JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 71, NO. 5, 2018

PUBLISHED BY ELSEVIER

Ticagrelor for Secondary Prevention of Atherothrombotic Events in Patients With Multivessel Coronary Disease

Sameer Bansilal, MD, MS,[a] Marc P. Bonaca, MD, MPH,[b] Jan H. Cornel, MD, PhD,[c] Robert F. Storey, MD,[d] Deepak L. Bhatt, MD, MPH,[b] Ph. Gabriel Steg, MD,[e,f] Kyungah Im, PhD,[b] Sabina A. Murphy, MPH,[b] Dominick J. Angiolillo, MD, PhD,[g] Robert G. Kiss, MD,[h] Alexander N. Parkhomenko, MD, PhD,[i] Jose Lopez-Sendon, MD, PhD,[j] Daniel Isaza, MD,[k] Assen Goudev, MD, DSc,[l] Frederic Kontny, MD, PhD,[m,n] Peter Held, MD, PhD,[o] Eva C. Jensen, MD, PhD,[o] Eugene Braunwald, MD,[b] Marc S. Sabatine, MD, MPH,[b] A.J. Oude Ophuis, MD, PhD[c,p]

ABSTRACT

BACKGROUND Patients with prior myocardial infarction (MI) and multivessel coronary disease (MVD) are at high risk for recurrent coronary events.

OBJECTIVES The authors investigated the efficacy and safety of ticagrelor versus placebo in patients with MVD in the PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54) trial.

METHODS Patients with a history of MI 1 to 3 years before inclusion in the PEGASUS-TIMI 54 trial were stratified in a pre-specified analysis based on the presence of MVD. The effect of ticagrelor (60 mg and 90 mg) on the composite of cardiovascular death, MI, or stroke (major adverse cardiovascular events [MACE]), as well as the composite of coronary death, MI, or stent thrombosis (coronary events), and on TIMI major bleeding, intracranial hemorrhage (ICH), and fatal bleeding were evaluated over a median of 33 months.

RESULTS A total of 12,558 patients (59.4%) had MVD. In the placebo arm, compared with patients without MVD, those with MVD were at higher risk for MACE (9.37% vs. 8.57%, adjusted hazard ratio [HR_{adj}]: 1.24; $p = 0.026$) and for coronary events (7.67% vs. 5.34%, HR_{adj}: 1.49; $p = 0.0005$). In patients with MVD, ticagrelor reduced the risk of MACE (7.94% vs. 9.37%, HR: 0.82; $p = 0.004$) and coronary events (6.02% vs. 7.67%, HR: 0.76; $p < 0.0001$), including a 36% reduction in coronary death (HR: 0.64; 95% confidence interval: 0.48 to 0.85; $p = 0.002$). In this subgroup, ticagrelor increased the risk of TIMI major bleeding (2.52% vs. 1.08%, HR: 2.67; $p < 0.0001$), but not ICH or fatal bleeds.

CONCLUSIONS Patients with prior MI and MVD are at increased risk of MACE and coronary events, and experience substantial relative and absolute risk reductions in both outcomes with long-term ticagrelor treatment relative to those without MVD. Ticagrelor increases the risk of TIMI major bleeding, but not ICH or fatal bleeding. For patients with prior MI and MVD, ticagrelor is an effective option for long-term antiplatelet therapy. (Prevention of Cardiovascular Events [e.g., Death From Heart or Vascular Disease, Heart Attack, or Stroke] in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin [PEGASUS]; NCT01225562) (J Am Coll Cardiol 2018;71:489-96) © 2018 by the American College of Cardiology Foundation.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the [a]Zena and Michael Weiner Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York; [b]TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [c]Department of Cardiology, Noordwest Ziekenhuisgroep, Alkmaar and Dutch Network for Cardiovascular Research (WCN), the Netherlands; [d]Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, United Kingdom; [e]DHU (Département Hospitalo-Universitaire)-FIRE (Fibrosis, Inflammation, REmodelling), Hôpital Bichat, AP-HP (Assistance Publique-Hôpitaux de Paris), Université Paris-Diderot, Sorbonne-Paris Cité, and FACT (French Alliance for Cardiovascular clinical Trials), an F-CRIN network, INSERM U-1148, Paris, France; [f]National Heart and Lung Institute, Institute of Cardiovascular Medicine and Science, Royal Brompton Hospital, Imperial College, London, United Kingdom; [g]Division of Cardiology, University of Florida College of Medicine, Jacksonville, Florida; [h]Department of Cardiology, Military Hospital, Budapest, Hungary; [i]Emergency Cardiology Department, Institute of Cardiology, Kiev, Ukraine; [j]Hospital Universitario La Paz, Madrid, Spain;

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2017.11.050

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft

CI = confidence interval

CV = cardiovascular

DAPT = dual antiplatelet therapy

HR = hazard ratio

ICH = intracranial hemorrhage

KM = Kaplan-Meier

MACE = major adverse cardiovascular event(s)

MI = myocardial infarction

MVD = multivessel disease

NNT_{3yr} = number needed to treat for 3 years

PAD = peripheral artery disease

PCI = percutaneous coronary intervention

TIMI = Thrombolysis In Myocardial Infarction

The PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54) trial evaluated the benefit of long-term treatment with 2 doses of ticagrelor (60 mg and 90 mg twice daily) compared with placebo in patients treated with low-dose aspirin who had a history of myocardial infarction (MI) between 1 and 3 years before randomization and who also had additional risk factors for recurrent atherothrombotic events. Ticagrelor reduced the risk of major adverse cardiovascular (CV) events (MACE) (CV death, MI, or stroke), with an increase in nonfatal major bleeding (1).

Patients with multivessel coronary artery disease (MVD) have more advanced atherosclerosis, with higher rates of in-hospital events, as well as recurrent atherothrombotic coronary events and death (2–6). Significant debate has centered on revascularization strategies in MVD patients; less attention has been paid to the intensity and duration of antithrombotic therapy. Recently, data from multiple small trials have provided some evidence of reduction in major ischemic events with more intense and longer duration antiplatelet therapy in patients with MVD (7).

SEE PAGE 497

In this pre-specified analysis from the PEGASUS-TIMI 54 trial, we evaluated the efficacy and safety of long-term ticagrelor therapy in patients with prior MI and MVD.

METHODS

The design and primary overall results of PEGASUS-TIMI 54 have been previously published (8). Patients with a history of MI 1 to 3 years previously and ≥1 additional atherothrombotic risk factor (age >65 years, diabetes mellitus requiring medication, second prior spontaneous MI, chronic renal dysfunction, or MVD) were randomized to ticagrelor (90 mg or 60 mg

[k]Fundacion Cardioinfantil, Instituto de Cardiología, Bogotá, Cundinamarca, Colombia; [l]Medical University Sofia, Queen Ioanna Hospital, Sofia, Bulgaria; [m]Department of Cardiology, Stavanger University Hospital, Stavanger, Norway; [n]Drammen Heart Center, Drammen, Norway; [o]AstraZeneca Research and Development, Mölndal, Sweden; and the [p]Department of Cardiology, CWZ Hospital, Nijmegen, the Netherland. Dr. Angiolillo is the recipient of funding from the Scott R. MacKenzie Foundation and the National Institute of Health/National Center for Advancing Translational Sciences Clinical and Translational Science Award to the University of Florida UL1 TR000064 and National Institutes of Health/National Human Genome Research Institute U01 HG007269, outside the submitted work. Dr. Bansilal has served on advisory boards of AstraZeneca, Merck, and Janssen; has received speaking or consulting fees from AstraZeneca and Janssen; has received research support from AstraZeneca; and is currently an employee of Bayer LLC, but not at the time of this research. Dr. Bonaca has received grant support to the TIMI Study Group from AstraZeneca and Merck; and has been a consultant to Aralez, AstraZeneca, Bayer, and Merck. Dr. Cornel has received personal fees from Merck, Eli Lilly, and AstraZeneca. Dr. Storey has received research grants and honoraria from AstraZeneca; research grants from PlaqueTec; and consultancy fees from Actelion, AstraZeneca, Avacta, Bayer, Bristol-Myers Squibb/Pfizer, Novartis, PlaqueTec, The Medicines Company, and Thermo Fisher Scientific. Dr. Bhatt has served on the advisory boards of Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences; has served on the board of directors of the Boston VA Research Institute and the Society of Cardiovascular Patient Care; served as chair of the American Heart Association Quality Oversight Committee; has served on data monitoring committees for the Cleveland Clinic, Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine, and Population Health Research Institute; has received honoraria from the American College of Cardiology (senior associate editor, *Clinical Trials and News*, ACC.org), Belvoir Publications (editor in chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (editor in chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (guest editor; associate editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (chief medical editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (secretary/treasurer), and WebMD (CME steering committees); has other relationships with *Clinical Cardiology* (deputy editor), NCDR-ACTION Registry Steering Committee (chair), and VA CART Research and Publications Committee (chair); has received research funding from Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Ironwood, Ischemix, Lilly, Medtronic, Pfizer, Roche, Sanofi, and The Medicines Company; has received royalties from Elsevier (editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); has been a site coinvestigator for Biotronik, Boston Scientific, and St. Jude Medical (now Abbott); has been a trustee for the American College of Cardiology; and has performed unfunded research for FlowCo, Merck, PLx Pharma, and Takeda. Dr. Steg has received research grants from Merck, Sanofi, and Servier; and speaking or consulting fees from Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, GlaxoSmithKline, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron, Sanofi, and Servier. Dr. Im and Ms. Murphy have received research grant support to their institution from AstraZeneca. Dr. Angiolillo has received individual fees or honoraria for consulting from Amgen, AstraZeneca, Bayer, Chiesi, Daiichi-Sankyo, Eli Lilly, Janssen, Merck, PLx Pharma, Pfizer, and Sanofi; and for participating in review activities from CeloNova and St. Jude Medical; and has institutional payments for grants from Amgen, AstraZeneca, Biosensors, CeloNova, CSL Behring, Daiichi-Sankyo, Matsutani Chemical Industry Co., Merck, Novartis, and Renal Guard Solutions. Dr. Kiss has served on speakers bureaus for Bayer AG, Pfizer, Boehringer Ingelheim, and