A
cute coronary syndrome (ACS) is the major cause of
morbidity and mortality in the world. Recent develop-
ments in ACS treatment have significantly im-
proved the prognosis of ACS patients, but the risk of recurrent
ischemic events remains still high.1 Even with dual antiplatelet
therapy (DAPT), death, myocardial infarction (MI), or stroke
occurs in 9–11% at 1 year after the ACS event.2 One potential
strategy is the addition of anticoagulant after initial hospital-
ized management.

**Previous studies have shown that the addition of a vitamin K antagonist (VKA), such as warfarin, reduces the risk of re-
current ischemic events.3 Despite proven efficacy, long-term
use of VKAs in ACS patients is very rare because of their
various limitations, such as narrow therapeutic window; nu-
merous food/drug interactions, and high propensity for bleeding
complications.4

Novel oral anticoagulants targeting factor Xa have been de-
developed in an attempt to overcome the limitations of VKAs.
Because of the favorable properties of direct Xa inhibitors and
their proven effectiveness in preclinical trials compared with
VKAs for prevention of stroke in patients with nonvalvular
atrial fibrillation (AF),5–7 prolonged oral anticoagulant therapy
in conjunction with antiplatelet therapy is theoretically an at-
tractive option for secondary prevention after an ACS.

To date, 2 oral Xa inhibitors, apixaban (APPRAISE-2 trial)8
and rivaroxaban (ATLAS ACS 2-TIMI 51 [ATLAS-2]),9 have been
evaluated in phase III clinical trials for secondary pre-
vention of ACS (Table). APPRAISE-2 was prematurely ter-
ninated because of an excess of bleeding and no evidence of benefit. ATLAS-2 met its primary objective.9

In APPRAISE-2, 7,392 patients with ACS (40% ST-elevation
MI; 60% non-ST-elevation ACS) and at least 2 additional risk
factors for ischemic events were randomized at a median 6 days
after ACS event to apixaban 5 mg twice daily (BID) (2.5 mg
BID in patients with creatine clearance (CrCl) <40 ml/min) or
placebo for mean follow-up of 241 days.8 Most patients (81%)
were taking DAPT. Apixaban failed to reduce ischemic events
compared with placebo (hazard ratio [HR] 0.95; 95% confi-
dence interval [CI] 0.80–1.11).8 Apixaban evidently increased
major bleeding events compared with placebo (HR 2.59; 95%
CI 1.50–4.46), including intracranial hemorrhage (HR 4.06;
95% CI 1.15–14.38) and fatal hemorrhage (5 vs. 0 events).8
The overall efficacy/safety balance considerations prompted the
Data and Safety Monitoring Board to terminate the trial
before completing enrollment.

In the ATLAS-2 trial, 15,526 patients with ACS were ran-
domized 1:1:1 to placebo or rivaroxaban 2.5 mg BID or 5 mg
BID for mean follow-up of 13.1 months.9 Patients with previ-
sous gastrointestinal bleeding, previous ischemic stroke or tran-
sient ischemic attack, and poor renal function were excluded.9
Rivaroxaban significantly improved the primary efficacy com-
posite of cardiovascular death, MI or stroke, compared with
placebo (HR 0.84, 95% CI 0.74–0.96).9 The 2.5 mg BID, but
not 5.0 mg BID, also significantly reduced death from cardio-
vascular cause (HR 0.66; 95% CI 0.53–0.87).10 Rivaroxaban in-
creased major bleeding events not associated with coronary
artery bypass grafting surgery (HR 3.96; 95% CI 2.46–6.38)
and intracranial hemorrhage (HR 3.28; 95% CI 1.28–8.42),
without an increase in fatal bleeding (HR 1.19, 95% CI 0.54–
2.59).9

In this issue of the Journal, Ogawa et al provide the results of
APPRAISE-J,10 which was conducted as part of APPRAISE-2
and focused on Japanese patients. Previous studies have re-
ported an increased risk of bleeding in Asian patients when
receiving similar strength VKA therapy.11 However, it remains
uncertain whether the risk of bleeding will be higher in Asian
populations with the use of Xa inhibitors.10 The result of AP-
PRAISE-J demonstrated that apixaban treatment was gen-
erally safe and tolerated in Japanese patients with ACS and the
bleeding rate was similar to that of the global APPRAISE-1
study.10

In the APPRAIS-2 trial, the addition of apixaban increased
major and fatal bleeding events, without a reduction in recur-
current ischemic events. Conversely, in ATLAS-2, rivaroxaban
significantly reduced recurrent ischemic events, cardiovascular
death, and all-cause mortality, in addition to increases in
bleeding.

There are several potential reasons for the differences.12
Firstly, this discrepancy might relate to differences between
the patient populations enrolled in the 2 trials. Compared with
ATLAS-2, APPRAISE-2 included a more high-risk population
of older ages, diabetes or renal dysfunction. Furthermore, pa-
tients with a history of stroke or transient ischemic attack who
were treated with DAPT were excluded from ATLAS-2, but
not from APPRAISE-2. This group of patients might be be-
yond the threshold of deriving benefit from intense antithrom-
bolic therapy, and gain only an increased risk of bleeding.13
A secondary possible explanation is dose selection. APPRAISE-2
used the same 5-mg BID apixaban dose tested in AF,5 whereas
ATLAS-2 used 2 doses, 2.5 mg BID and 5 mg BID, that were

The opinions expressed in this article are not necessarily those of the editors or of the Japanese Circulation Society.

Received July 16, 2013; accepted July 16, 2013; released online July 31, 2013
Department of Cardiology, Teikyo University Chiba Medical Center, Ichihara, Japan
Mailing address: Masayasu Ikutomi, MD, PhD, Department of Cardiology, Teikyo University Chiba Medical Center, 3426-3 Anegasaki,
Ichihara 299-0111, Japan. E-mail: mikutomi@gmail.com
All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp
Xa Inhibitors in ACS

Both AF and ACS remain unclear. Further study is required to evaluate the potential use of apixaban in place of warfarin for patients with AF. As a result of the 2 phase III trials, the addition of an Xa inhibitor to standard antiplatelet therapy might narrow the therapeutic window, particularly in high-risk patients. Larger clinical trials are required to fully assess their efficacy/safety of bleeding in patients already receiving conventional ACS therapy.

Disclosures

None.

Table. Summary of 2 Phase III Clinical Trials of Xa Inhibitors in Patients With ACS

<table>
<thead>
<tr>
<th>Drug</th>
<th>APPRAISE-2</th>
<th>ATLAS ACS2-TIMI 51</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria</td>
<td>Apixaban 5mg twice daily (or 2.5mg in renal dysfunction) vs. placebo in addition to standard ACS therapy</td>
<td>Rivaroxaban 2.5mg or 5mg BID vs. placebo in addition to standard ACS therapy</td>
</tr>
<tr>
<td></td>
<td>ACS within the previous 7 days</td>
<td>Patients ≥18 years of age</td>
</tr>
<tr>
<td></td>
<td>Receiving standard medical therapy with antiplatelet therapy</td>
<td>Receiving standard medical therapy with antiplatelet therapy</td>
</tr>
<tr>
<td></td>
<td>Two or more of the high-risk characteristics (age &gt;65 years, diabetes mellitus, MI within previous 5 years, cerebrovascular disease, peripheral vascular disease, clinical heart failure or a left ventricular ejection fraction &lt;40%, CrCl &lt;60ml/min, no vascularization after the index event)</td>
<td>Patients under 55 years of age with either diabetes mellitus or previous MI</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>Hemoglobin &lt;9g/dl</td>
<td>Hemoglobin &lt;10g/dl</td>
</tr>
<tr>
<td></td>
<td>Platelet count &lt;100,000/mm³</td>
<td>Platelet count &lt;90,000/mm³</td>
</tr>
<tr>
<td></td>
<td>CICr &lt;20ml/min</td>
<td>CICr &lt;30ml/min</td>
</tr>
<tr>
<td></td>
<td>History of intracranial hemorrhage</td>
<td>History of intracranial hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Persistent severe hypertension</td>
<td>Significant gastrointestinal bleeding within 12 months</td>
</tr>
<tr>
<td></td>
<td>Ischemic stroke within 7 days</td>
<td>Ischemic stroke or transient ischemic attack who were taking DAPT</td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td>NYHA class IV heart failure</td>
<td>Age: 67 years (median)</td>
</tr>
<tr>
<td></td>
<td>STEMI: 39.6%</td>
<td>STEMI: 50.3%</td>
</tr>
<tr>
<td></td>
<td>NSTEMI: 41.6%</td>
<td>NSTEMI: 25.5%</td>
</tr>
<tr>
<td></td>
<td>uAP: 18.1%</td>
<td>uAP: 24.2%</td>
</tr>
<tr>
<td></td>
<td>PCI for index ACS event: 44%</td>
<td>PCI for index ACS event: 60.6%</td>
</tr>
<tr>
<td></td>
<td>≥65 years: 58.9%</td>
<td>≥65 years: 36.5%</td>
</tr>
<tr>
<td></td>
<td>previous MI 26.2%</td>
<td>previous MI 26.9%</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus: 47.8%</td>
<td>Diabetes mellitus: 32.0%</td>
</tr>
<tr>
<td></td>
<td>History of stroke or TIA: 10.0%</td>
<td>History of stroke or TIA: 2.7%</td>
</tr>
<tr>
<td></td>
<td>Concomitant aspirin only: 16%</td>
<td>Concomitant aspirin only: 6.8%</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Concomitant DAPT: 81%</td>
<td>Concomitant DAPT: 93.2%</td>
</tr>
<tr>
<td>Primary efficacy endpoint</td>
<td>8 months</td>
<td>13 months</td>
</tr>
<tr>
<td>Composite of cardiovascular death, MI or ischemic stroke</td>
<td>7.5% vs. 7.9%; P=0.51</td>
<td>8.9% vs. 10.7%; P=0.008</td>
</tr>
<tr>
<td>Secondary efficacy endpoint</td>
<td>Composite of cardiovascular death, MI, stroke or uAP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.2% vs. 7.5%; P=0.87</td>
<td>Death from cardiovascular cause</td>
</tr>
<tr>
<td></td>
<td>Death from any cause:</td>
<td>2.7% vs. 4.1%; P=0.002</td>
</tr>
<tr>
<td></td>
<td>for both at 2.5mg BID arms</td>
<td>2.1% vs. 4.1%; P&lt;0.001</td>
</tr>
<tr>
<td>Primary safety endpoint</td>
<td>Major bleeding</td>
<td>Major bleeding not related to CABG</td>
</tr>
<tr>
<td></td>
<td>1.3% vs. 0.5%; P=0.001</td>
<td>2.1% vs. 0.6%; P&lt;0.001</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; BID, twice daily; CABG, coronary artery bypass grafting; CICr, creatinine clearance; DAPT, dual antiplatelet therapy; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation MI; uAP, unstable angina pectoris.

one-quarter to one-half of the total daily dose of rivaroxaban tested in AF. Low doses of Xa inhibitor might be preferable in this patient population. Finally, the lack of significance of the reduction in ischemic events in the APPRAISE-2 might be related to the early termination of the trial. In ATLAS-2, the efficacy gain for rivaroxaban was greater in the later part of the study, rather than the earlier. Therefore, the wide CIs in APPRAISE-2 do not exclude a residual potential for a reduction in event rates.

The current JCA guidelines recommend concomitant warfarin and antiplatelet therapy for prevention of secondary cardiovascular events after MI in patients with AF. In 2 trials, patients who required continuous anticoagulant therapy were excluded. Therefore, the benefits and risks for patients with both AF and ACS remain unclear. Further study is required to evaluate the potential use of apixaban in place of warfarin for patient with AF. As a result of the 2 phase III trials, the addition of an Xa inhibitor to standard antiplatelet therapy might narrow the therapeutic window, particularly in high-risk patients. Larger clinical trials are required to fully assess their efficacy/safety of bleeding in patients already receiving conventional ACS therapy.
References


