

Review

Ultrathin Struts Drug-Eluting Stents: A State-of-the-Art Review

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Abstract: New-generation drug-eluting stents (DESs) represent the standard of care for patients undergoing percutaneous coronary intervention (PCI). Recent iterations in DES technology have led to the development of newer stent platforms with a further reduction in strut thickness. This new DES class, known as ultrathin struts DESs, has struts thinner than 70 μm . The evidence base for these devices consists of observational data, large-scale meta-analyses, and randomized trials with long-term follow-up, which have been conducted to investigate the difference between ultrathin struts DESs and conventional new-generation DESs in a variety of clinical settings and lesion subsets. Ultrathin struts DESs may further improve the efficacy and safety profile of PCI by reducing the risk of target-lesion and target-vessel failures in comparison to new-generation DESs. In this article, we reviewed device characteristics and clinical data of the Orsiro (Biotronik, Bülach, Switzerland), Co-roflex ISAR (B. Braun Melsungen, Germany), BioMime (Meril Life Sciences Pvt. Ltd., Gujarat, India), MiStent (MiCell Technologies, USA), and Supraflex (Sahajanand Medical Technologies, Surat, India) sirolimus-eluting stents.

Keywords: coronary artery disease; drug-eluting stents; percutaneous coronary intervention; ultrathin struts



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1. Introduction

Percutaneous coronary intervention (PCI) is the technique most frequently used to treat flow-limiting coronary artery stenoses. PCI is a continually evolving field, primarily as a result of the development, refinement, and iterations of technologies and devices [1]. The transition from early-generation to new-generation stents entailed a wide range of design changes in the metallic stent platform and its geometry [2,3]. While bare metal stents (BMSs) are usually made of stainless steel, most new-generation drug-eluting stents (DESs) consist of a cobalt-chromium alloy (CoCr) or a platinum-chromium alloy (PtCr) metallic platform. These improvements enabled the reduction of the strut thickness from 130–140 μm to 60–80 μm , resulting in greater deliverability and faster endothelial coverage following implantation. Differences among the platforms exist also with respect to the antiproliferative drug and the drug load. Newer stents use a lower drug load to facilitate the endothelialisation process with a “limus” derivative as an antiproliferative drug (i.e., sirolimus, everolimus, zotarolimus, novolimus, biolimus, umirolimus). DESs were initially developed to reduce neointimal hyperplasia and restenosis ensuing after PCI with BMSs. However, when compared with BMSs, the use of early-generation DESs was associated with an increased risk of stent thrombosis (ST) [4]. To address this issue, new-generation DESs were designed with improved biocompatibility of the permanent polymer coating or with biodegradable polymer along with better safety of the released drug [5]. New-generation DESs outperformed BMSs in numerous endpoints, including cardiac death, myocardial infarction (MI), ST, and repeat revascularization [6,7]. As a result, new-generation DESs are currently recommended for all patients undergoing PCI irrespective of the anticipated duration of dual antiplatelet therapy [8]. Over the past few years, refinements in device technology prompted a further reduction of strut thickness with the introduction of a

new class called “ultrathin strut DESs”. Despite the lack of a standardized definition, ultrathin DESs are defined as stents with a strut thickness less than 70 µm. The potential benefits of these device include deliverability, reduced vessel injury, and side branches’ flow disturbance. In this article, we provided a comprehensive overview of ultrathin DESs that are currently available (Figure 1).

	Orsiro	CoroFlex IsarNeo	Biomime	Biomime Morph	Evermine 50	MiStent	Supraflex Cruz
Company	Biotronik	B. Braun	Meril	Meril	Meril	Stentys	Sahajanand Medical Technologies (SMT)
Platform material and Strut thickness (µm)	2.5 to 3 mm 3.5 to 4 mm 60 80	2 to 3 mm 3.5 to 4 mm 55 65	65	65	50	64	60
Crossing Profile	0.95 mm	0.79 to 0.96 mm	0.83 to 1.19 mm	0.93 to 1.03	0.83 to 1.19	n.a.	0.95 mm
Available diameters (mm)	2.25, 2.5, 2.75, 3.0, 3.5, 4.0	2.0, 2.25, 2.5, 2.75, 3.0, 3.5, 4.0	2.0, 2.25, 2.75, 3.0, 3.5, 4.0, 4.5	2.75-2.25, 3.0-2.5, 3.5-3.0	2.0, 2.25, 2.50, 2.75, 3.0, 3.5, 4.0, 4.5	n.a.	2.0, 2.25, 2.5, 2.75, 3.0, 3.5, 4.0, 4.5
Lengths available (mm)	9 to 40	9 to 38	8 to 48	30 to 60	8 to 48	n.a.	8 to 48 mm
Polymer type	Biodegradable (proBIO®)	Polymer free	Biodegradable Biocompatible	Biodegradable Biocompatible	Biodegradable Biocompatible	Biodegradable	Biodegradable
Coating distribution	Circumferential	-	Circumferential	Circumferential	Circumferential	Circumferential	Circumferential
Polymer material and thickness	3.5 µm abluminal 7.5 µm luminal	-	2 µm	2 µm	2 µm	5 µm/15 µm	4-5 µm
Polymer absorption	15 months	-	60 days	60 days	60 days	3 months	9-12 months
Eluted drug	Sirolimus	Sirolimus and Probucol	Sirolimus	Sirolimus	Everolimus	Sirolimus (microcrystals)	Sirolimus
Drug dose	1.4 µg/mm ²	1.2 µg/mm ²	1.25 µg/mm ²	1.25 µg/mm ²	1.25 µg/mm ²	2.4 µg/mm ²	1.4 µg/mm ²
Drug release	50% by 1 month 80% by 3 months	80% by 28 days 100% by 90 days	30-40 days	30-40 days	30-40 days	9 months	70% by 1 week 100% by 3-4 months

Cobalt-Chromium
 PLLA
 PLLA and PLGA
 PLLA + PCL + PVP

Figure 1. Comparison of currently available ultrathin drug-eluting stents (DESs). CoCr: cobalt chrome; n.a.: not available, PCL: poly-caprolactone; PLGA: poly-D,L-lactide-co-glycolide; PLLA: poly-L-lactic acid; proBIO: amorphous hydrogen-rich silicon carbide; PVP: poly vinyl pyrrolidone.

2. Orsiro

The Orsiro coronary stent (BIOTRONIK, Bülach, Switzerland) consists of an ultrathin strut, cobalt-chromium platform, with a bioresorbable, sirolimus-eluting polymer (biodegradable polymer sirolimus-eluting stent (BP-SES)). It is available in diameters ranging from 2.25 to 4.0 mm and in lengths between 9 and 40 mm. Stents with diameters of 2.25 to 3.0 mm have a strut thickness of 60 µm, whereas stents with diameters of 3.5 to 4.0 mm have a strut thickness of 80 µm [9]. The Orsiro BP-SES consists of different layers. The innermost layer is a cobalt-chromium alloy (the PRO-Kinetic energy™ stent) arranged in a double-helix pattern, designed to improve deliverability by lowering the crossing profile. Due to the proBIO coating, the metallic platform of the stent is not in direct contact with the blood vessel or bloodstream. This is an amorphous-hydrogen-rich silicon carbide coating bonded to the metallic platform. The proBIO coating is a specific feature of this device, and it may have positive effects related to a lowered rate of metallic stent corrosion and less tissue inflammation, including allergic reactions to the metal. Of interest, this “passive shield” offered by the proBIO coating is permanent (i.e., the coating does not delaminate over time). The outer layer is made of a bioabsorbable poly-L-lactic acid (PLLA)

polymer containing sirolimus. The active BIOLute™ coating is distributed asymmetrically with a thickness of 7.5 µm on the abluminal side and a thinner, 3.5 µm layer on the luminal portion of the stent. The sirolimus load is 1.4 µg/mm². The PLLA degrades over 2 years, releasing 50% of the drug within 30 days and 80% during the first three months. The safety and efficacy of the Orsiro SES has been evaluated in a number of clinical trials involving multiple clinical settings (acute and chronic coronary syndromes) and subsets of lesions (de novo, small vessel disease, chronic total occlusions, in-stent restenosis).

The BIOFLOW I was the first-in-man trial evaluating the Orsiro BP-SES in patients with single de novo coronary artery lesions and showed excellent results in terms of 9-month late lumen loss (LLL) [10]. The BIOFLOW II trial showed the non-inferiority of the Orsiro BP-SES compared with a durable polymer (DP) everolimus-eluting stent (Xience EES Abbott Vascular, Santa Clara, California) in terms of target-lesion failure (TLF) and lower mortality in vessels from 2.25 to 2.75 mm, suggesting a potential benefit of ultrathin struts up to 5-years follow-up [11,12]. The BIOFLOW IV trial was designed for regulatory submission in Japan and confirmed the non-inferiority of the Orsiro BP-SES with the Xience EES among 575 patients with de novo lesions [13]. The BIOFLOW V was designed to test the performance of Orsiro in all-comers PCI patients across 13 countries. A total of 1334 patients were randomly assigned to either Orsiro or Xience in a 2:1 ratio. About 50% presented with an acute coronary syndrome. At 1-year follow-up, the Orsiro SES outperformed the Xience EES, demonstrating consistently lower clinical event rates in TLF ($p = 0.0399$) and significantly lower rates of target-vessel myocardial infarction (TV-MI) ($p = 0.0155$). These results were confirmed up to 5-years follow-up. In order to improve statistical significance, the authors of BIOFLOW V combined the results with those of the BIOFLOW II and IV trials with a Bayesian approach, reporting a posterior probability for non-inferiority of 100% and a posterior probability of superiority of 97% for the Orsiro [14,15]. The BIOSCIENCE was a non-inferiority trial that randomized 2119 patients (3139 lesions) to receive either the Orsiro SES or the Xience EES. The Orsiro was shown to be not inferior in terms of the primary endpoint of TLF at 12 months (p-non-inferiority < 0.0004). As a novel finding, a subgroup analysis of patients treated for ST-segment elevation myocardial infarction (STEMI) showed a lower risk of TLF with the Orsiro SES than the Xience EES at 12 months ($p = 0.024$) [16]. However, this superiority was not confirmed by the BIOSCIENCE 5-year follow-up, where no differences were found between the two stents in terms of TLF, suggesting that the advantage of ultrathin struts and biodegradable polymer may decrease after complete degradation of the polymer and endothelial healing [17]. An individual, patient-level, meta-analysis of five randomized trials (BIOFLOW-II, BIOFLOW-IV, BIOFLOW-V, BIOSCIENCE, and BIOSTEMI) showed a similar risk of TLF among 5780 patients randomly allocated to BP-SES or DP-EES up to 5-years follow-up [18]. The BIO-RESORT trial randomized patients to receive one of three stents: the Orsiro BP-SES, the Synergy BP-EES (74 µm), or the Resolute Integrity DP zotarolimus-eluting stent (91 µm). The trial showed the non-inferiority of the Orsiro BP-SES at 1-, 2-, and 3-years follow-up [19–21]. In the BIONYX trial, the Orsiro BP-SES served as the control stent for the newly designed Resolute Onyx DP-ZES. No differences were found among the two devices in clinical outcomes, although definite or probable stent thrombosis was less frequent in the experimental arm [22]. Conversely, the Orsiro BP-SES was associated with a significantly lower risk of definite or probable stent thrombosis and TLF against the Nobori and the Biofreedom biolimus-eluting stents, respectively, in the SORTOUT VII and IX trials. This difference in clinical outcomes could be explained by the thicker struts (120 µm) of the two platforms made of stainless steel [23,24].

3. Coroflex ISAR Neo

Coroflex ISAR (B. Braun, Melsungen, Germany) is a polymer-free, cobalt-chromium, sirolimus-eluting stent. The stent platform is based on the CX-Blue Ultra stent for 2.0 to 3.0 mm diameters (55 µm) and on the CX-Blue Neo stent for 3.5 to 4.0 mm diameters (65 µm). The polymer-free matrix is contained on the abluminal aspect of the microporous stent surface and consists of sirolimus at a concentration of 1.2 µg/mm² and probucol to control the drug

release. Probucol serves as matrix-builder and is a highly lipophilic, lipid-lowering agent, with antioxidant effects [25]. Approximately 80% of sirolimus is released within 30 days, while the process is completed at 90 days. The device is available in diameters ranging from 2.0 to 4.0 mm and lengths between 9 and 38 mm. The Coroflex has been tested in the Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucol- and Zotarolimus Eluting Stents (ISAR-TEST-5) study, a non-inferiority trial including 3002 patients. According to the primary endpoint, a composite of cardiac death, target-vessel-related myocardial infarction, or target lesion revascularization (TLR), the Coroflex ISAR stent was non-inferior to the Resolute ZES (P-non-inferiority = 0.006; P-superiority = 0.74) [26]. These findings were confirmed at 5- and 10-years follow-up with a low incidence of probable/definite ST in both groups and consistent results through pre-specified subgroups of age, gender, diabetes mellitus, and vessel size [27,28].

4. Biomime, Biomime Morph, and Evermine 50

BioMime (Meril Life Sciences Pvt. Ltd., Gujarat, India) is an ultrathin (65 μm), cobalt-chromium, biodegradable polymer, sirolimus-eluting stent. The device presents a hybrid design with closed cells at both ends and open cells in the middle, potentially favouring a better stent expansion and lesser likelihood of edge dissection. The open cell design in the mid-part of the stent should also facilitate side branch access and treatment. The BioPoly biodegradable polymer has a low thickness (~ 2 μm), is composed by poly-L-lactic acid (PLLA) and poly-D,L-lactide-co-glycolide (PLGA), and degrades in approximately 60 days. The sirolimus concentration is 1.25 $\mu\text{g}/\text{mm}^2$ and is released over 30–40 days after stent implantation. The BioMime SES is available in lengths from 8 to 48 mm and diameters from 2.00 to 4.50 mm.

The MeriT-1, MeriT-2, and MeriT-3 trials established the safety and efficacy of the Biomime SES in treating single de novo and complex coronary lesions [29,30]. In the meriT-1 study, a first-in-human, single-centre trial, the Biomime SES showed a low LLL at 8-months angiographic follow-up in 30 patients (30 lesions) [29]. The meriT-2 trial was a larger, single-arm study including 250 patients (355 lesions) with a higher prevalence of diabetes and multivessel disease. At 1-year follow-up, major adverse cardiac events (MACE) occurred in 8.9% of patients [31]. The meriT-3 study included 1161, all-comers patients undergoing PCI with Biomime SES across 15 centres in India and showed a low rate (2.35%) of MACE at 1-year follow-up [30]. The meriT-V trial was the first to randomly compare in a 2:1 ratio the Biomime SES with the Xience EES among 256 patients. At 9-months angiographic follow-up, the Biomime SES resulted in being non-inferior to the Xience EES with respect to the primary endpoint of LLL [32].

The Biomime Morph (Meril Life Sciences Pvt. Ltd., Gujarat, India) is a further iteration of the Biomime SES technology featuring a tapered stent system with two different proximal and distal diameters (e.g., 2.75–2.25 mm; 3.00–2.50 mm, etc). The tapered stent system together with the long available lengths (30, 40, 50, 60 mm) allows the treatment of diffuse, long lesions.

The Evermine 50 (Meril Life Sciences Pvt. Ltd., Gujarat, India) presents the same hybrid cell stent design, but the cobalt-chromium platform is thinner (50 μm). The stent releases everolimus, which is loaded with a concentration of 1.25 $\mu\text{g}/\text{mm}^2$.

5. Mi Stent

The MiStent sirolimus-eluting stent (MiStent SES) (MiCell Technologies, Durham, NC, USA) is an ultrathin (64 μm), biodegradable polymer, sirolimus-eluting stent. The sirolimus is built in the vessel wall as microcrystals, and its crystalline form enables a controlled drug release. Indeed, the polymer (PLGA) is reabsorbed within 3 months after implantation, minimizing the risk of vascular inflammation, while the sirolimus is continuously delivered up to 270 days.

The Mistent has been evaluated in the Dessolve trials. Dessolve I was the first-in-man study and enrolled 30 patients with de novo lesions. At 18-months follow-up, the

primary endpoint of LLL was attested to be 0.08 mm. Of interest, 27 underwent optical coherence tomography, which showed complete strut coverage [33]. In the Dessolve II trial, 184 patients were randomized 2:1 to Mistent vs. Endeavor ZES. No difference was found between groups in terms of TLF up to 5-years follow-up [34]. In the Dessolve III trial, the MiStent SES was non-inferior to the Xience EES with respect to the primary endpoint of cardiac death, target-vessel MI, or clinically indicated target lesion revascularization at 12 months among 1398 all-comers patients enrolled across 20 European centres [35].

6. The Supraflex Family

The Supraflex (Sahajanand Medical Technologies, Surat, India) system is an ultrathin strut (60 μm) stent made of a cobalt-chromium alloy and a biodegradable polymer releasing sirolimus. The stent diameters range from 2.0 to 4.5 mm and the lengths from 8 to 48 mm. Sirolimus has a concentration of 1.4 $\mu\text{g}/\text{mm}^2$, and the polymer gradually degrades over 9–12 months. Approximately 70% of the drug is released within 7 days. The latest iteration of the Supraflex is the Supraflex Cruz with two long dual-Z connectors from “valley to valley” between the struts, to enhance deliverability and increase the flexibility of the stent and a re-designed proximal shaft to allow a better pushability. The Supraflex was first evaluated in a large-scale, multicentre observational registry. The FLEX registry included 995 patients (1242 lesions) in nine Indian centres and reported a low rate (3.7%) of MACE at 1-year follow-up (3.7%) [36]. The S-FLEX UK registry was conducted across different U.K. centres and showed a low rate of TLF (2.4%) and no definite stent thrombosis among 469 patients undergoing PCI with the Supraflex SES [37]. The TALENT trial randomly compared the Supraflex SES with the Xience EES among 1430 patients. At 12-months follow-up, there was no difference between the groups for the primary endpoint, a composite of cardiac death, target-vessel myocardial infarction, or clinically indicated TLR [38]. Although the trial was not powered for all-cause mortality, a significantly higher mortality rate was found in the experimental arm (2.0% vs. 0.6%), which might be due to the play of chance. At 2- and 3-years follow-up, the primary endpoint occurred at similar rates in the Supraflex SES and Xience EES arms (6.9% vs. 7.9%, $p = 0.491$; 8.1% vs. 9.4%, $p = 0.406$, respectively) [39,40]. Several ongoing studies will provide evidence on the performance of Supraflex Cruz SES in different settings, including acute coronary syndromes, multivessel-disease and high-bleeding-risk patients [41,42]. The FIRE trial (Clinical trial.gov: NCT03772743) is an all-comers, prospective, randomized, multicentre trial, using the SUPRAFLEX/SUPRAFLEX Cruz SES to evaluate the outcomes of a functionally driven complete revascularization in elderly patients with MI and multivessel disease [34].

The trial has completed the enrolment phase. Differently, the ongoing multivessel TALENT trial will compare clinical outcomes between the SUPRAFLEX Cruz SES and the SYNERGY EES, in 1550 patients with three-vessel disease. The primary endpoint is a composite of all-cause death, stroke, myocardial infarction, or any repeat revascularization, whereas the secondary endpoints include a superiority comparison of the SUPRAFLEX Cruz SES versus the control arm at 24 months [35].

Eventually, the Cruz HBR registry will enrol 1200 patients to prove that the Supraflex Cruz is not inferior to the BioFreedom stent in HBR patients with respect to a device-oriented composite endpoint (DOCE) at 1 year.

7. Benefit of Strut Thickness Reduction: A Class Effect?

Ultrathin struts have been implemented to further enhance PCI outcomes. In recent years, a number of large-scale randomized trials have assessed their potential benefits. In addition, two large-scale systematic meta-analyses have been performed to investigate the differences between the available ultrathin platforms. Bangalore et al. conducted a meta-analysis of >11,500 patients. Out of 10 trials included, 8 evaluated the Orsiro SES (5444 patients), 1 the Mistent SES (703 patients), and 1 the Biomime SES (170 patients) [43]. At 1-year follow-up, the ultrathin strut DES reduced by 16% the risk of TLF compared with a conventional new-generation DES (relative risk, 0.84; 95% CI, 0.72–0.99). The results were

consistent across trials, and no differences emerged according to the type of ultrathin DES used. The risk reduction in TLF was driven by lower rates of MI, mainly attributed to a lower rate of ST and periprocedural MI. These findings were confirmed by a subsequent larger meta-analysis including 16 randomized trials with 20,701 patients [44]. The ultrathin DESs were the Orsiro (12 trials, 17,658 patients), the MiStent (2 trials, 1582 patients), the BioMime (1 trial, 256 patients), and the Supraflex (1 trial, 1435 patients). At a mean follow-up of 2.5 years, ultrathin-strut DESs were associated with a lower risk of TLF and TVF. There was no significant interaction according to stent type in the ultrathin strut group.

Because the stent comparators in these meta-analyses were all new-generation DESs with biocompatible polymers, the observed differences might be due to the reduction of greater than 10 μm in strut thickness [45,46]. This difference may potentially enhance strut endothelialization due to a reduction in vessel injury and vascular inflammation and reduced periprocedural MI due to less flow disturbance to the side branches [47].

8. Ultrathin Stents in High-Risk Subgroups

8.1. STEMI

STEMI setting is burdened by an increased risk of early ST due to the prothrombotic milieu of the culprit lesions. At 12- and 24-months follow-up, the BIOSCIENCE trial demonstrated lower rates of TLF in STEMI patients receiving the Orsiro SES than in patients receiving the Xience EES (3.3% vs. 8.7%, $p = 0.024$ at 12 months; 5.4% vs. 10.8%, $p = 0.043$ at 24 months) [48–50]. The BIOSTEMI trial was specifically designed to demonstrate the superiority of the Orsiro SES in patients with STEMI. At 12 months, the Orsiro SES resulted in lower rates of TLF compared with the Xience EES (4% vs. 6%, posterior probability of superiority = 0.986) [17]. The experience with the Supraflex Cruz stent from multicentre word registries demonstrated initial favourable outcomes in different subsets of lesions and clinical and patient characteristics [36]. The Supraflex SES proved safe and effective in 229 STEMI patients from the Talent trial and 198 from the Flex registry with a low incidence of TLR and stent thrombosis [36,38].

8.2. Chronic Total Occlusions

The performance of Orsiro in CTO lesions was evaluated in the Prison IV trial [51]. A total of 330 patients were randomized in a 1:1 ratio to the Orsiro SES or the Xience EES. Although underpowered for clinical outcomes, the trial failed to show the non-inferiority of the Orsiro SES in terms of LLL at 9 months. These results were confirmed at 3-years follow-up with a higher rate of MACE in the Orsiro SES arm. Anyway, the subgroup analysis of patients with CTO included in the BIOFLOW III and SORT-OUT VII trials showed a low rate of TLF and TLR [52]. Out of 185 patients with CTO treated with Supraflex Cruz SES from the Flex registry, the rate of MACE at 1 year was as low as 6.6% [36].

8.3. Diabetes Mellitus

In an analysis of the Talent trial, the rate of DOCE in diabetic patients was 5.8% in the Supraflex arm vs. 8.5% in the Xience arm. The 1-year clinical outcomes with the Orsiro DES in diabetic patients were assessed in a patient-level pooled analysis of the diabetic population from the BIOFLOW II, IV, and V trials. A similar rate of 1-year TLF was observed among 494 patients treated with the ultrathin BP-SES and 263 patients treated with the thin-strut DP-EES (6.3% vs. 8.7%) [53]. Similar results were found in a subgroup analysis of the SORT OUT VII trial [54]. In the ISAR-TEST 5 Trial, out of 3002 patients, 28.7% treated with the Coroflex ISAR Neo were diabetics; across such a subgroup, the outcomes were consistent with those of non-diabetic patients up to 10-years follow-up [28].

8.4. Small Vessel Disease

Small vessel coronary artery disease is common among patients undergoing PCI, and myocardial revascularization in this subset remains challenging owing to an increased risk of restenosis and technical failure. Evidence in this field is limited for new-generation

DESs, including ultrathin struts DESs in view of a lack of dedicated trials. As such, the evidence is mainly limited to subgroup or post hoc analyses of randomized trials [55]. In the BIORESORT trial, out of 3514 patients, 1506 were in the small vessel subgroup (defined as vessels ≤ 2.75 mm). Patients treated with Orsiro experienced a lower rate of TLR in comparison with the other treatment groups [56]. In contrast, in the Bioscience trial, where small vessel disease was defined as a vessel diameter ≤ 3 mm, no difference was observed in the 5-year rate of TLF between the BP-SES and DP-EES groups [57]. No outcome difference was observed in a prespecified analysis according to the vessel size in patients treated with the Coroflex ISAR Neo in the ISAR-TEST 5 [28]. Patients from the TALENT trial had small vessel disease in 44.9% of cases with a rate of DOCE of 8% at 1 year, not significantly different from patients treated with Xience.

8.5. In-Stent Restenosis

While data about new-generation DESs for the treatment of in-stent restenosis showed improved performance in comparison to drug-eluting balloons [58], data on the performance of ultrathin DESs in this setting are lacking. When compared with the drug-coated balloon in the BIOLUX trial, Orsiro resulted in being non-inferior in terms of LLL and TLF. However, further data are necessary in this subgroup of patients [59].

8.6. Limitations of Ultrathin DES

When a high radial force is required, such as CTO or calcific lesions, the presence of the ultrathin struts might potentially reduce the performance of the stent in terms of stent expansion. However, specific data on this issue are scant. Of interest, stent expansion capacity is more limited with ultrathin DESs than other new-generation DESs, and therefore, their use in large vessels may be challenging [60].

9. Future Directions

The search for the ideal stent continues, enhancing research in improving DESs design and their performance in real-world challenging settings. The outcomes of the previous generation DESs, along with the impact of specific PCI techniques, ancillary techniques (e.g., intracoronary imaging), and structural features, have been investigated in different complex clinical scenarios such as left main stem disease, in-stent restenosis, and coronary bifurcation lesions [61–63]. Differently, data regarding the safety and efficacy of ultrathin struts DESs in left main or coronary bifurcations are still scarce. Once these safety data in real-world cohorts become available, it is likely that ultrathin stents will be the standard of care for most revascularization procedures. We may anticipate that, in the near future, research in stent design will focus on the development of novel and more biocompatible drugs, alloys, and polymers. Future DESs are also supposed to be characterized by a progressive improvement in deliverability and flexibility. Whether such enhancements will entail further strut thickness reduction largely depends on the evidence that modification of DES structure would not come at the cost of an insufficient radial force, as discussed above.

10. Conclusions

The introduction of ultrathin struts DESs constituted a further iteration in the field of PCI technology with the potential to further hone the safety and efficacy profile of PCI. The results of multiple studies enrolling a huge number of patients and providing long-term follow-up may make ultrathin struts stents the preferred stent strategy in several clinical scenarios and lesion subsets. Ongoing randomized trials will increase evidence on the efficacy and safety of ultrathin DES.

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Abbreviations

BMS	bare metal stents
BP	biodegradable polymer
CI	confidence interval
CoCr	cobalt-chromium
CTO	chronic total occlusions
DES	drug-eluting stents
DOCE	device-oriented composite endpoint
DP	durable polymer
EES	everolimus-eluting stent
HBR	high bleeding risk
LLL	late lumen loss
MACE	major adverse cardiac events
MI	myocardial infarction
PCI	percutaneous coronary interventions
PLGA	poly-D,L-lactide-co-glycolide
PLLA	poly-L-lactic acid
PtCR	platinum-chromium
SES	sirolimus-eluting stent
ST	stent thrombosis
STEMI	ST-segment elevation myocardial infarction
TLF	target-lesion failure
TLR	target-lesion revascularization
TVF	target-vessel failure
TV-MI	target-vessel myocardial infarction
ZES	zotarolimus-eluting stent.

References

- Piccolo, R.; Giustino, G.; Mehran, R.; Windecker, S. Stable Coronary Artery Disease: Revascularisation and Invasive Strategies. *Lancet* **2015**, *386*, 702–713. [[CrossRef](#)]
- Piccolo, R.; Pilgrim, T.; Heg, D.; Franzone, A.; Rat-Wirtzler, J.; Räber, L.; Silber, S.; Serruys, P.W.; Jüni, P.; Windecker, S. Comparative Effectiveness and Safety of New-Generation Versus Early-Generation Drug-Eluting Stents According to Complexity of Coronary Artery Disease. *JACC Cardiovasc. Interv.* **2015**, *8*, 1657–1666. [[CrossRef](#)]
- Piccolo, R.; Franzone, A.; Windecker, S. From Bare Metal to Barely Anything: An Update on Coronary Stenting. *Heart* **2018**, *104*, 533–540. [[CrossRef](#)]
- Tada, T.; Byrne, R.A.; Simunovic, I.; King, L.A.; Cassese, S.; Joner, M.; Fusaro, M.; Schneider, S.; Schulz, S.; Ibrahim, T.; et al. Risk of Stent Thrombosis Among Bare-Metal Stents, First-Generation Drug-Eluting Stents, and Second-Generation Drug-Eluting Stents. *JACC Cardiovasc. Interv.* **2013**, *6*, 1267–1274. [[CrossRef](#)]
- Chisari, A.; Pistrutto, A.; Piccolo, R.; la Manna, A.; Danzi, G. The Ultimaster Biodegradable-Polymer Sirolimus-Eluting Stent: An Updated Review of Clinical Evidence. *Int. J. Mol. Sci.* **2016**, *17*, 1490. [[CrossRef](#)]
- Piccolo, R.; Bona, K.H.; Efthimiou, O.; Varenne, O.; Baldo, A.; Urban, P.; Kaiser, C.; Remkes, W.; Räber, L.; de Belder, A.; et al. Coronary Stent Trialists' Collaboration. Drug-Eluting or Bare-Metal Stents for Percutaneous Coronary Intervention: A Systematic Review and Individual Patient Data Meta-Analysis of Randomised Clinical Trials. *Lancet* **2019**, *393*, 2503–2510. [[CrossRef](#)]
- Piscione, F.; Piccolo, R.; Cassese, S.; Galasso, G.; Chiariello, M. Clinical Impact of Sirolimus-Eluting Stent in ST-Segment Elevation Myocardial Infarction: A Meta-Analysis of Randomized Clinical Trials. *Catheter. Cardiovasc. Interv.* **2009**, *74*, 323–332. [[CrossRef](#)]
- Neumann, F.-J.; Sousa-Uva, M.; Ahlsson, A.; Alfonso, F.; Banning, A.P.; Benedetto, U.; Byrne, R.A.; Collet, J.-P.; Falk, V.; Head, S.J.; et al. ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on Myocardial Revascularization. *Eur. Heart J.* **2019**, *40*, 87–165. [[CrossRef](#)]
- Iglesias, J.F.; Muller, O.; Zuffi, A.; Eeckhout, E. Performance of the Orsiro Hybrid Drug-Eluting Stent in High-Risk Subgroups. *Minerva. Cardioangiol.* **2016**, *64*, 55–73.

10. Hamon, M.; Niculescu, R.; Deleanu, D.; Dorobantu, M.; Weissman, N.J.; Waksman, R. Clinical and Angiographic Experience with a Third-Generation Drug-Eluting Orsiro Stent in the Treatment of Single de Novo Coronary Artery Lesions (BIOFLOW-I): A Prospective, First-in-Man Study. *EuroIntervention* **2013**, *8*, 1006–1011. [[CrossRef](#)]
11. Windecker, S.; Haude, M.; Neumann, F.-J.; Stangl, K.; Witzenbichler, B.; Slagboom, T.; Sabaté, M.; Goicolea, J.; Barragan, P.; Cook, S.; et al. Comparison of a Novel Biodegradable Polymer Sirolimus-Eluting Stent with a Durable Polymer Everolimus-Eluting Stent: Results of the Randomized BIOFLOW-II Trial. *Circ. Cardiovasc. Interv.* **2015**, *8*, e001441. [[CrossRef](#)]
12. Lefèvre, T.; Haude, M.; Neumann, F.-J.; Stangl, K.; Skurk, C.; Slagboom, T.; Sabaté, M.; Goicolea, J.; Barragan, P.; Cook, S.; et al. Comparison of a Novel Biodegradable Polymer Sirolimus-Eluting Stent With a Durable Polymer Everolimus-Eluting Stent: 5-Year Outcomes of the Randomized BIOFLOW-II Trial. *JACC Cardiovasc. Interv.* **2018**, *11*, 995–1002. [[CrossRef](#)]
13. Saito, S.; Toelg, R.; Witzenbichler, B.; Haude, M.; Masotti, M.; Salmeron, R.; Witkowski, A.; Uematsu, M.; Takahashi, A.; Waksman, R.; et al. BIOFLOW-IV, a Randomised, Intercontinental, Multicentre Study to Assess the Safety and Effectiveness of the Orsiro Sirolimus-Eluting Stent in the Treatment of Subjects with de Novo Coronary Artery Lesions: Primary Outcome Target Vessel Failure at 12 Month. *EuroIntervention* **2019**, *15*, e1006–e1013. [[CrossRef](#)]
14. Kandzari, D.E.; Mauri, L.; Koolen, J.J.; Massaro, J.M.; Doros, G.; Garcia-Garcia, H.M.; Bennett, J.; Roguin, A.; Gharib, E.G.; Cutlip, D.E.; et al. BIOFLOW V Investigators. Ultrathin, Bioresorbable Polymer Sirolimus-Eluting Stents versus Thin, Durable Polymer Everolimus-Eluting Stents in Patients Undergoing Coronary Revascularisation (BIOFLOW V): A Randomised Trial. *Lancet* **2017**, *390*, 1843–1852. [[CrossRef](#)]
15. Doros, G.; Massaro, J.M.; Kandzari, D.E.; Waksman, R.; Koolen, J.J.; Cutlip, D.E.; Mauri, L. Rationale of a Novel Study Design for the BIOFLOW V Study, a Prospective, Randomized Multicenter Study to Assess the Safety and Efficacy of the Orsiro Sirolimus-Eluting Coronary Stent System Using a Bayesian Approach. *Am. Heart J.* **2017**, *193*, 35–45. [[CrossRef](#)]
16. Pilgrim, T.; Heg, D.; Roffi, M.; Tüller, D.; Müller, O.; Vuilliomenet, A.; Cook, S.; Weilenmann, D.; Kaiser, C.; Jamshidi, P.; et al. Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent versus Durable Polymer Everolimus-Eluting Stent for Percutaneous Coronary Revascularisation (BIO-RESORT): A Randomised, Single-Blind, Non-Inferiority Trial. *Lancet* **2014**, *384*, 2111–2122. [[CrossRef](#)]
17. Iglesias, J.F.; Müller, O.; Heg, D.; Roffi, M.; Kurz, D.J.; Moarof, I.; Weilenmann, D.; Kaiser, C.; Tapponnier, M.; Stortecky, S.; et al. Biodegradable Polymer Sirolimus-Eluting Stents versus Durable Polymer Everolimus-Eluting Stents in Patients with ST-Segment Elevation Myocardial Infarction (BIOSTEMI): A Single-Blind, Prospective, Randomised Superiority Trial. *Lancet* **2019**, *394*, 1243–1253. [[CrossRef](#)]
18. Pilgrim, T.; Rothenbühler, M.; Siontis, G.C.; Kandzari, D.E.; Iglesias, J.F.; Asami, M.; Lefèvre, T.; Piccolo, R.; Koolen, J.; Saito, S.; et al. Biodegradable Polymer Sirolimus-Eluting Stents vs Durable Polymer Everolimus-Eluting Stents in Patients Undergoing Percutaneous Coronary Intervention: A Meta-Analysis of Individual Patient Data from 5 Randomized Trials. *Am. Heart J.* **2021**, *235*, 140–148. [[CrossRef](#)]
19. Von Birgelen, C.; Kok, M.M.; van der Heijden, L.C.; Danse, P.W.; Schotborgh, C.E.; Scholte, M.; Gin, R.M.T.J.; Somi, S.; van Houwelingen, K.G.; Stoel, M.G.; et al. Very Thin Strut Biodegradable Polymer Everolimus-Eluting and Sirolimus-Eluting Stents versus Durable Polymer Zotarolimus-Eluting Stents in Allcomers with Coronary Artery Disease (BIO-RESORT): A Three-Arm, Randomised, Non-Inferiority Trial. *Lancet* **2016**, *388*, 2607–2617. [[CrossRef](#)]
20. Kok, M.M.; Zocca, P.; Buiten, R.A.; Danse, P.W.; Schotborgh, C.E.; Scholte, M.; Hartmann, M.; Stoel, M.G.; van Houwelingen, G.; Linssen, G.C.M.; et al. Two-Year Clinical Outcome of All-Comers Treated with Three Highly Dissimilar Contemporary Coronary Drug-Eluting Stents in the Randomised BIO-RESORT Trial. *EuroIntervention* **2018**, *14*, 915–923. [[CrossRef](#)]
21. Buiten, R.A.; Ploumen, E.H.; Zocca, P.; Doggen, C.J.M.; Danse, P.W.; Schotborgh, C.E.; Scholte, M.; van Houwelingen, K.G.; Stoel, M.G.; Hartmann, M.; et al. Thin, Very Thin, or Ultrathin Strut Biodegradable or Durable Polymer-Coated Drug-Eluting Stents: 3-Year Outcomes of BIO-RESORT. *J. Am. Coll. Cardiol. Interv.* **2019**, *12*, 1650–1660. [[CrossRef](#)]
22. Von Birgelen, C.; Zocca, P.; Buiten, R.A.; Jessurun, G.A.J.; Schotborgh, C.E.; Roguin, A.; Danse, P.W.; Benit, E.; Aminian, A.; van Houwelingen, K.G.; et al. Thin Composite Wire Strut, Durable Polymer-Coated (Resolute Onyx) versus Ultrathin Cobalt-Chromium Strut, Bioresorbable Polymer-Coated (Orsiro) Drug-Eluting Stents in Allcomers with Coronary Artery Disease (BIONYX): An International, Single-Blind, Randomi. *Lancet* **2018**, *392*, 1235–1245. [[CrossRef](#)]
23. Jensen, L.O.; Thayssen, P.; Maeng, M.; Ravkilde, J.; Krusell, L.R.; Raungaard, B.; Junker, A.; Terkelsen, C.J.; Veien, K.T.; Villadsen, A.B.; et al. Randomized Comparison of a Biodegradable Polymer Ultrathin Strut Sirolimus-Eluting Stent With a Biodegradable Polymer Biolimus-Eluting Stent in Patients Treated With Percutaneous Coronary Intervention: The SORT OUT VII Trial. *Circ. Cardiovasc. Interv.* **2016**, *9*, e003610. [[CrossRef](#)]
24. Jensen, L.O.; Maeng, M.; Raungaard, B.; Engstrøm, T.; Hansen, H.S.; Jensen, S.E.; Bøtker, H.E.; Kahlert, J.; Lassen, J.F.; Christiansen, E.H. Comparison of the Polymer-Free Biolimus-Coated BioFreedom Stent with the Thin-Strut Biodegradable Polymer Sirolimus-Eluting Orsiro Stent in an All-Comers Population Treated with Percutaneous Coronary Intervention: Rationale and Design of the Randomized SO. *Am. Heart J.* **2019**, *213*, 1–7. [[CrossRef](#)] [[PubMed](#)]
25. Kim, W.; Jeong, M.H.; Cha, K.S.; Hyun, D.W.; Hur, S.H.; Kim, K.B.; Hong, Y.J.; Park, H.W.; Kim, J.H.; Ahn, Y.K.; et al. Effect of Anti-Oxidant (Carvedilol and Probuco) Loaded Stents in a Porcine Coronary Restenosis Model. *Circ. J.* **2005**, *69*, 101–106. [[CrossRef](#)] [[PubMed](#)]
26. Massberg, S.; Byrne, R.A.; Kastrati, A.; Schulz, S.; Pache, J.; Hausleiter, J.; Ibrahim, T.; Fusaro, M.; Ott, I.; Schömig, A.; et al. Polymer-free sirolimus- and probucol-eluting versus new generation zotarolimus-eluting stents in coronary artery disease: The

- Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus-and Probucoel-Eluting versus Zotarolimus-eluting Stents (ISAR-TEST 5) trial. *Circulation* **2011**, *124*, 624–632. [[CrossRef](#)]
27. Kufner, S.; Sorges, J.; Mehilli, J.; Cassese, S.; Repp, J.; Wiebe, J.; Lohaus, R.; Lahmann, A.; Rheude, T.; Ibrahim, T.; et al. ISAR-TEST-5 Investigators. Randomized Trial of Polymer-Free Sirolimus- and Probucoel-Eluting Stents Versus Durable Polymer Zotarolimus-Eluting Stents: 5-Year Results of the ISAR-TEST-5 Trial. *JACC Cardiovasc. Interv.* **2016**, *9*, 784–792. [[CrossRef](#)]
 28. Kufner, S.; Ernst, M.; Cassese, S.; Joner, M.; Mayer, K.; Colleran, R.; Koppa, T.; Xhepa, E.; Koch, T.; Wiebe, J.; et al. ISAR-TEST-5 Investigators. 10-Year Outcomes From a Randomized Trial of Polymer-Free Versus Durable Polymer Drug-Eluting Coronary Stents. *J. Am. Coll. Cardiol.* **2020**, *76*, 146–158. [[CrossRef](#)]
 29. Dani, S.; Costa, R.A.; Joshi, H.; Shah, J.; Pandya, R.; Virmani, R.; Sheiban, I.; Bhatt, S.; Abizaid, A. First-in-Human Evaluation of the Novel BioMime Sirolimus-Eluting Coronary Stent with Bioabsorbable Polymer for the Treatment of Single de Novo Lesions Located in Native Coronary Vessels—Results from the MeriT-1 Trial. *EuroIntervention* **2013**, *9*, 493–500. [[CrossRef](#)]
 30. Jain, R.K.; Chakravarthi, P.; Shetty, R.; Ramchandra, P.; Polavarapu, R.S.; Wander, G.S.; Mohan, B.; Banker, D.N.; Dharmadhikari, A.; Bansal, S.S.; et al. One-Year Outcomes of a BioMime™ Sirolimus-Eluting Coronary Stent System with a Biodegradable Polymer in All-Comers Coronary Artery Disease Patients: The MeriT-3 Study. *Indian Heart J.* **2016**, *68*, 599–603. [[CrossRef](#)]
 31. TCT-650. Impact of the New BioMime™ Sirolimus-Eluting Stent in Complex Patients of Daily Practice—Preliminary Results of the MeriT-2 Study. *J. Am. Coll. Cardiol.* **2012**, *17*, B189.
 32. Abizaid, A.; Kedev, S.; Kedhi, E.; Talwar, S.; Erglis, A.; Hlinomaz, O.; Masotti, M.; Fath-Ordoubadi, F.; Lemos, P.A.; Milewski, K.; et al. Randomised Comparison of a Biodegradable Polymer Ultra-Thin Sirolimus-Eluting Stent versus a Durable Polymer Everolimus-Eluting Stent in Patients with de Novo Native Coronary Artery Lesions: The MeriT-V Trial. *EuroIntervention* **2018**, *14*, e1207–e1214. [[CrossRef](#)] [[PubMed](#)]
 33. Ormiston, J.; Webster, M.; Stewart, J.; Vrolix, M.; Whitbourn, R.; Donohoe, D.; Knape, C.; Lansky, A.; Attizzani, G.F.; Fitzgerald, P.; et al. First-in-Human Evaluation of a Bioabsorbable Polymer-Coated Sirolimus-Eluting Stent: Imaging and Clinical Results of the DESSOLVE I Trial (DES with Sirolimus and a Bioabsorbable Polymer for the Treatment of Patients with de Novo Lesion in the Native Coron. *JACC Cardiovasc. Interv.* **2013**, *6*, 1026–1034. [[CrossRef](#)]
 34. Wijns, W.; Vrolix, M.; Verheye, S.; Schoors, D.; Slagboom, T.; Gosselink, M.; Benit, E.; Kandzari, D.; Donohoe, D.; Ormiston, J.A. Long-Term Clinical Outcomes of a Crystalline Sirolimus-Eluting Coronary Stent with a Fully Bioabsorbable Polymer Coating: Five-Year Outcomes from the DESSOLVE I and II Trials. *EuroIntervention* **2018**, *13*, 2147–2151. [[CrossRef](#)] [[PubMed](#)]
 35. De Winter, R.J.; Katagiri, Y.; Asano, T.; Milewski, K.P.; Lurz, P.; Buszman, P.; Jessurun, G.A.J.; Koch, K.T.; Troquay, R.P.T.; Hamer, B.J.B.; et al. A Sirolimus-Eluting Bioabsorbable Polymer-Coated Stent (MiStent) versus an Everolimus-Eluting Durable Polymer Stent (Xience) after Percutaneous Coronary Intervention (DESSOLVE III): A Randomised, Single-Blind, Multicentre, Non-Inferiority, Phase 3 Trial. *Lancet* **2018**, *391*, 431–440. [[CrossRef](#)]
 36. Lemos, P.A.; Chandwani, P.; Saxena, S.; Ramachandran, P.K.; Abhyankar, A.; Campos, C.M.; Marchini, J.F.; Galon, M.Z.; Verma, P.; Sandhu, M.S.; et al. Clinical Outcomes in 995 Unselected Real-World Patients Treated with an Ultrathin Biodegradable Polymer-Coated Sirolimus-Eluting Stent: 12-Month Results from the FLEX Registry. *BMJ Open* **2016**, *6*, e010028. [[CrossRef](#)]
 37. Choudhury, A.; Garg, S.; Smith, J.; Sharp, A.; Nabais de Araujo, S.; Chauhan, A.; Patel, N.; Wrigley, B.; Chattopadhyay, S.; Zaman, A.G. Prospective Evaluation of an Ultrathin Strut Biodegradable Polymer-Coated Sirolimus-Eluting Stent: 12 Months' Results from the S-FLEX UK Registry. *BMJ Open* **2019**, *9*, e026578. [[CrossRef](#)]
 38. Zaman, A.; de Winter, R.J.; Kogame, N.; Chang, C.C.; Modolo, R.; Spitzer, E.; Tonino, P.; Hofma, S.; Zurakowski, A.; Smits, P.C.; et al. TALENT trial investigators. Safety and Efficacy of a Sirolimus-Eluting Coronary Stent with Ultra-Thin Strut for Treatment of Atherosclerotic Lesions (TALENT): A Prospective Multicentre Randomised Controlled Trial. *Lancet* **2019**, *393*, 987–997. [[CrossRef](#)]
 39. Gao, C.; Kogame, N.; Sharif, F.; Smits, P.C.; Tonino, P.; Hofma, S.; Moreno, R.; Choudhury, A.; Petrov, I.; Cequier, A.; et al. Prospective Multicenter Randomized All-Comers Trial to Assess the Safety and Effectiveness of the Ultra-Thin Strut Sirolimus-Eluting Coronary Stent Supraflex: Two-Year Outcomes of the TALENT Trial. *Circ. Cardiovasc. Interv.* **2021**, *14*, e010312. [[CrossRef](#)] [[PubMed](#)]
 40. De Winter, R.J.; Zaman, A.; Hara, H.; Gao, C.; Ono, M.; Garg, S.; Smits, P.C.; Tonino, P.A.L.; Hofma, S.H.; Moreno, R.; et al. Sirolimus-Eluting Stents with Ultrathin Struts versus Everolimus-Eluting Stents for Patients Undergoing Percutaneous Coronary Intervention: Final Three-Year Results of the TALENT Trial. *EuroIntervention* **2022**, *18*, 492–502. [[CrossRef](#)]
 41. Biscaglia, S.; Guiducci, V.; Santarelli, A.; Amat Santos, I.; Fernandez-Aviles, F.; Lanzilotti, V.; Varbella, F.; Fileti, L.; Moreno, R.; Giannini, F.; et al. Physiology-Guided Revascularization versus Optimal Medical Therapy of Nonculprit Lesions in Elderly Patients with Myocardial Infarction: Rationale and Design of the FIRE Trial. *Am. Heart J.* **2020**, *229*, 100–109. [[CrossRef](#)]
 42. Hara, H.; Gao, C.; Kogame, N.; Ono, M.; Kawashima, H.; Wang, R.; Morel, M.-A.; O'Leary, N.; Sharif, F.; Möllmann, H.; et al. A Randomised Controlled Trial of the Sirolimus-Eluting Biodegradable Polymer Ultra-Thin Supraflex Stent versus the Everolimus-Eluting Biodegradable Polymer SYNERGY Stent for Three-Vessel Coronary Artery Disease: Rationale and Design of the Multivessel TAL. *EuroIntervention* **2020**, *16*, e997–e1004. [[CrossRef](#)]
 43. Bangalore, S.; Toklu, B.; Patel, N.; Feit, F.; Stone, G.W. Newer-Generation Ultrathin Strut Drug-Eluting Stents Versus Older Second-Generation Thicker Strut Drug-Eluting Stents for Coronary Artery Disease. *Circulation* **2018**, *138*, 2216–2226. [[CrossRef](#)]
 44. Madhavan, M.V.; Howard, J.P.; Naqvi, A.; Ben-Yehuda, O.; Redfors, B.; Prasad, M.; Shahim, B.; Leon, M.B.; Bangalore, S.; Stone, G.W.; et al. Long-Term Follow-up after Ultrathin vs. Conventional 2nd-Generation Drug-Eluting Stents: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Eur. Heart J.* **2021**, *42*, 2643–2654. [[CrossRef](#)]

45. Palmerini, T.; Biondi-Zoccai, G.; Della Riva, D.; Mariani, A.; Sabaté, M.; Smits, P.C.; Kaiser, C.; D'Ascenzo, F.; Frati, G.; Mancone, M.; et al. Clinical Outcomes with Bioabsorbable Polymer- versus Durable Polymer-Based Drug-Eluting and Bare-Metal Stents: Evidence from a Comprehensive Network Meta-Analysis. *J. Am. Coll. Cardiol.* **2014**, *63*, 299–307. [[CrossRef](#)]
46. Bangalore, S.; Toklu, B.; Amoroso, N.; Fusaro, M.; Kumar, S.; Hannan, E.L.; Faxon, D.P.; Feit, F. Bare Metal Stents, Durable Polymer Drug Eluting Stents, and Biodegradable Polymer Drug Eluting Stents for Coronary Artery Disease: Mixed Treatment Comparison Meta-Analysis. *BMJ* **2013**, *347*, f6625. [[CrossRef](#)]
47. Kolandaivelu, K.; Swaminathan, R.; Gibson, W.J.; Kolachalama, V.B.; Nguyen-Ehrenreich, K.-L.; Giddings, V.L.; Coleman, L.; Wong, G.K.; Edelman, E.R. Stent Thrombogenicity Early in High-Risk Interventional Settings Is Driven by Stent Design and Deployment and Protected by Polymer-Drug Coatings. *Circulation* **2011**, *123*, 1400–1409. [[CrossRef](#)]
48. Pilgrim, T.; Piccolo, R.; Heg, D.; Roffi, M.; Tüller, D.; Müller, O.; Moarof, I.; Siontis, G.C.M.; Cook, S.; Weilenmann, D.; et al. Ultrathin-Strut, Biodegradable-Polymer, Sirolimus-Eluting Stents versus Thin-Strut, Durable-Polymer, Everolimus-Eluting Stents for Percutaneous Coronary Revascularisation: 5-Year Outcomes of the BIOSCIENCE Randomised Trial. *Lancet* **2018**, *392*, 737–746. [[CrossRef](#)]
49. Piccolo, R.; Heg, D.; Franzone, A.; Roffi, M.; Tüller, D.; Vuillimienet, A.; Müller, O.; Cook, S.; Weilenmann, D.; Kaiser, C.; et al. Biodegradable-Polymer Sirolimus-Eluting Stents Versus Durable-Polymer Everolimus-Eluting Stents in Patients With Acute ST-Segment Elevation Myocardial Infarction: Insights From the 2-Year Follow-Up of the BIOSCIENCE Trial. *JACC Cardiovasc. Interv.* **2016**, *9*, 981–983. [[CrossRef](#)] [[PubMed](#)]
50. Pilgrim, T.; Piccolo, R.; Heg, D.; Roffi, M.; Tüller, D.; Vuillimienet, A.; Müller, O.; Cook, S.; Weilenmann, D.; Kaiser, C.; et al. Biodegradable Polymer Sirolimus-Eluting Stents versus Durable Polymer Everolimus-Eluting Stents for Primary Percutaneous Coronary Revascularisation of Acute Myocardial Infarction. *EuroIntervention* **2016**, *12*, e1343–e1354. [[CrossRef](#)] [[PubMed](#)]
51. Teeuwen, K.; van der Schaaf, R.J.; Adriaenssens, T.; Koolen, J.J.; Smits, P.C.; Henriques, J.P.S.; Vermeersch, P.H.M.J.; Tjon Joe Gin, R.M.; Schölzel, B.E.; Kelder, J.C.; et al. Randomized Multicenter Trial Investigating Angiographic Outcomes of Hybrid Sirolimus-Eluting Stents With Biodegradable Polymer Compared With Everolimus-Eluting Stents With Durable Polymer in Chronic Total Occlusions: The PRISON IV Trial. *JACC Cardiovasc. Interv.* **2017**, *10*, 133–143. [[CrossRef](#)] [[PubMed](#)]
52. Jensen, L.O.; Maeng, M.; Raungaard, B.; Hansen, K.N.; Kahlert, J.; Jensen, S.E.; Hansen, H.S.; Lassen, J.F.; Bøtker, H.E.; Christiansen, E.H. Two-Year Outcome after Biodegradable Polymer Sirolimus- and Biolimus-Eluting Coronary Stents (from the Randomised SORT OUT VII Trial). *EuroIntervention* **2018**, *13*, 1587–1590. [[CrossRef](#)]
53. Waksman, R.; Shlofmitz, E.; Windecker, S.; Koolen, J.J.; Saito, S.; Kandzari, D.; Kolm, P.; Lipinski, M.J.; Torguson, R. Efficacy and Safety of Ultrathin, Bioresorbable-Polymer Sirolimus-Eluting Stents Versus Thin, Durable-Polymer Everolimus-Eluting Stents for Coronary Revascularization of Patients With Diabetes Mellitus. *Am. J. Cardiol.* **2019**, *124*, 1020–1026. [[CrossRef](#)] [[PubMed](#)]
54. Ellert, J.; Christiansen, E.H.; Maeng, M.; Raungaard, B.; Jensen, S.E.; Kristensen, S.D.; Veien, K.T.; Junker, A.B.; Jakobsen, L.; Aarøe, J.; et al. Impact of Diabetes on Clinical Outcomes after Revascularization with Sirolimus-Eluting and Biolimus-Eluting Stents with Biodegradable Polymer from the SORT OUT VII Trial. *Catheter. Cardiovasc. Interv.* **2019**, *93*, 567–573. [[CrossRef](#)] [[PubMed](#)]
55. Siontis, G.C.M.; Piccolo, R.; Praz, F.; Valgimigli, M.; Räber, L.; Mavridis, D.; Jüni, P.; Windecker, S. Percutaneous Coronary Interventions for the Treatment of Stenoses in Small Coronary Arteries. *JACC Cardiovasc. Interv.* **2016**, *9*, 1324–1334. [[CrossRef](#)]
56. Buiten, R.A.; Ploumen, E.H.; Zocca, P.; Doggen, C.J.M.; van der Heijden, L.C.; Kok, M.M.; Danse, P.W.; Schotborgh, C.E.; Scholte, M.; de Man, F.H.A.F.; et al. Outcomes in Patients Treated With Thin-Strut, Very Thin-Strut, or Ultrathin-Strut Drug-Eluting Stents in Small Coronary Vessels: A Prespecified Analysis of the Randomized BIO-RESORT Trial. *JAMA Cardiol.* **2019**, *4*, 659–669. [[CrossRef](#)]
57. Iglesias, J.F.; Heg, D.; Roffi, M.; Tüller, D.; Noble, S.; Müller, O.; Moarof, I.; Cook, S.; Weilenmann, D.; Kaiser, C.; et al. Long-Term Effect of Ultrathin-Strut Versus Thin-Strut Drug-Eluting Stents in Patients With Small Vessel Coronary Artery Disease Undergoing Percutaneous Coronary Intervention: A Subgroup Analysis of the BIOSCIENCE Randomized Trial. *Circ. Cardiovasc. Interv.* **2019**, *12*, e008024. [[CrossRef](#)]
58. Piccolo, R.; Galasso, G.; Piscione, F.; Esposito, G.; Trimarco, B.; Dangas, G.D.; Mehran, R. Meta-Analysis of Randomized Trials Comparing the Effectiveness of Different Strategies for the Treatment of Drug-Eluting Stent Restenosis. *Am. J. Cardiol.* **2014**, *114*, 1339–1346. [[CrossRef](#)]
59. Jensen, C.J.; Richardt, G.; Tölg, R.; Erglis, A.; Skurk, C.; Jung, W.; Neumann, F.J.; Stangl, K.; Brachmann, J.; Fischer, D.; et al. Angiographic and Clinical Performance of a Paclitaxel-Coated Balloon Compared to a Second-Generation Sirolimus-Eluting Stent in Patients with in-Stent Restenosis: The BIOLUX Randomised Controlled Trial. *EuroIntervention* **2018**, *14*, 1096–1103. [[CrossRef](#)]
60. Öner, A.; Rosam, P.; Borowski, F.; Grabow, N.; Siewert, S.; Schmidt, W.; Schmitz, K.-P.; Stiehm, M. Side-Branch Expansion Capacity of Contemporary DES Platforms. *Eur. J. Med. Res.* **2021**, *26*, 121. [[CrossRef](#)]
61. D'Ascenzo, F.; Omedè, P.; de Filippo, O.; Cerrato, E.; Autelli, M.; Trabattoni, D.; Ryan, N.; Venuti, G.; Muscoli, S.; Montabone, A.; et al. Impact of Final Kissing Balloon and of Imaging on Patients Treated on Unprotected Left Main Coronary Artery With Thin-Strut Stents (From the RAIN-CARDIOGROUP VII Study). *Am. J. Cardiol.* **2019**, *123*, 1610–1619. [[CrossRef](#)] [[PubMed](#)]
62. Gaido, L.; D'Ascenzo, F.; Imori, Y.; Wojakowski, W.; Saglietto, A.; Figini, F.; Mattesini, A.; Trabattoni, D.; Rognoni, A.; Tomassini, F.; et al. Impact of Kissing Balloon in Patients Treated With Ultrathin Stents for Left Main Lesions and Bifurcations. *Circ. Cardiovasc. Interv.* **2020**, *13*, e008325. [[CrossRef](#)] [[PubMed](#)]
63. Iannaccone, M.; D'Ascenzo, F.; Gallone, G.; Mitomo, S.; Parma, R.; Trabattoni, D.; Ryan, N.; Muscoli, S.; Venuti, G.; Montabone, A.; et al. Impact of Structural Features of Very Thin Stents Implanted in Unprotected Left Main or Coronary Bifurcations on Clinical Outcomes. *Catheter. Cardiovasc. Interv.* **2020**, *96*, 1–9. [[CrossRef](#)] [[PubMed](#)]