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RESEARCH LETTER

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Reasons for nonadherence to the direct oral anticoagulant apixaban for atrial fibrillation

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INTRODUCTION

Direct-acting oral anticoagulants (DOACs) have surpassed warfarin as the most commonly prescribed oral anticoagulants in the United States.[1] Yet, DOAC nonadherence occurs in 26–45% of patients.[2,3] This study aimed to understand the reasons patients with atrial fibrillation (AF) are nonadherent to the most often-prescribed DOAC, apixaban.[1]

METHODS

We identified University of California, Los Angeles (UCLA) and University of California, San Francisco (UCSF) adult patients with nonvalvular AF who were prescribed apixaban from August 2019 to July 2020, through large-scale Clinical and Translational Science Institute data pulls. Participants reported nonadherence to apixaban and no significant problems in the prior 12 months with memory or thinking.[4] One-time 30–45 min semi-structured telephone interviews occurred from August 2020 to January 2021. Patients were asked about their interactions with healthcare providers, beliefs about apixaban, and contexts surrounding reasons for missed or skipped doses. Interviews were analyzed in ATLAS.ti 9 using thematic analysis,[5–7] with theoretical saturation[8] reached after 15 interviews. The UCLA Institutional Review Board approved this study. UCSF relied on the UCLA IRB.

RESULTS

The 42 participants had mean age of 69.6 years (SD = 12.4; range 33–93). Sixteen (38%) were female, and 30 (71%) were non-Hispanic whites. Over half self-reported paroxysmal AF, and about one-fourth reported persistent AF. Thirty-five participants (83.3%) started but stopped, skipped, or decreased apixaban dosing; 16.7% never started apixaban. We identified six major themes related to nonadherence (Table 1).

Theme 1: Cost

Two-thirds mentioned cost as a potential concern, even if it did not personally affect their ability to obtain the prescription. For some, nonadherence was solely cost-related, with several noting nonadherence during their Medicare prescription drug coverage gap. Some participants remarked that physicians were not particularly helpful with cost concerns; a few said physician-provided discount coupons did not always work. Even if cost was not limiting, it contributed to participant decisions about apixaban use.

TABLE 1 Major themes and illustrative quotes related to nonadherence to apixaban

Major themes and subthemes	Example quotes
Theme 1: Cost: Cost can be a direct obstacle to nonadherence or may "tip the balance"	
	"Of course, I'm sure everyone's going to tell you that the cost of Eliquis is absurd." (P652)
	"I think I skipped two or three doses when the price went up to $150 bucks a month. I'm on social security." (P40)
	"If the insurance would have paid for it, I would have been taking it." (P187)
	"The reason I stopped for the last two or three months is because when I went to pick up the medication, I had to meet the stopgap. It caused my medication to go up three times as high so I didn't take them." (P296)
	"I thought, 'Well, it's expensive. I guess I'll just do it once a day, and maybe I'll get along with that.'" (P1510)
	"I don't really want to take it, it's really expensive and I'm not convinced that I needed it." (P1500)
Theme 2: Bleeding: Bleeding created a major obstacle to adherence	
Fear of bleeding	"Risk of hemorrhage, risk of bleeding especially if you fall and hit your head. I live alone. I really didn't want to have to be on it." (P380)
	"Then I read about the bleeding problems and that scares me more than anything." (P1019)
	"You know when you're a couple thousand feet or 3,000 feet, and then you got to get down, I don't know what the chances of internal bleeding is if I fall, but there is a good chance because I do hike every week." (P1020)
	"My sister had a hemorrhagic brain bleed ... a great-grandfather and a grandfather both actually died of aneurysms, so I'm pretty leery of taking [apixaban]." (P1286)
Experiences with bleeding	"These lesions that are on my arm are really worrisome. Like yesterday, I just had a minor fall, and now I have these, you know, big bruise type things...If I stop getting these bruises, then I'll go back to twice-a-day." (P590)
	"I just could not stop a small nick in my arm from bleeding. That prompted me to reduce the amounts [of apixaban] that I was taking and then eventually I just stopped taking it." (P850)
	"I started to get bloody noses more frequently. I started to have vaginal bleeding again. I just felt like my body doesn't really need that." (P1627)
Theme 3: Lack of symptoms: Need for apixaban questioned when participants lacked symptoms	
No symptoms of atrial fibrillation	"In the last couple of months...maybe I've had one instance where I might, think it might have been atrial fibrillation for 20 seconds but that's it. It's disappeared. There's no sense in me taking anything." (P593)
	"I'm not fibrillating, I can usually tell if I am." (P479)
	"[I think apixaban is] pretty important, but I also am not quite as great about taking it as I would be if I knew that I was constantly in Afib [*sic*]. I think just knowing that I had paroxysmal Afib—I think it's slightly less important for me to take it than if I were full-time in Afib." (P264)
Feels healthy	"I really, really, really felt in my heart that I didn't need a blood thinner. I just felt that because, again, I was straight from the hospital. I had a clean bill of health. My heart was in rhythm. They said I had no blood clots." (P1601)
Uncertainty about medication effects	"I don't even notice that I'm taking it. There's no blood pressure fluctuation or heart palpitations or anything like that. I never even really notice any difference in my physical receptiveness to Eliquis." (P514)
Atrial fibrillation caused by mutable factors	"What I really was trying to do then was more trying to figure out if my AFib was not being caused by ingesting certain chemicals in processed foods, for example, that may cause a AFib condition. Sometimes when I eat certain things that have heavy amounts of preservatives and stuff, my heart races and stuff. Like sulfites. I remember when MSG was around, it affected me negatively. That was the reasoning." (P969)
Theme 4: Safe to skip doses: Participants believed it was safe to skip doses	
Medication stays in your body for a while	"... most medicines, as I was told once, circulate through your blood and if you miss a dose, you still had it circulating so it's not that critical to miss a dose of most medication. No one ever talked to me about missing it specifically in Eliquis, but my concept is most medications are circulating and you miss a dose, it's still in your blood." (P40)
	"The residual effects [of Eliquis] would carry me through a few days when I'm not taking it." (P118)

TABLE 1 (Continued)

Major themes and subthemes	Example quotes
Physician recommends stopping briefly	"I figure if you have a surgery or something, you have to be off medication sometimes." (P332)
	"My cardiologist told me, he said, 'Well, if you have to stop it for a day or two, it's no big deal.' With that in mind, I said, well, why not?" (P1373)
Theme 5: Confusion about measurable effects: Confusion about and desire for measurable effects	
	"I'm not saying it didn't do anything, but I'm saying I still had [atrial fibrillation] episodes here and there." (P187)
	"We have to have measurable and replicable [lab] results [to take apixaban as prescribed]." (P978)
Theme 6: Incomplete, discordant physician-patient communication: resulted in nonadherence	
	"I don't normally tell him I missed a dose. If he asked, I would tell him." (P332)
	"[I had a physician tell me that I] didn't need to be on [apixaban] anymore. Now this new, this other doctor just said, 'Yes, you do [have to take it] and you'll need to be on it the rest of your life. Once you have Afib, you have to be on it.'" (P1500)
Minor theme: Alternative or natural treatments were sometimes used in place of apixaban	
	"I started taking omega-3 early before people did it. I'm still doing it. I understand that that has to be a bit of a blood-thinning effect." (P1319)
	"I had told [my doctor], at that time, when I saw her the first time, that I was taking turmeric and it pretty much works as a blood thinner. It's more natural, and I was really hesitant about taking more medication." (P1019)

Theme 2: Bleeding

Participants worried about both major life-threatening and minor bleeding. Some feared major bleeding because they engaged in motorcycle riding, hiking, or construction work. Family member experiences with major bleeding scared others. Troublesome minor bleeding included prolonged bleeding, bruising, bloody noses, and vaginal bleeding.

Theme 3: Lack of symptoms

Participants questioned the need for apixaban if AF was paroxysmal of if they perceived that they lacked AF symptoms. Several felt their stroke risk was small, given infrequent AF episodes.

Theme 4: Safe to skip doses

Some participants reduced their dosing from twice to once daily, believing that apixaban was still effective. Others interpreted physician recommendations to stop apixaban for a few days before surgery or for excess bleeding as tacit approval for occasional nonadherence.

Theme 5: Confusion about measurable effects

Some believed apixaban was used to reduce AF symptoms or episodes, and were confused because they had continued episodes of AF. Several felt few effects when taking apixaban and desired measurable laboratory results.

Theme 6: Incomplete, discordant communication

Several participants remarked they had not informed their physicians about their nonadherence, and were not asked during encounters. Several commented that had their physician given explicit instructions about taking apixaban regularly, they would have done so. A few expressed uncertainty about taking apixaban because they received differing physician opinions on chronic administration.

DISCUSSION

AF patients with nonadherence to apixaban expressed multiple reasons for nonadherence. Patients often

mentioned cost either as a primary reason for nonadherence or as tipping the balance for those with other reasons for nonadherence. Importantly, physicians often did not discuss or help patients resolve cost difficulties. Physicians typically consider the risks of major bleeding, but our data suggest that patients have significant concerns about bothersome minor bleeding such as bruising or nosebleeds. Fear of bleeding was also a major factor in nonadherence. This concern likely extends to all anticoagulants and bleeding discussions should accompany all anticoagulant prescriptions.

Consistent with studies demonstrating patient desire for DOAC monitoring,[9,10] some patients in this study wanted information on whether apixaban was working for them. DOAC concentration measurements with anti-Factor Xa activity assays are available, but monitoring is not routine. For certain patients, monitoring might increase adherence.

Study limitations include little racial diversity, patient self-selection for participation, and self-report regarding nonadherence. All participants received care in academic health centers, and health literacy and education were not assessed.

In conclusion, this study describes patient-reported reasons underlying nonadherence to the DOAC apixaban that include cost, concerns about bleeding, uncertainty about the need for anticoagulation, and beliefs that skipping doses is inconsequential. Patients did not always tell their physicians about their nonadherence. This work identifies targets for interventions to increase adherence.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Study concept and design: Drs Tarn and Schwartz; acquisition of data: Drs Tarn and Shih; analysis and interpretation of data: all authors; manuscript preparation and revisions: all authors.

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The contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. The study investigators are the sponsors for the study. The BMS/Pfizer Alliance ARISTA-USA external multidisciplinary review committee reviewed the design and methods of the study. They were not involved in subject recruitment, data collection, or analysis of the data.

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