

Is intraprocedural intravenous aspirin safe for patients who require emergent extracranial stenting during mechanical thrombectomy?

Adam Ingleton ¹, Marko Raseta,² Rui-En Chung,³ Kevin Jun Hui Kow,³ Jake Weddell,⁴ Sanjeev Nayak,⁵ Changez Jadun,⁵ Zafar Hashim,⁵ Noman Qayyum,⁵ Phillip Ferdinand,¹ Indira Natarajan,¹ Christine Roffe^{1,6}

To cite: Ingleton A, Raseta M, Chung R-E, *et al.* Is intraprocedural intravenous aspirin safe for patients who require emergent extracranial stenting during mechanical thrombectomy?. *Stroke & Vascular Neurology* 2023;**0**. doi:10.1136/svn-2022-002267

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/svn-2022-002267>).

Received 23 December 2022
Accepted 6 September 2023



© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

¹Neurosciences, University Hospitals of North Midlands NHS Trust, Stoke-on-Trent, UK

²Statistics and Mathematical Modelling, Department of Molecular Genetics, Erasmus Medical Center, Rotterdam, Zuid-Holland, The Netherlands

³Radiology, University Hospitals of North Midlands NHS Trust, Stoke-on-Trent, UK

⁴School of Medicine, Keele University, Keele, UK

⁵Interventional Radiology, University Hospitals of North Midlands NHS Trust, Stoke-on-Trent, UK

⁶Stroke Research, Keele University, Keele, UK

Correspondence to

Dr Adam Ingleton;
atingleton@gmail.com

ABSTRACT

Background Intraoperative antiplatelet therapy is recommended for emergent stenting during mechanical thrombectomy (MT). Most patients undergoing MT are also given thrombolysis. Antiplatelet agents are contraindicated within 24 hours of thrombolysis. We evaluated outcomes and complications of patients stented with and without intravenous aspirin during MT.

Methods All patients who underwent emergent extracranial stenting during MT at the Royal Stoke University Hospital, UK between 2010 and 2020, were included. Patients were thrombolysed before MT, unless contraindicated. Aspirin 500 mg intravenously was given intraoperatively at the discretion of the operator. Symptomatic intracranial haemorrhage (sICH) and the National Institutes for Health Stroke Scale score (NIHSS) were recorded at 7 days, and mortality and functional recovery (modified Rankin Scale: mRS ≤ 2) at 90 days.

Results Out of 565 patients treated by MT 102 patients (median age 67 IQR 57–72 years, baseline median NIHSS 18 IQR 13–23, 76 (75%) thrombolysed) had a stent placed. Of these 49 (48%) were given aspirin and 53 (52%) were not. Patients treated with aspirin had greater NIHSS improvement (median 8 IQR 1–16 vs median 3 IQR –9–8 points, $p=0.003$), but there were no significant differences in sICH (2/49 (4%) vs 9/53 (17%)), mRS ≤ 2 (25/49 (51%) vs 19/53 (36%)) and mortality (10/49 (20%) vs 12/53 (23%)) with and without aspirin. NIHSS improvement (median 12 IQR 4–18 vs median 7 IQR –7–10, $p=0.01$) was greater, and mortality was lower (4/33 (12%) vs 6/15 (40%), $p=0.05$) when aspirin was combined with thrombolysis, than for aspirin alone, with no increase in bleeding.

Conclusion Our findings based on registry data derived from routine clinical care suggest that intraprocedural intravenous aspirin in patients undergoing emergent stenting during MT does not increase sICH and is associated with good clinical outcomes, even when combined with intravenous thrombolysis.

BACKGROUND

Endovascular treatment improves outcomes in patients with intracranial large artery occlusion.¹ Emergent intraprocedural stenting of extracranial or intracranial arteries is often necessary to overcome an atherosclerotic

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Emergent intraprocedural stenting of extracranial or intracranial arteries is often necessary to achieve vessel patency or improve cerebral flow. Intraprocedural antiplatelet agents are considered necessary to maintain stent patency but are also associated with increased bleeding risk, when given in patients who have been thrombolysed.

WHAT THIS STUDY ADDS

⇒ This observational study compares outcomes with and without intraprocedural aspirin in relation to thrombolysis in patients undergoing emergent stenting during mechanical thrombectomy. Early neurological recovery and functional outcome at 90 days were better in patients who received intraprocedural aspirin 500 mg intravenously than in those who were not given aspirin, irrespective of thrombolysis and with no increase in intracerebral haemorrhage.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study suggests that the current guidance not to give antiplatelet agents within the first 24 hours of thrombolysis may not apply to patients undergoing emergent stenting during mechanical thrombectomy.

plaque or thrombosis and to provide access, maintain sufficient flow and prevent reocclusion.^{2,3} Most stents are placed in the carotid artery,^{2 4–7} but smaller intracranial and extracranial arteries are also included in some series.^{8,9}

Bridging therapy with intravenous alteplase prior to thrombectomy is given in most patients undergoing emergent or rescue stenting. Intravenous heparin is administered throughout the procedure to flush the lines and contributes to haemorrhage risk.¹⁰ Antiplatelet agents are required intraoperatively to ensure patency of the stent.¹¹ However, there is evidence of increased haemorrhage risk if given concurrently with alteplase.¹²

The European Stroke Organization Guidelines for intravenous thrombolysis after stroke state that antiplatelet agents should not be given within 24 hours after thrombolysis.¹³ There are no randomised controlled trials to guide antiplatelet management for emergent stenting, and practice varies.^{7 14} While there is consensus among interventional neuroradiologists that intraoperative antiplatelets are required for emergent stenting,¹¹ accepted practice among neurologists is to avoid antiplatelets within 24 hours of thrombolysis.¹³

The aim of this study was to assess the safety, complications and outcomes of intraprocedural intravenous aspirin during mechanical thrombectomy with emergent stenting in patients with and without thrombolysis before the procedure.

METHODS

All patients treated with mechanical thrombectomy for a large vessel occlusive stroke between January 2010 and December 2020 at the Royal Stoke University Hospital, a large comprehensive stroke centre in the UK were included. Data were extracted from a prospective database of all patients who received mechanical thrombectomy. Patients who had an extracranial stent placed during the procedure were included in the analysis. Details of thrombectomy pathways and service configuration have previously been described.^{15 16} Standard treatment before thrombectomy included intravenous thrombolysis with alteplase 0.9 mg/kg body weight (up to 6 hours from onset for anterior circulation infarcts and up to 12 hours for posterior circulation infarcts), unless contraindicated (most commonly anticoagulation with warfarin and an INR >1.7).¹⁷ Indications for thrombectomy are shown in figure 1.

Thrombectomies were conducted using a Stentriever, aspiration or a combination of both. Heparin (1000 iu/L) was given as per standard protocol to flush the catheters during the procedure. Emergent stenting was performed if necessary to provide access to distal occlusions, if patency could not be maintained without a stent and if deemed technically feasible. The decision for stenting, additional treatment with angioplasty and use of intravenous aspirin during the procedure was at the discretion of the treating interventional neuroradiologist. Use of aspirin reflected preferences of the operator and the treating stroke physician rather than differences in perceived bleeding risk. If antiplatelets were required intraoperatively, aspirin 500 mg intravenously was used. No other antiplatelet agents were used intraoperatively or postoperatively for the first 24 hours. Intraoperative aspirin was not given in patients who had a thrombectomy but were not stented. Once intracerebral haemorrhage was excluded at 24 hours using a CT head scan dual antiplatelet therapy (clopidogrel and aspirin) was given for 3 months, followed by long-term clopidogrel. Patients with minor asymptomatic haemorrhage (haemorrhagic transformation 1 (HT1) or 2 (HT2) or small subarachnoid

Figure 1. Flow diagram for clinical decision making

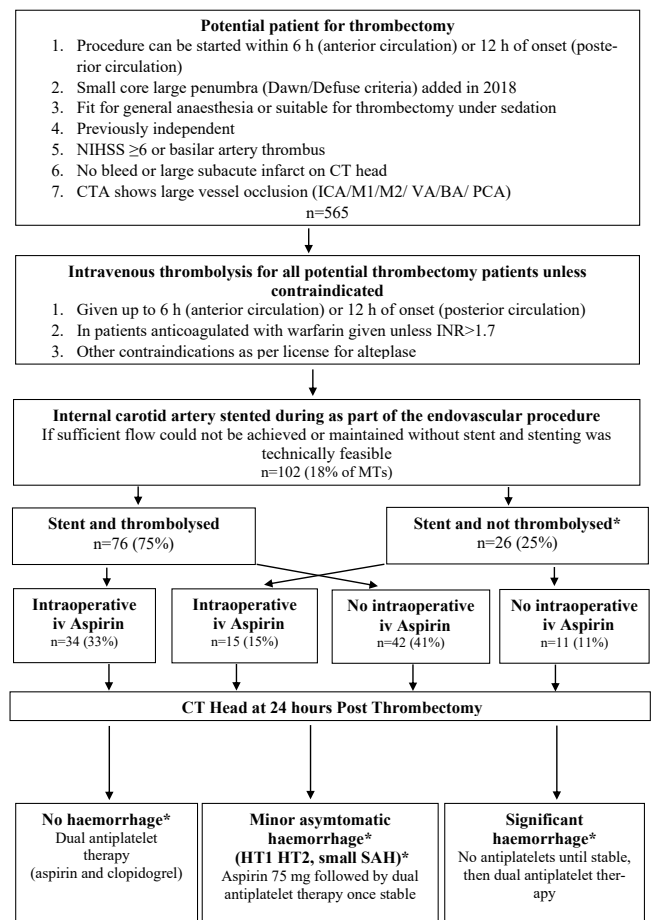


Figure 1 *Clinical thrombectomy pathway. Patients who had contraindications to thrombolysis were given oral antiplatelets (aspirin or clopidogrel, if aspirin intolerance) before thrombectomy, unless fully anticoagulated. The indications and contraindications were for guidance, with final treatment decisions made by the responsible clinician. BA, basilar artery; HT1, haemorrhagic transformation 1; HT2, haemorrhagic transformation 2; INR, International Normalised Ratio; iv Aspirin, intravenous aspirin at a dose of 500mg; ICA, internal carotid artery; MT, mechanical thrombectomy; M1, proximal segment of the middle cerebral artery; M2, Sylvain Segment of the middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; PCA, posterior cerebral artery; SAH, subarachnoid haemorrhage; VA, vertebral artery.

haemorrhages) with good recanalisation were given aspirin 75 mg until clinically stable. In patients with clinically significant post-thrombectomy haemorrhage antiplatelet agents were delayed for a week or more at the discretion of the treating clinician. Functional outcome was assessed using the modified Rankin Scale (mRS) at 90 days over the phone or in person by a member of the stroke team not involved in the procedure. A good functional outcome was defined as an mRS of 0–2. For patients who were intubated or in coma, a National Institutes for

Table 1 Baseline demographics and clinical details

| | All thrombectomies (n=565) | | | Thrombectomies with stenting (n=102) | | | | | |
|--|----------------------------|------------------|---------|--------------------------------------|-------------------|---------|---------------------|------------------------|---------|
| | Stent (n=102) | No stent (n=463) | P value | Aspirin (n=49) | No aspirin (n=53) | P value | Thrombolysis (n=76) | No thrombolysis (n=26) | P value |
| Age (years) median (IQR) | 67 (57–72) | 70 (60–77) | 0.004* | 68 (55–75) | 66 (57–70) | 0.40* | 62 (55.75–71) | 68.5 (60–78) | 0.03* |
| Male sex (n (%)) | 70 (69%) | 233 (50%) | 0.001† | 27 (55%) | 43 (81%) | 0.009† | 60 (79%) | 10 (38%) | 0.0003† |
| Hypertension (n (%)) | 51 (50%) | 234 (51%) | 1† | 21 (43%) | 30 (57%) | 0.23† | 36 (47%) | 15 (58%) | 0.50† |
| Atrial fibrillation (n (%)) | 4 (4%) | 153 (33%) | <0.001† | 2 (4%) | 2 (4%) | 1† | 2 (3%) | 2 (8%) | 0.27† |
| Hyperlipidaemia (n (%)) | 27 (26%) | 124 (27%) | 1† | 10 (20%) | 17 (32%) | 0.27† | 19 (25%) | 8 (31%) | 0.75† |
| Diabetes (n (%)) | 18 (18%) | 70 (15%) | 0.63† | 7 (14%) | 11 (21%) | 0.55† | 15 (20%) | 3 (12%) | 0.55† |
| Previous stroke/TIA (n (%)) | 13 (13%) | 69 (15%) | 0.69† | 7 (14%) | 6 (11%) | 0.88† | 9 (12%) | 4 (15%) | 0.73† |
| Thrombolysis (n (%)) | 76 (75%) | 354 (76%) | 0.77† | 34 (69%) | 42 (79%) | 0.36† | NA | NA | NA |
| NIHSS at baseline (median (IQR)) | 18 (13–23) | 18 (14–22) | 0.87* | 19 (15–23) | 18 (9–23) | 0.22* | 19(14–23) | 15.5 (10–22.5) | 0.20* |
| Anterior circulation (n (%)) | 94 (92%) | 416 (90%) | 0.60† | 45 (92%) | 49 (92%) | 1† | 70 (92%) | 24 (92%) | 1† |
| Posterior circulation (n (%)) | 8 (8%) | 47 (10%) | 0.60† | 4 (8%) | 4 (8%) | 1† | 7 (8%) | 2 (8%) | 1† |
| Onset to groin time (min) (median (IQR)) | 269 (195–343) | 261 (201–332) | 0.93* | 277 (204–359) | 260 (195–325) | 0.36* | 253 (195–322.5) | 287 (195–500) | 0.30* |
| Onset to lysis time (min) (median (IQR)) | 123 (90–160) | 135 (105–182) | <0.001* | 115 (90–152) | 123 (94–168) | <0.001* | 123(90–160) | na | na |
| Collateral score (n (%)) | | | | | | 1† | | | 0.11† |
| Level 1 | | | | 17 (44%) | 17 (41%) | | 29 (49%) | 5 (24%) | |
| Level 2 | | | | 17 (44%) | 19 (46%) | | 24 (41%) | 12 (57%) | |
| Level 3 | | | | 5 (12%) | 5 (13%) | | 6 (10%) | 4 (19%) | |
| ASPECTS score | | | | 7 (6.75–9) | 8 (6–9) | 0.88* | 8 (6–9) | 7 (7–9) | 1* |

*Mann-Whitney U test.

†Z-test.

‡Fisher's exact test.

ASPECTS, The Alberta Stroke Programme Early CT Score; NIHSS, National Institutes for Health Stroke Scale score; TIA, Transient ischemic attack.

Table 2 Complications and outcomes in patients who were stented during thrombectomy with or without intraoperative aspirin

| | All thrombectomies (n=565) | | | Thrombectomies with stenting (n=102) | | |
|--|----------------------------|------------------|---------|--------------------------------------|-------------------|---------|
| | Stent (n=102) | No stent (n=463) | P value | Aspirin (n=49) | No aspirin (n=53) | P value |
| Thrombolysis in cerebral infarct score $\geq 2b$ (n (%)) | 92 (90%) | 414 (90%) | 0.96* | 43 (88%) | 49 (92%) | 0.51* |
| NIHSS at 7 days median (IQR) | 10 (3–20) | 6 (2–16) | 0.08† | 5 (2–17) | 15 (4–32) | 0.03† |
| NIHSS difference baseline to 7 days median (IQR) | 6 (-3–13) | 9 (1–14) | 0.02† | 8 (1–16) | 3 (-9–8) | 0.003† |
| Infarction at 24 hours (n (%)) | 79 (77%) | 331 (72%) | 0.27* | 35 (71%) | 44 (83%) | 0.25* |
| Malignant middle cerebral artery syndrome (n (%)) | 6 (6%) | 36 (8%) | 0.65* | 1 (2%) | 5 (9%) | 0.21‡ |
| Hemicraniectomy (n (%)) | 2 (2%) | 9 (2%) | 1‡ | 1 (2%) | 1 (2%) | 1‡ |
| Symptomatic intracerebral haemorrhage (n (%)) | 11 (11%) | 30 (7%) | 0.19* | 2 (4%) | 9 (17%) | 0.08* |
| Subarachnoid haemorrhage (n (%)) | 10 (10%) | 42 (9%) | 0.97* | 6 (12%) | 4 (7%) | 0.51‡ |
| Stroke within 90 days (n (%)) | 0 (0.0%) | 9 (2%) | 0.37‡ | 0 (0.0%) | 0 (0.0%) | 1‡ |
| Death at 90 days (n (%)) | 22 (22%) | 76 (16%) | 0.27* | 10 (20%) | 12 (23%) | 0.97* |
| mRS 0–2 at 90 days (n (%)) | 44 (43%) | 221 (48%) | 0.46* | 25 (51%) | 19 (36%) | 0.18* |

*Z-test.

†Mann-Whitney U test.

‡Fisher's exact test.

NIHSS, National Institutes for Health Stroke Scale score.

Health Stroke Scale score (NIHSS) of 35 was assigned. Death was recorded as a NIHSS of 42 and an mRS of 6.¹⁸

Successful recanalisation was defined by thrombolysis in cerebral infarct (TICI) score 2b–3. Symptomatic intracranial haemorrhage (sICH) was defined using Safe Implementation of Thrombolysis in Stroke Monitoring Study criteria,¹⁹ as a local or remote parenchymal haemorrhage type 2 on the 22–36 hour post-treatment head scan, combined with a neurological deterioration of four or more points from the lowest NIHSS within admission or leading to death. Malignant middle cerebral artery syndrome was defined as cerebral oedema causing midline shift with associated clinical deterioration of four or more NIHSS points.²⁰

The Alberta Stroke Programme Early CT Score (ASPECTS) was determined retrospectively using RAPID software on existing CT head scans.²¹ Where this was not possible, scans were scored visually by two independent assessors. Collaterals were graded by the two independent assessors using single-phase CT angiogram collateral scoring,²² since perfusion imaging was not available in the first years of the study to allow collateral calculation.²³

The study was reviewed by the Institutional Review Board at the Tertiary Centre and considered a service review analysing routinely collected data. Use of the registry data without individual informed consent was approved by the information governance team.

Statistical analysis

Data were summarised using medians, and percentages, where appropriate. Categorical variables were compared by means of Z-test (binary variables) and Fisher's exact test (low expected per-cell observations). All continuous variables (age, onset to groin time, NIHSS at onset, 1

week and difference of the two) are reported as medians and IQRs and were compared by means of Mann-Whitney U-test. Moreover, ordinal numerical variable ASPECTS score was treated as a continuous variable in statistical analysis as it takes more than five different levels.²⁴ Statistical analysis was done in R statistical software tool (R Core Team, 2018). Significance was accepted at $p < 0.05$ level.

RESULTS

Demographics

A flow diagram showing patients who had thrombectomy, thrombolysis and aspirin is given in figure 1. In total, 565 thrombectomies were included. In 102 (18%), an emergent or rescue extracranial stent was placed (table 1). Stented patients were younger (median 67 vs median 70 years IQR 60–77, $p = 0.004$), more likely to be men (69% vs 50%, $p = 0.001$), less likely to have atrial fibrillation (4% vs 33%, $p < 0.001$), and onset to lysis time was shorter (123 vs 135 min, $p < 0.001$). There were no other significant differences between stented and non-stented patients. In the stented group, most strokes were severe (median NIHSS 18 (IQR 13–23) at baseline), affected the anterior circulation in 92%, and occurred in patients with multiple comorbidities.

Just under 50% of stented patients ($n = 49$, 48%) were given intraoperative aspirin, with 53 (52%) patients not receiving aspirin during the procedure. The only significant difference in demographic and clinical characteristics between the patients given aspirin and those not given aspirin were more men (55% vs 81% $p = 0.009$) and shorter onset to lysis times (115 vs 123 min, $p < 0.001$) for the aspirin group.

Table 3 Complications and outcomes in stented patients in relation to aspirin and thrombolysis

| | Aspirin given intraoperatively (n=49) | | | No aspirin given intraoperatively (n=53) | | |
|--|---------------------------------------|-------------------------|---------|--|-------------------------|---------|
| | Thrombolysed (n=34) | Not thrombolysed (n=15) | P value | Thrombolysed (n=42) | Not thrombolysed (n=11) | P value |
| Thrombolysis in cerebral infarct score $\geq 2b$ (n (%)) | 33 (97%) | 10 (67%) | 0.008* | 39 (93%) | 10 (90%) | 1* |
| NIHSS at 7 days median (IQR) | 5 (2–14) | 16 (2–36) | 0.09† | 15 (3–34) | 15 (5–21) | 0.63† |
| NIHSS difference baseline to 7 days median (IQR) | 12 (4–18) | 7 (–7–10) | 0.01† | 4 (–6–9) | 2 (–12–4) | 0.24† |
| Infarction at 24 hours (n (%)) | 26 (76%) | 9 (60%) | 0.31* | 34 (81%) | 10 (91%) | 0.67* |
| Malignant middle cerebral artery syndrome (n (%)) | 0 (0%) | 1 (7%) | 0.31* | 5 (12%) | 0 (0%) | 0.57* |
| Hemicraniectomy (n (%)) | 0 (0%) | 1 (7%) | 0.31* | 1 (2%) | 0 (0%) | 1* |
| Symptomatic intracerebral haemorrhage (n (%)) | 1 (3%) | 1 (6%) | 1* | 4 (10%) | 5 (46%) | 0.01* |
| Subarachnoid haemorrhage (n (%)) | 4 (12%) | 2 (13%) | 1* | 2 (5%) | 2 (18%) | 0.19* |
| Stroke within 90 days (n (%)) | 0 (0%) | 0 (0%) | 1* | 0 (0%) | 0 (0%) | 1* |
| Death at 90 days (n (%)) | 4 (12%) | 6 (40%) | 0.05* | 8 (19%) | 4 (36%) | 0.24* |
| mRS 0–2 at 90 days (n (%)) | 20 (59%) | 5 (33%) | 0.18‡ | 16 (38%) | 3 (27%) | 0.73* |

*Fisher's exact test.
 †Mann-Whitney U test.
 ‡Z-test.
 mRS, modified Rankin Scale; NIHSS, National Institutes for Health Stroke Scale score.

The majority of stented patients (n=76, 75%) were thrombolysed. Apart from age (62.0 vs 68.5 years, p=0.03) and male sex (79% vs 38%, p<0.001), there were no significant differences between thrombolysed and non-thrombolysed patients.

There were no differences in stroke severity (eg, baseline NIHSS, infarct size on baseline CT head (ASPECTS) and collateral status) and delay between onset and the start of intervention (onset to groin time) between patients treated and not treated with aspirin and between patients thrombolysed and not thrombolysed.

Complications and outcomes in patients who were stented during thrombectomy

Outcomes and complications up to 90 days are shown in table 2. Procedural outcome was similar in patients who were stented to patients not requiring a stent with a high rate of successful recanalisation in both groups (90% TICI 2b or higher). While there was less reduction of neurological deficits at 1 week (median NIHSS difference from baseline 6 IQR –3–13 vs 9 IQR 1–14, p=0.02) in stented patients, longer term stroke recurrence, functional independence and mortality at 90 days were similar in both groups. Of those stented 11% had an sICH.

Complications and outcomes of stented patients with and without intraoperative aspirin

Patients who were given aspirin during the procedure had better NIHSS scores at 1 week (median 5 IQR 2–17 vs median 15 IQR 4–32, p=0.03), and a greater fall from baseline median 8 IQR 1–16 versus median 3 IQR –9–8,

p=0.003 (table 2). There was no significant difference for any of the other outcomes. The rate of stroke recurrence and mortality at 90 days were very similar for both groups.

Complications and outcomes in relation to aspirin and thrombolysis

Table 3 compares patients who received aspirin with and without thrombolysis (n=34 and n=15, respectively) and those who received no aspirin during the procedure and did or did not get thrombolysis (n=42 and n=11, respectively). As these are further subgroups, numbers in each are small. Rate of successful recanalisation (97% vs 67% p=0.008), neurological recovery (NIHSS difference median 12 IQR 4–18 vs median 7 IQR –7–10, p=0.01) and mortality at 90 days (12% vs 40%, p=0.05) were significantly better when aspirin was combined with thrombolysis, than for aspirin alone, with no increase in bleeding.

For the group not given aspirin, outcomes are generally worse than for those given aspirin, with similar results in those thrombolysed and not thrombolysed. The only statistically significant difference in outcomes for this comparison was for sICH, which was more frequent in those given neither thrombolysis nor aspirin (n=5 (46%) vs n=4 (10%), p=0.01). The 34 patients who received both aspirin and thrombolysis had the lowest NIHSS at 1 week. This group also achieved the highest rate of functional independence at 90 days with 20 patients (59%) achieving an mRS ≤ 2 .

The number of stented patients over time span of this study is shown in online supplemental appendix.



Apart from the first 2 years, when only very few stents were placed, there is no clear trend in the proportion who received intraoperative intravenous aspirin (online supplemental appendix).

DISCUSSION

The main findings of this study are that neurological recovery at 1 week was significantly better in patients undergoing emergent stenting during mechanical thrombectomy given aspirin intraoperatively than in those not receiving this treatment. At 90 days mortality was similar, with a weak trend towards better functional outcome with aspirin. Aspirin was not associated with an increase in intracerebral haemorrhage, whether given alone, or with intravenous thrombolysis.

The study population included all 102 patients treated with an emergent or rescue stent to an extracranial vessel representing 18% of patients treated by mechanical thrombectomy at our centre. As expected for patients with large-vessel stenosis, most strokes were severe (median NIHSS 18). Mortality was 22%, with the lowest rate (12%) in the subgroup receiving both thrombolysis and intraprocedural aspirin. This is similar to other studies examining emergent stenting with mortality ranging from 9.5%⁵ to 37.5%.^{2 4-9 24-34} Baseline NIHSS is a key determinant of mortality and functional outcome, and the results presented here reflect the higher baseline NIHSS (median 18) in our cohort than in cohort studies (medians 13–17) and meta-analyses (medians 13–17).^{9 26} Intraoperative aspirin did not affect functional independence at 90 days, with 43.0% achieving this in our study and 36%–57.9% in the other recent studies. Patients who received both thrombolysis and intraprocedural aspirin had the best outcomes with 12% mortality and 59% attaining functional independence at 90 days. While these outcomes could potentially have been confounded by more late presenters in those not given thrombolysis, our data show no significant differences in onset to groin time, baseline neurological deficit, infarct size on the CT head (ASPECTS) or collateral status for either the aspirin/no aspirin or the thrombolysis/no thrombolysis groups, suggesting major outcome predictors and bleeding risk were comparable. The results provide reassuring evidence that there are no major adverse interactions between thrombolysis and intravenous aspirin.

We found no excess of intracranial bleeding with aspirin or the combination of aspirin and thrombolysis, with haemorrhage rates. The rate of sICH among those who had thrombolysis and aspirin was 3%. A similarly low haemorrhage rate was reported in the TITAN registry, where the subgroup treated with thrombectomy, stent, antiplatelets and thrombolysis had an sICH haemorrhage rate of 2.4%.⁵ This contrasts with the findings of the 'Antiplatelet in combination with rtPA thrombolysis in Ischemic Stroke' (ARTIS) trial in thrombolysed patients who did not undergo thrombectomy showed that the risk of sICH is significantly increased by giving aspirin intravenously

within 90 min of thrombolysis,¹² especially as the dose of intravenous aspirin given in this research study is 500 mg, this is higher than the 300 mg given in ARTIS. More recently the open-label MR CLEAN-MED study showed an increased risk of haemorrhage in patients given intraprocedural aspirin during mechanical thrombectomy.³⁵ These studies provide evidence that giving aspirin soon after intravenous thrombolysis and/or during mechanical thrombectomy increases haemorrhage risk. This should be a reason to avoid aspirin soon after thrombolysis or during thrombectomy. However, neither has examined the effect in patients stented during thrombectomy, where intraoperative aspirin is part of routine care. Our study provides observational evidence to suggest that intraoperative aspirin may be safe even in the presence of thrombolysis in patients who require emergent stenting during mechanical thrombectomy.

In this study, we used aspirin 500 mg intravenously, as previously reported in a case series of emergent stenting during mechanical thrombectomy.² A recent consensus statement by interventional neuroradiologists declared that aspirin should be used at a dose of 500 mg intravenously and also highlighted the lack of evidence to support this dose.¹¹ The ARTIS RCT used aspirin 300 mg intravenously or no aspirin within 90 min of thrombolysis and reported an excess of intracranial haemorrhages.¹² The same dose was used in the MR Clean MED thrombectomy RCT.

Neither of these studies examined outcomes in patients who were treated by emergent stenting. Table 4 shows that details of intraprocedural antiplatelet administration are poorly reported in studies and meta-analyses of emergent stenting, with aspirin 500 mg intravenously, cangrelor intravenously, dual antiplatelet therapy, tirofiban, GPIIb/IIIa inhibitors, heparin and abciximab used in different studies, while other studies provide no detail of antiplatelet therapy.

A major strength of this paper is the presentation of data from a single centre with consistent documentation of thrombolysis, use of a single antiplatelet regimen (intravenous aspirin) and the presence of a contemporaneous control group not given antiplatelets intraoperatively. Limitations of the study are that it is observational and that treatment with aspirin and thrombolysis was determined by the treating clinician rather than by chance, thus potentially introducing bias by indication. This could be particularly relevant for thrombolysis, where clear indications and contraindications exist, with patients not thrombolysed likely to have more complex comorbidities and presenting later. However, our data show no significant differences in comorbidities, baseline neurological deficit, extent of the infarct on CT, collateral status or onset to groin time between those thrombolysed and not thrombolysed.

As there is no definite evidence to guide aspirin use in this setting, choice of treatment was not systematic, but determined by clinical uncertainty, and this is confirmed by similar distributions of risks and outcome predictors

Table 4 Studies of emergent stenting during mechanical thrombectomy with details of the use of intraprocedural antiplatelet agents.

| Observational Studies | | | | | | | | | | | |
|---|--------------------------------|------------|-----------|-----------------------------------|-------------|---------------|--------------------------------|--|---|----------------------------|--------------------------|
| Paper | Number stented/ total cases | Indication | Centres | NIHSS before MT (median) | Territory | TICI ≥ 2 | Key outcome mRS ≤ 2 | Symptomatic intracranial haemorrhage | Antiplatelet choice | Thrombolysis | Mortality at 3 months |
| Behme <i>et al</i> ² | 170/170 | ES | Multi (4) | 15 | Carotid | 77% | 36% | 9% | Eptifibatid or tirofiban or aspirin 500 intravenous and clopidogrel via nasogastric tube | 72% | 19% (discharge) |
| Papanagiotou <i>et al</i> ⁴ | 322/482 | ES | Multi | 16 | Carotid | 81.1% | 55.0% | 7.1% | Variable intravenous aspirin, intravenous GP IIb/IIIa Inh, clopidogrel heparin | 62% | 11.2% |
| Zhu <i>et al</i> /TITAN registry ⁵ | 256/295 | ES | Multi | ND | Carotid | 83.1% | 57.9% | 5.1% | All below | 60% | 9.5% |
| Anadani <i>et al</i> / TITAN Registry ⁶ | 205/205 | ES | Multi | ND | Carotid | 81% | 56.6% | 5.9% | Type of antiplatelet regime not reported | 60% | 12.7% |
| | | | | | | | | 4.4% | Antiplatelet and lysis (136) | | |
| | | | | | | | | 8.6% | Antiplatelet alone (92) | | |
| Hadler <i>et al</i> ⁷ | 73/548 | xx | Single | xx | Carotid | xx | 40.6% | 16% | Tirofiban, dual antiplatelet therapy | 65.8% | 28.1% |
| Chang <i>et al</i> ⁸ | 48/148 | RS | Multi | 14 | Carotid, M1 | 64.6% | 39.6% | 16.7% | GP IIb/IIIa Inh and /or antiplatelets | 46% intravenous, 15% ia | 12.5% |
| Stracke <i>et al</i> ⁹ | 210/210 | RS | Multi | 13 | Any | 82.9% | 44.8% | 10.5% | At least one agent, detail not fully reported | 31% | 18.5% |

Continued

Table 4 Continued

| Observational Studies | | | | | | | | | | | |
|------------------------------------|----------------------------|------------|---------------------------------------|--------------------------|----------------------|---------------|--------------------------|--------------------------------------|--|-----------------------|-----------------------|
| Paper | Number stented/total cases | Indication | Centres | NIHSS before MT (median) | Territory | TICI ≥ 2 | Key outcome mRS ≤ 2 | Symptomatic intracranial haemorrhage | Antiplatelet choice | Thrombolysis | Mortality at 3 months |
| Delvoe et al ²⁵ | 60/218 | ES | Single | 16 | Carotid | ND | 58.1% | 9.3% | Aspirin intravenous 250 mg (43) or | 53.5% | 18.6% |
| | | | | 12 | | | 37.5% | 25% | abciximab 0.25 mg/kg (8) | 50.0% | 37.5% |
| | | | | 17 | | | 33.3% | 11.1% | Bolus and infusion (9) | 33.3% | 11.1% |
| Peng et al ²⁶ | 90/339 | RS | Multi (16) | 17 | Anterior circulation | ND | 36.4% | 13.6% | Tirofiban | Yes | 31.9% |
| Schaefer et al ²⁷ | 26/122 | RS | Single | 15* | ND | ND | ND | 3.6% | ND | 39% | 36% (discharge) |
| Mohamedan et al ²⁸ | 107/499 | RS | Multi (14) | 16 | Carotid | ND | 34.6% | 7.5% | Not specified | 29% intravenous 2% ia | 29.9% |
| Ingleton et al | 102/565 | RS | Single | 18 | Carotid, VA | 90% | 43% | 11% | All 102 (100%) | 75% | 22% |
| | | | | 19 | | 88% | 51% | 4% | Aspirin 500 mg intravenous in 49 (48%) | 69% | 20% |
| | | | | 18 | | 92% | 51% | 4% | No aspirin I in 53 (52%) | 79% | 23% |
| Metanalyses and systematic Reviews | | | | | | | | | | | |
| Paper | Number stented/total cases | Indication | Centres | NIHSS before MT (median) | Territory | TICI ≥ 2 | Key outcome mRS ≤ 2 | Symptomatic intracranial haemorrhage | Antiplatelet choice | Thrombolysis | Mortality at 3 months |
| Dufort et al ²⁹ | 1635 | ES | Meta-analysis of 16 studies | ND | Anterior circulation | ND | 53.7% | 8.3% | Variable | Not specified | 13.4% |
| Paul et al ³⁰ | 129 | ES | Pooled analysis | ND | Any | 100% | ND | 6.2% | IV cangrelor | 23.4% | ND |
| Sadeh-Gonik et al ³¹ | 338 | ES | Meta-analysis of 14 studies | 16* | Anterior circulation | 76% | 53% | 7% | Not specified | 65% | 14% |
| Maingard et al ³² | 365 | RS | Meta-analysis of 12 studies | 16* | Anterior circulation | 35.7% | 48.5% | 9.7% | Tirofiban, heparin, abciximab, aspirin, clopidogrel, | | 21.9% |
| Sivan-Hoffman et al ³³ | 193 | ES | Meta-analysis of 11 studies 2010–2015 | 17* | Carotid | 63.8% | 44% | 7% | Not specified | 54% | 13% |

Continued

Table 4 Continued

| Metanalyses and systematic Reviews | | NIHSS before MT (median) | | Territory | | TICI ≥ 2 | Key outcome mRS ≤ 2 | Symptomatic intracranial haemorrhage | Antiplatelet choice | Thrombolysis | Mortality at 3 months |
|------------------------------------|----------------------------|--------------------------|-----------------------------|-----------|-----|---------------|--------------------------|--------------------------------------|---------------------|--------------|-----------------------|
| Paper | Number stented/total cases | Indication | Centres | Any | Any | 78.5% | 37.8%† | 8.3%† | Not specified | 31.8% median | 22.5%** |
| Cai <i>et al</i> ⁸⁴ | 774/1595 | ES | Meta-analysis of 15 studies | ND | Any | 78.5% | 37.8%† | 8.3%† | Not specified | 31.8% median | 22.5%** |

Observational studies including 20 or more patients and meta-analyses of emergent or rescue stenting after mechanical thrombectomy.

*Study used mean as measure of NIHSS baseline, TICI.

†Total number of participants is 1595. The total number of stented patients is 774. Percentages were calculated, where information available in tables and figures.

BA, basilar artery; ES, emergent stenting; GP IIb/IIIa Inh, glycoprotein IIb/IIIa inhibitors; M1, proximal segment of the middle cerebral artery; mRS, modified Rankin Scale; MT, mechanical thrombectomy; ND, not disclosed within article; NIHSS, National Institutes of Health Stroke Scale; RS, rescue stenting; TICI, thrombolysis in cerebral infarct; VA, vertebral artery; xx, unavailable.

in patients given and not given aspirin. While thrombectomy and stenting techniques have evolved over time, the level of uncertainty relating to antiplatelets in our centre has remained largely unchanged, as shown in online supplemental appendix. A larger multicentre randomised controlled trial of intraoperative antiplatelet administration would be desirable to confirm our results, but given current interventional practice is to administer antiplatelets intraprocedurally and the encouraging results of our study, it is unlikely that operators would have sufficient equipoise to consider such a trial.

CONCLUSION

The findings of our study based on registry data from routine clinical care suggest that intraprocedural intravenous aspirin is safe in patients undergoing emergent stenting during mechanical thrombectomy, but interpretation should be tempered by the possibility of bias, as the study was non-randomised. There was no excess of intracerebral haemorrhage, even when combined with intravenous thrombolysis, and neurological recovery was better at one week. Our work highlights the need for further research in this area to inform guidelines for antiplatelet therapy during emergent stenting.

Twitter Noman Qayyum @drNoman_Qayyum

Acknowledgements Previous contribution to the Mechanical Thrombectomy registry, Nasar Ahmad, Peter Ward, Adrian Craig, Emma Parr, Stacey Knight.

Contributors Study concept and design: ATI, CR. Project administration: ATI CR. Data acquisition and management: ATI, CR. Neuroradiology data generation: R-EC, KJHK. Data analysis: MR, CR, ATI. Drafting the manuscript: ATI, MR, CR. Peer-review or research concept and paper from selected interventional radiologists and stroke physicians: JW, SN, CJ, ZH, NQ, PF, IN. All authors reviewed, edited and approved the manuscript. ATI is the author responsible for the overall content and is the guarantor for the paper.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests CR has received personal remuneration for educational and advisory work from Allergan and Daiichi Sankyo and her institution has received educational grants from Medtronic, Brainomix, Firstkind Medical, and Johnson & Johnson for stroke-related activities. She was the National coordinator for the ECASS-4 study and is the National lead for SITS International, both of which are partially funded by Boehringer Ingelheim. She holds grants from the National Institute for Health Research and the British Heart Foundation.

Patient consent for publication Not applicable.

Ethics approval The study was reviewed by the Institutional Review Board (University of North Midlands NHS Trust) and considered a service review analysing routinely collected data. Use of the registry data without individual informed consent was approved by the information governance team. The study was reviewed by the Institutional Review Board (University of North Midlands NHS Trust) and considered a service review analysing routinely collected data. The use of the registry data without individual informed consent was approved by the information governance team.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

The datasets generated and analysed during the current study are not publicly available, but anonymised data may be available from the corresponding author on reasonable request.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content

includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Adam Ingleton <http://orcid.org/0000-0002-8151-9714>

REFERENCES

- Goyal M, Menon BK, van Zwam WH, *et al.* Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 2016;387:1723–31.
- Behme D, Mpotsaris A, Zeyen P, *et al.* Emergency stenting of the extracranial internal carotid artery in combination with anterior circulation thrombectomy in acute ischemic stroke: a retrospective multicenter study. *AJNR Am J Neuroradiol* 2015;36:2340–5.
- Wilson MP, Murad MH, Krings T, *et al.* Management of tandem occlusions in acute ischemic stroke - intracranial versus extracranial first and extracranial stenting versus angioplasty alone: a systematic review and meta-analysis. *J Neurointerv Surg* 2018;10:721–8.
- Papanagiotou P, Haussen DC, Turjman F, *et al.* Carotid Stenting with antithrombotic agents and intracranial thrombectomy leads to the highest recanalization rate in patients with acute stroke with Tandem lesions. *JACC Cardiovasc Interv* 2018;11:1290–9.
- Zhu F, Bracard S, Anxionnat R, *et al.* Impact of emergent cervical carotid stenting in tandem occlusion strokes treated by thrombectomy: a review of the TITAN collaboration. *Front Neurol* 2019;10:206.
- Anadani M, Spiotta AM, Alawieh A, *et al.* TITAN (Thrombectomy in tandem lesions) investigators. emergent carotid stenting plus thrombectomy after thrombolysis in tandem strokes: analysis of the TITAN registry. *Stroke* 2019;50:2250–2.
- Hadler F, Singh R, Wiesmann M, *et al.* Increased rates of hemorrhages after endovascular stroke treatment with emergency carotid artery stenting and dual antiplatelet therapy. *Cerebrovasc Dis* 2021;50:162–70.
- Chang Y, Kim BM, Bang OY, *et al.* Rescue stenting for failed mechanical thrombectomy in acute ischemic stroke: a multicenter experience. *Stroke* 2018;49:958–64.
- Stracke CP, Fiehler J, Meyer L, *et al.* Emergency intracranial stenting in acute stroke: predictors for poor outcome and for complications. *J Am Heart Assoc* 2020;9:e012795.
- Benali F, Hinsenveld WH, van der Leij C, *et al.* Effect of heparinized flush concentration on safety and efficacy during endovascular thrombectomy for acute ischemic stroke: results from the MR CLEAN Registry. *Cardiovasc Intervent Radiol* 2021;44:750–5.
- Goyal M, Yoshimura S, Milot G, *et al.* Considerations for antiplatelet management of carotid stenting in the setting of mechanical thrombectomy: a Delphi consensus statement. *AJNR Am J Neuroradiol* 2020;41:2274–9.
- Zinkstok SM, Roos YB, ARTIS investigators. ARTIS investigators. early administration of aspirin in patients treated with Alteplase for acute ischaemic stroke: a randomised controlled trial. *Lancet* 2012;380:731–7.
- Berge E, Whiteley W, Audebert H, *et al.* European stroke organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *Eur Stroke J* 2021;6:1–LXII.
- Heck DV, Brown MD. Carotid Stenting and intracranial Thrombectomy for treatment of acute stroke due to Tandem occlusions with aggressive antiplatelet therapy may be associated with a high incidence of intracranial hemorrhage. *J NeuroInterv Surg* 2015;7:170–5.
- Ahmad N, Nayak S, Jadun C, *et al.* Mechanical thrombectomy for ischaemic stroke: the first UK case series. *PLoS One* 2013;8:e82218.
- Weddell J, Parr E, Knight S, *et al.* Mechanical thrombectomy: can it be safely delivered out of hours in the UK *BMC Neurol* 2020;20:326.
- Gandhi CD, Al Mufti F, Singh IP, *et al.* Standards and guidelines committee of the society of neurointerventional surgery (SNIS). neuroendovascular management of emergent large vessel occlusion: update on the technical aspects and standards of practice by the standards and guidelines committee of the society of neurointerventional surgery. *J Neurointerv Surg* 2018;10:315–20.
- Chalos V, van der Ende NAM, Lingsma HF, *et al.* National Institutes of health stroke scale: an alternative primary outcome measure for trials of acute treatment for ischemic stroke. *Stroke* 2020;51:282–90.
- Wahlgren N, Ahmed N, Dávalos A, *et al.* Thrombolysis with Alteplase for acute ischaemic stroke in the safe implementation of thrombolysis in stroke-monitoring study (SITS-MOST): an observational study. *Lancet* 2007;369:275–82.
- Hacke W, Schwab S, Horn M, *et al.* Malignant middle cerebral artery territory infarction: clinical course and prognostic signs. *Arch Neurol* 1996;53:309–15.
- Barber PA, Demchuk AM, Zhang J, *et al.* Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. *Lancet* 2000;355:1670–4.
- Tan JC, Dillon WP, Liu S, *et al.* Systematic comparison of perfusion-CT and CT-angiography in acute stroke patients. *Ann Neurol* 2007;61:533–43.
- Lin L, Chen C, Tian H, *et al.* Perfusion computed tomography accurately quantifies collateral flow after acute ischemic stroke. *Stroke* 2020;51:1006–9.
- Rhemtulla M, Brosseau-Liard PÉ, Savalei V. When can categorical variables be treated as continuous? A comparison of robust continuous and categorical SEM estimation methods under suboptimal conditions. *Psychol Methods* 2012;17:354–73.
- Delvoe F, Maier B, Escalard S, *et al.* Antiplatelet therapy during emergent extracranial internal carotid artery stenting: comparison of three intravenous antiplatelet perioperative strategies. *J Stroke Cerebrovasc Dis* 2021;30:105521.
- Peng F, Wan J, Liu W, *et al.* Efficacy and safety of rescue stenting following failed mechanical thrombectomy for anterior circulation large vessel occlusion: propensity score analysis. *J Neurointerv Surg* 2020;12:271–3.
- Schaefer J, Sweid A, Gooch A, *et al.* Rescue stenting for failed mechanical thrombectomy procedures (abstract). Neurology commons. 2020 phase 1. paper 5. Available: https://jdc.jefferson.edu/si_dh_2022_phase1/5 [Accessed 24 Jun 2023].
- Mohammaden MH, Haussen DC, Al-Bayati AR, *et al.* Stenting and angioplasty in neurothrombectomy: matched analysis of rescue intracranial stenting versus failed thrombectomy. *Stroke* 2022;53:2779–88.
- Dufort G, Chen BY, Jacquin G, *et al.* Acute carotid stenting in patients undergoing thrombectomy: a systematic review and meta-analysis. *J Neurointerv Surg* 2021;13:141–5.
- Paul AR, Entezami P, Holden D, *et al.* Use of intravenous cangrelor and stenting in acute ischemic stroke interventions: a new single center analysis and pooled-analysis of current studies. *Interv Neuroradiol* 2021;27:837–42.
- Sadeh-Gonik U, Tau N, Friehmann T, *et al.* Thrombectomy outcomes for acute stroke patients with anterior circulation Tandem lesions: a clinical registry and an update of a systematic review with meta-analysis. *Eur J Neurol* 2018;25:693–700.
- Maingard J, Phan K, Lamanna A, *et al.* Rescue intracranial Stenting after failed mechanical thrombectomy for acute ischemic stroke: a systematic review and meta-analysis. *World Neurosurgery* 2019;132:e235–45.
- Sivan-Hoffmann R, Gory B, Armoiry X, *et al.* Stent-retriever thrombectomy for acute anterior ischemic stroke with Tandem occlusion: a systematic review and meta-analysis. *Eur Radiol* 2017;27:247–54.
- Cai J, Xu H, Xiao R, *et al.* Rescue intracranial Stenting for acute ischemic stroke after the failure of mechanical thrombectomy: a systematic review, meta-analysis, and trial sequential analysis. *Front Neurol* 2023;14:1023089.
- van der Steen W, van de Graaf RA, Chalos V, *et al.* Safety and efficacy of aspirin, unfractionated heparin, both, or neither during endovascular stroke treatment (MR CLEAN-MED): an open-label, multicentre, randomised controlled trial. *Lancet* 2022;399:1059–69.

APPENDIX 1**Number of Thrombectomies with Stenting Per Year**

| Year | Number of Stented Patients | Number of Patients who received IV Aspirin Perioperatively |
|------|----------------------------|--|
| 2010 | 2 | 0 |
| 2011 | 5 | 0 (0%) |
| 2012 | 6 | 1 (18%) |
| 2013 | 9 | 5 (56%) |
| 2014 | 8 | 5 (63%) |
| 2015 | 13 | 9 (79%) |
| 2016 | 18 | 12 (67%) |
| 2017 | 11 | 3 (27%) |
| 2018 | 12 | 6 (50%) |
| 2019 | 9 | 5 (56%) |
| 2020 | 9 | 3 (33%) |