International Journal of
Clinical Cardiology & Research

Research Article

Bleeding Risk with Apixaban when Using Cardiac P-Glycoprotein Inhibitors

Daniel Howell[1]*, Lynn Zaremski[2], John Fisher[2], Kevin Ferrick[2], Luigi DiBiase[2] and Andrew Krumerman[2]

[1]Icahn School of Medicine, Department of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, USA
[2]Montefi ore Medical Center, Bronx, New York

***Address for Correspondence:** Daniel Howell MBBS MSc, Icahn School of Medicine, Department of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, USA, ORCID ID: orcid.org/0000-0002-7083-0136; E-mail: Daniel.howell@mountsinai.org

Submitted: 04 October 2018; **Approved:** 23 October 2018; **Published:** 25 October 2018

Cite this article: Howell D, Zaremski L, Fisher J, Ferrick K, DiBiase L, et al. Bleeding Risk with Apixaban when Using Cardiac P-Glycoprotein Inhibitors. Int J Clin Cardiol Res. 2018;2(3): 061-065.

ISSN: 2639-3786

ABSTRACT

Background: Apixaban is increasingly being used for anticoagulation. The primary risk of treatment with Apixaban is bleeding. Overall patients treated with Apixaban have fewer bleeding events than those treated with warfarin. Apixaban is a substrate of P-glycoprotein (P-gp) and P-gp inhibition increases drug exposure.

Strong P-gp inhibitors are commonly used in combination with Apixaban.

Methods: We retrospectively studied patients who had been prescribed Apixaban using a hospital informatics database. We compared patients prescribed Apixaban without any cardiac P-gp inhibitors (Amiodarone, Carvedilol and Verapamil) to those who had received one of them. Our primary outcome was any bleeding event which included blood transfusion, gastrointestinal bleeding and intracranial haemorrhage. Patients were followed for one year. Cox regression analysis was used to model the impact of P-gp inhibitor use on any bleeding event controlling for potential confounders.

Results: 1350 patients received a prescription for Apixaban. 291 of these patients were treated with a cardiac P-gp inhibitor. There were no significant differences in bleeding rates between the groups. There were 103 (9.73%) bleeds in patients not receiving a P-gp inhibitor compared to 32 bleeds (11.00%) in patients receiving a P-gp inhibitor (p = 0.522). P-gp inhibitor use was not a significant predictor for any bleeding event.

Conclusions: There was no evidence of increased bleeding when Apixaban was co-administered with commonly utilized rate and rhythm control agents that inhibit P-gp. These findings are consistent with the limited data available to date. Our findings add to evidence that Amiodarone, Carvedilol and Verapamil can be safely co-administered with Apixaban

Keywords: Atrial fibrillation; Thrombosis; P-glycoprotein; Apixaban; Bleeding

INTRODUCTION

The direct oral anticoagulants including apixaban were introduced to the market in the past decade, marking a significant step forward in drug discovery. For more than 60 years, vitamin K antagonists were the only oral anticoagulation option. Apixaban is increasingly used to prevent strokes and systemic embolism in atrial fibrillation and for the prevention and treatment of venous thromboembolism [1-3].

Apixaban is a potent, highly selective reversible Factor Xa inhibitor with antithrombotic activity [4]. It has a high affinity for Factor Xa and low affinity for thrombin which made it an attractive compound for development [5]. Apixaban is used in stroke and systemic embolism prevention in patients with atrial fibrillation and for the treatment and prevention of venous thromboembolism. Compared to warfarin, it has favorable outcomes in terms of both efficacy and safety [6,7].

The P-glycoprotein (P-gp) transporter is an important potential site of significant drug-drug interactions for all the Direct Oral Anti-Coagulants (DOACs) [8-10]. P-gp is a transporter present in multiple tissue sites including the gut, kidney, blood-brain barrier and liver [9]. P-gp transporters in the intestinal lumen and the renal tubules are believed to be the sites of pre-dominant importance for potential apixaban interaction [8]. P-gp inhibition will lead to increased apixaban exposure, potentially increasing the anticoagulation effect. Several commonly prescribed antiarrhythmic agents including amiodarone, verapamil and carvedilol are all strong P-gp inhibitors. Amiodarone and verapamil also inhibit Cytochrome P450 (CYP450) enzymes [11]. CYP450 enzyme modulation is of minimal importance for apixaban as there is little potential for clinically significant interaction [12]. The Apixaban metabolite M2 is formed via CYP3A4 and co-administration of CYP-450 inhibitors reduces metabolite formation. However, there are multiple metabolic pathways that exist and thus there is a low likelihood of clinically significant drug-drug interaction. Despite this, co-administration of apixaban with other dual CYP 450/P-gp inhibitors, such as Ketoconazole or Diltiazem can lead to increased apixaban exposure in healthy subjects [13].

Data from ARISTOTLE did not demonstrate increased bleeding rates in patients who were treated with both apixaban and amiodarone as compared to those treated with apixaban alone [14]. The FDA Clinical Pharmacology and Biopharmaceutics review recommends dose reduction when there is evidence of a greater than 50% increase in apixaban exposure [15].

STUDY OBJECTIVE

Experience with P-gp and CYP450 inhibitors is modest and so we aimed to evaluate commonly used medications in the treatment of atrial fibrillation that modulate these pathways. It is not possible to isolate the effect of P-gp from CYP450 modulation when a drug (such as verapamil or amiodarone) inhibits. However, P-gp inhibition has a much greater impact on apixaban pharmacokinetics by increasing exposure as described above.

We hypothesized that there is an increased risk of bleeding with apixaban therapy when one of the P-gp inhibitors amiodarone or verapamil or carvedilol are co-administered.

METHODS

Data source

In this retrospective study, data was obtained from a hospital network located in the Bronx, New York. Montefiore is the University Hospital for the Albert Einstein College of Medicine (AECOM). A diverse range of patients are treated in this hospital system. Diagnoses are coded using ICD-9 (international classification of diseases, 9th revision) until September 2015 after which point ICD-10 diagnostic codes are used. Clinical Looking Glass™ software was utilized to obtain data from the electronic medical record system.

Subjects

Ethics approval was obtained from the Institutional Review Board (IRB) at AECOM. Inclusion criteria included all patients prescribed apixaban between 2013 and 2015. This group was then divided into those treated with apixaban alone and those treated with apixaban co-administered with carvedilol or verapamil or amiodarone. Patients included were aged 18 years or older at the time of their apixaban prescription. The index date for the study was the first date they were prescribed apixaban. We then searched for all patients who were prescribed amiodarone or carvedilol or verapamil within 365 days

of their first apixaban prescription. There was, therefore, a group of patients prescribed apixaban only to compare with a separate group of patients prescribed apixaban in addition to any one of the included P-gp inhibitors.

Outcomes

The primary outcome was any bleeding event defined as the need for a blood transfusion, gastrointestinal bleeding, or intracranial haemorrhage. Due to possible overlap between gastrointestinal bleeding and blood transfusion any blood transfusion that occurred within 72 hours of a gastrointestinal bleeding diagnosis was considered as a single bleeding event. The ICD-9 and ICD-10 codes used to define both gastrointestinal bleeding and intracranial haemorrhage are included in the supplementary materials.

Variables

Data was collected on variables that had a potential impact on bleeding. Demographic data on patients were collected including age, sex and ethnicity. Other variables included weight, height, and diastolic Blood Pressure (BP) and medications that increase bleeding risk such as aspirin, clopidogrel, prasugrel and ticagrelor. Comorbidities were recorded using the Charlson comorbidity index [16]. ICD-9 and ICD-10 codes that make up the Charlson index were collected including congestive heart failure, peripheral vascular disease, myocardial infarction, cerebrovascular disease, peptic ulcer disease, renal disease and diabetes mellitus (with or without complication). For purposes of analysis myocardial infarction, peripheral vascular disease and cerebrovascular disease were combined to a new variable of any Cardiovascular (CV) disease. Additional variables included hypertension and atrial fibrillation.

Statistical analysis

Baseline characteristics were presented and compared between groups using appropriate statistical tests (Chi-squared/ Fishers/ unpaired t-tests and Mann-Whitney tests). Comparisons in bleeding events between the unexposed and exposed groups (i.e. no P-gp inhibitor versus any P-gp inhibitor) were made using chi-squared testing. Cox proportional hazards modelling was used to explore the relationship between use of any P-gp inhibitor and any bleeding events while adjusting for significant co-variables. A process of backward elimination was utilized, retaining only those variables with a p-value of less than 0.05 in the final model. To ensure adequate power of the model, ten outcome events (i.e. bleeding events) per variable included were required. Otherwise univariate analysis was undertaken prior to multivariate analysis to eliminate non-significant variables.

RESULTS

Baseline characteristics

A total of 1350 patients received apixaban between 2013 and 2015 with 291 (21.56%) of these patients receiving a prescription for one of the cardiovascular P-gp inhibitors. Baseline characteristics between groups are shown in table 1. Patients treated with both apixaban and P-gp inhibitor agents tended to be older and have significant co-morbidities as compared to those treated with apixaban alone. These included cardiac and renal disease.

Bleeding risk

The primary outcome, any bleeding event, occurred at a rate of 10.29 per 100 patient-years with apixaban only compared to 11.48 per 100 patient-years with apixaban and P-gp inhibitor. These differences were not statistically significant (p = 0.529, Chi-squared). Likewise, there were no significant differences between groups in any bleeding sub-type as shown in table 2. Values were missing for BMI in 123 patients and 142 patients for diastolic blood pressure. A univariate analysis of each variable was undertaken prior to multivariate analysis as described in the methods.

A univariate analysis of each predictor variable was undertaken prior to multivariate analysis as described in the methods. Table 3 shows the hazard ratios with p-values for each of the predictor variables derived from Cox proportional hazards modelling for the primary outcome (any bleeding event). Variables with a p-value of less than 0.2 on univariate analysis were included in the initial multivariate model. These included ethnicity, renal disease, aspirin use, other anti-platelet use, hypertension, Charlson index, any cardiovascular disease and heart failure. After backward elimination, heart failure was the only significant predictor of any bleeding event when treated with apixaban as shown in table 4. However, given the violation of the proportional hazards model for this Cox regression model we do not conclude heart failure to be a significant predictor of any bleeding event. P-gp inhibitor use did not significantly impact the hazard of any bleeding event (HR 0.89 (0.59-1.34) p = 0.585) with apixaban.

DISCUSSION

Interpretation of results

This study provides real world data suggesting that co-administration of amiodarone, or carvedilol or verapamil with apixaban does not significantly increase bleeding. Several studies have demonstrated safety with co-administration of apixaban and amiodarone therapies. Our study also evaluated bleeding risk when co-administration of other commonly used cardiac P-gp inhibitor medications were co-administered with apixaban.

Table 1: Baseline characteristics of apixaban group by P-gp inhibitor use.

		Apixaban/ No Pgp inhibitor (%)	Apixaban/Any Pgp inhibitor (%)	p-value
Total patients		1059 (78.44)	291 (21.56)	
Age (years)		70.61 (SD = 14.13)	72.99 (SD = 12.50)	0.009
Gender	Male	472 (44.57)	154 (52.92)	0.011
Ethnicity	White	333 (31.44)	95 (32.65)	0.587
	African-American	318 (30.03)	76 (26.12)	
	Hispanic	104 (9.82)	33 (11.34)	
	Other or unknown	304 (28.71)	87 (29.90)	
P-gp inhibitor	Amiodarone	-	147	
	Carvedilol	-	148	
	Verapamil	-	22	
Co-morbidities	Atrial Fibrillation	709 (66.95)	231 (79.38)	< 0.001
	Myocardial infarction	108 (10.20)	62 (21.31)	< 0.001
	Stroke	233 (22.0)	60 (20.62)	0.612
	Any cardiovascular disease[1]	400 (37.77)	135 (46.39)	0.008
	Heart Failure	339 (32.01)	177 (60.82)	< 0.001

Table 2: Bleeding with apixaban by P-gp inhibitor use.

	Apixaban only		Apixaban and *P*-gp inhibitor		*p*-value
	N (%)	Event rate (per 100 patient-years)	N (%)	Event rate (per 100 patient-years)	
Blood Transfusion	54 (5.10)	5.29	19 (6.53)	6.74	0.339
Gastrointestinal bleeding	60 (5.67)	5.90	17 (5.84)	5.91	0.909
Intracranial Haemorrhage	6 (0.60)	0.57	5 (1.82)	1.72	0.066
Any bleeds[2]	103 (9.73)	10.29	32 (11.00)	11.48	0.523

Table 3: Univariate Cox proportional hazards modelling for each variable for any bleeding event with apixaban.

Variable	HR (95% confidence interval)	*p*-value
Any p-gp inhibitor	1.07 (0.72-1.59)	0.736
Age	0.99 (0.98-1.01	0.374
Gender	0.92 (0.65-1.29)	0.619
Ethnicity (African-American/ Hispanic/other)	1.99 (1.28-3.11)/1.36 (0.71-2.61)/1.40(0.87-2.26)	0.022
Renal disease	1.68 (1.19 - 2.37)	0.003
Aspirin use	1.87 (1.33 - 2.64)	< 0.001
Other anti-platelet use	1.71 (0.99 - 2.98)	0.056
Atrial fibrillation	1.16 (0.79 - 1.69)	0.451
Hypertension	1.44 (0.96 - 2.14)	0.077
Charlson index (5-10/10 +)	2.08 (1.44 - 3.00)/ 2.07 (1.16-3.70)	0.003
Any CV disease	1.44 (1.02-2.01)	0.036
CHF	1.81 (1.29-2.54)	0.001
BMI	0.99 (0.97-1.01)	0.434
Diastolic BP value	0.99 (0.98-1.01)	0.359

Table 4: Hazard ratios for any bleeding event with apixaban.

Variable	Hazard ratio (95% confidence intervals)	*p*-values
Any P-gp occurred	0.89 (0.59-1.34)	0.585
Heart failure [1]	1.86 (1.31-2.63)	< 0.001

Population characteristics: In our study there were significant differences in the prevalence of atrial fibrillation between groups when stratified by P-gp inhibitor use. This is likely explained by the dual indication of apixaban (stroke prevention in AF and treatment/ prevention VTE). The ARISTOTLE population was similar in age to this study population but had fewer males. The rates of heart failure in this population were much higher than those in the GARFIELD-AF and PREFER-AF registries where rates were around 20% compared to rates as high as 61% in our study [1,2]. The increased rate of heart failure in our study is most likely due to the fact that patients with congestive heart failure are more likely to be treated with carvedilol and amiodarone therapy. The percentage of patients using amiodarone with apixaban was 10.89% which is similar to the percentage use in the ARISTOTLE population. However, rates of amiodarone use in the PREFER-AF are much higher, as high as 40% in France. As amiodarone is one of the only rhythm control medications that is safe for use in atrial fibrillation with heart failure there may be higher rates with real-world use as seen in the PREFER-AF population.

Bleeding events: For the primary outcome, any bleeding event, there were no significant differences by P-gp inhibitor use with apixaban. With apixaban, any bleeding occurred at a rate 18.1% per year in ARISTOTLE and major bleeding occurred in 2.33 per 100 patient years in US Medicare data compared to an event rate of 10.29 per 100 patient-years in this study with apixaban only [17]. The finding that P-gp inhibitor use did not affect bleeding events with apixaban is consistent with an analysis of bleeding rates by amiodarone use from the ARISTOTLE trial [14]. While the study was aimed at comparing efficacy and safety outcomes between amiodarone users with apixaban versus warfarin, data is presented on bleeding rates for those treated with apixaban only and those with apixaban and amiodarone. There is no statistical comparison of this data. The major bleeding incidence was similar: with apixaban and amiodarone major bleeding occurred with a rate of 1.86% per year compared to 2.18% per year when apixaban was given without amiodarone. There were also similar rates of clinically relevant non-major bleeds and intracranial hemorrhage.

To our knowledge, the effect of carvedilol and verapamil use on bleeding events with apixaban has not previously been studied. It is known from pre-clinical work that apixaban is a substrate of P-gp. P-gp inhibitors increase apixaban exposure however this is unlikely clinically relevant and CYP450 inhibition likely has little clinical impact given the multiple metabolic pathways for apixaban metabolism. The lack of impact on the primary outcome with apixaban and P-gp inhibitor use is consistent with available clinical data.

Limitations

This was a retrospective study using a hospital database and as such these findings can be used to generate further hypotheses and study in this area. Limiting event follow-up to one year may have limited the number of bleeding events and diminished the differences between groups observed. This study did not by its retrospective nature confirm medication adherence nor did it consider the dose or formulation of apixaban or P-gp inhibitor. This study considered three P-gp inhibitors but did not evaluate other P-gp inhibitors that the patients included may have been taking. These factors may have led to unmeasured confounding biases. There is a limited ability to compare this data with other data given differing definitions of bleeding. Other commonly used definitions such as the International society on thrombosis and Haemostasis include a drop in haemoglobin of 2g/DL as part of their definition. This dynamic change in laboratory data could not be obtained from our Hospital database. The majority of patients in the P-gp inhibitor group were treated with either amiodarone or carvedilol. Data regarding Verapamil co-administration with apixaban is limited to 22 individuals. This may have diminished any increased risk of bleeding associated with verapamil.

Future directions

This retrospective study provides supporting evidence for the safe use of the strong cardiac P-gp inhibitors: amiodarone, or verapamil or carvedilol with apixaban. The low event rate of intracranial haemorrhage in randomized trials and this study means that larger studies with greater patient numbers are needed to understand if P-gp inhibitors (which may impact central nervous system drug

concentrations) impact its risk. While largely reassuring regarding clinically relevant bleeding, pharmacokinetic data had confirmed the interaction of P-gp inhibitors when used with apixaban. There is a paucity of evidence for real-world use of apixaban with P-gp inhibitors and pharmacovigilance for these interactions is required. Large international registries for the atrial fibrillation and venous thromboembolism, such as GARFIELD and PREFER-AF, exist and perhaps data will be available from these populations to further evaluate apixaban and P-gp inhibitor interactions. Prospective clinical trials with apixaban and P-gp inhibitors would also help with developing guidelines for apixaban use. These data sources would allow for higher levels of evidence to make more comprehensive and robust recommendations.

CONCLUSIONS

In this study we found no increased risk of any bleeding events when apixaban was co administered with the cardiac P-gp inhibitors: amiodarone or verapamil or carvedilol. We therefore reject the hypothesis that co-administration of apixaban and P-gp inhibitors increases the risk of bleeding. To our knowledge this is the first study to compare apixaban bleeding rates between those who are treated with cardiac P-gp inhibitors and those who are not. Further prospective study and registry data in the future should help with developing informed guidelines for management of patients needing these combinations of drugs to maximize benefit and minimize harm [18].

REFERENCES

1. Kirchhof P, Ammentorp B, Darius H, De Caterina R, Le Heuzey JY, Schilling RJ, et al. Management of atrial fibrillation in seven European countries after the publication of the 2010 ESC Guidelines on atrial fibrillation: primary results of the PREvention oF thromboemolic events--European Registry in Atrial Fibrillation (PREFER in AF). Europace. 2014; 16: 6-14. https://goo.gl/oJgQnq

2. Bassand JP, Accetta G, Camm AJ, Cools F, Fitzmaurice DA, Fox KA, et al. Two-year outcomes of patients with newly diagnosed atrial fibrillation: results from GARFIELD-AF. Eur Heart J. 2016; 37: 2882-2889. https://goo.gl/ecHmm6

3. Camm AJ, Accetta G, Ambrosio G, Atar D, Bassand JP, Berge E, et al. Evolving antithrombotic treatment patterns for patients with newly diagnosed atrial fibrillation. Heart. 2017; 103: 307-314. https://goo.gl/wSomfL

4. He K, Luettgen JM, Zhang D, He B, Grace JE Jr, Xin B, et al. Preclinical pharmacokinetics and pharmacodynamics of apixaban, a potent and selective factor Xa inhibitor. Eur J Drug Metab Pharmacokinet. 2011; 36: 129-139. https://goo.gl/VriLJU

5. Pinto DJ, Orwat MJ, Wang S, Fevig JM, Quan ML, Amparo E, et al. Discovery of 1-[3-(aminomethyl)phenyl]-N-3-fluoro-2'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl]-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide(DPC423), a highly potent, selective, and orally bioavailable inhibitor of blood coagulation factor Xa. J Med Chem. 2001; 44: 566-578. https://goo.gl/x5dX8w

6. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013; 369: 799-808. https://goo.gl/BuCpWo

7. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011; 365: 981-992. https://goo.gl/1qoj2m

8. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener HC, Hacke W, 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: 1467-1507. https://goo.gl/ujtC2x

9. Stöllberger C, Finsterer J, Relevance of P-glycoprotein in stroke prevention with dabigatran, rivaroxaban, and apixaban. Herz. 2015; 40: 140-145. https://goo.gl/BKnHYS

10. Voukalis C, Lip GY, Shantsila E, Drug-drug interactions of non-vitamin K oral anticoagulants. Expert Opin Drug Metab Toxicol. 2016; 12: 1445-1461. https://goo.gl/xPfGM5

11. Wessler JD1, Grip LT, Mendell J, Giugliano RP. The P-glycoprotein transport system and cardiovascular drugs. J Am Coll Cardiol. 2013; 61: 2495-2502. https://goo.gl/yekNcj

12. Wang L, Zhang D, Raghavan N, Yao M, Ma L, Frost CE, et al. In vitro assessment of metabolic drug-drug interaction potential of apixaban through cytochrome P450 phenotyping, inhibition, and induction studies. Drug Metab Dispos. 2010; 38: 448-458. https://goo.gl/13T8vA

13. Frost CE, Byon W, Song Y, Wang J, Schuster AE, Boyd RA, et al. Effect of ketoconazole and diltiazem on the pharmacokinetics of apixaban, an oral direct factor Xa inhibitor. Br J Clin Pharmacol. 2015; 79: 838-846. https://goo.gl/rbNik8

14. Flaker G, Lopes RD, Hylek E, Wojdyla DM, Thomas L, Al-Khatib SM, et al. Amiodarone, anticoagulation, and clinical events in patients with atrial fibrillation: insights from the ARISTOTLE trial. J Am Coll Cardiol. 2014; 64: 1541-1550. https://goo.gl/uT6ruC

15. Food and Drug Administration, Apixaban: Clinical Pharmacology and biopharmaceutics review(s). 2010.

16. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005; 43: 1130-1139. https://goo.gl/rp4Duy

17. Yao X, Abraham NS, Sangaralingham LR, Bellolio MF, McBane RD, Shah ND, et al. Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. J Am Heart Assoc. 2016; 5. https://goo.gl/vPBS2D

18. Weitz JI, Semchuk W, Turpie AG, Fisher WD, Kong C, Ciaccia A, et al. Trends in prescribing oral anticoagulants in canada, 2008-2014. Clin Ther. 2015; 37: 2506-2514. https://goo.gl/eN1phj