# Impact of ARCH-ARC's Standardized Endpoint Definitions on Aortic Arch Trials

Standardized definitions for anatomy, procedural outcomes, clinical events, imaging findings, and durability provide the foundation for the next generation of aortic arch clinical trials.

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The treatment of aortic arch disease is entering a period of extraordinary change. For decades, open surgical reconstruction was the standard against which all other approaches were judged. Hybrid procedures have since expanded the options available to patients who are considered poor candidates for conventional arch replacement. Branched, fenestrated, and other endovascular technologies are now advancing rapidly, extending treatment to increasingly complex pathology involving the ascending aorta and arch.

This innovation is exciting, but it creates an important challenge: How do we determine whether these new therapies improve patient care, and what metrics should we use to establish safety and efficacy? The answers require more than successful device implantation. They require agreement about what disease is being treated, how anatomy is described, what constitutes technical success, which complications matter, how they are measured, when they are measured, and what constitutes a durable treatment result. Without this foundation, even well-conducted trials may be difficult to compare or interpret.

This was the motivation for the Aortic Arch Academic Research Consortium (ARCH-ARC) and our recently published consensus report on standardized endpoint definitions for clinical trials in thoracic aortic repair. Our goal was not to create clinical practice guidelines or dictate how arch disease should be treated. Rather, because ARCH-ARC is fundamentally an evidence-generation framework, we sought to establish a common language for evaluating open, hybrid, and endovascular approaches to ascending aortic and arch disease.[1]

## WHY ARCH-ARC WAS NEEDED

Early studies of new aortic technologies tend to be (necessarily) relatively small, highly selected, and single arm. This is particularly true in the arch, for which disease prevalence is lower than in many other cardiovascular conditions, anatomy is extraordinarily heterogeneous, and patients may present with very different pathologies and levels of acuity.

A degenerative arch aneurysm, chronic dissection with aneurysmal degeneration, acute dissection, penetrating aortic ulcer, and pseudoaneurysm are not interchangeable disease states. Likewise, zone 2 single-branch repair, complete three-vessel endovascular arch replacement, hybrid debranching with thoracic endovascular aortic repair, frozen elephant trunk, and conventional open arch reconstruction are profoundly different procedures. Despite these differences, all might appear in the literature broadly described as "aortic arch repair."

As a consequence, outcomes can be difficult to compare. Investigators may define technical success or capture neurologic complications differently. Planned staged procedures might be counted as reinterventions in one study and components of the intended treatment strategy in another. Endoleaks, branch-related events, dissection-related false lumen perfusion, and device failures can all be categorized inconsistently as well. Before we can conduct better trials, we must first ensure we're all speaking the same language.

## STANDARDIZING WHAT WE'RE TREATING

One of the less obvious but important contributions of ARCH-ARC is that endpoint standardization starts before trial planning begins or the procedure occurs.

A trial cannot meaningfully compare outcomes unless the populations being treated are adequately characterized. ARCH-ARC provides standardized approaches to describing anatomy, pathology, disease chronicity, and the extent of treatment. This includes refinement of ascending aortic zone 0 into zones 0A through 0D. As devices move proximally toward the aortic root, the traditional concept of "zone 0" becomes insufficiently granular. A device interacting with the sinotubular junction, coronary arteries, or aortic valve complex presents fundamentally different challenges from one landing immediately proximal to the innominate artery.

Similarly, the proposed ARCH-ARC dissection classification combines familiar concepts from the Stanford system with aortic zones to describe both the location and extent of disease in a way that is more applicable to contemporary endovascular therapy.[1,2]

This is important for future trials because, for example, if two studies enroll anatomically or biologically different patients but label both populations as "arch disease," comparing their outcomes may be misleading regardless of how precisely those outcomes are measured.

## BEYOND "TECHNICAL SUCCESS"

Perhaps the most important conceptual contribution of the ARCH-ARC document is its distinction between technical, procedural, and treatment success.[1]

Primary technical success is an immediate endpoint: Was the device successfully delivered, positioned, deployed, and functioning as intended after deployment? Were intended branches patent? Was there freedom from major device deformation or type I or III endoleak? Did the procedure avoid an unanticipated corrective intervention?

ARCH-ARC also distinguishes primary from assisted technical success. This is particularly useful in complex endovascular procedures. A procedure requiring an unplanned adjunctive maneuver may ultimately produce an excellent result, but it is not equivalent to one performed exactly as intended. Capturing that distinction provides a more transparent assessment of device and procedural performance, and it can allow for intentional future innovation to improve upon the procedure or device.

Procedural success moves the assessment to 30 days or the duration of hospitalization and incorporates major clinical events such as death, disabling stroke, permanent spinal cord injury, dialysis-requiring renal failure, myocardial infarction, bowel ischemia, respiratory failure, major bleeding, major vascular complications, and important cardiac structural complications.

Finally, treatment success is longitudinal, which may ultimately be the most important concept for evaluating arch technologies. Implanting an endograft is not the objective of therapy; preventing death due to aortic disease and providing durable control of the underlying disease process are the objectives. Treatment success therefore incorporates both clinical and imaging outcomes, including prevention of rupture, lesion-related mortality, aortic enlargement, persistent failure to exclude the lesion, migration, occlusion, dissection-related failure, and secondary aortic intervention.[1]

This framework should help future trials distinguish a procedure that was successfully completed from a treatment that was ultimately clinically successful for the patient.

## MORE COMPREHENSIVE NEUROLOGIC OUTCOMES

Neurologic injury remains one of the defining concerns in aortic arch intervention, and simply reporting "stroke: yes or no" is inadequate. ARCH-ARC builds substantially on prior NeuroARC work by emphasizing the occurrence of stroke as well as its timing, severity, and subsequent recovery. Spinal cord ischemia is similarly characterized, including functional severity and bowel or bladder dysfunction.[3]

The ARCH-ARC framework also recognizes neurocognitive function, an outcome that has historically received much less attention. Delirium and delayed neurocognitive recovery are common after complex cardiovascular procedures and can matter enormously to patients and families. Such postprocedure outcomes can prolong hospitalization and complicate recovery. Future arch trials should increasingly include standardized baseline and postoperative neurologic and neurocognitive assessments, particularly when comparing less invasive endovascular approaches with open surgical reconstruction.

A therapy that produces similar mortality and major stroke rates but substantially reduces cognitive impairment, loss of independence, or recovery time could offer important patient benefit. Conversely, those potential advantages cannot be demonstrated if we do not measure them.

## IMAGING AS AN ENDPOINT, NOT JUST SURVEILLANCE

Aortic intervention differs from many other cardiovascular therapies in that treatment success cannot be determined from clinical events alone. A patient may feel perfectly well while developing loss of seal, branch instability, persistent false lumen perfusion, device migration, structural device failure, or progressive aortic

enlargement. Standardized imaging assessment must be integral to trial design.

ARCH-ARC provides definitions for endoleak, device-related target vessel instability, persistent false lumen opacification, loss of device integrity, and related imaging outcomes. Consistent imaging methodology and independent core laboratory assessment for pivotal trials will become increasingly important as the field matures.[1] This is particularly relevant to arch devices with multiple modular or branch components, where the durability of the entire construct matters, not simply the patency of the main aortic endograft.

## WHAT WILL THIS CHANGE IN FUTURE TRIALS?

The most immediate benefit of standardized definitions is comparability. Investigators, regulators, clinicians, patients, and industry should be able to examine different studies and know that stroke, technical failure, target vessel instability, secondary intervention, and treatment success are consistently defined. However, the longer-term implications are more important. Standardization should allow us to develop credible historical controls and, eventually, performance goals for specific aortic pathologies and specific patient risk groups. This is particularly valuable when randomized trials are impractical because of uncommon disease, rapidly evolving technology, or patients for whom equipoise between open and endovascular therapy may be limited. It should also improve clinical event adjudication. Prospective specification of events, timing, severity, and attribution reduces ambiguity for independent clinical events committees and makes regulatory evaluation more reproducible.

The ARCH-ARC framework should facilitate registry-based research as well. If clinical trials and major aortic registries collect compatible variables using compatible definitions, registries could eventually support long-term device surveillance, identification of external control populations, development of pragmatic or embedded trials, and evaluation of outcomes well beyond the time horizon of conventional pivotal studies. Standardized collection of variables may also facilitate integration of artificial intelligence approaches to risk stratification and precise identification of candidates for particular trials.

Finally, standardized definitions should make comparative trials more achievable. Open and endovascular arch repair will never have identical complication profiles. An open operation may carry greater risks of bleeding, prolonged ventilation, or recovery time, while an endovascular reconstruction introduces other concerns surrounding seal/fixation, branch durability, device integrity, and reintervention. The goal should not be to force fundamentally different therapies into an artificial definition of equivalence but rather to measure the outcomes of each therapy objectively and transparently enough to understand their tradeoffs.

## UNRESOLVED QUESTIONS IN TRIAL DESIGN

ARCH-ARC provides the vocabulary but does not answer every question about how future trials should be designed, and several major issues remain. Each of the following is an important question for the next phase of ARCH-ARC:

- Should a cohort of patients undergo randomized comparison with open surgery?
- When are single-arm studies with predefined performance goals more appropriate?
- How should prohibitive-, high-, intermediate-, and lower-risk surgical candidates be defined?
- Should trials be organized primarily around a device, an anatomic treatment zone, or a specific disease such as aneurysm versus dissection?
- What duration of follow-up is sufficient to establish durability?
- How should quality of life, functional recovery, neurocognition, and patient preferences be incorporated into primary or hierarchical endpoints?

Arch pathology often presents acutely, creating a particular challenge for this population that deserves emphasis in trial design. A patient with an acute dissection may be unstable, unable to consent, and in the operating room within the hour, and yet this is often where novel therapy is deployed and the stakes are highest. Such patients often cannot be enrolled and randomized in a trial, and future trial designs will need mechanisms for emergent enrollment and deferred consent. A framework that captures only elective patients describes only half the disease.

Importantly, future trial design should not simply ask whether an endovascular procedure can reproduce or approximate the early results of open surgery. Less invasive therapy may offer benefits that are not captured by mortality and disabling stroke alone, including shorter recovery, preservation of functional status, avoidance of sternotomy/circulatory arrest, or treatment of patients who otherwise have no reasonable therapeutic option. At the same time, these benefits must be balanced against device durability, secondary procedures, need for long-term surveillance, and the lifelong consequences of placing increasingly complex endovascular constructs into younger or lower-risk patients. Ultimately, the appropriate endpoints will depend on the clinical question being asked.

## CONCLUSION

Aortic arch therapy is moving faster than the evidence infrastructure that has been traditionally used to evaluate it. Although this is not unusual during periods of major technologic innovation, it does make rigorous evidence generation even more important.

The experience of other ARC initiatives illustrates what can happen when investigators, regulators, clinicians, and industry agree on a common framework. Standardized definitions do not determine whether a technology succeeds or fails. Rather, they make it possible for us to determine that answer more reliably. For the aortic arch, this is the real potential of ARCH-ARC.[3-5]

The first generation of endovascular arch studies appropriately asked, "Can we do this?" The next generation must ask more difficult questions:

- For whom should we do it?
- Is it better than the alternatives?
- What outcomes matter most to patients and clinicians?
- Will the repair remain successful 5, 10, or more years later?

Answering will require better trials, longer follow-up, harmonized registries, rigorous imaging, and meaningful patient-centered outcomes. We need to agree on what we are measuring before we can answer those questions, and ARCH-ARC gives us that starting point. ■

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