Apixaban, an Oral, Direct, Selective Factor Xa Inhibitor, in Combination With Antiplatelet Therapy After Acute Coronary Syndrome

Results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) Trial

APPRAISE Steering Committee and Investigators

Background—After an acute coronary syndrome, patients remain at risk of recurrent events. Apixaban, an oral direct factor Xa inhibitor, is a novel anticoagulant that may reduce these events but also poses a risk of bleeding.

Methods and Results—Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) was a phase 2, double-blind, placebo-controlled, dose-ranging study. Patients (n=1715) with recent ST-elevation or non–ST-elevation acute coronary syndrome were randomized to 6 months of placebo (n=611) or 1 of 4 doses of apixaban: 2.5 mg twice daily (n=317), 10 mg once daily (n=318), 10 mg twice daily (n=248), or 20 mg once daily (n=221). Nearly all patients received aspirin; 76% received clopidogrel. The primary outcome was International Society of Thrombosis and Hemostasis major or clinically relevant nonmajor bleeding. A secondary outcome was cardiovascular death, myocardial infarction, severe recurrent ischemia, or ischemic stroke. At the recommendation of the Data Monitoring Committee, the 2 higher-dose apixaban arms were discontinued because of excess total bleeding. Compared with placebo, apixaban 2.5 mg twice daily (hazard ratio, 1.78; 95% confidence interval, 0.91 to 3.48; P=0.09) and 10 mg once daily (hazard ratio, 2.45; 95% confidence interval, 1.31 to 4.61; P=0.005) resulted in a dose-dependent increase in major or clinically relevant nonmajor bleeding. Apixaban 2.5 mg twice daily (hazard ratio, 0.73; 95% confidence interval, 0.44 to 1.19; P=0.21) and 10 mg once daily (hazard ratio, 0.61; 95% confidence interval, 0.35 to 1.04; P=0.07) resulted in lower rates of ischemic events compared with placebo. The increase in bleeding was more pronounced and the reduction in ischemic events was less evident in patients taking aspirin plus clopidogrel than in those taking aspirin alone.

Conclusions—We observed a dose-related increase in bleeding and a trend toward a reduction in ischemic events with the addition of apixaban to antiplatelet therapy in patients with recent acute coronary syndrome. The safety and efficacy of apixaban may vary depending on background antiplatelet therapy. Further testing of apixaban in patients at risk of recurrent ischemic events is warranted. (Circulation. 2009;119:2877-2885.)

Key Words: anticoagulants • acute coronary syndromes • clinical trial • factor Xa inhibitor

Clinical Perspective on p 2885

Apixaban (Bristol-Myers Squibb, New York, NY) is a direct, selective, factor Xa inhibitor. It has a half-life of ≈12 hours and is eliminated predominantly through nonrenal mechanisms. Apixaban is effective in preclinical models of venous and arterial thrombosis and has shown encouraging results in the treatment and prevention of venous thromboembolism. The Apixaban for Prevention of Acute Ischemic Safety Events (APPRAISE) trial investigated a range of doses of apixaban compared with placebo over 26 weeks in patients receiving contemporary evidence-based care after a recent ACS.

Methods

Study Design

APPRAISE was an international, multicenter, randomized, double-blind, placebo-controlled, dose-escalation trial.
Patients

Patients were enrolled at 151 sites in 14 countries in Europe, the Middle East, and North America. Eligible patients were between 18 and 90 years of age, had a recent (within 7 days) ST-elevation or non–ST-elevation ACS, were clinically stable receiving evidence-based care, and had at least 1 additional risk factor for recurrent ischemic events. The diagnosis of ACS required symptoms of myocardial ischemia lasting 10 minutes and either elevated cardiac markers or ≥1.0-mm ST-elevation or depression. Additional risk factors included age ≥65 years, elevated cardiac markers and ST deviation, diabetes mellitus, prior myocardial infarction (MI) within 12 months, cerebrovascular disease, peripheral vascular disease, congestive heart failure or a left ventricular ejection fraction ≤40%, nonrevascularized multivessel coronary artery disease, and mild to moderate renal insufficiency.

Exclusion criteria included aspirin allergy; planned catheterization, percutaneous coronary intervention, coronary bypass surgery, or other invasive procedure; persistent severe hypertension; severe renal insufficiency; active bleeding or a high risk for bleeding; coagulopathy; acute pericarditis or pericardial effusion; stroke within 3 months; New York Heart Association class IV heart failure; thrombocytopenia; anemia; an indication for ongoing anticoagulation; long-term nonsteroidal antiinflammatory drug or high-dose aspirin use; ongoing treatment with strong CYP3A4 inhibitors; and participation in an investigational drug or device trial within 30 days. Women of childbearing potential also were excluded. The trial was reviewed by institutional review boards or ethics committees at all participating sites, and all patients gave written informed consent before participating.

Randomization and Study Drug

Patients were randomized via a centralized interactive voice response system to 1 of 4 blinded doses of apixaban or matching placebo for 26 weeks. Randomization was stratified by planned single or dual antiplatelet therapy. Because the safety of apixaban with dual antiplatelet therapy was unknown, the trial was conducted in 2 phases (Figure 1). In phase A, patients were randomly assigned 1:1:1 to apixaban 2.5 mg twice daily, apixaban 10 mg once daily, or placebo. After 450 patients had received study drug for at least 30 days, an independent data monitoring committee reviewed bleeding and adverse event data and recommended inclusion of the 2 planned higher doses of apixaban. In phase B, patients were randomly assigned 1:1:2:2:3 to apixaban 2.5 mg twice daily, apixaban 10 mg once daily, apixaban 10 mg twice daily, apixaban 20 mg once daily, or placebo. The final planned sample size was 1800 patients.

Study drug was stopped in patients who required invasive procedures or had adverse events requiring study drug discontinuation. Patients who discontinued study drug for >30 days could restart it if the reason for stopping resolved.

Concomitant Treatments

All patients were to receive aspirin ≤165 mg/d. The use of clopidogrel and other care was left to the discretion of the treating physician. Use of evidence-based care as outlined in clinical practice guidelines was recommended.1–3

Trial Outcomes

Patients were seen for follow-up at weeks 1, 3, 9, 18, and 26 and had telephone follow-up at weeks 6, 13, and 22. All suspected major and clinically relevant nonmajor bleeding, deaths, and suspected cases of MI, severe recurrent ischemia, and stroke were reviewed by a blinded independent clinical events committee using prespecified criteria.

Bleeding

The primary outcome of the trial was the incidence of major or clinically relevant nonmajor bleeding. Major bleeding was assessed by the International Society of Thrombosis and Hemostasis (ISTH) definition.24 It included bleeding that was fatal, occurred in a critical location (intracranial, intraspinal, intraocular, retroperitoneal, intravascular with compartment syndrome, or pericardial), or was associated with a fall in hemoglobin of 2 g/dL or a transfusion of ≥2 units of packed red blood cells. Clinically relevant nonmajor bleeding was defined as bleeding that required medical or surgical
intervention. ISTH major bleeding events were retrospectively classified by Thrombolysis in Myocardial Infarction (TIMI) definitions of TIMI major or TIMI minor bleeding.25

**Efficacy Outcomes**

The main efficacy outcome was the composite of cardiovascular death, MI, severe recurrent ischemia, or ischemic stroke. MI was defined as elevation of creatine kinase-MB or troponin at least 2 times the local upper limit of normal, total creatine kinase at least 2 times the upper limit of normal if no creatine kinase-MB or troponin values were available, or new significant Q waves in at least 2 contiguous leads.26 After percutaneous coronary intervention, MI was defined as an elevation of creatine kinase-MB or troponin at least 3 times the upper limit of normal or new significant Q waves in at least 2 contiguous leads. After coronary artery bypass surgery, MI was defined as elevation of creatine kinase-MB or troponin at least 5 times the upper limit of normal or new significant Q waves in at least 2 contiguous leads. Severe recurrent ischemia was defined as worsening anginal symptoms lasting at least 10 minutes and associated with at least 2 of the following: dynamic ≥1-mm ST depression or elevation, hospitalization, or unplanned cardiac catheterization with evidence of significant coronary stenosis. Ischemic stroke was defined as a new focal neurological deficit lasting at least 24 hours that had a nonvascular cause and was not associated with imaging evidence of intracranial bleeding.

**Data Monitoring Committee**

An independent data monitoring committee reviewed unblinded bleeding and adverse event data at the completion of phase A and after 50% and 75% of patients were enrolled and treated for 30 days; it also assessed limited safety data every 2 weeks. On the basis of data for 1498 randomized patients, the data monitoring committee recommended discontinuation of the 2 higher-dose apixaban arms because of an excess in total bleeding among patients receiving these doses of apixaban and dual antiplatelet therapy.

**Statistical Analysis**

Continuous variables are summarized as medians and 25th and 75th percentiles. Categorical variables are summarized as numbers and percentages.

Baseline characteristics and qualifying event data are presented for all randomized patients. Study drug and concomitant medication data are presented for all patients who received at least 1 dose of study drug. All bleeding and other safety analyses include patients who received at least 1 dose of study drug and events that occurred from the first dose of study drug until 2 days after discontinuation of study drug. Patients were analyzed in the group to which they were randomized. Bleeding rates are presented for the overall population and by baseline clopidogrel use. Rate differences were calculated for the apixaban 2.5 mg twice daily and the apixaban 10 mg once daily arms compared with placebo. Kaplan–Meier curves were generated.
for the primary outcome, and Cox proportional-hazards modeling was used to determine hazard ratios (HRs) and 95% confidence intervals (CIs) for each lower-dose apixaban arm compared with the placebo arm for the primary outcome. Analyses were stratified by baseline clopidogrel use and by trial phase.

Efficacy analyses were by intention to treat and included all randomized patients and events that occurred from randomization through 26 weeks. Patients were analyzed in the group to which they were randomized. Efficacy data are included for patients assigned to placebo, apixaban 2.5 mg twice daily, or apixaban 10 mg once daily in the combined phase A and B population overall and by baseline clopidogrel use. Kaplan–Meier curves were generated for the main efficacy outcome, and Cox proportional-hazards modeling was used to determine HRs and 95% CIs for each lower-dose apixaban arm compared with the placebo arm for the main efficacy outcome. Analyses were stratified by baseline clopidogrel use and by trial phase.

Given the desire to compare concurrently randomized groups with similar exposure, 2 sets of analyses are reported. The first includes patients assigned to placebo, apixaban 2.5 mg twice daily, or apixaban 10 mg once daily in the combined phase A and B population. The second includes patients assigned to placebo, apixaban 2.5 mg twice daily, apixaban 10 mg once daily, apixaban 10 mg twice daily, or apixaban 20 mg once daily in phase B and includes only patients randomized and events that occurred before October 1, 2007, when the 2 higher-dose arms were discontinued.

The sample size was based on precision of event rate estimates rather than power considerations. We projected a rate of major or clinically relevant nonmajor bleeding of between 3% and 5% in the placebo arm and between 3% and 10% in the apixaban arms during the treatment period. With 300 patients per arm, the half-length of the 95% CI for the difference between each apixaban arm and the placebo arm would be between 2.4% and 3.9%.

Table 2. Concomitant Medications During Treatment Period

<table>
<thead>
<tr>
<th>Drug</th>
<th>Placebo (n=599), %</th>
<th>2.5 mg BID (n=315)</th>
<th>10 mg BID (n=315)</th>
<th>10 mg BID (n=244)</th>
<th>20 mg QD (n=218)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>100</td>
<td>99.7</td>
<td>99.7</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>92.0</td>
<td>92.7</td>
<td>92.1</td>
<td>91.8</td>
<td>91.3</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>87.3</td>
<td>85.1</td>
<td>82.9</td>
<td>85.7</td>
<td>85.3</td>
</tr>
<tr>
<td>Calcium blocker</td>
<td>20.5</td>
<td>25.1</td>
<td>19.7</td>
<td>22.5</td>
<td>16.5</td>
</tr>
<tr>
<td>Nitrate</td>
<td>36.7</td>
<td>41.3</td>
<td>41.3</td>
<td>30.7</td>
<td>29.8</td>
</tr>
<tr>
<td>Statin</td>
<td>88.3</td>
<td>87.0</td>
<td>87.9</td>
<td>92.2</td>
<td>89.0</td>
</tr>
</tbody>
</table>

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

All analyses are considered exploratory. A value of $P<0.05$ was considered nominally significant. Because of the small number of patients and events, no statistical interaction tests have been performed. All analyses were performed with SAS statistical software version 8.2 (SAS Inc, Cary, NC).

Role of the Funding Source

The Steering Committee participated in the design and oversaw the conduct of the trial collaboratively with the trial sponsors, Bristol-Myers Squibb and Pfizer. The clinical trial data were managed at Bristol-Myers Squibb, but the locked database was transferred in full to the Duke Clinical Research Institute for analysis. All analyses were performed independently by statisticians at the Duke Clinical Research Institute. The sponsors reviewed and commented on the manuscript, but their approval was not required for submission.

Results

A total of 1715 patients were randomized between May 31, 2006, and October 26, 2007. The 6-month follow-up was completed on May 30, 2008, and the database was locked on July 11, 2008. Preliminary data were presented at the European Society of Cardiology Meeting in Munich, Germany, on September 2, 2008. The disposition of patients is shown in Figure 2.

Figure 2. Proportion of patients with major or clinically relevant nonmajor bleeding by baseline clopidogrel status.
Figure 1. In the placebo, apixaban 2.5 mg twice daily, and apixaban 10 mg once daily arms, >75% of randomized patients completed the 26-week treatment period. Of those who did not, most either withdrew consent (9.1%) or were discontinued as a result of an adverse event (8.4%) (Figure 1).

Baseline Characteristics

The population is typical of moderate- to high-risk patients with a recent ST-elevation or non–ST-elevation ACS (Table 1). Of the 1715 patients randomized, 63% were enrolled after an ST-segment elevation MI, 30% after a non–ST-elevation MI, and 8% after unstable angina. A total of 65% underwent percutaneous coronary intervention before randomization. The median time from the onset of the qualifying ACS to randomization was 4 days (25th and 75th percentiles, 3 and 6 days), suggesting that most patients were enrolled near the completion of their index hospitalization. The median time from discontinuation of parenteral antithrombotic therapy to the start of study drug was 30 hours (25th and 75th percentiles, 14 and 64 hours).

The 76% of patients receiving clopidogrel at randomization were younger (median age, 59 versus 65 years); less likely to be female (19% versus 40%) and to have cerebrovascular disease (3.2% versus 7.5%), renal insufficiency (20% versus 62%), and prior congestive heart failure or left ventricular dysfunction (7.0% versus 27%); more likely be smokers (61% versus 43%); more likely to have had a qualifying MI (96% versus 81%); and more likely to have undergone percutaneous intervention for their qualifying event (84% versus 64%) than those not receiving clopidogrel. The majority of patients (80%) not receiving clopidogrel at randomization were enrolled in Russia.

Study Drug

All but 24 patients received at least 1 dose of study drug (Figure 1). The total and mean study drug exposure periods for each of the arms were 2988 patient-months and 21.7 weeks (SD, 9.1 weeks) for placebo, 1598 patient-months and 22.1 weeks (SD, 8.6 weeks) for apixaban 2.5 mg twice daily, 1555 patient-months and 21.5 weeks (SD, 9.1 weeks) for apixaban 10 mg once daily, 715 patient-months and 12.7 weeks (SD, 8.3 weeks) for apixaban 10 mg twice daily, and 546 patient-months and 10.9 weeks (SD, 8.2 weeks) for apixaban 20 mg once daily.

Concomitant Medications

Enrolled patients received contemporary evidence-based post-ACS care (Table 2). Nearly all patients received aspirin, and >75% received dual antiplatelet therapy. Among those taking clopidogrel at randomization, 236 of 1303 (18%) discontinued clopidogrel during the 6-month treatment period a median of 58 days (25th and 75th percentiles, 28 and 95 days) after randomization. Among those not taking clopidogrel at randomization, 22 of 412 (5.0%) started clopidogrel a median of 42 days (25th and 75th percentiles, 16 and 94 days) after randomization.

Bleeding

A dose-dependent increase in ISTH major or clinically relevant nonmajor bleeding was observed with apixaban 2.5 mg twice daily (5.7%; 95% CI, 3.4 to 8.9) and 10 mg once daily (7.9%; 95% CI, 5.2 to 11.5) compared with placebo.
Table 4. Locations of Bleeding

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=599), %</th>
<th>Apixaban, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.5 mg BID (n=315)</td>
<td>10 mg QD (n=315)</td>
</tr>
<tr>
<td>Bruising</td>
<td>2.7 5.1 7.3</td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>2.7 4.8 6.3</td>
<td></td>
</tr>
<tr>
<td>Hematoma</td>
<td>2.0 2.9 3.8</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1.7 2.2 2.9</td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td>1.3 1.6 3.2</td>
<td></td>
</tr>
<tr>
<td>Gingival</td>
<td>1.3 2.9 3.8</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>0.8 5.7 2.5</td>
<td></td>
</tr>
<tr>
<td>Intraocular</td>
<td>0.5 0.3 0.0</td>
<td></td>
</tr>
<tr>
<td>Intraartricular</td>
<td>0.2 0.0 0.0</td>
<td></td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>0.0 0.3 0.6</td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>0.0 0.6 1.0</td>
<td></td>
</tr>
<tr>
<td>Intraspinal</td>
<td>0.0 0.0 0.0</td>
<td></td>
</tr>
<tr>
<td>Pericardial</td>
<td>0.0 0.0 0.0</td>
<td></td>
</tr>
<tr>
<td>Retropertoneal</td>
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<td></td>
</tr>
<tr>
<td>Intracranial</td>
<td>0.0 0.0 0.0</td>
<td></td>
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</tbody>
</table>

(3.0%; 95% CI, 1.8 to 4.7%; Table 3). The dose-related increases in bleeding were more apparent in patients taking clopidogrel (Figure 2). The adjusted rate difference in major or clinically relevant nonmajor bleeding was 2.2% (95% CI, −1.0 to 5.4) for the apixaban 2.5 mg twice daily arm and 3.8% (95% CI, 0.4 to 7.3) for the apixaban 10 mg once daily arm. These differences were more pronounced among patients taking clopidogrel (apixaban 2.5 mg twice daily, 3.2% [95% CI, −0.5 to 7.0]; apixaban 10 mg once daily, 5.5% [95% CI, 1.3 to 9.8]) than among patients not taking clopidogrel (apixaban 2.5 mg twice daily, −0.7% [95% CI, −6.3 to 4.9]; apixaban 10 mg once daily, 0.8% [95% CI, −4.9 to 6.5]). The increase in bleeding with apixaban 10 mg once daily and apixaban 2.5 mg twice daily was evident immediately after randomization with separation of the 2 apixaban dose curves after ∼8 weeks (Figure 3). Over the 6-month treatment period, the risk of major or clinically relevant nonmajor bleeding was higher with apixaban 2.5 mg twice daily (HR, 1.78; 95% CI, 0.91 to 3.48; P=0.09) and with apixaban 10 mg once daily (HR, 2.45; 95% CI, 1.31 to 4.61; P=0.005) than with placebo.

Although overall rates are lower, similar relative increases in ISTH major and TIMI bleeding are seen with apixaban compared with placebo (Table 3). The most frequent locations of bleeding were cutaneous bruising and hematomas, epistaxis and gingival bleeding, hematuria, and gastrointestinal bleeding (Table 4).

Patients taking apixaban 10 mg twice daily and apixaban 20 mg once daily had substantially higher rates of ISTH major bleeding and total bleeding than patients taking either of the lower doses of apixaban or placebo (Table 5). One intracranial hemorrhage occurred 3 months after randomization in a 48-year-old man taking aspirin, clopidogrel, and apixaban 20 mg once daily. Correcting for similar exposure, higher rates of major or clinically relevant nonmajor bleeding were observed with apixaban 10 mg twice daily and 20 mg once daily than with placebo among the majority of patients taking clopidogrel (15 of 190 [7.9%] and 15 of 169 [8.9%] versus 2 of 280 [0.7%]) and, to a lesser extent, those not taking clopidogrel (4 of 54 [7.4%] and 1 of 49 [2.0%] versus 1 of 82 [1.2%]).

Other Safety

Similar proportions of patients receiving apixaban 2.5 mg twice daily (0.3%), 10 mg once daily (1.3%), 10 mg twice daily (0.9%), and 20 mg once daily (0.5%) and placebo (3.4%) had alanine aminotransferase or aspartate aminotransferase elevations >3 times the upper limit of normal.

Efficacy

The incidence of cardiovascular death, MI, severe recurrent ischemia, or ischemic stroke was numerically but not significantly lower in patients assigned to apixaban 2.5 mg twice daily (7.6%) and 10 mg once daily (6.0%) compared with placebo (8.7%) (Table 6). The risk of recurrent ischemic events continued to accrue over time in all groups with a reduction in ischemic events with apixaban compared with placebo after ∼10 weeks of treatment (Figure 4). Overall event rates and the benefits of apixaban were greater among patients not taking clopidogrel (Figure 5). Patients not taking clopidogrel also tended to have lower rates of cardiovascular death, MI, or ischemic stroke with either apixaban 2.5 mg twice daily or 10 mg once daily compared with placebo.

Patients assigned to receive apixaban 10 mg twice daily (8 of 248 [2.8%]; HR, 0.71; 95% CI, 0.30 to 1.66) and apixaban 20 mg twice daily (7 of 221 [3.2%]; HR, 0.72; 95% CI, 0.30 to 1.74) tended to have lower rates of the composite ischemic outcome than patients taking placebo (16 of 368 [4.3%]).

Discussion

This is the first experience with an oral, direct, selective factor Xa inhibitor in patients with recent ST-elevation or non–ST-elevation ACS treated with contemporary antiplatelet therapy. We found that the addition of apixaban to contemporary antiplatelet therapy results in a dose-dependent increase in ISTH
major or clinically relevant nonmajor bleeding and a trend toward a reduction in clinically important ischemic events. These findings from APPRAISE are consistent with the findings with warfarin and ximelagatran and those recently presented with the oral factor Xa inhibitor rivaroxaban.10,12,13,15,28

Interaction With Antiplatelet Therapy

In patients receiving dual antiplatelet therapy, there was a clear increase in ISTH major or clinically relevant nonmajor bleeding with apixaban. In contrast, in the absence of clopidogrel, increases in bleeding with apixaban were less apparent, particularly with 2.5 mg twice daily. In contrast, the dose-related reduction in ischemic events was more pronounced in patients not receiving clopidogrel. Caution is necessary, however, in interpreting these subgroup results as being related only to clopidogrel because these groups were different in baseline characteristics, region of enrollment, ACS management (including percutaneous intervention), and overall rates of bleeding and ischemic events. In addition, clopidogrel status was ascertained at baseline, and not all patients stayed on or off clopidogrel for the duration of the study. These results suggest, however, that the balance between incremental benefit and incremental risk with apixaban may depend on antiplatelet therapy. Alternatively, apixaban might be downtitrated over time or uptitrated after an acute ischemic event. In the future, as other more potent antiplatelet agents become available, additional studies will need to investigate how antiplatelet and anticoagulant agents should be combined, recognizing that the optimal antithrombotic regimen may change over time, may be dependent on revascularization strategy, and may vary on the basis of a patient’s individual risk of bleeding or thrombosis.29

High-Dose Apixaban

Total daily doses of apixaban between 5 and 20 mg have been studied in short-duration clinical trials in the prevention and treatment of venous thromboembolism.21,23 In APPRAISE, the 2 highest doses of apixaban had substantially higher rates of both total and ISTH major bleeding. Knowing that a total daily dose of 20 mg of apixaban results in significant increases in bleeding helps to define the upper bound of the therapeutic window.

Impact of Bleeding Definitions

We used the ISTH definition of major bleeding in APPRAISE.24 This definition is more sensitive than a number of
other bleeding scales commonly used to assess bleeding in ACS care. Even minor “nuisance” bleeding, however, is a significant issue in the outpatient setting where patient satisfaction and compliance are important issues. Further work is needed to define predictors of bleeding with factor Xa inhibition and to determine whether specific populations of patients have a more favorable risk-benefit tradeoff with higher or lower doses of apixaban.

Risk Versus Benefit

The tradeoff between efficacy and bleeding is an issue with all effective antithrombotic agents. Given the small number of severe bleeding and ischemic events, any estimation of the potential balance between benefit and risk needs to be done with caution. The question of measuring “net clinical benefit” also is challenged by the differing severities of the various safety and efficacy outcomes. If one compares the increase in ISTH major bleeding and the reduction in ischemic events, however, then apixaban 2.5 mg twice daily and apixaban 10 mg once daily result in absolute net reductions of 0.3% and 1.6% in clinical events in the overall population, mostly from severe bleeding and ischemic events, any estimation of the potential benefit and risk needs to be done with caution.

Conclusions

We observed an increase in ISTH major or clinically relevant nonmajor bleeding and a reduction (although not statistically significant) in clinically important ischemic events with the addition of apixaban to contemporary antiplatelet therapy in patients with ACS. The increase in bleeding is more pronounced and the reduction in ischemic events is smaller in patients receiving contemporary dual antiplatelet therapy. Given the balance between reducing clinically important ischemic events and increasing the risk of bleeding, apixaban at a total daily dose of 10 mg appears attractive and warrants further evaluation in patients at high risk of ischemic events, possibly with dose adjustment for a patient’s individual risk of bleeding.

Acknowledgments

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Sources of Funding

The APPRAISE trial was funded by the sponsors Bristol-Myers Squibb (New York, NY) and Pfizer (New York, NY).

Disclosures

All members of the Writing Group served on the Steering Committee for the APPRAISE study and received research funding, honoraria, or travel support from the sponsor to support this role. None of the members of the Writing Group received shares or share options in the sponsor company. Dr Alexander had full access to all the data from the study.

References


Patients with acute coronary syndromes continue to have recurrent ischemic events despite revascularization and current antiplatelet therapy. Several novel oral anticoagulants that may reduce recurrent ischemic events are being developed but come with an increased risk of bleeding. Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) is the first phase 2 trial exploring several doses of the oral factor Xa inhibitor, apixaban, in patients, with a recent acute coronary syndrome who received, in many cases, both aspirin and clopidogrel. With the addition of apixaban, there was an increase in bleeding but also promising reductions in clinically important ischemic events, including cardiovascular death, myocardial infarction, stroke, and recurrent ischemia requiring hospitalization or revascularization. The results of APPRAISE set the stage for adequately powered phase 3 trials of apixaban in patients with recent acute coronary syndromes, which, depending on their results, may establish oral anticoagulation as a new standard approach for preventing recurrent ischemic events in patients with acute coronary syndromes.
Apixaban, an Oral, Direct, Selective Factor Xa Inhibitor, in Combination With Antiplatelet Therapy After Acute Coronary Syndrome: Results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) Trial
APPRAISE Steering Committee and Investigators

_Circulation_. 2009;119:2877-2885; originally published online May 26, 2009;
doi: 10.1161/CIRCULATIONAHA.108.832139
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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