

Choice and Selection of Treatment Modalities for Cardiac Patients: An Interventional Cardiology Perspective

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Scope of the Problem

Cardiovascular disease represents a leading cause of death in the United States and is responsible for 17% of national healthcare expenditures.^{1,2} The field of cardiology, especially interventional cardiology, has witnessed significant advancement with several innovations in the last decades. However, within the current transformative period of healthcare delivery, financial support, revenue, and margins are a major concern for health systems everywhere. Financial support for clinical care and research appears to be decreasing, and more and more hospitals are working with negative operating margins due to declining revenues.

In addition, an increasing gap between research and clinical practice seems to be widespread in cardiology. Although this specialty abounds in clinical trials and outcomes research, the current guidelines are mostly not based on robust evidence. In 2009, only 11% of the recommendations made by the joint cardiovascular practice guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) were classified as highest level of evidence (Level A).³ In fact, a majority of the recommendations are based on expert opinion or consensus or case studies, rather than high-quality clinical research.³ With an expansion of the therapeutic armamentarium with sparse definitive evidence to determine the standard of care, the management of patients in cardiology has been characterized by significant variation and resultant disparities in care.⁴⁻⁹ The technologic advancement in cardiovascular medicine has truly been “fast and furious”; however, the supporting evidentiary base often lags

behind, requires considerable financial backing, and is frequently insufficient.

The role of the patient in healthcare delivery is another important element in the ongoing discussion. The relationship between the caregiver and the patient has evolved over the last half century. Patients are the most important stakeholders, and they have grown to become experienced “consumers” of healthcare “services.” Most patients understand that they have rights and are much less inclined than they used to be to leave medical decisions solely to the experts. The widespread and easily available information, media coverage, political trends, ethical overtones, and the research-related underpinnings have all contributed to this change in patient attitudes and behavior. We have indeed entered the era of “collaborative decision-making” with our patients that is more complex and requires more attention to the realities of clinical practice than are currently evident. Our review has aimed to characterize some of these inherent problems and to evaluate proposed solutions in the determination of appropriate therapy for an individual patient. We have provided lessons learned from some of the most controversial areas in interventional cardiology such as transcatheter aortic valve replacement (TAVR), transcatheter patent foramen ovale (PFO) closure, carotid artery stenting (CAS), and percutaneous coronary intervention (PCI) for complex coronary artery disease (CAD).

Healthcare Provider Aspects

Multispecialty Collaborations

The field of cardiology has lived with the concept of “gatekeeper” for decades. The “gatekeeper” was traditionally the physician who was responsible for deciding the optimal treatment choice and referring the patient to specialists of his/her choice. As the field of interventional cardiology moves forward by invention of new devices, drugs, and therapeutic modalities, there is an increasing need for multispecialty collaborations for several reasons. First, the knowledge and expertise from different specialties provides perspectives that are useful in performing the procedure safely and effectively. Second, collaboration with surgical specialties is invaluable

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for surgical bailout during complications that might otherwise be catastrophic. Third, perspectives from different specialties often help determine the appropriateness of the procedure, as well as provide an unbiased assessment of “therapeutic futility” in several cases. Multidisciplinary “heart-teams” consisting of interventional cardiologists, surgeons, imaging cardiologists, anesthesiologists, geriatricians, and nurses have been instrumental in the success of the TAVR programs worldwide. Similarly, “heart-teams” consisting of interventional cardiologists and cardiothoracic surgeons have become important for deciding optimal revascularization strategies in patients with complex CAD. The controversial arena of PFO closure has witnessed a partnership between interventional cardiologists, imaging cardiologists, and neurologists, and the field of CAS has seen the emergence of collaboration between peripheral interventionists and vascular surgeons. One of the challenges that all institutions currently face regarding multispecialty collaboration is determination of reimbursement structures for time and effort of multiple physicians investing time into a single albeit complex procedure. However, this is likely to be the norm in the future, and the payment structures would likely have to adapt to accommodate this practice.

Learning Curve

With the emergence of several new technologies in various subspecialties of interventional cardiology, concerns about “learning curve” are often expressed by patients, operators, and payers. Rapid evolution of existing devices and development of new iterative designs makes it even more challenging to ensure meeting of learning curve requirements. There is now a large armamentarium of devices to choose from in each arena, and each device possesses specific relative advantages over its counterparts. It is now incumbent upon the operators to know the nuances and subtleties of each of these devices and become facile with their use. With an increase in awareness of learning curve requirements, there have been systematic analyses using large national representative databases to look at optimal case volume needed for CAS, PCI, or PFO closure.^{10–13} A 4-society expert consensus statement published in 2012 details the recommended criteria for existing as well as new TAVR programs, especially pertaining to program and practitioner case volumes.¹⁴ These guidelines serve as a basis for safe and effective adoption of TAVR into new centers and ensuring excellent quality of care at existing centers.

Expert Opinion

Although evidence-based clinical practice is the highest standard of medical practice, it is often unavailable or fails

to conform to the clinical scenario at hand. Expert opinion, even in the current era, forms the basis of a substantial proportion of our medical practice and hence cannot be dismissed. In addition, it is not always possible to amass evidence for every clinical scenario experienced in routine practice. Expert opinions are derived from personal clinical experiences and accumulated clinical knowledge that includes the expert’s personal assessment of published literature, opinion of colleagues, and often unpublished reports and experiences. The current clinical practice guidelines often include expert opinion in areas where there is scant evidence or conflicting evidence. An effective strategy to improve the value and validity of expert opinion may be by combining opinion from multiple experts through consensus panels. Collective expert opinion strengthens the credibility of a practice guideline and adds validation to individual expert opinions. Development of appropriateness criteria in several aspects of cardiovascular medicine represents a good example of collective expert opinion.

Appropriateness Criteria

Recent years have witnessed the development of appropriate use criteria (AUC) to guide rational use of cardiovascular therapeutic modalities for delivery of high-quality care to patients. The main purpose of AUC is to assist clinicians in making decisions, when they are faced with common as well as uncommon clinical situations during everyday practice. AUC guidelines typically provide a foundation for delivering evidence-based cardiovascular care, and when evidence is lacking, provide expert consensus opinion that is approved in review by a panel consisting of multispecialty experts. Although there is a significant uncertainty in several areas of cardiology, AUC provide a practical standard upon which to assess and better understand variability.

The process of constructing AUC can be well exemplified using the AUC for PCI.¹⁵ To construct the AUC, the technical panel reviewed and independently rated the appropriateness of PCI in several clinical scenarios. After independent rating, there was collective discussion on appropriateness of PCI in each clinical scenario, to come up with a consensus document that reflects latest evidence-based practices or expert consensus, where the former is lacking. Besides serving as a decision-making tool, AUC have facilitated rational discussion with patients and/or referring physicians about the utility and need for revascularization. In addition, these criteria have begun to be used by facilities and payers to gauge quality of cardiovascular care delivered and determine reimbursement. Furthermore, the AUC also identifies clinical scenarios where there is lack of evidence and uncertainty regarding the utility of therapeutic modalities that might serve as avenues for further research.

Research-Related Aspects

Utilization of Registries for Research

Although randomized control trials (RCT) represent the most rigorous method of experimentation to evaluate a causal link between a treatment and outcome, it is becoming increasingly difficult to conduct and complete good trials due to rising complexities and soaring costs of performing trials in the current era. One of the simple and inexpensive alternatives to RCTs might be large multicenter registries, which have been instrumental in many areas of cardiology. The national cardiovascular disease registry maintains several registries pertaining to CAD, PCI, peripheral vascular disease, and so on in the United States. The Society of Thoracic Surgeons database collects in-hospital outcomes on valvular surgery and coronary artery bypass grafts (CABG). There have been several large national registries that have furthered our understanding of TAVR.^{16–18} The most recent addition to the series of large national registries has been the US Transcatheter Valve Therapy registry, which aims to collect outcomes following interventions on aortic as well as mitral valves.¹⁹ Registry-based randomized trials represent a rather innovative style of answering important clinical questions by designing a randomized trial on the platform of an already existing high-quality observational registry. Using clinical information that is already being collected for a registry or a pre-existing database, the investigators are able to enroll many patients in little time and obtain accurate follow-up at a significantly lower cost. One of the important prerequisites for maintaining veracity of the results would be utilization of meticulously maintained high-quality registries for this research.²⁰

Stakeholder Involvement and Engagement

The term “stakeholder” is defined in the management literature as any individual, group of people, or organization involved in or affected by policymaking, development, implementation, or management of a process or system.²¹ With shrinking financial support for research and declining revenues in clinical care, decision-making on important issues should ideally be performed by a diverse group of stakeholders including those who affect and are affected by these decisions. The first issue is actually identifying these key stakeholders. The selected group should represent a broad range of clinical, policy, payer, and patient perspectives. After identifying the relevant stakeholders, the second issue is to gain access to them and eliciting their views. Stakeholder engagement has been recognized as critical to achieving the goals of comparative effectiveness research (CER), and several federal grant announcements have encouraged or required the involvement of advisory groups representing

multiple stakeholders. The Institute of Medicine has emphasized the importance of engaging stakeholders in setting research priorities, as well as in designing and conducting studies to meet the needs of various stakeholders including decision-makers.²² Stakeholder engagement in interventional cardiology is still in its nascent stages, and many questions remain to be answered in this relatively uncharted territory.

Comparative Effectiveness Research Initiatives

The divide between research and decision-making is apparent by the minority of the ACC/AHA guidelines based on high-quality research.³ This critical gap has received significant scrutiny and public attention, and there is a need for a process or a program that can fill this gap, ensuring benefit to all involved stakeholders.²³ CER is one possible solution to bridge this gap that matters to stakeholders and facilitate good healthcare decision-making. It follows that the success of CER requires participation of all stakeholders in all aspects of the research process including setting priorities and goals, study design, study conduct, as well as dissemination of results and subsequent policymaking. CER involves both synthesis of existing evidence as well as production of new scientific data. CER offers a systematic approach to critically appraise existing research and to identify areas of remaining clinical uncertainty. Moreover, the Patient Protection and Affordable Care Act of 2010 mandates the creation of a patient-centered outcomes research institute to set priorities for CER based on multistakeholder engagement.²⁴ Patient-Centered Outcomes Research Institute was established in response to a widespread concern that patients and their families, along with their immediate caregivers, often do not have the information they need to make decisions about treatment alternatives to attain desired health outcomes.²⁴ Although there has been some fear that CER may lead to rationing of care, or the fact that it might negatively impact quality of care, the formal involvement of the public, through initiatives like “citizens forums,” might help alleviate some of those concerns. Utilizing the systematic approach of CER toward data interpretation and evidence synthesis in cardiovascular disease might ultimately reduce morbidity and mortality, reduce costs of care, and improve quality of care for our patients.

Patient Aspects

Collaborative Decision-Making With the Patient

Over the years, there has been a growing consensus that patients should be more involved in their own care. There is now evidence to support that greater involvement of patients in care results in better health outcomes.²⁵ We have now

entered the era of collaborative decision-making with our patients, wherein the physicians educate their patients about the disease process, the treatment options available, and the inherent risks and outcomes associated with each approach. Subsequently, the physicians engage in a dialogue with the patient to determine the expectations of the patient and choose a treatment plan to suit those expectations. Family values and cultural beliefs have a profound influence on these expectations. However, not all patients want to make those decisions themselves. The desire for active engagement in medical care varies with a patient's background, cultural beliefs, and perceived clinical situation. Yet the desire for information is universal. Most patients prefer to see the "roadmap," even if they don't want to "take over the wheel." Education of patients and eliciting their preferences is often time-consuming and complex and sometimes unrealistic for a 30- to 45-minute outpatient visit with a specialist. Hospitals have started utilizing allied healthcare personnel such as nurse practitioners or physician assistants to help with this process. However, the optimal reimbursement pattern to account for time spent on this complex decision-making for several of these high-risk procedures is still in very nascent stages. In addition to these facets, it is also important that the "success" versus "failure" or "futility" of a therapeutic decision must reflect patient perspectives, which are traditionally lacking in the clinical trials.

Lessons Learned From Transcatheter Aortic Valve Replacement

TAVR has emerged as an attractive alternative for treatment of patients with severe symptomatic aortic stenosis who are inoperable or high-risk for surgical aortic valve replacement (Figure 1). TAVR technology has indeed transformed the arena of treatment of severe aortic stenosis and has expanded the range of options for high-risk or sick patients who were once referred for palliative care. Despite the expeditious acceptance and the clinical appeal of TAVR, there are still several obstacles to be overcome and prospective opportunities explored.

One of the key factors that has led to the success of TAVR worldwide is a universal adoption of multidisciplinary heart teams for patient selection, risk stratification, procedure, and postprocedural care.²⁶ In addition, postmarket surveillance of the TAVR devices is an extremely important function of the heart team, as the heart team is intimately involved in the longitudinal care of these patients. These heart teams traditionally included interventional cardiologists, cardiac surgeons, imaging cardiologists, anesthesiologists, nursing personnel, and case managers, with a clear understanding of the role that they are supposed to play in the care of the patient. Patient selection and risk stratification is one of the

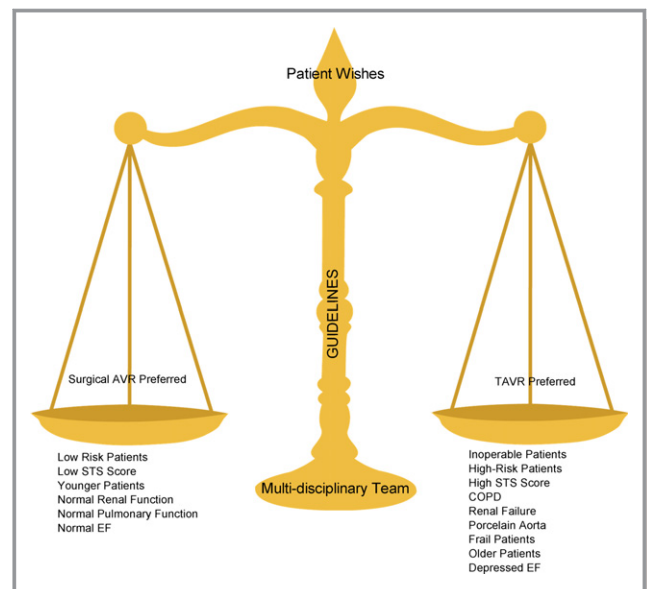


Figure 1. Key factors important in determining the choice of surgical AVR or TAVR in patients with severe symptomatic aortic stenosis. AVR indicates aortic valve replacement; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement.

most difficult things that a heart team faces during evaluation of patients for TAVR. Risk assessment is often guided by risk scores like the Society of Thoracic Surgeons score or EuroScore, which have not been fully validated in this population.²⁷ These risk scores fail to include important comorbidities that experienced surgeons often take into account before operating on patients, such as malnutrition and cachexia, chronic kidney disease and dialysis, physical deconditioning or wheelchair-bound status, history of solid tumor malignancies, dementia or history of stroke, and other debilitating conditions that preclude patients returning to a reasonable functional status. Frailty, which refers to decline in resiliency and homeostatic reserve, has been associated with poor outcomes post TAVR and is not entirely captured in current risk stratification metrics.²⁸

An important facet of the evolution of TAVR technology was the fact that definitive RCTs such as the Placement of Aortic Transcatheter Valves trial established the role of TAVR in the treatment of severe aortic stenosis patients, prior to dissemination of the technology in the community.^{29,30} Although performed using first-generation devices that had higher complication rates compared to current devices, the Placement of Aortic Transcatheter Valves trial was instrumental in demonstrating efficacy of this new technology in inoperable and severe aortic stenosis patients.^{29,30} The next few years witnessed the publication of multiple large multi-center registries, which helped understand the utilization of this new technology and the outcomes in real-world settings.

For the growth and maturation of this technology, it is important that all sites in the United States should embrace meticulous data collection and participate in the national Transcatheter Valve Therapy registry.¹⁹ This registry would be crucial to benchmark performance standards, determine appropriateness of case selection, monitor device-related complications, and provide the substrate for reimbursement decisions currently and in the future.

With the rapid evolution of TAVR devices, significant concern has been expressed over the “learning curve” and maintaining case volumes to stay adept at TAVR implantation. A 4-society expert consensus statement published in 2012 details the recommended criteria for existing as well as new TAVR programs, especially pertaining to program and practitioner case volumes.¹⁴ This document details the programmatic as well as operator requirements for new and continued certification for performing TAVR. In addition, the ACC and the Society of Thoracic Surgeons have been working together with other professional societies to help promote “rational dispersion” of this truly transformative technology. The goal of these guidelines is to provide criteria that maximize the safe and effective utilization of TAVR in more and more centers, yet not to restrict access to care for patients in need of this therapy. The establishment of the US–Transcatheter Valve Therapy registry is crucial to “rational dispersion” of TAVR technology, as it will help ensure the appropriateness of the case selection and detect any “indication creep” that might happen over time.

Although there is a considerable survival and quality of life benefit with TAVR, clinical experience has demonstrated that many patients die soon after the procedure or have little improvement in quality of life or functional status.^{29–32} Therapeutic futility has been defined as lack of therapeutic efficacy, especially when the therapy is unlikely to produce the desired clinical result, as judged by a group of competent physicians, or lack of meaningful survival as judged according to the personal values of the patient.^{33–35} Several clinical comorbidities like a high Society of Thoracic Surgeons score, impaired left ventricular function, and severe pulmonary hypertension increase the chances of adverse outcomes following TAVR.³³ Besides these traditional risk factors, a number of other issues such as frailty, disability, mobility impairment, cognitive impairment, malnutrition, polypharmacy, mood disturbances, fall risk, and social isolation have a potential to cause poor outcomes and are often overlooked. Also, the assessment of therapeutic futility is inherently value driven and must consider a patient’s goals, values, attitudes, and preferences. Through comprehensive risk stratification, estimation of clinical benefit, and assessment of patient’s goals, the heart team should determine who will benefit from TAVR and who will not, and those who lie in the gray zone need further assessment and engagement before definitive decisions are made (Figure 2). The decision of not performing TAVR should not be viewed as abandoning care; at this time, it is important for the physician, patient, and family to be realistic about the poor prognosis and to provide appropriate

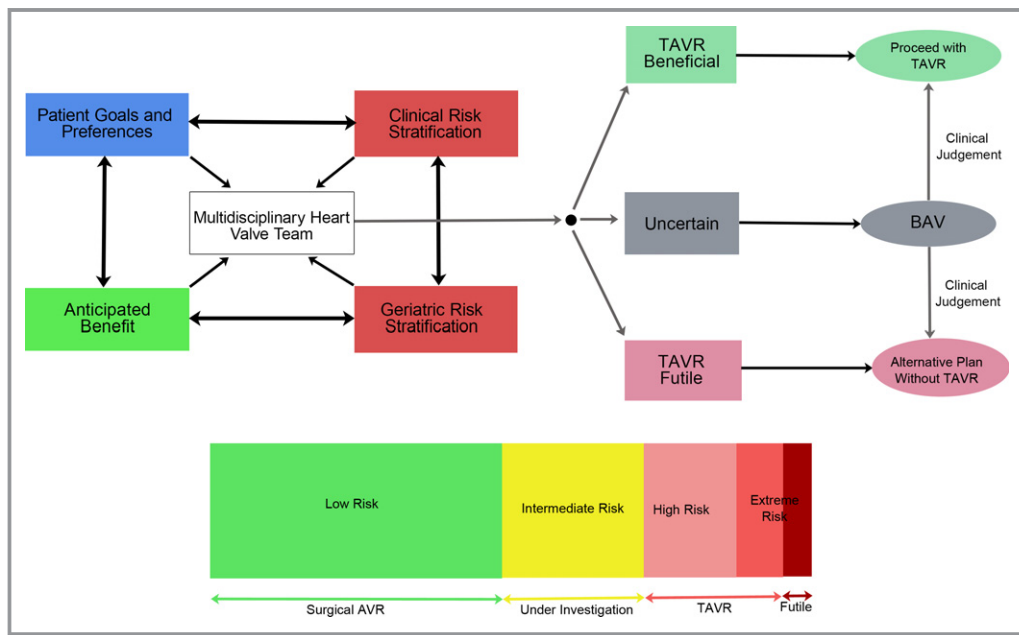


Figure 2. Decision-making by the multidisciplinary heart team on patients referred for transcatheter aortic valve replacement (TAVR). The multidisciplinary team considers and weighs the various risk factors shown and makes a decision regarding whether TAVR would be beneficial or futile. Adapted with permission from the BMJ Publishing Group Limited from Agarwal et al²⁶. BAV indicate balloon aortic valvuloplasty.

palliative care resources. TAVR therapy holds immense future promise, but as the technology matures further, we must use it responsibly within a framework that enables collaborative decision-making with the ultimate objective of realizing patient goals and promote their well-being.

Lessons Learned From Carotid Artery Stenting

Over the past 2 decades, CAS has been proposed as an alternative to carotid endarterectomy (CEA) for treatment of severe carotid stenosis (Figure 3). For several reasons, the emergence of CAS has provided an interesting opportunity to assess the impact of a new technology on the relationship within and between various specialties. First, the data comparing CAS and CEA are heterogeneous and subject to highly variable interpretations. The current literature has been used by professional societies and practitioners to both support as well as raise concern about the use of CAS for treatment of carotid stenosis.^{36–39} Second, there are huge financial incentives at stake in the treatment of severe carotid disease. Third, CEA and CAS have traditionally been performed by professionally distinct specialties, and this offers an opportunity to examine how physicians could collaborate to harness a new technology to optimize patient care. Management of carotid stenosis highlights the importance of multidisciplinary collaborations between vascular surgery, interventional cardiology, radiology,

and neurology, as each of these specialties has discrete skills and expertise that is necessary for treatment.

CAS has evolved partly as an alternative to CEA for patients with prohibitively high risk for operative complications. CAS is less invasive compared to CEA with reduced risk for cranial nerve damage and has the ability to treat distal lesions that cannot be treated using CEA. Unlike CEA, CAS is the modality of choice among patients with “hostile neck” or those with radiotherapy or prior surgical interventions in this area. The French Endarterectomy Versus Angioplasty in Patients With Severe Symptomatic Carotid Stenosis (EVA-3S) trial demonstrated a higher rate of death or stroke at 1- and 6-month follow-up with CAS as compared to CEA, among patients with symptomatic carotid stenosis.⁴⁰ The German counterpart Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial failed to demonstrate noninferiority of CAS in comparison to CEA during short-term follow-up.⁴¹ However, the caveats to a fair comparison of the 2 strategies in the literature include a lower than optimal utilization of emboli protection devices as well as relatively inexperienced operators included as a part of these earlier trials.⁴² The pivotal Carotid Revascularization Endarterectomy versus Stenting (CREST) trial randomly assigned patients with symptomatic or asymptomatic carotid stenosis to undergo CEA or CAS and compared the occurrence of primary composite end point of stroke, myocardial infarction (MI), or death from any cause during the periprocedural period or any ipsilateral stroke within 4 years after randomization.⁴³ Although the primary outcome was similar between the 2 groups, there was an increased rate of stroke with CAS that was offset by a reduced rate of MI as compared to CEA.⁴³ The question of equivalence of MI and stroke outcomes following carotid revascularization has been the crux of the debate following CREST. In addition, CREST also demonstrated a significant interaction between age and efficacy of therapy. CAS tended to be more efficacious at younger ages, and CEA was more efficacious in older subjects. Updated Cochrane collaboration review of long-term outcome comparisons between CAS and CEA demonstrated that CAS was associated with an increased risk of periprocedural stroke or death compared with CEA.⁴⁴ However, this excess risk appeared to be limited to older patients. It must be noted that although CAS is considered to be more difficult among older patients, rigorous patient selection criteria were not routinely employed in several of these trials. In the longer term, the data demonstrated that the difference was caused by an excess in nondisabling procedural strokes associated with CAS and did not appear to translate into lower functional capacity, as compared to CEA.⁴⁴ Despite this suggestion, the long-term efficacy of CAS and the risk of restenosis are unclear and require further follow-up of existing trials.

Besides the controversies that surround the management of patients with symptomatic carotid stenosis, treatment of

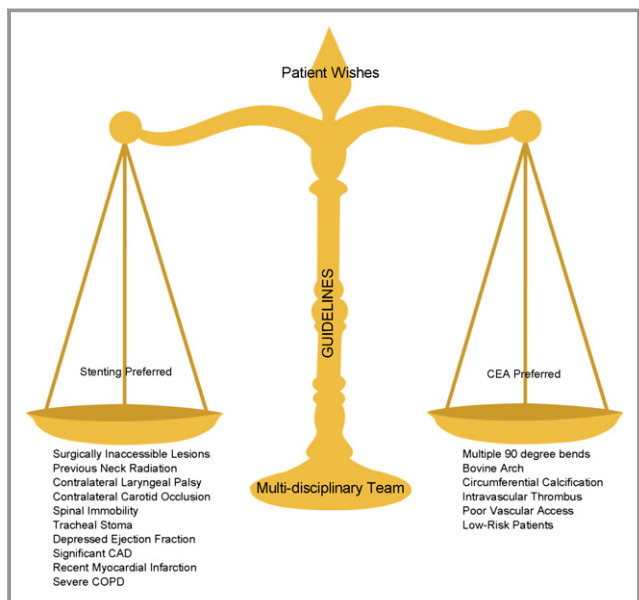


Figure 3. Key factors important in determining the choice of carotid artery stenting or CEA for treatment of severe carotid artery stenosis. CAD indicates coronary artery disease; CEA, carotid endarterectomy; COPD, chronic obstructive pulmonary disease.

patients with asymptomatic carotid stenosis is even more controversial. In the current era of optimal medical therapy, the role of carotid revascularization by CAS or CEA is unclear and is being sought by the CREST-2 trial.⁴⁵ Furthermore, there is ongoing controversy regarding the role of operator experience while comparing CAS and CEA, along with differing certification requirements for the 2 interventions. The rate of periprocedural stroke among symptomatic patients undergoing CAS was 6% in the CREST trial as compared to 9.6% in the EVA-3S trial,^{40,43} emphasizing the importance of training, credentialing, and auditing the CAS operators.

So, how do we put all this information into perspective for decision-making? Overall, it has been demonstrated that CAS and CEA are durable procedures that are effective in preventing major strokes that lead to death or disability in the majority of patients. CAS seems to have the disadvantage of causing minor nondisabling strokes in the postprocedural period and possibly in the long term. However, this increased risk of minor strokes must be weighed against the increased risk of MI, cranial nerve palsies, and access site complications associated with CEA. The choice between CAS and CEA should take into account the different procedure-related risks, demographic characteristics such as age and sex, patient preferences, along with other comorbidities that may relatively or absolutely contradict a procedure. We have established that there is a complementary role for both CAS and CEA but have not been able to establish clearly as to who will benefit the most from which procedure. The risk–benefit issue is a little complex at the moment and should be discussed with patients in a transparent fashion to facilitate collaborative and individualized choice of treatment. The current ACC/AHA guidelines recommend CEA as the revascularization strategy of choice among low- or medium-risk patients with significant carotid stenosis presenting with stroke or transient ischemic attack (Class I recommendation).³⁶ However, the guidelines also recognize CAS as an alternative to CEA (Class I recommendation) among patients who are at low risk for endovascular intervention, giving rise to controversy about patient selection.³⁶ Finally, the importance of optimal medical therapy and control of modifiable traditional cardiovascular risk factors cannot be ignored. However, according to the current guidelines, in symptomatic or asymptomatic patients at high risk of complications for carotid revascularization by either CEA or CAS because of comorbidities, the effectiveness of revascularization versus medical therapy alone is not well established.³⁶

Lessons Learned From Transcatheter Patent Foramen Ovale Closure

In several epidemiologic studies, a higher prevalence of PFO in patients with cryptogenic stroke suggests that at least in

some patients with cryptogenic stroke, the cause of stroke may be paradoxical thromboembolism occurring through a PFO.⁴⁶ Transcatheter PFO closure has been available for over 10 years with very little hard evidence to guide patient and device selection (Figure 4). In the past, investigators have used their own clinical judgment to decide when and how to percutaneously close the PFO. The published literature in this arena has been confusing and controversial. On one side, the observational data indicate an overwhelming benefit of transcatheter closure as compared to medical therapy.⁴⁷ On the other side, the RCTs have shown a controversial and questionable efficacy of transcatheter closure over medical therapy.⁴⁸ In addition, the literature only gives us some insights regarding event rates on medical therapy, as well as the impact and the management of high-risk anatomical features such as interatrial aneurysm. Although the strength of RCT is to minimize unmeasured biases, entry bias introduced by investigators' and patients' preferences, especially when the same therapy is available outside the clinical trial, can play an important role in the adequacy of final study population (Figure 5). This is of particular relevance in this population where the chance of PFO being an innocent bystander is high. In addition to paradoxical thromboembolism, PFO closure has been attempted as a therapeutic modality for migraines, decompression syndrome, and platypnea–orthodeoxia syndrome. However, convincing clinical data are currently lacking for use of PFO closure for these indications. In addition, when there are multiple clinical manifestations of these diseases, it is even more difficult to get granularity for efficacy in individual subsets.

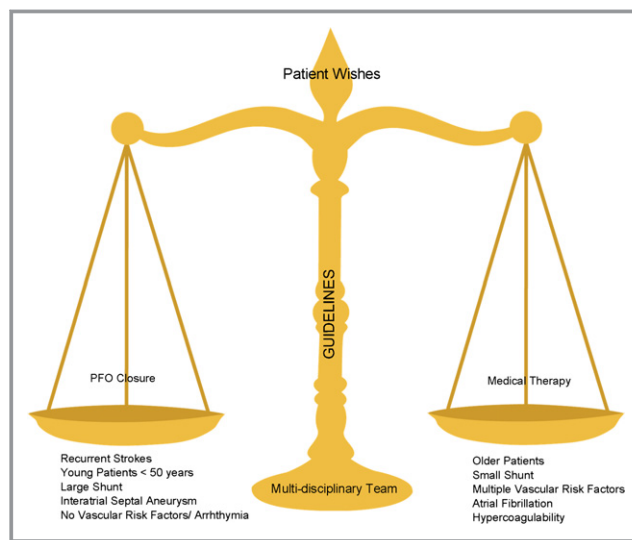


Figure 4. Key factors important in determining the choice of transcatheter closure of PFO or medical therapy in patients with paradoxical thromboembolism. PFO indicates patent foramen ovale.

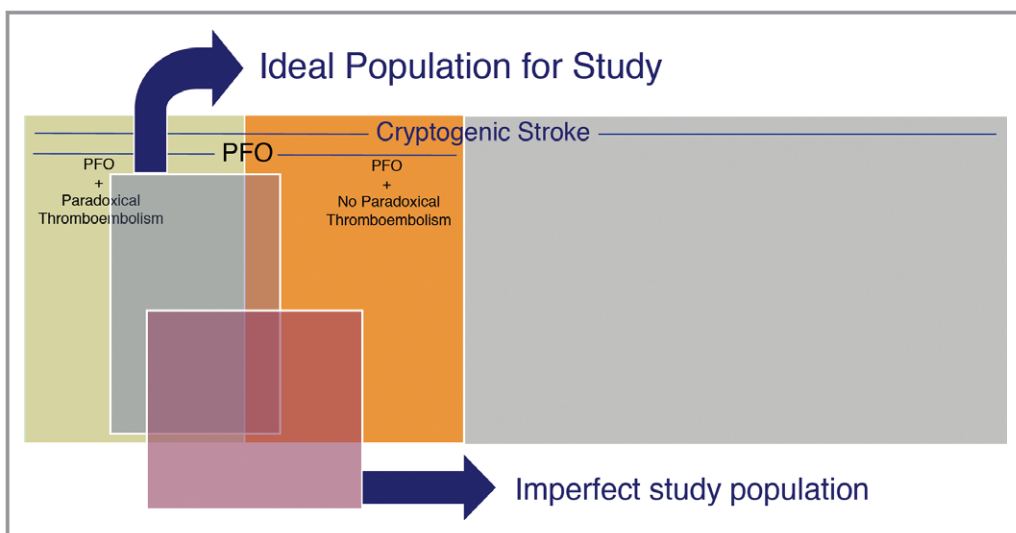


Figure 5. Schematic diagram depicting an ideal population for transcatheter closure of patent foramen ovale (PFO) that would likely benefit from this treatment. On the contrary, the “imperfect population” where PFO is not the cause of thromboembolism is unlikely to derive any benefit from transcatheter PFO closure. Reprinted from Agarwal et al,⁴⁷ with permission from Elsevier.

One of the main questions that arise in the choice of treatment therapy for PFO is why RCTs have been so difficult and controversial in this arena. One of the biggest reasons is the fact that the clinical trials related to cryptogenic stroke and transcatheter PFO closure were formulated after the closure devices were already commercially available. All RCTs were significantly hampered by slow enrollment despite multiple pleas to limit off-label use from several professional societies.⁴⁹ Interestingly, during 1998–2004, Optowsky et al reported that there was a 50-fold increase in the number of percutaneous PFO devices inserted in the United States.⁵⁰ In addition, after a review by the Food and Drug Administration, the human device exemptions for the 2 percutaneous closure devices granted in 2000 and 2002 were withdrawn in 2006, because the number of patients undergoing this procedure after “conventional medical therapy failure” was significantly in excess of 4000 patients per year.⁵¹ Why did the physicians choose to do this? If one looks at the scenario from a practicing physician’s point of view who is faced with a young patient with cryptogenic stroke with a PFO, a rather grave situation comes to light. Even though it is apparent that an evidence-based recommendation cannot be made to the patient, the physician certainly has an obligation to make a recommendation based on experience, temperament, professional judgment, and common sense. In addition, physicians who are keen on enrolling patients into clinical trials are faced with a “real-world” issue, in that if patients are refused transcatheter PFO closure unless enrolled in the trial, they often choose to go to another medical center where such treatment is readily available without the pressure of being enrolled into the clinical trial. Although it may seem

unjustifiable on scientific grounds to forego recruitment in clinical trials, physicians have managed to circumvent these 6 constraints based on humanitarian, pragmatic, and compassionate grounds.

Taken together, the evidence from all 3 RCTs (Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale-CLOSURE I, Randomized evaluation of recurrent stroke comparing PFO closure to established current standard of care-RESPECT, Percutaneous closure of PFO versus medical management in patients with cryptogenic stroke-PC), each of which failed to demonstrate the benefit of transcatheter PFO closure over medical therapy, does not support the use of percutaneous closure for prevention of recurrent neurological events among patients with PFO and cryptogenic stroke.^{52–54} However, the per-protocol analysis from RESPECT, which is at the root of ongoing controversy, leaves open the possibility that closure with an Amplatzer PFO occluder might be superior to medical therapy (primarily antiplatelet) in carefully screened patients with cryptogenic stroke.⁵² One of the primary reasons for the discrepancy between the RCT and observational data might emanate from the “recruitment bias,” wherein lower-risk patients with equivocal symptoms are enrolled into the trials secondary to physician reluctance, patient reluctance, concerns regarding the pitfalls of a lifelong medical therapy, and widespread off-label use of closure devices (Figure 5). One of the solutions might be to create a large, prospective multicenter registry, which allows comparison between various treatment strategies and helps determine the clinical utility of transcatheter PFO closure. It is well known that

registries provide a unique insight to our understanding when a relatively rare clinical problem is investigated and “clinical judgment” is exerted to select the treatment approach. This large registry can help gather data on device complications, residual leak rates, and rates of recurrent neurological events along with understanding the utilization patterns across the country.

Subsequently, what should we tell our patients at this time? The current evidence and the trial results should be discussed with all patients in an unbiased fashion. We should acknowledge the absence of solid clinical guidelines, which direct the management of these patients. Pending such guidelines and based on the pooled results from CLOSURE I and RESPECT trials, it would be reasonable to discuss transcatheter PFO closure with the Amplatzer device in young patients <50 years with a large shunt, without vascular risk factors and a demonstrable cortical infarct on reliable brain imaging such as magnetic resonance imaging. In older individuals, the current evidence would support antithrombotic/antiplatelet therapy along with intensive modification of traditional cardiovascular risk factors. It is also important to realize the anticoagulant therapy may be more efficacious in preventing recurrent strokes than antiplatelet therapy, should medical therapy be adopted.⁴⁷ Before a strategy is embarked upon, it is vitally important to establish that the stroke is truly “cryptogenic.” This entails ensuring all relevant investigations including computed tomography of the brain, neck vessels, and aorta; prolonged continuous rhythm monitoring (CardioNet for 30 days) and hypercoagulable workup are performed to rule out known etiologies of stroke, which might change the course of treatment. Lastly, regardless of the treatment alternative chosen, we should reassure all our patients that the annual risk of recurrent stroke is low with both medical therapy and device therapy, and intensive control of cardiovascular risk factors is of paramount importance in improving their cerebrovascular health.

Lessons Learned From Complex Percutaneous Coronary Interventions

CABG has been traditionally regarded as the treatment of choice for complex multivessel CAD. However, advances in the percutaneous therapies including drug-eluting stents (DES), and newer antithrombotic and antiplatelet regimens with aggressive medical therapy have led to marked improvement in outcomes following nonsurgical treatment of CAD. In addition, there have been considerable improvements in the surgical techniques including greater use of arterial grafts, greater use of off-pump CABG, along with better postoperative care, which has antiquated the bulk of surgical outcomes data published earlier.^{55,56} As the PCI technology continues to evolve and the surgical outcomes improve, we are more often

than not faced with the ultimate question “What is the best revascularization strategy for patients with complex multivessel CAD?” (Figure 6).

Two seminal RCTs—Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) and Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM)—have influenced our practice in a major way.^{57,58} The primary aim of SYNTAX was to assess the optimal revascularization strategy for patients with 3-vessel disease or left main trunk disease, by randomizing patients to PCI with paclitaxel-eluting DES or CABG.⁵⁸ This trial demonstrated a significantly higher occurrence of major adverse cardiovascular and cerebrovascular events among patients treated with PCI as compared to CABG.⁵⁸ In contrast to the complex 3-vessel disease group, the outcomes among patients with left main trunk disease appeared to be more comparable,⁵⁸ introducing heterogeneity in the applicability of the results of this trial. Furthermore, the results appeared comparable between the PCI and the CABG groups among patients with low SYNTAX scores, suggestive of moderately complex disease. The key difference between the 2 strategies was a higher risk of stroke with CABG, which was compensated by a higher rate of revascularization with PCI. The FREEDOM trial, which evaluated the optimum revascularization strategy among diabetics with multivessel CAD, also demonstrated a significantly lower incidence of death, MI, and stroke with CABG as compared to PCI.⁵⁷ In contrast to the SYNTAX trial, the difference was chiefly driven by significant differences in all-cause mortality and MI.⁵⁷

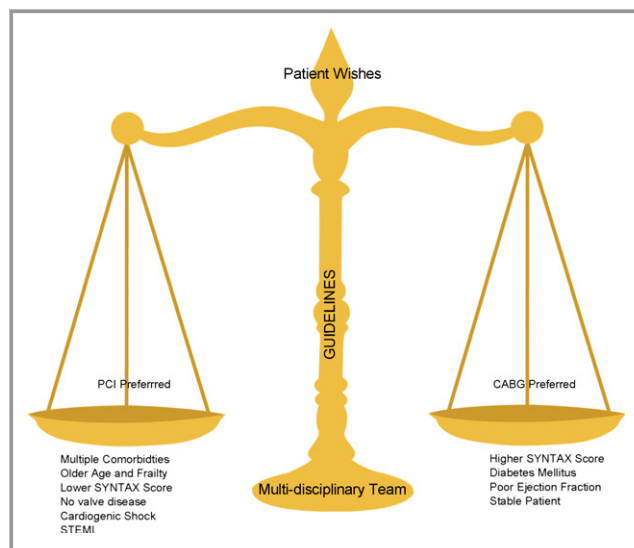


Figure 6. Key factors important in determining the choice of PCI or CABG in patients with complex coronary artery disease. CABG indicates coronary artery bypass graft; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; SYNTAX, Synergy between PCI with Taxus and Cardiac Surgery.

One of the important features that we learned from the SYNTAX trial, which is now incorporated in current guidelines, was the use of a “heart team” approach for deciding the optimal revascularization strategy, in collaboration with the patient who should be educated about the evidence behind each approach. Ad hoc PCI in clinically stable patients with complex CAD should be avoided, and each case should be discussed by the heart team before a definitive strategy is embarked upon. The ad hoc procedures afford little procedural planning and may be biased as the same physician makes the diagnosis, recommends the treatment, as well as performs the procedure. An attractive approach is the hybrid coronary revascularization, which theoretically provides the best of both worlds. The premise is based on the excellent patency rates and survival benefits associated with the durable left internal mammary artery graft to the left anterior descending artery along with the good patency rates of DES, which generally are superior to saphenous vein grafts to non-left anterior descending vessels. Despite its appeal, the technology and its application are still in their nascent stages and much work remains to be done in this area.

Although a majority of management in complex CAD is guided by large RCTs, we must acknowledge encountering patients who did not meet the inclusion criteria for these trials. Perhaps the toughest scenario in the post-FREEDOM era is the emergent management of ST-segment elevation MI patients with diabetes and 3-vessel disease. Emergency reperfusion of the infarct-related artery is usually the norm. It is unclear whether the practicing interventionists should think about altering their practices with respect to obtaining emergent surgical consultations in these scenarios, choice of stent (DES versus bare metal stents), using glycoprotein inhibitors to avoid use of thienopyridines for urgent surgery, or even considering hybrid coronary revascularization in these cases. Furthermore, after revascularizing the infarct-related artery, should we “reset the clock” to determine the need for further revascularization of non-infarct-related arteries? In addition, if left internal mammary artery conduit cannot be utilized, the long-term benefit of CABG over PCI remains questionable. Furthermore, from a logistic and practical point of view, PCI might offer timely revascularization among patients with cardiogenic shock.

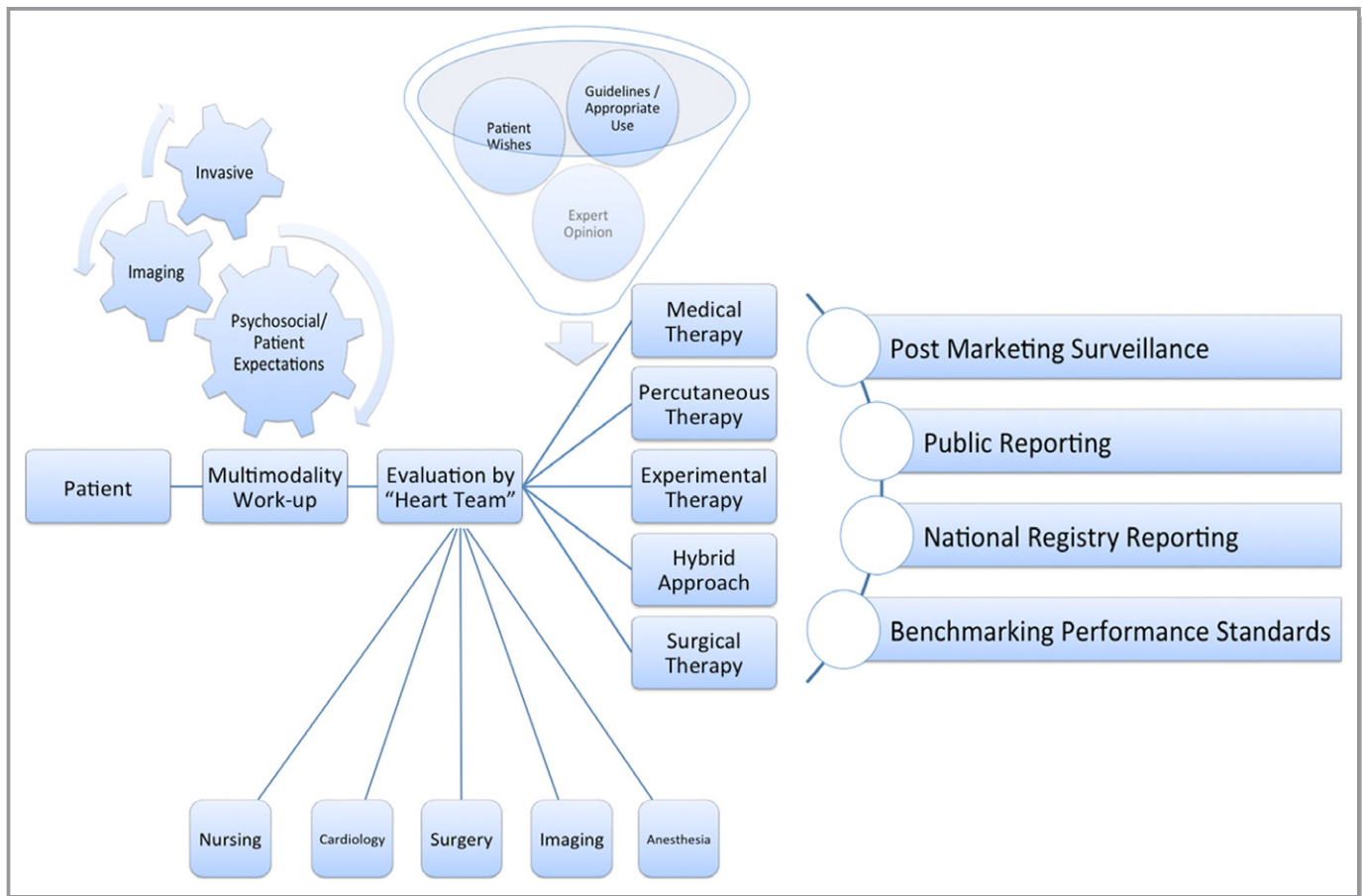


Figure 7. Key elements of decision-making in interventional cardiology on complex patients.

One of the major challenges encountered, while comparing different therapies, is the fact that both therapies continuously evolve, but at different paces. A rise in total arterial revascularization, especially the use of bilateral internal thoracic artery (BITA) grafting, off-pump CABG without aortic manipulation, improved graft harvesting techniques, and better postoperative care will help improve the outcomes after CABG. In addition, use of antiplatelet therapy after CABG, use of epi-aortic scanning, avoidance of aortic manipulation, and perhaps ligation of the left atrial appendage in patients with atrial fibrillation will be some measures to prevent postoperative stroke. These advances in CABG have been met by similar advances in the PCI field, including newer-generation DES with better deliverability, fractional flow reserve-guided revascularization, bioresorbable stent scaffolds, and several modalities for adjunctive imaging.

So, what do we tell our patients with complex multivessel CAD? The majority of patients with complex multivessel CAD are still best treated with CABG. There are always patients who are either ineligible for surgery or refuse surgery or who express a strong desire for noninvasive treatment. PCI can and should be considered in patients thought to be inoperable due to multiple comorbidities, in those with left main trunk disease with moderate SYNTAX scores, or in those with low SYNTAX scores. An important factor for making the decision is the scenario in which revascularization is being attempted. As mentioned above, cardiogenic shock or ST-segment elevation MI may be best treated with PCI based on logistical and practical concerns. In patients with chronic heart failure, the choice between PCI or CABG should include a meticulous evaluation of the extent of CAD, expected completeness of revascularization, comorbidities, and associated valvular heart disease. Among elderly patients, an accurate determination of frailty should be made prior to embarking on the choice of revascularization, as frailty is a better determinant of outcomes following both PCI and CABG.^{59,60} Female sex was an important predictor of long-term mortality in the PCI arm of the SYNTAX trial, despite risk factor adjustment,⁶¹ and hence, the threshold to send female patients to CABG might be slightly lower than for men. Among patients with chronic kidney disease, it is advisable to use the off-pump CABG if CABG is the preferred strategy. That being said, the patient should always be at the heart of all decision-making regarding treatment strategy. We must all understand that every patient has different preferences in life and will interpret risk and benefit differently, and hence, it is of utmost importance to use collaborative decision-making at every step of rendering health care.

Conclusions

Interventional cardiology has embarked on an exciting era—an era that is filled with innovation, and rapidly evolving

technology that has opened multiple avenues and options for our patients. However, we are also faced with the difficult task of determining the most optimal treatment strategy, often in areas of uncertainty (Figure 7). As evidenced by important lessons in multiple areas discussed above, we all realize that there are several areas of uncertainty in key areas of interventional cardiology. Based on all the experiences in various fields in interventional cardiology, there are 5 basic principles that one should use in cases of medical uncertainty.⁶²

- 1 Acknowledge ignorance and lack of definitive clinical data
- 2 Involve the patient and family in all clinical decision-making
- 3 Work in collaboration with other experts to consider all possible treatment strategies
- 4 Prioritize sound clinical evidence, before adopting unproven clinical therapies
- 5 Caution must be exercised if extrapolating from results of low-grade/anecdotal evidence, because of intrinsic biases

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Disclosures

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