Core Evidence

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Apixaban: An Update of the Evidence for Its Place in the Prevention of Stroke in Patients with Atrial Fibrillation

This article was published in the following Dove Press journal:
Core Evidence

Julia Seeger
Jochen Wöhrle

Medical Campus Lake Constance, Department of Cardiology, Friedrichshafen, Germany

Abstract: Oral anticoagulant therapy for stroke prevention in atrial fibrillation patients has been remarkably changed by the introduction of non-vitamin k oral anticoagulants (NOAC). Apixaban was the third NOAC introduced to clinical practice. Aim was to outline the current evidence for Apixaban in stroke prevention in atrial fibrillation patients in the randomized trials and real-world data. Apixaban has been shown to be superior to warfarin in preventing stroke and systemic embolism and causes significantly less major bleeding based on large randomized trials. These data are confirmed in real-world studies. Apixaban has been shown to be safe and effective in atrial fibrillation patients in acute coronary syndrome or undergoing PCI in combination with a $P2Y_{12}$ inhibitor. Regarding expanded use of apixaban also in valvular heart disease patients, there is still missing knowledge in relation to the safety and efficacy of apixaban which is being addressed by ongoing randomized clinical trials.

Keywords: apixaban, stroke, oral anticoagulants, atrial fibrillation

Core Evidence Clinical Impact Summary

Outcome Measure	Evidence	Implications
Disease-oriented evidence	Clinical trials	Apixaban has been shown to be safe and effective in non-valvular atrial fibrillation patients
Patient-oriented evidence	Clinical trials	Apixaban has been shown to be effective in the prevention of stroke and thromboembolic events. On the other hand, it has been shown to be superior to warfarin regarding major bleeding events.
Economic evidence	Articles	Apixaban has been shown to be cost-effective compared to warfarin in patients with non-valvular atrial fibrillation and increased risk of stroke

Introduction

Stroke prevention in atrial fibrillation is a major issue. Atrial fibrillation, the arrhythmia with the highest prevalence in the population, is getting even more frequent in the elderly population[1] and is associated with an increased all-cause mortality.[2] In the elderly population over one third of strokes are linked to atrial fibrillation.[3] Atrial fibrillation is

Correspondence: Julia Seeger
Medical Campus Lake Constance, Friedrichshafen 88048, Germany
Tel +49-7541-96-71257
Email Julia.seeger@t-online.de

submit your manuscript | www.dovepress.com
DovePress
http://doi.org/10.2147/CE.S172935

associated with a two to seven-fold increase in the risk of stroke which is dependent on the CHA_2DS_2VASC Score.[4] Thus preventing stroke is crucial in these patients. Second, atrial fibrillation patients are more likely to suffer from other cardiovascular diseases which makes safety and reduced bleeding risk compared to the therapy with vitamin k antagonist an important issue. Lately, four non-vitamin k oral anticoagulants, namely apixaban, dabigatran, edoxaban and rivaroxaban, have been approved for stroke prevention in non-valvular atrial fibrillation patients,[5–8] showing non-inferiority to vitamin k antagonists (VKA). Apixaban is the third non-vitamin k oral anticoagulant approved. Lately, growing evidence for its use in patients with atrial fibrillation undergoing percutaneous coronary interventions (PCI) for acute coronary syndrome (ACS), real-world data and first hypothesis generating data in patients with valvular heart disease undergoing percutaneous valve procedures have emerged. We will discuss the current evidence for apixaban in atrial fibrillation patients.

Role of Apixaban in Prevention of Stroke in Atrial Fibrillation Patients

The first double-blind, randomized controlled trial of apixaban compared to acetylsalicylic acid in the prevention of stroke or systemic embolism was the AVERROES trial[9] (Table 1). This study included patients who were unable to take vitamin k antagonists (VKA) or failed VKA therapy. The trial enrolled 5599 patients randomized to either apixaban or aspirin. In 2010 the trial was discontinued early due to a clear significant benefit of apixaban in stroke prevention with an annual rate of stroke or systemic embolism of 1.6% in patients on apixaban compared to 3.7% in patients on aspirin.[10] There was no difference in all-cause mortality. In a post hoc analysis, there was a significant reduction of rehospitalization for cardiovascular reasons in the apixaban group with 12.3% per year compared with 15.4% in the aspirin group. Rehospitalization was an independent predictor of mortality in this analysis.[11] Risk of major bleeding (HR1.13) and minor bleeding (HR 1.24) was slightly higher on apixaban, with no difference in rate of intracranial haemorrhage.

The apixaban for reduction in stroke and other thrombotic events in atrial fibrillation (ARISTOTLE) trial was published in 2011[5] (Table 1). In this double-blind randomized non-inferiority trial apixaban was compared to warfarin in the prevention of stroke and systemic embolism in 18.201 patients with atrial fibrillation. Median age at enrolment was 70 years. Included where patients with ≥2 episodes of atrial fibrillation within the last 12 months and ≥1 of the following risk factors: ≥75 years of age, history of stroke or systemic embolism, symptomatic heart failure in the last 3 months, diabetes or hypertension requiring pharmacologic treatment.[5,12] In this large randomized trial,

Table 1 Summary of ARISTOTLE and AVERROES Trials

	ARISTOTLE	**AVERROES**
Study design	Noninferiority, Phase III, randomized double blind, double dummy trial	Superiority, Phase III, randomized, double blind, double dummy trial
Study objective	Apixaban 5 mg BD versus warfarin (INR range 2.0–3.0)	Apixaban 5mg BD versus aspirin (81–324 mg daily)
Inclusion criteria	Patients with NVAF and at least one other stroke risk factor	Patients with NVAF unsuitable for VKA
Randomized subjects	18,201	5599
Primary efficacy endpoint	Fewer strokes/systemic embolism: 21% RRR, 0.33% ARR (1.27% per year [n=212] with Apixaban vs 1.60% per year [n=265] with warfarin; HR=0.79 [95% CI: 0.66–0.95] p=0.01).	Fewer strokes/systemic embolisms: 55% RRR, 2.1% ARR (1.62% per year [n=51] with Apixaban vs 3.63% per year [n=113] with aspirin; HR=0.45 [95% CI: 0.32–0.62] p<0.0001).
Primary safety endpoint	Apixaban demonstrated fewer major bleeds:31% RRR, 0.96% ARR (2.13% per year (n=327) with Apixaban vs 3.09% per year (n=462) with warfarin; HR=0.69 (95% CI: 0.60–0.80) p<0.001).	Comparable rate of major bleeding: 1.41% per year (n=45) with Apixaban vs 0.92% per year (n=29) with aspirin; HR=1.54 (95% CI: 0.96–2.45) p=0.0716
Key secondary endpoint	Deaths from any cause were observed in 603 patients treated with Apixaban (3.52% per year) and in 669 patients treated with warfarin (3.94% per year); HR=0.89 (95% CI: 0.80–0.99; p=0.047)	All-cause mortality: 3.5% per year in the apixaban group, 4.4% per year in aspirin group (p = 0.07).

apixaban did not only meet its primary goal of noninferiority but was superior to warfarin in the prevention of stroke or systemic embolism, major bleeding and all-cause mortality. Rate of stroke or systemic embolism was significantly lower (1.27%/year) on apixaban compared with warfarin (1.6%/year, hazard ratio (HR) 0.79, p<0.001). Rate of all-cause mortality was significantly lower on apixaban (3.52%/year) compared with warfarin (3.94%/year, HR 0.89, p=0.047).[5] These findings are in line with the results of the other trials on NOACS, where mortality was lower compared with warfarin.[5–8]

Major Bleeding

Major bleeding still is the most relevant adverse event. Apixaban was associated with a significantly lower risk of major bleeding (2.13%/year) compared with warfarin (3.09%/year, HR 0.69, p<0.001) in ARISTOTLE.[5,11] Moreover, 30 days risk of mortality after a major bleeding event was significantly lower on apixaban compared with warfarin (HR 0.5, 95% CI 0.33–0.74).[13] Intracranial haemorrhage was lower on apixaban, which is in line with the data from other NOACS.[5–8] Age, prior stroke or transient ischemic attack (TIA), diabetes, anemia, prior haemorrhage, aspirin and nonsteroidal anti-inflammatory drugs (NSAID) were independent predictors of major hemorrhage.[13] For risk evaluation, the HAS-BLED score had a predictive value for major haemorrhage in patients on apixaban. Patients with a HAS-BLED score of ≥3 derived the most benefit from apixaban compared with warfarin in the reduction of intracranial haemorrhage.[14] Risk of gastrointestinal bleeding was similar for apixaban and warfarin.[5,15]

Real-World Data on Apixaban

Real-world studies on the use of apixaban compared with warfarin and other NOACS help to understand in less selected patient populations the efficacy and safety in certain clinical conditions. A large meta-analysis on the real-world use of apixaban in the prevention of stroke in atrial fibrillation patients[16] included a total of 170.814 patients of 16 studies. Included were three single-center cohorts, 6 studies from insurance databases, 1 regional database and 6 nationwide registries. Mean age was 70 years. In 4 studies patients with a high thromboembolic risk based on a CHA_2DS_2-VASc score ≥4 were enrolled. Dose reduction to 2.5mg bid ranged from 13.5% to 37.8% in these studies. Real-world studies confirmed a lower risk of stroke or systemic embolism compared with warfarin[17–19] (Table 2) and lower risk of major bleeding. In a metaanalysis[16] there was a significant reduction in thromboembolic risk (OR, 0.77; 95% CI, 0.64–0.93) compared with warfarin in the regular dose group, however, in the reduced dose group, there was a 27% relative risk increase in any thromboembolic events. Regarding rate of stroke, there was no significant difference between apixaban and warfarin in the regular as well as the reduced dose group.

Consistent with the ARISTOTLE trial major bleeding was significantly lower on apixaban compared with warfarin (OR, 0.62; 95% CI 0.51–0.75), in both dosing groups and the risk of intracranial haemorrhage was also significantly reduced with apixaban (36% relative risk reduction). Compared with the other NOACS apixaban was comparable to rivaroxaban and dabigatran regarding stroke and systemic embolism, however, risk of major bleeding was significantly lower on apixaban.[20–23]

Apixaban in Atrial Fibrillation Patients in Acute Coronary Syndrome and Undergoing Percutaneous Coronary Interventions (PCI)

Triple therapy in atrial fibrillation patients undergoing PCI has been shown to carry a higher risk of major bleeding compared to dual therapy. In the WOEST trial VKA plus Clopidogrel, in PIONEER-AF Rivaroxaban plus Clopidogrel and in RE-DUAL-PCI Dabigatran plus Clopidogrel or Ticagrelor were associated with a lower rate of major bleeding compared to triple therapy.[24–26] In the AUGUSTUS trial, an international randomized controlled trial with a 2x2 factorial design[27] 4614 patients were assigned to apixaban or vitamin K antagonist and aspirin or placebo for 6 months. Patients were eligible for inclusion with an acute coronary syndrome or undergoing PCI and in need for a $P2Y_{12}$ inhibitor. Clinically relevant or major bleeding within 6 months of follow-up was significantly lower on apixaban compared with warfarin (10.5% vs 14.7%, HR 0.69, p<0.0001). Adding aspirin compared with placebo resulted in a significant increase in bleeding complications (16.1% vs 9.0%; HR 1.89, p< 0.0001). Compared to warfarin rate of death and rehospitalization was significantly lower on apixaban (23.5% vs 27.4%; HR 0.83; p=0.002), driven by a lower rehospitalization rate on apixaban (22.5% vs 25.3%) Regarding ischemic events (stroke, myocardial infarction, stent thrombosis and revascularization) there was no significant difference between groups. Event rates were highest under triple therapy with VKA, $P2Y_{12}$ inhibitor and aspirin (27.5%) and lowest on apixaban plus $P2Y_{12}$ inhibitor (22.0%).

Table 2 Real-World Studies on the Use of Apixaban Compared with Warfarin and Other NOACS

	Proietti et al[16]	Coleman et al[17]	Yoa et al[18]	Li et al[19]
Study design	Meta-analysis on the real-world use of apixaban in the prevention of stroke in atrial fibrillation patients three single-center cohorts, 6 studies from insurance databases, 1 regional database and 6 nationwide registries	Retrospective study using MarketScan claims from January 2012 to October 2014 1:1 propensity-score matched	Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation	Retrospective study used four large US claims databases of NVAF patients newly initiating apixaban or warfarin from January 1, 2013 to September 30, 2015. 1:1 warfarin-apixaban propensity score matching
Inclusion criteria	Patients with NVAF	Patients with NVAF	Patients with NVAF	Patients with NVAF
Subjects	170,814	4083 apixaban and 4083 warfarin users were matched	15,390	76,940 (38,470 warfarin and 38,470 apixaban)
Results	Significant reduction for apixaban in thromboembolic risk (OR, 0.77; 95% CI, 0.64–0.93) compared with warfarin in the regular dose group, however in the reduced dose group there was a 27% relative risk increase in any thromboembolic events major bleeding was significantly lower on apixaban compared with warfarin (OR, 0.62; 95% confidence interval (CI), 0.51–0.75), in both dosing groups and the risk of intracranial haemorrhage was also significantly reduced with apixaban (36% relative risk reduction).	Apixaban was found to nonsignificantly reduce the combined endpoint of ischemic stroke or Intracranial hemorrhage versus warfarin. Ischemic stroke risk was nonsignificantly increased with apixaban (HR = 1.13, 95% CI = 0.49–2.63) versus warfarin.	HR and CI: For Apixaban vs warfarin: Stroke/systemic embolism 0.67 (0.46–0.98) Any bleeding 0.45 (0.34–0.59) Intracranial hemorrhage 0.24 (0.12–0.50) Gastrointestinal bleeding 0.51 (0.37–0.70)	Apixaban initiators had a significantly lower risk of stroke/SE (HR: 0.67, 95% CI: 0.59–0.76) and major bleeding (HR: 0.60, 95% CI: 0.54–0.65) than warfarin initiators. Compared to warfarin, apixaban use was associated with a 40% lower risk of major bleeding (HR: 0.60, 95% CI: 0.54–0.65, p<0.001) within one year of treatment initiation.

The AUGUSTUS trial supports the idea of dual therapy with apixaban and a $P2Y_{12}$ inhibitor in atrial fibrillation patients undergoing PCI. Larger randomized powered trials are needed to prove or decline the slight increase in ischemic events seen in the trial on dual therapy.

Apixaban After Structural Heart Interventions

Optimal anticoagulation regimen in atrial fibrillation patients undergoing structural heart interventions is still unclear. However, rate of atrial fibrillation in patients undergoing transfemoral aortic valve replacement (TAVR) ranges from 32.9% in the PARTNER trial[28] to 46.8% in the Core Valve high-risk study. In patients undergoing cardiac surgery atrial fibrillation is an independent predictor of stroke, death and heart failure.[29] Single-center experiences point at a significantly higher 30-day early safety endpoint in TAVR patients in atrial fibrillation. Whereas apixaban was superior to warfarin in the prevention of thromboembolic events at a lower bleeding rate in the ARISTOTLE trial, subgroup analysis in patients with valvular heart disease demonstrated comparable results to warfarin.[30] A single-center study in 617 TAVR patients, with 272 in atrial fibrillation or with new-onset atrial fibrillation after TAVR demonstrated a significantly lower earl safety endpoint ($p< 0.01$) and a significantly lower rate of life-threatening bleeding ($p<0.01$) on apixaban compared with a vitamin K antagonist.[31] In a second publication including 21 patients treated with NOAC for atrial fibrillation after TAVR, no thromboembolic event was reported.[32] Large randomized trials evaluating the efficacy and safety of NOACS in atrial fibrillation patients undergoing TAVR are ongoing. The ATLANTIS trial, a multicenter, randomized, phase IIIb, prospective,

open-label, superiority study comparing standard of care (SOC Group) versus an apixaban-based strategy (Anti-Xa Group) after successful TAVR (ClinicalTrials.gov NCT 02664649) is ongoing.[33]

Conclusion

Apixaban has been shown to be superior to warfarin in preventing stroke and systemic embolism and causes significantly less major bleeding based on large randomized trials. These data are confirmed in real-world studies. Apixaban has been shown to be safe and effective in atrial fibrillation patients in acute coronary syndrome or undergoing PCI in combination with a $P2Y_{12}$ inhibitor. Regarding the expanded use of apixaban in valvular heart disease patients there is still missing knowledge in relation to the safety and efficacy of apixaban which is being addressed by ongoing randomized clinical trials.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Mozaffarian D, Benjamin E, Go A, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics – 2015 update: a report from the American Heart Association. *Circulation*. 2015;131:e29–322. doi:10.1161/CIR.0000000000000152
2. Miyasaka Y, Barnes M, Bailey K, et al. Mortality trends in patients diagnosed with first atrial fibrillation: a 21-year community-based study. *J Am Coll Cardiol*. 2007;49:986–992. doi:10.1016/j.jacc.2006.10.062
3. Psaty B, Manolio T, Kuller L, et al. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation*. 1997;96:2455–2461. doi:10.1161/01.CIR.96.7.2455
4. Fuster V, Rydén LE; European Heart Rhythm Association; Heart Rhythm Society, et al. ACC/AHA/ESC 2006 guidelines 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 European Society of Cardiology Committee for Practice Guidelines (Writing committee to revise the 2001 guidelines for the management of patients with atrial fibrillation). *J Am Coll Cardiol*. 48;2006:854–906. doi:10.1016/j.jacc.2006.07.009
5. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992. doi:10.1056/NEJMoa1107039
6. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151. doi:10.1056/NEJMoa0905561
7. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891. doi:10.1056/NEJMoa1009638
8. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369:2093–2104.
9. Eikelboom J, O'Donnell M, Yusuf S, et al. Rationale and design of AVERROES: apixaban versus acetylsalicylic acid to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment. *Am Heart J*. 2010;159:348–353.e1. doi:10.1016/j.ahj.2009.08.026
10. Connolly S, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011;364:806–817. doi:10.1056/NEJMoa1007432
11. Hohnloser S, Shestakovska O, Eikelboom J, et al. The effects of apixaban on hospitalizations in patients with different types of atrial fibrillation: insights from the AVERROES trial. *Eur Heart J*. 2013;34:2752–2759. doi:10.1093/eurheartj/eht292
12. Lopes R, Alexander J, Al-Khatib S, et al. Apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (ARISTOTLE) trial: design and rationale. *Am Heart J*. 2010;159:331–339. doi:10.1016/j.ahj.2009.07.035
13. Hylek E, Held C, Alexander J, et al. Major bleeding in patients with atrial fibrillation receiving apixaban or warfarin: the ARISTOTLE trial (Apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation): predictors, characteristics, and clinical outcomes. *J Am Coll Cardiol*. 2014;63:2141–2147. doi:10.1016/j.jacc.2014.02.549
14. Lopes R, Al-Khatib S, Wallentin L, et al. Efficacy and safety of apixaban compared with warfarin according to patient risk of stroke and of bleeding in atrial fibrillation: a secondary analysis of a randomised controlled trial. *Lancet*. 2012;380:1749–1758. doi:10.1016/S0140-6736(12)60986-6
15. Hess C, Al-Khatib S, Granger C, Lopes R. A review of apixaban for stroke prevention in atrial fibrillation: insights from ARISTOTLE. *Expert Rev Cardiovasc Ther*. 2013;11:1105–1114. doi:10.1586/14779072.2013.824181
16. Proietti M, Romanazzi I, Romiti GF, Farcomeni A, Lip GYH. Real-world use of apixaban for stroke prevention in atrial fibrillation: a systematic review and meta-analysis. *Stroke*. 2018;49:98–106. doi:10.1161/STROKEAHA.117.018395
17. Coleman CI, Antz M, Bowrin K, et al. Real-world evidence of stroke prevention in patients with nonvalvular atrial fibrillation in the United States: the REVISIT-US study. *Curr Med Res Opin*. 2016;32:2047–2053. doi:10.1080/03007995.2016.1237937
18. Yao X, Abraham NS, Sangaralingham LR, et al. Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. *J Am Heart Assoc*. 2016;5:e003725. doi:10.1161/JAHA.116.003725
19. Li XS, Deitelzweig S, Keshishian A, et al. Effectiveness and safety of apixaban versus warfarin in nonvalvular atrial fibrillation patients in "real-world" clinical practice. A propensity-matched analysis of 76,940 patients. *Thromb Haemost*. 2017;117:1072–1082. doi:10.1160/TH17-01-0068
20. Al-Khalili F, Lindström C, Benson L. The safety and persistence of nonvitamin-K-antagonist oral anticoagulants in atrial fibrillation patients treated in a well structured atrial fibrillation clinic. *Curr Med Res Opin*. 2016;32:779–785. doi:10.1185/03007995.2016.1142432
21. Noseworthy PA, Yao X, Abraham NS, Sangaralingham LR, McBane RD, Shah ND. Direct comparison of dabigatran, rivaroxaban, and apixaban for effectiveness and safety in non valvular atrial fibrillation. *Chest*. 2016;150:1302–1312. doi:10.1016/j.chest.2016.07.013
22. Abraham NS, Noseworthy PA, Yao X, Sangaralingham LR, Shah ND. Gastrointestinal safety of direct oral anticoagulants: a large population-based study. *Gastroenterology*. 2017;152:1014–1022.e1. doi:10.1053/j.gastro.2016.12.018
23. Altay S, Yıldırımtürk Ö, Çakmak HA; NOAC-TURK Study Collaborators., et al. New oral anticoagulants-TURKey (NOAC-TURK): multicenter cross-sectional study. *Anatol J Cardiol*. 17;2017:353–361. doi:10.14744/AnatolJCardiol.2016.7472
24. Dewilde WJ, Oirbans T, Verheugt FW, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet*. 2013;381:1107–1115. doi:10.1016/S0140-6736(12)62177-1
25. Gibson CM, Mehran R, Bode C, et al. An open-label, randomized, controlled, multicenter study exploring two treatment strategies of rivaroxaban and a dose-adjusted oral vitamin K antagonist treatment strategy in subjects with atrial fibrillation who undergo percutaneous coronary intervention (PIONEER AF-PCI). *Am Heart J*. 2015;169:472–8.e5.

26. Cannon CP, Bhatt DL, Oldgren J, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med*. 2017;377:1513–1524. doi:10.1056/NEJMoa1708454
27. Lopes RD, Heizer G, Aronson R, et al.; AUGUSTUS Investigators. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation.mN. *Engl J Med*. 2019;380:1509–1524. doi:10.1056/NEJMoa1817083
28. Kodali SK, Williams MR, Smith CR, et al.; PARTNER Trial Investigators. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med*. 2012;366:1686–1695. doi:10.1056/NEJMoa1200384
29. Stortecky S, Windecker S. Stroke: an infrequent but devastating complication in cardiovascular interventions. *Circulation*. 2012;126:2921–2924. doi:10.1161/CIRCULATIONAHA.112.149492
30. 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;132:624–632. doi:10.1161/CIRCULATIONAHA.114.014807
31. Seeger J, Gonska B, Rodewald C, Rottbauer W, Wöhrle J. Apixaban in patients with atrial fibrillation after transfemoral aortic valve replacement. *JACC Cardiovasc Interv*. 2017;10:66–74. doi:10.1016/j.jcin.2016.10.023
32. Hendricks AK, Nei SD, Greason KL, Scott RA. Direct oral anticoagulant use following transcatheter aortic valve replacement: a case series. *J Cardiovasc Pharmacol*. 2019. doi:10.1097/FJC.0000000000000755
33. Collet JP, Berti S, Cequier A, et al. Oral anti-Xa anticoagulation after trans-aortic valve implantation for aortic stenosis: the randomized ATLANTIS trial. *Am Heart J*. 2018;200:44–50. doi:10.1016/j.ahj.2018.03.008