


Critical Analysis of Apixaban Dose Adjustment Criteria

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Abstract

Apixaban is indicated for the prevention of ischemic stroke in non-valvular atrial fibrillation (NVAf), as well as for the prevention and treatment of venous thromboembolism (VTE). Dose adjustment is based on age, weight, and serum creatinine in NVAf, while there are no recommended adjustment criteria for VTE. Such adjustment is unconventional compared to other commonly used medications. The objective of this manuscript is to critically analyze each apixaban dosing adjustment criterion and its associated outcomes. PubMed articles from March 2013 to March 2020 were selected with search terms “apixaban,” and “dose adjustment,” “adjustment,” or “adjustment criteria.” Pharmacokinetic studies demonstrated increased apixaban exposure in patients >65 years of age, those with extreme body weights, and those with advanced renal impairment, though post-hemodialysis dosing may off-set the elevated apixaban exposure. However, clinical data show that among patients ≥ 75 years, ≤ 60 kg, and with estimated glomerular filtration rate < 50 mL/min, including those on dialysis, there is no reduction in apixaban safety or efficacy. Published literature describes variable dosing strategies utilized in clinical practice. Overall, apixaban dose adjustment criteria may need to be re-evaluated.

Keywords

apixaban, anticoagulation, dosing

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Introduction

Apixaban is a direct-acting oral anticoagulant (DOAC) initially approved in 2012 for stroke prevention in patients with non-valvular atrial fibrillation (NVAf) and for the prevention and treatment of venous thromboembolism (VTE) in 2014. The dose adjustment criteria are not consistent across indications. For NVAf, apixaban is dosed at 5 mg orally twice daily and is reduced to 2.5 mg twice daily in patients who meet 2 of the following criteria: age ≥ 80 years, body weight ≤ 60 kg, and serum creatinine (SCr) ≥ 1.5 mg/dL.¹ Placement of these criteria within the Cockcroft-Gault formula would provide an estimated glomerular filtration rate (eGFR) of approximately 30 mL/min. Perhaps these parameters were chosen to present a practical method for determining dose adjustment, as opposed to requiring clinicians to calculate the creatinine clearance (CrCl). However, for the treatment of VTE, the dose is 10 mg orally twice daily for 7 days, followed by 5 mg twice a day with no dose adjustment recommendations.¹ The rationale for why the dose adjustment criteria only apply in NVAf is uncertain. In real-world practice, off-label dosing has not been

uncommon, likely due to this lack of clarity.^{2,3} The objective of this article is to explore each dose adjustment criterion and its effect on pharmacokinetic and clinical outcomes.

Methods

PubMed was used to search for articles published between March 2013 and March 2020. Search terms included:

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“apixaban,” and “dose adjustment,” “adjustment,” or “adjustment criteria.” During an initial screening, 192 articles were identified and after the use of filters such as human, English, and full-text, 121 articles were screened. Studies on indications other than NVAf and VTE, studies on pediatric patients, case reports or case series, and commentaries or editorials were excluded.

Rationale for Dose Adjustment Criteria

Patients with NVAf and at least 2 of the dose adjustment criteria have demonstrated higher risk for major bleeding and all-cause death compared to patients with ≤ 1 dose adjustment criterion.⁴ Regardless, this does not fully explain the selection of the specific dose adjustment criteria. We begin our exploration of each criterion by evaluating the pharmacokinetic data.

Clinical Pharmacokinetics of Each Dose Adjustment Criteria

Age ≥ 80 years. An open-label study assigned 2 groups of participants to receive a single dose of apixaban 20 mg: 1) patients between 18 and 40 years of age, and 2) patients >65 years. The maximum plasma concentration (C_{max}) was similar between the 2 groups, but the area under the concentration-time curve (AUC) was 32% higher among those >65 years. The mean elimination half-life was longer in those >65 years (15.45 vs. 11.98 hours).⁵ Thus, patients >65 years displayed higher apixaban exposure and reduced drug clearance. This age cut-off is inconsistent with the dose adjustment criterion of ≥ 80 years per the drug manufacturer.

Weight ≤ 60 kg. In an open-label randomized controlled trial that enrolled patients with extremes of body weight, patients with low body weight (<50 kg) had approximately 27% higher C_{max} and 20% higher AUC. Those with high body weight (≥ 120 kg) had approximately 31% and 23% lower C_{max} and AUC, respectively.⁶ There appears to be a slight, but notable discrepancy between the weight cut-off of <50 kg in this study and the ≤ 60 kg recommended by the manufacturer.

SCr ≥ 1.5 mg/dL. In an open-label study, a 10 mg oral dose of apixaban was given to patients with normal renal function, mild renal impairment with CrCl >50 to 80 mL/min, moderate renal impairment (CrCl 30 to 50 mL/min), and severe renal impairment (CrCl <30 mL/min). The C_{max} was not significantly different, but the AUC increased by 16%, 29%, and 38%, respectively, compared to those with normal renal function.⁷ The manufacturer chose a different measure of renal function (SCr) for dose adjustment. Another open-label study compared a 5 mg oral apixaban dose in patients with normal renal function to those on hemodialysis (HD) in whom a 5 mg dose was given 2 hours pre-HD and a 5 mg dose was given 7 days post-HD. When apixaban was given pre-HD, the C_{max} and AUC were 13% and 14% lower, respectively, versus non-HD patients.⁸ When apixaban was administered post-HD, C_{max}

was decreased by 10%, but AUC was increased by 36% compared to non-HD patients. Although patients on HD may be at higher risk for bleeding due to heparin exposure during HD and a higher level of Von Willebrand factor, HD may offset the temporarily elevated AUC from post-HD dosing. Therefore, it may not be necessary to dose adjust in this population.

Drug Interactions

The apixaban package labeling advises on the importance of drug interactions, as apixaban is a substrate of both cytochrome P450 3A4 (CYP3A4) and efflux transporter permeability-glycoprotein (P-gp). Co-administration of strong CYP3A4 and P-gp inhibitors or inducers may result in increases or decreases of apixaban exposure, respectively.^{9,10} Apixaban should not be used with dual strong CYP3A4 and P-gp inducers, such as rifampin, carbamazepine, phenytoin, and phenobarbital.^{11,12} Concomitant dual strong CYP3A4 and P-gp inhibitors should also be avoided or a 50% dose reduction is recommended when concurrent use is needed.¹ CYP3A4 inhibitors and inducers are thought to have a more significant drug interaction with apixaban compared to those of P-gp. With commonly used cardiology medications that are CYP3A4 inhibitors, such as amiodarone, verapamil, or diltiazem, there appear to be no clinically significant interactions.¹²

Overall, pharmacokinetic data support the idea that apixaban plasma concentrations are affected by each of the NVAf dose adjustment criterion; however, the cutoffs do not appear to be consistent with those currently recommended by the manufacturer. Next, we will dive into the available clinical data focusing on subgroups of age, weight, and renal function.

Review of Clinical Trial Data as It Pertains to Apixaban Dose Adjustment Criteria

AVERROES randomized 5,599 patients with NVAf to standard dose apixaban or aspirin 81-324 mg per day. The dose adjustment criteria for reduced dose apixaban was applied. Apixaban users had significantly fewer stroke events, with no difference in major bleeding. Subgroup analyzes evaluating age and renal function, including patients ≥ 75 years and eGFR <50 mL/min found no significant interactions.¹³

ARISTOTLE was a double-blind, randomized trial that compared apixaban to warfarin in 18,201 patients with NVAf. Stroke events and death from any cause occurred significantly less in the apixaban group compared with warfarin. Subgroup analyzes demonstrated consistent efficacy and safety with apixaban among patients age ≥ 75 years and weight ≤ 60 kg, and reduction in major bleeding was maintained in those with renal impairment. A total of 428 patients met criteria for reduced dose apixaban. The reduced apixaban dose did not meet statistical significance in stroke reduction, though the confidence interval was wide and the P -value for the interaction between standard and reduced dose apixaban was not significant.^{14,15}

A secondary analysis of ARISTOTLE evaluated standard dose apixaban in patients meeting 1 dose-reduction criterion versus none.¹⁶ Among 3,966 patients with only 1 dose-reduction criterion, 41.3% were ≥ 80 years of age, 36.0% weighed ≤ 60 kg, and 22.8% had SCr ≥ 1.5 mg/dL. Findings when compared with warfarin were consistent with the original ARISTOTLE trial, suggesting that the presence of 1 dose-reduction criterion does not significantly impact stroke or bleeding events with standard dosing. Another subgroup analysis of the ARISTOTLE trial analyzed patients who met ≥ 2 dose-reduction criteria ($n = 751$) and 17,322 patients who met standard-dose criteria (0 or 1 criteria).⁴ Of the 751 patients, 93% were ≥ 80 years of age, 70% patients weighed ≤ 60 kg, 39.3% patients had SCr ≥ 1.5 mg/dL. A total of 386 patients were given apixaban 2.5 mg twice daily, and 365 were given warfarin. Patients with ≥ 2 dose-reduction criteria (receiving either apixaban or warfarin) had significantly higher rates of stroke and major bleeding than patients with 0 or 1 criterion. When looking only at apixaban, though not statistically significant, there was a trend toward a higher rate of stroke in the ≥ 2 dose-reduction criteria group who received 2.5 mg twice daily, compared with the standard dose group who received 5 mg twice daily. A post-hoc analysis of ARISTOTLE found no significant interactions for stroke or bleeding outcomes across age groups (<65 , 65 to <75 , and ≥ 75 years), a continuum of eGFR, and dosing (2.5 and 5 mg twice daily).¹⁷ Additionally, another post-hoc analysis of ARISTOTLE showed that in patients weighing ≤ 60 kg, only 27% were on a reduced dose of apixaban and these patients were found to have a lower risk of hemorrhagic stroke and major bleeding compared to warfarin.¹⁸ Evaluation of only those dosed according to the package labeling within the ARISTOTLE trial demonstrated reduced apixaban concentrations among patients who received 2.5 mg twice daily compared to standard dosing, but similar effect on clinical efficacy and safety outcomes versus warfarin, which provides some reassurance regarding the suitability of dose adjustment to the reduced dose.⁴ However, standard versus reduced dose apixaban was not evaluated with respect to age, weight, and renal function in any of these trials.

To evaluate apixaban use for the treatment of acute VTE, 2,691 patients were randomized to receive 10 mg of apixaban twice daily for the first 7 days, then subsequently 5 mg twice daily or enoxaparin at a dose of 1 mg/kg subcutaneously twice daily for 5 days bridging to warfarin for 6 months.¹⁹ Fixed-dose apixaban was non-inferior to conventional therapy with enoxaparin for the treatment of acute VTE and significantly reduced major bleeding. Again, the effect of apixaban on each outcome did not differ within subgroups of age, weight, or renal function though $<5\%$ of patients were >75 years of age, 231 (8.6%) weighed ≤ 60 kg, and 14 (0.5%) had CrCl ≤ 30 mL/min. Approximately 10% of patients would have qualified for the lower apixaban dose if the dose adjustment recommendations for NVAF were followed. These same dose adjustment criteria were not applied for VTE treatment to avoid underdosing patients with active clots and high risk of recurrent VTE.^{13,14} A subgroup analysis of AMPLIFY defined

“fragile” patients as those who met at least 2 of 3 dose adjustment criteria for NVAF.²⁰ No VTE or VTE-related deaths were reported for the “fragile” patients receiving apixaban compared with “non-fragile” patients and the lower incidence of bleeding was consistent with the overall AMPLIFY study results. This subgroup analysis did not report the individual accountability of age, weight, and SCr, which requires further investigation.

Apixaban Renal Dose Adjustment

Most renal dosing recommendations are based on calculated CrCl using the Cockcroft-Gault formula, and limited drugs utilize eGFR for dosing. Interestingly, the apixaban renal dose adjustment recommendation is based on SCr, and is the only drug on the market with such dose adjustment criteria. While the most accurate and reliable index of kidney function for drug dosing is still debated, SCr is not a reliable indicator of renal function because it requires stable kidney function and can be confounded by muscle mass, age, race, gender, and tubular secretion. It is not clear why apixaban is dose adjusted based on SCr instead of CrCl or estimated GFR.

All trials leading to apixaban approval excluded patients with SCr >2.5 mg/dl or CrCl <25 mL/min. Apixaban is excreted in both feces and urine as metabolites (27% of total clearance).⁵ Thus, in patients taking apixaban with renal impairment, less drug clearance may cause more anticoagulant effects and a higher risk of bleeding; however, this was not seen clinically.¹⁷ Additional literature challenges the role of renal impairment for apixaban dosing.²¹⁻²³

An inpatient retrospective cohort study compared apixaban ($n = 73$) to warfarin ($n = 73$) in patients with severe renal impairment (CrCl of <25 mL/min or SCr of >2.5 mg/dL), including patients on peritoneal dialysis ($n = 4$) or HD ($n = 38$).²² Patients receiving continuous renal replacement therapy (CRRT) were excluded. Indications for apixaban included NVAF (72.6%) and VTE (26%). Approximately 62% received the reduced dose of apixaban 2.5 mg twice daily, 37% received apixaban 5 mg twice daily, and 1.4% received apixaban 10 mg twice daily. No statistically significant differences were seen for bleeding or stroke/systemic embolism. Seven of 39 patients who were taking apixaban before admission were taking an inappropriate dose (e.g. dose reduction for VTE treatment).

Another retrospective cohort study compared the safety and efficacy of apixaban vs warfarin in dialysis patients.²¹ Patients with acute kidney injury and those on CRRT were excluded. Among inpatient end-stage renal disease (ESRD) patients ($n = 124$) on peritoneal dialysis or HD who received apixaban ($n = 74$) or warfarin ($n = 50$), 34 (46%), 29 (39.2%) and 11 (14.9%) patients received apixaban for VTE, NVAF, and prophylaxis of VTE, respectively. Almost 80% of patients were on the standard apixaban dose for either VTE treatment or NVAF, while the remaining patients were on the reduced apixaban dose (20.3%) and met criteria for either dose reduction ($n = 4$) or lifelong prophylactic anticoagulation dosing

Table 1. Summary of Pharmacokinetic and Clinical Data.

Dose adjustment criteria	Pharmacokinetic data	Clinical data
Age	Similar C _{max} between age 18 to 40 and >65 years with higher AUC and longer half-life in patients >65 years ⁵	No difference in stroke/systemic embolism or major bleeding between age ≤ 65, 65 to 75, and ≥75 years ¹⁷ Age may not have a large impact on clinical outcomes and dose adjustment for age may not be necessary
Body weight	Higher C _{max} and AUC in patients <50 kg vs ≥120 kg ⁶	Weight ≤60 kg associated with a lower risk of hemorrhagic stroke and major bleeding ¹⁸ Low body weight may not have large impact on the clinical outcomes and dose adjustment for low body weight may not be necessary
Severe renal impairment	Similar C _{max} among varying degrees of renal function (CrCl 50-80 mL/min, 30-50 mL/min, and <30 mL/min) with higher AUC in the <30 mL/min group ⁷	Apixaban standard dose is safe in patients with severe renal impairment ²² Renal impairment may not have a large impact on the clinical outcomes and dose adjustment for renal function may not be necessary.
Hemodialysis	Lower C _{max} and AUC when given pre-HD, but lower C _{max} and higher AUC when given post-HD ⁸	Apixaban standard dose is safe and effective in ESRD patients on dialysis. ²¹ Standard dose apixaban significantly reduced thromboembolic events and mortality in ESRD patients compared to the reduced dose ²³ Renal dose adjustment for apixaban in dialysis patients may not be necessary.

(n = 11). Apixaban users had a non-significantly lower VTE recurrence rate and significantly fewer bleeding events compared to warfarin users. Thus, standard dose apixaban appears to be safe and effective in patients with ESRD on dialysis.

A larger retrospective cohort study evaluated the safety and effectiveness of standard dose apixaban (n = 1,034) versus reduced apixaban dose (n = 1,317) in ESRD patients on dialysis for NVAF only.²³ Only the standard dose apixaban was associated with a significantly lower risk of stroke or systemic embolism compared to warfarin. Both apixaban doses showed a significantly greater reduction in major bleeding compared to warfarin. Notably, standard dose apixaban demonstrated greater reduction in thromboembolic events and mortality in ESRD patients compared to the reduced apixaban dose suggesting again that standard dosing of apixaban is safe in these patients.

These studies of apixaban in renal impairment demonstrated the safety of apixaban use in this population compared to warfarin.²¹⁻²³ Importantly, when compared with reduced dose apixaban, standard dose apixaban not only significantly reduced the stroke rate, but was also associated with reduced mortality.²³ Overall, it appears that apixaban dose adjustment for severe renal impairment, including those on dialysis, may not be necessary and available literature suggests that SCr or CrCl should not be considered for dose adjustment.

More recently, a retrospective cohort study was conducted in patients with NVAF and ESRD on dialysis. Interestingly, compared to no anticoagulation, apixaban use was not associated with a lower rate of stroke or systemic embolism (HR 1.24, 95% CI 0.69 to 2.23), but was associated with a higher rate of fatal or intracranial bleeding (HR 2.74, 95% CI 1.37 to 5.47).²⁴ This study suggests that apixaban use in this patient population should be re-evaluated to determine the net clinical benefit.

Real-World Apixaban Dosing

A retrospective cohort study of 27 patients who received apixaban 2.5 mg twice daily for VTE treatment (15%) and for NVAF or atrial flutter (85%) was conducted.²⁵ More than half of the patients had 1 dose-reduction criterion leading to a manufacturer-recommended dose adjustment adherence rate of about 10% in NVAF patients. Most of the adjustments were made due to history of bleeding, renal dysfunction, and concomitant medications such as nonsteroidal anti-inflammatory drugs or other agents that increase bleed risk. In contrast, in a multicenter trial, 420 patients were given standard dose apixaban, and 136 received reduced dose apixaban for NVAF.² Adherence to apixaban dosing recommendations per the manufacturer was 87%, illustrating the variability in adherence to manufacturer-recommended dose adjustment in real life. Reasons for deviating from the manufacturer-recommended dose were continuation of home dose (38.9%), perception of increased bleeding risk (25%), unspecified (20%), history of gastrointestinal bleeding (5.6%), dosing error (5.6%), and anticipated need for dose-reduction in the future (4.2%). It seems that lower-than-recommended dosing is clinician-specific and not standardized.

When dosed according to the package labeling, some have identified large overlap in plasma apixaban levels between those receiving 5 mg twice daily and those reduced to 2.5 mg twice daily dosing, suggesting appropriateness of dose adjustment criteria, even among those deemed to be at high-risk for bleeding.^{26,27} However, those receiving the lower dose off-label had median trough apixaban levels almost half that of patients receiving the lower dose according to manufacturer recommendations (66 vs 102 ng/ml, *P* = 0.014).²⁶ The clinical relevance of decreased apixaban exposure in those receiving

the lower dose off-label remains uncertain. To capture real-world data on use of lower doses, a Danish database included 88,141 patients of which 69.9% of patients received warfarin, 7.9% received apixaban 2.5 mg twice daily, 15.9% received dabigatran 110 mg twice daily, and 6.3% received rivaroxaban 15 mg daily.²⁸ In contrast to the previous trials, patients receiving apixaban demonstrated a trend toward increased ischemic stroke and no difference in bleeding when compared to warfarin. However, patients receiving apixaban were older (mean age 83.9 vs. 73.9 years) with more comorbidities and higher mean scores for CHA₂DS₂-VASc (4.3 vs. 3.3) and HAS-BLED (2.8 vs 2.4). Sensitivity analyzes of cohorts with an indication for dose reduction and patients ≥80 years of age showed reduced bleeding, but did not differ from an efficacy standpoint. With the lack of reporting on weight or SCr, it remains difficult to assess whether the dose adjustment criteria are clinically necessary, though it is plausible that 2.5 mg may be too low of a dose for adequate stroke prevention.

Conclusion

Dosing apixaban can be complicated and the appropriateness of its dose adjustment criteria remains unclear. Current package labeling generally recommends reduced-dose apixaban based on older age, lower weight, and higher SCr, and only when prescribed for NVAF. The rationale provided by the manufacturer is that patients with these characteristics are anticipated to have higher apixaban drug exposure.¹⁵ After a thorough literature review including both PK and clinical data, the clinical relevance of applying such criteria requires additional analysis (summarized in Table 1), and is difficult to evaluate given the discordance between dose adjustment criteria and reported cut-points within studies. In real-world utilization, the dose may be reduced in patients presumed to have a higher bleeding risk and this is not standardized in clinical practice. Though renal function may not be a relevant criterion for dose adjustment, the net clinical benefit of anticoagulation in HD patients must be re-examined. Overall, the clinical significance of dose reducing apixaban may require further investigation and confirmation in well-designed randomized controlled trials.

While apixaban fixed dosing is advantageous, there is clear need for improvement from the standpoint of criteria for dose adjustment. As we continue to learn more about what role certain criteria or specific drug interactions play in the dosing of apixaban, we can optimize dosing for each patient. We are also still learning about the role of coagulation test monitoring as there are limited data evaluating anti-FXa assays and the association with clinical outcomes.²⁹⁻³² The lack of routine monitoring is another benefit to using DOACs and perhaps there are certain criteria that warrant closer monitoring, but the therapeutic index of DOACs has yet to be fully elucidated. When these aspects are clear, we will be able to individualize and optimize apixaban therapy.

Authors' Note

Our institution did not require ethical approval. Informed consent for patient information to be published in this article was not obtained because human subject research was not conducted for this manuscript.


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References

1. Apixaban [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2012.
2. Gibson CM, Smith CB, Davis S, Scalese MJ. Assessment of apixaban prescribing patterns for nonvalvular atrial fibrillation in hospitalized patients. *Ann Pharmacother* 2018;52(1):54-59. doi:10.1177/1060028017726795
3. Buchholz A, Ueberham L, Gorczynska K, et al. Initial apixaban dosing in patients with atrial fibrillation. *Clin Cardiol*. 2018; 41(5):671-676. doi:10.1002/CLC.22949
4. Zeitouni M, Giczewska A, Lopes R, et al. Clinical and pharmacological effects of apixaban dose adjustment in the ARISTOTLE trial. *J Am Coll Cardiol*. 2020;75(10):1145-1155.
5. Frost C, Song Y, Shenker A, et al. Effects of age and sex on the single-dose pharmacokinetics and pharmacodynamics of apixaban. *Clin Pharmacokinet*. 2015;54(6):651-662. doi:10.1007/s40262-014-0228-0
6. Upreti VV, Wang J, Barrett YC, et al. Effect of extremes of body weight on the pharmacokinetics, pharmacodynamics, safety and tolerability of apixaban in healthy subjects. *Br J Clin Pharmacol*. 2013;76(6):908-916.
7. Chang M, Yu Z, Shenker A, et al. Effect of renal impairment on the pharmacokinetics, pharmacodynamics, and safety of apixaban. *J Clin Pharmacol*. 2016;56(5):637-645. doi:10.1002/jcph.633
8. Wang X, Tirucherai G, Marbury T, et al. Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end-stage renal disease on hemodialysis. *J Clin Pharmacol*. 2016;56(5): 628-636. doi:10.1002/jcph.628
9. Byon W, Garonzik S, Boyd RA, Frost CE. Apixaban: a clinical pharmacokinetic and pharmacodynamic review. *Clin Pharmacokinet*. 2019;58(10):1265-1279. doi:10.1007/s40262-019-00775-z
10. Chin P. Which patients may benefit from dose adjustment of non-vitamin K antagonist oral anticoagulants? *Semin Thromb Hemost*. 2015;41(2):195-207.
11. Chang S, Chou IJ, Yeh YH, et al. Association between use of non-vitamin K oral anticoagulants with and without concurrent medications and risk of major bleeding nonvalvular atrial fibrillation. *JAMA*. 2017;318(13):1250-1259. doi:10.1001/jama.2017.13883

12. Wiggins B, Dixon D, Neyens R, Page R, Gluckman T. Select drug-drug interactions with direct oral anticoagulants. *J Am Coll Cardiol*. 2020;75(11):1341-1350.
13. Connolly S, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation [supplementary appendix]. *N Engl J Med*. 2011;364(9):806-817.
14. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-992.
15. Lopes RD, Alexander JH, Al-Khatib SM, et al. Apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (ARISTOTLE) trial: design and rationale. *Am Heart J*. 2010;159(3):331-339. doi:10.1016/j.ahj.2009.07.035
16. Alexander J, Andersson U, Lopes R, et al. Apixaban 5 mg twice daily and clinical outcomes in patients with atrial fibrillation and advanced age, low body weight, or high creatinine: a secondary analysis of a randomized clinical trial. *JAMA Cardiol*. 2016;1(6):673-681. doi:10.1001/jamacardio.2016.1829
17. Halvorsen S, Atar D, Yang H, et al. Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial. *Eur Heart J*. 2014;35(28):1864-1872.
18. Hohnloser SH, Fudim M, Alexander JH, et al. Efficacy and safety of apixaban versus warfarin in patients with atrial fibrillation and extremes in body weight: insights from the ARISTOTLE trial. *Circulation*. 2019;139(20):2292-2300.
19. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369(9):799-808.
20. Data on File APIX047 [Fragile subanalysis outcomes in AMPLIFY]. Princeton NJ: Bristol-Myers Squibb Company; 2011.
21. Reed D, Palkimas S, Hockman R, Abraham S, Le T, Maitland H. Safety and effectiveness of apixaban compared to warfarin in dialysis patients. *Res Pract Thromb Haemost*. 2018;2(2):291-298.
22. Stanton BK, Barasch NS, Tellor KB. Comparison of the safety and effectiveness of apixaban versus warfarin in patients with severe renal impairment. *Pharmacotherapy*. 2017;37(4):412-419.
23. Siontis K, Zhang X, Eckard A, et al. Outcomes associated with apixaban use in patients with end-stage kidney disease and atrial fibrillation in the United States. *Circulation*. 2018;138(15):1519-1529. doi:10.1161/CIRCULATIONAHA.118.035418
24. Mavrakanas T, Garlo K, Charytan D. Apixaban versus no anticoagulation in patients undergoing long-term dialysis with incident atrial fibrillation. *Clin J Am Soc Nephrol*. 2020;15(8):1146-1154.
25. Barra ME, Fanikos J, Connors JM, Sylvester KW, Piazza G, Goldhaber SZ. Evaluation of dose reduced direct oral anticoagulant therapy. *Am J Med*. 2016;129(11):1198-1204. doi:10.1016/j.amjmed.2016.05.041
26. Bhagirath VC, Chan N, Hirsh J, Ginsberg J, de Vries TAC, Eikelboom J. Plasma apixaban levels in patients treated off label with the lower dose. *J Am Coll Cardiol*. 2020;76(24):2906-2907.
27. Cirinzione B, Kowalski K, Nielsen J, et al. Population pharmacokinetics of apixaban in subjects with nonvalvular atrial fibrillation. *CPT Pharmacometrics Syst Pharmacol*. 2018;7(11):728-738. doi:10.1002/psp4.12347
28. Nielsen P, Skjioth F, Sogaard M, Kjaeldgaard J, Lip G, Larsen T. Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ*. 2017;356:j510. doi:10.1136/bmj.j510
29. Conway SE, Hwang AY, Ponte CD, Gums JG. Laboratory and clinical monitoring of direct acting oral anticoagulants: what clinicians need to know. *Pharmacotherapy*. 2017;37(2):236-248.
30. Testa S, Legnani C, Antonucci E, et al. Drug levels and bleeding complications in atrial fibrillation patients treated with direct oral anticoagulants. *J Thromb Haemost*. 2019;17(7):1064-1072. doi:10.1111/jth.14457
31. Jakowenko N, Nguyen S, Ruegger M, Dinh A, Salazar E, Donahue KR. Apixaban and rivaroxaban anti-Xa level utilization and associated bleeding events within an academic health system. *Thromb Res*. 2020;196:276-282. doi:10.1016/j.thromres.2020.09.002
32. Liu Z, Zhang H, Xie Q, et al. Different coagulation indicators in predicting clinical outcomes for patients with direct oral anticoagulants: a systematic review and meta-analysis. *Clin Ther*. 2020;42(10):2066-2081.e9. doi:10.1016/j.clinthera.2020.08.001