The ATLAS ACS 2-TIMI 51 Study

What is the ATLAS ACS 2-TIMI 51 Study?

♦ The ATLAS ACS 2-TIMI 51 (Anti-Xa Therapy to Lower cardiovascular events in Addition to aspirin with/without thienopyridine therapy in Subjects with Acute Coronary Syndrome) was a global, double blind, Phase III clinical study involving 15,526 acute coronary syndrome (ACS) patients hospitalised with unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI) or ST segment elevation myocardial infarction (STEMI), evaluating the efficacy and safety of Xarelto® (rivaroxaban) for secondary prevention of ACS

♦ This study was conducted in collaboration with the Thrombolysis in Myocardial Infarction (TIMI) Study Group

♦ The efficacy of ‘Xarelto’ was compared to placebo in preventing the most devastating threats ACS patients face after leaving the hospital, including cardiovascular (CV) death, myocardial infarction (MI), or stroke. In addition to standard antiplatelet therapy — low-dose aspirin with or without a thienopyridine such as clopidogrel — patients were given ‘Xarelto’ dosed at 2.5 mg BID or 5 mg BID, or placebo. Of the patients randomised into the study, 93% received standard antiplatelet therapy in addition to ‘Xarelto’ or placebo, and the balance were treated with aspirin plus ‘Xarelto’ or placebo

ATLAS ACS 2-TIMI 51 Results: Summary

The study delivered improved outcomes for ACS patients through a dual pathway treatment strategy combining ‘Xarelto’ and standard antiplatelet therapy, compared to standard antiplatelet therapy alone.

♦ The results of the ATLAS ACS 2-TIMI 51 study showed that both 2.5 and 5 mg of ‘Xarelto’ dosed twice daily (BID) in addition to standard antiplatelet therapy were superior to standard antiplatelet therapy plus placebo in both study arms in the primary efficacy endpoint of preventing recurrent major CV events (CV death, MI or stroke) in patients after an ACS [combined doses 8.9% vs. 10.7% (P=0.008), Relative Risk Reduction (RRR)=16%]. Additionally and importantly, ‘Xarelto’ significantly reduced stent thrombosis compared with placebo [2.3% vs. 2.9% (P=0.016)]
Patients dosed with 2.5 mg BID of ‘Xarelto’ showed a significant reduction in risk of the composite primary endpoint [9.1% vs. 10.7% (P=0.020)], driven by a significant 34% RRR in the rate of cardiovascular death [2.7% vs. 4.1% (P=0.002)]. There was also a significant reduction in deaths from any cause [2.9% vs. 4.5% (P=0.002)]. In addition, the 5 mg BID dose of ‘Xarelto’ reduced the rate of the primary efficacy endpoint in the study [8.8% vs. 10.7% (P=0.028)].

The principal safety endpoint for the study was TIMI major bleeding not associated with coronary artery bypass graft (CABG) surgery. In patients receiving ‘Xarelto’ in addition to standard antiplatelet therapy, bleeding rates were low overall, yet statistically significantly increased versus those treated with standard therapy plus placebo [2.1% vs. 0.6% (p<0.001)]. Similarly, ‘Xarelto’ resulted in higher rates of TIMI major bleeding events not associated with CABG surgery at both the 2.5mg and 5mg BID doses compared to placebo [1.8% vs. 0.6% (p<0.001)] and 2.4% vs. 0.6% (p<0.001), respectively.

Importantly, there was no increase in fatal ICH or fatal bleeding.

Other treatment-emergent adverse events were generally balanced across treatment groups.

Full data from ATLAS ACS 2-TIMI 51 were presented at the American Heart Association (AHA) Scientific Sessions meeting and published in the New England Journal of Medicine (NEJM) in November 2011.

A major sub-analysis of the ATLAS ACS 2-TIMI 51 study in 7,817 ACS patients with a recent STEMI demonstrated that ‘Xarelto’ 2.5 mg twice daily, when added to standard antiplatelet therapy, provides a significant mortality benefit. Efficacy and safety data are consistent with results of the overall ATLAS ACS 2-TIMI 51 study, which demonstrated the effectiveness of rivaroxaban in secondary prevention after an ACS. The sub-analysis results were presented at ESC Congress 2012.
ATLAS ACS 2-TIMI 51^2,3

Study design
♦ Multi-centre, randomised, event-driven, double-blind, parallel-group, placebo controlled study
♦ Conducted in 44 countries and at 766 sites worldwide

Interventions
♦ Stratum 1: Standard antiplatelet therapy of low-dose aspirin and either:
  • One of two doses of oral ‘Xarelto’ (2.5 mg and 5 mg) taken twice daily
  • Placebo
♦ Stratum 2: Low-dose aspirin and a thienopyridine, such as clopidogrel and either:
  • One of two doses of oral ‘Xarelto’ (2.5 mg and 5 mg) taken twice-daily
  • Placebo

Number of patients
♦ 15,526 patients worldwide

Primary efficacy endpoint
♦ Reduction in the risk of the composite of CV death, MI or stroke

Primary safety endpoint
♦ TIMI major bleeding events and intracranial haemorrhages not associated with coronary artery bypass graft (CABG) surgery

RESULTS
Primary efficacy endpoint
♦ ‘Xarelto’ met its primary efficacy endpoint with significant reductions in the rates of CV death, MI or stroke
♦ In both strata, ‘Xarelto’ 2.5 mg BID in addition to antiplatelet therapy showed:
  • A significant 16% RRR in the composite of CV death, MI or stroke: HR 0.84 (0.72-0.97) p=0.020
  • A significant 34% RRR in cardiovascular mortality: 2.7 vs 4.1%; HR 0.66 (95% CI 0.51–0.86); p=0.002
  • A significant 32% RRR in all-cause mortality: 2.9 vs 4.5%; HR 0.68 (95% CI 0.53–0.87); p=0.002
♦ In both strata, compared with placebo, ‘Xarelto’ 5.0 mg BID in addition to antiplatelet therapy showed:
  • A significant 15% RRR in the composite of CV death, MI or stroke: 8.8 vs 10.7%; HR 0.85 (95% CI 0.73–0.98); p=0.028

Primary safety endpoint
♦ There was a dose-dependent statistically significant increase in the risk of non-CABG-related TIMI major bleeding and intracranial haemorrhages with ‘Xarelto’ plus standard of care compared with standard of care plus placebo:
  • TIMI major bleeding not associated with CABG: ‘Xarelto’ 2.5mg BID 1.8% vs. 0.6% HR 3.46 (p<0.001); ‘Xarelto’ 5mg BID 2.4% vs. 0.6% HR 4.47 (p<0.001)
  • Intracranial haemorrhage: ‘Xarelto’ 2.5mg BID 0.4% vs. 0.2% HR 2.83 (p=0.04); ‘Xarelto’ 5mg BID 0.7% vs. 0.2% HR 3.74 (p=0.005)
♦ The rate of fatal bleeding was low and there was no significant difference with ‘Xarelto’ plus standard of care compared with standard of care plus placebo: ‘Xarelto’ 2.5mg BID 0.1% vs. 0.2% HR 0.67 (p=0.45); ‘Xarelto’ 5mg BID 0.4% vs. 0.2% HR 1.72 (p=0.20)

*The TIMI scale is one of the most well-known risk scoring methods for a patient hospitalised with a heart attack. Using a patient’s current vital health information as a guide, the TIMI scale provides a numeric value for the patient’s potential prognosis, including short-term risk of death.
 References

About Xarelto® (Rivaroxaban)
Rivaroxaban is the most broadly indicated novel oral anticoagulant and is marketed under the brand name Xarelto®. To date, Xarelto has been approved for use in the following venous arterial thromboembolic (VAT) indications:

- The prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) with one or more risk factors in more than 70 countries worldwide
- The treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) in adults in more than 70 countries worldwide
- The prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery in more than 120 countries worldwide

Since the first approval of Xarelto in 2008 in the orthopaedic setting, more than two and a half million patients worldwide have received Xarelto in daily clinical practice in this indication alone.

Rivaroxaban was discovered by Bayer HealthCare, and is being jointly developed with Janssen Research & Development, LLC. Xarelto is marketed outside the U.S. by Bayer HealthCare and in the U.S. by Janssen Pharmaceuticals, Inc. (a Johnson & Johnson Company).

Anticoagulant medicines are potent therapies used to prevent or treat serious illnesses and potentially life threatening conditions. Before initiating therapy with anticoagulant medicines, physicians should carefully assess the benefit and risk for the individual patient.

Responsible use of Xarelto is a high priority for Bayer, and the company has developed a Prescribers Guide for physicians and a Xarelto Patient Card for patients to support best practices. To learn more, please visit: https://prescribe.xarelto.com.

To learn more about thrombosis, please visit www.thrombosisadviser.com
To learn more about VAT, please visit www.VATspace.com
To learn more about Xarelto, please visit www.xarelto.com

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