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Stroke in Children With Cardiac Disease: Report From the International Pediatric Stroke Study Group Symposium

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Abstract

BACKGROUND—Cardiac disease is a leading cause of stroke in children, yet limited data support the current stroke prevention and treatment recommendations. A multidisciplinary panel of clinicians was convened in February 2014 by the International Pediatric Stroke Study group to identify knowledge gaps and prioritize clinical research efforts for children with cardiac disease and stroke.

RESULTS—Significant knowledge gaps exist, including a lack of data on stroke incidence, predictors, primary and secondary stroke prevention, hyperacute treatment, and outcome in children with cardiac disease. Commonly used diagnostic techniques including brain computed tomography and ultrasound have low rates of stroke detection, and diagnosis is frequently delayed. The challenges of research studies in this population include epidemiologic barriers to research such as small patient numbers, heterogeneity of cardiac disease, and coexistence of multiple risk factors. Based on stroke burden and study feasibility, studies involving mechanical circulatory support, single ventricle patients, early stroke detection strategies, and understanding secondary stroke risk factors and prevention are the highest research priorities over the next 5-10 years. The development of large-scale multicenter and multispecialty collaborative research is a critical next step. The designation of centers of expertise will assist in clinical care and research.

CONCLUSIONS—There is an urgent need for additional research to improve the quality of evidence in guideline recommendations for cardiogenic stroke in children. Although significant barriers to clinical research exist, multicenter and multispecialty collaboration is an important step toward advancing clinical care and research for children with cardiac disease and stroke.

Keywords

cardiac; stroke; arterial ischemic; congenital heart disease

Introduction

Children with congenital and acquired cardiac disease are at an increased risk of arterial ischemic stroke (AIS). The risk varies depending on age, comorbidities, underlying cardiac diagnosis, and factors that can vary over time, including changing hemodynamics, new cardiac procedures, and/or the need for mechanical circulatory support devices. Children

with particular cardiac lesions, such as single ventricle physiology and cardiomyopathy appear to be at greater risk. In spite of the increased risk of stroke in children with heart disease, diagnosis is frequently delayed, and high-level evidence on prevention and treatment of stroke in this group is lacking. In combination with other factors that influence neurological outcome, including other cardiac-related brain injury, stroke in this population leads to significant morbidity and mortality. The International Pediatric Stroke Study group organized a symposium in 2014, comprising pediatric subspecialists in neurology, cardiology, hematology, and critical care medicine, to address stroke in this vulnerable population. The aims of the meeting were as follows: to foster multidisciplinary collaboration, to review current knowledge, to identify important gaps in knowledge, and to outline priorities for further research. This report summarizes the findings and recommendations from the symposium.

Current knowledge and knowledge gaps

Incidence—Stroke has been associated with both congenital and acquired heart disease in children. Congenital heart disease occurs in 4-10 per 1000 live births.[1] Approximately 85% of patients survive into adult life and within this decade, in North America, approximately 1 in 150 adults are expected to have some form of congenital heart disease.[2] Although stroke has been associated with most types of cardiac disease, those with cyanotic and complex congenital heart disease appear to be at greatest risk.

Reported incidence rates for stroke in children with cardiac disease are primarily based on single- or dual-center studies. These data are summarized in Table 1. There is considerable variability in reported rates, and caution should be used when interpreting studies because of limitations related to small sample size, non-population-based data, variable stroke definitions, ascertainment bias, and variability in the definition of cardiac disease. Also as indicated in the table, some studies considered AIS independently, whereas others looked at combined rates of AIS and other neurological injury such as hemorrhagic stroke and cerebral sinovenous thrombosis.

Hoffman et al.[3] estimated the overall incidence of AIS in children with cardiac disease based on a cohort in the Intermountain Pediatric Stroke Database, United States. Their reported incidence rate was 132 of 100,000 per year, which is dramatically higher than the general incidence of AIS in children of 2-8 of 100,000 per year.[4-6] Among cohorts of neonates and children with AIS, the prevalence of cardiac disease ranges from 10%-31%[6-13]; however, studies varied as to whether they included isolated patent foramen ovale (PFO) as a cardiac disease. In the vast majority of patients, cardiac disease is known before the onset of stroke. In the International Pediatric Stroke Study cohort, Dowling et al.[13] found that children with cardiac disease and AIS tended to be younger at presentation and were more likely to have strokes in a “cardioembolic stroke pattern,” defined as strokes that were multiple, bilateral, and involved both the anterior and posterior circulations, compared with those with AIS and no cardiac disease. A higher rate of hemorrhagic transformation was also seen in those with AIS and cardiac disease.[14] The increased rate of hemorrhagic transformation may be related to the underlying embolic mechanism or the greater prevalence of anticoagulation therapy at the time of stroke in children with cardiac disease.

Children with mechanical circulatory support devices including extracorporeal membrane oxygenation (ECMO) and ventricular assist devices (VADs) are at particularly high risk of stroke. Neurological dysfunction, most commonly ischemic stroke, occurred in 29% and was the leading cause of death or withdrawal of care in the pediatric Berlin Heart EXCOR trial.[15,16] Comparison of VAD-supported patients versus ECMO-supported patients requires caution. Published data on stroke prevalence in ECMO cohorts (including the ECMO comparator group in the Berlin EXCOR VAD cohort) come from the Extracorporeal Life Support Organization registry, which is based on voluntary reporting from centers with widely varying approaches to diagnosis and classification of events, and without central adjudication. The published data on stroke prevalence in the Berlin Heart EXCOR VAD cohort are more reliable because neurological event ascertainment was mandated, centrally defined, and adjudicated. Moreover, there is a shorter exposure period for stroke risk in a patient on ECMO, because ECMO duration is typically <14 days compared with VAD duration, which typically exceeds 30 days. Although the prevalence of stroke on ECMO (7-11%) appears to be lower than the prevalence on the EXCOR (29%), the incidence rate of stroke on ECMO (1-2 events per 100 days of support)[17] is significantly higher than on EXCOR events per 100 days of support).[16] Adult VADs, such as the Heartware HVAD (Heartware, Framingham, MA) and Heartmate II left VAD (Thoratec, Pleasanton, CA), used widely in adolescent heart failure patients appear to have a significantly lower risk of stroke (6-12%) based on small pediatric studies.[18]

Diagnosis/diagnostic delay

Prompt stroke diagnosis is critical for the initiation of neuroprotective care and secondary stroke prevention and for close monitoring of stroke complications. However, the diagnosis of AIS in children is frequently delayed.[19] Children with cardiac disease appear to be no exception, despite many of these strokes occurring in children who are already hospitalized at the time of the stroke.

A number of factors may lead to delays in diagnosis. Prolonged postsurgical sedation, pharmacologic paralysis, and/or anesthesia may mask symptoms associated with stroke and reduce reliability of clinical detection. More commonly appreciated signs of stroke, such as acute hemiparesis, are often lacking in the neonatal period and early infancy, and this is a common time for cardiac surgery. Seizures are a common presenting feature of childhood stroke,[20-22] and lack of awareness of this may delay diagnosis. Obtaining definitive neuroimaging in children with complex cardiac disease postoperatively is challenging given potential hemodynamic instability. Cardiac anesthesia is usually required for patient safety and monitoring when performing MRI of the brain. Permanent or temporary pacing wires and/or mechanical circulatory support devices are contraindications to MRI. Cranial ultrasound is frequently relied on for screening of intracranial events including stroke because of its noninvasive nature and bedside facility. Yet, in infants with AIS, it is known that cranial ultrasound misses the diagnosis of stroke in up to two-thirds of cases.[23,24] Head computed tomography is usually obtained when MRI cannot be safely performed; however, 50%-80% of strokes eventually detected on MRI are missed on initial head computed tomography.[19,25]

Limited family and health practitioner awareness of the risk of stroke in children with cardiac disease is another factor that may lead to delays in diagnosis. Anecdotally, families report not having been aware that children with complex cardiac disease are at increased risk of stroke. Health practitioners may be reluctant to burden families with this information given the already complex medical situations that many of these children face. There may also be a lack of awareness of the common presenting features of stroke in children amongst parents and health practitioners.

Stroke mechanisms and risk factors

Approximately one-quarter to one-third of children with cardiac disease and stroke have their stroke in the peri-procedural period related to cardiac surgery or other cardiac interventions.[13,26] The remainder occurs spontaneously. Multiple stroke risk factors often exist for an individual child with cardiac disease. Cardioembolic stroke may be because of mural thrombus in a dyskinetic atrium or ventricle, clot formation or vegetation on an abnormal heart valve, or from paradoxical embolism in the presence of right to left shunting or a univentricular heart. In children with cardiac disease, intracardiac thrombus is rarely identified on echocardiography after an AIS event.[11]

The propensity to thrombosis in an individual child with cardiac disease can vary over time. Virchow's Triad describes three broad variables that contribute to thrombosis: alterations in blood flow, injury to the vessel wall, and alterations in blood components. In the setting of cardiac disease, some or all of these factors may be at play (Figure).[27,28]

Genetic and acquired thrombophilias (prothrombotic disorders) have been reported to occur at a greater frequency in children with cardiac disease and stroke compared with age-matched healthy controls.[7] Specific abnormalities include elevated lipoprotein (a), protein C deficiency, anticardiolipin antibodies, and combined prothrombotic disorders among others. Based on pooled data from 1764 children with stroke due to AIS or cerebral sinovenous thrombosis from all causes and 2799 control children, the odds ratios for index AIS is increased 1.5-9 times in children with a single prothrombotic disorder and by 12-fold in children with two or more abnormalities.[29] Practices vary regarding testing for thrombophilias. More research is required in this area to determine whether screening for a thrombophilia before cardiac surgery could reduce the risk of stroke through selective administration of more intensive perioperative anticoagulation. Primary stroke prevention in children with cardiac disease and thrombophilia undergoing procedures would lend itself well to a multicenter collaborative study.

In spite of numerous refinements over the years optimizing safety and morbidity from cardiopulmonary bypass, stroke risks persist secondary to microembolism and macroembolism of particulate (including thrombotic) and gaseous material. Given that oxygenated blood is delivered directly to the (cannulated) aorta, emboli originating in the bypass circuit can enter the cerebral circulation directly thereby bypassing the normal pulmonary filtration mechanism. Also, children with prolonged surgery, hypoperfusion, or cardiac arrest can have watershed pattern strokes. There is overlap in the neuroimaging features between watershed pattern and arterial occlusive stroke.[30] Differentiating "white matter injury" from arterial occlusive stroke can also be challenging. Detailed neuroimaging

analysis employing a uniform classification system across a large and diverse group of children with cardiac disease and stroke is lacking.

In neonates and infants with surgically treated congenital heart disease, numerous studies have examined the preoperative and postoperative risk factors for MRI-ascertained brain injury, including stroke.[31-39] Risk factors across studies vary and most report on brain injury as a whole, including white matter injury—the most common form of brain injury in infants with congenital heart disease.[34,35,37] In one single-center study of children undergoing cardiac surgery with bypass, reoperation was independently associated with an increased risk of stroke.[40] In another study, significant risk factors for stroke were as follows: lower birth weight, preoperative intubation, lower intraoperative hematocrit, and higher blood pressure at admission to the cardiac intensive care unit post-operatively.[31] However, the preceding studies employed varying age groups (all pediatric versus only neonates/infants) and stroke definitions (clinical versus silent). Recent studies suggest that in infants with congenital heart disease, brain structure and metabolism are relatively immature compared with other infants. This may be one explanation for the increased propensity to brain injury that is seen in children with congenital heart disease.[34] There have been contradictory findings as to whether ballon atrial septostomy is an independent risk factor for preoperative stroke.[34-37,39] Block et al.[35] found that ballon atrial saptostomy was significantly associated (relative risk, 4; 95% confidence interval, 1.5-9.3) with preoperative stroke in infants with transposition of the great arteries. This remains an important issue because in practice the use of prophylactic anticoagulation during ballon atrial septostomy is another area that would benifit from a standardized protocol or clinical trial.

There are limited data on stroke recurrence in children with cardiac disease. In a single-center longitudinal study of 135 neonates and children, the risk of stroke recurrence was 27% at 10 years by competing risk analysis.[26] The recurrence risk was highest in the period immediately following the sentinel stroke and decreased with time. Neonates were at similar risk to older children for stroke recurrence, which is quite different than neonatal stroke without cardiac disease, where recurrence risk is very low.[41] Half of the children with a recurrence had a stroke while they were not receiving therapeutic anticoagulation or antiplatelet agents. Predictors of recurrent stroke included the presence of a mechanical valve, a prothrombotic condition (including genetic and acquired thrombophilias/ prothrombotic states, e.g., factor V Leiden gene mutation, protein C/S deficiency, presence of indwelling catheter, and protein losing enteropathy) and an acute infection at the time of the sentinel stroke.[26]

Cerebral vasculopathy is identified in a significant proportion of children with cardiac disease.[11,13] In the International Pediatric Stroke Study cohort, cerebral vasculopathy was present in 25.8% of children with cardiac disorders compared with 52.1% of those without cardiac disorders.[13] However, the International Pediatric Stroke Study data are not population-based and vasculopathy frequently coexisted with cardiac disease as part of an associated underlying genetic syndrome. Syndromes with both cardiac disorders and cerebral vasculopathy include Down syndrome, William syndrome, neurofibromatosis type I, Posterior fossa brain malformations, Hemangiomas, Arterial abnormalities, Cardiac anomalies and Coarctation of the aorta, Eye abnormalities, Alagille syndrome, and rarely

Noonan syndrome. The associated vasculopathy may be steno-occlusive, typically moyamoya like, or may manifest with increased tortuosity or increased frequency of congenital/developmental variants (e.g., fetal posterior cerebral artery, hypoplasia of A1 segment of the anterior cerebral artery).

Improved knowledge of the risk factors and mechanisms of stroke in children with cardiac disease is critical for successful preventative strategies. To date, relatively low patient numbers and the heterogeneous nature of the population have hindered studies. Analysis based on a very large multicenter database with standardized collection of data would be required to define more precisely the risk factors for stroke in this population.

Treatment and review of recommendations in published guidelines

Current guidelines for prevention and treatment of stroke in children with cardiac disease.[28,42,43] are based on a low level of evidence in spite of the fact that the volume of cited papers in these guidelines has risen significantly overtime. Most recommendations are based on expert consensus. There is an urgent need for additional research to improve the quality of evidence and confidence in guideline recommendations.

Recent guidelines with recommendations on treatment of cardioembolic stroke in children are summarized (Table 2). Differences in antithrombotic treatment recommendations exist between the American College of Chest Physicians, Antithrombotic therapy in Neonates and Children guidelines, and the American Heart Association scientific statement on the *Management of Stroke in Infants and Children*.[42,43] Results from the International Pediatric Stroke Study, 2003-2007, found that 52% of children with stroke and cardiac disease received anticoagulation at some point in their poststroke care; however, 25% of children received no antithrombotic therapy.[44]

The recommendations for closure of isolated PFO in the setting of AIS in children also differ between the two guidelines. This clinical situation is particularly challenging for physicians. Although studies in young adults have suggested a role for isolated PFO as a risk factor for stroke, further research is required in children.[45] Recent randomized trials in adults have not demonstrated benefit for percutaneous closure of PFO compared with medical therapy alone for prevention of recurrent transient ischemic attack or stroke.[46-48] Although it is possible that children may benefit differently from percutaneous PFO closure, there is currently no evidence to support this idea and replicating these PFO closure trials in children is probably not possible because of sample size limitations.

The published guidelines conclude that there are insufficient data from which to make recommendations regarding hyperacute stroke treatments such as tissue plasminogen activator (tPA) or endovascular therapy because of the lack of evidence in children. Unfortunately, a safety and dose finding study for tPA in pediatric stroke was recently closed because of lack of patient accrual. The Thrombolysis in Pediatric Stroke trial included children 2-17 years with stroke of all types and required confirmation of a partial or complete cerebral vessel occlusion to be eligible for thrombolysis.[49] In spite of significant pediatric stroke expertise at the study sites, there were many challenges including the following: the need for continuous 24-hour availability of acute stroke teams for children

and 24/7 sedated neuroimaging capability.[50] The challenges in a cardioembolic stroke treatment trial might be slightly different, but clearly the Thrombolysis in Pediatric Stroke Study showed how difficult it is to mount a stroke-related clinical trial in children.

Hyperacute treatments such as tPA and thrombectomy therefore remain off-label treatments in children. However, there are reports of their use, including in children with cardiac disease.[51-53] Systematic reporting in a central registry of patients receiving off-label use of these hyperacute treatments would be beneficial.

Recommendations for primary prevention of thrombosis in children with heart disease are provided in the American Heart Association Prevention and Treatment of Thrombosis in Pediatric and Congenital Heart Disease guidelines.[28] A special focus has been placed on the Fontan population, a challenging and high-risk group. The recommendations for prevention of clinically evident systemic thrombosis (and possibly stroke) in children following Fontan procedure have been informed by one randomized controlled trial. Monagle et al.[54] performed a multicenter randomized trial comparing aspirin to heparin or a vitamin K antagonist in prevention of thrombosis following Fontan procedure. The overall rate of thrombosis (venous or arterial and symptomatic or detected on routine echocardiography) was 19% at 2 years with no significant difference between the aspirin and the heparin/vitamin K antagonist groups. However, this study was relatively underpowered (111 children were randomized). In addition, no clinical stroke events were observed, and routine neuroimaging was not included in the study protocol. There remains a need for large multicenter trials of antithrombotic agents in pediatric patients with cardiac disease for both clinical and silent stroke outcomes. In addition, because this study evaluated patients up to 2 years post-Fontan, by study design, stroke in the very late postoperative period was not evaluated. In a 2005 retrospective review of risk factors for cerebrovascular events following Fontan procedure, the use of aspirin or aspirin and/or warfarin, compared with no antithrombotic therapy was associated with a significantly decreased risk of cerebrovascular events.[55] No significant difference was seen in comparing aspirin with anticoagulation. A more recent study of thrombotic complications (intravascular thrombosis, cardioembolic strokes, or pulmonary embolism) at different stages of single ventricle palliation has shown a trend toward potential benefit of warfarin as thromboprophylaxis.[56] AIS has, however, been reported in children up to 5-9 years[57-59] following the Fontan procedure in spite of prophylaxis with either aspirin or warfarin, and clinical practice varies both within and among centers. The ongoing long-term risk of stroke in this population poses a significant challenge in prevention studies.

The recommendations for primary prevention of thrombosis and stroke in other groups of children with cardiac disease are also based on a low level of evidence. In children with a VAD, where there is a particularly high risk of stroke, multiple antithrombotic agents are used concurrently to prevent thrombosis.[15]

Neurodevelopmental outcomes in congenital heart disease

Neurodevelopmental abnormalities described in children with congenital heart disease include developmental delay,[60-62] intellectual disability,[33] behavioral problems,[63] socialization problems,[64] and functional limitations.[65] A variety of pre- and post-operative

factors are thought to increase the risk of these problems including the type of cardiac lesion,[66] preoperative hypoxia,[64] low pH,[67] age at surgery,[65] palliative versus corrective operative procedure,[62] deep hypothermic cardiac arrest,[68] and length of cardiac intensive care unit stay.[65]

More recent studies have described the temporal and anatomic lesion patterns associated with various types of brain injury including stroke in infants with cyanotic forms of congenital heart disease.[35,37,69] However, there are limited data exploring the relationship between the different patterns of brain injury and neurodevelopmental outcome.

Priorities for research and quality improvement: challenges and opportunities

Significant gaps exist in our current knowledge regarding stroke in children with cardiac disease. Ideas for future research were identified and are summarized in Table 3. The development of a large multicenter registry and a multicenter transdisciplinary collaborative network was recognized as a priority for any future research.

A multicenter collaboration with centralized review of neuroimaging in children with cardiac disease and stroke would be helpful for improving understanding of types, timing, mechanisms, and evolution of brain injury in this population and how they these factors to neurodevelopmental outcomes. It would be beneficial to establish minimum neuroimaging requirements to detect ischemic or hemorrhagic brain injury. Guidelines would need to take into account the imaging requirements of varied clinical scenarios. For example, the clinical decision making, and hence the imaging needs, for the child on a VAD with acute new hemiparesis would be quite different from those of an infant with complex congenital heart disease with subclinical seizures detected on video electroencephalography on Postoperative day 1. In the first case, a very narrow time window for hyperacute reperfusion intervention (e.g., thrombectomy) and the unavailability of MRI would dictate the choice of imaging. In the second case, a role for hyperacute reperfusion intervention is not likely and the priority might more appropriately be placed on treating status epilepticus. MRI would be the preferred imaging modality to definitively characterize the basis for the neurological symptoms for the purposes of making decisions about ongoing intensive care unit supportive care, secondary stroke prevention, and prognosis. Although a consensus was not reached at the symposium regarding the minimum MRI dataset for children with acute cardiac stroke, diffusion weighted imaging, a blood sensitive sequence such as susceptibility-weighted imaging, T1 and T2 sequences, and time of flight magnetic resonance angiography should be strongly considered.

Bedside neuromonitoring strategies, for example with near infrared spectroscopy, continuous electroencephalography (cEEG) and transcranial Doppler ultrasound may hold some promise for early detection of stroke or cerebral emboli in high-risk patients such as those undergoing cardiac surgery. The advantage of these diagnostic modalities is that they can be performed at the bedside in the cardiac intensive care unit or the operating room, and their use may inform decisions about the need for neuroimaging. A systematic review in 2012 found that there has been insufficient research to date to determine whether cEEG, transcranial Doppler ultrasound, or near infrared spectroscopy as neuromonitoring strategies may improve neurological outcome in infants undergoing cardiac surgery.[70] These

neuromonitoring strategies, including cEEG, are currently used in some centers, and a multicenter study of cEEG for early stroke detection was proposed at the symposium.

The critical challenges for clinical trials in pediatric cardiac disease are sample size and the heterogeneity of the population in terms of patient age and cardiac diagnosis. Both factors would be addressed by conducting collaborative research across a large multicenter network. The grouping of children with similar diagnoses and the utilization of adaptive trial designs to maximize sample size are potentially useful strategies.[71] The Berlin Heart EXCOR Pediatric trial is one example of a successful trial in a particularly complex group of children with cardiac disease,[15] hopefully paving the way for future clinical trials.

Along with sample size and population heterogeneity, a number of other challenges exist for conducting trials in this population. Individual centers become familiar with their own clinical practice, leading to a reluctance to change and randomize away from their “comfort zone.” Newer anticoagulant and antiplatelet agents lack pharmacokinetic data and pediatric drug formulations for pediatric dosing, although some pediatric pharmacokinetic trials are underway. The new antithrombotic agents may hold promise, but efficacy and comparison data of aspirin, heparin, and warfarin/vitamin K antagonist for primary and secondary prevention of stroke and transient ischemic attack in childhood remain limited. Furthermore, the irreversible and rapid-onset anticoagulant effects of oral direct thrombin inhibitors may pose excess risk for children where the risk of bleeding is increased and the need for urgent reversal may be present, especially in the toddler years when the risk of falls is high.

Measuring neurological outcome in children with cardiac disease poses a number of challenges and makes clinical trial design more difficult. Only one measure of neurological outcome is specifically validated for pediatric stroked—the Pediatric Stroke Outcome Measure.[72] However, in pediatric stroke studies many different outcome measures have been used. Consensus outcome measures for pediatric stroke research would improve the ability to compare groups between and across studies.[73] Differentiating outcomes related to stroke versus other neurological injury related to cardiac disease also poses a challenge. The high rate of pre-existing brain injury or genetic syndromes in children with congenital heart disease necessitates baseline neurological assessments to better interpret end point/outcome measurements. However, baseline neurological assessments may be difficult to obtain because of resource constraints or critical illness. The American Heart Association scientific statement, “Neurodevelopmental Outcomes in Children with Congenital Heart Disease: Evaluation and Management”, makes a suggestion that periodic developmental surveillance, screening, evaluation, and re-evaluation throughout childhood may enhance identification of neurodevelopmental deficits.[74] Ideally, stroke studies in this population should include long-term neurological follow-up of ≥5 years.

A key issue is defining “acceptable outcomes.” This was highlighted in the recent Berlin Heart EXCOR trial of a VAD for children with severe heart failure.[16] In this trial, the Food and Drug Administration and funding agencies required that the trial sponsor incorporate in the study design a definition for “acceptable” versus “unacceptable outcome”. This was particularly challenging considering that the alternative to use of a VAD in many children would have been death. As pediatric cerebrovascular disease independently remains one of

the top ten causes of mortality in children aged 1-18 years,[75] there are similar challenges in this population. Defining an “acceptable” outcome is a heavily value-loaded process in any particular clinical trial and in this very vulnerable population where the costs are high and the stakes are life and death. As such, arriving at these end point definitions might best be done through collaborations that include the study sponsors, regulatory agencies, treating providers as well as families, and the wider community. Recurrent stroke is an important outcome to identify; however, children with cardiac disease may have recurrent silent infarcts only detected on neuroimaging.[26] Follow-up neuroimaging should therefore be considered as research protocols are designed. Non-neurological outcomes, such as extracerebral bleeding related to anticoagulation, should also be sought.

Development of centers of expertise in pediatric cardiac disease and stroke treatment and prevention could improve standardization of practice and monitoring of outcomes. An ideal “center of expertise” would have multidisciplinary collaborations between pediatric experts in cardiology, vascular neurology/stroke, hematology, anesthesiology, perfusion, surgery, and critical care. Such centers could develop, follow, and periodically review adherence to clinical guidelines and update these as new evidence becomes available. Guidelines could be shared between centers and the International Pediatric Stroke Study could serve as a central repository. Routine multidisciplinary case management review at individual centers is recommended to highlight the relationships between practices and patient outcomes; this practice should optimize clinical care, add to interdivisional education, and enhance communication. Quality improvement efforts help to assure that best practices are implemented.

When making patient decisions in the absence of high-level evidence, collaboration and communication among pediatric cardiologists, neurologists, and hematologists to understand an individual’s cardiac physiology, thrombosis, and stroke risk is perhaps more critical than strict adherence to guidelines. Decisions in both the inpatient and outpatient settings require a multispecialty approach. Involvement of caregivers at all stages of decision making is also critical, and education of families and health practitioners regarding the increased risk and identification of stroke in children with cardiac disease is a priority. The International Pediatric Stroke Study and International Alliance for Pediatric Stroke could serve as repositories for educational resources regarding stroke in cardiac disease.

Conclusions

Multispecialty collaborations are a priority for both clinical care and research in pediatric cardiac stroke. Collaboration among pediatric neurologists, cardiologists, hematologists, and critical care physicians is crucial, and existing collaborations should expand to include neonatologists, cardiothoracic surgeons, and neuroradiologists. Laying the groundwork through collaborative effort is critical to address research priorities for children with cardiac disease. The International Pediatric Stroke Study group cardiac stroke symposium is an important start, and the publication of a joint summary of our current views demonstrates multidisciplinary alliance. The suggested immediate “next steps” to further research in this area are summarized in Table 4. Sustained collaborative efforts, both at an individual center

and multicenter level, will be required to advance clinical care and research priorities for neonates, infants, and children with cardiac disease and stroke.

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References

1. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. Circulation. 2014; 129:e28–e292. [PubMed: 24352519]
2. Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 Guidelines for the Management of Adults with Congenital Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease). Circulation. 2008; 118:e714–833. [PubMed: 18997169]
3. Hoffman JL, Mack GK, Minich LL, et al. Failure to impact prevalence of arterial ischemic stroke in pediatric cardiac patients over three decades. Congenit Heart Dis. 2011; 6:211–218. [PubMed: 21450034]
4. Fullerton HJ, Wu YW, Zhao S, Johnston SC. Risk of stroke in children: ethnic and gender disparities. Neurology. 2003; 61:189–194. [PubMed: 12874397]
5. Giroud M, Lemesle M, Gouyon JB, Nivelon JL, Milan C, Dumas R. Cerebrovascular disease in children under 16 years of age in the city of Dijon, France: a study of incidence and clinical features from 1985 to 1993. J Clin Epidemiol. 1995; 48:1343–1348. [PubMed: 7490597]
6. Mallick AA, Ganesan V, Kirkham FJ, et al. Childhood arterial ischaemic stroke incidence, presenting features, and risk factors: a prospective population-based study. Lancet Neurol. 2014; 13:35–43. [PubMed: 24304598]
7. Strater R, Vielhaber H, Kassenbohmer R, von Kries R, Gobel U, Nowak-Gottl U. Genetic risk factors of thrombophilia in ischaemic childhood stroke of cardiac origin. A prospective ESPED survey. Eur J Pediatr. 1999; 158:S122–125. [PubMed: 10650850]
8. Lanthier S, Carmant L, David M, Larbrisseau A, de Veber G. Stroke in children: the coexistence of multiple risk factors predicts poor outcome. Neurology. 2000; 54:371–378. [PubMed: 10668698]
9. Lee YY, Lin KL, Wang HS, et al. Risk factors and outcomes of childhood ischemic stroke in Taiwan. Brain Dev. 2008; 30:14–19. [PubMed: 17573220]
10. Lo W, Stephens J, Fernandez S. Pediatric stroke in the United States and the impact of risk factors. J Child Neurol. 2009; 24:194–203. [PubMed: 19182157]
11. Ganesan V, Prengler M, McShane MA, Wade AM, Kirkham FJ. Investigation of risk factors in children with arterial ischemic stroke. Ann Neurol. 2003; 53:167–173. [PubMed: 12557282]
12. Barnes C, Newall F, Furmedge J, Mackay M, Monagle P. Arterial ischaemic stroke in children. J Paediatr Child Health. 2004; 40:384–387. [PubMed: 15228568]
13. Dowling MM, Hynan LS, Lo W, et al. International Paediatric Stroke Study: stroke associated with cardiac disorders. Int J Stroke. 2013; 8:39–44. [PubMed: 23231361]
14. Rovira A, Grive E, Rovira A, Alvarez-Sabin J. Distribution territories and causative mechanisms of ischemic stroke. Eur Radiol. 2005; 15:416–426. [PubMed: 15657788]
15. Fraser CD Jr, Jaquiss RD, Rosenthal DN, et al. Prospective trial of a pediatric ventricular assist device. N Engl J Med. 2012; 367:532–541. [PubMed: 22873533]
16. Almond CS, Morales DL, Blackstone EH, et al. Berlin Heart EXCOR pediatric ventricular assist device for bridge to heart transplantation in US children. Circulation. 2013; 127:1702–1711. [PubMed: 23538380]

17. Almond CS, Singh TP, Gauvreau K, et al. Extracorporeal membrane oxygenation for bridge to heart transplantation among children in the United States: analysis of data from the Organ Procurement and Transplant Network and Extracorporeal Life Support Organization Registry. Circulation. 2011; 123:2975–2984. [PubMed: 21670232]
18. Cabrera AG, Sundareswaran KS, Samayoa AX, et al. Outcomes of pediatric patients supported by the HeartMate II left ventricular assist device in the United States. J Heart Lung Transplant. 2013; 32:1107–1113. [PubMed: 24002006]
19. Srinivasan J, Miller SP, Phan TG, Mackay MT. Delayed recognition of initial stroke in children: need for increased awareness. Pediatrics. 2009; 124:e227–234. [PubMed: 19620205]
20. Chadehumbe MA, Khatri P, Khoury JC, et al. Seizures are common in the acute setting of childhood stroke: a population-based study. J Child Neurol. 2009; 24:9–12. [PubMed: 18923086]
21. Singh RK, Zecavati N, Singh J, et al. Seizures in acute childhood stroke. J Pediatr. 2012; 160:291–296. [PubMed: 21911225]
22. Abend NS, Beslow LA, Smith SE, et al. Seizures as a presenting symptom of acute arterial ischemic stroke in childhood. J Pediatr. 2011; 159:479–483. [PubMed: 21429519]
23. Golomb MR, Dick PT, MacGregor DL, Armstrong DC, DeVeber GA. Cranial ultrasonography has a low sensitivity for detecting arterial ischemic stroke in term neonates. J Child Neurol. 2003; 18:98–103. [PubMed: 12693775]
24. Cowan F, Mercuri E, Groenendaal F, et al. Does cranial ultrasound imaging identify arterial cerebral infarction in term neonates? Arch Dis Child Fetal Neonatal Ed. 2005; 90:F252–256. [PubMed: 15846018]
25. McGlennan C, Ganesan V. Delays in investigation and management of acute arterial ischaemic stroke in children. Dev Med Child Neurol. 2008; 50:537–540. [PubMed: 18611205]
26. Rodan L, McCrindle BW, Manlhiot C, et al. Stroke recurrence in children with congenital heart disease. Ann Neurol. 2012; 72:103–111. [PubMed: 22829272]
27. Wolberg AS, Aleman MM, Leiderman K, Machlus KR. Procoagulant activity in hemostasis and thrombosis: Virchow's triad revisited. Anesth Analg. 2012; 114:275–285. [PubMed: 22104070]
28. Giglia TM, Massicotte MP, Tweddell JS, et al. Prevention and treatment of thrombosis in pediatric and congenital heart disease: a scientific statement from the American Heart Association. Circulation. 2013; 128:2622–2703. [PubMed: 24226806]
29. Kenet G, Lutkhoff LK, Albisetti M, et al. Impact of thrombophilia on risk of arterial ischemic stroke or cerebral sinovenous thrombosis in neonates and children: a systematic review and meta-analysis of observational studies. Circulation. 2010; 121:1838–1847. [PubMed: 20385928]
30. Gottesman RF, Sherman PM, Grega MA, et al. Watershed strokes after cardiac surgery: diagnosis, etiology, and outcome. Stroke. 2006; 37:2306–2311. [PubMed: 16857947]
31. Chen J, Zimmerman RA, Jarvik GP, et al. Perioperative stroke in infants undergoing open heart operations for congenital heart disease. Ann Thorac Surg. 2009; 88:823–829. [PubMed: 19699905]
32. Beca J, Gunn JK, Coleman L, et al. New white matter brain injury after infant heart surgery is associated with diagnostic group and the use of circulatory arrest. Circulation. 2013; 127:971–979. [PubMed: 23371931]
33. Mahle WT, Tavani F, Zimmerman RA, et al. An MRI study of neurological injury before and after congenital heart surgery. Circulation. 2002; 106:I109–114. [PubMed: 12354718]
34. Dimitropoulos A, McQuillen PS, Sethi V, et al. Brain injury and development in newborns with critical congenital heart disease. Neurology. 2013; 81:241–248. [PubMed: 23771484]
35. Block AJ, McQuillen PS, Chau V, et al. Clinically silent preoperative brain injuries do not worsen with surgery in neonates with congenital heart disease. J Thorac Cardiovasc Surg. 2010; 140:550–557. [PubMed: 20434174]
36. Petit CJ, Rome JJ, Wernovsky G, et al. Preoperative brain injury in transposition of the great arteries is associated with oxygenation and time to surgery, not balloon atrial septostomy. Circulation. 2009; 119:709–716. [PubMed: 19171858]
37. McQuillen PS, Barkovich AJ, Hamrick SE, et al. Temporal and anatomic risk profile of brain injury with neonatal repair of congenital heart defects. Stroke. 2007; 38:736–741. [PubMed: 17261728]

38. Bertholdt S, Latal B, Liamlahi R, et al. Cerebral lesions on magnetic resonance imaging correlate with preoperative neurological status in neonates undergoing cardiopulmonary bypass surgery. Eur J Cardiothorac Surg. 2014; 45:625–632. [PubMed: 24031043]
39. Beca J, Gunn J, Coleman L, et al. Pre-operative brain injury in newborn infants with transposition of the great arteries occurs at rates similar to other complex congenital heart disease and is not related to balloon atrial septostomy. J Am Coll Cardiol. 2009; 53:1807–1811. [PubMed: 19422989]
40. Domi T, Edgell DS, McCrindle BW, et al. Frequency, predictors, and neurologic outcomes of vaso-occlusive strokes associated with cardiac surgery in children. Pediatrics. 2008; 122:1292–1298. [PubMed: 19047248]
41. Fullerton HJ, Wu YW, Sidney S, Johnston SC. Risk of recurrent childhood arterial ischemic stroke in a population-based cohort: the importance of cerebrovascular imaging. Pediatrics. 2007; 119:495–501. [PubMed: 17332202]
42. Monagle P, Chan AK, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141:e737S–801S. [PubMed: 22315277]
43. Roach ES, Golomb MR, Adams R, et al. Management of stroke in infants and children: a scientific statement from a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young. Stroke. 2008; 39:2644–2691. [PubMed: 18635845]
44. Goldenberg NA, Bernard TJ, Fullerton HJ, Gordon A, deVeber G. Antithrombotic treatments, outcomes, and prognostic factors in acute childhood-onset arterial ischaemic stroke: a multicentre, observational, cohort study. Lancet Neurol. 2009; 8:1120–1127. [PubMed: 19801204]
45. Dowling MM, Ikemba CM. Intracardiac shunting and stroke in children: a systematic review. J Child Neurol. 2011; 26:72–82. [PubMed: 21212453]
46. Carroll JD, Saver JL, Thaler DE, et al. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. N Engl J Med. 2013; 368:1092–1100. [PubMed: 23514286]
47. Furlan AJ, Reisman M, Massaro J, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. N Engl J Med. 2012; 366:991–999. [PubMed: 22417252]
48. Wolfrum M, Froehlich GM, Knapp G, et al. Stroke prevention by percutaneous closure of patent foramen ovale: a systematic review and meta-analysis. Heart. 2014; 100:389–395. [PubMed: 23793373]
49. Hospital SCs. ClinicalTrials.gov [Internet]. National Library of Medicine (US); Bethesda (MD): 2000. Thrombolysis in Pediatric Stroke (TIPS). [cited 2014 Sept 7]. Available from: http://clinicaltrials. gov/show/NCT01591096. NLM Identifier: NCT01591096
50. Bernard TJ, Rivkin MJ, Scholz K, et al. Emergence of the primary pediatric stroke center: impact of the thrombolysis in pediatric stroke trial. Stroke. 2014; 45:2018–2023. [PubMed: 24916908]
51. Amlie-Lefond C, deVeber G, Chan AK, et al. Use of alteplase in childhood arterial ischaemic stroke: a multicentre, observational, cohort study. Lancet Neurol. 2009; 8:530–536. [PubMed: 19423401]
52. Alnaami I, Buchholz H, Ashforth R, et al. Successful use of Solitaire FR for stroke in a pediatric ventricular assist device patient. Ann Thorac Surg. 2013; 96:e65–67. [PubMed: 23992733]
53. Rhee E, Hurst R, Pukenas B, et al. Mechanical embolectomy for ischemic stroke in a pediatric ventricular assist device patient. Pediatr Transplant. 2014; 18:E88–92. [PubMed: 24646292]
54. Monagle P, Cochrane A, Roberts R, et al. A multicenter, randomized trial comparing heparin/warfarin and acetylsalicylic acid as primary thromboprophylaxis for 2 years after the Fontan procedure in children. J Am Coll Cardiol. 2011; 58:645–651. [PubMed: 21798429]
55. Barker PC, Nowak C, King K, Mosca RS, Bove EL, Goldberg CS. Risk factors for cerebrovascular events following Fontan palliation in patients with a functional single ventricle. Am J Cardiol. 2005; 96:587–591. [PubMed: 16098317]
56. Manlhiot C, Brandao LR, Kwok J, et al. Thrombotic complications and thromboprophylaxis across all three stages of single ventricle heart palliation. J Pediatr. 2012; 161:513–519. e513. [PubMed: 22513267]

57. Oski JA, Canter CE, Spray TL, Kan JS, Cameron DE, Murphy AM. Embolic stroke after ligation of the pulmonary artery in patients with functional single ventricle. Am Heart J. 1996; 132:836–840. [PubMed: 8831374]
58. Chun DS, Schamberger MS, Flaspohler T, et al. Incidence, outcome, and risk factors for stroke after the Fontan procedure. Am J Cardiol. 2004; 93:117–119. [PubMed: 14697484]
59. Mahnke CB, Boyle GJ, Janosky JE, Siewers RD, Pigula FA. Anticoagulation and incidence of late cerebrovascular accidents following the Fontan procedure. Pediatr Cardiol. 2005; 26:56–61. [PubMed: 14994183]
60. Bellinger DC, Jonas RA, Rappaport LA, et al. Developmental and neurologic status of children after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. N Engl J Med. 1995; 332:549–555. [PubMed: 7838188]
61. Rappaport LA, Wypij D, Bellinger DC, et al. Relation of seizures after cardiac surgery in early infancy to neurodevelopmental outcome. Boston Circulatory Arrest Study Group. Circulation. 1998; 97:773–779. [PubMed: 9498541]
62. Dittrich H, Buhrer C, Grimmer I, Dittrich S, Abdul-Khaliq H, Lange PE. Neurodevelopment at 1 year of age in infants with congenital heart disease. Heart. 2003; 89:436–441. [PubMed: 12639876]
63. Majnemer A, Limperopoulos C. Developmental progress of children with congenital heart defects requiring open heart surgery. Semin Pediatr Neurol. 1999; 6:12–19. [PubMed: 10098225]
64. Hovels-Gurich HH, Konrad K, Wiesner M, et al. Long term behavioural outcome after neonatal arterial switch operation for transposition of the great arteries. Arch Dis Child. 2002; 87:506–510. [PubMed: 12456550]
65. Limperopoulos C, Majnemer A, Shevell MI, et al. Functional limitations in young children with congenital heart defects after cardiac surgery. Pediatrics. 2001; 108:1325–1331. [PubMed: 11731655]
66. Majnemer A, Limperopoulos C, Shevell M, Rohlicek C, Rosenblatt B, Tchervenkov C. Developmental and functional outcomes at school entry in children with congenital heart defects. J Pediatr. 2008; 153:55–60. [PubMed: 18571536]
67. Karl TR, Hall S, Ford G, et al. Arterial switch with full-flow cardiopulmonary bypass and limited circulatory arrest: neurodevelopmental outcome. J Thorac Cardiovasc Surg. 2004; 127:213–222. [PubMed: 14752433]
68. Newburger JW, Jonas RA, Wernovsky G, et al. A comparison of the perioperative neurologic effects of hypothermic circulatory arrest versus low-flow cardiopulmonary bypass in infant heart surgery. N Engl J Med. 1993; 329:1057–1064. [PubMed: 8371727]
69. Miller SP, McQuillen PS, Hamrick S, et al. Abnormal brain development in newborns with congenital heart disease. N Engl J Med. 2007; 357:1928–1938. [PubMed: 17989385]
70. Hirsch JC, Jacobs ML, Andropoulos D, et al. Protecting the infant brain during cardiac surgery: a systematic review. Ann Thorac Surg. 2012; 94:1365–1373. discussion 1373. [PubMed: 23006704]
71. O'Rourke PP, Crone RK, Vacanti JP, et al. Extracorporeal membrane oxygenation and conventional medical therapy in neonates with persistent pulmonary hypertension of the newborn: a prospective randomized study. Pediatrics. 1989; 84:957–963. [PubMed: 2685740]
72. Kitchen L, Westmacott R, Friefeld S, et al. The pediatric stroke outcome measure: a validation and reliability study. Stroke. 2012; 43:1602–1608. [PubMed: 22474056]
73. Engelmann KA, Jordan LC. Outcome measures used in pediatric stroke studies: a systematic review. Arch Neurol. 2012; 69:23–27. [PubMed: 22232344]
74. Marino BS, Lipkin PH, Newburger JW, et al. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. Circulation. 2012; 126:1143–1172. [PubMed: 22851541]
75. Heron M. Deaths: leading causes for 2009. Natl Vital Stat Rep. 2012; 61:1–93. [PubMed: 24964584]
76. Odegard KC, Zurakowski D, Hornykewycz S, et al. Evaluation of the coagulation system in children with two-ventricle congenital heart disease. Ann Thorac Surg. 2007; 83:1797–1803. [PubMed: 17462402]

77. Rask O, Hanseus K, Ljung R, Strandberg K, Berntorp E. Lower incidence of procoagulant abnormalities during follow-up after creation of the Fontan circulation in children. Cardiol Young. 2009; 19:152–158. [PubMed: 19195416]

78. Odegard KC, Zurakowski D, DiNardo JA, et al. Prospective longitudinal study of coagulation profiles in children with hypoplastic left heart syndrome from stage I through Fontan completion. J Thorac Cardiovasc Surg. 2009; 137:934–941. [PubMed: 19327521]

79. McLeod KA, Martin P, Williams G, Walker DR. Neutrophil activation and morbidity in young adults with cyanotic congenital heart disease. Blood Coagul Fibrinolysis. 1994; 5:17–22. [PubMed: 8180336]

80. Firdouse M, Agarwal A, Chan AK, Mondal T. Thrombosis and thromboembolic complications in Fontan patients: a literature review. Clin App Thromb Hemost. 2014; 20:484–492.

81. Atz AM, Travison TG, McCrindle BW, et al. Late status of Fontan patients with persistent surgical fenestration. J Am Coll Cardiol. 2011; 57:2437–2443. [PubMed: 21658565]

82. Tweddell JS, Nersesian M, Mussatto KA, et al. Fontan palliation in the modern era: factors impacting mortality and morbidity. Ann Thorac Surg. 2009; 88:1291–1299. [PubMed: 19766824]

83. Mathews K, Bale JF Jr, Clark EB, Marvin WJ Jr, Doty DB. Cerebral infarction complicating Fontan surgery for cyanotic congenital heart disease. Pediatr Cardiol. 1986; 7:161–166. [PubMed: 3492707]

84. Cengiz P, Seidel K, Rycus PT, Brogan TV, Roberts JS. Central nervous system complications during pediatric extracorporeal life support: incidence and risk factors. Crit Care Med. 2005; 33:2817–2824. [PubMed: 16352965]

85. Liu XY, Wong V, Leung M. Neurologic complications due to catheterization. Pediatr Neurol. 2001; 24:270–275. [PubMed: 11377101]

86. Weissman BM, Aram DM, Levinsohn MW, Ben-Shachar G. Neurologic sequelae of cardiac catheterization. Cathet Cardiovasc Diagn. 1985; 11:577–583. [PubMed: 4092235]

87. Niwa K, Nakazawa M, Tateno S, Yoshinaga M, Terai M. Infective endocarditis in congenital heart disease: Japanese national collaboration study. Heart. 2005; 91:795–800. [PubMed: 15894782]

88. Venkatesan C, Wainwright MS. Pediatric endocarditis and stroke: a single-center retrospective review of seven cases. Pediatr Neurol. 2008; 38:243–247. [PubMed: 18358401]

89. Chen K, Williams S, Chan AK, Mondal TK. Thrombosis and embolism in pediatric cardiomyopathy. Blood Coagul Fibrinolysis. 2013; 24:221–230. [PubMed: 23429248]

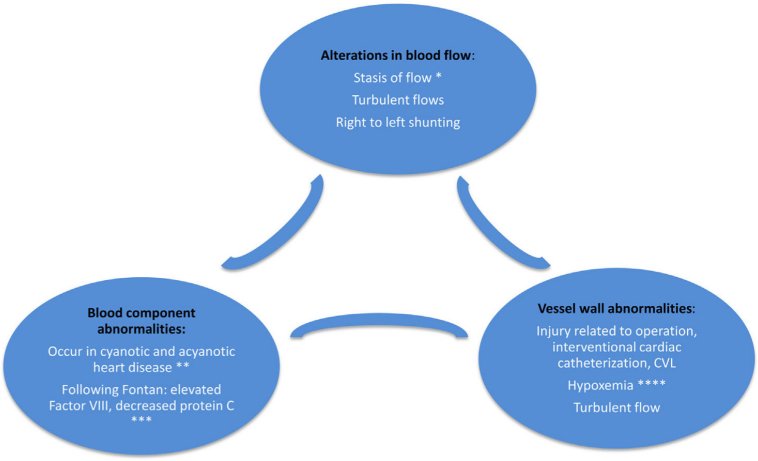

FIGURE.

Propensity to thrombosis in children with cardiac disease based on Virchow's triad. *Stasis can occur because of nonpulsatile flow, vessel or chamber dilatation, decreased systolic performance, immobility, arrhythmia, or hyperviscosity. ** [76,77] *** [78] **** Hypoxemia is thought to activate neutrophils, and via the inflammatory cascade, cause endothelial injury.[79] (The color version of this figure is available in the online edition.)

TABLE 1

Published Incidence or Prevalence of Stroke in Children With Cardiac Disease

Population with Cardiac Disease	Incidence or prevalence of Stroke	Limitations/Caveats of Incidence/Prevalence Data
All children with cardiac disease	AIS: 132 of 100,000 per yr[3]	Cardiac disease defined as CHD, arrhythmia, or cardiomyopathy
Neonates/infants with surgically treated CHD	Preoperative AIS 5%-25%, postoperative AIS 0%-19%[31-35,37,38]	Vast majority of strokes clinically silent and detected on neuroimaging
Post-Fontan procedure	1.4%-19%[55,58,59,80-83]	Variability in stroke definition and length of follow-up
Berlin Heart EXCOR VAD	AIS and HS: 28%-34 %[15,16]	Ischemic stroke not clearly differentiated from hemorrhagic stroke. VAD IDE trial mandated neurologic assessments, adjudicated centrally. Including silent infarcts and global ischemic encephalopathy (events excluded from the neurological dysfunction definition in the trial), the overall stroke risk was 34%
ECMO	AIS and HS: 7%-11%[17,84]	From ELSO registry, voluntary reporting, nonadjudicated neurological events. Data include ischemic and hemorrhagic strokes, with each stroke subtype accounting for ~50% of the cases
Cardiac surgery with bypass	AIS and CSVT: 5.4 of 1000 per cardiac surgeries with bypass[40]	Incidence of both AIS and CSVT-related stroke during first 72 hours after surgery
Cardiac catheterization	AIS: 0.38%-1.3%[85,86]	Liu et al study was 1977-1981; stroke diagnosed by CT and no children received anticoagulation for catheterization procedure
Endocarditis	AIS and HS: 6%-11%[87,88]	
Cardiomyopathy	4.8%[89]	Rate of cerebral embolism

Abbreviations:

AIS = Arterial ischemic stroke

CHD = Congenital heart disease

CSVT = Cerebral sinovenous thrombosis

CT = Computed tomography

ECMO = Extracorporeal membrane oxygenation

ELSO = Extracorporeal Life Support Organization

HS = hemorrhagic stroke

IDE = Investigational device exemption

VAD = Ventricular assist device

TABLE 2

Comparison of Guidelines for the Treatment, Prevention, and Evaluation of Cardiac Stroke in Children

Stroke Mechanism	Chest Antithrombotic Therapy in Neonates and Children 2012 Recommendations[42]	American Heart Association (AHA) Management of Stroke in Infants and Children 2008 Recommendations[43]	American Heart Association Prevention and Treatment of Thrombosis in Pediatric and Congenital Heart Disease 2013 Recommendations[28]
AIS secondary to cardiac embolism	For AIS secondary to cardioembolic causes, suggest anticoagulant therapy for at least 3 mo (Grade 2C)	Reasonable to start anticoagulation in children with cardiac embolism unrelated to PFO, who are judged to be at high risk of recurrence. Where there is a risk of cardiac embolism, it is reasonable to continue anticoagulation for at least 1 yr or until the lesion responsible for the risk has been corrected. For those with a suspected cardiac embolism unrelated to PFO where there is a lower or unknown risk of stroke, it is reasonable to start aspirin and continue for at least 1 yr (Class IIa, level of evidence C)	Refers to 2008 AHA Management of Stroke in Infants and Children recommendations
Endocarditis	No recommendations, case-by-case basis	Anticoagulant therapy not recommended for individuals with native valve endocarditis (Class III, level of evidence C)	Not addressed
Isolated PFO	For children with AIS secondary to cardioembolic causes where there is a demonstrated right to left shunt (e.g., PFO), surgical closure * of the shunt suggested (Grade 2C)	Surgical repair or transcatheter closure is reasonable in those with *a major atrial septal defect*. (Class IIa, level of evidence C). This recommendation does not apply to individuals with a PFO pending additional data	Addressed regarding adults but not children because of insufficient data in children
Prothrombotic risk factor assessment in child with congenital heart disease and AIS	Not addressed	It is reasonable to evaluate for the more common prothrombotic states even when another stroke risk factor has been identified (Class IIa, Level of Evidence C).	Expanded evaluation for inherited or acquired prothrombotic risk factors is reasonable (*Class IIa; Level of Evidence B*). It would be reasonable to include the following factors in an initial evaluation: protein C, protein S, AT III, lipoprotein(a), homocysteine level, anticardiolipin antibodies, lupus anticoagulant, mutations of factor V Leiden, and prothrombin genes

Abbreviations:

AIS = Arterial ischemic stroke

AT III = antithrombin III

PFO = Patent foramen ovale

Chest Grade 2C: weak recommendation, low, or very-low quality evidence.

AHA Class IIa: conflicting evidence and/or a divergence of opinion about the usefulness/efficacy ofa procedure or treatment. The weight of evidence oropinion is in favor of the procedure or treatment.

AHA Class III: evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful.

AHA Level of evidence C: consensus opinion of experts.

* Recommendation made before publication of adult randomized controlled trials of medical therapy versus PFO closure.

TABLE 3

Identified Research Questions

General
Can a secondary risk factor(s) analysis establish predictors for initial or recurrent stroke in children with cardiac disease? For example, does addition of a particular risk factor(s) (yet to be identified) significantly increase the risk of stroke beyond the risk of cardiac disease alone?
What is the ideal minimum dataset for the collection of multicenter data on stroke risk factors in the cardiac population?
Does neuromonitoring with cEEG in high-risk situations, such as in neonates and infants following cardiac surgery, result in earlier stroke detection or improved neuroprotection following acute stroke?
Does the use of bedside imaging modalities, such as transcranial Doppler ultrasound or optical imaging, for neuromonitoring in high-risk situations result in earlier stroke detection?
Would the development and implementation of a standardized brief neurological assessment for bedside caregivers (e.g., intensive care nurses) improve stroke detection?
When is it safe to perform cardiac bypass surgery following an ischemic or hemorrhagic stroke?
What further improvements in cardiopulmonary bypass and cardiac catheterization protocols can reduce the risk of procedure-related stroke?
Neuroimaging
What are the neuroimaging characteristics of cardiogenic stroke in children?
What is the ideal minimum neuroimaging dataset for the collection of multicenter data for suspected stroke in the cardiac population?
Should certain populations of children have screening neuroimaging (population, imaging modality, and timing are important factors to consider)?
Are children with other brain injury (e.g., white matter injury) at increased risk of stroke?
What is the incidence and what are the typical neuroimaging abnormalities in children with a VAD (pre/post)?
Does having an incomplete circle of Willis increase the risk of perioperative stroke?
Hematological
Does the presence of an inherited or an acquired thrombophilia predict stroke recurrence and/or worse outcome?
What is the best method of serum antithrombotic monitoring in patients with a VAD/ECMO?
Does antithrombotic monitoring for patients with a VAD/ECMO reduce complications?
What is the risk of bleeding when using multiple antithrombotic agents concurrently?
What is the best practice for antithrombotic therapy in cardiomyopathy?
Would a prothrombotic evaluation performed before cardiac surgery alter management and improve outcome?
What is the role of new antithrombotic agents in stroke prevention in children with cardiac disease?
Is anticoagulation superior to antiplatelet therapy for secondary stroke prevention in children with cardiac AIS? Do particular subgroups respond differently?
After cardiac stroke, how long should a child remain on antithrombotic treatment for secondary stroke prophylaxis?
Would procedural anticoagulation given during cardiac catheterization with venous access only (particularly when there is a potential for right to left shunting) reduce the risk of procedure related stroke?
Subgroups
What are the risk factors for stroke in the Fontan population?
Does anticoagulation reduce the risk of stroke after Fontan procedure in older children and young adults?
What is the best practice regarding management of fenestration and residual right to left shunting after Fontan procedure?
What are the risk factors for stroke in children with arrhythmia?
How long should antithrombotic therapy be withheld in children with intracranial hemorrhage who have a VAD?
Is balloon atrial septostomy independently associated with stroke?

Abbreviations:

AIS = Arterial ischemic stroke

cEEG = Continuous electroencephalography

ECMO = Extracorporeal membrane oxygenation

VAD = Ventricular assist device

TABLE 4

The “next steps” to Advance Research and Clinical Care in Pediatric Cardiac Stroke

Development of a multicenter pediatric cardiac stroke registry to assess secondary risk factors for stroke in children with cardiac disease
Development of a multicenter collaborative network
Designation of centers of expertise, where clinical guidelines are in place and are monitored through quality improvement activities
Development of parent education resources regarding stroke in children with cardiac disease