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Application of Drug-Coated Balloons in Complex High Risk and Indicated Percutaneous Coronary Interventions

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ABSTRACT

There is a growing trend of patients with significant comorbidities among those referred for percutaneous coronary intervention (PCI). Consequently, the number of patients undergoing complex high risk indicated PCI (CHIP) is rising. CHIP patients frequently present with factors predisposing to extensive drug-eluting stent (DES) implantation, such as bifurcation and/or heavily calcified coronary lesions, which exposes them to the risks associated with an increased stent burden. The drug-coated balloon (DCB) may overcome some of the limitations of DES, either through a hybrid strategy (DCB and DES combined) or as a leave-nothing-behind strategy (DCB-only). As such, there is a growing interest in extending the application of DCB to the CHIP population. The present review provides an outline of the available evidence on DCB use in CHIP patients, which comprise the elderly, comorbid, and patients with complex coronary anatomy. Although the majority of available data are observational, most studies support a lower threshold for the use of DCBs, particularly when multiple CHIP factors coexist within a single patient. In patients with comorbidities which predispose to bleeding events (such as increasing age, diabetes mellitus, and hemodialysis) DCBs may encourage shorter dual antiplatelet therapy duration—although randomized trials are currently lacking. Further, DCBs may simplify PCI in bifurcation lesions and chronic total coronary occlusions by reducing total stent length, and allow for late lumen enlargement when used in a hybrid fashion. In conclusion, DCBs pose a viable therapeutic option in CHIP patients, either as a complement to DES or as stand-alone therapy in selected cases.

1 | Introduction

Percutaneous coronary intervention (PCI) for chronic coronary syndromes in contemporary practice has become progressively selective [1], as the treatment target has shifted to cardiac symptom relief following large randomized trials [2, 3]. Those patients referred to the catheterization laboratory for revascularization are characterized by increasing complexity [4, 5]. Indeed, the prevalence of complex high risk indicated PCI (CHIP) is growing, a classification which is known to encompass a heightened risk at in-hospital and major adverse cardiac or cerebrovascular events (MACCE) [6, 7]. The definition of CHIP generally comprises three clinical spheres [1]: patient characteristics and comorbidities [2], coronary anatomical

Abbreviations: BMS, bare metal stent; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHIP, complex high risk and indicated PCI; CTO, chronic total coronary occlusion; DAPT, dual antiplatelet therapy; DCB, drug-coated balloon; DES, drug-eluting stent; HBR, high bleeding risk; ICA, invasive coronary angiography; ISR, in-stent restenosis; LLL, late luminal loss; LM, left main; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac or cerebrovascular events; MACE, major adverse cardiovascular events; MB, main branch; MI, myocardial infarction; MVD, multivessel disease; PCI, percutaneous coronary intervention; PTX, paclitaxel; SB, side branch; SVD, small vessel disease; TLR, target lesion revascularization.

complexity, and [3] ventricular hemodynamics [8]. Importantly, the coexistence of multiple risk factors may pose a dilemma for the physician; anatomically complex lesions often require extensive stent deployment, which exposes a CHIP patient to an increased risk of in-stent restenosis (ISR) [9, 10]. In addition, the required duration of dual antiplatelet therapy (DAPT) could magnify the risk of bleeding in conjunction with other CHIP factors [11]. These limitations of DES have revived the interest in drug-coated balloons (DCB). The benefit of a DCB lies in the absence of a metallic cage, while facilitating a rapid and uniform antiproliferative drug transfer to the coronary vessel wall [12]. Furthermore, DCB use may drive a less aggressive antithrombotic regime [13]. DCBs have recently been appointed a guideline Class II recommendation (evidence level A) for the management of ISR [14], but its potential has prompted research into de novo coronary artery disease (CAD). The heightened risk profile of CHIP patients demands alternative therapeutic options which reduce stent burden, either through a combination of DES and DCB (hybrid strategy) or with DCB-only treatment. In this review, we discuss the definition of CHIP and its role in clinical practice, followed by a comprehensive overview of the current evidence on the safety and feasibility of DCB utilization in CHIP patients in the first (patient characteristics and comorbidities) and second (coronary anatomical complexity) clinical spheres.

2 | CHIP

2.1 | Definitions

The term complex high risk and indicated PCI has been introduced as early as 2016 [8], with various definitions mentioned throughout literature (Table 1). In general, CHIP is considered to be a composite of three spheres: patient characteristics, coronary complexity, and ventricular hemodynamics (Figure 1) [8]. The primary sphere "patient characteristics" pertains to the presence of (concomitant) comorbidities, or prior medical history favoring PCI over coronary artery bypass grafting (CABG) due to an increased surgical risk. The second sphere "coronary complexity" includes (but is not limited to) left main (LM) disease, severe calcification, bi- or trifurcation lesions, chronic total coronary occlusions (CTOs), ostial lesions, thrombus, and disease of saphenous vein grafts (SVG) [8, 15, 16]. The final sphere considers "ventricular hemodynamics"; risk factors which may predispose to hemodynamic decompensation during intervention (e.g., impaired ventricular function or valvular disease). An example of a typical CHIP patients is shown in Figure 2.

2.2 | CHIP in Clinical Practice

Several studies have reported an increase in comorbidities in patients eligible for angioplasty [1, 28], along with a rise in coronary disease complexity [29]. In contrast, the landscape of interventional cardiology is evolving as revascularization rates are declining [30]. This change has been attributed to recent insights into the efficacy of revascularization in patients with stable CAD, which suggest that PCI leads to cardiac symptom relief but does not reduce the occurrence of major adverse cardiovascular events (MACE) [2, 3, 31, 32]. Nevertheless, patients with CHIP characteristics are often excluded from the aforementioned clinical trials. Although CABG is preferred in certain cases (e.g., complex multivessel disease [MVD] or LM CAD) [33, 34], there remains a proportion of patients who are ineligible for surgery and in whom invasive treatment is deemed appropriate. The treatment of these patients partly relies on dedicated interventionalists.

2.3 | Determining Risk Profile and Outcome

Most studies concur that CHIP patients are at an increased risk for adverse events, as reflected by a higher rate of in-hospital complications [22], higher incidence of MACE at follow-up (FU) [7], and reduced long-term survival rate [18, 23]. Factors which mark a CHIP patient (e.g., age and bifurcation lesions) are associated with ISR and ischemia-driven target lesion revascularization (TLR) [10]. Extensive stenting, suboptimal stent expansion, and malapposition are at the root of these adverse events [9, 35, 36]. To identify which CHIP patients are most at risk for a poor clinical outcome, various risk scores have been developed [6, 18]. These studies emphasized an increased all-cause mortality rate in CHIP patients, as well as an exponential rise in in-hospital MACCE rate with increasing CHIP score. Reducing stent burden may directly impact the risk associated with CHIP PCI, which makes DCB-angioplasty a compelling alternative therapeutic option. The potential advantages and limitations of a DCB strategy in CHIP PCI are summarized in the Central illustration (Figure 3).

3 | Rise of the DCB

3.1 | Introduction to DCB Technology

Delayed healing after permanent caging of a vessel is an important disadvantage of DES, and may lead to ISR and stent thrombosis [37]. Indeed, TLR rates following DES implantation show an annual increase without plateau [38]. These risks sparked the reintroduction of the DCB as a surrogate for DES [39]. The DCB has a variable degree of compliance, and adequate lesion preparation is imperative in achieving optimal antiproliferative drug delivery [40]. The efficacy of a DCB is the product of the interaction between the excipient, drug, and coating procedure. Paclitaxel (PTX) is the most common agent in DCB technology, usually applied at a concentration of $3\,\mu g/mm^2$. PTX acts through the disruption of cell division by binding to (and stabilizing) microtubules, preventing mitosis and smooth muscle cell proliferation as the cell is arrested in the M-phase [41]. PTX coated balloons have been shown to be safe both in the treatment of CAD and peripheral artery disease [42–44]. Given the earlier concerns of the safety of PTX, rapamycin (sirolimus) was opted as an alternative. This drug, known for its widespread application in DES, acts through the inhibition of mammalian target of rapamycin (mTOR), a key kinase which regulates cell growth and proliferation [45]. Although prior trials have reported a good efficacy of the sirolimus coated balloon [46–48], recent studies suggested that

TABLE 1 | Definitions of CHIP throughout literature.

Definitions of complex high risk indicated percutaneous coronary interventions					
Authors	**Sample size†**	**Study design**	**Definition**	**Primary endpoint**	**Relevant outcomes**
Kirtane et al. [8]	—	Literature review	Composite risk derived from the integration of three clinical spheres: (1) patient risk factors and comorbid conditions*, (2) location and complexity of coronary anatomy**, (3) hemodynamics, ventricular function, and concomitant valvular disease	—	—
Kinnaird et al. [17]	30,268 (100%)	National registry (BCIS), observational, retrospective	Defined by patient characteristics (age ≥ 80 years, LVEF ≤ 30%, prior CABG, or chronic renal failure) and/or procedural characteristics (LM, CTO, LV support, use of rotational atherectomy, or laser atherectomy)	Temporal changes in CHIP-PCI volume; relationship between operator CHIP-PCI volume and outcome	CHIP-PCI volume increased over time (28% in 2007 to 36% in 2014). Higher operator volumes were associated with higher rates of patient comorbidity and procedural complexity. Improved 12-month survival was not associated with higher operator volumes.
Brener et al. [18]	4,478 (38.6%)	Single-center, observational, retrospective	Defined as any of the following: age > 80 years, LVEF < 30% before PCI, dialysis, prior CABG, LM, CTO, or > 2 lesions in > 1 coronary artery	Identification of risk factors for 1-year all-cause mortality to develop a CHIP score	All-cause mortality at 1 year FU is 2.5-fold higher in CHIP patients compared to non-CHIP patients. Increasing risk score translates to higher mortality rates.
Leick et al. [19]	—	Literature review	Defined by patient related criteria (age, diabetes, COPD, CKD, peripheral vascular disease, heart failure, prior cardiac surgery, concomitant valve disease), coronary anatomy (MVD, CTO, unprotected LM, last remaining vessel, calcified lesions, long lesions, complex bifurcation lesions), and hemodynamic status (increased LV end-diastolic pressure, anticipated prolonged ischemic time, impaired cardiac output, large area of myocardium at risk, lower mean arterial pressure, ventricular arrhythmias).	—	—

(Continues)

TABLE 1 | (Continued)

Definitions of complex high risk indicated percutaneous coronary interventions					
Authors	**Sample size†**	**Study design**	**Definition**	**Primary endpoint**	**Relevant outcomes**
Protty et al. [6]	313,054 (64.1%)	National registry (BCIS), observational, retrospective	Includes patient factors (age ≥ 80 years, female sex, previous stroke, previous MI, peripheral vascular disease, EF < 30%, and chronic renal disease) and procedural factors (rotational atherectomy, LM PCI, 3-vessel PCI, dual arterial access, LV support, and total lesion length > 60 mm)	Identification of variables associated with in-hospital MACCE (composite of death, periprocedural CVA or MI) to construct a CHIP score	seven patient and six procedural factors were identified. In-hospital MACCE increased exponentially as the CHIP score increased.
Shamkhani et al.‡ [20]	424,290 (33%)	National registry (BCIS), observational, retrospective	Presence of at least one high-risk feature in the clinical sphere (prior CABG, chronic renal failure, severely impaired LV function) or procedural sphere (LM, CTO, severe vascular calcification treatment, LV support)	Stratified to age: in-hospital all-cause mortality, MACCE (composite of death, periprocedural CVA or MI), and in-hospital complications	Mortality, MACCE, and major bleeding increased by age group (adjusted for baseline risk). MACCE and major bleeding trends significantly declined, with the greatest decline in octogenarians.
Van den Buijs et al. [21]	41 (100%)	Multicenter, observational, retrospective	Patients with an unprotected LM artery, last patent vessel, or complex 3-vessel CAD, with a LVEF of ≤30%–40%, and severe comorbidities (e.g., severe valve disease(s), renal, pulmonary, or cerebrovascular) that were declined for CABG	MACE and mortality at hospital discharge and 30-day mortality following CHIP with MCS (VA-ECMO or Impella CP)	In CHIP patients, there were no differences in MACE rate and hemodynamic instability between VA-ECMO or Impella CP device.
Fujimoto et al. [22]	989 lesions (140 definite CHIP)	Single-center, observational, retrospective	Definite CHIP was defined as the presence of one complex PCI feature (LM, CTO, rotational atherectomy, orbital atherectomy, three-vessel disease with ≥ 90% stenosis or proven ischemia), together with patient factors* and complicated heart disease**. *Frailty, active malignancy, use of immunosuppressive drugs (incl. corticosteroids), pulmonary disease requiring inhalants, liver cirrhosis, chronic renal failure on hemodialysis, and previous cerebral infarction **unstable hemodynamics, LVEF ≤ 40%, and moderate or severe valvular disease	Major complication rate (composite endpoint) in PCI in patients with definite CHIP, possible CHIP, and non-CHIP	The major complications incidence of PCI was highest in the definite CHIP group, followed by the possible CHIP group and lowest in the non-CHIP group. Among CHIP factors, immunosuppressive drugs, unstable hemodynamics and frailty were associated with major complications.

(Continues)

TABLE 1 | (Continued)

Definitions of complex high risk indicated percutaneous coronary interventions					
Authors	**Sample size†**	**Study design**	**Definition**	**Primary endpoint**	**Relevant outcomes**
Satake et al. [23]	695 (46.3%)	Single-center, observational, retrospective	At least one criterion for both patient and procedure characteristics. Patient characteristics include: age ≥ 75 years old, LVEF ≤ 35%, DM, ACS, prior CABG, PAD, CKD, COPD, severe valvular disease (aortic stenosis or mitral regurgitation). Procedural characteristics include: unprotected LM disease, degenerated SVGs or radial artery grafts, severely calcified lesions requiring rotational atherectomy, last patent coronary conduit, CTO, MVD, use of MCS	All-cause mortality during FU; secondary endpoints include nonfatal MI, new restenosis lesions receiving repeat revascularization, stroke, and congestive HF leading to hospital admission	The survival was significantly lower in CHIP patients than in non-CHIP patients. Age, COPD, LVEF, severe CKD, and use of MCS after CHIP-PCI were significant predictors of all-cause mortality after adjustment for several prognostic variables
Tyczynski et al. [24]	232 (35%)	Single-center, observational, retrospective	Defined as having at least one clinical criterion and one anatomical high-risk criterion. Clinical criteria include: advanced age (≥75 years), DM, ACS, heart failure with LVEF ≤ 35%, prior cardiac surgery, PVD, advanced chronic kidney disease (eGFR < 30 mL/min/1.73 m^2), COPD, concomitant severe aortic valvulopathy, or severe mitral regurgitation. Anatomical criteria include: unprotected LM disease, degenerated SVGs, severely calcified lesions requiring rotational atherectomy, last patent conduit, or CTO in a patient with MVD	Performance and safety of PCI in CHIP and HBR patients at 4-years follow-up	Compared to the whole population, CHIP and HBR patients had a higher rate of MACE and cardiac death at FU. PCI in CHIP and HBR patients is feasible with a low rate of periprocedural complications

Note: Definitions used in previous studies are linked by color. †Total sample size (percentage of CHIP patients). ‡Definition has been used in previous publications of the same research group [25–27]. For simplicity, only one study is depicted in this overview.

Abbreviations: ACS, acute coronary syndrome; BCIS, British cardiovascular intervention society; CAD, coronary artery disease; CHIP, complex high risk indicated PCI; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CTO, chronic total coronary occlusion; CVA, cerebral vascular accident; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate, HBR, high bleeding risk; HF, heart failure; HR, hazard ratio; LV, left ventricle; LVEF, left ventricular ejection fraction; MAC(C)E, major adverse cardiovascular (cerebrovascular) events, MCS, mechanical circulatory support; MI, myocardial infarction; MVD, multivessel disease; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; RCT, randomized controlled trial; SVG, saphenous vein graft.

*Including those that preclude surgical or percutaneous revascularization

**Including adequacy of vessels for PCI or for surgical targets.

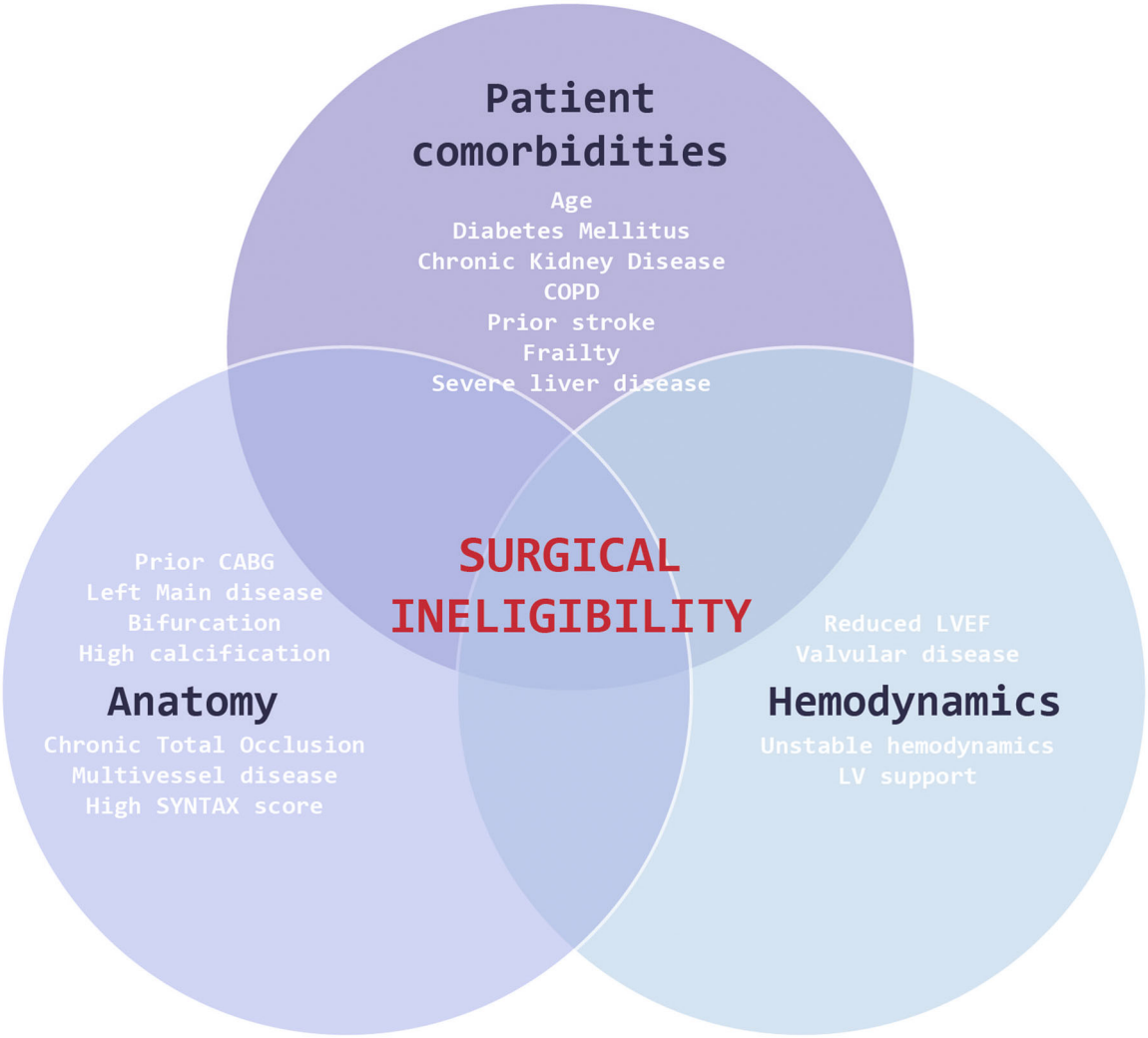

FIGURE 1 | Three spheres of CHIP. [Color figure can be viewed at wileyonlinelibrary.com]

PTX has more potential in the late positive remodeling of the treated artery [49, 50]. Figure 4 shows the difference in drug penetration between both agents.

3.2 | Role of DCB in Current Practice

3.2.1 | ISR

The interest in DCBs was driven by clinical scenarios in which stenting was not clinically feasible or desirable. In addition, very-late stent-related adverse events has been reported to occur in ~2%, regardless of stent type [51]. The earliest trials on DCB can be traced back to its use in ISR. Scheller et al. [52] compared PTX-coated balloons to uncoated balloon catheters in ISR. At 6 months FU, angiographic in-segment late luminal loss (LLL) was lower in the PTX arm (0.03 ± 0.48 mm vs. 0.74 ± 0.86 mm, $p = 0.002$). Importantly, the 12-month MACE rate was 4% in the PTX group (vs. 31% in the uncoated arm, $p = 0.01$). These findings were confirmed at 5 year FU [53]. Unverdorben et al. [54] extended the comparison to an older generation PTX-eluting stent (Taxus Liberté), demonstrating reduced rates of binary restenosis and improved event-free survival in the DCB arm. A myriad of studies evaluated DCB in ISR of BMS [55, 56], DES [57–59], or both [60, 61]. These trials led to the consensus that DCB in BSM-ISR and DES-ISR is safe [62], resulting in a European Class I recommendation with Level A of evidence [63]. Importantly, a recent update of the ESC guideline downgraded DCB-angioplasty in ISR to a Class IIa recommendation [14]. Possibly, this change may impact the uptake of DCB for ISR in clinical practice in Europe. Treatment of DES-ISR remains highly challenging, and it should be noted that successful DCB-angioplasty warrants careful lesion optimization (defined as a residual % diameter stenosis $\leq 20\%$, balloon-to-stent ratio of >0.91, and an inflation time of >60 s [64]) and may benefit from the use of intravascular imaging (to guide balloon sizing and dilation) [65]. Future studies should incorporate these key methodological steps, so we may fully appreciate the therapeutic efficacy of DCBs in ISR.

3.2.2 | Small Vessel Disease (SVD) and High-Bleeding Risk (HBR)

Parallel to its application in ISR, there is a growing body of evidence on DCB in SVD and patients with HBR. In SVD, the capacity to adapt to neointima formation without compromising blood flow is hampered following stenting, resulting in

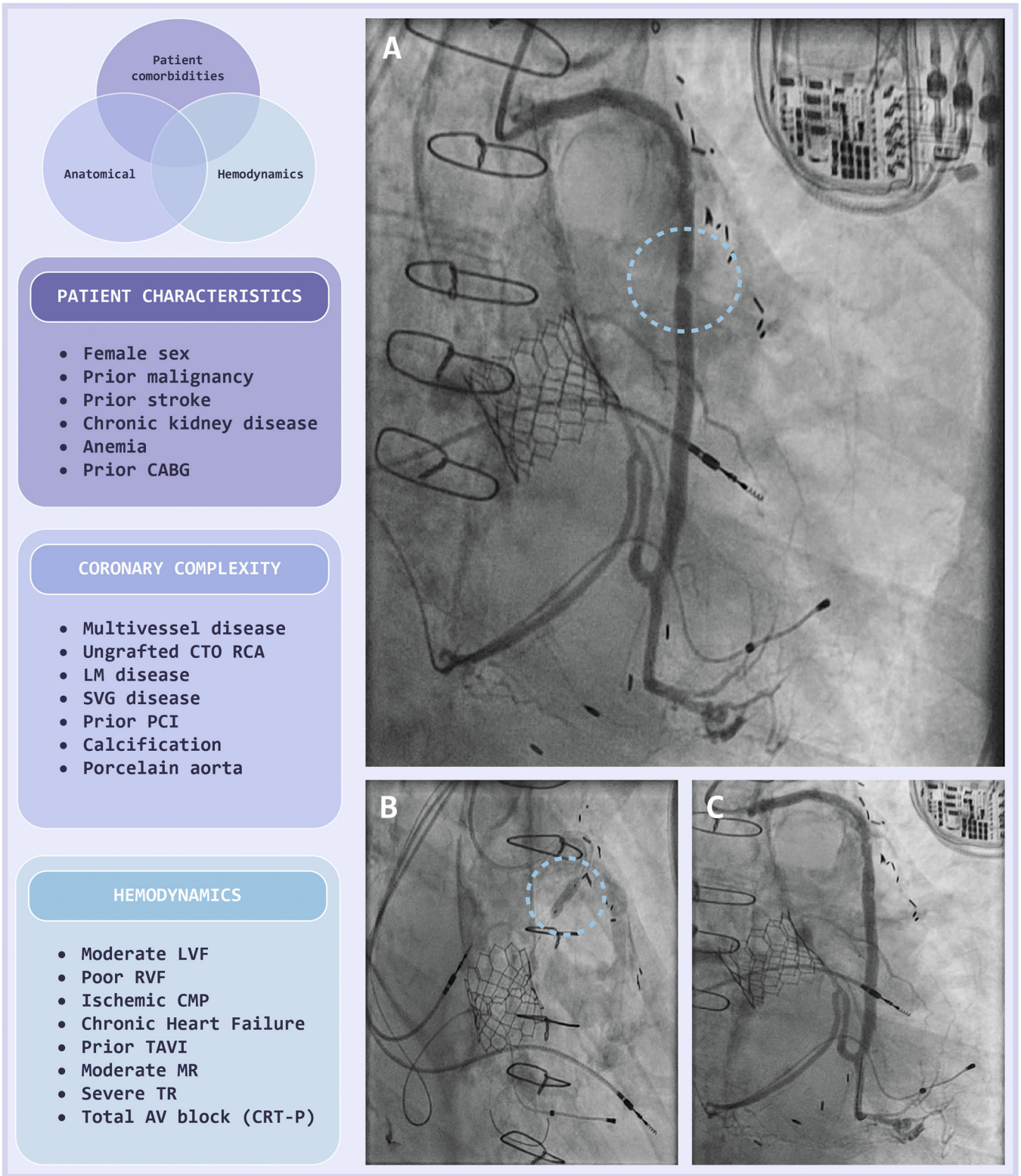

FIGURE 2 | Case example of CHIP patient. Case example of a patient with CHIP factors pertaining to all clinical spheres. A significant stenosis in the SVG (A, dotted circle) was treated with PCI (B, C). AV, atrioventricular; CMP, cardiomyopathy; CRT-P, cardiac resynchronization therapy pacemaker; MR, mitral regurgitation; RCA, right coronary artery; RVF, right ventricular function; TAVI, transcatheter aortic valve implantation; TI, tricuspid regurgitation. [Color figure can be viewed at wileyonlinelibrary.com]

higher clinical event rates [66]. Late lumen enlargement (LLE) following DCB treatment could therefore prove beneficial [67]. Interestingly, a recent meta-analysis including all relevant RCTs on DCB use in SVD showed similar rates of angiographic restenosis and LLL [68]. In interpreting these studies, one should consider the varying definitions for SVD across trials, the observed heterogeneity of the investigated patient population and collected clinical endpoints, and absence of routine

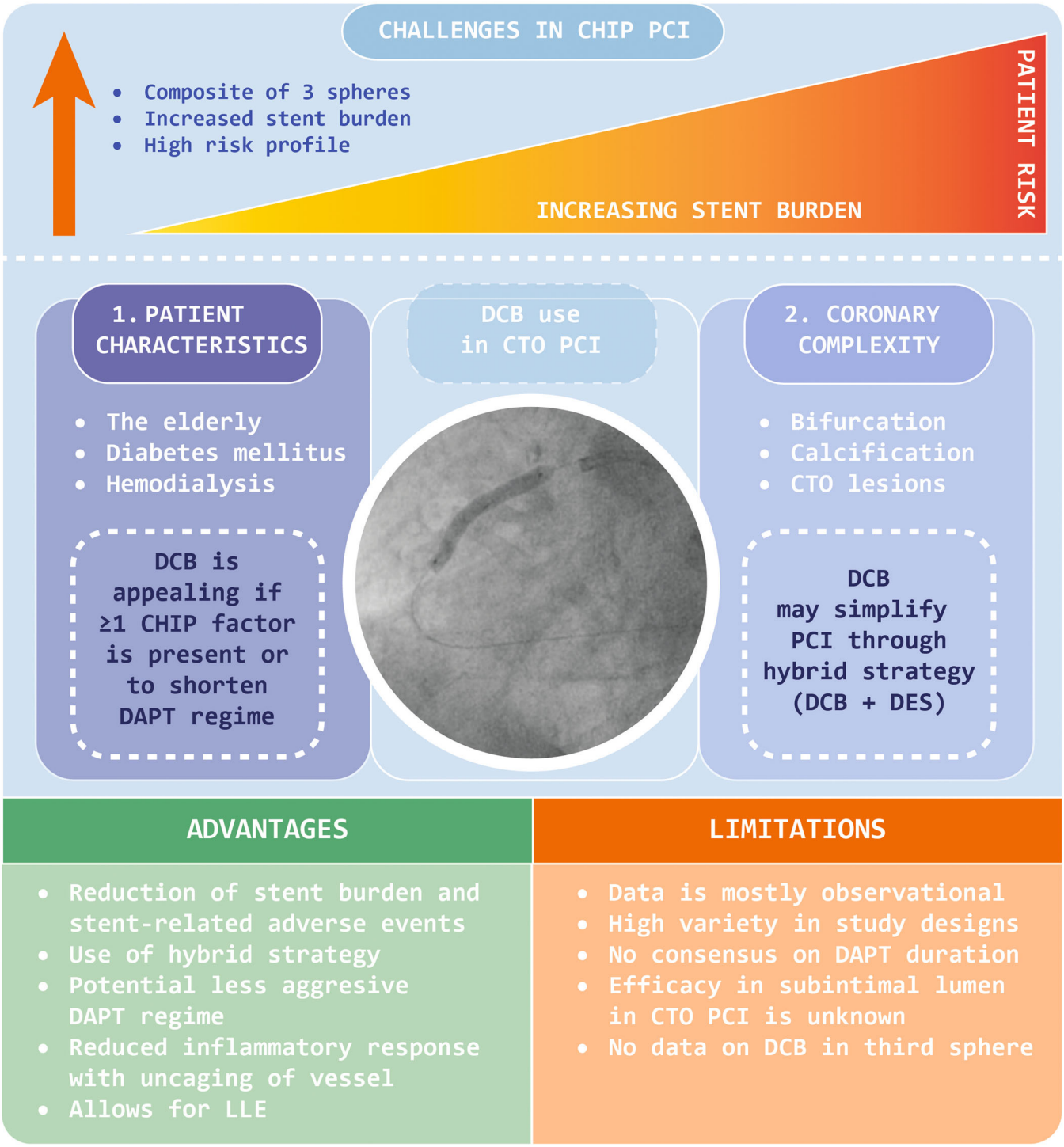

FIGURE 3 | Central illustration. The present review investigated the application of drug-coated balloon (DCB) angioplasty in complex high risk and indicated percutaneous coronary intervention (CHIP). There exist numerous advantages to DCB-angioplasty in CHIP, such as the reduction of stent burden and the potential for a less aggressive dual antiplatelet therapy regime. These benefits should be weighed against the known limitations of DCB. As the data is mostly observational, caution is advised when using DCB-angioplasty in complex coronary lesions where randomized data are lacking. [Color figure can be viewed at wileyonlinelibrary.com]

angiographic FU with a high variety in follow-up time [69]. Regardless of these limitations, DCB in SVD is considered an attractive alternative to DES in reducing stent burden [69]. Regarding HBR, Rissanen and colleagues explored the use of DCB in the DEBUT (DCB for Treatment of De-novo Coronary Artery Lesions in Patients With HBR) trial. The authors compared PTX-DCB to BMS, both options which allow a shortened DAPT duration of 1 month in patients with stable CAD. This study demonstrated lower MACE rate at 9 months follow-up in the DCB arm. As the DAPT regime was similar between groups, it is unsurprising that bleeding events did not differ [70]. In the BASKET-SMALL 2 (Basel Kosten-Effektivitäts trial, DCBs for Small CAD) trial, the potential effects of a less aggressive DAPT regime are better appreciated. This cohort of SVD patients (20%

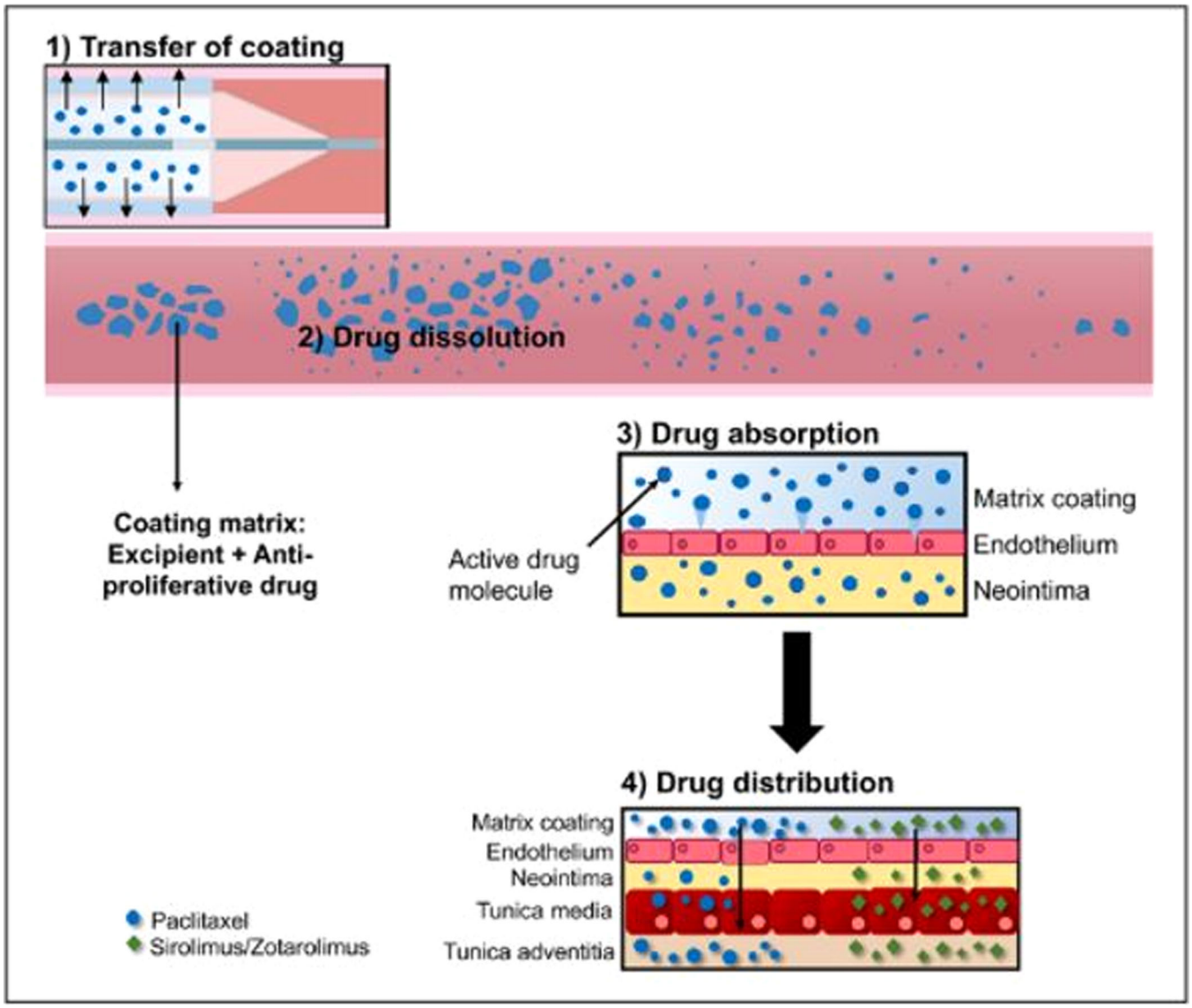

FIGURE 4 | Drug penetration of paclitaxel and sirolimus. Paclitaxel predominantly penetrates into the tunica adventitia, whereas sirolimus shows an equal drug distribution in the tunica adventitia and tunica media. Image by Ang et al. [12]. [Color figure can be viewed at wileyonlinelibrary.com]

HBR) demonstrated a numerical reduction of bleeding events at 3 years FU after DCB use [71]. Although the use of a reduced DAPT period or single antiplatelet therapy appear feasible and safe [13, 72], this remains to be confirmed in a randomized setting. Current ESC guidelines propose a DAPT regime of 6 months following DCB (Class IIa, evidence level B), but shorter DAPT duration (≤3 months) may be considered in HBR [73]. The International DCB consensus group advocates 1 month DAPT based on expert opinion [74]. The DEBATE (DCB in Anticoagulated and Bleeding Risk Patients Undergoing PCI) trial (ClinicalTrials.gov identifier: NCT04814212) will explore the combination of DCB-treatment and shortened DAPT duration in de novo lesions of HBR patients.

3.2.3 | De Novo Lesions

At present, data on the use of DCB in de novo lesions in large coronary vessels are expanding. Shin et al. [75] reported a lower MACE rate in patients treated with the hybrid strategy (DCB and DES) versus DES-only in MVD. Although the authors did not elaborate on the applied DAPT regime, major bleeding events were reportedly lower in the hybrid strategy arm. Furthermore, the reduced or complete lack of stent burden may facilitate treatment with either DCB or DES if TLF occurs, without resulting in multiple stent layers. To expand the role of DCB in de novo lesions, Gao et al. [76] investigated the efficacy of DCB angioplasty with rescue stenting compared to intended stenting in an all-comer, de novo, non-complex patient population in the important REC-CAGEFREE I trial. Notably, DCB did not achieve non-inferiority compared to DES in terms of the device oriented composite endpoint at 2 years. Notwithstanding these results, the trial was able to confirm the safety of DCB-only angioplasty: no acute occlusion occurred in the DCB arm, and the rate of definite or probable device or vessel thrombosis was extremely low. Moreover, subgroup analyses of bifurcation lesions and SVD showed that DCB angioplasty was non-inferior to DES. Future RCTs are needed to explore the potential of DCB angioplasty in more complex patients and anatomical settings, as well as different DCBs with novel coating technologies.

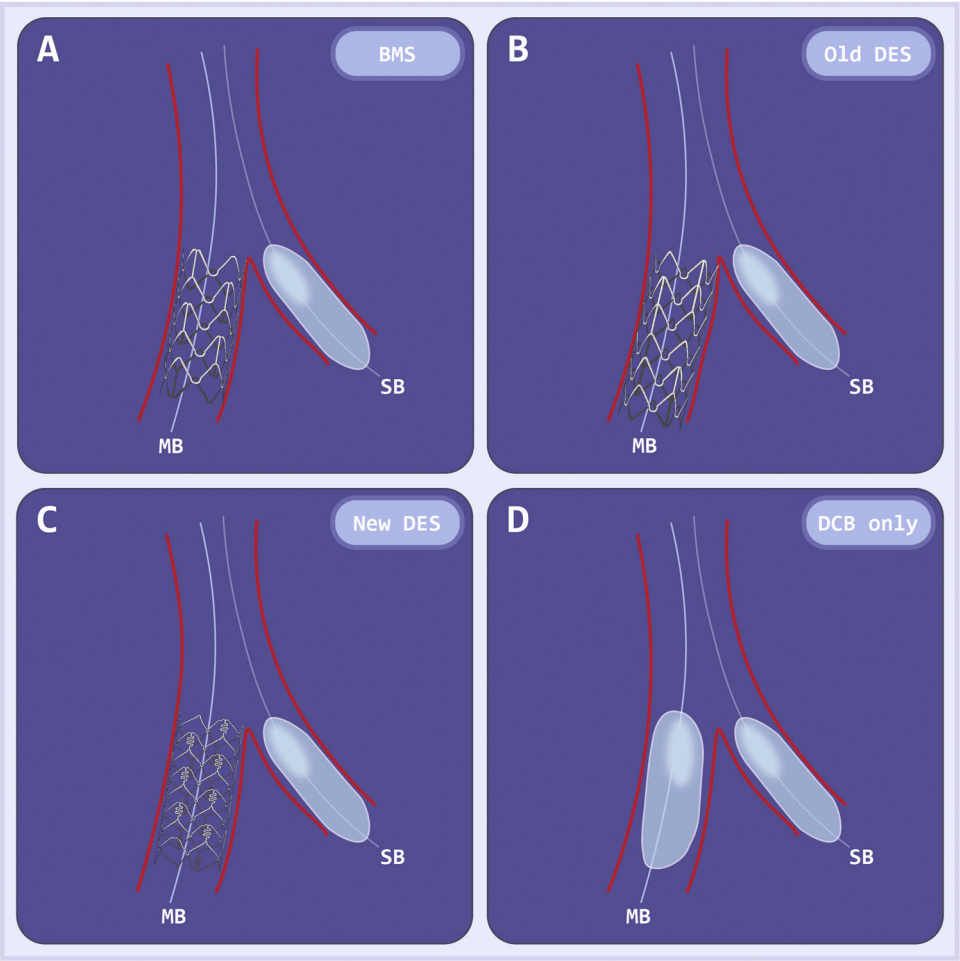

FIGURE 5 | Location of DCB in bifurcation studies. (A) DCB in SB and MB, followed by BMS in MB [96, 102, 103]. (B) DCB in SB, old generation DES in MB [94, 95]. (C) DCB in SB, new generation DES in MB [97, 98, 104–108]. (D) DCB-only strategy, with or without DCB treatment of the MB [109–115]. Comparison of DCBs (old- and new generation) was conducted versus POBA, BMS, old generation DES, and new generation DES. [Color figure can be viewed at wileyonlinelibrary.com]

4 | DCB in CHIP-PCI

4.1 | The Elderly and Comorbid

4.1.1 | Increasing Age

The incidence of CHIP-PCI is rising in conjunction with age [20]. Data on the utilization of DCB in the elderly are scarce, and most trials investigated age in conjunction with other risk factors. For instance, Sinaga et al. [77] investigated the use of PTX-DCB in elderly patients with SVD, and found that patients ≥ 75 years old had more comorbidities, yet a statistically equal and acceptable MACE rate compared to patients < 75 years old at 9 months FU. In line with these findings, the previously highlighted DEBUT and BASKET-SMALL 2 trial provided insight in DCB use in an older population, as the mean age were 77 years and 71 years (in HBR group), respectively [70, 78]. Although neither trial provided a sub-analysis on age, the efficacy of DCB (in HBR) was confirmed. The analysis by Sella et al. [79], a retrospective analysis on DCB use in patients < 70 and >80 years old with de novo CAD and ISR, appears to deviate from these findings. The authors reported a much higher MACE rate at 24 months FU (37.1% and 41.6% in both arms), which they attributed to the inclusion of cardiac hospitalization in the composite endpoint. Further, the TLR rate (7.6%) was twice as high as the previously mentioned analysis by Sinaga et al. (3.6%), a point which was not addressed by the authors. An important gap in the aforementioned data is investigation into a reduced DAPT duration or single antiplatelet therapy regime in the elderly. Treatment with DES requires DAPT, varying from 1 month to 1 year, which may pose a risk in older patients who are prone to bleeding [80, 81]. While DCB use in the elderly may appear feasible and safe, its potential benefit is hypothesized to be driven by a more liberal DAPT therapy, but this has not been investigated to date. Therefore, alterations in DAPT regime in conjunction with DCB-only therapy in the elderly should be considered carefully in anticipation of more conclusive data.

4.1.2 | Diabetes Mellitus

Diabetics are known to experience higher rates of target lesion failure and TLR compared to non-diabetic patients [82]. Indeed, the pro-inflammatory state of diabetics may favor a reduction in stent burden, as caging of the vessel might promote

TABLE 2 | Advantages and limitations of DCB in CHIP-PCI.

	Advantages	Limitations
Elderly and comorbid	Reduction of stent burden in high event rate population	Randomized data on DCB in elderly and comorbid is scarce
	Uncaging of vessel in diabetics may reduce inflammatory response	Challenging to distill the isolated impact of DCB use in a high risk population
	Possibility of shorter DAPT duration	No clear consensus on DAPT duration
	Accumulative benefit of DCB in case of multiple CHIP factors	Longer FU time warranted
Bifurcation lesions	Reduction of stent burden in high event rate lesions	High variety in study design of available data
	May support the adage "Keep it Simple, Swift and Safe (KISS)" through DES in MB and DCB in SB (if indicated)	Current trials do not include all relevant factors predisposing to SB occlusion
	May be preferred in specific lesions, such as stent-in-stent, prior stenting with old generation DES, and small caliber SB	Future RCTs with larger sample sizes and angiographic FU (incl. invasive coronary imaging or intracoronary measurements) are warranted
	DCB-only strategy appears to yield comparable results to DES treatment	
Calcified lesions and CTOs	May reduce risk at stent-related adverse events	Aggressive lesion preparation is essential
	While dissection may occur, evidence supports that non-flow limiting dissection frequently heals without intervention	Calcification may impair drug infiltration and therefore positive vascular remodeling
	Uncaging of the vessel in CTO PCI may allow for LLE	Increased risk at perforation and dissection may require (bail-out) stenting
	A hybrid strategy (combined DES and DCB) may reduce stent burden	Degree of calcification is not clearly defined and often angiographically determined, hampering clinical translatability
		The efficacy of DCBs in the subintimal lumen in CTO PCI has been scarcely explored

Note: Abbreviations as previously described.

inflammation and subsequent stent-related adverse events [82]. An interesting study conducted by Her et al. [83] found that the benefit of reduced stenting in conjunction with DCB use was most evident in patients with diabetes and MVD. Patients with diabetes who were treated with a hybrid strategy experienced lower rates of MACE and cardiac death. Furthermore, a meta-analysis showed a trend toward lower TLR in diabetics following DCB versus DES angioplasty in de novo SVD [84]. The presented data was hampered by their observational nature (2 of the 3 included studies), in which a high (>95%) rate of stenting with BMS in the DCB arm may have impacted the angiographic outcomes. These studies emphasized the cumulative risk for stent-related events in diabetes patients in conjunction with (a) SVD, (b) diffuse disease or MVD, and (c) prior (extensive) stenting. As such, the combination of one or more of these clinical factors may support a lower threshold for DCB therapy in diabetics [85].

4.1.3 | Hemodialysis (HD)

HD patients, like diabetics, are prone to worse clinical outcomes following stent implantation [86]. It is not surprising that TLR and MACE rate are persistently high following both DES and DCB use in HD compared to non-HD patients [87–89]. Perhaps the advantage of DCB use in HD patients lies not in the reduction of stent-related adverse events or MACE, but in the possibility of reducing bleeding events. Increased thrombogenicity and a predisposition to severe bleeding coexist in the HD patient, and DCB use may enforce a less aggressive DAPT regime. However, this hypothesis remains to be clarified, as the aforementioned trials did not explore shortened DAPT duration and its potential impact on bleeding events. In summary, the accumulative risk of adverse events in the primary CHIP sphere may encourage a lower threshold for the utilization of DCBs. Whether this can be applied in conjunction with a less aggressive DAPT regime warrants further investigation.

4.2 | Complex Anatomical Lesions

4.2.1 | Bifurcation Lesions

Bifurcation lesions pertain to all lesions occurring at or adjacent to a significant sidebranch (SB), which the operator wants to preserve during PCI. Bifurcation PCI is highly prevalent (15−20%), and associated with a higher rate of procedural complications and inferior clinical outcomes compared to

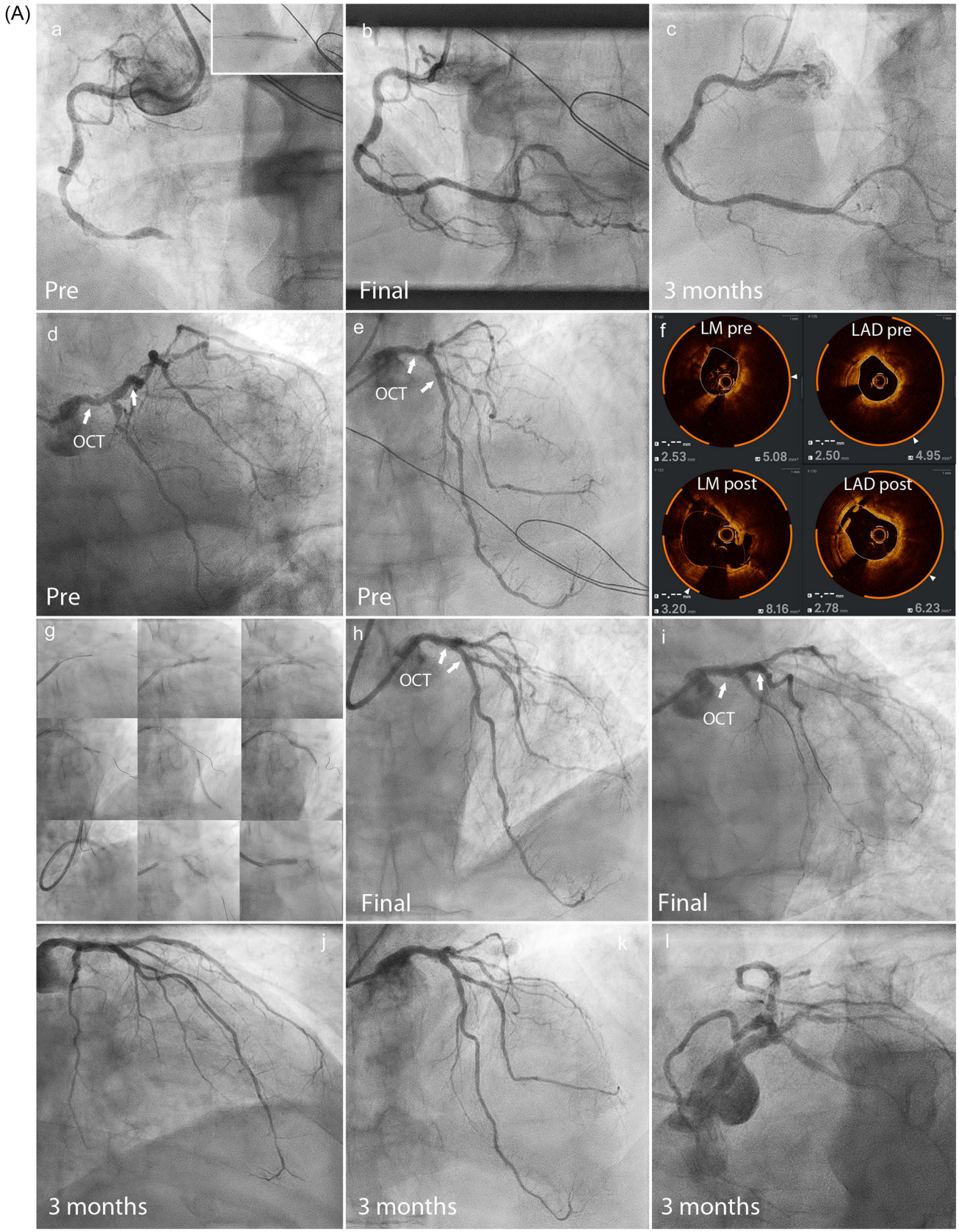

FIGURE 6 | Case examples of DCB in complex anatomical lesions. (A) Multivessel (incl. bifurcation) PCI. Treatment of acute coronary syndrome and multivessel disease using DCB-only angioplasty. 74 years-old male at high bleeding risk (chronic kidney disease and anemia) presented with ST-elevation myocardial infarction. (a) The culprit lesion was predilated using non-compliant (NC) balloon of 1:1 balloon-to-vessel ratio, followed by paclitaxel-iopromide DCB (inset). (b) Final result with TIMI 3 flow. (c) Follow-up angiography three months later. (d, e) Angiography of the left coronary artery revealed diffuse multivessel disease involving significant stenoses in the left main (LM), left anterior descending artery (LAD), left

non-bifurcation lesions [90, 91]. Although a simple stenting technique is favored above a double stenting technique [92], some SB lesions require a complex two-stent technique—especially if there is significant flow limitation in the SB, difficult SB access, or if the SB covers considerable myocardial territory [91]. There are drawbacks to bifurcation stenting, such as stent deformation and multiple layers of metal and polymers [90]. The DCB may tackle some of these limitations, as well as obviate a need for re-wiring or kissing balloon inflation. Further, it has been suggested that DCB use may prevent carina shift; a significant cause of SB narrowing following treatment of the main branch (MB) [90, 93]. Most importantly, the DCB has the potential to simplify bifurcation PCI, as the DCB may either be deployed in the SB (with stenting of the MB), or in both the MB and SB [74]. The numerous options for DCB placement in bifurcation PCI has resulted in an abundance of study designs (Figure 5). Recently, the hybrid strategy was explored in bifurcation lesions. After the DCB had been studied in conjunction with a PTX-stent [94–96], Worthley et al. [97] moved to a combination of a newer generation DES (everolimus-eluting) in the MB and a DEB in the SB. Although the LLL in the SB was low (0.10 ± 0.43 mm) paired with a low clinical event rate, the small sample size ($n = 35$) and low rate of true bifurcations (31.4%) were important limitations of this study. Equally, Pellegrini and colleagues reported a low clinical event rate in a small sample size ($n = 50$) with a combined strategy of DCB (in SB) and DES (in MB), but managed to include solely true bifurcation lesions based on the Medina classification [98]. A final category worth mentioning is the application of DCB versus plain-old balloon angioplasty (POBA). A meta-analysis by Corballis et al. [99] showed that DCB in the SB outperformed POBA in terms of lower LLL. The aforementioned data illustrate the high variety in study design, and with it the difficulty of interpreting the data in a clinical setting. Nevertheless, several conclusions can be drawn from these studies. First, the major advantage of DCB in bifurcation PCI is its ability to simplify a procedure. This is in line with the European Bifurcation Club, who advocate the adage "Keep It Simple, Swift and Safe (KISS)" [100]. If SB treatment is pursued on the basis of significant disease, compromised TIMI flow, or considering myocardial territory subtended by the SB, this may be easily solved by DCB-therapy. Second, when a provisional approach with stenting of the MB is performed, DCB in a significantly diseased SB may be preferred over POBA [100], which was recently confirmed by Gao and colleagues [101] in the multicenter randomized DCB-BIF trial. In patients with a simple and true coronary bifurcation lesion undergoing provisional stenting of the MB, Gao et al. demonstrated a lower MACE rate following DCB-treatment of the compromised SB, compared to treatment with an uncoated non-compliant balloon of the SB. Finally, there may be scenarios in which a DCB may be preferred over stenting, such as in stent-in-stent bifurcation lesions, prior stenting with older generation DES, or small caliber SB lesions. Minimization of stent deployment may be

circumflex artery (LCX), first diagonal branch (D1) and a subtotal occlusion of the intermediate branch (IM). In a staged procedure—during the same index hospitalization—full revascularization was done. Arrows point to the sites of optical coherence tomography (OCT) images. (f) In OCT, LM and proximal LAD were found to have minimal lumen areas (MLA) of approx. 5 mm^2 and severe calcification (upper row). Lower row: OCT after predilatation using 4.0 mm cutting balloon and 5.0 mm NC balloon in the LM and 3.5 mm NC balloon in the LAD shows therapeutic medial dissections and increase in MLAs (automatic measurement in LM underestimates MLA) (g) Occluded IM was wired using a high weight polymer jacket wire and a microcatheter. IM, LCX and D1 were predilated using 1:1 balloon-to-vessel ratio NC balloons. (g) Altogether eight paclitaxel-iopromide coated DCBs were used, and several bifurcations were treated. (h, i) The final angiograms showed non-flow limiting dissections in all treated branches, and less than 30% angiographic recoil. (j–l) Follow-up angiography 3 months after revealed a good result of the "leaving nothing behind" approach in the revascularization of calcified and diffuse multivessel disease and LM bifurcation. The patients was asymptomatic with normal ejection fraction. (B) Calcified lesion (incl. rotatripsy) PCI. Treatment of calcified LAD using rotatripsy followed by a DCB-only approach. 74 year old male with high bleeding risk (oral anticoagulation, anemia, and frailty) was admitted to the hospital due to new onset heart failure with poor left ventricular ejection fraction (20%). (a) Coronary angiogram showed severely calcified lesions (arrows) in LAD and in the first diagonal branch. The LAD lesions were debulked with upfront rotational atherectomy (insets), using 1.25 mm (proximal and distal) and 1.75 mm burrs (proximal). (b) After rotablation, NC balloons at 20 ATM were used for predilatation (2.5 mm for the distal LAD and diagonal branch, and 3.0 mm for proximal LAD). (c) Angiography after rotablation and predilations with NC balloons. OCT after predilations did not show adequate cracks in the calcium or sufficient lumen areas (inset). (d) Intravascular lithotripsy using 3.0 mm balloon and 120 pulses was performed in the LAD followed by repeated predilations using NC balloons. (e) Sirolimus-coated DCBs with microreservoir technology were used for the diagonal branch (2.5×20 mm) and LAD (2.75×30 mm, 3.0×40 mm and 3.5×20 mm). (f) Final result showing normal flow and less than 30% angiographic recoil. OCT confirmed sufficient cracks in the calcium and lumen areas in the LAD (inset). (g–i) Control angiography 3 months later demonstrated a good result of DCB-only treatment in the calcified complex lesion. (C) CTO PCI with a hybrid approach. Treatment of calcified CTO RCA. 59 year old male with a history of diabetes mellitus type II and ambulant myocardial infarction in the inferior territory. Patient presented with refractory anginal symptoms. Angiography revealed a CTO of the distal RCA, J-CTO score = 2 (calcification, length ≥ 20 mm). Due to persisting symptoms under optimal medical therapy, the patient was accepted for CTO PCI. (a, b) Set-up shots with dual catheter injection of the RCA, revealing ample retrograde filling by the LAD (Rentrop III, CCS 2) via septal collaterals. (c) Successful recanalization of the CTO via antegrade wire escalation. (d) After wiring of the CTO vessel, the entire coronary artery was predilated at high pressure (20 atm). (e, f) Intravascular ultrasound (IVUS) was performed from the right posterior descending artery (RPD) to the ostium. Besides extensive adjacent disease in all segments of the RCA (proximal, mid, distal, RPD, and posterolateral branch [RPL]), IVUS also revealed almost 360 calcium ring. G) PCI was performed with a short drug-eluting stent (SYNERGY, 3.5 x 38 mm, left upper corner) to cover the CTO body, followed by 4 paclitaxel-DCBs (AGENT, twice 2.75 x 30 mm in RPL and RPD (with kissing balloon inflation), 4.0 x 30 mm mid-RCA, 4.0 x 20 mm in proximal RCA). A second DES (3.5 x 8 mm) was placed at the distal edge due to edge dissection. H-J) Final result with good stent expansion (confirmed by IVUS), and non-flow limiting dissection in the proximal RCA, mid-RCA, RPL, and RPD. J-L) Follow-up at 12 months shows late lumen enlargement in the proximal RCA, mid-RCA, RPL and RPD, as well as good stent result—confirmed by IVUS. [Color figure can be viewed at wileyonlinelibrary.com]

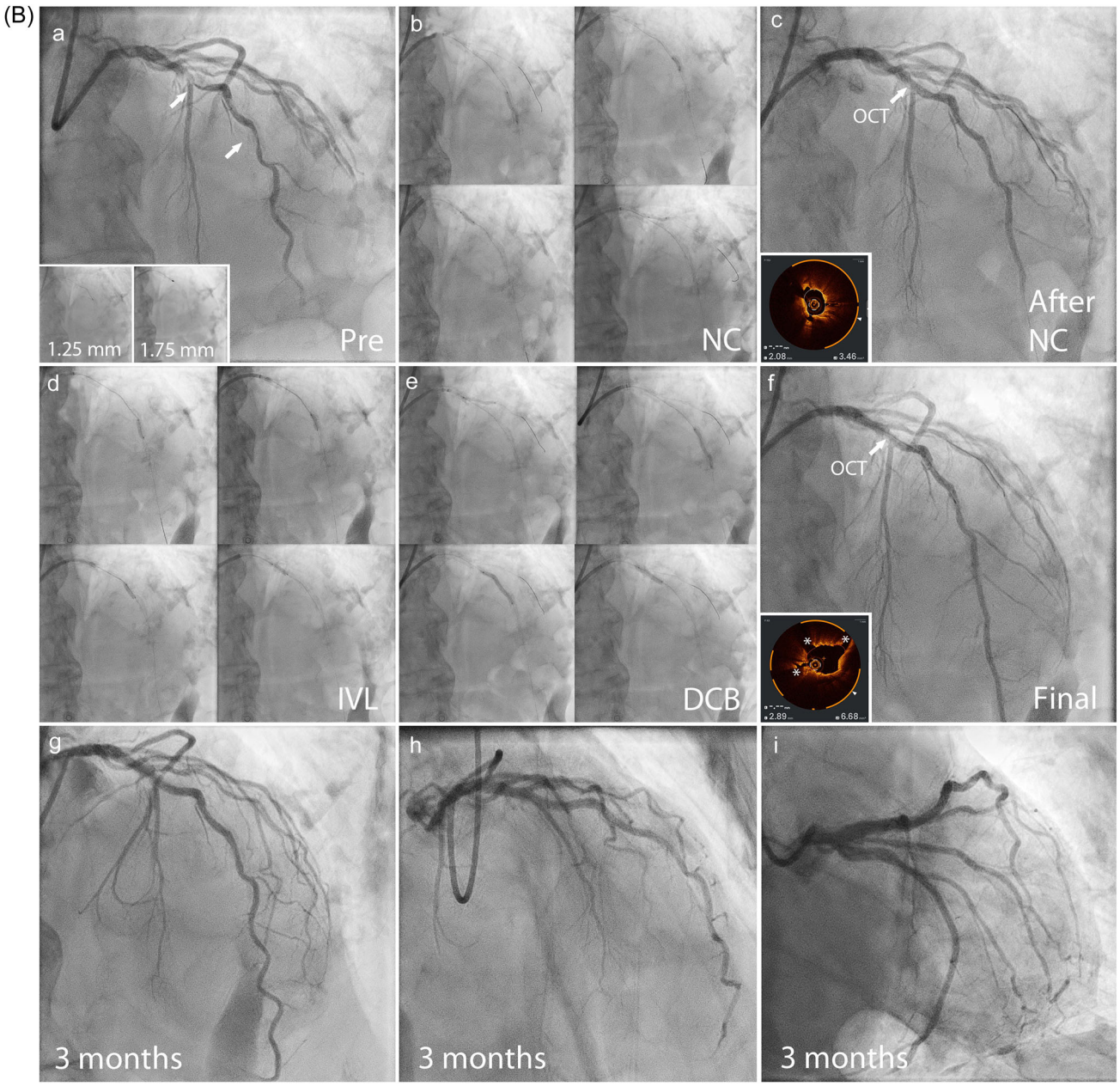

FIGURE 6 | (Continued)

appealing in these cases, and can be justified as the applicability of DCB in ISR and SVD has been confirmed.

4.2.2 | Calcified Lesions

Calcified lesions account for one-third of patients in the cardiac catheterization laboratory. The presence of calcification is associated with DES underexpansion and malapposition following implantation [116, 117], both independent risk factors for stent thrombosis and ISR [118]. To reduce these risks, aggressive lesion preparation is essential, either through (high-pressure) POBA, cutting or scoring balloons, lithotripsy, or ablative techniques such as rotational atherectomy (RA) [118]. In calcified lesions, the application of DCBs may defer complications associated with stent implantation [77]. In a retrospective single-center study, Rissanen et al. [119] explored DCBs in calcified de novo coronary lesions extensively prepared with RA, followed by ballooning (semi-, non-compliant or cutting) at the discretion of the operator. The overall MACE rate at 24 months was high (20%) and mostly driven by cardiovascular mortality (12.3%). Possibly, this is a result of the high lesion complexity, patient risk factors (82% had one HBR risk factor), and the inclusion of ACS patients (32%). In another study, the use of DCB in calcified lesions showed lower rates of LLE compared to non-calcified lesions, with comparable LLL and restenosis rates. The authors hypothesized that the presence of calcification may impair drug infiltration and therefore positive vascular remodeling [120]. Another potential pitfall of calcified lesions is the increased risk of dissections or coronary perforation [116] which may require additional stenting. DES deployment is encouraged if flow-limiting dissection occurs

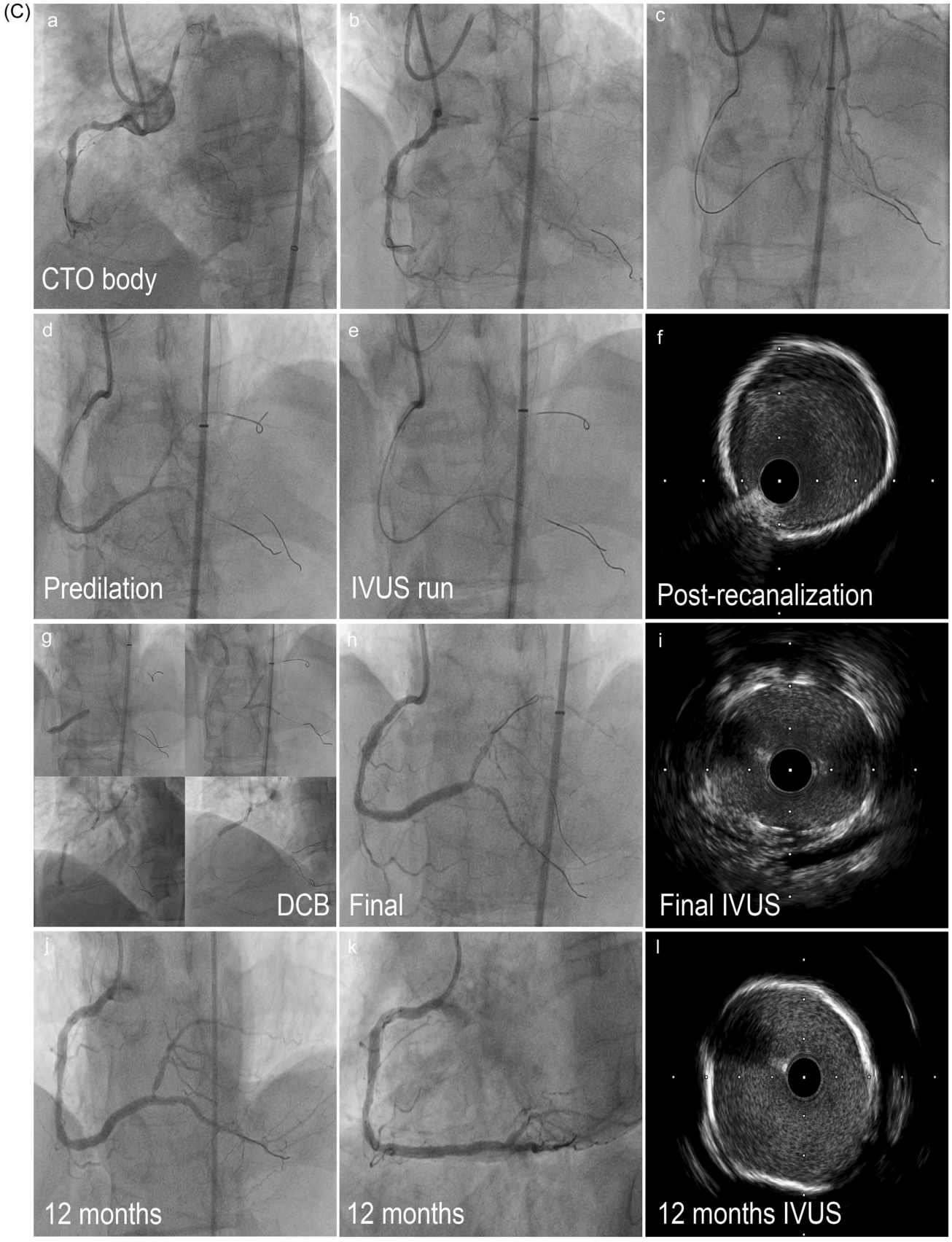

FIGURE 6 | (Continued)

TABLE 3 | Ongoing interventional trials on DCBs.

Title	ID	Country	Study objective	Study design	Inclusion	Status
Bifurcation lesions						
DCB-BIF trial	NCT04242134	China	Efficacy of DCB versus POBA for SB after provisional stenting as measured by MACE at 12 months	Multi-center, randomized, single-blind, superiority	784	Active, not recruiting
Hybrid-DEB trial	NCT05731687	Netherlands	Non-inferiority of hybrid DEB approach to stepwise provisional two-stent strategy in bifurcation lesions as measured by MACE at 24 months	Multi-center, randomized, single-blind, non-inferiority	500	Recruiting
DCB in coronary bifurcation lesions	NCT05872074	Egypt	Impact of DCB in coronary bifurcation lesions as measured by MACE at 6 months	Single-center, randomized	50	Recruiting
Sirolimus DEB in bifurcation lesions	NCT04896177	China	Non-inferiority of SCB in bifurcation lesions as measured by lumen diameter stenosis at 9 months	Multi-center, randomized, non-inferiority	280	Recruiting
CTO lesions						
Co-CTO trial	NCT04881812	Netherlands	Non-inferiority of DCB versus DES in disease adjacent to the CTO body as measured by percentage diameter stenosis (IVUS) at 12 months	Single-center, randomized, non-inferiority	144	Recruiting
De novo lesions						
DCB in de novo coronary lesions	NCT03691675	China	Safety and efficacy of DCB in de novo lesions as measured by LLL at 3 months	Single-group assignment	45	Unknown
UNIQUE-DCB I trial	NCT04104854	China	Safety and efficacy of DCB versus DES in de novo lesions under QFR guidance as measured by LLL at 12 months	Multi-center, randomized	220	Not yet recruiting
DEBATE trial	NCT05516446	Tunisia	Non-inferiority of DEB (SEQUENT PLEASE) versus last generation DES as measured by LLL at 12 months	Single-center, randomized, open-label, non-inferiority	290	Recruiting
STENTLESS trial	NCT06084000	China	Safety ad efficacy of scheduled DCB and conventional DES as measured by MACE at 12 months	Multi-center, randomized, open-label	2700	Recruiting
REVERSE trial	NCT05846893	Korea, Taiwan, Malaysia, Singapore	Non-inferiority of DCB treatment versus DES in de novo lesions as measured by net adverse clinical events at 12 months	International, multi-center, randomized, non-inferiority	1436	Recruiting
DCB-HBR trial	NCT05221931	Korea	Non-inferiority of DCB versus DES for de novo lesions under intravascular imaging	Multi-center, randomized, open-label, non-inferiority	1350	Recruiting

(Continues)

TABLE 3 | (Continued)

Title	ID	Country	Study objective	Study design	Inclusion	Status
			guidance in HBR patients as measured by TVF at 24 months			
DES versus DCB in calcified de novo lesions	NCT05750771	China	Non-inferiority of DCB versus DES in calcified de novo lesions as measured by LLL at 12 months	Single-center, randomized, non-inferiority	200	Recruiting
LARGE ONE trial	NCT05961787	China	Non-inferiority of DCB versus DES (Firehawk family) in de novo large diameter lesions as measured by LLL at 13 months	Multi-center, randomized, non-inferiority	134	Recruiting
Sirolimus-eluting or -coated balloon						
SELUTION 4 ISR trial	NCT04280029	United States of America	Safety and efficacy of SELUTION SLR 04 DEB in ISR as measured by TLF at 12 months	Multi-center, randomized, single-blind, non-inferiority	418	Recruiting
SELUTION 4 IDE trial	NCT05946629	United States of America	Safety and efficacy of SELUTION SLR 014 DEB in SVD as measured by TLF at 12 months	Multi-center, randomized, single-blind	910	Recruiting
TRANSFORM II trial	NCT04893291	Italy, Bangladesh, Netherlands, France, Spain	Efficacy of MagicTouch SCB compared to gold standard treatment for native vessel disease as measured by TLF at 12 months	International, multi-center, randomized, open-label	1820	Recruiting
GINGER trial	NCT05471245	Italy	Performance of MagicTouch SCB in de novo CAD as measured by LLL at 9 months	Prospective, single-group assignment	100	Recruiting
MAGICAL ISR trial	NCT05908331	United States of America	Safety and efficacy of MagicTouch SCB in ISR as measured by TLF at 12 months	Multi-center, randomized, single-blind, superiority	492	Recruiting
Miscellaneous						
DEBATE trial	NCT04814212	Finland	Non-inferiority of DCB versus DES in stable CAD or ACS patients with HBR as measured by MACE at 12 months	Multi-center, randomized, non-inferiority	546	Recruiting
RESTORE trial	NCT06365502	China	Superiority of DCB on non-flow limited vulnerable plaque compared to GMDT in ACS patients as measured by TLF at 24 months	Multi-center, randomized, open-label	1860	Recruiting
PLAMI trial	NCT06080919	Spain	Assess changes in percentage atheroma volume evaluated by IVUS at 3 months	Investigator-initiated, single-arm, open-label, pilot	30	Recruiting

(Continues)

TABLE 3 | (Continued)

Title	ID	Country	Study objective	Study design	Inclusion	Status
ULTIMATE-III trial	NCT04255043	China	Impact of IVUS- versus angiography-guided DCB treatment in HBR patients as measured by LLL at 7 months	Multi-center, randomized	260	Recruiting
ISAR-DESIRE 5 trial	NCT05544864	Germany	Assess interaction in treatment effect between OCT pattern of neointima and type of PCI (DCB or DES) in ISR as measured by MACE at 24 months	Single-center, randomized	376	Recruiting
DCB in STEMI under OCT guidance	NCT05680051	China	Assess application of DCB under OCT guidance in STEMI patients as measured by LLL at 10 months	Multi-center, randomized	300	Recruiting

Abbreviations: DEB, drug-eluting balloon; OCT, optical coherence tomography; POBA, plain old balloon angioplasty; QFR, quantitative flow ratio; SCB, sirolimus-coated balloon, STEMI, ST-elevation myocardial infarction. Other abbreviations as previously described.

[74], while DCB treatment in non-flow limiting dissection is thought to facilitate drug penetration into the vessel wall and promote LLE [121, 122]. Ueno et al. [123] successfully avoided high rates of major, flow-limiting dissection by applying an aggressive rotablation strategy (to properly modify calcification), followed by DCB inflation at low pressure. Dissection warranting DES-placement occurred in only 2%. While this strategy is an interesting concept, there is also evidence that dissection frequently heals without intervention [122, 124], further reinforcing the notion that permanent caging of the vessel may not be necessary when (non-flow limiting) dissection occurs. Notwithstanding these data, adequate lesion preparation without causing flow-limiting dissection is imperative when considering DCB-angioplasty in calcified lesions. There are currently no robust, randomized data recommending the routine use of DCB over DES [118], and the extent of calcification may dilute the potential benefits of DCB treatment. Caution is advised when applying DCB-angioplasty in highly calcified lesions, as well as the careful implementation of calcium debulking methods, dedicated balloons (scoring or cutting), and intravascular imaging to guide intervention. Randomized studies incorporating these methods may further clarify the role of DCB in calcified lesions.

4.2.3 | Chronic Total Occlusions

Calcification is also highly prevalent in CTOs [125], and is associated with guidewire crossing failure [126]. CTOs are defined as an occlusion without antegrade flow through the lesion with a presumed or documented duration of ≥3 months [127]. The use of a DCB in CTO is tantalizing, considering that the presence of disease adjacent to the CTO lesion often warrants extensive stenting, which carries a higher risk of stent-related adverse events. The combination of extensive plaque in CTOs and negative remodeling due to chronic hypoperfusion might favor the use of DCBs [128]. Uncaging of the vessel allows for LLE, and may prevent stent-related adverse events caused by stent undersizing and malapposition [128]. The feasibility and safety of a DCB-only approach in CTO PCI was explored by Köln and colleagues. Of 27 patients with successfully recanalized lesions, 1 reocclusion and 1 restenosis occurred at a mean FU of 8.6 months, but no reported death or MI [129]. Another retrospective study by Jun et al. [130] explored a DCB-strategy in 84 patients (93 vessels). Dissection occurred in 73% following DCB use, of which only three vessels warranted bail-out stenting. Interestingly, 96% of all vessels showed no residual dissection at angiographic FU, and clinical outcomes were favorable at 1 and 2 years following CTO PCI. The aforementioned trials include cases with intraplaque wiring, whereas the efficacy of DCB in the subintimal space has been scarcely explored. The major concern with DCB use in the subintimal lumen is the pro-apoptotic effect of PTX, as this drives vessel enlargement (i.e., positive remodeling) which may cause vessel wall thinning and subsequent aneurysm formation [128, 131, 132]. Only Ybarra et al. [133] described the application of DCB in the subintimal lumen during an investment procedure with improved vessel healing at angiographic FU, although no definitive conclusions can be drawn from this case series. In summary, the various wiring approaches in CTO PCI require a different application of DCBs. In intraplaque wiring, a

DCB-only strategy has been shown to be safe and feasible. When dissection and re-entry techniques are deployed, the DCB may be utilized in combination with DES to reduce overall stent burden. This concept is the foundation of the randomized Co-CTO (DCB Coronary Angioplasty vs. Stenting for Treatment of Disease Adjacent to a Chronic Total Occlusion) trial (ClinicalTrials.gov identifier: NCT04881812). In this study, a minimal stenting strategy (stenting of the CTO lesion and DCB treatment of adjacent disease) will be compared to a complete stenting strategy, with the aim of testing non-inferiority. This study will provide insight in whether DCB use can be extended to CTO PCI (albeit in a hybrid fashion). As is paramount in all DCB trial designs, the Co-CTO trial warrants a 1:1 balloon-to-vessel ratio, and excludes vessels with unfavorable characteristics for DCB treatment (e.g. high-grade dissection, residual stenosis $\geq 30\%$, or reduced thrombolysis in myocardial infarction flow). An overview of the advantages and limitations of DCB in CHIP PCI is shown in Table 2. Case based examples of the aforementioned complex anatomical lesions (bifurcation, calcified, and CTO) are depicted in Figure 6a–c.

5 | Future Perspectives

The use of DCBs in the third sphere of CHIP (i.e., ventricular hemodynamics) has not been addressed in this review, as data on this area are lacking. Future studies may elucidate whether DCBs are a suitable therapeutic option for patients in this category, for example through simplification of complex procedures when ventricular hemodynamics are severely compromised. Finally, the current body of data on DCB use is rapidly expanding as a result of ongoing research, as summarized by Table 3.

6 | Conclusions

Extensive stent deployment in CHIP PCI is common, and stent-related adverse events remain a serious concern in contemporary PCI. The present review considered the rising application of DCB in CHIP, specifically in the first and second clinical sphere. Although mostly observational, the data suggest DCB could reduce stent burden and concomitant risk in CHIP PCI. Whether this could facilitate a less aggressive DAPT regime remains to be elucidated. Randomized controlled trials comparing a DCB-only or hybrid approach (DES + DCB) to a DES-only approach are steadily becoming available, yet caution is required in the routine uptake of DCBs in complex coronary lesions where randomized data are lacking.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Supporting Information

Review criteria are reported in the Supporting Information Material.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.