Therapeutic value of warfarin
and
INR remote monitoring

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ABSTRACT

Warfarin is a coumarin derivative and it produces an anticoagulant effect by interfering with the cyclic interconversion of vitamin K and its 2,3 epoxide. It is widely used in part because of its relatively predictable onset and duration of action and its excellent bioavailability. Whilst warfarin has been shown to be effective, it has a narrow therapeutic index that necessitates frequent monitoring and dose adjustments. The aim of monitoring is to ensure that the International Normalized Ratio (INR) is maintained within the target therapeutic range (2.0 and 3.0), where warfarin treatment has been shown to offer an acceptable benefit/risk ratio. TTR (time in therapeutic range) is calculated based on the proportion of time spent in the target INR range 2.0–3.0.

In 2010 the prevalence of anticoagulant (AC) treatment was 1.64% in a Finnish population study and the most common indication for warfarin use is atrial fibrillation. Randomised clinical trials have shown that anticoagulation with warfarin reduces the risk of stroke by up to two thirds. The effect of warfarin is usually stratified by stroke risk (CHADS2) and treatment status (TTR) in outcome analysis and best effect against stroke and survival has been shown when TTR > 80, which is also the suggested TTR limit in current Finnish AF treatment guidelines.

In real-world clinical setting the TTR-level varies and mostly the desirable target level is not met. The retrospective FinWAF-study showed an average TTR of 62% with a median of 67%. Another RWE-study in Finland showed that the average TTR was 65.2% but increased to 74.5% among patients using warfarin continuously, but still one-third of the patients in this study had a TTR of below 60%.

As INR-monitoring has been shown to be both necessary and time and resource consuming, the warfarin outpatient cost is also being estimated. The average outpatient costs in a patient cohort were €314.44 with the national unit costs and €560.26 with the service provider unit costs A higher TTR was associated with lower outpatient costs.

The guidelines state that direct anticoagulants are at least as effective and safer as warfarin in AF associated stroke. Comparisons between DOACs and warfarin has been done in multiple studies, but most of the comparative and efficacy studies of warfarin compared to DOACs show that TTR among warfarin-treated patients is mostly under 70% This leads to a difficult comparison between the effect of different anticoagulants. Compared to warfarin, the lack of laboratory monitoring to assess therapeutic levels, it is important to assess adherence to DOACs and the extent to which it varies by patient characteristics and different DOACs currently available. Adherence studies show that the amount of DOAC non-adherence varies from 25 to 29%.

Studies show that adding electronic communication channels has reduced patients' attachment to healthcare, facilitated communication and reduced unnecessary contacts. Patient self-monitoring is used in a setting where the patient self-measures the INR-value and makes dose adjustments independently or they are done by healthcare professionals. In both types of settings most studies show that TTR-values have elevated, and patients can successfully measure their own INRs, adjust their own warfarin dosage, and achieve a degree of therapeutic effectiveness at least as good, if not better than patients managed in an anti-coagulation clinic. Patient self-management or self-testing of oral anticoagulation has lead even to a significant 50% reduction in thromboembolism in a Cochrane review. The effect of self-monitoring to TTR-values shows 5,1% improvement for AF patients compared to standard care.

In Sweden it has been studied that the first year of self-management is the most expensive due to training and measurement equipment cost, in the UK cost-effectiveness of self-monitoring, and in particular self-management, of anticoagulation status appeared cost-effective when pooled estimates of clinical effectiveness were applied. Remote monitoring seems to be a good option to protomote effective anticoagulation with warfarin and ii is also favoured by patients.

CONTENTS

1. INTRODUCTION

Warfarin is a coumarin derivative and it produces an anticoagulant effect by interfering with the cyclic interconversion of vitamin K and its 2,3 epoxide (vitamin K epoxide) (Hirsh et al. 2003). It is widely used in part because of its relatively predictable onset and duration of action and its excellent bioavailability (Giugliano et al. 2013)

Main indication for warfarin use is atrial fibrillation (Viitaniemi et al 1999). Whilst warfarin has been shown to be effective, it has a narrow therapeutic index that necessitates frequent monitoring and dose adjustments (Hirsh et al. 2003). The narrow therapeutic window may be further complicated by drug-drug and drug-food interactions; therefore, regular monitoring is required which is costly and inconvenient for patients (Menzin et al. 2005). The aim of monitoring is to ensure that the International Normalized Ratio (INR) is maintained within the target therapeutic range (2.0 and 3.0), where warfarin treatment has been shown to offer an acceptable benefit/risk ratio (Fuster et al. 2006). A significant proportion of patients fail to achieve stability within the target range and suboptimal anticoagulation (AC) is associated with poor outcomes either in terms of thrombotic events, hemorrhage or mortality (Jones et al 2005).

Several new direct oral anticoagulants (DOAC) have been developed that dose-dependently inhibit thrombin or activated factor Xa and offer potential advantages over vitamin K antagonists, such as rapid onset and offset of action, absence of an effect of dietary vitamin K intake on their activity, and fewer drug interactions (Connolly et al. 2009; Patel et al. 2011; Granger et al. 2011; Giugliano et al. 2013). The predictable anticoagulant effects of DOACs enable the administration of fixed doses without the need for routine monitoring, thereby simplifying treatment. Individually, direct oral anticoagulants are at least as safe and effective as warfarin for prevention of stroke and systemic embolism in patients with atrial fibrillation, but adherence to this treatment is continuously under discussion. DOACs are increasingly used as the first choice for anticoagulation in patients with AF, but warfarin is still widely used and remains the only option for patients with mechanical valve prosthesis (Eikelboom et al. 2013).

Implementation of anticoagulation treatment is nationally inconsistent, but there is a constant attempt to harmonize treatment in Finland (Puhakka 2011). Treatment practices have a great operational potential and qualitative importance for both customers and healthcare providers. Current mode of operation is burdening and uneconomic, as anticoagulation can not be so far in all indications implemented. For example, in the city of Helsinki, it is estimated that the care is provided approximately to 10 000 patients, with an annual 124 000 INR laboratory tests per year. Each test involves an average of 2.5 contacts with healthcare. As INR-monitoring has been shown to be both necessary and time and resource consuming, the therapeutical value of remote monitoring should be considered and it's therapeutical value estimated.

2. INR AND TTR

The prothrombin time (PT) is the most common test used to monitor oral anticoagulant therapy (Horsti 2009). The INR calibration model, adopted in 1982, is now used to standardize reporting by converting the PT ratio measured with the local thromboplastin into an INR, calculated as follows: INR = (patient PT/mean normal PT)^{ISI}, where ISI denotes the International Sensitivity Index of the thromboplastin used at the local laboratory to perform the PT measurement. The ISI reflects the responsiveness of a given thromboplastin to reduction of the vitamin K–dependent coagulation factors (Poller 1987). The more responsive the reagent, the lower the ISI value.

In Finland warfarin treatment area of thromboembolic complications in artificial valve patients INR range should be 2.5-3.5 and in other indications 2.0-3.0 (Marevan SPC). The INR is usually checked daily until the therapeutic range has been reached and sustained for 2 consecutive days, then 2 or 3 times weekly for 1 to 2 weeks, then less often, according to the stability of the results. Once the INR becomes stable, the frequency of testing can be reduced to intervals as long as 4 weeks. Studies has also been done to assess INR measurement intervals and in some studies assessment of warfarin dosing every 12 weeks seems to be safe and noninferior to assessment every 4 weeks (Schulman et al. 2011). In Finland most warfarin-patients measure INR-values every 4 weeks (Käypähoito-suositus).

When dose adjustments are required, frequent monitoring is resumed. Some patients on long-term warfarin therapy experience unexpected fluctuations in dose-response due to changes in diet, concurrent medication changes, poor compliance, or alcohol consumption. Subgroup analyses of other cohort studies also have shown a sharp increase in the risk of bleeding when the INR is higher than the upper limit of the therapeutic range, and the risk of thromboembolism increased when the INR fell to 2.0 (James et al. 1992; Hylek and Singer 1994; Hylek et al. 1996).

TTR (time in therapeutic range) is calculated based on the proportion of time spent in the target INR range 2.0–3.0 (Figure 1). In routine clinical practice the time individual patients spend in this target range varies considerably (Baglin and Rose 1998). Patients with well controlled INR survived on average more than a year and a half longer than patients with poor control, whose survival was indistinguishable from the non-warfarin treatment group.

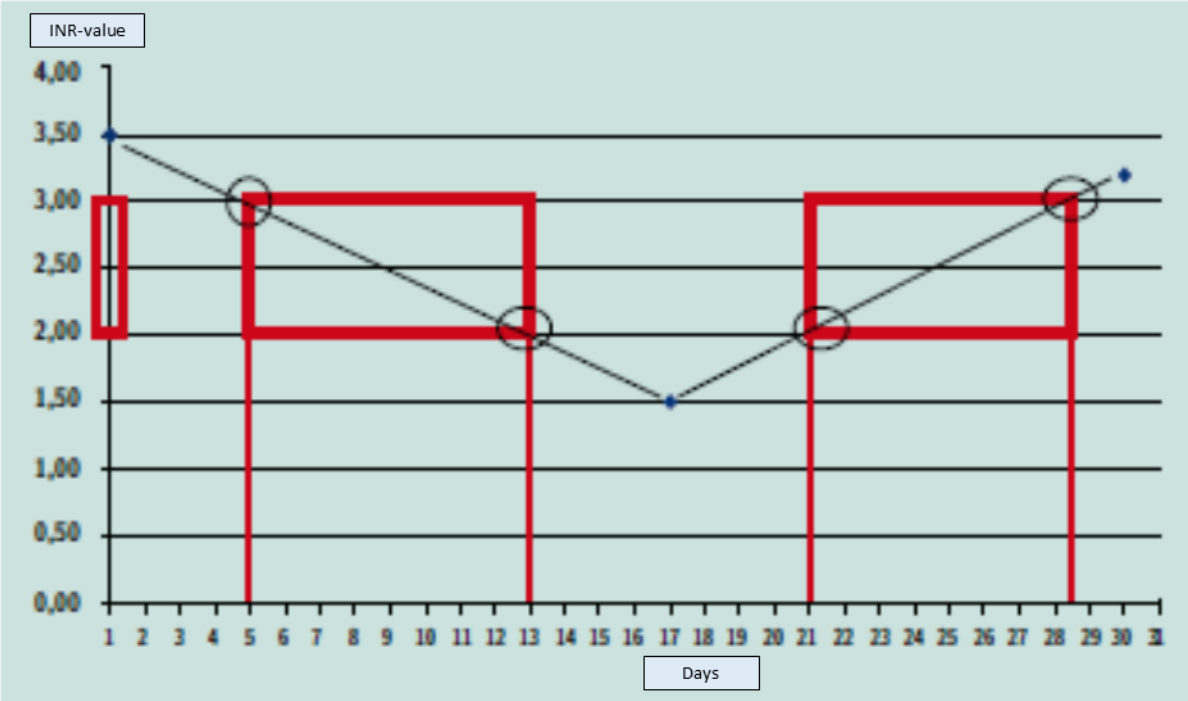

FIGURE 1. HOW TTR-VALUE IS CALCULATED (HALINEN 2013). ON THE FIRST DAY THE INR WAS 3.5, ON THE 17TH 1.5 AND ON THE 30TH DAY 3.2. THE SEGMENT OF INR-VALUES AT DETERMINATION DAY CUTS THE INR VALUE 3 (UPPER LIMIT OF THE TREATMENT AREA) ON DAY 5. BEFORE THAT, ON THE FIRST FOUR DAYS, THE INR WAS NOT IN THE TREATMENT AREA. ON DAYS 5-13 THE INR WAS IN THE TREATMENT AREA FOR EIGHT DAYS. FROM DAY 13 TO 21, INR WAS FOR EIGHT DAYS BELOW THE TREATMENT AREA. INR WAS FROM 21 DAYS IN THE TREATMENT AREA FOR SEVEN AND A HALF DAYS. FROM DAY 28-29 TO DAY 30 INR WAS OVER A TREATMENT AREA FOR ONE AND A HALF DAYS. THE INR VALUE WAS 13.5 DAYS OUTSIDE THE TREATMENT AREA AND 15.5 DAYS IN THE TREATMENT AREA =TTR% WAS 54% IN THIS EXAMPLE.

The current Finnish AF treatment guidelines state that if the TTR is <80%, the cause of the poor balance should be investigated and assessed whether the condition can be corrected by warranting warfarin or by directly replacing the anticoagulant (Käypähoito-suositus).

3. ATRIAL FIBRILLATION (AF)

Atrial fibrillation (AF) is the most common cardiac arrhythmia of clinical significance, with around 5 million new cases each year and the incidence of AF is increasing (Chugh et al. 2014; Kannel et al. 1998). In adjusted models, AF is associated with increased morbidity, especially stroke and heart failure, as well as increased mortality. AF constitutes a significant public health problem and has also significant effect on healthcare cost. The most common indication for warfarin treatment is atrial fibrillation and the need for anticoagulation treatment will increase as the incidence and prevalence of AF increases.

3.1 FINNISH CARE GUIDELINES IN ATRIAL FIBRILLATION

In Finland a current guideline of atrial fibrillation was given in 2017 (Käypähoito-suositus). It states that for the prediction of atrial fibrillation, the most important thing is proper anticoagulation treatment. The need for AC treatment is evaluated with the CHA_2DS_2VASc-score always with atrial fibrillation patients (Table 1). For high risk patients (CHA_2DS_2VASc-score ≥ 2), AC treatment is usually justified even if the risk of haemorrhage has increased. In general oral anticoagulation treatment is recommended for patients whose CHA_2DS_2-VASc score is at least 1, and whose risk of stroke equals or exceeds 1% per annum. In a clinical setting the risk of haemorrhage is evaluated with the HAS-BLED-score (Table 2). The need of AC therapy is carefully evaluated if HAS-BLED > CHA_2DS_2VASc. When treating with warfarin, in terms of stroke prevention and haemorrhagic complications, INR 2-3 is the ideal treatment level and frequent monitoring is necessary. The current Finnish AF treatment guidelines state that if the TTR is <80%, the cause of the poor balance should be investigated and assessed whether the condition can be corrected by warranting warfarin or by directly replacing the anticoagulant (Käypähoito-suositus).

TABLE 1. EVALUATION OF THE RISK OF THROMBOEMBOLIC COMPLICATIONS WITH THE MODIFIED CHA_2DS_2VASc-SCORE (KÄYPÄHOITO-SUOSITUS).

Risk factor	Points
Congestive heart failure	1
Hypertension	1
Age ≥ 75 years	2
Diabetes	1
Stroke or TIA	2
Vascular disease	1
Age 65-75 years	1
Sex category female	1

TABLE 2. RISK OF HAEMORRHAGE IS EVALUATED WITH THE HAS-BLED-SCORE (KÄYPÄHOITO-SUOSITUS).

Risk factor	Points
Hypertension	1
Abnormal liver or kidney function	2
Stroke or TIA	1
Bleeding [1)]	2
Labile INR	1
Elderly	1
Drugs or alcohol	1

[1)] Cancer, anemia, thrombocytopenia, thrombocyte dysfunction, earlier bleeding

In Finland there are four different direct oral anticoagulants (DOAC) in clinical use: a direct thrombin inhibitor: dabigatran and direct inhibitors of the factor Xa, apixaban, edoxaban and rivaroxaban (Table 3). The choice between DOACs and warfarin is made by the clinician and the advantages and disadvantages of DOACs compared to warfarin is taken into consideration (Table 4).

TABLE 3. CHARACTERISTICS OF DIRECT ANTICOAGULANTS AND DOSING INSTRUCTIONS (KÄYPÄHOITO-SUOSITUS).

	Dabigatran	Abixaban	Edoxaban	Rivaroxaban
Mechanism of action	Direct thrombin (factor II) inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Bioavailability	3–7 %	50 %	62 %	66 %*
The effect of nutrition on absorption	No effect	No effect	6–22 % more with nutrition	39 % more with nutrition
Top concentration (hours)	2	1–4	1–2	2–4
Elimination	80 % via renal and 20 % other	27 % via renal and 73 % other	50 % via renal and 50% other	35% via renal and 65 % other
Elimination half-life (hours)	12–17	9–14	10–14	5–13
Normal dosage in AF	150 mg x 2 Age and weight of patient must be taken into consideration	5 mg x 2 Age and weight of patient must be taken into consideration	60 mg x 1 Age and weight of patient must be taken into consideration	20 mg x1 (Must be taken with nutrition)
Dosage with kidney deficiency:				
eGRF > 50 ml/min	150 mg x 2	5 mg x 2	60 mg x 1	20 mg x 1
eGRF 30–49 ml/min	110 mg x 2	5 mg x 2	30 mg x 1	15 mg x 1
eGRF 15–29 ml/min	Contraindicated	2,5 mg x 2	30 mg x 1	Avoid use
eGRF < 15 ml/min	Contraindicated	Contraindicated	Contraindicated	Contraindicated
Interactions:				
P-glykoprotein	Yes	Yes	Yes	Yes
CYP3A4	No	Yes (moderate)	Yes (minor)	Yes (moderate)

eGFR= Estimated glomerular filtration rate

TABLE 4. A COMPARISON OF THE ADVANTAGES AND DISADVANTAGES OF DIRECT ANTICOAGULANTS COMPARED WITH WARFARIN (KÄYPÄHOITO-SUOSITUS).

Benefits
Less intracranial haemorrhage
Standard dosage and more predictable dose effect
Variation in vitamin-K intake (nutrition) does not alter the effect
Less medicine interactions
No need for routine medicine effect monitoring (easier and more comfortable to implement)
Significant disadvantages
Contraindications in mitral valve narrowing and in patients with mechanical artificial valve
Contraindications in severe renal insufficiency (dose reduction in less severe cases)
Other things to consider
Lower availability of monitoring methods (monitoring of drug effects and therapeutic intake is more demanding when needed)
The age and weight of the patient affect the delivery of some products
Other side effects than haemorrhage more common (e.g. dyspepsia)
A specific antibody only available for dabigatran
Cost
Shorter user experience

4. PATIENT POPULATION

In 1992 the prevalence of anticoagulant (AC) treatment was 0.65% in a Finnish population study (Eskola et al. 1996). A more recent study from Finland states that the prevalence has more than doubled since, being 1.64 % in 2010 (Virjo et al. 2010). In Finland, it has been estimated that 8–16 % of the elderly use warfarin in 2010. The proportion of atrial fibrillation among indications has increased to 67% and 70 different indications for AC treatment was found altogether (Table 5). In this study the mean age of patients with warfarin was 72.4 years and the proportion of patients 59 years or younger was 13.2% (Figure 2).

Warfarin usage in Helsinki has also been studied and it is estimated that approximately 10 000 patients are monitored by primary healthcare (Holvitie et al. 2014). The most common main indication for warfarin treatment was atrial fibrillation (38%) (Viitaniemi et al. 1999).

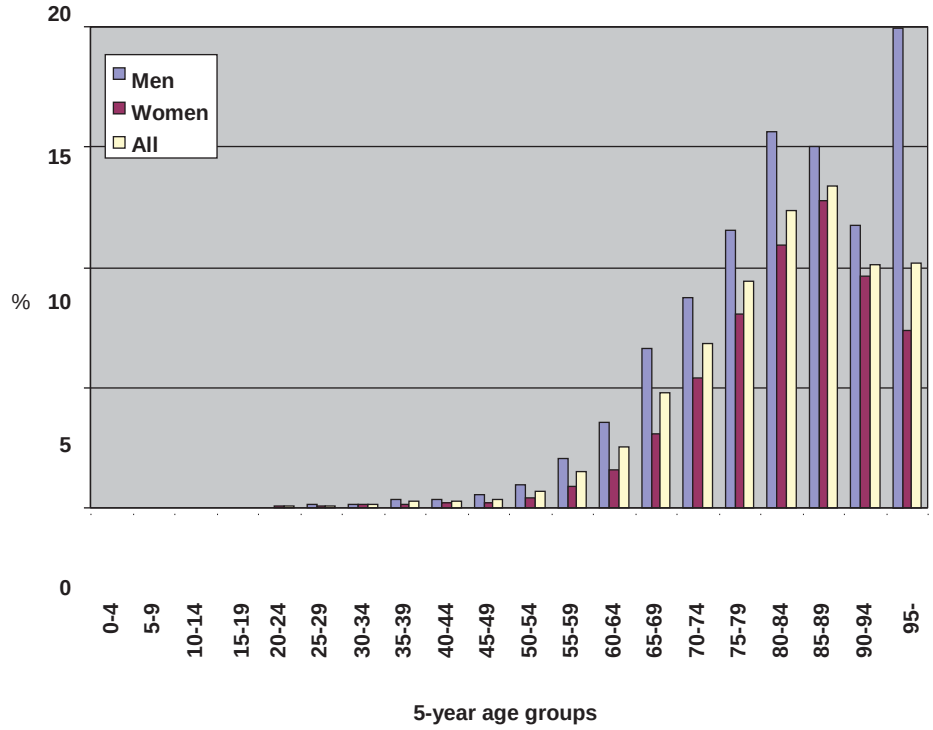

FIGURE 2. PREVALENCE OF AC TREATMENT IN THE POPULATION OF 15 MUNICIPALITIES IN SOUTH OSTROBOTHNIA AS AT 1 APRIL 2004 BY FIVE-YEAR AGE GROUPS AND GENDER. (FOR MEN 95 YEARS AND OLDER THE PREVALENCE WAS 31%). (VIRJO ET AL. 2010)

TABLE 5. DISTRIBUTION OF MAIN AND SECOND INDICATIONS FOR AC TREATMENT OF ALL AC PATIENTS BY AGE GROUP IN 15 MUNICIPALITIES IN SOUTH OSTROBOTHNIA IN FINLAND, 1 APRIL 2004 (VIRJO ET AL. 2010).

	Age < 60 years n = 317		Age ≥ 60 years n = 2072		All n = 2389	
Indications ICD 10 code and name	Main indication (%)	Second indication (%)	Main indication (%)	Second indication (%)	Main indication (%)	Second indication (%)
I48 Atrial fibrillation	32.5	4.4	64.5	7.6	60.2	7.2
I80 Deep vein thrombosis of lower extremity	18.3	2.5	8.1	1.1	9.4	1.3
I63 Brain infarction	8.5	0.6	7.0	4.3	7.2	3.8
I26 Pulmonal emboli	8.2	3.2	5.7	1.4	6.0	1.6
I35 Lesions of aortic valve	15.5	1.6	4.3	1.0	5.8	1.1
I65 Occlusion and stenosis of precerebral arteries which has not caused brain infarction	0.6	0.6	2.3	0.8	2.1	0.8
Other diagnoses	16.1	14.9	8.0	8.9	9.2	9.7
No indication	0.3	72.2	0.1	74.9	0.1	74.5
Altogether	100	100	100	100	100	100

Since old age is the most significant risk factor in atrial fibrillation, the amount of AF patients will grow in the future as the population in Finland ages. Among patients treated with warfarin, age has also been shown to be continuously and independently associated with increased bleeding risk (Wallvik et al. 2007). It has been estimated that the proportion of over 65-year-old people will almost double by the year 2060 (Statistics Finland: population projection 2008-2060). AF can thus be seen as a growing public health problem and a huge challenge to primary health care to offer safe and high-quality care for patients needing oral AC treatment.

It has been argued that fewer than half of patients eligible for warfarin treatment actually receive it (Bungard et al. 2000; Viitaniemi et al. 1999). Retrospective studies also support this claim; many patients with nonvalvular AF remain untreated and the patient population requiring AC treatment is higher that AC prevalence. In Finland the underuse of AC has been shown in the FibStroke Study (Palomäki et al. 2016). This retrospective registry included 3404 high thromboembolic complication-risk patients with previously diagnosed AF. This patient population suffered a total of 2955 ischaemic strokes and 895 TIAs during 2003–2012. The results also showed that 25% of these patients had sufficient AC-treatment, 30% were outside warfarin-care area and 45% did not have AC-treatment at all. In 2003 51% of these patients did not have any treatment for AF at all, but in 2012 this had decreased to 35% showing improvement in AC coverage.

5. DOSAGE

Usually warfarin dosing may be separated into initial and maintenance phases (Hirsh et al. 2003). After treatment is started, the INR response is monitored frequently until a stable dose-response relationship is obtained; thereafter, the frequency of INR testing is reduced. An anticoagulant effect is observed within 2 to 7 days after beginning oral warfarin, according to the dose administered. Care level is typically reached in 5-6 days (Marevan SPC). When rapid anticoagulation is required, heparin can be given together with warfarin until the desired INR-level is reached with warfarin.

In long-term monitoring, the frequency of measurement depends among other things on patient compliance and clinical condition, but the goal for monitoring interval is 4 weeks (Marevan SPC). If there are significant changes in INR levels in the monitoring or if the patient has a liver or disease affecting the absorption of vitamin K, the follow-up range must be shorter. Many medicines may potentiate or weaken the effect of warfarin, which should be monitored when other medications are started or discontinued. The interactions of warfarin are more thoroughly presented in the interactions- chapter.

There are theoretical reasons for beginning treatment with the average maintenance dose of 5 mg daily, which usually results in an INR of 2.0 after 4 or 5 days (Harrison et al 1997). Lower starting doses should be used in patients sensitive to warfarin, including the elderly, and in those at increased risk of bleeding (James et al. 1992). The SPC of Marevan (warfarin) says that a normal weighted patient with spontaneous INR of less than 1.2 is given for three consecutive days 10 mg of warfarin (Marevan SPC). Dosing will be continued on the fourth day of the measured INR according to the following table (Table 6). For outpatients and for patients with congenital protein C or protein S deficiency 5 mg of warfarin (*) is recommended as the starting dose for three consecutive days. For elderly, small-sized patients, for patients with spontaneous INR above 1.2 or having a disease or medication affecting the effect on anticoagulation therapy starting dose of 5 mg warfarin (*) is recommended for two consecutive days. After the initiation, the therapy continues according to Table 6.

TABLE 6. WARFARIN DOSAGE IS BASED ON THE INR-VALUE AND THE DOSE SHOULD BE TITRATED ACCORDING TO THIS TABLE IN THE BEGINNING OF THE TREATMENT (MAREVAN SPC).

Treatment day	INR	Warfarin dose mg/day
1.	-	10 (5*)
2.	-	10 (5*)
3.	< 2.0	10 (5*)
	2.0–2.4	5
	2.5–2.9	3
	3.0–3.4	2,5
	3.5–4.0	1,5
	> 4.0	A day off
4.-6.	< 1.4	10
	1.4–1.9	7,5
	2.0–2.4	5
	2.5–2.9	4,5
	3.0–3.9	3
	4.0–4.5	A day off, then 1,5
	> 4.5	2 days off, then 1,5
7.-		Weekly dose
	1.1–1.4	Add weekly dose 20%
	1.5–1.9	Add weekly dose 10%
	2.0–3.0	Same dose
	3.1–4.5	Decrease weekly dose 10%
	> 4.5	Pause until INR < 4.5, then continue with 20% smaller dose

6. EFFECT

Randomised clinical trials have shown that anticoagulation with warfarin reduces the risk of stroke by up to two thirds (Atrial Fibrillation Investigators 1994). Among patients treated with warfarin who are below the target range at the time of a stroke event, severity is greater and 30-day survival is reduced compared with patients at an INR greater than 2.0. (Käypähoito-suositus; Pastori et al. 2015). The effect of warfarin is usually stratified by stroke risk ($CHADS_2$) and treatment status (TTR) in outcome analysis (Table 7).

TABLE 7. STROKE AND MORTALITY RATES PER 1 000 PATIENT YEARS STRATIFIED BY STROKE RISK AND TREATMENT STATUS (MORGAN ET AL. 2009).

Event rate	Warfarin	Non warfarin
CHADS<2		
Stroke	46.0	44.5
Mortality	84.9	211.5
CHADS >=2		
Stroke	116.5	113.9
Mortality	227.6	402.8
All		
Stroke	59.1	57.5
Mortality	104.2	237.7

Best effect against stroke and survival has been shown when TTR > 80 (Figure 3, Figure 4). International treatment guidelines suggest warfarin substitution if TTR is below 70 despite repairing attempts of balance-reducing factors, such as drug interactions (ESC 2016). In Finland the current recommendation is to have TTR-values over 80 (Käypähoito-suositus).

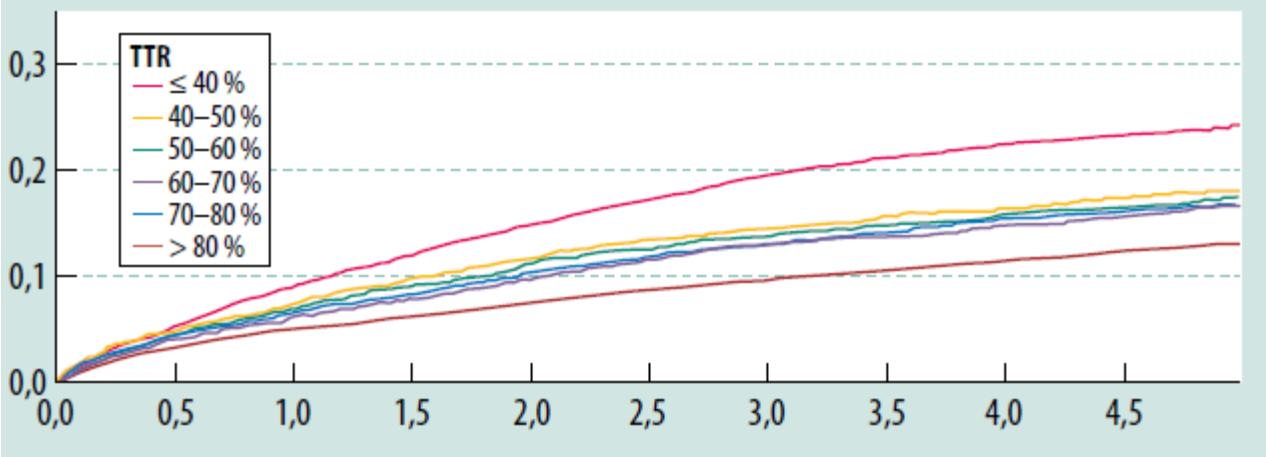

FIGURE 3. EFFECT OF WARFARIN THERAPY (TTR, %) TO CUMULATIVE APPEARANCE OF STROKE (LEHTO ET AL. 2017).

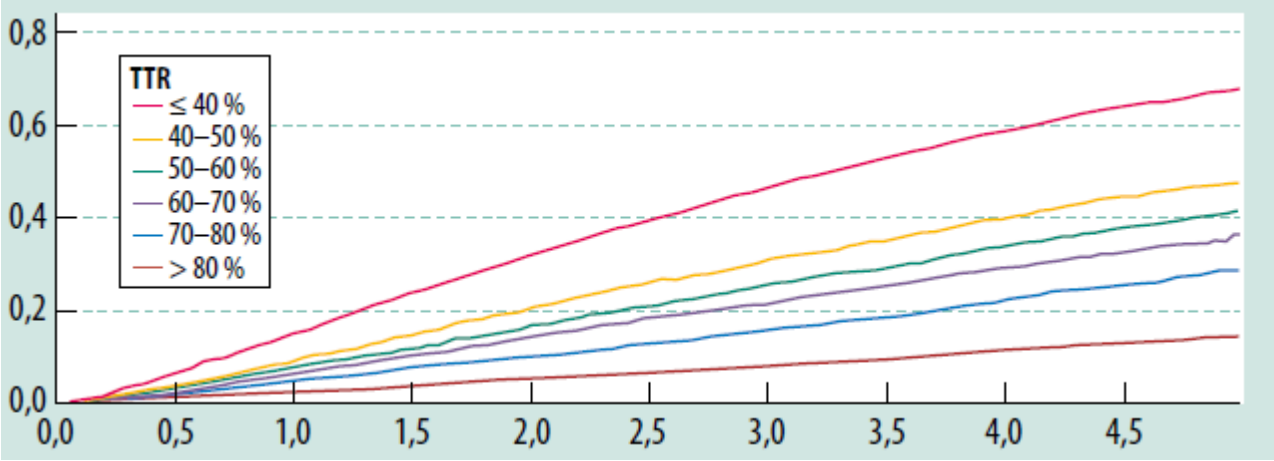

FIGURE 4. EFFECT OF WARFARIN THERAPY (TTR, %) TO CUMULATIVE MORTALITY (LEHTO ET AL. 2017).

Significant improvement in time to stroke compared with non-warfarin-treated groups has been proven with the greatest TTR-group (71% and above) (Figure 5). Mortality has been shown to be significantly reduced for all warfarin treated patient groups with INR-control of over 40% when compared with the non-warfarin treatment group after adjusting for age, sex and $CHADS_2$ score.

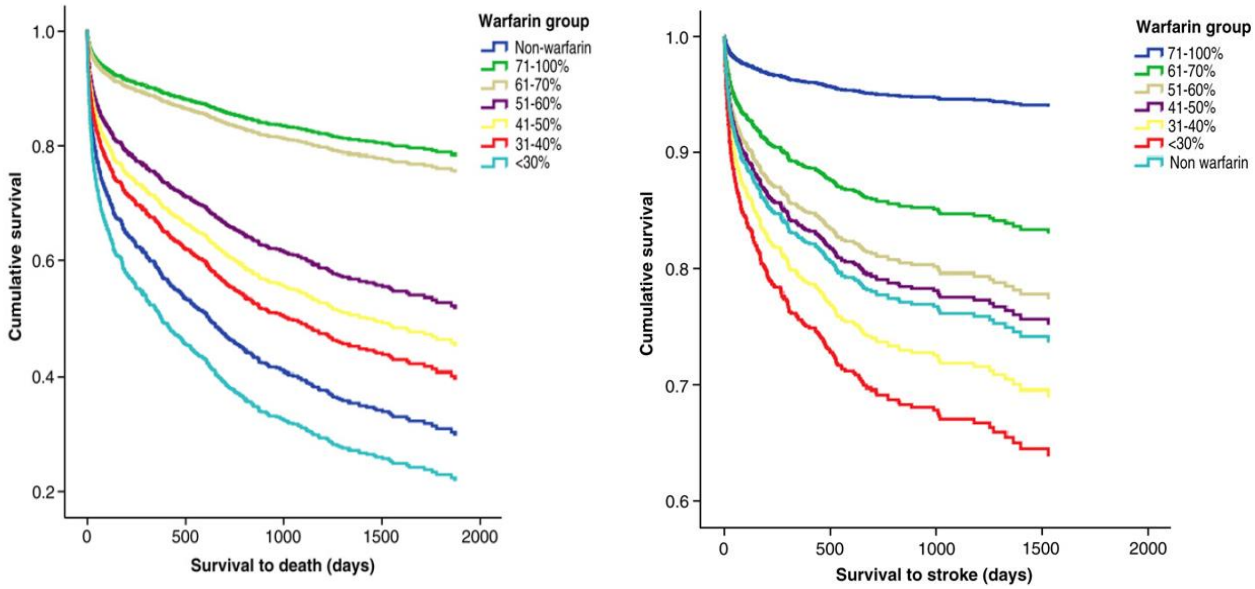

FIGURE 5. COX PROPORTIONAL HAZARDS MODEL FOR SURVIVAL TO POST ATRIAL-FIBRILLATION DEATH AND STROKE FOR PATIENTS AT MODERATE OR HIGH RISK OF STROKE $CHADS_2 \geq 2$ BY LEVEL OF WARFARIN CONTROL (MORGAN ET AL. 2009).

The level of warfarin treatment has slowly improved in Finland (Mustonen et al. 2018). The retrospective FinWAF-study showed an average TTR of 62% with a median of 67% (Lehto et al. 2017). In 2016 a quality control in Jyväskylä area showed an average TTR of 76% (Mustonen et al. 2018). The FinWaf study also showed that patient outcomes continued to improve with increasing TTR values up to a TTR ≥80%; therefore, the target for the TTR should exceed 80% instead of the traditional range of at least 60–70% (Table 8).

TABLE 8. RESULTS FROM THE FINWAF-STUDY ON TTR-RANGE EFFECT ON ANNUAL STROKE RISK, BLEEDING EVENTS AND OVERALL MORTALITY. ALL DIFFERENCES AMONG THE TTR GROUPS WERE HIGHLY SIGNIFICANT (P < 0.001) (LEHTO ET AL. 2010).

TTR	Annual Stroke Risk	Bleeding events	Overall mortality
≤ 40%	9.3%	7.5%	20.9%
60 - 70%	4.7%	4.5%	8.5%
70 - 80%	4.6%	4.3%	6.4%
> 80%	3.1%	2.6%	3.1%

6.1 TTR IN RWE-STUDIES

In real-world clinical setting the TTR-level varies and mostly the desirable target level is not met (Currie et al. 2006; Ruff et al. 2014; Holvitie et al. 2014). In Finland the city of Helsinki conducted a project aimed at improving patient sel-care and electronic services in primary healthcare (Holvitie et al. 2014). At baseline of the study, the TTR was 70%, INR was measured on average 13,4 times per year and the patients were mostly over 65-years old. As a result the TTR rose to 74% and among self-care patients from 74% to almost 80%. Also, the introduction of electronic communication channels has reduced patients' attachment to healthcare, facilitated communication and reduced unnecessary contacts. The empowerement of trained patients is apparent and appears to be improved in the management balance, especially in self-help patients. Another RWE-study in Finland showed that the average TTR was 65.2% but increased to 74.5% among patients using warfarin continuously (Hallinen et al. 2014). One-third of the patients in this study had a TTR of below 60%.

In Oulu outpatient healthcare TTR-values have been studied retrospectively in 2013 (Leskelä et al. 2013). There were 2,940 patients in the patient population to be analyzed. The rates of INR-values in patients undergoing warfarin therapy and the maintenance of results at treatment level have been reviewed by age group and individual level. An average of 15.9 INR-tests was taken per year from patients, 63.8% of the test results were at treatment level and 77.6% at the extended treatment level (INR-values 1.9-3.5). Most of the INR values outside the treatment range were below with and INR-value less than 2.0. Warfarin therapy was at a good level (TTR> 70%) in 54.7% of patients. The total TTR of the material was 66.4% (95% confidence interval 66.3-66.5%), which is slightly better than in many international studies. The highest level of treatment was the test results of 70-80 years of age.

In a Swedish registry study 77 423 unselected patients with 100 952 treatment periods of warfarin, constituting 217 804 treatment years (Sjögren et al. 2015). Atrial fibrillation was the most common indication (68%) and the mean time in therapeutic range of the INR 2.0-3.0 was 76.5%. The annual incidence of severe bleeding was 2.24% and of thromboembolism 2.65%. The incidence of intracranial bleeding was 0.37% per treatment year in the whole population, and 0.38% among patients with atrial fibrillation.

A retrospective study of a large UK population compared the risk of serious thromboembolic and bleeding events and survival in patients with NVAF treated with or without warfarin (Currie et al. 2006). Survival was increased in patients treated with warfarin, and this was related to the proportion of time they spent within the target INR range (2.0–3.0). Warfarin treatment was found to be associated with a lower risk of ischaemic and thromboembolic events and an increase in bleeding events. However, in this study, the risk reduction observed (26%) was substantially lower than in clinical trials where reductions in risk of stroke of up to two thirds have been reported (Atrial fibrillation investigators 1994). This suggests that in routine medical management such reductions are not achieved, and the level of INR-control may explain this discrepancy. The results show that the mean survival of patients treated with warfarin was more than a year longer than that of the group who did not receive warfarin (Currie et al. 2006). The differences in survival are apparent even in the oldest patients.

6.2 EXCESSIVE ANTICOAGULATION

Excessive anticoagulation and hemorrhage are well known complications of warfarin therapy (Marevan SPC). High international normalized ratio (INR) level predisposes to significant bleeds and independently increases morbidity and mortality also through mechanisms other than bleeding (Hylek et al. 2003).

Since there aren't many large-scale studies on very high INR values in warfarin patients, Excessive Warfarin Anticoagulation (EWA) study from Finnish registries sought to evaluate the incidence, patient characteristics and predictors of excessive anticoagulation in patients with atrial AF on warfarin treatment in a large well-defined patient population (Jaakkola et al. 2017). The EWA-researchers screened all patients (n = 13 618) in the Turku University Hospital region with an INR≥ 2 between years 2003–2015. The aim of this study was to investigate the occurrence and predicting factors for episodes with very high (≥ 9) INR-values in warfarin treated patients with atrial fibrillation. As a result, 4,1% of the patients with an INR ≥ 2 had a very high INR (≥ 9), but only 25.5% had a significant bleeding related to high INR. The EWA- study shows that severe overanticoagulation is a rare phenomenon during warfarin treatment and that the first months after introduction of the treatment carry the highest risk. Overanticoagulation can also be predicted with many patient characteristics together with temporary predisposing factors highlighting the complexity and multifactorial etiology of excessive anticoagulation. By identifying these risk factors, it is possible to improve the safety of warfarin anticoagulation.

6.3 REVERSAL OF ANTICOAGULATION

Prevalence of anticoagulation therapy increases with aging population and reversal of anticoagulation is required prior to surgery. The reversal strategies include the temporary withholding of warfarin and the administration of vitamin K, fresh frozen plasma (FFP), or prothrombin complex concentrate (PCC) (Ageno et al. 2009). The choice of treatment method depends on the urgency of the anticoagulant effect reversal. Withholding warfarin is not a feasible method because the international normalized ratio (INR) may take 3–7 days to normalize. It is also less predictable and requires meticulous organization and monitoring prior to the procedure if bridging anticoagulation is needed. If 3 mg of intravenous vitamin K is administered in addition to withholding warfarin, appropriate hemostatic function can be restored within 24 h in most patients with a therapeutic INR (Burbury et al. 2011). A budget impact analysis has been done in Finland regarding these three reversal strategies and this analysis favored vitamin K as an anticoagulation reversal therapy (Purmonen et al. 2015).

Reversal of DOACs' anticoagulation effect is more difficult, since dabigatran is at the moment the only DOAC with a specific antidote (idarucizumab) to be used in emergency situations like vitamin K is for warfarin (Pollack et al. 2015).

7. WARFARIN OUTPATIENT COST

As INR-monitoring has been shown to be both necessary and time and resource consuming, the warfarin outpatient cost should also be estimated (Hallinen et al. 2014). In Finland (in Joensuu) this has been estimated with data collected on healthcare resource use, warfarin use, individually defined target INR range and INR test results from the primary healthcare database for patients with AF diagnosis. The analysed dataset consisted of a 1-year follow-up. Warfarin treatment balance was estimated with the proportion of time spent in the therapeutic INR range (TTR) and patients were considered to be warfarin users during the follow-up period if their TTR was analysable from the database. The cost of used healthcare resources was valued separately with national and service provider unit costs to estimate the total outpatient treatment costs. The factors potentially impacting the treatment costs were assessed with a generalised linear regression model.

The results show that approximately 50% of the patients with AF with CHADS-VASc ≥1 used warfarin (Hallinen et al. 2014). The average TTR was 65.2% but increased to 74.5% among patients using warfarin continuously during followup (Table 9). One-third of the patients had a TTR of below 60%.

TABLE 9. AVERAGE TIME IN TTR AMONG WARFARIN USERS (HALLINEN ET AL. 2014).

Outcome variable	N	Mean	SD
Individual TTR	1271	65.2	26.8
Standard TTR	1271	64.4	26.9
Individual TTR, continuous use of warfarin	474	72.3	19.9
Standard TTR, continuous use of warfarin	474	70.9	20.7
Individual TTR, continuous use of warfarin and 1-year follow-up	420	74.5	17.8
Standard TTR, continuous use of warfarin and 1-year follow-up	420	72.8	19.0

Individual TTR calculated on the basis of individually specified target INR range when available and on the basis of assumed 2.0–3.0 target range when individually specified target ranges were not defined. Standard TTR calculated on the basis of assumed 2.0–3.0 target INR range for all warfarin users. Continuous use, no gaps exceeding 56 days between two successive INR test results.
INR, international normalised ratio; TTR, time in therapeutic range.

The average outpatient costs in the patient cohort were €314.44 with the national unit costs and €560.26 with the service provider unit costs (Table 10). The costs among warfarin users were, on average, €524.11 or €939.54 higher compared with the costs among non-users, depending on the used unit costs. A higher TTR was associated with lower outpatient costs.

TABLE 10. HEALTHCARE RESOURCE USE AND AVERAGE COST (2011 VALUE) (HALLINEN ET AL. 2014).

	Resourse use, mean (SD)			National unit costs, mean (SD)			Service provider costs, mean (SD)		
	All (n=2 746)	Warfarin (n=1271)	No warfarin (n=1 475)	All	Warfarin	No warfarin	All	Warfarin	No warfarin
Physician visits	1.8 (3.0)	3.3 (3.4)	0.6 (1.8)	130.37 (213.7)	234.94 (242.3)	40.27 (130.03)	219.34 (359.52)	395.24 (407.65)	67.74 (218.76)
Physician phone consultations	0.4 (1.0)	0.8 (1.2)	0.1 (0.6)	8.43 (19.8)	15.04 (24.9)	2.73 (11.4)	20.43 (48.08)	36.46 (60.30)	6.61 (27.54)
Nurse visits	2.6 (5.6)	4.8 (7.1)	0.7 (2.7)	81.18 (176.3)	149.97 (223.4)	21.91 (85.4)	145.12 (315.17)	268.08 (399.31)	39.17 (152.75)
Nurse phone consultations	2.8 (5.9)	6.0 (7.5)	0.2 (0.8)	25.13 (52.03)	52.61 (66.2)	1.44 (7.2)	53.35 (110.47)	111.70 (140.58)	3.07 (15.30)
Inpatient days	10.9 (50.4)	17.4 (59.5)	5.2 (40.1)	1795.19 (8327.84)	2880.29 (9834.83)	860.16 (6627.74)	1661.10 (7705.83)	2665.16 (9100.26)	795.91 (6132.71)
INR tests	8.8 (13.3)	19.1 (13.7)	0 (0.1)	69.33 (105.5)	149.75 (107.5)	0.04 (0.6)	122.04 (184.0)	263.60 (189.3)	0.07 (1.1)
Average total costs				2109.62 (8352.22)	3482.59 (9808.79)	926.54 (6632.42)	2221.37 (7764.31)	3740.24 (9064.49)	912.56 (6145.70)
Average outpatient costs				314.44 (419.4)	602.30 (424.2)	66.38 (198.8)	560.26 (744.60)	1075.08 (750.65)	116.65 (348.65)

INR, international normalised ratio.

8. INTERACTIONS

Many factors have been reported as barriers to treatment with warfarin, including interactions between warfarin and other medications and foods, concerns over the risk of bleeding, and practical problems relating to frequent INR monitoring (Sudlow et al. 1998). Many medicines may potentiate or weaken the effect of warfarin, which should be monitored when other medications are started or discontinued (Marevan SPC, Table 11).

TABLE 11. LEVEL 1 EVIDENCE OF DRUG AND FOOD INTERACTIONS WITH WARFARIN* (WELLS ET AL. 1994).

Interaction	Antibiotics	Cardiac	Anti-Inflammatory	Central Nervous System	Gastrointestinal	Miscellaneous
Potentiation	cotrimoxazole (8), erythromycin (8), fluconazole (6), isoniazid (1), metronidazole (8), miconazole (6)	amiodarone (28), clofibrate (8), propafenone (8), proprano-lol (12), sulfinpyrazone† (13)	phenylbutazone† (14), piroxicam (1)	alcohol (with liver disease) (1)	cimetidine‡ (50), omeprazole (19)	
Inhibition	griseofulvin† (2), nafcillin (1), rifampin (31)	cholestyramine (27)		barbiturates (12), carbamazepine (3), chlordiazepoxide (1)	sucralfate (1)	High vitamin K content foods/enteral feeds (5), large amounts of avocado (2)
No effect	enoxacin (5)	atenolol (6), bumetanide (10), felodipine (2), metoprolol (6), moricizine (1)	diflunisal (5), ketorolac (10), naproxen (5)	alcohol (15), fluoxetine (3), nitrazepam (3)	antacids (6), famotidine (8), nizatidine (7), psyllium (6), ranitidine§ (14)	

* Numbers in parentheses are numbers of patients, volunteers, or both.
† Supporting level 1 evidence (see Appendix 1 for criteria) from patients and volunteers.
‡ In a small number of volunteers, an inhibitory drug interaction occurred.
§ Level 2 evidence of potentiation in patients.

Drugs that appear highly probable to interact with warfarin are not absolutely contraindicated (Wells et al. 1994). Instead, patients and clinicians should be aware of the interaction potential, individual variability in the response to interactions and add INR-monitoring and possible dose changes accordingly.

9. DIRECT ORAL ANTICOAGULANTS (DOACS)

The advantages and disadvantages of DOACs have been tabulated in the current treatment guidelines-chapter (Table 4). The guidelines state that direct anticoagulants are at least as effective and safer as warfarin in AF associated stroke (Käypähoito-suositus). Because of better treatment compliance, safety and comfort, direct anticoagulant is a good choice for new atrial fibrillation patients. Well-operated warfarin treatment in long-term treatment can be continued, but rapid replacement to direct

anticoagulants is recommended if warfarin cannot be continued because of allergies or other disadvantages or INR tracking is not successful. The Finnish guidelines give also a recommendation that DOAC is the primary choice in short-term treatment (including cardioversion or ablation therapy), because of the slow progression of warfarin treatment balance and anticoagulation efficacy.

Comparisons between DOACs and warfarin has been done in multiple studies (Ruff et al. 2014). Table 12 shows the results of a meta-analysis done from phase III clinical trials of warfarin versus dabigatran, rivaroxaban, apixaban and edoxaban in 2009-2013.

TABLE 12. BASELINE CHARACTERISTICS OF THE INTENTION-TO-TREAT POPULATIONS OF THE INCLUDED TRIALS AND COMBINED COMPARISON BETWEEN DOAC (=NOAC) AND WARFARIN (RUFF ET AL. 2014).

	RE-			ROCKET-AF[6]		ARISTOTLE		ENGAGE AF-TIMI			Combined	
	Dabigatran 150 mg (n=6076)	Dabigatran 110 mg (n=6015)	Warfarin (n=6022)	Rivaroxaban (n=7131)	Warfarin (n=7133)	Apixaban (n=9120)	Warfarin (n=9081)	Edoxaban 60 mg (n=7035)	Edoxaban 30 mg (n=7034)	Warfarin (n=7036)	NOAC (n=42 411)	Warfarin (n=29 272)
Age (years)	71·5 (8·8)	71·4 (8·6)	71·6 (8·6)	73 (65–78)	73 (65–78)	70 (63–76)	70 (63–76)	72 (64–68)	72 (64–78)	72 (64–78)	71·6	71·5
≥75 years	40%	38%	39%	43%	43%	31%	31%	41%	40%	40%	38%	38%
Women	37%	36%	37%	40%	40%	36%	35%	39%	39%	38%	38%	37%
Atrial fibrillation type												
Persistent or permanent	67%	68%	66%	81%	81%	85%	84%	75%	74%	75%	76%	77%
Paroxysmal	33%	32%	34%	18%	18%	15%	16%	25%	26%	25%	24%	22%
CHADS2*	2·2 (1·2)	2·1 (1·1)	2·1 (1·1)	3·5 (0·94)	3·5 (0·95)	2·1 (1·1)	2·1 (1·1)	2·8 (0·97)	2·8 (0·97)	2·8 (0·98)	2·6 (1·0)	2·6 (1·0)
0–1	32%	33%	31%	0	0	34%	34%	<1%	<1%	<1%	17%	17%
2	35%	35%	37%	13%	13%	36%	36%	46%	47%	47%	35%	33%
3–6	33%	33%	32%	87%	87%	30%	30%	54%	53%	53%	48%	50%
Previous stroke or TIA*	20%	20%	20%	55%	55%	19%	18%	28%	29%	28%	29%	30%
Heart failure†	32%	32%	32%	63%	62%	36%	35%	58%	57%	58%	46%	47%
Diabetes	23%	23%	23%	40%	40%	25%	25%	36%	36%	36%	31%	31%
Hypertension	79%	79%	79%	90%	91%	87%	88%	94%	94%	94%	88%	88%
Prior myocardial infarction	17%	17%	16%	17%	18%	15%	14%	11%	12%	12%	15%	15%
Creatinine clearance‡												
<50 mL/min	19%	19%	19%	21%	21%	17%	17%	20%	19%	19%	19%	19%
50–80 mL/min	48%	49%	49%	47%	48%	42%	42%	43%	44%	44%	45%	45%
>80 mL/min	32%	32%	32%	32%	31%	41%	41%	38%	38%	37%	36%	36%
Previous VKA use§	50%	50%	49%	62%	63%	57%	57%	59%	59%	59%	57%	57%
Aspirin at baseline	39%	40%	41%	36%	37%	31%	31%	29%	29%	30%	34%	34%
Median follow-up (years)¶	2·0	2·0	2·0	1·9	1·9	1·8	1·8	2·8	2·8	2·8	2·2	2·2
Individual median TTR	NA	NA	67 (54–78)	NA	58 (43–71)	NA	66 (52–77)	NA	NA	68 (57–77)	NA	65 (51–76)

Data are mean (SD), median (IQR), or percent, unless otherwise indicated. NOAC=new oral anticoagulant. $CHADS_2$=stroke risk factor scoring system in which one point is given for history of congestive heart failure, hypertension, age ≥75 years, and diabetes, and two points are given for history of stroke or transient ischaemic attack. TIA=transient ischaemic attack. VKA=vitamin K antagonist. TTR=time in therapeutic range. NA=not available. *ROCKET-AF and ARISTOTLE included patients with systemic embolism. †ROCKET-AF included patients with left ventricular ejection fraction <35%; ARISTOTLE included those with left ventricular ejection fraction <40%. ‡RE-LY <50 mL/min, 50–79 mL/min, ≥80 mL/min; ARISTOTLE ≤50 mL/min, >50–80 mL/min, >80 mL/min. §RE-LY, ARISTOTLE, and ENGAGE AF-TIMI 48 patients who used VKAs for ≥61 days; ROCKET AF patients who used VKAs for ≥6 weeks at time of screening. ¶IQRs not available.

New oral anticoagulants had a favourable risk–benefit profile, with significant reductions in stroke, intracranial haemorrhage, and mortality, and with similar major bleeding as for warfarin, but increased gastrointestinal bleeding (Ruff et al. 2014). The relative efficacy and safety of new oral anticoagulants was consistent across a wide range of patients. Median TTR for the warfarin group in these studies varied

from 58 to 68 indicating that INR monitoring wasn't on a sufficient level in these clinical trials. Reversal of DOAC's anticoagulation effect is more difficult, since dabigatran is the only DOAC with a specific antidote (idarucizumab) to be used in emergency situations like vitamin K is for warfarin (Pollack et al. 2015).

Direct anticoagulants have not been compared with each other, and the Finnish treatment guidelines doesn't take a stand for the choice between them (Käypähoito-suositus). There is no research evidence available that well-balanced warfarin-treatment should be replaced with a direct oral anticoagulant. Most of the comparative and efficacy studies of warfarin compared to DOACs show that TTR among warfarin-treated patients is mostly under 70% (Ruff et al. 2014). This leads to a difficult comparison between the effect of different anticoagulants. In studies where warfarin patients spend a high proportion of time in the therapeutic range, warfarin is safe and effective and will continue to be a valid treatment option in the era of newer oral anticoagulants (Sjögren et al. 2015, Figure 5).

9.1 DOAC ADHERENCE

Concerns remain about DOACs because of their shorter half-lives and the potential for reductions in effectiveness with poor adherence (Borne et al. 2017). Compared to warfarin, the lack of laboratory monitoring to assess therapeutic levels, it is important to assess adherence to DOACs and the extent to which it varies by patient characteristics and different DOACs currently available.

A retrospective registry study with 2 882 patients between 2010-2015 has been done in order to evaluate adherence to newly prescribed DOACS. The adherence was calculated in the first year of therapy. As a result, more than one quarter of patients had sub-optimal adherence with DOACs (Table 13). While there were differences in adherence between DOAC and patient characteristics, these were not clinically significant. Outcomes including all-cause mortality and stroke were associated with medication adherence and several patient factors were associated with greater medication adherence (e.g. older age, diabetes, stroke).

TABLE 13. CHARACTERISTICS DESCRIBING MEDICATION ADHERENCE OF DOACS IN A RETROSPECTIVE REGISTRY STUDY (BORNE ET AL. 2017).

	All n = 2882	Dabigatran n = 2096 (72.7%)	Rivaroxaban n = 571 (19.8%)	Apixaban n = 215 (7.5%)	p
Mean (SD) pill count per dispensed supply	38.1 (20.9)	38.2 (20.8)	38.2 (22.0)	36.4 (18.7)	<0.01
Proportion of Days Covered (PDC)* (mean + SD)	0.85 (0.19)	0.84 (0.20)	0.86 (0.18)	0.89 (0.14)	<0.01
PDC < 80% n (%)	796 (27.6%)	604 (28.8%)	143 (25.0%)	49 (22.8%)	0.05

* The PDC was defined as the number of doses dispensed in relation to the dispensing period. The numerator was based on the prescription fill dates and number of pills dispensed to determine the number of outpatient days for which each DOAC was supplied. Patients were considered adherent if they achieved a PDC > 80%.

Similar trends to DOAC medication adherence can be seen in other registry studies (Tsai et al. 2013; Shore et al. 2014). E.g. in an overall study-population, 39.9% of 17,691 patients were nonpersistent to dabigatran and two in 5 patients discontinued dabigatran therapy within 6 months, and the majority of these patients were not anticoagulated with warfarin upon discontinuation (Tsai et al. 2013). Another adherence study on dabigatran showed that 27,8% of the study population had a PDC < 80% and were classified as non-adherent.

These findings highlight potential gaps in the care of patients treated with DOACs in routine practice and suggest that medication nonadherence is common among many chronic illnesses and highly impacts outcomes.

10. THERAPEUTIC VALUE OF INR- REMOTE MONITORING

Previous studies show that adding electronic communication channels has reduced patients' attachment to healthcare, facilitated communication and reduced unnecessary contacts (Holvitie et al. 2014). The empowerement of trained patients is apparent and appears to be improved in the management balance, especially in self-help patients. It has been demonstrated that 50–60% of patients can be expected to remain in their target range if monitoring of INR occurs monthly, 77–85% if monitored weekly and up to 92% if monitored every 3 days (Oral anticoagulation monitoring study group 2001). It has been postulated that a threshold may exist beyond which there is no further beneficial effect of increased testing and this has been suggested to be between 2 and 4 days (Samsa 2000). It would be unrealistic to expect an anticoagulation clinic to monitor patients with such frequency, but home monitoring does allow for this. Self-testing and self-management are associated with a rate of testing that is higher than with usual care (Ansell et al. 2005). Remote monitoring can be devided to patient self-management and self-testing. Patient self-management is used in a setting where the patient self-measures the INR-value and makes dose adjustments independently. Patient self-testing is used when the patient tests the INR-value remotely but result interpretation and dosage adjustments are done by healthcare professionals.

10.1 PATIENT SELF-MANAGEMENT

In some countries, such as Germany, UK and Canada self-monitoring and self-management with portable monitors are established therapeutic methods add Cochrane review of self monitoring has been done (Heneghan et al. 2016). There are several available point-of-care devices and the most well known is the CoaguChek® monitor. Other available monitors are the ProTime®Microcoagulation System, INRatio® Monitor, Hemochron Junior Signature, and the TAS near-patient test system. Patient self-monitoring means that patients self-monitor and self-adjust the dose of their oral anticoagulants guided by a capillary whole-blood prothrombin time (PT) monitor. The study results vary, some studies show superiority of self-monitoring over other monitoring methods, other show no significant difference between monitoring practices.

In the first long-term study of patient self-management patients monitored their PTs 2153 times during a mean interval of 44.7 months compared with 1608 PTs in matched control patients receiving oral anticoagulation at a tertiary medical institution during a mean interval of 42.5 months (Regier et al. 2006). Study patients made an average of 11.5 dosage changes per patient, contrasted with 22.7 changes per control patient ($P<0.001$). The PTs in study patients were within the recommended therapeutic range in 88.6% (95% confidence interval, 87.2 to 89.9) of the determinations compared with 68.0% (95% confidence interval, 65.7 to 70.3; $P<0.001$) of the determinations made by the matched control patients. In response to the 2153 PTs, study patients made 67 (3.1%) dosage decisions that were considered incorrect based on physician guidelines. None of these changes led to adverse outcomes. There was no significant difference in complication rates between the two groups. This result suggests that patients can successfully measure their own PTs, adjust their own warfarin dosage, and achieve a degree of therapeutic effectiveness at least as good, if not better than patients managed in an anti-coagulation clinic.

The Cochrane review pooled together 28 relevant clinical trials comparing patient self-management, patient self-testind and standard care (Heneghan et al. 2016). The summary of findings are presented in

Table 14 and Table 16.

TABLE 14. SUMMARY OF FINDINGS IN THE COCHRANE REVIEW COMPARISON BETWEEN STANDARD CARE AND PATIENT SELF-MONITORING (SELF-MANAGEMENT) (HENEGHAN ET AL. 2016). PATIENT OR POPULATION: PATIENTS ON LONG-TERM ANTICOAGULANT THERAPY (TREATMENT DURATION LONGER THAN TWO MONTHS) IRRESPECTIVE OF THE INDICATION FOR TREATMENT. SETTINGS: PRIMARY CARE, SPECIALIST CLINICS (EUROPE, AMERICA, CANADA)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Standard care	Self-management			
Thromoembolic events (Follow-up: 3 to 57 months)	Study population		RR 0.47 (0.31 to 0.70)	3497 (11 studies)	Moderate[2]
	36 per 1000	17 per 1000 (12 to 25)			
	Moderate risk population				
	16 per 1000	7 per 100 (5 to 11)			
All-cause mortality (Follow-up: 6 to 57 months)	Study population		RR 0.55 (0.36 to 0.84)	3058 (8 studies)	Moderate[2]
	33 per 1000	18 per 1000 (12 to 28)			
	Moderate risk population				
	17 per 1000	7 per 100 (6 to 14)			
Major haemorrhage (Follow-up: 4 to 57 months)	Study population		RR 1.08 (0.79 to 1.47)	3980 (13 studies)	Low[1]
	33 per 1000	36 per 1000 (22 to 44)			
	Moderate risk population				
	18 per 1000	19 per 100 (14 to 26)			
Minor haemorrhage (Follow-up: 4 to 57 months)	Study population		RR 0.91 (0.47 to 1.76)	1862 (7 studies)	Low[3]
	137 per 1000	125 per 1000 (64 to 241)			
	Moderate risk population				
	2 per 1000	2 per 1000 (1 to 4)			

* The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% conf idence interval) is
based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI).
CI: Conf idence interval; RR: Risk Ratio
GRADE Working Group grades of evidence
High quality: We are very conf ident that the true ef fect lies close to that of the estimate of the ef fect.
Moderate quality: We are moderately conf ident in the ef fect estimate: The true ef fect is likely to be close to the estimate of the ef fect, but there is a possibility that it is substantially dif ferent.
Low quality: Our conf idence in the ef fect estimate is limited: The true ef fect may be substantially dif ferent f rom the estimate of the ef fect.

1 Downgraded f rom high to low because of serious risk of bias and imprecision of ef fect estimate.
2 Downgraded f rom high to moderate because of serious risk of bias.
3 Downgraded f rom high to low because of serious risk of bias and substantial heterogeneity.

Patient self-managament or self-testing of oral anticoagulation leads to a significant 50% reduction in thromboembolism but no reduction in all-cause mortality (Heneghan et al. 2016). However, trials of self-management led to a significant reduction in all-cause mortality. Self-management did not reduce major haemorrhages nor did self-testinging.

The results of other studies show the equivalence of the monitoring methods (Cromheecke et al. 2000; Sunderji et al. 2004; Fitzmaurice et al. 2002). For long-term oral anticoagulation treatment the comparison between self-managed and anticoagulation clinic management showed that no significance difference in the overall quality of control of anticoagulation between the two study periods (Figure 6). Self-management of INR appears to result in control of anticoagulation that is at least equivalent to management by specialist clinic (

Table 15.). It is also better appreciated by patients.

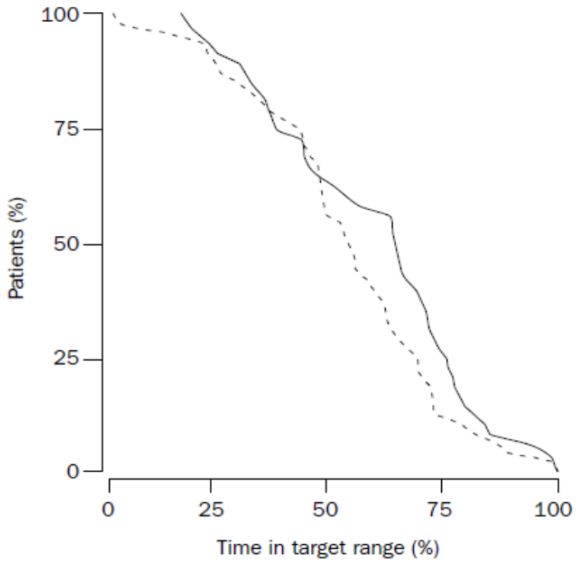

FIGURE 6. COMPARISON OF CONTROL OF ANTICOAGULATION (EXPRESSED AS PERCENTAGE OF THE TIME IN THE THERAPEUTIC TARGET RANGE) IN PATIENTS DURING SELF-MANAGEMENT (UNBROKEN LINE) AND DURING ANTICOAGULATION CLINIC-GUIDED MANAGEMENT (BROKEN LINE). OVERALL THERE IS NO SIGNIFICANCE DIFFERENCE BUT THE PROPORTION OF PATIENTS MORE THAN 50% OF THE TIME IN THE THERAPEUTIC RANGE IS LARGER DURING SELF-MANAGEMENT THAN DURING ANTICOAGULATION-CLINIC-BASED MANAGEMENT ($P<0.005$) (CROMHEECKE ET AL. 2000).

TABLE 15. PATIENTS' CHARACTERISTICS AND COMPARISON OF SUBJECTIVE QUALITY-OF-CARE ASSESSMENT (CROMHEECKE ET AL. 2000).

	Self-management group (n=45)	Conventional-care group (n=44)	p	Cronbach-α
Age	42 (16)	42 (12)	. .	. .
M/F ratio	28:17	25:19	. .	. .
Indication for anticoagulation				
Artificial heart valve	23 (51%)	21 (48%)		
Arterial thromboembolism	12 (24%)	10 (23%)		
Venous thromboembolism	10 (22%)	12 (27%)		
Target range INR				
2·0–3·0	2 (4%)	2 (5%)		
2·5–3·5	13 (29%)	16 (36%)		
3·0–4·0	24 (53%)	22 (50%)		
3·5–4·5	6 (13%)	4 (9%)		
Years on anticoagulant treatment	3·9 (2·2)	4·1 (2·1)		
Highest school education				
University/advanced education	20 (44%)	19 (43%)		
Intermediate education	21 (47%)	21 (48%)		
Primary education	4 (9%)	4 (9%)		
General treatment satisfaction	4·8 (1·2)	4·0 (1·5)	0·015	0·74
Self-efficacy	5·4 (0·6)	4·5 (1·0)	<0·001	0·70
Daily worries	1·8 (0·5)	2·6 (0·5)	<0·001	0·83
Distress	2·5 (0·8)	2·9 (1·1)	0·022	0·76
Social issues	1·7 (0·6)	2·7 (0·9)	<0·001	0·79

The comparison is made between patients participating in the cross-over study at the end of the self-management period and a matched control group receiving conventional care, ie, management of oral anticoagulation by the specialised anticoagulation clinic. Values are mean (SD).

Similar result of clinical trials in AC-treatment self-monitoring has been reported in the UK and Canada (Sunderji et al. 2004; Fitzmaurice et al. 2002). Data from these studies demonstrate that patient self-management is as safe as primary care management for a selected population.

10.2. PATIENT SELF-TESTING

Studies have also been published on patient self-testing, where patients measure their prothrombin time/INR-value and raport the result to healthcare professionals, who make treatment decisions based on these measurements (White et al. 1989). The monitors differ between studies, but the monitor results are comparable with the clinical laborarity results in each of these studies.

46 patients has completed a 8-week study, where oral anticoagulation therapy managed using a portable prothrombin time monitor compared with specialized anticoagulation clinic care (White et al. 1989). The

median percentage of time that patients in the home-monitor group (n = 23) were within a range equal to the target prothrombin ratio ± 0. 3, but always above 1.25, was 93%, compared with 75% for patients in the clinic group (n = 23) (P = 0.003). There was no significant difference between groups in the percentage of time above the therapeutic range; however, the percentage of time that patients were subtherapeutic was significantly greater in the clinic group (P < 0.001). There were no major thromboembolic or hemorrhagic complications in either group. Patients doing home monitoring have achieve superior anticoagulation control compared with those receiving standard anticoagulation clinic care.

Another study of patient self-testing has been done in 2013, where the primary objective was to evaluate the effect of a system combining frequent INR self-testing with online remote monitoring and management ($STORM_2$) (Bussey et al. 2013). Additionally the researchers assessed the impact of $STORM_2$ on clinician time. As a result TTR improvement with $STORM_2$ was 25% and $STORM_2$ required a minimum amount of clinician time with less than 10 minutes per four patient visits per month. This study shows significant benefit to warfarin patients in a self-testing environment with minimal healthcare resources.

In the Cochrane review in 2016 self-testing was also compared to standard care in relevant clinical trials (Heneghan et al. 2016). Summary of findings are presented in Table 16 and for clarification in this review patient self-testing is called patient self-monitoring. These result suggest that self-testing reduces thromboembolis events also significantly.

TABLE 16. SUMMARY OF FINDINGS IN THE COCHRANE REVIEW COMPARISON BETWEEN STANDARD CARE AND PATIENT SELF-TESTING (SELF-MONITORING) (HENEGHAN ET AL. 2016). PATIENT OR POPULATION: PATIENTS ON LONG-TERM ANTICOAGULANT THERAPY (TREATMENT DURATION LONGER THAN TWO MONTHS) IRRESPECTIVE OF THE INDICATION FOR TREATMENT. SETTINGS: PRIMARY CARE, SPECIALIST CLINICS (EUROPE, AMERICA, CANADA).

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Standard care	Self-monitoring			
Thromoembolic events (Follow-up: 3 to 57 months)	Study population		RR 0.69 (0.49 to 0.97)	4097 (7 studies)	Moderate[2]
	35 per 1000	24 per 1000 (17 to 34)			
	Moderate risk population				
	34 per 1000	23 per 100 (17 to 33)			
All-cause mortality (Follow-up: 6 to 57 months)	Study population		RR 0.94 (0.78 to 1.15)	3300 (3 studies)	Moderate[2]
	90 per 1000	85 per 1000 (70 to 104)			
	Moderate risk population				
	0 per 1000	0 per 0 (0 to 0)			
Major haemorrhage (Follow-up: 4 to 57 months)	Study population		RR 0.90 (0.74 to 1.09)	4038 (7 studies)	Low[1]
	97 per 1000	82 per 1000 (67 to 99)			
	Moderate risk population				
	49 per 1000	44 per 100			

		(36 to 53)			
Minor haemorrhage (Follow-up: 4 to 57 months)	**Study population**		RR 1.16 (0.95 to 1.42)	3503 (6 studies)	Moderate[2]
	275 per 1000	319 per 1000 (259 to 391)			
	Moderate risk population				
	188 per 1000	218 per 1000 (177 to 267)			

* The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% conf idence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI).
CI: Conf idence interval; RR: Risk Ratio
GRADE Working Group grades of evidence
High quality: We are very conf ident that the true ef fect lies close to that of the estimate of the ef fect.
Moderate quality: We are moderately conf ident in the ef fect estimate: The true ef fect is likely to be close to the estimate of the ef fect, but there is a possibility that it is
substantially dif ferent.
Low quality: Our conf idence in the ef fect estimate is limited: The true ef fect may be substantially dif ferent f rom the estimate of the ef fect.
1 Downgraded f rom high to low because of serious risk of bias and strong suspicion of publication bias.
2 Downgraded f rom high to moderate because of serious risk of bias.

10.3 PATIENT SELF-MONITORING

In many studies patient self-testing anf self-management has been pooled together and compared with standard care (Heneghan et al. 2016; Heneghan et al. 2012; Ansell et al. 1995). The most significant difference in hazard ratios between these two monitoring methiods can be seen for thrombotic events (Figure 7). The same results are present also in the Cochrane review when PSM and PST results are combined (Heneghan et al. 2016).

THE EFFECT OF SELF-MONITORING TO TTR-VALUES HAS ALSO BEEN STUDIED AND AT 1 YEAR, 2,7% AND 5,1% IMPROVEMENTS WERE REPORTED FOR TTR FOR HEART VALVE AND AF PATIENTS, RESPECTIVELY, COMPARED TO STANDARD CARE (HENEGHAN ET AL. 2012). AT YEAR 1 PARTICIPANTS WITH AF TOOK AN AVERAGE OF 21 MORE TESTS THAN THE STANDARD CARE GROUP (TABLE 17. MEAN DIFFERENCE BETWEEN SELF-MONITORING AND CONTROL GROUP IN TIME IN THERAPEUTIC RANGE AND NUMBER OF TESTS FOR PARTICIPANTS WITH A MECHANICAL VALVE (HENEGHAN ET AL. 2012). AND

Table 18.).

TABLE 17. MEAN DIFFERENCE BETWEEN SELF-MONITORING AND CONTROL GROUP IN TIME IN THERAPEUTIC RANGE AND NUMBER OF TESTS FOR PARTICIPANTS WITH A MECHANICAL VALVE (HENEGHAN ET AL. 2012).

	Time in therapeutic range			Number of tests		
	Mean difference between self-monitoring and control group (95% CI)	Heterogeneity	p value	Mean difference between self-monitoring and control group (95% CI)	Heterogeneity	p value
7 days	12·25% (8·99 to 15·51)	0	<0·001	0·25 (0·10 to 0·39)	77%	0·001
30 days	6·13% (–0·09 to 12·35)	72%	0·05	2·28 (1·59 to 2·97)	94%	<0·001
6 months	5·13% (–1·13 to 11·40)	79%	0·11	12·71 (9·33 to 16·10)	96%	<0·001
1 year	2·71% (–6·10 to 11·51)	94%	0·55	24·22 (18·40 to 30·04)	93%	<0·001

Data % or % (95% CI).

TABLE 18. MEAN DIFF ERENCE BETWEEN SELF-MONITORING AND CONTROL GROUP IN TIME IN THERAPEUTIC RANGE AND NUMBER OF TESTS FOR PARTICIPANTS WITH ATRIAL FI BRILLATION (HENEGHAN ET AL. 2012).

	Time in therapeutic range			Number of tests		
	Mean difference between self-monitoring and control group (95% CI)	Heterogeneity	p value	Mean difference between self-monitoring and control group (95% CI)	Heterogeneity	p value
7 days	10·38% (8·56 to 12·20)	0%	<0·001	0·01 (–0·25 to 0·28)	92%	0·91
30 days	3·16% (–4·07 to 10·39)	77%	0·39	1·78 (0·97 to 2·60)	97%	<0·001
6 months	4·40% (–0·86 to 9·67)	79%	0·10	12·03 (7·46 to 16·60)	99%	<0·001
1 year	5·13% (0·97 to 9·28)	57%	0·02	21·74 (13·11 to 30·37)	98%	<0·001

Data % or % (95% CI).

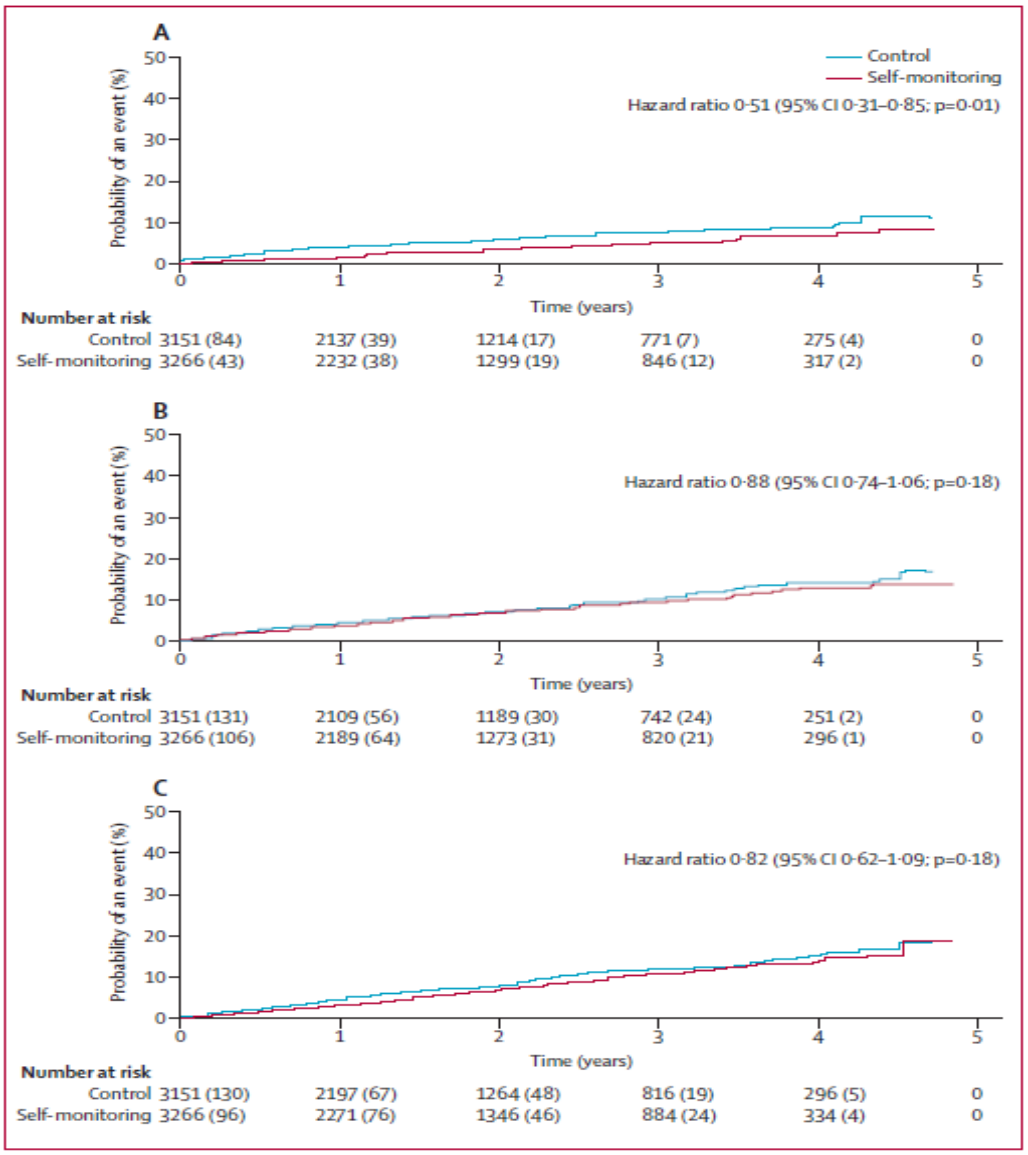

FIGURE 7. HAZARD RATIOS FOR MAJOR OUTCOMES. HAZARD RATIOS FOR THROMBOTIC EVENTS (152 EVENTS IN THE CONTROL GROUP, 114 IN THE SELF-MONITORING GROUP; A), HAEMORRHAGIC EVENTS (244 IN THE CONTROL GROUP, 230 IN THE SELF-MONITORING GROUP; B), AND DEATH (274 IN THE CONTROL GROUP, 247 IN THE SELF-MONITORING GROUP; C) (HENEGHAN ET AL. 2012).

10.4 COST-EFFECTIVENESS OF SELF-MANAGED ANTICOAGULANT THERAPY

Cost-effectiveness of anticoagulation self-management has been studied in Canada (Regier et al. 2006). The researchers developed a Bayesian Markov model comparing the costs and quality-adjusted life years (QALYs) accrued to patients receiving oral anticoagulation therapy through self-management or physician management for atrial fibrillation or for a mechanical heart valve. Five health states were defined: no events, minor hemorrhagic events, major hemorrhagic events, thrombotic events and death. Data from

published literature were used for transition probabilities. Canadian 2003 costs were used, and utility estimates were obtained from various published sources.

Self-management resulted in 3.50 fewer thrombotic events, 0.78 fewer major hemorrhagic events and 0.12 fewer deaths per 100 patients than physician management (Regier et al. 2006). The average discounted incremental cost of self-management over physician management was found to be $989 (95% confidence interval [CI] $310–$1655) per patient and the incremental QALYs gained was 0.07 (95% CI 0.06–0.08). The cost-effectiveness of self-management was $14 129 per QALY gained (Table 19). There was a 95% chance that self-management would be cost-effective at a willingness to pay of $23 800 per QALY. Results were robust in probabilistic and deterministic sensitivity analyses. The researcher interpret that this model suggests that self-management is a cost-effective strategy for those receiving long-term oral anticoagulation therapy for atrial fibrillation or for a mechanical heart valve.

TABLE 19. EXPECTED INCREMENTAL COSTS AND HEALTH BENEFITS OF SELF-MANAGED ANTICOAGULATION THERAPY (REGIER ET AL. 2006).

	Events avoided per 100 patients					
Period	Major thrombotic	Major hemorrhagic	Death	Mean cost,* $ (95% CI)	Mean Δ QALY† (95% CI)	ICER, $
1 yr	0.72	0.17	0	1420 (1041 to 1807)	0.006 (0.005-0.008)	236 667
5 yr‡§	3.5	0.79	0.12	989 (310 to 1655)	0.07 (0.056-0.084)	14 129
10 yr§	5.67	1.25	4.1	599 (-459 to 1677)	0.20 (0.160-0.240)	2995

Note: CI = confidence interval, QALY = quality-adjusted life years, ICER = incremental cost-effectiveness ratio. All costs are reported in 2003 Canadian dollars.
*Incremental costs for self-management strategy.
†QALYs gained for self-management strategy.
‡Base case time period.
§Costs and QALYs were discounted at a rate of 3% beyond the first year.

In UK a randomised trial was done to compare routine primary care management of oral anticoagulation with patient self management and calculate their cost (Fitzmaurice et al. 2002). Cost data were collected over the six month follow up period on a per patient basis, allowing the estimation of health service costs for each study patient. The data focused on key resource use items where variation by trial arm was hypothesised a priori. These items, along with the unit costs used in this analysis, are listed in

Table 20. The mean cost each year for each group (control versus intervention, intervention being the self monitoring group) was compared using standard parametric methods (t-test), given that the cost distributions were not highly skewed.

TABLE 20. RESOURCE ITSEMS AND UNIT COST (FITZMAURICE ET AL. 2002).

Resource item	Unit cost (£)	Source
Control group		
Follow up attendance at anticoagulation clinic	8.84	Parry *et al*[24]
Intervention group		
Test strip (for each strip)	2.30	Manufacturer
Advice by practice nurse (for each 15 minute consultation)	5.75	Netten[25]
Internal quality control (for each assessment)	2.30	Manufacturer
External quality control (for each assessment)	30.00	NEQAS
Training session (for each patient)*		
Room hire	6.00	Parry *et al*[24]
Staff time	20.00	Parry *et al*[24]
Test strips	23.00	Manufacturer
Quality control	1.46	Manufacturer
Equipment (per machine)	400.00r	Manufacturer

*Assuming 5 patients for each training session.
NEQAS, National External Quality Assessment Scheme.

The mean cost each year for patients in the intervention arm in this study was £425 compared with £90 for patients in the control arm ($p < 0.001$) (Fitzmaurice et al. 2002). Intervention costs were based on capital costs (spread over five years at a rate on interest of 6%) and running costs of the equipment, quality control, training, and support from the practice. Control costs were based on average cost for each patient attending a primary care clinic. These costs included capital costs of equipment, training of the general practitioner and practice nurse (spread over five years at a rate on interest of 6%), running costs to include time spent by practice nurse in running the clinic, general practitioner support, test strips, and service charge for room usage (

Table 21). Indirect costs to the patient were not included. The high cost for patients in the intervention arm is a function of the number of tests undertaken and the consumable and equipment costs of self management tests. If this technology becomes more more widely available and its associated costs fall over time then the costs for patient self management could become more favourable.

TABLE 21. TOTAL COST FOR EACH PATIENT CALCULATED FOR EACH YEAR (FITZMAURICE ET AL. 2002).

	Intervention group	Control group
Number	23	26
Mean	425.23*	89.71*
SD	52.65	38.58
Median	413.53	88.40
Interquartile range	388.23–459.53	53.04–123.76
Range	342.23–563.03	17.68–141.44

*$p<0.001$, *t* test.

Sharma et al. have done a HTA assessment in the UK of self-monitoring (self-testing and self-management) (Sharma et al. 2015). The researchers came to the following conclusion: "Compared with standard monitoring, self-monitoring appears to be safe and effective, especially for people with AHVs (artificial heart valve). Self-monitoring, and in particular self-management, of anticoagulation status appeared cost-effective when pooled estimates of clinical effectiveness were applied. However, if self-monitoring does not result in significant reductions in thromboembolic events, it is unlikely to be cost-effective, based on a comparison of annual monitoring costs alone. Trials investigating the longer-term outcomes of self-management are needed, as well as direct comparisons of the various point-of-care coagulometers.

In Sweden it has been studied that the first year of self-management is the most expensive due to training and measurement equipment cost (Kunskapunderlag 2015). Self-management becomes a cost-saving alternative to routine care when the patient has used the analysis tool for at least 18 months. The result of self-testing shows that the cost is higher compared to routine care in the first four years. Like self-management, the biggest cost item for self-testing in the first year is to initiate self-testing at home, i.e. the cost of the analytical instrument and the initial education effort. This despite the fact that the education effort is lower for self-testing. What drives the cost is the consumption of test strips. Furthermore, the amount of time spent by healthcare professionals on drug dosage adds cost. Only direct cost related to warfarin treatment has been taken into concideration in this health economic calculation and i. e. travel cost and possible cost of working time loss are missing.

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