

Go Implant-Free in De Novo Lesions: DCB-Only Strategy

Experts share their thoughts on DCB-only angioplasty as an implant-free alternative to DES implantation. Based on their clinical practice, the experts offer their distinct perspectives on recently published data, future expectations, and much more.

WITH ROBERT A. BYRNE, MD, PhD; RABAN JEGER, MD; AND BRUNO SCHELLER, MD, WITH ADDITIONAL COMMENTARY PROVIDED BY TUOMAS T. RISSANEN, MD, PhD

Clinical DCB Practice of Experts

Dr. Byrne: We treat ISR in 80% of cases with DCBs. In de novo lesions, we only use DCBs in selected clinical situations. Less than 10% of our patients are treated with DCB-only.

Prof. Jeger: Almost 100% of ISR cases are treated with DCBs. We treat de novo lesions increasingly with the DCB-only strategy, especially bifurcations and small vessel disease.

Prof. Scheller: We treat about 50% of all patients with at least one DCB. The feasibility of the DCB-only approach is based on the lesion preparation result; we do not differentiate between ISR and de novo lesions.

Tell us about your background and how you currently practice drug-coated balloon (DCB) angioplasty. Do you consider the DCB technology to be your primary treatment option?

Dr. Byrne: Our experience with DCB angioplasty at the German Heart Centre in Munich, Germany, stretches back about 10 years. We initially investigated DCBs in a randomized trial called ISAR-DESIRE 3, which we subsequently published in 2013.¹ In this trial, we exclusively studied patients with in-stent restenosis (ISR) and demonstrated non-inferiority in angiographic outcomes compared with repeat stenting with drug-eluting stents (DESs).

In coronary ISR, angioplasty with DCB is our default, and we treat approximately 80% of lesions with this approach. Only in patients in whom the mechanical integrity of the underlying stent is clearly compromised do we prefer repeat stenting. In de novo disease, the situation is reversed. Pending the availability of further clinical trial

data and in light of the generally excellent results with new-generation stents, stenting with a DES is our default approach, with DCBs reserved for selected clinical situations such as diffuse, distal vessel disease or bifurcations. Overall, $\leq 10\%$ of our patients are treated with DCB alone.

Prof. Jeger: I began my work in interventional cardiology 15 years ago when DESs were entering clinical practice. At that time, I was involved in many trials comparing bare-metal stents (BMSs) and DESs, and I was happy with the results of second-generation DESs for a long time. However, due to the limitations of stents in some clinical and anatomic situations, I was using more and more DCBs.

DCBs should always be the first step in the treatment plan. Sometimes, the DCB-only approach is not possible, and stents should be used instead. DCBs and DESs are complementary but not contrary treatment options.

I currently try to use the DCB-only strategy as much as possible—in almost 100% of ISR cases, bifurcations, and small vessel disease, as well as, increasingly, large native vessels.

Prof. Scheller: I started my training in interventional cardiology 23 years ago. I had experienced the transition from post-stent treatment with anticoagulants to dual platelet inhibition. However, the stents were far from safe to use at that time. Stent loss in the coronary vessels was common, and many lesions could only be treated with balloons. At the same time, the first concepts for local drug delivery were published. In 1999, we started our own first projects on the local application of drugs. The result was a coating consisting of paclitaxel and a contrast agent (Figure 1). The first coronary clinical study was conducted in patients with BMS ISR (PACCOCATH ISR trial).

DCBs are already my primary treatment option. Today, we use at least one DCB in close to half of all percutaneous coronary interventions (PCIs) in our clinic, with de novo lesions accounting for > 85% of all DCB interventions. The decision to use a DCB is made after lesion preparation. This has significantly reduced the number of newly implanted stents, which also means less ISR. I see few limitations for DCB angioplasty.

When performing DCB-only angioplasty in ISR or de novo lesions, what are the primary considerations concerning technique and usage?

Dr. Byrne: The key to successful DCB therapy is performing a meticulous angioplasty procedure—taking time to prepare the lesion well and deliver the DCB device in as efficient a manner as possible. There are two central considerations when performing DCB angioplasty. First, the lesion (ISR or de novo) must be adequately dilated with conventional catheter techniques, achieving a satisfactory acute result in the absence of major flow-limiting dissection. One must bear in mind that the DCB catheter is primarily a local drug-delivery vehicle, which should be used when the mechanical dilation work has been accomplished. Non-compliant, super-high-pressure, and cutting or scoring balloons are excellent choices for safe and effective lesion preparation. Rotablation may occasionally be necessary, and experience is increasing with intracoronary lithotripsy.

Second, it is important to handle the catheter very carefully during preparation and introduce it as rapidly as

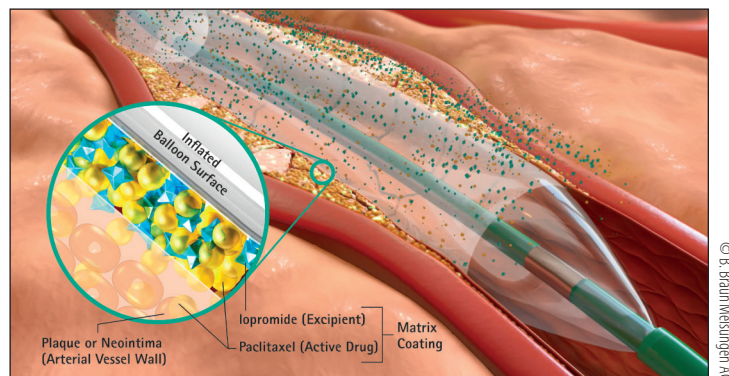


Figure 1. Mechanism of SeQuent® Please NEO's matrix coating.

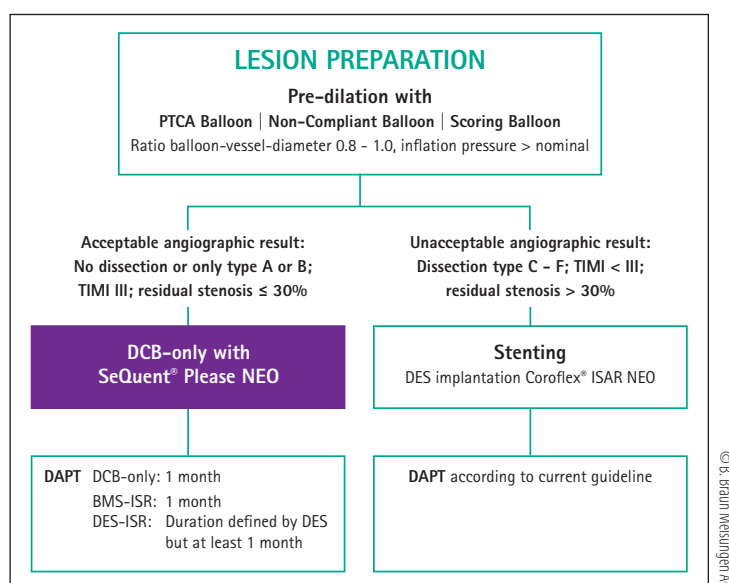


Figure 2. DCB-only treatment methodology according to the German Consensus Group with products from B. Braun's coronary angioplasty portfolio. PTCA, percutaneous transluminal coronary angioplasty; TIMI, thrombolysis in myocardial infarction. Kleber FX, et al. Clin Res Cardiol. 2013;102:785-797.

possible to the target lesion. This is because the coating is quite fragile and can be removed by manual contact with the balloon or washed off in transit if the dwell time in the guide catheter and vessel is too long. Thus, in addition to thorough lesion preparation, good guide catheter support, resolution of any proximal tortuosity prior to balloon delivery, and use of mother-child catheters are important considerations in planning an effective procedure.

Prof. Jeger: The main requirement for a successful DCB-only intervention is an acceptable angiographic result after pre-dilatation (Figure 2), irrespective of localization or lesion type. If no acceptable result is possible, the lesion should be treated with DESs.



Figure 3. The SeQuent® Please NEO.

Prof. Scheller: In individual cases, fractional flow reserve measurements can be very helpful in assessing the result after pre-dilatation. The focus here is on the functional result; non-flow-limiting dissections are accepted and may even improve the long-term outcome. Following the rules of the German Consensus Group, > 70% of all lesions can be treated with DCB-only. The risk of acute and subacute vascular occlusions is well below the comparable rate of modern DESs.

What concerns did you have when you started with DCB-only angioplasty, and how did you manage them?

Dr. Byrne: Our main concern was that the therapy would prove ineffective and patients would return with restenosis. We had worked a lot with novel DES technologies and realized that with stent technology, control of drug-release kinetics in the initial 14 to 28 days after intervention was critical to the therapy's success. We wondered how a simple 60-second dilation with a balloon catheter could be effective. However, once we saw the data that emerged from ISAR-DESIRE 3, we realized that DCB therapy was a very effective way to treat patients presenting with ISR, and this impression has been underlined by the general experience from several clinical trials since then.

Prof. Jeger: The main concern was that lesions treated without stents might be subject to acute vessel closure or restenosis. However, after positive clinical results in the ISR field, I went on and used DCBs in de novo lesions as well—with good clinical results. The positive results of the BASKET-SMALL 2 trial corroborated our clinical impression and did not show any acute vessel closure after DCB use, although stent thrombosis was quite frequent.

Prof. Scheller: At the beginning of the DCB clinical research, I was still of the opinion that stents were needed and the combination of DCB and stents would be a good idea. We had to learn that results of this com-

bination therapy were often disappointing. Factors like geographic mismatch between stent and balloon played a role. The advantage of the DCB, namely to avoid permanent implants, was non-existent in this concept. The resulting strategy was the DCB-only principle, which was initially intended as a decision-making aid to choose either a DCB or stent. Later, the aspect of lesion preparation as an integral part of the intervention became more important.

Did the published data on the DCB-only approach in de novo lesions—such as the randomized BASKET-SMALL 2 and DEBUT trials—change your approach? If so, how?

Dr. Byrne: In contrast to ISR, the field of intervention for de novo disease has been limited by a lack of convincing data from randomized clinical trials (RCTs). Nevertheless, a minority of interventionalists have accumulated extensive experience with the DCB-only approach and have shown excellent results in observational studies. However, for professional societies and clinical practice guideline task forces, randomized trial data are the gold standard for evaluating treatment modalities. The recent publication of encouraging results from the two clinical trials has reawakened interest in DCB use for de novo disease, particularly for lesions in small vessels and patients with high bleeding risk. At the same time, further trials are urgently needed, in more broadly inclusive patient populations and testing directly against high-performance new-generation DESs.

Prof. Jeger: For my clinical practice, the two trials did not change my preferences, because I used DCBs before. However, cardiologists now have the certainty that DCBs are a good alternative to DESs in many situations. Thus, I see increasing confidence in the technique, which is very positive.

Prof. Scheller: We were one of the main centers for BASKET-SMALL 2, and I was able to write the comment in *The Lancet* for DEBUT.² Although the studies did not change my daily work, they help in discussions with colleagues who are still critical of DCB technology. Moreover, these data and publications facilitate reimbursement, especially when discussing the benefits with health insurance companies.

What do you believe will be the role of the DCB-only approach in the future?

Dr. Byrne: In my opinion, DCBs will continue to play an important role in treating patients with ISR, at least in the first instance. It is clear that in patients with stent failure, avoiding implantation of additional stent layers

is a preferable strategy over the medium to long term. If a patient subsequently fails after treatment with DCB angioplasty, then repeat stenting may be considered. In de novo disease, a critical mass of data is being generated. Further supportive data from a large-scale trial enrolling relatively unselected patient populations would give more physicians confidence in using DCBs for this indication.

Prof. Jeger: I think that the DCB-only approach is here to stay. After the failure of bioabsorbable scaffolds, we now have a technique that is fulfilling the dream of “leaving nothing behind.” In many clinical and anatomic situations, a primary approach of treating the vessel with DCB-only and just implanting a stent when necessary may be beneficial for the patient. DCBs will increasingly be used when operators get comfortable with the technique and the good clinical results become apparent. The next step will be to expand the technique to other indications, such as larger de novo vessels. Although DCBs are already used for these lesion types, we need RCTs to give the community confidence that the DCB-only approach is feasible and safe in any kind of coronary lesions.

Prof. Scheller: DCB use in coronary lesions is still considered a niche indication by many interventional cardiolo-

gists. However, this wonderful technology does not deserve a niche role. The currently recognized indications for ISR, small vessel disease, side branches of bifurcations, and patients with a high risk of bleeding make up more than half of all PCIs. It is time for DCBs to be accepted as mainstream therapy, not just as an emergency solution when stents appear to be unfavorable. However, the real benefits of the technology will only become apparent in the long term. Unlike bioresorbable vascular scaffolds, the long-term advantage of DCBs is not traded in with a disadvantage in the first years after the initial intervention.

Current-generation DCBs, such as the SeQuent® Please NEO (Figure 3), have significantly improved mechanical properties so that the initial issue of deliverability is solved. To minimize wash-off in transit to the lesion, the transfer time should not exceed 2 minutes. With the current DCB generation, this is usually possible with experienced operators. The question of whether other drugs, such as sirolimus, will play a role in DCB technology is the subject of ongoing clinical research. Until then, DCBs with paclitaxel coating and sufficient clinical evidence—particularly the SeQuent® Please NEO—are the gold standard. ■

1. Byrne RA, Neumann FJ, Mehilli J, et al. Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): a randomised, open-label trial. *Lancet*. 2013;381:461-467.
2. Scheller B. Drug-coated balloons for patients with increased risk of bleeding. *Lancet*. 2019;394:P190-P192.

DCB-only Strategy Broadens Indications

De novo lesions in large vessels, bifurcations, and patients with high bleeding risk can now be treated with DCB angioplasty. By Tuomas T. Rissanen, MD, PhD

Implanting a DES has become the standard of PCI during the last two decades. Target lesion revascularization of the treated arterial segment after PCI using newer-generation DESs is quite rare, occurring in approximately 5% of cases at 1 year after intervention. However, there are still significant drawbacks to using a DES as a permanent coronary implant. Most importantly, dual antiplatelet therapy (DAPT)-related bleeding complications remain a significant issue, especially in elderly patients or those using oral anticoagulation, in whom the risk of death is increased up to seven-fold.¹ After stenting, DAPT often cannot be safely shortened. There is also a small but often fatal risk of stent thrombosis (ranging from 0.5%–1%) after implantation of a metallic DES in a coronary artery.

Balloons coated with paclitaxel and iopromide as an excipient were originally developed for treating ISR; however, their potential for treating de novo coronary artery lesions was later demonstrated in large registry trials.²⁻⁷ The BASKET-SMALL 2 trial (n = 758) was the first RCT with a

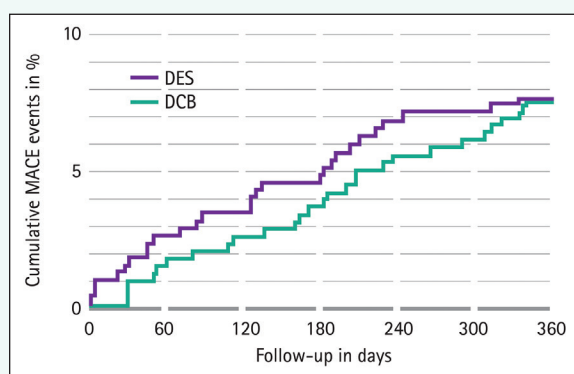


Figure 4. Graph depicting the percentage of major adverse cardiac events (MACE) in the BASKET-SMALL 2 trial.

primary clinical endpoint showing non-inferiority of DCBs in comparison with second-generation DESs in de novo lesions (Figure 4). Although this study was restricted to small vessels (reference diameter < 3 mm),⁸ randomized

data on larger vessels are already available. The recently published DEBUT trial (n = 208) was initiated in five Finnish centers in 2013. It was the first RCT where the DCB-only strategy was tested in de novo lesions of large coronary vessels (reference diameter $\leq$ 4 mm) in patients with high bleeding risk. Only a few clinical scenarios were excluded, such as PCI in the left main stem, ST-segment elevation myocardial infarction, and chronic total occlusions.⁹ The DEBUT trial demonstrated that it is safe and effective to defer stenting in patients with high bleeding risk, resulting in a low rate of MACE (3.9% at 1 year) and target lesion revascularization (2% at 1 year).⁹

The advantages of the implant-free DCB-only approach are highlighted in these trials: no acute vessel closures or thrombotic events occurred in lesions treated with DCB-only in either the BASKET-SMALL 2 or DEBUT trial, even when an antithrombotic regimen was stopped.

Future RCTs should focus on three topics: optimal antiplatelet treatment, bifurcations, and diffuse lesions in distal segments. The lack of metal inside the coronary artery may allow single-agent antiplatelet therapy in patients with very high bleeding risk and in patients undergoing emergent or urgent surgery. An RCT comparing DCB with newer-generation DESs in patients with high bleeding risk is warranted. The full clinical benefit of the DCB-only strategy over DES implantation requires shorter or even no DAPT after DCB angioplasty.

PCI of bifurcations is quicker and less complex when performed with a DCB in one or both target branches as

compared with a two-stent strategy. Stenting versus the DCB-only strategy in bifurcations should be evaluated in an RCT. Finally, for diffuse atherosclerosis in vessels with proximal lesions (eg in chronic total occlusions), stenting in combination with DCB treatment is a promising new application of DCBs. This kind of hybrid procedure using both a DES and DCB in the same vessel is already daily clinical practice in experienced DCB centers. This also leads to shorter vessel segments caged by a metallic stent.

To date, only paclitaxel-coated DCBs have shown clinical potential in RCTs. Future trials will show whether sirolimus-based DCBs will be as effective as paclitaxel-coated balloons in the treatment of de novo lesions.

1. Palmerini T, Bacchi Reggiani L, Della Riva D, et al. Bleeding-related deaths in relation to the duration of dual-antiplatelet therapy after coronary stenting. *J Am Coll Cardiol*. 2017;69:2011-2022.
2. Scheller B, Hehrlein C, Bocksch W, et al. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *N Engl J Med*. 2006;355:2113-2124.
3. Bondesson P, Lagerqvist B, James SK, et al. Comparison of two drug-eluting balloons: a report from the SCAAR registry. *EuroIntervention*. 2012;8:444-449.
4. Wöhrle J, Zadura M, Möbius-Winkler S, et al. SeQuent Please world wide registry: clinical results of SeQuent Please paclitaxel-coated balloon angioplasty in a large-scale, prospective registry study. *J Am Coll Cardiol*. 2012;60:1733-1738.
5. Zeymer U, Waliszewski M, Spiecker M, et al. Prospective 'real world' registry for the use of the 'PCB only' strategy in small vessel de novo lesions. *Heart*. 2014;100:311-316.
6. Venetsanos D, Lawesson SS, Panayi G, et al. Long-term efficacy of drug coated balloons compared with new generation drug-eluting stents for the treatment of de novo coronary artery lesions. *Catheter Cardiovasc Interv*. 2018;92:E317-E326.
7. Rosenberg M, Waliszewski M, Chin K, et al. Prospective, large-scale multicenter trial for the use of drug-coated balloons in coronary lesions: the DCB-only all-comers registry. *Catheter Cardiovasc Interv*. 2019;93:181-188.
8. Jeger RV, Farah A, Ohlwe MA, et al. Drug-coated balloons for small coronary artery disease (BASKET-SMALL 2): an open-label randomised non-inferiority trial. *Lancet*. 2018;392:849-856.
9. Rissanen TT, Uskela S, Eränen J, et al. Drug-coated balloon for treatment of de-novo coronary artery lesions in patients with high bleeding risk (DEBUT): a single-blind, randomised, non-inferiority trial. *Lancet*. 2019;394:230-239.

Robert A. Byrne, MD, PhD

Deputy Director
Department of Cardiovascular Diseases
German Heart Centre Munich
Munich, Germany
byrne@dhm.mhn.de

Disclosures: Reports lecture fees from B. Braun Melsungen AG, Biotronik, Boston Scientific Corporation, and Micell Technologies; research funding to the institution from Boston Scientific Corporation and Celonova Biosciences.

Raban Jeger, MD

Head of Structural Cardiology
University Hospital of Basel, University of Basel
Basel, Switzerland
raban.jeger@usb.ch

Disclosures: Received research support from B. Braun Melsungen AG; received lecture honoraria from B. Braun Melsungen AG and Cardionovum.

Bruno Scheller, MD

Professor of Clinical and Experimental Interventional Cardiology
Saarland University Medical Center
Homburg, Germany
bruno.scheller@uks.eu

Disclosures: Named as co-inventor on patent applications submitted by Charite hospital in 2000/01; travel support by B. Braun Melsungen AG.

Tuomas T. Rissanen, MD, PhD

Head of Cardiology
Heart Center
North Karelia Central Hospital, Siun Sote
Joensuu, Finland
tuomas.rissanen@siunsote.fi

Disclosures: Research grant and honoraria from B. Braun Melsungen AG.