. The assessment of sirolimus in blood is crucial for determining its therapeutic levels and possible toxicity because of its distinct pharmacokinetic profile.(18) Blood samples were obtained from the main catheter ten minutes following coated balloon treatment, and sirolimus levels were concurrently assessed. Because blood pressure is anticipated to peak following intravascular delivery, the first time point was selected. Before being subjected to high-performance liquid chromatography (HPLC) analysis, two milliliters of blood were extracted using two milliliters of methyl tert-butyl ether, the extract was evaporated, and the dried material was dissolved in methanol.

3.8. Efficiency of Different Types of Sirolimus Ballon Coatings

In myocardial tissue histology, a mixture of edema, vasculitis, myocarditis, scar tissue, diffuse inflammation, and degeneration was observed. No thrombotic occlusion, necrosis, or endocarditis was found.(18) Most of these findings were minimal, mild, and some were moderate in severity. No severe histopathological changes were observed. These changes were evident across all treatments, including those with uncoated balloons. No vascular obstruction due to foreign material was found.

4. Conclusion

Both DCB angioplasty and repeat stent implantation with DES are similarly safe and efficacious for long-term follow-up in patients with bare metal stent-in-stent restenosis (BMS-ISR). Repeat DES implantation is far more successful and seems to be just as safe as DCB angioplasty for long-term follow-up in patients with DES-ISR. DES-ISR is often linked to a greater rate of target lesion revascularization than BMS-ISR. In contrast to PCB, which has been clinically regarded as the gold standard and first-line therapy for coronary ISR, this literature study methodically determined the anti-restenosis efficacy of SCB. Remarkably, after 6 months, both DCBs treated DES restenosis in this high-risk cohort with essentially comparable angiographic courses and very little lumen narrowing. At least in this indication and during a rather brief follow-up period, this is the first proof that SCB is just as effective as the best-in-class PCB.

Compliance with ethical standards

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Disclosure of Conflict of interest

The authors declare no financial or personal relationships that could influence the work presented in this study.

References

[1] Shahjehan RD, Sharma S, Bhutta BS. Coronary Artery Disease. Medical Nursing [Internet]. 2024 Oct 9 [cited 2024 Dec 6];110–4. Available from: https://www.ncbi.nlm.nih.gov/books/NBK564304/

[2] Zhang G, Yu C, Zhou M, Wang L, Zhang Y, Luo L. Burden of Ischaemic heart disease and attributable risk factors in China from 1990 to 2015: findings from the global burden of disease 2015 study. BMC Cardiovasc Disord [Internet]. 2018 Feb 2 [cited 2023 Apr 1];18(1). Available from: /pmc/articles/PMC6389214/

[3] Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020 Dec 22;76(25):2982–3021.

[4] Gaziano T, Reddy KS, Paccaud F, Horton S, Chaturvedi V. Cardiovascular Disease. Disease Control Priorities in Developing Countries [Internet]. 2006 [cited 2024 Dec 6]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK11767/

[5] Rafieian-Kopaei M, Setorki M, Doudi M, Baradaran A, Nasri H. Atherosclerosis: Process, Indicators, Risk Factors and New Hopes. Int J Prev Med [Internet]. 2014 [cited 2024 Dec 6];5(8):927. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC4258672/

[6] Alraies MC, Darmoch F, Tummala R, Waksman R. Diagnosis and management challenges of in-stent restenosis in coronary arteries. World J Cardiol [Internet]. 2017 [cited 2024 Dec 6];9(8):640. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC5583537/

[7] Giacoppo D, Alfonso F, Xu B, Claessen BEPM, Adriaenssens T, Jensen C, et al. Drug-Coated Balloon Angioplasty Versus Drug-Eluting Stent Implantation in Patients With Coronary Stent Restenosis. J Am Coll Cardiol [Internet]. 2020 Jun 2 [cited 2023 Apr 1];75(21):2664–78. Available from: https://pubmed.ncbi.nlm.nih.gov/32466881/

[8] Talanas G, Lorenzoni G, Fiore G, Terrosu P. Coronary stent dislodgment after deployment during bifurcation treatment with the double kissing crush technique: A case report. Journal of Indian College of Cardiology. 2015 Jun 1;5(2):168–72.

[9] Jon C. George MD DFM and RBM of CMUHPP. Management of Dislodged Coronary Stent Using Intravascular Ultrasound. Cath Lab Digest [Internet]. 2009 Nov 5 [cited 2024 Dec 6];17(11). Available from: https://www.hmpgloballearningnetwork.com/site/cathlab/articles/management-dislodged-coronary-stent-using-intravascular-ultrasound

[10] Oktaviono YH. STENT DISLODGEMENT. Vol. 52, Folia Medica Indonesiana. 2016.

[11] Buccheri D, Piraino D, Andolina G, Cortese B. Understanding and managing in-stent restenosis: a review of clinical data, from pathogenesis to treatment. J Thorac Dis [Internet]. 2016 [cited 2023 Apr 1];8(10):E1150. Available from: /pmc/articles/PMC5107494/

[12] BC Cancer Agency. Paclitaxel BC Cancer Drug Manual. 2019 Dec.

[13] Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACTS Guidelines on myocardial revascularizationThe Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J [Internet]. 2014 Oct 1 [cited 2023 Apr 1];35(37):2541–619. Available from: https://academic.oup.com/eurheartj/article/35/37/2541/581070

[14] Klumb C, Lehmann T, Aschenbach R, Eckardt N, Teichgräber U. Benefit and risk from paclitaxel-coated balloon angioplasty for the treatment of femoropopliteal artery disease: A systematic review and meta-analysis of randomised controlled trials. EClinicalMedicine [Internet]. 2019 Nov 1 [cited 2023 Apr 1];16:42–50. Available from: http://www.thelancet.com/article/S2589537019301658/fulltext

[15] Cortese B, Fouladvant F. Is Paclitaxel-Eluting Stent Use Justified by an Adequate Risk Profile? JACC Cardiovasc Interv [Internet]. 2021 Mar 22 [cited 2023 Apr 1];14(6):702–3. Available from: https://pubmed.ncbi.nlm.nih.gov/33736777/

[16] Caiazzo G, De Michele M, Golino L, Manganiello V, Fattore L. Sirolimus-Eluting Balloon for the Treatment of Coronary Lesions in Complex ACS Patients: The SELFIE Registry. J Interv Cardiol [Internet]. 2020 [cited 2023 Apr 1];2020. Available from: /pmc/articles/PMC7586180/

[17] Ali RM, Abdul Kader MASK, Wan Ahmad WA, Ong TK, Liew HB, Omar AF, et al. Treatment of Coronary Drug-Eluting Stent Restenosis by a Sirolimus- or Paclitaxel-Coated Balloon. JACC Cardiovasc Interv. 2019 Mar 25;12(6):558–66.

[18] Clever YP, Peters D, Calisse J, Bettink S, Berg MC, Sperling C, et al. Novel sirolimus-coated balloon catheter. Circ Cardiovasc Interv [Internet]. 2016 Apr 1 [cited 2023 Apr 1];9(4). Available from: http://ahajournals.org