Bleeding and Ischemic Outcomes With Ticagrelor Monotherapy According to Body Mass Index

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LIST OF ABBREVIATIONS AND ACRONYMS

ARC: Academic Research Consortium

ARD: absolute risk difference

ARR: absolute risk reduction

ACS: acute coronary syndrome

BARC: Bleeding Academy Research Consortium

BMI: body mass index

CABG: coronary artery bypass graft

CI: confidence interval

CKD: chronic kidney disease

DAPT: Dual antiplatelet therapy

ESC: European Society of Cardiology

GUSTO: Global Use of Strategies to Open Occluded Arteries

HR: hazard ratio

ISTH: International Society of Thrombosis or Hemostasis

MI: myocardial infarction

NACE: net adverse clinical event

PCI: percutaneous coronary intervention

SD: standard deviation

TIMI: Thrombolysis in Myocardial Infarction

ABSTRACT

Background

Among patients with cardiovascular disease, available evidence suggests a U-shaped relationship between body mass index (BMI) and the risk of bleeding or cardiovascular events. Furthermore, BMI affects pharmacokinetics of antithrombotic drugs.

Methods

The TWILIGHT trial randomized high-risk patients to ticagrelor plus aspirin or ticagrelor plus placebo at 3 months after percutaneous coronary intervention (PCI). In this secondary analysis, ischemic and bleeding outcomes at 1 year after randomization were evaluated according to standardized BMI categories.

Results

Among 7038 patients randomized and with available BMI, 1807 (25.7%) had normal weight (BMI=18.5-24.99 kg/m^2), 2927 (41.6%) were overweight (BMI=25-29.99 kg/m^2), and 2304 (32.7%) were obese (BMI≥30 kg/m^2). Ticagrelor monotherapy, compared with ticagrelor plus aspirin, reduced the primary endpoint of Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding (HR 0.48, 95% CI 0.32-0.73; HR 0.57, 95% CI 0.41-0.78; HR 0.63, 95% CI 0.44-0.91; p-interaction=0.627) without any increase in the composite ischemic endpoint of all-cause death, myocardial infarction (MI), or stroke (HR 1.36, 0.84-2.19; HR 0.92, 95% CI 0.63-1.35; HR 0.84, 95% CI 0.56-1.25; p-interaction=0.290) in normal weight, overweight and obese patients (p-interaction>0.10 for all other outcomes). Obese subjects experienced a greater

absolute risk reduction in BARC 3 or 5 bleeding (p-interaction=0.030) and net clinical adverse events, composite of BARC type 3 or 5, all-cause death, MI, or stroke (p-interaction=0.040).

Conclusion

Among high-risk patients undergoing PCI, ticagrelor monotherapy, compared with ticagrelor plus aspirin, reduced bleeding events without any increase in the ischemic risk across different BMI categories and might be particularly beneficial in obese subjects.

INTRODUCTION

Obesity represents a global health issue, affecting both high- and low-income countries. [1,2] As of today, about one out of three adults in the USA can be defined obese, and these rates are expected to increase worldwide. [1,2] In the European Union, 53% of population are considered overweight (36% pre-obese, 17% obese). [3] There is high prevalence of obesity among patients with coronary artery disease and there is pharmacological interaction between antithrombotic medications and adipose tissue. [4–6] Available evidence suggests a U-shaped relation between the incidence of bleeding [7–11] or cardiovascular events [12–17] and body mass index (BMI), with extreme categories, namely underweight or obese, being at higher risk of adverse events. Furthermore, there is a paucity of data regarding the safety and efficacy of different antiplatelet regimens, including different DAPT durations and P2Y12 inhibitor monotherapy, according to BMI. As a consequence, a recent consensus document from the European Society of Cardiology (ESC) Working Group on Thrombosis recommended that data of antithrombotic trials should be reported with respect to established BMI categories. [4]

The TWILIGHT trial evaluated a novel therapeutic strategy for high risk patients undergoing percutaneous coronary intervention (PCI) with drug eluting stent where, after 3 months of dual antiplatelet therapy (DAPT) with aspirin plus ticagrelor, aspirin was dropped. Ticagrelor monotherapy, compared with ticagrelor plus aspirin, significantly reduced the risk of bleedings by 44% without any ischemic trade-off. [18,19] As such, this strategy might be appealing for those subjects who are particularly at increased odds of adverse events. We sought to evaluate the benefit of ticagrelor monotherapy versus ticagrelor plus aspirin among the patients included in the TWILIGHT trial based on the different standardized BMI categories. [1,4]

METHODS

Study Design and Population

The trial rationale, design, and principal results have been reported elsewhere. [18,19] TWILIGHT was a randomized, placebo-controlled trial (187 sites, 11 countries) enrolling patients that underwent a successful PCI with the implantation of drug-eluting stent and that were at high risk of ischemic or bleeding events based on the presence of at least one clinical (age ≥65 years, female sex, troponin positive acute coronary syndrome [ACS], prior myocardial infarction [MI], prior coronary revascularization, peripheral arterial disease, diabetes mellitus requiring medication, or chronic kidney disease [CKD]) and one angiographic (multivessel coronary artery disease, total stent length >30 mm, thrombotic target lesion, bifurcation lesion requiring 2 stents, obstructive left main or proximal left anterior descending lesion, or calcified target lesion requiring debulking devices) high risk feature. Need for oral anticoagulation, prior stroke, ST-segment elevation myocardial infarction, or cardiogenic shock were key exclusion criteria. After three months of uneventful and tolerated DAPT with open-label ticagrelor (90 mg twice daily) and enteric-coated aspirin (81-100 mg daily), patients were randomized 1:1 to enteric-coated aspirin or matching placebo for an additional 12 months on a background open-label ticagrelor therapy. Follow-up visits were scheduled via telephone at 1 month, and in-person at 6 and 12 months after randomization.

The protocol was approved by national regulatory agencies and institutional review boards or ethics committees of participating sites.

Study Outcomes

The primary endpoint was Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding up to 1 year after randomization. The key secondary ischemic endpoint was the composite of all-cause death, MI, or stroke. Secondary bleeding endpoints included BARC type 3 or 5 bleeding, Thrombolysis in Myocardial Infarction (TIMI) major bleeding, Global Use of Strategies to Open Occluded Arteries (GUSTO) moderate or severe or bleeding, and International Society of Thrombosis or Hemostasis (ISTH) major bleeding. [20–23] Other secondary ischemic endpoints included the composite of cardiovascular death, MI, or ischemic stroke, its individual components, definite or probable stent thrombosis. Net adverse clinical event (NACE) was the composite of BARC type 3 or 5 bleeding, death, MI, or stroke. MI was defined according to the third universal definition, and stent thrombosis were classified according to the Academic Research Consortium (ARC) criteria. [24,25] All clinical events were adjudicated by an independent committee, blinded to treatment assignment.

BMI Categories

For the purpose of this analysis, the population was stratified in the following established BMI categories as recommended by the ESC Working Group on Thrombosis: normal weight (BMI=18.5-24.99 kg/m^2), overweight (BMI=25-29.99 kg/m^2), and obese (BMI≥30 kg/m^2). [1,4] BMI was derived using the standard formula (BMI=weight [kg]/[height (m)]^2). Underweight subjects (BMI <18.5 kg/m^2) were excluded from the present study because of the very limited sample size (n=52, 0.7%) preventing any statistical inference. Furthermore, patients were also stratified by median BMI, which was 27.7 kg/m^2, as pre-specified in the trial protocol. [18]

Statistical Analyses

Clinical and procedural characteristics are presented by mean ± standard deviation (SD) or number of patients (%) as appropriate. The cumulative incidence of primary and secondary

endpoints was estimated using the Kaplan-Meier method. Survival analyses were based on the time to first event and patients were censored at the time of death, last known contact, or 365 days, whichever came first. The intention-to-treat population was used for all the analyses on bleeding events (including NACE), while ischemic outcomes were analyzed in the per protocol cohort. Hazard ratios (HRs) and adjusted HRs with 95% confidence intervals (CIs) were generated using Cox proportional hazards models. Prognostically relevant variables that were significantly different among normal weight, overweight and obese subjects were used for adjustment in the final multivariable model which included age (years), gender, race, enrolling region, diabetes, CKD, anemia, current smoker, hypercholesterolemia, hypertension, previous PCI, previous coronary artery bypass graft (CABG), indication for PCI, and complex PCI. [26] Absolute risk differences (ARDs) for the treatment effect of ticagrelor monotherapy were generated by the differences in the Kaplan–Meier event rates for 1-year outcomes between the two treatment arms among normal weight, overweight and obese patients. Heterogeneity of both the relative and absolute treatment effects according to the different BMI categories was analyzed with a test for treatment-by-subgroup interaction.

A two-sided p-value of <0.05 was considered statistically significant. All analyses were performed using Stata version 16.0 (College Station, Texas).

RESULTS

Standardized BMI Categories in the TWILIGHT population

Among the 7119 patients randomized in the parental trial, 29 (0.4%) did not have information on BMI. After excluding 52 (0.7%) underweight patients, the final study cohort included 7038 patients: 1807 (25.7%) normal weight, 2927 (41.6%) overweight and 2304 (32.7%) obese (**Table 1**). Patients with a higher BMI were more frequently younger, of white race, and they had a higher burden of cardiovascular risk factors including diabetes mellitus, CKD, hypercholesterolemia, hypertension and prior coronary revascularization. Although ACS was overall the most frequent indication to PCI, obese patients had a higher prevalence of stable coronary artery disease as compared with normal body weight patients. Furthermore, obese patients were more frequently enrolled in North America, overweight in Europe and patients with normal weight in Asia. As it relates to procedural characteristics, the use of radial artery access was lower among obese patients, who were also less likely to undergo complex PCI. Baseline clinical and procedural characteristics were overall balanced between the two treatment arms in each BMI category (**Supplementary Table 1** and **2**).

Standardized BMI categories and risk of adverse event in the TWILIGHT population

The primary endpoint of BARC type 2, 3, or 5 bleeding occurred in 101 (5.7%) patients with a normal weight, 164 (5.7%) overweight patients and 120 (5.3%) obese patients ($p_{log\text{-}rank}$=0.830) (**Figure 1A**, **Table 3**). There were no significant differences in all secondary bleeding endpoints according to the TIMI, GUSTO, and ISTH scale across BMI categories (p>0.20 for all outcomes). The adjusted multivariable Cox model provided consistent results (**Table 3**).

The key secondary ischemic endpoint (composite of all-cause death, MI, or stroke) occurred in 68 (3.8%) patients with a normal weight, 106 (3.7%) overweight, and 94 (4.2%) obese patients ($p_{log\text{-}rank}$=0.680) (**Figure 1B**, **Table 3**). Similar to bleeding events, there was no significant association between BMI and any of the secondary ischemic endpoints (p>0.10 for all outcomes) both before and after adjustment (**Table 3**).

The occurrence of NACE (composite of BARC type 3 or 5 bleeding, death, MI, or stroke) in normal weight (4.9%) was similar to overweight (5.0%; HR 1.03, 95% CI 0.79-1.34) and obese subjects (5.2%; HR 1.06, 95% CI 0.80-1.39).

Standardized BMI categories and clinical safety and efficacy of ticagrelor monotherapy

Ticagrelor monotherapy, compared with ticagrelor plus aspirin, reduced the primary endpoint of BARC type 2, 3, or 5 bleeding consistently in normal weight, overweight and obese patients (HR 0.48, 95% CI 0.32-0.73; HR 0.57, 95% CI 0.41-0.78; HR 0.63, 95% CI 0.44-0.91, respectively; p-interaction=0.627) (**Figure 2**). The benefit of ticagrelor monotherapy was confirmed also for BARC type 3 or 5 bleeding (normal weight: HR 0.70; 95% CI 0.30-1.63; overweight: HR 0.65, 95% CI 0.37-1.16; obese: HR 0.25, 95% CI 0.1-0.60; p-interaction=0.129) and for other bleeding endpoints according to the TIMI, GUSTO and ISTH scale with no effect of heterogeneity across the BMI categories (p-interaction>0.10 for all bleeding outcomes) (**Figure 2**).

Patients randomized to ticagrelor monotherapy versus ticagrelor plus aspirin were not at higher risk of composite ischemic endpoint of all-cause death, MI, or stroke (normal weight: HR 1.36, 0.84-2.19; overweight: HR 0.92, 95% CI 0.63-1.35; obese: HR 0.84, 95% CI 0.56-1.25; p-interaction=0.290), ischemic events or NACE irrespective of the BMI category (p-interaction>0.20 for all ischemic outcomes and for NACE) (**Figure 3** and **4**).

The adjusted multivariable Cox model provided consistent results (**Supplementary Table 3**). While treatment effects on the relative scale (HRs) were consistent, patients with higher BMI realized a greater absolute risk reduction with ticagrelor monotherapy as compared with ticagrelor plus aspirin in terms of BARC type 3 or 5 bleeding (normal weight: ARD -0.4%, 95% CI -1.5%, 0.6%; overweight: ARD -0.7%, 95% CI -1.6%, 0.2%; obese: ARD -1.6%, 95% CI -2.5%, -0.6%; p-interaction=0.030) and NACE (normal weight: ARD 0.5%, 95% CI -1.5%, 2.5%; overweight: ARD -0.8%, 95% CI -2.4%, 0.7%; obese: ARD -2.0%, 95% CI -3.8%, -0.1%; p-interaction=0.040). There was no heterogeneity in the treatment effect as measured by ARD for any of the other outcomes across the BMI categories (p-interaction> 0.05 for all other outcomes) (**Table 4**).

Prespecified BMI analysis

Among a total of 7090 patients with available information on BMI in TWILIGHT, the median BMI was 27.7 kg/m^2. Baseline clinical and procedural characteristics of patients by median BMI are reported in **Supplementary Table 4** and **5**, and the risks for adverse events are shown in **Supplementary Table 6**. Overall baseline characteristics were consistent with those by standardized BMI categories and the risks of adverse events were similar between patients with a BMI below or above median. **Supplementary Table 7** summarize the treatment effect of ticagrelor monotherapy vs ticagrelor plus aspirin by median BMI at one year after randomization. The experimental strategy reduced the occurrence of bleeding events without increasing the ischemic risk irrespective of having a BMI below or above median.

DISCUSSION

We herein report the data from the TWILIGHT trial with respect to established BMI categories, as recommended by the ESC Working Group on Thrombosis. [4]

We showed that, compared to ticagrelor plus aspirin, ticagrelor monotherapy reduced bleeding events without any increase in the ischemic risk across different BMI categories. Although the relative bleeding risk reduction was similar in each category, subjects with a higher BMI, experienced greater absolute risk reductions in terms of major bleeding (BARC type 3 or 5) and NACE as compared with those with a normal weight.

Obesity is a known important and modifiable risk factor for coronary artery disease. [27] The excess in adipose tissue has been shown to favor a prothrombotic and inflammatory milieu [28,29] that may predispose to atherothrombotic events, plaque rupture and increased risk in all-cause and cardiovascular mortality. [12–17] However, in individuals with established vascular disease the association between obesity and ischemic events is more complex and not fully understood. [4] In some studies, overweight BMI has been shown to be associated with the lowest risk of cardiovascular events, the so called obesity paradox. [5,30–32] Furthermore, obese patients are also at higher risk for spontaneous major bleeding, including hemorrhagic strokes and major extracranial bleeding, the latter partly explained by the positive correlation between BMI and blood pressure. [11,33,34] In the TWILIGHT population, enriched with both clinical and procedural characteristics indicative of high bleeding and ischemic risk, we did not observe any association between BMI categories and adverse events, whether ischemic or hemorrhagic. This finding, also observed in the COMPASS trial, suggests that the high risk profile of the included population might attenuate this clinical association. [5]

Obesity is known to have an impact on the pharmacokinetic and pharmacodynamic of both aspirin and P2Y12 inhibitors. [4,35–37] However, very few trials evaluating the clinical safety and efficacy of antithrombotic therapy reported data with respect to standardized BMI categories, making comparisons across reports challenging. [4] In the PLATO trial, non-obese patients (<30 kg/m^2) treated with ticagrelor or clopidogrel on a background of aspirin therapy experienced a similar rate of major bleeding (11.6% vs 11.6%, HR 0.99, 95% CI 0.89-1.09). Conversely, the risk of major bleeding was higher in obese subject (BMI≥30 kg/m^2) treated with ticagrelor plus aspirin as compared with those treated with clopidogrel plus aspirin (11.6% vs 10.0%, HR 1.21, 95% CI 1.02-1.45, p-interaction=0.05). [38] This finding may be partially explained by the higher hemorrhagic risk of this subset of patients, but also because obesity is a known independent predictor of high on-treatment platelet reactivity in individuals treated with clopidogrel. [4,35,36] Conversely, ticagrelor has shown to have a wide therapeutic window and although the plasmatic concentration of both ticagrelor and its active metabolite are influenced by body weight, there is no evidence that obesity may impact on its safety and efficacy. [4,37,39]

Prior trials evaluated a strategy of short DAPT followed by ticagrelor monotherapy in patients undergoing PCI. [40,41] However, these trials enrolled a lower risk population and had an open-label design. Furthermore they did not report data with respect to standardized BMI categories, therefore they did not take in consideration the different risk profiles of underweight, normal weight, overweight and obese patients. [41,42] This is noteworthy because pooling together underweight, normal weight and even overweight subjects might represent a source of bias. Indeed, an underweight status in patients with coronary artery disease might be associated with severe conditions such as “cardiac cachexia”, cancer or other comorbidities that may not be fully captured and accounted for. [27] Nevertheless, overall findings from these prior studies were

consistent with the pre-specified analysis by median BMI herein reported, and suggest that BMI does not influence the safety and efficacy of ticagrelor monotherapy. [41,42] We proved that the benefit of ticagrelor monotherapy observed in the parental trial are preserved across different BMI categories but obese subjects, which represent an ever-growing subgroup, [1,2] experienced greater absolute benefit in terms of major bleeding (BARC type 3 or 5) and NACE. Although we cannot provide a mechanistic explanation as pharmacodynamic and pharmacokinetic measurements were not collected in the main trial, available evidence supports our clinical data and suggests that BMI may have less impact on the efficacy of ticagrelor as compared with aspirin or clopidogrel. [4,35–38,38,39] Hence, among high risk obese patients, ticagrelor monotherapy may provide an ideal trade-off between bleeding and ischemic risk, allowing to reduce the bleeding events while preserving the antithrombotic benefit of DAPT.

Limitations

The present study should be interpreted in light of the following limitations. First, the analysis according to the recommendations from the ESC Working Group on Thrombosis was not pre-specified in the protocol and therefore should be interpreted as hypothesis-generating. [4] Second, limitations of the main trial should be considered also for this sub-analysis and the present findings cannot be extrapolated to patients who were not enrolled at the time of PCI because of exclusion and inclusion criteria or to those who were not randomized because of adverse events occurring in the first three months. Third, as for most subgroup analyses, we were likely underpowered to detect significant differences, especially for ischemic events. Furthermore, we did not account for multiplicity thereby increasing the risk of type 1 error. Finally, given the very low prevalence of underweight subject (0.7% of the randomized cohort), we could not reliably

assess the effect of ticagrelor monotherapy in this subset of patients. However, BMI analyses from other trials also excluded this subgroup due to the extremely low prevalence among patients with cardiovascular disease. [5,6]

CONCLUSION

Among high-risk patients undergoing PCI, ticagrelor monotherapy, compared with ticagrelor plus aspirin, reduced bleeding events without any increase in the ischemic risk across different BMI categories. Although risk reduction in major bleeding and NACE was similar on a relative scale, the absolute risk reduction was larger in obese patients.

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FIGURE LEGENDS

Figure 1. Rates of BARC type 2, 3, or 5 bleeding and composite of death, MI, or stroke at 1 year after randomization.

Kaplan-Meier curves for incidence of BARC type 2, 3, or 5 bleeding (panel A) and the composite of death, MI, or stroke (panel B) at 1 year after randomization according to the following standardized BMI categories: normal weight (BMI=18.5-24.99 kg/m^2), overweight (BMI=25-29.99 kg/m^2), and obese (BMI≥30 kg/m^2).

BARC: Bleeding Academic Research Consortium, BMI: body mass index, HR: hazard ratio, CI: confidence interval, MI: myocardial infarction.

Figure 3. Risk of bleeding events at 1 year.

Forest plots showing the effect of ticagrelor plus placebo versus ticagrelor plus aspirin on the bleeding endpoints according to the following standardized BMI categories: normal weight (BMI=18.5-24.99 kg/m^2), overweight (BMI=25-29.99 kg/m^2), and obese (BMI≥30 kg/m^2). Event rates at one year were estimated using the Kaplan-Meier method in the intention-to-treat cohorts. Hazard ratios (HR) and 95% confidence intervals (CI) with interaction p-values generated using Cox regression.

BARC: Bleeding Academic Research Consortium; BARC: Bleeding Academic Research Consortium, TIMI: Thrombolysis in Myocardial Infarction, GUSTO: Global Utilization of Streptokinase and TPA for Occluded Arteries, ISTH: International Society on Thrombosis and Hemostasis; Tica: ticagrelor.

* P value is for the interaction between randomized treatment assignment and BMI categories.

Figure 4. Risk of ischemic events at 1 year.

Forest plots showing the effect of ticagrelor plus placebo versus ticagrelor plus aspirin on the ischemic events according to the following standardized BMI categories: normal weight (BMI=18.5-24.99 kg/m^2), overweight (BMI=25-29.99 kg/m^2), and obese (BMI≥30 kg/m^2). Event rates at one year were estimated using the Kaplan-Meier method in the per-protocol cohorts. Hazard ratios (HR) and 95% confidence intervals (CI) with interaction p-values generated using Cox regression.

BMI: body mass index; CV: cardiovascular; MI: myocardial infarction; ST: stent thrombosis; Tica: ticagrelor.

* P value is for the interaction between randomized treatment assignment and BMI categories.

Figure 5. Risk of NACE at 1 year.

Forest plots showing the effect of ticagrelor plus placebo versus ticagrelor plus aspirin on the NACE according to the following standardized BMI categories: normal weight (BMI=18.5-24.99 kg/m^2), overweight (BMI=25-29.99 kg/m^2), and obese (BMI≥30 kg/m^2).

Event rates at one year were estimated using the Kaplan-Meier method in the intention-to-treat cohorts. Hazard ratios (HR) and 95% confidence intervals (CI) with interaction p-values generated using Cox regression.

BARC: Bleeding Academic Research Consortium; BMI: body mass index; NACE: net adverse clinical events, including BARC type 3 or 5, all-cause death, MI, and stroke; Tica: ticagrelor.

* P value is for the interaction between randomized treatment assignment and BMI categories.

Graphical Abstract. Benefit of ticagrelor monotherapy vs ticagrelor plus aspirin by standardized BMI categories.

Effects of ticagrelor plus placebo versus ticagrelor plus aspirin on bleeding and ischemic events across standardized BMI categories (normal weight: BMI 18.5-24.99 kg/m^2; overweight: BMI 25-29.99 kg/m^2; obese: BMI≥30 kg/m^2) in patients who tolerated 3 months of DAPT after PCI with a drug-eluting stent.

ARR: absolute risk reduction, BARC: Bleeding Academic Research Consortium, CI: confidence interval, DAPT: dual antiplatelet therapy, HR: hazard ratio, MI: myocardial infarction, NACE: net adverse clinical events (including BARC type 3 or 5, all-cause death, MI, and stroke), PCI: percutaneous coronary intervention.

P-interaction is for the treatment-by-subgroups interaction with respect to events ARR of ticagrelor monotherapy vs ticagrelor plus placebo among standardized BMI categories.

The percentages represent Kaplan-Meier rates at 12 months after randomization.

TABLES

Table 1. Baseline clinical characteristics by standardized BMI categories.

Clinical parameters	Overall N=7038	Normal N=1807 (25.7%)	Overweight N=2927 (41.6%)	Obese N=2304 (32.7%)	P-value
Age, years	63.9±10.2	65.4±10.2	64.1±10.2	62.3±9.9	<.001
Female sex	1677 (23.8%)	498 (27.6%)	578 (19.7%)	601 (26.1%)	<.001
Nonwhite race	2147 (30.5%)	845 (46.8%)	893 (30.5%)	409 (17.8%)	<.001
Enrolling region					<.001
North America	2952 (41.9%)	474 (26.2%)	1078 (36.8%)	1400 (60.8%)	
Europe	2489 (35.4%)	592 (32.8%)	1159 (39.6%)	738 (32.0%)	
Asia	1597 (22.7%)	741 (41.0%)	690 (23.6%)	166 (7.2%)	
Diabetes	2605 (37.0%)	516 (28.6%)	1018 (34.8%)	1071 (46.5%)	<.001
Diabetes treated with insulin	707 (27.1%)	115 (22.3%)	256 (25.1%)	336 (31.4%)	<.001

Clinical parameters	Overall N=7038	Normal N=1807 (25.7%)	Overweight N=2927 (41.6%)	Obese N=2304 (32.7%)	P-value
Chronic kidney disease	1102 (16.3%)	255 (14.7%)	442 (15.7%)	405 (18.3%)	0.005
Anemia	1309 (19.4%)	426 (24.6%)	501 (17.8%)	382 (17.3%)	<.001
Current smoker	1521 (21.6%)	420 (23.2%)	647 (22.1%)	454 (19.7%)	0.017
Hypercholesterolemia	4274 (60.7%)	806 (44.6%)	1753 (59.9%)	1715 (74.4%)	<.001
Hypertension	5109 (72.6%)	1148 (63.6%)	2092 (71.5%)	1869 (81.1%)	<.001
Peripheral arterial disease	484 (6.9%)	122 (6.8%)	203 (6.9%)	159 (6.9%)	0.969
Previous MI	2017 (28.7%)	488 (27.0%)	834 (28.5%)	695 (30.2%)	0.082
Previous PCI	2975 (42.3%)	644 (35.6%)	1273 (43.5%)	1058 (45.9%)	<.001
Previous CABG	708 (10.1%)	119 (6.6%)	281 (9.6%)	308 (13.4%)	<.001
Previous major bleed	60 (0.9%)	15 (0.8%)	26 (0.9%)	19 (0.8%)	0.963
Indication for PCI					<.001
Stable CAD	2488 (35.4%)	569 (31.5%)	1045 (35.7%)	874 (37.9%)	

Clinical parameters	Overall N=7038	Normal N=1807 (25.7%)	Overweight N=2927 (41.6%)	Obese N=2304 (32.7%)	P-value
ACS	4548 (64.6%)	1236 (68.5%)	1882 (64.3%)	1430 (62.1%)	

BMI: body mass index, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, CAD: coronary artery disease, ACS: acute coronary syndrome.

Table 2. Baseline procedural characteristics by standardized BMI categories.

Procedural characteristics	**Overall N=7038**	**Normal N=1807 (25.7%)**	**Overweight N=2927 (41.6%)**	**Obese N=2304 (32.7%)**	**P-value**
Radial artery access	5123 (72.8%)	1403 (77.6%)	2164 (73.9%)	1556 (67.5%)	<.001
Multivessel CAD	4414 (62.7%)	1124 (62.2%)	1844 (63.0%)	1446 (62.8%)	0.858
Target vessel					
Left Main	344 (4.9%)	103 (5.7%)	145 (5.0%)	96 (4.2%)	0.075
LAD	3952 (56.2%)	1085 (60.0%)	1636 (55.9%)	1231 (53.4%)	<.001
LCX	2265 (32.2%)	582 (32.2%)	947 (32.4%)	736 (31.9%)	0.951
RCA	2470 (35.1%)	614 (34.0%)	1040 (35.5%)	816 (35.4%)	0.512
Number of vessels treated	1.3±0.5	1.3±0.5	1.3±0.5	1.2±0.5	<.001
Number of lesions treated	1.5±0.7	1.6±0.8	1.5±0.7	1.5±0.7	0.010
Lesion morphology					

Procedural characteristics	Overall N=7038	Normal N=1807 (25.7%)	Overweight N=2927 (41.6%)	Obese N=2304 (32.7%)	P-value
Moderate/severe calcification	978 (13.9%)	228 (12.6%)	424 (14.5%)	326 (14.1%)	0.179
Bifurcation	858 (12.2%)	242 (13.4%)	349 (11.9%)	267 (11.6%)	0.181
Total occlusion	435 (6.2%)	116 (6.4%)	194 (6.6%)	125 (5.4%)	0.178
Thrombotic	739 (10.5%)	160 (8.9%)	315 (10.8%)	264 (11.5%)	0.022
Total stent length, mm	39.8±24.1	43.0±26.0	40.2±24.0	36.7±22.4	<.001
Minimum stent diameter, mm	2.8±0.5	2.8±0.4	2.9±0.5	2.9±0.5	0.016
Complex PCI*	2304 (32.7%)	652 (36.1%)	979 (33.4%)	673 (29.2%)	<.001

BMI: body mass index, CAD: coronary artery disease, LAD: left anterior descending, LCX: left circumflex, RCA: right coronary artery, PCI: percutaneous coronary intervention.

*Complex PCI is defined as any of the following: 3 vessels treated, ≥ 3 lesions treated, total stent length > 60 mm, bifurcation with 2 stents implanted, atherectomy device use, left main PCI, surgical bypass graft or chronic total occlusion as target lesions.

Table 3. Adverse events by standardized BMI categories at one year randomization.

	Event (%)	HR (95% CI)	p-value	AHR (95% CI)*	p-value
Bleeding outcomes *					
BARC 2, 3, or 5					
Normal weight	101 (5.7%)	Ref.		Ref.	
Overweight	164 (5.7%)	1.00 (0.78 - 1.28)	0.985	1.03 (0.79 - 1.34)	0.821
Obese	120 (5.3%)	0.94 (0.72 - 1.22)	0.626	0.84 (0.63 - 1.14)	0.265
BARC 3 or 5					
Normal weight	22 (1.2%)	Ref.		Ref.	
Overweight	48 (1.7%)	1.35 (0.81 - 2.23)	0.245	1.44 (0.85 - 2.44)	0.176
Obese	30 (1.3%)	1.08 (0.62 - 1.87)	0.793	0.96 (0.52 - 1.78)	0.898
TIMI major					
Normal weight	10 (0.6%)	Ref.		Ref.	

	Event (%)	HR (95% CI)	p-value	AHR (95% CI)*	p-value
Overweight	23 (0.8%)	1.42 (0.68 - 2.98)	0.354	1.45 (0.68 - 3.09)	0.339
Obese	17 (0.8%)	1.34 (0.61 - 2.93)	0.460	1.27 (0.54 - 3.00)	0.583
GUSTO moderate or severe					
Normal weight	18 (1.0%)	Ref.		Ref.	
Overweight	32 (1.1%)	1.10 (0.62 - 1.95)	0.753	1.29 (0.71 - 2.35)	0.409
Obese	24 (1.1%)	1.05 (0.57 - 1.94)	0.871	1.15 (0.58 - 2.30)	0.685
ISTH major					
Normal weight	26 (1.5%)	Ref.		Ref.	
Overweight	51 (1.8%)	1.21 (0.76 - 1.94)	0.426	1.28 (0.78 - 2.11)	0.335
Obese	31 (1.4%)	0.94 (0.56 - 1.58)	0.816	0.79 (0.44 - 1.42)	0.428
Ischemic outcomes †					
Death, MI, or stroke					

	Event (%)	HR (95% CI)	p-value	AHR (95% CI)*	p-value
Normal weight	68 (3.8%)	Ref.		Ref.	
Overweight	106 (3.7%)	0.96 (0.71 - 1.31)	0.811	0.81 (0.59 - 1.12)	0.203
Obese	94 (4.2%)	1.09 (0.80 - 1.49)	0.591	0.80 (0.57 - 1.14)	0.216
Cardiovascular death, MI or ischemic stroke					
Normal weight	61 (3.4%)	Ref.		Ref.	
Overweight	102 (3.6%)	1.03 (0.75 - 1.42)	0.837	0.88 (0.63 - 1.23)	0.455
Obese	89 (4.0%)	1.15 (0.83 - 1.59)	0.400	0.88 (0.61 - 1.26)	0.470
All-cause death					
Normal weight	19 (1.1%)	Ref.		Ref.	
Overweight	29 (1.0%)	0.94 (0.53 - 1.68)	0.845	0.79 (0.44 - 1.43)	0.440
Obese	27 (1.2%)	1.12 (0.62 - 2.01)	0.714	0.77 (0.40 - 1.45)	0.413
Cardiovascular death					

	Event (%)	HR (95% CI)	p-value	AHR (95% CI)*	p-value
Normal weight	12 (0.7%)	Ref.		Ref.	
Overweight	25 (0.9%)	1.29 (0.65 - 2.56)	0.471	1.09 (0.54 - 2.20)	0.804
Obese	22 (1.0%)	1.45 (0.72 - 2.92)	0.304	1.07 (0.50 - 2.28)	0.863
MI					
Normal weight	45 (2.5%)	Ref.		Ref.	
Overweight	77 (2.7%)	1.06 (0.73 - 1.53)	0.765	0.87 (0.59 - 1.28)	0.479
Obese	66 (3.0%)	1.16 (0.79 - 1.69)	0.454	0.82 (0.54 - 1.25)	0.353
Ischemic stroke					
Normal weight	8 (0.5%)	Ref.		Ref.	
Overweight	9 (0.3%)	0.70 (0.27 - 1.80)	0.455	0.75 (0.28 - 1.98)	0.558
Obese	7 (0.3%)	0.69 (0.25 - 1.90)	0.474	0.77 (0.25 - 2.40)	0.657
Stent thrombosis (definite/probable)					

	Event (%)	HR (95% CI)	p-value	AHR (95% CI)*	p-value
Normal weight	6 (0.3%)	Ref.		Ref.	
Overweight	11 (0.4%)	1.13 (0.42 - 3.07)	0.804	0.86 (0.31 - 2.36)	0.771
Obese	16 (0.7%)	2.11 (0.82 - 5.39)	0.119	1.12 (0.40 - 3.09)	0.834
NACE *					
Normal weight	88 (4.9%)	Ref.		Ref.	
Overweight	146 (5.0%)	1.03 (0.79 - 1.34)	0.849	0.90 (0.68 - 1.19)	0.465
Obese	118 (5.2%)	1.06 (0.80 - 1.39)	0.692	0.80 (0.59 - 1.09)	0.162

HR: hazard ratio, AHR: adjusted hazard ratio, CI: confidence interval, BARC: Bleeding Academic Research Consortium, TIMI: Thrombolysis in Myocardial Infarction, GUSTO: Global Utilization of Streptokinase and TPA for Occluded Arteries, ISTH: International Society on Thrombosis and Hemostasis, MI: myocardial infarction, NACE: net adverse clinical events, including BARC 3 or 5, all-cause death, MI, and stroke.

*Bleeding outcomes and NACE were analyzed in the intention-to-treat cohort.

†Ischemic outcomes were analyzed in the per-protocol cohort.

Model adjusted for age (years), gender, nonwhite race, enrolling region, diabetes, chronic kidney disease, anemia, current smoker, hypercholesterolemia, hypertension, previous PCI, previous CABG, indication for PCI, and complex PCI.

The percentages mentioned above represent K-M rates at 12 months after randomization.

Table 4. Absolute risk differences between ticagrelor monotherapy and ticagrelor plus aspirin by standardized BMI category at one year after randomization.

	Ticagrelor+Placebo	Ticagrelor+Aspirin	ARD (95% CI)	p-value	p-interaction
	no. of events (%)				
Bleeding outcomes*					
BARC 2, 3, or 5					
Normal weight	33 (3.7%)	68 (7.6%)	-3.9% (-6.0%, -1.7%)	< 0.001	0.371
Overweight	60 (4.1%)	104 (7.2%)	-3.1% (-4.7%, -1.4%)	< 0.001	
Obese	47 (4.2%)	73 (6.5%)	-3.1% (-4.7%, -1.4%)	< 0.001	
BARC 3 or 5					
Normal weight	9 (1.0%)	13 (1.4%)	-0.4% (-1.5%, 0.6%)	0.402	0.030
Overweight	19 (1.3%)	29 (2.0%)	-0.7% (-1.6%, 0.2%)	0.140	
Obese	6 (0.5%)	24 (2.1%)	-1.6% (-2.5%, -0.6%)	0.001	
TIMI major					

	Ticagrelor+Placebo	Ticagrelor+Aspirin	ARD (95% CI)	p-value	p-interaction
	no. of events (%)				
Normal weight	3 (0.3%)	7 (0.8%)	-0.4% (-1.1%, 0.2%)	0.206	0.386
Overweight	9 (0.6%)	14 (1.0%)	-0.4% (-1.0%, 0.3%)	0.286	
Obese	5 (0.4%)	12 (1.1%)	-0.6% (-1.3%, 0.1%)	0.090	
GUSTO moderate or severe					
Normal weight	7 (0.8%)	11 (1.2%)	-0.4% (-1.4%, 0.5%)	0.351	0.182
Overweight	12 (0.8%)	20 (1.4%)	-0.6% (-1.3%, 0.2%)	0.150	
Obese	7 (0.6%)	17 (1.5%)	-0.9% (-1.7%, -0.0%)	0.041	
ISTH major					
Normal weight	10 (1.1%)	16 (1.8%)	-0.7% (-1.8%, 0.5%)	0.245	0.135
Overweight	22 (1.5%)	29 (2.0%)	-0.5% (-1.4%, 0.5%)	0.315	
Obese	7 (0.6%)	24 (2.1%)	-1.5% (-2.5%, -0.5%)	0.002	

	Ticagrelor+Placebo	Ticagrelor+Aspirin	ARD (95% CI)	p-value	p-interaction
	no. of events (%)				
Ischemic outcomes†					
Death, MI, or stroke					
Normal weight	39 (4.4%)	29 (3.3%)	1.1% (-0.7%, 2.9%)	0.215	0.126
Overweight	51 (3.5%)	55 (3.9%)	-0.3% (-1.7%, 1.1%)	0.651	
Obese	43 (3.8%)	51 (4.6%)	-0.7% (-2.4%, 0.9%)	0.384	
Cardiovascular death, MI or ischemic stroke					
Normal weight	33 (3.7%)	28 (3.2%)	0.6% (-1.1%, 2.3%)	0.506	0.312
Overweight	50 (3.5%)	52 (3.6%)	-0.2% (-1.5%, 1.2%)	0.794	
Obese	41 (3.6%)	48 (4.3%)	-0.6% (-2.3%, 1.0%)	0.437	
All-cause death					
Normal weight	10 (1.1%)	9 (1.0%)	0.1% (-0.8%, 1.1%)	0.821	0.152

	Ticagrelor+Placebo	Ticagrelor+Aspirin	ARD (95% CI)	p-value	p-interaction
	no. of events (%)				
Overweight	12 (0.8%)	17 (1.2%)	-0.4% (-1.1%, 0.4%)	0.330	
Obese	10 (0.9%)	17 (1.5%)	-0.6% (-1.5%, 0.3%)	0.173	
Cardiovascular death					
Normal weight	5 (0.6%)	7 (0.8%)	-0.2% (-1.0%, 0.5%)	0.567	0.420
Overweight	11 (0.8%)	14 (1.0%)	-0.2% (-0.9%, 0.5%)	0.526	
Obese	8 (0.7%)	14 (1.3%)	-0.5% (-1.4%, 0.3%)	0.194	
MI					
Normal weight	26 (2.9%)	19 (2.2%)	0.8% (-0.7%, 2.3%)	0.292	0.242
Overweight	37 (2.6%)	40 (2.8%)	-0.2% (-1.4%, 0.9%)	0.694	
Obese	31 (2.8%)	35 (3.1%)	-0.4% (-1.8%, 1.0%)	0.597	
Ischemic stroke					

	Ticagrelor+Placebo	Ticagrelor+Aspirin	ARD (95% CI)	p-value	p-interaction
	no. of events (%)				
Normal weight	5 (0.6%)	3 (0.3%)	0.2% (-0.4%, 0.9%)	0.475	0.584
Overweight	6 (0.4%)	3 (0.2%)	0.2% (-0.2%, 0.6%)	0.325	
Obese	5 (0.4%)	2 (0.2%)	0.3% (-0.2%, 0.7%)	0.253	
Stent thrombosis (definite/probable)					
Normal weight	4 (0.5%)	2 (0.2%)	0.2% (-0.3%, 0.8%)	0.414	0.096
Overweight	5 (0.3%)	6 (0.4%)	-0.1% (-0.5%, 0.4%)	0.742	
Obese	5 (0.4%)	11 (1.0%)	-0.5% (-1.2%, 0.2%)	0.130	
NACE*					
Normal weight	46 (5.2%)	42 (4.7%)	0.5% (-1.5%, 2.5%)	0.629	0.040
Overweight	67 (4.6%)	79 (5.5%)	-0.8% (-2.4%, 0.7%)	0.295	
Obese	48 (4.2%)	70 (6.2%)	-2.0% (-3.8%, -0.1%)	0.036	

ARD: absolute risk difference, CI: confidence interval, BARC: Bleeding Academic Research Consortium, TIMI: Thrombolysis in Myocardial Infarction, GUSTO: Global Utilization of Streptokinase and TPA for Occluded Arteries, ISTH: International Society on Thrombosis and Hemostasis, MI: myocardial infarction, NACE: net adverse clinical events, including BARC 3 or 5, all-cause death, MI, and stroke.

*Bleeding outcomes and NACE were analyzed in the intention-to-treatment cohort

†Ischemic outcomes were analyzed in the per-protocol cohort.

P-interaction is the p-value for the interaction test between randomized treatment assignment and BMI categories.

The percentages mentioned above represent K-M rates at 12 months after randomization.

Figure 1

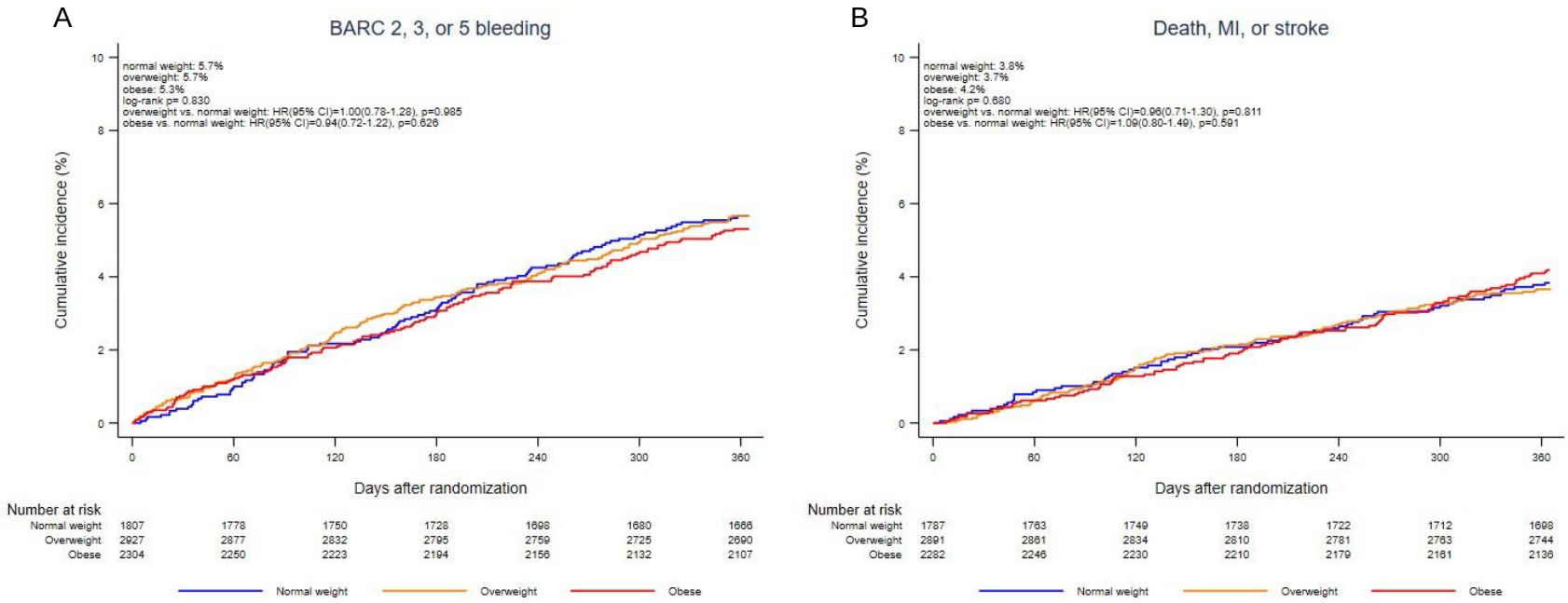

A
BARC 2, 3, or 5 bleeding
normal weight: 5.7%
overweight: 5.7%
obese: 5.3%
log-rank p= 0.830
overweight vs. normal weight: HR(95% CI)=1.00(0.78-1.28), p=0.985
obese vs. normal weight: HR(95% CI)=0.94(0.72-1.22), p=0.626
Cumulative incidence (%)
0
2
4
6
8
10
0
60
120
180
240
300
360
Days after randomization
Number at risk
Normal weight 1807 1778 1750 1728 1698 1680 1666
Overweight 2927 2877 2832 2795 2759 2725 2690
Obese 2304 2250 2223 2194 2156 2132 2107
Normal weight
Overweight
Obese
B
Death, MI, or stroke
normal weight: 3.8%
overweight: 3.7%
obese: 4.2%
log-rank p= 0.680
overweight vs. normal weight: HR(95% CI)=0.96(0.71-1.30), p=0.811
obese vs. normal weight: HR(95% CI)=1.09(0.80-1.49), p=0.591
Cumulative incidence (%)
0
2
4
6
8
10
0
60
120
180
240
300
360
Days after randomization
Number at risk
Normal weight 1787 1763 1749 1738 1722 1712 1698
Overweight 2891 2861 2834 2810 2781 2763 2744
Obese 2282 2246 2230 2210 2179 2161 2136
Normal weight
Overweight
Obese

Figure 2

Bleeding events	No. of patients	Tica+Placebo no. of events (%)	Tica+Aspirin no. of events (%)	HR (95% CI)	Interaction p-value *
BARC 2, 3, or 5					
Normal BMI	1807	33 (3.7%)	68 (7.6%)	0.48 (0.32 - 0.73)	
Overweight	2927	60 (4.1%)	104 (7.2%)	0.57 (0.41 - 0.78)	0.627
Obese	2304	47 (4.2%)	73 (6.5%)	0.63 (0.44 - 0.91)	
BARC 3, or 5					
Normal BMI	1807	9 (1.0%)	13 (1.4%)	0.70 (0.30 - 1.63)	
Overweight	2927	19 (1.3%)	29 (2.0%)	0.65 (0.37 - 1.16)	0.129
Obese	2304	6 (0.5%)	24 (2.1%)	0.25 (0.10 - 0.60)	
TIMI major					
Normal BMI	1807	3 (0.3%)	7 (0.8%)	0.43 (0.11 - 1.67)	
Overweight	2927	9 (0.6%)	14 (1.0%)	0.64 (0.28 - 1.48)	0.779
Obese	2304	5 (0.4%)	12 (1.1%)	0.41 (0.15 - 1.17)	
GUSTO moderate or severe					
Normal BMI	1807	7 (0.8%)	11 (1.2%)	0.64 (0.25 - 1.66)	
Overweight	2927	12 (0.8%)	20 (1.4%)	0.60 (0.29 - 1.22)	0.736
Obese	2304	7 (0.6%)	17 (1.5%)	0.41 (0.17 - 0.98)	
ISTH major					
Normal BMI	1807	10 (1.1%)	16 (1.8%)	0.63 (0.29 - 1.39)	
Overweight	2927	22 (1.5%)	29 (2.0%)	0.76 (0.43 - 1.31)	0.144
Obese	2304	7 (0.6%)	24 (2.1%)	0.29 (0.12 - 0.67)	

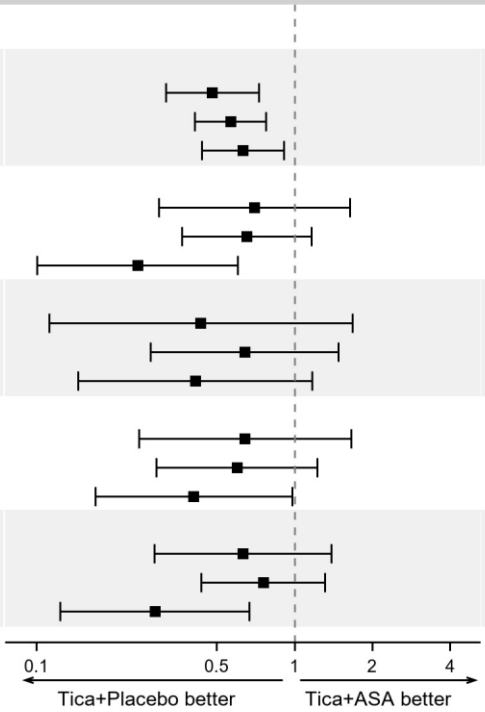


Figure 3

Ischemic events´	No. of patients	Tica+Placebo no. of events (%)	Tica+Aspirin no. of events (%)	HR (95% CI)	Interaction p-value *
Death, MI or stroke					
Normal BMI	1787	39 (4.4%)	29 (3.3%)	1.36 (0.84 - 2.19)	
Overweight	2891	51 (3.5%)	55 (3.9%)	0.92 (0.63 - 1.35)	0.290
Obese	2282	43 (3.8%)	51 (4.6%)	0.84 (0.56 - 1.25)	
CV-death, MI or ischemic stroke					
Normal BMI	1787	33 (3.7%)	28 (3.2%)	1.19 (0.72 - 1.96)	
Overweight	2891	50 (3.5%)	52 (3.6%)	0.95 (0.65 - 1.41)	0.596
Obese	2282	41 (3.6%)	48 (4.3%)	0.85 (0.56 - 1.28)	
All-cause death					
Normal BMI	1787	10 (1.1%)	9 (1.0%)	1.11 (0.45 - 2.73)	
Overweight	2891	12 (0.8%)	17 (1.2%)	0.70 (0.33 - 1.46)	0.562
Obese	2282	10 (0.9%)	17 (1.5%)	0.59 (0.27 - 1.28)	
CV-death					
Normal BMI	1787	5 (0.6%)	7 (0.8%)	0.72 (0.23 - 2.25)	
Overweight	2891	11 (0.8%)	14 (1.0%)	0.78 (0.35 - 1.72)	0.866
Obese	2282	8 (0.7%)	14 (1.3%)	0.57 (0.24 - 1.35)	
MI					
Normal BMI	1787	26 (2.9%)	19 (2.2%)	1.38 (0.76 - 2.49)	
Overweight	2891	37 (2.6%)	40 (2.8%)	0.92 (0.59 - 1.43)	0.457
Obese	2282	31 (2.8%)	35 (3.1%)	0.88 (0.54 - 1.42)	
Ischemic stroke					
Normal BMI	1787	5 (0.6%)	3 (0.3%)	1.67 (0.40 - 7.00)	
Overweight	2891	6 (0.4%)	3 (0.2%)	1.98 (0.50 - 7.93)	0.937
Obese	2282	5 (0.4%)	2 (0.2%)	2.49 (0.48 - 12.8)	
Definite/probable ST					
Normal BMI	1787	4 (0.5%)	2 (0.2%)	2.00 (0.37 - 10.9)	
Overweight	2891	5 (0.3%)	6 (0.4%)	0.83 (0.25 - 2.71)	0.310
Obese	2282	5 (0.4%)	11 (1.0%)	0.45 (0.16 - 1.30)	

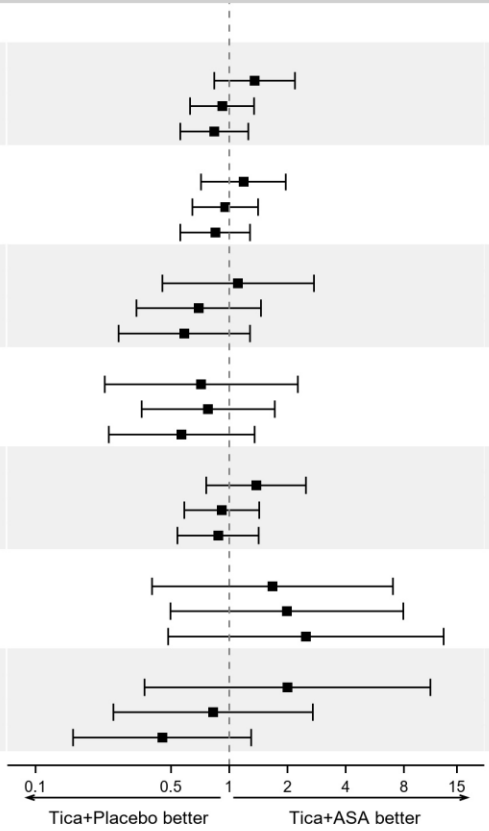
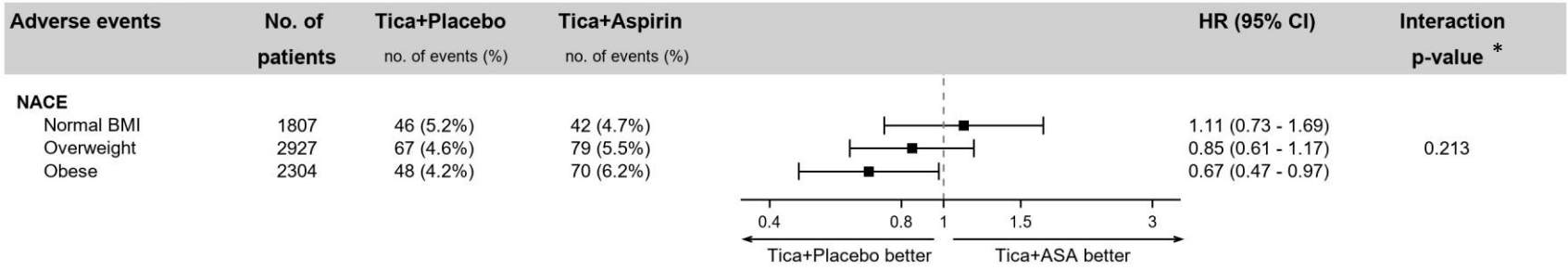


Figure 4


Adverse events
No. of patients
Tica+Placebo
no. of events (%)
Tica+Aspirin
no. of events (%)
HR (95% CI)
Interaction p-value *
NACE
Normal BMI 1807 46 (5.2%) 42 (4.7%) 1.11 (0.73 - 1.69)
Overweight 2927 67 (4.6%) 79 (5.5%) 0.85 (0.61 - 1.17) 0.213
Obese 2304 48 (4.2%) 70 (6.2%) 0.67 (0.47 - 0.97)
0.4
0.8
1
1.5
3
Tica+Placebo better
Tica+ASA better

Graphical abstract