Lower Extremity Revascularization: Recent Past and Future Directions

Commentary on five key articles related to peripheral artery disease published over the past year, top headlines, and critical questions to be answered for the future.

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This article outlines five important publications in lower extremity peripheral artery disease (PAD) within the past year and provides a forecast of important questions that will need to be answered to determine where the field is headed in the next 10 years.

Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Katsanos K, Spiliopoulos S, Kitrou P, et al. J Am Heart Assoc. 2018;7:e011245.

The article of 2019 was actually published at the end of 2018. Katsanos et al conducted a meta-analysis of randomized controlled trials of paclitaxel-coated devices (PCDs) that showed an increase in mortality beginning at 2 years in patients treated with PCDs.[1] The authors also posited an association between mortality and the dose of paclitaxel delivered. This article was an earthquake to the field of PAD intervention and prompted an extensive reanalysis of existing data sets, an FDA panel meeting, and several professional societies to issue guidance statements regarding the future use of PCDs. Regardless of the deficiencies in the methodology of the meta-analysis (lack of accounting of crossover, limited data sets with follow-up out to 2–5 years, among others), this article appropriately sparked serious concern within the field and served as a stark reminder about the need for adequately powered clinical trials.

In response, a patient-level meta-analysis of the In.Pact Admiral (Medtronic) data sets was conducted, which failed to demonstrate any correlation between the level of paclitaxel exposure and mortality out to 5 years.[2] Similarly, the Lutonix (BD Interventional) and Stellarex (Philips) programs reanalyzed their data without any identifiable signal for increased long-term mortality.[3,4] An independent retrospective cohort of 16,560 Medicare beneficiaries treated with PCDs revealed a lower rate of mortality through 600 days when compared with patients treated with percutaneous transluminal angioplasty (PTA) alone.[5] Cook Medical announced that a previous article from 2016 looking at the 5-year results from the company's paclitaxel-coated Zilver PTX stent had inadvertently reversed the mortality data such that all-cause mortality at 5 years was higher for the primary Zilver PTX group than the PTA-only group.[6,7] This correction served only to heighten the suspicion about the safety of paclitaxel use in peripheral interventions.

Ultimately, the Katsanos et al article dominated the academic discourse surrounding lower extremity peripheral arterial intervention in 2019 and figures to consume much of the academic attention in 2020 as well. Did this meta-analysis set the field back years or is the signal for mortality proof that an entire line of devices could be harmful?

In the coming year, a larger Medicare analysis is set to be published that should help either con-

firm the results of the Katsanos et al meta-analysis or add to the body of literature refuting the mortality signal. The completion of ongoing trials (SWEDEPAD, among others), ongoing FDA efforts with both industry and professional societies, and analysis of registry databases including the Vascular Quality Initiative and the National Cardiovascular Data Registry Peripheral Vascular Intervention registries will help clarify the role of PCDs in the treatment of PAD. Meanwhile, nonpaclitaxel-based technologies (sirolimus and everolimus) may be poised to assume the mantle of the go-to antirestenotic drug therapy of choice in endovascular treatment.

Retrograde Tibioperoneal Access for Complex Infrainguinal Occlusions: Short- and Long-Term Outcomes of 554 Endovascular Interventions

Schmidt A, Bausback Y, Piorkowski M, et al. JACC Cardiovasc Interv. 2019;12:1714–1726.

This article is a fascinating look into the safety and efficacy of a relatively new endovascular approach that may make the "best endovascular techniques" employed in BEST-CLI noncontemporary within the endovascular community.[8] Much like the radial approach has improved the safety profile of coronary interventions when compared with femoral access, tibioperoneal access in the field of lower extremity interventions, as first described by Mustapha et al,[9] has the potential to improve on the safety profile of lower extremity interventions. The tibioperoneal or "TAMI" (tibiopedal arterial minimally invasive) approach can be combined with an antegrade approach to successfully cross the most challenging complex lesions. Although there has understandably been much enthusiasm for tibioperoneal access, concerns regarding access vessel patency are real. This article by Schmidt et al is the largest data set to explore the safety of tibioperoneal access. In this single-center, retrospective cohort study, technical success was high (98.6% successful access, 95.1% successful wire crossing), and puncture site complications were rare (3.3%).

Although the usual caveats for such a study apply (single center, retrospective design), the accompanying editorial noted that the authors are operators at a high-volume referral center and the high rates of success may not be generalizable to the peripheral interventional community at large.[10] Additional important details include the use of a 4-F system (13.5% of cases) at largest, and only a support catheter was used in most cases (59.5%) to aid in retrograde wire crossing while treatment was then largely done from the antegrade approach. Nevertheless, this publication has helped establish the safety of the tibioperoneal approach; additional multicenter trials with a prospective design should be undertaken to more clearly establish its safety and efficacy. If this article's excellent safety and efficacy profile is confirmed, peripheral operators will have another weapon in their arsenal against chronic limb-threatening ischemia (CLTI).

TOP HEADLINES OF 2019 IN LOWER EXTREMITY PAD

- **Vascular Community Responds as Safety of PCDs Is Called Into Question**
  Much of the talk in lower extremity disease in 2019 centered around whether or not the use of PCDs is associated with increased mortality. Government agencies, society leadership, and industry all weighed in with recommendations and data updates. Trials that paused enrollment have since been resumed. This will likely continue to be a talking point in 2020.
- **CLTI Guidelines Published**
  The Society for Vascular Surgery CLTI guidelines outline new terminology for comprehensive assessment of patients with PAD.
- **The American College of Cardiology Releases Appropriate Use Criteria for Peripheral Artery Interventions**
  The new guidance from the American College of Cardiology outlines the roles of different revascularization options, rating them as "appropriate," "may be appropriate," or "rarely appropriate."
- **Sirolimus Platforms Gain FDA Breakthrough Device Designation**
  We may soon have approved devices for use below the knee (BTK). A host of sirolimus-based balloons were granted FDA Breakthrough Device designation in the treatment of BTK PAD.
- **Favorable Data Presented for BTK Therapies**
  Studies such as ABSORB BTK, TOBA II BTK, and DETOUR I have shown improved outcomes in patients with PAD and CLTI. Optimizing these therapies will continue to be of interest in this complex patient population, with pivotal trials underway.

Endovascular-First Treatment Is Associated With Improved Amputation-Free Survival in Patients With Critical Limb Ischemia

Lin JH, Brunson A, Romano PS, et al. Circ Cardiovasc Qual Outcomes. 2019;12:e005273.

This retrospective, propensity-matched analysis of 16,800 patients with lower extremity ulcers without previous revascularization undergoing revascularization procedures in California hospitals found that an open surgical–first approach was associated with worse amputation-free survival rates (hazard ratio [HR], 1.16; 95% confidence interval [CI], 1.13–1.20) when compared with an endovascular approach.[11] Reintervention rates were higher in the endovascular-first group (HR, 1.19; 95% CI, 1.14–1.23). Overall mortality was not different between the two groups.

The baseline comorbid conditions were worse for the endovascular-first group, but because these data were drawn retrospectively from ICD-9 coding and used propensity-matched scoring, they are not without limitations. The anatomic pattern and severity of disease cannot be reliably extracted from this data set, which may have influenced the up-front treatment strategy. Wound healing could not be adjudicated.

Nevertheless, this article is an encouraging signal for an endovascular-first approach for the treatment of patients with CLTI while we await the results of adequately powered, prospective, randomized controlled trials.

Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischemia

Conte MS, Bradbury AW, Kolh P, et al. J Vasc Surg. 2019;69:3S–125S.e40.

This guideline document contains an entirely new conceptual framework for the evaluation and management of the sickest PAD patients.[12] The guidelines incorporate the WIfI (Wound, Ischemia, and foot Infection) score and introduce the terms GLASS (Global Limb Anatomic Staging System), TAP (target artery path), PLAN (patient risk, limb severity, and anatomic pattern of disease), and LBP (limb-based patency) to more clearly classify patients who would benefit from revascularization as well as potentially help decide whether to undertake an endovascular-first approach or surgical revascularization as the first option. Additionally, the classification schema will help organize this heterogeneous group of patients into more easily studied groups for future research.

These recommendations regarding the revascularization options for various subsets of CLTI served to highlight the ongoing need for high-quality data in the CLTI subset. This raises the question as to whether BEST-CLI, BASIL-2, and BASIL-3 will be able to answer the question of "endo versus open."

CRITICAL QUESTIONS FOR THE FUTURE

- Will payers reimburse for the use of unique technologies at a level that encourages further research and development?
- What technologies or combination of technologies will allow for 1-, 3-, or even 5-year primary patency rates > 90%?
- Will we have adequately powered prospective studies on CLTI that evaluate revascularization techniques as well as wound care strategies and risk factor control of comorbid conditions (ie, diabetes, atherosclerotic disease)?
- Will appropriate use criteria and guidelines actually govern practice, or will endovascular intervention remain the "Wild West"?
- Will more patients with lower extremity PAD be treated in office-based labs and ambulatory surgical centers than in hospitals? If so, how will this affect treatments rendered and the long-term health of our patients?

Major Bleeding in Patients With Coronary or Peripheral Artery Disease Treated With Rivaroxaban Plus Aspirin

Eikelboom JW, Bosch JJ, Connolly SJ, et al. J Am Coll Cardiol. 2019;74:1519–1528.

Revascularization devices and techniques are undoubtedly exciting and important, but the mainstay of chronic disease management is medical therapy. This article by Eikelboom et al should provide some reassurance about the safety of low-dose rivaroxaban.[13]

Although the COMPASS trial did not exclusively evaluate patients with PAD,[14] low-dose rivaroxaban plus low-dose aspirin therapy in patients with PAD was a welcome addition to the options for more aggressive medical management. The biggest hurdle that clinicians face with respect to widespread adoption of a low-dose rivaroxaban plus low-dose aspirin approach is the concern regarding the elevated bleeding risk. This article looked at the timing, severity, and management of bleeding events in patients in the COMPASS trial, and the authors found that most of the bleeding occurred within the first year of randomization, originating from the gastrointestinal tract and only mild to moderate in intensity.

The results of the COMPASS PPI substudy are awaited, but this article by Eikelboom et al should give a degree of reassurance to clinicians who are concerned about the bleeding risk with this medication strategy. Patients who can tolerate this combination for the first year without a bleeding event will continue to accrue benefits while the risk of bleeding remains consistently low. If the clinical community is poised to make strides in the treatment of PAD, the widespread adoption of all best medical therapies will no doubt be at the forefront of this effort. ■

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