Nonvitamin K Antagonist Oral Anticoagulants Use in Patients with Atrial Fibrillation and Bioprosthetic Heart Valves/Prior Surgical Valve Repair: A Multicenter Clinical Practice Experience

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Abstract

This is an observational study to investigate the efficacy and safety of nonvitamin K antagonist oral anticoagulants (NOACs) in atrial fibrillation (AF) patients with bioprosthetic valves or prior surgical valve repair in clinical practice. A total of 122 patients (mean age: 74.1 ± 13.2; 54 females) with bioprosthetic heart valve or surgical valve repair and AF treated with NOACs were included in the analysis. The mean CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age >75 years, Diabetes mellitus, prior Stroke or transient ischemic attack, Vascular disease) and HAS-BLED (Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR [international normalized ratio], Elderly, Drugs or alcohol) score values were 3.6 ± 1.2 and 2.6 ± 1.4, respectively. Of the total study population, 28.6% was taking apixaban 5 mg twice daily (BID), 24.5% apixaban 2.5 mg BID, 18% dabigatran 150 mg BID, 13% dabigatran 110 mg BID, 9.8% rivaroxaban 20 mg daily (QD), and 5.7% rivaroxaban 15 mg QD. Also, 92% of the study population previously had warfarin replaced with NOACs due to lack compliance and labile INR control (time in therapeutic range < 60%). NOAC therapy for AF was started on average 934 ± 567 days after bioprosthetic heart valve implantation or surgical repair for an average duration of 835 ± 203 days. The study population included 24 (19.6%) patients with bioprosthetic mitral valve, 52 (43%) patients with bioprosthetic aortic valve, 41 (33.6%) patients with previous surgical mitral repair, 5 (4%) patients with previous surgical aortic repair, and concomitant use of NOACs. All patients were evaluated for thromboembolic events (ischemic stroke, transient ischemic attack, systemic embolism) as well as major bleeding events during the follow-up period. In our study population, we recorded a low mean annual incidence of thromboembolism (0.8%) and major bleeding (1.3%). According to our data, anticoagulation therapy with NOACs seems to be an effective and a safe treatment strategy for nonvalvular AF patients with bioprosthetic valves or prior surgical valve repair.

Keywords
- atrial fibrillation
- bioprosthetic valve
- surgical valve repair
- NOACs
- dabigatran
- apixaban
- rivaroxaban
- stroke
- major bleedings

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The general increase in life expectancy leads to a more frequent association between atrial fibrillation (AF) and valvular heart disease (VHD) in clinical practice.[1] Bioprosthetic valve implantation is a common and an increasingly utilized treatment for VHD.[2] Patients with AF and bioprosthetic valves require anticoagulation therapy to prevent thromboembolic events. Nonvitamin K antagonist oral anticoagulants (NOACs) are safe and efficacious alternatives to vitamin K antagonists for anticoagulation in AF.[3] However, there is no clear worldwide consensus about indications for NOACs in patients with AF and bioprosthetic valves or with prior valve repair due to the lack of prospective controlled data.[4–6]

In the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) and ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trials, a small number of AF patients with previous valve surgery was included,[7,8] but only the ENGAGE AF (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation) trial explicitly enrolled AF patients with bioprosthetic valves.[9]

The aim of our study was to describe the efficacy and safety of NOACs in AF patients with bioprosthetic valves or prior surgical valve repair in clinical practice, defined as one outside the arena of a randomized clinical trial. We therefore report a multicenter experience in this area of clinical management.

Materials and Methods

Patient Population

Data for this study were obtained from the prospectively maintained Atrial Fibrillation Research Database shared by five Italian cardiologic centers (Monaldi Hospital, Naples, University of Campania "Luigi Vanvitelli,"Caserta; University of Naples Federico II, Naples; Buonconsiglio Hospital, Naples; Maggiore Hospital, Trieste), which includes all AF patients followed by these centers. All patients provided written, informed consent before inclusion in the database. The study was approved by the local institutional review committee.

The database was queried for patients with AF who were prescribed NOACs (dabigatran, rivaroxaban or apixaban) and had a history of bioprosthetic heart valve replacement or surgical valve repair from July 2013 to January 2016. There were no patients taking edoxaban because it was not available in Europe before 2016.

In total, 133 patients with AF and bioprosthetic heart valve or surgical valve repair (mitral or aortic) and treated with NOACs were included, and 11 patients were excluded due to follow-up $<$ 1 year (n: 6) or lost at follow-up $<$ 1 year (n: 5).

Follow-up data were obtained through outpatient visits each 3 to 6 months. During the follow-up visits the clinical status, adherence to treatment, occurrence of stroke, transient ischemic attack (TIA), major and minor bleeding events, other side effects, and major cardiovascular complications were evaluated.

Ischemic stroke was defined as a focal neurologic deficit lasting for at least 24 hours with no signs of hemorrhage on cerebral imaging and was verified radiologically. TIA was defined as an acute focal neurologic deficit lasting less than 24 hours. Systemic embolism was defined as an acute vascular insufficiency associated with clinical or radiographic evidence of arterial occlusion and not associated with another likely cause. Major bleeding was defined as a fatal bleeding or symptomatic bleeding in a critical area or organ or bleeding causing a fall in hemoglobin level of 2 g/dL or more or leading to transfusion of two or more units of whole blood or red cells.[10]

Statistical Analysis

Descriptive statistics of patient characteristics were carried out; in particular, frequency and percentage were reported for the categorical variables, and mean and the standard deviation were used to summarize continuous variables. The incidence of bleeding was calculated both as incidence rate (the ratio between the number of new events occurred during the follow-up and the person-time accrued from the study members) every 100 patient-years and as cumulative incidence. Continuous variables were compared using t-tests, and categorical variables were compared using χ^2 tests. All statistical analyses were performed using IBM SPSS Version 19 (SPSS, Armonk, NY).

Results

Study Population

In the analysis, 122 patients with bioprosthetic heart valve or surgical valve repair and AF treated with NOAC were included. The characteristics of the patients are shown in ►**Table 1**. Of the study population, 28.6% (n: 35) was taking apixaban 5 mg twice daily (BID), 24.5% (n: 30) apixaban 2.5 mg BID, 18% (n: 22) dabigatran, 13% (n: 16) dabigatran 110 mg BID, 150 mg BID, 9.8% (n: 12) rivaroxaban 20 mg daily (QD), and 5.7% (n: 7) rivaroxaban 15 mg QD. Also, 92% of the study population previously had warfarin replaced with NOACs due to lack compliance and labile international normalized ratio (INR) control (time in therapeutic range $<$ 60%).

NOAC therapy for AF was started on average 934 $\pm$ 567 days after bioprosthetic heart valve implantation or surgical repair for an average duration of 835 $\pm$ 203 days. The study population included 24 (19.6%) patients with bioprosthetic mitral valve, 52 (42.6%) patients with bioprosthetic aortic valve, 41 (33.6%) patients with previous surgical mitral repair, 5 (4%) patients with previous surgical aortic repair, and concomitant use of NOACs. ►**Table 2** shows the NOAC therapy in relation to type of heart valve surgery in the study population.

Thromboembolic Events

Thromboembolic events occurred in two (1.6%) patients. Mean annual incidence of thromboembolism was 0.8%. One patient with medium thromboembolic and hemorrhagic risk (CHA_2DS_2-VASc score: 2, HAS-BLED [Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs or alcohol] score: 3) experienced a TIA

Table 1 Patient baseline characteristics and prevalence of stroke risk factors

Characteristic[a]	$N = 122$
Age	74 ± 13.2
Female	54 (44)
CHA_2DS_2-VASc	3.6 ± 1.2
HAS-BLED	2.6 ± 1.4
Type of atrial fibrillation	***n* (%)**
Paroxysmal	48 (39)
Persistent	19 (16)
Permanent	50 (41)
Atrial Flutter	5 (4)
Comorbidity and risk factors	***n* (%)**
Previous stroke	7 (6)
Previous TIA	7 (6)
Previous acute coronary syndrome	14 (11)
Heart failure	54 (44)
Arterial hypertension	88 (72)
Diabetes mellitus	19 (16)
Dyslipidemia	16 (13)
Previous hemorrhage	7 (6)
Liver disease	3 (2)
Chronic kidney failure	37 (30)
Obesity	12 (10)
Peripheral vascular disease	16 (13)
Coronary artery disease	7 (6)
Smoking	37 (30)
Additional pharmacological therapy	***n* (%)**
Aspirin	20 (17)
Clopidogrel	17 (13)
Beta-blockers	86 (70)
ACE-I/ARB	49 (40)
Calcium channel blocker	12 (10)
Diuretics	81 (67)
Digitalis	29 (23)
Class 1 antiarrhythmics	20 (17)
Amiodarone	24 (20)
Sotalol	9 (7)
Proton-pump inhibitors	94 (77)
Statin	37 (30)

Abbreviations: ACE-I, angiotensin converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin receptor blockers; CHA_2DS_2-VASc: score for AF stroke risk including Congestive heart failure, Hypertension, Age > 75 years, Diabetes mellitus, prior Stroke or transient ischemic attack, Vascular disease; HAS-BLED: score for major bleeding risk including Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR (international normalized ratio), Elderly, Drugs or alcohol; TIA, transient ischemic attack.
[a]Results are shown as mean ± standard deviation or *n* (%).

8 days after temporary suspension of dabigatran 110 mg BID for abdominal surgery. The other one with high thromboembolic and hemorrhagic risk (CHA_2DS_2-VASc score: 3; HAS-BLED score: 4) experienced an embolic stroke 10 days after direct current cardioversion on apixaban 2.5 mg BID.

Major Bleedings

In our study population, we reported only four cases of major bleeding (3.3%) comprising symptomatic anemia (*n*: 2), melena (*n*: 1) and bladder bleeding (*n*: 1). Mean annual incidence of major bleeding was 1.3%. The two patients with symptomatic anemia were affected by diverticulosis, one patient (CHA_2DS_2-VASc = 4 and HAS-BLED = 3) was taking dabigatran 150 mg BID and one (CHA_2DS_2-VASc = 3 and HAS-BLED = 4) was taking apixaban 5 mg BID; these patients required multiple transfusions. The patient with melena suffered from peptic ulcer disease and was taking rivaroxaban 15 mg OD (CHA_2DS_2-VASc = 3 and HAS-BLED = 4), but the suspension of NOAC therapy was adequate to control melena. The patient with bladder bleeding had bladder cancer in active state and was taking dabigatran 150 mg BID (CHA_2DS_2-VASc = 4 and HAS-BLED = 4). For this patient, the suspension of NOAC therapy was adequate to control bladder bleeding. In particular, patients with major bleeding differed from the rest of the study population for older age (86 ± 7 vs. 71 ± 10 years; $p = 0.03$) and higher HAS-BLED score (3.75 ± 0.5 vs. 2.2 ± 0.9; $p = 0.004$). No hemorrhagic stroke or subarachnoid hemorrhage was observed.

Adverse Events

Fourteen (11.4%) patients reported adverse events: dyspepsia in three (2.4%) patients, diarrhea in two (1.6%) patients, minor bleeding in six (4.9%) patients, headache in one (0.8%) patient, and dermatitis in two (1.6%) patients. Cases of minor bleeding included hemarthrosis of the shoulder, vaginal bleeding, head laceration, bleeding hemorrhoid, and minor hematochezia and hemoptysis not requiring transfusion. Two patients reported resolution of dyspepsia with concomitant intake of food, copious amounts of water, proton pump inhibitors, or H2-blocking agents. The temporary anticoagulant therapy discontinuation rate was 9%. Seven patients switched to another NOAC. The total definitive anticoagulant therapy discontinuation rate was 4%.

Mortality and Hospitalization

No death was reported. The hospitalization rate was 3.3% (four cases: one patient on apixaban 5 mg BID, one patient on dabigatran 150 mg BID, one patient on rivaroxaban 15 mg QD, and one patient on dabigatran 110 mg BID).

Discussion

The use of NOACs in AF patients with bioprosthetic heart valves or surgical valve repair is still controversial because there is no clear consensus about the definition of "valvular" AF used in the literature and contemporary clinical practice. The American cardiology guidelines define valvular as AF in the presence of rheumatic mitral stenosis, a mechanical or

Table 2 NOAC therapy and related heart valve surgery in the study population

	Overall, *N* (%)	Apixaban, *N* (%)	Rivaroxaban, *N* (%)	Dabigatran, *N* (%)
Any heart valve surgery	122 (100)	65 (53)	19 (16)	38 (31)
Bioprosthetic heart valve	**76 (62)**	**42 (55)**	**10 (13)**	**24 (32)**
Bioprosthetic mitral valve	24 (20)	12 (50)	6 (25)	6 (25)
Bioprosthetic aortic valve	52 (43)	42 (58)	4 (8)	18 (35)
Surgical valve repair	**46 (38)**	**23 (50)**	**9 (20)**	**14 (30)**
Surgical mitral repair	41 (34)	21 (51)	8 (20)	12 (29)
Surgical aortic repair	5 (4)	2 (40)	1 (20)	2 (40)

Abbreviation: NOAC, nonvitamin K antagonist oral anticoagulant.

bioprosthetic heart valve or mitral valve repair, and do not recommend NOACs in these patients;[4] these are different to European guidelines that consider valvular as AF in the presence of mechanical prosthetic heart valve or moderate to severe mitral stenosis.[5] According to the practice guidelines of the European Heart Rhythm Association, patients with bioprosthetic heart valve or surgical valve repair are eligible to receive NOACs, expectedly for the first 3 to 6 months postoperatively.[6] Few clinical practice data are available in literature about the efficacy and safety of NOACs in AF patients with bioprosthetic heart valves or surgical valve repair,[11,12] and these patients were relatively underrepresented in trials performed to date.

The RELY (Randomized Evaluation of Long-term Anticoagulant Therapy) trial excluded AF patients with prosthetic heart valve (biological or mechanical) and valvular disease requiring an intervention before study.[13]

The ROCKET AF trial excluded patients with prosthetic heart valve and planned invasive interventions with a major risk of uncontrolled bleeding. A posthoc analysis from the ROCKET AF trial has shown that 14.1% (*n*: 1,992) of the study population had significant native aortic or mitral valve disease (SVD) and, among them, 106 patients (5.6%) underwent valvuloplasty (n:64) or other cardiac procedure (*n*: 42). AF patients with SVD experienced the same stroke-prevention benefit from rivaroxaban as did AF patients without SVD; however, the observed risk of bleedings was higher with rivaroxaban than with warfarin in patients with SVD. No information about safety and efficacy of rivaroxaban in comparison with warfarin was given for the patient subgroup with previous valve surgery.[14]

The ARISTOTLE trial excluded patients with conditions other than AF that required anticoagulation (e.g., a prosthetic heart valve). A posthoc analysis from the ARISTOTLE trial has shown that 26.4% (*n*: 4,808) of the study population had at least moderate valvular disease; of these, 251 (5.2%) patients had previous valve surgery, although it was not specified how many of these surgeries were bioprosthetic implants or valve repair. AF patients with VHD had a higher risk of thromboembolism and bleeding, but the relative benefit of apixaban over warfarin was preserved for both efficacy and bleeding. Similar benefits of apixaban in comparison with warfarin were also seen in patients with prior valve surgery; however, the data were not shown.[15]

In the ENGAGE AF trial, 824 (13%) had a history of moderate or severe VHD or had undergone prior valve surgery; of these, 191 (0.9%) patients had prior bioprosthetic heart valve implantation ($n = 131$ [68.6%] mitral, $n = 60$ [31.4%] aortic) and 123 (0.6%) had prior valve repair. The presence of VHD increased the risk of death, major adverse cardiovascular events, and major bleeding but did not affect the relative efficacy or safety of higher-dose edoxaban versus warfarin in AF patients. Patients with bioprosthetic valves treated with higher-dose edoxaban had similar rates of stroke/systemic embolism and major bleeding compared with warfarin. Patients treated with lower-dose edoxaban had similar rates of stroke/systemic embolism but lower rates of major bleeding compared with warfarin. Compared with warfarin, patients with bioprosthetic valves treated with higher-dose edoxaban had lower rates of major adverse cardiac events and primary net clinical outcome. Compared with warfarin, patients treated with lower-dose edoxaban had lower rates of primary net clinical outcome. This analysis suggests that edoxaban appears to be a reasonable alternative to warfarin in patients with AF and remote bioprosthetic valve implantation.[16]

In a recent phase II, prospective, open-label, randomized, pilot study, Durães et al evaluated the use of dabigatran 110 mg BID versus warfarin in 27 patients with bioprosthetic mitral and/or aortic valve replacement and AF postoperatively.[17] The trial was prematurely terminated because of low enrollment; however, the efficacy of dabigatran appears to be similar to warfarin in preventing the formation of intracardiac thrombus in patients after mitral and/or aortic bioprosthesis valve replacement and with documented AF postoperatively. In the clinical practice setting, there is only a retrospective single-center cohort study performed on 73 AF patients with bioprosthetic heart valve implantation on NOAC therapy.[11] Forty-four (60.3%) patients were on dabigatran, 25 (34.2%) on rivaroxaban, and 4 (5.5%) on apixaban. The authors showed that the use of NOACs in AF patients with bioprosthetic valves was effective with regard to low occurrence of thromboembolic events (1.4%); however, it was characterized by high rate of major bleeding (6.9%). In 127 consecutive patients with a biological valve undergoing AF ablation with uninterrupted NOAC use, Di Biase et al showed that periprocedural and long-term administration of NOACs in patients with biological heart valve and AF appears as safe as warfarin therapy.[12] In their study, the majority of

Table 3 Overview of the population study characteristics, rates of thromboembolism, and major bleeding in all published studies which included AF patients with bioprosthetic valves or prior surgical valve repair

Authors	Study design	NOACs	Bioprosthesis, *n* (%)	Surgical valve repair, *n* (%)	Stroke/TIA/SE	Major bleedings	Follow-up
Breithardt et al[14]	Posthoc analysis phase III trial	Rivaroxaban	–	64 valvuloplasty (60.4%) 42 other cardiac procedure (39.6%)	2.01% per year	6.14% per year	1.9 y
Avezum et al[15]	Posthoc analysis phase III trial	Apixaban	132 previous valve surgery		1.31% per year	4.55% per year	1.8 y
Carnicelli et al[16]	Posthoc analysis phase III trial	Edoxaban	191 Aortic bioprosthesis (31.4%) Mitral bioprosthesis (68.6%)	–	1.19% per year (60 mg od) 2.57% per year (30 mg od)	Similar to warfarin 6.27% per year 0.76% per year (30 mg od)	2.8 y
Durães et al[17]	Phase II prospective, open-label, randomized, pilot study	Dabigatran	15 Isolated mitral bioprosthesis (73.3%)	–	6.7%	–	90 d
Yadlapati et al[11]	Retrospective single-center cohort study	Dabigatran (60.3%) Rivaroxaban (34.2%) Apixaban (5.5%)	60 Aortic bioprosthesis (65.8%) Mitral bioprosthesis (16.4%)	13 Root reconstruction with aortic bioprosthesis (17.8%)	1.4%	6.9%	511.8 ± 400.8 d
Di Biase et al[12]	Prospective single-center cohort study	Rivaroxaban (70%) Apixaban (30%)	127 Aortic bioprosthesis (59%) Mitral bioprosthesis (41%)	–	0% per year	1.6% per year	1 y
Russo et al (current study)	Retrospective multicenter cohort study	Apixaban (54%) Dabigatran (31%) Rivaroxaban (15%)	76 Aortic bioprosthesis (42.6%) Mitral bioprosthesis (19.7%)	46 Aortic repair (33.6%) Mitral repair (4.1%)	0.8% per year	1.3% per year	835 ± 203 d

Abbreviation: AF, atrial fibrillation; NOACs, nonvitamin K antagonist oral anticoagulants; od, once a day; TIA, transient ischemic attack.

patients had aortic valve replacement (*n*: 75; 59%), whereas mitral valve was replaced in 52 (41%) patients, which did not differ from control. Predominantly, patients underwent ablation with uninterrupted rivaroxaban (*n*: 89; 70%), whereas the remaining 38 (30%) patients underwent the ablation while on apixaban. Only two groin hematomas were observed periprocedurally in both groups. No stroke/TIA was observed periprocedurally or during long-term follow-up.

Our multicenter observational study reported the safety and efficacy of NOAC use in nontrial AF patients with bioprosthetic heart valves or prior surgical valve repair during 3-year follow-up. The bioprosthetic aortic valve implantation was the most common interventional procedure (43%) following by the surgical mitral repair (34%) and bioprosthetic mitral valve implantation (20%). We identified a low annual incidence of thromboembolic events (0.8%) and major bleedings (1.3%). The thromboembolic events were mainly related to temporary suspension of NOAC therapy for noncardiac surgical procedure and for direct current cardioversion. All major bleedings were conservatively treated. Moreover, the patients who experienced major bleeding were older than the rest of the study population and showed an increased HAS-BLED score. After comparing our bleeding rate results to previous observations[11] in a similar population, we hypothesize that our lower rate might be related to the "patient centered tailoring approach" in the use of NOACs and to the careful monitoring of the patients on NOAC therapy in our clinical practice.[18,19] ►**Table 3** summarizes the population study characteristics, rates of thromboembolism, and major bleeding in all published studies that included AF patients with bioprosthetic valves or prior surgical valve repair.

Limitations

Despite the novelty, our study is limited by small sample size, heterogeneous anticoagulation management, different procedures, retrospective design, and lack of warfarin control group.

Conclusion

According to our clinical practice data, anticoagulation therapy with NOACs seems to be an effective and a safe treatment strategy for nonvalvular AF patients with bioprosthetic heart valves or prior surgical valve repair. This is supported by retrospective subgroup analyses of the large randomized trials with NOAC in AF. Further randomized prospective controlled studies are necessary to confirm our preliminary findings.

Conflicts of Interest
None.

References

1 Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet 2006;368(9540):1005–1011
2 Isaacs AJ, Shuhaiber J, Salemi A, Isom OW, Sedrakyan A. National trends in utilization and in-hospital outcomes of mechanical versus bioprosthetic aortic valve replacements. J Thorac Cardiovasc Surg 2015;149(05):1262–9.e3
3 Russo V, Rago A, Proietti R, et al. Efficacy and safety of the target-specific oral anticoagulants for stroke prevention in atrial fibrillation: the real-life evidence. Ther Adv Drug Saf 2017;8(02):67–75
4 January CT, Wann LS, Alpert JS, et al; ACC/AHA Task Force Members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation 2014;130(23):2071–2104
5 Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace 2016;18(11):1609–1678
6 Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace 2015;17(10):1467–1507
7 Patel MR, Mahaffey KW, Garg J, et al; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365(10):883–891
8 Granger CB, Alexander JH, McMurray JJ, et al; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365(11):981–992
9 Giugliano RP, Ruff CT, Braunwald E, et al; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369(22):2093–2104
10 Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3(04):692–694
11 Yadlapati A, Groh C, Malaisrie SC, et al. Efficacy and safety of novel oral anticoagulants in patients with bioprosthetic valves. Clin Res Cardiol 2016;105(03):268–272
12 Di Biase L, Trivedi C, Mohanty P, et al. Periprocedural and long term safety and feasibility of treatment with novel oral anticoagulants in patients with biological valve and atrial fibrillation. Presented at the American College of Cardiology 64th Annual Scientific Session [P-255]; March 14–16, 2015, San Diego, CA
13 Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361(12):1139–1151
14 Breithardt G, Baumgartner H, Berkowitz SD, et al; ROCKET AF Steering Committee & Investigators. Clinical characteristics and outcomes with rivaroxaban vs. warfarin in patients with non-valvular atrial fibrillation but underlying native mitral and aortic valve disease participating in the ROCKET AF trial. Eur Heart J 2014;35(47):3377–3385
15 Avezum A, Lopes RD, Schulte PJ, et al. Apixaban in comparison with warfarin in patients with atrial fibrillation and valvular heart disease: findings from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial. Circulation 2015;132(08):624–632
16 Carnicelli AP, De Caterina R, Halperin JL, et al; ENGAGE AF-TIMI 48 Investigators. Edoxaban for the prevention of thromboembolism in patients with atrial fibrillation and bioprosthetic valves. Circulation 2017;135(13):1273–1275
17 Durães AR, de Souza Roriz P, de Almeida Nunes B, et al. Dabigatran versus warfarin after bioprosthesis valve replacement for the management of atrial fibrillation postoperatively: DAWA pilot study. Drugs R D 2016;16(02):149–154
18 Russo V, Bianchi V, Cavallaro C, et al. Efficacy and safety of dabigatran in a "real-life" population at high thromboembolic and hemorrhagic risk: data from MonaldiCare registry. Eur Rev Med Pharmacol Sci 2015;19(20):3961–3967
19 Russo V, Di Napoli L, Bianchi V, et al. A new integrated strategy for direct current cardioversion in non-valvular atrial fibrillation patients using short term rivaroxaban administration: the MonaldiVert real life experience. Int J Cardiol 2016;224:454–455