Irish Journal of Medical Science (1971 -) (2019) 188:689–698
https://doi.org/10.1007/s11845-018-1899-6

ORIGINAL ARTICLE

A systematic review of the clinical effectiveness of emergency endovascular therapy using mechanical thrombectomy in acute ischaemic stroke: implications for service delivery

Ronan W. Glynn [1] · Conor Teljeur [1] · Joseph Harbison [2] · David J. Williams [3] · Patricia Harrington [1] · Mairin Ryan [1]

Received: 6 March 2018 / Accepted: 5 September 2018 / Published online: 15 September 2018

Abstract

Background Twelve randomised controlled trials (RCTs) comparing mechanical thrombectomy against traditional treatment options for patients experiencing acute ischaemic stroke (AIS) have been published.

Aims To evaluate whether this technology is more effective and/or safer than traditional treatment options and to assess the potential for implementation of this technology as a treatment strategy for acute ischaemic stroke in Ireland.

Methods RCTs published up to February 2017 were included. Meta-analysis was performed for two primary (mortality at 90 days, mRS at 90 days) and four secondary outcomes. Cumulative meta-analysis was used to investigate the point at which a consistent treatment effect was observed for outcomes that had a statistically significant pooled effect.

Results Mechanical thrombectomy was associated with higher likelihood of being independent (mRS, $p < 0.01$; Barthel index, $p < 0.01$) at 90 days post-AIS ($p < 0.001$). Cumulative meta-analysis demonstrated a consistent treatment effect in favour of mechanical thrombectomy after each trial was added to the analysis. There was no evidence of a difference in mortality rates ($p = 0.21$) or rates of SICH ($p = 0.71$) between patients randomised to intervention and control arms. Although the intervention appears to be associated with higher rates of any cerebral haemorrhage ($p < 0.01$) and recurrent ischaemic stroke ($p = 0.03$), considerable uncertainty remains as to these treatment effects.

Conclusions The trials published most recently have acted as a 'watershed' for mechanical thrombectomy, and while there are significant caveats, the data suggests that mechanical thrombectomy needs to be factored into the planning and delivery of services for the management of patients with acute ischaemic stroke in Ireland.

Keywords Aspiration · Endovascular · Ischaemic stroke · Meta-analysis · Stent retriever · Thrombectomy

Introduction

It has been estimated that approximately 7000 individuals experience a stroke each year in Ireland, of which 85% are acute ischaemic stroke (AIS). An estimated 2000 people die as a result of stroke each year in Ireland, giving an age-standardised death rate of 34.6 per 100,000 population [1]. In 2014, it was predicted that there would be a 20% increase in the prevalence of chronic diseases by 2020, primarily due to population ageing, with the number of people experiencing stroke predicted to increase by between 4 and 5% per annum between 2015 and 2020 [2].

Intravenous thrombolysis with tissue plasminogen activator (IV tPA) has traditionally been regarded as the gold standard treatment for patients experiencing AIS, albeit with modest clinical efficacy. Thrombolysis, administered within 4.5 h of symptom onset, is associated with a recanalisation rate of approximately 46% and good functional recovery (as defined by a modified Rankin score of 0 or 1) in approximately 35% of patients [3, 4]. The narrow time window and strict exclusion criteria associated with thrombolysis has meant that only a small proportion of potentially eligible patients receive this therapy.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11845-018-1899-6) contains supplementary material, which is available to authorized users.

✉ Ronan W. Glynn
ronanglynn@doctors.net.uk

[1] Health Technology Assessment Directorate, Health Information and Quality Authority, George's Court, Dublin 7, Ireland

[2] St. James' Hospital, Dublin, Ireland

[3] Geriatric Medicine, Royal College of Surgeons in Ireland (RCSI) and Beaumont Hospital, Dublin, Ireland

A potential alternative involves the use of mechanical thrombectomy, a catheter-based technology, to approach and remove a clot from a blocked cerebral artery. Mechanical thrombectomy devices aim to retrieve thrombi and rapidly restore blood flow in patients experiencing AIS. These devices can also be considered in terms of their time of development and approval for use, and may be separated into 'first-' and 'second-generation' (stent retriever) devices, and those whose mechanism of action is based on aspiration/suction.

The first randomised controlled trials (RCTs) to compare thrombolysis with mechanical thrombectomy for patients experiencing AIS were published in 2013 [5–7]. The following years saw opinion swing back and forth regarding its potential, but the publication of five additional trials in 2015 saw increasing acceptance that mechanical thrombectomy provides additional benefit, when compared with standard medical therapy, including IV tPA.

Four additional RCTs were published in 2016–2017 [8–11]. The aim of this work is to incorporate this latest evidence into a meta-analysis of published RCTs and to assess whether mechanical thrombectomy plus traditional treatment options (which may include intravenous (IV) and/or intraarterial (IA) thrombolysis where appropriate) is more effective and/or safer than these options alone in the management of AIS.

Patient and methods

Search strategy and selection criteria

A systematic literature search identified RCTs published between January 2005 and February 2017, inclusive (a full history of this work is included in the supplementary appendix). Studies were identified via electronic searches in databases PubMed [Medline] and Embase. Studies of any language were considered. References from the included studies and review articles were reviewed. The full search strategies are outlined in Appendix 1. This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12].

Eligibility criteria

Inclusion and exclusion of studies was based on the Patients, Interventions, Comparisons, Outcomes (PICO) protocol. The population of interest were adults aged 18 years or older with acute ischaemic stroke in the anterior and/or posterior region. The intervention was mechanical thrombectomy (which could be used in combination with IV and/or IA thrombolysis, or as an alternative to it in patients experiencing an AIS who are not candidates for thrombolysis, or in patients in whom thrombolysis appears to have failed) plus traditional treatment options. The comparator was these traditional options alone.

Study selection and analysis of quality and bias

Two investigators (RWG, CT) reviewed and selected articles according to pre-defined selection criteria. Researchers then met and discussed areas of agreement and completeness, and disagreements were resolved by consensus. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to assess the quality of the evidence. The risk of bias was assessed using the Cochrane risk of bias tool for RCTs, which considers the presence or absence of selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting of outcomes) and other bias (any other important concerns noted).The assessment of bias was based on author judgement. Two authors assessed the risk of bias and disagreements were resolved by consensus.

Outcome measures

The pre-specified primary outcome measures were all-cause mortality at 90 days and functional independence at 90 days as measured by a modified Rankin score (mRS) score of 0–2. The pre-specified secondary outcomes were ability to perform activities of daily living (ADLs) at 90 days as measured by Barthel index, symptomatic intra-cerebral haemorrhage (SICH) (as defined by the individual studies), any cerebral haemorrhage and recurrent ischaemic stroke at 90 days.

Data analyses

Meta-analysis was performed for the two primary and four secondary outcomes. Cumulative meta-analysis was used to investigate the point at which a consistent treatment effect was observed for outcomes that had a statistically significant pooled effect.

Meta-analyses were conducted using R statistical software, version 3.2.2, and the metafor 1.9-8 package within R [13, 14]. Due to the expected heterogeneity across studies in terms of devices used and time to procedure, random effects meta-analysis was used. Binary outcomes were pooled as risk ratios. Heterogeneity was assessed on the basis of I^2 values. Values in excess of 75% were interpreted as considerable heterogeneity, and values between 50 and 90% were interpreted as potentially substantial heterogeneity.

The first three trials included in this assessment [5–7] had a number of important methodological differences when compared with the latter nine (see discussion). Therefore, subgroup analyses, including the latter nine trials only, were also performed. Most of these second-generation trials ceased early. Due to concerns over potential bias introduced by early trial cessation, meta-regression was used to explore whether there was an association between the proportion of planned patient enrolment which was completed and treatment effect.

Results

Electronic searches yielded 8620 unique records; 12 studies were included in the final analysis (Table 1).

Study characteristics

The stroke was confined to the anterior circulation in the majority of the included trials; IMS III (14/656), SYNTHESIS (25/362), THRACE (4/414) and EASI (10/77) included patients with posterior circulation occlusions.

Neither MR RESCUE nor SYNTHESIS used non-invasive arterial imaging to identify patients for enrolment. IMS III did not begin using computed tomography angiography (CTA) to identify the site of occlusion until after 284 participants had undergone randomisation. Although vascular imaging was not mandated in the protocol for EASI, proximal occlusion was confirmed in 80% of patients prior to enrolment. The other eight trials used either CTA and/or magnetic resonance angiography (MRA) to guide patient selection.

The proportion of patients randomised to the intervention group who received IV tPA ranged from 0 to 100%. The proportion of patients randomised to the intervention group who actually received thrombectomy ranged from 31 to 100%.

Eight trials provided data on median time from onset of symptoms to commencement of thrombolysis with IV tPA for both their control and intervention arms [8, 9, 11, 15–19]. The median time from symptom onset to thrombolysis in the intervention arms ranged from 85 to 150 min; in the control groups, it ranged from 87 to 155 min.

Eight trials provided median times from symptom onset to the start of the procedure for those randomised to the intervention (range 210 to 269 min). MR RESCUE and IMS III reported mean times from symptom onset to procedure commencement for those randomised to the intervention of 381 min (standard deviation (SD) 74) and 208 min (SD 47), respectively. ESCAPE did not report this information directly, but noted the median times from symptom onset to study computed tomography (CT) (134 min) and from study CT to groin puncture (51 min). The Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) reported that the median time from symptom onset to the end of the procedure was 251 min.

Quality assessment

While the risk of bias overall for each of the RCTs was rated as low (see risk of bias figure, supplementary appendix), a number of issues which could potentially have affected the outcome data were identified. The quality of the evidence (see grade table, supplementary appendix) was rated as moderate for mRS and for the other outcomes of effectiveness. With the exception of mortality at 90 days and SICH, there was inconsistency in how trials reported their safety outcomes, making comparability and interpretation difficult.

A further concern is the number of trials, which were stopped early (nine); trials which stop early for benefit may under- or over-estimate the treatment effect of the intervention and truncated RCTs have previously been demonstrated to be associated with greater effect sizes than RCTs not stopped early [20].

Primary outcomes

All-cause mortality

All trials reported all-cause mortality at 90 days ($n = 3066$). There were 266 deaths in 1639 (16.2%) patients in the intervention arm, and 252 deaths in 1427 (17.7%) patients in the control arm (Fig. 1). One study found a statistically significant reduction in mortality associated with the intervention (ESCAPE). The pooled risk ratio for mortality was 0.90 (95%CI: 0.77 to 1.06; $p = 0.21$). There was no evidence of a difference in mortality rates at 90 days between patients randomised to intervention and control arms.

A subgroup analysis was performed using data from the nine trials commenced from 2010 onwards. In these trials, there were 145 deaths in 960 patients in the intervention arm (15.1%) and 173 deaths in 970 patients in the control arm (17.8%). The pooled risk ratio for mortality was 0.86 (95%CI: 0.70 to 1.07; $p = 0.17$).

mRS at 90 days

All trials reported data for mRS at 90 days ($n = 3035$). In total, 715 of 1620 (44.1%) patients in the intervention arm achieved an mRS of 0–2 at 90 days, compared with 475 of 1415 (33.6%) patients in the control arm (Fig. 2). The risk ratio for achieving an mRS of 0–2 at 90 days was 1.34 (95%CI: 1.14 to 1.58; $p < 0.01$) in favour of the intervention. The evidence suggests that the intervention is associated with higher likelihood of being independent at 90 days post AIS.

A statistically significant difference was noted between mRS scores reported for the first three trials versus those for trials commenced from 2010 onwards ($p < 0.01$). While these studies exhibit a potentially substantial statistical heterogeneity overall ($I^2 = 62\%$; $p < 0.01$), this heterogeneity is

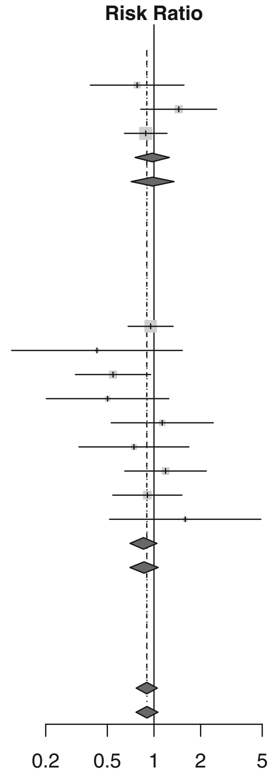
Table 1 Study characteristics of twelve included randomised controlled trials

Study name year	No. centres	Products used	Years of enrolment	Location of stroke	Baseline NIHSS score	Stopped early	% protocol sample enrolled	% randomised to intervention who received…	
								IV tPA	Thrombectomy
MR RESCUE 2013 [5]	22	Merci Retriever; Penumbra System®;	2004–2011*	Anterior circulation	≥ 6 and < 30	No	98.3 (118/120)	43.7	100 (64/64)
IMS3 2013 [6]	58	Merci Retriever; Penumbra System®; Solitaire™ FR	2006–2012	M1, ICA or Basilar	≥ 10 at start of IV tPA or > 7 and < 10 with occlusion in M1/ICA/BA	Yes	72.8 (656/900)	100	39.1 (170/434)
SYNTHESIS 2013 [7]	24	Included Solitaire™, Penumbra System® Trevo®, Merci	2008–2012	–	No pre-defined cut-off	No	> 100 (362/350)	0	30.9 (56/181)
MR CLEAN 2015 [15]	16	Retrievable stents 81.5%	2010–2014	ICA, M1, M2	≥ 2	No	100 (500/500)	87.1	81.5 (190/233)
EXTEND IA 2015 [16]	10	Solitaire™ FR	2012–2014	Anterior circulation	Control group median 13 (IQR 9–19) Group median 17 (range 13–20)	Yes	70.0 (70/100)	100	77.1 (27/35)
REVASCAT 2015 [17]	4	Solitaire™ FR	2012–2014	Anterior circulation	≥ 6	Yes	29.9 (206/690)	68	95.1 (98/103)
SWIFT PRIME 2015 [18]	39	Solitaire™ FR; Solitaire™ 2	2012–2014	ICA, M1	≥ 8	Yes	26.1 (196/750)	–$	88.8 (87/98)
ESCAPE 2015 [19]	22	Solitaire™ FR + unspecified others	2013–2014	Anterior circulation	> 5	Yes	63.2 (316/500)	72.7	91.5 (151/165)
THRACE 2016 [8]	26	Retrievable stents (83%) Aspiration systems (16%)	2010–2015	ICA, M1, Superior third BA	≥ 10 and ≤ 25	Yes	86.3 (414/480)	100	71.1 (145/204)
THERAPY 2016 [10]	36	Penumbra System®, Solitaire™, Trevo®	2012–2014	ICA, M1, M2	≥ 8	Yes	15.6 (108/692)	98	81.8 (45/55)
PISTE 2017 [9]	10	Any CE marked device (68% stent retriever, 32% aspiration systems)	2013–2015	ICA, M1, M2	No pre-defined cut-off	Yes	16.3 (65/400)	100	96.7 (32/33)
EASI 2017 [11]	1	Any approved device 97% stent retrievers	2013–2014	ICA, M1, M2, intracranial/vertebral/BA	≥ 8	Yes	16.0 (77/480)	Not specified	75.0 (30/40)

*The MR RESCUE trial began enrolment in June 2004. It finished enrolling in 2011 but the exact month is not clear. The duration of 80 months is based on the trial having completed enrolment in January 2011

$ Although not clearly stated in the paper, a number of pervious reviews have interpreted that 100% of patients received IV tPA

Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%-CI
First generation						
MR RESCUE (2004 – 2011)	12	64	13	54	0.78	[0.39; 1.56]
SYNTHESIS Expansion (2008 – 2012)	26	181	18	181	1.44	[0.82; 2.54]
IMS III (2006 – 2012)	83	434	48	222	0.88	[0.64; 1.21]
Fixed effect model	**121**	**679**	**79**	**457**	**0.97**	**[0.75; 1.26]**
Random effects model					**0.98**	**[0.71; 1.35]**
Heterogeneity: $I^2 = 24\%$, $\tau^2 = 0.0211$, $p = 0.27$						
Test for effect in subgroup (fixed effect): $z = -0.20$ ($p = 0.84$)						
Test for effect in subgroup (random effects): $z = -0.12$ ($p = 0.90$)						
Second generation						
MR CLEAN (2010 – 2014)	49	233	59	267	0.95	[0.68; 1.33]
EXTEND IA (2012 – 2014)	3	35	7	35	0.43	[0.12; 1.52]
ESCAPE (2013 – 2014)	17	164	28	147	0.54	[0.31; 0.95]
THERAPY (2012 – 2014)	6	50	11	46	0.50	[0.20; 1.25]
EASI (2013 – 2014)	11	40	9	37	1.13	[0.53; 2.42]
SWIFT PRIME (2012 – 2014)	9	98	12	97	0.74	[0.33; 1.68]
REVASCAT (2012 – 2014)	19	103	16	103	1.19	[0.65; 2.18]
THRACE (2010 – 2015)	24	204	27	208	0.91	[0.54; 1.52]
PISTE (2013 – 2015)	7	33	4	30	1.59	[0.52; 4.90]
Fixed effect model	**145**	**960**	**173**	**970**	**0.86**	**[0.70; 1.05]**
Random effects model					**0.86**	**[0.70; 1.07]**
Heterogeneity: $I^2 = 4\%$, $\tau^2 = 0.0043$, $p = 0.40$						
Test for effect in subgroup (fixed effect): $z = -1.52$ ($p = 0.13$)						
Test for effect in subgroup (random effects): $z = -1.37$ ($p = 0.17$)						
Fixed effect model	**266**	**1639**	**252**	**1427**	**0.90**	**[0.77; 1.05]**
Random effects model					**0.90**	**[0.77; 1.06]**



Heterogeneity: $I^2 = 3\%$, $\tau^2 = 0.0025$, $p = 0.42$
Test for overall effect (fixed effect): $z = -1.34$ ($p = 0.18$)
Test for overall effect (random effects): $z = -1.25$ ($p = 0.21$)
Test for subgroup differences (fixed effect): $\chi^2_1 = 0.62$, df = 1 ($p = 0.43$)
Test for subgroup differences (random effects): $\chi^2_1 = 0.42$, df = 1 ($p = 0.52$)

Fig. 1 Meta-analysis of all-cause mortality at 90 days

eliminated by only including the nine studies, which began enrolling from 2010 onwards ($I^2 = 0\%$; $p = 0.56$) (Fig. 2). The interpretation of treatment effect was unchanged after the inclusion of the seventh trial (SWIFT PRIME).

Limiting analysis to the latter 9 studies, 454 of 960 (47.3%) of patients in the intervention arm were reported to have achieved an mRS of 0–2 at 90 days, compared with 295 of 966 (30.5%) of patients who were assigned to the control arm. The absolute benefit of the intervention on mRS at 90 days across these nine trials ranged from 7.6% in THERAPY to 31.4% in EXTEND IA. In a subgroup analysis of these nine trials, the risk ratio for achieving a mRS of 0–2 at 90 days was 1.51 (95%CI: 1.35 to 1.69; $p < 0.01$) in favour of the intervention. The cumulative meta-analysis demonstrated a consistent treatment effect in favour of mechanical thrombectomy after each trial was added to the analysis.

Secondary outcomes

Barthel index at 90 days

Four trials (MR CLEAN, REVASCAT, ESCAPE, THRACE) reported the proportion of patients in the control and intervention groups who achieved a Barthel index score of 95 or more at 90 days ($n = 1251$); 332 of 612 (54.2%) patients achieved this score in the intervention groups with 224 of 639 (35.1%) achieving it in the control arms (Table 2) (risk ratio = 1.57, 95%CI: 1.27 to 1.95; $p < 0.01$). This suggests that the intervention is associated with better outcomes in relation to activities of daily living (ADL), as measured using the Barthel index, at 90 days. All four studies individually demonstrated a statistically significant benefit from the intervention. The cumulative meta-analysis demonstrated a consistent treatment effect on Barthel index in favour of mechanical thrombectomy after each trial was added to the analysis.

Symptomatic intracerebral haemorrhage (SICH)

All 12 trials reported data on SICH ($n = 3081$) (Table 2). Eighty of 1633 (4.9%) patients in the intervention arm and 68 of 1448 (4.7%) of patients in the control arm experienced a SICH. This evidence suggests no difference between intervention and control with respect to SICH (risk ratio = 1.06; 95%CI: 0.77 to 1.47; $p = 0.71$).

Subgroup analysis was performed using data from the nine trials commenced from 2010 onwards. In these trials, there were 40 events in 954 patients in the intervention arm (4.2%) and 43 events in 991 patients in the control arm

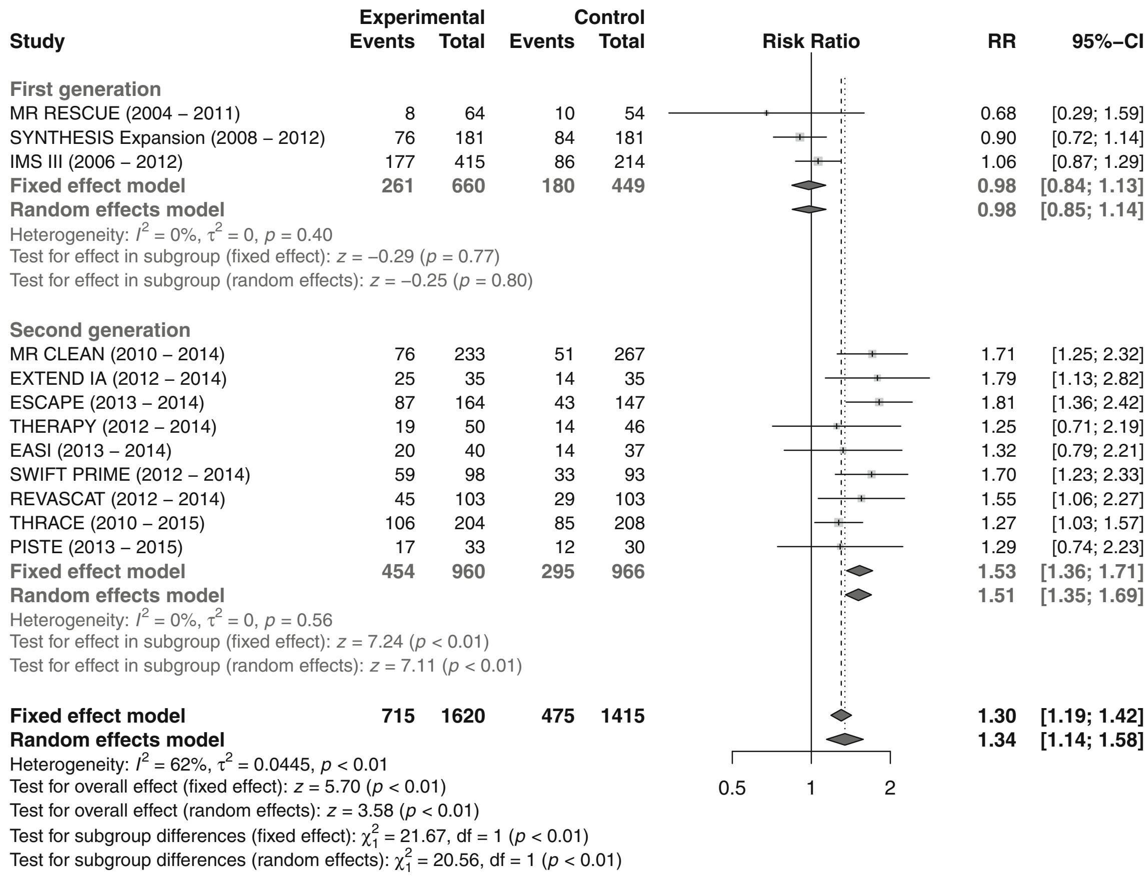


Fig. 2 Meta-analysis of modified Rankin scale at 90 days

(4.3%). The pooled risk ratio for SICH was 1.07 (95%CI: 0.70 to 1.63; $p = 0.76$).

Any cerebral haemorrhage

Nine of the 12 trials reported comparable data on any cerebral haemorrhage. Five hundred and sixty-three of 1369 (41.1%) patients in the intervention arm and 309 of 1168 (26.5%) patients in the control arm experienced some form of cerebral haemorrhage (Table 2) (risk ratio = 1.37, 95% CI: 1.22 to 1.55; $p < 0.01$), indicating that the intervention is associated with a higher overall rate of any cerebral haemorrhage when compared with the control. Individual studies differed substantially from one another, with rates of any cerebral haemorrhage in intervention and control groups varying from 7.7 and 6.4% in MR CLEAN, respectively, to 70.3 and 51.9% in MR RESCUE, respectively. Interpretation of the treatment effect has been consistent since the second trial was published.

Subgroup analysis of any cerebral haemorrhage was performed using data from seven of the nine trials commenced from

Table 2 Summary estimates for secondary outcomes of interest

	No. trials	No. events/total patients		Risk ratio (95%CI)	*P* value
		Intervention group	Control group		
Barthel index	4	332/612	224/639	1.57 (1.27–1.95)	< 0.01
SICH	12	80/1633	68/1448	1.06 (0.77–1.47)	0.71
Subgroup analysis	9	40/954	43/991	1.07 (0.70 to 1.63)	0.76
Any cerebral haemorrhage	9	563/1369	309/1168	1.37 (1.22–1.55)	< 0.01
Subgroup analysis	7	257/871	188/892	1.34 (1.10 to 1.65)	< 0.01
Recurrent stroke	5	50/968	21/774	2.21 (0.77–6.34)	0.14
Subgroup analysis	4	28/534	7/552	3.27 (1.13 to 9.42)	0.03

SICH symptomatic intracerebral haemorrhage

2010 onwards (no data available for EASI or THERAPY). In these trials, there were 257 events in 871 patients in the intervention arm (29.5%) and 188 events in 892 patients in the control arm (21.1%). The pooled risk ratio for any cerebral haemorrhage at 90 days was 1.34 (95% CI: 1.10 to 1.65; $p < 0.01$). Excluding the first generation trials, there is greater uncertainty about the treatment effect, and a consistent statistically significant effect has only been observed since the publication of the REVASCAT trial (2015).

Recurrent ischaemic stroke within 90 days

Five trials (IMS III, MR CLEAN, ESCAPE, REVASCAT, PISTE) provided data on recurrent ischaemic stroke within 90 days. 50 of 968 (5.2%) patients in the intervention arm and 21 of 774 (2.7%) patients in the control arm experienced a recurrent event (Table 2). The pooled data do not suggest that the intervention is associated with a higher overall rate of recurrent ischaemic stroke within 90 days (risk ratio = 2.21; 95% CI: 0.77 to 6.34; $p = 0.14$).

Potentially substantial statistical heterogeneity was noted between the five included studies ($I^2 = 62\%$; $p = 0.03$), although this was reduced by excluding the earliest trial (IMS III). Subgroup analysis including only the later four trials again suggests that the intervention is associated with a higher overall rate of recurrent ischaemic stroke within 90 days, when compared with the control (risk ratio = 3.27; 95%CI: 1.13 to 9.42; $p = 0.03$). The direction of effect is consistent across second-generation trials, although none of the individual trials found a statistically significant effect. This outcome may be sensitive to the inclusion of additional trials.

One additional trial, SYNTHESIS reported that 2.2% (4/181) of patients in the intervention group had experienced a new stroke at 7 days.

The effect of early cessation of trials and the potential impact on estimated treatment effect was explored using meta-regression. Analyses were carried out in relation to the outcomes of functional independence (mRS 0–2) and mortality (mRS 6). The covariate was defined as the proportion of the planned patients that were actually enrolled. For both outcomes, the coefficient associated with the covariate was close to zero and was not statistically significant ($p = 0.68$ for functional independence; $p = 0.76$ for mortality).

Discussion

This meta-analysis suggests that mechanical thrombectomy, when used in conjunction with non-invasive arterial imaging, in selected patients with anterior circulation AIS, and when using second-generation devices, has a beneficial effect on morbidity and function but no effect on all-cause mortality at 90 days. While the publication of the first three trials in 2013 met with widespread pessimism in the stroke community about the value of endovascular treatment for patients experiencing AIS [21], subsequent publication of the latter nine trials has transformed opinion around this issue, and it has been suggested that clinical equipoise no longer exists [22].

It has been argued that the methodology and devices (predominantly stent retrievers) employed in the later nine trials are those which are most relevant to current clinical practice. It is therefore pertinent that subgroup analysis of these trials demonstrated an improved effect of the intervention on mRS at 90 days, when compared with its overall effect across all 12 trials, and this subgroup analysis correlates well with the results of the individual patient meta-analysis of data from the five trials published in 2015 [23].

Importantly, however, the achievement of statistical significance for the primary outcome in any clinical trial, while typically a prerequisite for the adoption of a new therapy, is not in itself sufficient [24]. In relation to mechanical thrombectomy specifically, while this and previous analyses have suggested that the procedure is not associated with an increased risk of mortality, the trials upon which these analyses were based were not powered to detect a difference in mortality and were unlikely to have detected a difference unless it was very substantial. Study size is also important in evaluating the significance of trial results; small trials lack power such that positive treatment effects are susceptible to exaggeration. In addition, while some trials stop early because of treatment effect, this practice tends to exaggerate treatment efficacy, while simultaneously truncating the evidence for important secondary (and safety) outcomes [24]. These caveats are of particular relevance in the case of mechanical thrombectomy, where 9 of the 12 trials stopped early, and where 5 of the 12 trials enrolled less than one third of their intended study sample. However, meta-regression demonstrated no evidence to suggest that stopping early had introduced a systematic bias to the estimates of treatment effect for outcomes of functional independence and mortality at 90 days.

In addition to the caveats around mortality and safety data, the many limitations inherent in this present analysis and in previous meta-analyses on this subject—the variability seen between the trials with respect to device types, use/non-use of imaging, time to intervention, proportions receiving thrombectomy—need to be addressed in individual patient meta-analyses using pooled data from the published trials and a number of these have already been published [23, 25]. Furthermore, as all included trials focused either exclusively or predominantly on patients with proximal anterior circulation AIS, the results presented here should be taken to be indicative of the effectiveness or otherwise of mechanical thrombectomy in this context; further studies are required before a determination can be made regarding the efficacy of mechanical thrombectomy in the posterior circulation and in the management of distal intracranial occlusions [26].

These limitations notwithstanding, the results presented here do suggest that mechanical thrombectomy and other endovascular interventions need to be factored into the planning and delivery of services for the management of patients with acute ischaemic stroke in Ireland. At present, approximately 200 endovascular procedures are carried out annually, with over 85% of these are performed in just one institution [27]. A total of 355 patients underwent thrombectomy in this latter institution in the 6-year period from 2010 to 2016, inclusive [28]. There are a number of issues which need to be addressed if the estimated 14% of patients with acute ischaemic stroke, who could potentially benefit from receipt of this therapy are to be facilitated in receiving it; these may be categorised into pre-hospital, individual hospital and system wide (including community) factors (a full discussion of these factors, together with an assessment of the likely organisational, budget and ethical issues to be considered is available as part of the full Health Technology Assessment of which this work formed a part (https://www.hiqa.ie/reports-and-publications). [27].

A key consideration in assessment of eligibility for mechanical thrombectomy is the time elapsed from symptom onset to the time of intervention. The evidence presented in this meta-analysis is based on trials involving cohorts of patients who were managed within 6 h of symptom onset. It is therefore concerning that the time of onset of symptoms is unknown in 38% of patients presenting with acute stroke in Ireland and that nationally the median time from onset of symptoms to presentation varies appreciably by hospital (national median 2 h 26 min, range 1 h 21 min–6 h 6 min) [29]. Indeed, 22% of patients arrive at hospital greater than 6 h after symptom onset [29].

Where patients do present within 6 h of onset, the hospitals to which they present must be equipped to manage their stroke in a timely manner. As seen in the data presented in this work, access to appropriate and timely imaging is central to maximising outcome. Unfortunately, while all hospitals managing stroke in Ireland have 24 h access to on-site CT scanning, the median time from onset of symptoms to performance of neuro-imaging is 15 h and 44 min, and over 30% of patients are not scanned within 24 h. While some of this delay can be accounted for by the delay in patients presenting at the hospital, there is also evidence of substantial delays in care within institutions—the 2015 National Stroke Audit reported that the median time from presentation to scan ('door to scan time') was 9 h and 23 min [29].

Imaging is just one component of the care pathway in mechanical thrombectomy, but the issues outlined above are illustrative of the challenges faced by individual units providing care for stroke patients. The majority of the hospitals which participated in the RCTs included in this analysis are high-volume stroke centres, where the procedures were carried out in ideal circumstances [30]. It is doubtful if the stroke management systems in these institutions could be replicated on a widespread basis in hospitals around Ireland. While stroke units are available in 78% (21/27) of receiving hospitals, less than one third of patients (29%) are admitted to these units at presentation [29]. Even if all patients were admitted to these units at presentation, it is unrealistic to expect that each of these units would have trained interventional neuro-radiologists on-site or that the volume of patient throughput at individual sites would be sufficient to maintain expertise. Furthermore, it will not be feasible from a health system perspective to provide 24 h, 7 day cover for mechanical thrombectomy in all of these stroke units. Therefore, if the encouraging results demonstrated in this meta-analysis are to be replicated in Ireland, the procedure will need to be developed and offered in a small number of centres, sited to maximise patient access and workforce expertise and coverage. As noted in the full Health Technology Assessment (HTA) of mechanical thrombectomy for the management of AIS in Ireland—of which this current work formed a part—the provision of this national service would have significant organisational and resource implications in order to ensure timely transfer of patients for treatment and repatriation post-intervention [27].

One potential solution is the development of a "hub and spoke" model with referral to "comprehensive" centres of excellence helping to improve workflow, treatment times and, ultimately, clinical outcomes [31]. The most appropriate configuration of this model for Ireland remains to be elucidated, but there are precedents upon which to base this, including the Acute Coronary Syndromes Model of Care, which designated six hospitals as Primary Percutaneous Coronary Intervention (PPCI) centres in 2012 [32]. A mapping exercise undertaken as part of the role out of this model reported that 81% of the Irish population, aged over 55 years, lives within a 90-min drive time to Dublin, Cork and Galway [32]. Therefore, a combination of approaches—arrangements for emergency care and transport, and designation of comprehensive stroke centres whose workflow practices have been maximised—can ensure that a substantial majority of those who would benefit from mechanical thrombectomy receive it.

Coordination of these approaches and, in particular, designation and efficient working of "comprehensive" stroke centres will require a number of "foundation stones", as was evidenced during roll-out of the Acute Coronary Syndromes Model of Care [32]:

- Ensure national agreement
- Implement the programme robustly
- Ensure readiness in pre-hospital sector
- Understand and deal with the knock on effects on various parts of the system
- Understand and plan for staffing requirements
- Clarify costs of implementation
- Set out clear monitoring and evaluation parameters.

Many of these elements are already in place for stroke care in Ireland. The National Clinical Programme for Stroke was launched in 2010 and has resulted in dramatic improvements in the organisation and delivery of stroke care in Ireland. This is perhaps best illustrated by improvements in rates of thrombolysis nationally; between 2007 and 2015, there was a tenfold increase in these rates and, at the end of 2016 13.9% of patients with AIS were benefitting from this treatment [29]. However, the implementation of a coordinated service for mechanical thrombectomy will bring unique and additional challenges, and the exact model for its delivery in Ireland has yet to be defined. However, the aforementioned HTA outlined these challenges and estimated that the budget impact of moving from the current ad hoc level of service provision to an organised national service would be approximately €2.8 million over 5 years [27].

Finally, this meta-analysis has demonstrated improved outcomes for patients with acute ischaemic stroke in relation to disability, morbidity and function at 90 day follow-up. The benefits of this at the individual and societal level are obvious. However if more patients are being discharged back in to the community (as opposed to step down or long-term residential care facilities) this may place additional burden on community-based post-stroke service provision. A 2012 study of this service in Ireland noted that there were "major gaps in the provision of community-based interdisciplinary team services for people with stroke….(and) where services existed, they were generic in nature, rarely interdisciplinary in function and either deficient in (or completely deprived of) input from salient disciplines" [33]. Just as integration of pre-hospital and hospital-based care is essential to improving outcomes in the acute phase of stroke management, so too must hospital and community-based services be integrated to ensure optimal outcomes in the post-acute phase. As noted in the 2011 National Policy and Strategy for the Provision of Neuro-Rehabilitation Services in Ireland, "neuro-rehabilitation teams cannot function successfully without close links and associated referral pathways forged with other sectors of the HSE not directly involved in neuro-rehabilitation" [34]. It is therefore recommended that the proposals contained in the Policy for the Provision of Neuro-Rehabilitation Services are implemented as a matter of urgency. In particular, it is central recommendation—that regional and local neuro-rehabilitation networks should be developed—needs to be advanced, such that the ability of stroke survivors to participate physically, psychologically, socially and economically in everyday life in Ireland is optimised.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Health in Ireland - Key trends. 2014, Department of Health and Children: Dublin
2. Smyth B, et al. (2015) Planning for health: trends and priorities to inform health service planning 2016. Health Service Executive: Dublin
3. Rha JH, Saver JL (2007) The impact of recanalization on ischemic stroke outcome: a meta-analysis. Stroke 38(3):967–973
4. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, Brott T, Cohen G, Davis S, Donnan G, Grotta J, Howard G, Kaste M, Koga M, von Kummer R, Lansberg M, Lindley RI, Murray G, Olivot JM, Parsons M, Tilley B, Toni D, Toyoda K, Wahlgren N, Wardlaw J, Whiteley W, del Zoppo G, Baigent C, Sandercock P, Hacke W, Stroke Thrombolysis Trialists' Collaborative Group (2014) Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet 384(9958):1929–1935
5. Kidwell CS, Jahan R, Gornbein J, Alger JR, Nenov V, Ajani Z, Feng L, Meyer BC, Olson S, Schwamm LH, Yoo AJ, Marshall RS, Meyers PM, Yavagal DR, Wintermark M, Guzy J, Starkman S, Saver JL, MR RESCUE Investigators (2013) A trial of imaging selection and endovascular treatment for ischemic stroke. N Engl J Med 368(10):914–923
6. Broderick JP, Palesch YY, Demchuk AM, Yeatts SD, Khatri P, Hill MD, Jauch EC, Jovin TG, Yan B, Silver FL, von Kummer R, Molina CA, Demaerschalk BM, Budzik R, Clark WM, Zaidat OO, Malisch TW, Goyal M, Schonewille WJ, Mazighi M, Engelter ST, Anderson C, Spilker J, Carrozzella J, Ryckborst KJ, Janis LS, Martin RH, Foster LD, Tomsick TA, Interventional Management of Stroke (IMS) III Investigators (2013) Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. N Engl J Med 368(10):893–903
7. Ciccone A, Valvassori L (2013) Endovascular treatment for acute ischemic stroke. N Engl J Med 368(25):2433–2434
8. Bracard S, Ducrocq X, Mas JL, Soudant M, Oppenheim C, Moulin T, Guillemin F, THRACE investigators (2016) Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. Lancet Neurol 15(11):1138–1147
9. Muir KW, Ford GA, Messow CM, Ford I, Murray A, Clifton A, Brown MM, Madigan J, Lenthall R, Robertson F, Dixit A, Cloud GC, Wardlaw J, Freeman J, White P, PISTE Investigators (2017) Endovascular therapy for acute ischaemic stroke: the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial. J Neurol Neurosurg Psychiatry 88(1):38–44
10. Mocco J, Zaidat OO, von Kummer R, Yoo AJ, Gupta R, Lopes D, Frei D, Shownkeen H, Budzik R, Ajani ZA, Grossman A, Altschul D, McDougall C, Blake L, Fitzsimmons BF, Yavagal D, Terry J, Farkas J, Lee SK, Baxter B, Wiesmann M, Knauth M, Heck D, Hussain S, Chiu D, Alexander MJ, Malisch T, Kirmani J, Miskolczi L, Khatri P, THERAPY Trial Investigators* (2016) Aspiration thrombectomy after intravenous alteplase versus intravenous alteplase alone. Stroke 47(9):2331–2338
11. Khoury NN, et al. (2017) Endovascular thrombectomy and medical therapy versus medical therapy alone in acute stroke: a randomized care trial. J Neuroradiol
12. Moher D et al (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 4:1
13. (2015) R: a language and environment for statistical computing. Available from: https://www.R-project.org/
14. Wiechtbauer W (2010) Conducting meta-analyses in R with the metafor package. J Stat Softw 36(3):1–48
15. Berkhemer OA, Fransen PS, Beumer D, van den Berg L, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, van Walderveen M, Staals J, Hofmeijer J, van Oostayen J, Lycklama à Nijeholt GJ, Boiten J, Brouwer PA, Emmer BJ, de Bruijn SF, van Dijk L, Kappelle LJ, Lo RH, van Dijk E, de Vries

J, de Kort PL, van Rooij W, van den Berg J, van Hasselt B, Aerden LA, Dallinga RJ, Visser MC, Bot JC, Vroomen PC, Eshghi O, Schreuder TH, Heijboer RJ, Keizer K, Tielbeek AV, den Hertog H, Gerrits DG, van den Berg-Vos R, Karas GB, Steyerberg EW, Flach HZ, Marquering HA, Sprengers ME, Jenniskens SF, Beenen LF, van den Berg R, Koudstaal PJ, van Zwam W, Roos YB, van der Lugt A, van Oostenbrugge R, Majoie CB, Dippel DW, MR CLEAN Investigators (2015) A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 372(1):11–20
16. Campbell BCV et al (2015) Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 372(11): 1009–1018
17. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, San Román L, Serena J, Abilleira S, Ribó M, Millán M, Urra X, Cardona P, López-Cancio E, Tomasello A, Castaño C, Blasco J, Aja L, Dorado L, Quesada H, Rubiera M, Hernandez-Pérez M, Goyal M, Demchuk AM, von Kummer R, Gallofré M, Dávalos A, REVASCAT Trial Investigators (2015) Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 372(24):2296–2306
18. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, Albers GW, Cognard C, Cohen DJ, Hacke W, Jansen O, Jovin TG, Mattle HP, Nogueira RG, Siddiqui AH, Yavagal DR, Baxter BW, Devlin TG, Lopes DK, Reddy VK, du Mesnil de Rochemont R, Singer OC, Jahan R, SWIFT PRIME Investigators (2015) Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 372(24):2285–2295
19. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, Roy D, Jovin TG, Willinsky RA, Sapkota BL, Dowlatshahi D, Frei DF, Kamal NR, Montanera WJ, Poppe AY, Ryckborst KJ, Silver FL, Shuaib A, Tampieri D, Williams D, Bang OY, Baxter BW, Burns PA, Choe H, Heo JH, Holmstedt CA, Jankowitz B, Kelly M, Linares G, Mandzia JL, Shankar J, Sohn SI, Swartz RH, Barber PA, Coutts SB, Smith EE, Morrish WF, Weill A, Subramaniam S, Mitha AP, Wong JH, Lowerison MW, Sajobi TT, Hill MD, ESCAPE Trial Investigators (2015) Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 372(11):1019–1030
20. Bassler D, Briel M, Montori VM, Lane M, Glasziou P, Zhou Q, Heels-Ansdell D, Walter SD, Guyatt GH, STOPIT-2 Study Group, Flynn DN, Elamin MB, Murad MH, Abu Elnour NO, Lampropulos JF, Sood A, Mullan RJ, Erwin PJ, Bankhead CR, Perera R, Ruiz Culebro C, You JJ, Mulla SM, Kaur J, Nerenberg KA, Schünemann H, Cook DJ, Lutz K, Ribic CM, Vale N, Malaga G, Akl EA, Ferreira-Gonzalez I, Alonso-Coello P, Urrutia G, Kunz R, Bucher HC, Nordmann AJ, Raatz H, da Silva SA, Tuche F, Strahm B, Djulbegovic B, Adhikari NK, Mills EJ, Gwadry-Sridhar F, Kirpalani H, Soares HP, Karanicolas PJ, Burns KE, Vandvik PO, Coto-Yglesias F, Chrispim PP, Ramsay T (2010) Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. Jama 303(12):1180–1187
21. Campbell BCV, Donnan GA, Lees KR, Hacke W, Khatri P, Hill MD, Goyal M, Mitchell PJ, Saver JL, Diener HC, Davis SM (2015) Endovascular stent thrombectomy: the new standard of care for large vessel ischaemic stroke. Lancet Neurol 14(8):846–854
22. Furlan AJ (2015) Endovascular therapy for stroke - it's about time. N Engl J Med 372(24):2347–2349
23. Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, Dávalos A, Majoie CBLM, van der Lugt A, de Miquel MA, Donnan GA, Roos YBWEM, Bonafe A, Jahan R, Diener HC, van den Berg LA, Levy EI, Berkhemer OA, Pereira VM, Rempel J, Millán M, Davis SM, Roy D, Thornton J, Román LS, Ribó M, Beumer D, Stouch B, Brown S, Campbell BCV, van Oostenbrugge RJ, Saver JL, Hill MD, Jovin TG (2016) Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 387:1723–1731
24. Pocock SJ, Stone GW (2016) The primary outcome is positive - is that good enough? N Engl J Med 375(10):971–979
25. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CBLM, Dippel DW, Campbell BC, Nogueira RG, Demchuk AM, Tomasello A, Cardona P, Devlin TG, Frei DF, du Mesnil de Rochemont R, Berkhemer OA, Jovin TG, Siddiqui AH, van Zwam WH, Davis SM, Castaño C, Sapkota BL, Fransen PS, Molina C, van Oostenbrugge RJ, Chamorro Á, Lingsma H, Silver FL, Donnan GA, Shuaib A, Brown S, Stouch B, Mitchell PJ, Davalos A, Roos YBWEM, Hill MD, for the HERMES Collaborators (2016) Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. Jama 316(12):1279–1288
26. Grossberg JA, Rebello LC, Haussen DC, Bouslama M, Bowen M, Barreira CM, Belagaje SR, Frankel MR, Nogueira RG (2018) Beyond large vessel occlusion strokes: distal occlusion thrombectomy. Stroke 49(7):1662–1668
27. (2017) Health technology assessment of a national emergency endovascular service for mechanical thrombectomy in the management of acute ischaemic stroke. Health Information and Quality Authority: Dublin
28. Motyer R, Kok HK, Asadi H, O'Hare A, Brennan P, Power S, Looby S, Nicholson P, Williams D, Murphy S, Hill MD, Goyal M, McManus J, O'Brien P, Thornton J (2017) Outcomes of endovascular treatment for acute large-vessel ischaemic stroke more than 6 h after symptom onset. J Intern Med 282(6):537–545
29. McElwaine P, McCormack J, Harbison J, Irish Heart Foundation/ HSE National Stroke Audit (2015) 2016, Irish Heart Foundation. Health Service Executive, Dublin
30. McGee H (2010) Changing Cardiovascular Health. National Cardiovascular Health Policy 2010-2019. Department of Health and Children, Dublin
31. Palaniswami M, Yan B (2015) Mechanical thrombectomy is now the gold standard for acute ischemic stroke: implications for routine clinical practice. Interv Neurol 4(1–2):18–29
32. Acute Coronary Syndromes Programme. Model of Care. 2012: Dublin
33. Hickey A, Horgan F, O'Neill D, McGee H, Steering Committee of the Irish National Audit of Stroke Care (INASC) (2012) Community-based post-stroke service provision and challenges: a national survey of managers and inter-disciplinary healthcare staff in Ireland. BMC Health Serv Res 12:111
34. National Policy and Strategy for the Provision of Neuro-Rehabilitation Services in Ireland (2011) Health Service Executive. Department of Health, Dublin