ASK THE EXPERTS

How Do You Define 'High Risk for Restenosis'?

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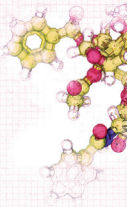
The FDA's most recent communication on paclitaxel device use for peripheral artery disease (PAD) recommends, "For individual patients judged to be at particularly high risk for restenosis and repeat femoropopliteal interventions, clinicians may determine that the benefits of using a paclitaxel-coated device outweigh the risk of late mortality." However, the criteria for high-risk determinations are not specified. In your experience, what high-risk anatomic features would potentially be best treated with paclitaxel-delivering balloons and stents in the superficial femoral artery (SFA)? Is there evidence to support this?



Prof. Holden: For many years, we've known that more complex femoropopliteal disease is not only associated with a higher incidence of suboptimal acute results when treated by plain balloon angioplasty (PTA) but also a higher risk of restenosis. Complex disease includes longer lesion length, a greater component of chronic total occlusion (CTO), moderate-to-severe calcification, and restenosis (after previous angioplasty or within a stent). One striking finding from "real-world" registries is that these complex lesions do surprisingly well in terms of short- and midterm patency with drug-eluting technologies. Given this background, it is reasonable to treat complex femoropopliteal disease with paclitaxel-delivering technologies.

The challenge is that we have no clear, evidence-based definitions of what lesion length, occlusive component, or calcification severity constitutes a complex lesion. For example, is a 10-cm CTO with moderate calcification complex or not?

Dr. Rundback: The current regulatory recommendation regarding high-risk characteristics for which paclitaxel-coated balloons and stents would provide a favorable risk strategy is clearly subject to personal interpretation. Restenotic lesions represent an anatomic cohort for which these devices would be expected to provide substantially more durable results, mitigating the inherent risk of recurrent interventions for these patients.

The DEBATE-SFA trial supports this strategy for in-stent restenosis (ISR) and suggests that paclitaxel delivery as a secondary intervention may provide similar mid- and long-term results as primary drug-coated balloon (DCB) or drug-eluting stent (DES) use. Another anatomic scenario favoring paclitaxel devices is in patients with markedly impaired infrapopliteal runoff; although there have been no data sets evaluating this, a poor runoff score has repeatedly been associated with endovascular failure, and the improved patency with paclitaxel delivery can be clinically important. We also use DES for ostial SFA lesions with longer flow-limiting dissections after optimized angioplasty due to strong patency data and the ability for precise positioning.

Although I agree with Prof. Holden that DCBs and DESs provide much better patency than PTA or bare-metal stents in CTOs, moderately calcified lesions, and long stenoses, there are also reasonable alternative therapies that we use first, including biomimetic stents, vessel preparation with optimized angioplasty and dissection repair, and stent grafts.

Prof. Brodmann: Such anatomic scenarios include CTOs, long lesions, calcified lesions, restenotic lesions (including ISR), impaired outflow, large disease "deployment" (meaning atherosclerotic disease from the iliac to the below-the-knee arteries), and small vessel diameter. It is important to note that the proof of concept for paclitaxel-coated devices in femoropopliteal lesions has been achieved in lesions with a maximum lesion length up to 18 cm if stenotic and 10 cm if CTOs. Also, restenotic lesions, ISR, and calcium were exclusion criteria. In the more demanding real-world patient cohorts seen in various registries, this was completely different. In these really complex patients with regard to lesion morphology as well as patient characteristics, DCBs have achieved outstanding results in the range of randomized controlled trial (RCT) data.

Noncomplex lesions in the femoropopliteal region are nice as a discussion topic at the podium but not as relevant in the real world. In real-world conditions, I would classify noncomplex lesions under the term "rare disease."

Dr. Schneider: We can identify patients at high risk due to anatomic features based on numerous studies of a variety of technologies in both investigational device exemption trials and observational studies. These include recurrence after PTA or atherectomy, ISR (especially if presenting as in-stent occlusion), bypass graft stenosis, severe calcification, and long lesions (TASC C/D or D+). Locations where stents are undesirable should also be considered. This may include the popliteal artery or an

SFA origin lesion where stenting is not desirable. Among patients with multilevel occlusive disease requiring treatment, I would consider using paclitaxel for inflow disease of the SFA disease prior to distal endovascular reconstruction or distal bypass.

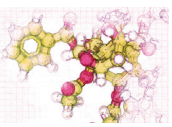
Dr. Aronow: Anatomic features such as heavy calcification, longer lesions, smaller-diameter vessels, CTOs, poor below-the-knee runoff, and ISR all increase subsequent restenosis risk. These associations have been confirmed in numerous large case series, registry studies, and clinical trials.

Dr. Ansel: Randomized trials have demonstrated a very significant decrease in need for short- and long-term repeat procedures for all lesion lengths > 4 cm in claudicants. However, there is not much trial data for CLI patients, though registry data are available for more complex disease based on anatomy. We would typically classify long lesions, small-diameter vessels, restenosis, and territories unfriendly for stents to be indicated for drug-eluting technologies, as these are associated with much higher need for repeat procedures. Calcification is still a murky area. However, the definition could also be expanded to vessels with significant postpredilation dissection, as there are also data that demonstrate a higher need for repeat procedures.

Dr. Deloose: It is important to note that the recent paclitaxel meta-analysis focused on the ideal circumstances observed in RCTs. When we look at the 2-year data, we notice a mean lesion length of 9.6 cm and 35.9% of patients having CTOs. And, in the three RCTs comprising the 4- and 5-year endpoint with the mortality signal, we see even more "ideal" lesions: a mean lesion length of 7.6 cm and 25% CTOs. In the IN.PACT (Medtronic), Lutonix (BD), and ILLUMENATE (Philips) global registries, the Ranger (Boston Scientific Corporation) data, and the Zilver PTX long-lesion SFA registry (Cook Medical), Zilver PTX Japan postmarket study, and the long lesion subanalysis from IMPERIAL (Boston Scientific Corporation), no safety signal has yet been observed. These real-world complex populations also showed substantial benefit from being treated with drug-eluting technologies.

As my daily vascular service mainly treats these real-world lesions, I feel there is no current concern for me to continue with drug-eluting technologies, based on the FDA's recommendations in its third letter. The pathology we encounter on a daily basis is typically at high risk for restenosis and reintervention. For the "exceptional" short, moderate-graded stenosis, I'm willing to use other non–drug-eluting technologies such as interwoven stents, low chronic outward force stents, dissection repair devices such as the Tack (Intact Vascular), and local atherectomies.

Are there high-risk clinical circumstances for which DCBs or DESs represent a particularly favorable therapy?



Dr. Schneider: Patients at higher risk of death or limb loss are dramatically less likely to be affected by any potential mortality signal and may have a substantial amount to gain by achieving limb salvage and avoiding reinterventions. Critical limb ischemia (CLI; including rest pain), chronic renal failure, patients with multiple recurrences, and uncontrolled diabetes are all at high risk for recurrence due to clinical circumstances. Patients with extensive medical comorbid conditions whose life expectancies may be limited but who also require lower extremity revascularization and are not candidates for open surgery should also be considered for a drug-delivering therapy.

Dr. Rundback: There are clearly patient groups in whom we favor drug delivery technologies based on clinical characteristics. This includes patients with CLI (Rutherford class 4–6), in whom the short-term risk of death after major amputation as a result of recurrent arterial reocclusion well exceeds any reported mortality hazard of paclitaxel. Similarly, I believe elderly patients and those with substantial cardiovascular risk factors and anticipated high 5-year death rates should be treated with paclitaxel DCB or DES to avoid the need for dangerous reintervention. This includes diabetic patients with poor glycemic control, patients with advanced coronary artery disease, ischemic cardiomyopathy, prior cerebrovascular event, severe chronic obstructive pulmonary disease, and malignancies, to name a few. Finally, in patients who cannot be treated with or are intolerant to antiplatelet or statin therapy, both of which have been shown to enhance patency after vascular intervention, we prefer paclitaxel-delivery devices to provide a different mechanism of improved lesion durability.

Prof. Brodmann: Yes, indeed there are clearly patient cohorts in which we should favor drug delivery based on clinical characteristics, including patients with a high number of comorbidities, renal insufficiency, obesity, CLI, and a high number of cardiovascular risk factors, especially if we see that they are poorly controlled. We should also favor the patients who are challenging with regard to returning to the cath lab. We also forget female patients, who have done very well with DCBs.

Dr. Aronow: Demographic and clinical characteristics associated with higher restenosis risk include female sex, diabetes, chronic kidney disease, and CLI. Patients with multiple clinical or anatomic characteristics are at even greater risk and are likely to derive the most benefit from paclitaxel-containing technology.

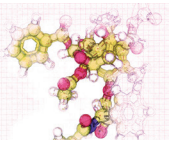
Dr. Deloose: Following the third letter issued by the FDA, we need to continue to treat people who are at high risk for restenosis and repeat intervention with drug-eluting technologies. Everybody knows the populations that we don't want to have to retreat: obesity, cardiopulmonary comorbidities, chronic kidney disease (from stage 3B on), poorly controlled diabetes, vascular access difficulties, and female patients with smaller-diameter vessels. If we can decrease the reintervention rate at 5 years with 25% to 50% in these categories by using drug-eluting therapies (as seen in the freedom from target lesion restenosis results in the IN.PACT SFA and Zilver PTX trials), I'm in.

Dr. Ansel: Unfortunately, the randomized data sets were not powered to provide us with definitive information regarding clinical subgroups. To date, the only group that may not see as beneficial of an effect is female patients. Again though, the data were not powered to look specifically at this group, and there are mixed results. The calcification issue is murky due to various definitions in the different trials. However, there is a general consensus that DCBs may not be as effective in severe calcification as DESs seem to be. Thus, drug-based therapy offers decreased and delayed need for repeat procedure benefit for most groups to date.

Prof. Holden: As we previously discussed, more complex femoropopliteal disease is associated with higher rates of restenosis and clearly benefits from paclitaxel-based balloon and stent technology in terms of patency and freedom from reintervention. However, the patency advantage that these devices offer over nondrug technologies (20%–30% over 3–5 years) is present for all femoropopliteal lesions, including relatively simple disease.

It is important to remember that reintervention is not benign, placing patients at risk of additional vascular access, procedural, contrast, and radiation-related complications. This is why I discuss the risks and benefits of DCBs and DESs with all patients undergoing femoropopliteal intervention, including simple lesions. One particular treatment concern I have is the performance of atherectomy without an antirestenotic therapy. We learned more than 20 years ago that restenosis is profound after atherectomy. Although atherectomy device technology has improved since then, their combination with paclitaxel-based devices has largely contributed to the clinical results reported. To return to treatment algorithms that failed 20 years ago would be regrettable.

Given the current guidance, are there scenarios where you might have treated with paclitaxel devices but have now changed your practice? What strategies have you adopted in these cases?



Dr. Aronow: In the past, I would utilize paclitaxel-containing technologies routinely in patients with claudication or CLI. Under the current FDA guidance, I feel it is best to use these devices primarily in the latter group until we gain a better understanding of the mortality signal. In the former group, lesion preparation should not change but the ultimate procedural intervention might involve non–paclitaxel-containing devices instead.

Prof. Brodmann: We have only changed our way of consenting the patients. We inform them about the meta-analysis and the FDA letter published in August 2019. The number of patients not signing the informed consent and denying DCB treatment after receiving this information is one within a monthly period.

Dr. Ansel: First, we take patient risk very seriously, including their possible prognoses and outcomes with and without being treated. Vascular disease significantly affects the patient's quality of life and comes with significant mortality concerns as well. We also discuss with patients the various scenarios for the different devices

that may be used and how these may affect the need for coming back for more procedures. This is important for many of our patients both logistically and financially due to insurance copays, time off from work, etc. So, this current issue is much more complex than is often discussed.

There is also no current mechanistic etiology for paclitaxel mortality in drug device use. The issue of delayed mortality was only able to be brought to presumed significance when mixing devices that are very different in multiple aspects, and I question the science of mixing devices to obtain a *P* value. There appears to be no dose response evident, and paclitaxel has not shown a similar delayed mortality effect in the coronary arteries, or in much larger doses as used in oncology (also considered to have acceptable safety in pregnant women). Large population data sets have also not demonstrated this mortality issue.

As a health care system, we have removed our previous moratorium of the use of these devices. We ask that the physicians utilize a shared decision model with the patients with gaining consent and discuss the risk versus benefit of the various approaches, which has typically been our standard process anyway. If there really is a delayed mortality risk, in our opinion, it was more likely due to different clinical treatment between the two groups. We have requested that our physicians strengthen the patients' education on the need for close clinical follow-up and risk factor modification to optimize their long-term outcomes.

Dr. Deloose: The Belgian authorities' (FAMHP) statements are even more strict than FDA recommendations, stating that paclitaxel devices not be used as preferred treatment for intermittent claudication until further notice. I strongly favor the FDA recommendations in their third letter over the unfounded Belgian advice: informing and consenting, identifying patient and lesion factors at high risk for restenosis and repeat intervention (as described here by myself and my colleagues), and treating them with drug delivery technologies and extension of close follow-up postprocedure up to 5 years. As mentioned earlier, in the rare simple lesions, I use modern scaffolds to overcome recoil, repair dissections, and tackle calcium.

Dr. Schneider: Even if I believe that paclitaxel is the best option in a given situation, a thorough patient-focused discussion of the potential benefits and possible risks of paclitaxel administration—including a discussion of the potential increase in long-term mortality—must be conducted. If the patient expresses concern or hesitation, I would not recommend its use. In younger patients without major comorbid conditions and with focal lesions, I would have offered paclitaxel in the past. In this situation, there are a variety of options with reasonable results, and the patient may have a longer life expectancy due to a paucity of severe comorbidities. Patients must be considered on an individual basis, but I would probably not recommend paclitaxel in this situation.

Dr. Rundback: Outside of the "high-risk" features described, our preference is to perform optimized angioplasty as the first-line approach. This consists of appropriate balloon sizing, often with intravascular ultrasound, atherectomy for calcified lesions, slow incremental balloon inflations, Tack dissection repair, and biomimetic stents or stent grafts depending on lesion length and location. For subintimal SFA recanalization, we generally rely on diligent angioplasty with a strategy of spot stenting for flow limitation, which has been shown to be preferable compared with long segment subintimal stents.

Prof. Holden: In the femoropopliteal segment, we continue to use a management algorithm that has provided excellent outcomes. This includes careful and prolonged predilatation to a nominal diameter with plain PTA. Based on those findings, patients receive either DCB or DES treatment. More complex disease such as heavily calcified lesions may be treated by atherectomy, intravascular lithotripsy, or a biomimetic stent. To date, this approach has not changed, as the antirestenotic benefit of paclitaxel-based devices is proven, and the causal relationship between paclitaxel and mortality is not.

Do you believe that the mortality concerns that have arisen from a meta-analysis of femoropopliteal interventions in claudicants can be applied to other clinical indications and anatomic locations?

Dr. Schneider: We should be judicious in the use of paclitaxel for any indication, including CLI and in patients with dialysis access failure, until it is better understood.

Prof. Holden: This is an interesting question! On the one hand, we know that the life expectancy of patients with other conditions (eg, CLI, renal failure patients

on hemodialysis) is very different from the claudicant population. Using this logic, the risk-benefit discussion is different in these patients, and one could consider it reasonable to use paclitaxel-delivering devices because the patient may not live long enough to experience any added mortality. I find this argument illogical and flawed. Even if the mortality risk is real, it has not been quantified, and we certainly can't accurately predict the life expectancy of CLI or hemodialysis patients on an individual patient-level basis. In my view, the result of the paclitaxel debate is binary—if added mortality is real, it should be excluded from all vascular devices. If, as I believe, it is not, it should be used in all clinical indications in which evidence shows a clear benefit.

Dr. Ansel: The current controversy arose in part due to the mixing of devices that have different characteristics (ie, a DES with a different form of paclitaxel and no excipient and DCBs). This appears to have been necessary to obtain a statistically significant *P* value in the original Katsanos et al manuscript, and the science remains confounded, with no mechanism and no dose relationship to date. To my knowledge, this would be the first pharmacologic agent to accomplish this feat. There are also a large amount of data from real-world populations not demonstrating any trend and numerically going in the opposite direction. Therefore, I reject the hypothesis and thus currently do not withhold this therapy where it has demonstrated benefit. Regarding additional populations, if the hypothesis is incorrect for the population studied, transferring the finding to other populations such as CLI and arteriovenous fistulas would also be incorrect.

If the patient-level data demonstrate a dose relationship, then I will change this opinion and work on finding the new science. However, such a mortality trend, if present, would more likely be related to investigator postprocedure treatment bias or from not needing to come back for medical care as often. Our institution has redoubled its efforts to provide these patients great medical care on a long-term basis.

Prof. Brodmann: To my knowledge, no causal relationship has been shown with regard to the higher mortality and paclitaxel usage, and therefore I see no restriction to use in any indication or patient cohort or anatomic lesion.

Dr. Aronow: It is hard to know whether the observed mortality signal represents a cause and effect relationship with paclitaxel. Until we better understand this association, I feel that our concerns should be limited to the disease state in which they were initially observed, namely patients with PAD.

Dr. Deloose: As I am a nonbeliever in the unexplained, noncausal mortality signal in femoropopliteal interventions in claudicants, how can I believe in applications to other clinical indications and anatomic locations?

Dr. Rundback: Limiting the use of paclitaxel-delivering balloons and stents based on the possible 5-year mortality signal should only be a concern in patients with normal actuarial survival estimates. There should be no impact on using these devices for individuals with CLI or other conditions threatening short-term survival or in whom restenosis or repeated interventions would be considered particularly dangerous. ■