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Effect of general anaesthesia on functional outcome among patients with anterior circulation ischaemic stroke undergoing endovascular thrombectomy versus standard care: a meta-analysis of individual patient data from seven randomised controlled trials~~The Association Between General Anaesthesia and Outcome of Endovascular Thrombectomy in Pooled Data from Seven Randomised Trials~~

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Abstract

Background: General anaesthesia (GA) during endovascular thrombectomy has been associated with worse patient outcomes in observational studies. We examined the association between GA and the outcome of endovascular thrombectomy in pooled data from seven available trials.

Methods: Patient-level data were pooled from randomiszed trials listed in Pubmed 1/Jan/2010-31/May/2017 comparing endovascular thrombectomy (performed predominantly using predominantly -stent-retrievers) with standard care in anterior circulation ischaemic stroke patients (HERMES Collaboration). The primary outcome was ordinal analysis of the modified Rankin scale (mRS) at 90 days in the GA and non-GA subgroups of endovascular-treated patients and patients randomised to standard care, adjusted for baseline prognostic variables. An alternative approach using propensity-score stratification was also used. To account for between-trial variance we used mixed-effects modeling with a random effect for trial incorporated in all models.

Findings: Of 1764 patients, 871 were allocated to endovascular thrombectomy. After exclusion of 74 patients (72 who did not undergo the procedure and 2 with missing data on anaesthetic strategy), 236/797 (30%) of endovascular patients were treated under GA. At baseline, GA patients were younger and had shorter time to randomization but similar pre-treatment clinical severity compared to non-GA. Endovascular thrombectomy improved functional outcome at 3 months versus standard care in both GA (adjusted common odds ratio (cOR) 1·52, 95%CI 1·09-2·11, p=0·014) and non-GA (adjusted cOR 2·33, 95%CI 1·75-3·10, p<0·001) patients. However, outcomes were significantly better for those treated under non-GA versus GA (covariate-adjusted cOR 1·53, 95%CI 1·14-2·04, p=0·004; propensity-stratified cOR 1·44 95%CI 1·08-1·92, p=0·012). The risk of bias and variability among studies was assessed to be low.

Interpretation: Worse outcomes after endovascular thrombectomy were associated with GA, after adjustment for baseline prognostic variables. These data support avoidance of GA whenever possible. The procedure did, however, remain effective versus standard care in patients treated under GA, indicating that treatment should not be withheld in those who require anaesthesia for medical reasons.

Funding: The HERMES collaboration was funded by an unrestricted grant from Medtronic to the University of Calgary.

Research in context

Evidence before this study

We searched Pubmed for studies examining the association of general anaesthesia with outcome in stroke patients undergoing endovascular thrombectomy between 1 Jan ~~2000-~~2010 and~~-~~ 31 May 2017. Multiple observational studies demonstrated worse outcome in patients treated under general anaesthesia. Individual randomised trials of thrombectomy versus standard care found conflicting results on the effect of general anaesthesia, varying between abolition of the thrombectomy treatment effect in MR CLEAN and no effect in THRACE. Three single-centre randomised trials of general anaesthesia versus conscious sedation found either no difference in functional outcome between groups or a slight benefit of general anaesthesia.

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Added value of this study

These data from contemporary, high quality randomised trials form the largest study to date of the association between general anesthesia and the benefit of endovascular thrombectomy versus standard care. We used two different approaches to adjustment for baseline imbalances (multivariable logistic regression and propensity-score stratification). We found that GA for endovascular thrombectomy, as practiced in contemporary clinical care across a wide range of expert centers during the randomised trials, was associated with worse outcome than avoiding GA, independent of patient co-morbidities. Patients still benefited from thrombectomy compared to standard care when treated under GA.

Implications of all the available evidence

The requirement for GA due to airway compromise or agitation that threatens the quality of revascularization should not deter clinicians from pursuing endovascular thrombectomy. The contrast between this analysis and the recent randomised trials comparing GA and conscious sedation suggests that, when GA is medically necessary, close attention should be paid to minimizing anaesthetic delays to commence the procedure and maintaining physiological parameters such as blood pressure. A multi-centre randomiszed trial to definitively address these issues is warranted.

Introduction:

Multiple observational studies have suggested that patients treated with endovascular thrombectomy under general anaesthesia (GA) have poorer outcomes than those treated without GA.[1] However, patients with more severe stroke or comorbidities may be more likely to be treated under GA, leading to the potential for confounding by indication. In MR CLEAN, sites specified their anaesthetic strategy prospectively and analysis of that trial found that the beneficial treatment effect of thrombectomy became non-significant in patients treated under GA.[2] These results could potentially lead to a reluctance to convert from an awake procedure to GA in cases where patient agitation or challenging vascular anatomy are preventing optimal revascularization. In contrast, three small single-center randomised trials which compared GA, performed using strict protocols to maintain blood pressure, with conscious sedation using the same agents at lower doses without intubation did not detect a signal of harm, and functional independence was either no different or slightly increased in the GA patients.[3-5] We analysed the pooled individual patient data from seven available randomised trials to assess whether a treatment benefit was preserved in patients treated under GA in broader contemporary practice.

Methods:

~~The Highly Effective Reperfusion using Multiple Endovascular Devices (HERMES) collaboration[6] pooled data from~~ We searched Pubmed for randomis~~z~~ed trials published between 1 Jan 2010 and 31 May 2017 comparing endovascular thrombectomy performed using predominantly stent-retrievers with standard care in anterior circulation ischaemic stroke patients - Pubmed search string: (("randomis~~z~~ed controlled trial"[Publication Type]) AND ((thrombectomy[Title/Abstract]) OR (clot retrieval[Title/Abstract]) OR intraarterial[Title/Abstract]) AND (stroke[Title/Abstract]) AND ("2010/01/01"[Date - Publication] : "2017/05/31"[Date - Publication])). The Highly Effective Reperfusion using Multiple Endovascular Devices (HERMES) collaboration[6] pooled individual patient data from the MR CLEAN,[7] ESCAPE,[8] EXTEND-IA,[9] SWIFT PRIME,[10] REVASCAT,[11] PISTE[12,13] and THRACE[14] trials. All participants provided informed consent according to each trial protocol and each study was approved by the local ethics board.

This meta-analysis was prospectively designed by the HERMES executive committee but not registered. The study protocol is included in the supplementary web appendix. Data were contributed by the authors of all the trials meeting eligibility criteria and collated by independent statisticians. All data relevant to the analyses presented were part of each study's individual design and data collection and are part of the general HERMES database. No standardization or translation of the fields employed for analysis and reporting was necessary. After collation of data, key fields were compared to original results, including published data. No major discrepancies were found and minor discrepancies were resolved in collaboration with the study authors/investigators. The study selection process is outlined in supplementary Figure SA1. Variability between studies is described in supplementary Table SA1 and heterogeneity assessed in supplementary figures SA2-4. Risk of bias in the individual studies was assessed using the Cochrane handbook methodology[15] and was low for all studies except THRACE which used unblinded assessment of day 90 functional outcome (supplementary Table SA2). The principal risk of bias derived from differences among individual studies' methods and inclusion criteria. A one-stage approach was employed, defined as use of individual patient data with analysis including covariates and random study effects to appropriately incorporate any between-study differences.

In MR CLEAN, the steering committee gave no recommendations about anaesthetic management. Nevertheless, the majority of centers adhered to a fixed protocol regarding type of anesthetic management throughout the trial. In the other trials, the use of anaesthesia was at the discretion of the treating team on a case by case basis, although two trials (ESCAPE and REVASCAT) discouraged GA where possible.

Patients treated under GA (sedation with intubation) were identified and their baseline characteristics compared to the non-GA patients who were managed with or without sedation and not intubated.

The primary outcome was the mRS at 3 months, which was analyzed using ordinal logistic regression to obtain the common odds ratio (cOR). Secondary outcomes were the proportion of patients reaching independence (mRS 0-2) and return to all usual activities (mRS 0-1) and the proportion with early neurological recovery defined as a ≥8 point reduction in National Institutes of Health Stroke Scale (NIHSS) or reaching 0-1 at 24 hours. Safety outcomes were the proportion of patients who had died at 90 days, the proportion with symptomatic intracerebral haemorrhage (SICH, as defined by each trial) and the proportion with parenchymal haematoma (PH, intracerebral blood clot with mass effect). The proportions of endovascular patients with vessel perforation and pneumonia were compared between GA and non-GA groups.

Regression analyses were adjusted for baseline prognostic factors including age, sex, NIHSS at baseline, ASPECTS, location of occlusion, treatment with intravenous alteplase (yes/no) and time to randomization. Treatment was included as a variable with three levels: defined as GA, non-GA and controls. To account for between-trial variance we used mixed-effects modeling with a random effect for trial incorporated in all models. In addition, as a sensitivity analysis, propensity scores were constructed using logistic regression with GA vs no GA as the outcome and employing the same set of baseline variables as in the regression models. Propensities were then incorporated into the outcome model for the ordinal modified Rankin scale (mRS) score by stratification into five groups.[16]

Role of the funding source

An unrestricted grant was provided to the University of Calgary by Medtronic who had no role in study design, the collection, analysis or interpretation of data, the writing of the report or the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results:

In the pooled data of 1764 patients, 871 were randomised to endovascular thrombectomy and 893 to standard medical care. After exclusion of 74 patients (72 who did not undergo the procedure and 2 with missing data on anaesthetic strategy), 236/797 (30%) of endovascular patients were treated under GA. At baseline, patients treated under GA were younger and had shorter time from stroke onset to randomization than those treated without GA (Table 1). Baseline clinical severity (NIHSS) was not significantly different between groups although there was a trend to greater severity in the GA patients. GA was used in 113/394 (29%) of right hemisphere and 119/392 (30%) of left hemisphere stroke patients (p=0·64). GA patients were more likely to receive alteplase and had a lower rate of diabetes mellitus.

Functional and neurological outcome

At 3 months, the patients who underwent endovascular treatment had significantly greater odds of improved functional outcome versus standard medical care in covariate-adjusted analysis in both GA (common odds ratio

[cOR] 1·52 CI_{95} 1·09-2·11, p=0·014) and non-GA (cOR 2·33 CI_{95} 1·75-3·10, p<0·001) groups, Table 2, Figure 1. There was no heterogeneity in the effect of GA on outcome among studies, although the small numbers limit power for this analysis. The odds of improved outcome using non-GA versus GA were significantly greater in ordinal analysis of the mRS, after adjustment for baseline prognostic factors (cOR 1·53 CI_{95} 1·14-2·04, p=0·004). For every 100 patients treated under GA versus no GA, 18 patients would have worse functional outcome, including 10 who would not achieve functional independence. The propensity-stratified analysis generated similar results and the common odds ratio for improved outcome for non-GA vs GA was 1·44, CI_{95} 1·08-1·92, p=0·012. Secondary outcomes followed similar trends (Table 2).

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Safety

The rate of SICH did not differ between endovascular patients treated under GA, those treated without GA or standard medical care patients. The~~re was a trend towards reduced~~ 90-day mortality was 13.4% in non-GA patients versus 17.3% in standard medical care (p=0·07) and 17.4% ~~that was not observed~~ in GA ~~versus standard medical care~~ patients (Table 2). Pneumonia occurred in a similar proportion of GA versus non-GA patients (11·4% versus 8·4% p=0·18), although the reported incidence of pneumonia was significantly different among studies (p<0·001), likely indicating differences in definition or in capture of adverse events. ~~Rates of v~~Vessel perforation ~~were similar~~occurred in 0.4% ~~in~~ GA ~~(0·4%)~~ versus 1.6% non-GA patients (~~1·6%,~~ p=0·30).

Procedural characteristics and time metrics

The proportion of patients with successful reperfusion post-procedure (modified Treatment in Cerebral Infarction mTICI 2b/3 i.e. reperfusion of greater than 50% of the affected territory) did not differ between GA and no GA patients (75.1% vs 76.1%, p=0.78). The time interval between randomization and reperfusion was significantly greater in GA versus non-GA patients (median 105 vs 85 min, p<0·001). However, there was an imbalance in the time from stroke onset to randomization which was median 5 minutes shorter in the GA group (p=0·04) and the difference in total onset to reperfusion time between both groups was therefore not significant (median 302 vs 288 min, p=0·57, Table 1).

Discussion

Patients treated under GA suffered poorer outcomes compared to those treated without GA, after adjustment for baseline characteristics. The magnitude of this effect was clinically significant – for every 100 patients treated under GA versus no GA, 18 patients would have worse functional outcome, including 10 who would not achieve functional independence However, a significant benefit of endovascular thrombectomy over standard care was retained in those patients treated under GA.

The randomised trials differed in their proportion of patients treated under GA but the experience in REVASCAT and ESCAPE, which discouraged GA, was that <10% of anterior circulation stroke patients had an absolute requirement for GA. MR CLEAN has previously reported that GA was associated with marked attenuation of treatment effect. It is possible that the lower rate of revascularization in MR CLEAN attenuated the potential treatment benefit compared to EXTEND-IA and SWIFT PRIME. However, the THRACE trial reported no difference in outcomes in patients treated with or without GA despite a similar effect size to MR CLEAN.[14]

The method of GA in these randomised trials was entirely at the discretion of the treating team and there were no formal protocols specifying anaesthetic agents, blood pressure targets or other aspects of physiological management. This is in contrast to the highly protocol-specified approach to both GA and conscious sedation in the SIESTA, ANSTROKE and GOLIATH trials.[3-5] In particular, strict attention to maintaining systolic blood pressure >140mmHg throughout the procedure (including during anaesthetic induction) may have been critical to preserving collateral blood flow to the ischaemic penumbra and preventing a harmful effect of GA. There were also specified criteria to prevent hyper or hypoventilation.

Each of the GA vs conscious sedation randomised trials also used the same medications in both treatment arms, the difference being lower dose and absence of intubation in the conscious sedation group. This contrasts with the HERMES non-GA patient group, in which treatment varied between no sedative medication at all and use of sedatives and anaesthetic agents but without intubation. The use of local anaesthetic agent at the arterial puncture site without any sedative agent, which is routine at many institutions, may have different implications for patient outcome compared to conscious sedation as described in the recent randomised trials. Different anaesthetic agents could also potentially vary in their protective or harmful effects on ischaemic brain, among other hypothetical differences between approaches.[17] The details of the medications given in the HERMES patients were not available for this analysis.

Although the main reasons given for using GA are procedural safety and securing the airway, there was no significant difference in the rate of vessel perforation or pneumonia between GA and non-GA patients. Our data therefore do not support GA as a safer approach to treatment and demonstrate the general technical safety of endovascular thrombectomy. There are potential advantages of avoiding GA, including the ability to assess neurological status during the procedure, reduced intensive care requirements post-procedure and reduced costs. In the HERMES trials, GA was also associated with a delay in reperfusion. However, this was not the case in the randomised trials where a slight delay to start the procedure in GA patients (on average <10 minutes) appeared to be offset by shorter procedural time. This may be plausible if reduced patient movement allows more efficient roadmap techniques. However, the three centers that performed the randomised trials of GA achieved exceptionally fast anaesthetic induction that may not be common practice at most institutions.

The main limitation of this study is that the choice to use GA versus non-GA was not randomised and the differentiation between medically required GA versus elective GA was not recorded in the trial databases. The important prognostic variables of age and time from stroke onset to randomization favoured the GA group, although the ~~trend to~~non-significantly greater clinical severity would partially offset that effect. We used two different methods of adjustment for baseline imbalances (multivariate regression and propensity-score stratification) which gave consistent results. Nonetheless, for both methods the possibility of unmeasured confounding remains. The anaesthetic practices in the HERMES trials were not pre-specified by protocol nor recorded in detail but are likely to have been substantially more variable than the recent single centre randomis~~z~~ed trials. However, this also represents a strength of our study as results are likely to be generalizable to current clinical practice. The risk of bias in component trials was overall assessed to be low.

In conclusion, the HERMES data suggest that GA for endovascular thrombectomy, as practiced in contemporary clinical care across a wide range of expert centers during the randomised trials, is associated with worse outcome ~~than~~ compared to avoiding GA, independent of patient co-morbidities. Patients still benefited from thrombectomy compared to standard care when treated under GA. Therefore, the requirement for GA due to airway compromise or agitation that threatens the quality of revascularization should not deter clinicians from pursuing endovascular thrombectomy. The contrast between the HERMES data and the recent randomised trials comparing GA and conscious sedation suggests that, when GA is medically necessary, close attention should be paid to minimizing anaesthetic delays to commence the procedure and maintaining physiological parameters such as blood pressure. A multi-centre randomis~~z~~ed trial to definitively address these issues is warranted.

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nil

Contributors

BCVC prepared the first draft of the report based on an analysis plan agreed by the HERMES Executive (BCVC, MG, DWJD, AMD, S Bracard, PW, AD, CBLM, FG, KWM, JLS, TJG, MDH, PJM) who also contributed to study interpretation. SB performed the statistical analyses. All authors participated in patient enrolment, data collection, critically reviewed the report and approved the final version. FG, KWM, RIvO, JLS, TGJ, MDH and PJM contributed equally.

Declaration of interests

B.C.V. Campbell: reports research support from the National Health and Medical Research Council of Australia (GNT1043242, GNT1035688), Royal Australasian College of Physicians, Royal Melbourne Hospital Foundation, National Heart Foundation, National Stroke Foundation of Australia and unrestricted grant funding for the EXTEND-IA trial to the Florey Institute of Neuroscience and Mental Health from Covidien (Medtronic).

W.H. van Zwam reports speaker's honoraria from Stryker and Codman (paid to institution).

M. Goyal reports grants from Medtronic and Stryker, personal fees from Microvention, Medtronic and Stryker, during the conduct of the study; In addition, Dr. Goyal has a patent systems and methods for diagnosing strokes (PCT/ CA2013/000761) licensed to GE Healthcare.

B. Menon: reports membership of the Steering and Executive Committee, ESCAPE trial that received support from Covidien Inc., Site Principal Investigator, SOCRATES Trial, sponsored by Astra Zeneca, honoraria from Penumbra Inc., a provisional patent 62/086077 for triaging systems in ischaemic stroke, research funding from CIHR, HSFC, AIHS, HBI and the Faculty of Medicine, University of Calgary and board membership of QuikFlo Health Inc. .

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P. White: Has nothing to disclose.

A. Dávalos: Consultant/Advisory Board; Modest; Medtronic Neurovascular (Steering Committee STAR).

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R.J. van Oosterbrugge: Has nothing to disclose

J. Saver is an employee of the University of California. Dr. Saver has served as an unpaid site investigator in multicenter trials run by Medtronic and Stryker for which the UC Regents received payments on the basis of clinical trial contracts for the number of subjects enrolled. Dr. Saver received stock options for services as a scientific consultant regarding trial design and conduct to Cognition Medical. Dr. Saver receives funding for services as a scientific consultant regarding trial design and conduct to Medtronic/Covidien, Stryker, Neuravi, BrainsGate, Pfizer, Squibb, Boehringer Ingelheim (prevention only), ZZ Biotech, and St. Jude Medical. Dr. Saver serves as an unpaid consultant to Genentech advising on the design and conduct of the PRISMS trial; neither the University of California nor Dr. Saver received any payments for this voluntary service. The University of California has released the Rankin Focused Assessment for free use under a Creative Commons u license, and has copyright for Rankin Scale training vignettes. The University of California has patent rights in retrieval devices for stroke.

T.G. Jovin: has consulted for Codman Neurovascular and Neuravi, holds stock in Silk Road and Blockade; has acted as an unpaid consultant to Stryker as PI of the DAWN trial and served as an unpaid member of a Medtronic Advisory Board.

M. Hill: reports unrestricted grant funding for the ESCAPE trial to University of Calgary from Covidien (Medtronic), and active/in-kind support consortium of public/charitable sources (Heart & Stroke Foundation, Alberta Innovates Health Solutions, Alberta Health Services) and the University of Calgary (Hotchkiss Brain Institute, Departments of Clinical Neurosciences and Radiology, and Calgary Stroke Program); personal fees from Merck, non-financial support from Hoffmann-La Roche Canada Ltd, outside the submitted work; In addition, Dr. Hill has a patent Systems and Methods for Assisting in Decision-Making and Triaging for Acute Stroke Patients pending to US Patent office Number: 62/086,077 and owns stock in Calgary Scientific Incorporated, a company that focuses on medical imaging software.

P.J. Mitchell: reports unrestricted grant funding for the EXTEND-IA trial to the Florey Institute of Neuroscience and Mental Health from Covidien (Medtronic), has served as an unpaid consultant to Codman Johnson and Johnson, his organization has received unrestricted research funding and grants from Codman Johnson and Johnson, Medtronic, and Stryker.

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Figure 1 – Distribution of modified Rankin Scale at 3 months in patients treated under general anaesthesia versus without general anaesthesia (no GA) versus the standard medical care group.

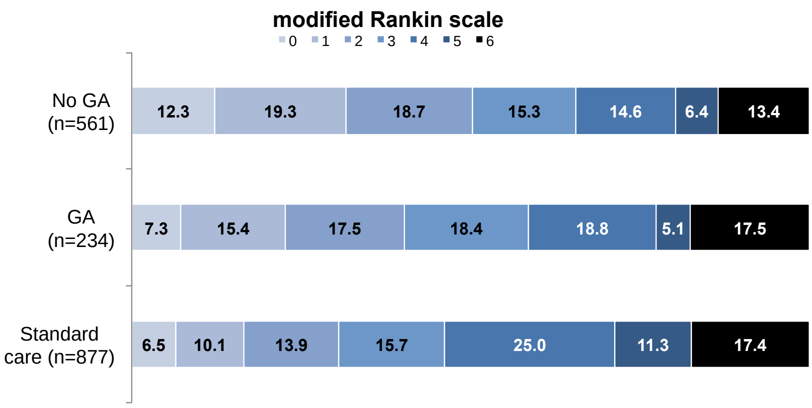

Table 1 – Baseline characteristics of endovascular patients treated under general anaesthesia (GA) versus without GA (no GA) and those who received standard care.

Characteristic	GA (n=236)	No GA (n=561)	p-value GA vs no GA	All Endovascular (n=871)	All Standard Care (n=893)
Age, mean (SD)	63·8 (14)	66·3 (13·3)	0·015	65·5 (13·5)	65·7 (13·5)
Female sex % (n)	42·8% (101/236)	48·7% (273/561)	0·14	47·3% (412/871)	47·3% (421/891)
NIHSS at baseline, median (IQR)	18 (15-21)	17 (14-20)	0·09	17 (14-20)	17 (13-21)
ASPECTS, median (IQR)	7 (6-8)	8 (7-9)	~~<~~0·~~001~~0005	8 (7-9)	8 (7-9)
Left hemisphere affected % (n)	51·3% (119/232)	49·3% (273/554)	0·64	49·5% (424/856)	50·2% (442/881)
Directly admitted to treating center %(n)	75·4% (178/236)	77·3% (432/559)	0·57	78·0% (678/869)	75·2% (668/888)
Onset to randomization, min median (IQR)	179 (137-238)	184 (144-246)	0·04	181 (141-241)	184 (140-250)
Randomization to reperfusion, min, median (IQR)	105 (80-149)	85 (51-118)	<0·0001	92 (61-128)	NA
Onset to reperfusion, min median (IQR)	302 (246-357)	288 (222-358)	0·57	291 (231,357)	NA
Site of arterial occlusion					
ICA occlusion %(n)	25·0% (59/236)	25·7% (144/561)	0·13	24·7% (215/871)	25·4% (227/893)
M1 occlusion %(n)	59·7% (141/236)	61·1% (343/561)		61·5% (536/871)	60·1% (537/893)
M2 occlusion %(n)	6·4% (15/236)	8·4% (47/561)		7·7% (67/871)	7·2% (64/893)
Unknown %(n)	8·9% (21/236)	4·8% (27/561)		6·1% (53/871)	7·2% (64/893)
Alteplase administered %(n)	92·4% (218/236)	84·3% (473/561)	0·002	87·6% (763/871)	90·6% (809/893)
Hypertension %(n)	50·9% (119/234)	56·1% (315/561)	0·18	53·6% (465/867)	58·8% (523/890)
Hyperlipidemia %(n)	29·7% (69/232)	36·9% (202/548)	0·06	35·5% (300/846)	40·2% (351/873)
Diabetes mellitus %(n)	8·9% (21/236)	18·2% (102/560)	~~<~~0·~~001~~0009	15·1% (131/867)	17·5% (156/889)
Smoking %(n)	39·0% (85/218)	36·3% (183/504)	0·503	37·8% (298/788)	36·6% (300/820)

SD standard deviation, IQR interquartile range, NIHSS National Institutes of Health Stroke Scale (standardized neurological examination) ranges from normal (0) to death (42). ASPECTS Alberta Stroke Program Early Computed Tomography Score (reflects extent of early ischemic change on CT brain: 10 is normal, 0 is involvement of the entire middle cerebral artery territory). ICA internal carotid artery, M1 first segment of middle cerebral artery (pre-bifurcation), M2 second segment of middle cerebral artery (from bifurcation to the circular sulcus of the insula in the Sylvian fissure).

Table 2 – Outcomes in patients treated with standard care versus endovascular thrombectomy with or without general anaesthesia (GA)

Outcome	Standard Care (n=893)	Thrombectomy with GA (n=236)	Thrombectomy without GA (n=561)	GA vs Standard *		No GA vs Standard *		No GA vs GA *	
				Effect size OR (95%CI)	P value	Effect size OR (95%CI)	P value	Effect size OR (95%CI)	P value
Primary outcome Functional outcome at 90 days (modified Rankin Scale – mRS) Ordinal analysis[†] – median (IQR) **– covariate adjusted common odds ratio**	4 (2, 5)	3 (2, 4)	2 (1, 4)	1·52 (1·09-2·11)	0·01	2·33 (1·75-3·10)	<0·0001	1·53 (1·14-2·04)	0·004
– propensity-score stratification common odds ratio				1·42 (1·09-1·84)	0·008	2·21 (1·65-2·95)	<0·0001	1·44 (1·08-1·92)	0·01
Secondary Outcomes Independent functional outcome (mRS0-2)	30·6%	40·2%	50·3%	1·62 (1·16-2·26)	0·005	2·72 (1·99-3·72)	<0·0001	1·65 (1·14-2·38)	0·008
Excellent functional outcome (mRS0-1)	16·6%	22·6%	31·6%	1·53 (1·02-2·31)	0·04	2·72 (2·00-3·69)	<0·0001	1·68 (1·12-2·52)	0·01
Early neurological improvement (NIHSS reduction ≥8 points or reaching 0–1 at 24h)[‡]	23·8%	38·1%	53·2%	2·02 (1·36-3·00	<0·00051	3·92 (2·73-5·62)	<0·0001	1·75 (1·23-2·48)	0·002
Safety									
Death within 90 days	17·3%	17·4%	13·4%	1·01 (0·67-1·52)	0·96	0·73 (0·52-1·02)	0·07	0·71 (0·44-1·14)	0·15
Symptomatic intracerebral haemorrhage[§]	3·5%	4·4%	3·8%	1·19 (0·56-2·51)	0·65	1·14 (0·62-2·10)	0·68	0·95 (0·41-2·19)	0·90
Parenchymal haematoma (PH)	10·2%	14·3%	11·4%	1·38 (0·86-2·22)	0·19	1·25 (0·72-2·16)	0·42	0·97 (0·60-1·58)	0·90

OR odds ratio, CI confidence interval, IQR interquartile range

[*] adjusted for age, sex, baseline stroke severity, site of occlusion, intravenous alteplase treatment, ASPECTS score, and time from onset to randomization

[†] Modified Rankin scale (mRS) ranges from normal (0) to death (6). Analysis combined mRS 5 & 6

[‡] National Institutes of Health Stroke Scale (NIHSS) score (standardized neurological examination) ranges from normal (0) to death (42), 8 point reduction is highly clinically significant.

[§] SICH - Symptomatic intracerebral haemorrhage defined by source trial