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Reduction of Stent Thrombosis in Patients With Acute Coronary Syndromes Treated With Rivaroxaban in ATLAS-ACS 2 TIMI 51

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Objectives The aim of this study was to determine if rivaroxaban is associated with a reduction in stent thrombosis among patients with acute coronary syndromes (ACS) in the ATLAS-ACS 2 TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome—Thrombolysis in Myocardial Infarction 51) trial.

Background Dual antiplatelet therapy (DAPT) has been the mainstay of efforts to prevent stent thrombosis. Because thrombin is a potent stimulant of platelet activation, we hypothesized that inhibition of thrombin generation via factor Xa inhibition may further reduce the risk of stent thrombosis.

Methods The ATLAS-ACS 2 TIMI 51 study was a placebo-controlled trial that randomly assigned 15,526 patients with recent ACS to receive twice-daily doses of either 2.5 mg or 5 mg of rivaroxaban or placebo for a mean of 13 months and up to 31 months.

Results Among patients who had a stent placed before or at the time of the index event, rivaroxaban significantly reduced independently adjudicated Academic Research Consortium definite and probable stent thrombosis in the pooled (1.9% vs. 1.5%; hazard ratio [HR]: 0.65; $p = 0.017$) and the 2.5 mg twice-daily (1.9% vs. 1.5%; HR: 0.61; $p = 0.023$) treatment groups when compared with placebo, with a trend toward a reduction in the 5 mg twice-daily treatment group (1.9% vs. 1.5%; HR: 0.70; $p = 0.089$). Among patients who received both aspirin and a thienopyridine (stratum 2), the benefit of rivaroxaban emerged during the period of active treatment with DAPT (HR: 0.68; 95% CI: 0.50 to 0.92, combined rivaroxaban group vs. placebo). Among stented patients who were treated with dual antiplatelet therapy, there was a mortality reduction among those treated with twice-daily rivaroxaban 2.5 mg (HR: 0.56; 95% CI: 0.35 to 0.89; $p = 0.014$).

Conclusions Among stented patients with ACS treated with DAPT, the administration of twice-daily rivaroxaban 2.5 mg was associated with a reduction in stent thrombosis and mortality. (An Efficacy and Safety Study for Rivaroxaban in Patients With Acute Coronary Syndrome; NCT00809965) (J Am Coll Cardiol 2013;62:286–90) © 2013 by the American College of Cardiology Foundation

Percutaneous coronary intervention (PCI) is the predominant revascularization strategy in patients with acute coronary syndromes (ACS), and intracoronary stents have improved procedural success and decreased rates of angiographic restenosis compared with conventional balloon angioplasty (1). Although stents have led to improvements in target lesion revascularization rates, they have also been associated with stent thrombosis, a highly morbid complication (2).

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The incidence of stent thrombosis is significantly reduced by the administration of dual antiplatelet therapy (DAPT), implicating platelet activation as an important mediator of this complication (3). Efforts to reduce stent thrombosis have therefore focused on minimizing the discontinuation of DAPT and identifying those patients who have a poor response to thienopyridine therapy (4).

There have been relatively few contemporary studies examining oral anticoagulation and its role in the prevention of thrombotic complications of ACS and stent thrombosis (3,5). Rivaroxaban is an oral anticoagulant that directly and selectively inhibits factor Xa, interrupts the coagulation cascade, and thereby reduces the formation of thrombin. Inhibition of factor Xa is an attractive mechanistic target because thrombin generated on the surface of the activated platelet induces further platelet activation through the thrombin receptor (protease-activated receptor 1) to form a local positive-feedback loop (6). Indeed, rivaroxaban successfully inhibited high-shear–induced stent thrombosis in a porcine ex vivo model; when combined with DAPT, rivaroxaban reduced stent thrombus weight to a nearly undetectable limit of 2% (vs. 21% with DAPT alone) (7). It was therefore hypothesized that rivaroxaban administration is associated with a reduction in stent thrombosis, and this hypothesis was prospectively tested among patients with ACS randomized in the ATLAS-ACS 2 TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome—Thrombolysis in Myocardial Infarction 51) trial.

Abbreviations and Acronyms

ACS = acute coronary syndrome(s)

DAPT = dual antiplatelet therapy

PCI = percutaneous coronary intervention

Methods

The ATLAS-ACS 2 TIMI 51 trial (8,9) enrolled patients (≥18 years of age) who presented with symptoms suggestive of ACS. The present analysis was restricted to patients with a history of stent placement, including those receiving stents before study enrollment and those who received stents during the index PCI. Enrollment occurred within 7 days (median: 4.3 days) of hospital admission, and patients were randomly assigned in a 1:1:1 fashion to twice-daily administration of either 2.5 mg or 5.0 mg of rivaroxaban or placebo, with a maximum follow-up of 31 months.

All patients were to receive standard medical therapy at the enrolling physician's discretion at a dose recommended in either national or local guidelines. Stratum 1 was defined as those patients whom the enrolling physician chose to treat with aspirin alone, and stratum 2 was defined as those patients treated with aspirin plus a thienopyridine (8,9).

The primary efficacy endpoint of the ATLAS-ACS 2 TIMI 51 trial was a composite of death from cardiovascular causes, myocardial infarction, and stroke (ischemic, hemorrhagic, and stroke of uncertain cause) (8). Complete definitions of the endpoints have been reported previously (9). Stent thrombosis was a predefined endpoint reported by the enrolling physician and was independently adjudicated based upon the Academic Research Consortium (ARC) designations of definite, probable, or possible (2).

Statistical analysis. Efficacy analyses were performed using a modified intention-to-treat (mITT) approach, which has been described previously (8,9). Sensitivity efficacy analyses were conducted with the use of an ITT approach, which included all patients and all endpoint events occurring after randomization until the global treatment end date.

Hazard ratios (HR) with 2-sided 95% confidence intervals (CI) were used to compare the study groups. Rates of the endpoints were expressed as Kaplan-Meier estimates through 24 months. Results were examined according to major subgroups for general consistency of treatment effect, and interaction testing was performed.

Results

Of the 15,342 patients included in the MITT analysis, 9,631 (63%) underwent PCI and had at least 1 stent inserted either before randomization or during their index event.

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