Ticagrelor and Major Adverse Limb Events: A Systematic Review and Meta-Analysis

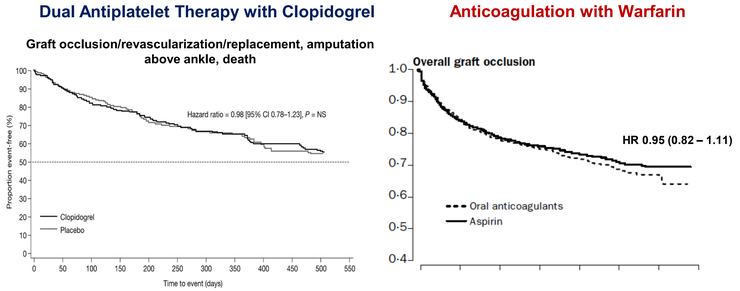
Marc P. Bonaca[1,2], Deepak L. Bhatt[3], Philippe Gabriel Steg[4], Thomas A. Zelniker[5], Warren Capell[1,2], William R. Hiatt[1,2], Connie N. Hess[1,2], Marc S. Sabatine[3,6]

[1]University of Colorado School of Medicine; [2]CPC Clinical Research, Aurora, CO, [3]Brigham and Women's Hospital, Boston, MA, [4]Hôpital Bichat, Université de Paris, INSERM Unité 1148 (P.G.S.), Paris, [5]Vienna General Hospital, Medical University of Vienna, [6]TIMI Study Group

BACKGROUND

- Major adverse limb events including acute limb ischemia (ALI), major amputation of vascular etiology and urgent peripheral revascularization for ischemia are morbid events associated with significant disability, limb loss and death
- Although thrombosis is a primary driver of these outcomes, prior trials of dual antiplatelet therapy (DAPT) with aspirin and clopidogrel or with therapeutic warfarin have not significantly reduced this risk (Figure 1).[1,2]

Figure 1



Belch et al. Journal of Vascular Sugery. 2010
Dutch Bypass Oral anticoagulants or Aspirin (BOA) Study Group. Lancet. 2000

- Ticagrelor is a 3rd generation $P2Y_{12}$ inhibitor that is more potent and less variable than clopidogrel and has been shown to reduce the risk of major adverse cardiovascular events in patients with acute coronary syndromes (ACS), prior myocardial infarction and diabetes with stable coronary disease.
- The effect of ticagrelor added to aspirin on major adverse limb events in patients with atherosclerosis is of clinical interest.

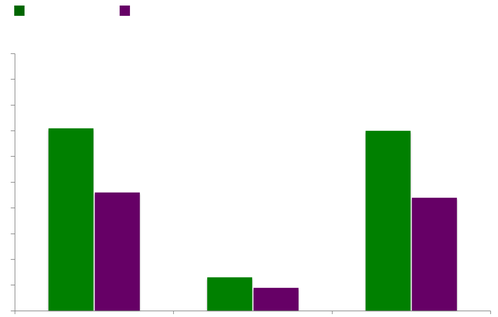
METHODS

- A search for randomized, double-blind, clinical trials of ticagrelor added to aspirin versus aspirin alone that had adjudicated limb outcomes, more than a year of follow up and at least 25 MALE events was performed
- Reported effects on MALE were meta-analyzed using a fixed effects model.

RESULTS – SYSTEMATIC REVIEW

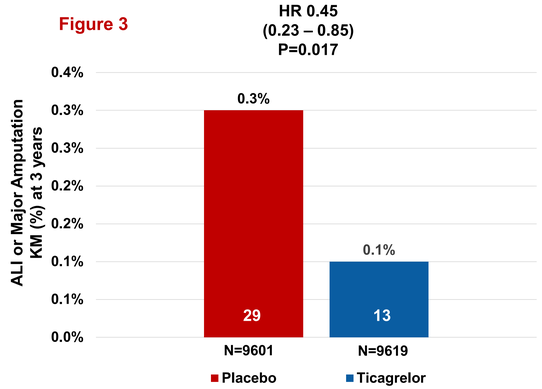
- Two trials were identified meeting criteria for meta-analysis
- ***PEGASUS-TIMI 54*** (Figure 2) included 21,162 patients with prior MI randomized to ticagrelor 60 mg twice daily, ticagrelor 90 mg twice daily, or placebo and reported rates at 3 years.[3]
- Major adverse limb events were adjudicated as acute limb ischemia or revascularization for ischemia with a total of 108 events.[4]
- With both doses pooled there was a ~35% reduction in major adverse limb events. [4]

Figure 2



- ***THEMIS*** (Figure 3) randomized 19,220 with diabetes mellitus and coronary disease to ticagrelor twice daily (initially 90 mg twice daily and later 60 mg twice daily) or placebo and reported rates at 3 years.[5,6]
- Major adverse limb events were adjudicated as acute limb ischemia or major amputation of a vascular cause with a total of 42 events. [5,6]
- Overall there was a ~55% reduction in major adverse limb events. [5,6]

Figure 3



1. Belch JJ, Dormandy J, Biasi GM…Leizorovicz A. et al. J Vasc Surg 2010
2. Dutch Bypass Oral anticoagulants or Aspirin (BOA) Study Group. Lancet 2000
3. Bonaca MP, Bhatt DL, Cohen M….Sabatine MS et al. NEJM 2015
4. Bonaca MP, Bhatt DL, Storey RF…Sabatine MS et al. NEJM 2016
5. Steg PG, Bhatt DL, Fox K…Leiter LA et al. NEJM 2019
6. Bhatt DL, Steg PG, Mehta SR…Harrington RA et al. Lancet 2019

RESULTS – META-ANALYSIS

- Across both trials there were a total of 150 first major adverse limb outcomes in a total of 40,392 patients with event rates of 0.7% and 0.3% in the placebo arms respectively.
- When combining the 60 mg and 90 mg doses, ticagrelor reduced the risk of major adverse limb events by 41% (HR 0.59, 95% CI 0.42 – 0.83, p=0.002), Figure 4

Figure 4

CONCLUSIONS

- Ticagrelor added to aspirin reduces major adverse limb events in stable patients with atherosclerosis by ~40%
- Although event rates in broad atherosclerosis populations and in the stable setting are relatively low, rates and absolute benefits would be expected to be greater in patients with lower extremity peripheral artery disease

DISCLOSURES

Disclosures: PEGASUS-TIMI 54 and THEMIS were funded through grants from AstraZeneca
Dr. Bonaca reports research grant support through CPC Clinical Research from Amgen, AstraZeneca, Bayer, Janssen, Merck, Pfizer. Dr. Hess reports research grant support to CPC Clinical Research from Amgen, Merck, and Bayer. Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Cereno Scientific; Elsevier Practice Update Cardiology; Medscape Cardiology, PhaseBio, PLx Pharma, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, Lexicon, Lilly, Medtronic, Pfizer, PhaseBio, PLx Pharma, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, Takeda.
Dr. Zelniker reports research grant support from the Deutsche Forschungsgemeinschaft (ZE 1109/1-1) and honoraria from AstraZeneca
Dr. Sabatine reports research grant support through Brigham and Women's Hospital from: Amgen; AstraZeneca; Bayer; Daiichi-Sankyo; Eisai; Intarcia; Janssen Research and Development; Jazz Pharmaceuticals; Medicines Company; MedImmune; Merck; Novartis; Pfizer; Quark Pharmaceuticals; Takeda, and consulting for: Amgen; Anthos Therapeutics; AstraZeneca; Bristol-Myers Squibb; CVS Caremark; DalCor; Dr. Reddy's Laboratories; Dynamix; Esperion; IFM Therapeutics; Intarcia; Janssen Research and Development; Medicines Company; MedImmune; Merck; Novartis.