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STATE-OF-THE-ART REVIEW

CEREBROVASCULAR DISEASE AND STROKE

The Heart Brain Team and Patient-Centered Management of Ischemic Stroke

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ABSTRACT

The multifaceted connections between the heart and the brain have been extensively studied at the anatomy, pathophysiology, and clinical levels. Studies have suggested a vital role for both cardiologists and neurologists in the management of various cardiovascular and neurological disorders. However, a true heart-brain team-based approach remained confined to large, specialized centers. In this paper, we review the various intersection areas of cardiology and neurology with regard to ischemic stroke. We focus our discussion on the challenges and opportunity for a heart-team approach to stroke in the context of atrial fibrillation, carotid disease, and patent foramen ovale, and in the setting of strokes complicating transcatheter endovascular interventions. (JACC Adv 2022;1:100014) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

The interplay between the heart and the brain has been a subject of fascination and debate for many decades. Numerous studies have documented the multifaceted interactions between neurological and cardiovascular disorders.[1] The impact of autonomic dysfunction on heart failure, arrhythmias, myocardial infarction, orthostatic hypotension, syncope, and sudden cardiac death is now well established.[2-5] Similarly, the effects of coronary disease, atrial fibrillation (AF), and cardiomyopathy on overt or subtle brain dysfunction (eg, stroke, neurocognition) are supported by indisputable epidemiological and clinical practice evidence.[6-12] Nonetheless, considerable gaps remain, necessitating a reconsideration of the critical role the "heart-brain team" can play in current and future practice. Herein, we review emerging concepts in the prevention and treatment of acute ischemic stroke from a heart-brain team perspective (**Central Illustration**).

PREVENTION OF ACUTE ISCHEMIC STROKE

Stroke is a leading cause of death and mortality. In the United States, stroke accounts for 5% of all deaths claiming >130,000 lives annually. Ischemic stroke accounts for 85% of all strokes, with cardioembolism being the most common mechanism.[13] Despite the advances in stroke management, the incidence of stroke and stroke-related mortality continue to rise in many parts of the world.[14] This is partially caused by the increasing complexity of stroke patients, the lack of a well-rounded multidisciplinary team approach to stroke prevention, and the paucity of stroke centers

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

ANS = autonomic nervous system

CAS = carotid artery stenosis

IPH = intraplaque hemorrhage

LAAC = left atrial appendage closure

OAC = oral anticoagulation

PFO = patent foramen ovale

RCT = randomized clinical trials

with more advanced capacities for treatment of acute stroke.[1] However, the decline in stroke rates and stroke-related mortality in the United States, especially among young patients, suggest that stroke could be preventable further emphasizing the role of heart-brain teams in preventing and managing this fatal disease.[15-17]

Here, we discuss the challenges of stroke prevention in patients with AF, patients with carotid artery stenosis (CAS), patients with patent-foramen ovale (PFO), and those undergoing transcatheter endovascular procedures.

HIGHLIGHTS

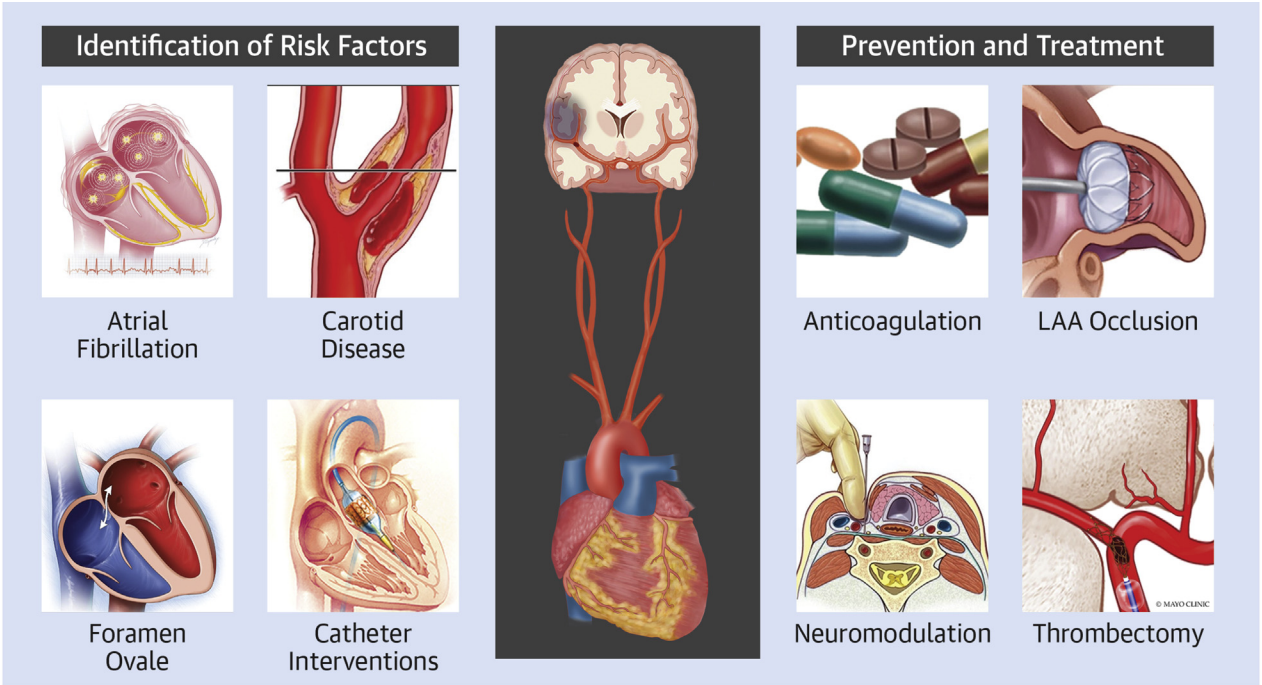
- The connections between the heart and the brain have been extensively studied at the anatomy, pathophysiology, and clinical levels.
- Multidisciplinary team-based approaches are now integral part of cardiovascular medicine practice.
- The heart-brain team can play a vital role in advancing the science and optimizing the provision of coordinated patient-centered care for ischemic strokes.
- Multistakeholder efforts are needed to develop, nurture, and scale up heart-brain teams that may can lead to further major advances in the field.

ATRIAL FIBRILLATION. AF is the most common arrythmia, and it is associated with a substantial increase in the risk of cardioembolic events. The prevalence of AF and its burden among patients hospitalized with acute ischemic stroke are rapidly increasing in the United States.[17,18] Lifelong management of stroke risk in AF patients requires a concerted team efforts to address several remaining issues in the following domains:

Risk stratification. Managing risk is an essential component of caring for patients with AF. Numerous efforts have been made to devise accurate user-friendly tools to estimate the risk of stroke and the risks and benefits of oral anticoagulation (OAC).[19,20] However, these risk prediction tools have significant limitations that hinder their effectiveness.[19-21] First, commonly used risk scores have a modest discrimination value. For example, CHA_2DS_2-VASc, the most common risk score for the prediction of stroke in the setting of AF, only achieved a C-statistics of 0.61 in the original validation cohort and C-statistics between 0.58 and 0.69 in subsequent confirmatory studies.[19] Similarly, the HASBLED score, a widely used score to predict bleeding risks with warfarin, attained C-statistics of 0.60-0.66 when externally validated in prospective cohorts.[22] Second, current risk prediction schemes omit key predictors of the event of interest. For example, CHA_2DS_2-VASc does not account for AF duration, left atrial size and function, left atrial appendage contractility, and morphology, all of which have been shown to strongly correlate with ischemic stroke risk. Likewise, the HASBLED score does not account for the type of anticoagulant used, and hence may not be applicable to modern practice where most AF patients receive direct OACs.[23] Third, although commonly used in daily practice, the CHA_2DS_2-VASc score was derived from observations made several decades ago. Since then, medical treatment has evolved, risk factors have changed, and stroke incidence has declined.[15-17] There is a dire need to revisit the value of these "historical" data and their applicability to current or future practice. Fourth, risk scores do not address the need of the growing number of "special AF populations" whose unique characteristics are not accounted for in these schemes. For instance, cerebral amyloid angiopathy, which affects 12%-36% of octogenarians and is associated with a several-fold increase in micro and overt intracranial hemorrhage, is not recognized by current risk scores (**Figure 1**).[24,25] Indeed, both the CHA_2DS_2-VASc and the HASBLED scores yielded a limited value in predicting stroke and bleeding in patients with cerebral amyloid angiopathy.[26] Similarly, these scores are inadequate to risk-stratify patients with end-stage renal disease, a rapidly growing population in whom the prevalence of AF exceeds 25%.[27] The increasing complexity of AF patients and of the available stroke prevention strategies along with the limitations of risk prediction tools highlight the need for a team approach to effectively appraise the evidence and provide individual patient-centered recommendations.

Identification of stroke mechanism. An important issue relates to the fact that there are several different mechanisms of "ischemic" stroke that may coexist in patients with AF. These may include concomitant carotid or cerebral vascular disease and PFO, among others. Consideration of all of these potential causes is essential to select the optimal short- and long-term management strategy. However, because of differences in expertise between cardiologists and neurologists, the identification of the likely etiology often requires input from both. For example, cardiologists

CENTRAL ILLUSTRATION **Heart Brain Team Management for Ischemic Stroke**



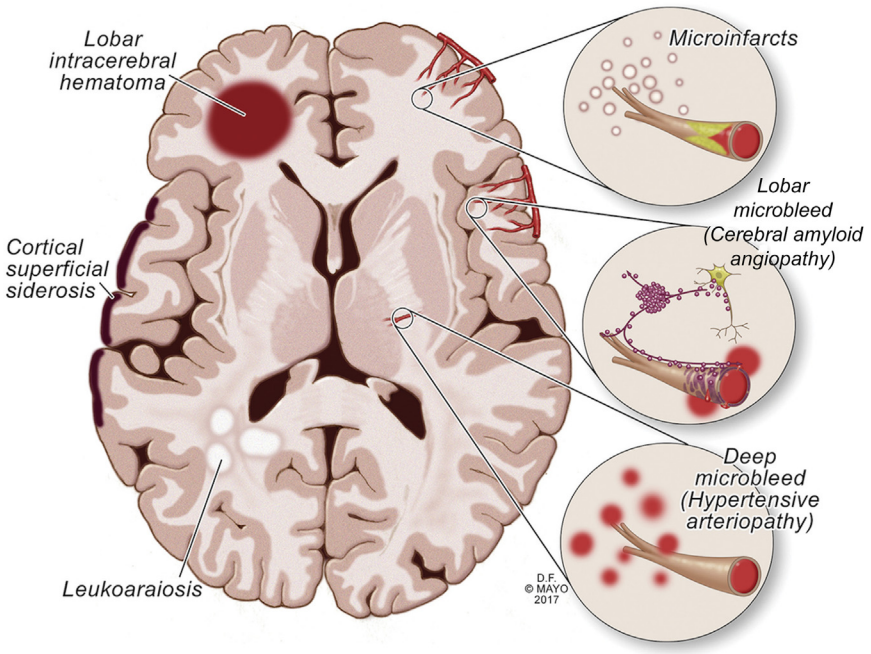
Alkhouli M, et al. JACC Adv. 2022;1(1):100014.

This figure illustrates the various potential venues for the heart-brain team to improve the care of patients at risk for or those who have already experienced an ischemic stroke. LAA = left atrial appendage.

are less attuned than neurologists with the nuances of ischemic stroke characteristics (lacunar vs embolic, single vs multiterritory), and have limited knowledge of noncardioembolic causes of stroke (eg, vasculitis, hypercoagulable states, hematologic disorders, intracranial atherosclerosis, nonatherosclerotic intracranial vasculopathies such as moyamoya disease, and so on). Hence, they are more likely to view all "ischemic strokes" as 1 entity, which may impact management decisions. On the other hand, neurologists may be less familiar with anatomical or physiological data (eg, AF duration, procedural risks, adequacy of device closure, high-risk features of a concomitant PFO), which may be important determinants of stroke risk and selection of the optimal prevention strategy in individual patients. An ongoing alliance between the 2 specialties on the training, research, and practice levels will facilitate knowledge sharing and likely lead to more accurate diagnoses and optimal care provision.

Selection of stroke prevention strategy. Up until 2016, either OAC or surgical excision/closure of the left atrial appendage was the only stroke prophylaxis strategy for patients with AF. However, nationwide cohort studies have shown that approximately two-thirds of AF patients are intolerant of or noncompliant with OAC, leading to suboptimal stroke prevention in most patients. To address this large unmet clinical need, percutaneous left atrial appendage closure (LAAC) was developed as an alternative stroke prevention in selected AF patients.[18] Since its approval in the United States, the adoption of LAAC in practice has been growing exponentially.[28,29] However, several issues remain, including appropriate patient selection for OAC vs LAAC, the potential role of LAAC in addition to OAC, incomplete device closure, and device-related thrombus (**Figure 2**).[30-33] One of the largest randomized trials on surgical LAAC has recently shown that LAAC in addition to OAC resulted in 33% reduction in the risk of ischemic stroke or systemic embolization in AF patients undergoing cardiac surgery.[34] This trial challenged the notion of perceiving medical (ie, OAC) and device therapies (ie, LAAC) as competitive.

FIGURE 1 Vascular Pathologies Associated With Cerebral Amyloid Angiopathy



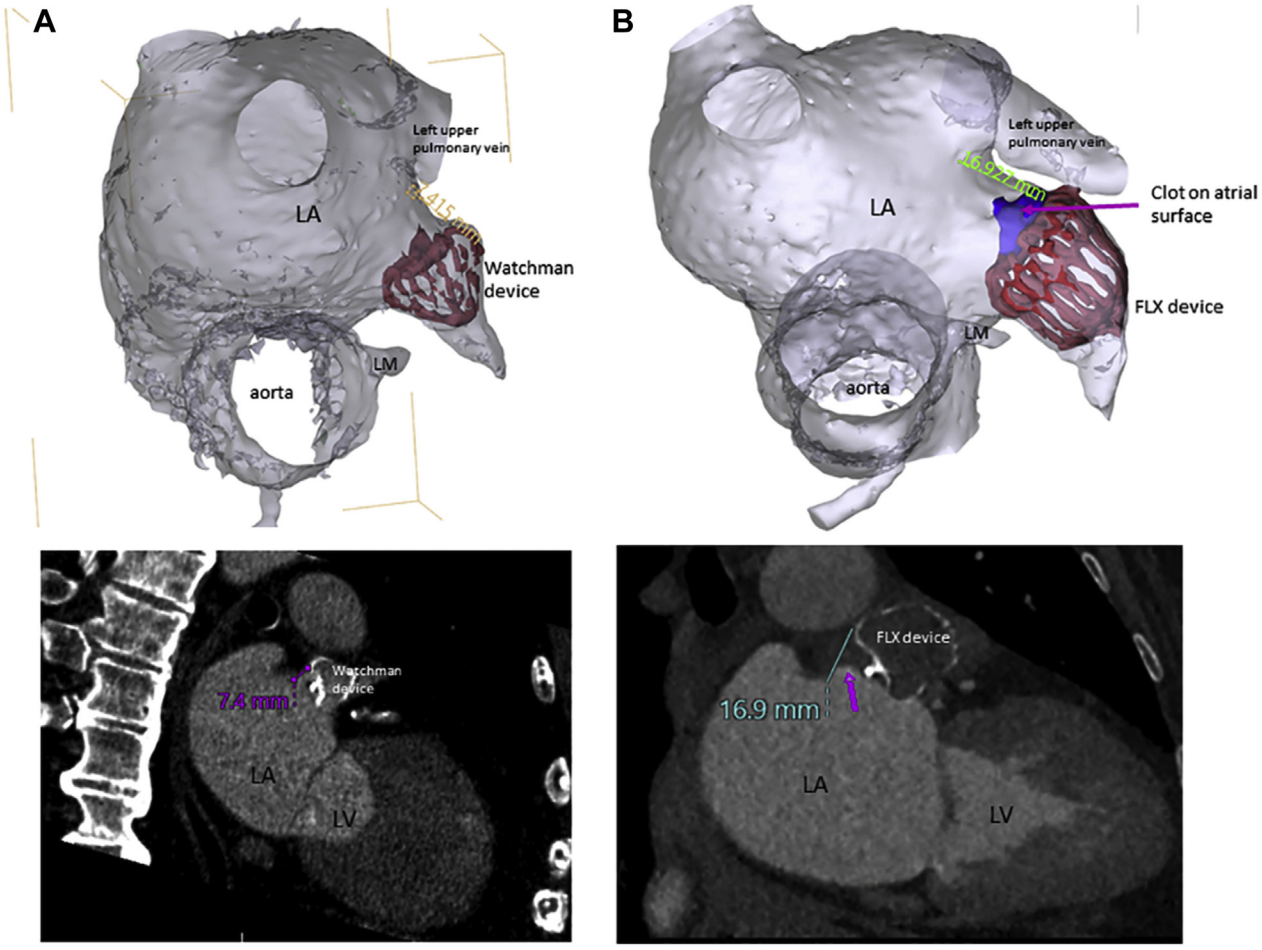
This figure illustrates the various pathologies that can be present in the setting of cerebral amyloid angiopathy in the aging brain. Reproduced with permission from DeSimone et al.[25]

Further studies are needed to explore the role of concomitant stroke prevention strategies in the increasingly complex era of precision medicine. Other important venues for interdisciplinary decisions in AF patients pertain to appropriate choice and timing of OAC after an acute ischemic stroke, selection of antithrombotic regiment after LAAC, management of OAC interruption in high-risk patients, and appraisal of the dynamic risk of stroke and bleeding in the geriatric population.[35-38]

Managing risk factors of ischemic stroke. Numerous studies have demonstrated the presence of atrial structural remodeling that precede clinical pathology and may be linked to thromboembolic risk even during sinus rhythm.[39-41] Although a survey of the literature yields conflicting conclusions, there is growing evidence that the optimal management of stroke risk is multifaceted and may include clinical risk factor modification (hypertension, dyslipidemia, diabetes, and so on), elimination or neutralization of thrombus source (OAC+/−LAAC), and modification of the inflammatory and/or arrhythmogenic milieu (catheter ablation, neuromodulation).[39-43] Herein, we focus on the evolving field of neuromodulation. At large, neuromodulation is based on 2 fundamental concepts: 1) the autonomic nervous system (ANS) plays a key role in the pathophysiology of AF; and 2) opportunities exist to affect the function of the ANS in multiple locations thought out the neurocardiac axis.[44] Modern advances in neurophysiology, 3-dimensional molecular imaging, and tissue ablation inspired many scientists to explore further the role of ANS neuromodulation to interrupt the initiation and perpetuation of AF (**Figure 3**). The impact of neuromodulation on modifying the risk of stroke has not yet been studied. However, the growing research on neuromodulation could potentially provide more insights into the issue of dissociation between rhythm control and stroke risk in patients with AF. Next, we summarize the emerging data on the various neuromodulation methods for AF (**Figure 4**).

- *Modulation of the autonomic ganglionic plexi.* The epicardial fat pads contain clusters of sympathetic and parasympathetic fibers that interconnect in the discrete plexi (autonomic ganglionic plexi [AGP]). Ablation of the AGP has shown some

FIGURE 2 **Device Thrombus After Left Atrial Appendage Occlusion**

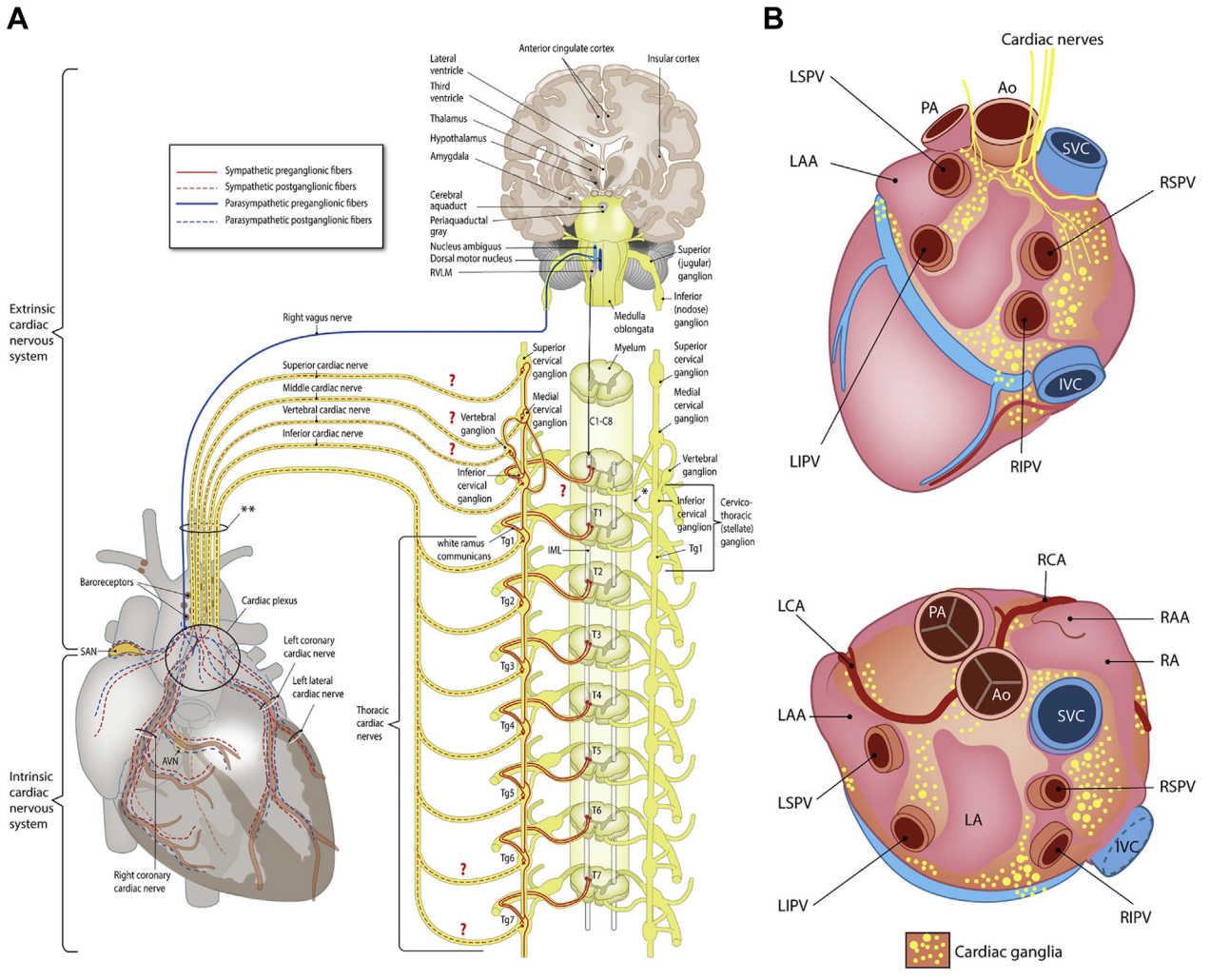


Computed tomography images of 2 patients without **(A)** and with **(B)** device-related thrombus. **Pink arrows** denote the location of the thrombus DRT. Reproduced with permission from Simard et al.[33] CT = computed tomography; LA = left atrium; LM = left main; LV = left ventricle.

promising results in treating AF in early proof-of-concept work. Concomitant AGP and pulmonary vein ablation resulted in higher freedom from recurrent AF in several randomized clinical trials (RCTs).[45-47] Other trials assessing the role of AGP ablation in various settings (recurrent AF, post-surgical AF, and so on) are ongoing.[44] Temporary modulation of the AGP has also been explored via local injection of neurotoxins into the epicardial fat. Studies evaluating the effect of epicardial Botulinum injection at the time of cardiac surgery yielded mixed results, although more RCTs are ongoing.[44,47]

- *Electrical stimulation of the carotid baroreceptors and the vagal nerve.* Altering the ANS via electrical stimulation of its afferent pathways is another potential method that may influence the genesis and burden of AF.
- Carotid stimulation: Baroreceptors are mechanoreceptors located in the carotid sinus and in the aortic arch. These "stretch" receptors sense blood pressure alterations and provide continuous feedback loops to the brainstem. Stimulation of the carotid baroreceptors attenuates the sympathetic tone, and enhances the parasympathetic tone. In canine models, low-level carotid baroreceptor stimulation suppresses AF by inhibiting the sympathetic activity in the left stellate ganglion.[44,48] However, the clinical usefulness of this approach has not yet been confirmed.

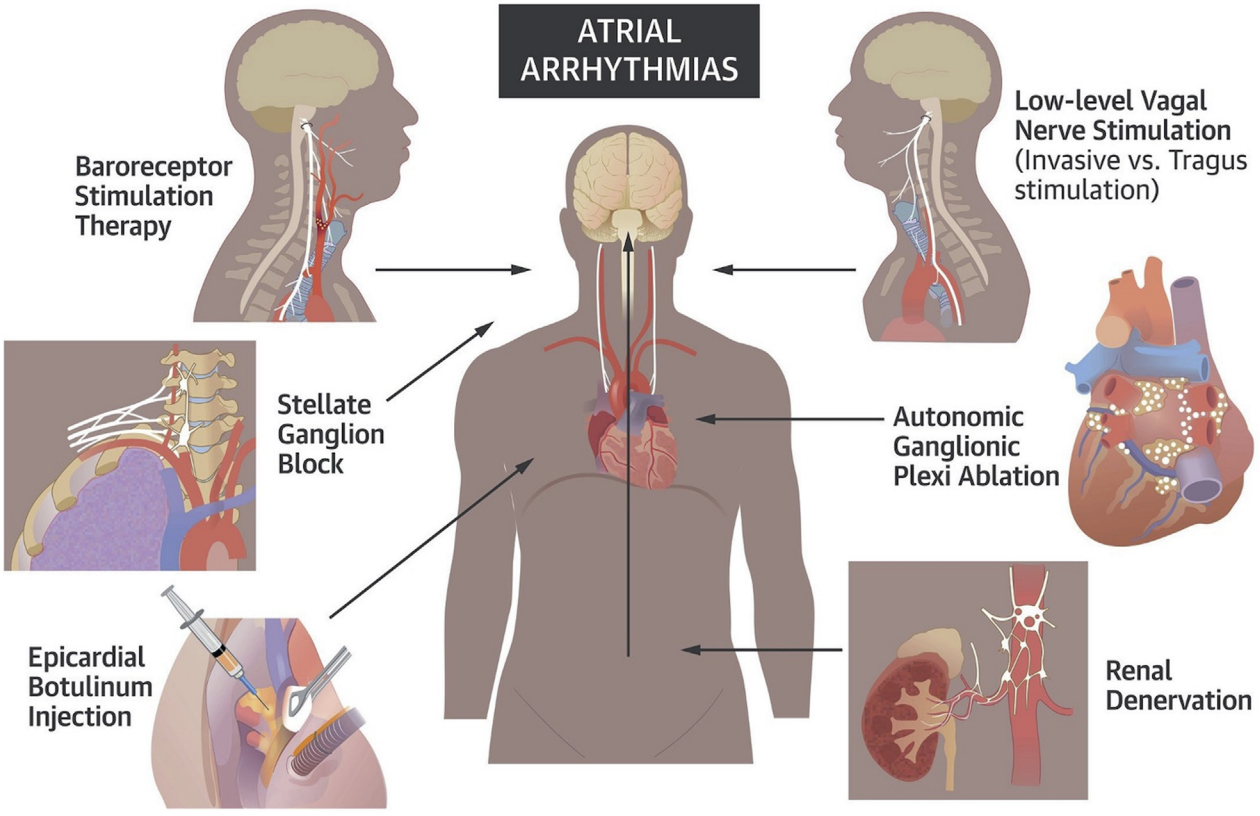
FIGURE 3 Anatomy of the Extrinsic and Intrinsic Cardiac Autonomous Nervous System



(A) Overview of the autonomous nervous system. **(B)** Overview of the cardiac plexus. The question marks refer to anatomical structures with questionable involvement in cardiac innervation. *Ansa subclavia. **Vagal and sympathetic nerves mix prior to entering the cardiac plexus. Reprinted with permission from Wink J, van Delft R, Notenboom RGE, et al. Human adult cardiac autonomic innervation: controversies in anatomical knowledge and relevance for cardiac neuromodulation. *Auton Neurosci.* 2020 Sep;227:102674. https://doi.org/10.1016/j.autneu.2020.102674. Creative Commons CC-BY license. Ao = aorta; IVC = inferior vena cava; LA = left atrium; LAA = left atrial appendage; LCA = left coronary artery; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; Pa = pulmonary artery; RA = right atrium; RAA = right atrial appendage; RCA = right coronary artery; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein; SVC = superior vena cava.

- Vagal stimulation: Both sympathetic and parasympathetic stimulation can promote the development of AF, although the latter is a more potent inciter of the arrhythmia. Studies have shown a dose-related effect of vagal stimulation on AF with high- and low-level stimulation leading to promotion vs inhibition of AF, respectively. Hence, the role of low-level vagal stimulation in managing AF has been extensively investigated. Stavrakis et al[49] showed that electrical stimulation of the left vagal nerve at 20 Hz (50% below the threshold for inducing bradycardia) reduced postoperative AF among patients undergoing cardiac surgery. Because the vagal nerve projects neural endings in the ear, it is possible to achieve vagal nerve modulation noninvasively by electrical stimulation of the tragus. In a sham-controlled trial,

FIGURE 4 Neuromodulation Techniques for the Treatment of Atrial Arrythmia



An overview of the emerging neuromodulation modalities to treat atrial fibrillation. Reproduced with permission from Waldron et al.[44]

20-Hz vagal stimulation delivered via an earlobe clip attached to the tragus for 1 hour daily over 6 months reduced the burden of AF by 85% in the active intervention arm.[50]

- *Renal denervation.* The renal vasculature is richly innervated with mechanosensitive and chemosensitive nerves that supply afferent input to the brainstem. A continuous feedback loop is then formed among the kidneys, central nervous system, and the heart to facilitate dynamic control of the cardiovascular ANS. The ERADICATE-AF (Evaluate Renal Denervation in Addition to Catheter Ablation to Eliminate Atrial Fibrillation) trial showed that in patients with paroxysmal AF, adding renal denervation to pulmonary vein isolation increased the freedom of recurrent AF at 12 months (72.1% vs 56.5%; HR: 0.57; 95% CI: 0.38-0.85; $P = 0.006$).[51,52] Other studies have shown similar findings and even demonstrated a potential benefit of renal denervation in preventing subclinical AF.[51-54] A few prospective trials are underway to confirm these findings and assess the efficacy of stand-alone renal denervation in treating AF.[44]
- *Stellate ganglion block.* Percutaneous injection of local anesthetic around the stellate ganglion is a commonly used intervention to treat pain in the ambulatory setting. Given that the stellate ganglion is a crucial center for regulating sympathetic afferent and efferent cardiac signals, its temporary block or permanent ablation can be another venue for neuromodulation. Pilot studies have shown this concept's feasibility and potential efficacy, but more extensive confirmatory trials are lacking.[44,55,56]

CAROTID ARTERY STENOSIS

Atherosclerotic CAS accounts for 15% of ischemic strokes in the United States.[57] Revascularization reduces the risk of incident or recurrent stroke. However, several issues related to the screening and

treatment of CAS remain open, making the management of CAS quite challenging, and highlighting the potential role of the heart-brain team in navigating this intricate entity.

SCREENING FOR ASYMPTOMATIC CAS. Screening for atherosclerotic CAS is an essential component in the management of patients with stroke or transient ischemic attacks. However, screening asymptomatic patients remains problematic. The U.S. Preventive Services Task Force recommends against routine screening for CAS in the absence of symptoms.[58] However, this recommendation is based on historical data that do not account for the advances in interventional therapies of CAS, and it does not address high-risk populations, such as those with concomitant coronary disease or those undergoing major cardiovascular procedures. Selective screening of these high-risk populations is indeed an area of ongoing debate.[59-61] The 2011 U.S. guidelines recommend screening for asymptomatic CAS among high-risk patients referred for coronary bypass grafting (Class IIa recommendation, Level of Evidence: C), but the recently published updated guidelines make no mention of carotid disease.[62,63] European guidelines do not support routine screening of CAS before bypass surgery.[64] These discordant recommendations mirror the variability in clinical practices: routine or selective screening is pursued in some institutions, whereas no screening at all is routine in others.[60] A similar theme can be observed in the field of transcatheter aortic valve replacement (TAVR). Although CAS is present in 22% and is severe in 5% of patients referred for TAVR, its association with postprocedural stroke remains controversial.[65,66] Hence, a wide variability exists in practice, with carotid ultrasound being performed in some but not all patients before TAVR.[65] In the context of the limited data and disparate guidelines, the partnership between neurologists and cardiologists becomes crucial to provide patient-centered recommendations and to design and lead clinical investigations that would address the remaining unanswered questions.

TREATMENT OF CAS. Cardiologists have played an instrumental role in studying CAS and its treatment for decades.[67] However, the controversies on the choice of carotid stenting vs endarterectomy dominated the field in recent years resulting in a fractionated specialty-centered approach to this important entity. Yet, many questions remain in the management of CAS, which represent an enticing opportunity for cross-discipline collaboration:

1. In the United States, <5% of patients with severe asymptomatic CAS undergo revascularization.[68] Should this practice be re-evaluated with new trials using contemporary medical therapy and revascularization techniques? The near-completion CREST-2 (Carotid Revascularization for Primary Prevention of Stroke) trial is randomizing patients with severe asymptomatic CAS to medical therapy vs stenting or to medical therapy vs surgery.[69] The trial will address the question of whether an intervention should be done for severe asymptomatic CAS, but will leave the issue of stenting vs endarterectomy open.[69]
2. The timing and mode of revascularization of severe symptomatic CAS in patients undergoing coronary bypass or valve surgery have been long debated, but no consensus exists on the optimal management of these patients.[70-72]
3. Should the classification of CAS now incorporate high-risk plaque characteristics and not just the degree of luminal stenosis considering the growing evidence of the association of high-risk plaque with stroke and ischemic heart disease?[73-75]
4. What can we learn from the similarities and differences in atherosclerotic plaques composition in the coronary and in the carotid vasculature?[76,77]

The high prevalence of multimorbidity in patients with carotid disease and the many uncertainties surrounding their management call for a team-based approach both to achieve optimal care and to address the unsettled questions in the field. This may include considering enhanced medical therapy as well as revascularization of carotid atherosclerotic lesions in selected patients (eg, patients with AF and a high-risk carotid plaque or panvascular disease). Although data on combined therapies are limited, one may speculate a holistic approach to the individual patient accounting for all potential risk factors and treatment options will become the dominant approach in the future. The heart-brain team is well poised to generate the evidence needed for and to implement such a "precision-medicine" patient-centered practice.

PATENT FORAMEN OVALE

Cohnheim and Litten first described paradoxical embolization via PFOs in 1877 and 1880.[78] However, a strong correlation between PFO and embolic strokes was not established until the early 1990s. Since then, numerous studies have investigated the role of percutaneous closure of PFO in reducing recurrent stroke risk. The initial enthusiasm for PFO closure was, nonetheless, tampered by the negative results of early RCTs comparing device closure to medical therapy. However, later RCTs published in 2017 all

showed a consistent benefit of PFO closure. A meta-analysis of early and later trials showed that PFO closure was associated with lower rates of recurrent stroke compared with antiplatelet therapy (2.38% vs 6.07%, number needed to treat ~27) refueling a broad interest in this topic.[78] In 2020, the American Academy of Neurology issued an updated practice guidelines document supporting the consideration of PFO closure in patients <60 years of age who experience an ischemic stroke without a clear alternative etiology.[79] Although these guidelines do not specifically recommend a team-based evaluation of potential candidates for the procedure, they suggest several practices that are not routinely in the scope of cardiologists (**Table 1**). Regardless, experts have long argued that optimal care of patients considered for PFO closure is best achieved by a heart-brain team familiar with the nuances of the current and emerging data and the remaining uncertainties in this highly dynamic field. In our practice, we implement a simple 3-step approach to patients with PFO referred for possible percutaneous closure:

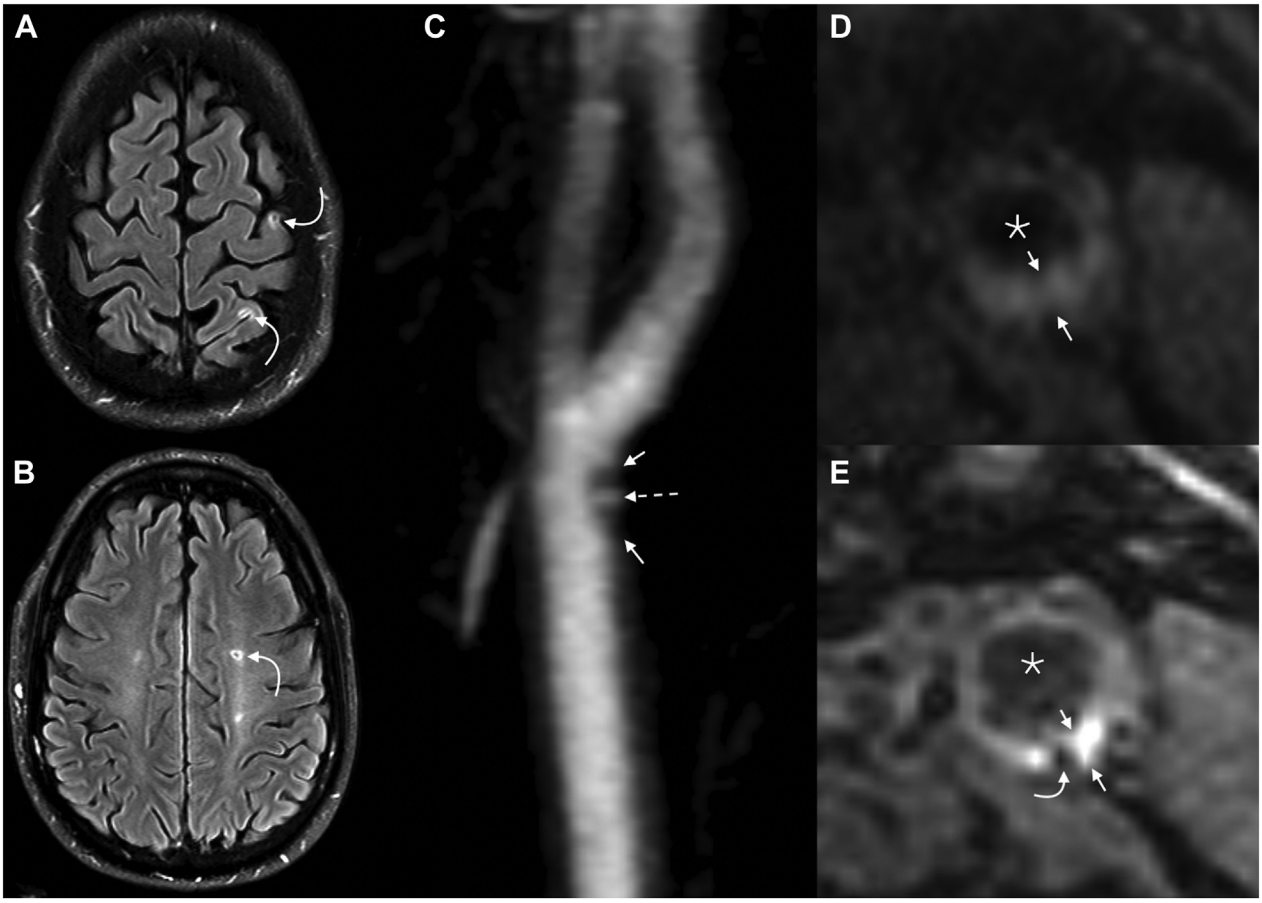
1. *Characterization of the stroke*: current guidelines recommend careful consideration of the ischemic stroke phenotype when evaluating patients for PFO closure. Therefore, baseline brain images are reviewed by a stroke neurologist to discern whether the reported stroke is consistent with a cardioembolic source (cortical and/or multi-territory infarcts) vs lacunar (involving a single deep perforator, <1.5 cm in diameter) or attributable to some other cause. Although this distinction seems relatively straightforward, it is often quite intricate even for expert neurologists. In addition, accurate phenotyping of the ischemic stroke has important implications:
   - The presence of "lacunar lesions" on brain imaging is usually viewed as mutually exclusive of cardioembolism. However, ~10%-15% of lacunar strokes have a potential embolic etiology.[80-83] PFO closure could be considered in a small subset of patients with larger lacunar strokes in whom an embolic event is strongly suspected.
   - Lacunar strokes are usually nonfatal. However, they are not inconsequential. Numerous studies have documented their association with high recurrence rates, progression of white matter lesions, cognitive decline, and cerebral microbleeds.[80,84] Hence, controlling risk factors and determining suitability for antiplatelet/antithrombotic therapy remain paramount. It is therefore evident that the subtle issues surrounding stroke phenotyping require special scrutiny and considerations that can only be realized by collaborative heart-brain teams.
2. *Characterization of the PFO*: RCTs on PFO closure showed mixed results, with some showing no advantage of the procedure while others demonstrating substantial benefit.[78] This led to much debate among cardiologists and neurologists alike.[85] This debate has mainly resolved with the emergence of new data from recent trials with more selective patient selection criteria and longer-term follow-up. Most experts now agree that the PFO anatomy played an essential role in determining outcomes of PFO closure.[78] Study- and patient-level meta-analyses repeatedly showed that certain PFO features such large right-to-left shunt and atrial septal aneurysm confer a higher risk of paradoxical embolization.[78,86] However, risk stratifying PFOs can be challenging because of issues surrounding imaging assessment under sedation conditions and bubble injection via peripheral upper extremity veins.[78,87,88]
3. *Excluding alternative etiologies:* the presence of a PFO, even one with high-risk features, does not prove its causative effect of cryptogenic strokes. Hence, the diagnosis of a PFO-related stroke is one of elimination. Excluding other common causes of stroke is crucial for rational use of PFO closure. Although some alternative embolic stroke etiologies such as AF are common and are typically screened for in most patients before the procedure, others are less familiar to most clinical cardiologists. For example, intraplaque hemorrhage (IPH) is an under-recognized but well-documented cause of ischemic stroke that is not usually considered by cardiologists (**Figures 5 and 6**). Patients with IPH may have nonocclusive carotid disease as well as a PFO. Many of the ischemic events in these patients would have been considered PFO-related if the treating physician is unfamiliar with IPH or had not

TABLE 1 Opportunities for Heart-Brain Team Collaboration in the American Academy of Neurology Guidelines

In patients being considered for PFO closure, clinicians should obtain brain imaging to confirm stroke size and distribution, assessing for an embolic pattern or a lacunar infarct (typically involving a single deep perforator, <1.5 cm in diameter) (Level of Evidence: B).
In patients being considered for PFO closure, clinicians should obtain complete vascular imaging (MRA or CTA) of the cervical and intracranial vessels to look for dissection, vasculopathy, and atherosclerosis (Level of Evidence: B).
Before undergoing PFO closure, patients should be assessed by a clinician with expertise in stroke to ensure that the PFO is the most plausible mechanism of stroke (Level of Evidence: B).

CTA = computed tomography angiography; MRA = magnetic resonance angiography; PFO = patent foramen ovale.

FIGURE 5 Magnetic Resonance Imaging of Carotid Intraplaque Hemorrhage



(A and B) Axial fluid attenuation inversion recovery (FLAIR) images showing chronic left-side infarcts of the frontal and parietal cortex and the centrum semi-ovale **(arrows)**. **(C)** 3-dimensional reformatted image of a contrast-enhanced magnetic resonance angiography demonstrates a nonstenotic plaque in the distal left common carotid artery **(between arrows)** with a small focal ulceration **(dashed arrow). (D)** Axial fat saturated T_1 cube showing the lipid-rich necrotic core in the plaque. **(E)** Axial Magnetization Prepared-Rapid Gradient Echo image (MPRAGE) shows superimposed hemorrhage in the lipid core; the ulceration **(curved arrow)** is better demonstrated on the MPRAGE sequence. The lumen **(asterisk)** is preserved, without significant narrowing. Reproduced with permission from Alkhouli M, Holmes D, Klaas JP, Lanzino G, Benson JC. Carotid intraplaque hemorrhage: an underappreciated cause of unexplained recurrent stroke. *J Am Coll Cardiol Intv.* 2021;14(17):1950-1952. https://doi.org/10.1016/j.jcin.2021.04.033.

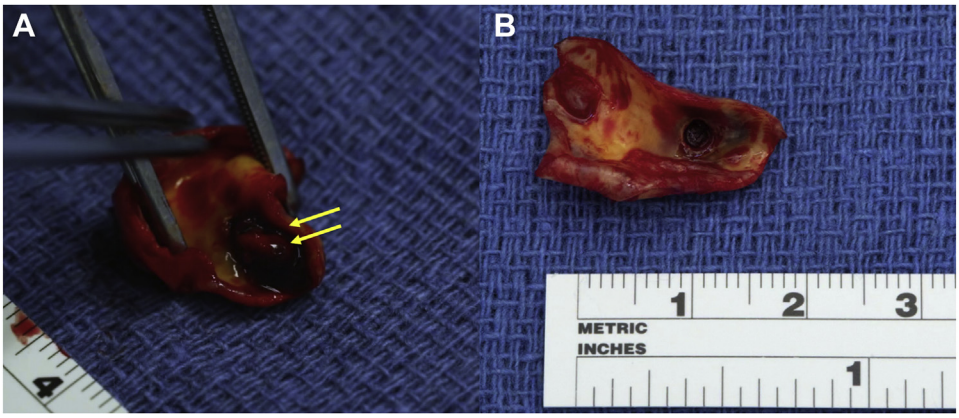
considered it as a possible stroke mechanism. Joint heart-brain assessment would ensure that this and other less common causes of stroke (eg, intracranial atherosclerosis, vasculitis, fibromuscular dysplasia, vascular spasm, arterial dissection, and so on) are considered before recommending PFO closure.

Once the stroke is phenotyped and the PFO is believed to be causal, shared-decision making is then undertaken with the patient weighing the attributable risks of concomitant risk factors (eg, hypertension, PFO, and so on) in the studied population and the risks and benefits of medical therapy and/or device closure.

PROCEDURAL STROKES

Acute ischemic strokes complicate ~1% of percutaneous coronary interventions (PCI) and 1%-2% of TAVRs.[6,89,90] Unfortunately, these events are associated with substantial morbidity and mortality. In large U.S. cohort studies, ischemic stroke after PCI or TAVR was associated with a 2-4-fold increase in short-term mortality.[6,89-91] In addition, despite the advances in transcatheter technology, the incidence

FIGURE 6 **Gross Anatomy of Carotid Intraplaque Hemorrhage**



Carotid plaque **(A)** with an associated internal hemorrhage **(B)** during endarterectomy. The **yellow arrows** indicate the intramural thrombus. Reproduced with permission from Alkhouli M, Holmes D, Klaas JP, Lanzino G, Benson JC. Carotid intraplaque hemorrhage: an underappreciated cause of unexplained recurrent stroke. *J Am Coll Cardiol Intv.* 2021;14(17):1950-1952. https://doi.org/10.1016/j.jcin.2021.04.033.

of postprocedural stroke has not decreased over time, raising major concerns in the field.[90] The growing issue of neurological complications of transcatheter procedures represent an opportunity for partnership between neurologists and cardiologists to address several open questions:

1. Should a neurologist-led evaluation be implemented in high-risk cases given the discrepancies in reported stroke rates between studies mandating/not mandating routine neurological assessments?
2. Should we be concerned about subclinical "silent" strokes considering the growing literature on their negative impact on cognitive function and long-term outcomes?
3. What is the role of routine cerebral embolic protection (CEP) with TAVR? Do all TAVR strokes occur because of intraprocedural catheter manipulations (**Figure 7**)? Are there neurological sequalae to the use of the CEP themselves? Can CEP be useful in all-comers, or should it be used judiciously in selected patients?[92-94]
4. What are the pathological features of postprocedural strokes? Are embolic materials in this context amenable to thrombolysis or mechanical thrombectomy?[7,95]

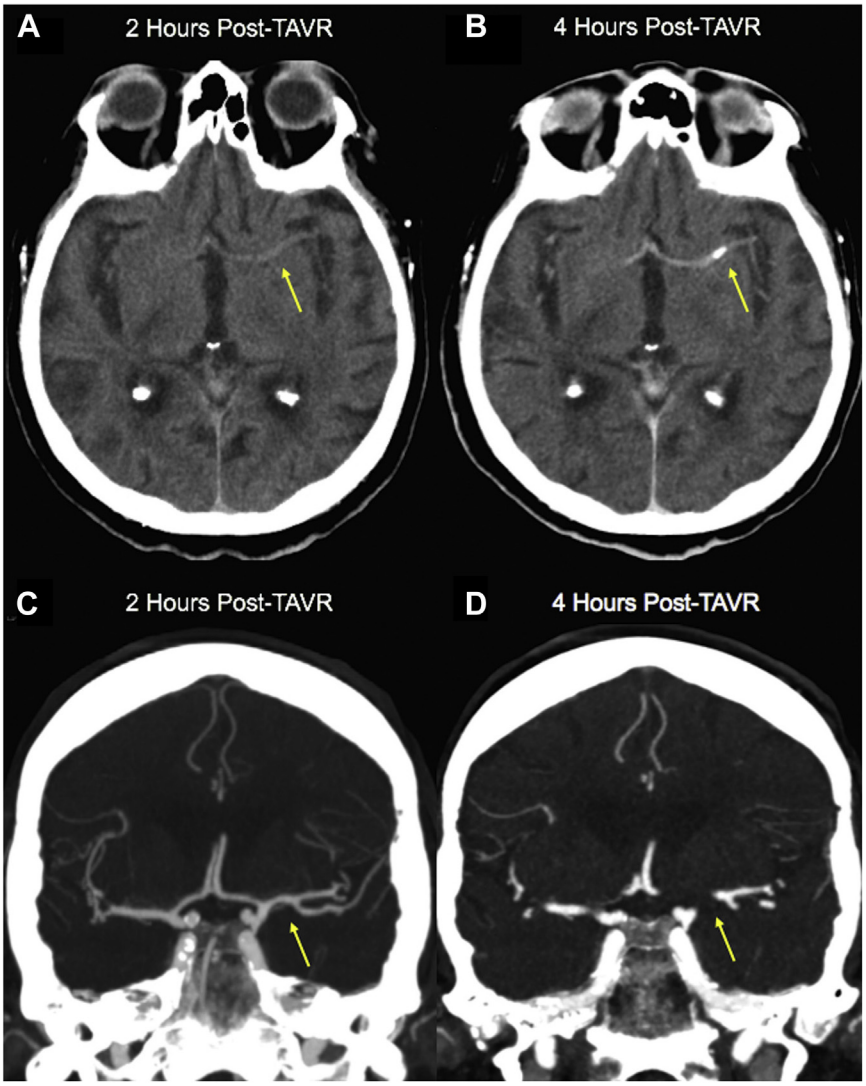
MANAGEMENT OF ACUTE ISCHEMIC STROKE

MEDICAL TREATMENT. Patients admitted with ischemic stroke typically have an enormous burden of cardiovascular comorbidities that confer a higher risk of in-hospital adverse events.[27,96,97] In addition, stroke is associated with major alterations in ANS and hemodynamics that may provoke atrioventricular block, AF, ventricular tachycardia, and acute myocardial infarction. Studies have shown that serious cardiac arrythmia and myocardial infarction complicate 25% and 2% of ischemic strokes, respectively.[9,96] This perplexes the acute management of stroke and emphasizes the need for an integrated team approach to address these challenges (**Table 2**).

MECHANICAL THROMBECTOMY. Endovascular mechanical thrombectomy (MT) has established its position as a key element of stroke care in contemporary practice.[98,99] However, whether to leverage the technical skills and the existing extensive catheterization laboratory infrastructure to facilitate timely provision of MT to all potential candidates remains an area of ongoing debate.[100-106] Implementation of the "interventional" heart-brain team is evidently more complicated than a "noninterventional" heart-brain team, and requires deliberate assessment of the following key questions:

Are the current systems and processes for acute stroke care adequate to accommodate the growing needs for endovascular interventions both in developed and in developing countries? If not, will there be a need for incorporating interventional cardiologists and established primary PCI centers in the stroke workforce? Will it increase patient access and improve overall outcomes, and what training, credentialing, and quality metric issues need to be considered? Are MT outcomes already optimized, or

FIGURE 7 Illustration of Post-TAVR Acute Ischemic Stroke Not Caused by Intraprocedural Embolization



Computed tomographic imaging illustrating the interval development of acute occlusion of the middle cerebral artery following transcatheter aortic valve replacement. **(A and B)** Computed tomography and computed tomographic angiography imaging at 2 hours after TAVR showing a patent middle cerebral artery. **(C and D)** Computed tomography and computed tomographic angiography at 4 hours after TAVR showing occlusion of the M1 segment of the middle cerebral artery. **Arrows** refer to the occluded segment of the middle cerebral artery. Reproduced with permission from Alkhouli et al.[95] TAVR = transcatheter aortic valve replacement.

is there room for improvement? Can the blending of the immense and diverse experiences that exist in each specialty lead to breakthrough innovations that would further revolutionize the management of stroke?

Open discourse to address these questions is important to identify opportunities for further improvement in acute stroke both in research and in clinical care.

THE HEART-BRAIN CLINIC: CHALLENGES AND OPPORTUNITIES

Potential impediments to the implementation of heart-brain teams are the unfamiliarity with the concept and its value, the limited dedicated resources, the complexities associated with the multifaceted care of cardiac patients, and the structure of subspecialization in cardiology and neurology. To

TABLE 2 The Role of the Heart Brain Team in the Medical Management of Acute Ischemic Stroke

Identify optimal blood pressure targets accounting for stroke subtype and cardiovascular comorbidities.
Assess candidacy and timing of surgery for patients who experience an acute ischemic stroke caused by endocarditis or large mobile intracardiac thrombi.
Evaluate the risks and benefits of invasive vs conservative approaches to acute myocardial infarction considering the underlying cause of ischemia, the risk of intracranial bleeding, and the likelihood of functional recovery.
Determine the appropriate work-up and treatment of known or newly diagnosed bradyarrhythmias and tachyarrhythmias weighing the hemodynamic impact and potential side effects of various antiarrhythmic medications.

mitigate these issues, a stepwide approach could be used.

First, adoption of the heart-brain concept needs to start in training. Medical students should be encouraged to approach the abstract knowledge on the interactions between the heart and the brain in the context of their clinical manifestation. Cross training among medicine and neurology trainee should become routine in residency programs.[107] A basic level of understanding of the heart-brain connections and their potential therapeutic implications can be achieved via well-designed multidisciplinary rotations that can be integrated in current training structures. Opportunities for advanced training in sophisticated areas (eg, neuromodulation) can be sponsored by key stakeholders and offered to individuals with further interest. Second, professional societies can leverage existing collaborations to lead the effort of bringing together the 2 specialties with initiatives that incorporate education, research, and practice. Third, although the previously mentioned strategies are being developed for the long-term advancement of the heart-brain field, individual institutions could use their current resources to initiate a disease-focused heart-brain team (eg, heart-brain clinic for stroke care). This infrastructure can then be then expanded to include larger and more comprehensive teams that can address the growing needs of our complex patients.

CONCLUSIONS

There is a growing recognition of the role of the heart-brain team in advancing knowledge and care of many cardiac and neurological diseases. In the case of stroke, a heart-brain team approach can leverage the neurologist's expertise in neuroanatomy, neurophysiology, and brain imaging and the cardiologist's knowledge in arrhythmias, vascular disease, and structural heart defects to advance the science and transform clinical care.

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