

Age dependency of ischaemic stroke subtypes and vascular risk factors in western Norway: the Bergen Norwegian Stroke Cooperation Study

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Objectives – Age dependency of acute ischaemic stroke aetiology and vascular risk factors have not been adequately evaluated in stroke patients in Norway. Aims of this study were to evaluate how stroke subtypes and vascular risk factors vary with age in a western Norway stroke population. **Materials and methods** – Patients aged 15–100 years consecutively admitted to our neurovascular centre with acute ischaemic stroke between 2006 and 2012 were included. The study population was categorized as young (15–49 years), middle-aged (50–74 years) or elderly (≥ 75 years). Stroke aetiology was defined by TOAST criteria. Risk factors and history of cardiovascular disease were recorded. **Results** – In total, 2484 patients with acute cerebral infarction were included: 1418 were males (57.3%). Mean age was 70.8 years ($SD \pm 14.9$), 228 patients were young, 1126 middle-aged, and 1130 were elderly. The proportion of large-artery atherosclerosis and of small-vessel occlusion was highest among middle-aged patients. The proportion of cardioembolism was high at all ages, especially among the elderly. The proportion of stroke of other determined cause was highest among young patients. Some risk factors (diabetes mellitus, active smoking, angina pectoris, prior stroke and peripheral artery disease) decreased among the elderly. The proportions of several potential causes increased with age. **Conclusion** – The proportion of stroke subtypes and vascular risk factors are age dependent. Age 50–74 years constitutes the period in life where cardiovascular risk factors become manifest and stroke subtypes change.

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Key words: age; cardiovascular disease; ischaemic stroke; stroke subtypes; stroke aetiology; trial of org 10172 in acute stroke treatment; vascular risk factors

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Introduction

The aetiology of stroke is influenced by sex, race and age, as well as by cultural and geographic factors (1–6). Stroke subtypes are commonly categorized as large-artery atherosclerosis (LAA), cardioembolism (CE), small-vessel occlusion (SVO), stroke of other determined cause (SOC) and stroke of undetermined cause (SUC) (TOAST

criteria) (7). Pathogenesis, prognosis and treatment vary among these subtypes, and evaluating vascular risk factors within each subtype may improve acute stroke treatment and secondary prevention (8).

Vascular risk factors may be classified as non-modifiable (e.g. age, sex, race, genetics), modifiable and well documented (e.g. cardiovascular disease, hypertension, diabetes mellitus, dyslipidaemia, atrial fibrillation, smoking), or potentially modifiable and less well documented (e.g. metabolic syndrome, hyperhomocysteinemia, migraine,

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malignancy) (9, 10). Risk factor profiles change with increasing age, as does the risk factor burden (11, 12). In Norway, recent studies have revealed a rather high-risk factor burden in the general population (13).

Adequate data on age dependency of acute ischaemic stroke aetiology and the prevalence of vascular risk factors are lacking in Norway. The aim of this study was to evaluate how ischaemic stroke subtypes and vascular risk factors vary with age in a well-defined western Norway ischaemic stroke population.

Materials and methods

Ischaemic stroke population and aetiology

The presented study is based on data from 2484 consecutive ischaemic stroke patients aged 15–100 years and admitted to Bergen Centre for neurovascular diseases between 2006 and 2012. All patients were prospectively registered in the Bergen NORSTROKE Registry. The study population was categorized as young (15–49 years), middle-aged (50–74 years) or elderly (≥ 75 years). The index stroke was documented by magnetic resonance imaging (MRI) or computed tomography (CT) confirming a lesion related to the clinical symptoms. Routine blood samples were collected on admission. Stroke aetiology was classified by an experienced stroke neurologist (HN) according to TOAST criteria (7). The proportion of different stroke aetiologies stratified by 10 years of age intervals is shown in Figs 1 and 2.

Vascular risk factors

Hypertension, diabetes mellitus, paroxysmal or chronic atrial fibrillation were considered present if diagnosed and/or treated prior to the index stroke or during the hospital stay (fasting plasma glucose >7.7 mmol/l; at least one ECG documenting atrial fibrillation). Current smoking was defined as smoking one or more cigarettes per day. A history of prior stroke, transitory ischaemic attack (TIA), myocardial infarction, pectoral angina or peripheral artery disease was considered present if diagnosed by a physician any time prior to index stroke onset.

The study was approved by the local ethics committee (REK Vest).

Statistics

STATA 13.1 (Statacorp 4905 Lakeway Drive, College Station, TX, USA) was used for analysis.

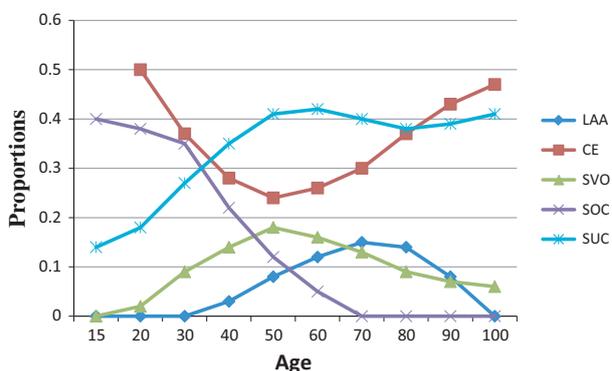


Figure 1. Proportions of TOAST subtypes stratified by age group. TOAST, Trial of Org 10172 in Acute Stroke Treatment; LAA, large-artery atherosclerosis; CE, cardioembolism; SVO, small-vessel occlusion; SOC, stroke of other determined cause; SUC, stroke of undetermined cause.

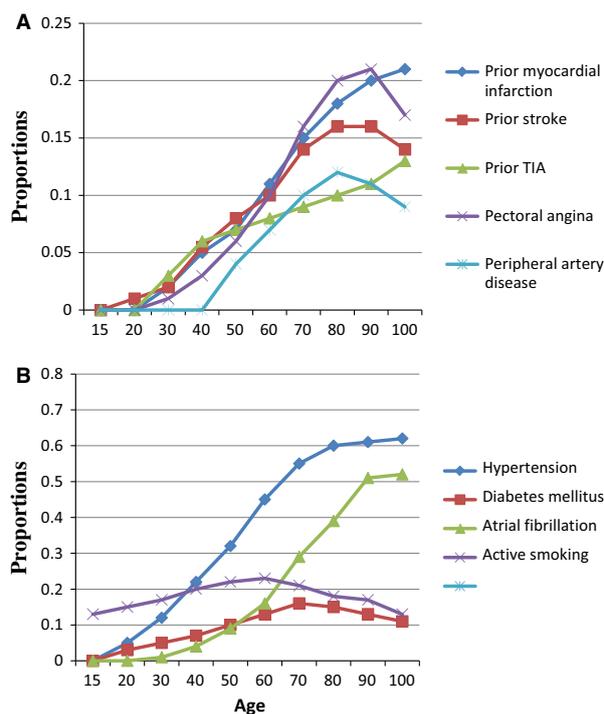


Figure 2. Proportions of prior cardiovascular disease (A) and vascular risk factors (B) stratified by age group. TIA, transitory ischaemic attack.

Chi-square test, Student's *t*-test, Spearman's correlation and Mann–Whitney *U*-test were used when appropriate. The proportion of TOAST subtypes was displayed by means of the Lowess function. Figures showing the proportion of prior cardiovascular disease (Fig. 2A) and vascular risk factors (Fig. 2B) stratified by age decades were made based on Lowess analyses.

Table 1 Socio-demographic characteristics and imaging stratified by age group

	15–49 years <i>n</i> = 228 <i>n</i> (%)	50–74 years <i>n</i> = 1126 <i>n</i> (%)	≥75 years <i>n</i> = 1130 <i>n</i> (%)	<i>P</i> <i>P</i> *
Socio-demographics				
Females	76 (33.3)	362 (32.1)	618 (54.7)	<0.001
Married	147 (64.5)	808 (71.8)	452 (40)	<0.001
Employed	183 (80.3)	431 (38.3)	20 (1.7)	<0.001
Imaging				
Computed tomography	178 (78.07)	932 (82.77)	1056 (93.45)	
Magnetic resonance imaging	214 (93.86)	1013 (90)	815 (72.12)	

*Chi-square test.

Table 2 Vascular risk factors, history of cardiovascular disease and stroke subtypes stratified by age group

	15–49 years <i>n</i> = 228	50–74 years <i>n</i> = 1126	≥75 years <i>n</i> = 1130	<i>P</i> <i>P</i> *
Vascular risk factors				
Hypertension	53 (23.2)	550 (48.9)	696 (61.6)	<0.001
Diabetes mellitus	16 (7.0)	161 (14.3)	173 (15.3)	0.004
Atrial fibrillation	9 (3.9)	203 (18.0)	487 (43.1)	<0.001
Active smoking	81 (35.5)	406 (36.1)	117 (10.3)	<0.001
History of CVD				
Prior stroke	10 (4.4)	148 (13.1)	187 (16.5)	<0.001
Prior TIA	9 (3.9)	75 (6.7)	105 (9.3)	0.005
Myocardial infarction	8 (3.5)	126 (11.2)	215 (19.0)	<0.001
Pectoral angina	6 (2.6)	102 (9.1)	204 (18.0)	<0.001
Peripheral artery disease	3 (1.3)	81 (7.2)	83 (7.4)	0.002
Stroke subtype (TOAST)				
Large-artery atherosclerosis	7 (3.1)	159 (14.1)	135 (11.9)	<0.001
Cardioembolism	65 (28.5)	280 (24.9)	460 (40.7)	<0.001
Small-vessel occlusion	32 (14.0)	181 (16.1)	93 (8.2)	<0.001
Stroke of other determined cause	44 (19.3)	21 (1.9)	3 (0.2)	<0.001
Stroke of undetermined cause	80 (35.1)	485 (43.1)	429 (37.9)	0.02

TIA, transient ischaemic attack; CVD, cardiovascular disease; TOAST, Trial of Org 10172 in Acute Stroke Treatment (1).

*Chi-square test.

Results

In total, 2484 patients with acute ischaemic stroke were included. Of these, 1418 were males (57.3%). The mean age was 70.8 years (SD ± 14.9), 228 patients were young, 1126 were middle-aged, and 1130 were elderly. Socio-demographic characteristics, CT and MRI imaging stratified by age group are given in Table 1. TOAST classification stratified by age group is shown in Fig. 1. In the total study population, SUC was the most frequent stroke subtype (40.2%), and CE (32.5%) dominated the determined causes (Table 2). Including only patients that underwent *full* assessment with CT, MRI, ECG, echocardiography and ultrasound of the

neck vessels (in total 32% of the patients) showed similar curves as in Fig. 1, except that of the frequency in LAA in patients >80 years old was not so steep and the frequency of SUC decreased in the elderly.

Figure 2 and Table 3 show the proportion of TOAST subtypes in accordance with age. LAA increased among middle-aged patients and declined among the elderly, with a peak proportion between 70 and 80 years. CE was a frequent cause at all ages and showed u-shaped correlation with decrease among the young, an increase among the middle-aged and among elderly patients (Table 3). The lowest proportion of CE was between 50 and 60 years. The SVO proportion peaked around 50 years and decreased thereafter both among mid-aged and elderly patients (Table 3). The SOC proportion was highest among the youngest patients with a peak proportion between 20 and 30 years and declined in the middle-aged. The SUC proportion increased among the young, peaked between age 50 and 60, and kept a steady proportion among the elderly (Table 3). The proportion of several potential causes in SUC increased with age, from 1% in the young, 9% in the middle-aged to 20% in the elderly (correlation factor 0.17, $P < 0.001$).

The proportions of prior cardiovascular disease according to age are shown in Fig. 2A and Table 3. The proportions of previous stroke, TIA, myocardial infarction, pectoral angina and peripheral artery disease consistently increased with age, predominantly in the middle-aged group (Table 3).

The proportion of vascular risk factors according to age is shown in Fig. 2B and Table 3. The proportion of hypertension increased consistently with age among young and middle-aged patients. Diabetes mellitus increased in the mid-age group and decreased in the elderly group, peaking between 70 and 80 years. The proportion of atrial fibrillation increased consistently with age. The proportion of active smoking increased with age among the young, and decreased among the middle-aged and elderly, with a peak proportion between 50 and 60 years.

Discussion

Our data demonstrate the correlation between age and different aetiologies and risk factors of ischaemic stroke for a well-defined western Norway population.

Cardioembolism was the most frequent determined cause of stroke in all age groups. This constellation may be explained by high rates of

Table 3 Spearman's correlation between proportions of risk factors and increasing age within three different age groups

	15–49 years	<i>P</i>	50–74 years	<i>P</i>	≥75 years	<i>P</i>
Risk factors						
Hypertension	0.19	0.005	0.16	<0.001	–0.01	0.60
Diabetes mellitus	0.11	0.09	0.07	0.01	–0.06	0.03
Atrial fibrillation	0.02	0.71	0.12	<0.001	0.02	0.37
Active smoking	0.14	0.03	–0.12	<0.001	–0.21	<0.001
History of CVD						
Prior stroke	–0.05	0.41	0.07	0.01	0.007	0.79
Prior TIA	0.06	0.32	0.06	0.04	0.02	0.40
Myocardial infarction	0.05	0.38	0.07	0.01	0.03	0.31
Pectoral angina	0.06	0.31	0.11	<0.001	0.05	0.05
Peripheral artery disease	0.03	0.64	0.12	<0.001	–0.03	0.29
Stroke subtype (TOAST)						
Large-artery atherosclerosis	0.08	0.20	0.12	<0.001	–0.13	<0.001
Cardioembolism	–0.26	<0.001	0.08	0.004	0.09	<0.001
Small-vessel occlusion	0.12	0.06	–0.11	<0.001	–0.06	0.02
Stroke of other determined cause	–0.10	0.12	–0.14	<0.001	0.0007	0.10
Stroke of undetermined cause	0.21	<0.001	–0.03	0.21	0.03	0.26

TIA, transient ischaemic attack; CVD, cardiovascular disease; TOAST, Trial of Org 10172 in Acute Stroke Treatment (1).

cardiac disorders with low or uncertain risk, such as patent foramen ovale, among young patients (5, 19, 20), whereas high-risk disorders, such as atrial fibrillation, increased dramatically with age (19, 20). The present data support this, as we identified AF as an important risk factor from the 4th decade, thereafter consistently increasing throughout the 10th decade. However, our data may be biased by diagnostics focusing mostly on cardiac arrhythmias among older patients, whereas investigation for right–left shunt with transesophageal echocardiography and neurosonographic bubble test was mostly performed among younger patients.

Stroke of other determined cause, predominantly cervical artery dissections (19, 21), has been described as the second most frequent cause of stroke in the young. In our study, the proportion of this subtype declined steeply during mid-age and was non-existent among the elderly. Other young stroke studies also support a decline of stroke of other determined cause towards mid-age, although their rates declined more gently than in our study (5, 17).

Small-vessel occlusion followed an inversed u-shaped curve with a peak in the 6th decade. This is in line with recent studies on young and middle-aged patients (5, 17), while others have observed a further increase in small-vessel occlusion at older ages (22). Large-artery atherosclerosis followed a similar time course as small-vessel occlusions. This corresponds to that of other stroke populations (18, 22). However, while some studies have observed higher proportions of large-artery atherosclerosis earlier in life (23, 24), our population shows that large-artery athero-

sclerosis appears in the 3rd decade, but was not a common finding before the 5th decade and thereafter increased until the 8th decade before decreasing again.

Vascular risk factors influence both small-vessel occlusion and large-artery atherosclerosis (25, 26). In our study population, all risk factors (except smoking and diabetes mellitus) increased consistently throughout the lifetime, but most distinctly among middle-aged patients. Risk factors increasing with age have been reported previously (10, 11, 27). We found hypertension as the most frequent risk factor at all ages. Hypertension plays a particular role in small-vessel occlusion (25) and is also frequently present in large-artery atherosclerosis (18, 22). There are some indications that large-artery atherosclerosis and small-vessel occlusion are coexisting subtypes of stroke (26), supporting the partly atherosclerotic aetiology of small-vessel occlusion. However, small-vessel occlusion is an imprecise subtype, which besides occlusions due to small artery microatheroma, lipohyalinosis and fibrinoid necrosis, most likely also includes misinterpreted occlusions due to embolic sources (28–32).

Large-artery atherosclerosis is classified according to rather rigid TOAST criteria, which requires occlusion or ≥50% stenosis in a related artery (7), not paying attention to atherosclerotic plaque instability which may lead to arterio-arterial embolism even from stenosis of low or moderate degree (33, 34). Hence, true large-artery atherosclerosis is in general likely to be underestimated due to an arbitrary TOAST definition.

In our total study population, stroke of undetermined cause was the most frequent subtype. This illustrates a well-known limitation of the TOAST classification, as the stroke of undetermined cause category not only includes cases of truly unknown cause, but also cases with several potential causes (14, 15). Stroke of undetermined cause comprised the largest subtype among young and middle-aged patients, which is in accordance with other studies (16, 17), whereas stroke of undetermined cause was outnumbered by cardioembolism among the elderly (18). The lowest proportion of stroke of undetermined cause was found among those younger than 30 years.

The clarification of stroke aetiology has an impact on optimal acute treatment, as well as optimal secondary prevention (8, 35), and thus comprises a crucial part of stroke workup. Our data show that ischaemic stroke entities change depending on age in western Norway, and stroke investigation needs accordingly to be focused in different directions during different periods of life.

The proportions of some risk factors (diabetes mellitus, active smoking, angina pectoris, prior stroke and peripheral artery disease) decreased among the elderly. One possible explanation is that many patients with these risk factors died before reaching old age.

The total number of patients in the mid-age and elderly group was approximately the same, but the proportions of cardiovascular disease and vascular risk factors tended to decrease with increasing age among the elderly as opposed to the middle-aged. This indicates that there may be important differences as to the underlying pathophysiological mechanisms between these age groups.

The strength of this study is a relatively large study population, investigated in a single stroke centre according to a predefined protocol. True stroke subtype classification is negatively affected by the TOAST classification's own limitations, such as oversizing the stroke of undetermined cause subgroup and undersizing the large-artery atherosclerosis subgroup. Another limitation is that TOE and neurosonographic bubble test were mainly performed among patients younger than 60 years, which may have introduced some bias by overlooking right-left shunts in the elderly. Also, elderly patients were examined with MRA in only 72% of the patients and some dissections, albeit rare, may have been missed. In stroke of other determined cause, we may have failed to look for some rare causes. This bias is likely small because of the rare occurrence of diseases such as Fabry's disease.

Conclusions

This study demonstrates the close correlation between age and ischaemic stroke subtypes as well as vascular risk factors. Mid-age constitutes the period of life where risk factors become manifest and the proportions of risk factors and stroke subtypes profoundly change among ischaemic stroke patients in western Norway.

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Authors' contributions

AN and AF contributed equally for this manuscript and both are first authors. HN and AN are responsible for the idea and design of the study. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors and were fully responsible for all content and editorial decisions. All authors critically reviewed the manuscript and approved the submitted version.

Conflict of interest and sources of funding

The authors declare no conflict of interests or sources of funding.

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