Available online at www.sciencedirect.com

ScienceDirect

Journal of the Chinese Medical Association 80 (2017) 277–282

www.jcma-online.com

Original Article

Association of warfarin with congestive heart failure and peripheral artery occlusive disease in hemodialysis patients with atrial fibrillation

Kuo-Hua Lee [a,b,c], Szu-Yuan Li [b,c], Jin-Sin Liu [d], Chi-Ting Huang [d], Ying-Ying Chen [c], Yao-Ping Lin [a,c], Chih-Cheng Hsu [f,g], Der-Cherng Tarng [c,e,*]

[a] *National Yang-Ming University, School of Medicine, Taipei, Taiwan, ROC*
[b] *Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan, ROC*
[c] *Division of Nephrology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[d] *Division of Geriatrics and Gerontology, Institute of Population Health Sciences, National Health Research Institutes, Taipei, Taiwan, ROC*
[e] *Institutes of Physiology and Clinical Medicine, National Yang-Ming University, Taipei, Taiwan, ROC*
[f] *Institute of Population Health Sciences, National Health Research Institutes, Zhunan, Taiwan, ROC*
[g] *Department of Health Services Administration, China Medical University, Taichung, Taiwan, ROC*

Received August 22, 2016; accepted October 11, 2016

Abstract

Background: The effect of warfarin on the risk of cardiovascular (CV) disease is unknown among chronic hemodialysis patients with atrial fibrillation (HD-AF).
Methods: Population-based propensity score and prescription time-distribution matched cohort study including 6719 HD-AF patients with CHA_2DS_2-VASc score ≥ 2 were divided into warfarin users and nonusers and followed-up for CV events and death.
Results: Warfarin treatment in HD-AF patients with AF preceding HD was associated with higher risks of developing congestive heart failure [hazard ratio (HR) = 1.82, 95% confidence interval (CI) = 1.29–2.58, $p < 0.01$], peripheral artery occlusive disease (HR = 3.42, 95% CI = 1.86–6.31, $p < 0.01$), and aortic valve stenosis (HR = 3.20, 95% CI = 1.02–9.98, $p < 0.05$). Warfarin users were not associated with risks of ischemic or hemorrhagic stroke and all-cause mortality as compared to nonusers.
Conclusion: Warfarin may be associated with vascular calcification, increasing the risks of congestive heart failure and peripheral artery occlusive disease among HD-AF patients.

Keywords: atrial fibrillation; hemodialysis; warfarin

1. Introduction

Patients with end-stage renal disease (ESRD) have an extremely high risk of developing cardiovascular (CV) diseases. Atrial fibrillation (AF) is the most common cardiac dysrhythmia in hemodialysis (HD) patients, with a prevalence rate of around 10%.[1] In the general population, clinical trial data supported the use of anticoagulants for stroke prevention in patients with a CHA2DS2-VASC score > 2.[2,3] However, due to the paucity of prospective trials in dialysis patients, the treatment strategy for this group was based on data obtained from retrospective observations. Although some studies have suggested that warfarin is beneficial for stroke prevention in HD patients with atrial fibrillation (HD-AF),[4] other studies have indicated that warfarin may actually increase the risk of stroke.[5,6] Furthermore, the risk of bleeding associated with

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

* Corresponding author. Dr. Der-Cherng Tarng, Division of Nephrology, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC.
E-mail address: dctarng@vghtpe.gov.tw (D.-C. Tarng).

http://dx.doi.org/10.1016/j.jcma.2016.10.012

warfarin treatment has been reported to be increased in patients with chronic kidney disease (CKD).[4] Consistent with the clinical uncertainty regarding the benefits of stroke prevention with warfarin, the most recent Kidney Disease Improving Global Outcomes recommendations neither supported nor rejected the use of warfarin therapy in HD patients.[7]

Apart from the potential effect on stroke, only a few studies have assessed the risks and benefits of warfarin on CV outcomes among chronic HD patients. Some preclinical studies have shown that warfarin inhibits vitamin K-dependent γ-carboxylase of matrix Gla protein (MGP) in arterial smooth muscle cells and is thus involved in the process of vascular calcification.[8–10] AF *per se* has been shown to impair cardiac performance,[11] and in combination with the potential negative effects of warfarin upon vascular health, the administration of warfarin in HD-AF patients may aggravate the severity of arterial stiffness, thereby increasing the risk of congestive heart failure (CHF) and electric instability of the heart leading to sudden cardiac death, which are the main causes of CV death in HD patients. Nevertheless, no large trials have yet analyzed the effect of warfarin on CHF and peripheral artery occlusive disease (PAOD) in HD-AF patients. Therefore, we used national registry data to investigate the effect of warfarin on the major CV outcomes among HD-AF patients.

2. Methods

2.1. Data source

The data used in this study were derived from the Taiwanese National Health Insurance (NHI) Research Database (NHIRD). Taiwan's NHI program, launched in 1995, currently covers 99.9% of the population of 23 million people. The de-identified information kept in the NHIRD includes date of birth, sex, residential area, diagnostic codes, drug prescriptions, and medical procedures. We used codes from the International Classification of Diseases, ninth revision (ICD-9) to define diseases. This study was approved by the Institutional Research Board of Taipei Veterans General Hospital (2015-08-003BC), and informed consent was waived due to the de-identified personal information in the NHIRD. We excerpted data from a specially ordered dataset that included all claims information from patients under the registry of catastrophic illnesses from January 2000 to December 2010. In Taiwan, patients with ESRD who need long-term dialysis can apply for catastrophic illness registration cards from the NHI Administration so that co-payments for medical services are exempted.

2.2. Design and study participants

This study was a propensity score and prescription time-distribution matched cohort study. We selected individuals who had chronic HD > 90 days and AF from January 1, 2000 through June 30, 2009. We excluded patients younger than 20 years, patients older than 90 years, and patients with a CHA2DS2-VASC score < 2. These high-risk HD-AF patients were then divided into warfarin users ($n = 744$) and nonusers ($n = 5975$). The number of days from AF diagnosis to first warfarin prescription was assessed for users. The date of first warfarin prescription was defined as the index date for users. To avoid the imbalance of the prescription time distribution between the two groups, an index date was randomly selected from this diagnosis-treatment distribution set for nonusers.[12] We presumed that a stable anticoagulation effect would be achieved 30 days after the first warfarin treatment, thus patients with major CV events that occurred within 30 days of warfarin initiation were considered to be nonusers. Patients with a follow-up of < 30 days were also excluded. A 1:3 (user vs. nonuser) propensity scored and prescription time-distribution matched cohort was followed to major CV events, death, or December 31, 2010, whichever occurred first. The primary outcomes were defined as death, major adverse cardiovascular events [(a composite outcome of hospitalization for ischemic stroke (ICD-9 code 433-434, 436-437) and acute myocardial infarction (AMI; ICD-9 code 410-414))], hospitalization for hemorrhagic stroke (ICD-9 code 430-432), CHF (ICD-9 code 428), PAOD (ICD-9 code 440.0, 440.2, 440.3, 440.8, 440.9, 443, 444.0, 444.22, 444.8, 444.9, 447.8, 447.9), and aortic valve stenosis (ICD-9 code 424.1). Fig. 1 illustrates the patient selection flow chart.

2.3. Statistical analysis

Baseline characteristics were compared by two-sided *t* tests or Chi-square tests. In multivariate Cox proportional hazards regression models, the effect of warfarin was further adjusted for age, sex, Charlson comorbidity index, AMI, CHF, cerebrovascular accident, transient ischemic attack, bleeding history, and use of aspirin and clopidogrel. Results were expressed as hazard ratios (HRs) compared with the warfarin nonusers. The proportional hazards assumption, the constant HR over time, was evaluated by comparing estimated log-log survival curves for all time-independent covariates. All the assessed log-log survival plots graphically showed two parallel lines, indicating no violation of the assumption. Adjusted HRs for major CV outcomes associated with warfarin use were analyzed among two subgroups based on the occurrence of AF before and after HD. All p values were two-sided, and the significance level was set at 0.05. All analyses were performed using the commercially available software, SAS (version 9.3 SAS Institute Inc., Cary, North Carolina) and Stata SE (version 13.0; StataCorp., College Station, Texas, USA).

3. Results

In total, 7208 HD-AF patients were identified from the NHIRD database. Compared to warfarin nonusers, the warfarin users were younger, had a higher proportion of heart failure, and took more antiplatelet drugs (all $p < 0.05$). After propensity matching, 589 HD-AF warfarin users with high CHA2DS2-VASC scores and 1767 warfarin nonusers were selected. The baseline demographic data and drug exposure were comparable after matching (Table 1).

With a mean follow-up of 2 years, the average warfarin dosage was 2 mg/d in the warfarin user group, and the drug

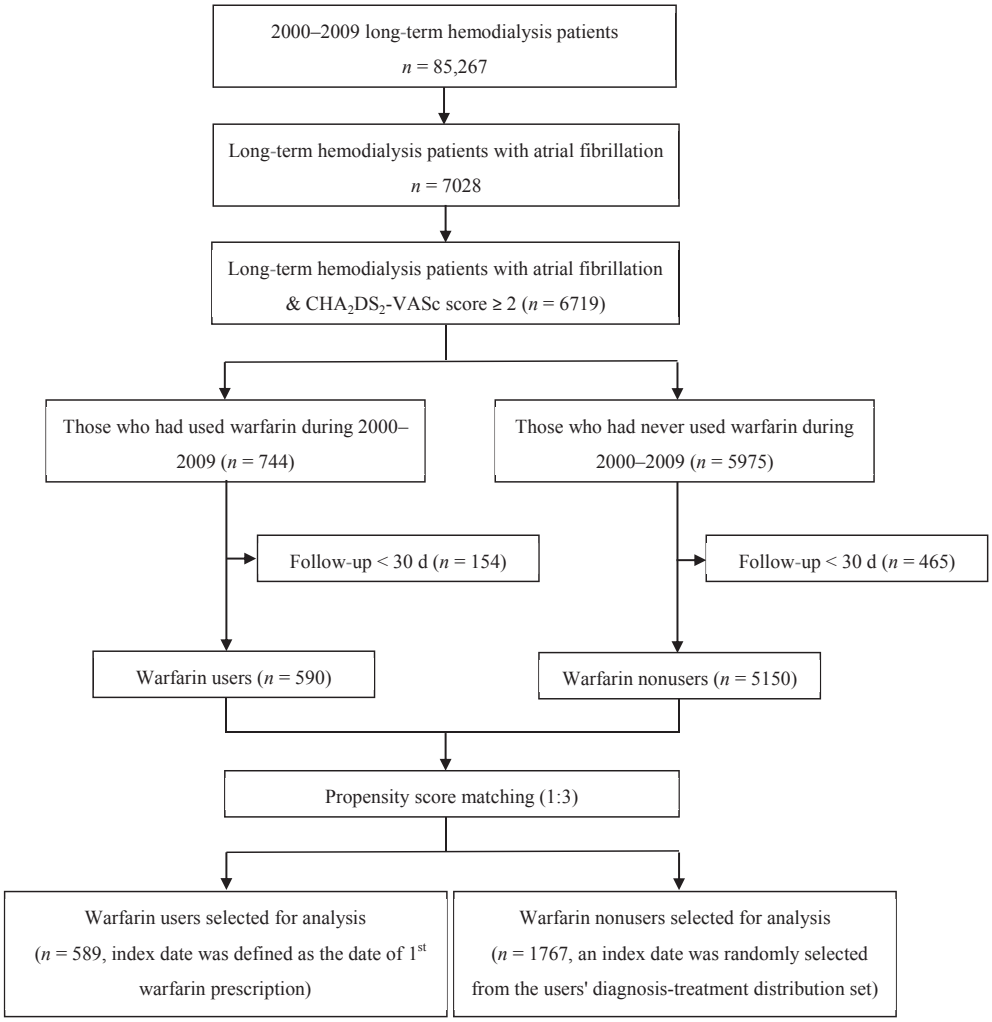

Fig. 1. Patient selection flow chart.

adherence rate was good (25% patients had drug discontinue > 30 days, only 10% patients had drug discontinue > 60 days during the study period). Patients in the warfarin user group averagely had 3.6- and 3.1-times the international normalized ratio (INR) check in the 1st year and 2nd year, respectively. In the fully matched cohort with AF developing before HD, the warfarin users were associated with higher risks of developing CHF [HR = 1.82, 95% confidence interval (CI) = 1.29–2.58, $p < 0.01$], PAOD (HR = 3.42, 95% CI = 1.86–6.31, $p < 0.01$), and aortic stenosis (HR = 3.20, 95% CI = 1.02–9.98, $p < 0.05$). The results in another subgroup with AF developing after HD were consistent, showing increased risks of CHF and PAOD in warfarin users (Table 2). Warfarin users were not associated with risks of ischemia or hemorrhagic stroke and all-cause mortality as compared to nonusers.

4. Discussion

4.1. Main findings

In the current study, we used the national registry data to show that warfarin was not able to prevent CV events in HD-AF patients. On the contrary, our data showed that warfarin use in HD-AF patients may lead to the development of PAOD, vascular calcification, and CHF, which are the main causes of CV morbidities in HD patients. Our findings highlight that warfarin should be prescribed to HD patients with great caution.

4.2. Association of warfarin use and ischemic stroke

Ischemic stroke is the main complication of AF, and various studies have proven that warfarin can efficiently prevent this complication. However, in HD-AF patients, the beneficial effect is not well recognized, mainly due to the exclusion of advanced CKD patients in large-scale prospective trials. In a retrospective study, Chan et al[5] reported that warfarin increased the ischemic stroke rate in HD patients, whereas Olesen et al[4] reported that warfarin prevented embolic stoke in this population. However, other studies have reported that warfarin had a neutral effect in stroke prevention in HD patients.[6,13,14] Inconsistent with most previous studies, our data showed a neutral effect of warfarin treatment in stroke prevention among HD-AF patients.

Table 1
Baseline characteristics of long-term hemodialysis patients with atrial fibrillation treated with and without warfarin.

	Before matching			After matching		
	Warfarin user	Warfarin nonuser		Warfarin user	Warfarin nonuser	
	$n = 590$	$n = 5150$	p	$n = 589$	$n = 1767$	p
Age (y)	68.8 (10.6)	71.2 (10.6)	0.018	69.3 (10.3)	70.3 (10.9)	0.782
Age (y)			0.032			0.982
20–39	2 (0.3)	29 (0.6)		2 (0.4)	5 (0.3)	
40–49	37 (6.3)	184 (3.6)		29 (5.0)	83 (4.8)	
50–59	72 (12.2)	558 (10.8)		67 (11.7)	216 (12.6)	
60–69	170 (28.8)	1316 (25.5)		167 (29.1)	505 (29.3)	
>70	309 (52.4)	3063 (59.5)		309 (53.8)	913 (53.0)	
Sex			0.149			0.462
Male	249 (42.2)	2334 (45.3)		243 (42.3)	699 (40.6)	
Female	341 (57.8)	2816 (54.7)		331 (57.7)	1023 (59.4)	
NHI Registration Location			0.285			0.677
City	134 (22.7)	1324 (25.7)		131 (22.8)	366 (21.3)	
Township	172 (29.2)	1446 (28.1)		168 (29.3)	500 (29.0)	
Rural area	284 (48.1)	2380 (46.2)		275 (47.9)	856 (49.7)	
Income			0.520			0.728
Poor	5 (0.8)	49 (0.9)		4 (0.7)	8 (0.4)	
Low income	142 (24.1)	1270 (24.7)		141 (24.6)	420 (24.4)	
Middle income	388 (65.8)	3440 (66.8)		376 (65.5)	1155 (67.1)	
High income	55 (9.3)	391 (7.6)		53 (9.2)	139 (8.1)	
CCI score			0.771			0.651
0	24 (4.1)	217 (4.2)		22 (3.8)	68 (3.9)	
1–2	127 (21.5)	1044 (20.3)		125 (21.8)	344 (20.0)	
> 2	439 (74.4)	3889 (75.5)		427 (74.4)	1310 (76.1)	
Comorbidity						
MI	163 (27.6)	1376 (26.7)	0.637	158 (27.5)	455 (26.4)	0.605
CHF	190 (32.2)	1395 (27.1)	0.009	186 (32.4)	527 (30.6)	0.420
TIA	10 (1.7)	60 (1.2)	0.267	10 (1.7)	29 (1.7)	0.926
CVA	43 (7.3)	297 (5.8)	0.138	39 (6.8)	101 (5.9)	0.420
Bleeding	32 (5.4)	391 (7.6)	0.056	32 (5.6)	81 (4.7)	0.403
Drug used						
Clopidogrel						
> 30 d	180 (30.5)	1416 (27.5)	0.122	172 (30.0)	491 (28.5)	0.506
Aspirin						
> 30 d	349 (59.2)	2598 (50.5)	< 0.001	336 (58.5)	1037 (60.2)	0.476
Y of follow-up						
Mean (SD)	2.28 (1.96)	2.15 (1.95)	0.1041	2.25 (1.94)	2.39 (2.08)	0.141

Data are presented as n (%), unless otherwise indicated.
CCI = Charlson Comorbidity Index; CHF = congestive heart failure; CVA = cerebrovascular accident; MI = myocardial infarction; NHI = national health insurance; SD = standard deviation; TIA = transient ischemic attack.

4.3. Association of warfarin use and bleeding risk

A major side effect of warfarin is bleeding. Taking into consideration the platelet dysfunction among dialysis patients, warfarin-induced bleeding could be a serious problem. However, the empirical evidence seems to be inconsistent. Two previous studies reported that warfarin increased the rate of gastrointestinal bleeding,[4,14] and another study reported that warfarin increased the rate of hemorrhagic stroke.[13] By contrast, there are studies showing that warfarin did not increase the risk of major bleeding.[13,15] From our registry database, we could not retrieve the INR data of each patient, an inevitable limitation in this claim-based big-data study, but in the setting of warfarin 2 mg/d and frequent INR monitoring, our results agreed with previous studies that major bleeding is not an issue; however, we could not clarify whether warfarin increased the minor bleeding rate due to the claim-based nature of the current study.

4.4. Association of warfarin use and mortality

Two previous studies have analyzed the association between warfarin usage and total mortality rate among HD-AF patients, and both found that warfarin did not affect the mortality rate.[5,13] One study showed that warfarin decreased mortality rate among AF patients with CKD and recent myocardial infarction. However, the benefit decreased as the kidney function deteriorated, and warfarin no longer provided survival benefits in CKD Stage 5.[15] Consistent with their results, the total mortality rate of HD-AF patients in our matched cohort was not associated with the use of warfarin.

4.5. Association of warfarin use and CV events

In patients with CKD, the elevated levels of calcium and phosphate in serum are associated with vascular calcification.[16] This process progressively narrows the arterial lumen

Table 2
Risk for cardiovascular events of warfarin users and nonusers during the follow-up period after propensity score and prescription time-distribution matching.

	Warfarin user		Warfarin nonuser		Patient developed AF before dialysis	Patient developed AF after dialysis
	n	IR	*n*	IR	Adjusted HR	Adjusted HR
CVA	56	5.6 (4.3–7.2)	188	5.3 (4.6–6.1)	0.91 (0.59–1.39)	1.23 (0.81–1.89)
Hemorrhagic stroke	8	0.8 (0.4–1.5)	37	1.0 (0.7–1.4)	0.84 (0.32–2.19)	0.45 (0.11–1.96)
Ischemic stroke	48	4.8 (3.6–6.3)	151	4.2 (3.6–5.0)	0.92 (0.57–1.48)	1.43 (0.91–2.24)
MACE[a]	22	2.1 (1.4–3.1)	126	3.5 (2.9–4.1)	0.87 (0.47–1.62)	0.62 (0.31–1.25)
CHF	82	8.5 (6.8–10.5)	205	5.8 (5.1–6.7)	1.82 (1.29–2.58)**	1.37 (0.92–2.03)
CHF/dead[b]	367	38.2 (34.4–42.2)	1104	31.5 (29.7–33.4)	1.23 (1.04–1.44)*	1.22 (1.02–1.46)*
PAOD	40	3.9 (2.8–5.2)	63	1.7 (1.3–2.2)	3.42 (1.86–6.31)**	2.00 (1.13–3.54)*
Aortic valve stenosis	12	0.9 (0.5–1.5)	8	0.2 (0.1–0.4)	3.20 (1.02–9.98)*	8.65 (1.4–51.24)*
All-cause mortality	340	32.0 (28.7–35.5)	1051	27.8 (26.1–29.5)	1.04 (0.88–1.23)	1.24 (1.03–1.50)*

Adjusted for age, sex, area, income, Charlson comorbidity index, myocardial infarction, congestive heart failure, cerebrovascular accident, transient ischemic attack, bleeding, and anti-platelet medications.
* $p < 0.05$.
** $p < 0.01$.
AF = atrial fibrillation; CHF = congestive heart failure; CVA = cerebrovascular accident; HR = hazards ratio; IR = incidence rate/1000 patient year; MACE = major adverse cardiovascular event; PAOD = peripheral arterial occlusive disease.
[a] Myocardial infarction or ischemic stroke.
[b] Composite endpoint of death and/or admission for heart failure.

and increases vascular stiffness, which deteriorates left ventricular loading and serves as an important pathological contributor to CHF.[17] In addition to the disordered mineral metabolism, warfarin has also been associated with vascular calcification in HD patients. Physiologically, MGP is carboxylated within the vasculature by vitamin K2. This peripheral carboxylation process has been shown to be inhibited by warfarin administration.[9] In human arteries, uncarboxylated MGP has been strongly associated with vascular calcification.[18] In the setting of HD-AF patients, warfarin might block the MGP-based vascular defense system, leading to vascular calcification and subsequent arterial stiffness. In the current study, the use of warfarin was associated with a 3.2-fold higher risk of developing aortic valve stenosis. Aortic valve calcification has been linked to warfarin in a small number of HD patients,[19] and the current study confirmed this finding. Our results indicate that in HD-AF patients, warfarin may induce CHF by increasing systemic vascular stiffness and aortic valve stenosis.

4.6. Time in therapeutic range on warfarin

To assess the adequacy of anticoagulant therapy for patients treated with warfarin, the time in therapeutic range (TTR) is an important indicator, defined as the percentage of time during which the patients have the INR values between 2 and 3, as recommended by the current treatment guidelines.[3] However, in consideration of bleeding tendency attributed to uremic toxins, anemia, platelet dysfunction, and regular heparin use in HD patients, the INR target of warfarin therapy in HD-AF patients was apparently conservative in clinical practice. In many countries, the average TTR is poor, and in a recent randomized trial, the average TTR in Taiwan was only 44%, much lower than the recommended TTR of > 70%.[20] Accordingly, even though the TTR data were not available from the NHIRD dataset, we could estimate a low TTR in HD-AF patients on warfarin, which reflects poor anticoagulation control with warfarin in HD patients. This might affect the outcomes in this study.

4.7. Strengths and limitations of this study

Compared to previous reports, the current study has the advantage of being a large-scale national registry data analysis. The results of this study may have implications for the prescription of warfarin in HD patients in clinical practice, and they also raise several questions, including at what stage of CKD is warfarin harmful, whether the dosage of warfarin is important, and whether other anticoagulation drugs have similar side effects in HD patients. Future large-scale prospective studies are needed to answer these questions.

In conclusion, the current study showed that warfarin use in HD-AF patients may lead to CHF, PAOD, and aortic valve stenosis due to the calcification tendency. Accordingly, warfarin should be prescribed with great caution to this population.

Acknowledgments

This study was supported in part by research grants from Taipei Veterans General Hospital (VGH-V102; Taipei, Taiwan) and the Foundation for Poison Control (E2-002).

References

1. Winkelmayer WC, Patrick AR, Liu J, Brookhart MA, Setoguchi S. The increasing prevalence of atrial fibrillation among hemodialysis patients. *J Am Soc Nephrol* 2011;**22**:349–57.
2. Estes 3rd NA, Halperin JL, Calkins H, Ezekowitz MD, Gitman P, Go AS, et al. ACC/AHA/Physician Consortium 2008 clinical performance measures for adults with nonvalvular atrial fibrillation or atrial flutter: a report of the American College of Cardiology/American Heart Association Task Force on performance measures and the physician consortium for

performance improvement (writing committee to develop clinical performance measures for atrial fibrillation) developed in collaboration with the heart rhythm society. *J Am Coll Cardiol* 2008;**51**:865−84.
3. Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, et al. Management of patients with atrial fibrillation (compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS recommendations): a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;**61**:1935−44.
4. Olesen JB, Lip GY, Kamper AL, Hommel K, Kober L, Lane DA, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med* 2012;**367**:625−35.
5. Chan KE, Lazarus JM, Thadhani R, Hakim RM. Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation. *J Am Soc Nephrol* 2009;**20**:2223−33.
6. Wizemann V, Tong L, Satayathum S, Disney A, Akiba T, Fissell RB, et al. Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. *Kidney Int* 2010;**77**:1098−106.
7. Herzog CA, Asinger RW, Berger AK, Charytan DM, Diez J, Hart RG, et al. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2011;**80**:572−86.
8. Holden RM, Booth SL. Vascular calcification in chronic kidney disease: the role of vitamin K. *Nat Clin Pract Nephrol* 2007;**3**:522−3.
9. Danziger J. Vitamin K-dependent proteins, warfarin, and vascular calcification. *Clin J Am Soc Nephrol* 2008;**3**:1504−10.
10. Kruger T, Oelenberg S, Kaesler N, Schurgers LJ, van de Sandt AM, Boor P, et al. Warfarin induces cardiovascular damage in mice. *Arterioscler Thromb Vasc Biol* 2013;**33**:2618−24.
11. Anter E, Jessup M, Callans DJ. Atrial fibrillation and heart failure: treatment considerations for a dual epidemic. *Circulation* 2009;**119**:2516−25.
12. Zhou Z, Rahme E, Abrahamowicz M, Pilote L. Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods. *Am J Epidemiol* 2005;**162**:1016−23.
13. Winkelmayer WC, Liu J, Setoguchi S, Choudhry NK. Effectiveness and safety of warfarin initiation in older hemodialysis patients with incident atrial fibrillation. *Clin J Am Soc Nephrol* 2011;**6**:2662−8.
14. Shah M, Avgil Tsadok M, Jackevicius CA, Essebag V, Eisenberg MJ, Rahme E, et al. Warfarin use and the risk for stroke and bleeding in patients with atrial fibrillation undergoing dialysis. *Circulation* 2014;**129**:1196−203.
15. Carrero JJ, Evans M, Szummer K, Spaak J, Lindhagen L, Edfors R, et al. Warfarin, kidney dysfunction, and outcomes following acute myocardial infarction in patients with atrial fibrillation. *JAMA* 2014;**311**:919−28.
16. Shroff R, Long DA, Shanahan C. Mechanistic insights into vascular calcification in CKD. *J Am Soc Nephrol* 2013;**24**:179−89.
17. Marti CN, Gheorghiade M, Kalogeropoulos AP, Georgiopoulou VV, Quyyumi AA, Butler J. Endothelial dysfunction, arterial stiffness, and heart failure. *J Am Coll Cardiol* 2012;**60**:1455−69.
18. Schurgers LJ, Teunissen KJ, Knapen MH, Kwaijtaal M, van Diest R, Appels A, et al. Novel conformation-specific antibodies against matrix gamma-carboxyglutamic acid (Gla) protein: undercarboxylated matrix Gla protein as marker for vascular calcification. *Arterioscler Thromb Vasc Biol* 2005;**25**:1629−33.
19. Holden RM, Sanfilippo AS, Hopman WM, Zimmerman D, Garland JS, Morton AR. Warfarin and aortic valve calcification in hemodialysis patients. *J Nephrol* 2007;**20**:417−22.
20. Wallentin L, Yusuf S, Ezekowitz MD, Alings M, Flather M, Franzosi MG, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet* 2010;**376**:975−83.