

# Surgical timing in infective endocarditis complicated by intracranial hemorrhage



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Given the growing incidence of infective endocarditis (IE), understanding the risks and benefits of valvular surgery is critical. This decision is particularly complex for the 1 in 10 cases complicated by intracranial hemorrhage (ICH). While guideline recommendations currently favor early surgery in general, delayed intervention of at least 4 weeks is still recommended for patients with ICH. To date, there are no randomized controlled trials that inform management of patients with an indication for surgery but concomitant ICH, and even reported observational data are rare. This paper reviews the current literature on timing of surgery with a specific focus on cases of ICH. It emphasizes a growing body of literature challenging the current paradigm that surgery within 4 weeks is associated with neurologic deterioration and high mortality rates by demonstrating favorable outcomes for patients with pre-operative ICH who undergo early valvular surgery. Based on these data, we propose a practical management algorithm to facilitate decisions on surgical timing in these complicated cases. Since more rigorous evidence may never be available, clinicians should make patient-specific surgical timing decisions that attempt to balance the competing risks of neurologic versus cardiac complications. (Am Heart J 2019;216:102-112.)

Infective endocarditis (IE) is a large and growing public health problem. From 2001 to 2010, IE hospitalizations increased by more than one third.<sup>1,2</sup> A national opioid epidemic has modified the epidemiology of native-valve endocarditis such that a larger proportion of cases are secondary to intravenous drug use (IVDU).<sup>3-5</sup> In 2008, the proportion of IE hospitalizations associated with IVDU was approximately 6%, a rate that nearly doubled to approximately 12% in 2013.<sup>2</sup> This has important implications for management, as IVDU-related cases are more likely to be caused by fungi and virulent bacteria that destroy cardiac tissue such as staphylococci (particularly *S. aureus*) and gram-negative organisms, factors which are associated with a failure of antibiotics alone.<sup>3,6,7</sup> With respect to cerebrovascular complications, IVDU-related cases of IE are significantly more likely to be associated with embolic events.<sup>8</sup> Furthermore, IVDU-associated IE

cases are more likely to be complicated by intracranial hemorrhage relative to other non-hemorrhagic neurologic complications.<sup>9</sup>

Generally speaking, medical management with antimicrobial therapy remains the cornerstone of initial treatment for IE. Nonetheless, up to 50% of patients will develop clinical complications that may warrant surgical intervention.<sup>10,11</sup> Accepted indications for surgery in left-sided, native-valve endocarditis (the focus of this review) include: signs of ongoing infection despite appropriate antimicrobials (more common in *S. aureus* and fungal endocarditis, as above), hemodynamic instability (eg, development of heart failure secondary to valvular dysfunction), mobile vegetations with size >10 mm in length (relatively weaker Class IIb indication), and recurrent embolic phenomena.<sup>10,12-15</sup> Vegetation characteristics associated with a high risk of embolization include vegetation length >13 mm, location on the mitral (more so than aortic) valve, and *S. aureus* as the etiological organism.<sup>8,16</sup>

Notably, a substantial proportion of IE patients with an indication for surgery will also have preoperative neurologic complications. In different analyses, this number varies between 15–60%.<sup>17-20</sup> In these cases, decisions regarding surgical timing become more difficult. The need for high-dose systemic anticoagulation at the time of cardiac surgery is particularly challenging for the one in 10 cases complicated by central nervous system (CNS) hemorrhage.<sup>21</sup> To date, there are no randomized, controlled trials that inform management of patients with surgical IE and intracranial hemorrhage (ICH). It must also be noted that the term “intracranial hemorrhage” generally represents a spectrum of disease

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ranging from incidental microbleeds (or microhemorrhage, defined as asymptomatic lesions detectable only by certain magnetic resonance imaging [MRI] sequences), ischemic stroke with hemorrhagic transformation, and intraparenchymal hemorrhage to more significant lesions including subarachnoid hemorrhage (SAH, ie, from ruptured aneurysm) and subdural hemorrhage (eg, from prior fall). In current observational studies in IE specifically, the type of ICH is inconsistently defined and includes a range of overlapping terminology in which specific lesion details are often lacking; terms include “hemorrhagic cerebral infarct,” “cerebral hemorrhage,” “hemorrhagic stroke,” “hemorrhage after ischemic stroke,” and “ischemic infarct with hemorrhagic transformation”.<sup>21-25</sup> Inconsistent, poorly defined terminology is a problem unto itself, but also represents a heterogeneity in presentations that can introduce selection bias. Thus, observational data for this population poses challenges. Decisions about whether to operate sooner or later are likely influenced by differences in presentation, potentially confounding associations between surgical timing and clinical outcomes.

Here, we will first review the literature favoring early surgery for IE patients in general and then will analyze the current data available for patients with concomitant ICH. As this patient population grows, the urgent need for better information to guide management is critical. The presence of ICH portends a much poorer prognosis, and these patients have higher mortality rates overall.<sup>23,24</sup> In the setting of competing risks for a complex population, understanding the adequacy of evidence about surgical timing becomes essential.

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## Early surgery in infective endocarditis

### Current management guidelines

The major guidelines currently informing surgical management of IE are those of the American Heart Association/American College of Cardiology (AHA/ACC) and the European Society of Cardiology (ESC). Notably, this is an area that generally lacks robust evidence upon which to base clinical decision-making. Even with Class I indications, both practice guidelines are based on level B evidence, consisting of either a single randomized trial or non-randomized observational data.<sup>10,12,13,15</sup> In light of these limitations, there is consistent emphasis on the importance of clinical context in deciding when to operate; these decisions should be made with a multidisciplinary team of specialists including cardiologists, cardiothoracic surgeons, infectious disease consultants, and when relevant, neurologists and neurosurgeons.

For left-sided native-valve endocarditis, practice guidelines support early surgical intervention, which for the AHA/ACC, is defined as taking place during the initial hospitalization and before completion of a full course of antibiotics.<sup>12</sup> The ESC also includes a recommendation for emergency surgery (defined as within 24 hours) in patients where IE is complicated by hemodynamic compromise, such as in refractory pulmonary edema or cardiogenic shock.<sup>13</sup> (Table 1)

### Literature supporting early surgery

Observational studies that initially supported early surgery in left-sided native-valve endocarditis were conducted in patients whose presentation was complicated by heart failure. In these cohort studies, patients who underwent early surgery (either during index admission or with a mean interval of 11.5 days from presentation) had lower in-hospital and one-year mortality rates.<sup>26,27</sup> Others provided more longitudinal support for early surgical treatment, defined as surgery during the active

**Table 1.** Guideline-directed indications for early surgery

AHA/ACC	LOE	ESC	LOE
IE with valve dysfunction resulting in symptoms of heart failure	IB	Surgery within 24 hours for severe acute regurgitation (aortic or mitral), obstruction, or fistula causing refractory pulmonary edema or cardiogenic shock	IB
Left-sided IE caused by <i>S. aureus</i> , fungal, or other highly resistant organisms	IB	Surgery within a few days for severe regurgitation (aortic or mitral) or obstruction causing symptoms of heart failure or echocardiographic signs of poor hemodynamic tolerance	IB
IE complicated by heart block, annular or aortic abscess, or destructive penetrating lesions	IB	Surgery within a few days for locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation)	IB
Evidence of persistent infection as manifested by persistent bacteremia or fevers lasting longer than 5 to 7 days after onset of appropriate antimicrobial therapy	IB	Surgery within a few days (or 1–2 weeks after antibiotics) in infection caused by fungi or multiresistant organisms	IC
In patients with IE who present with recurrent emboli and persistent vegetations despite appropriate antibiotic therapy	IIaB	Surgery within a few days in cases of persistently positive blood cultures despite appropriate antibiotic therapy and adequate control of septic metastatic foci	IIaB
Mobile vegetations greater than 10 mm in length (with or without clinical evidence of embolic phenomenon)	IIbB	Surgery within a few days with persistent vegetations >10 mm after one or more embolic episodes despite appropriate antibiotic therapy	IB

phase of infection when antibiotic administration was ongoing, demonstrating greater long-term survival at 10 years.<sup>28</sup>

The only prospective randomized controlled trial to date was published in 2012. The EASE trial (Early Surgery versus Conventional Treatment in Infective Endocarditis) included 76 patients with left-sided native-valve endocarditis with severe valve disease and large vegetations at high risk for embolization.<sup>29</sup> Patients were randomized to early surgery, defined as within 48 hours, or to conventional treatment, defined according to the 2005 AHA/ACC Guidelines (medical management with surgery only if symptoms persisted despite antibiotic therapy or in the case of a complication requiring urgent surgery). Inclusion criteria required a definitive diagnosis of IE, severe mitral or aortic valve disease, and a vegetation with a diameter greater than 10 mm. However notably, patients with a strong indication for surgical management were excluded, including those patients with a need for urgent surgery, patients with moderate-to-severe heart failure, cases complicated by annular or aortic abscess, and those with fungal endocarditis. As discussed in more detail below, patients with large embolic stroke at risk of hemorrhagic transformation and those with frank ICH were also excluded. In this intention-to-treat analysis, greater than two-thirds of patients randomized to conventional treatment ultimately underwent surgery, either on initial hospitalization or in follow-up. Study results demonstrated that early surgery reduced the composite primary endpoint of in-hospital death and embolic events within 6 weeks after randomization.<sup>29</sup>

Since the publication of the 2014 AHA/ACC Guidelines, 2 large meta-analyses have been published that attempt to better delineate the prognostic significance of early surgery at different specified time points. The first, published in December 2015, analyzed 16 cohort studies, including both prospective and retrospective studies comparing early surgical intervention to non-early surgical intervention (defined as both medical therapy or late surgery) and included a total of 8141 patients. For inclusion criteria, early surgery was broadly classified using the AHA/ACC definition (that taking place during initial hospitalization and before the completion of a full therapeutic course of antibiotics) but evaluated the endpoints of in-hospital mortality, long-term survival, and long-term mortality based on weekly subdivisions up to 4 weeks. This generated the finding that early surgery lowers the incidence of in-hospital and long-term mortality compared to non-early surgery, an effect size that was magnified for surgery performed within 2 weeks.<sup>30</sup> The second meta-analysis, published in February 2016, included 21 studies and generated similar conclusions. Early surgery was defined as surgery within 20 days of diagnosis or during initial hospitalization, but subgroup analyses further evaluated surgery within the first week or within the second and third weeks. All-cause

mortality for both time points favored early surgery over conventional therapy, with a greater effect size for surgeries performed within 7 days or less compared to those between eight and 20 days.<sup>31</sup> Neither of these studies comments on the presences or absence of neurologic complications, including ICH.

Notably, it is not clear from these meta-analyses if or how operative indication affects the survival benefit observed from early surgery. A newer prospective observational study sought to further evaluate this question by examining the endpoint of 6-month post-operative mortality based on timing of surgery in quartiles, including surgery performed within 1 day, between 2–6 days, between 7–15 days, and after 15 days, as well as by indication for surgery (including acute heart failure, embolic events, abscess, and persistent bacteremia). Study results failed to demonstrate a survival benefit across the quartiles of surgical timing. This was also true across operative indications, including heart failure; patients with acute heart failure who had earlier surgery exhibited no difference in in-hospital or 6-month mortality. However, in light of these negative results, it should be noted that the median time to surgery across all quartiles was 7 days with most surgeries occurring within 3 weeks of admission. Thus, within the context of this review, the vast majority of surgeries (even among the “late surgery” quartile) would still be considered relatively early.<sup>32</sup>

## **Surgical timing in cases of intracranial hemorrhage**

### **Challenges in the ICH population**

Understanding the extent to which results favoring early surgical intervention apply to patients with IE complicated by neurologic disease, especially ICH, is a critical but challenging dilemma. On the one hand, high-dose systemic anticoagulation carries the risks of further bleeding and neurologic deterioration, yet on the other hand, early surgery has been shown to prevent recurrent embolic events. In the only randomized controlled trial on surgical timing, the EASE trial described above, results favoring early surgery over conventional treatment were exclusively driven by a reduction in embolic phenomena. No patients randomized to early surgery experienced cerebral embolism compared to 13% of those randomized to conventional treatment. Furthermore, most embolic events occur early in the clinical course, with over half occurring within the first week of therapy.<sup>8</sup> Given that a major mechanism of ICH is related to septic cerebral emboli, definitive surgical repair may mitigate the risk of anticoagulation by decreasing ongoing cerebral injury.<sup>22,33</sup> Unfortunately, EASE trial results are not generalizable to the ICH population. While 30% of patients who underwent early surgery and 28% of patients randomized to conventional treatment had evidence of cerebral embolism on

admission, lesion characteristics for these patients are not available. Further, patients with large embolic stroke at risk of hemorrhagic transformation and those with frank ICH were excluded.<sup>29</sup>

### Early studies, current guidelines

Because of these limitations in available evidence, the AHA/ACC 2017 Guidelines were consistent with those of 2014, which assigned a Class IIb recommendation for delayed surgery, defined as at least 4 weeks, for patients with major ischemic stroke or ICH.<sup>12,34</sup> Importantly, this recommendation is based on only one study, a 2013 multicenter cohort study of 1345 patients that included 12 patients with “cerebral hemorrhage” who underwent surgery. While the study demonstrated high mortality and neurologic deterioration associated with early surgery, it was based on just four cases for whom surgery occurred within 2 weeks (75% mortality, 50% new bleeding events), three cases for whom surgery occurred within the third week (66% mortality, 33% new bleeding events), and five cases for whom surgery occurred after 3 weeks (40% mortality, 20% bleeding events).<sup>24</sup> Importantly, the study did not include further characterization of the size or nature of the hemorrhagic lesions for these 12 cases, nor information on pre-operative neurologic or functional status. Interpreting a causal relationship between surgical timing and clinical outcomes from these data is essentially impossible. This is not only because of the small number of included patients, but also because of treatment selection bias in which clinicians may decide that sicker patients, who are more likely to have poorer outcomes, need surgery earlier. As such, there is confounding between early surgery and clinical outcomes.

Another early cohort study similarly demonstrated worse outcomes for surgical patients with IE complicated by ICH but did not consistently demonstrate an association with early surgery. Eishi et al. analyzed 34 patients with preoperative “cerebral hemorrhage,” finding that none of the 12 patients who underwent surgery between two and 28 days of hemorrhage onset experienced neurologic deterioration, though four of 21 patients (19%) who received surgery more than 4 weeks later did experience exacerbation of cerebral complications. The paper does not include specifics on the nature of ICH lesions (with the exception of Figure 5, which contains the computed tomographic scans for one patient with cerebral hemorrhage who underwent mitral valve replacement 15 days after hemorrhage without complication).<sup>35</sup>

### Newer studies, better outcomes

Since that time, small studies in patients with cerebrovascular complications, including those with some degree of hemorrhage, have suggested that the risk of neurologic deterioration following early surgery may be overestimated. While those patients with microbleeds are not

consistently grouped within the ICH population, a retrospective study in 375 patients with septic cerebral emboli, including those with evidence of microhemorrhage (as above, defined as asymptomatic lesions detectable only by certain MRI sequences), found that early surgical intervention (within 14 days and a mean of 6 days) did not lead to significantly worse outcomes postoperatively, relative to patients without preoperative cerebral emboli.<sup>25,36</sup> These findings are particularly meaningful in the context of another study that looked at non-surgical IE patients, finding that the presence of cerebral microbleeds was an independent predictor of impending ICH over a three-month follow up period (OR 34.0, 95% CI 1.3–17,300).<sup>37</sup> If cerebral microbleeds truly are a predictor of more significant forms of ICH, evidence suggesting that early surgery is well tolerated in these patients becomes more applicable to the ICH population as a whole.

Diab et al analyzed which preoperative radiographic characteristics predicted postoperative ICH; with “post-operative ICH” defined specifically as primary intracerebral (intraparenchymal) bleeding, subdural hemorrhage, subarachnoid hemorrhage, and ischemic infarcts associated with hemorrhagic transformation. Their analysis included 24 patients with “pre-operative hemorrhagic cerebral infarcts,” which included patients with “hemorrhagic stroke” (by definition, accompanied by an acute neurologic deficit, N = 19) and “silent ischemic infarcts with small hemorrhagic transformation” (N = 3). While the group did demonstrate that preoperative infarcts associated with hemorrhage tended to have a higher incidence of postoperative ICH (4/24) compared to those without hemorrhage (5/94), these results were not statistically significant (OR: 3.56, 95% CI: 0.87–14.46,  $P = .082$ ). Patients who did develop postoperative ICH had a significantly higher in-hospital mortality rate (71% vs 22%,  $P < .001$ ).<sup>38</sup>

While these studies help to understand operative risk in patients with a range of cerebrovascular complications, only a subset of their study populations included those with some degree of pre-operative hemorrhage. There is now a small but growing body of literature focused specifically on patients with pre-operative ICH, including patients with more complicated lesions including subarachnoid hemorrhage from ruptured mycotic aneurysm. Accordingly, Yoshioka et al. analyzed 30 IE patients with pre-operative ICH who underwent surgery. In this study, ICH was defined as cerebral hemorrhage (N = 18, with median hemorrhage size reported as 20 mm in maximal length), subarachnoid hemorrhage (N = 8), and hemorrhagic infarction (N = 4, hemorrhage associated with low density infarct region). Eight of these patients had an associated preoperative mycotic aneurysm; one patient underwent surgical resection and six patients underwent clipping prior to cardiac surgery. Irrespective of the timing of valvular surgery, none of these 30 patients experienced neurological deterioration or died of

neurologic complications. Furthermore, postoperative neuroimaging did not demonstrate exacerbation of hemorrhagic lesions, even for those 11 patients who underwent surgery within 2 weeks of ICH diagnosis.<sup>39</sup>

In another, more recent study, Kume et al compared postoperative outcomes in 25 patients with preoperative ICH (N=25) to patients without pre-operative ICH (N=123). The preoperative ICH group included 13 patients with “hemorrhagic infarction” (volume of hemorrhage ranging from 1–10 mL) and 12 patients with hemorrhage without evidence of infarction (including intraparenchymal and subarachnoid hemorrhage). The study found that when comparing ICH to non-ICH patients, there was no significant difference in postoperative mortality ( $P=.134$ ) or postoperative hemorrhage ( $P=.429$ ). Furthermore, when comparing ICH patients operated on within 14 days of hemorrhage to those operated on after 14 days, there was no significant difference in postoperative hemorrhage, even up to 12 years after surgery ( $P=.904$ ).<sup>40</sup>

Notably, a subset of study participants (51/148) underwent dedicated vascular imaging including either magnetic resonance angiography (MRA) or computed tomography (CT) angiography (CTA), and of these, 14 patients had mycotic aneurysms (36% of ICH patients and 4% of non-ICH patients). While the study concluded that the only independent risk factor for postoperative cerebral hemorrhage was the presence of mycotic aneurysm preoperatively (when looking at all 14 patients), none of the 4/14 patients who underwent treatment of mycotic aneurysm prior to cardiac surgery experienced postoperative ICH.<sup>40</sup>

A meta-analysis was recently published by Tam et al., including 27 observational studies and comparing mortality and neurologic exacerbation in early and late surgery for IE complicated by neurologic events. The paper included studies in both ischemic and hemorrhagic stroke, with “hemorrhagic stroke” encompassing both transformed ischemic lesions and primary intraparenchymal hemorrhage. A sensitivity analysis examined the interaction between timing of surgery and mortality, finding that for patients with hemorrhagic stroke, there was no significant difference in perioperative mortality for surgery performed within 7 days, within 14 days, within 21 days, or within 28 days (overall interaction  $P=.47$ ). Furthermore, a separate subgroup analysis evaluated patients with intraparenchymal hemorrhage, in which there was no overall difference in postoperative neurologic deterioration when early surgery was performed <7 days, <14 days, <21 days, or <28 days compared to late surgery (overall interaction  $P=.27$ ).<sup>33</sup>

### Insights from stroke neurology

Both the Yoshioko and Kume studies above are novel in that they focus specifically on the preoperative ICH

population, and therefore, are better able to characterize this cohort. While not explicitly defined but implicit in their descriptions of preoperative ICH (and more explicitly stated in the meta-analysis by Tam et al), three distinct lesion categories emerge based on mechanism of hemorrhage: ischemic stroke with hemorrhagic transformation, primary intraparenchymal hemorrhage, and subarachnoid hemorrhage. Because of the small population of patients in these studies, it is very difficult to draw any definitive conclusions regarding operative/bleeding risk based on hemorrhage subtype. Yet these concepts are better defined within the non-IE stroke population. Drawing from this literature may prove highly informative and suggests that defining high-risk characteristics of a particular lesion likely depends on the mechanism of hemorrhage. With this in mind, we wish to explicitly discuss five lesion subtypes: cerebral microbleeds, ischemic stroke with hemorrhagic transformation, primary intraparenchymal hemorrhage, mycotic aneurysm, and subarachnoid hemorrhage.

Again, while microbleeds are not consistently included within the spectrum of ICH, existing non-IE stroke literature suggests that their identification may be highly meaningful from a prognostic standpoint. Specifically, the presence of lobar and/or cortical microhemorrhage may signify underlying cerebral amyloid angiopathy (CAA), a diagnosis which carries an elevated risk of spontaneous hemorrhage.<sup>41</sup> It is therefore important to identify patients with CAA prior to cardiac surgery, as the risks of anticoagulation in such cases may be prohibitive.

In the ischemic stroke population, systemic thrombolysis (eg, tissue-type plasminogen activator [tPA]) is known to increase the risk of intracranial hemorrhage. Hemorrhagic transformation is not uncommon in infarcted tissue even without thrombolytic therapy, and in one major study, the presence of ICH (both symptomatic and asymptomatic and as diagnosed by CT scan) was observed in 7% (12/168) of ischemic stroke patients treated with tPA and 1% (2/165) of patients treated with placebo.<sup>42,43</sup> Subsequently, a number of risk stratifiers have been devised to help identify which patients are at greatest risk for ICH; one of the most predictive factors seems to be stroke severity, defined by neurologic status at presentation.<sup>44</sup> The prognostic significance of ICH associated with ischemic stroke has also been well studied; the European Cooperative Acute Stroke Study provided an anatomic classification scheme for extent of bleeding in order to analyze which lesion severities were associated with poor clinical outcomes. Accordingly, the study found that for lesions defined as “hemorrhagic infarction” (ie, ischemic lesions with petechial or confluent hemorrhage within the infarct area), there was no association between early clinical deterioration and three-month mortality. This was also true in cases of parenchymal

hematoma (solid clot of blood) when the clot area comprised less than 30% of the infarct area.<sup>43</sup>

For non-IE primary intraparenchymal hemorrhage, a number of scoring systems have been developed for prognostication of long-term outcome. These generally incorporate lesion size, lesion location, neurologic function at presentation, age, and pre-morbid functional status. Accordingly, volume of hemorrhage greater than or equal to 30 mL and intraventricular/infratentorial location of origin tend to be associated with worse prognosis.<sup>45-47</sup>

While mycotic aneurysms do not strictly fall under the category of ICH, these lesions are common in IE and are the presumed source of bleeding in subarachnoid hemorrhage. For intracranial arterial aneurysms in the non-IE population, asymptomatic aneurysm >5–10 mm are generally considered high-risk, as are unsecured mycotic aneurysms.<sup>48</sup> In these cases, surgical or endovascular intervention should be strongly considered but is dependent on location (eg, basilar versus elsewhere) and aneurysm characteristics (eg, broad-versus narrow-based). The presence of subarachnoid hemorrhage without known structural lesion is highly suggestive of arterial/aneurysmal bleeding and warrants further investigation with dedicated vascular imaging (classically with CT angiogram or conventional angiography). Those cases that reveal a culprit vessel can then be managed with similar considerations as that for aneurysm. Those without a culprit vessel are termed “angiogram-negative SAH” and generally fall into two categories depending on the pattern of bleed (perimesencephalic SAH and diffuse classic SAH). While controversial, these patients (particularly with perimesencephalic SAH) seem to have very low rates of re-bleeding and disease-specific complications.<sup>49-51</sup>

A newer study in ICH patients with IE demonstrated this link between prognosis and mechanism of hemorrhage. The study, which included 68 patients with ICH, analyzed patient outcomes according to mechanism of hemorrhage including three main categories: “ruptured mycotic aneurysm” (N = 22), “hemorrhage after ischemic stroke” (N = 27), and “hemorrhage of undetermined etiology” (N = 19). Outcomes for the ICH population were then compared to IE patients with isolated ischemic stroke (N = 157) and IE patients without neurologic vascular complications (N = 738). The study found that patients with ICH of undetermined etiology had higher mortality rates overall. It also revealed quite compelling data with respect to surgical management. Of the 68 patients with ICH, 60 patients were noted to have an indication for cardiac surgery. Of those 60 patients, 38 underwent cardiac surgery at a median of 34 days post-ICH, and none experienced neurologic deterioration postoperatively (including 17 patients who underwent cardiac surgery within 4 weeks of ICH diagnosis). However what is most notable is that, for patients with

ICH who had an indication for surgical management but did not ultimately undergo surgery, time-to-event curves for death from any cause demonstrated a significantly worse prognosis for patients who were managed non-operatively ( $P = .005$ ). This again suggests that the key to successful management of this difficult population requires careful assessment of competing cardiac and neurologic risk.<sup>9</sup> See Table 2 for a summary of the studies highlighted above.

## Proposed algorithm for clinical decision making

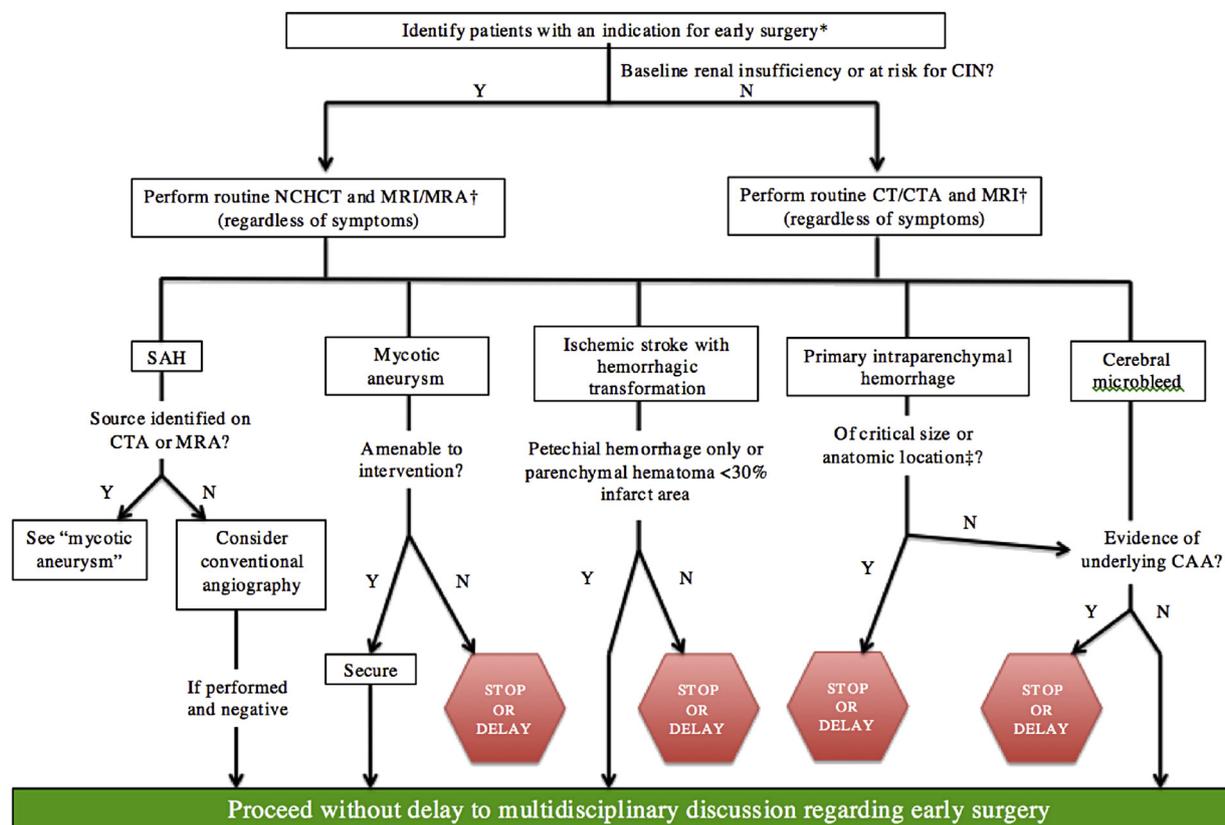
Based on the above review of data for both early surgery in IE and surgical timing in cases complicated by ICH, as well as insights from stroke neurology in non-IE cases, we propose the following management algorithm (Figure 1). For patients with left-sided native-valve endocarditis, initial clinical assessment should first seek to identify those patients with an indication for early cardiac surgery. As above, generally accepted indications include: heart failure secondary to valvular dysfunction, evidence of cardiac structural tissue compromise (ie, annular or aortic abscess, heart block, destructive lesion), need for source control (eg, persistent infection despite 5-7 days of antibiotics and/or recurrent embolic events), infection caused by fungal or highly resistant organisms, and vegetation size >10 mm. There is likely a greater benefit to early surgery for various indications, but this has not been rigorously studied. In general, vegetation size alone (eg, >10 mm) seems to be a weaker indication for surgery, though as noted above, it is known that larger vegetations (especially >13 mm) carry a higher risk of embolic complications.<sup>8</sup>

We propose that for all patients meeting the above criteria, optimal preoperative assessment should include CNS imaging to screen for asymptomatic ICH and aneurysm. The optimal upfront imaging modality will realistically be affected by a number of factors, including scanner availability, patient stability, etc. Noncontrast head computed tomography (NCHCT) is likely to be the most feasible upfront study and will identify the presence of hemorrhage (especially if large) and subacute, larger infarcts. In the absence of renal insufficiency or other contraindication to contrast administration, CTA should be performed, as this has a slightly higher sensitivity for the detection of small (<5 mm) and infectious aneurysms compared to three-dimensional time-of-flight MRA (which is a reasonable alternative in patients who cannot receive contrast).<sup>52,53</sup> Routine MRI will further identify patients with microhemorrhage (by definition, CT-negative and identified only on specific MRI sequences) in addition to relevant non-hemorrhagic lesions such as early/acute or small infarcts, which may require additional perioperative assessment and/or management.

**Table 2.** Summary of observational studies on cardiac surgery in endocarditis with preoperative intracranial hemorrhage

Publication (year)	Patient population	Lesion characteristics	Preoperative neurologic function	Timing of cardiac surgery	Outcomes
García-Cabrera (2013)	<ul style="list-style-type: none"> <li>- Total cohort (N = 1345)</li> <li>- ICH patients (N = 60)</li> <li>- ICH patients who underwent surgery (N = 12)</li> </ul>	<ul style="list-style-type: none"> <li>- Ischemic with hemorrhagic transformation (N = 9)</li> <li>- Primary intraparenchymal hemorrhage (N = 43)</li> <li>- SAH/ruptured mycotic aneurysm (N = 8)</li> </ul>	- Not specified	<ul style="list-style-type: none"> <li>- 2 weeks (N = 4)</li> <li>- 3 weeks (N = 3)</li> <li>- &gt;3 weeks (N = 5)</li> </ul>	High mortality and neurologic deterioration associated with early surgery
Eishi (1995)	<ul style="list-style-type: none"> <li>- Total cohort (N = 2523)</li> <li>- Pre-operative cerebrovascular complications (N = 244)</li> <li>- ICH patients (N = 57)</li> <li>- ICH patients who underwent surgery (N = 34)</li> </ul>	- Not specified	- Not specified	<ul style="list-style-type: none"> <li>- 2-28 days (N = 12)</li> <li>- &gt;4 weeks (N = 21)</li> </ul>	No neurologic worsening in 2-28 day group but 19% exacerbation >4 weeks
Sorabella (2015)	<ul style="list-style-type: none"> <li>- Total cohort (N = 308)</li> <li>- Pre-operative cerebrovascular complications (N = 54)</li> <li>- ICH patients who underwent surgery (N = 8)</li> </ul>	- Microhemorrhage (N = 8)	<ul style="list-style-type: none"> <li>- Focal deficit in 21 patients (39% of septic cerebral embolus cohort)</li> <li>- Non-focal deficit in 17 (32%)</li> <li>- Asymptomatic in 12 (22%)</li> </ul>	- <14 days (N = 8)	The presence of preoperative microhemorrhage is not a/w post-operative hemorrhage
Diab (2016)	<ul style="list-style-type: none"> <li>- Total cohort (N = 308)</li> <li>- Cerebral complications (N = 122)</li> <li>- ICH patients who underwent surgery (N = 43)</li> </ul>	<ul style="list-style-type: none"> <li>- Ischemic with hemorrhagic transformation (N = 21)</li> <li>- Primary intraparenchymal hemorrhage a(N = 3)</li> <li>- Microhemorrhage (N = 19)</li> </ul>	<ul style="list-style-type: none"> <li>- Neurologic deficit in 87 patients (19 with hemorrhage)</li> <li>- Asymptomatic in 31 patients (5 with hemorrhage)</li> </ul>	- Not specified	Pre-operative ICH is not a/w significantly increased post-operative stroke or hemorrhage (OR: 3.56, 95% CI: 0.87-14.46, P = .082)
Yoshioka (2014)	- Total cohort, all ICH patients who underwent surgery (N = 30)	<ul style="list-style-type: none"> <li>- Ischemic with hemorrhagic transformation (N = 4)</li> <li>- Primary intraparenchymal hemorrhage (N = 18, median diameter 20 mm)</li> <li>- SAH (N = 8)</li> </ul>	<ul style="list-style-type: none"> <li>- Paralysis of the extremities (N = 11)</li> <li>- Disturbance in consciousness (N = 6)</li> <li>- Constructional apraxia (N = 5)</li> <li>- Asymptomatic (N = 8)</li> <li>- Median modified Rankin score of 1.5</li> </ul>	<ul style="list-style-type: none"> <li>- &lt;7 days (N = 5)</li> <li>- 8-14 days (N = 6)</li> <li>- 15-28 days (N = 9)</li> <li>- &gt;29 days (N = 10)</li> </ul>	No neurologic deterioration, regardless of surgical timing
Kume (2018)	<ul style="list-style-type: none"> <li>- Total cohort (N = 148)</li> <li>- ICH patients who underwent surgery (N = 25)</li> </ul>	<ul style="list-style-type: none"> <li>- Ischemic with hemorrhagic transformation (N = 13, volume of hemorrhage ranging from 1-10 mL)</li> <li>- Primary intraparenchymal hemorrhage (N = 12)</li> <li>- Mycotic aneurysm (N = 14)</li> </ul>	<ul style="list-style-type: none"> <li>- ICH group with mean modified Rankin score of 2.1</li> </ul>	<ul style="list-style-type: none"> <li>- &lt;14 days (N = 17)</li> <li>- &gt;14 days (N = 8)</li> </ul>	No significant difference in post-operative hemorrhage between patients operated on within or after 14 days (log-rank P = .904)
Salaun (2018)	<ul style="list-style-type: none"> <li>- Total cohort (N = 963)</li> <li>- ICH patients (N = 68)</li> <li>- ICH patients who underwent surgery (N = 38)</li> </ul>	<ul style="list-style-type: none"> <li>- Ischemic with hemorrhagic transformation (N = 27)</li> <li>- Primary intraparenchymal hemorrhage (N = 19)</li> <li>- SAH/ruptured mycotic aneurysm (N = 22)</li> </ul>	- ICH group with mean Glasgow Coma Scale of 14.3	<ul style="list-style-type: none"> <li>- &lt;4 weeks (N = 17)</li> <li>- Overall median of 34 days (N = 38)</li> </ul>	<ul style="list-style-type: none"> <li>- No neurologic deterioration, regardless of surgical timing</li> <li>- For ICH patients with an indication for surgery, significantly worse outcomes for those managed non-operatively versus those managed surgically</li> </ul>

**Figure 1**



**Proposed Algorithm for Preoperative Assessment and Management** Abbreviations: CAA = cerebral amyloid angiopathy; CIN = contrast-induced nephropathy; CTA = computed tomography angiography; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; NCHCT = noncontrast head computed tomography; SAH = subarachnoid hemorrhage. \*Heart failure secondary to valvular dysfunction, evidence of cardiac structural tissue compromise (ie, annular or aortic abscess, heart block, destructive lesion), need for source control (eg, persistent infection despite 5–7 days of antibiotics and/or recurrent embolic events), infection caused by fungal or highly resistant organisms, and vegetation size >10 mm. †NCHCT is an effective and feasible study for the evaluation of SAH and subacute, larger infarcts. If not contraindicated, CTA is recommended over MRA, as it has a slightly higher sensitivity for the detection of small (<5 mm) and infectious aneurysms compared to three-dimensional time-of-flight MRA. Routine MRI will further identify patients with microhemorrhage, as well as early/acute or small infarcts. ‡While the non-IE stroke literature suggests that volume of hemorrhage <30 mL tends to be lower-risk, this has not been validated in studies with IE patients, which have only demonstrated acceptable surgical outcomes for lesions up to 10 mL. Higher risk locations include intraventricular, infratentorial, or proximity to critical functional areas such as language. Figure Legend: For patients with left-sided native-valve endocarditis, initial clinical assessment should first seek to identify those patients with an indication for early surgery. Routine pre-operative evaluation for these patients should optimally include CT/CTA + MRI (if no contraindication to contrast administration) or NCHCT + MRI/MRA (in cases of baseline renal insufficiency or risk factors for CIN). The finding of either arterial/mycotic aneurysm or ICH; including SAH, ischemic stroke with hemorrhagic transformation, intraparenchymal hemorrhage, and cerebral microbleeds; should not necessarily be considered a contraindication to early surgery. However, in higher-risk scenarios, further imaging modalities or intervention may be warranted prior to cardiac surgery.

The presence of subarachnoid hemorrhage is highly suggestive of mycotic aneurysm, which if not previously identified on CTA or MRA, may require additional investigation with conventional angiography (the gold standard for diagnosis). If aneurysm is present and amenable to surgical or endovascular repair, it should be secured prior to proceeding with cardiac surgery.

These preoperative imaging modalities will also identify patients with ischemic stroke with hemorrhagic transformation and primary intraparenchymal hemorrhage, in which operative risk will likely depend on lesion characteristics including size and anatomic location. While the non-IE stroke literature suggests that volume of hemorrhage <30 mL tends to be lower-risk, this has not

been validated in IE patients, which have only demonstrated acceptable surgical outcomes for lesions up to 10 mL. When no concerning lesions are identified on initial CT/A or MRI/A, we recommend proceeding without delay. While the definition of early surgery is variable, studies generally define this as <3 weeks.

In cases where significant concerns regarding the risk of early surgery remain (eg, upfront imaging reveals a large area of infarction or hemorrhage or hemorrhagic extension is being considered) or the decision is made to delay surgery for other reasons, serial neuroimaging may further inform surgical timing decisions. Though this method has not been published, our experience has demonstrated that a successful approach involves repeat head CT with and without contrast at 4–6 weeks to look for contrast extravasation. The presence of extensive contrast extravasation suggests that there is damage to the blood brain barrier, in which case further delay of up to 2 weeks with subsequent reassessment may be prudent. It is also reasonable to repeat CTA or MRA to evaluate for mycotic aneurysm just prior to surgery, as the risk of developing mycotic aneurysm increases as a function of duration of bacteremia exposure. More generally, because a significant portion of systemic blood flow goes to the brain, serial neuroimaging may provide information about the adequacy of medical management. In this way, serial neuroimaging can be thought of as akin to blood cultures in providing useful information regarding antibiotic effectiveness and source control. From this perspective and with respect to more general IE management, sensible times for routine neuroimaging may include: at baseline/pre-cardiac surgery (though optimal intervals for serial preoperative imaging are not known), post-cardiac surgery/valvular debridement, and/or prior to or after the discontinuation of antibiotics.

## Conclusion

Surgical timing for IE with ICH is a relatively common clinical dilemma that is without high-quality evidence to inform clinical practice. As such, substantial practice variation likely exists, related to local practice patterns and anecdotal experience. In this paper, we suggest that current guidelines, which recommend delayed surgery for ICH patients, are based on studies that likely over-estimate the risk of neurologic deterioration associated with early surgery. We further define a spectrum of ICH within the IE population based on mechanism of hemorrhage and outline a possible management algorithm for better evaluating preoperative neurologic risk.

It should be noted that this algorithm necessarily simplifies a complex clinical area, and there are many additional considerations that greatly impact the decision to proceed with surgery. These include both operative considerations (eg, complexity of valve repair/projected

duration of cardiopulmonary bypass and type of prosthetic valve/implications for duration of postoperative anticoagulation) and patient-specific factors (eg, age, medical co-morbidities/surgical risk, and refractory/recurrent drug use disorder). A patient characteristic that appears to be particularly relevant is preoperative neurologic symptoms, which in the non-IE stroke literature, seem to have prognostic significance in terms of bleeding risk. As highlighted in Table 2, most available studies in this space fail to provide information on patients' baseline neurologic function. These studies further lack explicit characterization of preoperative CNS lesions. We have attempted to address this gap in knowledge by incorporating management paradigms from non-IE stroke neurology.

For all of the above reasons, we emphasize that surgical timing decisions should be made on a case-by-case basis with a multidisciplinary team of specialists who can weigh the risks and benefits of early surgery, including consideration of both cardiac and neurologic risk, within each unique patient-specific context.

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