ISSN: 2469-5858

Powell et al. J Geriatr Med Gerontol 2018, 4:052
DOI: 10.23937/2469-5858/1510052
Volume 4 | Issue 3
Open Access

Journal of
Geriatric Medicine and Gerontology

RESEARCH ARTICLE

The Impact of Demographic Changes on the Presentation and Outcome of Stroke: Experiences of the Oldest Old in the Murrumbidgee Region

Alice Powell[1], Martin Jude[2], Stephen Kerr[3], Jenna Mewburn[2], Katherine Mohr[2] and Paul Finucane[2]*

[1]*Concord Repatriation General Hospital, NSW, Australia*

[2]*Wagga Wagga Rural Referral Hospital, Wagga Wagga, NSW, Australia*

[3]*The Kirby Institute, University of New South Wales, Australia*

***Corresponding author:** *Dr. Alice Powell, Concord Repatriation General Hospital, NSW, Australia, E-mail: alice.powell@health.nsw.gov.au*

Abstract

Objectives: To build a profile of the experiences of stroke in the oldest old in the Murrumbidgee region and compare variables with two younger cohorts to test hypotheses about background, treatment and outcomes.

Methods: Prospective data from 100 stroke patients consecutively admitted to the Wagga Wagga Rural Referral Hospital Acute Stroke Unit was reviewed from a stroke database. Comparisons were made between the young old (65-74), old-old (75 to 84) and oldest old (85 and older).

Results: Older stroke patients were predominantly female with poorer premorbid functional status. Atrial fibrillation ($p = 0.008$) and hypertension ($p = 0.01$) were more common with advancing age. Smoking rates ($p = 0.006$) were higher in younger patients. Stroke mechanism was predominantly cardioembolic in older patients. Outcomes were poorer with rates of dependency ($p = 0.03$) and residential aged care facility placement ($p = 0.06$) increased.

Conclusion: These data signal how stroke may manifest in our ageing population in the future.

Keywords

Stroke, Older people, Regional, Stroke risk factors, Functional prognosis, Post-stroke complications

Introduction

The proportion of older people in the Australian population is increasing [1], heralding a change in how illness presents as well as the profile of people presenting with illness. This changing disease profile is most strikingly observed in conditions which disproportionately affect the old and particularly the oldest old. It is exemplified by stroke which is a leading cause of death and disability in Australia with 70% of stroke patients aged 65 and older [2,3]. Those responsible for the organisation and provision of health and social services need to be aware not just of the current service demands for people following stroke but how these are likely to evolve over time.

Because of its particular demographic profile, the Murrumbidgee region of New South Wales (NSW) is well placed to predict the future and evolving demands for stroke services nationally. The area is served by a single tertiary referral hospital at Wagga Wagga which contains the only Acute Stroke Unit in the region. In 2017, 19.3% of the Murrumbidgee population were aged 65 years or over and 2.7% were aged 85 years or over [4]. This proportion of older people is appreciably more than the current national percentages of 15.2% and 2.0% respectively and approximates the percentages that are anticipated nationally in 2031 [4]. Therefore, the Murrumbidgee region is 14 years ahead of the national average in terms of population ageing meaning that health data collected from this population has future applications nationally.

Given that Australian society will increasingly be obliged to meet the needs of very old people following a stroke, we aimed to compare the profile of stroke in the oldest old with younger cohorts of older people. The

Citation: Powell A, Jude M, Kerr S, Mewburn J, Mohr K, et al. (2018) The Impact of Demographic Changes on the Presentation and Outcome of Stroke: Experiences of the Oldest Old in the Murrumbidgee Region. J Geriatr Med Gerontol 4:052. doi.org/10.23937/2469-5858/1510052

Accepted: August 08, 2018: **Published:** August 10, 2018

very old have been defined in many published studies as those aged 80 years and older. However, the three demographic categories of young old (65-74 years old), old-old (75-84 years old) and oldest old (85 years and over) have also been established in the gerontology literature [5-7]. These categories facilitate a straightforward comparison between the oldest old and the remainder of individuals considered as older persons. Therefore, they comprise the comparison groups in this study.

Stroke is broadly classified as either haemorrhagic or ischaemic with brain ischemia further defined by means of pathophysiological mechanism as that due to thrombosis, generally referring to *in situ* obstruction of an artery, embolism or hypoperfusion [8]. The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification classifies ischaemic strokes by cause as due to large artery atherosclerosis, cardioembolism, small vessel occlusion, stroke of other determined aetiology and stroke of undetermined aetiology [9]. In terms of large artery atherosclerosis, the presence of the cytokines fibroblast growth factor, transforming growth factor beta and tumour necrosis factor alpha within atheromatous plaque may accelerate the development of plaque and its destabilisation [10].

There are some recognised differences in stroke risk factor profiles and outcomes between younger and older demographic groups. Atrial fibrillation and cardioembolic stroke is more common in older patients and hypertension and dyslipidaemia are less important risk factors [11]. There is evidence of benefit with thrombolysis in ischaemic stroke patients over 80 years of age [12] but very few older people have been included in the large stroke clinical trials so data on stroke management in older people is otherwise scarce [11,12]. Individuals over 80 hospitalised with ischaemic stroke experience higher mortality, longer hospitalisation, a lower likelihood of being discharged home and higher rates of recurrent stroke than those aged under 80 [13,14].

The main aim of the study was to explore the key research question of whether stroke is a different disease in the very old. A number of specific hypotheses were developed before the data was collected and relate to differences between baseline variables, treatment and outcomes in the young old, old-old and oldest old. It was hypothesised that the oldest old were more likely to already be living in residential care and possibly have fewer social supports. They were thought more likely to have multiple stroke risk factors and that the types of risk factors were likely to differ between the groups with increasing rates of atrial fibrillation, in particular, being seen with increasing age. Correspondingly, it was thought likely that the older patients would be more likely to already be taking antiplatelet and anticoagulant medications. Haemorrhagic stroke was hypothesised to be more likely in the older age group. The older age group was considered less likely to be offered acute stroke treatment including thrombolysis and endovascular clot retrieval and more likely to have stroke complications and poor outcomes including dependency and death. The length of hospital stay was predicted to be longer for the oldest old.

Methods

Prospective stroke related data on all patients admitted to the Wagga Wagga Health Service Acute Stroke Unit since 2008 has been collated by a single Stroke Care Coordinator. This database was accessed in September 2017 and the last 34 patients aged over 85 admitted with either an ischaemic or haemorrhagic stroke were included after the diagnosis of stroke was confirmed on either computerised tomography or magnetic resonance imaging of the brain through review of their electronic medical records. 33 patients matched for approximate admission dates aged 65 to 74 and 33 patients similarly matched and aged 75 to 84 were also included to comprise a total of 100 patients. The data was verified and supplemented by additional information derived from individual patient's electronic medical records.

This additional data included age, gender, premorbid functional status (assessed by the Modified Rankin Scale, mRS), living situation including whether they were living in a Residential Aged Care Facility (RACF) and the level of care received (high or low care), previous stroke, stroke risk factors including atrial fibrillation, ischaemic heart disease, heart failure, hypertension, dyslipidaemia, diabetes and smoking status. Premorbid antiplatelet and anticoagulant use was also recorded. Additional data was collected on whether anticoagulant medication had been held prior to the stroke, whether the International Normalised Ratio (INR) was subtherapeutic for those on warfarin and whether Direct Oral Anticoagulant (DOAC) dosing was appropriate for their age and renal function. The second set of data included timing of presentation and any delays in accessing treatment, National Institutes of Health Stroke Scale (NIHSS) [15] score, whether the stroke was ischaemic or haemorrhagic, the Oxford Stroke Classification which classifies strokes by vascular territory [16] and Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification [9] which classifies ischaemic strokes by cause. Additionally, the presence of microhaemorrhages on magnetic resonance imaging was recorded.

Stroke treatment data collected included thrombolysis numbers, clot retrieval numbers and whether a palliative focus of care was instituted either initially or later during the patient's admission. Outcome data collected included inpatient complications, death, dependency which was defined as a mRS of 3 or above and Residential Aged Care Facility placement. Length of stay data was also collected for patients from each of the demographic groups.

Cognitive impairment was considered to be both an important premorbid variable and significant post stroke complication but documentation of this in the electronic medical record was variable and incomplete and therefore ultimately deemed unreliable and not included.

Ethics approval was obtained for this study from the New South Wales Greater Western Human Research Ethics Committee.

Statistical Analysis

Comparisons were made between the three demographic groups with regard to their baseline characteristics, stroke information, stroke treatment and outcomes. Categorical variables were expressed as numbers and percentages and formal comparisons between age groups made using a Fisher's exact test, or Chi-square test as appropriate. Continuous data were expressed as median (Interquartile Range [IQR]) and formal comparisons between age groups were made with a Kruskal-Wallis test. When significant differences were found between 3 groups, pairwise comparisons were made between the younger groups and the oldest age group as a reference using a Fisher's exact test for categories and Wilcoxon rank sum test for continuous covariates. Age between groups was compared with a t-test. Lastly, a Chi-square test was used for trend where there was evidence of a linear trend of categories across age groups. Analysis was conducted using Stata 15.1 (Statcorp LLC, College Station, TX, USA) software.

Results

Significant differences in baseline variables between the demographic groups included gender, functional status and living situation as well as the stroke risk factors of atrial fibrillation, hypertension and smoking status. Function declined with increasing age and fewer of the oldest old were living at home prior to admission. The proportions of female stroke patients increased with increasing age. Atrial fibrillation and hypertension became increasingly more prevalent with older age and higher proportions of younger stroke patients smoked or had ever smoked. The P values for atrial fibrillation and hypertension are expressed as the trend. Full details are shown in Table 1.

Stroke type and severity did vary between the age groups. Although a small number of patients had severe strokes, the majority were relatively mild on the basis of their initial NIHSS scores. The distribution of scores was skewed with a larger proportion of lower scores and therefore they were expressed by the median interquartile range. Stroke severity according to NIHSS did increase with advancing age. The majority of strokes in all age groups were anterior circulation. The commonest mechanism in the youngest patients was Embolic Stroke of Undetermined Source (ESUS) and cardioembolic in the oldest patients. Full details are shown in Table 2.

There were no significant differences in stroke treatment, access to rehabilitation or length of hospital stay between the groups. Full details are shown in Table 3.

Table 1: Baseline characteristics of patients by demographic group.

	Young old (65-74) (N = 33)	Old old (75-84) (N = 33)	Oldest old (> 85) (N = 34)	P value comparing 3 groups	P value young old vs. oldest old	P value old old vs. oldest old
Mean age (SD)	70.2 (2.62)	80.3 (2.28)	88.6 (3.30)	< 0.001	< 0.001	< 0.001
Gender						
- Female (%)	9 (27%)	11 (33%)	22 (65%)	0.004	0.003	0.02
- Male (%)	24 (73%)	22 (66%)	12 (35%)			
Function - mRS						
- 0	27 (82%)	20 (61%)	13 (38%)	0.003	< 0.001	0.19
- 1-2	6 (18%)	9 (27%)	15 (44%)			
- 3 and above	0 (0%)	4 (12%)	6 (18%)			
Living situation						
- Home	33 (100%)	30 (91%)	24 (71%)	0.004	0.001	0.13
- Residential care - low level	0	2 (6%)	6 (18%)			
- Residential care - high level	0	1 (3%)	4 (12%)			
Prior stroke (%)	7 (21%)	4 (12%)	5 (15%)	0.583		
Atrial fibrillation or flutter (%)	8 (24%)	12 (36%)	19 (56%)	0.008*	0.02	0.09
Ischaemic heart disease (%)	9 (27%)	13 (39%)	11 (32%)	0.58		
Cardiac failure (%)	3 (9%)	5 (15%)	8 (23%)	0.27		
Hypertension (%)	23 (70%)	25 (76%)	32 (94%)	0.01*	0.01	0.05
Dyslipidaemia (%)	18 (55%)	15 (45%)	15 (44%)	0.65		
Diabetes mellitus (%)	12 (36%)	7 (21%)	6 (18%)	0.17		
Smoker (%)						
- Never	10 (30%)	22 (67%)	23 (68%)	0.006	0.004	1.0
- Current	7 (21%)	2 (6%)	1 (3%)			
- Ex	16 (49%)	9 (27%)	10 (29%)			
Ever smoked	23 (70%)	11 (33%)	11 (32%)	0.002	0.003	1.0

Any stroke risk factor	31 (94%)	31 (94%)	34 (100%)	0.39		
3 or more risk factors	21 (64%)	15 (45%)	22 (65%)	0.20		
Anticoagulant (%)						
- Warfarin	4	4	7			
- DOAC	4	4	2			
- Any	8 (24%)	8 (24%)	9 (26%)	*0.97*[†]		
- DOAC underdosed	2	0	0			
- Subtherapeutic INR	2	3	2			
- Warfarin or DOAC held	0	1	1			

[*]*P value for trend;* [†]*Any use.*

Table 2: Stroke information by demographic group.

	Young old (65-74) (N = 33)	Old old (75-84) (N = 33)	Oldest old (> 85) (N = 34)	P value comparing 3 groups
NIHSS (median IQR)	2 (1-4)	3 (2-11)	3 (2-8)	0.06
Oxford classification				
- PACI	17	16	19	
- TACI	1	2	4	
- Anterior circulation (PACI + TACI)	18 (55%)	18 (55%)	23 (68%)	
- POCI	8 (24%)	5 (15%)	6 (18%)	
- LACI	2 (6%)	4 (12%)	1 (3%)	
- Multi-territory	2 (6%)	5 (15%)	1 (3%)	
- N/A (haemorrhagic)	3 (9%)	1 (3%)	3 (~9%)	
TOAST classification				
- Cardioembolic	9 (28%)	17 (52%)	23 (68%)	
- ESUS	14 (42%)	3 (9%)	2 (6%)	
- Large artery	4 (12%)	5 (15%)	3 (~9%)	
- Small vessel	3 (9%)	7 (21%)	3 (~9%)	
- N/A (haemorrhagic)	3 (9%)	1 (3%)	3 (~9%)	
Stroke type				
- Ischaemic (%)	30 (91%)	32 (97%)	31 (91%)	0.69
- Haemorrhagic (%)	3 (9%)	1 (3%)	3 (9%)	
Microhaemorrhages on SWI				
- Any	6	2	4	
- Suggestive of amyloid angiopathy	3	1	3	0.32
- None	25	22	21	
- MRI not performed	2	9	9	

Table 3: Stroke treatment by demographic group.

	Young old (65-74) (N = 33)	Old old (75-84) (N = 33)	Oldest old (> 85) (N = 34)	P value comparing 3 groups
Delay to presentation	16 (48%)	15 (45%)	18 (53%)	0.83
Thrombolysis (%)	1 (9%)	4 (12%)	5 (15%)	0.33
Endovascular clot retrieval (%)	0	2 (6%)	0	0.21
Rehabilitation				
- Inpatient	10	13	10	0.76[*]
- Outpatient	6	6	8	
- Any	16 (48%)	19 (58%)	18 (53%)	
Palliated				
- Initially	0	1	0	0.45[†]
- Later in admission	3	3	7	
- Total	3 (9%)	4 (12%)	7 (21%)	
Length of stay (median IQR); maximum in those who didn't die	6.5 (4-21); 123	18 (8-32); 95	17 (4-26); 270	0.15

[*]*Any rehabilitation;* [†]*Ever palliated.*

Older patients were more likely to have any stroke complication, although this did not reach statistical significance, but rates of individual complications did not vary. A higher proportion of older patients were either

Table 4: Outcomes by demographic group.

	Young old (65-74) (N = 33)	Old old (75-84) (N = 33)	Oldest old (> 85) (N = 34)	P value comparing 3 groups	P value young old vs. oldest old	P value old old vs. oldest old
Any complication (%)	14 (42%)	22 (67%)	23 (68%)	0.06		
Delirium	2 (6%)	8 (24%)	4 (12%)	0.11		
Depression	3 (9%)	2 (6%)	0 (0%)	0.20		
Pneumonia	4 (12%)	8 (24%)	6 (18%)	0.44		
Urinary tract infection	2 (6%)	6 (18%)	6 (18%)	0.30		
Venous thromboembolism	0 (0%)	0 (0%)	1 (3%)	1.0		
Falls	3 (9%)	3 (9%)	1 (3%)	0.56		
Pressure injury	1 (3%)	1 (3%)	2 (6%)	1.0		
Pain	0 (0%)	0 (0%)	2 (6%)	0.33		
Incontinence	5 (15%)	12 (36%)	6 (18%)	0.08		
Death	3 (9%)	4 (12%)	7 (21%)	0.45		
Dependency (mRS 3 and above)	6 (18%)	16 (48%)	10 (29%)	0.03	0.39	0.14
RACF placement	2 (6%)	9 (27%)	5 (15%)	0.06	0.43	0.24

placed in a residential aged care facility or experienced a functional decline rendering them dependent. Mortality rates did not vary. Full details are shown in Table 4.

Discussion

The majority of stroke patients over the age of 85 were female, which is unsurprising considering that women comprise 64 percent of Australians aged 85 years and over [17]. However, for the younger two demographic groups, the majority of stroke patients were male. This is more than would be expected for the population and may represent different stroke risk factor profiles between the genders. As expected, a significantly higher proportion of the younger demographic were living at home prior to admission. Functional status, expressed by the mRS, predictably also declined with advancing age. However, there was no significant difference in either living situation or baseline functional status when comparing the old-old and oldest old.

Unsurprisingly there was a statistically significant trend for the proportion of stroke patients with both atrial fibrillation and hypertension to increase with increasing age. Rates of diabetes declined in the older age groups although not significantly so and there were more smokers in the youngest age group. There was no difference in antiplatelet or anticoagulant use between the groups. However, a number of patients who were on anticoagulation prior to their stroke were either under-dosed or had this medication held at the time of the stroke. Half of the youngest demographic group on Direct Oral Anticoagulants (DOACs) were prescribed an inappropriately low dose for their age and renal function and seven out of the fifteen, or 47 percent, of those on warfarin had a subtherapeutic international normalised ratio, INR, at the time of their stroke. This reflects known pitfalls with the prescribing of anticoagulant medications for stroke prevention with under-dosing of DOACs recently linked with a higher risk of stroke [18].

Stroke severity on the basis of NIHSS increased with advancing age although this did not reach statistical significance and the majority of scores were low. The majority of ischaemic strokes were anterior circulation across all three demographic groups. However, multi-territory strokes, which are usually cardioembolic, were not increased in the oldest demographic group. The proportion of strokes designated as cardioembolic by mechanism did significantly increase with age while the number of Embolic Strokes of Undetermined Source (ESUS) decreased. Haemorrhagic strokes did not increase with age as had been predicted. There was no evidence of increased rates of amyloid angiopathy, defined as multiple microhaemorrhages restricted to lobar, cortical or cortico-subcortical regions on susceptibility weighted MRI [19], with increased age. However, a substantial proportion of patients in the two oldest demographic groups did not have an MRI, 27% and 26% respectively.

A substantial number, almost half of all patients, experienced a delay in accessing medical care for a variety of factors including delays in seeking help, being physically incapacitated by stroke and found by family or friends at a later time, geographical distance, delays in transfer from peripheral hospitals and delays in recognition of stroke both by patients and their caregivers and by medical staff. However, there did not appear to be significant differences between the age groups in these delays. There was no significant difference between the age groups in those treated with thrombolysis or endovascular clot retrieval although the overall numbers eligible for or offered these therapies were very low. This is likely reflective of the regional location and delays in presenting to and accessing specialised medical care.

Interestingly, the oldest old had the highest rate of thrombolysis at fifteen percent. This reflects the biological differences in the demographic groups and the relative robustness of the oldest old. Age in itself is no barri-

er to thrombolysis. Existing evidence demonstrates that the benefits of both thrombolysis and endovascular clot retrieval are not diminished in older patients [20,21].

There was no significant difference in those who participated in either inpatient or outpatient rehabilitation. The proportion of patients who were palliated during their admission did not vary with age.

Rates of individual stroke complications did not vary. However, the proportion of patients experiencing any complication was significantly higher in older patients. There was a slight trend toward increased mortality in the older demographic group but no significant difference in survival probabilities between the groups. Rates of dependency and placement in residential aged care facilities post hospital admission predictably increased with age. However, the difference lay between the youngest and middle demographic group highlighting the resilience of the oldest old.

The main limitation of this study was its small sample size. It is possible that expected significant differences in other variables may have been appreciated with larger numbers. Additionally, data was collected only from a regional cohort of patients and thus might not necessarily apply to patients who reside in other settings.

Conclusion

While many of the findings in this study were not surprising, they confirm established predictions relating to the evolving need for health and social care and then apply these predictions to a specific clinical problem. Our findings confirm that in the future, very old people with acute stroke in Australia will more likely be female, have poorer premorbid functional status and be more likely to be living in residential care. Atrial fibrillation and hypertension are set to become more prevalent risk factors. Reduced rates of diabetes and cigarette smoking are most likely a survival phenomenon with those particular risk factors reducing the chances of those affected from living sufficiently long to develop a stroke towards the extremes of old age.

Stroke severity and treatment will not necessarily differ, but our data suggests that the oldest old have a greater likelihood of a complicated outcome. However, they will be no more likely to die from their stroke and the likelihood of requiring to access residential care will not significantly increase. Further research into the needs and outcomes of older stroke patients is warranted as the Australian population continues to age.

References

1. Australian Institute of Health and Welfare. Ageing.
2. Knoflach M, Matosevic B, Rucker M, Furtner M, Mair A, et al. (2012) Functional recovery after ischemic stroke a matter of age: Data from the Austrian Stroke Unit Registry. Neurology 78: 279-285.
3. Australian Institute of Health and Welfare (2013) Stroke and its management in Australia: An update. Cardiovascular disease series cat. no. CVD 61. Canberra, AIHW.
4. Australian Bureau of Statistics (2013) Population Projections, Australia 2012 (base) to 2101.
5. Zizza CA, Ellison KJ, Wernette CM (2009) Total water intakes of community living middle old and oldest old adults. J Gerontol A Biol Sci Med Sci 64: 481-486.
6. Cho C, Han C, Sung M, Lee C, Kim M, et al. (2017) Six-month lower limb aerobic exercise improves physical function in young old, old old and oldest old adults. Tohoku J Exp Med 242: 251-257.
7. Gondo Y (2012) Longevity and successful ageing: Implications from the oldest old and centenarians. Asian J Gerontol Geriatr 7: 39-43.
8. Caplan LR (2009) Basic pathology, anatomy, and pathophysiology of stroke. Caplan's Stroke: A Clinical Approach. (4th edn), Saunders Elsevier, Philadelphia, 22.
9. Adams HP, Bendixen BH, Kappelle IJ, Biller J, Love BB, et al. (1993) Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 24: 35-41.
10. Janczak D, Ziolkowski P, Garcarek J, Janczak D, Dorobisz K, et al. (2014) The cytokines within the carotid plaque in symptomatic patients with internal carotid stenosis. J Cardiothorac Surg 9: 139.
11. Fustinoni O (2011) The case for an elderly targeted stroke management. Front Neurol 2: 1-6.
12. Mishra NK, Ahmed N, Andersen G, Egido JA, Lindsberg PJ, et al. (2010) Thrombolysis in very elderly people: Controlled comparison of SITS International Stroke Thrombolysis Registry and Virtual International Stroke Trials Archive. BMJ 341: 6046.
13. Sanossian N, Ovbiagele B (2009) Prevention and management of stroke in very elderly patients. Lancet Neurol 8: 1031-1041.
14. Saposnik G, Cote R, Phillips S, Gubitz G, Bayer N, et al. (2008) Stroke outcome in those over 80: A multicentre cohort study across Canada. Stroke 39: 2310-2317.
15. (2018) National Institute of Health, National Institute of Neurological Disorders and Stroke. Stroke Scale.
16. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C (1991) Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet 337: 1521-1526.
17. Australian Bureau of Statistics (2014) Australian Demographic Statistics.
18. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA (2017) Non-vitamin k antagonist oral anticoagulant dosing in patients with atrial fibrillation and renal dysfunction. J Am Coll Cardiol 69: 2779-2790.
19. Van Rooden S, Van der Grond J, Van den Boom R, Haan J, Linn J, et al. (2009) Descriptive analysis of the Boston criteria applied to a Dutch-type cerebral amyloid angiopathy population. Stroke 40: 3022-3027.
20. IST-3 collaborative group (2012) The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): A randomised controlled trial. Lancet 379: 2352-2363.
21. Goyal M, Menon BK, Van Zwam WH, Dippel DWJ, Mitchell PH, et al. (2016) Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. Lancet 387: 1723-1731.