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Analysis of oral anticoagulant treatment in patients with non-valvular atrial fibrillation: a population-based study in Estonia

Master's Thesis

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TALLINNA TEHNIKAÜLIKOOL

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Suukaudsete antikoagulantide kasutamine virvendusarütmiaga patsientide raviks Eestis

Magistritöö

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Tallinn 2018

I declare herewith, that this Master's Thesis is my own original work. All the used materials, references to the literature and the work of others have been clearly referenced. Current work has not been submitted for any other academic degree.

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Abstract

Background: Stroke is the major cause of death and disability worldwide. Atrial fibrillation (AF) is one of the main risk factors for stroke. AF prevalence in population has increased remarkably in recent years and the increase is predicted to continue due to ageing of the population. Oral anticoagulant (OAC) therapy is the key for stroke prevention in patients with AF.

Aim: To analyze the prevalence and trends of AF-related stroke in Estonia and to study OAC usage and side effects. *Method:* Nationwide retrospective registries based study in Estonia from January 1, 2010 to December 31, 2016. *Data collection:* Data from Estonian Health Insurance Fund, Health Statistics and Health Research database, pharmacy database and Statistics Estonia database was inquired. *Results:* Prevalence of AF was 4.2% in Estonia in 2010 - 2016. Prevalence increased from 1.1% in 2010 to 2.1% in 2016. 86% of AF patients had OAC treatment in year 2016 compared to 41% in 2010. Stroke prevalence in AF diagnosed patients decreased from 4.2% to 3.1% and side effects prevalence from 4.8% to 2.8% in a timeframe 2010 - 2016. *Conclusion:* Prevalence of AF has nearly doubled in Estonian population from 2010 to 2016. OAC treatment has increased remarkably in recent years. Prevalence of warfarin-related complications however has decreased. The cost of OAC treatments has increased significantly.

Thesis is written in English and is 55 pages long, including 6 chapters, 19 figures and 8 tables.

Annotatsioon

Maailma Terviseorganisatsiooni andmetel on insult surmapõhjuste hulgas teisel ja raske puude põhjustajana kolmandal kohal. Üheks suurimaks riskifaktoriks isheemilisele insuldile on kodade virvendusarütmia (AF). Kodade virvendusarütmia on südame rütmihäire, mille hinnanguline esinemissagedus üldrahvastikus on 1 – 2% (Andrade *et al*, 2014). Kuna virvendusarütmia esinemissagedus suureneb vanusega, siis lähiaastatel on oodata patsientide märkimisväärset kasvu rahvastiku vananemise tõttu. Insuldi ennetamiseks on virvendusarütmiaga patsientidel efektiivne vaid antikoagulantravi, kuid see ravi on ülemaailmselt alakasutatud.

Töö eesmärk: Analüüsida kodade virvendusarütmia esinemissagedust ja trende Eestis. Uurida suukaudsete antikoagulantide kasutamist virvendusarütmiaga patsientidel ja analüüsida ravi mõju tüsistuste esinemisele.

Meetod: Teostati üleriigiline retrospektiivne registripõhine uuring ajavahemikus 01.01.2010 – 31.12.2016. Andmeallikatena kasutati Eesti haigekassa (EHIF) mitteisikustatud andmeid, tervisestatistika ja terviseuuringute andmebaasi, apteegi andmebaasi ja Eesti statistika andmebaasi.

Tulemused: Kodade virvendusarütmia levimus on 4.2% 2010 - 2016. Levimus suurenes 1.1%-lt 2010 kuni 2.1%-le 2016. Insuldi levimus kodade virvendusarütmiaga patsientidel vähenes 4.2%-lt 3.1%-le. Antikoagulatsiooni kasutamine virvendusarütmiaga patsientidel näitas olulist suurenemist 41%-lt 2010 86%-le 2016 ja tüsistuste esinemine aga vähenemist 4.8%-lt 2.8%-le 2010 - 2016. Antikoagulantravi on muutunud oluliselt kallimaks.

Kokkuvõte: Kodade virvendusarütmia esinemissagedus on rahvastikus peaaegu kahekordistunud ajavahemikus 2010 – 2016. Samuti on oluliselt suurenenud virvendusarütmia ravi antikoagulantidega. Varfariinravil olevate patsientide tüsistuste teke on vähenenud. Uute antikoagulantide turuletulek on oluliselt suurendanud ravi maksumust.

Lõputöö on kirjutatud inglise keeles ja on 55 leheküljel, sisaldades 6 peatükki, 19 joonist ja 8 tabelit.

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Abbreviations

AF – atrial fibrillation

AHA – American Heart Association

b.i.d. or BID – twice a day

CHA_2DS_2-VASc – congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, and sex (female)

$CHADS_2$ – cardiac failure, hypertension, age ≥75, diabetes, stroke (doubled)

DDD – defined daily dose

DOAC – direct acting oral anticoagulant

EHIF – Estonian Health Insurance Fund

ESO – European Stroke Organization

ICD 10 – International Statistical Classification of Diseases and Related Health Problems (10th revision)

ICH – intracerebral hemorrhage

INR – international normalised ratio

ISTH – International Society on Thrombosis and Haemostasis

NOAC – novel oral anticoagulant

OAC – oral anticoagulant

PO – by mouth

qDay – once a day

VKA – vitamin K antagonist

1 Introduction

Stroke is the second leading cause of death and the third leading cause of disability in the world (Johnson *et al*, 2016). Therefore, stroke has caught attention by health authorities to undertake public health actions. According to the World Health Organization, 15 million people suffer from stroke worldwide each year, 5 million of them die and another 5 million are permanently disabled (*Stroke statistics*). Stroke prevention, effective management of stroke and accessible and high quality rehabilitation is a big challenge in any country all over the world. Guidelines provided by American Heart Association (AHA) and European Stroke Organization (ESO) help to align and improve the treatment of stroke. However, more importantly, it has to be emphasized that stroke can be prevented by using appropriate methods (*Eksperdid: Insuldi ravi on …* , 2017). One of the major risk factors for stroke is atrial fibrillation (AF).

AF is the most common cardiac rhythm disorder, occurring in 1 – 2% of the general population (Andrade *et al*, 2014). This figure is likely to increase in the next years due to the ageing of the population. As already mentioned, one of the most serious complications of AF is stroke. Unfortunately, stroke caused by AF is frequently either fatal or associated with remarkable permanent disability in the majority of patients (Wolf *et al*, 1991).

Increasing frequency of AF and severity of stroke caused by untreated AF is the major reason why both AF and stroke are important issues of public health policy. Also, consideration of stroke-related health care cost is important. The risk of death from AF-related stroke is twice higher and the cost of care is increased 1.5 times (Camm *et al*, 2010).

Stroke prevention is extremely important and adequate management of different risk factors is paramount. Although stroke prophylaxis is relatively standard for many patients, importantly, adequate stroke prevention strategies in AF needs totally different approach. In AF the risk of formation blood clots in the heart is very high. Blood clots can move to

brain blood vessels and cause occlusion, in other words – stroke. Anticoagulant therapy prevents blood clot formation (*Heart Rhythm Society*, 2016).

Anticoagulation therapy in AF as the only efficient prophylactic treatment to prevent strokes and is one of the most important health care quality indicators in Estonia (*Eesti haigekassa ravikvaliteedi raport*, 2017). Inclusion of anticoagulation treatment as a quality indicator demonstrates that specifically, prevention of AF-related strokes is one of the major health-related priorities to the state in order to improve the well-being of individuals and societies.

Anticoagulants, also called as blood thinners, interrupt the blood normal clotting (coagulation) process and prevent clot formation. Therefore, anticoagulants are highly effective for lowering the likelihood of stroke-related to AF. Anticoagulants target different parts of the coagulation cascade (cell proteins) so blood clots cannot form (*Heart Rhythm Society*, 2016). There are several oral anticoagulants (OAC) available to treat patients with AF. They are divided to OAC with warfarin sodium (vitamin K antagonists) and non-vitamin K antagonist OAC, by their ability to target different clotting factors (proteins, enzymes).

Primary prevention of stroke in patients with AF is based on identification of risk factors that have been incorporated into different scales ($CHADS_2$ or CHA_2DS_2-VASc) (Odum *et al*, 2012). Patients, who have no stroke risk factors (CHA_2DS_2-VASc score 0 in males or 1 in females) are considered 'low risk' and do not need any antithrombotic treatment. However, the only effective stroke prevention is with an oral anticoagulant if AF patients have ≥1 stroke risk factors (Lip, 2017). Importantly, stroke in history is already one risk factor indicating that all patients with AF after first stroke need anticoagulation.

To conclude, stroke prevention with anticoagulation is central in the management of patients with AF (Chao *et al*, 2016). Patients with AF have a five-fold risk of stroke (Wolf *et al*, 1991), and when they do have stroke it is frequently fatal or associated with substantial disability. It is important to provide effective stroke prevention to AF patients with ≥1 stroke risk factors according to CHA_2DS_2-VASc score (Lip, 2017). Effective stroke prevention in AF means only oral anticoagulants and standard treatment with aspirin is not recommended. Several analyses have shown that oral anticoagulants reduce AF-related stroke around 64% compared to 22% on aspirin therapy. Therefore, efficacy of

aspirin is comparable to placebo/control (Lip, 2012). Even more, it is pointed out that patients with AF who receive aspirin treatment may only attain harmful impact due to minimal or not effective stroke prevention, but have potential for dangerous side effects (major bleeding or intracranial hemorrhage) (*Aspirin still overprescribed …* , 2014).

Therefore, it is necessary to study what is the current situation in Estonia regarding the only one effective stroke prophylaxes for patients with AF.

Synthesis of data accessed from different public databases – Estonian Health Insurance Fund database, Health Statistics and Health Research database, database for pharmacy information and population statistics database was done.

Based on the data, prevalence of stroke, AF, AF-related strokes and the usage of oral anticoagulants, side effects and cost were evaluated.

Aim of my Master's Thesis is to analyze:

- the prevalence and trends of stroke, AF and AF-related strokes in Estonia
- the oral anticoagulant usage in Estonia in patients with AF
- the usage of different anticoagulants in Estonia
- side effects of anticoagulation in Estonia
- cost of anticoagulant treatments in Estonia

The thesis consists of three main parts. The first part gives an overview of background information relevant to the research topic. The second part defines the objectives, questions and research methodology. Third part provides results of the study, discussion and conclusions.

2 Background information

2.1 Ischemic stroke

Ischemic stroke is the most common accounting for 88% of all of strokes (*Stroke center*). Ischemic stroke occurs when a blood clot blocks blood vessel in the brain. When this happens, brain cells die and irreversible brain damage occurs if the vessel in not recanalized immediately. One of the major cause of ischemic stroke is irregular heartbeat due to AF.

2.2 Atrial fibrillation (AF)

Atrial fibrillation (AF) is a worldwide health care problem with an increasing incidence and prevalence (Chugh *et al*, 2014). Several studies have been conducted to evaluate the trends of AF in the population. Patients who had received an AF diagnosis during the previous 5 years were included in the population-based study in a region in Sweden with 1.56 million residents. All stroke events during 2010 were evaluated. The results demonstrated that AF is more common than expected, giving 2.5% of prevalence from the total population and 3.2% prevalence from the population aged ≥20 years (Figure 1) (Björck *et al*, 2013).

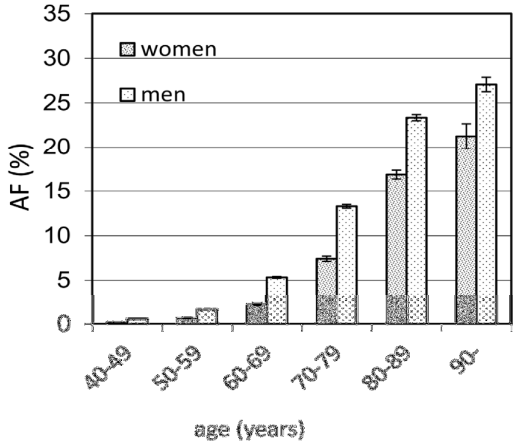

Figure 1. Prevalence of AF in the general population in relation to age and sex (Björck *et al*, 2013).

In addition, it was pointed out, that the risk of AF for stroke increases with age, showing that AF is more common among the elderly being diagnosed in at least 50% from 80 years of age (Figure 2).

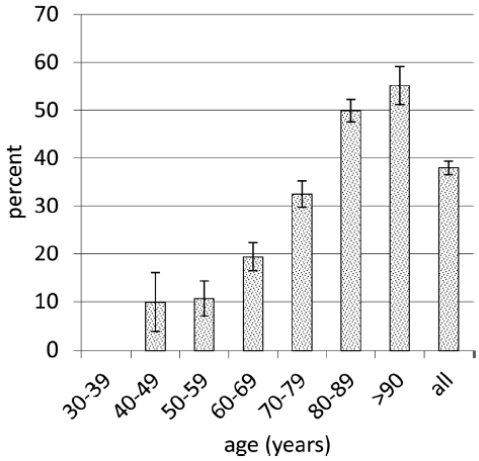

Figure 2. Prevalence of AF among 4565 acute ischemic stroke events (Björck *et al*, 2013).

AF patients have a 5-fold risk of stroke. Moreover, one in five of all strokes is attributed to AF (Camm *et al*, 2010). Stroke in AF is often fatal and results in long-term disability as well as high recurrence rate compared to patients with other causes of stroke.

2.3 Treatment – anticoagulation

Anticoagulant therapy is the key of stroke prevention in AF. Approximately 4500 strokes are diagnosed every year in Estonia making the rate of deaths from cardiovascular diseases 3.5 times higher than elsewhere in western Europe despite the management of stroke according to European and national stroke guidelines (Kõrv *et al*, 2013).

The risk of stroke and correspondingly appropriate prophylaxis of stroke in patients with AF is based on identification of risk score according to risk factors. $CHADS_2$ and CHA_2DS_2-VASc score tables have been developed in order to predict the risk of stroke (Figure 3) (*EPCCS*).

Condition	$CHADS_2$ score	Points	CHA_2DS_2-VASc score	Points
Congestive heart failure (or Left ventricular systolic dysfunction)	C	1	C	1
Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	H	1	H	1
Age ≥75 years	A	1	A_2	2
Diabetes Mellitus	D	1	D	1
Stroke or TIA or thromboembolism in history	S_2	2	S_2	2
Vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque)			V	1
Age 65–74 years			A	1
Sex category (i.e. female gender)			Sc	1

This table shows the components of the $CHADS_2$ (Gage et al., JAMA 2001 [36]) and CHA_2DS_2-VASc scores (Lip et al., Chest 2010 [41]) tools to assess stroke risk in patients with AF. These risk assessment tools help to determine who should and who should not receive anticoagulation. CHA_2DS_2-VASc improves risk stratification in patients with $CHADS_2$=0 or 1, and allows for identification of patients at truly low risk.

Figure 3. $CHADS_2$ vs CHA_2DS_2-VASc Score: Stroke Risk Assessment in AF (*EPCCS*).

Patients who have AF but no stroke risk factors according to CHA_2DS_2-VASc score (0 in males or 1 in females) are considered as 'low risk' and do not need any antithrombotic treatment, whether patients with ≥1 stroke risk factors need an oral anticoagulant for effective stroke prevention (Lip, 2017).

CHA_2DS_2-VASc score is an updated version of $CHADS_2$ score that gives a better stratification of low-risk patients. Additional conditions that help to assess stroke risk in patients with AF have been added to the table. It is important to stress that one of the new major risk factors is sex category, which gives an extra point for female patients. The sex-specific studies have shown that women with AF have higher risk of stroke and death than

men with AF (Reeves *et al*, 2008). Recently, it has been confirmed that the effective treatment of the AF especially in women is highly important to reduce the negative outcomes (Ko *et al*, 2017). Also, previous stroke is the most important risk factor in AF for stroke (Figure 3), followed by ≥ 75 years of age. All patients with AF and with prior to stroke need oral anticoagulant treatment to avoid new strokes.

Although critically important for preventing next stroke, anticoagulant therapy of discharged patients with ischemic stroke and AF ranged between 23.7% and 57.3% in different European countries (Wiedmann *et al*, 2015). Besides inadequate prescription of anticoagulants an important health care issue is treatment adherence. Nationwide follow-up study in Sweden showed, that after 2 years of stroke only 45 – 74% of the patients discharged with a specific preventive medication were still regularly using it (Glader *et al*, 2010).

It was brought out that during the first 2 years after stroke the use of secondary prevention treatments decreased drastically. The results were especially bad for warfarin that decreased to 45% (Figure 4).

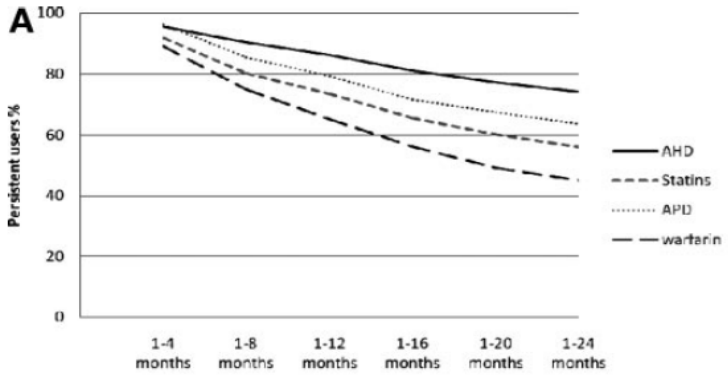

Figure 4. Proportion of stable users among patients prescribed with drugs (Glader *et al*, 2010).

In Estonia, anticoagulant therapy was prescribed during 30 days after the end of treatment bill for stroke invoiced for EHIF to 17 – 74% of AF-related ischemic stroke patients in regional and central hospitals and to 34% of patients in general hospitals in 2014 (*Eesti haigekassa ravikvaliteedi raport*, 2016), to 22 – 76% of patients in regional and central

hospitals and to 38% of patients in general hospitals in year 2015 (*Eesti haigekassa ravikvaliteedi raport*, 2017) (Figure 5).

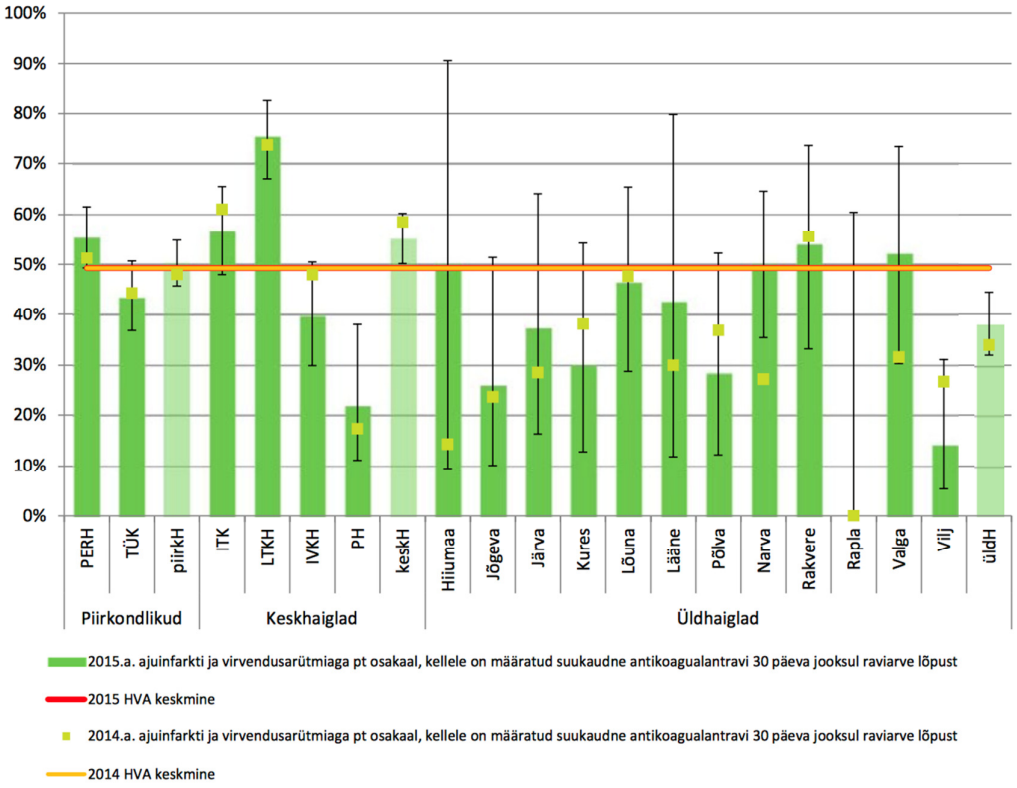

Figure 5. Proportion of patients with AF-related ischemic stroke, who had been assigned persistent (12 months) OAC treatment after 30 days after the end of treatment bill for EHIF (*Eesti haigekassa ravikvaliteedi raport*, 2017).

As seen in Figure 5 there has not been much improvement in the scope of treatment in two following years. Mean of OAC therapy implementation after 30 days from the end of treatment bill fo EHIF is around 50%. When comparing results from regional and central hospitals then majority of them are applying treatment moderately, only Pärnu hospital stands out with low level of prescriptions.

Since it is important to provide consistency of the treatment after the acute stroke (12 months after hospital treatment), results after 12 months and 1 day after hospitalization show that anticoagulant therapy was prescribed to 29 – 61% of patients in regional and

central hospitals and to 39% of patients in general hospitals in 2014 and to 48 – 66% of patients in regional and central hospitals and to 38% of patients in general hospitals in 2015 (Figure 6).

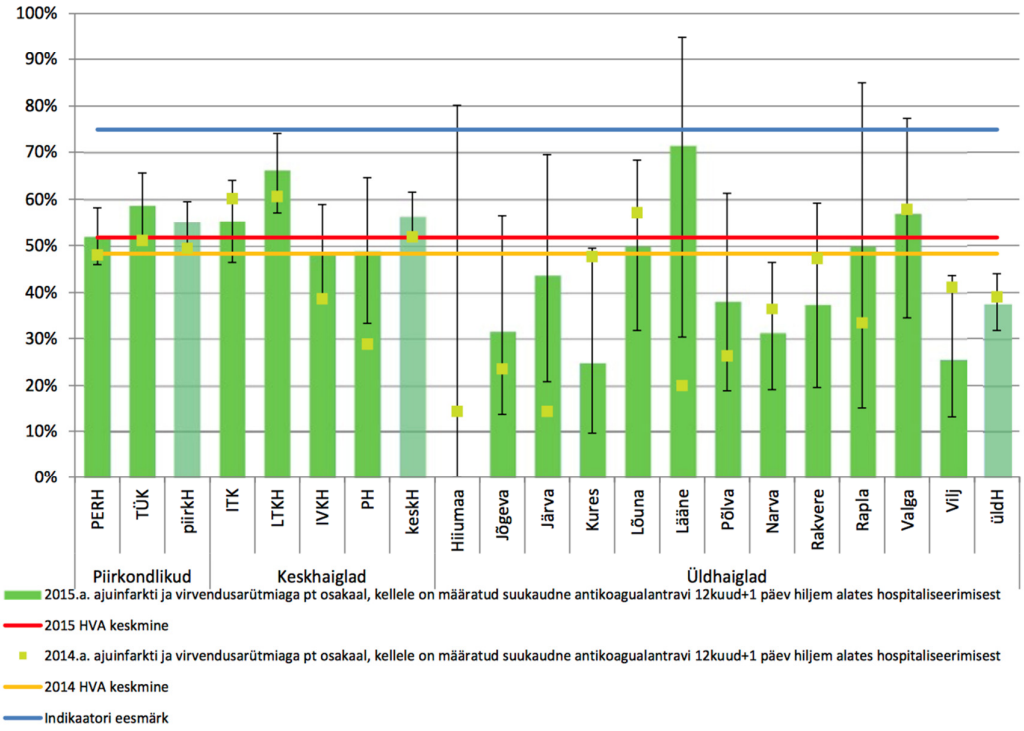

Figure 6. Proportion of patients with AF-related ischemic stroke, who had been assigned persistent OAC treatment after 12 months and 1 day after acute ischemic stroke (*Eesti haigekassa ravikvaliteedi raport*, 2017).

As seen on figure 6 there has been nearly 10 percent improvement in treatment in two following years. Mean of OAC therapy implementation after 12 months and 1 day after acute ischemic stroke has increased from 48% in 2014 to 52% in 2015 and much more uniform results from regional and central hospitals have been obtained.

These analysis show that patients receive less often anticoagulation than indicated in the AF-related stroke. Although, two consecutive studies in Estonia show that some improvement has been achieved. The goal for corresponding quality indicator (for 12 months and 1 day after hospitalization) is 75% in Estonia and 95% in Denmark (for 14 days after hospitalization) (*Eesti haigekassa ravikvaliteedi raport*, 2017).

It can be concluded based on the results from previous studies that effective measures to improve access and adherence to anticoagulant medications after stroke need to be developed.

2.4 Anticoagulants

There are several oral anticoagulants available to treat patients with AF. They are divided to OAC with warfarin sodium (vitamin K antagonists) and non-vitamin K antagonist OAC, by their ability to target different clotting factors (proteins, enzymes). Recently, the search for the best terminology for non-warfarin oral anticoagulants has gained attention. Originally term novel oral anticoagulant (NOAC) is recently not considered best term and DOAC (direct oral anticoagulants), TSOAC (target specific oral anticoagulants), NOAC (non-VKA oral anticoagulants) and non-VKA-OAC are all mentioned in recent literature. However, based on recommendations by the ISTH direct oral anticoagulants (DOAC) was chosen to be used in current thesis (Barnes *et al*, 2015).

2.4.1 Vitamin K antagonists - warfarin

Vitamin K antagonists interrupt the production of clotting proteins that rely on vitamin K for synthesis in the coagulation cascade (*Heart Rhythm Societ*y, 2016). Warfarin is a vitamin K antagonist and until recently it has been the only available oral anticoagulant. Warfarin's use in preventing stroke is supported by more than three decades of research. There have been a lot of studies showing the benefit for the patients with the treatment with warfarin and on the other hand, several times higher stroke incidence for the ones not having treatment at all (Björck *et al*, 2013; Azoulay *et al*, 2014).

Warfarin is highly efficacious in reducing the risk of stroke, but its effectiveness in clinical practice is challenged by variable dose response, need for frequent monitoring and dosage adjustment dependent on the INR (to keep it within the narrow therapeutic range of 2.0-3.0). Also, treatment complications, multiple food (dietary vitamin K intake) and drug

interactions and problems with adherence complicate the use (Hylek *et al*, 2014). Additionally, achievement of effective anticoagulation takes a long time (3-5 days) and is very individual (Little *et al*, 2012). On the other hand, if there is an emergency or a planned medical procedure, doctors can reverse warfarin treatment effects in order to normalize body's normal clotting abilities (*Heart Rhythm Society*, 2016). Importantly, warfarin is the most inexpensive anticoagulant.

2.4.2 Direct oral anticoagulants (DOAC) - dabigatran, rivaroxaban, apixaban, edoxaban

DOACs have been developed as alternatives to warfarin. DOACs can be divided into two groups based on their target site: direct thrombin inhibitors and factor Xa inhibitors.

Direct thrombin inhibitors (dabigatran)

Thrombin is one of the enzymes involved in the coagulation cascade and by inhibiting it, the coagulation cascade is interrupted, so blood clots form less readily (*Heart Rhythm Society*, 2016).

Factor Xa inhibitors (rivaroxaban, apixaban, edoxaban)

Factor Xa is another enzyme involved in the clot formation and by inhibiting factor Xa, the coagulation cascade is interrupted (*Heart Rhythm Society*, 2016).

DOACs are considered to be safe and effective, they don't require blood monitoring compared to warfarin and they have limited drug interactions. Additionally, DOACs have a direct mode of action against only one clotting factor and they have a rapid onset of action (peak onset within 1-4 hours) (Little *et al*, 2012). However, DOACs offer stroke protection for a certain period of time after intake, so patients must not skip a dose, since missing even one dose can lead to a non-anticoagulated state (*Heart Rhythm Society*, 2016). In addition, doctors are not so free in managing patients prescribed DOACs in emergency situations, since there are no specific antidotes to reverse the anticoagulant effect, except for dabigatran developed recently.

The approval of DOACs launched them into the clinical practice, providing alternative to warfarin treatment. DOACs don't require monitoring but they lack long-term safety data compared to warfarin (Peacock *et al*, 2016).

2.5 Efficacy

Unfortunately, the risk of stroke is still under-recognized and anticoagulation underused in patients with AF, despite the severe consequences.

Björk et al were able to demonstrate in the population-based study in a region in Sweden with 1.56 million residents that majority of AF patients with increased risk for stroke had not received anticoagulation therapy (Figure 7) (Björck *et al*, 2013).

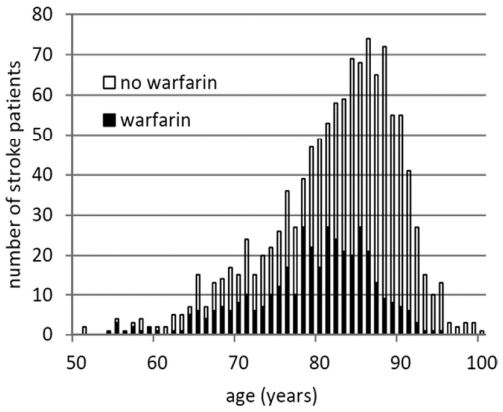

Figure 7. Number of patients with AF having a stroke in relation to age and warfarin treatment (Björck *et al*, 2013).

Furthermore, the study showed that AF patients treated with anticoagulation medications had a 54% lower risk of stroke compared to AF patients who did not receive a treatment. Studies regarding stroke prophylaxis conducted elsewhere have presented similar results, where over 60% of lower risk of stroke was found by using VKAs compared to no treatment at all (Hart *et al*, 1999; Azoulay *et al*, 2014).

It is proposed that strokes may be more severe in Estonia and lower the survival rate at one year due to insufficient use of anticoagulants in the prevention of stroke (Vibo *et al*, 2007).

2.6 Side-effects

In oral anticoagulant therapy bleeding is the major risk, but not all bleedings are equally severe. Common bleeding complications that occur are minor, such as nosebleeds or gum bleeding. Major bleedings are more serious, like ICH (Fang *et al*, 2007).

There are studies to evaluate the effect of increased warfarin use and warfarin-related ICH. Study, conducted in Finland, showed in contrast to many others that although the proportion of warfarin users nearly quadrupled in population, the annual incidence and case fatality of warfarin-related ICHs decreased (Figure 8) (Huhtakangas *et al*, 2011).

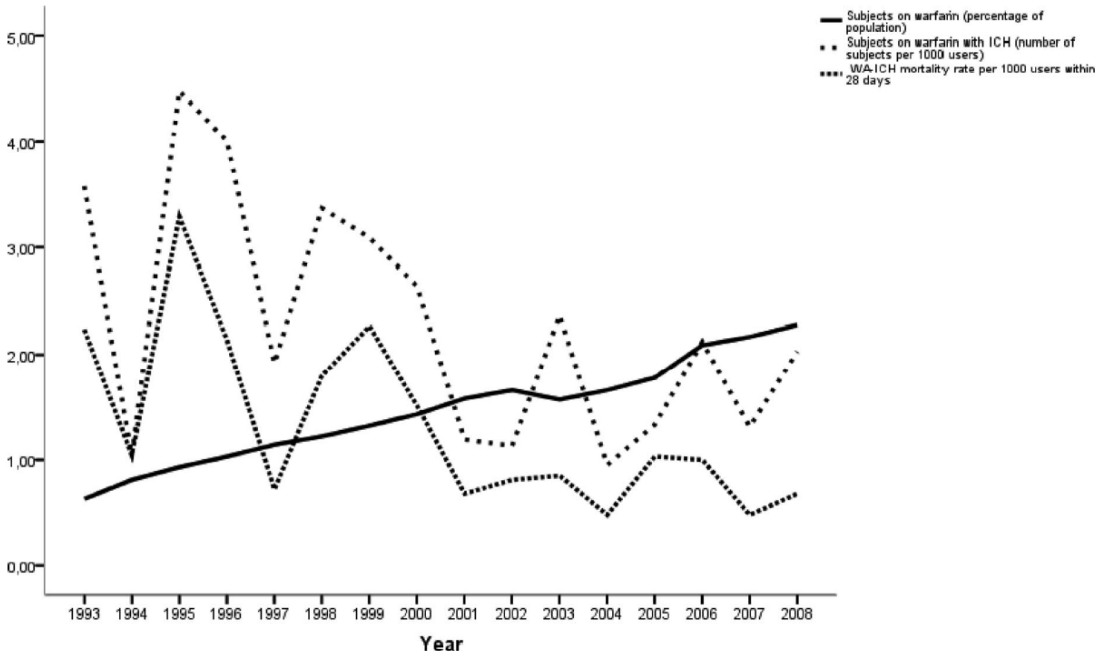

Figure 8. Annual increase of warfarin use in relation to the incidence of WA-ICHs and the annual 28-day mortality rates due to WA-ICHs (Huhtakangas *et al*, 2011).

On the other hand, evidence show that even a perfectly conducted VKA treatment in AF patients doubles the risk of ICH. The major cause being both: patient-related risk factors and anticoagulation intensity influences the rate of anticoagulation-related ICH (Hart *et al*, 1995).

Bleeding is especially alarming with the DOACs due to lack of antidotes (except for dabigatran).

Rivaroxaban is considered to be as effective as warfarin in preventing stroke, but a trend for lower mortality has been observed (4.5% and 4.9%/year, respectively). In addition, less ICH, but increased gastrointestinal hemorrhage has been detected (Hess et al, 2013). Dabigatran (150 mg b.i.d.) is more effective in reducing the rate of stroke compared to warfarin, but is as prone to major bleedings as warfarin and has increased levels of gastrointestinal bleeding. Dabigatran (110 mg b.i.d.) on the other hand is considered to be as effective as warfarin in reducing the rate of stroke, but significantly reduced rates of major bleeding can be observed. Both doses of dabigatran reduced rates of ICH by over two-thirds and a trend toward lower mortality compared with warfarin was observed (Hess et al, 2013). Third DOAC, apixaban is more effective in reducing the rate of stroke compared to warfarin and shows significantly lower rates of death. In addition, apixaban is associated with remarkably less major bleeding, ICH as well as gastrointestinal hemorrhage (Hess et al, 2013). Based on the comparison of DOACs, apixaban seems to have the most favorable profile for the treatment.

Extra-cranial bleeding (gastrointestinal bleeding), the most common side effect in DOACs, leads to death or disability in 3% of cases, whereas intracranial bleeding (ICH), the biggest shortcoming in warfarin treatment, leads to death or disability in 76% of cases (Fang *et al*, 2007).

Interestingly, a recent study has shown that restarting oral anticoagulation after ICH in patients with AF is associated with favorable outcomes. According to a meta-analysis conducted in US, proceeding with oral anticoagulation treatment after ICH decreases mortality and provides better functional outcome due to lower risk of thromboembolic complications with a similar risk of ICH recurrence (Biffi *et al*, 2017).

2.7 Cost

Ageing of the population is occurring worldwide. It is predicted that by 2050 the number of people aged 65 and over will be 17% (from 9% today) (He *et al*, 2016). Therefore, the use of oral anticoagulants will increase rapidly.

In cost-effectiveness and budget impact evaluation of DOACs in Estonia demonstrated that DOACs use would result in higher costs for multiple reasons. Several factors are involved: mainly, the overall use of anticoagulants would increase due to ageing of the population and higher population coverage due to convenience of use. DOACs are more expensive compared to warfarin and there would be increase in reimbursement (Reile *et al*, 2016). Another study conducted in US showed that by mid-2013 DOACs accounted for 62% of new prescriptions and 98% of total anticoagulant-related drug costs. This study demonstrated rapid adoption of DOACs into clinical practice and high health care cost consequences (Desai *et al*, 2014).

2.8 The register-based study

Collecting new research data might be time consuming and expensive, even more, desired data might have already been collected, but not analyzed. Historical follow-up studies based on data in existing registers can be carried out in less time than corresponding case-control studies. Fortunately, some countries have provided an opportunity to use national registers for certain types of research (Olsen, 2011). Register-based research is a research where at least one data source is a register. Register is an information system that repeatedly records subject-based data for certain complete set of subjects. In register-based research the data have not been collected primarily for the purposes of specific research question, but instead these registers are used for secondary analysis of data (Centre for research methods). Since the register data is available for research purposes only, a request for a register dataset must be sent with a research plan containing research question, a description of the data needed and methods that are required to answer them. In addition, researcher must consider whether the project needs a review by an ethics committee, that

will weigh whether the expected social benefits and knowledge gained by the project is associated with the risks and costs of violation of personal integrity (Mellander, 2017). Collected health data can be used for supporting a wide range of medical and health care functions, like disease surveillance or population health management (Bouzillé *et al*, 2017). EHIF database can be considered as healthcare register in Estonia, where the health data about the entire population is collected.

2.9 Conclusions

Literature review demonstrated that stroke is one of the leading cause of death and disability influencing severely a person's quality of life. One of the major risk factors for stroke is AF. AF prevalence increases with age being the most common cardiac arrhythmia in patients. Anticoagulant therapy is the key in stroke prevention in AF reducing the risk of stroke several times. Despite the effectiveness of the treatment insufficient anticoagulation in patients with AF was demonstrated. Studies showed that warfarin is highly efficacious in reducing the risk of stroke, but its usage amongst the patients is challenged by several behavioural and environmental factors. It leads to stopping the treatment in half of the patients during first years. The scope of anticoagulation treatment has shown improvement in recent years due to launch of DOACs. Compared to warfarin, DOACs have several advantages like a rapid onset of action, few drug interactions, and no need for regular monitoring. The disadvantage is lack of specific antidote, except for dabigatran. ICH is unpredictable complication in AF treatment with severe consequences, however restarting oral anticoagulation after ICH in patients with AF is associated with favorable outcomes. Due to the increasing number of patients in OAC treatment and high cost of DOACs the cost of AF treatment is increased drastically.

3 Research methodology

3.1 Research objectives and research questions

The objectives of this research is to analyze AF and stroke in Estonian population, compare the OAC usage in patients with AF based on data from public databases and evaluate in what extent the complications occurred during the treatment are related to OAC therapy.

Research questions:

- What are the trends of diagnosed stroke and AF in Estonia in 2010 – 2016?
- How many patients with diagnosed AF are treated with oral anticoagulants in Estonia in 2010 – 2016?
- What are the oral anticoagulants used in Estonia in 2010 – 2016?
- What is the influence of oral anticoagulation on stroke risk and side effects related to bleeding?
- What is the cost of treatment?

Research hypothesis:

- Number of AF patients has grown in Estonia.
- AF is more prevalent in age groups > 65 years as age being one of the risk factors for stroke based on $CHADS_2$ and CHA_2DS_2-VASc score tables.
- Number of AF patients on OAC treatment is increased due to better management of AF and the launch of DOACs.

- Warfarin is the most prescribed drug in treatment of AF.
- Number of strokes have decreased due to increase of OAC treatment.
- Number of side effects have remained the same or decreased due to better monitoring of warfarin treatment despite increasing number of patients having the treatment.
- The cost of treatment has increased due to introduction of DOACs.

3.2 Research method

For the research a nationwide retrospective registries based study regarding oral anticoagulant usage in Estonia from January 1, 2012 to December 31, 2016 was carried out.

Information from

- Estonian Health Insurance Fund (EHIF) database was analyzed to determine
    - the number of patients with AF and stroke
    - number of patients on warfarin
    - number of patients with side effects related to warfarin treatment
    - number of patients who restarted OAC treatment after ICH
- Health Statistics and Health Research database was analyzed to determine
    - warfarin and DOAC usage in Estonia
- Pharmacy database was analyzed to determine
    - the cost of DDD
- Statistics Estonia database was analyzed to determine
    - population statistics.

3.3 Research sample

The nationwide study covers more than 1.3 million residents in Estonia. For each subject, EHIF database was searched for a diagnosis of AF and ischemic stroke. Stroke (ICD 10: I63 or I64), AF-related strokes (ICD 10: I48 + I63 or I64).

Patients having AF are described in this study as persons who have been visiting doctor between January 1, 2010 and December 31, 2016 and having at least two treatment bills with main diagnosis of AF (ICD 10: I48). Existence of two treatment bills was required to ensure the accuracy of the diagnosis. Precondition for identifying the number of patients on warfarin treatment was pre-existing AF diagnosis (ICD 10: I48). Analyzed data included the number of patients whom the medicine was prescribed and how many purchased.

Prevalence of side effects caused by warfarin treatment (ICD 10: I48 + I60 - I64 or K92 + warfarin purchased at least once) in 2010 – 2016 were analyzed.

OAC treatment continuation after ICH (ICD 10: I48 + I61 + OAC prescription after diagnosis) in 2016 based on data inquired from EHIF.

From January 1, 2010 to December 31, 2016, 55 367 AF diagnosed patients were identified from the EHIF as the study population, from whom stroke events, warfarin users and side effect events were identified per year in the timeframe 2010 – 2016.

All data was obtained from EHIF database as non-personalized data, as a number of persons grouped by sex and age groups.

3.4 Analysis of data

Collected health data was analyzed by calculating AF and ischemic stroke prevalence in the general population per year in a timeframe 2010 - 2016. Health data from 2010 was compared to population on 1st of January 2011, data from 2011 was compared to population on 1st of January 2012 etc.

In addition, ischemic stroke prevalence in patients with AF, AF prevalence in patients with ischemic stroke and side effect prevalence in patients on warfarin treatment was calculated.

Usage of medicines was determined by comparing the number of patients gained from EHIF and the number of patients derived from DDD/1000 inhabitants/day calculations based on Health Statistics and Health Research data. The DDD is the assumed average dose per day for the medicine used in adults and since it is a technical unit it might not correspond to the clinical dose actually prescribed to patient (*WHO*).

DDD for warfarin is 7.5 mg, 300 mg for dabigatran, 20 mg for rivaroxaban and 10 mg for apixaban (*Appendix 2*).

Actual average clinical dose for warfarin was determined.

Calculation examples can be found in Appendices (*Appendix 1*).

4 Results

4.1 Prevalence of stroke, AF and AF-related stroke in Estonian population based on Estonian Health Insurance Fund data in 2010 – 2016

4.1.1 Stroke prevalence in general population

30 582 patients were detected from EHIF database with the main diagnosis of ischemic stroke (ICD 10: I63 and/or I64), making the prevalence 2.32% from population. Prevalence of stroke is stable for men (0.43%) and decreased for women (from 0.49% to 0.45%) during 2010 - 2016. Women comprised 57%.

Number of strokes was higher in older age groups, in the age group 70 - 79 for men and 80 - 89 for women.

Number of patients and prevalence of stroke are shown per year and in total in the timeframe 2010 - 2016 in Table 1 (page 31) and in relation to age and gender in Table 2 (page 32). Data on prevalence of AF and stroke is depicted on Figure 9.

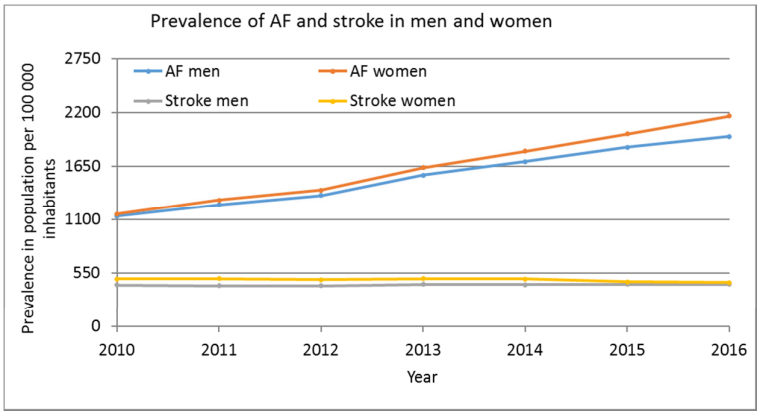

Figure 9. Prevalence of AF and stroke in Estonia in 2010 – 2016.

The number of AF diagnosed patients has increased nearly 80% in recent years. Stroke rate has stayed nearly the same in 2010 - 2016.

4.1.2 AF prevalence in general population

55 367 AF diagnosed patients (ICD 10: I48) were identified based on EHIF data in 2010 - 2016. This corresponds to 4.21% from the general population. In 2010 the prevalence of AF was 1.13% for men and 1.16% for women. In 2016, the figures were 1.95% and 2.16% respectively (Table 1).

The highest number of AF patients was in the age group 70 – 79, both for female and male patients and 55% were women of all the patients (Table 2).

The figure 10 demonstrates that the number of people aged 60 and older has increased nearly 10% in recent years compared to 80% increase in diagnosed AF (Figure 10).

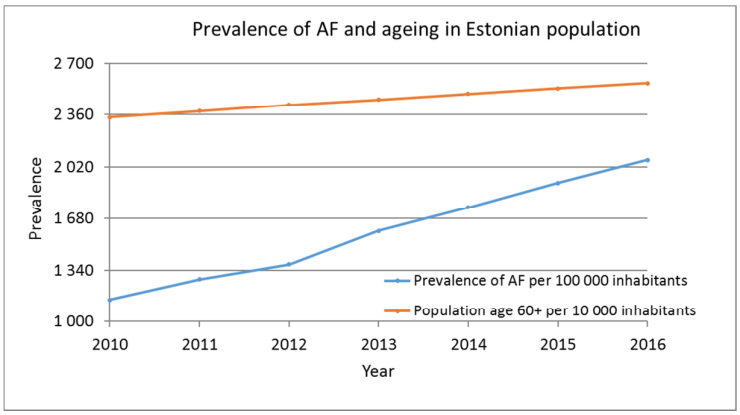

Figure 10. Prevalence of people aged 60+ per 10 000 people and prevalence of AF per 100 000 people in 2010 – 2016.

4.1.3 Ischemic stroke prevalence in patients with AF

7 422 patients were identified with the AF-related stroke diagnosis. Stroke events were detected more in women, in 60% (Table 1).

The prevalence of stroke among 55 367 AF patients in relation to age and gender in 2010 - 2016 is demonstrated on figure 11. Age groups up to 29 years have been excluded from the figure because of few patients. Prevalence of stroke is reaching up to 23% among women in the age group of 90 - 99 and 18% among men in age 80 - 89 years (Table 2; Figure 11).

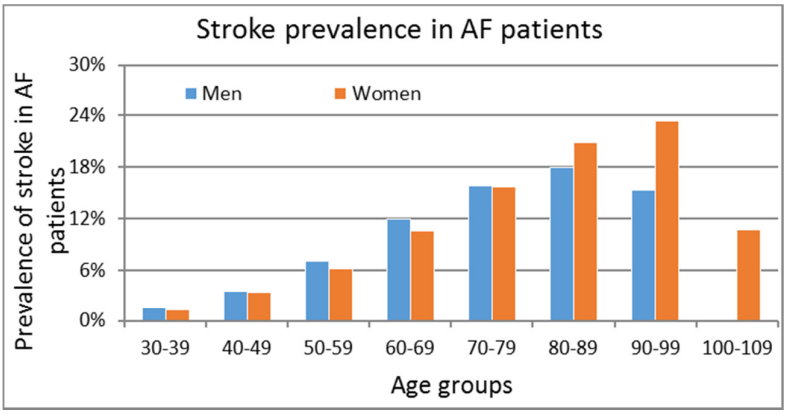

Figure 11. Prevalence of stroke among 55 367 AF patients in relation to age and gender in 2010 – 2016.

4.1.4 AF prevalence in ischemic stroke events

30 582 patients were detected with the diagnosis of stroke from whom 7422 (24%) had previous AF diagnosis.

In figure 12 the prevalence of AF among 30 582 ischemic stroke patients in relation to age and gender in 2010 - 2016 is presented (age groups up to 29 years have been excluded from the graph because of small representation of the disease). AF-related strokes comprise up to 40% from all ischemic stroke events and are the most common in patents aged 70 - 89 years.

Number of patients and prevalence of AF-related stroke are shown per year and in total in 2010 - 2016 in Table 1 and in relation to age and gender in Table 2 and Figure 12.

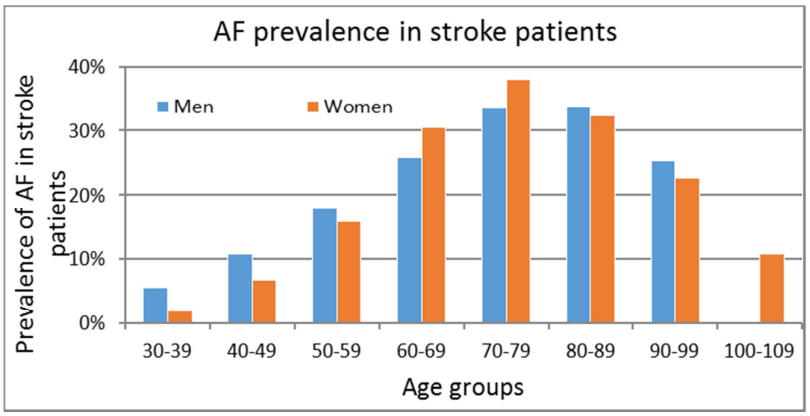

Figure 12. Prevalence of AF among 30 582 ischemic stroke events in relation to age and gender in 2010 – 2016.

Table 1. Number of patients and prevalence of stroke, AF and AF-related stroke Estonia in 2010 – 2016.

Year	2010	2011	2012	2013	2014	2015	2016	Total	Prevalence
Population	1 329 660	1 325 217	1 320 174	1 315 819	1 313 271	1 315 944	1 315 635	1 319 390***	
men	619 700	618 138	616 167	614 919	614 389	616 708	617 538		
women	709 960	707 079	704 007	700 900	698 882	699 236	698 097		
Stroke patients								30 582	2,32%
men	2 646	2 589	2 582	2 665	2 646	2 675	2 676	13 070	
%*	0,43%	0,42%	0,42%	0,43%	0,43%	0,43%	0,43%		
women	3 475	3 479	3 396	3 463	3 405	3 207	3 156	17 512	
%*	0,49%	0,49%	0,48%	0,49%	0,49%	0,46%	0,45%		
AF patients								55 367	4,21%
men	7 027	7 766	8 315	9 580	10 444	11 369	12 064	24 820	
%*	1,13%	1,26%	1,35%	1,56%	1,70%	1,84%	1,95%		
women	8 207	9 206	9 881	11 475	12 600	13 855	15 098	30 547	
%*	1,16%	1,30%	1,40%	1,64%	1,80%	1,98%	2,16%		
AF-related stroke								7 422	
men	265	278	312	352	394	366	357	2 953	
% **	3,77%	3,58%	3,75%	3,67%	3,77%	3,22%	2,96%	11,90%	
women	375	427	433	500	543	543	495	4 469	
% **	4,57%	4,64%	4,38%	4,36%	4,31%	3,92%	3,28%	14,63%	
Stroke prevalence from AF patients									13,4%
AF prevalence from stroke patients									24,3%
% - prevalence; * - from population; ** - from AF patients; *** - mean population 2010-2016									

Table 2. Number of patients and prevalence of stroke, AF and AF-related stroke in relation to age and gender in Estonia in 2010 – 2016.

Age groups	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99	100-109	80+	Total
Population													1 319 390
men	75 100	64 805	94 246	93 975	88 201	83 717	62 162	38 823				15 766	616 795
women	71 096	61 237	88 217	89 371	89 304	95 544	86 189	73 665				47 972	702 595
Stroke patients													30 582
men	24	11	34	146	473	1 765	3 838	4 621	2 654	272	9	2 935	13 070
%*	0,03%	0,02%	0,04%	0,16%	0,54%	2,11%	6,17%	11,90%				18,62%	
women	23	15	48	111	252	880	2 409	5 822	7 283	1 549	28	8 860	17 512
%*	0,03%	0,02%	0,05%	0,12%	0,28%	0,92%	2,80%	7,90%				18,47%	
AF patients													55 367
men	5	26	199	511	1 432	4 467	8 280	9 762	4996	449	5	5 450	24 820
%*	0,01%	0,04%	0,21%	0,54%	1,62%	5,34%	13,32%	25,14%				34,57%	
women	3	12	67	164	506	2 254	6 940	14 051	11 285	1 494	28	12 804	30 547
%*	0,00%	0,02%	0,08%	0,18%	0,57%	2,36%	8,05%	19,07%				26,69%	
AF-related stroke													7 422
men	24		2	8	51	315	993	1 548	895	69		964	2 953
%**				1,57%	3,56%	7,05%	11,99%	15,86%	17,91%	15,37%		17,69%	
women	12		1	2	17	138	735	2 212	2 355	350	3	2 708	4 469
%**				1,22%	3,36%	6,12%	10,59%	15,74%	20,87%	23,43%	10,71%	21,15%	

% - prevalence; * - from population; ** - from AF patients

4.2 The usage of warfarin treatment on AF diagnosed patients based on Estonian Health Insurance Fund data in 2010 – 2016 and Health Statistics and Health Research Database in 2012 – 2016

15 234 AF diagnosed patients and 6507 patients prescribed to warfarin were detected in 2010, making it only 43% from the patients. The number of prescribed medication increased significantly in the following two years reaching to 70% of patients in 2012. Percentage of the patients who purchased the medicine is high, yielding to 96% in year 2010 and 97% in following years (Table 3).

Table 3. Warfarin usage in Estonia in 2010 – 2016.

Year	AF patients	Patients on warfarin			
		Prescribed	Prescribed %	Purchased	Purchased %
2010	15 234	6 507	43	6 263	96
2011	16 972	10 587	62	10 302	97
2012	18 196	12 760	70	12 405	97
2013	21 055	14 126	67	13 709	97
2014	23 044	14 516	63	14 043	97
2015	25 224	14 335	57	13 852	97
2016	27 162	12 635	47	12 269	97

Warfarin use was also determined from Health Statistics and Health Research database in order to compare results from EHIF. Warfarin usage is given as DDD/1000 inhabitants/day.

Table 4. Warfarin and DOAC usage in Estonia in 2012 – 2016 as DDD/1000 inhabitants/day.

	2012	2013	2014	2015	2016
Warfarin	7.23	8.03	7.89	7.55	7.03
Dabigatran	0.20	0.40	0.60	0.96	1.36
Rivaroxaban	0.09	0.50	2.39	3.98	5.23
Apixaban	-	0.01	0.07	0.50	1.26

The difference of warfarin consumption based on two databases (Figure 13).

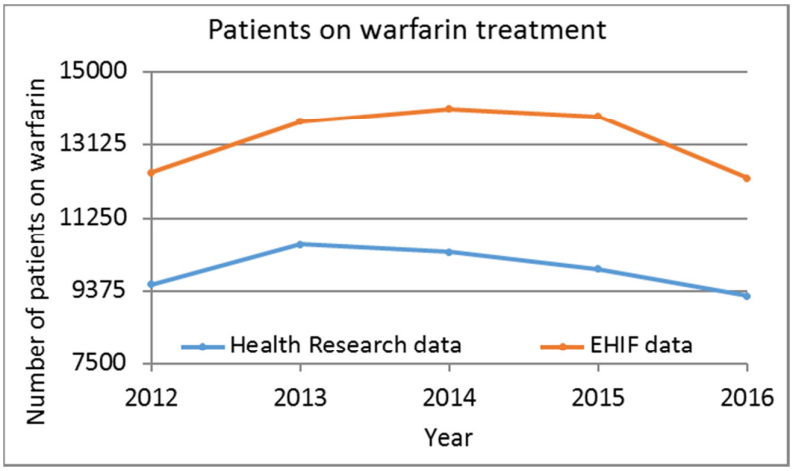

Figure 13. Number of patients on warfarin based on two different databases in 2012 - 2016.

Trend seen in the Figure 13 regarding consumption of warfarin is similar, but the number of patients on warfarin differ by 30 - 40%.

The reason for the difference in the number of patients on warfarin treatment according to different databases is caused by DDD specification. DDD for warfarin is 7.5 mg per patient, but actual dose used is in between 5.4 and 5.8 mg per patient in recent years in AF patients in Estonia according analysis of data from EHIF database (Table 5).

Table 5. Warfarin usage and actual average daily dose in Estonia in 2012 – 2016 based on two databases.

	Population	Warfarin EHIF	Warfarin Health Statistics and Health Research	Actual daily dose for warfarin, mg
2012	1 320 174	12 405	9 545	5,8
2013	1 315 819	13 709	10 566	5,8
2014	1 313 271	14 043	10 362	5,5
2015	1 315 944	13 852	9 935	5,4
2016	1 315 635	12 269	9 249	5,7

4.3 DOACs as a treatment for AF diagnosed patients based on Health Statistics and Health Research Database in 2012 – 2016 and EHIF data in 2016

Consumption of rivaroxaban has increased remarkably in recent years compared to the other DOACs (Table 4; Figure 14).

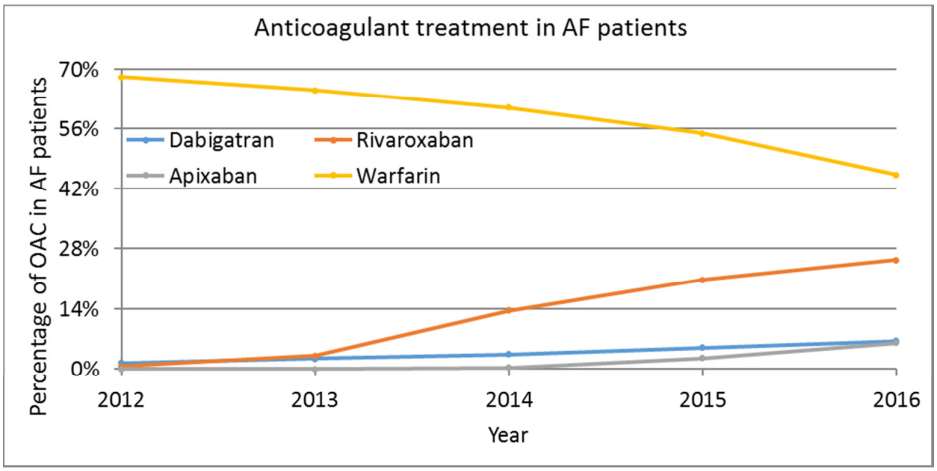

Figure 14. AF patients on OAC treatment based on EHIF (warfarin) and Health Statistics and Health Research (DOACs) database in 2012 - 2016.

Based on EHIF data DOACs were prescribed to 11 493 patients with AF diagnosis in the year 2016 and 11 149 purchased the medicine, which makes the purchase rate of the prescription 97% (Table 6). Based on Health Statistics and Health Research database DOAC-s were used for treatment for 10 328 patients in year 2016 (7,85 people per 1000 inhabitants according to Table 4).

OACs were prescribed to 24 128 AF patients, 89% of 27 162 AF diagnosed patients in 2016 (Table 6). 86% of the patients followed the treatment by purchasing the medicine.

Table 6. Warfarin and DOAC usage in Estonia in 2016.

	Patients on OAC in 2016			
	Prescribed	**Prescribed %**	**Purchased**	**Purchased %**
Warfarin	12 635	47	12 269	97
DOAC	11 493	42	11 149	97
Total	24 128	89	23 418	97

4.4 Prevalence of side effects in patients on warfarin treatment in Estonia based on data from EHIF database in 2010 – 2016 and continuing anticoagulation treatment after ICH in 2016

4654 patients on warfarin treatment who had side effect (ischemic stroke, intracranial or extra-cranial hemorrhage) during 2010 – 2016 were detected from EHIF database. In 2010 6263 patients were on warfarin treatment and 303 had any side effect with the prevalence 4.8%. In 2016 the corresponding figures were 12 269 patients on warfarin treatment and 344 side effects making the prevalence 2.8% (Table 7; Figure 15).

Table 7. Prevalence of side effects in AF patients on warfarin treatment in Estonia in 2010 – 2016.

Year	Patients on warfarin	Side effects	Side effect prevalence
2010	6263	303	4,8%
2011	10 302	434	4,2%
2012	12 405	490	4,0%
2013	13 709	521	3,8%
2014	14 043	463	3,3%
2015	13 852	392	2,8%
2016	12 269	344	2,8%

Figure 15 shows that the number of patients on warfarin treatment doubled while the number of side effects remained nearly the same in the given timeframe. Starting from 2013 the number of side effects have decreased by nearly 35%.

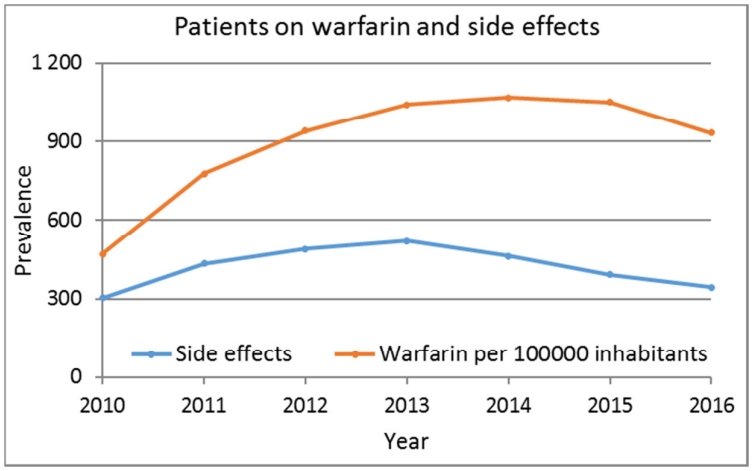

Figure 15. Annual increase of warfarin use and warfarin-related side effects.

The highest number of side effects was in the age group 70 – 79 for both, men and women and side effects were detected more in female patients (54%) (Table 8).

Table 8. Prevalence of side effects in AF patients on warfarin treatment in relation to age and gender in Estonia in 2010 – 2016.

	Patients on warfarin		Side effects		Prevalence, %	
Age groups	Men	Women	Men	Women	Men	Women
0-9		1				
10-19	2		1			
20-29	19	8	2		11%	0%
30-39	118	26	7	1	6%	4%
40-49	625	136	42	10	7%	7%
50-59	2 361	926	241	110	10%	12%
60-69	4 949	3 649	731	493	15%	14%
70-79	5 829	7 635	1 129	1 352	19%	18%
80-89	2 404	4 746	497	1 069	21%	23%
90-99	132	339	22	60	17%	18%
100-109		2				
All	**13 008**	**13 927**	**2 118**	**2 536**	**16%**	**18%**

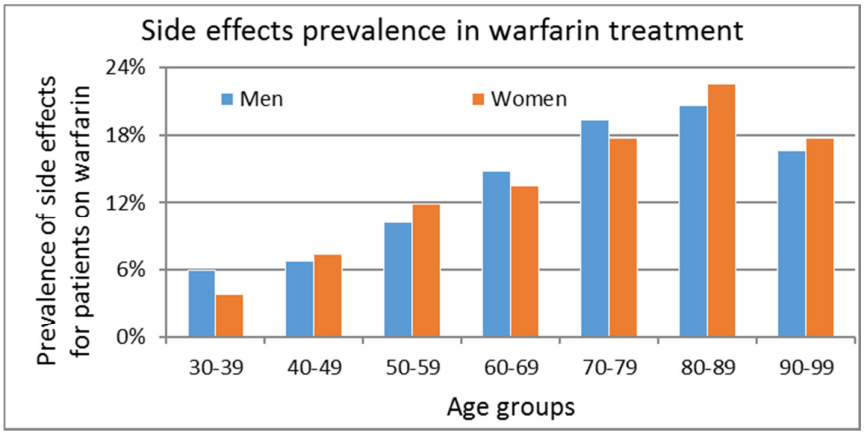

Figure 16. Prevalence of side effects among 26 935 patients on warfarin in relation to age and gender in 2010 – 2016.

In Figure 16 prevalence of side effects among 26 935 AF patients on warfarin treatment in relation to age and gender in 2010 – 2016 is given. Age groups up to 29 years have been excluded from the figure because of few patients. Side effects occur more often in patients in older age and reach around 20% of patients at the age 70 – 89 years (Table 8, Figure 16).

Continuing anticoagulation after ICH shows that in older age groups proceeding with the treatment is well accepted yielding to 35% in the age group 70-79 (Figure 17). OAC treatment is resumed in 14% of the patients after all the ICH events.

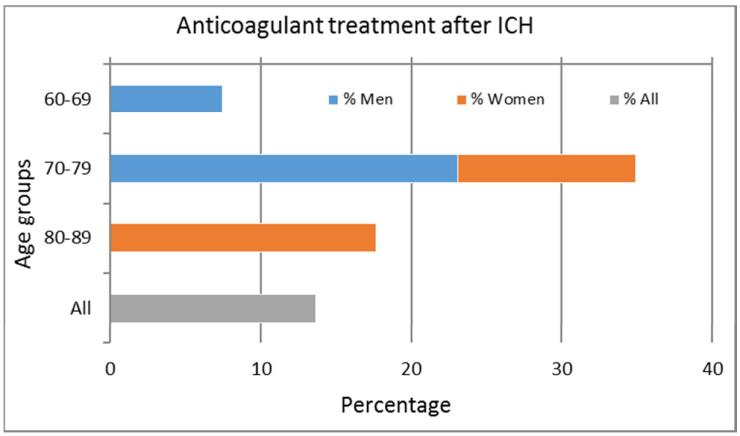

Figure 17. Resumption of OAC after ICH in 2016 in Estonia.

4.5 Cost of the treatment

Cost of the AF treatment has increased remarkably in recent years (Figure 18).

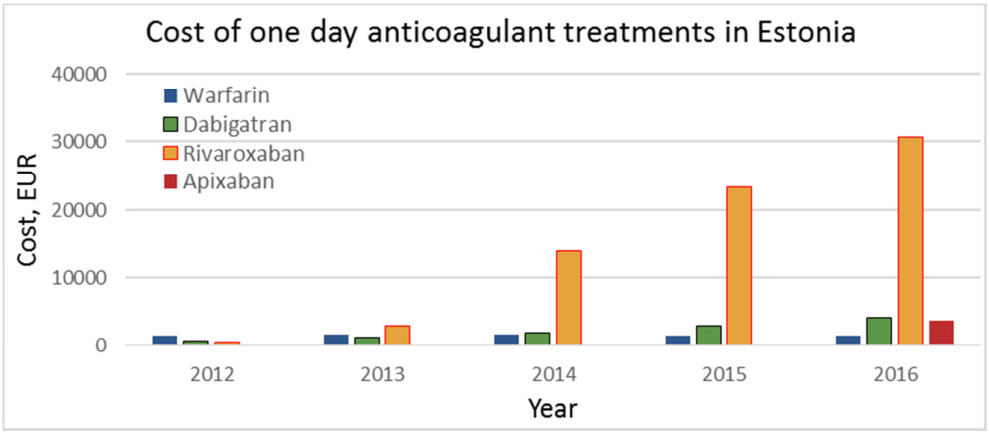

Figure 18. Cost of one day OAC treatment in Estonia in 2012 – 2016.

The cost of DDD for warfarin is 0.15 EUR, for dabigatran 2.28 EUR, for rivaroxaban 4.46 EUR and for apixaban 2.25 EUR.

The annual cost for warfarin is 506 620 EUR, 11 204 040 EUR for rivaroxaban, 1 489 565 EUR for dabigatran and 1 361 815 EUR for apixaban (Table 19).

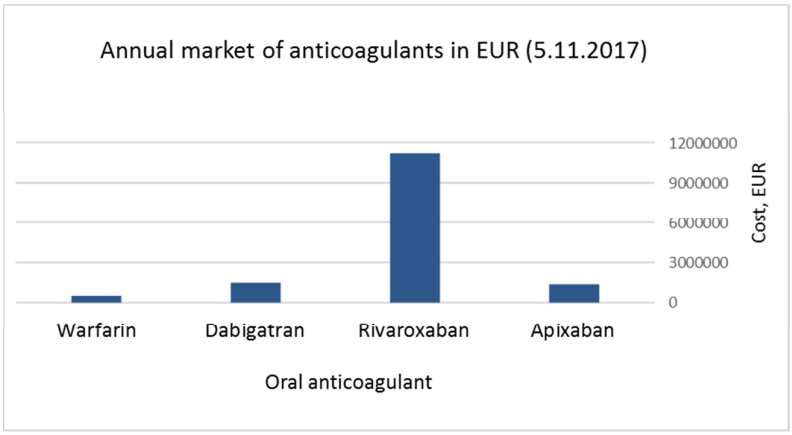

Figure 19. Annual market of OACs in Estonia in 2012 – 2016.

5 Discussion

5.1 Research results

Stroke is the major health care issue in the world. High quality epidemiological studies from South Estonia place Estonia in the high incidence region for first ever stroke (Kõrv *et al*, 2013). According to our data in 2010 – 2016 the prevalence of all stroke is 2.3% in all Estonian population with 57% of stroke victims being women. Prevalence of stroke has been stable for men, being 0.43% from population and has some tendency to decrease for women, from 0.49% to 0.45% from 2010 to 2016 (Table 1). Prevalence of stroke increased rapidly from the age of 60 and highest group of risk is the age group 70 – 79 for men and 80 - 89 for women (Table 2). Stroke is caused by blockage of cerebral blood vessels by blood clots and causes severe and irreversible disability. One of the major risk factors for stroke is AF. AF is the most common type of heart arrhythmia and causes formation of blood clots (*Heart Rhythm Society*, 2016).

Our data confirms that AF in Estonia is twice as prevalent as in other countries reaching to 4.2% from the population in the timeframe 2010 - 2016. Observed trends in AF prevalence in population revealed a sharp increase from 1.1% in 2010 to 2.1% in 2016. 72% increase among men and 86% among women was detected (Table 1). Prevalence of AF increased drastically from the age of 50 and was detected most frequently in the age group 70 – 79, both for man and women (Table 2). The numbers demonstrate that due to ageing of the population and increased AF in the older age groups the total number of AF patients has grown significantly. However, by comparing the increase in the number of people aged 60+ and AF diagnosed patients, we see that population aged 60+ has increased nearly 10% in recent years whether AF has increased more than 80% (Figure 10). So, ageing of the population is not the only factor responsible for the significant increase in the prevalence of AF. An additional factor why prevalence of AF is increasing is attributed to improved ability to suspect and diagnose AF (Zoni-Berisso *et al*, 2014).

The main complication of AF is stroke (Wolf *et al*, 1991), so it is important to evaluate ischemic stroke prevalence in patients with AF. Prevalence of stroke in AF diagnosed patients increases with age exceeding 10% in both of the patient groups over the age of 60 years and reaching to as high as 23% among women in age 90 - 99 and 18% among men in age 80 - 89 years (Figure 11). Stroke that occurs in patients with AF is often fatal or results in remarkable long-term disability in the majority of patients (Camm *et al*, 2010).

One in five of all strokes is attributed to AF in literature (Camm *et al*, 2010). Our data demonstrates that AF-related strokes are even more frequent - up to 40% from all ischemic stroke events are AF-related. In the patient group aged 60+ at least one of four of all strokes are related to AF (Figure 12). Our data in depicted in figure 12 demonstrate that if we are able to reduce the amount of AF-related strokes by effective treatment of AF we can significantly lower the stroke prevalence in the population.

Anticoagulant therapy is the cornerstone of stroke prevention in AF (Chao *et al*, 2016). The overall conclusion from different sources in literature led us to the conclusion that anticoagulants are prescribed significantly less frequently than indicated in Europe (Hart *et al*, 1999; Azoulay *et al*, 2014). Many years the only stroke prevention medication for AF patients has been warfarin (Björck *et al*, 2013). The frequent need for INR monitoring and fear of treatment side effects are probably the main factors contributing to the global underuse of warfarin treatment in AF patients (Hylek et al, 2014). The same is true for Estonia according to EHIF quality indicator analysis as well. Our analysis of warfarin prescription data are not very different and demonstrated that warfarin was prescribed to only 43% of the AF patients in 2010. However, a favorable trend was observed with the number of warfarin prescriptions increasing significantly during the following two years reaching to 70% of patients in 2012 (Table 3). The data of recent years certainly place Estonia among countries with high quality care for AF. From 2012 smooth decrease in the amount of prescribed warfarin started (Table 3). Literature analysis demonstrates that not only insufficient prescription of anticoagulation but also treatment adherence is a problem (Glader *et al*, 2010). Our data seems to demonstrate excellent treatment adherence: the percentage of the patients who purchased the medicine is high, yielding to 96% in year 2010 and 97% in following years (Table 3). However, according to the literature significant adherence problems are developing during at least 24-month follow-up (Glader *et al*,

2010). Our data demonstrate excellent adherence to treatment following the first prescription only (patients purchased the second prescription).

Interestingly, from methodological point of view we were able to observe discrepancies between data of two databases analyzing warfarin use. Internationally DDD for warfarin is 7.5mg. However, in Estonian clinical practice the mean daily dose is 5.4 mg - 5.8 mg, the difference is demonstrated on figure 13 between EHIF and Health Statistics and Health Research data.

Since the decrease of warfarin treatment was observed from 2012 inquiry to Health Statistics and Health Research database was made to see whether warfarin may be replaced by other oral anticoagulants.

Recently, a group of direct acting oral anticoagulants (DOAC) has been developed. DOACs are easy to use with no need for close monitoring or drug to drug interactions. DOACs have better safety profile than warfarin (Hess *et al*, 2013).

Our data confirms that really, the launch of DOACs has had positive influence on the AF treatment in Estonia. Number of AF patients receiving oral anticoagulation has grown remarkably and reached 86% in 2016 (Table 6). Although the prescribed rate of anticoagulation seems nearly perfect, it is important to keep in mind that patients changing their treatment during one year from warfarin or DOAC are counted double (in both of the samples). Still, the number of patients who dropped out from the warfarin treatment is smaller than patients using DOACs. So significant increase in OAC treatment can be observed (Figure 14). Most probably, the number of patients having the treatment is increased due to better diagnostics and management (Zoni-Berisso *et al*, 2014). Also, convenience of use is important – DOACs compared to warfarin do not require blood monitoring for INR values and they have limited drug interactions, so it is easier for patients to follow the treatment (Little *et al*, 2012).

In order to analyze how the DOACs have been accepted for the AF treatment in Estonia, data concerning three DOACs (dabigatran, rivaroxaban and apixaban) was obtained from Health Statistics and Health Research database. Edoxaban is not available in Estonian market. Surprisingly, consumption of rivaroxaban was remarkably higher compared to the other DOACs (Table 4; Figure 14), despite its launch to market at the same time with

dabigatran (apixaban became available one year later). Once daily rivaroxaban is mainly used for patients with AF diagnosis to prevent stroke, more frequently for patients with renal insufficiency (Hess *et al*, 2013). Other than this small difference, rivaroxaban does not seem to have significant advantages (plus once daily regimen). Based on the comparison of DOACs, dabigatran seems to be most efficient and apixaban seems to have the most favorable safety profile (Hess *et al*, 2013). So, we are unable to explain reasons for significant differences in DOAC use in Estonia.

In addition to Health Statistics and Health Research database consumption of DOACs were studied from EHIF database for comparison.

Based on EHIF data DOACs were prescribed to 11 493 patients with AF diagnosis in the year 2016 and 11 149 (97%) purchased the medicine. Based on Health Statistics and Health Research database DOAC-s were used for treatment for 10 328 patients according to DDD calculations in 2016. Nearly 8% difference can be observed. Similar to warfarin data but to the lesser extent with DOACs there are differences in DDDs and mean prescribed doses. The actual prescribed dosages may be smaller with DOACs than internationally agreed DDDs. For instance, for patients with renal impairment or when co-administrating with other medications the dosage of the DOACs is usually reduced (Hess *et al*, 2013).

Despite the benefit of warfarin treatment for stroke prevention in AF patients, side effects occur and limit its use. Warfarin cause mainly bleeding related side effects (Fang *et al*, 2007). In the current study, complications that affect efficacy as well as safety were evaluated. Safety was the data we collected by analyzing intra- or extra-cranial hemorrhage incidence in AF patients on warfarin treatment. The prevalence of complications in warfarin treatment showed gradual decrease from 4.8% in 2010 to 2.8% in 2016 (Table 7). The lower occurrence of complications might have been achieved by improved control of warfarin therapy (improved coagulation monitoring as well as medication and diet compliance) (Huhtakangas *et al*, 2011). In addition, side effects occur more often in patients in older age and reach around 20% for patients at the age of 70 - 89 years (Table 8, Figure 16). High risk in older age can be due to increase of patient-related risk factors, like high blood pressure (Hart *et al*, 1995).

Very complicated problem of restarting oral anticoagulation after ICH in patients with AF is discussed and finally recommended nowadays (Biffi *et al*, 2017). The findings of the current study show that OAC treatment is continued with a high rate, 35% in older patients (age group 70 - 79) after the ICH (Figure 17).

Oral anticoagulation treatment among AF patients has increased remarkably based on our data. DOACs have vigorously entered to the market and increased the cost of AF treatment tremendously. The cost of DDD for warfarin is 0.15 EUR, while DDD for dabigatran is 2.28 EUR, for rivaroxaban 4.46 EUR and for apixaban 2.25 EUR (Figure 18). Moreover, the annual cost for rivaroxaban was 11.2 million EUR compared to warfarin 0.5 million EUR in 2017 (Figure 19). Surveys conducted elsewhere demonstrate rapid adoption of DOACs and high health care cost burden (Desai *et al*, 2014).

5.2 Research limitations

One of the limitations of the research concern warfarin treatment in patients with AF diagnosis. Data on only once purchased warfarin prescription was inquired, but in order to have confidence about the medication adherence at least two prescriptions should have been followed, even adherence during 24 months would have been more informative.

In addition, medication consumption may vary even for patients who purchase the medicine, but do not follow the treatment plan – buying the medicine but not taking it, taking the medicine, but not in specified time and quantity. It is not easy to follow patients in that aspect, one way might be self-reporting obligation about day-to-day treatment.

In order to evaluate OAC treatment in recent years in Estonia, patients having warfarin and DOAC treatment were inquired from two health databases. Here some overlapping of the patients can appear due to changing the medication from warfarin to DOAC during the year. In this case patient is counted in both of the samples and somewhat better treatment coverage can be presented.

6 Summary

Stroke is the second leading cause of death in the world. It is one of the diseases which prevention, acute treatment and later rehabilitation are highly important in all of the countries worldwide. Patients with AF, one of the major risk factors for stroke, have a five-fold risk of stroke, and when the stroke occurs it is either fatal or associated with substantial disability (Wolf *et al*, 1991). Oral anticoagulant treatment has been proven to be most effective for the stroke prophylaxis in AF patients, but because of the complexity of the treatment, it has been underused.

The main results of my Master's Thesis are:

- The prevalence of all stroke was 2.3% in all Estonian population in 2010 - 2016. Stroke prevalence in AF diagnosed patients decreased from 4.2% in 2010 to 3.1% in 2016 and side effects prevalence decreased from 4.8% in 2010 to 2.8% in 2016.

- The prevalence of AF was 4.2% in Estonia in 2010 – 2016. Prevalence increased from 1.1% in 2010 to 2.1% in 2016. AF was detected most frequently in the age group 70 – 79, but rapid increase was already noticed starting from the age of 50.

- Oral anticoagulant treatment in Estonia has increased rapidly in recent years. 86% from the AF patients had oral anticoagulant treatment in 2016. Warfarin was still the most prescribed oral anticoagulant (47% of the patients), followed by rivaroxaban (25% of the patients).

- Cost of oral anticoagulant treatment has increased significantly during last years.

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Appendices

Appendix 1. Examples of calculations

Period prevalence measures the proportion of individuals in a defined population that have a disease of interest during a specified period of time (*Health Knowledge*).

Calculating the ischemic stroke prevalence in patients with AF

For calculating the prevalence of stroke in AF diagnosed patients in 2010 - 2016, number of stroke patients with AF diagnosis in the given period should be divided by the number of AF diagnosed patients in the same population at the same timeframe.

For example:

Of 55 367 AF patients in 2010 - 2016, 7 422 had stroke and previous AF diagnosis.

The prevalence of stroke among AF diagnosed patients in this timeframe is calculated as:

7422/55367 = 0.13 or 13%

Prevalence of ischemic stroke in patients with AF was calculated similarly for age groups in a timeframe 2010 - 2016 to see relevance of age (Table 2).

Calculating the AF prevalence in patients with ischemic stroke

For calculating the prevalence of AF in stroke diagnosed patients in 2010 - 2016, number of stroke patients with previous AF diagnosis in the given period should be divided by the number of total stroke diagnosed patients in the same population in the same timeframe.

For example:

Of 30 582 stroke patients in 2010 - 2016, 7 422 had AF-related stroke.

The prevalence of AF among stroke patients on this timeframe is calculated as:

7422/30582 = 0.24 or 24%

Prevalence of AF in patients with stroke diagnosis is calculated similarly for age groups in a timeframe 2010 - 2016 to see the trend (Table 3).

Calculating the deviation of defined daily dose from actual average dose for warfarin

DDD for warfarin is 7.5 mg per patient (*Eesti ravimistatistika*, 2016), but actual dose can be calculated based on gathered data from EHIF and Health Statistics and Health Research database.

For example:

In year 2012 there were 12 405 patients on warfarin treatment (purchased prescriptions) based on EHIF data.

In year 2012 7.23 inhabitants out of 1000 had warfarin treatment according to Health Statistics and Health Research database (it means they consumed DDD, 7.5 mg) and that makes 9545 inhabitants out of the total population in 2012 (1 320 174 people).

Based on the two figures we can calculate the actual average dose of warfarin used for AF treatment in 2012 as follows: DDD, 7.5mg of warfarin was consumed actually by 12 405 patients according to EHIF data, so it reduces the actual dose to 7.5*9545/12405 = 5.8 mg.

Number of people having warfarin treatment according to Health Statistics and Health Research database and actual average dose for warfarin in Estonian population was calculated in the same manner per year for 2012 - 2016 (Table 6).

Calculating the side effect prevalence in patients on warfarin treatment

For calculating the prevalence of side effects (ischemic stroke or major bleeding) in AF diagnosed patients having warfarin treatment in 2010 - 2016, number of ischemic stroke or intracranial or extra-cranial hemorrhage diagnosed patients on warfarin treatment and having previous AF diagnosis in the given period should be divided by the number of patients on warfarin treatment with previous AF diagnosis in the same population in the same timeframe.

For example:

Of 26 935 AF patients on warfarin treatment in 2010 - 2016, 4 654 had ischemic stroke or intracranial or extra-cranial hemorrhage.

The prevalence of side effects among AF patients on warfarin treatment on this timeframe is calculated as:

4654/26935 = 0.17 or 17%

Prevalence of side effects in AF patients on warfarin treatment is calculated similarly per years in a timeframe 2010 - 2016 to see the trend (Table 7).

Appendix 2. The recommended dosage scheme for DOACs

The recommended dose of dabigatran etexilate for AF patients is 150 mg PO BID or 75mg PO BID if patients have severe renal impairment (CrCl 15-30 mL/min) or moderate renal impairment (CrCl 30-50 mL/min) and co-administration with P-gp inhibitors (dronedarone or ketoconazole). DDD 300 mg. DDD (2012-2015) 220 mg.

The recommended dose of rivaroxaban for AF patients is 20 mg/day or 15 mg/day if moderate to severe renal impairment (CrCl 15-50 mL/min). DDD 20 mg. DDD (2013-2015) 10 mg.

The recommended dose of apixaban for AF patients is 5 mg PO BID or 2.5 mg PO BID if age ≥80 years, weight ≤60 kg, serum creatinine ≥1.5 mg/dL. DDD 10 mg. DDD (2013-2015) 5 mg, 2012 no data, not in the market.

The recommended dose of edoxaban for AF patients is 60 mg PO qDay or 30 mg qDay if patients have moderate to severe renal impairment (CrCl 15-50 mL/min) or if given with P-gp inhibitors. Not allowed to use if CrCl >95 mL/min - increased risk of ischemic stroke.

Source: Medscape