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REVIEW

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Intimal aortic atherosclerosis in cardiac surgery: surgical strategies to prevent embolic stroke

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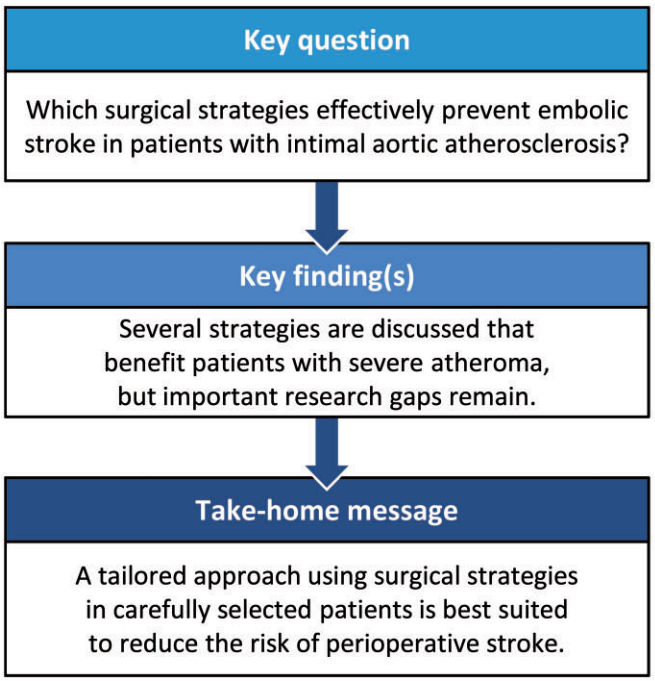

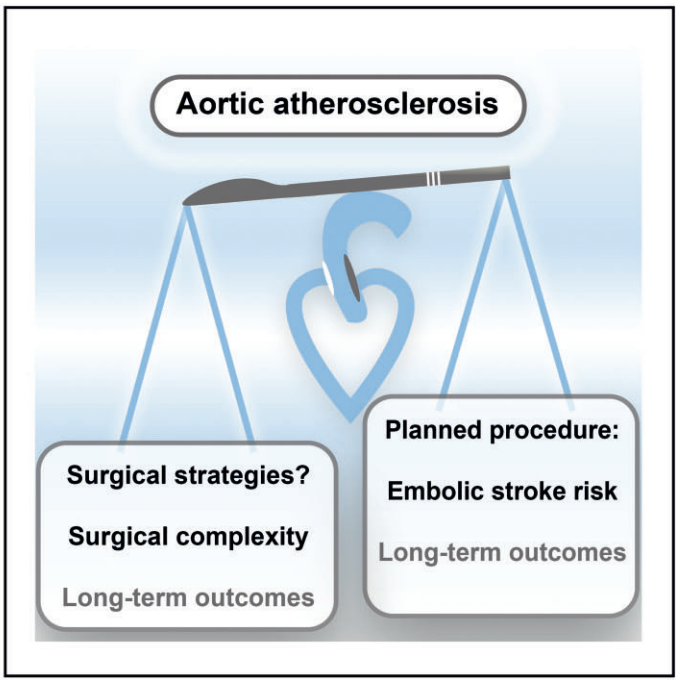

Abstract

OBJECTIVES: Although the incidence of perioperative stroke after cardiac surgery gradually decreased over the last decades, there is much variation between centres. This review aimed to create a concise overview of the evidence on possible surgical strategies to prevent embolic stroke in patients with intimal aortic atherosclerosis.

METHODS: The PubMed and EMBASE databases were searched for studies on surgical management of aortic atherosclerosis and the association with perioperative stroke in cardiac surgery, including specific searches on the most common types of surgery. Articles were screened with emphasis on studies comparing multiple strategies and studies reporting on the patients' severity of aortic atherosclerosis. The main findings were summarized in a figure, with a grade of the corresponding level of evidence.

RESULTS: Regarding embolic stroke risk, aortic atherosclerosis of the tunica intima is most relevant. Although several strategies in general cardiac surgery seem to be beneficial in severe disease, none have conclusively been proven most effective. Off-pump surgery in coronary artery bypass grafting should be preferred with severe atherosclerosis, if the required expertise is present. Although transcatheter aortic valve replacement is used as an alternative to surgery in patients with a porcelain aorta, the risk profile concerning intimal atherosclerosis remains poorly defined.

CONCLUSIONS: A tailored approach that uses the discussed alternative strategies in carefully selected patients is best suited to reduce the risk of perioperative stroke without compromising other outcomes. More research is needed, especially on the perioperative stroke risk in patients with moderate aortic atherosclerosis.

Keywords: Aortic atherosclerosis • Cardiac surgery • Perioperative stroke

ABBREVIATIONS

CABG	Coronary artery bypass grafting
EAU	Epiaortic ultrasound
MRI	Magnetic resonance imaging
OPCAB	Off-pump CABG
PCI	Percutaneous coronary intervention
SAVR	Surgical aortic valve replacement
TAVR	Transcatheter aortic valve replacement

INTRODUCTION

In cardiac surgery, perioperative stroke is a debilitating complication that increases mortality [1]. The incidence of perioperative stroke is frequently underestimated, as more cases are identified with systematic neurological screening and more cerebral damage is observed on postoperative magnetic resonance imaging (MRI) [2]. Nevertheless, over the last decades an increased understanding of mechanisms underlying perioperative stroke has led to a steady decline in the stroke rate, despite increasing complexity of the population [3]. However, there is high variation in risk-adjusted stroke rates and subsequent mortality between institutions [4]. Proven effective methods like intraoperative screening of the ascending aorta with epiaortic ultrasound (EAU) are being underused [5], potentially leading to suboptimal outcomes in patients with aortic atherosclerosis. Although many prior reviews have discussed the prevention of stroke in cardiac surgery, none have created a concise overview of the evidence on possible surgical strategies to prevent embolic stroke in patients with intimal aortic atherosclerosis.

METHODS

Search strategy

Between July and November 2020 literature searches were performed, closing on 1 November 2020 using PubMed and EMBASE (W.G.K.), focusing on studies on the association of aortic atherosclerosis and perioperative stroke, strategies in general cardiac surgical procedures and strategies in coronary artery bypass grafting (CABG) and surgical aortic valve replacement (SAVR) specifically. Articles were screened and relevant references were identified. No prior reviews with a specific focus on surgical management of intimal aortic atherosclerosis were found. The search strategies are described in the Supplementary Material. This document also contains tabulated data from the evaluated clinical studies.

Article selection

The articles were screened with regard to quality and relevance, with emphasis on studies either (i) comparing different strategies or a preventive strategy with a control group or (ii) evaluating the severity of aortic atherosclerosis. These emphases were chosen to deal with the variation in stroke risk among study populations, the confounding effect of different management policies between studies when encountering aortic atherosclerosis and the variable definitions and adjudication of stroke as an end point in studies published prior to the first standardized neurological end points consensus document [6, 7]. We focused on studies reporting the severity of atherosclerosis because the benefit of preventive strategies is very dependent on this. Clinical studies fulfilling these 2 criteria were tabulated (Supplementary Material). Studies were screened for overlapping reporting of study populations by comparing institution and enrolment period and subsequently excluded from tabulation. Right-sided valve surgery, mitral valve surgery, primary aortic surgery and reoperations were not included. The main findings are summarized in Fig. 1, grading the underlying evidence using the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence [8].

AORTIC ATHEROSCLEROSIS

Many different terms are used to describe atherosclerosis of the aorta, such as 'shaggy aorta', 'hostile aorta', 'porcelain aorta', aortic atheroma, aortic (soft) plaque and aortic calcification. Two types of aortic atherosclerosis should be distinguished.

Tunica intima versus tunica media disease

Intimal atherosclerosis is a pathophysiological process that is mainly mediated by low-density-lipid cholesterol [9]. This aspect of atherosclerosis is often referred to as soft plaque. Early in this process the role of calcification is limited, while later, spotty calcification can expand, forming larger lumps or even plates. A distinct process is calcification of the medial layer of arteries, which is more likely to expand to diffuse calcified plaques, that can extend to circumferential plaques. This is associated with general, rather than local inflammation, and is often associated with type-II diabetes or chronic kidney failure [10].

Intimal atherosclerosis as a risk factor for stroke

Distinction between these 2 entities has important clinical consequences. Medial calcification and porcelain aorta can lead to mechanical difficulties (e.g. incomplete occlusion, aortic dissection) in clamping the aorta but do not seem to increase the rate of perioperative stroke as much, once intimal atherosclerosis is ruled out [11, 12]. In this review, we will focus on atherosclerosis of the intimal layer (further referred to as aortic atherosclerosis), which can be present both with and without calcification. Aortic atherosclerosis is related to the risk of perioperative stroke in patients undergoing cardiac surgery [13]. Causality of this relationship is difficult to prove but seems likely, based on several findings. Most debris captured in the aorta during cardiac surgery was found to be fibrous atheroma tissue [14]. Aortic

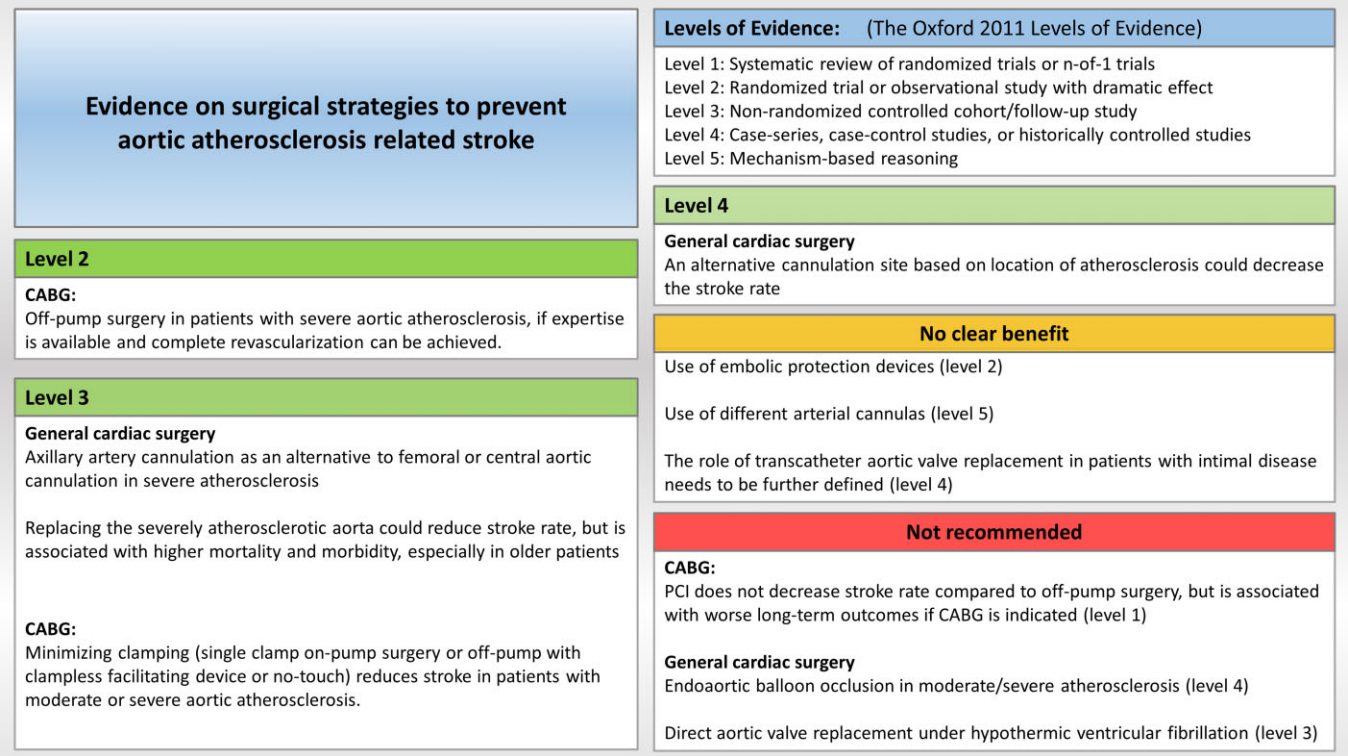

Figure 1: A visual summary of the strategies evaluated. CABG: coronary artery bypass grafting.

atherosclerosis was identified by numerous studies as an independent predictor of stroke, with a higher risk in patients with more severe atherosclerosis [2, 13, 15]. Most importantly, decreasing aortic manipulation in patients with aortic atherosclerosis decreases the rate of stroke [16, 17].

Diagnosis of aortic atherosclerosis

The golden standard for the diagnosis of intimal aortic atherosclerosis is intraoperative EAU [17, 18]. Transoesophageal echocardiography is less sensitive, as the view of the distal ascending aorta is blocked by the left main bronchus [18]. Contrast-enhanced computed tomography has the advantage of preoperative screening but exposes the patient to radiation and contrast medium [12].

Prevalence of aortic atherosclerosis

Aortic atherosclerosis is more frequent in patients undergoing cardiac surgery than in the general population, especially in patients undergoing CABG or SAVR [19, 20]. The severity is commonly categorized in 5 categories, based on the degree of intimal thickening, irregularity and mobility of the atheroma, using either of 2 classifications (Table 1) [18, 21]. Sample images of atherosclerosis severity are shown in Fig. 2. As an example, studies in patients undergoing CABG report somewhere between 27% and 68% for mild, 11% and 47% for moderate and 2% and 6% for severe atheroma [16, 22, 23]. The prevalence is influenced by variations in the classification used, population studied and type of imaging modality used.

Severity of aortic atherosclerosis

The risk of stroke increases with increasing severity of atherosclerosis [15]. In a study assessing aortic atherosclerosis with EAU before and after cannulation, new intima lesions after aortic manipulation were more frequent in moderate (11.8%) and severe (33.3%) atheroma, than in less than moderate atheroma (0.8%), implying that mainly moderate and severe atheroma are clinically relevant [23]. For severe atheroma this increased risk has been shown repeatedly [15, 21]. The risk is less well described for moderate atheroma, which is often combined with mild or severe

Table 1: Intimal atherosclerosis classifications

Grade	Severity	Katz [20]	ASE/EACVI guideline [21]
I	Normal	Normal aorta	Intimal thickness <2 mm
II	Mild	Extensive intimal thickening	Focal or diffuse intimal thickness 2–3 mm
III	Moderate	Sessile atheroma extending <5 mm into the lumen	3–5 mm (no mobile/ulcerated components)
IV	Severe	Sessile atheroma protruding >5 mm (protruding atheroma)	>5 mm (no mobile/ulcerated components)
V		Mobile atheroma	Complex grade 2–4 atheroma plus mobile or ulcer

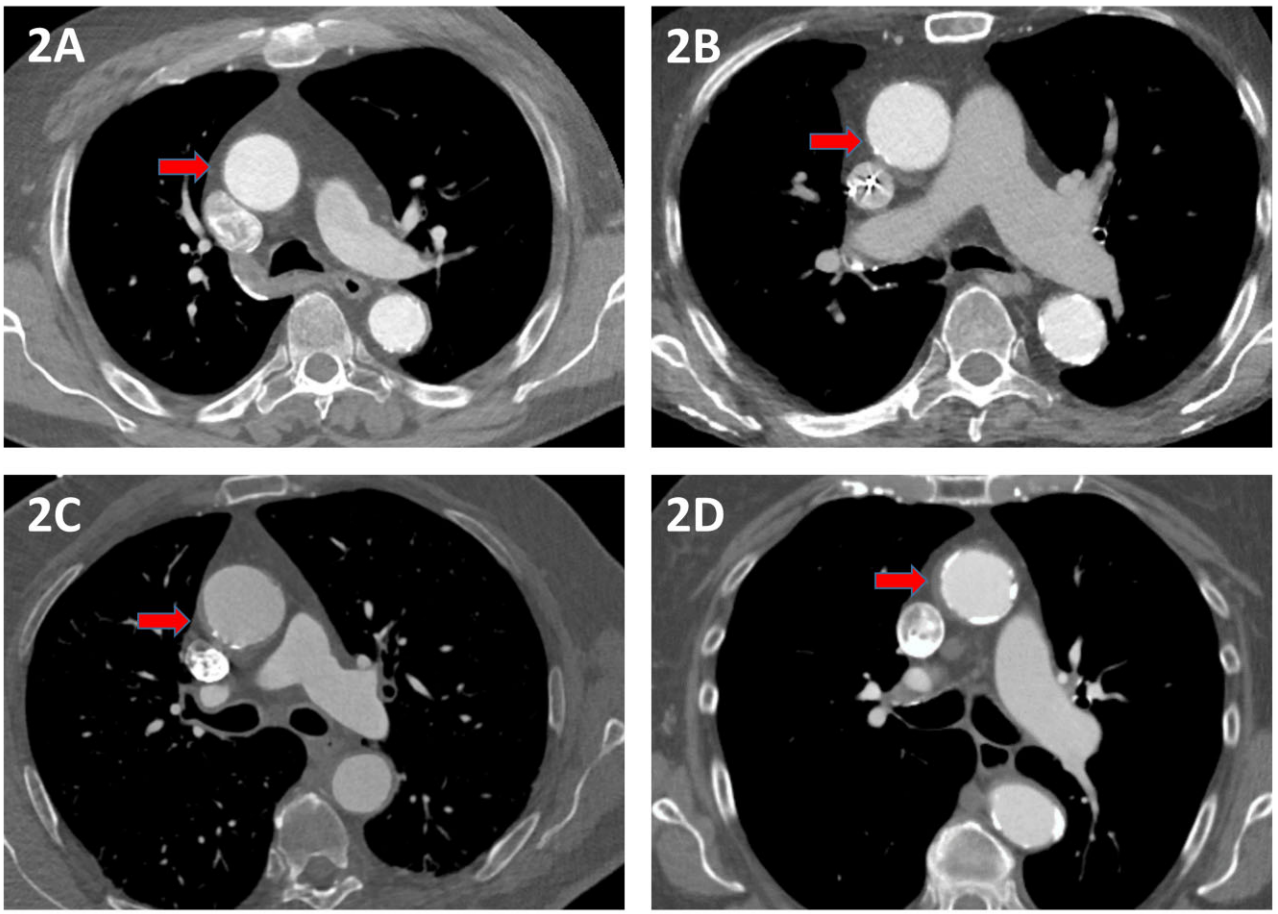

Figure 2: Computed tomography images of the grades of aortic atherosclerosis. The red arrows indicate (**A**) a normal aorta; (**B**) mild atherosclerosis with intimal irregularity but wall thickness <3 mm; (**C**) moderate atherosclerosis with irregularity and wall thickness <5 mm; and (**D**) severe atherosclerosis with pronounced intimal thickening >5 mm.

atheroma, masking the risk for this specific category. A case–control study in 1969 patients undergoing cardiac surgery with EAU found a significantly higher prevalence of severe atheroma (10.9% vs 4.8%), but not moderate atheroma (15.2% vs 12.6%) in stroke patients [24]. Similar results were observed in another case–control study where moderate atheroma was defined as wall thickness more than 3 mm in 1 of 3 segments of the ascending aorta [15]. Another study found no association between the number of particulate emboli captured by a filter and the aortic wall thickness in patients with mild or moderate atheroma [25]. However, the risk of stroke is also related to the extent and location of the plaque within the aorta [13]. Moreover, the benefit of different surgical strategies depends also on the effectiveness and risk profiles of these strategies. Thus, no uniform cut-off value necessitating change of the surgical strategy can be provided and this should be evaluated for each alternative strategy in particular.

GENERAL CARDIAC SURGERY

Many cardiac surgical procedures are performed with cardiopulmonary bypass and under cardiac arrest. This requires arterial cannulation and cross-clamping of the aorta. Several strategies have been proposed for patients with aortic atherosclerosis, when no substantial disease-free part can be identified.

Arterial cannulas

When direct aortic cannulation in a disease-free part of the ascending aorta is still possible, aortic arch atherosclerosis could increase the risk of stroke through a 'sandblasting effect' [26]. The arterial cannula's higher flow velocity can damage vulnerable plaques and dislodge debris. The extent to which this phenomenon contributes to the rate of embolic stroke is poorly defined. Several alterations on arterial cannulas have been suggested, to decrease the flow velocity and wall shear stress. No studies powered to find a clinically meaningful effect on stroke rate have been performed [27, 28]. While different types of arterial cannulas have different haemodynamic profiles, no clear recommendation can be provided on their role in preventing embolic stroke in patients with aortic atherosclerosis [29].

Embolic protection devices

Filtration or suction-based devices have been developed to capture dislodged debris before leaving the aorta. Indeed, these devices capture embolic tissue in up to 97% of patients [14]. A first randomized trial using a suction-based device observed a reduction in brain lesions on postoperative MRI [30]. A large randomized trial evaluating the filtration-based device did not observe a reduction in stroke [14]. The most recent trial

randomized 383 patients undergoing SAVR between the filtration and suction-based devices or a control group. The trial was halted after the interim analysis for expected futility in observing a difference in central nervous system infarction between the 3 groups [31]. Taken together, there is some evidence that these devices can decrease the number and volume of lesions on postoperative MRI, but no clear reduction of perioperative stroke has been established.

Alternatives to clamping the diseased aorta

Instead of capturing debris after embolization, other methods aim to prevent embolization during clamping, for instance occluding the aorta with an endoaortic balloon. Instead of externally compressing and deforming the aortic walls, a balloon catheter is inflated in the ascending aorta to obstruct blood flow. In patients undergoing minimally invasive mitral valve surgery, this procedure has shown similar stroke rates compared to external clamping [32]. However, patients with significant ilio-aortic atherosclerosis are usually excluded from minimally invasive surgery. Only one study evaluated this method specifically in 52 patients with aortic atherosclerosis, reporting unfavourable outcomes [33]. A higher mortality rate was observed, both compared to a preoperative risk score and to unmatched patients with a regular approach. The stroke rate was also marginally increased (3.8% vs 0.8%, $P = 0.067$). Thus, currently no studies support the use of endoaortic balloon occlusion in patients with aortic atherosclerosis.

Another, more radical alternative to clamping is the use of hypothermia and ventricular fibrillation to enable intracardiac surgery. Two cohorts of 24 and 13 patients have been described performing direct SAVR under deep hypothermic circulatory arrest [34, 35]. The outcomes were not compared to a control group, but high stroke rates of 17% and 15% were observed, leading the authors of the latter study to largely abandon the strategy of direct SAVR without performing concomitant aortic surgery [36].

Alternative cannulation sites

To avoid manipulation of the ascending aorta, other sites are available for arterial cannulation. The most pragmatic alternative, especially when atherosclerosis has been diagnosed intraoperatively, is the aortic arch. Besides the increased technical complexity, a problem with this approach is that the severity of aortic atherosclerosis usually increases along the length of the aorta. Few patients with a diseased ascending aorta will have a disease-free aortic arch [19]. The same problem occurs with femoral cannulation, as the descending aorta is even more prone to atherosclerosis [19]. Despite being a safe and frequently used location in selected patients undergoing minimally invasive surgery, retrograde perfusion from the femoral artery has been associated with increased stroke rates in patients with aortic atherosclerosis [37, 38]. This association was not observed in studies on minimally invasive mitral valve surgery, when femoral cannulation was changed to aortic or axillary cannulation in patients with severe aortic atherosclerosis [39, 40]. Retrograde perfusion thus seems to be safe as long as these patients are excluded. A suitable alternative for patients with severe atheroma is the axillary artery. An experimental study showed that the altered blood flow from axillary cannulation, significantly decreased embolization of microparticles released in the ascending aorta, compared to cannulation of the ascending aorta [41]. This was supported by a recent study using computed tomography angiography screening prior to minimally invasive surgery . In 270 patients, no strokes were observed, despite rigorous postoperative neurological assessment including MRI, when switching from femoral to axillary cannulation in patients with aortoiliac wall thickness >3 mm. However, in most procedures, there remains a need for clamping, thereby decreasing, but not obviating manipulation of the diseased aorta.

Aortic replacement

A more frequently used strategy when applying deep hypothermic circulatory arrest for severe atherosclerosis is to replace the aorta altogether [34]. Circulatory arrest is usually required, as the distal ascending aorta is rarely spared, preventing the use of cross-clamping. Aortic replacement is associated with higher risks of mortality and stroke in patients with aortic atherosclerosis, when compared to other indications [43]. Supplementary Material, Table S2 shows studies that evaluated this approach in patient with severe aortic atherosclerosis. In the larger cohorts, the stroke rate ranged from 2.8% to 18%. Although these stroke rates were higher compared to control groups with less severe atherosclerosis, they were equal or lower compared to other surgical strategies, including aortic endarterectomy. However, some studies observed higher rates of other postoperative morbidity, such as postoperative bleeding and acute renal failure [35, 44, 45]. Mortality rates were also high, ranging from 3% to 25%. In a cohort where 73% of patients with severe aortic calcification underwent aortic replacement, there was a large age-related difference in mortality and stroke rates between patients aged below (3.8% and 6.4%) or above 80 years old (15.9% and 18.2%, respectively) [36]. Without larger studies and reliable control groups, mortality and stroke rates are difficult to interpret. Aortic replacement was often used as a last resort in patients with exclusively severe aortic atherosclerosis, reflecting a high surgical risk. Aortic replacement adds significant complexity to the surgery and requires surgical experience, which could influence surgical outcome in low-volume centres.

CORONARY ARTERY BYPASS GRAFTING

Surgical strategies in CABG, mainly regarding the use of clamping and extracorporeal bypass, have extensively been studied. These strategies have not demonstrated lower stroke rates when used routinely [46, 47]. However, in selected patients, there is substantial evidence that they effectively reduce stroke rate.

On-pump coronary artery bypass grafting

A randomized trial compared a clampless versus partial clamp strategy in off-pump CABG (OPCAB) and single versus double clamp strategy in on-pump CABG patients with no or only mild atherosclerosis [48]. In these patients, the more extensive clamping strategies did not result in more microemboli, suggesting that clamping is safe in most patients undergoing CABG. In 2 propensity-matched studies comparing CABG with a single or multiple clamping strategy for the proximal anastomosis, no difference in stroke risk was observed [49, 50]. However, both propensity

scores in these registry-based studies did not control for aortic atheroma. Increased use of the single clamp technique in patients with aortic atherosclerosis could have obscured the potential benefit of less clamping. No studies evaluated single or additional partial clamping specifically in high-risk patients. One study evaluating patients strictly operated on with either strategy by 1 surgeon who changed preference suggested a possible benefit of single clamping [51]. Overall, in patients with more severe atherosclerosis, the additional use of a partial clamp has not definitely been proven safe. Use of single clamping will increase clamp time by ~15 min and measuring the graft length is performed on an empty heart, but this is not expected to have clinical consequences. The question therefore remains whether a partial clamp should be applied in patients with more severe aortic atherosclerosis.

Off-pump coronary artery bypass grafting

Similar to on-pump CABG, in OPCAB, the use of a partial clamp has not unequivocally been linked to a higher stroke rate, compared to no-touch OPCAB. In Supplementary Material, Table S3, the studies have been listed that compare these strategies and report on the severity of aortic atherosclerosis. Only one study observed an increasing stroke rate with increasing degree of aortic manipulation [52]. Interestingly, the prevalence of severe aortic atherosclerosis in the on-pump CABG group was only 0.6%, while the decrease in stroke rate compared to the no-touch group was 1.3% (2.0–0.7%). This suggests a benefit of avoiding aortic manipulation in patients with moderate aortic atherosclerosis. In 3 studies, aortic atherosclerosis was identified as an independent predictor using multivariate regression analyses [52–54]. This correlation was not observed in 2 studies evaluating the use of a clampless proximal anastomosis facilitating device [55, 56]. Apparently the use of these devices helps to prevent the increase in stroke rate associated with increasing aortic atherosclerosis severity. This is supported by the increase in benefit ratio between observed and expected stroke rate with increasing severity of aortic atherosclerosis observed when using these devices [56].

It is important to note that none of the studies included in Supplementary Material, Table S3 focused exclusively on patients with moderate or severe aortic atherosclerosis and all studies described a bias towards using the no-touch approach in patients with more severe aortic atherosclerosis [22, 52, 54]. This effect is likely to be present throughout all non-randomized studies reporting on stroke rate differences between different clamping and bypass strategies in CABG.

This and several other confounders must also be taken into account when comparing the outcomes of OPCAB to on-pump CABG. Individual randomized controlled trials in unselected study populations using either no-touch or partial clamping OPCAB have not been able to show a benefit of OPCAB over on-pump CABG [46, 47, 57]. A network meta-analysis of studies that did differentiate the degree of aortic manipulation in OPCAB showed that the rate of stroke is lowest in no-touch OPCAB and highest in on-pump CABG [58]. This finding is supported by the studies in Supplementary Material, Table S4, none of which were included in the network meta-analysis. All 3 studies included only patients with severe aortic atherosclerosis and all observed a benefit of OPCAB over on-pump CABG [59–61]. The use of OPCAB in patients with a calcified aorta has become a class I recommendation in the latest guidelines on myocardial revascularization by the European Association of Cardiothoracic Surgery [62]. Based on the studies included in Supplementary Material, Table S4, this should be extrapolated to patients with severe non-calcified aortic atherosclerosis. However, the long-term results of OPCAB are comparable to on-pump surgery only when performed by experienced surgeons and when complete revascularization is achieved [63]. Furthermore, maintaining adequate perfusion pressures and circulation during OPCAB is of special importance in patients with aortic atherosclerosis, as they are likely to suffer from cerebrovascular atherosclerosis as well. Whether this influences the risk of haemodynamic stroke in these patients remains to be investigated.

Percutaneous coronary intervention (PCI), as an alternative strategy to CABG, suffers from inherent intra-aortic manipulation. Although an analysis of pooled individual patient data from several trials randomizing patients to PCI or CABG showed a lower perioperative stroke risk after PCI, the 30-day stroke rate of no-touch OPCAB was lower when compared to PCI in a network meta-analysis, with an odds ratio of 0.92 (95% confidence interval: 0.47–1.78) [64, 65]. Moreover, PCI is associated with lower survival in patients with an indication for CABG [66]. Therefore, while PCI could be a reasonable alternative when the required surgical experience is not present, it should not be the first choice for patients with an indication for CABG.

AORTIC VALVE REPLACEMENT

In a study among 196 patients >65 years old undergoing SAVR, any aortic atherosclerosis was observed in 86% of both patients with and without perioperative stroke [6]. This highlights the high prevalence of atherosclerosis in these patients and shows that the mere presence of atherosclerosis is not enough to discriminate stroke risk. A further substudy in 129 patients who underwent postoperative cerebral MRI showed embolic type lesions in 59% of patients, accounting for 97% (77/79) of the total number of acute infarcts observed. In a multivariable model, aortic arch atheroma was correlated with embolic infarcts (odds ratio 3.4, 1.0–12.0) [2]. Another study confirmed the relevance of moderate or severe aortic atherosclerosis. A substudy of a randomized trial evaluating embolic protection devices in 326 patients undergoing SAVR observed a higher stroke rate in patients with moderate or severe atherosclerosis (8.6% vs 5.9%), although this did not reach statistical significance ($P = 0.38$) [67].

Unlike in CABG, no small modifications are available to avoid aortic manipulation in SAVR, as cardiopulmonary bypass, cardiac arrest and an aortotomy are imperative. Aside from the options of peripheral cannulation and aortic replacement discussed above, it is difficult to adjust the procedure upon diagnosing severe aortic atherosclerosis intraoperatively.

With the advent of transcatheter aortic valve replacement (TAVR), a new minimally invasive alternative has become available, and it has been proposed as an alternative in patients with a porcelain aorta [68]. However, despite its use in patients diagnosed with a porcelain aorta, few studies have evaluated the stroke risk of TAVR specifically in patients with intimal aortic atherosclerosis. Theoretically, extensive intra-aortic wire manipulation could dislodge atherosclerotic debris and cause embolization. Indeed, total atheroma volume was associated with stroke after TAVR in 2 case–control studies [69, 70]. Although TAVR is an alternative in some patients with a

porcelain aorta, the benefit over other surgical strategies of SAVR in patients with predominantly intimal atherosclerosis remains to be investigated.

LIMITATIONS AND IMPLICATIONS FOR FUTURE RESEARCH

As this review focused on the risk of embolic stroke, the trade-off in terms of other outcomes of the surgical alternatives was not evaluated. Also, the deliberate focus on embolic stroke associated with aortic atherosclerosis prevented further discussion of other contributing aetiologies, including other embolic causes and haemodynamic stroke.

The key to successfully minimizing stroke risk in patients with aortic atherosclerosis is careful patient selection. The alternative approaches are usually technically more challenging, time-consuming or are even associated with unfavourable outcomes in the short or long term. Evidence in this field mainly consists of retrospective studies with limited sample sizes. More insight is needed in the stroke risk associated with aortic atherosclerosis in general, but mainly in patients with moderate atherosclerosis. Surgical strategies should be evaluated specifically in patients with aortic atherosclerosis. Due to low event rates and the efforts needed to evaluate aortic atherosclerosis, studies are seldom powered to evaluate individual atherosclerosis grades. In this regard, large-scale registries, such as the STS database, could be an accessible and valuable source, but only if reliable data on atherosclerosis are collected. In addition, the role of TAVR in patients with intimal atherosclerosis needs to be evaluated and compared to other alternative strategies in SAVR. As many of these patients undergo preoperative contrast-enhanced computed tomography, data should be readily available.

CONCLUSIONS

The association between aortic manipulation in patients with intimal aortic atherosclerosis and the risk of perioperative stroke have been well defined. Many strategies have been proposed to mitigate this risk, but only few have consistently been proven effective. Currently, these strategies are not consistently employed, causing variation in the perioperative stroke rates. A tailored approach, using alternative strategies in carefully selected patients, is needed to reduce the risk of perioperative stroke without compromising other outcomes. More insight in the effectiveness of alternative surgical strategies, especially in patients with moderate aortic atherosclerosis, is needed. Collecting reliable data on aortic atherosclerosis in large-scale registries is necessary.

Conflict of interest: none declared.

Author contributions

Wiebe G. Knol: Conceptualization; Data curation; Methodology; Writing—original draft. **Ricardo P.J. Budde:** Conceptualization; Methodology; Supervision; Writing—review & editing. **Edris A.F. Mahtab:** Methodology; Writing—review & editing. **Jos A. Bekkers:** Methodology; Writing—review & editing. **Ad J.J.C. Bogers:** Conceptualization; Methodology; Supervision; Writing—review & editing.

Reviewer information

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