ESC European Society of Cardiology

European Heart Journal (2022) **00**, 1–9
https://doi.org/10.1093/eurheartj/ehab898

STATE OF THE ART REVIEW
Valvular heart disease

Current recommendations and uncertainties for surgical treatment of infective endocarditis: a comparison of American and European cardiovascular guidelines

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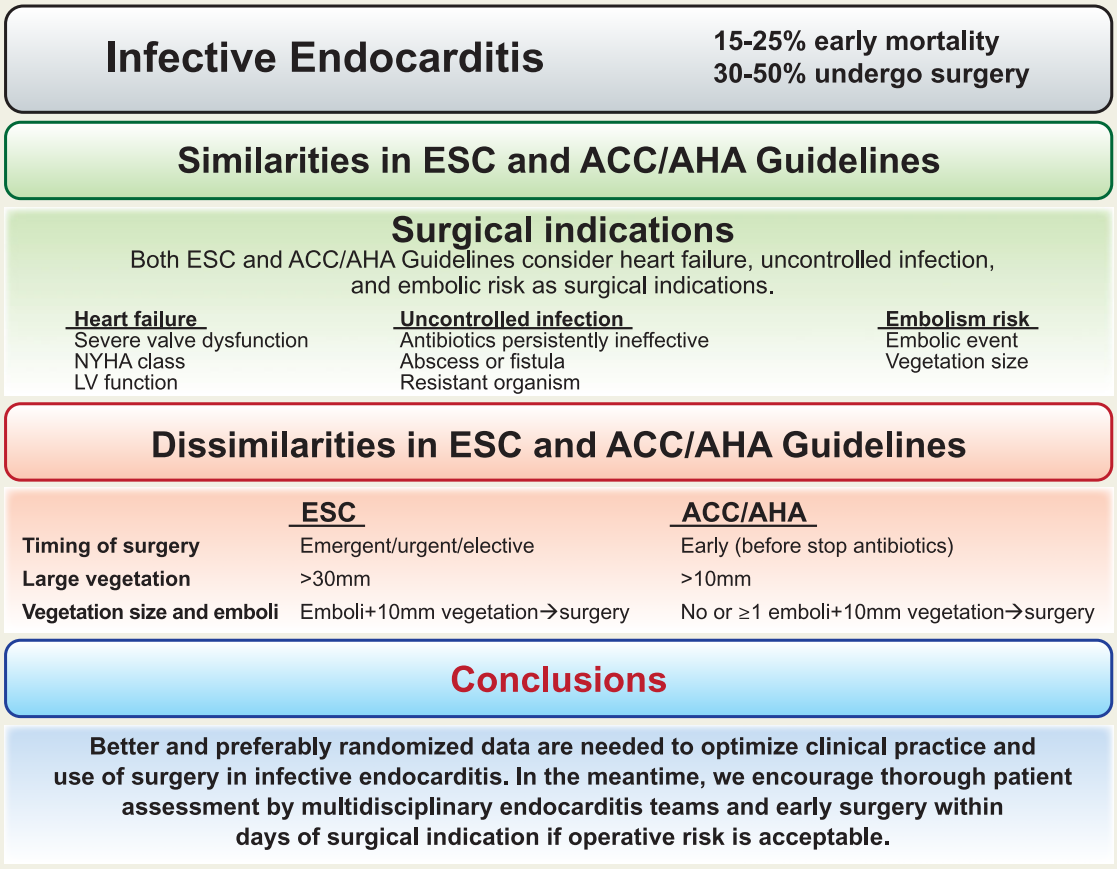
Received 2 July 2021; revised 11 December 2021; accepted 21 December 2021



Graphical Abstract An overview of the interplay between surgical indication, risk, and timing and where current European and American guidelines differ.

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Surgery is an effective therapy in the treatment of left-sided infective endocarditis (IE) in patients for whom antibiotic treatment alone is unlikely to be curative or may be associated with ongoing risk of complications. However, the interplay between indication for surgery, its risk, and timing is complex and there continue to be challenges in defining the effects of surgery on disease-related outcome. Guidelines published by the American College of Cardiology/American Heart Association and the European Society of Cardiology provide recommendations for the use of surgery in IE, but these are limited by a low level of evidence related to predominantly observational studies with inherent selection and survival biases. Evidence to guide the timing of surgery in IE is less robust, and predominantly based on expert consensus. Delays between IE diagnosis and recognition of an IE complication as a surgical indication and transfers to surgical centres also impact surgical timing. This comparison of the two guidelines exposes areas of uncertainty and gaps in current evidence for the use of surgery in IE across different indications, particularly related to its timing and consideration of operative risk.

Keywords Endocarditis • Surgery • Guideline • Valve • Heart

Introduction

Infective endocarditis (IE) is a disease with high morbidity and mortality, despite improvements in diagnostic testing, antibiotic therapy, and surgical treatment. In contemporary studies of left-sided IE, the effect of these advancements in the management and outcome has been attenuated by changes in both host and microbiological factors, such as the increase in healthcare-associated and *Staphylococcus aureus* infections.

Surgery treatment of complicated left-sided IE is performed in ~50% of cases in tertiary centres.[1] In general, surgery is recommended in cases in which antibiotic treatment alone may not be curative or may be associated with worse outcomes. The decision to perform surgery in IE is complex in its balance between predicted benefit vs. operative risk, and multidisciplinary care of IE patients has been associated with appropriate (not necessarily more frequent) use of surgery and lower mortality.

Our objective is to describe the recommendations for surgery in IE, including indications, patient selection and operative risk, and timing of surgery with comparisons between the recommendations of major cardiovascular professional societies, the American College of Cardiology/American Heart Association (ACC/AHA),[2] and the European Society of Cardiology (ESC).[3] Although the ESC have recently updated their guideline for the management of valvular heart disease,[4] IE management recommendations have not changed since 2015.[3] In this review, we highlight areas with different recommendations and uncertainties for the use of surgery in IE.

Surgical indications in infective endocarditis

A comparison of surgical indications in IE as recommended by the ACC/AHA and ESC guidelines is shown in *Table 1*. Importantly, both guidelines are limited by relatively low level of evidence predominantly from observational studies or expert consensus rather than randomized trials, with an increasing percentage of recommendations with the lowest level of evidence.[5] Recommendations for the use and timing of cardiac surgery in IE are inherently confounded by both selection and survival biases of retrospective, observational studies. The ACC/AHA societies have recently updated recommendations for surgical treatment of IE in the 2020 ACC/AHA Guideline for the Management of Valvular Heart Disease,[2] which was previously revised in 2017. However, even in comparison with the earlier 2014 ACC/AHA guideline, the recommendations for surgery in IE have remained unchanged. In considering specific IE complications as separate indications for surgery with different levels of recommendation, it should be noted that patients may have more than one simultaneous complication [e.g. heart failure (HF) with large vegetation; intracardiac abscess in *S. aureus* aortic valve IE].

Heart failure and shock

Based on observational studies that have reported over a two-fold higher in-hospital mortality in IE complicated by HF without surgical intervention,[6] patients with valve dysfunction resulting in symptoms of HF are recommended to undergo surgery. Both ESC and ACC/AHA treatment guidelines have similar recommendations for surgery for these patients with IE and HF. Few studies have described the relationship between HF severity, surgical treatment, and outcome. In a large, multinational study of left-sided IE, HF occurred in one-third of cases, and the majority of these cases had severe, NYHA 3 or 4 HF.[6] The relative risk reduction in mortality was greater in patients with severe HF symptoms than those with mild symptoms, although surgery was found to be associated with a survival benefit across the spectrum of HF severity.[6] The ESC guideline favours cardiac surgery for IE complicated by HF, but states that for IE patients with NYHA 1 or 2 HF symptoms, 'medical management with antibiotics under strict clinical and echocardiographic observation is a good option'.[3] However, because the rate of HF progression in IE may be rapid because of the acute nature of aortic or mitral valve regurgitation and the lack of ventricular adaptation as present in chronic valvular regurgitation, we favour proceeding with cardiac surgery within a few days when acute, severe left-sided regurgitation is present regardless of NYHA class.

At the extreme of HF severity, surgery for cardiogenic shock in IE has been associated with higher 30-day mortality than patients without shock (19.5 vs. 14.6%), but this mortality is significantly lower than mitral valve IE complicated by septic shock who underwent surgery (65.8%).[7] Because septic shock was a strong independent predictor of both short-term mortality and postoperative complications compared with cardiogenic shock, identifying the primary

Table 1 Comparison of cardiology society guideline recommendations for surgery in native valve infective endocarditis

Surgical indication	Class of recommendation and level of evidence	
	ACC/AHA	ESC
Valve dysfunction resulting in HF symptoms	1, B	I, B
Highly resistant organism	1, B Including *S. aureus*	I, C Fungi or multiresistant organism
Heart block, annular, or aortic abscess or destructive penetrating lesion	1, B	I, B
Persistent bacteraemia or fever lasting >5 days after onset of appropriate antibiotic therapy	1, B	IIa, B
Recurrent emboli and persistent vegetations despite appropriate antibiotic therapy	2a, B	I, B[a]
Left-sided valve IE who exhibit mobile vegetations >10 mm in length with or without clinical evidence of embolic event	2b, B	IIb, C[b]
Prosthetic valve IE caused by staphylococci or non-HACEK gram-negative bacteria	NA	IIa, C
Prosthetic valve IE and relapsing infection without other identifiable source	1, C	NA

[a]ESC guideline specifies 'persistent vegetations >10 mm after one or more embolic episode'.
[b]ESC guideline specifies for large vegetations (>15 mm) without embolic event or other indication for surgery (Class IIb recommendation).

aetiology of shock in these haemodynamically unstable patients carries important treatment and prognostic implications.[7] Septic shock in IE with end-organ failure is associated with lower selection for surgical intervention due to high operative risk and poor long-term outcome.[8] Therefore, we recommend careful, multidisciplinary decisions about surgery and its timing by a multidisciplinary team of endocarditis specialists (as per ESC guideline)[3] and surgical intervention for septic shock when another recognized indication, such as HF, abscess, or persistent bacteraemia, is present.

Microorganism and persistent bacteraemia

It is noteworthy that *S. aureus*, the most common cause of IE in the current era, is highlighted among the different microbiological causes of IE in both guidelines.[2,3] In the updated ACC/AHA guideline, IE caused by highly resistant organisms such as *S. aureus* or fungal organisms remains a Class 1 indication for early surgery in IE.[2] In contrast, the ESC guideline recommends surgery in native valve IE caused by *S. aureus* if a favourable early response to antibiotics is not achieved.[3]

Although *S. aureus* IE is associated with more frequent and severe IE complications, this infection often occurs in patients with other comorbid medical conditions and in the setting of healthcare-associated bacteraemia, such as patients requiring haemodialysis.[9] *Staphylococcus aureus* IE is strongly associated with higher in-hospital and 6-month mortality in left-sided IE,[10–12] but patients with *S. aureus* are less likely to undergo cardiac surgery during the index hospitalization because of adverse host factors, higher rates of stroke and sepsis, and overall higher operative risk.[1] Although *S. aureus* is the most common cause of IE and often associated with IE complications, among patients in the society of thoracic surgeons (STS) database of 21 388 operations for left-sided IE, Streptococcus species (28%) was as common as for Staphylococcal (27%) species.[13] In the prospective, multinational International Collaboration on Endocarditis (ICE) registry of IE, *S. aureus* IE complicated by sepsis was not generally treated with surgery.[1] Yet, carefully selected patients with complicated *S. aureus* IE treated with surgery do have similar survival benefits compared with IE caused by other bacterial species[14] and lower mortality compared with *S. aureus* IE treated with medical therapy.[15] A recent study from the STS database found significantly higher operative mortality for patients with fungal [adjusted odds ratio (OR) 2.9] and Staphylococcus (adjusted OR 1.4) compared with Streptococcal IE.[13] Because of the presence of adverse host factors and resulting higher operative risk in patients with *S. aureus* IE, we agree with the European guideline that surgery in left-sided *S. aureus* IE may not reduce morbidity or mortality unless another surgical indication is present.

In most cases of non-fungal IE, the clinical decision to surgically intervene in IE for persistent infection would likely be the more frequent clinical indication, independent of the specific microorganism. Both the ACC/AHA and ESC guidelines recommend surgery for IE with persistent bacteraemia, defined as continued positive blood cultures for the causative microorganism after 5 days of appropriate antibiotic therapy. In general, the use of surgery for this complication as the only indication is more strongly considered in left-sided IE caused by resistant organisms and when other sources of metastatic infection are controlled.

Embolic risk reduction

In the absence of a prior embolic event, surgery for left-sided vegetation >10 mm has been found to reduce future embolic events in the Early Surgery versus Conventional Treatment for Infective Endocarditis (EASE) trial which included patients with low operative risk and severe valvular regurgitation.[16] In 2015, the ESC IE guideline incorporated this finding to recommend (Class IIa)

urgent surgery for aortic or mitral valve IE vegetation >10 mm with severe stenosis or regurgitation and low operative risk.[3] The ACC/AHA guideline suggests considering early surgery (during initial hospitalization and before completion of antibiotic therapy) as Class IIb recommendation for left-sided, mobile vegetation >10 mm, without respect to valve lesion severity or operative risk.[2] In contrast, the ESC guideline uses size >15 mm as a threshold to consider surgery without other indications.[3] Other characteristics of the vegetation, including location (mitral valve), mobility, and microorganism, have been associated with a higher risk of the embolic event, but these are not explicitly described as criteria for surgery in either guideline. For secondary prevention of recurrent embolic events, both the ACC/AHA and ESC guidelines support surgery for patients with embolic events despite appropriate antibiotic therapy who have persistent vegetation, regardless of vegetation size.[2,3]

For the prevention of embolic events, it is important to recognize that appropriate antibiotic therapy reduces the risk of the embolic event within 1 week of treatment.[17] Thus, the benefit of surgery for reducing embolic risk is greatest during the first week of antibiotic treatment and surgery for vegetation >10 mm as the sole indication should not be delayed.

Prosthetic valve endocarditis

For patients with prosthetic valve endocarditis (PVE), the outcomes are poor for medically managed patients, yet the benefit of routine surgical treatment is not strongly supported. Patients with PVE have a higher rate of prior IE, healthcare-associated infection, and intracardiac abscess, but lower rates of new valvular regurgitation.[18] Heart failure is similarly common in PV as in native valve IE.[18] Surgery in PVE is associated with a lower unadjusted risk of in-hospital mortality compared with medical therapy, but the characteristics of these patients undergoing different treatments are dissimilar.[19] After propensity adjustment for surgery selection and survival bias, Lalani *et al.*[19] found that surgery for PVE was not associated with lower 1-year mortality for all PVE cases, while smaller and older studies found varying results.[20–24] However, in complicated PVE, surgery has been associated with lower mortality.[25] The ESC IE guideline recommends urgent or elective surgery in PVE complicated by HF, severe prosthetic dysfunction, abscess, or staphylococcal or non-HACEK gram-negative PVE.[3] The ACC/AHA guideline generally does not differentiate indications for surgery in native vs. PVE but does recommend early surgery for PVE with 'relapsing infection (defined as recurrence of bacteremia after a complete course of appropriate antibiotics and subsequent negative blood culture results) without other identifiable source of infection'.[2] In summary, we favour surgical intervention in PVE when other IE complication is present and with similar timing as for native valve IE recommendations.

Right-sided infective endocarditis

Although the ACC/AHA guideline does not include a specific recommendation for surgery in right-sided IE, similar clinical indications as for surgery in left-sided IE should apply, including recurrent emboli (septic pulmonary) and persistent bacteraemia.[26] Other indications for surgery in left-sided IE, such as HF or abscess formation, are less likely to complicate right-sided IE.[26] *Staphylococcus aureus* is the most common microbiological cause (60–90%) of right-sided IE.[3] Tricuspid valve IE is commonly associated with a cardiac implantable electronic device (CIED) IE and its outcome.[25] Extraction of the infected CIED is strongly recommended[2] and is associated with lower mortality,[25] but cardiac surgery is typically not needed for CIED removal. Because right-sided IE is often caused healthcare-associated bacteraemia or injection drug use,[9] patients with right-sided IE are at higher risk of recurrent IE and interventions should be pursued to reduce their risk of future bacteraemia.

In contrast, the ESC does include specific guideline recommendations for right-sided IE and surgery,[3] although supporting data are weak. Surgical treatment for right-sided IE is generally recommended by the ESC when medical treatment fails: (i) bacteraemia despite appropriate antibiotics, (ii) persistent large tricuspid vegetation above 20 mm and pulmonary emboli despite appropriate antibiotics, and (iii) HF despite aggressive treatment. We note that these recommendations are categorized as Class of recommendation as IIa with a level of evidence of C.[3]

Surgical patient selection and operative risk assessment

After an indication for surgical treatment of complicated IE has been identified, assessment of the patient's operative risk and the potential benefit of surgery is performed. Both the American and European guidelines recommend that all decisions regarding the indication and timing of surgical intervention for IE should be made by a multidisciplinary endocarditis team of infectious disease, cardiology, and cardiac surgery specialists. Several observational studies have found that implementation of this multidisciplinary care team for IE cases was associated with lower in-hospital and 1-year mortality in IE.[27,28] In these studies, the use of surgery in the active treatment phase of IE has been high. The use of this endocarditis team has included a shorter duration of time between surgical indication and surgical intervention,[28] but it is unclear whether the earlier intervention was independently associated with lower mortality. It is important to qualify that this IE multidisciplinary team should include specialists in cardiology, cardiac surgery, and infectious disease with an understanding of IE treatment options and their appropriate and optimal use in the individual case, not simply a heart team of sub-specialists.

In studies evaluating the timing and outcome of surgery in IE, adjustment for operative risk has not been routinely applied in observational studies, though many of these clinical characteristics are similarly related to in-hospital mortality with medical treatment of IE and longer-term survival.[1,29] A number of risk models have been developed to predict the operative risk of surgery specifically in IE (*Table 2*), with the most common endpoint of in-hospital mortality.[30–33] All operative risk models are limited by inherent bias in the selection of patients for surgical treatment. These risk models have been derived in different numbers of patients, number of surgical centres, and across a wide range of observed operative mortality.

In general, among these risk scores, patient age and haemodynamic instability, especially cardiogenic shock, are the strongest predictors of operative risk, similar to all cardiac surgeries. The

Table 2 Comparison of infective endocarditis-specific operative risk models

Risk score	Year	Derivation cohort	AUC	Mortality endpoint	Comments
Society of thoracic surgeons-infective endocarditis (STS-IE)[31]	2011	19 543 native or prosthetic IE surgeries in USA	0.76	30 days = 8.2%	• 48% had healed IE • Includes surgical urgency status (elective, urgent, or emergent) • No microbiological or echocardiographic data • Strongest predictors were shock/emergency status, creatinine ≥2.0, active IE
De Feo *et al.*[33]	2012	440 native valve IE surgeries at single Italian centre	0.88	In-hospital = 9.1%	• No prosthetic IE • 17% had healed IE • Predominantly streptococcal IE • 10% right-sided IE • Strongest predictors were ventilatory support and NYHA IV
PALSUSE[30]	2014	437 cases of native, prosthetic, and CIED IE at 26 Spanish centres	0.84	In-hospital = 24.3%	• Includes logistic EuroSCORE as dichotomous variable • Strongest predictors were Staph IE, PVE, urgent surgery
RISK-E[32]	2017	671 left-sided IE surgery cases at 3 Spanish centres	0.82	In-hospital = 28.6%	• Strongest predictors were age and presence of shock • Type of surgery not included • AUC 0.76 in external validation
EndoSCORE[48]	2018	2715 native or prosthetic valve IE at 26 Italian centres	0.85	30 days = 11.0%	• Strongest predictors were shock, organism (fungal, Pseudomonas, *S. aureus*), multiple valve surgery

STS-IE risk score includes a higher number of variables including comorbid medical conditions, whereas other risk scores focus predominantly on acute status and IE complications.[31] As a result, the STS-IE score has also been associated with longer-term mortality in IE.[1] Because of selection bias in each of these different IE cohorts, the discrimination of the scores in external validation in other IE cohorts is not as optimal as in the derivation cohorts.[32,34,35] However, the calibration of several of the IE-specific risk scores have been found to be more accurate than global cardiac surgery risk scores in external IE cohorts.[33]

The STS-IE score identified the urgency of surgery (defined as surgery clinically needed before hospital discharge) as independently associated with higher mortality, but none of the risk scores evaluated the timing of surgery as a discrete variable. These risk scores may be applied to characterize different cohorts of patients undergoing surgery for IE, and to assess the observed vs. expected mortality. Furthermore, many of the specific variables included in these models are also associated with survival independent of surgical intervention and beyond the index hospitalization.[1] Therefore, these operative risk models may be valuable for defining host factors, particularly those that are not modifiable, that may affect the relative benefit of surgery in IE.

In clinical practice, the calculation of operative risk may not alter the management of the patient with IE, even when operative risk is high (e.g. STS-IE predicted risk of mortality ≥8%). Another risk model, derived and validated from two cohorts of the International Collaboration on Endocarditis (ICE), includes both surgically and medically treated IE patients to predict 6-month mortality.[29] However, even in cases of high operative risk, most IE complications that are indications for surgery are associated with a very high rate of mortality if treated with medical therapy only. Furthermore, many of the conditions associated with operative risk in IE are not modifiable, and thus, delaying surgery may result in a higher operative risk if haemodynamic instability, worsening HF, or other end-organ complications occur. Lastly, these operative risk models to date have not included other clinically meaningful outcomes than operative (short-term) mortality. As opposed to the use of a specific model in clinical practice to perform or withhold surgery in complicated IE, we favour using an IE-specific risk model (i) for shared decision-making with the individual patient when surgery is indicated and (ii) to describe the operative risk of a patient cohort in studies evaluating the use and outcome of surgery in IE. Additionally, as a more disease-related composite endpoint than in-hospital mortality alone, we propose that freedom from all-cause death, disabling stroke, or IE relapse at 6 months is a more comprehensive outcome for surgery in IE.

Surgical timing

The optimal timing of surgical treatment should be based on the patient's clinical status as related to operative risk and the goal to prevent new or further morbidity or mortality related to an IE complication. The ACC/AHA guideline recommends early surgical intervention, defined as during the initial hospitalization and

before completion of a full therapeutic course of antibiotics, for IE complications related to destructive cardiac lesions, inadequate response to antibiotic treatment, or for the prevention of new or recurrent embolic events.[2] Similarly, the STS defines urgent surgery as that which is required during the same hospitalization in order to minimize the risk of further clinical deterioration,[36] but without more defined time intervals. The ESC guideline is more specific when it comes to the timing of surgery and stratifies timing into the following categories: emergency (<24 h), urgent (within days), and elective (after at least 1–2 weeks of antibiotic treatment).[3] Both of these IE guideline recommendations are predominantly based on expert consensus, with very limited studies to support a strong level of evidence.

To evaluate the relationship between surgery timing and outcome in IE, an accurate determination of the surgical procedure date relative to a preceding clinically relevant and definable event is necessary. Although the day of surgery is easily captured in observational studies, the initiating date, whether the day of hospital admission, diagnosis of definite IE, or the finding of a complication that is an indication for surgery, is less precisely recorded to calculate the time to surgery. For instance, in a typical case of IE, blood cultures may identify bacteraemia 24–48 h after admission; a transthoracic echocardiogram may be performed on the same or next day to confirm evidence of endocardial infection (vegetation or new or worsening valve regurgitation). Although the diagnosis of definite IE will be fulfilled by modified Duke criteria, the timing of surgical indication may be delayed by several days until a complication occurs (e.g. HF symptoms, embolic event, or persistent bacteraemia) or is visualized (e.g. intracardiac abscess). This time interval between IE diagnosis and indication for surgery is further complicated if a patient is initially diagnosed and treated at another hospital before referral and transfer to the surgical centre.

Because of these confounding factors, the appropriate timing of surgery in complicated IE is not well defined. To date, only one small, randomized study has evaluated earlier surgery compared with usual care (delayed surgery or antibiotic treatment alone) in left-sided IE with large valvular vegetations (>10 mm) and severe regurgitation for the composite primary endpoint of the systemic embolic event or in-hospital death within 6 weeks of randomization.[16] In the EASE trial ($n = 76$), patients without other surgical indications who were treated with surgery within 48 h of randomization (after transoesophageal echocardiogram) had significantly fewer embolic events with clinical signs or symptoms compared with conventional therapy (0 vs. 21%, respectively).[16] Almost all embolic events occurred within the first few weeks after randomization. Of note, 77% of the patients randomized to conventional treatment underwent surgery during the index hospitalization for worsening IE complications. Although 13% of patients in the conventional treatment arm had cerebral embolic events, the severity of these neurologic events was not reported. There was no difference in overall mortality at 6 weeks between the two treatment groups, and overall mortality was very low (only two deaths in-hospital and three deaths at 6 months in the overall cohort).[16] Importantly, the cohort of patients was young (mean age 46 years), had predominantly streptococcal IE, and low operative risk.[16]

In clinical practice, surgical treatment in IE is more commonly performed after a complication has occurred, rather than prophylactically to reduce the risk of a future complication. Surgery within 1 week of antibiotic treatment has been associated with lower 6-month mortality among patients with more IE complications (higher propensity for surgery treatment).[37] Although expedited surgery may reduce the risk of additional complications or worsening clinical status, surgical urgency is strongly associated with higher in-hospital mortality. In a larger, multinational registry of left-sided IE, surgery was performed at a median of 7 days from hospital admission, after an IE complication had occurred as the indication for surgery.[38] Shorter time to surgery was associated with hospital transfer, acute HF, and urgent clinical status. With propensity adjustment for earlier surgery timing, there was a trend towards higher 6-month mortality with early surgery compared with later surgery [hazard ratio = 1.68, 95% confidence interval (CI) 0.97–2.96; $P = 0.065$], which may reflect the surgical urgency and higher operative risk of these acutely ill patients.[38]

A comparison of guideline recommendations for timing of surgery in left-sided IE is shown in *Table 3*. In contrast to the very broad time interval described by the ACC/AHA ('during initial hospitalization and before completion of a full therapeutic course of antibiotics'),[39] the ESC guideline recommends surgery within a few days for most every IE complication, with some uncertainty in cases due to resistant infection or relapse of PV IE.[3] It is unclear whether this narrower window of time from IE complication to surgery (e.g. 2 vs. 4 days) is associated with lower operative mortality, as unstable or clinically worsening patients are more likely to undergo urgent surgery. However, for the prevention of new embolic events in the presence of vegetation size >10 mm, the results of the EASE trial support surgery within 48 h of transoesophageal echocardiography. Although the findings from the EASE study[16] need confirmation in larger trials, we recommend surgery within 48 h of the diagnosis for the prevention of embolic events in patients with left-sided vegetation >10 mm, although this suggested timing differs from the current ESC guidelines (where surgery within 7 days is recommended).[3] In summarizing the ACC/AHA and ESC recommendations for surgery timing, three general categories of indications can be thus considered: (i) HF due to severe valvular regurgitation, (ii) refractory infection, and (iii) prevention of embolic events, either first or recurrent (*Figure 1*).

Surgery timing in relation to stroke in infective endocarditis

In the absence of neurologic signs complicating IE, neither the ACC/AHA or ESC guideline recommends routine brain imaging to detect evidence of infarction or haemorrhage, but brain imaging is recommended by the American Association of Thoracic Surgery prior to cardiac surgery.[40] The ACC/AHA guideline offers two recommendations for the timing of cardiac surgery in IE in the setting of stroke as an IE complication, both with Class 2b status.[2] In patients with IE and recent stroke but without evidence of intracranial haemorrhage or extensive neurologic damage (such as major

Table 3 Comparison of ACC/AHA and ESC guideline recommendations for timing of surgery in complicated left-sided infective endocarditis

Surgical indication	Recommendation for timing of surgery	
	ACC/AHA	ESC
Valve dysfunction resulting in HF symptoms	Early ('during initial hospitalization and before completion of a full therapeutic course of antibiotics')	Emergency (<24 h)
Highly resistant organism	Early	Urgent/elective
Heart block, annular or aortic abscess, or destructive penetrating lesion	Early	Urgent ('within a few days')
Persistent bacteraemia or fever lasting >5 days after onset of appropriate antibiotic therapy	Early	Urgent
Recurrent emboli and persistent vegetations despite appropriate antibiotic therapy	Early	Urgent
Left-sided valve IE who exhibit mobile vegetations >10 mm in length with or without clinical evidence of embolic event	Early	Urgent
Prosthetic valve IE caused by staphylococci or non-HACEK gram-negative bacteria	NA	Urgent/elective
Prosthetic valve IE and relapsing infection without other identifiable source	Early	NA

deficit in function), surgery may be performed without delay when a surgical indication is present. This recommendation is based on observational studies,[41,42] which have found similar survival and neurologic outcome in patients without cerebral haemorrhage or major neurologic impairment. In contrast, for patients with IE and either haemorrhagic stroke or ischaemic stroke with extensive neurological damage, delay of surgery for at least 4 weeks is advised.[2] The ESC guideline is consistent with these recommendations for surgery after stroke in IE.[3]

Surgical timing, risk of infective endocarditis relapse, and antibiotic therapy after surgery

A consideration in the timing of surgery in IE is whether early surgery, especially in the setting of persistent bacteraemia, may increase the risk of IE relapse. Relapse of IE is a feared outcome and will often require surgical treatment. Extended intravenous

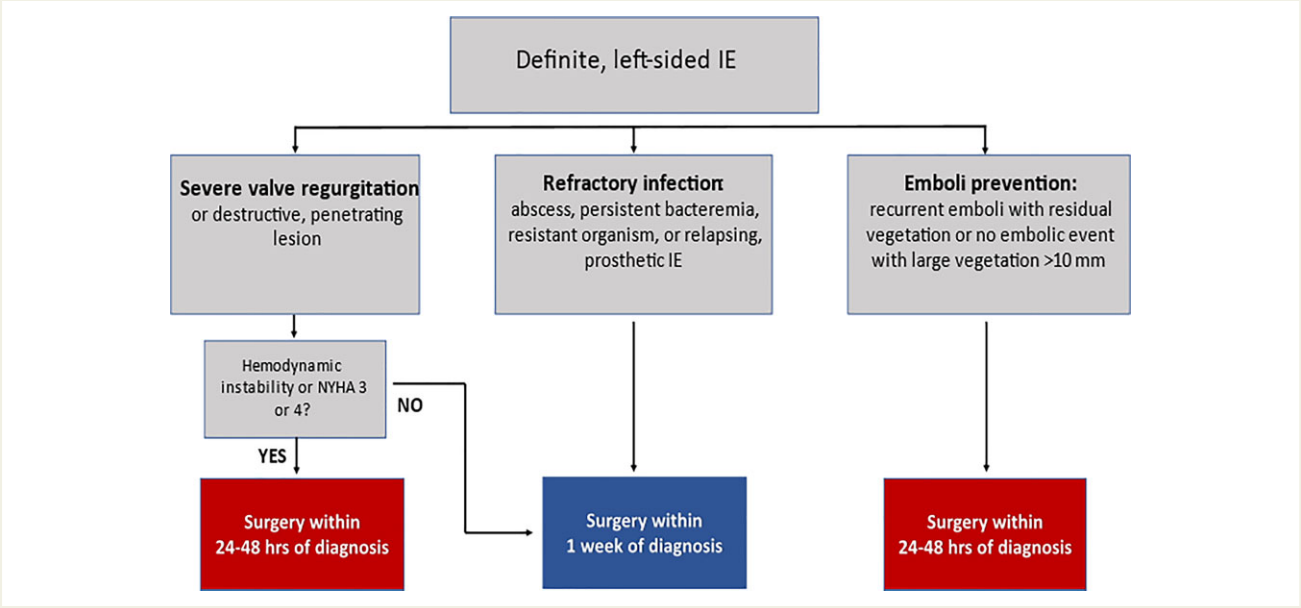

Figure 1 Guideline-based summary of surgical indications and timing in left-sided infective endocarditis. The figure shows a summary of guideline recommendations for surgery according to the three overarching indications for surgery. For the prevention of embolic events in patients with large (>10 mm) left-sided vegetations, it is the authors' recommendation that surgery should be performed within 48 h of diagnosis based on the EASE trial. This recommendation for timing of surgery is different from the current guidelines (ESC guidelines recommend surgery <7 days).

antibiotic regimens for the total duration of 4–6 weeks has therefore been advocated since the 1950s,[43] with rates of relapse currently <5%.[44] In the setting of active IE, the result of valve specimen culture has been studied as a variable to tailor the duration of antibiotic therapy after surgery. An observational study by Morris *et al.*[45] suggests that after surgery, a shortened duration of intravenous antibiotic treatment when valve culture was negative was associated with a low risk of IE relapse.

The ESC IE guideline does not consider IE relapse or recurrence an indication for surgery; the ACC/AHA guideline only refers to relapsing infection in PVE as an indication for surgery. In cases of IE relapse within 6 months of index IE diagnosis with the same organism after initial clearance of bacteraemia, we favour surgical intervention when there is a residual vegetation or other intracardiac source of infection (e.g. abscess or prosthetic implant) when operative risk is acceptable.

More recently, a shorter duration of intravenous antibiotic therapy before surgery has been associated with a higher frequency of positive valve culture.[46] In this situation, a 4- to 6-week duration of intravenous antibiotic therapy after surgery is generally recommended.[3,39] Post-surgical treatment may even be changed from an intravenous to oral antibiotic regimen in accordance with the criteria of the recent POET (partial oral treatment of endocarditis) randomized, controlled trial.[47] This trial tested whether oral treatment was non-inferior to intravenous treatment after an initial period of stabilization with intravenous antibiotics. Approximately 40% of the study patients underwent surgical therapy. In IE patients who had satisfactory clinical responses to initial antibiotic treatment administered intravenously for at least 10 days (and at least 7 days post-operatively if valve surgery was performed), completion of treatment with oral antibiotics was non-inferior to intravenous antibiotic therapy for the primary composite endpoint of all-cause mortality, unplanned cardiac surgery, embolic events, or relapse of bacteraemia with the primary pathogen, from randomization until 6 months after antibiotic treatment was completed.[47]

Conclusions

Current recommendations for surgical intervention in IE focus on IE complications associated with higher mortality if treated with medical therapy alone. To date, there is no strong evidence that earlier surgery within a few days of IE diagnosis is associated with lower mortality. In clinical practice, the timing and urgency of surgery are generally related to the haemodynamic status of the patient, which significantly impacts the patient's operative risk as well. Surgery for the prevention of complications, specifically embolic events in left-sided IE with large vegetation, carries a modest recommendation for benefit, but surgery in this setting should be expedited and performed within a few days of IE diagnosis before any embolic event has occurred. Surgery for PVE is indicated for similar complications of native valve IE, with the exception of uncomplicated Staphylococcal infection.

The predominance of evidence supporting the use and timing of surgery in IE is based on observational studies with inherent selection and survival biases, which may reduce their generalizability. There continue to be important differences in cardiovascular societal guidelines for the use and timing of surgery in IE. Observational studies and guidelines for surgical treatment of IE can be strengthened by the prospective, multidisciplinary, and multinational collaboration to address these uncertainties. To improve the level of evidence for the use and timing of surgery in IE, more randomized trials are greatly needed.

Conflict of interest: none declared.

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