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Review

Is a high calcific burden an indication, or a contraindication for Drug Coated Balloon?

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Drug coated balloons (DCB) are increasingly being used in coronary intervention. Most of their use is currently restricted to in stent restenosis, however, they are also being used to treat some de novo lesion subsets (especially small vessels) and in patients unable to take dual antiplatelet therapy beyond a month. Calcified lesions pose a significant challenge to coronary intervention from lesion preparation to the delivery of drug to the vessel wall. There are limited data on the use of DCB in calcified lesions. In this article, we have provided a detailed literature review on calcified lesions and the use of DCB including a case example.

Keywords

Coronary artery calcification; High calcific burden; Drug coated balloons; Drug eluting stents

1. Introduction

The use of DCB in coronary intervention is escalating in both restenotic and de-novo lesions [1–8]. Unlike DES, delivering the anti-restenotic drug without metal and polymer appears attractive. The drug (Paclitaxel or Sirolimus) coated on the balloon gets transferred to the vessel wall upon inflation to deliver its anti-restenotic action. The current European Society of Cardiology guidelines provides class IA recommendation for the use of DCB in restenotic lesions, but there are no such recommendations for de novo lesions [9]. There is increasing evidence in the literature to support the use of DCB in de novo coronary lesions. In the recently reported Basket Small 2 trial, clinical outcomes following the use of DCB in small vessel de novo lesions (<3.0 mm) was non-inferior to drug eluting stents (DES) during the long-term follow-up (3-years) [4]. This has encouraged the use of DCB in certain de novo lesion subsets where the operators prefer to avoid implanting stents (small vessel, diffuse disease, ostium of side-branch and patients unable to take dual anti-platelet therapy beyond 1-month) [10]. In addition, there is also data on the use of DCB in de novo large vessels in acute ST-segment elevation myocardial infarction, where DCBs have been shown to be non-inferior to DES [11]. The presence of coronary calcification poses several challenges to coronary intervention, from lesion preparation to delivery of the drug into the vessel wall [12]. In this article, we have provided a detailed literature review on the use of DCB in calcified lesions and our opinion based on the experience in treating calcified lesions.

2. Coronary artery calcification

Coronary artery calcification (CAC) is a natural progression of advanced atherosclerosis. CAC pathogenesis is initiated with microcalcifications, growing to form calcified sheets which finally evolve to form nodular deposits [13]. The predominant type of vascular calcification recognised in CAC is in the intimal layer and is thought to be secondary to smooth muscle cell apoptosis. Inflammatory states such as the metabolic syndrome, diabetes, chronic kidney disease and smoking increase the calcific burden in coronary arteries [14]. Calcific burden is proportional to age and is more common in men; >90% of lesions are found in males over the age of 70 as compared with 67% in females in females over the age of 70-years. Therefore, incidence of coronary calcification is clearly propagated by an aging population, with moderate to severe calcification being associated with approximately 30% of all coronary lesions [13–15]. As we are increasingly embarking complex coronary intervention owing to improvement in device technology, pharmacotherapy and skill set, we will encounter calcified lesions in day-to-day clinical practice. Coronary artery calcification is an independent risk-factor for in-stent restenosis (ISR) and stent thrombosis [16–19].

3. Use of DCB in calcified coronary lesions

The introduction of DES in coronary intervention has resulted in amplified number of cases treated percutaneously and trials designed to prove superiority or at-least non-inferiority to surgical revascularization [20–22]. Despite consistent improvement in stent technology and pharmacotherapy, restenosis remains a concern following stent use. The risk of restenosis escalates with complex stenosis (calcified lesions, chronic total occlusion, multi-vessel disease) and patient subsets (diabetes, chronic kidney disease, acute coronary syndrome) [17, 19, 23, 24]. Once restenosis is established, it is often difficult to treat with high rates of recurrence. The idea of leaving nothing behind following coronary intervention appears exciting and was explored with ab-

sorbable scaffolds, but with disappointing long-term results [25, 26]. Moreover, scaffolds can take up-to 3-years or even longer for complete resorption. Drug coated balloons offers an alternative to stents, which does not "cage" the vessel with struts or polymer. Additionally, drug delivery is uniform from the balloon surface unlike stents. The use DCB is mainly confined to restenosis which results in avoiding another layer of metal, however, recent reports have explored its use in de novo subsets (small vessels and diffuse lesions) [2, 4]. It's use in large vessels (>3.0 mm) has been poorly studied and the data are derived from non-randomized studies [7, 27] and such vessels are predominantly treated with DES unless patients have contra-indications to DES such as bleeding risk or the requirement for urgent surgery.

Calcified lesions pose significant challenges to angioplasty from lesion preparation to delivery of stent or balloons to the lesion site. In this section, we provide literature review on use of DCB in such complex lesions and opinion from our experience including a case-based example. There is very limited data on the use of DCB in de novo lesions more so with calcified lesions in specific.

3.1 Calcified versus non-calcified de novo lesions

It is well known that calcified lesions do have higher incidences of restenosis and stent thrombosis than non-calcified lesions following PCI with DES [17, 18, 23, 24]. There are limited data on use of DCB in calcified lesions. In a retrospective study by Ito *et al.* [28], they have evaluated 81-patients with de novo lesion who were treated with DCB. Of the 81-patients; 46 had calcified lesions and 35 with no calcification on the angiogram. During the angiographic follow-up, the late lumen loss and rates of restenosis were higher in the calcified group but was not significant (late lumen loss; 0.03 in calcified group versus –0.18 mm in the non-calcified group, $p = 0.09$ and 14% in calcified group versus 3% in non-calcified groups, $p = 0.1$). This difference did not translate into adverse clinical endpoints at 2-years in the calcified lesions group. The survival rates of target lesion revascularization (TLR) and MACE at 2-years were not significant (85.3% versus 93.4%, $p = 0.6$ and 81.4% versus 88.5%, $p = 0.57$). It is important to note that 82% of these calcified lesions were prepared with rotational atherectomy (RA) pre-DCB. Similarly, Nagai *et al.* [29] conducted a cohort study that treated 190 severely calcified lesions with DCBs following rotablation. During a median follow-up period of 199 days, they reported a TLR rate of 16.3%. Numbers in these studies are small to draw any significant conclusions and in addition, these are retrospective, non-randomized studies. Nevertheless, there are some signs that use of DCB can be considered in calcified lesions.

3.2 DCB versus DES in calcified lesions

There are trials, which have compared DCB versus DES in de novo coronary lesions, however very little data exists in calcified lesions. Ueno *et al.* [30], carried out a single-centre cohort study, which compared the clinical outcomes for a total of 166 severely calcified lesions either treated with DCB or DES following RA with a median follow up of 3 years. TLR rate was not significantly different in the DCB group compared to the DES group at 15.6% and 16.3% ($p = 0.99$) respectively. In addition, the late lumen loss was recorded to be lower in DCB-RA; 0.09 mm versus 0.52 mm in the DES-RA ($p = 0.009$). This is further supported by a single-centre cohort study carried out by Rissanen *et al.* [31] that treated 82 complex calcified large vessel de novo lesions with DCBs following lesion preparation by RA and predilatation. They reported an overall MACE rate of 14% and 20% at 12 months and 24 months respectively and an ischaemia driven TLR rate of 1.5% and 3.1% at 12 and 24-months respectively. Although, these results are encouraging, but numbers are small and randomized control trials are required to confirm these findings. In the interim, such data may instil confidence for operators to consider DCB in calcified lesions especially if they are in small vessels, where implanting a stent can enhance the risk for restenosis or if there are contraindications for DES (unable to take dual anti-platelet therapy beyond a month).

4. Challenges in use of DCB in calcified lesions

Although there is little in the literature to suggest a contraindication to the treatment of severely calcified lesions with DCBs, but there are technical limitations that may be faced when employing such a strategy. The delivery of antiproliferative drugs and their retention within the tissue upon balloon inflation is determined by adequate lesion preparation. Calcified lesions usually need aggressive lesion preparation with use of non-compliant, scoring and cutting balloons and/or rotational atherectomy. These aggressive lesion preparation strategies are important irrespective of the strategy (DES or DCB) as failure to prepare the lesions results in in-adequate stent expansion or in-adequate drug delivery in case of DCB. Aggressive lesion preparation also results in dissections, which is considered a good sign of lesion preparation, which then gets sealed with stents. However, if operator is considering DCB, dissections have to carefully evaluated as flow-limiting dissections (type C or more) is a contraindication for DCB and may lead to sub-optimal long-term results [32]. If, however the dissection is not flow-limiting, DCB can be considered. There is some data to support late lumen enlargement during angiographic follow-up post DCB especially in de novo lesions [33]. Kelber *et al.* [33] evaluated 58 consecutive native coronary artery lesions directly after DCB angioplasty and at a routine target follow-up angiography by QCA. A total of 69% of patients showed luminal enlargement whereas 29% had minor luminal loss [33].

Re-coil after lesion preparation is a well-known phenomenon and this can be negated with metallic stents. If re-coil is >50% it is not advisable to use DCB as it results in target lesion failure [32]. Further aggressive lesion preparation can be undertaken prior to DCB or switch the strat-

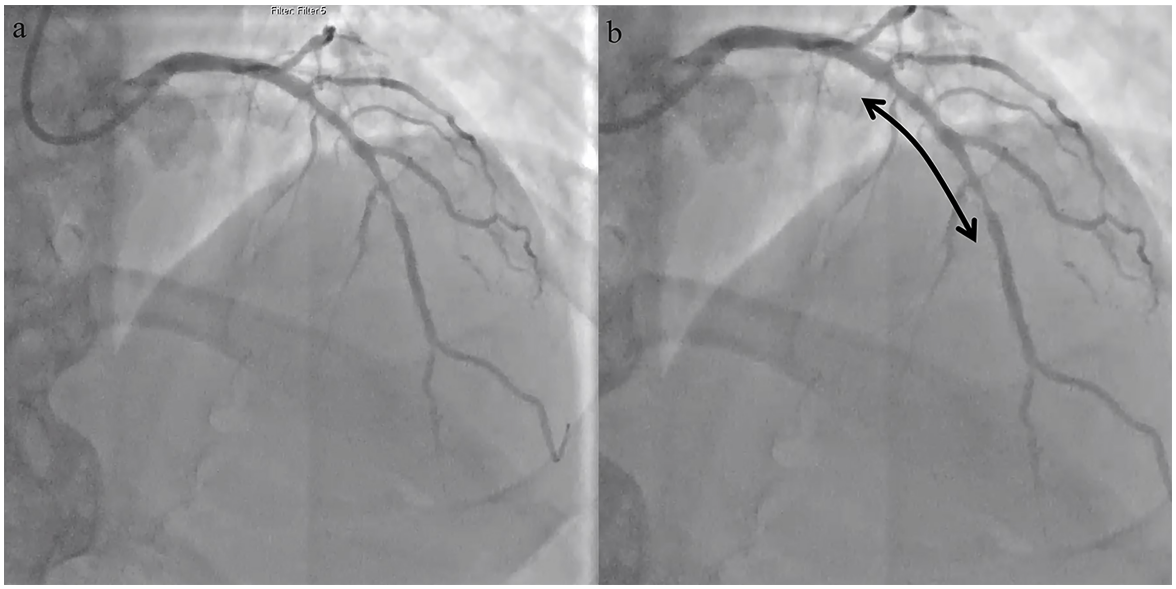

Fig. 1. Coronary angiogram showing a significant calcified disease in the mid-segment of left anterior descending artery. (a) Coronary angiogram showing a significant calcified disease in the mid-segment of left anterior descending artery. (b) Arrow highlighting the lesion.

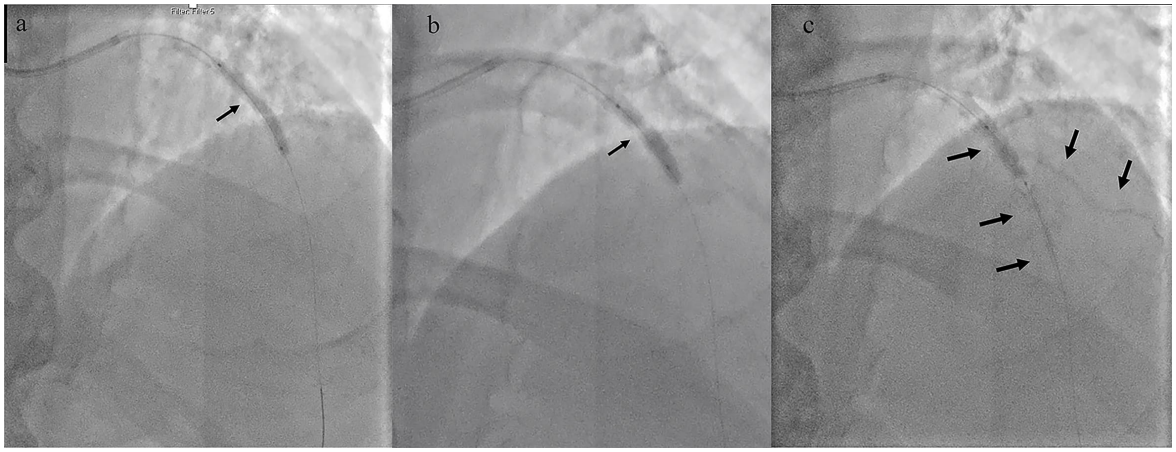

Fig. 2. Fluroscopic image showing the inability to prepare the lesions. (a,b) Using non-compliant balloons (2.5 mm and 3.0 mm) at high-pressures giving rise to dog-bone appearance (shown by the arrows). (c) Burst of a 3.5 mm non-compliant balloon when inflated at high-pressure (20 atm) with escape of contrast into the distal LAD and diagonal (shown by the arrows).

egy to stents. Finally, delivery of intracoronary devices and equipment can be challenging in calcified lesions. There is no time limit to the delivery of stents, which can be attempted multiple times by enhancing the support techniques (supportive guiding catheter, buddy wires, guide-extension devices). DCBs must be delivered within certain set-time (usually within 2-minutes) as there is drug loss during transit [32]. So, for calcified lesions requiring longer-lengths of DCB, operators have to anticipate obstacles and ensure adequate support is obtained prior to delivery of DCB.

5. Case

A 62-year old man awaiting cancer surgery and angina (CCS class III) was found to have a significant ischaemia in the anterior wall of the left ventricle on the stress echocardiogram. His background included; hypertension, hyperlipidaemia and previous smoking. At the time of presentation, he was on aspirin (primary prevention), atorvastatin and amlodipine. The coronary angiogram demonstrated a significant calcified disease in the mid-segment of left anterior descending artery (Fig. 1). His haemoglobin was 90 gm/dL, but was stable. Trial of medical therapy was not an option as time was not on our side given the urgency of cancer surgery. Since he was having CCS class 3 angina with large area of ischaemia in one of the major epicardial territories (LAD), we felt there was enough indication to undertake percutaneous intervention. The angioplasty was undertaken with a view to using a DCB to avoid the use of dual anti-platelet therapy beyond a month. Although, there is data for a month of dual antiplatelet therapy (DAPT) for certain DES, we felt, given

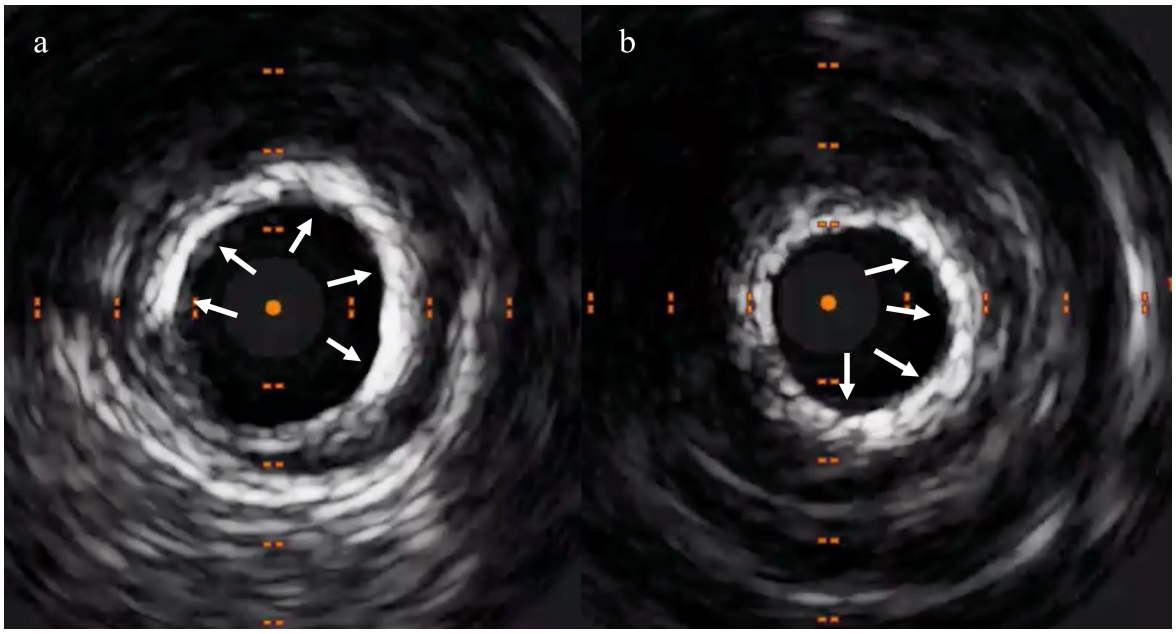

Fig. 3. IVUS exhibiting concentric calcification at the site of lesion, which was not yielding. (a) Calcium arc extending from 9'o clock to 5'o clock positions (shown by the arrows). (b) Calcium arc extending from 1'o clock to 6'o clock positions (shown by the arrows).

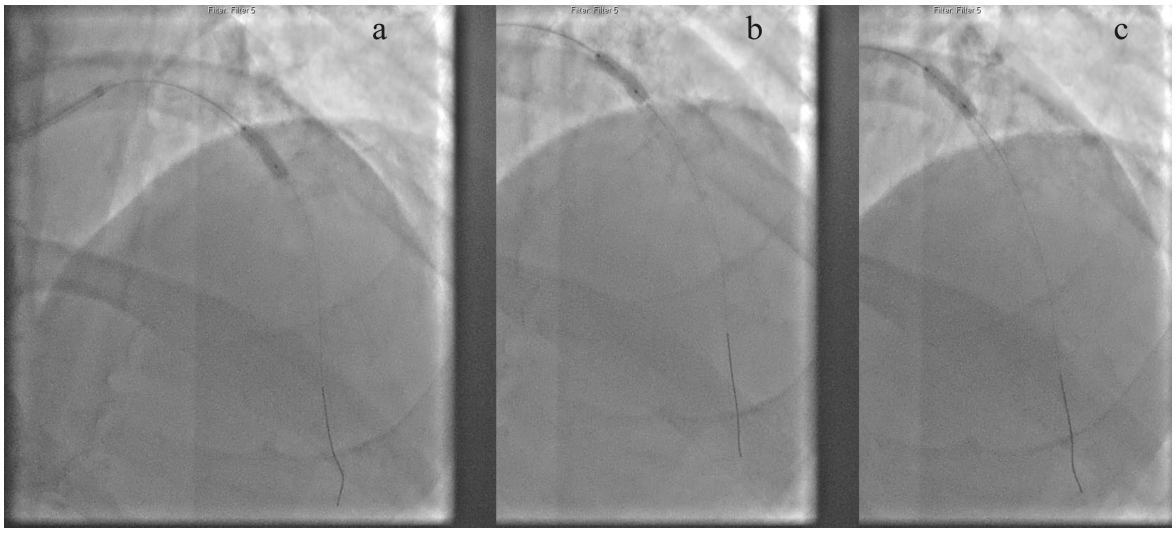

Fig. 4. 3.5 mm intra-vascular lithotripsy successfully cracked the lesion. (a) 3.5 mm IVL balloon successfully inflated in the mid-segment. (b) IVL balloon expanding in the proximal segment. (c) IVL balloon fully expanded in the proximal segment.

the calcified nature, the risk of stent thrombosis was high if the DAPT was interrupted at one month. Patient was loaded with 300 mg of clopidogrel prior to the procedure. The calcified lesion failed to yield with conventional non-compliant balloons (Fig. 2). High pressure inflation resulted in bursting of a 3.5 mm non-compliant balloon (Fig. 3). Intravascular imaging visualised concentric calcium (Fig. 4). Subsequently, we used a 3.5 mm intra-vascular lithotripsy (IVL) balloon (Fig. 5), which fractured the calcium which was confirmed on repeat intra-vascular imaging (Fig. 6). A long DCB (3.5 × 40 mm) was used to achieve excellent final result (Fig. 6). The clopidogrel was stopped at 2-weeks post PCI and patient subsequently underwent successful cancer surgery 3-weeks later on a single antiplatelet therapy (Aspirin). He remains free of angina at 6-months post-PCI. This demonstrates the potential value of DCB use in a patient awaiting a cancer surgery with a heavily calcified coronary lesion. Despite significant circumferential calcium, we were able to use a DCB to achieve a satisfactory result without significant recoil (<30%) or flow limiting dissection. Our patient underwent cancer surgery just after 3-weeks of the PCI with DCB. We had stopped the clopidogrel 2-weeks post PCI with DCB implying DAPT was interrupted at 2-weeks without any adverse effect. If we had used DES, we would not have had that liberty.

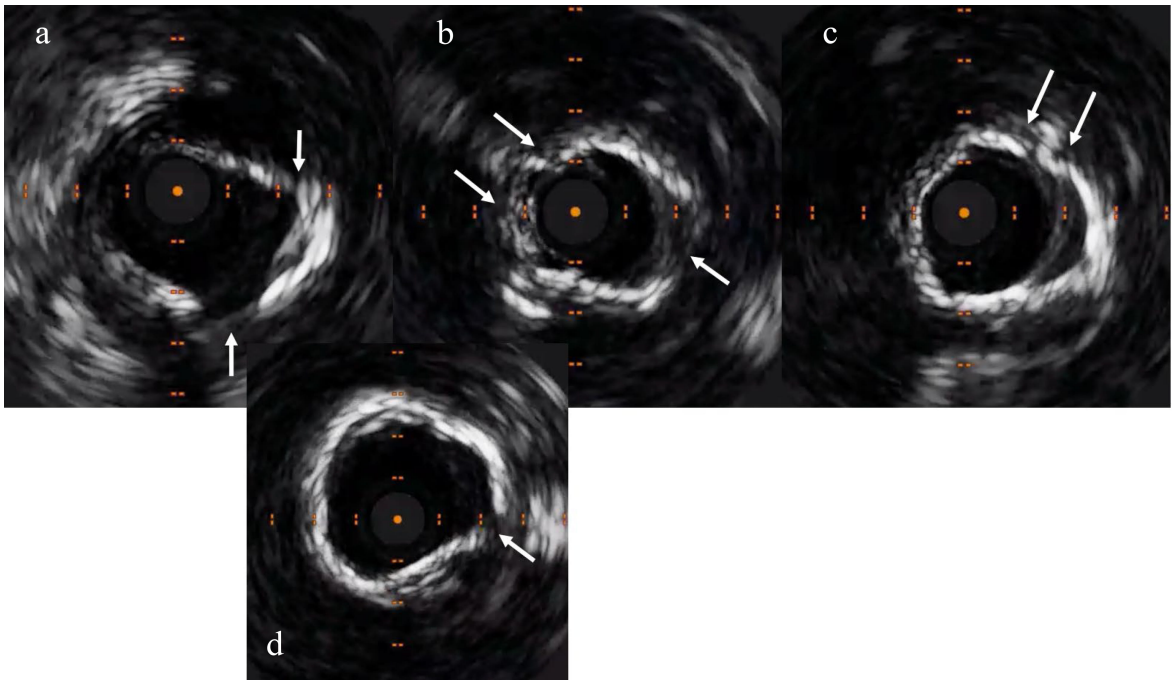

Fig. 5. Repeat IVUS exhibiting crack in the calcium (shown by the arrows). (a) Cracks at 2 and 5'o clock positions. (b) Cracks at 4 and 10'o clock positions. (c) Crack at 1'o clock position. (d) Crack at 3'o clock position (shown by the arrows).

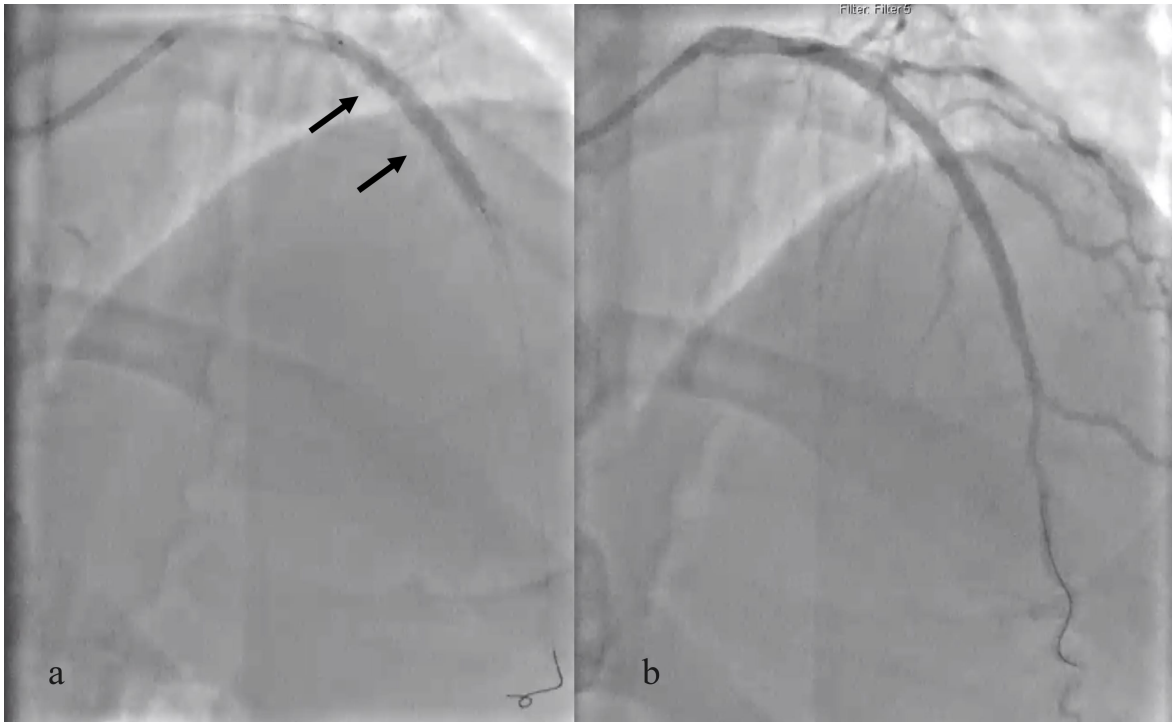

Fig. 6. Successful use of a long DCB (3.5 × 40 mm) to achieve excellent final result. (a) Successful use of a long DCB (3.5 × 40 mm). (b) Excellent final angiographic result.

6. Conclusions

Drug coated balloons offers an alternative modality in treatment of coronary stenosis especially in restenotic lesion and small vessel. Calcified lesions per se are not a contraindication for use of DCB, although there is no strong data to support use of DCB over DES. Henceforth, we are not recommending DCB routinely in the treatment of calcified lesions. However, if lesion(s) are long and located in a small vessel, then perhaps DCB can be considered over DES especially if adequate lesion preparation is achieved with no flow limit-

ing dissections. In addition, DCB can also be considered in patients with high-bleeding risk and those who cannot take DAPT beyond a month. The notion of performing percutaneous coronary revascularization leaving nothing behind in the vessel is attractive and is worthy of further evaluation.

Author contributions

SB—Manuscript preparation and case preparation, BHLW—Manuscript preparation and literature search, RW—Manuscript preparation, SA—Literature search and case preparation.

Ethics approval and consent to participate

Informed consent was obtained from all subjects involved in the study.

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Conflict of interest

The authors declare no conflict of interest.

References

[1] Cortese B, Micheli A, Picchi A, Coppolaro A, Bandinelli L, Severi S, *et al.* Paclitaxel-coated balloon versus drug-eluting stent during PCI of small coronary vessels, a prospective randomised clinical trial. The PICCOLETO study. Heart. 2010; 96: 1291–1296.

[2] Cortese B, Di Palma G, Guimaraes MG, Piraino D, Orrego PS, Buccheri D, *et al.* Drug-Coated Balloon Versus Drug-Eluting Stent for Small Coronary Vessel Disease: PICCOLETO II Randomized Clinical Trial. JACC: Cardiovascular Interventions. 2020; 13: 2840–2849.

[3] Habara S, Mitsudo K, Kadota K, Goto T, Fujii S, Yamamoto H, *et al.* Effectiveness of paclitaxel-eluting balloon catheter in patients with sirolimus-eluting stent restenosis. JACC: Cardiovascular Interventions. 2011; 4: 149–154.

[4] Jeger RV, Farah A, Ohlow MA, Mangner N, Möbius-Winkler S, Weilenmann D, *et al.* Long-term efficacy and safety of drug-coated balloons versus drug-eluting stents for small coronary artery disease (BASKET-SMALL 2): 3-year follow-up of a randomised, non-inferiority trial. Lancet. 2020; 396: 1504–1510.

[5] Rittger H, Brachmann J, Sinha AM, Waliszewski M, Ohlow M, Brugger A, *et al.* A randomized, multicenter, single-blinded trial comparing paclitaxel-coated balloon angioplasty with plain balloon angioplasty in drug-eluting stent restenosis: the PEPCAD-DES study. Journal of the American College of Cardiology. 2012; 59: 1377–1382.

[6] Scheller B, Clever YP, Kelsch B, Hehrlein C, Bocksch W, Rutsch W, *et al.* Long-Term Follow-up after Treatment of Coronary in-Stent Restenosis with a Paclitaxel-Coated Balloon Catheter. JACC: Cardiovascular Interventions. 2012; 5: 323–330.

[7] Lu W, Zhu Y, Han Z, Sun G, Qin X, Wang Z, *et al.* Short-term outcomes from drug-coated balloon for coronary de novo lesions in large vessels. Journal of Cardiology. 2019; 73: 151–155.

[8] Rosenberg M, Waliszewski M, Krackhardt F, Chin K, Wan Ahmad WA, Caramanno G, *et al.* Drug Coated Balloon-only Strategy in De Novo Lesions of Large Coronary Vessels. Journal of Interventional Cardiology. 2019; 2019: 6548696.

[9] Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, *et al.* 2018 ESC/EACTS Guidelines on myocardial revascularization. European Heart Journal. 2019; 40: 87–165.

[10] Basavarajaiah S, Athukorala S, Kalogeras K, Panoulas V, Loku Waduge BH, Bhatia G, *et al.* Mid-term clinical outcomes from use of Sirolimus coated balloon in coronary intervention; data from real world population. Catheterization and Cardiovascular Interventions. 2021; 98: 57–65.

[11] Vos NS, Fagel ND, Amoroso G, Herrman JR, Patterson MS, Piers LH, *et al.* Paclitaxel-Coated Balloon Angioplasty Versus Drug-Eluting Stent in Acute Myocardial Infarction: The REVELATION Randomized Trial. JACC: Cardiovascular Interventions. 2019; 12: 1691–1699.

[12] Farag M, Costopoulos C, Gorog DA, Prasad A, Srinivasan M. Treatment of calcified coronary artery lesions. Expert Review of Cardiovascular Therapy. 2016; 14: 683–690.

[13] Madhavan MV, Tarigopula M, Mintz GS, Maehara A, Stone GW, Généreux P. Coronary artery calcification: pathogenesis and prognostic implications. Journal of the American College of Cardiology. 2014; 63: 1703–1714.

[14] Mori H, Torii S, Kutyna M, Sakamoto A, Finn AV, Virmani R. Coronary Artery Calcification and its Progression. JACC: Cardiovascular Imaging. 2018; 11: 127–142.

[15] Otsuka F, Sakakura K, Yahagi K, Joner M, Virmani R. Has our understanding of calcification in human coronary atherosclerosis progressed? Arteriosclerosis, Thrombosis, and Vascular Biology. 2014; 34: 724–736.

[16] Buchanan GL, Basavarajaiah S, Chieffo A. Stent thrombosis: incidence, predictors and new technologies. Thrombosis. 2012; 2012: 956962.

[17] Dangas GD, Claessen BE, Caixeta A, Sanidas EA, Mintz GS, Mehran R. In-stent restenosis in the drug-eluting stent era. Journal of the American College of Cardiology. 2010; 56: 1897–1907.

[18] Iakovou I. Incidence, Predictors, and Outcome of Thrombosis after Successful Implantation of Drug-Eluting Stents. JAMA. 2005; 293: 2126–2130.

[19] Stolker JM, Kennedy KF, Lindsey JB, Marso SP, Pencina MJ, Cutlip DE, *et al.* Predicting restenosis of drug-eluting stents placed in real-world clinical practice: derivation and validation of a risk model from the EVENT registry. Circulation Cardiovascular Interventions. 2010; 3: 327–334.

[20] Head SJ, Davierwala PM, Serruys PW, Redwood SR, Colombo A, Mack MJ, *et al.* Coronary artery bypass grafting vs. percutaneous coronary intervention for patients with three-vessel disease: final five-year follow-up of the SYNTAX trial. European Heart Journal. 2014; 35: 2821–2830.

[21] Holm NR, Mäkikallio T, Lindsay MM, Spence MS, Erglis A, Menown IBA, *et al.* Percutaneous coronary angioplasty versus coronary artery bypass grafting in the treatment of unprotected left main stenosis: updated 5-year outcomes from the randomised, non-inferiority NOBLE trial. Lancet. 2020; 395: 191–199.

[22] Stone GW, Kappetein AP, Sabik JF, Pocock SJ, Morice MC, Puskas J, *et al.* Five-Year Outcomes after PCI or CABG for Left Main Coronary Disease. The New England Journal of Medicine. 2019; 381: 1820–1830.

[23] Cosgrave J, Melzi G, Biondi-Zoccai GGL, Airoldi F, Chieffo A, Sangiorgi GM, *et al.* Drug-eluting stent restenosis the pattern predicts the outcome. Journal of the American College of Cardiology. 2006; 47: 2399–2404.

[24] Latib A, Mussardo M, Ielasi A, Tarsia G, Godino C, Al-Lamee R, *et al.* Long-term outcomes after the percutaneous treatment of drug-eluting stent restenosis. JACC: Cardiovascular Interventions. 2011; 4: 155–164.

[25] Ali ZA, Gao R, Kimura T, Onuma Y, Kereiakes DJ, Ellis SG, *et al.* Three-Year Outcomes with the Absorb Bioresorbable Scaffold: Individual-Patient-Data Meta-Analysis from the ABSORB Randomized Trials. Circulation. 2018; 137: 464–479.

[26] Goel S, Pasam RT, Chava S, Sharma A, Malik BA, Ayzenberg S, *et al.* Three to four years outcomes of the absorb bioresorbable vascular scaffold versus second-generation drug-eluting stent: a

meta-analysis. Catheterization and Cardiovascular Interventions. 2020; 95: 216–223.
[27] Lin Y, Sun X, Liu H, Pang X, Dong S. Drug-coated balloon versus drug-eluting stent for treating de novo coronary lesions in large vessels: a meta-analysis of clinical trials. Herz. 2021; 46: 269–276.
[28] Ito R, Ueno K, Yoshida T, Takahashi H, Tatsumi T, Hashimoto Y, *et al.* Outcomes after drug-coated balloon treatment for patients with calcified coronary lesions. Journal of Interventional Cardiology. 2018; 31: 436–441.
[29] Nagai T, Mizobuchi M, Funatsu A, Kobayashi T, Nakamura S. Acute and mid-term outcomes of drug-coated balloon following rotational atherectomy. Cardiovascular Intervention and Therapeutics. 2020; 35: 242–249.
[30] Ueno K, Morita N, Kojima Y, Takahashi H, Kawasaki M, Ito R, *et al.* Safety and Long-Term Efficacy of Drug-Coated Balloon Angioplasty following Rotational Atherectomy for Severely Calcified Coronary Lesions Compared with New Generation Drug-Eluting Stents. Journal of Interventional Cardiology. 2019; 2019: 9094178.
[31] Rissanen TT, Uskela S, Siljander A, Kärkkäinen JM, Mäntylä P, Mustonen J, *et al.* Percutaneous Coronary Intervention of Complex Calcified Lesions with Drug-Coated Balloon after Rotational Atherectomy. Journal of Interventional Cardiology. 2017; 30: 139–146.
[32] Jeger RV, Eccleshall S, Wan Ahmad WA, Ge J, Poerner TC, Shin E, *et al.* Drug-Coated Balloons for Coronary Artery Disease: Third Report of the International DCB Consensus Group. JACC: Cardiovascular Interventions. 2020; 13: 1391–1402.
[33] Kleber FX, Schulz A, Waliszewski M, Hauschild T, Böhm M, Dietz U, *et al.* Local paclitaxel induces late lumen enlargement in coronary arteries after balloon angioplasty. Clinical Research in Cardiology. 2015; 104: 217–225.