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APIXABAN: A NEW ORAL DIRECT XA INHIBITOR

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For more than half a century warfarin has been the predominant oral anticoagulant for prevention of venous thromboembolic events (VTE) in patients with atrial fibrillation (AF). Although warfarin effectively lowers the risk of stroke by 66% in patients with AF,[1] it possesses limitations including drug interactions, dietary restrictions, regular and lifelong therapeutic monitoring, and an inherent risk of bleeding.[2,3] During the last decade, new oral anticoagulants that are potentially more effective, more convenient, and safer have been developed. To date, two new anticoagulants have entered the U.S. market. In October 2010, the FDA approved dabigatran (Pradaxa®), a direct thrombin inhibitor (DTI), for nonvalvular AF. Rivaroxaban (Xarelto®), a factor Xa (FXa) inhibitor, was approved for deep venous thrombosis (DVT) prophylaxis after orthopedic surgery in July, 2011.

Apixaban is an FXa inhibitor developed by Pfizer and Bristol-Myers for the prevention of VTE in nonvalvular AF. However, under the brand name Eliquis®, it has been used in Europe since June, 2011 for VTE prevention in adult patients after hip or knee replacement surgery.[4]

This article will review apixaban's pharmacology and pharmacokinetics, summarize apixaban's efficacy and safety data, and describe apixaban's dosing and monitoring.

Pharmacology

Apixaban is a selective, reversible, oral, direct FXa inhibitor that blocks the central protease, FXa, common to both the intrinsic and extrinsic pathways in the coagulation cascade. Apixaban inactivates both free FXa and bound FXa within a clot and the prothrombinase complex that is responsible for the conversion of prothrombin to thrombin.[5-7] Apixaban stops thrombin generation, not thrombin activity. Apixaban does not affect existing levels of thrombin and may not completely suppress the production of thrombin as it binds to FXa reversibly, permitting small amounts of thrombin for physiological regulation of thrombin hemostasis. This is thought to be the reason why apixaban has a lower risk of bleeding when compared with direct thrombin inhibitors.[8-11]

Inhibiting the same enzyme, direct FXa inhibitors (i.e. apixaban and rivaroxaban) differ from the indirect FXa inhibitors (i.e. fondaparinux and idraparinux). While direct inhibitors directly bind to the catalytic site of FXa, indirect inhibitors bind to antithrombin III (ATIII) and potentiate its ATIII-mediated anti-FXa activity. Indirect Fxa inhibitors are not able to inhibit FXa bound within the prothrombinase complex. In ad-

Inside This Issue:

dition, indirect inhibitors require subcutaneous administration.[12-15]

Pharmacokinetics

Apixaban is orally active and rapidly absorbed in the stomach and small intestine with a bioavailability of approximately 66% (**Table 1**). After oral administration, the peak plasma concentration is reached within 1-3 hours and steady state concentration is achieved by day three.[16-19] Apixaban's mean elimination half-life is 8-15 hours in healthy young subjects and is administered twice daily.[19-20]

Apixaban is oxidized to several inactive metabolites, mostly via CYP3A4 dependent mechanisms. However, less than 32% of the parent drug is metabolized and apixaban does not induce or inhibit CYP3A4.[19-21] Apixaban and its metabolites are eliminated by multiple pathways, including 27% via renal excretion, <3% via the biliary route, and largely (56%) via the fecal route. These multiple elimination pathways, together with a low rate of metabolism, suggest that potential for an interaction between apixaban and co-administered drugs may be relatively low (**Table 2**).[19-20]

Co-administration with ketoconazole (400 mg once daily), a strong inhibitor of both CYP3A4 and P-glycoprotein (P-gp, cell membrane-associated efflux transporter) increases the mean apixaban AUC and C_{max} by 2-fold and 1.6-fold, respectively.[4,22] Co-administration of apixaban with rifampin, a strong inducer of both CYP3A4 and P-gp, led to an approximate 54% decrease in mean apixaban AUC and 42% decrease in mean apixaban C_{max}.[4,23] Concomitant use of strong CYP34A and P-gp inhibitors such as azole-antimycotics (e.g. ketoconazole, itraconazole, voriconazole and posaconazole) and HIV proteases inhibitors (e.g. ritonavir) are not recommended and inducers such as phenytoin, carbamazepine, phenobarbital, or St. John's Wort should be used with caution. Co-administration with a moderate CYP3A4 and/or weak P-gp inhibitor such as diltiazem or naproxen (P-gp inhibitor) did not significantly affect the pharmacokinetics of apixaban. No dose adjustment for apixaban is required with less potent inhibitors of CYP3A4 and/or P-gp.[4, 24,25]

Table 1 | Pharmacokinetic properties of apixaban [18,20]

Property	Data
Oral bioavailability	66%
Time to Peak	1-3 hours
Half-life (h)	~12 hours
Protein Binding	87%
Metabolism	CYP3A4 (<32% of parent drug)
Excretion	27% renal, 56% fecal, ~3% biliary

Clinical Trials

Two major trials (AVERROES and ARISTOTLE) were conducted to evaluate the safety and efficacy of apixaban for the prevention of stroke and systemic thromboembolic events in AF patients (**Table 3**).[26, 27] Other completed or ongoing studies to evaluate the

Table 2 | Drug interactions with apixaban [4,22-25]

Interacting Drug	Interaction Mechanism	Effect of interaction on Apixaban	Recommendation
Ketoconazole 400mg	Strong CYP3A4 and P-gp inhibitor	↑ AUC 100%, ↑ C_{max} 60%	Avoid combination
Diltiazem 360mg	Moderate CYP3A4 and weak P-gp inhibitor	↑ AUC 40%, ↑ C_{max} 30%	No adjustment
Rifampin 600mg	Strong CYP3A4 and P-gp inducer	↓ AUC 54%, ↓ C_{max} 42%	No adjustment; caution
Naproxen 500mg	P-gp inhibitor	↑ AUC 50%, ↑ C_{max} 60%	No adjustment; caution
Digoxin 0.25mg	P-gp substrate	no clinically significant changes for either drug	No adjustment
Famotidine 40mg	Weak CYP1A2 inhibitor	no clinically significant changes for either drug	No adjustment
Atenolol 100mg	Renal excretion	↓ AUC 15%, ↓ C_{max} 18%	No adjustment
Clopidogrel 75mg	Potentiation of bleeding	No significant changes	No adjustment; caution

AUC: area under the curve; C_{max}: maximum serum concentration; P-gp: p-glycoprotein

safety and efficacy of apixaban for VTE prophylaxis and for the treatment and prevention of Acute Coronary Syndrome are included **in Tables 4, 5,** and **6**.[28-35]

AVERROES: phase III

AVERROES (Apixaban versus Acetylsalicylic Acid to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; phase III) was a double-blind, double-dummy, superiority trial that tested the efficacy and safety of apixaban against aspirin (ASA) for the prevention of stroke or systemic embolism in patients with AF.[26] Eligible patients had at least one risk factor for stroke and had either failed or were unsuitable for vitamin K antagonist therapy. A total of 5,599 patients from 522 centers in 36 countries were recruited and randomized to apixaban 5 mg twice daily (2.5 mg twice daily if patients had at least two of the following: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL) or ASA 81 to 324 mg once daily, with the dose selection at the discretion of local investigators. Initial ASA dose was maintained throughout the study unless a change was clinically indicated.

The trial was terminated early on February 19, 2010 after an interim analysis showed the benefit of apixaban for the primary outcome. Only outcomes through May 28, 2010 were included in the primary analyses resulting in the mean duration of follow up for the study of 1.1 years.

The primary efficacy outcome was the occurrence of stroke or systemic embolism. Stroke was diagnosed clinically on the basis of typical symptoms lasting at least 24 hours with or without confirmation by brain imaging. Apixaban was found to be superior to ASA for the primary efficacy outcome (1.6% per year (51/2808) vs. 3.7% per year (113/2791) respectively; HR: 0.45; 95% CI: 0.32-0.62; P<0.001). Ischemic stroke rates were 1.1% per year and 3.0% per year (HR: 0.37; 95% CI: 0.25-0.55; P<0.001) in the apixaban and ASA groups, respectively. Hemorrhagic strokes (intracerebral) occurred in 6 cases in the apixaban group and in 9 cases in the ASA group. Apixaban was also found to be superior to ASA for hospitalizations due to cardiovascular causes (12.6% per year vs. 15.9% per year, P<0.001) and the rate of death in the apixaban group was less than in the ASA group, but this difference was not statistically significant (3.5% per year vs. 4.4% per year; HR: 0.79; 95% CI: 0.62-1.02; P=0.07).[26]

Although not statistically significant, clinically overt major bleeding (> 2 g/dL decrease of hemoglobin level, transfusion of 2 or more units of packed red cells over a 24-hour period, bleeding at critical sites, or fatal bleeding) occurred more often in the apixaban group than in the ASA group (1.4% per year (44 events) vs. 1.2% per year (39 events), respectively;

Table 3 | Summary of apixaban clinical trials in patients with non-valvular atrial fibrillation [26, 27]

Study	Patients	Design	Outcomes	Interventions	Results
AVERROES 2011[26]	AF and failed or unsuitable for VKA	N = 5599 PG DB DD	1° efficacy: stroke or systemic embolism 1° safety: major bleeding events	A 5mg (or 2.5mg) BID vs. ASA 81-324 mg QD	1° efficacy: A: 1.6%/yr ASA: 3.7%/yr HR (95% CI): 0.45(0.32-0.62)[a] 1° safety: A: 1.4%/yr ASA: 1.2%/yr HR (95% CI): 0.74-1.75[b]
ARISTOTLE 2011[27]	AF	N = 18201 PG DB	1° efficacy: stroke or systemic embolism 2° efficacy: all cause death 1° safety: major bleeding events	A 5mg (or 2.5mg) BID vs. warfarin	1° efficacy: A: 1.27%/yr W: 1.60% /yr HR: 0.79; 95% CI: 0.66-0.95[c] 2° efficacy: A: 3.52% /yr W: 3.94%/yr HR: 0.89; 95% CI: 0.80-0.99[d] 1° safety: A: 2.13% /yr W: 3.09% /yr HR: 0.69; 95% CI: 0.60-0.80[e]

1° = primary ; 2° = secondary; A = apixaban; AF = atrial fibrillation; ASA = aspirin; BID = twice daily; CI = confidence interval; DB = double blind; DD = double dummy; f/u = follow up; HR = hazard ratio; INR = international normalized ratio; ITT = intention to treat; PG = parallel groups; QD = once daily; VKA = vitamin K antagonist; W = warfarin; yr = year; [a] P<0.001; [b] P=0.57; [c] P<0.001 for non-inferiority and p=0.01 for superiority; [d] P=0.047; [e] P<0.001

Table 4 | Apixaban for VTE prophylaxis in knee and hip replacement [28-30]

Study	Patients	Design	Outcomes	Interventions	Results
ADVANCE1 2008[28] US regimen	knee-replacement	N = 3195 PG DB DD	1° efficacy: DVT, nonfatal PE, and all-cause death 1° safety: bleeding events	[a]A 2.5mg BID for 10 to 14 days vs. E 30mg SC every 12 hours for 10-14 days	1° efficacy: A: 9% E: 8.8% RR: 1.02; 95% CI: 0.78-1.32; (P = 0.06) 1° safety: A: 2.9% E: 4.3% (P = 0.03)
ADVANCE2 2010[29] Europe regimen	unilateral or bilateral total knee replacement	N = 3057 PG DB	1° efficacy: DVT, nonfatal PE, and all-cause death 1° safety: bleeding events	[b]A 2.5mg BID for 12 days vs. E 40mg SC QD for 12 days	1° efficacy: A: 15% E: 24% RR: 0.62; 95% CI: 0.51-0.74; (P <0.0001) 1° safety: A: 4%; E: 5% (P = 0.09)
ADVANCE3 2010[30]	total hip replacement	N = 5407 PG DB	1°efficacy: DVT, nonfatal PE, and all-cause death 1° safety: bleeding events	[c]A 2.5mg BID for 35days vs. E 40mg QD for 35 days	1°efficacy: A: 1.4% E: 3.9% RR: 0.36; 95% CI: 0.22-0.54; (P <0.001) 1° safety: A: 4.8%; E: 5.0% (P = 0.34)

1° = primary ; 2° = secondary; A = apixaban; BID = twice daily; CI: confidence interval; DB = double blind; DD = double dummy; DVT = deep vein thrombosis; E = enoxaparin; f/u = follow up; PE = pulmonary embolism; PG = parallel groups; QD = once daily; RR = relative risk; [a] both medications started 12 to 24 hours after surgery and continued for 10 to 14 days; [b] apixaban started 12-24 hours after wound closure; enoxaparin started before 12 hours before surgery; [c] apixaban started 12-24 hours following surgery; enoxaparin started the evening before surgery

Table 5 | Apixaban for secondary prevention in Acute Coronary Syndrome (ACS) [31, 32]

Study	Patients	Design	Outcomes	Interventions	Results
[a]APPRAISE-1 [31]	ACS	N = 1715 PG DB DF	1° efficacy: CV death, MI, severe recurrent ischemia, or ischemic stroke 1° safety: major or clinically relevant nonmajor bleeding	Placebo A 2.5mg BID A 10mg QD [b]A10mg BID [b]A 20mg BID	1° efficacy: A 2.5mg BID: 7.6%; placebo: 8.7% HR: 0.73; 95% CI: 0.44-1.19 (P=0.21). A 10mg QD: 6.0%; placebo: 8.7% HR: 0.61; 95% CI: 0.35-1.04 (P=0.07). A 10mg BID: 2.8%; placebo: 8.7% HR: 0.71; 95% CI: 0.30-1.66. A 20mg BID: 3.2% ; placebo: 8.7%. HR: 0.72; 95% CI: 0.30-1.74 1° safety: A 2.5mg BID: 5.7%; placebo: 3.0% HR: 1.78; 95% CI: 0.91-3.48 (P=0.09). A 10mg QD: 7.9%; placebo: 3.0% HR: 2.45; 95% CI: 1.31-4.61 (P=0.005). A 10mg BID: 7.8%; A 20mg BID: 7.3%
[c]APPRAISE-2 [32]	ACS	N = 7392 PG DB	1° efficacy: CV death, MI or ischemic stroke 1° safety: major bleeding	A 5mg BID vs. placebo	1° efficacy: A: 7.5%; placebo: 7.9% HR: 0.95; 95% CI: 0.80-1.11 (P=0.51). 1° safety: A: 1.3%; placebo: 0.5% HR: 2.59; 95% CI: 1.50-4.46 (P=0.001)

1° = primary ; 2° = secondary; A = apixaban; BID = twice daily; CI = confidence interval; CV = cardiovascular; DB = double blind; DD = double dummy; DR = dose-finding study; DVT = deep vein thrombosis; f/u = follow up; HR = hazard ratio; MI = myocardial infarction; PE = pulmonary embolism; PG = parallel groups; QD = once daily; [a] Nearly all patients received aspirin(≤165mg/d) and 76% received clopidogrel.; [b]2 higher-dose apixaban arms were discontinued because of excess total bleeding by the recommendation of the Data Monitoring Committee; [c]Trial was terminated prematurely due to an increase in major bleeding events with apixaban in the absence of a counterbalancing reduction in recurrent ischemic events.

HR: 1.13; 95% CI: 0.74-1.75; P=0.57). Apixaban demonstrated more minor bleeding events than ASA (188 events vs. 153 events, respectively; HR: 1.24; 95% CI: 2.00 to 1.53; P=0.05). Among the major bleeding events, there were 11 cases of intracranial bleeding with apixaban vs. 13 with ASA. Overall, apixaban was associated with a significantly lower number of serious adverse events compared to ASA (22% vs. 27%, respectively, P<0.001).[26]

Results from the intention-to-treat analysis found that apixaban was superior to ASA for the composite rate of stroke, systemic embolism, MI, death from vascular causes, or major bleeding (5.3% per year vs. 7.2% per year; HR: 0.74; 95% CI: 0.60-0.90; p=0.003). The authors concluded that apixaban was superior to ASA in reducing the risk for stroke or systemic embolism with no significant increase in the risk of major or intracranial bleeding.[26]

ARISTOTLE: phase III

ARISTOTLE (The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) was a double-blind intention-to-treat study that randomized 18,201 patients with AF plus at least one additional risk factor for stroke from 1,034 centers in 39 countries.[27] Patients were randomized to apixaban 5 mg twice daily (2.5 mg twice daily if patients had at least two of the following: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL) or a dose adjusted warfarin to a target INR range of 2.0 to 3.0. Both warfarin naïve (57% of total patients) and warfarin-experienced patients were included. If the subjects were on warfarin before randomization, they were instructed to discontinue warfarin 72 hours before randomization and to not take the study drug until the INR was < 2.0.[27]

The primary objective of ARISTOTLE was to determine whether apixaban was non-inferior to dose-adjusted warfarin for the primary efficacy outcome of stroke or systemic embolism. The secondary objective was to determine if apixaban was superior to INR-adjusted warfarin for all-cause mortality. The primary safety outcome was major bleeding. During a median follow-up of 1.8 years, fewer patients in the apixaban group discontinued the drug (25.3%, with 3.6% due to death in the apixaban group vs. 27.5% with 3.8% due to death in the warfarin group; P=0.001). The time in the therapeutic range (TTR) in the warfarin group was a mean of 62.2% with a median of 66.0% over the entire study period.[27]

For the primary efficacy outcome apixaban was non-inferior to warfarin. Ischemic stroke, hemorrhagic stroke, or systemic embolism occurred in 212 patients assigned to apixaban compared to 265 patients assigned to warfarin (1.27% per year vs. 1.60% per year, respectively; HR: 0.79; 95% CI: 0.66-0.95; P<0.001 for non-inferiority and P=0.01 for superiority). The rate of ischemic or uncertain stroke was 8% lower in the apixaban group (0.97% per year vs. 1.05% per year; HR: 0.92; 95% CI: 0.74-1.13; P=0.42). The rate of hemorrhagic stroke was 49% lower in the apixaban group (0.24% per year vs. 0.47% per year; HR: 0.51; 95% CI: 0.35-0.75; P<0.001). Importantly, the rate of death from any cause was significantly lower in the apixaban group compared to the warfarin group (603 patients vs. 669 patients; 3.52% per year vs. 3.94% per year, respectively; HR: 0.89; 95% CI: 0.80-0.99; P=0.047). This was the first statistically significant mortality out-

Table 6 | Summary of ongoing apixaban trials [33-35]

Study	Indications/ patients	Design	Outcomes	Interventions
ADOPT [33]	DVT prevention/ acutely ill medical patients	N = 6524 PG DB	1° efficacy : VTE and VTE-related death 1° safety: all cause death, major bleeding, and clinically relevant non-major bleeding	A 2.5mg BID for 30 days vs. enoxaprin 40mg QD 6-14 days
AMPLYFY-Ext [34]	DVT prevention/ patients who have completed their intended treatment for DVT or PE	N = 2430 PG DB	1° efficacy: venous thromboembolic recurrence or death 1° safety: bleeding	A 5 or 2.5mg BID for 12 months vs. placebo
AMPLYFY [35]	DVT or PE treatment	N = 4816 PG DB	1°efficacy: venous thromboembolic recurrence or death 1° safety: bleeding	A 10mg BID for 7 days then 5mg BID for 6 months vs. enoxaparin 1mg/kg BID + warfarin for an INR between 2-4 for 6 months

1° = primary ; 2° = secondary; A = apixaban; BID = twice daily; DB = double blind; DVT = deep vein thrombosis; f/u = follow up; HR = hazard ratio; PE = pulmonary embolism; PG = parallel groups; QD = once daily; VTE = venous thromboembolism events

come of superiority over warfarin among the new oral anticoagulants.[27]

The rate of major bleeding was significantly lower in the apixaban group than in the warfarin group (327 vs. 462; 2.13% per year vs. 3.09% per year; HR: 0.69; 95% CI: 0.60-0.80; P<0.001). Apixaban also reduced the rate of major intracranial bleeding (0.33 % per year vs. 0.80% per year; HR: 0.42; 95% CI: 0.30-0.58; P<0.001), clinically overt bleeding at other locations (0.1.79% per year vs. 2.27%; HR: 0.79; 95% CI: 0.68-0.93; P=0.004), and major GI bleeding (0.76% per year vs. 0.86% per year; HR: 0.89; 95% CI: 0.70-1.15; P=0.37) compared to the warfarin group.[27]

The net clinical outcome analysis which included all efficacy and safety data (stroke, systemic embolism, major bleeding or death from any cause) demonstrated that apixaban was significantly superior to warfarin (6.13% per year vs. 7.20% per year, respectively; HR: 0.85; 95% CI: 0.78-0.92; P<0.001). The authors concluded that apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality in patients with AF.[27]

Table 7 | Adverse reactions in 5,924 apixaban patients undergoing elective hip or knee replacement surgery [4]

Common (≥1% to <10%)	Uncommon (≥0.1% to <1%)	Rare (≥0.01% to <0.1%)
Anemia[a]	Thrombocytopenia	Hypersensitivity
Hemorrhage[b]	Hypotension	Ocular hemorrhage[g]
Nausea	Epistaxis	Hemoptysis
Contusion	Gastrointestinal hemorrhage[d]	Rectal hemorrhage
	Hematochezia	Gingival bleeding
	ALT/AST increase	Muscle hemorrhage
	Bilirubin increase	
	Blood alkaline phosphatase increase	
	Gamma-glutamyltransferase increase	
	Hematouria[e]	
	Post procedural hemorrhage[f]	

[a] including postoperative and hemorrhagic anemia, and respective laboratory parameters; [b] including hematoma, and vaginal and urethral hemorrhage; [c] including procedural hypotension; [d] including hematemesis and melena; [e] including respective laboratory parameters; [f] including wound secretion, incision site hemorrhage; [g] including conjunctival hemorrhage

Adverse Events

In ARISTOTLE,[27] 7.6% (688/9088) of patients in the apixaban group discontinued the study drug vs. 8.4% (758/9052) in the warfarin group. Overall adverse events, however, occurred equally in both apixaban and warfarin groups (81.5% vs. 83.1%), including serious adverse events (35.0% vs. 36.5%). Patients with co-morbid diabetes or moderate (CrCl = 30-50 ml/min) or severe (CrCl = 15-29 ml/min) renal impairment had significantly more bleeding events (P=0.03). The rate of abnormal liver function tests and liver-related adverse events was approximately <0.1% (> 20X upper limit of normal (ULN)), roughly 1.1% (> 3X ULN) in the apixaban group and 0.1% (> 20X ULN) and approximately 1.0% (> 3X ULN) in the warfarin group.[36]

Other adverse events reported during the relevant phase II and III studies are summarized in **Table 7**.[4]

Dosing and Administration

The usual dose range of apixaban is 2.5 mg to 10 mg with or without food.[4,37-39] The dose of apixaban used in clinical trials for AF was 5 mg twice daily or 2.5 mg in select patients (if two of the following criteria were met: age ≥ 80 years, body weight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dL).[26, 27] It is reasonable to assume the same dosing regimen will be approved by the FDA for AF patients. As apixaban prolongs clotting time in a dose-dependent manner and it is not recommended in patients with severe renal or hepatic impairment.[4,19,40] Apixaban does not have an antidote to reverse its anticoagulant effect in the case of uncontrolled bleeding.[4] Laboratory coagulation tests with improved sensitivity such as anti-FXa assay or mPT are considered suitable for monitoring the anticoagulant effect and plasma levels of apixaban.[40, 41]

Summary

Apixaban is well tolerated with more pharmacodynamic and pharmacokinetic stability than warfarin. Apixaban is superior to warfarin in preventing stroke or systemic embolism in AF patients and reduces all-cause mortality and the risk for major bleeding. The observed efficacy and safety of apixaban reflects its potential to join the new oral anticoagulants in the US market.

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Clinical Trial Update

ADHD Medications and Risk of Serious Cardiovascular Events in Young and Middle-aged Adults [1]—In a retrospective, population-based cohort study using electronic health records from four sources (OptumInsight Epidemiology, Tennessee Medicaid, Kaiser Permanente California, and HMO Research Network) Habel et al evaluated whether currently used medications to treat attention-deficit/hyperactivity disorder (ADHD) increased the risk for cardiovascular (CV) events.[1] Eligible patients were aged 25 to 64 years old and received prescriptions for methylphenidate, amphetamine, atomoxetine, or pemoline; each medication user (n = 150,659) was matched to two non-users for study site, birth year, sex, and calendar year for a total of 443,198 patients; melthyphenidate and amphetamine accounted for 89% of the medications. There were 806,182 person-years of follow-up (median, 1.3 years) and 107,322 years of current use (median, 0.33 years). The primary outcome was the occurrence of myocardial infarction (MI), sudden cardiac death (SCD), or stroke compared between current or new users of ADHD medications to remote users. A cardiovascular risk score (CRS) was calculated to account for a potential difference in CV risk between groups and included CV disease, medications, mental health conditions (except ADHD), use of psychotropic medications, and other health conditions (e.g. diabetes, obesity, smoking), and health care utilization. Also for each event a separate score was created from a Poisson regression model adjusted for ADHD medications and matching baseline variables (age, sex, site, calendar year).

During the study 1357 cases of MI, 296 cases of SCD, and 575 cases of stroke were observed. For current users, the incidence of an event per 1000-person years was 1.34 for MI, 0.30 for SCD, and 0.56 for stroke. After adjustment for baseline matching variables the relative risk (RR) of MI, SCD, and stroke for current users compared to non-users was 0.97 (95% Confidence Interval [CI], 0.84-1.12); adjustment for the CRS decreased the RR to 0.83 (95% CI, 0.72-0.96).

In a comparison of users, either current use or remote use (defined as greater than 364 days since the end of the last days supply of an ADHD medication prescription), the adjusted risk for CV events did not differ between current use or during follow-up after remote use (RR 1.03; 95% CI, 0.86-1.24). Also, the authors did not observe an increased risk of CV events with increasing durations of use.

The study is not without it's limitations. The retrospective design does not allow causality to be determined, but the large sample size and person-years of follow-up provide a large sample to analyze. However, power was limited as the outcome events are rare. The short duration of current use (median of 0.33 years) may limit interpretation of long-term risk, but the authors did not find an association between increasing risk with longer durations of use. Also, white college educated patients comprised the majority of the study patients which may have influenced the results as the medications appeared to have a protective effect on the risk of stroke and SCD. Noting this potential healthy-user bias the authors performed additional analysis to control for baseline demographic characteristics which eliminated the apparent protective effect but did not indicate an increased risk.

This large study provides evidence that stimulants used for the treatment of ADHD may not be associated with substantial CV risks. However, proper patient selection remains paramount as the authors note a modestly increased risk cannot be completely ruled out.

1. Habel LA, Cooper WO, Sox CM, et al. ADHD Medications and Risk of Serious Cardiovascular Events in Young and Middle-aged Adults. JAMA. 2011 Dec 12. [Epub ahead of print]

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