International Journal of Cardiology 370 (2023) 51–57

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

External applicability of the Effect of ticagrelor on Health Outcomes in diabEtes Mellitus patients Intervention Study (THEMIS) trial: An analysis of patients with diabetes and coronary artery disease in the REduction of Atherothrombosis for Continued Health (REACH) registry

Jeremie Abtan [a,b], Deepak L. Bhatt [b,*], Yedid Elbez [a], Gregory Ducrocq [a], Shinya Goto [c], Sidney C. Smith Jr [d], E. Magnus Ohman [e], Kim A. Eagle [f], Kim Fox [g,h], Robert A. Harrington [i], Lawrence A. Leiter [j], Shamir R. Mehta [k], Tabassome Simon [l], Ivo Petrov [m], Peter R. Sinnaeve [n], Prem Pais [o], Eli Lev [p], Héctor Bueno [q], Peter Wilson [r], Philippe Gabriel Steg [a,g], on behalf of the REACH Registry Investigators [1]

[a] FACT (French Alliance for Cardiovascular clinical Trials), Université de Paris, Hôpital Bichat (Assistance Publique – Hôpitaux de Paris) and INSERM U-1148, all in Paris, France
[b] Brigham and Women's Hospital Heart & Vascular Center, Harvard Medical School, Boston, MA, USA
[c] Department of Medicine (Cardiology), Tokai University School of Medicine, Isehara, Kanagawa, Japan
[d] Division of Cardiology, Department of Medicine, University of North Carolina, Chapel Hill, USA
[e] Division of Cardiology, Department of Medicine, Duke University School of Medicine, Durham, North Carolina; Duke Clinical Research Institute, Durham, NC, USA
[f] University of Michigan Cardiovascular Center, Ann Arbor, USA
[g] National Heart and Lung Institute, Imperial College, London, United Kingdom
[h] Institute of Cardiovascular Medicine and Science, Royal Brompton Hospital, London, United Kingdom
[i] Stanford Center for Clinical Research, Department of Medicine, Stanford University, California, USA
[j] Division of Endocrinology and Metabolism, Li Ka Shing Knowledge Institute, St Michael's Hospital, University ot Toronto, Ontario, Canada
[k] Population Health Research Institute and Department of Medicine, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada
[l] Plateforme de Recherche Clinique de l'Est Parisien (URCEST-CRCEST-CRB), Saint-Antoine Hospital, AP-HP, Paris, France
[m] University Hospital Acibadem City Clinic Sofia, Sofia University St. Kliment Ohridski, Bulgaria
[n] Department of Cardiovascular Medicine, University Hospitals Leuven, Belgium
[o] Division of Clinical Research and Training, St. John's Research Institute, Bangalore, India
[p] Department of Cardiology, Rabin Medical Center, Petach Tikva, Department of Cardiology, Assuta Ashdod University Hospital, Ashdod, Faculty of Medicine, Ben Gurion University, Be'er Sheva, all in, Israel
[q] Cardiology Department, Hospital Universitario 12 de Octubre, Centro Nacional de Investigaciones Cardiovasculares, and CIBER de enfermedades CardioVasculares (CIBERCV), Madrid, Spain
[r] Mayo Clinic, Rochester, MN, USA

ARTICLE INFO

Keywords:
Diabetes mellitus
Stable coronary artery disease
Ticagrelor

ABSTRACT

Aims: THEMIS is a double-blind, randomized trial of 19,220 patients with diabetes mellitus and stable coronary artery disease (CAD) comparing ticagrelor to placebo, in addition to aspirin. The present study aimed to describe the proportion of patients eligible and reasons for ineligibility for THEMIS within a population of patients with diabetes and CAD included in the Reduction of Atherothrombosis for Continued Health (REACH) registry.
Methods and results: The THEMIS eligibility criteria were applied to REACH patients. THEMIS included patients ≥50 years with type 2 diabetes and stable CAD as determined by either a history of previous percutaneous coronary intervention, coronary artery bypass grafting, or documentation of angiographic stenosis of ≥50% of at least one coronary artery. Patients with prior myocardial infarction or stroke were excluded. In REACH, 10,156 patients had stable CAD and diabetes. Of these, 6515 (64.1%) patients had at least one exclusion criteria. From the remaining population, 784 patients did not meet inclusion criteria (7.7%) mainly due to absence of aspirin

* Corresponding author at: Brigham and Women's Hospital Heart & Vascular Center, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA.
E-mail address: DLBhattMD@post.Harvard.edu (D.L. Bhatt).

[1] A full list of the REACH Registry Investigators can be found in Bhatt DL, Steg PG, Ohman EM, et al. JAMA 2006;295:180–9.

https://doi.org/10.1016/j.ijcard.2022.10.132
Received 13 September 2021; Received in revised form 5 August 2022; Accepted 16 October 2022
Available online 19 October 2022

treatment (7.2%), yielding a 'THEMIS-eligible population' of 2857 patients (28.1% of patients with diabetes and stable CAD). The main reasons for exclusion were a history of myocardial infarction (53.1%), use of oral anticoagulation (14.5%), or history of stroke (12.9%). Among the 4208 patients with diabetes and a previous PCI, 1196 patients (28.4%) were eligible for inclusion in the THEMIS-PCI substudy.
Conclusions: In a population of patients with diabetes and stable coronary artery disease, a sizeable proportion appear to be 'THEMIS eligible.'
Clinical trial registration: http://www.clinicaltrials.gov identifier: NCT01991795

1. Introduction

Type 2 diabetes mellitus (T2DM) is a major risk factor for atherosclerosis, and patients with diabetes and documented atherosclerosis have a high risk of ischemic events [1,2], comparable to that of patients with prior myocardial infarction (MI). Antiplatelet therapy is used to mitigate that risk. In patients with diabetes in primary prevention, the most recent data support aspirin use in carefully selected patients [3–6]. For patients with documented coronary artery disease, aspirin is recommended regardless of the presence of diabetes mellitus [7–9].

The THEMIS (Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study, NCT01991795) trial is the first randomized controlled trial designed to test a strategy of a dual antiplatelet therapy with aspirin and ticagrelor in patients treated for diabetes mellitus with known coronary artery disease but without prior MI or stroke [10]. The trial met its primary endpoint with a reduction in the composite of cardiovascular death, non-fatal MI, or non-fatal stroke: 8.5% in the placebo arm versus 7.7% in the ticagrelor arm (HR: 0.90; [95% CI], 0.81 to 0.99; $p = 0.04$). However, there was an increase in the risk of major bleeding and a small, but statistically significant increase in the risk of intracranial hemorrhage (0.5% in the placebo group versus 0.7% in the ticagrelor group (HR: 1.71; [95% CI], 1.18 to 2.48; $p = 0.005$) events [11]. In the prespecified population with a history of percutaneous coronary intervention (PCI), the benefit of the addition of ticagrelor was even more clear with the reduction of the primary endpoint: 7.3% in the placebo arm versus 8.6% (HR 0.85; [95% CI], 0.74 to 0.97; $p = 0.013$), no increase in fatal bleeding (0.1% in both groups, (HR: 1.13; [95% CI], 0.36 to 3.50; $p = 0.83$) or intracranial hemorrhage (0.6% in both groups, (HR:1.21; [95% CI], 0.74 to 1.97; $p = 0.45$) [12,13]. In that population with a history of prior PCI, there was a 15% reduction in net irreversible harm, with a statistically significant interaction compared with patients without a history of PCI ($p = 0.012$).

Large randomized controlled trials (RCTs) raise the issue of the generalizability of their results in unselected patients from routine clinical practice [14–16]. Patients enrolled in RCTs are often highly selected and may not be representative of the actual target population. Therefore, the interpretation of trial findings of RCTs hinges, to some extent, on the representativeness of the trial population versus the target population [16–21]. Therefore, despite being the largest trial performed in patients with diabetes ($n = 19{,}220$), the applicability of THEMIS in a non-selected population merits evaluation.

In the present analysis, we sought to use the REduction of Atherothrombosis for Continued Health (REACH) registry [2,22], a large international observational registry of people with atherosclerotic CVD or its risk factors, to determine the proportion of THEMIS-eligible patients as well as the reasons for non-eligibility within the population of patients with diabetes, documented CAD, and no prior MI or stroke. In addition, we compared the clinical characteristics and outcomes of the THEMIS-eligible and non-eligible patients from REACH with those from patients actually randomized in the placebo arm of the THEMIS trial.

2. Methods

2.1. THEMIS trial design

The THEMIS trial is a phase-3 randomized controlled trial, in which ticagrelor twice daily (bid) was compared with placebo, on top of aspirin, in patients 50 years of age or older with T2DM treated by hypoglycemic medications for at least 6 months, and with documented coronary artery disease but without previous MI or stroke. The study enrolled participant from February 2014 and was completed in January 2019. Coronary artery disease was defined as a history of percutaneous coronary intervention, coronary artery bypass graft surgery, or angiographic evidence of at least 50% stenosis of at least 1 coronary artery. The detailed THEMIS inclusion and exclusion criteria are described in **Supplementary Table 1** [11,23]. The primary outcome was a composite of myocardial infarction, stroke, or cardiovascular death. Follow up visits were scheduled 90 days, 180 days, and 360 days after randomization. In a prespecified subgroup analysis, patients with a history of PCI were analyzed [12].

2.2. The REACH registry

The design of the Reduction of Atherothrombosis for Continued Health (REACH) registry has been previously described [2,22,24,25]. Briefly, from December 2003 and December 2004 it recruited over 69,000 consecutive patients who were 45 years of age or older with documented atherothrombosis (coronary, cerebrovascular, or peripheral artery disease) or at least 3 risk factors for atherothrombosis in 5587 centers from 44 countries across 6 major regions. Coronary artery disease was defined by a history of at least one of the following: myocardial infarction, unstable angina, stable angina, previous percutaneous coronary intervention, or previous coronary artery bypass grafting. Standardized case report forms were used in order to centrally collect the baseline characteristics of patients, including medical history, risk factors and medications. Clinical follow-up was collected each year for a minimum of 2 years and up to 4 years in selected countries. The protocol of the REACH registry was approved by institutional review boards and each patient gave informed consent. The detailed inclusion criteria are described in **Supplementary Table 2**.

2.3. 'THEMIS evaluable' population in REACH

In order to identify 'THEMIS eligible' patients in the REACH registry, we first excluded patients without documented CAD and patients without a history of diabetes **(Supplementary Fig. 1).** Then, we excluded the patients with missing information regarding the THEMIS inclusion or exclusion criteria. The remaining population constitutes the 'REACH CAD population with diabetes', which is the study population.

2.4. 'THEMIS eligible' population in REACH

The exclusion and exclusion criteria of THEMIS were applied to the 'REACH CAD population with diabetes.' The selection criteria had to be adjusted due to discrepancies between the information available in REACH and the requirements for inclusion in THEMIS. A full list of inclusion and exclusion criteria and adjustments is available in **Supplementary Table 3**. Patients meeting exclusion criteria represented the 'THEMIS excluded' population. The main exclusion criteria were: history of MI, history of stroke, treatment with dual antiplatelet therapy in the first 12 months after a stent implantation, treatment with anticoagulant therapy, treatment with non-steroidal anti-inflammatory drugs,

estimated glomerular filtration rate (eGFR) < 15 mL/min, and uncontrolled hypertension (defined as a systolic BP ≥180 mmHg and/or diastolic BP ≥100 mmHg). Then, the 'THEMIS eligible' population corresponded to the patients fulfilling the following inclusion criteria: age 50 years old or more, treatment by aspirin, and history of revascularization (PCI and/or CABG) or a history of stable angina. The patients not excluded but not fulfilling inclusion criteria were defined as the 'THEMIS not included' population.

2.5. Patients included in the THEMIS trial

We compared the baseline characteristics and outcomes of the 'THEMIS eligible' population in REACH to those of actual patients randomized to the placebo arm of the THEMIS trial. In addition, we compared baseline characteristics and outcomes of the 'THEMIS-PCI eligible' population in REACH to those of actual patients randomized to the placebo arm of the THEMIS-PCI substudy.

2.6. Outcomes

The outcomes defined in THEMIS were used for this analysis. The primary efficacy outcome of THEMIS was a composite outcome of cardiovascular death, myocardial infarction, or stroke. The secondary outcomes were each component of the composite as well as all-cause mortality, lower limb amputation, angioplasty and/or stenting for peripheral artery disease, bypass surgery for PAD, and intra-cranial hemorrhage. The irreversible harm outcome was prespecified as the composite of all-cause mortality (including fatal bleeding), myocardial infarction, stroke, or intracranial hemorrhage. Bleeding definitions differed between THEMIS and REACH so that no direct comparison could be made. As a consequence, the bleeding and transfusion rates are reported in each group separately for exploratory purposes. In REACH, serious bleeding was defined as any bleeding leading to hospitalization and/or transfusion. In the THEMIS trial, the BARC and PLATO definitions were used. To match with the serious bleeding definition from REACH, we took the BARC ≥3 and PLATO major as a threshold.

2.7. Statistical analysis

Baseline characteristics are described using mean ± standard deviation for continuous variables and frequencies and percentages for categorical variables. Continuous and categorical baseline variables were compared between REACH subgroups using ANOVA and Chi-square tests, respectively. All outcomes are described by Kaplan-Meier estimates at 4 years, with 95% confidence intervals (CI).

In order to allow statistical comparisons between THEMIS trial participants and THEMIS-eligible REACH participants, baseline characteristics were compared by Student and Chi-square tests for continuous and categorical variables respectively, and outcomes were also expressed as incidence rates by 100 patients-year with 95% CI.

3. Results

3.1. 'THEMIS-eligible' population in REACH

Among 65,531 patients enrolled in REACH, 13,068 (19.94%) had coronary artery disease and were pharmacologically treated for diabetes. Of these, 2912 were excluded from the analysis due to missing data regarding eligibility for THEMIS, yielding an 'evaluable' population of 10,156 patients constituting the 'REACH CAD population with diabetes'. A first group of 6515 patients (64.1%) had at least one THEMIS exclusion criteria and constitute the 'THEMIS excluded' population; a second subset of 784 patients (7.7%) did not fulfill one or more of the THEMIS inclusion criteria (among the following: age ≥ 50 years/old; a history of PCI or CABG or angiographic evidence of ≥50% lumen stenosis in one coronary artery or more; the use of aspirin) and constituted the 'THEMIS non-included' population. The remaining 2857 patients (27.7% of the evaluable population) constitute the 'THEMIS-eligible' population. The flow chart is presented in **Supplementary Fig. 1.**

The main reasons for exclusion were a history of MI (n = 5391 patients, 53.1%), the use of anticoagulation therapy (n = 1468, 14.5%) and a history of stroke (n = 1310 patients, 12.9%), and severe renal failure (n = 101, 0.9%). The main reasons for non-inclusion were the absence of aspirin use (n = 696, 19.1%) or age below 50 years (n = 101, 2.7%).

The baseline characteristics of the 'THEMIS-eligible' population are presented in **Supplementary Table 4** while those of 'THEMIS excluded' and 'THEMIS non-included' patients are presented in **Supplementary Table 5.**

3.2. Participants of the THEMIS trial included in the placebo arm

A total of 19,620 participants were included in THEMIS, and 9601 in the placebo arm. Their baseline characteristics are presented in **Supplementary Table 4**. In comparison with 'THEMIS-eligible' patients, they were younger (66.3 ± 7.75 years-old vs 68.8 years-old ±8.66), p < 0.001), more frequently male (68.9% vs 64.3%, p < 0.001) with a higher prevalence of hypertension (92.4% vs 89.2%, p < 0.001), and similar frequency of active smoking. They had higher rates of coronary revascularization (79.9% vs 70.39%, p < 0.001) driven by higher rates of previous PCI (58.3% vs 42.01%, p < 0.001) but lower rates of previous CABG (28.5% vs 36.83%, p < 0.001).

Guideline-recommended secondary prevention drug therapies were more frequently used among patients included in THEMIS, with higher rates of use of statin, beta blockers, and ACE-inhibitors or ARBs than in 'THEMIS eligible' patients from REACH.

3.3. Outcomes for THEMIS-eligible patients

'THEMIS-eligible' patients in REACH experienced a substantially higher primary outcome rate (per 100 patient/years) than patients enrolled in the placebo arm of THEMIS (4.0% versus 2.7%, p < 0.0001). The rates of all the components of the primary outcome were also higher in the 'THEMIS-eligible' population than in THEMIS participants (1.84% versus 1.13%, p < 0.001 for cardiovascular death, 2.27% versus 0.99%, p < 0.001 for non-fatal MI, and 1.15 versus 0.71, p < 0.001 for non-fatal stroke), as well as all-cause mortality (3.11% in THEMIS-eligible patients in REACH versus 1.86% in patients enrolled in the placebo arm of THEMIS, p < 0.001). The results are summarized in **Supplementary Table 6**, **Supplementary Table 7**, and Fig. 1.

Among the 'THEMIS-eligible' REACH patients, serious bleeding according to the definition in REACH occurred in 3.95% and the rate of transfusion was 3.67%. In patients enrolled in the THEMIS placebo arm, BARC ≥3 serious bleeding occurred in 2.56%, PLATO major bleeding in 2.27%, and transfusion was required in 1.43%.

3.4. 'THEMIS-PCI eligible' population in REACH

Among the 10,156 patients in the 'REACH CAD population with diabetes', 4208 (41.43%) had an history of previous PCI. Among them, 2742 had at least one exclusion criteria and 270 did not fulfill inclusion criteria, yielding a population of 1196 patients from the REACH registry eligible for THEMIS-PCI substudy (28.4% of patients with analyzable data). The flow-chart for this THEMIS-PCI analysis is presented in **Supplementary Fig. 2.** The main reasons for exclusion were a history of MI (n = 2415, 57.39%) followed by a history of stroke (n = 441, 10.48%) and treatment with an oral anticoagulant (n = 559, 13.28%) **(**Fig. 2**).** The main reasons for non-inclusion were the absence of aspirin use (n = 218, 14.9%), or an age below 50 years (n = 57, 3.9%). The characteristics of 'THEMIS-PCI eligible' patients in REACH are presented in **Supplementary Table 8**.

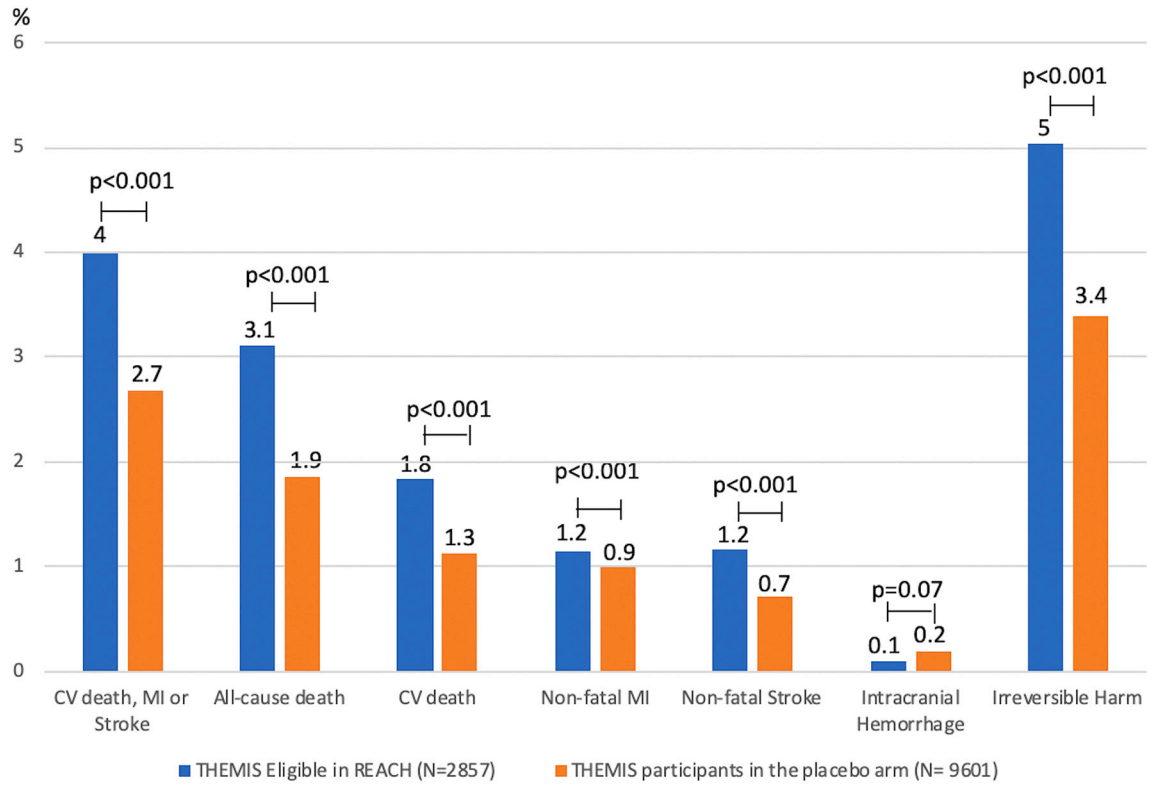

Fig. 1. Comparison of main CV event rate per 100 patient/years for the 'THEMIS eligible' patients from REACH and THEMIS patients in the placebo arm (%).

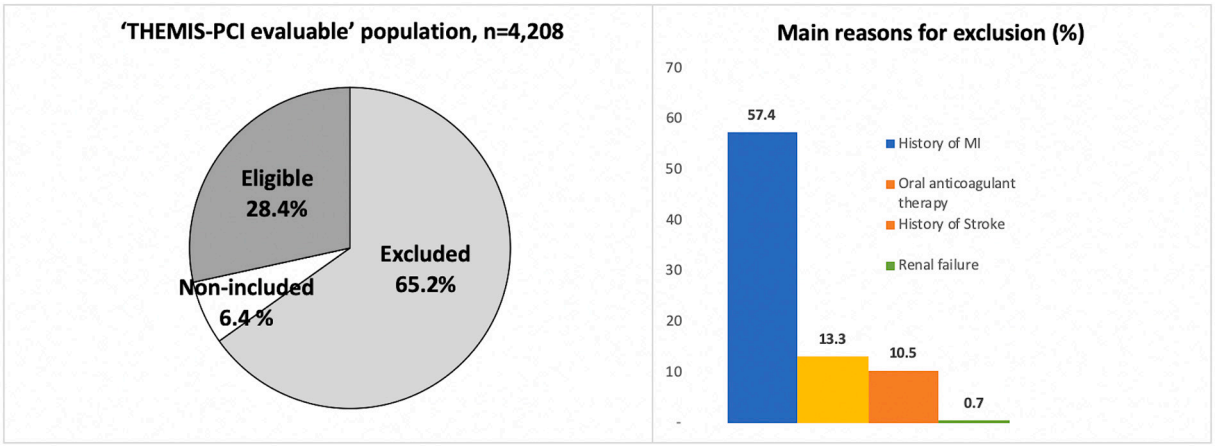

Fig. 2. Proportion of 'THEMIS-PCI' eligible and excluded in REACH registry and reasons for exclusion.

3.5. Participants of THEMIS PCI included in the placebo arm

A total of 11,154 patients were included in the THEMIS-PCI analysis representing 58.0% of the overall THEMIS trial and 5596 in the placebo arm. Their baseline characteristics are presented in **Supplementary Table 8.**

Compared with 'THEMIS-PCI eligible' patients from REACH, participants of THEMIS-PCI were younger (67.59 ± 8.53 years-old vs 66.4 years-old ±7.73), $p < 0.001$), more frequently male (69.3% vs 66.6%, p < 0.001) with a higher prevalence of hypertension (91.8% vs 88.0%, p < 0.001), current smoking (11.8% vs 11.2%, p < 0.001) and heart failure (13.7% vs 13.2%, p < 0.001) but lower prevalence of previous CABG (12.0% vs 19.9%, p < 0.001) and PAD (8.3% vs 11.0%, p < 0.001). As in the main comparison, guideline-recommended secondary prevention drug therapies were more frequently used among patients included in THEMIS-PCI, with higher rates of use of statins, beta-blockers, and ACE-inhibitors or ARBs than in 'THEMIS-PCI eligible' patients from REACH.

3.6. Outcomes for THEMIS-PCI eligible patients

'THEMIS-PCI eligible' patients in REACH experienced higher rates per 100 patient/years of the primary outcome compared with patients included in the placebo arm of the THEMIS-PCI trial THEMIS (3.80% versus 2.64%, $p < 0.0001$). The rate of cardiovascular death was also higher in the 'THEMIS-PCI eligible' population in REACH than in THEMIS-PCI participants (1.38% versus 0.99%, $p = 0.043$) as well as those of non-fatal stroke (1.35% versus 0.59%, $p < 0.001$) and all-cause mortality (2.58% in 'THEMIS-PCI eligible' patients in REACH versus 1.73% in patients enrolled in the placebo arm of THEMIS-PCI, $p =$

0.001). The rates of non-fatal MI were not different 1.15% for 'THEMIS-PCI eligible' patients versus 1.14% for THEMIS-PCI, $p = 0.97$, nor were the rates of intracranial hemorrhage (0.15 versus 0.22%, $p = 0.43$). The irreversible harm was significantly higher in the THEMIS-PCI population in REACH than in THEMIS-PCI enrolled in the placebo arm (4.74 versus 3.47 respectively, $p < 0.001$). The results are summarized in **Supplementary Table 9** and Fig. 3. The rate of amputation did not differ significantly between 'THEMIS-PCI eligible' patients and THEMIS-PCI participants (0.21% versus 0.80%, $p = 0.25$ whereas angioplasty and/or stenting for PAD and bypass surgery for PAD were more frequently used in the 'THEMIS-PCI eligible' patients. Lower limb outcomes are presented in **Supplementary Table 10.**

In 'THEMIS-PCI eligible' patients, serious bleeding occurred in 3.01% and the rate of transfusion was 2.54%. In THEMIS-PCI placebo arm patients, the rate of bleeding according to BARC≥3 definition occurred in 2.55%, PLATO major bleeding in 2.32%, and transfusion was required in 1.32%.

4. Discussion

In this analysis, over a quarter of patients with diabetes and CAD in the international REACH registry would have been eligible for the THEMIS randomized control trial and approximately the same proportion in THEMIS-PCI. In the interpretation of RCTs, and application of trial findings to routine practice, generalizability is critical [17–21]. One frequent criticism of RCTs is the concern over participants' selection criteria being so stringent that trial participants may no longer be representative of patients encountered in routine clinical practice and trial results may not be applicable to "real world" patients. In the present analysis, the 'THEMIS and THEMIS-PCI eligible' patients represented a sizeable fraction of the population of patients with coronary artery disease and diabetes.

The main reasons for exclusion were a history of MI (in approximately half of the patients), followed by the need for oral anticoagulation, and a prior history of stroke. More than 50% of CAD outpatients treated for diabetes had a history of a prior ischemic event in REACH, emphasizing the high ischemic risk of this population.

Compared with patients enrolled in the placebo arm of THEMIS and THEMIS-PCI, 'THEMIS eligible' and 'THEMIS-PCI eligible' patients from the REACH registry were older, with more comorbidities such as previous CABG, PAD, and atrial fibrillation. They were less likely to receive the evidence-based secondary prevention drugs. As a consequence, as observed in previous analyses pertaining to other trials [17,26,27], 'THEMIS eligible' patients from REACH represent a subset with a higher ischemic and hemorrhagic risk and have a poorer prognosis in comparison to patients actually enrolled THEMIS. These higher event rates suggest that in routine clinical practice, with a similar relative treatment effect, 'THEMIS eligible' patients may derive an even greater absolute benefit from ticagrelor than the more selected trial participants in terms of ischemic outcomes reduction, but a higher bleeding risk might in part counterbalance some of this benefit.

Recently, the US Food and Drug Administration updated the label of ticagrelor based on the THEMIS results. The label states ticagrelor is now additionally approved "to reduce the risk of a first MI or stroke in patients with coronary artery disease at high risk for such events." [28] Based on the label, the vast majority of patients with CAD (with or without diabetes) in REACH would be eligible for therapy with ticagrelor.

A limitation of the present analysis is that REACH participants were enrolled in 2003–2004 and followed up until 2008–2009; the data therefore antedate the start of THEMIS by approximately 10 years. Meanwhile, improvement in the management of diabetes and atherothrombosis has resulted in improved outcomes. Therefore, when comparing outcomes between 'THEMIS eligible' REACH patients and actual THEMIS participants, it is difficult to disentangle secular trends in outcome improvement from the genuine differences in prognosis between these two populations. However, this would not be expected to have an important impact on trial eligibility. In addition, given differences in data capture between REACH and THEMIS, analysis of eligibility required modification of some criteria, which may have impacted the outcome of the comparison. Specifically, the THEMIS trial required angiographic documentation of CAD. In REACH, since angiographic data were not required, CAD was defined using broad criteria (a history of MI, unstable angina, stable angina, or previous coronary

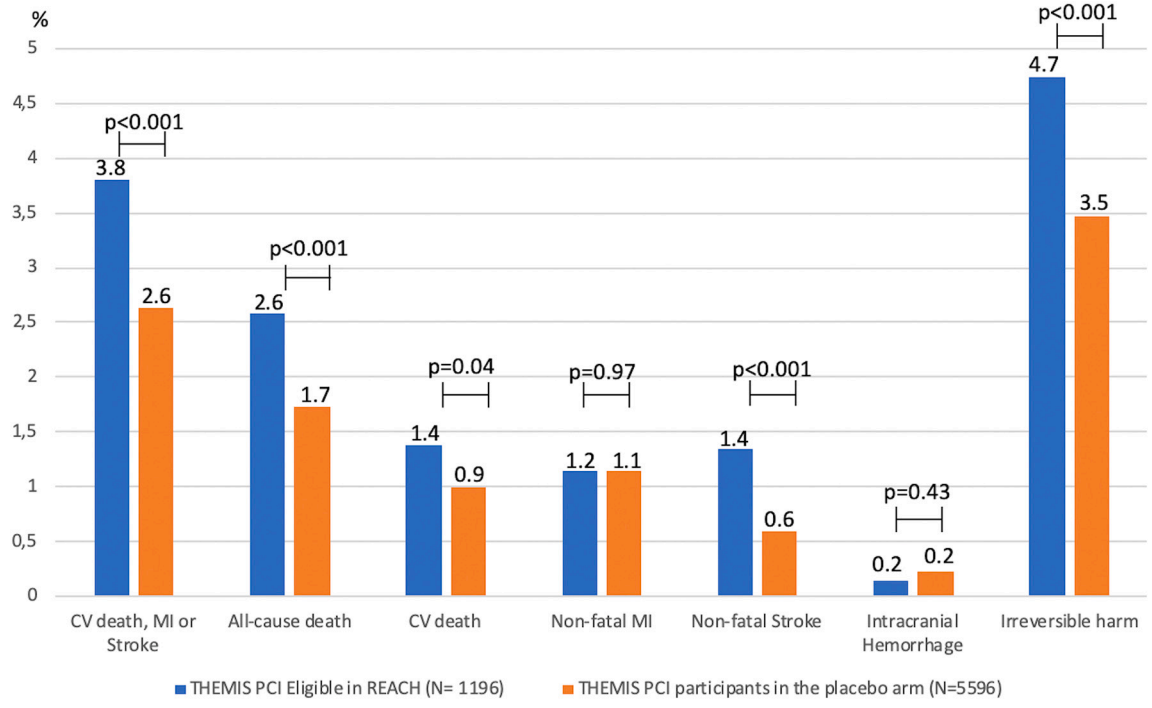

Fig. 3. Comparison of main CV event rate per 100 patient/years for the 'THEMIS-PCI' eligible patients from REACH and THEMIS PCI patients in the placebo arm (%).

revascularization), hypothetically leading to an overestimation of the REACH CAD population with diabetes and therefore an underestimation of the eligibility. The evolution of treatment strategies and drug therapies that have occurred between inclusion in the REACH registry and THEMIS trial might have influenced the categorization of the patients. In addition, the higher use of secondary prevention drug therapies in the placebo group of THEMIS compared to the patients from the REACH registry may have affected the outcomes. Finally, the bleeding definitions used in the REACH registry and in the THEMIS trial differed such that no direct comparison can be made. BARC $\geq$2 is a more sensitive definition of bleeding, but these data were not captured in the REACH registry.

In conclusion, in the REACH registry, over a quarter of patients with diabetes and stable coronary artery disease were 'THEMIS eligible' - a sizeable population. Given their higher event rates compared with actual trial participants, they may derive a greater absolute benefit from ticagrelor than the more selected trial participants.

Funding

The THEMIS trial was funded by AstraZeneca. The REACH registry was sponsored by Sanofi, Bristol-Myers Squibb, and the Waksman Foundation (Tokyo, Japan) and is endorsed by the World Heart Federation.

Disclosures

Dr. Jeremie Abtan discloses the following relationships: research grant from Federation Française de Cardiologie, research grant from Institut Servier.

Dr. Bhatt served as co-Chair of THEMIS and THEMIS-PCI, with funding from AstraZeneca paid to Brigham and Women's Hospital. Dr. Bhatt discloses the following relationships - Advisory Board: Angio-Wave, Bayer, Boehringer Ingelheim, Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, High Enroll, Janssen, Level Ex, McKinsey, Medscape Cardiology, Merck, MyoKardia, NirvaMed, Novo Nordisk, PhaseBio, PLx Pharma, Regado Biosciences, Stasys; Board of Directors: AngioWave (stock options), Boston VA Research Institute, Bristol Myers Squibb (stock), DRS.LINQ (stock options), High Enroll (stock), Society of Cardiovascular Patient Care, TobeSoft; Chair: Inaugural Chair, American Heart Association Quality Oversight Committee; Consultant: Broadview Ventures; Data Monitoring Committees: Acesion Pharma, Assistance Publique-Hôpitaux de Paris, Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Boston Scientific (Chair, PEITHO trial), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo; for the ABILITY-DM trial, funded by Concept Medical), Novartis, Population Health Research Institute; Rutgers University (for the NIH-funded MINT Trial); Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol-Myers Squibb clopidogrel litigation), 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), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), Cowen and Company, 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), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Oakstone CME (Course Director, Comprehensive Review of Interventional Cardiology), Piper Sandler, 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), Wiley (steering committee); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Patent: Sotagliflozin (named on a patent for sotagliflozin assigned to Brigham and Women's Hospital who assigned to Lexicon; neither I nor Brigham and Women's Hospital receive any income from this patent.) Research Funding: Abbott, Acesion Pharma, Afimmune, Aker Biomarine, Amarin, Amgen, AstraZeneca, Bayer, Beren, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cardax, CellProthera, Cereno Scientific, Chiesi, CinCor, CSL Behring, Eisai, Ethicon, Faraday Pharmaceuticals, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Garmin, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, Javelin, Lexicon, Lilly, Medtronic, Merck, Moderna, MyoKardia, NirvaMed, Novartis, Novo Nordisk, Owkin, Pfizer, PhaseBio, PLx Pharma, Recardio, Regeneron, Reid Hoffman Foundation, Roche, Sanofi, Stasys, Synaptic, The Medicines Company, Youngene, 89Bio; Royalties: Elsevier (Editor, Braunwald's Heart Disease); Site Co-Investigator: Abbott, Biotronik, Boston Scientific, CSI, Endotronix, St. Jude Medical (now Abbott), Philips, SpectraWAVE, Svelte, Vascular Solutions; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Takeda.

Dr. Ducrocq reports receiving speaker's and/or consulting fees from Amgen, Astra Zeneca, Bayer, BMS, Janssen, Sanofi, Terumo, proctoring fees from Boston Scientific, fee for Clinical Events Committee participation from Novo Nordisk, and travel fees from Astra Zeneca, Bayer, BMS.

Dr. Shinya Goto discloses the following: financial support from MEXT/JSPS KAKENHI 19H03661, grant support for translational research provided by the Agency for Medical Research and Development in Japan, grant support from The Vehicle Racing Commemorative Foundation, Nakatani Foundation for Advancement of Measuring Technologies in Biomedical Engineering, Bristol-Myers Squibb from their independent research support project (33999603) and research funding from Sanofi, Pfizer, and Ono. Shinya Goto is received quality fee from the American Heart Association as an Associate Editor for Circulation and received Steering Committee member fee from the Thrombosis Research Institute, London, UK. Shinya Goto associate Editor for Journal of Biorheology, and section Editor for Archives of Medical Science and Thrombosis and Hemostasis.

Dr. Kim Fox receives fees, honoraria and/or travel expenses from AstraZeneca,CellAegis, Celixir,Servier,UCB,and Broadview Ventures.He is a Director of Vesalius Trials Ltd.

Dr. Harrington reports grants from AstraZeneca, during the conduct of the study; grants from Sanofi Aventis, Portola, Janssen, Bristol-Myers Squibb, Novartis, The Medicines Company, CSL Behring, outside the submitted work; and consulting (before July 1, 2018) for Amgen, Gilead, and MyoKardia.

Dr. Lawrence Leiter reports grants and personal fees from AstraZeneca, grants and personal fees from Bayer, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Eli Lilly, grants from Esperion, grants from GSK, personal fees from HLS, grants and personal fees from Janssen, grants from Kowa, grants from Lexicon, personal fees from Merck, grants and personal fees from Novartis, grants and personal fees from Novo Nordisk, grants and personal fees from Sanofi, personal fees from Servier, and grants from The Medicines Company.

Dr. Mehta reports research grants to Population Health Research Institute from AstraZeneca, Abbott, Boston Scientific, and Sanofi, and is a consultant to AstraZeneca, Bayer, Biosensors, and Sanofi.

Dr. Simon reports grants from AstraZeneca, Bayer, Daichi-Sankyo,

GSK, MSD, Novartis and personnel fees from AstraZeneca, BMS, Novartis, and Sanofi.

Dr. Sinnaeve: institutional grants and/or consultancy fees from Astra-Zeneca, Daiichi-Sankyo, Bayer Sanofi, Amgen, Abbott Vascular, Idorsia, Pfizer, BMS, GSK, Itreas.

Dr. Bueno reports receiving research funding from the Instituto de Salud Carlos III, Spain (PIE16/00021 & PI17/01799), Sociedad Española de Cardiología, AstraZeneca, Bayer, BMS and Novartis; having received honoraria for consultancy fees from AstraZeneca, Bayer, BMS-Pfizer, Novartis; and speaking fees or support for attending scientific meetings from Amgen, AstraZeneca, Bayer, BMS-Pfizer, Novartis, and MEDSCAPE-the heart.org;

Dr. Ph. Gabriel Steg serves as co-Chair of THEMIS and THEMIS-PCI. Dr. Steg discloses the following relationships - Research grants (to INSERM U1148): Bayer, Merck, Servier, Sanofi; speaker or consultant (including steering committee, DMC and CEC memberships): Amarin, Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, BristolMyersSquibb, Idorsia, Mylan, NovoNordisk, Novartis, Pfizer, Regeneron, Sanofi, Servier.

Drs Smith, Pais and Lev have no relevant disclosures or conflicts of interest.

Take-home message

Over a quarter of patients with diabetes and CAD in the REACH registry were eligible for the THEMIS or THEMIS-PCI trials - a sizeable population.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.10.132.

References

[1] M.A. Cavender, P.G. Steg, S.C. Smith, et al., Impact of diabetes on hospitalization for heart failure, cardiovascular events, and death: outcomes at 4 years from the REACH registry, Circulation 132 (2015) 923–931.

[2] D.L. Bhatt, K.A. Eagle, E.M. Ohman, et al., for the REACH Registry Investigators. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis, JAMA 304 (2010) 1350–1357.

[3] H.K. Abdelaziz, M. Saad, N.V.K. Pothineni, et al., Aspirin for primary prevention of cardiovascular events, J. Am. Coll. Cardiol. 73 (2019) 2915–2929.

[4] G. De Berardis, M. Sacco, G.F.M. Strippoli, et al., Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials, BMJ 339 (2009) b4531.

[5] L. Bowman, M. Mafham, K. Wallendszus, et al., ASCEND Study Collaborative Group, Effects of aspirin for primary prevention in persons with diabetes mellitus, N. Engl. J. Med. 379 (2018) 1529–1539. Massachusetts Medical Society.

[6] I. Raber, C.P. McCarthy, M. Vaduganathan, et al., The rise and fall of aspirin in the primary prevention of cardiovascular disease, Lancet 393 (2019) 2155–2167.

[7] American Diabetes Association, 10. Cardiovascular disease and risk management: standards of medical Care in Diabetes-2019, Diabetes Care 42 (2019) S103–S123. American Diabetes Association.

[8] Authors/Task Force Members, L. Rydén, P.J. Grant, S.D. Anker, et al., ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD), Eur. Heart J. (2013) 3035–3087.

[9] Arnold SV, Bhatt DL, Barsness GW, et al., American Heart Association Council on Lifestyle and Cardiometabolic Health and Council on Clinical Cardiology. Clinical management of stable coronary artery disease in patients with type 2 diabetes mellitus: a scientific statement from the American Heart Association. *Circulation* Lippincott Williams & Wilkins Hagerstown, MD; 2020;139: CIR0000000000000766.

[10] P. Held, A. Himmelmann, M. Ditmarsch, Ticagrelor for the treatment of atherosclerotic disease: insights from the PARTHENON clinical development program, Futur. Cardiol. 12 (2016) 405–418.

[11] P.G. Steg, D.L. Bhatt, T. Simon, et al., for theTHEMIS Steering Committee and Investigators. Ticagrelor in patients with stable coronary disease and diabetes, N. Engl. J. Med. 381 (2019) 1309–1320. Massachusetts Medical Society.

[12] D.L. Bhatt, P.G. Steg, S.R. Mehta, et al., for the THEMIS Steering Committee and Investigators. Ticagrelor in patients with diabetes and stable coronary artery disease with a history of previous percutaneous coronary intervention (THEMIS-PCI): a phase 3, placebo-controlled, randomised trial, Lancet 394 (2019) 1169–1180.

[13] D.L. Bhatt, P.G. Steg, THEMIS and THEMIS-PCI, Eur. Heart J. 40 (2019) 3378–3381.

[14] P.G. Steg, J. Lopez-Sendon, E. López-de-Sá, et al., for the GRACE Investigators. External validity of clinical trials in acute myocardial infarction, Arch. Intern. Med. 167 (2007) 68–73.

[15] P.M. Rothwell, External validity of randomised controlled trials: "to whom do the results of this trial apply?", Lancet 365 (2005) 82–93.

[16] D.L. Bhatt, Advancing the care of cardiac patients using registry data: going where randomized clinical trials dare not, JAMA American Medical Association 303 (2010) 2188–2189.

[17] A. Darmon, D.L. Bhatt, Y. Elbez, et al., External applicability of the COMPASS trial: an analysis of the reduction of atherothrombosis for continued health (REACH) registry, Eur. Heart J. 39 (2018) 750–757a.

[18] M. Würtz, K.K.W. Olesen, T. Thim, S.D. Kristensen, J.W. Eikelboom, M. Maeng, External applicability of the COMPASS trial: the Western Denmark Heart registry, Eur. Heart J. Cardiovasc. Pharmacother. 373 (2019) 1849.

[19] F. Schiele, E. Puymirat, J. Ferrières, et al., for the FAST-MI investigators. The FAST-MI 2005-2010-2015 registries in the light of the COMPASS trial: the COMPASS criteria applied to a post-MI population, Int. J. Cardiol. 278 (2019) 7–13.

[20] X. Jia, J.M. Akeroyd, K. Nasir, et al., Eligibility and cost for icosapent ethyl based on the REDUCE-IT trial, Circulation 139 (2019) 1341–1343. Lippincott Williams & Wilkins Hagerstown, MD.

[21] A. Darmon, E. Sorbets, G. Ducrocq, et al., for the REACH Registry Investigators. Association of multiple enrichment criteria with ischemic and bleeding risks among COMPASS-eligible patients, J. Am. Coll. Cardiol. 73 (2019) 3281–3291.

[22] D.L. Bhatt, P.G. Steg, E.M. Ohman, et al., for the REACH Registry Investigators. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis, JAMA 295 (2006) 180–189.

[23] D.L. Bhatt, K. Fox, R.A. Harrington, et al., for the THEMIS Steering Committee. Rationale, design and baseline characteristics of the effect of ticagrelor on health outcomes in diabetes mellitus patients Intervention study, Clin. Cardiol. 42 (2019) 498–505. John Wiley & Sons, Ltd.

[24] P.G. Steg, D.L. Bhatt, P.W.F. Wilson, et al., for the REACH Registry Investigators. One-year cardiovascular event rates in outpatients with atherothrombosis, JAMA 297 (2007) 1197–1206.

[25] M.J. Alberts, D.L. Bhatt, J.-L. Mas, et al., REduction of Atherothrombosis for Continued Health Registry Investigators. Three-year follow-up and event rates in the international REduction of Atherothrombosis for Continued Health Registry, Eur. Heart J. 30 (2009) 2318–2326.

[26] H.G.C. Van Spall, A. Toren, A. Kiss, R.A. Fowler, Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review, JAMA 297 (2007) 1233–1240. American Medical Association.

[27] A. Britton, M. McKee, N. Black, K. McPherson, C. Sanderson, C. Bain, Threats to applicability of randomised trials: exclusions and selective participation, J. Health Serv. Res. Policy 4 (1999) 112–121.

[28] Brilinta Prescribing Information, AstraZeneca, Accessed April 6, 2021 at, https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022433s028lbl.pdf#page=29, 2020.