European Heart Journal - Cardiovascular Pharmacotherapy (2017) **3**, 147–150
doi:10.1093/ehjcvp/pvx003

ORIGINAL ARTICLE
Atrial fibrillation

Changes in oral anticoagulation for elective cardioversion: results from a European cardioversion registry

Judit Papp[1]*, Endre Zima[2], Ramon Bover[3], Rasa Karaliute[4], Andrea Rossi[5], Catherine Szymanski[6], Rossella Troccoli[7], Jonas Schneider[8], Morten Wang Fagerland[9], A. John Camm[10], and Dan Atar[11]

[1]Department of Cardiology, Medical Center Hungarian Defence Forces, 44 Robert Karoly Krt., 1134 Budapest, Hungary; [2]Heart and Vascular Center, Semmelweis University, 68 Varosmajor u., 1122 Budapest, Hungary; [3]Cardiology Department, University Hospital Clinico San Carlos, Profesor Martin Lagos s/n, 28040 Madrid, Spain; [4]Lithuanian University of Health Sciences, Cardiology Clinic, 2 Eiveniu str., 50161 Kaunas, Lithuania; [5]Cardiothoracic Department, Tuscany Foundation Gabriele Monasterio, 1 Via G. Moruzzi, 56124 Pisa, Italy; [6]Cardiology Department, Amiens University Hospital, Avenue Rene Laennec, 80000 Salouel Amiens, France; [7]Cardiologia Ospedaliera Polyclinic of Bari, 11 Piazza Giulio Cesare, 70124 Bari, Italy; [8]Bayer Healthcare, 178 Müllerstrasse, 13353 Berlin, Germany; [9]Oslo Centre for Biostatistics and Epidemiology, Research Support Services, Oslo University Hospital, Postboks 4950 Nydalen, 0424 Oslo, Norway; [10]Molecular and Clinical Research Institute and Cardiology Clinical Academic Group, St. George's University of London and Imperial College, London SW17 0RE, UK; and [11]Cardiology Department B and Faculty of Medicine, Oslo University Hospital, University of Oslo, 166 Kirkeveien, Building 3-A, 0407 Oslo, Norway

Received 28 November 2016; revised 23 January 2017; editorial decision 8 February 2017; accepted 9 March 2017; online publish-ahead-of-print 17 March 2017

Aims In patients with atrial fibrillation (AF) pharmacological or electrical cardioversion may be performed to restore sinus rhythm. The procedure is associated with an increased risk of thromboembolic events, which can be significantly reduced by adequate anticoagulation (OAC). Our aim was to create a partly prospective, partly retrospective cardioversion registry, particularly focusing on OAC strategies in different European countries, and on emerging choice of OAC over time.

Methods From September 2014 to October 2015, cardioversions due to AF performed in six European city hospitals in five European countries (Hungary: Budapest-1 and -2; Italy: Bari and Pisa; France: Amiens; Spain: Madrid; and Lithuania: Kaunas) were recorded in the registry.

Results A total of 1101 patients (retrospective/prospective: 679/422, male/female: 742/359, mean age: 67.3 years ± 11.2) were registered. Most of the cardioversions were electrical (97%). Oral anticoagulants were administered in 87% of the patient, the usage of non-VKA oral anticoagulants (NOACs) vs Vitamin K antagonists (VKA) was 31.5% vs 68.5%, respectively. Seventy seven percent of the patients were given oral anticoagulants more than 3 weeks prior to the procedure, and 86% more than 4 weeks after the procedure. When using VKA, international normalized ratio (INR) at cardioversion was above 2.0 in 76% of the cases. A decline in VKA usage ($P = 0.033$) in elective cardioversion over approximately 1 year was observed. During the observation period, there was an increase in apixaban ($P < 0.001$), a slight increase in rivaroxaban ($P = 0.028$) and no changes in dabigatran ($P = 0.34$) usage for elective cardioversion. There were differences in use of OAC between the countries: Spain used most VKA (89%), while France used least VKA (39%, $P < 0.001$).

Conclusion According to current AF guidelines, NOACs are adequate alternatives to VKA for thromboembolic prevention in AF patients undergoing elective cardioversion. Our results indicate that NOAC use is increasing and there is a significant decrease in VKA use.

Keywords Atrial fibrillation • Cardioversion • Registry • Anticoagulation • NOACs

* Corresponding author. Tel: 0036 14651800, Fax: 0036 14651857, Email: jucapapp@gmail.com

Introduction

Atrial fibrillation or flutter (AF) is the most common type of sustained cardiac arrhythmia. To restore sinus rhythm one option is to perform a cardioversion. There are two types of cardioversions: pharmacological and electrical. The procedure is associated with a risk of thromboembolic events, most commonly ischaemic stroke.[1] Adequate anticoagulation can significantly reduce the incidence of thromboembolic complications. According to current AF guidelines (ESC 2016[2] and AHA/ACC 2014[3]) adequate oral anticoagulation (OAC) is recommended for at least 3 weeks prior to and for 4 weeks after cardioversion in patients with AF of $\geq$ 48 h or unknown duration. As an alternative to OAC, transoesophageal echocardiography can be performed before cardioversion to rule out left atrial thrombus.

Vitamin K antagonists (VKA) can prevent thromboembolic episodes during cardioversion.[4] A great amount of clinical experience is available on VKA,[5] but there are some limitations to their usage, such as the requirement of continuous laboratory monitoring and the numerous drug and food interactions. Since the advent of non-VKA oral anticoagulants (NOACs) there are now several alternatives used for prevention of stroke in patients with AF.[6–12] The NOACs comprize dabigatran, a direct thrombin inhibitor, and rivaroxaban, apixaban and edoxaban, which are direct Xa factor antagonists.

With regards to cardioversion, X-VERT was the first prospective randomized trial to show that rivaroxaban can prevent thromboembolic complications as effectively as VKA in patients undergoing cardioversion.[13] Also the recently published ENSURE-AF[14] trial and the *post hoc* analyses of the RE-LY[15] and ARISTOTLE[16] trials proved that edoxaban, dabigatran, and apixaban can be safely used as well. In addition, several single-centre trials and meta-analyses confirmed the low number of thromboembolic events and safe use of NOACs during cardioversion.[17-20]

Aims

Our aim was to create a partly prospective and partly retrospective cardioversion registry, particularly focusing on OAC strategies in different European countries (Hungary, Italy, France, Spain, Lithuania), and on emerging choices over time for anticoagulants in this setting.

Methods

Design and patients

All patients in the study centres who underwent electrical or pharmacological cardioversion of AF or flutter were included in the registry. Patient records were collected in seven cardiology departments of six different European cities in five European countries, namely (i) Budapest—Hungary, (ii) Budapest—Hungary, (iii) Pisa—Italy, (iv) Bari—Italy, (v) Madrid—Spain, (vi) Amiens—France, and (vii) Kaunas—Lithuania.

Data were recorded between September 2014 and October 2015, in the 7 months prior to start date of the registry, and in the 6 months following the start date of the registry. The retrospective and prospective design was chosen in order to align the timing to the 12 months following the presentation of the X-VERT trial, in order to assess whether its publication would influence NOAC uptake in the cardioversion setting.

Data collection was performed in in-patient and out-patient cardiology departments. All cardioversions during electrophysiological procedures were excluded; also data from emergency departments were not collected. Cardioversions were performed according to local protocols. The study was approved by the ethics committee in participating centres/country. For all patients a case report form was completed, and subsequently databased. Cardiovascular endpoints were not assessed in this registry.

Statistical methods

We used the Pearson chi-squared test to compare NOAC vs. VKA in *de novo* prescriptions prior to scheduled cardioversion (yes/no), duration of OAC before cardioversion (more/less than 3 weeks), and duration of OAC after cardioversion (more/less than 4 weeks). The Pearson chi-squared test was also used to compare Spain and France in use of anticoagulants (yes/no). To analyse changes in OAC usage over time, we used logistic regression with OAC (yes/no) as the outcome variable and the number of months since 1 January 2014 as explanatory variable. The plots of OAC usage over time were smoothed with 1-nearest-neighbour and 2-nearest-neighbour averaging. Stata 14 (StataCorp LP) and Matlab 2014 (Mathworks, Inc) were used to perform the statistical analyses.

Results

A total of 1101 patients (male/female: 742/359, mean age: 67.3 years ± 11.2) were included in the registry. Six hundred and seventy-nine retrospective and 422 prospective cases were collected. Most of the cardioversions were elective (1050 cases), acute cardioversions were done only 51 times, where acute procedure was defined as a cardioversion performed on a haemodynamically unstable patient. Nearly all cardioversions were electrical (97%), only 3% were pharmacological. 405 patients were recorded in Hungary, 200 in Italy, 193 in Lithuania, 186 in Spain, and 116 in France.

Oral anticoagulants were administered in 87% of the patients. The usage of NOACs vs. VKA was 31.5% vs. 68.5%, respectively. Thirteen percent of the subjects were cardioverted without oral anticoagulants, because of an AF duration of <48 h in most cases (83.3%).

OAC prescription habits were also documented. No differences were found between NOACs and VKA in *de novo* prescriptions prior to scheduled cardioversions (NOAC: 20% vs. VKA: 19%; $P = 0.68$). Also we analysed previously anticoagulated and treatment-naive patients, and there were no differences in the use of NOACs and VKA between the groups (previously prescribed: 30.2% NOACs vs. new treatment: 30.3% NOACs, $P = 0.99$).

Also there were no differences between the duration of OAC before cardioversion, i.e. most of the patients received 3 or more weeks of OAC in both the NOACs and the VKA groups (86% vs. 84%; $P = 0.51$). In 87% of the patients taking NOACs and in 84% of those taking VKA, the anticoagulants were given for more than 4 weeks after the procedure ($P = 0.14$). When using VKA, international normalized ratio (INR) at cardioversion was above 2.0 in 76% of the cases.

When examining OAC strategies over time a decline in VKA usage ($P = 0.033$) in elective cardioversion over approximately 1 year was observed (*Figure 1A*). During the observation period an increase in apixaban ($P < 0.001$), a slight increase in rivaroxaban ($P = 0.028$) and no changes in dabigatran ($P = 0.34$) usage for elective cardioversion was recorded (*Figure 1B*).

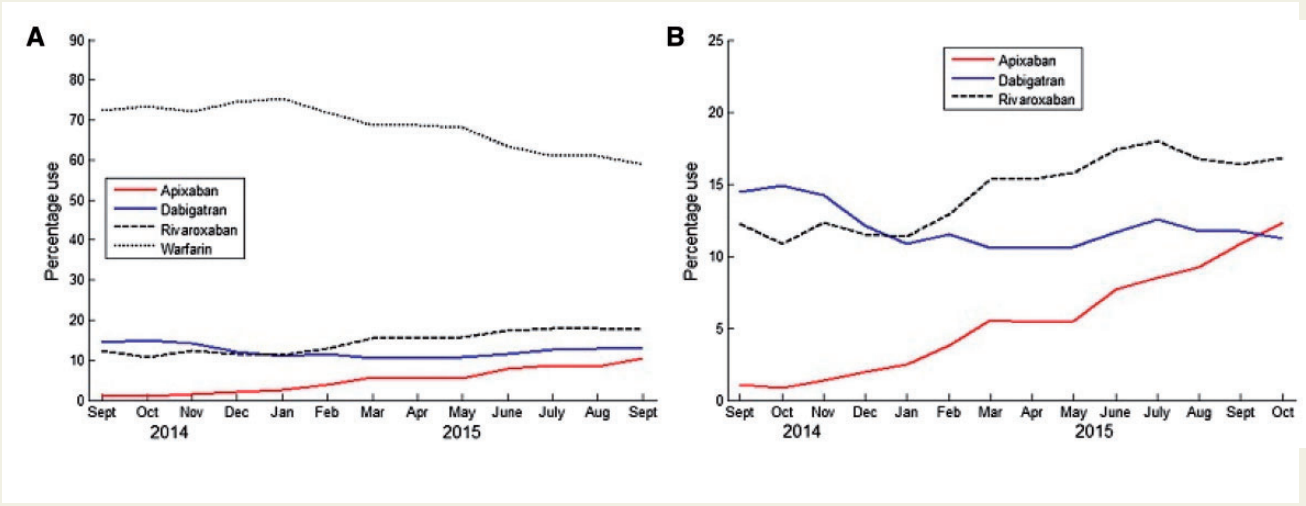

Figure 1 (*A*) Changes in OAC usage over time. (*B*) Changes in NOAC usage over approximately 1 year (enlarged portion of *Figure 1A*).

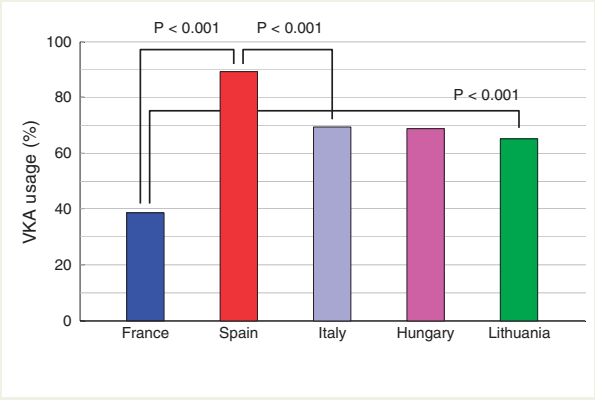

Figure 2 VKA usage in different European countries.

There were differences in use of anticoagulants between the countries: Spain used most VKA (89%), while France used least VKA (39%, $P < 0.001$). There were no large differences in VKA usage between Italy, Hungary and Lithuania (*Figure 2*).

Discussion

According to large randomized prospective clinical studies, NOACs were shown to be at least non-inferior to VKA in the prevention of stroke in patients with AF.[6–9] Further, NOACs have been shown to be safe alternatives to VKA during cardioversion.[13–16]

To examine anticoagulation strategies in different European countries our research group created a cardioversion registry of 1101 patients enrolled over approximately 1 year. According to our results only approximately 3/4 of the patients receiving VKA reached therapeutic INR levels during cardioversion, which is a concern given the predominantly elective and iatrogenic nature of cardioversion and the known increased risk for thromboembolism. On the other hand, in our registry most patients received anticoagulation more than 3 weeks before and more than 4 weeks after cardioversion which is similar to the results of the European Heart Rhythm Association Survey.[21] No differences were observed between the NOACs and VKA groups in the duration of OAC. In the X-VERT[13] trial a significantly shorter time to cardioversion was observed in the rivaroxaban group as opposed to the VKA group. According to the ENSURE-AF[14] trial there was no difference in time to cardioversion between the edoxaban and warfarin group, which was explained by optimized warfarin dosing and enoxaparin bridging therapy. In our study, the exact duration from start of treatment to the cardioversion procedure was not registered. However, the relatively low number of subjects reaching therapeutic INRs may indirectly suggest that patients underwent a longer treatment period in the VKA group, and hence a reduced time to cardioversion in the NOAC group after the initial 3 weeks.

One of the conclusions of our registry is that despite several practical advantages of NOACs over VKAs, clinicians appear to hesitate to embrace their usage during cardioversions. According to a Norvegian registry in total 32 675 patients with AF 65.1% was given NOACs, but in our cardioversion registry the usage of NOACs was only 31.5%.[22] One of the reasons may be that compliance (persistence and adherence) is harder to monitor in NOACs than in VKAs, which is of extreme importance when performing cardioversion.

The slight increase in rivaroxaban usage over time might well be a reflection of the publication of the X-VERT trial in 2014, the first prospective trial to show the safety and efficacy of a NOAC during cardioversion when compared to warfarin. Dabigatran was the first choice in most of the countries in the first 4 months of our observational period, and it remained at a stable usage ratio. Apixaban was the least prescribed NOAC during the first few months, but a substantial increase throughout the observational period of one year was recorded. In a Danish registry between 2011 and 2015, a decreasing usage of VKA in general AF management was observed, and among

NOACs a rise of apixaban and a decrease of dabigatran was noticed.[23] Similarly, an expanding use of NOACs was reported in the GARFIELD-AF registry, and there were differences between countries similar to our results in the cardioversion population.[24] Differences of NOAC usage between countries depend predominantly on regulatory as well as economic factors.

The design of this registry purposely focused on the use of oral anticoagulants, however outcome data of stroke and systemic embolism and safety endpoints such as bleeding events would be of great additional value to this work. These will be subject for future research and will receive highest priority.

Conclusions

Taken together, our study shows that most patients did receive oral anticoagulants during cardioversion. VKAs were used more often (2/3 vs. 1/3) than NOACs in this particular setting. However, our results show a significant decrease in VKA usage over time, while NOAC usage displays a gradual increase. As NOACs are more and more widely used in AF in general, further studies in the cardioversion setting will be needed to understand their optimal role in this aspect of AF patient management.

Funding

Open access to this publication was supported by Bayer AG.

Conflict of interest: none declared.

References

1. Overvad TF, Nielsen PB, Lip GY. Treatment thresholds for stroke prevention in atrial fibrillation: observations on the CHA2DS2-VASc score. *Eur Heart J Cardiovasc Pharmacother* 2017;**3**:37–41.
2. 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. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–2962.
3. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014;**64**:e1–76.
4. Stellbrink C, Nixdorff U, Hofmann T, Lehmacher W, Daniel WG, Hanrath P, Geller C, Mugge A, Sehnert W, Schmidt-Lucke C, Schmidt-Lucke JA. Safety and efficacy of enoxaparin compared with unfractionated heparin and oral anticoagulants for prevention of thromboembolic complications in cardioversion of nonvalvular atrial fibrillation: the Anticoagulation in cardioversion using enoxaparin (ACE) trial. *Circulation* 2004;**109**:997–1003.
5. Chan PH, Li WH, Hai JJ, Chan KH, Tse HF, Cheung BM, Chan EW, Wong IC, Leung WK, Hung IF, Lip GY, Siu CW. Gastrointestinal haemorrhage in atrial fibrillation patients: impact of quality of anticoagulation control. *Eur Heart J Cardiovasc Pharmacother* 2015;**4**:265–272.
6. 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.
7. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–1151.
8. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**:981–992.
9. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;**369**:2093–2104.
10. Hinojar R, Jiménez-Natcher JJ, Fernández-Golfín C, Zamorano JL. New oral anticoagulants: a practical guide for physicians. *Eur Heart J Cardiovasc Pharmacother* 2015;**2**:134–145.
11. Ezekowitz JA, Lewis BS, Lopes RD, Wojdyla DM, McMurray JJ, Hanna M, Atar D, Cecilia Bahit M, Keltai M, Lopez-Sendon JL, Pais P, Ruzyllo W, Wallentin L, Granger CB, Alexander JH. Clinical outcomes of patients with diabetes and atrial fibrillation treated with apixaban: results from the ARISTOTLE trial. *Eur Heart J Cardiovasc Pharmacother* 2015;**2**:86–94.
12. Dogliotti A, Giugliano RP. A novel approach indirectly comparing benefit-risk balance across anti-thrombotic therapies in patients with atrial fibrillation. *Eur Heart J Cardiovasc Pharmacother* 2015;**1**:15–28.
13. Enomoto Y, Ito N, Fujino T, Noro M, Ikeda T, Sugi K. The efficacy and safety of oral rivaroxaban in patients with non-valvular atrial fibrillation scheduled for electrical cardioversion. *Intern Med* 2016;**55**:1953–1958.
14. Goette A, Merino JL, Ezekowitz MD, Zamoryakhin D, Melino M, Jin J, Mercuri MF, Grosso MA, Fernandez V, Al-Saady N, Pelekh N, Merkely B, Zenin S, Kushnir M, Spinar J, Batushkin V, de Groot JR, Lip GY; ENSURE-AF Investigators. Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. *Lancet* 2016;**388**:1995–2003.
15. Renda G, Zimarino M, Ricci F, Piccini JP, Ezekowitz MD, Patel MR, Cappato R, Giugliano RP, De Caterina R. Efficacy and safety of non-vitamin K antagonist oral anticoagulants after cardioversion for nonvalvular atrial fibrillation. *Am J Med* 2016;**129**:1117–1123.
16. Cappato R, Ezekowitz MD, Klein AL, Camm AJ, Ma CS, Le Heuzey JY, Talajic M, Scanavacca M, Vardas PE, Kirchhof P, Hemmrich M, Lanius V, Meng IL, Wildgoose P, van Eickels M, Hohnloser SH, on Behalf of the X-VeRT Investigators. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. *Eur Heart J* 2014;**35**:3346–3355.
17. Nagarakanti R, Ezekowitz MD, Oldgren J, Yang S, Chernick M, Aikens TH, Flaker G, Brugada J, Kamensky G, Parekh A, Reilly PA, Yusuf S, Connolly SJ. Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. *Circulation* 2011;**123**:131–136.
18. Flaker G, Lopes RD, Al-Khatib SM, Hermosillo AG, Hohnloser SH, Tinga B, Zhu J, Mohan P, Garcia D, Bartunek J, Vinereanu D, Husted S, Harjola VP, Rosenqvist M, Alexander JH, Granger CB; ARISTOTLE Committees and Investigators. Efficacy and safety of apixaban in patients after cardioversion for atrial fibrillation: insights from the ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation). *J Am Coll Cardiol* 2014;**63**:1082–1087.
19. Saliba W. Non-vitamin K antagonist oral anticoagulants: new choices for patient management in atrial fibrillation. *Am J Cardiovasc Drugs* 2015;**15**:323–335.
20. Coleman CM, Khalaf S, Mould S, Wazni O, Kanj M, Saliba W, Cantillon D. Novel oral anticoagulants for DC cardioversion procedures: utilization and clinical outcomes compared with warfarin. *Pacing Clin Electrophysiol* 2015;**38**:731–737.
21. Larsen TB, Potpara T, Dagres N, Proclemer A, Sciarrafia E, Blomström-Lundqvist C; Scientific Initiative Committee, European Heart Rhythm Association. Preference for oral anticoagulation therapy for patients with atrial fibrillation in Europe in different clinical situations: results of the European Heart Rhythm Association Survey. *Europace* 2015;**17**:819–824.
22. Halvorsen S, Ghanima W, Fride Tvete I, Hoxmark C, Falck P, Solli O, Jonasson C. A nationwide registry study to compare bleeding rates in patients with atrial fibrillation being prescribed oral anticoagulants. *Eur Heart J Cardiovasc Pharmacother* 2017;**3**:28–36.
23. Staerk L, Fosbøl EL, Gadsbøll K, Sindet-Pedersen C, Pallisgaard JL, Lamberts M, Lip GY, Torp-Pedersen C, Gislason GH, Olesen JB. Non-vitamin K antagonist oral anticoagulation usage according to age among patients with atrial fibrillation: Temporal trends 2011-2015 in Denmark. *Sci Rep* 2016;**6**:31477.
24. Ten Cate V, Ten Cate H, Verheugt FW. The Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF): Exploring the changes in anticoagulant practice in patients with non-valvular atrial fibrillation in the Netherlands. *Neth Heart J* 2016;**24**:574–580.