Accepted Manuscript

Associations between Complex PCI and Prasugrel or Clopidogrel use in Patients with Acute Coronary Syndromes undergoing PCI: From the PROMETHEUS Study

Jaya Chandrasekhar, MBBS, MS, Usman Baber, MD MS, Samantha Sartori, PhD, Melissa Aquino, MS, Annapoorna S. Kini, MBBS, Sunil Rao, MD, William Weintraub, MD, Timothy D. Henry, MD, Serdar Farhan, MD, Birgit Vogel, MD, Sabato Sorrentino, MD, Zhen Ge, MD, Samir Kapadia, MD, Joseph B. Muhlestein, MD, Sandra Weiss, MD, Craig Strauss, MD, Catalin Toma, MD, Anthony DeFranco, MD, Mark B. Effron, MD, Stuart Keller, BS Pharm, Brian A. Baker, PharmD, Stuart Pocock, PhD, George Dangas, MD, PhD, Roxana Mehran, MD

PII: S0828-282X(17)31248-5
DOI: 10.1016/j.cjca.2017.12.023
Reference: CJCA 2691

To appear in: Canadian Journal of Cardiology

Received Date: 28 November 2017
Revised Date: 19 December 2017
Accepted Date: 19 December 2017


This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Associations between Complex PCI and Prasugrel or Clopidogrel use in Patients with Acute Coronary Syndromes undergoing PCI: From the PROMETHEUS Study

Jaya Chandrasekhar, MBBS, MS; Usman Baber MD MS; Samantha Sartori PhD; Melissa Aquino MS; Annapoorna S. Kini MBBS; Sunil Rao MD; William Weintraub MD; Timothy D. Henry MD; Serdar Farhan, MD; Birgit Vogel, MD; Sabato Sorrentino, MD; Zhen Ge, MD; Samir Kapadia MD; Joseph B. Muhlestein MD; Sandra Weiss MD; Craig Strauss MD; Catalin Toma MD; Anthony DeFranco MD; Mark B. Efron MD; Stuart Keller BS Pharm; Brian A. Baker PharmD; Stuart Pocock PhD; George Dangas, MD, PhD; Roxana Mehran MD

1 Icahn School of Medicine at Mount Sinai, New York, New York
2 Mount Sinai Hospital, New York, New York
3 Duke University, Durham, North Carolina
4 Christiana Care Health System, Newark, Delaware
5 Cedars-Sinai Heart Institute, Los Angeles, California
6 Cleveland Clinic, Cleveland, Ohio
7 Intermountain Heart Institute, Salt-Lake city, Utah
8 Minneapolis Heart Institute, Minneapolis, Minnesota
9 University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania
10 Aurora Cardiovascular Services, Milwaukee, Wisconsin
11 Eli Lilly and Company, Indianapolis, Indiana
12 John Ochsner Heart and Vascular Center, Ochsner Medical Center, New Orleans, Louisiana
13 Daiichi Sankyo, Inc, Parsippany, New Jersey
14 London School of Hygiene and Tropical Medicine, London, United Kingdom

Correspondence to:
Roxana Mehran, MD, FACC
Professor of Medicine (Cardiology)
Director of Interventional Cardiovascular Research and Clinical Trials

The Zena and Michael A. Wiener Cardiovascular Institute

The Icahn School of Medicine at Mount Sinai

One Gustave L. Levy Place, Box 1030, New York, NY 10029-6574

Tel: 1-212-659-9641; Fax: 1-646-537-8547

Roxana.mehran@mountsinai.org

**Running title:** Effect of PCI complexity in ACS

**Key words:** percutaneous coronary intervention, acute coronary syndrome, complex PCI, prasugrel versus clopidogrel

**Word count:** 5640
ABSTRACT

Background: Potent P2Y₁₂ inhibitors may offer enhanced benefit against thrombotic events in complex percutaneous coronary intervention (PCI). We examined prasugrel use and outcomes by PCI complexity, as well as analyzing treatment effects by thienopyridine type.

Methods: PROMETHEUS was a multicenter observational study comparing clopidogrel vs. prasugrel in acute coronary syndrome patients undergoing PCI (n = 19,914). Complex PCI was defined as PCI of the left main, bifurcation lesion, moderate-severely calcified lesion or total stent length ≥30mm. Major adverse cardiac events (MACE) were a composite of death, myocardial infarction, stroke or unplanned revascularization. Outcomes were adjusted using multivariable Cox regression for impact of PCI complexity and propensity-stratified analysis for effect of thienopyridine type.

Results: The study cohort included 48.9% (n=9,735) complex and 51.1% (n=10,179) non-complex patients. Second generation DES were used in 70.1% complex and 66.2% non-complex PCI patients (p <0.0001). Complex PCI was associated with greater adjusted risk of 1-year MACE (HR 1.29, 95% CI 1.20-1.39, p <0.001). Prasugrel was prescribed in 20.7% of complex and 20.1% of non-complex PCI patients (p=0.30). Compared to clopidogrel, prasugrel significantly decreased adjusted risk for 1-year MACE in complex PCI (HR 0.79, 95% CI 0.68-0.92) but not non-complex PCI (HR 0.91, 95% CI 0.77-1.08), albeit there was no evidence of interaction (p interaction =0.281).

Conclusions: Despite the use of contemporary techniques, ACS patients undergoing complex PCI had significantly higher rates of 1-year MACE. Adjusted magnitude of treatment effects with prasugrel versus clopidogrel were consistent in complex and non-complex PCI without evidence of interaction.

Funding sources: The PROMETHEUS study was sponsored and funded by Daiichi Sankyo, Inc. and Eli Lilly and Company.
BRIEF SUMMARY:

In this analysis from the PROMETHEUS ACS registry (n = 19,914), complex PCI (PCI of left main/bifurcation/moderate-severely calcified lesion/stent length ≥30mm) was associated with greater risk of 1-year MACE (death, myocardial infarction, stroke or unplanned revascularization; HR 1.29 [1.20-1.39]). Treatment effects with prasugrel vs. clopidogrel for risk of 1-year MACE were consistent in complex (HR 0.79 [0.68-0.92]) and non-complex PCI (HR 0.91 [0.77-1.08] (p interaction =0.281).
INTRODUCTION

Percutaneous coronary intervention (PCI) in complex lesion subsets is associated with high thrombotic risk and greater susceptibility for both stent related and non-related short and long-term adverse events [1-3]. There is no universal definition for complex PCI and different classifications using combinations of lesion and procedural characteristics account for 10%-50% of all PCI patients in current clinical practice [2-4]. In particular, PCI of the left main, bifurcation target lesion, moderate or severely calcified lesion or stent implantation of $\geq 30$mm are procedural parameters correlated with greater event rates in prior studies [5-8]. Other authors have also attributed complex PCI status to chronic total occlusion (CTO) PCI, saphenous vein graft (SVG) PCI, use of rotablation atherectomy, target lesion with thrombus, tortuous target vessel, ultralong stent length $>60$mm, or factors based on total number of lesions treated or stents implanted [3, 4, 9-11]. Notwithstanding these anatomical variances in definition, risk may be further compounded in the setting of acute coronary syndromes (ACS) [12]. There are currently no outcomes data by PCI complexity in large ACS cohorts treated with contemporary PCI technologies. Furthermore, whether use of potent antiplatelet therapies provides preferential benefit to mitigate risk of recurrent thrombotic events following PCI in such high-risk patients has not been investigated.

Potent P2Y$_{12}$ therapies such as prasugrel and ticagrelor result in rapid, uniform and more potent platelet inhibition than clopidogrel with significantly reduced risk of 1-year ischemic outcomes [13, 14]. These agents are also recommended in guidelines for treatment of ACS patients undergoing PCI[15, 16]. However, the potential role of these potent agents has not been systematically examined by PCI complexity in randomized trials, thus specific recommendations by anatomical risk are presently lacking. Moreover, the decision for selection of potent inhibitors following complex PCI may be outweighed by concomitant risk of bleeding, thus negating the net benefit of such therapies [13, 14, 17].

We conducted a post-hoc analysis from a multicenter observational study of 19,914 patients undergoing ACS PCI in 8 academic US centers 1) to analyze 1-year outcomes by PCI complexity,
and 2) to examine the patterns of prasugrel use and to assess 1-year outcomes by thienopyridine type and PCI complexity.

**METHODS**

**Study sample**

The PROMETHEUS study was a multicenter observational study including patients undergoing PCI between 1 January 2010 to 30 June 2013 at 8 academic US centers that maintained a prospective PCI database with 1-year follow-up [18]. The institutional ethics committees of all centers approved the study. All data were prospectively collected and then retrospectively extracted and harmonized for analysis. The data fields extracted followed standardized definitions of the National Cardiovascular Data Registry (NCDR) Catheterization PCI database and were jointly agreed to by the study investigators. The main study was designed to compare use of prasugrel and clopidogrel in all-comer ACS PCI. Management of data quality, statistical analyses and results reporting were the responsibility of the Data Coordinating Center at the Icahn School of Medicine at Mount Sinai, New York. The sponsors did not have access to patient-level data.

The study population included all patients undergoing PCI for ACS and treated with dual antiplatelet therapy (DAPT) with aspirin and either clopidogrel or prasugrel. The current analysis was stratified by the PCI complexity as complex vs. non-complex using the study definition (Figure 1). The PCI procedure and related management was carried out per usual standard of care and at the discretion of the treating physicians at each site. Prescription of prasugrel or clopidogrel in individual patients was also directed by the treating physician.

**Endpoints and Definitions**

Complex PCI was defined as PCI with any 1 of the following characteristics: left main PCI location, bifurcation target lesion treated with any technique, moderate or severely target calcified target lesion or total implanted stent length ≥30mm. This definition was agreed on by the study authors based on prior studies indicating higher risk in these patient subsets [5-8]. The univariate and
multivariate adjusted risk associated with each component of the complex PCI definition for 90-day and 1-year MACE is shown in Supplementary Figure 1. All lesion characteristics including American College of Cardiology/ American Heart Association (ACC/AHA) lesion type were site reported and not adjudicated by an angiographic core laboratory. Variables used in other complex PCI definitions such as CTO PCI, SVG PCI, lesion length, vessel tortuosity, presence of thrombus, calcified lesions treated with rotablation atherectomy and bifurcation PCI requiring 2 stents were not available or could not be reliably ascertained from the dataset. SYNTAX score was not collected.

The primary endpoint of the main study was 90-day major adverse cardiac events (MACE), composite of death, spontaneous myocardial infarction (MI), stroke or unplanned revascularization. This time point was selected since adherence at this stage was expected to continue to be high with low rates of thienopyridine switching. Secondary endpoints included the individual components of the primary endpoint, stent thrombosis (ST), and clinically significant bleeding which was defined as bleeding needing hospitalization or transfusion. Study endpoints were site reported in each center’s database and internally validated at site level but not centrally adjudicated.

For this analysis we evaluated MACE and all secondary endpoints at 90 days and 1-year. Follow up was completed by phone, clinic visit or chart review as per standard of care by trained research staff at each site.

We also examined the frequency of prasugrel use, prevalence of high-risk baseline features and the incidence of MACE and clinically significant bleeding in the overall population by number of complex features (0 to ≥3 for none, left main PCI, bifurcation PCI, moderate or severely calcified lesion, ≥30mm stent length).

**STATISTICAL ANALYSIS**

Patients were grouped and compared by PCI complexity. Categorical data are presented as numbers and percentages and compared using the chi-square test. Continuous data are presented as means and standard deviations and compared using the parametric Student’s t test. Clinical event rates are presented using the Kaplan Meier method and compared using the log rank test.
Hazard ratios and confidence intervals for adjusted risk of 90-day and 1-year outcomes between patients with complex vs. non-complex PCI were generated using multivariable Cox regression methods (reference = non-complex PCI), adjusting for the following variables: age, African-American or other race, body mass index (BMI), diabetes, hypertension, estimated glomerular filtration rate, hemoglobin, prior PCI, coronary artery disease (CAD) presentation, multivessel disease, bivalirudin use, stent type, prasugrel use and center. Similarly adjusted hazard ratios and confidence intervals for MACE associated with each component of complex PCI were generated using multivariable Cox regression methods accounting for the following variables: age, African-American or other race, body mass index (BMI), diabetes, hypertension, estimated glomerular filtration rate, hemoglobin, prior PCI, coronary artery disease (CAD) presentation, bivalirudin use, stent type, prasugrel use and center.

Further, adjusted hazard ratios and confidence intervals for risk of 90-day and 1-year outcomes with prasugrel vs. clopidogrel (reference = clopidogrel) among complex and non-complex PCI patients were generated using Cox proportional hazards regression stratified by propensity to receive prasugrel, with formal interaction testing between P2Y_{12} inhibitor treatment and PCI complexity. The propensity model included the following main effects: center, CAD presentation, diabetes, age, age squared, bivalirudin, smoking, gender, African-American race, hypertension, family history of CAD, prior PCI, prior coronary artery bypass surgery (CABG), prior peripheral arterial disease, prior congestive heart failure, prior cerebrovascular disease (CVD), stent length, stent diameter, glycoprotein IIb/IIIa inhibitor use, hypercholesterolemia, prior myocardial infarction, estimated glomerular filtration rate, stent type, body mass index (BMI), hemoglobin and the following interaction terms: center*procedural glycoprotein IIb/IIIa inhibitor use; BMI*hemoglobin; prior CVD*prior PCI; prior CVD*prior CABG.

All data were analyzed using Stata version 14.0 (College station, Texas) or SAS version 9.4 (Cary, NC); p-values < 0.05 were considered significant.

**RESULTS**
A total of 19,914 patients were included in the study, of whom 48.9% (n=9,735) underwent complex PCI and 51.1% (n=10,179) underwent non-complex PCI per the study definition. Tables 1 and 2 show the baseline and procedural characteristics by PCI complexity. Complex PCI patients were older than non-complex PCI patients with a higher prevalence of diabetes, multi-distribution vasculopathy and multivessel disease. In the complex group, left main PCI was performed in 6.9%, bifurcation PCI in 20.1% and moderate or severe target lesion calcification was present in 28.9%. The mean stent length was 42.9mm in complex vs. 18.9mm in non-complex patients (p < 0.0001). Second generation drug eluting stents (DES) were used more often in complex PCI patients (70.1% vs. 66.2%, p <0.001). Complex PCI patients were more likely to be treated with glycoprotein IIb/IIIa inhibitors (24.0% vs. 21.9%, p =0.0002). Prasugrel was used in 20.7% of complex and 20.1% of non-complex PCI patients (p=0.30). The frequency of prasugrel by CAD presentation is shown in Figure 2.

Loss to follow up was 8.4% at 90-days and 17.1% at 1-year. Supplementary Table 1 and Figure 3 shows the clinical outcomes in complex and non-complex PCI groups. Both at 90-days and 1-year the incidences of MACE, death, MI, ST and unplanned revascularization were significantly greater in complex PCI patients. At 90-days the incidence of MACE was 10.6% in complex patients vs. 7.2% in non-complex patients, adjusted HR 1.42, 95% CI 1.28-1.58, p <0.001. Analogously, the incidence of death in complex vs. non-complex patients was 3.1 vs. 1.7%, adjusted HR 1.48, 95% CI 1.20-1.83, p <0.001. At 1-year, the incidence of MACE was 22.0% in complex patients vs. 16.0% in non-complex patients, adjusted HR 1.29, 95% CI 1.20-1.39, p <0.001. The incidence of 1-year death in complex vs. non-complex patients was 6.7 vs. 4.6%, adjusted HR 1.25, 95% CI 1.09-1.43, p=0.002. A borderline trend was observed for greater clinically significant bleeding in complex PCI patients at 1-year (5.0% vs. 3.8%, adjusted HR 1.16, 95% CI 0.99-1.34, p =0.061).

When we examined patients by increasing number of complex features from 0 to ≥ 3, the prevalence of baseline risk factors, and the incidence of both MACE and bleeding increased, whereas prasugrel use decreased in the same manner (Figure 4 and Supplementary Figure 2).
Effect of PCI complexity and thienopyridine type

Supplementary Tables 2 and 3 show the baseline differences by PCI complexity and thienopyridine type. Prasugrel treated patients were younger and more often males in both groups with higher BMI and fewer comorbidities such as prior revascularization. However, prasugrel treated patients were more likely to present with troponin positive events. With respect to anatomical features, prasugrel treated complex patients had lower frequency of left main PCI and fewer moderate or severely calcified lesions compared to clopidogrel treated complex patients.

Supplementary Table 4 and Figures 5-6 show the clinical outcomes by PCI complexity and thienopyridine type. At 90-days the incidence of MACE was lower with prasugrel vs. clopidogrel in complex and non-complex PCI patients, however adjusted treatment effects were not significantly different in both groups (complex PCI: 6.7% vs. 11.6%, HR 0.81, 95% CI 0.66-1.01, p = 0.057; non-complex PCI: 4.8% vs. 7.7%, HR 0.99, 95% CI 0.76-1.27, p =0.910; p-interaction =0.624). At 1-year, adjusted risk of MACE was lower with prasugrel vs. clopidogrel in complex PCI (13.3% vs. 24.3%, HR 0.79, 95% CI 0.68-0.92, p = 0.002) but not in non-complex PCI (10.9% vs. 17.3%, HR 0.91, 95% CI 0.77-1.08, p =0.292). Nevertheless, no evidence of interaction was observed between P2Y<sub>12</sub> treatment and PCI complexity (p-interaction = 0.281). The effect of lowered MACE with prasugrel compared to clopidogrel in complex PCI patients was driven by lower risk of death. At 90-days, adjusted risk of death was significantly lower with prasugrel vs. clopidogrel in complex PCI (0.8% vs. 3.7%, HR 0.48, 95% CI 0.27-0.85) but not non-complex PCI (0.4% vs. 2.0%, HR 0.75, 95% CI 0.35-1.59); p-interaction=0.896. Similar results were noted for 1-year death with prasugrel vs. clopidogrel (complex PCI: 2.0% vs. 8.0%, HR 0.55, 95% CI 0.38-0.79; non-complex PCI: 1.6% vs. 5.4%, HR 0.76, 95% CI 0.50-1.16; p-interaction = 0.463). There were no adjusted differences in other secondary endpoints including MI or ST by thienopyridine type, regardless of PCI complexity.

DISCUSSION
The main findings of the current analysis are as follows 1) complex ACS PCI comprising PCI of the left main, bifurcation target lesion, moderate or severely calcified target lesion or implantation of stent length ≥30mm was associated with significantly greater adjusted risk of 90-day and 1-year MACE, death, MI, ST and unplanned revascularization; 2) prasugrel was used in only one-fifth of ACS PCI patients regardless of PCI complexity; 3) compared to clopidogrel, prasugrel significantly decreased risk of 1-year MACE and death in complex PCI patients, albeit the adjusted magnitude of treatment effect with prasugrel versus clopidogrel was consistent in complex and non-complex PCI without evidence of interaction; 4) with increasing number of complex PCI features, the incidence of both ischemic and bleeding events increased whereas prasugrel use decreased, highlighting the counteracting risks and thus the unwillingness to prescribe potent P2Y_12 inhibitors when perceived risk outweighs benefit. While decision for prasugrel prescription may be clear in the majority of ACS PCI patients presenting with a single complex PCI characteristic, physicians may perceive equipoise between ischemic benefit and potential harm from bleeding related to other comorbidities in patients with multiple complex features, necessitating more careful assessment for tailored prescription.

**Risks associated with complex PCI**

Complex PCI has been the subject of many recent reports [3, 4, 9-11] and although a universal definition is lacking several descriptions have been used, including some of the characteristics we utilized in our study definition, which have been shown to be associated with long-term adverse events in prior studies [4-9]. The left main subtends 100% of the left ventricular myocardial territory in a left dominant circulation and 70% in right dominant circulation [19]. While we did not have precise information on protected vs. unprotected left main lesions, nearly half of the left main lesions (n=301) were noted in patients without prior history of CABG. Majority of left main PCI involves the distal bifurcation, which is associated with the highest risk [5, 20, 21]. Indeed, bifurcation lesions remain associated with high rates of target lesion failure, even though use of 2nd generation DES has been observed to be protective [22]. Further, bifurcation lesions treated with a simple or complex strategy may be associated with greater risk than a non-bifurcation lesion due to procedure
related plaque shift, alteration of flow and risk of poor stent apposition[23]. Calcified lesions increase procedural technical difficulty requiring adjunctive use of intravascular imaging, rotablation atherectomy, guideliner support and higher inflation pressures to achieve stent optimization[24]. Further, several studies have shown that stent length >30mm is linked with greater risk for MACE, ST and target vessel revascularization [3, 7, 25]. Total stent length also serves as a surrogate for number of lesions and vessels treated and number of stents implanted. Although studies have also shown that number of vessels treated and number of stents implanted are associated with greater risk [4, 26], we were limited by missingness of information for number of stents. Furthermore multivessel PCI and number of stents were strongly associated with stent length ≥30mm, therefore we used the latter as a proxy variable.

Indeed, we observed each component of our definition of complex PCI to be associated with higher adjusted risk of MACE both at 90-days and 1-year. However, other experts contend that lesion complexity should be considered in conjunction with systemic comorbidities, to allow comprehensive assessment of predicted risk[2]. Certainly patients undergoing complex PCI in the current study were more likely to have greater atherothrombotic risk factors including diabetes, prior MI and history of smoking, but they presented more frequently with unstable angina rather than troponin positive ACS.

Both at 90-days and 1-year, complex PCI correlated with greater adjusted risk for MACE driven by death, MI and unplanned revascularization. Despite predominant 2nd generation DES use, complex patients were at significantly higher risk of MI and ST, thus PCI complexity was independently associated with both stent related and non-stent related thrombotic outcomes following PCI. Other studies have noted similar findings of greater adverse event rates attributed to PCI complexity [3, 4, 9]. However, mortality reductions exceeding reductions in MI observed in our study strongly suggest that residual confounding from unmeasured parameters may account for greater mortality in complex PCI patients. Although we observed a borderline trend for greater adjusted risk of bleeding in complex patients, this was not statistically significant. The recent complex PCI patient-level pooled analysis from 6 randomized controlled trials also did not
demonstrate greater hazard for bleeding in complex PCI, however the eligibility criteria of the included trials may have precluded enrollment of patients at highest risk of bleeding [4].

Selecting patients for prasugrel

Despite higher adjusted risk of MACE in complex PCI patients, use of prasugrel was notably similar in both groups. However, when examined by the number of complex PCI features, prasugrel use declined with rising PCI complexity. Conversely a stepwise increase was noted in the incidence of both MACE and bleeding from 0 to ≥3 complex features. Additionally, we observed that with advancing PCI complexity, the frequency of risk factors for bleeding where prasugrel use is generally not recommended per the Food and Drug administration label [27], specifically, age ≥ 75 years, weight <60kg and history of prior cerebrovascular disease, gradually increased, providing a plausible explanation for the decrease in prescription rates. Moreover, other risk factors associated with bleeding such as prevalence of chronic kidney disease (CKD) and pre-existing anemia were higher in increasingly complex patients [28, 29]. In fact, these bleeding risks may not only influence prescription rates, but also adherence to antiplatelet therapy [30, 31]. Our study suggests that prasugrel, while prescribed more frequently in patients with one complex PCI characteristic, was less often used in the setting of multiple complex PCI features. Ongoing studies will examine whether a novel strategy of aspirin withdrawal and continued potent antiplatelet monotherapy yields benefit in complex PCI patients [32, 33]. Alternatively whether switching down from potent P2Y12 therapy to clopidogrel after the first month is beneficial in high bleeding risk complex PCI patients is not known [34]. Importantly, the recent complex PCI pooled analysis suggested that longer DAPT duration was beneficial for MACE reduction in complex but not in non-complex PCI patients, albeit prolonged DAPT resulted in greater bleeding irrespective of PCI complexity[4]. In addition, DAPT included clopidogrel in majority of the patients in this meta-analysis, rather than potent P2Y12 therapy.

Interestingly, on propensity stratified analysis although we observed a benefit for lower 1-year MACE and death with prasugrel vs. clopidogrel in complex patients, there was no evidence of
P2Y$_{12}$ treatment interaction by PCI complexity. Moreover, there was no reduction in risk of MI or ST. This may be due to 1) limited sample size to demonstrate interaction; 2) selection bias resulting in healthier patients receiving prasugrel, who may not be at highest risk, affirming the well-described risk-benefit paradox [35]; 3) consideration of only high risk procedural characteristics in the study definition rather than high risk patient factors such as STEMI, diabetes or prior PCI where prasugrel may be most beneficial [13, 36, 37]; 4) other mechanisms at play to increase platelet reactivity and ischemic risk in complex PCI patients with diabetes and CKD, which may not be attenuated by P2Y$_{12}$ inhibitors [38]; 5) adherence to medications was not assessed and decreased compliance or cessation of prasugrel and switching to clopidogrel may have been a contributor to the observed outcomes. However, adherence at 90-days is expected to be $\geq 90\%$; sensitivity analysis excluding patients switching treatment prior to discharge observed similar outcomes in the main study [18].

**Limitations**

PROMETHEUS was an observational study and prospectively collected data were retrospectively extracted and although validated at site level, were not centrally adjudicated. Information on cardiovascular and non-cardiovascular causes of death was not available. We considered a definition for complex PCI based on site reported standard high-risk angiographic/procedural characteristics, which were not validated by a core lab. However each component was associated with greater adjusted hazard for early and late MACE. SYNTAX scores were not available and could not be used to support our definition of complex PCI. Although certain variables used in other reported definitions of complex PCI were unavailable, our results confirm the internal validity of the study definition demonstrating significantly greater risk of early and late outcomes in complex PCI patients. The sample size for this subgroup analysis was limited and hence the findings for the role of prasugrel in complex PCI are merely exploratory. Comparisons between prasugrel and clopidogrel may be influenced by unmeasured confounders resulting in treatment selection bias. We did not have information on adherence to antiplatelet therapy through 1-year follow-up.

**CONCLUSIONS**
Complex PCI per the study definition comprised nearly 50% of ACS patients and was an independent predictor of 90-day and 1-year adjusted risk of MACE, MI, ST and death despite contemporary PCI techniques. Real world uptake of prasugrel across the participating academic centers from the United States was low in both complex and non-complex ACS PCI patients, in contrast to current ACS guidelines. Although prasugrel significantly decreased risk of 1-year MACE in complex PCI patients compared to clopidogrel, a P2Y$_{12}$ treatment interaction was not observed by PCI complexity, therefore adequately powered randomized trial data are required to confirm these findings.
DISCLOSURES

The PROMETHEUS study was sponsored and funded by Daichii Sankyo, Inc and Eli Lilly and Company. We have the following financial disclosures to report: Dr. Mehran has received institutional grant support from The Medicines Company, Bristol-Myers Squibb/Sanofi, and Eli Lilly and Company/Daiichi Sankyo; and is a consultant to Abbott Vascular, AstraZeneca, Boston Scientific, Covidien, Janssen Pharmaceuticals, Regado Biosciences, Mayo Medical, Merck & Co., and The Medicines Company. Dr. Kini serves on the speaker’s bureau of the ACC and has received consulting fees from WebMD. Dr. Henry has received research grant support from Eli Lilly and company, and Daiichi Sankyo. Mr. Keller is employed by Eli Lilly and Company and Dr. Effron is a previous employee of Eli Lilly and Company. Mr. Baker is employed by Daiichi Sankyo, Inc. All other authors report no relevant conflicts of interest.
REFERENCES


27. FDA, U. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022307s002lbl.pdf. 2016,


FIGURE LEGENDS

Figure 1: Study Flow
Figure 2: Frequency of prasugrel use by CAD presentation in complex and non-complex PCI groups
Figure 3: Adjusted risk of 90-day and 1-year clinical outcomes in patients with complex vs. non-complex PCI
Figure 4: Frequency of prasugrel use, and incidence of MACE and clinically significant bleeding by increasing number of complex PCI features
MACE, major adverse cardiovascular events
Figure 5: Cumulative incidence of MACE and clinically significant bleeding by thienopyridine type and PCI complexity during 1-year follow-up
MACE, major adverse cardiovascular events
Figure 6: Propensity stratified 90-day and 1-year outcomes by thienopyridine type and PCI complexity
Supplementary Figure 1: Unadjusted and adjusted risk of complex PCI components on 90-day and 1-year MACE
MACE, major adverse cardiovascular events
Supplementary Figure 2: Frequency of baseline clinical risks by increasing number of complex PCI features
CKD, chronic kidney disease; CVD, cerebrovascular disease
19,914 patients undergoing ACS PCI in 8 academic centers from 1 January 2010 to 30 June 2013

- 9,735 (48.9%) Complex PCI patients
  - 7720 patients treated with Clopidogrel (79.3%)
  - 2015 patients treated with Prasugrel (20.7%)

- 10,179 (51.1%) Non-Complex PCI patients
  - 8133 patients treated with Clopidogrel (79.9%)
  - 2046 patients treated with Prasugrel (20.1%)
Fig. 2

Frequency of prasugrel use by CAD presentation

Complex PCI | Non-complex PCI
---|---
Unstable angina | 20.2% | 17.7%
NSTEMI | 20.7% | 22.1%
STEMI | 22.7% | 24.2%
Fig. 3

**Adjusted risk of clinical outcomes with complex vs. non-complex PCI**

### 90-days

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>1.42 (1.28-1.58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death</td>
<td>1.48 (1.20-1.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>1.50 (1.26-1.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unplanned revascularization</td>
<td>1.30 (1.10-1.52)</td>
<td>0.002</td>
</tr>
<tr>
<td>Clinically significant bleeding</td>
<td>1.15 (0.95-1.39)</td>
<td>0.145</td>
</tr>
<tr>
<td>Def/ Prob stent thrombosis</td>
<td>1.86 (1.09-2.18)</td>
<td>0.023</td>
</tr>
</tbody>
</table>

### 1-year

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>1.29 (1.20-1.39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death</td>
<td>1.25 (1.09-1.43)</td>
<td>0.002</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>1.35 (1.18-1.55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unplanned revascularization</td>
<td>1.30 (1.17-1.43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinically significant bleeding</td>
<td>1.16 (0.99-1.34)</td>
<td>0.061</td>
</tr>
<tr>
<td>Def/ Prob stent thrombosis</td>
<td>1.57 (1.01-2.44)</td>
<td>0.043</td>
</tr>
</tbody>
</table>
Frequency of prasugrel use, Incidence of 1-year MACE and bleeding by increasing number of complex PCI features

**Complex PCI components include:**
- Left main PCI
- Bifurcation target lesion
- Moderate or severely calcified target lesion
- Stent length ≥30mm

![Graph showing frequency of prasugrel use](image)

**Prasugrel use**

- 0 features: 20.1%, P < 0.0001
- 1 feature: 22.0%
- 2 features: 17.2%
- ≥3 features: 16.3%

![Graph showing MACE incidence](image)

**MACE**

- 0 features: 16.0%, P < 0.00001
- 1 feature: 20.1%
- 2 features: 25.9%
- ≥3 features: 32.4%

![Graph showing clinically significant bleeding](image)

**Clinically significant bleeding**

- 0 features: 3.8%
- 1 feature: 4.6%
- 2 features: 6.2%
- ≥3 features: 6.2%
Fig. 5

A

Cumulative MACE

Log-rank p value <0.001

Number at risk
Non-complex/ clop  8134 6791 6306 6032 5830 5642 5270
Non-complex/ pras 2045 1756 1661 1615 1564 1510 1392
Complex/ clop  7722 6190 5628 5290 5042 4816 4389
Complex/ pras 2013 1730 1623 1554 1509 1460 1304

B

Cumulative Bleeding

Log-rank p value <0.001

Number at risk
Non-complex/ clop  8134 6980 6580 6403 6264 6122 5771
Non-complex/ pras 2045 1791 1718 1687 1658 1621 1497
Complex/ clop  7722 6401 5973 5741 5569 5409 5020
Complex/ pras 2013 1776 1623 1554 1509 1460 1304
Adjusted outcomes by PCI complexity and thienopyridine type

90-days

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR (95% CI)</th>
<th>P-int</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>0.81 (0.66-1.01)</td>
<td>0.624</td>
</tr>
<tr>
<td>Death</td>
<td>0.99 (0.76-1.27)</td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0.48 (0.27-0.85)</td>
<td>0.896</td>
</tr>
<tr>
<td>Unplanned revascularization</td>
<td>0.48 (0.35-0.85)</td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>1.03 (0.71-1.49)</td>
<td>0.698</td>
</tr>
</tbody>
</table>

1-year

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR (95% CI)</th>
<th>P-int</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>0.79 (0.68-0.92)</td>
<td>0.281</td>
</tr>
<tr>
<td>Death</td>
<td>0.91 (0.77-1.08)</td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0.55 (0.38-0.79)</td>
<td>0.463</td>
</tr>
<tr>
<td>Unplanned revascularization</td>
<td>0.48 (0.35-0.85)</td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>0.95 (0.70-1.29)</td>
<td>0.969</td>
</tr>
</tbody>
</table>

Fig. 6
### TABLE 1: Baseline characteristics in patients undergoing Complex and Non-Complex PCI

<table>
<thead>
<tr>
<th></th>
<th>Complex PCI N = 9,735</th>
<th>Non-Complex PCI N = 10,179</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>65.23 ± 12.18</td>
<td>63.60 ± 12.31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>3045(31.3%)</td>
<td>3259(32.0%)</td>
<td>0.2630</td>
</tr>
<tr>
<td>African-American, n (%)</td>
<td>933(9.6%)</td>
<td>1192(11.7%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>29.82 ± 6.17</td>
<td>30.02 ± 6.18</td>
<td>0.0226</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>3946(40.5%)</td>
<td>3634(35.7%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>• Diabetes on insulin</td>
<td>1283(13.2%)</td>
<td>1251(12.3%)</td>
<td>0.0781</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>8228(84.5%)</td>
<td>8153(80.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>8394(86.2%)</td>
<td>8295(81.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>2345(24.1%)</td>
<td>2661(26.1%)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Prior MI, n (%)</td>
<td>3100(31.8%)</td>
<td>2863(28.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prior PCI, n (%)</td>
<td>2520(25.9%)</td>
<td>2518(24.7%)</td>
<td>0.0623</td>
</tr>
<tr>
<td>Prior CABG, n (%)</td>
<td>1866(19.2%)</td>
<td>1567(15.4%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prior cerebrovascular disease, n (%)</td>
<td>1294(13.3%)</td>
<td>1091(10.7%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prior CHF, n (%)</td>
<td>2328(23.9%)</td>
<td>1923(18.9%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %, mean (SD)</td>
<td>50.90 ± 13.86</td>
<td>52.31 ± 12.78</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prior PAD, n (%)</td>
<td>1328(13.6%)</td>
<td>1103(10.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anemia, n (%)</td>
<td>1560 (16.0%)</td>
<td>1332 (13.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CAD Presentation, n (%)</td>
<td>5627(57.8%)</td>
<td>5589(54.9%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>• Unstable angina</td>
<td>2666(27.4%)</td>
<td>2746(27.0%)</td>
<td></td>
</tr>
<tr>
<td>• NSTEMI</td>
<td>1441(14.8%)</td>
<td>1844(18.1%)</td>
<td></td>
</tr>
</tbody>
</table>

BMI: Body Mass Index; CABG: Coronary Artery Bypass grafting; CAD: Coronary Artery Disease; CHF: Congestive Heart Failure; CKD: Chronic Kidney Disease; MI: Myocardial Infarction; NSTEMI: Non ST-segment elevation myocardial infarction; PAD: Peripheral Artery Disease; PCI: Percutaneous Coronary Intervention; STEMI: ST-segment elevation myocardial infarction.
TABLE 2: Procedural characteristics in patients undergoing Complex and Non-Complex PCI

<table>
<thead>
<tr>
<th></th>
<th>Complex PCI (N = 9,735)</th>
<th>Non-Complex PCI (N = 10,179)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multivessel disease, n (%)</strong></td>
<td>5119(52.6%)</td>
<td>3277(32.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>PCI vessel, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Left Main</td>
<td>667(6.9%)</td>
<td>0(0.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>• Left anterior descending</td>
<td>4736(48.6%)</td>
<td>4159(40.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>• Circumflex</td>
<td>3169(32.6%)</td>
<td>2725(26.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>• Right coronary artery</td>
<td>3631(37.3%)</td>
<td>3166(31.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>At least one B2/C type lesion, n (%)</strong></td>
<td>8235(84.6%)</td>
<td>5371(52.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>At least one lesion with moderate/severe calcification, n (%)</strong></td>
<td>2771(28.5%)</td>
<td>0(0.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Stent length ≥30mm, mean (SD)</strong></td>
<td>7329 (75.6%)</td>
<td>0 (0.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Total stent length, mm, mean (SD)</strong></td>
<td>42.94 ± 23.25</td>
<td>18.55 ± 5.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Minimum stent diameter, mm, mean (SD)</strong></td>
<td>2.91 ± 0.48</td>
<td>3.02 ± 0.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Multivessel PCI, n (%)</strong></td>
<td>2331(23.9%)</td>
<td>337(3.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>≥3 vessels treated</strong></td>
<td>291(3.0%)</td>
<td>8(0.07%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Number of lesions treated, mean (SD)</strong></td>
<td>1.81 ± 0.85</td>
<td>1.12 ± 0.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Number of stents implanted, mean (SD)</strong></td>
<td>2.07 ± 1.03</td>
<td>1.09 ± 0.33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>≥3 lesions treated</strong></td>
<td>1515 (17.1%)</td>
<td>72 (0.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>≥3 stents implanted</strong></td>
<td>2036(24.5%)</td>
<td>50(0.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>&gt;60mm total stent length</strong></td>
<td>1654(17.0%)</td>
<td>0(0.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Stent type, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one 1\textsuperscript{st} generation DES</td>
<td>1819(18.7%)</td>
<td>973(9.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>At least one 2\textsuperscript{nd} generation DES</td>
<td>6825(70.1%)</td>
<td>6736(66.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>At least one BMS</td>
<td>1786(18.3%)</td>
<td>2709(26.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Procedural anticoagulation, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>7004(71.9%)</td>
<td>7465(73.3%)</td>
<td>0.0269</td>
</tr>
<tr>
<td>GPI</td>
<td>2341(24.0%)</td>
<td>2225(21.9%)</td>
<td>0.0002</td>
</tr>
<tr>
<td>LMWH</td>
<td>102(1.0%)</td>
<td>105(1.0%)</td>
<td>0.6153</td>
</tr>
</tbody>
</table>

Numbers are presented as n (%) unless indicated otherwise.

BMS, bare metal stent; DES, drug eluting stent; GPI, glycoprotein 2b3a inhibitor; LMWH, low molecular weight heparin;