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Understanding Clinical Data and Its Application to Clinical Practice

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The emphasis on evidence-based medical practice emerged in response to the potential hazards and inconsistencies of empirical clinical decision making and reinforced the importance of critical data interpretation. Randomized controlled trials (RCTs) remain the gold standard when performed by trained investigators blinded to treatment arms in multiple centers, with predetermined endpoints and adjudicated through independent core labs and clinical events committees (CECs). RCTs provide the most rigorous and unbiased answers for the safety and effectiveness of a study treatment versus a predefined control group in a specified population. However, there are criticisms of RCTs, including their applicability to real-world populations because of the inclusion/exclusion criteria used to limit confounding variables that would ultimately create heterogeneity in study arms and potentially drive confounding results. Additionally, RCTs are generally costly given the rigorous inclusion/exclusion requirements, data monitoring, and close clinical follow-up.

To overcome the methodologic challenges, regulatory RCTs* designed for device approval to treat peripheral artery disease (PAD) narrowly define the PAD patient cohort studied (age, symptoms, comorbidities) and restrict angiographic inclusion/exclusion criteria (lesion length, chronic total occlusion length, calcification) to reduce confounding variables and maximize approval probability. Due to the perceived irrelevance to the general patient population frequently treated by clinicians, the RCT data can be misinterpreted or dismissed.

Regardless of the limitations of regulatory RCTs, the IN.PACT DEEP trial† is a striking example of their importance to the field. Prior to Medtronic's IN.PACT DEEP trial, which compared the IN.PACT™ Amphirion™ 0.014-inch Paclitaxel-Eluting PTA Balloon Catheter (DEB) versus percutaneous transluminal angioplasty (PTA), two single-center, self-adjudicated registries[1,2] reported the marked improved clinical results in patients with infrapopliteal occlusive disease and various degrees of critical limb ischemia (CLI). However, to further define the device's safety and effectiveness and promote market adoption, trial investigators enrolled 358 patients with Rutherford classification stages 2 to 6 at 13 sites in six European countries. Study patients were randomized 2:1 to treatment with IN.PACT™ Amphirion™ 0.014-inch DEB (n = 239) or PTA (n = 190). Baseline clinical characteristics were similar across both groups. Much to the surprise of both trial investigators, United States physicians, and the trial sponsor, the trial failed to meet the two primary effectiveness endpoints: The coprimary efficacy endpoints of clinically driven target lesion revascularization (CD-TLR) and late lumen loss were noninferior to PTA at 12-month follow-up. Additionally, no difference was observed in the composite 6-month safety endpoints of all-cause mortality, major amputation, and CD-TLR between the two treatment groups.[3] Importantly, monitoring of clinical events in all patients will continue through 5 years to assess any potential safety issues.

The lack of efficacy led Medtronic to withdraw the IN.PACT™ Amphirion™ 0.014-inch DEB from the market‡; however, lost in the conversation were the lessons learned from subjecting an approved device to a randomized, prospective, adjudicated trial, which only came to light after the trial's completion. In "failing forward," Medtronic understood key contributing factors in the trial's unanticipated and unimpressive results:

1. Using a different balloon material and coating process in the IN.PACT™ Amphirion™ 0.014-inch DEB platform versus the IN.PACT™ Admiral™ 0.035-inch Drug-Coated Balloon (DCB) platform resulted in a higher coating retention, which likely prevented the transfer of paclitaxel to the vessel wall.
2. The trial design was underpowered to discern a difference between the control and treatment groups.
3. Patient compliance to required clinical follow-up and procedures was poor.
4. Vessel angioplasty technique or "vessel preparation" was not standardized prior to randomization, which may have adversely impacted paclitaxel transfer into the vessel wall in patients randomized to the IN.PACT™ Amphirion™ 0.014-inch DEB.
5. Standardized wound care and assessment across all sites was difficult.

Armed with these important learnings and the proven IN.PACT™ Admiral™ 0.035-inch DCB platform, which has been extensively studied in superficial femoral artery (SFA) trials, Medtronic plans to reenter the clinical field with a randomized trial to address these shortcomings while advancing the care of CLI patients.

RCTs AND THE COMPLEMENTARY VALUE OF ADJUDICATED REGISTRIES

Well-designed, independently adjudicated real-world registries are crucial for characterizing new technologies in more challenging patient cohorts not included in regulatory RCTs. In this regard, close scrutiny of multicenter registry design and reporting methodologies is essential as it reveals the credibility of reported data. Individual site- or investigator-reported assessments of device safety and effectiveness endpoints, clinical events attributed to the device or procedure, and ultrasound assessment of vessel primary patency may introduce considerable site-to-site variability. To minimize such circumstances, specific registry design elements are essential:

1. Independent core lab adjudication is imperative. The blinded, independent evaluation of procedural angiographic parameters and endpoints (eg, pre- and postprocedure lesion percent diameter stenosis, lesion length, dissection grade) using computerized edge-detection software ensures uniformity of these important parameters. Importantly, self-reported assessments of these angiographic parameters versus an independent core lab assessment may vary as much as 20% to 25% in coronary vessels.[4] Likewise, and not surprisingly, physician "eyeball" assessments in peripheral vessels enrolled in clinical trials tend to overestimate percentage stenoses and lesion lengths to a similar degree (SynvaCor Core Lab; personal observations). Importantly, the duplex Doppler core lab assessment of the primary patency endpoint by trained, certified ultrasound technicians blinded to the vessel treatment (eg, angioplasty vs DEB/DCB) adds substantial rigor to registry data.
2. A CEC composed of independent physician experts and a statistician ensures the uniform and blinded adjudication of clinical occurrences and promotes registry credibility. Whether a clinical incident is related directly or indirectly to the device or procedure or is independent or unrelated is another assurance that important safety-related issues are adjudicated in a dispassionate and unbiased manner.

In addition to independent core lab and CEC adjudication, a well-executed registry must also closely adhere to specific—although expanded—inclusion/exclusion criteria, close patient follow-up, and independent core lab adjudication to maintain the registry's veracity. The IN.PACT Global study is an important contribution to our field and establishes a new paradigm in the design and execution of a large global adjudicated study that characterizes a device's safety and effectiveness in patients typically excluded from regulatory trials but encountered regularly in our daily practice.

Through its commitment to RCTs and large adjudicated studies, Medtronic intends to provide physicians with high-quality clinical data in complex angiographic and patient populations. Future data will help define the patient cohorts for whom clinicians can confidently offer DCB technologies and expanded indications.

It cannot be assumed that all DCBs are equal in their clinical effectiveness and safety. Although head-to-head randomized studies of various DCBs are desirable, it is unlikely due to the sample sizes needed to demonstrate superiority instead of noninferiority, which could be prohibitive. Also, rapid technology evolution and/or technology combinations could prove the trial to be irrelevant.

It is essential that we critically evaluate the specifics of any study, including safety and effectiveness definitions, clinical and functional outcomes, and inclusion and exclusion criteria, and how these factors relate to one's individual clinical practice. In analyzing the results of prospective registries, the reader must discern whether the outcomes were independently monitored and core lab assessed. Physicians can make the most appropriate patient care–related decisions only after careful interpretation of the medical literature and device claims.

* The term *regulatory RCT* is used in this article to describe the RCTs that are designed for and used to support regulatory device approval, as described in this section.
†The IN.PACT DEEP trial was not a trial for regulatory approval, but a trial to further define the device's safety and effectiveness and promote market adoption, as described in this section. The data from the IN.PACT DEEP trial were intended to be used to guide the US regulatory strategy.
‡IN.PACT™ Amphirion™ DEB 0.014-inch was not approved for use in the United States.

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