Essential Innovation and Clinical Trial Needs in Vascular Care

Experts from a variety of specialty backgrounds comment on hurdles and opportunities for future clinical trials to explore.

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The treatment of aortic aneurysms has a robust body of evidence compared to many other vascular pathologies. Hallmark studies in infrarenal aneurysm disease such as the ADAM and the UK Small Aneurysm trials have clearly defined our threshold diameter for repair.[1,2] The evolution of endovascular aneurysm repair (EVAR) over the last 3 decades since Parodi's initial publication in 1991 is a tremendous demonstration of rigorously studied innovation.[3] The EVAR-1 and OVER studies established the safety and efficacy of EVAR.[4,5] More recently, there have been tremendous advances toward the analogous adoption of endovascular techniques for treatment of complex aortic aneurysms. Complex endovascular repair will continue to push the limits as total endovascular repair from aortic valve to the external iliacs becomes a reality. Despite the incredible work that has been done to study infrarenal EVAR and complex EVAR, many clinical trial needs are unmet. It is an exciting time in the field of vascular surgery!

Critical unanswered questions could be addressed with prospective clinical trials rather than just retrospective case series and expert opinion. In the infrarenal space, the significance of sac stability remains unknown. Current aneurysm guidelines utilize sac stability as an endpoint for successful EVAR; however, recent studies have suggested that a stable (not shrinking) sac may in fact portend increased mortality with time.[6,7] The reasons for this are unknown. The implications of this association also raise important questions. Is sac stability a consequence of type II endoleaks, either visualized or not? Is there a role for "sac filling" techniques at the time of EVAR? Should we be more aggressive in treating type II endoleaks postoperatively? Do our current Society for Vascular Surgery aneurysm guidelines leave patients vulnerable to long-term post-EVAR mortality

that is currently undefined? Critical evaluation of the best measure of "success" after EVAR is needed.

Intimate to the concept of sac shrinkage is the optimal strategy for management of type II endoleaks, which occur in up to 20% of patients after EVAR.[8] Although type II endoleaks have been identified as an independent predictor of sac expansion, intervention has not consistently been shown to halt aneurysm growth.[9] Several different treatment strategies—transarterial embolization of the inferior mesenteric or lumbar arteries with coils or glue, direct translumbar injection of the aneurysm sac, transcaval embolization, and laparoscopic ligation of feeding vessels—have all been met with variable success. Despite multiple interventions, many aneurysms continue to expand with an overall unclear understanding of why we are failing to alter the underlying biology.[10] The lack of clarity regarding how and when to treat is exemplified in the United States and European guidelines, which are discordant and equally vague.[11,12] Given the widespread use of EVAR and increasing adoption of branched and fenestrated grafts, redefining our measure of successful aneurysm exclusion through longitudinal, large studies should be a top priority in aortic clinical trial needs.

Complex EVAR for aortic disease involving the visceral vessels has quickly become widespread due to the high morbidity and mortality of open thoracoabdominal repair and the equally high-risk comorbidities of the patient population this disease process affects. Although it is intuitive that the perioperative morbidity and mortality of complex EVAR are favorable compared to open repair, current analyses of complex EVAR outcomes have been restricted to the use of historical controls. No randomized controlled trials (RCTs) exist to directly compare the two groups, and the current literature may underrepresent the benefits of EVAR given that many patients in the endovascular group are medically unfit to undergo open repair. Although large meta-analyses have failed to conclusively demonstrate safety and effectiveness of EVAR in this patient population, there are tremendous limitations to those studies. RCTs could settle the matter, but realistically, they are unlikely to be conducted. Fortunately, although not an RCT, the United States Aortic Research Consortium (US ARC) holds promise for providing robust data collected prospectively in the context of multicenter, pooled, FDA-regulated trials. Along with establishing the safety and efficacy of fenestrated/branched EVAR, the US ARC has begun nesting clinical trials within its study population, which holds tremendous promise for optimizing complex aneurysm care.

Finally, a multitude of recent publications have highlighted gender disparities across all research and the resultant bias in evaluating the effects of disease and therapies in women versus men. The field of vascular surgery has been no exception to this data void. Women comprise 15% to 20% of the total abdominal aortic aneurysm (AAA) burden and account for one-third of ruptures yet have been significantly underrepresented in trials that guide current AAA repair. A recent study evaluating FDA aortic device trial inclusion of women and ethnic minority groups found gross underrepresentation of both groups, in particular demonstrating that women comprised only 11% of enrollment in major EVAR trials.[13] Women present later, rupture at smaller sizes, and consistently demonstrate worse outcomes with EVAR, suggesting that aneurysmal disease is more virulent in this demographic. Although the WARRIORS trial, a multinational randomized trial organized by investigators at the Imperial College London, may help define optimal size threshold for intervention in women, this will not answer the question of whether device design can be improved to overcome the inferior outcomes seen in women. Ongoing commitment from major funding sources and industry partners to study device design in women, along with commitment from our major journals to publish this literature, can address this unmet need. As a corollary to this, the authors hypothesize that better representation of women patients in clinical trials, and expansion of device trials focused on outcomes of women, may be achieved by increasing the proportion of women principal investigators.

As a subspecialty, we must continue to critically assess our innovations to ensure their benefits. In partnership with industry, the next decade of aortic clinical trials should focus on lingering research gaps. We suggest the following priorities: (1) how success of EVAR is defined in terms of sac behavior; (2) the optimal timing, indication, and technique for type II endoleak management; (3) whether complex EVAR should be first-line therapy, and how that should be operationalized; and (4) how device design can be optimized to achieve equal outcomes for men and women after EVAR. These investigations offer the potential to meaningfully improve the care we provide to all patients with aneurysmal disease.

Disclosures
Dr. Endicott: Receives consulting fees from Gore & Associates.
Dr. Simons: None.

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PULMONARY EMBOLISM

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The interventional management of pulmonary embolism (PE) has been completely transformed in the last 2 decades with the advent of new devices and clinical trials. Although many original studies analyzed the use of anticoagulation for treating PE, the expansion of thrombolysis and thrombectomy devices has created a new research space to explore both the use and efficacy of these devices for PE management and their relationship with anticoagulation.

Many prospective, single-arm studies have evaluated the safety and efficacy of percutaneous thrombectomy/thrombolysis devices such as EXTRACT-PE and STRIKE-PE for the Indigo aspiration system (Penumbra, Inc.), FLASH and FLARE for the FlowTriever system (Inari Medical), SEATTLE II for EkoSonic endovascular system (Boston Scientific Corporation), and RESCUE for the Bashir endovascular catheter (Thrombolex, Inc.).[1-6] These studies all focused on safety, measuring major adverse events, major bleeding, device-related injuries, and efficacy, quantified as a change in the right ventricular/left ventricular (RV/LV) ratio.

Although many single-arm or prospective nonrandomized clinical trials have studied interventional treatment for PE, few have conducted a level 1 RCT. The ULTIMA trial was the first randomized trial to test catheter intervention in patients with acute PE and is now over a decade old.[7] ULTIMA enrolled 59 patients with acute main or lower lobe PE and randomized patients to two groups: (1) unfractionated heparin alone and (2) unfractionated heparin and ultrasound-assisted catheter-directed thrombolysis. ULTIMA concluded that intermediate-risk PE responded significantly better (with an endpoint of RV/LV ratio) to anticoagulation with thrombolysis compared to the anticoagulation alone.

The CANARY trial was another level 1 RCT in which 94 patients with intermediate-risk PE were randomly assigned to conventional catheter-directed thrombolysis (alteplase for 24 hours) plus heparin versus anticoagulation monotherapy.[8] Although the clinical trial was prematurely terminated due to the COVID-19 pandemic, their initial findings suggest an improved short-term echocardiographic RV recovery and fewer major bleeding complications for patients in the thrombolysis and heparin group compared to the heparin-only group.

For such an ample space and with such a significant burden on PE morbidity and mortality, only having two relatively small RCTs in interventional PE therapy is not optimal. HI-PEITHO, STORM-PE, and PEERLESS II are all ongoing RCTs comparing gold standard anticoagulation versus anticoagulation plus a thrombectomy/thrombolysis device.[9-11] As these studies continue to acceler-

ate enrollment, increase global centers, and include more clinical endpoints, single-arm PE trials continue to emerge and, unfortunately, remain the norm.

Beyond the current PE clinical trials, more innovation is drastically needed in the PE space. To understand and resolve current knowledge gaps, improve patient care and advocacy, and advance research and innovation, a multidisciplinary PE response team (PERT) organization, The PERT Consortium, was created. The Consortium has developed many initiatives ranging from online and in-person seminars and bootcamps, culminating in the annual meeting, the largest meeting of physicians from all subspecialities involved in PE care. The launch of the PERT Quality Assurance Database created a multicenter directory of PE patients with their treatment modalities and outcomes. One of The Consortium's newer initiatives is the Pulmonary Embolism Research Collaborative (PERC), a group including physicians, industry leaders, and the FDA tasked with addressing the need for endpoints in future trials that are relevant to clinical practice and achievable. While the results are soon to be published, there is a general consensus that the PE space needs more long-term outcomes, looking at quality of life (QOL) and mortality beyond the 90-day and 1-year time points. Although studies like STORM-PE are already incorporating additional outcomes by providing participants with a wearable device and using QOL questionnaires, these advanced and novel secondary outcomes need to become more standard.[9]

Additionally, there is a dire need for clinical trials—both retrospective and RCTs—to compare outcomes between different devices in the market. For example, does one specific thrombectomy device have better safety and efficacy outcomes in a saddle PE while another has better results for a lobar PE? Although extremely important, these differences have yet to be studied and determined. The PERT Consortium has made significant strides, being at the forefront of a movement to improve the quality and robustness of clinical trials; nonetheless, there remain substantial gaps in PE research.

In summary, PE trials have made much progress in the past few years; however, there is so much more to be done. Although The PERT Consortium is implementing significant advancements through the PERC and STORM-PE trials, the PE space needs innovation: an increase in the number of RCTs, device comparison

studies, implementation of longer-term outcomes, and QOL endpoints.

Disclosures
Ms. Ramakrishnan: None.
Ms. Youssef: None.
Dr. Ranade: Unavailable at the time of publication.
Dr. Moriarty: Receives research grants from Penumbra, Inc.; consultant to Penumbra, Inc., AngioDynamics, Innova Vascular, Boston Scientific Corporation, and Inquis Medical.

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PAD

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Peripheral artery disease (PAD) and its myriad manifestations have demonstrated major negative health effects on our patients by causing lack of mobility or chronic limb-threatening ischemia (CLTI) or limb loss. This is a growing problem for a variety of demographic reasons, and the need for innovative solutions in clinical trials of PAD is significant.

Clinical trials in PAD have increased significantly in the past 10 years, including femoropopliteal RCTs comparing plain old balloon angioplasty versus stent, or versus drug-coated balloon (DCB) or drug-eluting stent (DES), or covered stent, and some head-to-head trials of different DESs or different DCBs and DES versus DCB. Although clinical trials in the below-the-knee (BTK) space have been less frequent, the recent publication of both the BEST-CLI and BASIL-2 trials have provided needed information.[1,2] There are numerous options for treatment of the femoropopliteal arteries and fewer for the BTK arteries.

FUTURE DIRECTIONS IN PAD CLINICAL TRIALS

Algorithms of Care

The best value for our research efforts may be in studying algorithms of care that might be the most successful. For example, an algorithm might be the proposed most effective vessel preparation given the patient's clinical situation and anatomic disease morphology, followed by the proposed most effective clinical treatment. There are fewer tools available for BTK, and we benefit from comparative trials to evaluate the effectiveness of new tools, as well as proposed algorithms for therapy. BTK arteries are notable in that they are small-caliber, diffusely diseased, slow-flow arteries, typically with high outflow resistance, and this appears to require different approaches than what has tended to be successful in the femoropopliteal arteries.

CLTI Versus Claudication

Patients with claudication and those with CLTI have different enough conditions that they should not be combined in the same trial with the same endpoints. Claudication patients may have multiple competing reasons for poor ambulation. The negative effects of an inability to ambulate include loss of independence and negative effects on conditioning, exercise tolerance, and QOL, but it usually does not progress to limb threat. CLTI is by definition limb-threatening and could lead to major amputation in any patient. The larger issue in trials of CLTI is the wide range of severity of the condition and presentation of the patient. No one trial design is likely to work efficiently in all these circumstances of CLTI presentations. We should expect the continued need to focus on answering spe-

cific research questions. Clinical trials may be performed to evaluate various therapeutic approaches, or specific devices, drugs, or underlying comorbid conditions (like diabetes) but will not likely be useful to answer everything at once.

Use of Real-World Data

To the extent possible, real-world data supported by artificial intelligence (AI) should be used to help design prospective clinical trials. Real-world data could be used to model trial outcomes, estimate enrollment requirements, and evaluate inclusion/exclusion criteria prior to trial initiation. Pragmatic trial design is something that we are likely to see more of—that is, patients will more often be treated in a manner that they would receive in the real world or standard medical care. Criticisms of prospective RCTs in the vascular space include the question of applicability of the trial population to the broader clinical population, whether the exclusion of patients has created an unrealistic patient population, whether care could be consistently delivered in the same manner in community practice, cost, the time to enroll, and whether the technology has evolved, thus making the trial result less applicable.

Optimal Performance Goals

In general, we learn the most by comparing two different therapies in a prospective RCT. Single-arm trials are faster, more efficient, and avoid the use of an outmoded therapy in the control group. In the past, we have used objective performance goals (OPGs), usually constructed from existing published literature. One concern about OPGs is that they often are constructed from literature in which the successful cases tend to be included, which thereby inflates the OPG result. Going forward, we may be able to construct OPGs using real-world data.

Clinical Trial Endpoints

Efficacy endpoints for claudication trials, usually after revascularization of the femoropopliteal arteries, has traditionally been patency as determined by duplex ultrasound. This is not likely to change. Freedom from clinically driven target lesion revascularization (CD-TLR) is often included in the endpoint but should always include specific parameters for recurrence of symptoms, decrease in hemodynamics, and angiographic evidence of restenosis. Claudication trials should also include QOL and cost measures, data on medical management, and long-term follow-up for up to 3 to 5 years. Optimal endpoints for CLTI trials remain a challenge and are still in development. As mentioned previously, this patient population has a substantial attrition rate due to mortality and this has a significant effect on powering the trial, the inclusion/exclusion criteria, and the long-term follow-up. Patency and freedom from CD-TLR do not tell the whole story. A focus on limb-related events makes sense. If incidence of major adverse limb events is used, it must have strict parameters by which the event can be adjudicated.

Trial Population and Trial Sites

The need for a diversity of patient population in our trials that more closely reflects the populations for which we care is apparent. We need to make specific efforts to recruit centers in areas of populations at risk. Sites may need assistance with study personnel and clinical trial management.

Trial Content and Management

Many clinical trial needs have been identified over the past 5 years that we will continue to address. Some of these include monitoring of medical management, QOL, patient-centered activities, a better understanding of mortality causes and events, better assessment of wound healing, and more complete follow-up.

These are some ideas about trials in PAD and how these trials are likely to evolve.

Disclosures

Dr. Schneider: Consultant to Medtronic, Philips, Boston Scientific, Cagent, LimFlow, Surmodics, and Silk Road.

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INTERVENTIONAL ONCOLOGY

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Sven Seldinger, Charles Dotter, Andreas Grüntzig, and Julio Palmaz are credited as being the founding fathers of interventional radiology. They developed fundamental techniques (including the Seldinger technique in 1953), performed the first therapeutic endovascular procedures (angioplasty on January 16, 1964), and developed unique devices—including the angioplasty balloon and Palmaz stent (Cordis Corporation)—that have revolutionized medicine.[1] Interventional oncology (IO) was founded by Ryusaku Yamada and Luigi Solbiati, who transformed cancer care globally when they performed the first intra-arterial therapies for liver cancer in 1977 and the first percutaneous ablation in 1982, respectively.[2,3] By 1999, these minimally invasive therapies became the mainstay of treatment for hepatocellular carcinoma (HCC), as evidenced by their integration into the Barcelona Clinic Liver Cancer (BCLC) guidelines.[4] Seven years later, in 2006, approximately 25 years after these techniques were first performed, the term IO was introduced at the first World Conference of Interventional Oncology in Cernobbio, Italy. A specialty built on innovation, creativity, and disruptive approaches to medical care had been adopted worldwide and was now being practiced as part of the cancer care continuum. Other specialties had taken notice and patients were asking for these procedures by name. In 2023, we have a Society of Interventional Oncology and many annual stand-alone meetings dedicated solely to the practice of IO.

Despite this revolution in cancer care, IO therapies are vastly underrepresented in cancer guidelines. The National Comprehensive Cancer Network (NCCN) develops guidelines for cancer care, which sets the standards of care and drives insurance reimbursement. The NCCN includes over 1,700 clinicians and scientists, yet only eight of those are interventional radiologists (0.4%). Why is this the case? IO is desperately behind in producing data supporting the safety and efficacy of IO therapies, making it difficult to support the integration of therapies into guidelines. Medical oncology patients easily enroll in trials for two reasons. First, patients are unable to get study drugs off trial. Second, their trials typically compare two different systemic therapy (ST) regimens. IO trials often are designed such that one group gets ST, and the other gets ST with the addition of an IO procedure. Patients are often reluctant to enroll in a trial where the fate of them getting a procedure is left to randomization. Additionally, IO therapies are also available off trial, so patients do not need to be enrolled to get the treatment. In interventional radiology, we are a specialty rooted in innovation, but now we need to work to find creative solutions to acquire the data necessary to change guidelines.

Traditionally, RCTs have been the gold standard for evidence-based treatment. In IO, several pivotal clinical trials were able to propel IO procedures into the mainstream of cancer care. Llovet et al's landmark trial comparing intra-arterial therapies to best supportive care (BSC) in patients with unresectable HCC in 2002 included 112 patients randomized into three arms: transarterial embolization, transarterial chemoembolization (TACE), and conservative treatment.[5] This trial was the first study that demonstrated a significant survival benefit of TACE over BSC with level 1 data. A similar trial by Lo et al, also in 2002, randomized patients with unresectable HCC to TACE versus symptomatic treatment.[6] This study included 80 patients and substantiated the trial by Llovet et al by also demonstrating a significant survival benefit with TACE.

Likewise, in the realm of ablation, in 2006, Chen et al demonstrated that ablation had similar outcomes to surgery, the gold standard.[7] The group randomized 180 patients with solitary HCC < 5 cm to percutaneous radiofrequency ablation (RFA) or surgical resection. The results demonstrated no statistically significant difference in overall survival (OS) or disease-free survival between the two groups. Similarly, Feng et al in 2012 randomized 168 patients with HCC < 4 cm to treatment with RFA or surgical resection, also demonstrating no significant difference in survival rates between the two groups.[8] These trials

expanded the treatment options for patients with HCC, resulting in ablation being integrated into the BCLC guidelines. Even though both latter studies showed reduced morbidity with ablation, they did not show a survival benefit compared to surgery, the ultimate cancer outcome. To show superiority, Xu et al reported that this would require 40,000 patients, > 200 times the number included in these trials.[9] In addition to challenges with patient numbers, the technology in ablation is evolving rapidly, which can have a large impact on trial design and outcomes, making a trial of this size, which could demonstrate the superiority of ablation over surgery, nothing short of impossible.

This leaves us to evaluate early phase trials. There are many phase 2 trials being conducted to demonstrate efficacy of IO therapies. For example, the MISPHEC trial was a single-arm phase 2 trial that evaluated the response rate after selective internal radiotherapy (SIRT) combined with chemotherapy in the first-line setting in patients with unresectable intrahepatic cholangiocarcinoma (ICC).[10] This trial demonstrated a doubling of OS, 22 versus 11.7 months, in the historical ABC-02 trial with ST alone.[11] Additionally, the toxicities were the same when comparing the MISPHEC patient population to the ABC-02 cohort (adverse events 71% vs 70.7%). Though not randomized, this phase 2 provides very compelling data to support the utilization of SIRT concurrently with first-line therapy for ICC.

Even more compelling is the LEGACY study evaluating TheraSphere (Boston Scientific Corporation) for the treatment of HCC. LEGACY was a multicenter, single-arm, retrospective study evaluating patients with solitary HCC treated with SIRT.[12] This study demonstrated a 24-month OS, which far surpassed any OS previously reported. Though this study was retrospective, it was submitted to the FDA by Boston Scientific Corporation as support to get labelling for an HCC indication, which the FDA ultimately approved in 2021.[13] This study demonstrates that innovative approaches to research and strong collaboration with industry can ultimately change treatment paradigms, which in the past was left to randomized trials alone.

RCTs are the gold standard; however, these trials require idealized patients that are treated at large high-volume academic centers. Because of the strict inclusion criteria and treatment conditions, the data are difficult to translate to real-world patients and drug/device usage. IO has attempted to meet the unmet need for generalizable real-world data with another innovative approach to research. Registries are a powerful tool that allow data to be gathered both prospectively and retrospectively and represent utilization of therapies being performed every day in patients undergoing IO procedures by physicians in all clinical practice settings and with all levels of training. There are multiple examples of such registries, including the RESIN registry by Sirtex Medical and the CIRSE registry for SIR-Spheres therapy (Sirtex Medical), both studying outcomes in patients after SIRT.[14,15] Additionally, our industry partners are also developing postmarket surveillance registries to obtain data to show safety and efficacy of their devices, such as XACT ACE Robotic system (XACT Robotics) and the Histosonics platform (Histosonics, Inc.).

Given the explosion of new therapies and the speed with which new innovations arise, relying on traditional RCTs with small numbers, long lead times, and narrow patient populations is no longer the most effective way to bring treatments from bench to bedside. Phase 2 trials, retrospective multicenter trials, and clinical registries are innovative approaches to demonstrating the relevance of IO therapies. Our specialty was founded on innovation and creativity, and as we move forward in this world with rapidly evolving technology, drug development and treatment algorithms, we need to continue to harness our founding fathers' spirit in our approach to research to move our specialty forward.

Disclosures
Dr. Taylor: None.
Dr. White: Consultant to Cook, AstraZeneca; research funding from Guerbet; speakers bureau for Penumbra.

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DVT/CVO

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The treatment of both acute deep vein thrombosis (DVT) and chronic venous obstruction (CVO) has been plagued by a lack of high-quality data, an issue clearly highlighted in the recently updated European Society for Vascular Surgery guidelines for the treatment of acute and chronic disease.[1,2]

Several studies have now been published on DVT, all controversial, but to date only a single, small RCT has been published in CVO.[3-5] The results of the STEVECO study will soon become available, but data have been presented that have already highlighted that this study finished early and failed to recruit patients to meet the primary recruitment goal.[6] This was as a consequence of both the pandemic but also significant difficulties in recruitment.

These recruitment problems were evident in both ATTRACT and CAVA, which took 10 years to complete and are an issue in C-TRACT and BEST PTS—two current CVO trials underway in the United States and United Kingdom.[3,4,7,8] In addition, funding was withdrawn for IGUIDEU after recruitment did not meet expectations.[9]

This highlights the significant difficulty of conducting studies in disease states where the equipoise of both clinicians and patients is beyond the point at which RCTs are easily performed. The age-old adage of "it's too early to perform a randomized trial until it's too late" seems to be clearly appropriate.

RCTs will continue to be the gold standard, but we clearly need to address the issues faced in conducting these trials or waste more effort in a fruitless endeavor.

In STEVECO recruitment dropped to zero, partly due to the COVID-19 pandemic, but significantly also due to the problem that patients referred to tertiary centers often refuse randomization. This difficulty in recruitment afflicted ATTRACT and CAVA and is clearly a problem in the ongoing C-TRACT study. Indeed, BEST PTS, a similar study to STEVECO in the United Kingdom, is threatened with suspension due to recruitment difficulties. In addition, patients referred to centers where there is little financial incentive to not treat have induced often insurmountable bias.

The second and often more difficult dilemma with studies has been the choice of primary endpoint. The ATTRACT study would have been totally different had the outcome been symptom improvement rather than a binary yes or no answer. In the absence of a clear and uniform primary outcome measure for these studies, it is impossible to determine if the study design or treatment is the primary reason for negative outcomes. The future of studies rests with considering different options.

Societies play an important role in facilitating the establishment of large-scale registries in DVT and CVO. The Venous Quality Initiative was a laudable initial attempt; however, the move to this becoming a "for-profit" venture has likely hampered the long-term value. Societal backing may allow registry data and outcomes to be broadly acceptable to payers and regulators alike which enhances data collection; however, these registries are often compromised by the absence of genuine control groups and can therefore not answer the fundamental question of superiority of intervention over conservative treatment. This flaw prevents clinicians who are not treatment enthusiasts from referring their patients.

The solution may lie in the emerging fields of so-called big data analytics. If large enough data cohorts are collected that include patients who undergo intervention as well as—critically—conservative management, direct causal inference can be drawn. The methods of analytics allow for bias to be as mitigated as you would achieve in an RCT but without the equipoise compromise. Patients can be treated as they or their physician determine.[6]

Ultimately, all interested in furthering treatment options for patients need to commit to better data or the errors we have made in history with technology outpacing evidence will continue to bite. However, perhaps there are options that overcome the difficulties we have faced with RCT.

Disclosures
Prof. Black: None.

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STROKE

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Since the publication of the landmark RCTs in 2015 demonstrating the efficacy of mechanical thrombectomy (MT) over standard medical therapy in patients presenting early with acute ischemic stroke (AIS) caused by an anterior circulation large vessel occlusion (LVO), the pace of innovation in stroke care and expansion in indications for endovascular intervention has grown significantly. In 2018, the publication of the DAWN and DEFUSE 3 trials expanded the treatment window from 6 to 24 hours. In 2022, the BAOCHE and ATTENTION trials demonstrated the safety and efficacy of MT in the treatment of basilar artery occlusion.[1,2] More recently, the indications for MT were expanded again with the publication of the three large core trials (ANGEL-ASPECT, SELECT2, RESCUE-Japan LIMIT), which demonstrated the efficacy of MT in patients with LVOs and larger infarct burdens,[3-5] and despite limitations and criticisms regarding their generalizability given differences in patient selection, the TESLA trial recently presented at the European Stroke Organisation Conference confirmed the benefit in that patient population, with one additional trial (LAST) underway and expected to be published soon.

Currently, there are several trials investigating the efficacy of MT in patient populations excluded from the landmark studies, such as medium and distal vessel occlusions (DISTALS, DISTAL, ESCAPE-MeVO, DISCOUNT) and LVOs with low National Institutes of Health Stroke Scale (NIHSS) scores or mild symptoms (ENDOLOW and MOSTE).

Another area that has seen tremendous progress is the field of neuroprotection and reperfusion augmentation. The CHOICE trial showed that the use of intra-arterial tissue plasminogen activator (tPA) in patients undergoing successful MT resulted in improved functional outcomes.[6] The ESCAPE-NA1 trial signaled that nerinetide might reduce mortality in patients receiving tPA and undergoing MT.[7] The APRIL trial demonstrated that the administration of ApTOLL prior to MT resulted in improved clinical outcomes.[8] Trials investigating the safety and efficacy of adjunctive medical therapy are also ongoing, including the use of nerinetide in patients undergoing MT without thrombolysis (ESCAPE-NEXT) and the use of colchicine to prevent secondary stroke risk in noncardioembolic ischemic infarcts (CONVINCE). Within this era of stroke innovation, where else can we go from here? What

will be the next frontier of AIS trials? We propose two areas in ischemic cerebrovascular disease that are well-positioned for the next wave of clinical trials, including (1) procedural intervention for stroke due to intracranial atherosclerotic disease (ICAD) and (2) timing and management of cervical carotid occlusions in tandem strokes.

STROKE INTERVENTION DUE TO ICAD

ICAD is a leading cause of stroke worldwide. Currently, the mainstay of treatment is medical, as prior trials (SAMMPRIS, VISSIT, and CASSIS) investigating stenting for symptomatic intracranial artery stenosis have failed to show improved outcomes with percutaneous transluminal angioplasty and stenting (PTAS) compared to best medical management.[9-11] In SAMMPRIS, the 30-day rate of stroke or death in the stenting cohort was 14.7%, and in VISSIT, the 30-day rate of stroke, intracranial hemorrhage (ICH), or death in the stenting cohort was 24.1%.[9,11] On the other hand, the WEAVE postmarket surveillance registry demonstrated a periprocedural event rate of 2.6% after Gateway balloon angioplasty (Boston Scientific Corporation) and Wingspan stenting (Stryker) of ICAD lesions, suggesting that with proper patient selection, evaluation of antiplatelet resistance, and by delaying intervention by a median of 22 days from last infarct, a low periprocedural event rate is possible in the hands of experienced neurointerventionalists.[12] Even so, the CASSIS trial did not demonstrate superiority of PTAS over best medical therapy despite adhering to most WEAVE inclusion guidelines,[10] although it did not require testing for antiplatelet resistance and did not utilize the new generation of rapid-exchange drug-eluting balloon-expandable coronary stents, which have been utilized off-label in intracranial arteries with success.[13] Furthermore, a new interventional trial for symptomatic ICAD should also consider submaximal angioplasty without stenting,[14-16] which may further decrease the risk of periprocedural events compared to stenting. Thus, we believe a new trial comparing submaximal angioplasty and/or stenting with drug-eluting, balloon-mounted, rapid-exchange stents with maximal medical therapy should be considered. Such a trial could also utilize fractional flow reserve (FFR) as a novel outcome metric—the FFR is a measure of translesional pressure and can be used not only to determine the functional significance of lesion stenosis but also as an outcome measure of angioplasty or stenting as opposed to percent diameter of stenosis. We and others have shown that improvements in FFR correlate well with improvements in percent stenosis after intervention.[17-19] Of course, any new trial comparing PTAS with medical therapy should consider recent advances in optimal medical therapy being evaluated in the ongoing CAPTIVA trial, which is investigating the use of ticagrelor plus aspirin or rivaroxaban plus aspirin versus clopidogrel plus aspirin for ICAD. Ultimately, however, we believe we are on the precipice of a new interventional trial for symptomatic ICAD.

MANAGEMENT OF CERVICAL CAROTID OCCLUSIONS IN TANDEM ANTERIOR CIRCULATION OCCLUSIONS

The timing and management of cervical carotid occlusions in cases of tandem anterior circulation occlusions also retains clinical equipoise and should be considered for the next wave of interventional stroke clinical trials. Although it is well-known that endovascular therapy is associated with favorable outcome in patients with cervical internal carotid artery occlusion compared to intravenous (IV) thrombolysis alone,[20] the timing of extracranial carotid intervention (pre- or postintracranial thrombectomy) and the form of management (stenting vs angioplasty vs endarterectomy) remains controversial.[21] Our own experience suggests that proximal stenting followed by intracranial thrombectomy compares favorably with other series in terms of angiographic results and clinical outcomes,[22] and a recent multicenter, cross-sectional study reaffirmed these findings[23] (although importantly did not address the issue of timing of treatment of the extracranial lesion). On the other hand, a recent systematic review suggested that intracranial thrombectomy followed by extracranial carotid stenting may have favorable outcomes compared to antegrade treatment of the extracranial carotid lesion and also showed that IV thrombolysis did not increase the rate of symptomatic ICH.[24] Thus, future trials assessing management of tandem occlusions should include analysis of antegrade versus retrograde intervention of the cervical carotid lesion, evaluation of angioplasty alone versus stenting, and the role of monotherapy versus dual antiplatelet therapy after stenting. Additional trials could evaluate the role of IV thrombolysis in the setting of tandem occlusions; however, recent registries have suggested that the use of IV thrombolytics is not associated with an increased rate of symptomatic ICH in cases of acute carotid stenting.[24,25]

CONCLUSION

Ultimately, the landscape of stroke intervention has changed considerably over the last 20 years, and we patiently await the many high-quality studies that remain ongoing. In addition to the trials examining MT for low NIHSS patients, MT for medium and distal ves-

sel occlusions, and adjunctive use of neuroprotectants, interventional trials aimed at understanding ideal treatment paradigms for patients with symptomatic ICAD and acute tandem occlusions are needed. Such trials will have considerable impact for stroke management internationally, and we are excited about the potential they have to change practice patterns for all. ■

Disclosures
Dr. Raygor: None.
Dr. Bouslama: None.
Dr. Levy: Shareholder/Ownership Interest: NeXtGen Biologics, Rapid Medical, Claret Medical, Cognition Medical, Imperative Care, Rebound Therapeutics, StimMed, Three Rivers Medical; Patent: Bone Scalpel; Honorarium for Training & Lectures: Medtronic, Penumbra, MicroVention, Integra, Consultant: Clarion, GLG Consulting, Guidepoint Global, Imperative Care, Medtronic, StimMed, Misionix, Mosiac; Chief Medical Officer: Haniva Technology; National PI: Medtronic-Steering Committees for SWIFT Prime and SWIFT Direct Trials; Site PI Study: MicroVention (CONFIDENCE Study) Medtronic (STRATIS Study-Sub 1); Advisory Board: Stryker (AIS Clinical Advisory Board), NeXtGen Biologics, MEDX, Cognition Medical, Endostream Medical, IRRAS AB (Consultant/Advisory Board); Medical Legal Review: render medical/legal opinions as an expert witness; Leadership or fiduciary roles in other board society, committee or advocacy group, paid and unpaid: CNS, ABNS, UBNS.

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