Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 61, No. 18, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.01.066

Rivaroxaban in Patients Stabilized After a ST-Segment Elevation Myocardial Infarction

Results From the ATLAS ACS-2–TIMI-51 Trial (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis In Myocardial Infarction-51)

Jessica L. Mega, MD, MPH,* Eugene Braunwald, MD,* Sabina A. Murphy, MPH,* Alexei N. Plotnikov, MD,† Paul Burton, MD, PhD,† Robert Gabor Kiss, MD, PhD,‡ Alexander Parkhomenko, MD, PhD,§ Michal Tendera, MD, PhD,‖ Petr Widimsky, MD, PhD,¶ C. Michael Gibson, MS, MD*#

Boston, Massachusetts; Raritan, New Jersey; Budapest, Hungary; Kiev, Ukraine; Katowice, Poland; and Prague, Czech Republic

Objectives The present analysis reports on the pre-specified subgroup of ST-elevation myocardial infarction (STEMI) patients, in whom anticoagulant therapy has been of particular interest.

Background In 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), rivaroxaban reduced cardiovascular events across the spectrum of acute coronary syndrome (ACS).

Methods Seven thousand eight hundred seventeen patients in ATLAS ACS-2-TIMI 51 presented with a STEMI. After being stabilized (1 to 7 days), they underwent randomization to twice daily rivaroxaban 2.5 mg, rivaroxaban 5 mg, or placebo. Data are presented as 2-year Kaplan-Meier rates, and for intention-to-treat (ITT) and modified ITT (mITT) analyses.

Results Among STEMI patients, rivaroxaban reduced the primary efficacy endpoint of cardiovascular death, myocardial infarction, or stroke, compared with placebo (ITT: 8.4% vs. 10.6%, hazards ratio [HR]: 0.81, 95% confidence interval [CI]: 0.67 to 0.97, $p = 0.019$; mITT: 8.3% vs. 9.7%, HR: 0.85, 95% CI: 0.70 to 1.03, $p = 0.09$). This reduction emerged by 30 days (ITT and mITT: 1.7% vs. 2.3%, $p = 0.042$) and was evident in analyses that included events while patients received background dual antiplatelet therapies (ITT: 7.9% vs. 11.9%, $p = 0.010$; mITT: 7.7% vs. 10.1%, $p = 0.061$). In terms of the individual doses, rivaroxaban 2.5 mg reduced cardiovascular death (ITT: 2.5% vs. 4.2%, $p = 0.006$; mITT: 2.2% vs. 3.9%, $p = 0.006$), which was not seen with 5 mg of rivaroxaban. Rivaroxaban versus placebo increased non-coronary artery bypass grafting Thrombolysis In Myocardial Infarction major bleeding (2.2% vs. 0.6%, $p < 0.001$) and intracranial hemorrhage (0.6% vs. 0.1%, $p = 0.015$) without a significant increase in fatal bleeding (0.2% vs. 0.1%, $p = 0.51$).

Conclusions In patients with a recent STEMI, rivaroxaban reduced cardiovascular events. This benefit emerged early and persisted during continued treatment with background antiplatelet therapies. Rivaroxaban compared with placebo increased the rate of major bleeding, but there was no significant increase in fatal bleeding. (An Efficacy and Safety Study for Rivaroxaban in Patients With Acute Coronary Syndrome; NCT00809965) (J Am Coll Cardiol 2013;61:1853–9) © 2013 by the American College of Cardiology Foundation

From the *TIMI Study Group, Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; †Johnson & Johnson Pharmaceutical Research and Development, Raritan, New Jersey; ‡Department of Cardiology, Military Hospital, Budapest, Hungary; §National Scientific Center Institute of Cardiology, Kiev, Ukraine; ‖Medical University of Silesia, Katowice, Poland; ¶Charles University, Prague, Czech Republic; and the #Cardiovascular Division, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts. This study was supported by research grants from Johnson & Johnson Pharmaceutical Research and Development and Bayer Healthcare. Dr. Mega has received research grant support from Johnson & Johnson, Bayer Healthcare, Bristol-Myers Squibb/sanofi-aventis, Daiichi Sankyo, Eli Lilly; research supplies from Accumetrics and Nanosphere; and honoraria

JACC Vol. 61, No. 18, 2013
May 7, 2013:1853–9

Abbreviations and Acronyms

ACS = acute coronary syndrome

CABG = coronary artery bypass grafting

CI = confidence interval

HR = hazard ratio

ITT = intention-to-treat

MI = myocardial infarction

mITT = modified intention-to-treat

NSTEMI = non–ST-elevation MI

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

Morbidity and mortality rates following ST-segment elevation myocardial infarction (STEMI) have declined over time due in part to the delivery of timely reperfusion and in-hospital treatment with anticoagulant and antiplatelet therapies (1,2). Nonetheless, the cumulative risk of death and ischemic events persists during the initial treatment period and after the acute STEMI event (3). Thus, ways to prevent future complications in this at-risk patient population continue to be explored.

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) is the largest study to date to test a novel Xa inhibitor, rivaroxaban, in patients with an acute coronary syndrome (ACS). In the trial, as a whole, rivaroxaban reduced recurrent cardiovascular events across the spectrum of ACS (4,5). The present analysis focuses on the results of rivaroxaban versus placebo in the pre-specified subgroup of patients following a STEMI, in whom long-term anticoagulant therapy has been of particular interest. In addition, this analysis addresses several other key aspects of the trial: 1) the results of rivaroxaban versus placebo early after initiation of therapy, during a time when the post-STEMI event rates are at their highest; 2) the effect of rivaroxaban among patients who continued their background antiplatelet therapies, thus providing a particularly rigorous test of the additive role of this novel anticoagulant; and 3) further material on data completeness.

Methods

Study population. ATLAS ACS-2-TIMI-51 was a randomized, double-blind, placebo-controlled, event-driven trial that included 15,526 patients (≥18 years of age without an upper age limit) who presented with symptoms suggestive of ACS and a diagnosis of STEMI, non–ST-elevation MI (NSTEMI), or unstable angina. Patients were enrolled within 1 to 7 days after hospital admission. They needed to be stabilized before enrollment, with the initial management strategies completed. Patients were randomized in a 1:1:1 fashion to twice daily administration of either rivaroxaban 2.5 mg, rivaroxaban 5 mg, or placebo. They received standard care, including low-dose aspirin therapy and a thienopyridine (either clopidogrel or ticlopidine per the national or local guidelines). The key eligibility criteria and definitions of the endpoints have been published (4).

Statistical analysis. Rates of the endpoints were expressed as Kaplan-Meier event rates through 24 months. Treatment groups were evaluated using hazard ratios (HRs) and 2-sided 95% confidence intervals (CIs) using Cox proportional hazard models. Testing occurred between doses of rivaroxaban and placebo, based on the log-rank test, stratified by the intention to use a thienopyridine. The term rivaroxaban refers to the combined doses unless the individual doses are indicated. As pre-specified, this analysis focused on a subgroup of patients based on the index event (i.e., STEMI). Additionally, analyses were conducted that included events that occurred while patients were continuing on dual antiplatelet therapy. Exploratory analyses were conducted through 30 days. Data for the efficacy endpoints are presented for the intention-to-treat (ITT) analysis to provide complete accounting of events and for the modified intention-to-treat (mITT) analysis. The ITT analysis consists of all randomized patients and all first endpoint events through the global treatment end date. The mITT analysis consists of all randomized patients and the first endpoint events that occurred no later than: 1) the global treatment end date; 2) 30 days following early permanent discontinuation of the study drug; or 3) 30 days following randomization for patients who did not receive study drug. Thus, the mITT events are a subset of the ITT events. Before unblinding, 90 patients within the STEMI subgroup were excluded from the efficacy analyses due to trial misconduct at 3 sites. Data for the safety endpoints corresponds to the safety analysis set (4).

Results

In ATLAS ACS-2–TIMI-51, a total of 7,817 patients presented with a STEMI. The baseline characteristics of the STEMI patients were well matched across the treatment groups (Table 1). Background therapy included aspirin and a thienopyridine in 98.8% and 96.8% of the patients, respectively. Among the STEMI population, the median time from index STEMI to randomization was 4.7 days (interquartile range: 3.3 to 6.0 days).

for consulting from American Genomics, Boehringer Ingelheim, Janssen, and Merck. Dr. Braunwald has received research grant support from Abbott, AstraZeneca, Amgen, Bayer Healthcare, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Merck (SPRI), Pfizer, Roche (Diagnostics), sanofi-aventis, Johnson & Johnson; and has been a consultant for Merck (no compensation), Amorcyte, Daiichi Sankyo, The Medicines Co., Ikaria, CardioRentis, sanofi-aventis, and CVRx (no compensation). Ms. Murphy has received research grant support from Bayer Healthcare, Johnson & Johnson; and honoraria for consulting from Amarin Pharmaceuticals, and Eli Lilly and Company. Drs. Kiss, Parkhomenko, Tendera, and Widimsky have received research grant support from Johnson & Johnson and Bayer Healthcare. Drs. Burton and Plotnikov are employed by and own stock in Johnson & Johnson. Dr. Gibson has received research grant support from Johnson & Johnson, Bayer Healthcare, Bristol-Myers Squibb; honoraria for consulting from Portola Pharmaceuticals, sanofi-aventis, The Medicines Co., Daiichi Sankyo Company, Eli Lilly and Company, Biogen IDEC, Bristol-Myers Squibb, Ischemix, Inc., Johnson & Johnson, Bayer Healthcare, GlaxoSmithKline, Merck Schering Plough, Ortho McNeil, Medicure, Inc., Archemix, Inc., Genentech, Inc., and Boeringer Ingelheim; payment for lectures from Daiichi Sankyo Company, Eli Lilly and Company, Medicines Co.; and payment for development of educational presentations from Daiichi Sankyo Company and Eli Lilly and Company.

Manuscript received November 21, 2012; revised manuscript received January 7, 2013, accepted January 15, 2013.