ESC HEART FAILURE
ESC Heart Failure 2019; **6**: 10–15
Published online 9 October 2018 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12365

ORIGINAL RESEARCH ARTICLE

Effectiveness and safety of rivaroxaban vs. warfarin in patients with non-valvular atrial fibrillation and heart failure

Brandon K. Martinez[1,2], Thomas J. Bunz[3], Daniel Eriksson[4], Anna-Katharina Meinecke[4], Nitesh A. Sood[5] and Craig I. Coleman[1,2]*

[1]*Department of Pharmacy Practice, University of Connecticut School of Pharmacy, 69 North Eagleville Road, Unit 3092, Storrs, CT, USA;* [2]*Evidence-Based Practice Center, Hartford Hospital, Hartford, CT, USA;* [3]*Department of Pharmacoepidemiology, New England Health Analytics, LLC, Granby, CT, USA;* [4]*Real-World Evidence Strategy and Outcomes Data Generation, Bayer AG, Berlin, Germany;* [5]*Department of Cardiac Electrophysiology, Southcoast Health System, Fall River, MA, USA*

Abstract

Aims Heart failure (HF) is a common co-morbidity in non-valvular atrial fibrillation (NVAF) patients and a potent risk factor for stroke, bleeding, and a decreased time-in-therapeutic range with warfarin. We assessed the real-world effectiveness and safety of rivaroxaban and warfarin in NVAF patients with co-morbid HF.

Methods and results Using US Truven MarketScan Commercial and Medicare supplemental database claims data from 11/2011 to 12/2016, we identified oral anticoagulant (OAC)-naïve NVAF patients with HF (International Classification of Diseases, 10th Revision codes of I50 or I09.81) and ≥12 months of insurance coverage prior to the qualifying OAC dispensing. Rivaroxaban users (20 or 15 mg once daily) were 1:1 propensity score matched to warfarin users, with residual absolute standardized differences <0.1 being achieved for all covariates after matching. Patients were followed up until an event, OAC discontinuation/switch, insurance disenrolment, or end of follow-up. Rates [events per 100 person-years (PYs) of follow-up] for stroke or systemic embolism and major bleeding (using the Cunningham algorithm) were compared between the matched cohorts using Cox proportion hazard regression and reported as hazard ratios (HRs) with 95% confidence intervals (CIs). We matched 3418 rivaroxaban (32% receiving the reduced dose) and 3418 warfarin users with NVAF and HF with a median (interquartile range) available follow-up of 1.4 (0.6, 2.5) years. Median age was 74 (63, 82) years, and median CHA_2DS_2-VASc and HASBLED scores were 4 (3, 5) and 2 (2, 3). Common HF medications included beta-blockers (64%), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (62%), loop diuretics (46%), digoxin (11%), and aldosterone receptor antagonists (10%). The hazard of developing stroke or systemic embolism (0.98 events/100PY vs. 1.28 events/100PY; HR = 0.82, 95% CI = 0.47–1.44), ischaemic stroke (0.70 events/100PY vs. 1.02 events/100PY; HR = 0.77, 95% CI = 0.41–1.46), or major bleeding (3.86 events/100PY vs. 4.23 events/100PY; HR = 0.98, 95% CI = 0.73–1.31) was not found to be different between rivaroxaban and warfarin users. Intracranial haemorrhage was infrequent in both cohorts and numerically less with rivaroxaban (0.27 events/100PY vs. 0.36 events/100PY; HR = 0.73, 95% CI = 0.25–2.08).

Conclusions Effectiveness and safety of rivaroxaban vs. warfarin are sustained in NVAF patients with co-morbid HF treated in routine practice. The general consistency between this real-world study and those from phase III randomized trial data of rivaroxaban should provide additional reassurance to clinicians regarding the use of rivaroxaban in NVAF patients with HF.

Keywords Rivaroxaban; Warfarin; Atrial fibrillation; Heart failure; Anticoagulation; Stroke

Received: 31 May 2018; Revised: 26 July 2018; Accepted: 30 August 2018
**Correspondence to: Craig I. Coleman, University of Connecticut School of Pharmacy, 69 North Eagleville Road, Unit 3092, Storrs, CT 06269, USA. Tel: +1 860-972-2096; Fax: +1 860-545-2277. Email: craig.coleman@hhchealth.org*

Introduction

Heart failure (HF) is recognized as a risk factor for thromboembolic events in patients with non-valvular atrial fibrillation (NVAF).[1,2] It is estimated ~40% of patients with either atrial fibrillation (AF) or HF will develop the other condition, with an incidence of HF in individuals with AF up to 4.4/100 person-years (PYs) of follow-up.[3] Furthermore, patients with

NVAF and HF treated with vitamin K antagonists spend less time-in-therapeutic range (TTR) than those without HF, potentially increasing their risk of thrombo-embolism and/or bleeding.[4–7] In the Rivaroxaban Once-daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism (ROCKET AF) trial,[8] approximately two-thirds of patients had concomitant HF, with similar treatment-related efficacy and safety for rivaroxaban vs. warfarin in patient with and without HF.[9]

A paucity of data evaluating the real-world effectiveness and safety of rivaroxaban compared with warfarin in people with NVAF and co-morbid HF exists. Therefore, we sought to assess the effectiveness and safety of rivaroxaban vs. warfarin in people with NVAF and HF treated in routine practice.

Methods

We performed a retrospective claims database analysis of US Truven MarketScan data from 11/1/2011 to 12/31/2016. Truven MarketScan combines two separate databases, a commercial and a Medicare supplemental database, to cover all age groups and contains claims from 260 contributing employers, 40 health plans, and government and public organizations representing ~240 million lives.[10] Truven MarketScan captures enrolment records, demographics, International Classification of Diseases, 9th and 10 Revision (ICD-9 and ICD-10) diagnosis codes, procedure codes, admission and discharge dates, outpatient medical services data, and prescription dispensing records. All Truven MarketScan data were de-identified and are in compliance with the Health Insurance Portability and Accountability Act of 1996 to preserve participant anonymity and confidentiality. This study was determined to not constitute research involving human subjects according to 45 CFR 46.102(f) and, therefore, deemed exempt from institutional review board oversight.

We included people who were oral anticoagulant (OAC) naïve during the 12 months before the day of the first qualifying rivaroxaban or warfarin dispensing (index date); had ≥2 inpatient or outpatient ICD codes in any position for AF (ICD-10 = I48) without codes suggesting valvular disease; an inpatient or outpatient diagnosis code in any position for HF (ICD-10 = I50, I09.81)[11]; and ≥12 months of continuous medical and prescription coverage prior to OAC initiation (baseline period). Individuals were excluded if they had a history of venous thrombo-embolism or orthopaedic arthroplasty, were pregnant, had a transient cause of NVAF, or were prescribed >1 OAC.

Propensity scores were calculated using multivariable logistic regression incorporating frequently used variables and potential risk factors for differential OAC exposure (*Table 1*) including demographics, co-morbidities,[11] components of the CHA_2DS_2-VASc and HASBLED scores,[12] and concomitant non-OAC medications identified during the 12 month baseline period.

Each eligible rivaroxaban user (20 or 15 mg once daily) was 1:1 propensity score matched (using greedy nearest-neighbour matching without replacement, calliper = 1%) to a warfarin user to minimize the presence of baseline differences between cohorts.[13] Residual differences in covariates between matched cohorts were assessed via absolute standardized differences (<0.1 considered well balanced).[14]

Our primary effectiveness outcome was the combination of stroke or systemic embolism (SSE) including ischaemic stroke (ICD-10 = I63, I64.9), haemorrhagic stroke (ICD-10 = I60–I62), or systemic embolism (ICD-10 = I74).[15] The occurrence of SSE during the observation period was determined by the presence of an appropriate inpatient discharge diagnosis code in the primary position. Major bleeding was our primary safety outcome and was determined using the Cunningham algorithm.[16] Individuals were followed up until outcome occurrence, OAC discontinuation/switch (30 day permissible gap), insurance disenrolment, or end-of-study follow-up.

Baseline characteristics were analysed using descriptive statistics. Categorical data were reported as proportions and continuous data as medians with interquartile ranges. The rate of outcomes was reported as events/100PYs. Cox proportional hazards regression was performed on the matched cohorts using PROC PHREG and a robust sandwich estimator in SAS version 9.4 (SAS Inc., Cary, NC, USA). Because all characteristics were balanced after propensity score matching, regression included only the OAC used as a covariate. Results are reported as hazard ratios (HRs) with 95% confidence intervals (CIs).

Results

We initially identified 4533 rivaroxaban and 8222 warfarin users with NVAF and HF. Of these, 3418 rivaroxaban (32% received the 15 mg once daily dose) and 3418 warfarin users were matched. Baseline covariates were well balanced after matching (absolutes standardized differences ≤0.04 for all). The propensity score-matched cohort had a median available follow-up of 1.4 (0.6, 2.5) years, age of 74 (63, 82) years, and CHA_2DS_2-VASc and modified HASBLED scores of 4 (3, 5) and 2 (2, 3). The most common HF medications prescribed included beta-blockers (64%), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (62%), loop diuretics (46%), digoxin (11%), and aldosterone receptor antagonists (10%).

Rivaroxaban was associated with non-significant 18% and 23% hazard reductions in SSE and ischaemic stroke alone vs. warfarin (*Figure 1*). No difference in overall major bleeding (HR = 0.98) was observed between cohorts. Intracranial haemorrhage occurred less frequently with rivaroxaban compared with warfarin (0.27 events/100PY vs. 0.36 events/100PY); however, the 95% CIs for the HR included 1.0.

DOI: 10.1002/ehf2.12365

Table 1 Baseline characteristics in propensity score-matched rivaroxaban and warfarin patients

Variable	Rivaroxaban N = 3418 %	Warfarin N = 3418 %	Absolute standardized difference
Age, years, median (IQR)[a]	74 (63, 82)	74 (63, 82)	
65–74 years	22.3	22.1	0.00
≥75 years	55.8	56.1	0.01
Male sex	58.6	58.8	0.00
Co-morbidities			
Diabetes mellitus	35.2	35.6	0.01
Hypertension	82.9	83.3	0.01
Peripheral vascular disease	4.9	4.7	0.01
Ischaemic stroke	7.7	8.1	0.01
Myocardial infarction	13.2	12.8	0.01
Percutaneous coronary intervention	5.1	5.1	0.00
Coronary artery bypass grafting	16.2	16.2	0.00
History of major bleeding	5.1	4.6	0.02
Gastrointestinal bleeding	1.7	1.5	0.02
Intracranial haemorrhage	0.2	0.2	0.01
Acute kidney injury	13.1	12.7	0.01
Chronic kidney disease	17.2	16.6	0.02
End-stage renal disease	12.4	12.1	0.01
Liver disease	4.4	4.5	0.01
Coagulopathy	5.2	5.1	0.00
Gastroesophageal reflux disease	12.8	12.4	0.01
Upper gastrointestinal testing	6.9	7.3	0.01
Anaemia	21.9	21.1	0.02
Asthma	9.6	8.8	0.03
Chronic obstructive pulmonary disease	27.0	27.3	0.01
Sleep apnoea	18.0	17.7	0.01
Smoker	8.2	7.7	0.02
Haemorrhoids	3.7	3.3	0.02
Alcohol abuse	2.8	2.6	0.01
Anxiety	9.6	9.9	0.01
Depression	11.9	11.8	0.01
Psychosis	4.3	4.6	0.01
Obesity	20.3	19.5	0.02
Osteoarthritis	23.2	22.4	0.02
Back pain	18.6	18.5	0.00
Joint pain and stiffness	37.2	38.0	0.02
Headache	7.0	6.9	0.01
Diverticulitis	7.3	6.9	0.02
Crohn's disease or ulcerative colitis	2.5	2.4	0.01
Helicobacter pylori	0.5	0.3	0.04
Hypothyroidism	16.8	17.2	0.01
Solid tumour	11.5	11.9	0.01
Lymphoma	1.9	2.0	0.01
Metastatic cancer	1.7	1.9	0.01
Medication use			
Antiplatelet drugs	16.9	17.9	0.03
NSAIDs	17.3	17.2	0.00
COX-2-specific NSAIDs	2.6	2.8	0.01
ACE-inhibitors or ARBs	61.6	62.3	0.01
Aldosterone receptor antagonists	10.2	10.0	0.01
β-Blockers	64.5	64.3	0.00
Diltiazem	12.0	12.9	0.03
Verapamil	2.0	1.9	0.00
Dihydropyridine calcium channel blockers	25.3	25.3	0.00
Loop diuretic	45.8	45.6	0.00
Thiazide diuretic	27.0	27.2	0.00
Digoxin	11.1	11.1	0.00
Amiodarone	8.7	8.5	0.01
Dronedarone	1.4	1.1	0.03
Other antiarrhythmic drugs	5.7	5.0	0.03
Statins	54.0	54.1	0.00
Other cholesterol lowering drugs	10.2	10.3	0.01
Benzodiazepines	16.4	16.2	0.01
SSRIs or SNRIs	16.1	16.9	0.02

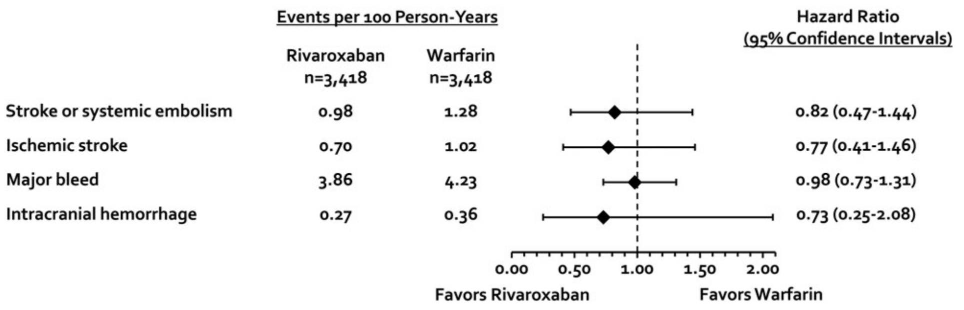
(*Continues*)

Table 1 (continued)

Variable	Rivaroxaban N = 3418 %	Warfarin N = 3418 %	Absolute standardized difference
Other antidepressants	9.2	8.8	0.01
Proton pump inhibitors	25.6	24.9	0.02
Histamine-2 receptor antagonists	5.0	5.3	0.01
Systemic corticosteroids	25.3	24.9	0.01
Warfarin inducer	31.8	30.8	0.02
Warfarin inhibitor	67.6	68.3	0.02
Metformin	16.9	16.9	0.00
Sulfonylureas or glinides	11.6	12.2	0.02
Thiazolidinediones	2.5	2.2	0.02
Dipeptidyl peptidase-4 inhibitors	4.7	4.5	0.01
Glucagon-like peptide-1 agonists	1.2	1.2	0.00
SGLT2 inhibitors	0.2	0.2	0.01
Insulin	11.1	10.9	0.00
Alpha-glucosidase inhibitor	0.2	0.1	0.01
Risk stratification scores			
$CHADS_2$[a,b], median (IQR)	3 (2,3)	3 (2,3)	
Mean ± standard deviation	2.8 ± 1.0	2.9 ± 1.0	
1	8.6	7.7	0.03
2	27.9	27.8	
3	42.7	43.9	
≥4	20.8	20.5	0.01
CHA_2DS_2-VASc[a,c], median (IQR)	4 (3, 5)	4 (3,5)	
Mean ± standard deviation	3.9 ± 1.4	4.0 ± 1.4	
1	4.5	3.8	0.04
2	13.0	12.8	
3	19.7	19.7	0.00
≥4	62.7	63.6	0.02
Modified HAS-BLED[a,d], median (IQR)	2 (2,3)	2 (2,3)	
Mean ± standard deviation	2.3 ± 1.2	2.3 ± 1.1	
≥3	37.7	37.1	0.01

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; COX-2, cyclooxygenase-2; IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drugs; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
[a]Median age and $CHADS_2$, CHA_2DS_2-VASc, and modified HASBLED risk scores were not included in the propensity score model; instead, individual components of CHA_2DS_2-VASc and modified HASBLED were used.
[b]$CHADS_2$ = congestive heart failure, 1 point; hypertension, 1 point; age ≥ 75 years, 1 point; diabetes mellitus, 1 point; previous stroke or transient ischaemic attack, 2 points.
[c]CHA_2DS_2-VASc = congestive heart failure, 1 point; hypertension, 1 point; age ≥ 75 years, 2 points; diabetes mellitus, 1 point; previous stroke, transient ischaemic attack, or thrombo-embolism, 2 points; vascular disease, 1 point; age 65–74 years, 1 point; female sex, 1 point.
[d]Modified HASBLED = hypertension, 1 point; age > 65 years, 1 point; stroke history, 1 point; bleeding history or predisposition, 1 point; liable international normalized ratio, not assessed; ethanol or drug abuse, 1 point; drug predisposing to bleeding, 1 point.

Figure 1 Event[*,†] rates, hazard ratios, and 95% confidence intervals for rivaroxaban vs. warfarin users with non-valvular atrial fibrillation and heart failure. n = number. [*]Stroke or systemic embolism included ischaemic stroke [International Classification of Diseases, 10th Revision (ICD-10) = I63, I64.9], haemorrhagic stroke (ICD-10 = I60–I62), or systemic embolism (ICD-10 = I74).[15] [†]Major bleeding was determined using the Cunningham algorithm.[16]



Discussion

In this large US claims database analysis of people with NVAF and co-morbid HF, rivaroxaban was associated with similar rates of SSE, ischaemic stroke, and major bleeding vs. warfarin. Our findings are consistent with those from a sub-analysis of the ROCKET AF trial, which showed the relative efficacy of rivaroxaban and warfarin for prevention of SSE was similar in people with HF or a left ventricular ejection fraction (LVEF) of <40% (SSEs/100PYs = 1.90 vs. 2.09; HR = 0.91, 95% CI = 0.74–1.13) as were the relative risk of developing bleeding complications (major or non-major clinical relevant bleeds/100PYs = 14.22 vs. 14.02; HR = 1.05, 95% CI = 0.95–1.15).[9]

A complex interrelationship exists between NVAF and HF. The two diseases share similar predisposing risk factors such as hypertension, diabetes, and coronary artery disease. Furthermore, both disease states are fostered by changes in neurohormonal activation, cellular and extracellular alterations, and electrophysiological changes.[17] For this reason, it is not uncommon to observe the coexistence of these two disease states. The prevalence of NVAF increases as the severity of HF increases, with patients with New York Heart Association (NYHA) functional class I symptoms exhibiting an AF prevalence of ≤5% and those with NYHA class IV symptoms having a prevalence of ~50%. The prevalence of both disease states also increases with advanced age. In patients with a LVEF < 40%, the AF prevalence is 22% in patients <70 years old compared with 41% in patients >70 years old.[17]

Both NVAF and HF treatment guidelines recommend direct-acting OACs be used preferentially over warfarin in people with concomitant NVAF and HF.[12,18] This recommendation is based on existing evidence demonstrating direct-acting OACs to be at least as effective as vitamin K antagonists in this patient population with a substantial decrease in intracranial haemorrhage risk.[19,20] Additionally, patients with NVAF and HF have been shown to have lower TTRs than those without HF.[4–7] Of particular note, a multivariate analysis of the US Outcomes Registry for Better Informed Treatment of Atrial Fibrillation suggested HF was a risk factor for patients falling into the lowest (0–53%) TTR quartile (odds ratio range: 1.25–1.72), with NYHA class III–IV status associated with the greatest odds of falling into the lowest TTR quartile (odds ratio = 1.72; 95% CI = 1.36–2.16).[6]

Our study has limitations worth discussion. First, both misclassification and selection bias may impact a claims database study's internal validity.[13] Second, we used US data[10]; and therefore, our results are most generalizable to an American population with concomitant NVAF and HF. Third, regardless of the sophistication of the methodology and the number of covariates used in developing propensity scores, residual confounding cannot be fully excluded because of the possibility of confounding from unobserved or unmeasured covariates.[14] Fourth, we were only able to match ~75% of rivaroxaban users to warfarin users in our analysis. This is due to the small propensity score calliper utilized. Using a small calliper makes it more difficult to match patients but likely results in a higher quality of matching. Next, international normalized ratio data were not available in our data set, and thus, TTR could not be calculated. Fifth, ICD-9 or ICD-10 diagnosis coding does not allow for adequate assessment of LVEF or NYHA class, and the lack of coding specificity was further compounded by the lack of laboratory data available in our Truven MarketScan data set. As a result, we were unable evaluate what impact HF severity or functional status may have had on our study's conclusions.[10] Interestingly, the HF patient sub-analysis of ROCKET AF did not show a statistical interaction by LVEF (≥40% vs. <40%) or NYHA classification (I–II vs. III–IV) and trial endpoints (including SSE and clinical relevant bleeding).[9] Consequently, it is less likely the lack of specific detail on HF severity in our data set would substantially impact our study's findings.

Conclusions

Rivaroxaban has at least as good effectiveness and safety as warfarin in NVAF with co-morbid HF treated in routine practice. The fact that our real-world findings are generally consistent with those from phase III randomized trial data of rivaroxaban should provide additional reassurance to clinicians regarding the use of rivaroxaban in NVAF patients with HF.

Conflict of interest

C.I.C. has received grant funding and consultancy honorarium from Bayer AG, Janssen Scientific Affairs LLC, and Boehringer Ingelheim Pharmaceuticals Inc. D.E. and A.-K.M. are employees of Bayer AG.

Funding

This study was supported by Bayer AG, Berlin, Germany.

References

1. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification of schemes for predicting stroke results from the National Registry of Atrial Fibrillation. *JAMA* 2001; **285**: 2864–2870.
2. Chao TF, Lip GY, Liu CJ, Tuan TC, Chen SJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Chen TJ, Chiang CE, Chen SA. Validation of a modified CHA_2DS_2-VASc score for stroke risk stratification in Asian patients with atrial fibrillation: a nationwide cohort study. *Stroke* 2016; **47**: 2462–2469.
3. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiuve SE, Cushman M, Delling FN, Deo R, de Ferranti SD, Ferguson JF, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Lutsey PL, Mackey JS, Matchar DB, Matsushita K, Mussolino ME, Nasir K, O'Flaherty M, Palaniappan LP, Pandey A, Pandey DK, Reeves MJ, Ritchey MD, Rodriguez CJ, Roth GA, Rosamond WD, Sampson UKA, Satou GM, Shah SH, Spartano NL, Tirschwell DL, Tsao CW, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P, American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2018 update: a report from the American Heart Association. *Circulation* 2018; **137**: e67–e492.
4. Rose AJ, Hylek EM, Ozonoff A, Ash AS, Reisman JI, Berlowitz DR. Patient characteristics associated with oral anticoagulation control: results of the Veterans AffaiRs Study to Improve Anticoagulation (VARIA). *J Thromb Haemost* 2010; **8**: 2182–2191.
5. Witt DM, Delate T, Clark NP, Martell C, Tran T, Crowther MA, Garcia DA, Ageno W, Hylek EM, Warfarin Associated Research Projects and other EnDeavors (WARPED) Consortium. Outcomes and predictors of very stable INR control during chronic anticoagulation therapy. *Blood* 2009; **114**: 952–956.
6. Pokorney SD, Simon DN, Thomas L, Fonarow GC, Kowey PR, Chang P, Singer DE, Ansell J, Blanco RG, Gersh B, Mahaffey KW, Hylek EM, Go AS, Piccini JP, Peterson ED, Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Investigators. Patients' time in therapeutic range on warfarin among US patients with atrial fibrillation: results from ORBIT-AF registry. *Am Heart J* 2015; **170**: 141–148.
7. Apostolakis S, Sullivan RM, Olshansky B, Lip GYH. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: the SAMe-TT_2R_2 score. *Chest* 2013; **144**: 1555–1563.
8. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; **365**: 883–891
9. van Diepen S, Hellkamp AS, Patel MR, Becker RC, Breithardt G, Hacke W, Halperin JL, Hankey GJ, Nessel CC, Singer DE, Berkowitz SD, Califf RM, Fox KA, Mahaffey KW. Efficacy and safety of rivaroxaban in patients with heart failure and nonvalvular atrial fibrillation: insights from ROCKET AF. *Circ Heart Fail* 2013; **6**: 740–747.
10. Hansen L. The Truven Health MarketScan Databases for life sciences researchers. **https://truvenhealth.com/Portals/0/Assets/2017-MarketScan-Databases-Life-Sciences-Researchers-WP.pdf (10 April 2018)**
11. Moore BJ, White S, Washington R, Coenen N, Elixhauser A. Increased risk of readmission and in-hospital mortality using hospital administrative data: the AHRQ Elixhauser comorbidity index. *Med Care* 2017; **55**: 698–705.
12. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016; **37**: 2893–2962.
13. Gandhi SK, Salmon W, Kong SX, Zhao SZ. Administrative databases and outcomes assessment: an overview of issues and potential utility. *J Manag Care Spec Pharm* 1999; **5**: 215–222.
14. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivar Behav Res* 2011; **46**: 399–424.
15. Lip GYH, Skjøth F, Nielsen PB, Kjældgaard JN, Larsen TB. Effectiveness and safety of standard-dose nonvitamin K antagonist oral anticoagulants and warfarin among patients with atrial fibrillation with a single stroke risk factor: a nationwide cohort study. *JAMA Cardiol* 2017; **2**: 872–881.
16. Cunningham A, Stein CM, Chung CP, Daugherty JR, Smalley WE, Ray WA. An automated database case definition for serious bleeding related to oral anticoagulant use. *Pharmacoepidemiol Drug Saf* 2011; **20**: 560–566.
17. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. *Am J Cardiol* 2003; **91**: 2D–8D.
18. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**: 2129–2200.
19. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomized trials. *Lancet* 2014; **383**: 955–962.
20. Xiong Q, Lau YC, Senoo K, Lane DA, Hong K, Lip GY. Non-vitamin K antagonist oral anticoagulants (NOACs) in patients with concomitant atrial fibrillation and heart failure: a systematic review and meta-analysis of randomized trials. *Eur J Heart Fail* 2015; **17**: 1192–1200.