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Arterial ischemic stroke secondary to cardiac disease in neonates and children


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Abstract:

Objective: To describe risk factors for peri-procedural and spontaneous arterial ischemic stroke (AIS) in children with cardiac disease.

Methods: We identified children with cardiac causes of AIS enrolled in the International Pediatric Stroke Study registry from January 2003 to July 2014. Isolated patent foramen ovale was excluded. Peri-procedural AIS (those occurring during or within 72 hours of cardiac surgery, cardiac catheterization or mechanical circulatory support) and spontaneous AIS that occurred outside of these time periods were compared.

Results: We identified 672 patients with congenital or acquired cardiac disease as the primary risk factor for AIS. Among these, 177 patients (26%) had peri-procedural AIS and 495 patients (74%) had spontaneous AIS. Among non-neonates, spontaneous AIS occurred at older ages (median 4.2 years, IQR 0.97–1 2.4) compared to peri-procedural AIS (median 2.4 years, IQR 0.35 – 6.1, P<0.001). About a third of patients in both groups had a systemic illness at the time of AIS. Patients that had spontaneous AIS were more likely to have a preceding thrombotic event (16 % vs. 9 %, p = 0.02) and to have a moderate or severe neurologic deficit at discharge (67% vs. 33%, p = 0.01) compared to those with peri-procedural AIS.

Conclusions: Children with cardiac disease are at risk for AIS at the time of cardiac procedures but also outside of the immediate 72 hours after procedures. Many have acute systemic illness or thrombotic event preceding AIS, suggesting that inflammatory or prothrombotic conditions could act as a stroke trigger in this susceptible population.

Keywords: Pediatric stroke; Pediatric arterial ischemic stroke; Cardiac disease; Stroke; Embolism; Cardiac procedure
Introduction:

Neonates and children with cardiac disease comprise one of the highest risk populations for pediatric arterial ischemic stroke (AIS), with a reported annual incidence rate ranging from 132/100,000 children to 1/100 children (1, 2) compared to 2-8/100,000 in the general pediatric population (3, 4). This risk persists beyond childhood. The prevalence of ischemic or hemorrhagic stroke in adults with congenital heart disease is estimated to be 10-100 times higher than expected in healthy adults of similar age (5). The prevalence of cardiac disease among children with AIS did not change between 1978 and 2009 despite improvement in acute medical and surgical management and outcomes in children with cardiac disease during this time period (1).

Underlying heart disease contributes to AIS risk through right to left shunting of blood, increased systemic venous pressure, depressed heart function with aberrant flow dynamics, arrhythmias, infective endocarditis, or thrombophilies (6). In addition, life-saving interventions such as cardiac surgery, cardiac catheterization and mechanical circulatory support come with the cost of AIS as a potential complication (2, 7-11). Infection and thrombosis are also complications of cardiac interventions and influence AIS risk (12). Infection has been shown to play a major role in childhood AIS pathogeneses of all causes, including spontaneous cardioembolic stroke (13). Both acute infection and prothrombotic conditions at the time of initial AIS presentation are predictive of AIS recurrence within a 10-year period in children with congenital heart disease (14). At a 2014 symposium of Stroke in Children with Cardiac Disease, a collaborative group of pediatric cardiologists, hematologists, and neurologists prioritized further study of co-existing multiple risk factors as critical for the development of successful AIS prevention strategies (15).

In a population-based study of children with ischemic or hemorrhagic stroke, the index stroke occurred more than 5 years after the last cardiac procedure in almost half of patients who had a congenital heart defect (CHD) as the primary stroke risk factor (16). Stroke risk related to
CHD continues to be elevated in adulthood, years after cardiac surgery (5, 17-19). Among 204 children with AIS and cardiac disease enrolled between 2003-2007 in the International Pediatric Stroke Study (IPSS), approximately one quarter had the index AIS with 72 hours of cardiac surgery or cardiac catheterization(7).

Most children with AIS have multiple converging risk factors. Understanding the conditions that influence the risk of stroke in peri-operative and non-surgical settings is a critical first step towards a more honed approach to stroke prevention. Since the first IPSS report on children with cardiac disorders, the registry has grown to include 4294 children with AIS or venous sinus thrombosis from 87 sites in 24 countries(20), allowing a stratified examination of children with peri-procedural versus spontaneous cardioembolic AIS. The IPSS collects standardized data regarding acute systemic illness at stroke onset, prior thrombosis, hypercoagulable conditions, and family history of thrombosis. Using these data, we sought to compare the reported frequencies of these potential risk factors in two groups with pediatric AIS related to CHD: those with a AIS occurring within 72 hours of a cardiac procedure versus those with spontaneous cardioembolic AIS. In both groups, we also described initial anti-thrombotic management and short-term outcomes.

Methods:

The IPSS is a multinational registry of prospectively gathered data on neonates and children with AIS or venous sinus thrombosis enrolled between January 1, 2003 and July 31, 2014. Study approval was obtained from the Institutional Review Board at each study site and informed consent (and if applicable, assent) was obtained from participating parents/guardian and patients.

Inclusion criteria: 1) neonates or children with AIS that occurred from birth to <19 years, 2) AIS identified by the site investigator to have cardiac disease as a primary etiology for the AIS.
Children with isolated patent foramen ovale (PFO) or presumed perinatal AIS were excluded (Figure 1).

Local site investigators collected data as previously described (20). Presumptive risk factors for stroke are identified and recorded by site investigators onto standardized forms, and include cardiac disease (categorized as congenital, acquired or isolated PFO), prothrombotic states, acute systemic illnesses, and family history of coagulopathy among others. Definitions: Cardiac disease was defined as an acquired heart disease (AHD) such as myocarditis or cardiac mass, or congenital heart defects (CHD). Peri-procedural AIS were defined as arterial ischemic stroke that occurred during or within 72 hours of cardiac surgery or catheterization or, if noted, during mechanical circulatory support such as a ventricular assist device (VAD) or extracorporeal membrane oxygenation (ECMO). Spontaneous AIS were defined as arterial ischemic stroke that occurred >72 hours after cardiac surgery, cardiac catheterization, decannulation from ECMO, VAD removal or outside of interventional cardiac treatment. Patients with AIS occurring beyond 72 hours post cardiac procedure performed were classified as “spontaneous” but noted to have a history of cardiac surgery or other cardiac procedure. Acute systemic illnesses at the time of the AIS were identified by site investigators; these included sepsis, viral gastroenteritis, fever lasting >48 hours, acidosis, shock and anoxia/asphyxia. Chronic medical disorder included genetic syndromes, malignancies or underlying medical conditions other than primary cardiac disease. Prothrombotic states included inherited or acquired pro-thrombotic conditions such as those identified on laboratory testing, reported use of oral contraceptives, treatment with L-asparaginase. Thrombotic events were intra-cardiac, pulmonary or systemic venous or arterial clots, transient ischemic attacks (TIA), additional AIS, or cerebral sinovenous thrombosis (CSVT). These were considered preceding thrombotic events if they were identified more than 24 hours preceding or concurrent if within 24 hours of the index AIS. Short-term outcome refers to recurrent thrombotic events (if they occurred 24 hours or more after the index AIS) and status at hospital discharge categorized by local
investigators as normal; mild, moderate, or severe neurologic deficit, or death. Poor outcome at discharge was considered moderate or severe neurologic deficit at time of discharge. Neonatal AIS occurred from birth to 28 days, childhood AIS occurred from 29 days to 18 years.

Statistical analysis: Data analysis was performed using SAS 9.3 (SAS Institute, Cary, NC) and GraphPad Prism (GraphPad Software, Inc, La Jolla, CA). We used summary statistics to examine demographics and pre-specified variables including stroke presentation, CHD, AHD, family history, acute systemic illness, chronic conditions, prior cardiac surgery (as a marker for disease severity and completeness of treatment of cardiac disease), anti-thrombotic management and outcomes in patients with peri-procedural or spontaneous AIS. We compared the two groups using Fisher’s exact or chi-square tests for categorical variables and t-test to compare continuous variables if normally distributed. Data were < 5% missing except where indicated. Anti-thrombotic management and congenital versus acquired heart disease data were missing unequally in the spontaneous and peri-procedural groups, so statistical comparisons for these variables were not presented.

Results:

Overall study group: Among 3253 patients with AIS, 903 (28%) were identified as having cardiac disease as the primary etiology for AIS. After excluding 231 with isolated PFO, our study population included 672 patients (Figure 1). The majority (n=495, 74%) had a spontaneous AIS. In the 177 patients with peri-procedural AIS, the index stroke occurred within 72 hours of: cardiac surgery in 92, diagnostic cardiac catheterization in 33, interventional cardiac catheterization in 30, support with VAD or ECMO in 24. In two patients, the index stroke occurred within 72 hours of both a cardiac surgery and interventional cardiac catheterization. CHD was identified in 504, while 105 had acquired heart disease and 4 had both congenital and acquired heart disease (variable missing
AIS in n=59). Demographics and characteristics of the study group are provided in Table 1, and were similar to prior IPSS reports (20).

*Peri-procedural vs. Spontaneous AIS*

In the majority of patients (n=495, 74%), AIS was spontaneous rather than peri-procedural. The proportion of neonates was similar in both groups (23% of spontaneous AIS and 19% of periprocedural AIS, Table 2). Among those with childhood AIS, spontaneous AIS occurred in older children (median age 4.2 years, IQR 0.97 – 12.4) compared to the age of those with peri-procedural AIS (median age 2.4 years, IQR 0.35 – 6.1, P< 0.001). Acute systemic illness at the time of the AIS was common overall (documented in 37% of those with spontaneous AIS and 31% of those with peri-procedural AIS, p=0.17), and was more frequent in patients with AHD compared to patients with CHD (49% vs. 34%, p = 0.01). A prothrombotic state was identified in 41 patients, including 34/495 (7%) patients with spontaneous AIS and 7/177 (4%) patients with peri-procedural AIS (P=0.7). Preceding thrombotic events were more common among those with spontaneous AIS (16%) compared to peri-procedural AIS (9%, P=0.02). Twenty-two patients (4%) with spontaneous AIS had preceding or concurrent intra-cardiac thrombi documented. A family history of thrombosis or hypercoaguability was reported in 11% of patients with spontaneous AIS and 18% with a peri-procedural AIS (P=0.2).

Within the group of 146 neonates, there was no difference between the peri-procedural and spontaneous AIS groups with regard to preceding thrombotic events, acute systemic illness, location of the infarct, number of infarcts (single or multiple).

*Anti-thrombotic management after AIS:*

Data were available regarding antithrombotic management in 643 patients. Providers initiated anti-thrombotic treatment after AIS in 460/643 patients. Of these patients, 236 (51%)
initially received anticoagulation alone (low molecular weight heparin, coumadin or unfractionated heparin). Another 164 patients (36%) received antiplatelet agents (aspirin or clopidogrel) alone, and 36 patients (8%) received combined antiplatelet agents and anticoagulation (6%). No other types of anti-coagulation or antiplatelet agents were utilized. The initial antithrombotic treatment was not available for 24 (5%) patients. At discharge, over half of patients (58%) remained on an anti-thrombotic medication, with aspirin as the most common choice followed by low molecular weight heparin (Figure 2). Patients with CHD were more likely to be discharged home on an anti-thrombotic therapy (84.3% of CHD patients) than patients with AHD (15.7%), $p = 0.02$.

**Short-term outcomes after AIS:**

Stroke recurrence was reported after peri-procedural AIS (n=7, 4%) and spontaneous AIS (n=36, 7%). There were no differences between the groups in the frequency of recurrent AIS, recurrent thrombotic events or outcome at the time of discharge (Table 2). Nine neonates (8%) with spontaneous AIS had recurrent thrombotic events, and eight of these were recurrent AIS or TIA. Two neonates (6%) in the peri-procedural group had a recurrent thrombotic event, neither of which were AIS. There were 47 in-hospital deaths (7%). Of the patients that survived to hospital discharge, 392 (58%) had a moderate or severe neurological deficit.

**Discussion:**

In this large, international registry of children with AIS, nearly one third of the patients had cardiac disease as the primary underlying etiology. Children with cardiac disease are at known risk for AIS following cardiac procedures, especially children with cyanotic CHD(8, 21). Spontaneous AIS was reported three times more frequently than peri-procedural AIS. However, our study was not designed to directly compare peri-procedural versus spontaneous stroke risk; thus this finding should not be used to de-emphasize the risk of cardiac procedures. The short time at-risk for peri-procedural stroke represents only a small percentage of a child’s lifetime, yet 26% of the strokes in
this study occurred during this period. Our data show that both peri-procedural and spontaneous AIS are important morbidities of pediatric heart disease. Stroke mechanisms are often multifactorial in children with cardiac disease, related to co-morbid polycythemia, chronic hypoxia, embolic or thrombotic disease, and abnormal flow and foreign devices or materials. Identifying and addressing risk factors for AIS that are not directly procedure-related and those that increase stroke risk at the time of a cardiac procedure are the first steps towards improving stroke prevention in these children.

Children with peri-procedural AIS tended to be younger (median age 2.4 years) than those with spontaneous strokes (4.2 years). While a number of factors may contribute to this age discrepancy, we speculate that this is primarily driven by the typical timing of invasive cardiac procedures and complicated cardiac surgeries during the first few years of life in children with single ventricle physiology and more severe forms of congenital heart disease. Although stroke risk is not homogenous across all cardiac procedures, we had limited details to differentiate between the procedures in the registry. For example, ECMO was included as a cardiac procedure, but has associated with uniquely high stroke risk (22). In some cases, more than one procedure (for example, ECMO and a catheterization or surgery) may have occurred in the preceding 72 hours that were not captured separately.

Acute systemic illness was frequently reported in both groups of patients. Mackay et al found that post-procedural infection increases the odds of stroke fivefold in children with CHD after a cardiac procedure (8). Acute infection at the time of sentinel stroke also has been reported to increase the risk of recurrent stroke in neonates and children with CHD (14). Acute illness may further exacerbate risk of thrombosis in children with cardiac disease by worsening acidosis (and potentially cardiac function), and/or decreasing oxygenation (e.g. those with pulmonary hypertension). In the Vascular effects of Infection in Pediatric Stroke study, infection within the
A week prior to stroke increased the risk of AIS 6.3 fold, and was reported in 22% of the children with spontaneous cardioembolic AIS (13). We cannot draw a causal relationship between acute systemic illness and AIS from our data, but further investigation into the role of acute systemic illness in AIS in children with cardiac disease is warranted. Elucidation of the mechanisms whereby infection might lead to AIS, including endocarditis or acquired prothrombotic states may improve early identification of cardiac patients who are at high risk for AIS.

Among the children with spontaneous AIS, we found that preceding or concurrent thrombotic events were common. However, the group with spontaneous AIS was older with more time at risk for a preceding thrombotic event. Approximately half of the children with spontaneous AIS had a remote history of cardiac surgery. Although some surgical interventions such as Fontan surgery are associated with increased risk of thromboembolic events (23), we did not have the specific surgeries performed in all of the patients and are unable to compare spontaneous AIS risk for particular sub-types of surgical procedures. Stroke risk after palliative cardiac surgery may differ from stroke risk after completed surgical repair (8). We were unable to precisely determine how many had an acquired or congenital underlying thrombophilic condition due to incomplete testing, but some studies suggest these are (24) common in neonates and children with complex cardiac defects (25-28). Neonates and children with cardiac disease and stroke were more likely to have an elevated lipoprotein a, protein C deficiency, or positive anti-cardiolipin antibodies than age-matched controls (28). D-dimer level, a functional measurement of coagulation activation, is acutely elevated in children with cardioembolic AIS compared to other types of AIS, and remains persistently elevated over months (12). Markers of active thrombosis were transiently elevated in 18 out of 18 children after cardiac surgery (27). Cardiac surgery itself may induce an imbalance between pro and antithrombotic states in the coagulation cascade, especially in single ventricle patients who are considered to be at higher risk for thrombosis than patients with other CHD (24, 25).
A thromboembolic recurrence was only reported in a small number of patients. Generally, recurrent stroke after neonatal AIS overall is uncommon, but we found that 8% of neonates with CHD had a recurrent AIS. Because the length of follow-up after hospitalization varied, this proportion should be considered a minimum proportion. Prothrombotic states predict stroke recurrence in children with CHD (14), yet investigators reported thrombophilia testing in only a small percentage of patients with cardiac disease in the IPSS (12.4%). Thrombophilia testing may have been underreported; these studies are often completed in a delayed fashion and may have been captured later. The American Heart Association (AHA) Guidelines on Management of Stroke in Infants and Children suggests reasonable evaluation for the more common prothrombotic states even when another stroke risk factor has been identified (Class IIa, Level of Evidence C). (29) The updated 2019 AHA guidelines for Management of Stroke in Neonates and Children (30) and the AHA Guidelines on Prevention and Treatment of Thrombosis in Pediatric and Congenital Heart Disease concur with these recommendations, and suggest considering evaluation for inherited or acquired prothrombotic risk factors in children with heart disease who have a stroke (Class IIa, Level of Evidence B)(6). Although routine testing for hypercoaguability after neonatal stroke may not be indicated the absence of cardiac disease (31), in neonates and children with CHD, a thrombophilia evaluation may be appropriate. Consistent thrombophilia testing in children with cardiac disease may help identify children with additional risk factors for AIS who accordingly, should be considered for more intensive or longer term antithrombotic treatment for primary or secondary AIS prevention.

We noted substantial variation in anti-thrombotic treatment, finding that only 60% of patients were discharged home on an anti-thrombotic medication. Among patients who received antithrombotic treatment, the majority initially received anticoagulation rather than antiplatelet agents. In contrast, the majority of patients were discharged with an antiplatelet agent (usually aspirin) rather than anticoagulation. Some of the patients in the IPSS may have had prior
indications for aspirin related to stents or their cardiac disease, or may have had a contraindication to anti-coagulation. However, small studies suggest aspirin may not be an adequate agent for AIS prevention in these children. In a series of 20 children with single ventricle palliative shunt surgery who were monitored with thromboelastography to measure platelet function, 80% were aspirin resistant in the post-operative period (32). Aspirin resistance is associated with increased risk of thrombosis in pediatric patients undergoing cardiac surgery (26). AHA guidelines suggest that low molecular weight heparin or warfarin treatment for at least one year (or until the lesion responsible for the risk has been corrected) is reasonable in children with a risk of cardiac embolism (29), but in practice it appears that a limited proportion of patients with cardiac disease and AIS are managed in this way.

Among neonates and children with AIS in the IPSS registry, congenital heart disease is associated with a higher rate of in-hospital mortality than other stroke etiologies (20). We found that 58% of survivors of cardiac-related stroke had a poor outcome at the time of discharge. We only reported short-term outcomes (at hospital discharge) because longer follow-up was not included in the initial IPSS data collection. This finding should be interpreted cautiously. Stroke outcome at hospital discharge may not be representative of the ultimate degree of neurologic recovery, particularly in children who may also be recovering from a cardiac surgery. Conversely, language or motor deficits may become more prominent over time in infants or young children with a stroke.

There are several limitations in the use of the IPSS database. The definition we used for peri-procedural AIS (one that occurs within 72 hours of a cardiac procedure) is narrow, and the proportion of patients with peri-procedural AIS may have been higher if a longer interval had been allowed. Estimating the time that AIS occurred can be difficult and imprecise because sedation limits the discovery of clinical symptoms, and imaging is often delayed in post-surgical or critically
ill patients. The database only includes patients captured by the site investigators and does not represent all pediatric patients with AIS secondary to cardiac disease during this time period; thus the prevalence of variables analyzed may have been over or under-represented in the IPSS database. Differentiation of cyanotic versus non-cyanotic heart disease and single ventricle status were not available. Follow-up after hospital discharge varied, and the prevalence of recurrent thrombotic events in our study is likely underestimated.

Summary:

Many cardiac-related pediatric AIS occur outside the immediate peri-procedural window. A high proportion of the patients in our study appeared to have an acute systemic illness as an additional trigger for the AIS or a prior thrombotic event. Choice and duration of treatment with antithrombotic therapy was inconsistent. These findings reflect uncertainties in optimal clinical care for a complicated and heterogeneous group; additional data is required to guide evidence-based management. Further multi-center prospective studies are needed to determine best practices for secondary stroke prevention in this vulnerable population.

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Contributing IPSS investigators are listed in the appendix.

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References.


Table 1: Demographics, characteristics and secondary stroke prevention in 672 neonates and children with stroke due to complex cardiac disease.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total, N=672</th>
<th>Spontaneous, N=495</th>
<th>Periprocedural, N=177</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal</td>
<td>146 (22)</td>
<td>112 (23)</td>
<td>34 (19)</td>
<td>0.34</td>
</tr>
<tr>
<td>Male sex</td>
<td>387 (58)</td>
<td>298 (60)</td>
<td>91 (51)</td>
<td>0.04</td>
</tr>
<tr>
<td>Congenital heart disease (of N = 619)</td>
<td>508 (75)</td>
<td>368 (79)</td>
<td>140 (93)</td>
<td></td>
</tr>
<tr>
<td>Preceding events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preceding thrombotic event</td>
<td>97 (14)</td>
<td>81 (16)</td>
<td>16 (9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Chronic disorder</td>
<td>217 (32)</td>
<td>176 (36)</td>
<td>41 (23)</td>
<td>0.002</td>
</tr>
<tr>
<td>Prior cardiac surgery</td>
<td>252 (36)</td>
<td>241 (49)</td>
<td>11 (6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Presentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemiparesis (of n = 641)</td>
<td>391 (63)</td>
<td>291/456 (64)</td>
<td>100/162 (62)</td>
<td>0.64</td>
</tr>
<tr>
<td>Seizures</td>
<td>267 (40)</td>
<td>179 (36)</td>
<td>88 (50)</td>
<td>0.001</td>
</tr>
<tr>
<td>Acute systemic illness at time of stroke</td>
<td>237 (35)</td>
<td>182 (37)</td>
<td>55 (31)</td>
<td>0.17</td>
</tr>
<tr>
<td>Stroke location and type</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Anterior circulation only</td>
<td>429 (64)</td>
<td>322 (65)</td>
<td>107 (60)</td>
<td>0.46</td>
</tr>
<tr>
<td>Large vessel stroke</td>
<td>289 (43)</td>
<td>211 (43)</td>
<td>78 (44)</td>
<td>0.22</td>
</tr>
<tr>
<td>Bilateral</td>
<td>182 (27)</td>
<td>120 (24)</td>
<td>62 (35)</td>
<td>0.006</td>
</tr>
<tr>
<td>Multiple strokes (of n = 551)</td>
<td>262 (48)</td>
<td>186/403 (46)</td>
<td>76/148 (51)</td>
<td>0.33</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died prior to discharge</td>
<td>47 (7)</td>
<td>37 (7)</td>
<td>10 (6)</td>
<td>0.4 &lt;</td>
</tr>
<tr>
<td>Poor outcome at discharge (of N=625 survivors)</td>
<td>392 (58)</td>
<td>333 (67)</td>
<td>59 (33)</td>
<td>0.001</td>
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<tr>
<td>Recurrent thrombotic events</td>
<td>52 (8)</td>
<td>42 (8)</td>
<td>10 (6)</td>
<td>0.22</td>
</tr>
<tr>
<td>Recurrent stroke or TIA</td>
<td>43 (6)</td>
<td>36 (7)</td>
<td>7 (4)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

* Values do not always add up to 672 total as data was missing for some patients. TIA=Transient ischemic attack
Figure 1: Among 672 neonates and children with cardiac disease in the International Pediatric Stroke Study, 26% had an arterial ischemic stroke within 72 hours of a cardiac procedure and 74% had a spontaneous cardio-embolic arterial ischemic stroke.
Figure 2: Among 672 neonates and children with arterial ischemic stroke related to cardiac disease, antithrombotic therapy data was available for 643 patients. 57% (n=371) were discharged from the hospital with an anti-thrombotic medication. Antithrombotic management did not vary whether the stroke was peri-procedural or a spontaneous cardio-embolic stroke.