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Diagnostics, treatment and secondary prevention of ischemic stroke in the Silesian Province, Poland between 2009 and 2015



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ABSTRACT

Background: The available data on diagnostics and treatment of ischemic stroke (IS) in Poland come mainly from non-representative cohorts or are outdated.

Objective: Therefore, the current study was done to access the most recent data on IS in the industrial region that covers 12% of the country's population.

Materials & methods: Analysis of the data from stroke questionnaires, obligatory for all patients hospitalized due to acute stroke and administered by the National Health Fund (the only public health insurer in Poland) between 2009 and 2015 ($n = 81,193$).

Results: The number of hospitalizations due to IS in the Silesian Province was 69,403 and constituted 85.5% of all stroke cases reported to the NHF between 2009 and 2015. Neuroimaging of the brain (CT/MRI) was performed in 68,696 (99%) subjects, while ultrasonography of extra- and/or intracranial arteries in 57,886 (83.4%). The rtPA therapy was applied in 3282 patients (4.7% of all IS subjects). The rate of patients treated with rtPA gradually increased (1.2% in 2009, 9.3% in 2015). Among all patients with IS, 57,636 (83.1%) subjects were administered antiplatelet drugs, 16,199 (23.3%) – oral anticoagulants, and 55,971 (80.7%) – antihypertensive drugs. Also, 2260 (3.3%) patients were referred for vascular intervention. In subjects with cardioembolic stroke etiology, 37.8% were treated with anticoagulants.

Conclusions: There has been observed a significant improvement in the quality of diagnosis and treatment of acute ischemic stroke during recent years. However, further actions are

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required both in terms of reperfusion treatment (thrombolysis and/or thrombectomy) and secondary prevention of stroke.

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1. Introduction

Stroke constitutes the third cause of death and the main cause of permanent disability in adults in Europe. Due to poor prognosis, high costs of treatment and chronic care, stroke is not only a medical problem, but also a social issue.

Based on the studies conducted in various countries it was documented that immediate hospitalization and treatment of patients according to an approved standard in specialized stroke units contributes to decreased mortality and lower treatment costs. In Poland, including the Silesian Province, there is a comprehensive network of stroke units and most patients diagnosed with stroke are treated in such specialized facilities [1,2].

Patients with ischemic stroke (IS) have had access to causal treatment for several years. It consists in administering a single dose of intravenous medication (alteplase – a recombinant tissue plasminogen activator – rtPA) which dissolves blood clots in an occluded cerebral artery [3–5]. The treatment is known as intravenous thrombolytic therapy. In 1996 the use of rtPA in AS was approved by the FDA, in 2002 this therapy was registered by the European Commission, in 2003 it was registered in Poland and since 2009 it has been fully reimbursed to all patients by the NHF, which is the only public health insurer in Poland.

There exist some reports concerning data on treatment of stroke in certain hospitals, cities, districts and provinces of Poland [6–8]. However, there is no comprehensive analysis concerning diagnostics and treatment of IS in the Silesian Province which is the second largest province in Poland with approximately 4,600,000 citizens (nearly 12% of Poland's population).

Therefore, the aim of this study was to analyze the use of diagnostic methods (neuroimaging, ultrasonography) and treatment of acute IS, as well as secondary stroke prevention in the Silesian Province between 2009 and 2015.

2. Patients and methods

The study was based on the data obtained from stroke questionnaires ($n = 88,425$) which were mandatorily reported to the NHF by all Silesian hospital departments for stroke patients (homogeneous patient groups: A48–A51). The analyzed period was between 2009 and 2015. The study was done with the approval of the Silesian division of the NHF and the Consultant in Neurology for the Silesian Province.

The questionnaire data were verified for incomplete or recurring data (e.g. recurring records of the same hospitalization were excluded). Finally, 81,193 stroke questionnaires were

enrolled for the analysis. Diagnosis of stroke was made according to the International Classification of Diseases version 10 (ICD-10).

The following data from the stroke questionnaires were used in the present study: age, sex, admission date, date of the first occurrence of stroke symptoms, date of death or discharge, number of hospitalization days, etiology of IS (according to the Trial Org 10172 in Acute Stroke Treatment – TOAST), clinical symptoms (consciousness disorders, hemiparesis/hemiplegia, speech disorders, sensory disorders, posterior circle syndrome), secondary stroke prevention (antiplatelets, anticoagulants, antihypertensives), information on referral for vascular intervention due to artery stenosis, application of rtPA, use of neuroimaging (CT/MRI) and ultrasonography of intra- and extracerebral arteries.

According to the Bioethics Committee, the study was not a medical experiment. Therefore, no approval of the Committee was required.

The statistical analysis was done using the statistical package SAS version 9.4 (SAS Institute Inc., Cary, NC). The level of statistical significance was set at $P < 0.05$.

The quantitative data were characterized using the mean and the standard deviation. For nominal data the percentage values were used. The correlation between the nominal variables was verified using the χ^2 test. The verification of the distribution of the variables and the agreement with the normal distribution were made using the Shapiro–Wilk test. The mean difference significance was verified using the Student's *t*-test for two groups and the ANOVA test for three or more groups. The consistency of the distribution was verified using the Mann–Whitney *U* test for groups and the Kruskal–Wallis test for skewed distributions. Multiple comparisons were made based on post hoc test results for variance analysis (ANOVA) and the Kruskal–Wallis test with the Bonferroni correction to assess significance of the percentage difference in the case of two or more groups. The test for trend was also calculated for consecutive years by means of Jonckheere–Terpstra and Cochran–Armitage tests for continuous and categorical variables, respectively.

3. Results

Based on the analysis of data obtained from the stroke questionnaires it was shown that the number of hospitalizations due to IS in the Silesian Province between 2009 and 2015 was 69,403 (35,880 women and 33,107 men; $P < 0.001$) which constituted 85.5% of all stroke cases reported to the NHF ($n = 81,193$). In 416 cases the data on sex were not available. The mean age of subjects hospitalized due to IS was 72.2 ± 11.8 years ($F - 75.4 \pm 11.5$ years, $M - 68.8 \pm 11.2$ years; $P < 0.05$). The

Table 1 – Percentage of hospitalizations due to ischemic stroke (I63) with performed diagnostic procedures (Brain CT/MRI and USG of extra- and/or intracranial arteries) in the Silesian Province between 2009 and 2015.

Year	Number of all hospitalizations due to ischemic stroke (I63) N	Brain CT/MRI [%]	USG of extra- and/or intracerebral arteries [%]
2009	9275	98.9	65.2
2010	10,058	98.7	81.6
2011	10,223	98.6	84.2
2012	10,187	99.2	86.1
2013	10,289	99.1	87.6
2014	9850	99.1	88.7
2015	9521	99.3	89.3
P ^a	–	<0.001	<0.001
All	69,403	99	83.4

^a Trend test Cochran–Armitage.

mean period from first symptoms of ischemic stroke to hospitalization was 0.74 ± 3.4 days, and it was stable over years.

Neuroimaging of the brain (CT/MRI) was performed in 68,696 (99.1%), and ultrasonography of extra- and/or intracranial arteries – in 57,886 (83.4%) of patients. The frequency of use of diagnostic methods in subjects with IS is shown in Table 1.

The rtPA therapy was applied to 3282 patients with IS (I63) treated in hospitals of the Silesian Province between 2009 and 2015. It constituted 4.7% of all cases of I63-diagnosed hospitalizations. The number of patients who received thrombolytic therapy was increasing gradually in the subsequent years (Fig. 1).

The mean hospitalization time in patients with IS treated with rtPA was 14.4 ± 11.7 days. It was statistically significantly longer than in patients with IS not receiving intravenous thrombolytic therapy (13.6 ± 10.8 days; $P = 0.01$). Table 2

presents the length of in-hospital stay for patients with IS treated and untreated with rtPA in the consecutive years.

The overall number of male and female patients treated with rtPA was 1690 (51.9%) and 1565 (48.1%), respectively (for 27 patients data concerning sex were not available) ($P < 0.001$). Table 3 shows sex distribution of patients treated with rtPA in the consecutive years.

The mean age of all patients who received rtPA therapy in the analyzed period was statistically significantly lower (70.2 ± 12.4 years) when compared to the mean age of patients untreated with rtPA (72.3 ± 11.8 years; $P < 0.001$). The mean age of patients treated with rtPA was gradually increasing in the subsequent years ($P < 0.001$) (Fig. 2).

The overall in-hospital mortality in patients treated with rtPA (number of deaths = 514; 15.7%) was not statistically significantly higher when compared to the in-hospital mortality of patients untreated with rtPA (number of deaths = 9825; 14.9%) ($P = 0.210$). Fig. 3 shows the in-hospital mortality for patients treated and untreated with rtPA in the consecutive years.

The in-hospital mortality in patients treated with rtPA was similar in men (15.6%) and women (15.8%) ($P = 0.899$).

The etiology of IS in patients who received intravenous thrombolysis and the in-hospital mortality depending on stroke etiology is presented in Table 4.

Data obtained from the stroke questionnaires allowed to determine the secondary stroke preventive therapy applied in patients with IS (I63); 57,636 (83.1%) subjects were administered antiplatelet drugs, 16,199 (23.3%) – oral anticoagulants, and 55,971 (80.7%) – antihypertensive drugs. Furthermore, 2260 (3.3%) patients were referred for vascular intervention due to artery stenosis. Table 5 shows the application of secondary stroke prevention in the consecutive years.

In patients with cardioembolic stroke etiology ($n = 12,973$), 4902 (37.8%) subjects were administered anticoagulants. The percentage of patients with cardioembolic stroke treated with anticoagulants were gradually increasing in the subsequent years ($P = 0.014$) while the negative trend was observed for antiplatelet drugs (Fig. 4).

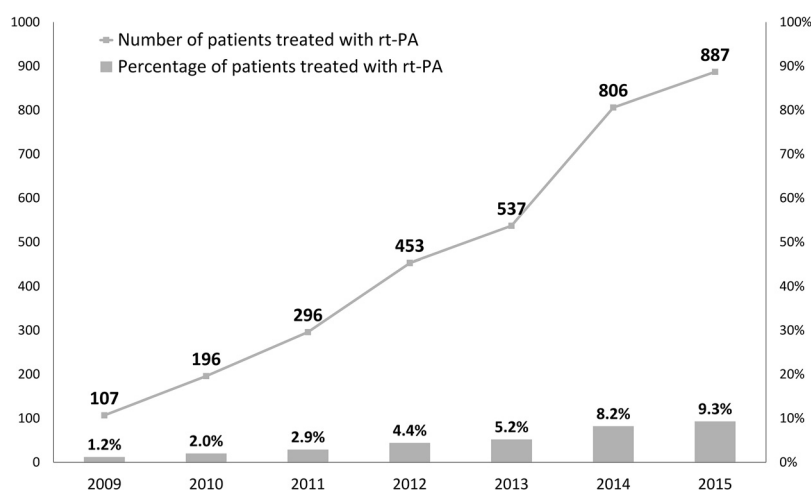


Fig. 1 – Intravenous thrombolytic therapy (rt-PA) in patients with ischemic stroke (I63) treated in hospitals of the Silesian Province between 2009 and 2015. Data presented as N (%) (Trend test Cochran–Armitage; $P < 0.001$).

Table 2 – Hospitalization time of patients with ischemic stroke (I63) treated and untreated with intravenous thrombolytic therapy (rtPA) in the Silesian Province between 2009 and 2015. Data presented as mean \pm SD in days.

Year	Hospitalization time in treated with rt-PA [days]	Hospitalization time in untreated with rt-PA [days]	p ^a
2009	13.9 \pm 8.1	14.0 \pm 10.1	0.878
2010	14.9 \pm 11.1	13.9 \pm 10.4	0.236
2011	16.6 \pm 17.1	13.9 \pm 11.9	<0.001
2012	14.4 \pm 11.7	13.6 \pm 13.4	0.141
2013	14.4 \pm 11.2	13.2 \pm 9.7	0.016
2014	14.2 \pm 11.2	13.6 \pm 10.2	0.181
2015	13.7 \pm 10.7	13.1 \pm 9.1	0.090
p ^b	0.001	<0.001	–
All	14.4 \pm 11.7	13.6 \pm 10.8	<0.001

^a ANOVA post hoc tests.
^b Trend test Jonckheere–Terpstra.

4. Discussion

The stroke incidence rate in the Silesian Province is very high – it varied from 169/100,000 to 187/100,000 per year (data from the paper of authors in press). It constitutes a major diagnostic and therapeutic issue. Most strokes are ischemic (85.5%) with atherosclerotic etiology, thus primary prevention of atherosclerosis is of great importance.

The rtPA therapy significantly increases the chance of minimal or no disability (by approximately 30%) at three months after stroke onset [3]. In the Silesian Province the number of patients treated with rtPA gradually increased since intravenous thrombolysis was reimbursed by the NHF in Poland. In 2009 only 1.2% of patients with IS were treated with intravenous thrombolytic therapy. However, in 2015 this percentage reached 9.3% of all subjects with IS. Generally, in the analyzed period 4% of patients with IS were treated with rtPA in the Silesian hospitals.

To compare, there are some data from rare recent studies conducted in other Polish regions: the percentage of patients treated with rtPA in the Swietokrzyskie Province was 8.8% (2009) whereas in the Pomeranian Province – 2.9% (2009) [7]. It should be stressed that the number of patients analyzed in these studies was much lower and the analyzed period significantly shorter than in the present study.

In some Western European countries the percentage of patients with IS treated with rtPA was higher than in the Silesian Province. For instance, the use of thrombolysis in England, Wales and Northern Ireland increased from 1.8% in 2008 to 12.2% in 2014 [9] and in Dutch hospitals from 6.4% in 2005 to 14.6% in 2012 [10]. There are also regions where thrombolysis rates are much higher, e.g. 15.7% in South London and, up to 35% in the German state of Hesse (2007–2008) [11,12]. However, in other regions the situation seemed to be similar, e.g. in Scotland it increased from 3% to 9% from 2008 to 2013 [13].

In the United States, where rtPA has been used since 1996 (6 years earlier than in Europe), the percentage of thrombolized patients reached 20–30% in some hospitals and quality

Table 3 – Rt-PA therapy in patients hospitalized due to ischemic stroke (I63) in the Silesian Province between 2009 and 2015. Results presented for all patients, men (M) and women (F).

Year	Number of all hospitalizations due to ischemic stroke (I63) ^a N	Number of male hospitalizations due to ischemic stroke (I63) N (%)	Number of female hospitalizations due to ischemic stroke (I63) N (%)	Number of patients treated with rt-PA/percentage of treated patients to all patients with I63 diagnosis	Number of men treated with rt-PA (percentage of treated men to all men with I63 diagnosis)	Number of women treated with rt-PA (percentage of treated women to all women with I63 diagnosis)	P ^b F vs M treated with rt-PA
2009	9275	4486 (48.4%)	4789 (51.6%)	107/1.2%	52 (48.6%)/1.2%	55 (51.4%)/1.2%	0.962
2010	10,058	4774 (47.5%)	5284 (52.5%)	196/1.9%	103 (52.6%)/2.2%	93 (47.5%)/1.8%	0.150
2011	10,223	4920 (48.1%)	5303 (51.9%)	296/2.9%	165 (55.7%)/3.4%	131 (44.3%)/2.5%	0.008
2012	9771	4693 (48.0%)	5078 (51.9%)	426/4.4%	232 (54.5%)/4.9%	194 (45.5%)/3.8%	0.007
2013	10,289	4896 (47.6%)	5393 (52.4%)	537/5.2%	273 (50.8%)/5.6%	264 (49.2%)/4.9%	0.121
2014	9850	4707 (47.8%)	5143 (52.2%)	806/8.2%	417 (51.8%)/8.9%	389 (48.3%)/7.6%	0.019
2015	9521	4631 (48.6%)	4890 (51.4%)	887 (9.3%)	448 (50.5%)/9.7%	439 (49.5%)/8.9%	0.243
All	68,987	33,107 (48%)	35,880 (52%)	3282 (4.7%)	1690 (51.9%)/5.1%	1565 (48.1%)/4.5%	P < 0.001

^a We considered only hospitalizations with I63 diagnosis where sex of the patient was known (no data about sex in 416 patients, including 27 patients treated with rtPA).
^b Chi² test (Bonferroni correction – significance level set at 0.007).

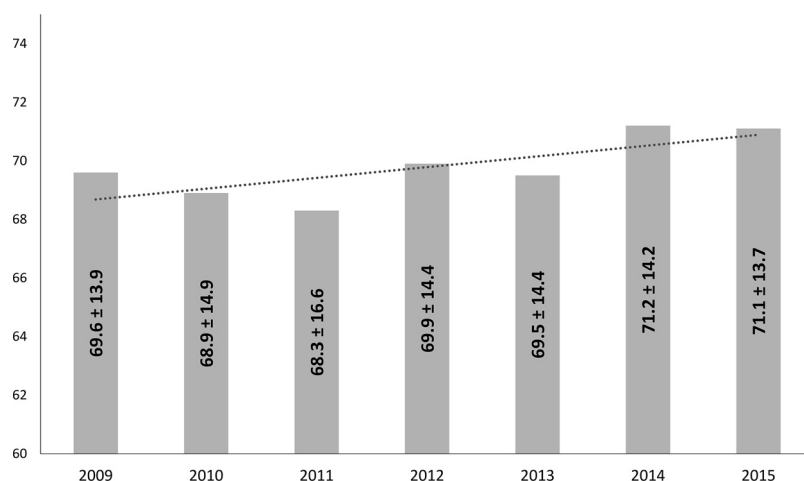


Fig. 2 – Mean age of patients with ischemic stroke (I63) treated with intravenous thrombolytic therapy (rt-PA) in hospitals of the Silesian Province between 2009 and 2015. Data presented as mean ± SD (Trend test Jonckheere-Terpstra; $P < 0.001$).

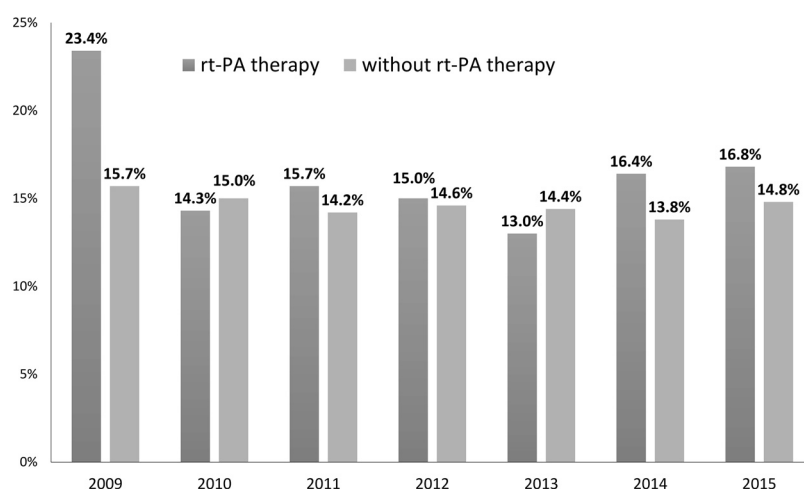


Fig. 3 – In-hospital mortality in patients treated with intravenous thrombolytic therapy (rt-PA) compared to in-hospital mortality of patients untreated with rt-PA in the Silesian Province between 2009 and 2015 (test χ^2 with the Bonferroni correction – significance level set at 0.007: 2009: $P = 0.031$; 2010: $P = 0.771$; 2011: $P = 0.485$; 2012: $P = 0.799$; 2013: $P = 0.395$; 2014: $P = 0.048$; 2015: $P = 0.104$).

registries but the national general estimates only ranged from 3% to 5% in the last decade [14–18]. It should be stressed that also in some Silesian hospitals (mostly university) the percentage of rtPA treated patients has reached almost 20% in the recent years [6]. However, there are still neurological departments in the Silesian Province where intravenous thrombolysis is very rarely used.

The main factor that limits the availability of thrombolytic therapy, not only in the Silesian Province, is a short period of time (small time windows) when the drug can be administered – 4.5 h (initially 3 h) from the occurrence of stroke symptoms [3–5]. The social awareness of stroke symptoms and available treatment options is still insufficient, and as a result many patients are admitted to hospital when it is already too late [19].

We found that the in-hospital mortality in patients treated and untreated with rtPA was similar, which is consistent with other reports [18]. The results from the SITS-ISTR and VISTA

combined ($n = 29,500$) revealed a reduction of death in patients receiving alteplase in a prospective observation which lasted longer (3 months) compared to our study. [18]

In our study the percentage of men treated with rtPA was higher than the similar percentage of women, which is consistent with other studies [20]. But the in-hospital mortality was similar both in thrombolized women and men. However, some other researchers reported that women achieved better results after intravenous thrombolysis [20]. In our study we were not able to establish the functional status but some authors reported that a 3-month functional outcome was significantly better in women compared to men [21–23]. Contrary to the above studies, other authors described a reverse situation – the outcome in women after rtPA was worse than in men [24].

Our study revealed that the in-hospital mortality in patients with cardioembolic etiology of IS was lower in subjects treated with rtPA (16.9%) than in those untreated

Table 4 – In-hospital mortality in patients with ischemic stroke (I63) treated (N = 3282) and untreated (N = 66,121) with rtPA according to the etiology of stroke. Data presented as N (%).

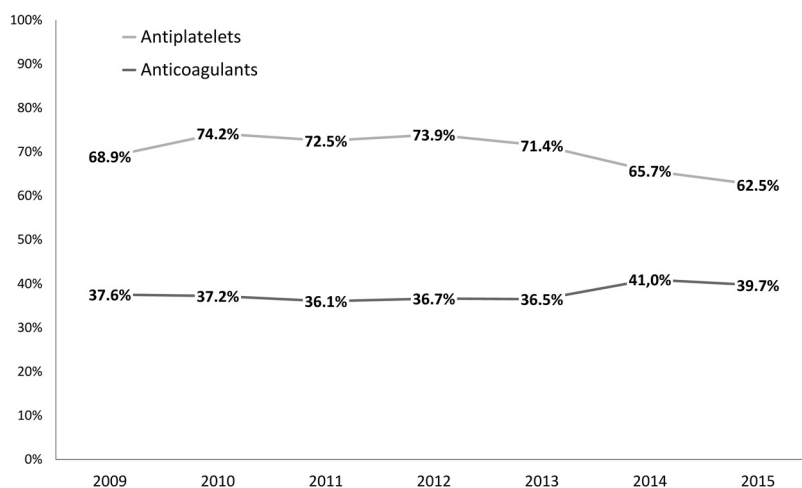
Etiology of ischemic stroke (TOAST)	Patients treated with rtPA	In-hospital mortality in patients treated with rtPA	Patients untreated with rtPA	In-hospital mortality in patients untreated with rtPA	P ^a In-hospital mortality in treated vs untreated with rtPA
Large-artery atherosclerosis	1127 (34.4%)	178 (15.8%)	23,927 (36.2%)	3421 (14.3%)	0.161
Cardioembolism	884 (26.9%)	149 (16.9%)	12,089 (18.3%)	2351 (19.5%)	0.050
Small artery occlusion (lacunar)	234 (7.1%)	21 (8.9%)	6512 (9.9%)	345 (5.3%)	0.015
Other determined etiology	45 (1.4%)	4 (8.9%)	1220 (1.8%)	145 (11.9%)	0.540
Undetermined etiology	992 (30.2%)	162 (16.3%)	22,373 (33.8%)	3563 (15.9%)	0.733
Total	3282 (100%)	514 (15.7%)	66,121 (100%)	9825 (14.9%)	0.210

^a Chi² test.

Table 5 – Secondary stroke prevention in patients with ischemic stroke (I63) in the Silesian Province between 2009 and 2015. Data presented as N (%).

Year	Oral antiplatelet drugs	Oral anticoagulant drugs	Antihypertensive drugs	Direction for vascular intervention due to artery stenosis ^b
2009	7303 (78.7%)	2194 (23.6%)	7095 (76.5%)	202 (2.1%)
2010	8383 (83.3%)	2650 (26.3%)	7939 (78.9%)	350 (3.4%)
2011	8535 (83.4%)	2608 (25.5%)	8233 (80.5%)	315 (3.0%)
2012	8655 (84.9%)	2593 (25.4%)	8193 (80.4%)	379 (3.7%)
2013	8682 (84.3%)	2301 (22.3%)	8331 (80.9%)	344 (3.3%)
2014	8248 (83.7%)	1965 (19.9%)	8187 (83.1%)	344 (3.3%)
2015	7830 (82.2%)	1888 (19.8%)	7993 (83.9%)	326 (3.4%)
All	57,636 (83.0%)	16,199 (23.3%)	55,971 (80.6%)	2260 (3.2%)
P ^a	<0.001	<0.001	<0.001	<0.001

^a Trend test Cochran–Armitage.
^b Endarterectomy or angioplasty of cervical artery.

**Fig. 4 – Secondary stroke prevention in patients with ischemic stroke (I63) of cardioembolic etiology. Data presented as percentage of patients with ischemic stroke after discharge from hospital receiving the given drug (Trend test Cochran–Armitage for antiplatelets $P < 0.001$; for oral anticoagulants $P = 0.014$).**

(19.5%) ($P = 0.05$). Cardioembolic strokes are usually associated with a more severe neurological impairment and higher mortality [20,25]. However, fibrin-rich and smaller volume embolic clots, often observed in cardioembolism, might be

relatively better for recanalization after intravenous thrombolysis and it might be the reason why patients with cardioembolic etiology of IS benefit more from the rtPA treatment than patients with large artery atherosclerosis.

Additionally, our study revealed that the vast majority of patients with IS – regardless of its etiology (atherosclerosis or cardioembolic) – had antiplatelet drugs prescribed as secondary stroke prevention (in 2009 – 78.7%; in 2015 – 82.2%). However, the number of patients with cardioembolic stroke receiving anticoagulants gradually increased over years (2009 – 37.6%, 2015 – 39.7%) with concomitant decrease in patients treated with antiplatelets (2009 – 68.9%, 2015 – 62.5%).

The number of Silesian patients after IS receiving secondary pharmacological stroke prevention seemed to be high, when compared to the results from previous Polish studies (e.g. multicenter, population-based PolSenior study conducted between 2008 and 2010). In the PolSenior study ($n = 5696$), among 426 subjects with a history of a previous stroke, 261 people (61.3%) used at least one drug as a secondary prevention; oral antiplatelets were regularly used by 237 people (55.6%), and oral anticoagulants – by 25 people (5.9%). Also the number of PolSenior patients with IS and atrial fibrillation receiving oral anticoagulants was much lower than in our study – 20% [26].

However, in other European countries many more patients have been instructed on stroke prevention. In the PREFER in AF registry (Prevention of Thromboembolic Events – European Registry in Atrial Fibrillation) the authors collected data from several European countries (Austria, France, Germany, Italy, Spain, Switzerland, and the UK) [27]. They described that oral anticoagulants were used by 82.3% of all subjects with atrial fibrillation and by 84% of patients with at least 1 point in CHA₂DS₂VASc. Anticoagulants were the least frequently used in Italy (71%), whereas in France they were the most often administered (90%) [27].

Other studies also showed similar trends [28,29]. GARFIELD-AF registry (an ongoing prospective, multicenter, international registry of patients newly diagnosed AF) demonstrated that preventive therapy with oral anticoagulants was generally higher in other European countries (41.9%–55.5%) than in Poland (36.9%–41.7%).

Our study may help in the implementation of proper health education initiatives in the Silesian Province, thus contributing to better health of the society. People should be instructed how to detect symptoms of stroke and call for help in a timely manner, as the rate of patients treated with intravenous thrombolysis is still relatively low despite the continuous increase.

5. Conclusions

1. The frequency of application of diagnostic methods in stroke (CT/MRI, USG) has still been increasing since 2009, particularly in the case of ultrasound of extra- and or intracranial arteries.
2. The rate of patients treated with rtPA in the Silesian Province has been continuously growing since 2009 although it is still too low. Statistically significantly more men were treated with rtPA than women.
3. The in-hospital mortality in patients receiving intravenous thrombolytic therapy is similar to those who were not treated with rtPA.

4. As secondary stroke prevention, antiplatelet drugs were used most often, also for strokes of cardioembolic etiology. However, the number of patients receiving oral anticoagulants has still been growing.

6. Limitations of the study

There are a few limitations to this study. First, in our paper we analyzed only stroke-related hospitalizations but in Poland almost all patients with AS are admitted to hospitals. It is also possible that in the case of some ASs the questionnaires might not have been sent to the NHF. Third, we only analyzed the questionnaire data and only information given in them. As a result, some human errors could have been made.

Contribution statement

BLR and AST contributed to this study design, data interpretation, and manuscript draft. MS and MG performed statistical analysis. ALS and MGa contributed to data interpretation, and literature review. All authors edited and approved the final version of the manuscript.

Conflict of interest

None declared.

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