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# Bleeding risk in patients with cardiac disease from ischaemic stroke reperfusion therapy: an update

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## ABSTRACT:

**Background** Intravenous tissue plasminogen activator (rtPA) and arterial endovascular therapy (ET) rapidly restore cerebral perfusion in eligible patients who had an acute ischaemic stroke (AIS). It is unknown whether patients who had an AIS with premorbid cardiac disease respond differently to reperfusion therapies than those without. These patients may have risk factors that worsen outcomes or may represent those who would most benefit from reperfusion therapy.

**Objective** To determine whether patients who had an AIS with the most frequently encountered pre-existing cardiac conditions, atrial fibrillation (AF), heart failure (HF), left ventricular assist devices (LVADs), or taking anticoagulation for cardiac indications, are at increased risk for poor outcome, such as symptomatic intracranial haemorrhage (sICH), after reperfusion therapy.

**Results** Although AF is an independent risk factor for poor poststroke outcomes, intravenous rtPA is not associated with increased risk of sICH for those not on anticoagulants. Likewise, HF is independently associated with mortality post stroke, yet these patients benefit from reperfusion therapies without increased rates of sICH. Patients with LVADs or who are on anticoagulation should not be given IV rtPA; however, ET remains a viable option in those who meet criteria, even patients with LVAD.

**Conclusion** There is no evidence of an increased risk for sICH after intravenous rtPA or ET for those with AF or HF. Intravenous rtPA should not be given to patients on anticoagulation or with LVADs, but ET should be offered to them when eligible. Whenever possible, future AIS reperfusion research should include patients with premorbid cardiac disease as they are frequently excluded, representing a gap in evidence.

## INTRODUCTION

Bleeding is a feared complication after administration of intravenous tissue plasminogen activator (rtPA) or arterial endovascular therapy (ET) in eligible acute ischaemic stroke patients. Certain stroke characteristics, such as a high National Institute of Health Stroke Scale (NIHSS) and large infarct size, increase the risk of symptomatic intracranial haemorrhage (sICH).[1] Understanding how specific premorbid cardiac conditions affect the risk of sICH after either intravenous rtPA or ET for patients who had an acute stroke is prudent, particularly given data projecting that the proportion of cardioembolic strokes will increase.[2]

Since the 1995 National Institute of Neurological Disorders and Stroke (NINDS) trial cited a 30% chance of minimal disability at 90 days and a sICH rate of 6.4%, intravenous rtPA has become standard-of-care in acute stroke treatment in eligible patients.[3] In 2015, stroke treatment further advanced with the discovery that ET benefits patients with large-vessel occlusion meeting certain criteria.[4] As a result, rapid perfusion-based cerebral imaging is now used to select patients to receive ET up to 24 hours post onset.

There were however notable exclusions from these trials, including patients with cardiac disease, such as heart failure (HF) resulting in a gap in the evidence; especially considering that patients with these conditions are not uncommonly encountered, and treated post stroke. It may be that patients who had a stroke with premorbid cardiac disease are uniformly at increased risk for a poor outcome secondary to shared vascular risk factors that independently portend a poor prognosis.[5] Conversely, it may be that patients with cardiac disease may represent those who would most benefit from reperfusion therapy secondary to the fact that cardioembolic strokes tend to be severe without treatment and can occur with anterior circulation, large-vessel occlusion.[6]

The aim of this descriptive review is to leverage the most relevant data from the past decade to determine how the most frequently encountered premorbid cardiac conditions, specifically atrial fibrillation (AF), HF, a left ventricular assist device (LVAD) and the use of anticoagulation (AC) for a cardiac indication, influence the risk of poor outcomes, such as sICH, in patients who had an acute ischaemic stroke after reperfusion therapy.

## METHODS

The literature review was performed by searching the PubMed database from 21 June to 13 July 2020, then again on 11 March 2021 to identify articles that met our inclusion criteria: full-length, English, original research articles published in the last decade from randomised, retrospective, or prospective, single or multicentre cohort studies involving adult, patients who had an acute ischaemic stroke with concomitant cardiac disease that assessed study-defined sICH as a primary or secondary outcome after intravenous rtPA or ET treatment. The principal summary measures for outcome of sICH were reported in ORs or percentage rates of sICH, depending on how the study reported the effect estimate. This work represents a descriptive review with all aforementioned variables and concepts defined on the study level, which may complicate or bias comparisons of reported effect estimates. Our review aims to report and resynthesise these risk ratios and effect estimates through discussion, rather than through means of either a formal systematic review or a meta-analysis.

The specific search query or search terms represented one of each of the four key concepts in the manuscript: an acute ischemic stroke reperfusion therapy (*IV rtPA, IVT, intravenous tissue plasminogen activator, IV thrombolysis, intravenous thrombolysis, tPA, thrombolysis, systemic thrombolysis, IV thrombolysis, EVT, MT, Endovascular therapy, Mechanical thrombectomy, thrombectomy, Intra-arterial therapy*), one of the four cardiac conditions examined in the review (*atrial fibrillation, AF, heart failure, systolic heart failure, diastolic heart failure, anticoagulation, direct oral anticoagulant, DOAC, novel oral anticoagulant, NOAC, VKA, Vitamin K Antagonists, Warfarin, Heparin, Dabigatran, Apixaban, Rivaroxaban, left ventricular assist device, LVAD, ventricular assist device*), a term for bleeding risk (*bleeding, hemorrhage, symptomatic intracranial hemorrhage, sICH, intracranial hemorrhage, ICH, outcomes*), and lastly a term for stroke (*acute ischemic stroke, ischemic stroke, stroke, AIS*). We supplemented our PubMed primary literature search by finding systematic or meta-analysis review articles and extracting from their reference lists other primary research articles that met inclusion criteria, to recapitulate their findings into our review article and to catalogue any relevant references in our summary tables. The electronic search results were imported into RefWorks and duplications were automatically removed. The studies were screened independently by BJC and MCJ with disagreements for inclusion resolved by discussion. We extracted the patient outcomes and the adjusted effect estimates for inclusion in the study. If different criteria of sICH were used in one study, then the numerical data from the one that was used more frequently were included.

## RESULTS

After duplicates were removed, electronic search revealed 150 publications that were suitable for title and abstract screening, from which 88 were selected for full-text review. Forty-five papers were discarded due to the patients not having ischaemic strokes; there was no extractable effect estimates or the results were already reflected in another paper. Forty-three papers fulfilled the eligibility criteria and were included.

### Atrial fibrillation

Haemorrhagic transformation can occur in AF-related stroke and is more common in acute cardioembolic strokes, frequency caused by AF, compared with other stroke etiologies.[7] The reported incidence of haemorrhagic transformation after intravenous rtPA ranges between 10% and 30%, likely depending on the criteria used.[8] The proposed mechanism of the haemorrhage is that the soft, red thromboembolus may be more easily and rapidly resolved, thereby increasing rates of recanalisation and subsequent haemorrhage into the stroke bed.[9] Among 230 patients who were not on premorbid AC and were eligible for reperfusion therapy (defined as intravenous rtPA, ET or both), 37 (16.1%) had haemorrhagic transformation (8 symptomatic), which included 23 (10.0%) haemorrhagic infarctions and 14 (6.1%) parenchymal haematomas (see also table 1).[10]

Patients who had a cardioembolic stroke have worse outcomes compared with patients with strokes of other aetiologies,[6] and it may be that AF itself represents an independent risk factor for poor clinical outcomes. In the Virtual International Stroke Trials Archive (VISTA), AF had no impact on stroke outcomes, and patients with AF experienced a similar benefit from acute thrombolysis.[11] In the original intravenous rtPA NINDS trial, AF was independently associated with worse global outcomes, but there was no significant interaction with treatment.[12] The European Cooperative Acute Stroke Study (ECASS) III trial demonstrated a trend among those with AF that favoured placebo over intravenous rtPA (OR 0.68), but it was ultimately not statistically significant (95% CI 0.30 to 1.55).[13] A systematic review and meta-analysis including VISTA, NINDS and ECASS suggest that AF increases the risk of death and sICH, as well as decreases the chance of favourable outcomes after thrombolysis.[14] Current stroke treatment guidelines, which include the extended time window for administration of intravenous rtPA to 4.5 hours after onset, do not consider AF an exclusionary criterion, and there is no evidence that reperfusion should be withheld to patients with AF.[5]

Among patients with AF, the data on outcomes after ET are less robust compared with after intravenous rtPA. In a recent meta-analysis from the HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials) collaboration, which also includes perfusion imaging, comprising six randomised clinical trials evaluating outcome of sICH after ET alone or with intravenous rtPA administration, there was no difference in the rate of sICH in patients with AF (3.4%) than without AF (4.5%).[15] They also did not find a difference in outcome between patients who had large vessel occlusion stroke with and without AF.[15] This result is further confirmed by another

**Table 1** Risk of studydefined symptomatic intracranial haemorrhage after acute ischaemic stroke reperfusion therapy in atrial fibrillation (AF)

| Cardiac condition<br>Reference name (number) (sICH timing) | Reperfusion type | Effect estimate (95% CI)* |
|---|---|---|
| Atrial fibrillation | | |
| AF versus no AF w/o additional risk factors | | |
| Frank *et al*, 2012[11] (<72 hours) | Intravenous rtPA | OR 1.20 (0.66 to 2.18) |
| Yue *et al*, 2016[14] (1–8 days) | Intravenous rtPA | OR 1.28† (1.08 to 1.52) |
| Nogueira *et al*, 2015[17] (24–36 hours) | Intravenous rtPA and/or ET | OR 1.61 (1.01 to 2.55) |
| Smaal *et al*, 2020[15] (<90 days) | Intravenous rtPA and/or ET | OR 0.57 (0.3 to 1.07) |
| Akbik *et al*, 2020[16] (<24 hours) | Intravenous rtPA and/or ET | OR 0.76 (0.49 to 1.18) |
| On warfarin | | |
| Zhao *et al*, 2016[39] (<24 hours) | Intravenous rtPA | OR 6.31† (1.18 to 33.87) |
| With heartfailure | | |
| Zhao *et al*, 2016[39] (<24 hours) | Intravenous rtPA | OR 1.54 (0.64 to 3.71) |
| With high NIHSS (>20) at admission | | |
| Zhao *et al*, 2016[39] (<24 hours) | Intravenous rtPA | OR 1.10† (1.03 to 1.17) |

*CIs were not reported for all studies
†Denotes statistical significance under the p<0.05 assumption.
d, days; ET, endovascular therapy (eg, arterial thrombectomy); h, hours; NIHSS, National Institutes of Health Stroke Scale; ; IV rtPA, intravenous recombinant tissue plasminogen activator; sICH, symptomatic intracranial haemorrhage; w/o, without.

study performed using the multicentre Stroke Thrombectomy and Aneurysm Registry, which concluded that the presence of premorbid AF in patients who achieved good recanalisation post ET did not impact sICH rates (aOR 0.69, 95% CI 0.43 to 1.12).[16] A large 2015 multicentre retrospective analysis searched for risk factors for ICH after ET and found that AF was associated with a higher risk of ICH, but this result did not persist after adjusting for vascular risk factors. Notably, there was also no significant difference in successful recanalisation rates between those who developed sICH versus those who did not.[17]

## Heart failure

Patients with HF are frequently excluded from stroke clinical trials, either as a result of clinical trial inclusion criteria or as a result of their poor premorbid functional status. Regardless of the reason, the best available evidence regarding outcomes after acute stroke reperfusion in HF is limited and the majority is from observational studies. HF is an independent predictor of unfavourable outcomes, as measured by the NIHSS at discharge and modified Rankin scale (mRS) at 90 days.[17] A lower ejection fraction appears to be associated with a higher mortality risk.[18] Notably, between patients who had a stroke with and without HF, there was no difference in the rate of successful vessel recanalisation after intravenous rtPA, ET or both.[18] There was also no difference in the rate of any intracranial bleeding or sICH (see table 2) or a difference in the need of mechanical ventilation in the first hours after ET.

The VISTA cohort also considered outcomes after intravenous rtPA among those with and without HF.[19] HF itself was an independent risk factor for poor outcomes after ischaemic stroke, but systemic thrombolysis treatment benefited patients with HF, compared with those without HF, and there was no significant difference in rates of sICH within the first 7 days after administration.

## Left ventricular assist devices

Patients with advanced HF awaiting heart transplants can be implanted with temporary VAD, typically in the left ventricle (LVAD), as a bridge-to-cardiac transplant. Because VAD patients necessitate prolonged AC, intravenous rtPA is contraindicated even if the patient presents within the time window for administration. To date, there are no randomised controlled trials examining the efficacy of ET for VAD patients who experience acute ischaemic stroke. In a 14 patient case series (2013–2019) that followed outcomes after ET, among survivors with complete follow-up data, 6 out of 9 patients had no adverse complications and remained eligible for heart transplantation.[20] None of the patients experienced sICH, though there was one case of asymptomatic subarachnoid haemorrhage. In a single-centre retrospective chart review of 216 LVAD patients, of the 19 with ischaemic stroke, 8 had evidence of large vessel occlusion, with 2 successfully opened outside the 6 hours window.[21] There are no studies evaluating LVAD patients and thrombectomy in the extended time window using perfusion imaging. It may be that nontechnical factors can affect contrast bolus characteristics including low cardiac output,[22] but how perfusion imaging is impacted in LVAD patients is not well described.

Table 2 Risk of study-defined symptomatic intracranial haemorrhage after acute ischaemic stroke reperfusion therapy in heart failure

| Cardiac condition<br>Reference name (number) (sICH timing) | Reperfusion type | Effect estimate<br>(95% CI)* |
|---|---|---|
| Heart failure | | |
| Heart failureversusno heartfailure | | |
| Siedler *et al*, 2019[18] (<24 hours) | Intravenous rtPA and/or ET | Rate 15%versus20% |
| Abdul-Rahim *et al*, 2014[19] (<7 days) | Intravenous rtPA | OR 1.16 (0.37 to 3.66) |
| Schnieder *et al*, 2019[40] (22–36 hours) | ET | Rate 4.4% versus 1% |
| Based on LVEF | | |
| Siedler *et al*, 2019[18] (<24 hours) | | |
| 40%–50% | Intravenous rtPA and/or ET | Rate 6% |
| 25%–35% | Intravenous rtPA and/or ET | Rate 0% |
| <25% | Intravenous rtPA and/or ET | Rate 0% |

*CIs were not reported for all studies.
ET, endovascular therapy; LVEF, left ventricular ejection fraction; rate, rate of sICH in %; rtPA, tissue plasminogen activator.

## AC use for cardiac indications

The American Stroke Association states that current AC use with an INR>1.7, PT>15 s or aPTT>40 s is an exclusion criterion for intravenous rtPA.[5] However, these guidelines contain the caveat that in the setting of a low suspicion for a bleeding diathesis, intravenous rtPA should be given rapidly, without waiting for coagulation test results.

AC is frequently used in the management of patients with cardiac disease, particularly those with AF or HF. A patient who is taking a vitamin K antagonist (VKA) with an INR≤1.7, with no other contraindications, who presents within the eligible time window should receive intravenous rtPA. However, if a patient is found to be therapeutic (ie, INR elevated above 1.7), there is no evidence to support rapid reversal in order to administer intravenous rtPA.[23] Of note, in the ECASS III trial that demonstrated the benefit of intravenous rtPA in the 3–4.5 hour time window, patients who were taking AC were excluded rather than tested for an anticoagulated state.

Patients with cardiac indications for AC are increasingly being prescribed direct oral anticoagulants (DOACs). Dabigatran was the first agent for which a rapid reversal strategy was developed (Idarucizumab, 2015) with data demonstrating safety if administered just prior to intravenous rtPA.[24] More recently, Andexanet alfa was approved in 2018 for rapid apixaban and rivaroxaban reversal.[25] While using these agents to rapidly reverse sICH in the setting DOAC use is important, the prevailing clinical experience does not support rapid reversal of one form of AC prior to administering another AC, intravenous rtPA, for ischaemic.

Rapid identification of whether a patient is taking a DOAC is imperative, particularly when medication reconciliation is not possible. Patients with normal aPTTs are considered unlikely to be taking dabigatran[26]; since aPTT remains the most common study ordered in a stroke code, rapid identification of therapeutic dabigatran usage is typically feasible. Dabigatran concentrations or ecarin clotting time can also be used to detect traces of this medication. Anti-Xa assays are also available to detect rivaroxaban and apixaban.

A systematic review that included 55 studies found that when intravenous rtPA was inadvertently administered to patients taking DOACs (dabigatran, 181; rivaroxaban, 215; apixaban, 40; unspecified NOAC, 56), the overall observed rate of sICH was 4.3% (20/462), a rate likely lower than some may anticipate (table 3). The same study demonstrated a mortality rate of 11.3% (48/423), and a favourable outcome (ie, low NIHSS or mRS) rate of 43.7% (164/375).[24] While it is important to follow the guidelines regarding intravenous rtPA administration, the sICH rates are non-threatening if testing for AC medication use is unknown and the clinical team administers intravenous rtPA while a patient is taking a medication, unknowingly.

Performing ET in the setting of therapeutic AC is not contraindicated, and several studies have examined its safety. A 5-year prospective cohort study (2010–2015) followed 46 patients, taking either VKAs or DOACs, who had undergone ET. When compared with patients with (1) normal hemostasis, or (2) patients receiving intravenous rtPA prior to ET, anticoagulated patients had similar rates of favourable angiographic and clinical outcomes.[27] Another study reports an increased risk of sICH after ET, but only in the group that was on VKA[28] with no association between DOAC use and either sICH or mortality. Interestingly, the INR on admission was not associated with sICH occurrence in this cohort. A 2020 meta-analysis, which included the aforementioned data (855 VKA cases, 318 DOAC cases, and 6289 controls), confirmed a significant difference in sICH rates for patients on VKAs, but again, not in the DOAC group.[28] Other work has suggested similar findings.[29] One caveat, however, is that there may be characteristics inherent to the patient, requiring the

**Table 3** Risk of study-defined symptomatic intracranial haemorrhage after acute ischaemic stroke reperfusion therapy in the setting of anticoagulation use

| Anticoagulation Use<br>Reference name (number) (sICH timing) | Reperfusion type | Effect estimate<br>(95% CI)* |
|---|---|---|
| Jin *et al*, 2018[24](<0.5–7 days) | | |
| DOACs | Intravenous rtPA | Rate 4.3%(2.7 to 6.4) |
| Dabigatran without Ida. reversal | Intravenous rtPA | Rate 7.4%(3.5 to 13.4) |
| Dabigatran with Ida. reversal | Intravenous rtPA | Rate 4.5%(0.8 to 13.4) |
| Dabigatran w/ versus w/o Ida. reversal | Intravenous rtPA | OR 0.60 (0.12 to 2.92) |
| Xian *et al*, 2017[41](<36 hour) | | |
| DOACs | Intravenous rtPA | Rate 4.8% |
| DOACs versus no DOACs | Intravenous rtPA | OR 0.92 (0.51 to 1.65) |
| Warfarin (INR<1.7) | Intravenous rtPA | Rate 4.9% |
| Warfarin (INR<1.7) versus no warfarin | Intravenous rtPA | OR 0.85 (0.66 to 1.10) |
| Cooray et al, 2019[42](<7 d) | | |
| LMW Heparin versus no LMWH | Intravenous rtPA | Rate 3.1% vs 4.2% |
| Rebello *et al*, 2015[25](<7 d) | | |
| OACs versus no OACs | ET | Rate 8% vs 5% |
| OACs versus no OACs+intravenous rtPA | ET | Rate 8% vs 4% |
| VKA versus DOACs | ET | Rate 9.2% vs 6.8% |
| Meinel *et al*, 2020[28](22 h-36h or<7 d) | | |
| VKAs versus no VKAs | ET | OR 1.62† (1.22 to 2.17) |
| DOACs versus no DOACs | ET | OR 1.03 (0.60 to 1.80) |
| Seiffge *et al*, 2015[43] (<7 days) | | |
| DOACs | intravenous rtPA and/or ET | Rate 3.2% |
| VKAs (all INRs) | intravenous rtPA and/or ET | Rate 6.1% |
| DOACs | intravenous rtPA | Rate 4% |
| VKAs (all INRs) | intravenous rtPA | Rate 3.6% |
| --VKAs+INR ≤ 1.7 | intravenous rtPA and/or ET | Rate 4.7% |
| --VKAs+INR >1.7 | intravenous rtPA and/or ET | Rate 11.2% |

*CIs were not reported for all studies
†Denotes statistical significance under the p<0.05 assumption
DOAC, direct oral anticoagulant (eg, dabigatran, rivaroxaban, apixaban, edoxaban); ET, endovascular therapy; Ida., idarucizumab; INR, international normalised ratio; LMWH, low molecular weight heparin; OAC, any oral anticoagulant (VKA and/or DOAC); rtPA, tissue plasminogen activator; VKA, vitamin K antagonist anticoagulant.

patient to be taking a VKA, which also put them at higher risk for sICH, rather than this effect being simply due to the medication use. Current guidelines are clear about avoiding treatment with intravenous rtPA in patients who had a stroke on AC for cardiac indications, but based on the evidence, ET-based reperfusion therapy should not be delayed. It is also encouraging that sequelae from accidental administration of intravenous rtPA appear to be minimal in patients taking DOACs.

## DISCUSSION

In this review, we have provided an overview of the most up-to-date data discussing the risk of sICH with reperfusion therapies in patients who had an acute ischaemic stroke with the most commonly encountered cardiac conditions, including patients with AF, HF, LVADs or AC for cardiac indications, which we hope will assist physicians treating patients who had an acute ischaemic stroke with comorbid cardiac disease, especially where guidelines are unspecified. We conclude that, broadly, ET is beneficial without increasing the risk of bleeding in patients who had a stroke with any of the cardiac conditions examined in this review. Intravenous rtPA should also be administered according to the guidelines, with the exception of patients on AC and more granular considerations should be made, especially when ET technology and expertise are not readily available.

When considering specific cardiac conditions, AF is the most common cause of cardioembolic stroke, with increasing incidence with age.[30] It has been suggested

that despite more aggressive control of risk factors and overall decline in stroke incidence, the proportion of cardioembolic strokes is increasing.[31] As demonstrated, patients who present with acute ischaemic stroke and have AF represent a unique group when considering reperfusion therapies, as many may be taking AC, a contraindication to intravenous rtPA.[5] Patients who had an AF-related cardioembolic stroke are at high risk for both stroke recurrence and sICH. The risk of sICH among those with AF is elevated among those with a high CHA2DS2-VASc score, a high NIHSS, and larger infarct size.[10] Our results suggest that while AF is an independent risk factor for worsened outcomes after stroke regardless of intravenous rtPA use, they do not suggest that intravenous rtPA should be contraindicated in patients with AF. Although the risks and benefits of acute stroke ET has not been studied only in participants with AF, the retrospective data and subgroup analyses of clinical trials, as well as real-world clinical experience would suggest that patients with AF do at least as favourably as other patients without AF.

HF represents a significant public health problem, with about 915 000 incident HF cases yearly in the USA alone.[32] When considering how a patient with HF may respond differently to acute stroke reperfusion therapy, a number of potential complexities emerge. It has been suggested that the efficacy of intravenous rtPA may be reduced in patients with a reduced ejection fraction, as their low cardiac outputs might decrease perfusion to the brain.[33] Additionally, management of patients with HF under anaesthesia is known to be more difficult, and anaesthesia is often required for ET.[34] Patients with HF can also have coagulation abnormalities that increase their bleeding risk, irrespective of ischaemic stroke.[35] Finally, HF with reduced ejection fraction is associated with the stasis of flow and an increased risk of AF, which can further complicate the decision-making in acute stroke if AC is being taken by the patient for stroke primary prevention at the time of the event. In our review of the available evidence, which is although limited, there is no evidence to delay in administering acute stroke reperfusion therapies in patients with HF. HF itself can portend a poorer prognosis but intravenous rtPA and ET appear to be equally as safe and effective in patients who had a stroke without HF.

Due to the abnormal blood flow in the hearts of these patients leading to increased susceptibility to thrombosis, ischaemic stroke is a non-infrequent complication of LVAD, with a 1-year post-VAD-implant stroke incidence ranging from 13% to 20%.[36] The 2019 INTERMACS report, a US-based VAD registry of>25 000 patients, cites stroke as the most common cause of death after VAD implantation.[36] However, even though the risk of stroke in LVAD patients is substantial, the number of prevalent LVAD patients is small so management is largely based on expert opinion. Although no guidelines currently recommend ET as a management strategy for this population, ET appears to be safe and efficacious and, importantly, the only viable option for individuals with VAD.[20] Interpretation of perfusion imaging in the expanded time window may need to be considered in light of LVAD placement, but data on this are lacking.

AC is a current contraindication to intravenous rtPA administration. Yet, in light of recent medical advances that have led to the expanded use of novel AC medications, the decision regarding administration of intravenous rtPA has become more complicated. For example, the specific AC reversal strategies when sICH develops and novel testing assays to rapidly identify a patient's AC status have become new considerations in the decision-making algorithm. With such scenarios, these considerations become relevant: the type of AC (VKA vs DOAC) a patient is taking, blood tests evaluating the patient's therapeutic level of AC (INR and aPTT tests), and viability of reversing a state of AC, which is not done at the authors' institution nor is endorsed, but is discussed in some of the publications included in this review. A full discussion of the decision to use antiplatelet therapy in addition to AC in the patient with cardiac disease is outside of the scope of this article, but can further complicated decision-making. In general, there is no evidence to continue antiplatelet therapy for stroke prevention once AC is initiated unless the patient has had a recent percutaneous coronary intervention or have AF with a mechanical heart valve.[37 38] Future studies with the aim of specifying optimal care of patients with these cardiac conditions among these considerations will be of great importance.

In summary, this review supports that patients with the specified cardiac conditions benefit from both acute stroke reperfusion therapies, with relatively low rates of sICH. We acknowledge that many of these studies were performed using older ET devices and did not include the expanded time window for patients presenting up to 24 hours after stroke onset, suggesting that the benefit from stroke reperfusion therapy in patients with cardiac disease may be even higher than currently realised. We also recognise that there are limitations in comparing patient populations from across different stroke trials, performed at different time periods, with different extents of inclusion or exclusion of cardiac patients and slightly differing definitions of sICH and diagnoses of cardiac disease; nonetheless, we anticipate a time when increased data will allow for a formal accounting of differences in variance and bias between studies.

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