Author/s:
Sim, K;Yan, B;Dowling, R;Bush, S;Mitchell, P

Title:
Endovascular clot retrieval in acute stroke with large ischaemic core is not always associated with poor outcomes

Date:
2019-04-01

Citation:
Sim, K., Yan, B., Dowling, R., Bush, S. & Mitchell, P. (2019). Endovascular clot retrieval in acute stroke with large ischaemic core is not always associated with poor outcomes. Internal Medicine Journal, 49 (4), pp.490-494. https://doi.org/10.1111/imj.14116.

Persistent Link:
https://hdl.handle.net/11343/285674

Sim Kenneth (Orcid ID: 0000-0001-5531-315X)

14

Title Page

Endovascular clot retrieval in acute stroke with large ischemic core is not always associated with poor outcomes.

Kenneth Sim[a], Bernard Yan[b], Richard Dowling[a], Steven Bush[a], Peter Mitchell[a]

Affiliations

[a]Department of Radiology, The Royal Melbourne Hospital, Parkville, Victoria, Australia

[b]Department of Medicine and Neurology, Melbourne Brain Centre at The Royal Melbourne Hospital, University of Melbourne, Parkville, Victoria, Australia

Correspondence

Dr Peter Mitchell, Department of Radiology, The Royal Melbourne Hospital, Parkville, Victoria, Australia.

Phone +613 9342 7000

Fax +613 9342 7482

Peter.Mitchell@mh.org.au

Acknowledgements, sources of funding and conflicts of interest

Dr Peter Mitchell receives research grants from Medtronic and Stryker.

Word count

Abstract: 231

Main text: 1755

Abstract

Background. The benefits of endovascular clot retrieval (ECR) for anterior circulation stroke with large ischemic cores remain uncertain. In spite of recent pooled analysis of randomized controlled studies, conclusions regarding the fate of large ischemic cores cannot be reached given the small number of included patients. **Methods.** This was a single centre retrospective study of patients treated with ECR in the period 2012 to 2017. The inclusion criteria were anterior circulation stroke with symptom onset less than 6 hours, baseline CT perfusion and 90 day clinical follow up defined by the Modified Rankin Score (mRS). **Results.** 261 patients were included. Median age of 72 (IQR 61-78) and 59% were male. The mean ischemic core volume was 27.6ml (SD 34.9ml). There were 235 patients with an ischemic core volume of <70ml and 26 patients with an ischemic core volume of e70ml. There was no statistically significant difference however in 90 day functional independence with 66% (154/235) in the <70ml core group and 54% (14/26) in the e70ml core group reaching a 90 day mRSd2. **Conclusions.** We found that patients selected for ECR with ischemic core size e70ml had clinical outcomes not significantly different compared with those with smaller ischemic cores. We recommend that large ischemic core size alone does not necessarily constitute an absolute contraindication for ECR. Randomized controlled studies are needed to better define the benefits for this group of patients.

Keywords

Acute stroke; Endovascular clot retrieval; Computed tomography perfusion; Ischemic core

Introduction

Endovascular clot retrieval (ECR) for anterior circulation ischemic stroke with large vessel occlusion results in improved functional outcomes at 90 days [1-6]. The HERMES collaboration, a meta-analysis of the five randomised trials, allowed further subgroup analysis and confirmed the benefits of ECR including those over the age of 80, patients ineligible for intravenous thrombolysis and those treated later than 300 minutes from symptom onset [7]. However, patients with evidence of large ischemic core on initial pre-treatment CT perfusion or MR perfusion were significantly under represented in this meta-analysis, and benefits of ECR in this subgroup could not be established [7]. Furthermore, recent trials demonstrating benefit of ECR beyond 6 hours after symptom onset which incorporated CT perfusion as inclusion criterion, excluded patients with ischemic cores greater than 70ml in DEFUSE 3 [8], and greater than 50ml in DAWN [9]. This resulted in uncertainty regarding the potential benefits of ECR in large ischemic cores.

Clarification of the role of ECR in this subgroup is important for several reasons. First, there is a prevailing understanding that there exists a strong association between ischemic core volume and clinical outcome [10, 11], with ischaemic core representing tissue that has undergone irreversible infarction, while penumbra is hypoperfused tissue at risk for infarction without early reperfusion[12, 13]. Second, in patients presenting within six hours of symptom onset, high variability in the volume of the ischemic core exists, likely related to individual differences in arterial collaterals [11, 14]. Third, despite the increasing awareness of the benefit of ECR, many regional hospitals are not equipped to provide ECR services [15], requiring a "drip and ship" approach to transfer patients to comprehensive stroke centres [16]. The consequence is that transfer patients are more likely to harbour larger ischemic cores.

The aim of this study is to retrospectively analyse patients treated with ECR for anterior circulation stroke and to assess the impact of pre-treatment ischemic core as defined on CT perfusion on clinical outcomes.

Materials and Methods

Patients

This was a single centre, retrospective analysis of patients who underwent endovascular treatment for acute ischemic stroke from 2012 to 2017. The study has been approved by the Human Research Ethics Committee of the Royal Melbourne Hospital. The inclusion criteria were: anterior circulation stroke, pre-treatment CT perfusion study processed with the use of fully automated software (RAPID, non-commercial research version, Stanford University) [17], ECR treatment and clinical follow up at 90 days defined by modified Rankin Score (mRS). Patient baseline characteristics included age, gender and vascular risk factors (hypertension, hypercholesterolaemia, smoking history, atrial fibrillation and diabetes mellitus). Initial stroke severity was assessed with the National Institute of Health Stroke Scale (NIHSS). Angiographic data included location of vessel occlusion, reperfusion was defined by the Thrombolysis in cerebral infarction (TICI) scale and presence of symptomatic intracerebral haemorrhage (sICH) were also assessed.

Statistical analysis

Student's t-test was used to evaluate between-group differences between the inclusion and exclusion arms with regards to age, gender and mean onset to recanalization. Fisher's exact test was used to evaluate differences in the baseline NIHSS score. Student's t-test was used to evaluate differences in 90 day mRS between the groups based on their ischemic core volumes.

Results

From January 2012 to May 2017, a total of 408 patients were treated by ECR for anterior circulation stroke. 98 patients were excluded due to no baseline CT perfusion study and 40 patients were excluded due to absence of post-processing of the CT perfusion study. 9 patients were excluded due to lack of 90 day mRS (Figure 1). A total of 261 patients were included for analysis, with no significant difference in age, gender or baseline NIHSS score between the inclusion and exclusion groups. Onset to recanalization however was significantly faster in the inclusion arm (Table 1).

Of the 261 patients, the median age was 72 (IQR 61-78), 59% were male, median NIHSS score was 17 (IQR 12-21) and mean stroke onset to recanalization time was 292 minutes. 61.7% had M1 occlusions, 21.1% had tandem ICA/MCA occlusions, 8.4% had ICA occlusions alone and 8.4% had an M2/3 occlusion. The mean ischemic core volume was 27.6ml (SD 34.9ml). There were 235 patients with an ischemic core volume of <70ml and 26 patients with an ischemic core volume of e 70ml. There was no statistically significantly difference (p = 0.24) in the 90 day clinical outcomes between these groups however with 66% (154/235) reaching an mRSd2 with an ischemic core of <70ml compared with 54% (14/26) reaching an mRSd2 with an ischemic core of e 70ml (Figure 2). Although the percentage of patients with poor clinical outcomes (90 day mRS 4–6) also increased as ischemic core volumes increased, even in patients with ischemic core volumes of >100mls, this only accounted for 36% of cases (Figure 3).

Discussion

The benefit of ECR in patients with large ischemic cores to date remains relatively uncertain. Despite the meta-analysis performed by the HERMES collaboration [7], the number of patients with large pre-treatment ischemic cores as assessed on baseline imaging in this pooled analysis is relatively low due to trial exclusion parameters. Furthermore, assessment of the ischemic core, as well as exclusion criteria on baseline imaging is variable. The Alberta Stroke program early CT score (ASPECTS) is a quantitative measure on non-contrast imaging for estimating the extent and distribution of early ischemic change within acute MCA strokes [18], with REVASCAT excluding patients with ASPECTS of less than 7 on non-contrast CT or less than 6 on DWI [4], and SWIFT-PRIME and ESCAPE excluding patient with ASPECTS of less than 6 [3, 5]. In MR CLEAN, only about 65% of patients underwent pre-treatment CT perfusion, while EXTEND-IA is the only trial of the five to require CT perfusion as an inclusion criteria, with exclusion of patients with ischemic cores of e70mls [2]. Even in more recent trials assessing ECR beyond 6 hours of symptom onset, patients with large ischemic cores were excluded with DEFUSE 3 limiting the initial ischemic core to less than 70ml, and DAWN having a threshold of less than 50ml and even lower in certain subgroups [8, 9]. Despite these exclusion thresholds, median volume of ischemic core in the ECR groups of these trials was also well below these cut-offs, calculated at 9.4ml in DEFUSE 3 and 7.6ml in DAWN.

Our results show that even in patients with large ischemic cores on baseline imaging as assessed by CT perfusion, a sizeable proportion attain good clinical outcomes with 54% of patients with an ischemic core of e70mls reaching an mRS of 0-2 at 90days. This appears significantly greater than the intravenous thrombolysis only arm of MR

CLEAN, of which 19.1% attained an mRS of 0-2 at 90 days [1]. When compared to the other four trials also analysed in the HERMES collaboration, this value also appears greater than the control groups in these studies (Table 2). Similarly, the THRACE study [6] demonstrated that patients with poor baseline ASPECTS (0-4) had worse clinical outcomes than those with better baseline ASPECTS (5-10), however 30% still achieved an mRS of 0-2 at 90 days. These findings suggest ECR may still confer benefit in patients with large ischemic cores over IV thrombolysis alone.

Assessment of the ischemic core and critically hypoperfused tissue on baseline imaging in order to aid selection for reperfusion therapies for each individual patient in the setting of acute ischemic stroke has been evaluated with CT perfusion as well as with magnetic resonance imaging (MRI) perfusion-diffusion mismatch [19]. Acute CT perfusion has been shown to provide similar accuracy in identifying ischemic core and penumbra when compared with MRI perfusion-diffusion imaging [20]. Clinical validation of CT perfusion results has also been demonstrated, with the calculated infarct core and tissue at risk measures strong predictors of clinical outcome [10]. The knowledge that CT perfusion can identify patients with large ischemic penumbras that with early successful reperfusion progress to more favourable clinical outcomes[10], aids management of acute stroke including decisions regarding reperfusion treatments offered at an individual patient level. This is particularly relevant in 'borderline' cases which would include M2 occlusions. Although the accuracy of MRI perfusion-diffusion imaging especially in identifying the acute infarct core may remain superior to CT perfusion [21, 22], often limited access to MRI in the emergency setting, as well as managing potential safety considerations and contraindications for MRI scanning, results in CT perfusion potentially being a more viable, but equally robust tool for assessment.

With the continual greater awareness of the benefit of ECR following the series of positive trials published in 2015, the number of cases and referrals for consideration for ECR continues to increase at our centre, a trend presumably reflected at many other ECR capable stroke centres. As such, consideration to perform ECR despite large ischemic cores on baseline CT perfusion will also likely continue to become more common. In addition, with Gerschenfeld et al. showing no significant difference in IV thrombolysis at a non-ECR capable centre, and then transfer to an ECR capable centre ('drip and ship') over direct transfer to an ECR capable centre ('mothership') [16], consideration for accepting patient transfers knowing the transfer delay will likely only extend the size of the ischemic core, will also likely become more frequent. Despite this, the extent of pre-treatment infarction is known to be a key factor of clinical outcome [11], and whether a threshold volume of ischemic core exists beyond which ECR confers no added benefit remains uncertain. Our results, albeit in a small cohort, have not however identified this potential threshold ischemic core volume.

An advantage of our single centre study in assessing outcomes in large ischemic cores is that our hospital is the state-wide stroke service for ECR in Victoria, which in turn inherently attracts referrals for consideration of cases with relatively large ischemic cores as well as consideration of 'mercy' cases. Despite this, there remains a relatively small number of patients in our research cohort with ischemic cores greater than 70mls, a limitation of the study. Furthermore, the relatively small numbers limited the ability to control for variables such as initial NIHSS, location of the occlusion, time to recanalization as well as final recanalization score as assessed by the thrombolysis in cerebral infarction (TICI) scale. In addition, whether these results can be broadly translated to centres with operators that are not performing high numbers of ECR is uncertain.

Conclusion

Clinical outcomes were not significantly different in patients selected for ECR with ischemic core size e 70ml compared with those with smaller ischemic cores. A more comprehensive understanding of the role of ECR in patients with large ischemic cores on baseline CT perfusion is required to help guide acute management decisions in this subgroup of patients. Future studies are required to investigate the role of ECR in anterior circulation stroke with large ischemic cores.

Acknowledgements

None to declare.

References

1. Berkhemer OA, Majoie CB, Dippel DW. Intraarterial treatment for acute ischemic stroke. The New England journal of medicine. 2015;372(12):1178-9.
2. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. The New England journal of medicine. 2015;372(11):1009-18.
3. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. The New England journal of medicine. 2015;372(24):2285-95.
4. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. The New England journal of medicine. 2015;372(24):2296-306.
5. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. The New England journal of medicine. 2015;372(11):1019-30.
6. Bracard S, Ducrocq X, Mas JL, Soudant M, Oppenheim C, Moulin T, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. Lancet Neurol. 2016;15(11):1138-47.
7. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016;387(10029):1723-31.
8. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. The New England journal of medicine. 2018.
9. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. The New England journal of medicine. 2018;378(1):11-21.
10. Bivard A, Spratt N, Levi C, Parsons M. Perfusion computer tomography: imaging and clinical validation in acute ischaemic stroke. Brain : a journal of neurology. 2011;134(Pt 11):3408-16.
11. Jovin TG, Yonas H, Gebel JM, Kanal E, Chang YF, Grahovac SZ, et al. The cortical ischemic core and not the consistently present penumbra is a determinant of clinical outcome in acute middle cerebral artery occlusion. Stroke. 2003;34(10):2426-33.
12. Campbell BC, Christensen S, Levi CR, Desmond PM, Donnan GA, Davis SM, et al. Cerebral blood flow is the optimal CT perfusion parameter for assessing infarct core. Stroke. 2011;42(12):3435-40.
13. Payabvash S, Souza LC, Wang Y, Schaefer PW, Furie KL, Halpern EF, et al. Regional ischemic vulnerability of the brain to hypoperfusion: the need for

location specific computed tomography perfusion thresholds in acute stroke patients. Stroke. 2011;42(5):1255-60.
14. Hwang YH, Kang DH, Kim YW, Kim YS, Park SP, Liebeskind DS. Impact of time-to-reperfusion on outcome in patients with poor collaterals. AJNR Am J Neuroradiol. 2015;36(3):495-500.
15. Adeoye O, Albright KC, Carr BG, Wolff C, Mullen MT, Abruzzo T, et al. Geographic access to acute stroke care in the United States. Stroke. 2014;45(10):3019-24.
16. Gerschenfeld G, Muresan IP, Blanc R, Obadia M, Abrivard M, Piotin M, et al. Two Paradigms for Endovascular Thrombectomy After Intravenous Thrombolysis for Acute Ischemic Stroke. JAMA neurology. 2017;74(5):549-56.
17. Straka M, Albers GW, Bammer R. Real-time diffusion-perfusion mismatch analysis in acute stroke. Journal of magnetic resonance imaging : JMRI. 2010;32(5):1024-37.
18. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. Lancet. 2000;355(9216):1670-4.
19. Sanelli PC, Sykes JB, Ford AL, Lee JM, Vo KD, Hallam DK. Imaging and treatment of patients with acute stroke: an evidence-based review. AJNR Am J Neuroradiol. 2014;35(6):1045-51.
20. Campbell BC, Christensen S, Levi CR, Desmond PM, Donnan GA, Davis SM, et al. Comparison of computed tomography perfusion and magnetic resonance imaging perfusion-diffusion mismatch in ischemic stroke. Stroke. 2012;43(10):2648-53.
21. Gonzalez RG, Schaefer PW, Buonanno FS, Schwamm LH, Budzik RF, Rordorf G, et al. Diffusion-weighted MR imaging: diagnostic accuracy in patients imaged within 6 hours of stroke symptom onset. Radiology. 1999;210(1):155-62.
22. Chalela JA, Kidwell CS, Nentwich LM, Luby M, Butman JA, Demchuk AM, et al. Magnetic resonance imaging and computed tomography in emergency assessment of patients with suspected acute stroke: a prospective comparison. Lancet. 2007;369(9558):293-8.

Figure Legends

Figure 1. Flow diagram depicting inclusion and exclusion group numbers.

Figure 2. Percentage and raw numbers of patients reaching functional independence based on size of the initial ischemic core. This did not reach statistical significance with a P value of 0.24.

Figure 3. Percentage and raw numbers of patients with poor clinical outcome (mRS 4-6) based on size of the initial ischemic core.

Tables

	Inclusion group	Exclusion group	P value
Age (years) – median (IQR)	72 (61-78)	71 (58-79)	0.85
Male sex – no. (%)	154 (59%)	78 (53%)	0.25
NIHSS – median (IQR)	17 (12-21)	17 (13-22)	0.36
Onset to recanalization (mins) - mean	292	347	<0.00001

Table 1. Characteristics of the inclusion and exclusion groups. There was no significant differences between the two groups with regards to age, gender or NIHSS. Onset to recanalization was however significantly faster in the inclusion group.

Current study: **mRS 0-2 at 90 days for endovascular clot retrieval in large ischemic cores (≥70ml)**	14/26 (54)
mRS 0-2 at 90 days for control groups (IV tpa only) of HERMES trials	
MR CLEAN	51/267 (19.1)
SWIFT PRIME	33/93 (35)
EXTEND-IA	14/35 (40)
REVASCAT	29/103 (28.2)
ESCAPE	43/147 (29.3)

Table 2. Clinical outcome in ECR for large ischemic cores compared with control arms of the HERMES trials

Abstract

Background. The benefits of endovascular clot retrieval (ECR) for anterior circulation stroke with large ischemic cores remain uncertain. In spite of recent pooled analysis of randomized controlled studies, conclusions regarding the fate of large ischemic cores cannot be reached given the small number of included patients. **Methods.** This was a single centre retrospective study of patients treated with ECR in the period 2012 to 2017. The inclusion criteria were anterior circulation stroke with symptom onset less than 6 hours, baseline CT perfusion and 90 day clinical follow up defined by the Modified Rankin Score (mRS). **Results.** 261 patients were included. Median age of 72 (IQR 61-78) and 59% were male. The mean ischemic core volume was 27.6ml (SD 34.9ml). There were 235 patients with an ischemic core volume of <70ml and 26 patients with an ischemic core volume of e70ml. There was no statistically significant difference however in 90 day functional independence with 66% (154/235) in the <70ml core group and 54% (14/26) in the e70ml core group reaching a 90 day mRSd2. **Conclusions.** We found that patients selected for ECR with ischemic core size e70ml had clinical outcomes not significantly different compared with those with smaller ischemic cores. We recommend that large ischemic core size alone does not necessarily constitute an absolute contraindication for ECR. Randomized controlled studies are needed to better define the benefits for this group of patients.

Keywords

Acute stroke; Endovascular clot retrieval; Computed tomography perfusion; Ischemic core

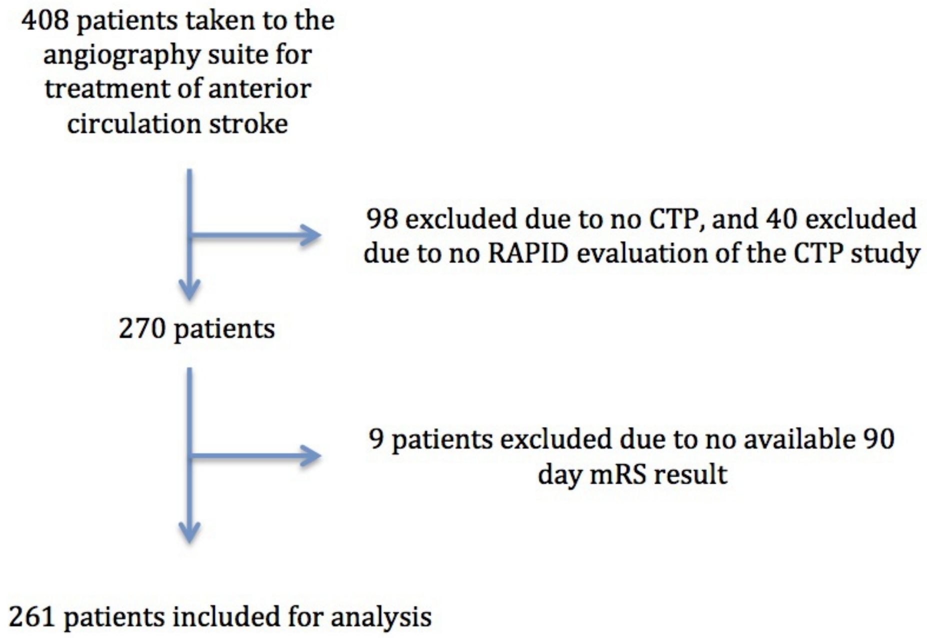

Figure 1. Flow diagram depicting inclusion and exclusion group numbers.

Figure 1.jpg

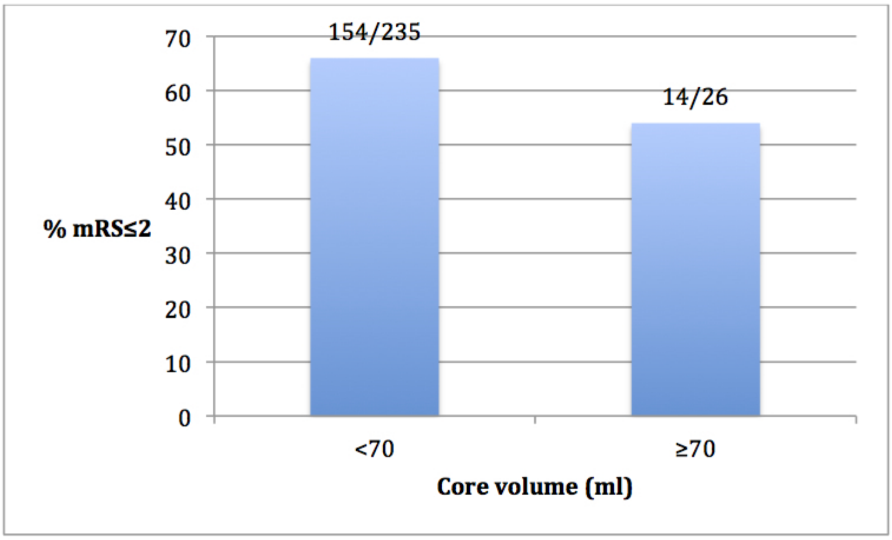

Figure 2. Percentage and raw numbers of patients reaching functional independence based on size of the initial ischemic core. This did not reach statistical significance with a P value of 0.24.

Figure 2 Revision.jpg

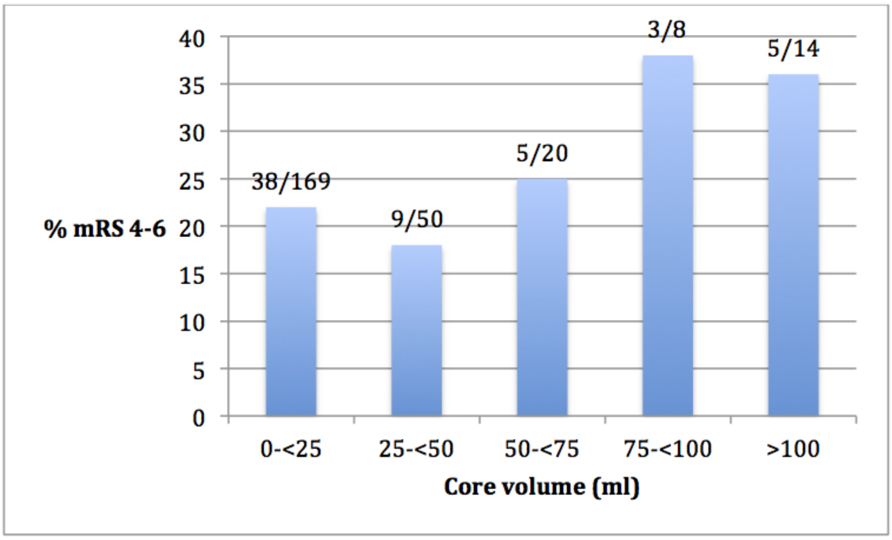

Figure 3. Percentage and raw numbers of patients with poor clinical outcome (mRS 4-6) based on size of the initial ischemic core.

Figure 3 Revision.jpg

Title Page

Endovascular clot retrieval in acute stroke with large ischemic core is not always associated with poor outcomes.

Kenneth Sim[a], Bernard Yan[b], Richard Dowling[a], Steven Bush[a], Peter Mitchell[a]

Affiliations

[a]Department of Radiology, The Royal Melbourne Hospital, Parkville, Victoria, Australia

[b]Department of Medicine and Neurology, Melbourne Brain Centre at The Royal Melbourne Hospital, University of Melbourne, Parkville, Victoria, Australia

Correspondence

Dr Peter Mitchell, Department of Radiology, The Royal Melbourne Hospital, Parkville, Victoria, Australia.

Phone +613 9342 7000

Fax +613 9342 7482

Peter.Mitchell@mh.org.au

Acknowledgements, sources of funding and conflicts of interest

Dr Peter Mitchell receives research grants from Medtronic and Stryker.

Word count

Abstract: 231

Main text: 1755