PANEL DISCUSSION

BTK Drug-Coated Balloons: Can They Clear the Hurdle?

Perspectives on the role of DCBs below the knee, current challenges, and considerations for future trials.

With Marianne Brodmann, MD; Edward Choke, MD; and Andrew Holden, MBChB, FRANZCR, EBIR

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First, to give readers a frame of reference of your experience, how would you briefly summarize your past and present use of drug-coated balloons (DCBs) below the knee (BTK), based on your investigational experience and availability in your region, as well as your own preferences?

Prof. Brodmann: We have had the opportunity to take part in several DCB BTK trials and, compared to the standard treatment (plain old balloon angioplasty [POBA]), we have seen better outcomes in the DCB arms in most of the trials. Of course, this is a site-related observation. In Europe, DCBs are CE Mark approved for BTK use, so we use DCBs in BTK treatment on a fairly regular basis, mainly in patients at high risk for reintervention or patients with restenosis. Because we have participated in DCB BTK trials, we are confident in using DCBs for this purpose, as we have not seen any local or systemic risks in our large patient cohort.

Dr. Choke: In the past, I have selectively used paclitaxel-coated balloons (PCBs) for specific areas of BTK arteries. Although PCBs are good at preventing restenosis from neointimal hyperplasia, this must be balanced against the risk of distal embolization, slow-flow phenomenon, and early arterial thrombosis. My personal preference is to selectively use PCBs for the proximal 100 mm of BTK arteries because BTK arteries here are larger and more tolerant of slow-flow phenomenon, whereas distal BTK arteries do not perform as well with PCB. I practice in Singapore and BTK arteries tend to be smaller in the Asian population. I avoid PCBs in small (< 2 mm) and inadequately prepared BTK arteries with poor runoff vessels because such vessels are less forgiving if slow-flow phenomenon were to occur.

I began using sirolimus-coated balloons (SCBs) for BTK arteries in a trial setting (XTOSI trial) when SCB became available as an investigational device in 2017 in Singapore. I initially started using them in proximal BTK arteries, and now I use them on a case-by-case basis in distal BTK arteries and even below-the-ankle arteries, where I have not encountered any adverse consequences of early thrombosis. For now, we are monitoring outcomes of PCBs and SCBs BTK using a prospective registry. In the longer term, the inclusion of PCBs and SCBs in the treatment algorithm of BTK will be guided by data from ongoing trials.

Dr. Holden: We are a major investigational site for early human vascular intervention device trials. We have been and are currently recruiting to several DCB trials BTK. In addition, we are involved in several vessel preparation device trials in tibial arteries that are followed by DCB treatment. Although these trials have shown safety and some signs of increased efficacy, it is still unclear exactly what the role of these technologies will be in BTK intervention. In our own clinical practice, while DCBs and drug-eluting stents are used in almost all patients undergoing femoropopliteal arterial interventions, we are more selective with DCBs BTK, primarily reserving these for restenotic lesions.

Based on what we have seen the clinical trial experience to date, what are your current thoughts on the potential applicability of DCBs in this setting?

Dr. Holden: I don't see any reason why DCBs in BTK arteries will not be associated with improved patency and reduced reintervention compared to standard percutaneous transluminal angioplasty. However, as we utilize an evidence-based approach to treating our patients, it is accurate to say there is inadequate evidence to support their routine use. I'm pleased to see a significant number of clinical trials currently being undertaken directly addressing this issue.

Prof. Brodmann: With regard to our own experience and the current data, we see varied effect as we have seen above the knee (ATK). A DCB needs to prove its efficacy, and therefore, some DCBs might be qualified and others not. It is unfortunate that some DCB BTK trials are stopped due to lack of enrollment, even though the DCBs used in these trial are of high quality and effective. The issue is that sufficient data are lacking.

Dr. Choke: Historically, there have been conflicting data for PCBs in BTK arteries. Following the negative results of the IN.PACT DEEP trial, it seemed for a while that companies and physicians alike were reluctant to apply PCBs for BTK disease.

More recently, PCBs BTK are making a comeback with new-generation devices. Catheter-based drug delivery technology has continued to evolve and improve, with novel innovative ways of maximizing the transfer of drugs while minimizing the downstream loss of drugs. With improved technology, PCBs may still have a role in BTK arteries, and we should watch this space for more data in the next 5 years. The In.Pact 014 PCB (Medtronic) showed lower late lumen loss (LLL) that approached statistical significance compared to standard balloon angioplasty in the IN.PACT BTK randomized controlled trial (RCT). Both ACOART II BTK RCTs (China and Italy) have recently reported superior primary patency and LLL with the Litos PCB (Acotec Scientific) BTK. The Lutonix BTK trial reported that the PCB group had a better primary efficacy endpoint using combination of freedom from vessel occlusion and freedom from above-ankle amputation at 6 months. Interestingly, the FDA has not approved the use of Lutonix 014 PCB (BD Interventional) for BTK arteries.

Data for the use of SCBs for BTK are limited to two small single-arm trials in Asian patients with chronic limb-threatening ischemia (CLTI), XTOSI (MagicTouch PTA, Concept Medical) and PRESTIGE (Selution SLR, MedAlliance). The XTOSI trial (of which I am Principal Investigator) results have been presented.[1] The 6-month primary patency was 74% for BTK arteries treated with the MagicTouch PTA SCB. The recently published PRESTIGE trial reported 6-month primary patency of 82%.[2] These were real-world, high-risk CLTI patients with long lesions (approximately 190 mm). These early data are promising but must be interpreted with caution, and we are currently running a BTK RCT of SCB versus standard balloon angioplasty (FUTURE BTK), which will provide further clarity.

Which of the challenges posed by this anatomy and of critical limb ischemia (CLI)/CLTI do you think are surmountable, and which will likely continue to hinder optimal results?

Dr. Choke: CLTI BTK lesions are long, diffuse, and often highly calcified. Furthermore, BTK arteries are small, and hence even minimal neointimal hyperplasia or recoil after conventional angioplasty will have a pronounced adverse effect compared to the larger superficial femoral arteries. These unfavorable features contribute to the notoriously high restenosis rates after standard balloon angioplasty. We are facing an epidemic of BTK disease, and the lack of effective treatment for BTK due to the above challenges means that there is a great unmet need.

Nevertheless, promising new technologies designed to overcome these challenges are being tested all over the world, so I think the BTK issues are surmountable.

For now, standard balloon angioplasty for BTK remains the standard of care, albeit with unsatisfactory results. I find that the use of noncompliant balloon catheters can reduce the rate of early recoil, but the solution to a more durable treatment fundamentally lies in the prevention of neointimal hyperplasia in the small BTK vessels. We are ever closer to a successful biologic antirestenotic therapy for BTK, and we look forward to RCT-level data for novel SCBs and newer-generation PCBs for BTK.

Prof. Brodmann: Some challenges in CLI are relevant, such as smaller vessel diameter, the different mode of calcium in BTK arteries, the high percentage of chronic total occlusions (CTOs), and the impaired outflow. As far as a patient-specific finding, the number of females with CLI is higher than claudicants.

Dr. Holden: Tibial artery disease is characterized by lesions that involve multiple arteries, are often long with a high incidence of CTOs as well as calcification. Postangioplasty dissection is also more common than has previously been appreciated. All of these challenges are surmountable, but the most significant areas that still need to be addressed include successful crossing of the majority of CTOs and management of intimal and medial calcification as well as postangioplasty dissection.

What are the differences in how operators might address factors such as calcium and CTOs in the real-world setting versus in a regulated trial aimed at gaining market clearances?

Dr. Holden: In many regulated trials, patients are selected based on relatively favorable anatomy. Long lesions, particularly long CTOs, and severely calcified lesions are often excluded. This is understandable as the role of these early trials is to show safety and efficacy of the technology being investigated. In the real world, technologies such as intraluminal crossing devices and debulking and calcium modification devices (such as atherectomy and intravascular lithotripsy) are often used, even though they have been excluded in many trials.

Prof. Brodmann: With regard to the real-world setting, I see treatment as very conservative: if a lesion can be crossed, then BTK treatment is mainly POBA. Calcium is not addressed specifically, and CTOs are mainly treated with a surgical approach.

What is currently known about how different anatomic locations within the BTK space respond to DCB therapy (ie, are there locations that fare better than others)? If so, how does this inform your thoughts on applicability?

Prof. Brodmann: Little is known about where DCBs might work best BTK. Some subgroup analyses from RCTs have suggested that DCBs might work better in proximal BTK lesions.

Dr. Choke: It has been acknowledged that the distal BTK arteries do not perform well after DCB therapy. For PCBs, this observation was first reported with In.Pact Amphirion in 2011 and also recently supported by the Lutonix BTK trial in which the "proximal segment" BTK group showed superior primary efficacy endpoint. When I used PCBs for BTK, I normally limited their use to the first proximal 100 mm of the tibial arteries because of the differential effects from proximal to distal and the worry of distal embolization when applied too distally. For SCBs, my personal observation is that they too work best in the proximal segments; however, from a practical viewpoint, I still apply SCBs to distal BTK arteries on the premise that they will still have a beneficial effect (albeit not as much as proximal segments), and the risk of slow-flow phenomenon or distal embolization is very low for SCBs, even when used very distally.

Has the discussion on paclitaxel-related mortality influenced how you view the potential use of DCBs BTK, and if so, in what ways?

Dr. Holden: As we all know, the discussion on paclitaxel-related mortality has primarily focused on the use of paclitaxel-coated devices in femoropopliteal arterial disease. It is pleasing that with more trial evidence and more complete patient follow-up, it is likely the previous mortality concerns with paclitaxel will be resolved. There has never been convincing evidence of a mortality concern with paclitaxel in CLI patients, including the use of DCBs in BTK arteries. In our practice, the use of DCBs is driven by data on efficacy, not paclitaxel-related mortality concerns.

Dr. Choke: The paclitaxel-related mortality in the original Katsanos et al meta-analysis in 2018 was derived from femoropopliteal trials that consisted of mainly claudicants (89%). For BTK, a second meta-analysis also by Katsanos et al on CLI patients reported a significantly decreased amputation-free survival (composite endpoint) after DCB use, although when evaluating the incidence of all-cause death and major amputation endpoints separately, no statistically significant difference

was seen. The PCB safety issue remains controversial, and the lack of individual patient-level data and the failure to consider the cross-over effect (patients initially treated with PTA who underwent subsequent reintervention with DCBs) were seen as major weaknesses in both meta-analyses. Furthermore, the longer 5-year outcomes of the IN.PACT DEEP BTK RCT as well as the long-term follow-up at 3 years of the Lutonix BTK study reported no increased risk of all-cause mortality with PCBs, but IN.PACT DEEP was not powered to assess amputations and mortality as endpoints, and the rate of loss of follow-up to 5 years was significant.

In their February 2021 update, the UK Medicines and Healthcare Products Regulatory Agency recommended the use of PCBs only in patients with CLI and to avoid their use in claudicants. This was based on the premise that benefits of PCBs may outweigh the risks (ie, prevention of restenosis could prevent limb loss and mortality). Considering this and the fact that PCBs have proven efficacy in preventing restenosis for femoropopliteal lesions, I would consider using PCBs for femoropopliteal lesions in CLI patients. Conversely, the concerns regarding safety of PCBs, in addition to the lack of strong data supporting the efficacy of PCBs for BTK, have made me more selective when using PCBs BTK. My stand on this may change in the future if there is evidence of efficacy for newer-generation PCBs for BTK. As mentioned previously, PCBs seem to be making a comeback for BTK vasculature.

Prof. Brodmann: Our use has not been influenced by the paclitaxel-related mortality discussions, as we have been involved in scientific evaluations of paclitaxel-coated DCB both ATK and BTK, follow our patients on a regular basis, and know the outcomes of the different treatment options.

Do you assume nonpaclitaxel antiproliferatives such as sirolimus will face the same hurdles as those limiting the efficacy of paclitaxel to date? How do you view the potential similarities and differences of these agents in this setting?

Dr. Choke: In the coronary arena, sirolimus is widely perceived as the superior antiproliferative agent and has displaced paclitaxel as the preferred antirestenotic agent of choice for coronary drug-eluting stents. Meta-analyses have reported superior angiographic patency and freedom from target lesion revascularization (TLR) with sirolimus-eluting stents compared to paclitaxel-eluting stents in the coronary space.

Sirolimus, as an alternative antiproliferative and antirestenotic agent, has been reported as advantageous to paclitaxel in several ways. First, sirolimus can inhibit smooth muscle cell migration from media into intima—a key step in neointimal hyperplasia.[3] Second, sirolimus was developed as an immunosuppressive drug and therefore has beneficial anti-inflammatory properties compared with paclitaxel, which was originally developed as an anticancer drug with no anti-inflammatory properties. Paclitaxel is cytotoxic—it impacts at the mitosis (M) phase and arrests the cell at a stage at which they are supposed to divide. These pro-apoptotic mechanisms eventually lead to apoptotic cell death. It therefore has a narrow therapeutic range in which it prevents restenosis but also causes cell death. On the other hand, sirolimus is cytostatic, which means it inhibits cell cycle in the G1 phase, at the initial phase of cell cycle progression, but does not kill the cell. It has a wide therapeutic range, does not cause apoptosis, and has a higher safety margin.

The disadvantage with sirolimus lies with its physical properties, which make it slower to be absorbed into tissues, coupled with shorter retention time. The major hurdles with sirolimus therefore lie with difficulties in delivering the drug to the lesion, and secondly, problems with retaining the drug in the arterial wall.

Prof. Brodmann: My opinion is that each drug-coated device must prove its efficacy and safety, irrespective of what kind of drug.

Dr. Holden: There is understandable interest in limus-based technologies for lower limb arterial intervention with many trials currently being performed. It is important that the same body of evidence that was gathered to demonstrate safety and efficacy for paclitaxel-coated devices is repeated for limus-coated devices. Given the challenges for sirolimus, such as a relative lack of drug persistence in the vessel wall without a stent or scaffold, longer-term patency results will be of particular interest.

What are the core components of a well-designed BTK trial in 2021 and beyond? For future trials, what are your opinions as to the essential endpoints necessary to show the utility of therapies used BTK? How have these evolved and why? What length of follow-up is needed?

Dr. Holden: The first key component is powering any trial to show the safety and particularly efficacy endpoints the trial is designed to evaluate. Modern BTK trials should use similar clinical and anatomic inclusion and exclusion criteria to enable objective

comparisons. Specific issues to consider include number of vessels treated, target lesion length, CTO and calcification limitations, management of inflow lesions, and restrictions on pedal artery anatomy. The frequency and duration of follow-up is also important. Although safety and efficacy results are usually focused at 6- and 12-month time points in BTK trials, longer follow-up should be considered, particularly given the experience gained from the recent paclitaxel controversy. Finally, an objective patency assessment is important when comparing the studied treatment modality to alternative techniques. In BTK arteries, patency is best assessed by catheter angiography, usually at the 6-month time point. Duplex ultrasound assessment is less accurate and objective, especially when a flow/no-flow binary parameter is used. Other noninvasive modalities such as CTA or MRA need further validation. Clinical parameters that should be included in any BTK trial include minor and major amputation-free survival, clinically driven TLR, ankle-brachial index and toe-brachial index measures, Rutherford score, and wound healing.

Prof. Brodmann: The endpoint must be efficacy with regard to primary patency. If we add clinically driven primary patency, we have to be careful, as worsening of wounds can be influenced by many cofactors. So, I still believe that an objective parameter such as primary patency is telling us the value of the device we are using. Other cofactors that can influence the local wound situation must be discussed. With regard to the length of a BTK/CLI trial, as a final follow-up period, I would stop at 2 years. For patients with CLI, this is a lengthy follow-up period and we have to take into consideration their health status.

Dr. Choke: The discussion of the ideal endpoint for BTK DCB trials is fascinating. At the most fundamental level, the sole function of DCBs is to reduce neointimal hyperplasia and prolong the patency of treated segment of the BTK artery. In my opinion, BTK DCB trials should therefore assess primary patency as the essential primary endpoint, defined by either angiographic quantification (< 50% restenosis or LLL) or duplex peak systolic velocity ratio < 2.4. The latter is commonly used in our practice because angiography is not well accepted given its invasiveness and risk of contrast-induced nephrotoxicity. Most wounds may take up to 6 months to heal, and therefore primary patency for BTK trials should be measured at 6 months, the key time point at which we want the BTK arteries to remain patent.

Some might argue for the use of wound healing as a clinically more meaningful endpoint for BTK trials. However, wound healing is dependent on wound care, and the heterogeneity of wound care between different units in multicenter BTK DCB trials would make it an inaccurate reflection of the DCB.

Using limb salvage rate as an endpoint is based on the premise that if DCBs can prolong BTK patency, then they can reduce rates of major limb amputations. However, in practice, most limb salvage units monitor their patients rigorously, and the loss of BTK patency can usually be compensated by expeditious reintervention (ie, TLR). This means that major amputation rates will remain low regardless of whether patients are in DCB or control arm. If one includes amputation as the primary endpoint, then this should be incorporated as a composite of major adverse limb event, which is met if participant has either major limb amputation or TLR.

Finally, the controversies regarding safety have meant that future trials need to consider mortality as their safety endpoint. However, this may mean a large sample size and a significant financial cost if followed for up to 5 years. For a mortality endpoint to be meaningful, trial protocols will also need to prevent cross-over treatment so that those patients initially assigned to uncoated balloon arm do not undergo subsequent reintervention with DCBs—not an easy feat to achieve over 5 years.

How has the study of DCBs in this setting been affected by limitations imposed in your region during the pandemic? Is there a clear picture as to how this might be reflected or borne out as the results of these trials are presented and published?

Prof. Brodmann: The pandemic has limited the start of new trials as everywhere, but we continued the ongoing trials and, with the help virtual observation, we were also able to test new technologies.

Dr. Holden: We have been very fortunate to have largely avoided community COVID-19 infection, so we have managed to continue clinical research relatively unscathed. However, as with many centers globally, we have seen a continued rise in the frequency of patients presenting with CLI requiring intervention, so the need for ongoing research and procedural evolution has never been greater. ■

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