PROBLEMS OF CARDIOEMBOLIC STROKE PRIMARY AND SECONDARY PREVENTION IN THE LATVIAN POPULATION

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Atrial fibrillation is one of major risk factors of cerebral infarction. The use of oral anticoagulants is the only evidence-based method of reducing the risk of cardioembolic accidents. The guidelines of oral anticoagulant admission and usage have been available since 2012. The results of this study show that of 550 stroke patients that were admitted to Pauls Stradiņš Clinical University Hospital, Rīga, Latvia, from 1 January 2014 until 1 July 2014, atrial fibrillation was diagnosed in 247 (45%) cases, and of these patients, only 8.5% used oral anticoagulants before the onset of stroke. Six months after discharge of 111 (44.9%) stroke survivors, five (4.5%) used no secondary prevention medication, 27 (24.3%) used antiplatelet agents, 54 (48.6%) warfarin, and 25 (22.5%) used target specific oral anticoagulants (TSOACs). The mortality rate was significantly higher in the patient group that used no secondary prevention medication or antiplatelet agents compared to the patient group that used oral anticoagulants. The use of oral anticoagulants for primary stroke prevention in Latvia is insufficient. The mortality of cardioembolic stroke in 180 days is very high — 40.4%. Secondary prevention is essential to prevent recurrent cardioembolic accidents.

Key words: *atrial fibrillation, cardioembolic stroke, primary stroke prevention, secondary stroke prevention.*

INTRODUCTION

Atrial fibrillation (AF) is the most common form of heart arrhythmias. Prevalence is about 1–2% in the general population with a tendency to increase in last 50 years. The prevalence tends to increase with age from 0.5% in 40–50 year-old patients to 5–17% in 80–85 year-old patients (Go *et al.*, 2001; Camm *et al.*, 2010; Stewart *et al.*, 2011; Camm, 2012). The possibility of developing AF at the age of 55 in the European population is 23.8% for men and 22.2% for women (Heeringa *et al.*, 2006). AF is associated with greater cardioembolic accident risk, such as cardioembolic stroke, left ventricle hypertrophy, chronic heart failure, which leads to lower quality of life and higher mortality rates (Kirchhof *et al.*, 2007). The use of oral anticoagulants decreases the risk of thromboembolic accidents in patients with non-valvular AF. To achieve effective cardioembolic accident prophylaxis, oral anticoagulants should be used regularly for prolonged period of time, which for most patients has proven to be difficult, considering the specific use of medication and possible side effects. The available oral anticoagulants in Latvia are the vitamin K antagonist (VKA) warfarin and target specific oral anticoagulants (TSOACs) — rivaroxaban, dabigatran and apixsaban.

Atrial fibrillation in one of the major risk factors of cerebral infarction and contributes to higher morbidity and mortality compared with non-AF-related strokes. Stroke etiology in patients with AF varies from 1–20% with a yearly average of 4.5% and mortality of 30%. Of all deaths associated with cardioembolism 80% are caused by cerebral infarction (Menke *et al.*, 2010; Furie *et al.*, 2012).

In 2012, the European society of cardiology (ESC) published the guidelines "2012 Focused Update of the ESC Guidelines for the Management of Atrial Fibrillation" for treatment of non-valvular atrial fibrillation, which recommended that patients with AF should be evaluated by the CHA_2DS_2-VASc score (Table 1). (Lane *et al.*, 2013). Patients with a CHA_2DS_2-VASc score of 2 or above should be

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ASSESSMENT OF STROKE (CHA$_2$DS$_2$-VASC) AND BLEEDING RISK (HAS-BLED) IN ATRIAL FIBRILLATION PATIENTS

CHA$_2$DS$_2$-VASc	Score	HAS-BLED	Score
Congestive heart failure	1	Hypertension (systolic blood pressure > 160 mm Hg)	1
Hypertension	1	Abnormal renal and liver function[*] (1 point each)	1 or 2
Age ≥ 75 y	2	Stroke	1
Diabetes mellitus	1	Bleeding tendency/ predisposition[*]	1
Stroke/TIA/TE	2	Labile INRs (if on warfarin)[*]	1
Vascular disease (prior MI, PAD, or aortic plaque)	1	Elderly (eg, age > 65 y)	1
		Drugs or alcohol (1 point each)[*]	1 or 2
Aged 65 to 74 y	1		
Sex category (ie, female sex)	1		
Maximum score	9	Maximum score	9

TIA, transient ischemic attack; TE, thromboembolic; INR, international normalized ratio; MI, myocardial infarction; PAD, peripheral artery disease.

*Abnormal renal function is classified as the presence of chronic dialysis, renal transplantation, or serum creatinine ≥ 200 mmol/L. Abnormal liver function is defined as chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (bilirubin 2 to 3 times the upper limit of normal, in association with aspartate aminotransferase/ alanine aminotransferase/alkaline phosphatase 3 times the upper limit normal, etc), history of bleeding or predisposition (anemia), labile INR (i. e, time in therapeutic range < 60%), concomitant antiplatelets or nonsteroidal anti-inflammatory drugs, or excess alcohol (Lane *et al.,* 2013).

offered anticoagulation. In patients with a CHA$_2$DS$_2$-VASc score of 1, consider anticoagulation and base any decision to treat or not treat on patient preference after balancing the benefits with risks of treatment. As a second step, HAS-BLED (Table 1) should be used to assess bleeding risk, with the aim of modifying this risk through addressing individual risk factors that can be altered (Lane *et al.,* 2013). HAS-BLED should not be used to decide whether to offer anticoagulation in someone with a CHA$_2$DS$_2$-VASc score of 2 or above, but to consider its use to balance the benefits of anticoagulation in patients with a CHA$_2$DS$_2$-VASc score of 1. On a regular basis, and at least once a year, the risk status of patients with AF should be re-evaluated depending on change in risk factors (change of age category, new hypertension, etc) (Camm *et al.*, 2012; Hobbs *et al.*, 2012).

The goal of our study was to evaluate the use of oral anticoagulants for primary and secondary stroke prevention in patients with atrial fibrillation.

MATERIALS AND METHODS

In the period between 1 January 2014 and 1 July 2014, in Latvia, 550 stroke patients were treated in the Clinic of Neurology, Pauls Stradiņš Clinical University Hospital, Rīga. Atrial fibrillation was diagnosed in 247 (45%) cases.

MODIFIED RANKIN SCALE (MRS)

Level	Description
0	No symptoms
1	No significant disability, despite symptoms; able to perform all usual duties and activities
2	Slight disability; unable to perform all previous activities but able to look after own affairs without assistance
3	Moderate disability; requires some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent, and requires constant nursing care and attention
6	Exitus letalis

Patients with haemorrhagic stroke, subarachnoid haemorrhage, or valvular AF were excluded from the study. Thus, a total of 247 patients were included in the data analysis. Average age of studied patients was 76.3 years, with range from 37 to 99. Information was collected about the use of medication. The CHA$_2$DS$_2$-VASc score (Table 1) was calculated before the onset of stroke (Lane *et al.*, 2013).

Modified Rankin's score (Table 2) was calculated on discharge from the hospital and 180 days after discharge, to assess functional outcome of patients (Sulter *et al.,* 1999).

Stroke survivors who were discharged from hospital were divided in four groups based on medication that was used for secondary prevention of stroke. Prescriptions for oral anticoagulants within a time frame of 180 days after discharge were used to determine therapeutic management for secondary stroke prevention. Standardised questions were asked about patient abilities and use of prescribed medication.

The data were analyzed using Microsoft Excel and SPSS. Absolute and relative frequencies were calculated based on cross-tables. Normal distribution of variables was tested using a Kolmogorov-Smirnof Test.

This study was approved by the local ethical board of Rīga Stradiņš University, Rīga, Latvia). Verbal consent was asked when contacting patients or their relatives by phone.

RESULTS

The CDA2DS2-VASc score (n = 247) was determined before the onset of stroke using non-parametric tests. The calculated median was 4 and mode was 4.

Antithrombotics use in primary stroke prevention was inappropriate. Before the onset of stroke, 127 (51.4%) patients had not used any antithrombotic medication, 99 (40.1%) used antiplatelet agents, 20 (8.1%) warfarin, and one (0.4%) used TSOACs (Fig. 1).

In-hospital mortality was 11% and 219 (89%) patients were discharged from hospital. In 12 (5.5%) patients no anti-
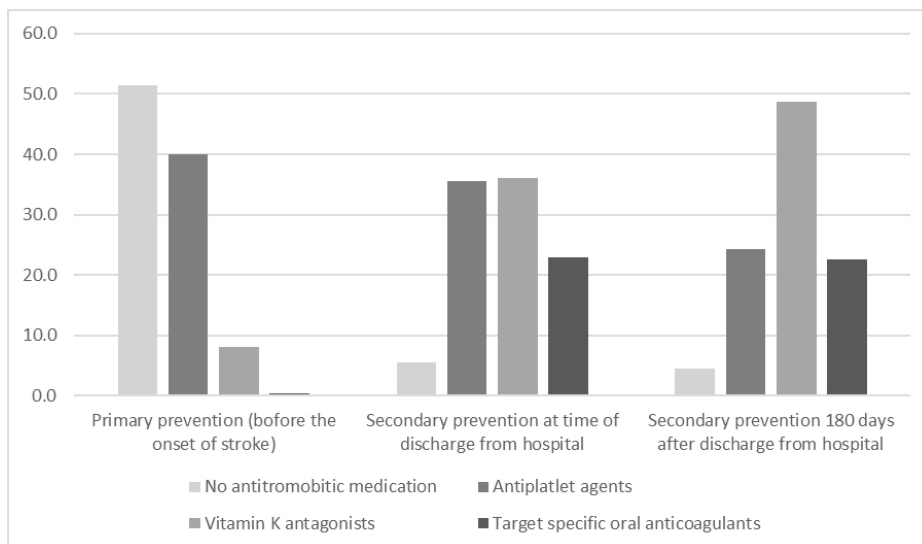
Fig. 1. The use of antithrombotic medication in different periods of the study.
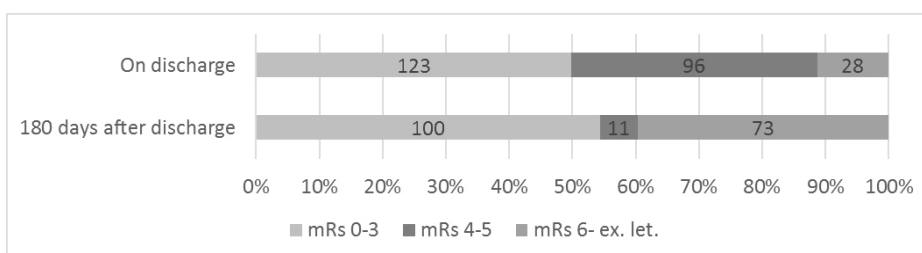

Fig. 2. Modified Rankin's scale at time of discharge from hospital and 180 days after discharge.

thrombotic therapy was prescribed for secondary prevention due to contraindications, 78 (25.6%) patients were discharged on antiplatelet agents, 79 (36.1%) on warfarin and the remaining 50 patients (22.8%) on TSOACs.

The Modified Rankin's score (mRs) was calculated at the time of discharge from hospital. A score of 1–3 was considered a satisfactorily outcome. At time of discharge 123 (49.8%) patients had satisfactory functional outcome (mRs 0–3), 96 (38.9%) had severe disability (mRs 4–5) and 28 (11.7%) had died in hospital. In the period up to 180 days after discharge, 100 (54.3%) patients had satisfactory outcome (mRs 0–3), 11 (5.9%) had severe disability (mRs 4–5) and 73 (39.8%) patients had died (Fig. 2).

The mortality rate in 180 days was as high as 40.4%. The most common causes of death were somatic complications due to severe disability and recurrent cardiovascular accidents. The mortality rate after 180 days in patients using no secondary prevention antithrombotic medication (67%) or antiplatelet agents (66%) was significantly higher than in the patient groups using warfarin (20%) or TSOACs (26%) ($p < 0.05$).

In the period of 180 days after discharge a change of secondary prophylaxis was documented. In the patient group for which secondary prophylaxis had not yet started, 75% began using antiplatelet agents and 25% warfarin. In the patients who were discharged using antiplatelet agents, 52% were still using antiplatelet agents, 33% ambulatory started using warfarin and 15% TSOACs, mainly because of significant neurological deficit and age. In the discharged patient group using warfarin, 5% stopped using any anti-

thrombotic medication, 15% started using antiplatelet agents, 63% were still using warfarin, and 17% had started using TSOACs. Patients who changed medication to TSOACs admitted that they experienced problems controlling INR. In the patient group that was discharged using NOACs, 9% stopped using any antithrombotic medication, without consulting a professional, 15% started using antiplatelet agents after consulting with a general practitioner, 38% were still using TSOACs, and 38% changed medication to warfarin, mainly because of financial aspects (Fig. 3).

Our study showed that 180 days after discharge, of 67 patients taking VKA, in 70.1% therapeutical anticoagulation (INR≥2.0) was observed, 22.4% had subtherapeutic INR (< 2.0) and 7.5% were not controlling INR (Table 3).

DISCUSSION

Primary cardioembolic stroke prevention in Latvia is insufficient. According to ESC guidelines, oral anticoagulants should be used if the CHA_2DS_2-VASc score is 1 for males and 2 for females. Median CHA_2DS_2-VASc was 4 and mode was 4. In our study group, 91.5% patients were using

Table 3

INTERNATIONAL NORMALISED RATIO (INR) IN 67 PATIENTS USING WARFARIN AT 180 DAYS AFTER DISCHARGE

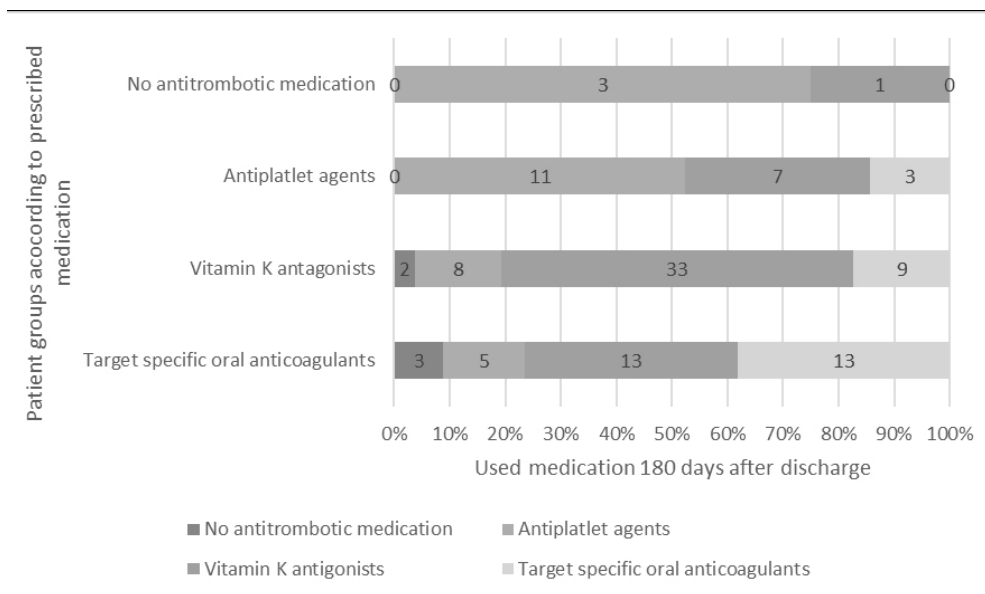| INR	n = 67	%
2.0–3.0	47	70.1
< 2.0	15	22.4
not measured	5	7.5

Fig. 3. The change of antithrombotic medication 180 days after discharge in different patient groups.

inadequate medication or were not using any preventive antithrombotic medication. (Camm *et al.*, 2012). According to the recent study by Friberg *et al.* (2015), patients with a CHA_2DS_2-VASc score of 1 are not required to use oral anticoagulants. According to European guidelines, women with a CHA_2DS_2-VASc score of 1 should not be given anticoagulation therapy on the basis of their sex alone. The risk in men and women with a CHA_2DS_2-VASc score of 1 is considered to be low and this group is not expected to benefit from anticoagulation therapy. Among men with a CHA_2DS_2-VASc score of 1, the annual stroke risk ranged between 0.5% and 0.7%, which indicates low risk for cerebral infarction (Friberg *et al.*, 2015). Overall, oral anticoagulant use was more common among low-risk patients than among patients with a CHA_2DS_2-VASc score ≥ 3 (Friberg *et al.*, 2015). European guidelines favour oral anticoagulant treatment at CHA_2DS_2-VASc scores of 1. The newly adapted US guidelines recommend treatment from a score of 2 and higher, with an option to treat cases with score 1 with oral anticoagulants, antiplatelet agents, or no medication (Friberg *et al.*, 2015).

In a Canadian study (Gladstone *et al.*, 2009) that included 597 stroke patients with previously diagnosed atrial fibrillation, 40% used anticoagulants, 30% used antiplatelet agents and 30% had not used antithrombotic medication before the onset of stroke. Of those taking warfarin, 75% had a subtherapeutic internationally accepted normalised ratio (INR) range (< 2.0) at the time of stroke admission. Only 10% of the patients with acute stroke with known atrial fibrillation were assessed with therapeutical anticoagulation (INR ≥ 2.0) at admission. (Gladstone *et al.*, 2009). Our study did not specify if a patient had previously diagnosed atrial fibrillation. Our results showed that 51.4% of patients had not used any antithrombotic medication, 40.1% of patients used antiplatelet agents, and use of anticoagulants was significantly less frequent — warfarin in 8.1% of cases and TSOACs in 0.4% of cases. In both studies, treatment of more than 90% of patients was inadequate for successful coagulation. Our study showed that 180 days after discharge

from the neurologic department, treatment of 70.1% of patients using VKA was considered as resulting in therapeutical anticoagulation (INR ≥ 2.0), 7.5% were not controlling their INR, and 22.4% had subtherapeutic INR (< 2.0).

Of 219 patients discharged from the hospital, in 5.5% antithrombotic medication was not recommended due to contraindications, 25.6% were discharged on antiplatelet agents, 36.1% on warfarin, and 22.8% on TSOACs. The reasons for avoiding oral anticoagulants in 31.1% of cases were severe neurologic deficit, noncompliance of patient or their relative, increased age and haemorrhagic transformation of cerebral infarction. A similar study conducted in Germany included 6261 patients after transistor ischemic attack or ischemic stroke, who had been diagnosed with atrial fibrillation (Tanislav *et al.*, 2014). They reported 45% of patients had been prescribed oral anticoagulants after discharge. According to our data, oral anticoagulants were prescribed more frequently (in 58.9% of patients), but even this proportion is insufficient. The use of antiplatelet agents to prevent cerebral infarction in patients with atrial fibrillation has been documented as ineffective (Camm *et al.*, 2010). Both studies show that antiplatelet agents are prescribed far too often in Latvia and in other countries. A German study reported that factors associated with reluctance in prescribing anticoagulants were increasing age, female sex, treatment at a non-neurological department, worsening disability, and dementia (Tanislav *et al.*, 2014).

In the United Kingdom, Moren *et al.* (2014) embarked on a retrospective case review of patients with first ever stroke or TIA, who had possibly preventable or curable disease before the onset. The study considered four categories of missed opportunities for stroke/TIA prevention are: untreated high blood pressure in patients eligible for treatment (either blood pressure ≥ 160/100 or ≥ 140/90 mm Hg in patients at high cardiovascular disease (CVD) risk); patients with atrial fibrillation with high stroke risk and no anticoagulant therapy; and no lipid modifying drug therapy prescribed in patients at high CVD risk or with familial hypercholesterolemia (Moren *et al.*, 2014). This study will

provide adequate data about primary stroke prevention for patients with AF in the UK, and will identify reasons for not taking oral anticoagulants in patients with AF.

Some studies suggest that usage of oral anticoagulants for elderly patients to prevent embolic accidents does not outweigh the risk for bleeding (Friberg *et al.*, 2015). In a study by Lip *et al.* (2014), 4130 elderly patients in France that were using VKA were compared to a group of patients who were not taking any antithrombotic therapy. A conclusion was made that elderly patients with AF have a higher risk of stroke and bleeding, but that the benefits of VKA therapy for stroke/thromboembolism or mortality were present regardless of increasing age. (Lip *et al.*, 2014). In our study, 94 (38%) patients had age 80 years or more. Of these patients, 11 (11.7%) died in hospital. Of 68 patients contacted, 21 (30.8%) had died in 90 days after leaving hospital and 42 (61.7%) had died within 180 days after discharge.

Of 83 patients discharged, 9 (10.8%) had no preventive antithrombotic medication prescribed, for 41 (49.3%) patients antiplatelet agents were prescribed, 18 (21.6%) VKA and 15 (18.0%) used TSOACs.

In our study in-hospital mortality was 11%, which is relatively high, and mortality at 90 days (27.1%) and 180 days (54.3%) were very high. High mortality was associated with severe disability due to stroke, poor compliance using prescribed medication and mistakes in the organization of national health care. In other European countries, for stroke patients, in-hospital mortality has been reported to be about 12.1%, the mortality rate at 30 days after onset in Switzerland was reported to be 13% (Nedeltchev *et al.*, 2010) and mortality at 90 days did not exceed 15.7% (Ois *et al.*, 2007).

In Latvia, primary and secondary prevention of cardioembolic stroke is insufficient and mortality in 90 and 180 days after stroke is catastrophically high. It is essential to raise patient awareness about cardioembolic stroke and its prevention, and to ensure that physicians prescribe oral anticoagulants for patients with atrial fibrillation and high risk for cerebral infarction, according to published guidelines (Camm *et al.*, 2012).

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KARDIOEMBOLISKA CEREBRĀLA INFARKTA PRIMĀRĀS UN SEKUNDĀRĀS PROFILAKSES PROBLĒMAS LATVIJĀ

Pētījuma mērķis bija izvērtēt perorālo antikoagulantu lietošanu cerebrālā infarkta pacientiem ar ātriju fibrilāciju. Ātriju fibrilācija ir viens no biežākajiem cerebrāla infarkta riska faktoriem. Perorālo antikoagulantu lietošana ir vienīgā uz pierādījumiem balstītā metode kardioembolisku notikumu riska samazināšanai. Perorālo antikoagulantu nozīmēšanas vadlīnijas ir pieejamas kopš 2012. gada, diemžēl mūsu pētījumā iegūtie dati liecina, ka no 550 pacientiem, kas ārstēti Paula Stradiņa Klīniskajā universitātes slimnīcā Neiroloģijas nodaļā no 2014. gada 1. janvāra līdz 2014. gada 1 jūlijam, 247 (45%) diagnosticēta mirdzaritmija. Tikai 8,5% pacientu pirms akūtā notikuma lietojuši perorālos antikoagulantus. Mirstība stacionārā bijusi relatīvi augsta — 11%. Savukārt mirstība 180 dienas pēc izrakstīšanās no slimnīcas šokējoši augsta — 40,4%. Kā galvenie nāves iemesli jāmin komplikācijas dziļā neiroloģiskā deficīta dēļ un atkārtoti kardioemboliski notikumi. Sešus mēnešus pēc izrakstīšanās no stacionāra, izdzīvojuši 111 (44,9%) pacientu, no tiem 5 (4,5%) nelieto nekādus antitrombotiskus medikamentus, 27 (24,3%) lieto antiagregantus, 54 (48,6%) vitamīna K antagonistus (*warfarin*) un 25 (24,3%) jaunos perorālos antikoagulantus. Mirstība bijusi augstāka pacientiem, kuri lietojuši antiagregantus vai nav lietojuši nekādus antirombotiskus medikamentus, salīdzinot ar pacientiem, kuri lietojuši perorālos antikoagulantus. Latvijā perorālo antikoagulantu lietošana primāra insulta profilaksei ir nepietiekoša. Ņemot vērā augsto kardioembolisko insultu mirstību 180 dienu laikā, ir nepieciešams informēt pacientus, kā arī medicīnas pārstāvjus par šo saslimšanu, apzināties riska faktorus un lietot atbilstošus medikamentus, lai samazinātu kardioembolisku notikumu risku.