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Non-interventional Study Report for Study CV185266

RISK OF STROKE AND OTHER CARDIOVASCULAR EVENTS AMONG WARFARIN-TREATED ATRIAL FIBRILLATION PATIENTS - A NATIONWIDE COHORT STUDY IN FINLAND

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SYNOPSIS

Report Type Non-interventional Study Report for Study CV185266

TITLE OF STUDY: Risk of stroke and other cardiovascular events among warfarin-treated atrial fibrillation patients - a nationwide cohort study in Finland.

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PUBLICATIONS:

STUDY INTIATION DATE: 15.10.2012

STUDY COMPLETION DATE: 1.4.2015

STUDY PERIOD: 1.1.2005 – 31.12.2011

OBJECTIVES:

Primary objectives:

1) To investigate and compare risk of stroke, systemic thromboembolism, and myocardial infarction among atrial fibrillation (AF) patients in relation to International Normalized Ratio (INR) levels: under 2.0, 2.0-3.0, and over 3.0.

2) To investigate and compare risk of bleeding events among AF patients in relation to INR levels: under 2.0, 2.0-3.0, and over 3.0.

3) To investigate and compare mortality risk among AF patients in relation to INR levels: under 2.0, 2.0-3.0, and over 3.0.

The primary objectives are evaluated separately for prevalent and new users of warfarin.

Secondary objectives:

1) To investigate risk of stroke, systemic thromboembolism, myocardial infarction, and bleeding events among AF patients during the first 90 days after initiation of warfarin treatment.

2) To investigate risk of stroke, systemic thromboembolism, myocardial infarction, and bleeding events among AF patients in relation to time from AF diagnosis to time of initiation of warfarin treatment.

3) To investigate risk of stroke, systemic thromboembolism, myocardial infarction, and bleeding events among AF patients who have stopped using warfarin.

METHODOLOGY: The study is conducted as a nationwide retrospective register-based linkage study using data obtained from the Finnish health care registers. The study population consists of all AF patients using warfarin with INR measurements in selected hospital district areas in Finland between 1.1.2007 and 31.12.2009 with up to 5 years follow-up.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Patients who:

- Had purchased warfarin (anatomical therapeutic chemical classification (ATC) code B01AA03) between 1.1.2007 and 31.12.2009 and
- Had at least one INR measurement between 1.1.2007 and 31.12.2009, and
- Had international classification of diseases, 10th revision (ICD-10) diagnosis I48 for AF between 1.1.2005 and 31.12.2009.

Exclusion criteria: permanent residence in Finland less than 12 months prior to index date, moving abroad during the study period or age below 18 years at index date.

Treatments warfarin, anatomical therapeutic chemical classification (ATC) code: B01AA03.

Duration of Follow-up

Index date was defined as the date of first purchase of warfarin after 1.1.2007. Follow-up of the patients started on the index date, and ended on 31.12.2011 or at time of death whichever occurred first. Treatment and comorbidity history was gathered from the period from 1.1.2005 to 31.12.2006.

NUMBER OF SUBJECTS (Planned and Analyzed): The anticipated study population size was 32 000 patients, but the actual study size was larger, 55072 patients. Of the 55072 patients that fulfilled all the three inclusion criteria, 54568 were analyzed. Those 504 who fulfilled the inclusion criteria but were not analyzed had either lived abroad during the study period, were under 18 years old at cohort entry date (CED), did not have AF diagnosis in the data, or did not have valid follow-up time (e.g. no INR measurements 60 days before or after CED).

CRITERIA FOR EVALUATION:

Primary Endpoints

- Stroke (including transient ischemic attack)
- Other systemic thromboembolic events excluding stroke
- Myocardial infarction
- Bleeding events
- Mortality, all-cause
- Mortality, stroke
- Mortality, myocardial infarction
- Mortality, systemic thromboembolic events excluding stroke
- Mortality, bleeding
- Mortality, cardiovascular causes

Secondary Endpoints

- Anemia
- Renal impairment

STATISTICAL CONSIDERATIONS:

Stratified incidence rates with 95% confidence intervals (CIs) were estimated for each endpoint within the strata of the INR levels, time in therapeutic INR range (TTR) categories, and other covariates. The crude and adjusted hazard ratio (HR) estimates with 95% CIs and P-values were estimated within the INR levels and TTR categories using the conventional Cox's proportional hazards model adjusting for other covariates.

SUMMARY OF RESULTS:

Demographics at CED.

	Prevalent warfarin users N = 31172 (57% of all)	**New warfarin users N = 23396 (43% of all)**
Age (years)		

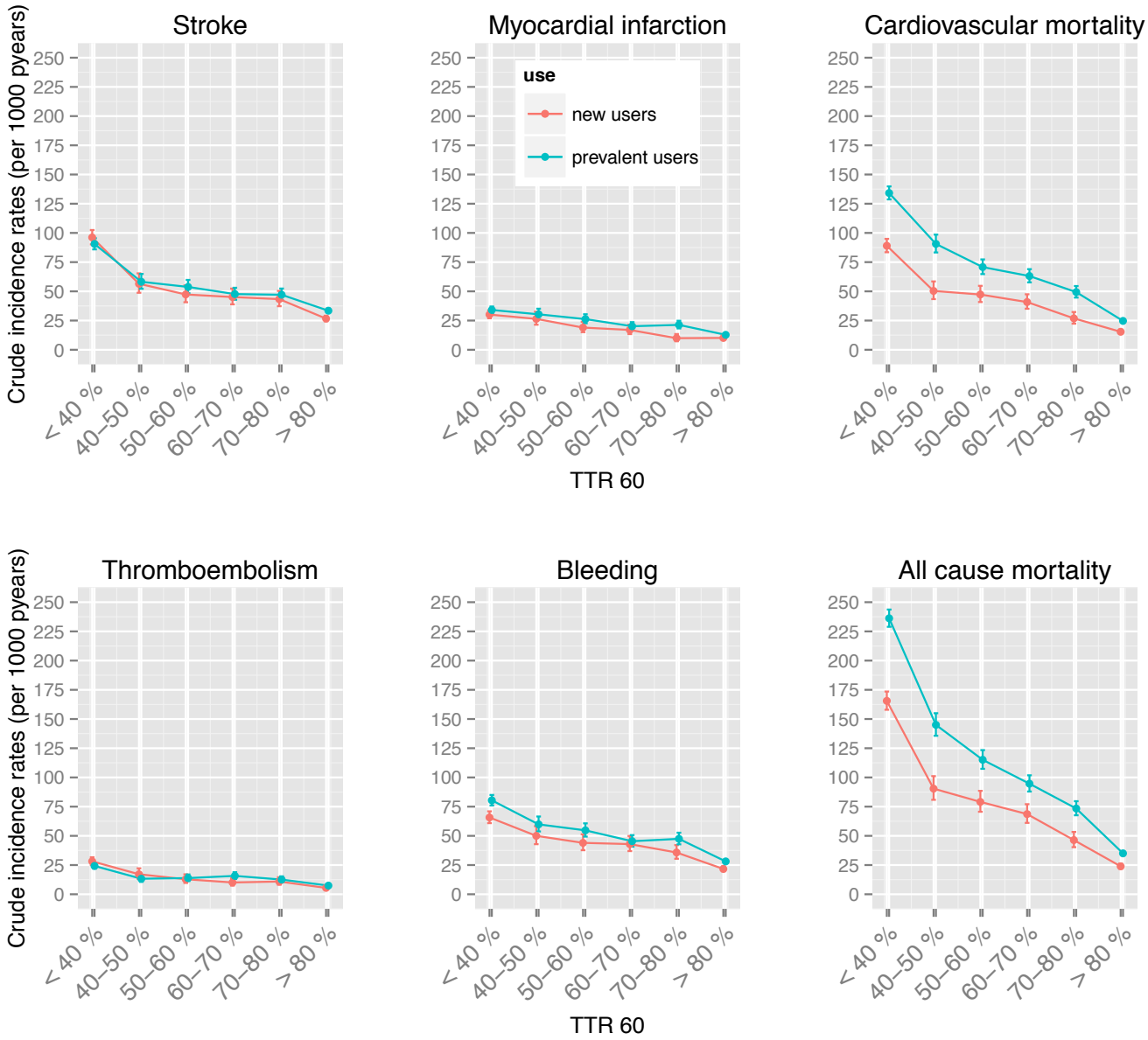
18-60	3235 (10.38%)	4006 (17.12%)
61-70	6426 (20.61%)	6097 (26.06%)
71-80	11895 (38.16%)	7923 (33.86%)
over 80	9616 (30.85%)	5370 (22.95%)
range (min,max)	(18.00, 101.00)	(18.00, 101.00)
mean (+/-sd)	74.45 (10.26)	71.38 (11.31)
median (Q1, Q3)	76.00 (68.00, 82.00)	73.00 (64.00, 80.00)
Gender		
Male	16255 (52.15%)	12467 (53.29%)
Female	14917 (47.85%)	10929 (46.71%)

Of the 31172 prevalent and 23396 new warfarin users, 3749 and 4974 discontinued the use, respectively. Discontinuation was defined as 60 days gap since the last INR measurement and warfarin exposure.

Results:

Primary objectives: Crude (unadjusted) incidence rates of stroke, systemic thromboembolism (excluding stroke), myocardial infarction, bleeding, cardiovascular mortality and all-cause mortality in relation to different TTR levels. Figures show the incidence rate (per 1000 person years) for TTR during the last 60 days together

with the 95% CI.



Secondary objectives: Risk of stroke, systemic thromboembolism, myocardial infarction and bleeding estimated using i) data from the first 90 days after CED ii) all follow-up data and iii) after stopping warfarin use, i.e., after 60 days gap since last INR measurement and warfarin exposure. All results are estimated among new warfarin users. Table presents incidence rates (per 1000 person years) together with its lower and upper 95% confidence intervals stratified by the CHA2DS2-Vasc score.

		First 90 days			All data			After stopping warfarin		
	CHA2DS2-Vasc	Rate	Lower limit	Upper limit	Rate	Lower limit	Upper limit	Rate	Lower limit	Upper limit
Stroke	0	29.75	17.94	49.35	13.83	10.11	18.93	1.6	0.51	4.95
	1	42.09	29.6	59.85	16.48	13.4	20.26	6.25	3.55	11
	2	91.5	73.88	113.32	26.81	23.51	30.58	13.07	8.61	19.86
	3	142.69	120.69	168.71	40.33	36.5	44.56	30.65	22.81	41.19
	4	215.17	183.45	252.38	58.21	53.09	63.82	41.92	31.5	55.8
	5	298.57	251.91	353.88	83.2	75.73	91.41	62.23	45.82	84.51
	6	382.92	308.4	475.45	123.62	110.76	137.99	90.89	64.94	127.2
	7	350.81	238.86	515.24	145.02	122.81	171.25	158.59	107.98	232.93
	8	521.21	271.19	1001.71	167.46	121.85	230.14	178.66	89.35	357.25
	9	869.64	280.48	2696.39	216.88	116.69	403.08	500.57	224.89	1114.21
Systemic thromboembolism	0	21.87	12.11	39.5	8.92	6.03	13.2	1.06	0.27	4.25
	1	28.64	18.67	43.93	10.17	7.81	13.25	3.13	1.4	6.96
	2	30.45	21.02	44.1	9.27	7.42	11.59	3.57	1.6	7.95
	3	46.45	34.68	62.22	12.03	10.05	14.41	9.04	5.25	15.58
	4	41.85	29.26	59.86	14.79	12.38	17.66	15.19	9.44	24.44
	5	54.2	36.63	80.22	15.83	12.9	19.42	14.46	7.78	26.87
	6	65.45	39.46	108.57	16.92	12.93	22.15	14.16	6.36	31.51
	7	75.01	33.7	166.97	20.9	14.43	30.27	32.42	14.56	72.16
	8	99	24.76	395.83	40.25	24.66	65.69	17.12	2.41	121.57
	9	0	NA	NA	25.48	6.37	101.86	0	NA	NA
Myocardial infarction	0	7.93	2.98	21.14	3.19	1.66	6.13	0.53	0.07	3.78
	1	13.59	7.31	25.26	4.96	3.40	7.23	2.61	1.09	6.27
	2	18.42	11.45	29.63	8.02	6.32	10.19	3.56	1.6	7.93
	3	33.96	24.15	47.77	13.16	11.08	15.62	13.17	8.4	20.65
	4	58.76	43.42	79.51	22.02	19.04	25.46	20.24	13.45	30.46
	5	47.66	31.38	72.39	29.05	24.98	33.8	26.21	16.51	41.6
	6	87.21	56.26	135.17	35.85	29.77	43.18	31.11	18.07	53.59
	7	88.12	42.01	184.84	41.15	31.52	53.73	37.92	18.08	79.54
	8	99.62	24.91	398.32	62.12	41.64	92.68	72.61	27.25	193.46
	9	269.56	37.97	1913.59	96.03	45.78	201.44	197.57	63.72	612.59
Bleeding	0	25.85	15.01	44.51	24.24	19.08	30.8	11.83	7.79	17.96
	1	39.59	27.51	56.97	26.21	22.2	30.93	16.93	11.98	23.95
	2	41.24	30.01	56.68	35.13	31.28	39.44	26.2	19.43	35.33
	3	55.8	42.74	72.86	37.7	34.01	41.8	38.65	29.6	50.47
	4	61.56	45.81	82.72	43.78	39.44	48.59	34.48	25.09	47.39
	5	56.27	38.31	82.65	41.81	36.82	47.47	53.12	38.14	73.99
	6	69.9	42.82	114.1	56.91	49.08	66	63.4	43.17	93.11

7	87.38	41.66	183.29	54.1	42.87	68.26	59.78	33.11	107.94
8	98.57	24.65	394.12	47.35	30.2	74.23	106.74	47.95	237.58
9	0	NA	NA	101.2	50.61	202.36	0	NA	NA

CONCLUSIONS: Among warfarin treated AF patients, the risks of stroke, systemic thromboembolism, myocardial infarction, bleeding, cardiovascular mortality and all-cause mortality were found to decrease as a function of TTR.

Incidence rates of stroke and systemic thromboembolism (excluding stroke), stratified by risk scores, were found to be high during the first 90 days after initiation of warfarin.