ESC European Society of Cardiology

European Heart Journal - Cardiovascular Pharmacotherapy (2018) **4**, 211–219
doi:10.1093/ehjcvp/pvy009

ORIGINAL ARTICLE
Atrial fibrillation

The quality of warfarin therapy and CHA_2DS_2-VASc score associate with the incidence of myocardial infarction and cardiovascular outcome in patients with atrial fibrillation: data from the nationwide FinWAF Registry

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Received 19 December 2017; revised 7 January 2018; editorial decision 16 February 2018; accepted 3 March 2018; online publish-ahead-of-print 5 March 2018

Aims The impact of the quality of warfarin therapy on cardiovascular outcomes excluding stroke is largely unknown. The aims of this study were to evaluate the association between the warfarin control and the incidence and outcome of myocardial infarction (MI) and to validate the predictive value of the CHA2DS2-VASc score for MI in atrial fibrillation (AF) patients taking warfarin.

Methods and results The nationwide FinWAF Registry consists of 54 568 AF patients (mean age 73.31 ± 10.7 years, 52% men) taking warfarin. The quality of warfarin therapy was assessed continuously by calculating the time in therapeutic range within a 60-day window using the Rosendaal method (TTR60). Adjusted Cox proportional hazards models were prepared for the incidence of MI and cardiovascular mortality in six different TTR60 categories. During the 3.2 ± 1.6 years of follow-up, the annual incidence of MI (95% confidence interval) was 3.3% (3.0–3.5%), 2.9% (2.6–3.3%), 2.4% (2.1–2.7%), 1.9% (1.7–2.2%), 1.7% (1.5–2.0%), and 1.2% (1.1–1.3%) among patients with TTR60 <40%, 40–50%, 50–60%, 60–70%, 70–80%, and >80%, respectively. Well-managed warfarin therapy (TTR60 > 80%) was associated also with a lower cardiovascular mortality, whereas a high CHA_2DS_2-VASc score correlated with poor outcome.

Conclusion Cardiovascular outcome was superior among AF patients with good warfarin control and in those with a low CHA_2DS_2-VASc score. The inverse association between the TTR60 and incidence of MI and cardiovascular mortality indicate that in AF patients the quality of warfarin therapy is critical not only for prevention of stroke but also with regard to cardiovascular outcome.

Keywords Atrial fibrillation • Myocardial infarction • Myocardial infarction mortality • Cardiovascular mortality warfarin • Time in therapeutic range

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Introduction

Atrial fibrillation (AF) is one of the major causes of stroke.[1,2] In addition, AF is associated with increased risk of heart failure, myocardial infarction (MI), cognitive impairment, and dementia.[3–8] Management of AF is focused on stroke prevention. According to the contemporary management guidelines, lifelong oral anticoagulation (OAC) therapy with a direct oral anticoagulant (DOAC) or a vitamin K antagonist (VKA) should be considered for all AF patients apart from those at very low stroke risk based on the CHA_2DS_2-VASc score.[9] Despite the outmost role of stroke prevention in management of AF, other cardiovascular outcomes should not be overlooked. Many cardiovascular diseases increase the risk of AF, and *vice versa*; patients with AF frequently develop cardiovascular disorders including MI.[2,6,10]

OAC therapy prevents more than two-thirds of ischaemic strokes in patients with AF.[11,12] On the other hand, the impact of the quality of VKA therapy on the incidence and outcome of other cardiovascular events such as MI has not been examined in detail. When using a VKA for stroke prevention, maintenance of the international normalized ratio (INR) at therapeutic level (INR 2.0–3.0) is essential. In clinical practice, the standard method to estimate the quality of long-term VKA remedy is to calculate the percentage of time that the INR values are in the therapeutic range (TTR).[9,13] The results of recent studies indicate that the higher the TTR, the better the outcome with regard to the incidence of stroke and total mortality.[14–17]

In the nationwide FinWAF Registry, clinical information of a large cohort of AF patients are linked to comprehensive laboratory data including INR values. The aims of the current analysis were to evaluate whether the quality of warfarin therapy was associated with incidence and outcome of MI and to validate the predictive value of the CHA_2DS_2-VASc score for MI in AF patients anticoagulated with warfarin.

Methods

Data sources

The FinWAF is a retrospective cohort study based on data obtained from seven nationwide health registries and six regional laboratory databases. In Finland, every permanent resident, regardless of citizenship, has personal identity code, which is used in all contacts with healthcare authorities, hospitals, outpatient clinics, and pharmacies. Hence, the code enables to link official data from healthcare registers and to investigate potential associations between the cause of death, hospital discharge diagnosis [10th revision of the International Statistical Classification of Diseases (ICD-10) code], medication, and laboratory values.

Ethical aspects

The study was performed in accordance with Declaration of Helsinki and the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct and registered to the ENCePP e-register (EU PAS Register Number EUPAS4700). The study protocol was approved by the local ethics committee. The permits to collect and link data from the registries and laboratory databases were received from the Social Insurance Institute, the National Institute for Health and Welfare, the Population Register Center, and the Statistics Finland.

Study population and follow-up

The inclusion criteria were (i) AF diagnosis, (ii) at least one warfarin purchase, and (iii) at least one INR measurement. The whole Finnish population was screened (*Figure 1*). A total of 55 072 patients fulfilled all the inclusion criteria. After implementing the exclusion criteria (age < 18 years at the cohort entry date, residence outside Finland during the study period, and no valid INR measurements during the follow-up), 54 568 patients remained eligible for the analysis. Of them 23 396 were new and 31 172 were previous warfarin users, respectively.

Cohort entry date (CED) was defined as the date of the first warfarin purchase after 1 January 2007. Data from 1 January 2005 to the CED were used to capture the baseline population characteristics. A patient was categorized into the previous or new warfarin user group if the initial warfarin purchase was made between 1 January 2005 and 31 December 2006 or after 1 January 2007, respectively. The follow-up began at CED and continued until the patient died or to the end of the study period on 31 December 2011. This scheme ensured at least 2 years of potential follow-up for every patient. When investigating the outcomes, the follow-up ceased at the time of the first event.

International normalized ratio measurements and time in the therapeutic range

INR data were collected from the databases of six accredited regional central laboratories. These laboratories analyse all blood samples taken in their district, and they cover about two-thirds of the Finnish population (3.5 million residents). Each of the laboratories complies with continuous internal and external quality assurance schemes as recommended by the Labquality (Helsinki, Finland).

The estimation of the quality of warfarin therapy was based on serial INR measurements.[16] Time-dependent TTR was calculated continuously via linear interpolation using the Rosendaal method and reported as the percentage of days that the INR values were between 2.0 and 3.0 within the previous 60 days (TTR60). When evaluating the association between the accomplishment of warfarin therapy and the incidence and outcome of MI and cardiovascular mortality, the patients were divided into six groups according to the TTR60 values: <40%, 40–50%, 50–60%, 60–70%, 70–80%, and >80%. TTR60 value 60–70% was used as a reference value. A summary therapeutic range value (sTTR) covering the entire study period was calculated for each patient to sum up the overall quality of warfarin therapy.

Background variables

Information on age, gender, co-morbidities, and medications was collected from seven nationwide healthcare registries (Supplementary material online, *Table S1*). The ICD-10 codes used for identification of the co-morbidities have been reported previously.[16] CHA_2DS_2-VASc risk score was used to summarize the background variables. It consists of *C*ongestive heart failure (1 point), *H*ypertension (1 point), *A*ge ≥75 (2 points), *D*iabetes mellitus (1 point), *S*troke, TIA or systemic thromboembolisation (2 points), *V*ascular disease (e.g. peripheral artery disease, prior MI), *A*ge 65–74 (1 point) and *S*ex category (female sex, 1 point).[9,18]

Endpoints

The endpoints were categorized according to the ICD-10. The primary endpoints included (i) first hospitalization due to MI (ICD-10 codes I21–I22), (ii) MI mortality (ICD10 codes I21–I22), and (iii) cardiovascular mortality (ICD-10 codes I00–I83, I99, Q20–Q28). In addition, we evaluated whether the CHA_2DS_2-VASc score was associated with the risk and outcome of MI. The diagnosis of MI was defined according to the

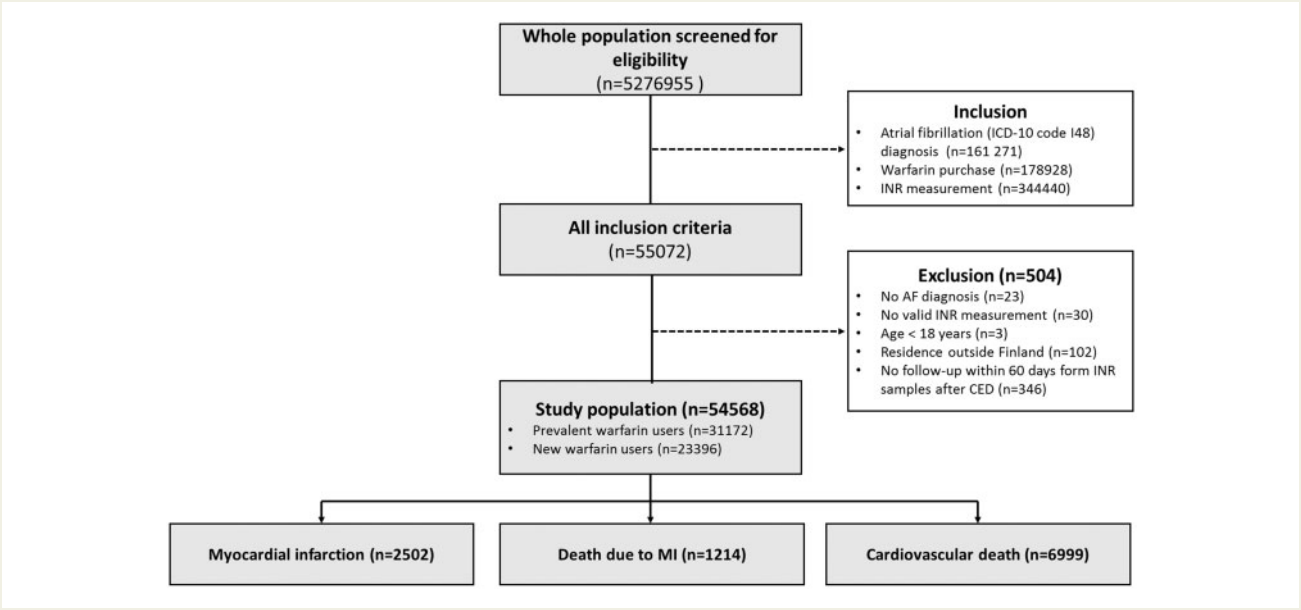

Figure 1 Schematic presentation showing the selection of the study population. Whole Finnish population was screened and those fulfilling all three inclusion criteria (warfarin purchase and INR measurement between 1 January 2007 and 31 December 2009 and AF diagnosis between 1 January 2005 and 31 December 2009) were eligible for the study. After exclusion (see Methods), a total of 54 568 patients were included in the study.

international criteria, which was valid at the time of the data input into the national registry.[19]

Statistical analyses

Baseline characteristics are reported as the mean ± standard deviation for continuous variables and percentages for categorical variables. Data management and all statistical analysis were performed using the R language.[20]

Stratified incidence rates were estimated in each time-dependent TTR category, and the 95% confidence intervals (CIs) were captured according to the Poisson assumption. Hazard ratios (HRs) for different time-dependent TTR levels compared with the reference group (TTR = 60–70%) were estimated using the Cox proportional hazards model adjusted for age, gender, and time-varying co-morbidities, including history of MI, congestive heart failure, hypertension, diabetes, previous stroke, previous transient ischaemic attack (TIA), renal impairment (serum creatinine > 90 μmol/l in women and > 100 μmol/l in men), vascular disease, and any previous hospitalization. The effects of adjusting covariates on the outcomes are provided in Supplementary material online, *Table S2*. HRs were accompanied by expected cumulative hazards, derived for an average study patient assumed to have a time-fixed TTR, and used to evaluate the predicted cumulative incidences as recommended by Therneau and Grambsch.[21]

To test for sensitivity, the results were rederived using the Cox proportional hazards model with 30-, 90-, 180-, and 360-day time frames for calculating the time-dependent TTR and by excluding patients who did not have at least two separate warfarin purchases within 120 days from the CED. Sensitivity analyses were also performed for previous and new warfarin users, and on cohorts that excluded patients who had an AF diagnosis only after the first purchase of warfarin, and patients who had a diagnosis of any valve disorder accompanied with their diagnosis of AF.

Results

Baseline characteristics and follow-up

The mean age of the study population was 73 ± 11 years (range 18–101 years), and 52% of them were men. The most common underlying diseases in the whole study population included hypertension (24.2%), vascular diseases (25.2%), congestive heart failure (18.1%), and diabetes (9.8%). A total of 12.3% and 4.4% of the patients had a history of stroke/TIA and MI, respectively. Detailed information on the baseline demographics among patients with the different TTR levels are presented in *Table 1*.

The mean follow-up time was 3.2 ± 1.6 years (interquartile range 2.0–4.7 years), and the total number of treatment years was 128 941. The median number of INR measurements was 1.36 per month (interquartile range 0.78–1.95). The monthly rate of INR measurements was lower among the previous warfarin users compared with the new ones (1.43 ± 1.13 vs. 1.65 ± 1.26, $P < 0.001$). During the follow-up period, 2502 MIs, 1214 deaths due to MI, and 6999 cardiovascular deaths were recorded. Hence, the annual incidence of MI, death due to MI, and cardiovascular mortality among the study population was 1.9% (95% CI 1.9–2.0), 0.9% (95% CI 0.9–1.0), and 5.3% (95% CI 5.2–5.4), respectively.

Time-dependent therapeutic range as a predictor of cardiovascular outcomes

The rate of MI was inversely related to the quality of warfarin therapy (*Table 2*). The HR for MI was more than 1.5 times higher among patients with TTR < 40% than in the reference population. In patients with TTR60 >80%, the risk of MI (HR 0.7, 95% CI 0.6–0.8) and MI

Table 1 Baseline characteristics of the total study population and patients with various summary TTR levels in patients with at least three international normalized ratio measurements

Variables	Summary TTR level						
	<40% (*n* = 8364)	40–50% (*n* = 4261)	50–60% (*n* = 6502)	60–70% (*n* = 9729)	70–80% (*n* = 11 547)	>80% (*n* = 11 224)	Total (*n* = 51 627)
Age (years)							
Mean (SD)	71.7 (12.3)	72.9 (11.7)	73.9 (11.0)	74.4 (10.6)	74.1 (9.8)	72.6 (9.7)	73.3 (10.7)
Median (range)	74 (18–101)	75 (25–98)	76 (25–100)	76 (18–101)	75 (22–99)	73 (18–98)	75 (18–101)
<65,[a,b] *n* (%)	2291 (27.45)	1065 (25.0)	1365 (21.0)	1759 (18.1)	1940 (16.8)	2255 (20.1)	10 675 (20.7)
65–74,[a,b] *n* (%)	2110 (25.2)	1000 (23.5)	1598 (24.6)	2532 (26.0)	3487 (30.2)	3803 (33.9)	14 530 (28.1)
≥75 years,[a,b] *n* (%)	3963 (47.4)	2196 (51.5)	3539 (54.4)	5438 (55.9)	6120 (53.0)	5166 (46.0)	26 422 (51.2)
Gender, *n* (%)							
Male[a,b]	4978 (59.5)	2316 (54.4)	3297 (50.7)	4731 (48.6)	5632 (48.8)	5997 (53.4)	26 951 (52.2)
Female[a,b]	3386 (40.5)	1945 (45.7)	3205 (49.3)	4998 (51.4)	5915 (51.2)	5227 (46.6)	24 676 (47.8)
Co-morbidities, *n* (%)							
CHF[a,b]	1859 (22.2)	948 (22.3)	1462 (22.5)	1906 (19.6)	1790 (15.5)	1367 (12.2)	9332 (18.1)
Cardiomyopathy[a,b]	266 (3.2)	153 (3.6)	227 (3.5)	253 (2.6)	289 (2.5)	237 (2.1)	1425 (2.8)
Hypertension[b]	2104 (25.2)	1063 (25.0)	1606 (24.7)	2380 (24.5)	2739 (23.7)	2607 (23.2)	12 499 (24.2)
Diabetes[a,b]	1043 (12.5)	479 (11.2)	791 (12.2)	1035 (10.6)	937 (8.1)	760 (6.8)	5045 (9.8)
Stroke or TIA[a]	937 (11.2)	472 (11.1)	834 (12.8)	1264 (13.0)	1460 (12.6)	1365 (12.2)	6332 (12.3)
Vascular disease[a,b]	2455 (29.4)	1239 (29.1)	1751 (26.9)	2553 (26.2)	2714 (23.5)	2273 (20.3)	12985 (25.2)
Prior MI[a,b]	505 (6.0)	212 (5.0)	301 (4.6)	406 (4.2)	431 (3.7)	405 (3.6)	2260 (4.4)
Renal impairment[a,b]	2021 (24.1)	1126 (26.4)	1605 (24.7)	2126 (21.9)	2097 (18.2)	1611 (14.4)	10 586 (20.5)
Pulmonary embolism[a,b]	169 (2.0)	76 (1.8)	92 (1.4)	164 (1.7)	173 (1.5)	108 (1.0)	782 (1.5)
DVT[a,b]	334 (4.00)	180 (4.2)	245 (3.8)	296 (3.0)	293 (2.5)	220 (2.0)	1568 (3.0)
Cancer[a,b]	1710 (20.4)	872 (20.5)	1335 (20.5)	1977 (20.3)	2131 (18.5)	1939 (17.3)	9964 (19.3)
CHA_2DS_2VASc score							
Mean (SD)	2. 7 (1.8)	2.8 (1.8)	3.0 (1.8)	3.0 (1.7)	2.8 (1.6)	2.6 (1.6)	2.8 (1.7)
Median (range)	3 (1–4)	3 (1–4)	3 (2–4)	3 (2–4)	3 (2–4)	2 (1–4)	3 (2–4)
0,[a,b] *n* (%)	1069 (12.8)	483 (11.3)	597 (9.2)	704 (7.2)	803 (7.0)	954 (8.5)	4610 (8.9)
1,[a,b] *n* (%)	1265 (15.1)	585 (13.7)	796 (12.2)	1239 (12.7)	1629 (14.1)	2006 (17.9)	7520 (14.6)
≥2,[a,b] *n* (%)	6030 (72.1)	3193 (74.9)	5109 (78.6)	7786 (80.0)	9115 (78.9)	8264 (73.4)	39 497 (76.5)
Medication, *n* (%)							
Previous warfarin user[a,b]	4137 (49.5)	2377 (55.8)	4016 (61.8)	5972 (61.4)	6937 (60.1)	6474 (57.7)	29 913 (57.9)
New warfarin user[a,b]	4227 (50.5)	1884 (44.2)	2486 (38.2)	3757 (38.6)	4610 (39.9)	4750 (42.3)	21 714 (42.1)
Clopidogrel[a,b]	454 (5.4)	190 (4.5)	273 (4.2)	415 (4.3)	412 (3.6)	354(3.2)	2098 (4.1)
Dipyridamole	238 (2.9)	104 (2.4)	176 (2.7)	273 (2.8)	309 (2.7)	253 (2.3)	1353 (2.6)
Beta-blockers[a,b]	6302 (75.4)	3283 (77.1)	5131 (78.9)	7749 (79.7)	9102 (78.8)	8687 (77.4)	40 254 (78.0)
Diltiazem/verapamil	399 (4.7)	227 (5.3)	396 (6.1)	550 (5.7)	700 (6.1)	651 (5.8)	2923 (5.7)
Class I or III AADs[a,b]	558 (6.7)	276 (6.5)	476 (7.3)	712 (7.3)	962 (8.3)	1060 (9.4)	4044 (7.8)

AAD, antiarrhythmic drug; CHF, congestive heart failure; DVT, deep venous thrombosis; MI, myocardial infarction; TIA, transient ischaemic attack.
[a]*P*-value <0.001 for test that proportion is equal in each TTR group.
[b]*P*-value <0.001 for test that there is a linear trend (either decreasing or increasing) in the variable by the summary TTR category.

mortality and cardiovascular mortality (HR 0.8, 95% CI 0.7–0.9) were significantly lower than in any other group.

The predicted cumulative incidence of MI is depicted in *Figure 2*, and cumulative incidence of MI mortality and cardiovascular mortality are shown in *Figure 3*. It was estimated that an average patient with TTR60 < 40% would have had 9.9% risk of having MI during a 5-year follow-up period. The corresponding numbers for MI mortality and cardiovascular mortality would have been 5.6% and 37.8%, respectively. In comparison, among patients with a TTR60 exceeding 80% the risk of MI, MI mortality and cardiovascular mortality would have been and 5.2%, 2.1% and 10.1%, respectively.

Sensitivity analyses testing different time frames (30, 90, 180, and 360 days) showed that a better TTR with any predefined time frame was associated with an improved patient outcome for all reported endpoint measures. The results also remained unchanged according to the sensitivity analysis under the following conditions: the exclusion of patients without at least two warfarin purchases within 120 days from CED, the exclusion of patients with an AF diagnosis

Table 2 Number of events, incidence rates, and hazard ratios (HR) of myocardial infarction, myocardial infarction mortality, and cardiovascular mortality among patients in the different time-dependent TTR categories

TTR60 (%)	Number of events	Rate per 100 patient-years (95% CI)	HR (95% CI)	*P*-value
Myocardial infarction				
≤40	859	3.3 (3.0–3.5)	1.6 (1.4–1.8)	<0.001
40–50	265	2.9 (2.6–3.3)	1.5 (1.2–1.7)	<0.001
50–60	248	2.4 (2.1–2.7)	1.2 (1.0–1.5)	0.033
60–70	218	1.9 (1.7–2.2)	1 (reference)	
70–80	203	1.7 (1.5–2.0)	0.9 (0.8–1.1)	0.447
>80	709	1.2 (1.1–1.3)	0.7 (0.6–0.8)	<0.001
Myocardial infarction mortality				
≤40	486	1.8 (1.6–2.0)	1.8 (1.5–2.2)	<0.001
40–50	144	1.5 (1.3–1.8)	1.6 (1.2–2.0)	<0.001
50–60	105	1.0 (0.8–1.2)	1.0 (0.8–1.4)	0.783
60–70	107	0.9 (0.8–1.1)	1 (reference)	
70–80	91	0.8 (0.6–0.9)	0.9 (0.7–1.1)	0.316
>80	281	0.5 (0.4–0.5)	0.6 (0.5–0.8)	<0.001
Cardiovascular mortality				
≤40	3162	11.7 (11.3 –12.1)	2.0 (1.8–2.2)	<0.001
40–50	714	7.6 (7.1–8.2)	1.3 (1.2–1.5)	<0.001
50–60	670	6.2 (5.8 –6.7)	1.1 (1.0–1.2)	0.084
60–70	647	5.5 (5.1–6.0)	1 (reference)	
70–80	497	4.1 (3.8–4.5)	0.8 (0.7–0.9)	<0.001
>80	1309	2.2 (2.0–2.3)	0.5 (0.4–0.5)	<0.001

The hazard ratios were adjusted for age, gender, congestive heart failure, hypertension, diabetes, stroke, transient ischaemic attack, vascular disease, previous hospitalization, and renal impairment.

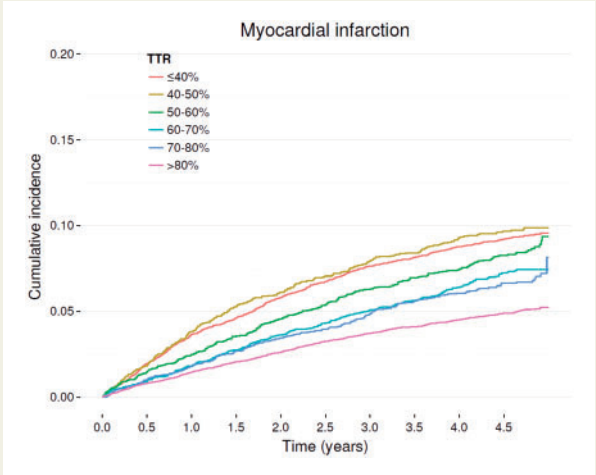

Figure 2 Cumulative incidence of myocardial infarction among the patients in the different time-dependent TTR60 categories.

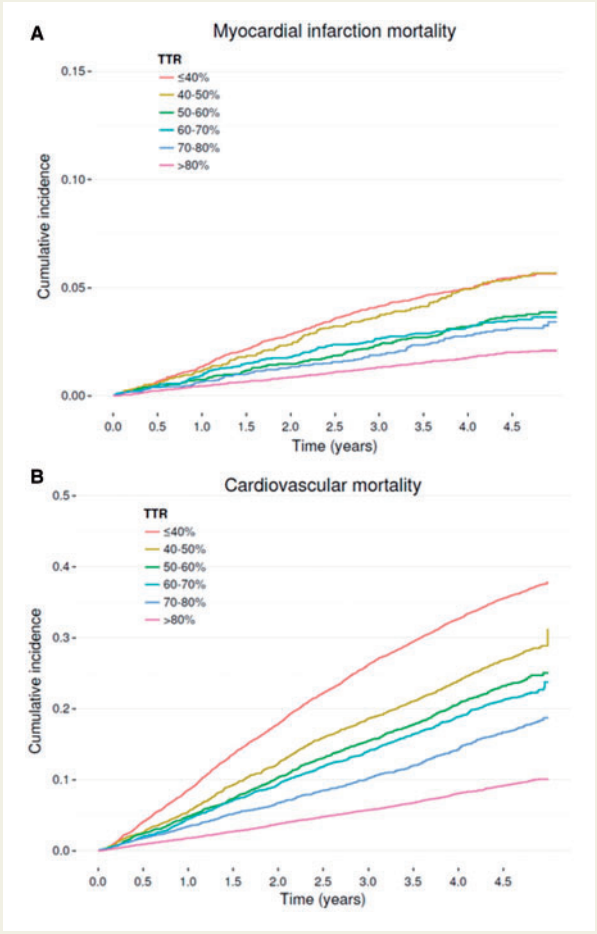

Figure 3 Cumulative incidence of myocardial infarction mortality (*A*) and cardiovascular mortality (*B*) among patients in the different time-dependent TTR60 categories.

after warfarin purchase, distinguishing previous from new warfarin users, and the exclusion of patients who were diagnosed with any valve disorders accompanied with a diagnosis of AF.

Association between the CHA_2DS_2-VASc score and risk of myocardial infarction

The mean CHA_2DS_2-VASc score in the entire study population was 2.8 ± 1.7. In the different TTR60 categories, the mean CHA_2DS_2-VASc score varied between 2.6 and 3.0, indicating clinically significant differences between the groups were unlikely. There was a strong association between the CHA_2DS_2-VASc score and the risk of MI (*Table 3*). Among patients with no risk factors, the incidence of MI (2.88 per 1000 patient-years, 95% CI 1.82–4.58) was lower than in any other group ($P < 0.001$). In comparison, among patients with CHA_2DS_2-VASc score >5, the incidence rate was 39–64 per 1000 patient-years. A high CHA_2DS_2-VASc score was also a strong predictor of MI mortality and cardiovascular death (*Table 3*). In patients with high CHA_2DS_2-VASsc score (>2 points) and low quality of warfarin therapy (TTR60 ≤ 40%), MI rate was almost 20 times higher (3.8 vs. 0.2 per 100 patient-years) than in those with no CHA_2DS_2-VASc

Table 3 Number of events and event rates (per 1000 person-years) stratified by the CHA_2DS_2-VASc risk score

CHA_2DS_2-VASc score	Number of patients	Number of events	Time at risk (years)	Event rate (95% CI)
Myocardial infarction				
0	4780	18	6244	2.9 (1.8–4.6)
1	9495	90	13 790	6.5 (5.3–8.0)
2	15 301	240	23 087	10.4 (9.2–11.8)
3	19 852	433	29 055	14.9 (13.6–16.4)
4	17 694	560	24 394	23.0 (21.1–24.9)
5	13 087	529	17 241	30.7 (28.2–33.4)
6	7771	380	9544	39.8 (36.0–44.0)
7	3506	162	4136	39.2 (33.6–45.7)
8	1165	74	1199	61.7 (49.1–77.5)
9	234	16	251	63.9 (39.1–104.2)
Myocardial infarction mortality				
0	4780	3	6244	0.5 (0.2–1.5)
1	9507	9	13 824	0.7 (0.3–1.3)
2	15 368	47	23 222	2.0 (1.5–2.7)
3	20 026	149	29 366	5.1 (4.3–6.0)
4	18 056	270	24 873	10.9 (9.6–12.2)
5	13 533	281	17 908	15.7 (14.0–17.6)
6	8136	259	10 067	25.7 (22.8–29.1)
7	3750	126	4411	28.6 (24.0–34.0)
8	1268	60	1322	45.4 (35.3–58.5)
9	263	10	283	35.4 (19.0–65.7)
Cardiovascular mortality				
0	4780	43	6244	6.9 (5.1–9.3)
1	9507	116	13 824	8.4 (7.0–10.1)
2	15 368	307	23 222	13.2 (11.8–14.8)
3	20 026	736	29 366	25.1 (23.3–26.9)
4	18 056	1440	24 873	57.9 (55.0–61.0)
5	13 533	1648	17 908	92.0 (87.7–96.6)
6	8136	1419	10 067	141.0 (133.8–148.5)
7	3750	820	4411	185.9 (173.6–199.1)
8	1268	384	1322	290.6 (262.9–321.1)
9	263	86	283	304.0 (246.1–375.6)

points and excellent warfarin control (TTR60 > 80%) (for details see Supplementary material online, *Table S3*).

A total of 2410 (4.4%) patients had prior MI, and 13 708 (25.1%) patients had been diagnosed with vascular disease. Beta-blocker therapy had favourable effect on MI rate [1.7 (1.6–1.8) with a beta-blocker vs. 1.8 (1.6–2.1) with no beta-blocker] and cardiovascular mortality [3.2 (3.1–3.4) vs. 7.4 (6.9–8.0)]. On the other hand, the rate of MI [1.6 (1.5–1.8) vs. 10.0 (7.5–13.5)] and cardiovascular mortality [4.0 (3.8–4.2) vs. 9.5 (7.2–12.6)] were higher among those using clopidogrel compared with those using no adenosine diphosphate (ADP) receptor antagonists.

Overall quality of warfarin therapy

The mean sTTR level capturing the entire follow-up period was 62 ± 25% (median 67%). sTTR was above 80% in 22% of the patients, whereas in 16% of the patients, it was below 40%. In patients with incident MI, the mean sTTR was lower than in patients without MI (56.5 ± 23.1% vs. 62.0 ± 23.7%, $P < 0.001$). Similarly, both the MI mortality (56.5 ± 24.3% vs. 61.9 ± 23.7%, $P < 0.001$) and the cardiovascular mortality (56.2 ± 22.5% vs. 62.6 ± 23.8%, $P < 0.001$) were associated with a lower sTTR.

Baseline characteristics associated with a low sTTR (≤40%) included age <65 years, history of congestive heart failure, vascular disease, diabetes, renal impairment, venous and pulmonary thromboembolism, cancer, and CHA_2DS_2-VASc Score 0. A good sTTR (>80%) was related to age 65–75 years and CHA_2DS_2-VASc Score 1.

Discussion

This is the first large-scale study showing that there is a strong association between the quality of warfarin therapy and incidence and outcome of MI in patients with AF. The risk of MI, death due to MI, and

cardiovascular mortality were significantly lower among patients with TTR60 over 80% than in the other TTR60 groups. Hence, the quality of VKA therapy relates not only to the risk of stroke but also to the risk and outcome of MI and overall cardiovascular mortality. Moreover, our data corroborated that a high CHA_2DS_2-VASc score is a powerful predictor of MI and cardiovascular outcome in AF patients anticoagulated with warfarin.

Association between time-dependent therapeutic range and incidence of myocardial infarction

The quality of warfarin therapy is inversely correlated with the risk of stroke in patients with AF.[16,22] On the other hand, data on the relationship between TTR and the incidence of MI in patients with AF are scant. Here, the risk of MI was lower among patients with TTR60 over 80% compared with the other TTR60 groups. It was estimated that an average patient with poor INR control (TTR60 < 40%) would have had almost 10% absolute risk of developing MI within the next 5 years. In contrast, in those with TTR above 80% the risk of MI would have been almost twice lower (i.e. 5.2%).

These findings concur with those from previously published smaller series. In the VKA arm of the SPORTIF III and IV trials, the rate of MI was significantly higher in patients with TTR < 60% than in those with TTR > 75%.[23] In the RE-LY trial, the patients with TTR ≥65% had lower MI rate compared with those with TTR <65%.[24] More recently, Pastori *et al.*[25] showed in a small prospective cohort that the rate of combined endpoint of major adverse cardiovascular events including fatal or nonfatal MI and cardiovascular mortality increased significantly across tertiles of TTR. None of these studies were powered to provide detailed information on the relationship between TTR levels and the incidence and outcome of MI. In contrast, the nationwide FinWAF cohort covered 3.5 million residents, i.e. 64% of the Finnish population. The large number of eligible patients (almost 55 000) allowed us to assess the associations between the incidence and outcome of MI and the quality of the warfarin treatment at six different TTR categories (10% steps from <40% to >80%). Another important advantage besides the size of the study population was that we reported continuous TTR calculations using a moving 60-day window, whereas in prior studies, TTR was expressed over the entire study period. It is evident that the detection of temporal associations between the quality of VKA remedy and clinical outcomes is more precise if TTR is calculated over a relative short time period before the event.

Association between therapeutic range and cardiovascular outcome

Atrial fibrillation is one of the major causes of stroke and systemic embolization.[1,9] In addition, AF has been associated with cardiovascular hospitalization and adverse outcome in many cardiovascular disorders.[3–8] In patients with acute coronary syndrome, concomitant AF predicts adverse outcome.[26,27] The results of the WARIS II trial indicate that warfarin is more effective than aspirin in secondary prevention after MI among patients without AF,[28] but the impact of warfarin therapy on the outcome of MI in patients with AF is sparsely characterized. In our study, the rate of MI mortality and cardiovascular mortality correlated inversely with the quality of warfarin therapy. That is, in AF patients with TTR60 over 80%, the outcomes were superior to any other TTR group. The estimated risk of dying for MI within the next 5 years was 5.6% in a patient with poor INR control (TTR60 < 40%) compared with 2.1% in a patient with good INR control (TTR > 80%). The corresponding number for cardiovascular mortality was 37.8% vs. 10.1%, respectively. These novel findings of this large-scale nationwide study are supported by the results of the above-mentioned smaller studies[23–25] and a recent meta-analysis.[22]

CHA_2DS_2-VASc score as a predictor of myocardial infarction

The introduction of the CHA_2DS_2-VASc score has simplified stratification of stroke risk.[9,18] In general, patients without any clinical risk factors for stroke do not need OAC therapy, while patients with stroke risk factors (i.e. CHA_2DS_2-VASc score of 1 or more for men and 2 or more for women) will benefit from OAC.[9] In line with prior data,[29] our findings indicate that the CHA_2DS_2-VASc score is a powerful predictor for MI and cardiovascular mortality in patients with AF receiving warfarin. The risk was highest among those with high CHA_2DS_2-VASsc score and poor warfarin control. Considering that CHA_2DS_2-VASc score components are also related to the risk of MI and cardiovascular death, this finding was rather anticipated.

Overall quality of warfarin therapy

In clinical practice, the standard method to estimate the quality of long-term VKA therapy is to calculate the TTR.[13] According to the contemporary AF management guidelines, TTR should be as good as possible.[9] Maintaining the INR within the target range is difficult and necessitates frequent monitoring of the INR and adjustment of the VKA dose. Here, the median summary TTR for the entire study period was 67%. Although it was in the same range or better than the TTR in recent randomized trials comparing warfarin and DOACs,[12] it was still far below the proposed minimum target level of more than 80%. In accordance with the results of previous studies,[30] young age, cardiovascular co-morbidities, and cancer were associated with a poor TTR.

Effect of concomitant medication

Beta-blocker use was associated with a lower MI rate and a better cardiovascular outcome as expected. Estimation of the net effect of ADP receptor antagonists is more difficult in a cohort of unselected AF patients. Higher risk of MI and worse cardiovascular outcome in patients using ADP receptor antagonists was most likely due to the preferable use of these agents in high-risk patients with recent ischaemic events or coronary interventions and not a true negative effect. The differences in the use of concomitant drugs in the various TTR60 categories were so small that any clinically significant effect is unlikely.

Limitations

All the nationwide registries used in our study have been validated and the diagnoses have proved to be accurate.[31] Nevertheless, a major limitation of our study was that no information on some cardiovascular risk factors such as smoking, alcohol consumption, and dietary habits were available. Moreover, data on some concomitant drugs that may have influenced the outcome were not accessible either because they were available over the counter (e.g. aspirin) or

not included in data collection permission (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers).

The exact reasons behind poor TTR remain to be established. Although the overall findings remained unchanged in the sensitivity analysis investigating the effects of previous hospitalizations, it is possible that in some cases TTR was low, because warfarin was discontinued on purpose (e.g. due to surgical interventions, cancer, bleeding). The impact of a particular factor or a risk score such as the CHA_2DS_2-VASc is best tested in non-anticoagulated patients with a broad range of risk factors. In our study, all patients were already using warfarin, which may have had some influence on the results. Finally, our study did not provide any information on the effect of DOACs on the risk and outcome of MI, because during the study period, no long-term data on clinical use of DOACs were available.

Clinical implications

According to the contemporary guidelines,[9,32] VKA monotherapy is sufficient in AF patients with stable coronary artery disease and concomitant antiplatelet therapy should be avoided in the absence of acute coronary syndrome or recent coronary stent implantation. Our findings underscore the importance of high-quality INR control. Calculating the TTR over a long-time period is not clinically practical, and physicians should be encouraged to use continuously calculated time-dependent TTR for follow-up of the quality of VKA therapy. Our data indicate that a 60-day TTR window provides a proper means for this purpose. A low continuously calculated TTR is not only a warning sign of stroke but also a predictor of MI and poor cardiovascular outcome in patients with AF. Given the sound relationship between the warfarin control and risk and outcome of MI, we recommend that the minimum TTR target in AF patients taking warfarin should be at least 80%. If good INR control is not possible, one should consider switching to DOAC therapy. Finally, the finding that a high CHA_2DS_2-VASc score is associated with elevated risk of MI indicates that management of other risk factors such as hypertension and dyslipidaemia is particularly important in anticoagulated AF patients.

Conclusions

In patients with AF, well-managed warfarin therapy is associated not only with a low risk of stroke but also that of MI and cardiovascular mortality. The inverse association between continuously evaluated TTR and the risk of MI and cardiovascular outcomes further support to our earlier conclusion that the TTR in AF patients using warfarin should be targeted at least at 80%. A high CHA_2DS_2-VASc score parallels with an elevated risk of MI among patients with AF.

Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

Acknowledgements

We thank Bristol-Myers Squibb, Finland, for the practical support during the study. Pia Annunen, Houssem Khanfir, and Fabian Hoti are acknowledged for their contribution to the study design. We also thank the regional laboratories: HUSLAB, Helsinki; TYKSLAB, Turku; FIMLAB, Tampere and FIMLAB, Central Finland; ISLAB, Kuopio; and NORDLAB, Oulu.

Funding

Bristol-Myers Squibb, Finland and Pfizer, Finland; the Finnish Foundation for Cardiovascular Research; Helsinki University Hospital District research fund [Y2016SK007].

Conflict of interest: none declared.

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