Baseline adiponectin concentration and clinical outcomes among patients with diabetes and recent acute coronary syndrome in the EXAMINE trial

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Abstract

Aim—To investigate adiponectin levels and cardiovascular (CV) outcomes in patients with diabetes and recent acute coronary syndrome (ACS).

Materials and methods—We analysed baseline adiponectin concentration and CV outcomes in 5213 patients with type 2 diabetes enrolled in the EXAMINE trial of alogliptin vs placebo 15 to 90 days (median 45 days) after ACS. Event rates at 18 months are reported.

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Results—The median (interquartile range) baseline adiponectin concentration was 5.2 (3.5–7.9) μg/mL. Patients with the highest baseline adiponectin concentration (quartile [Q]4) were at significantly higher risk of death from a CV event (8.4% vs 1.7%; *P* < .0001), hospitalization for heart failure (HF; 7.5% vs 1.7%; *P* < .0001), and all-cause mortality (10.8% vs 2.4%; *P* < .0001) compared with those in Q1. After adjusting for age, sex, index event, HF, estimated glomerular filtration rate and hypertension, adiponectin concentration in Q4 remained associated with an increased risk of death from CV causes (hazard ratio [HR] 2.43, 95% confidence interval [CI] 1.52, 3.88), all-cause mortality (HR 2.45, 95% CI 1.65, 3.64), and HF (HR 2.44, 95% CI 1.47, 4.05), without change after stratification by body mass index. There was no significant difference in the rate of myocardial infarction or stroke.

Conclusions—In this contemporary population of patients with diabetes and ACS, adiponectin concentration was independently associated with increased risk of death from CV causes, all-cause mortality, and hospitalization for HF. The relationship between adiponectin and CV outcomes is complex and deserves further study.

1 | INTRODUCTION

Adiponectin is the most abundant adipocytokine and is involved in numerous pathways impacting the metabolic syndrome and atherosclerosis.[1,2] Low adiponectin concentrations are associated with an unfavourable cardiovascular (CV) and metabolic risk profile, including insulin resistance, type 2 diabetes mellitus and obesity,[2–9] and strong inverse correlations have been observed between adiponectin, prevalent coronary artery disease,[10,11] and incident CV events.[2,12–14] Adiponectin has also been found in animal and *in vitro* studies to have directly beneficial anti-inflammatory and vasculo-protective actions.[2,15–17] As such, adiponectin has been considered a prognostic biomarker as well as an important potential mediator of protective vascular and metabolic effects.

Because adiponectin has been studied in increasingly diverse populations and clinical settings, however, the association with CV outcomes has been mixed.[1,10,14,18–29] Among patients with acute coronary syndrome (ACS) enrolled in the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Trial – Thrombolysis in Myocardial Infarction 22) trial,[30] patients with the highest adiponectin levels had a higher rate of death and CV events.[31] Similarly, adiponectin level drawn at the time of intervention correlates positively with CV events in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (STEMI).[23] Eighteen months after ACS, however, adiponectin may again have a protective association.[1]

While adiponectin has been studied immediately after and late after ACS, it has not been investigated in the sub-acute post-ACS phase or among patients with diabetes after ACS. Moreover, given the heterogeneity in the results across previous studies, further evaluation in a robustly sized data set is warranted. The EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care in Patients with Type 2 Diabetes Mellitus

and Acute Coronary Syndrome) trial, which randomized patients with type 2 diabetes 15 to 90 days after ACS to the dipeptidyl peptidase-4 (DPP-4) inhibitor alogliptin or to placebo, provides an opportunity to further the understanding of adiponectin in the post-ACS period.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

The design, baseline patient characteristics and primary results of the EXAMINE trial (NCT00968708) have been published previously.[32,33] EXAMINE was a multicentre, randomized, controlled, double-blind trial of the DPP-4 inhibitor alogliptin vs placebo among patients with type 2 diabetes and ACS within the preceding 15 to 90 days (median 45 days). Patients were followed for a median of 18 months. The diabetes inclusion criterion was glycated haemoglobin HbA1c 6.5% to 11.0% (48–97 mmol/mol), and 7.0% to 11.0% (53–97 mmol/mol) for patients on insulin, and ACS was defined as myocardial infarction (MI) or unstable angina requiring hospitalization.[32] Patients were excluded for New York Heart Association (NYHA) class IV heart failure (HF), uncontrolled hypertension, uncontrolled angina, and severe valvular heart disease, among other exclusion criteria.[32,33] All participants provided written informed consent.

2.2 | Endpoints

The primary trial endpoint was the composite of death from CV causes, MI or stroke. On the basis of our previous work,[31] the endpoints of death and HF were of principal interest in this analysis. An independent clinical events committee adjudicated each component of the primary endpoint according to prespecified criteria.[32,33] Hospitalization for HF was additionally recorded and adjudicated.

2.3 | Measurement of adiponectin

Venous blood samples were obtained in EDTA-treated tubes at study entry as part of the study protocol. Plasma samples were transported refrigerated to the TIMI Clinical Trials Laboratory (Boston, Massachusetts) and stored at −80°C or colder until analysed after one preceding freeze–thaw. Adiponectin was measured at baseline in all available samples (n = 5213) using a validated enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minnesota). Performance characteristics include a mean minimal detectable concentration of 0.246 ng/mL and inter-assay imprecision (coefficient of variation) values of 6.8%, 5.8% and 6.9% at adiponectin concentrations of 20.5, 74.4 and 157 ng/mL, respectively.

Prior to measurement of adiponectin, all specimens had been assayed for high-sensitivity C-reactive protein (hsCRP; Denka Seiken, Tokyo, Japan), high-sensitivity cardiac troponin I (hsTnI), B-type natriuretic peptide (BNP; Abbott Laboratories), LDL cholesterol, HDL cholesterol and triglycerides using validated methods. All assays were performed by laboratory personnel blinded to treatment allocation and clinical outcome.

2.4 | Statistical analysis

Adiponectin concentrations at baseline were categorized by quartiles (Q1–4). All patients with available adiponectin results were included. Baseline characteristics by adiponectin

quartile were recorded with mean ± standard deviation (s.d.) or median and interquartile range for continuous variables and number and percent for categorical variables. Comparisons of baseline characteristics were made with the Student t-test or Wilcoxon's rank sum test for continuous variables and the chi-squared or Fisher's exact test for categorical variables.

Event rates at 18 months were calculated using the Kaplan–Meier method. Cox proportional hazards and 95% confidence intervals (CIs) were calculated for each of the clinical outcomes. The covariates included in the adjusted model were age, sex, index event type, history of HF, estimated glomerular filtration rate (eGFR), prior hypertension, and randomized treatment. This analysis was repeated stratifying by baseline body mass index (BMI) category (<25, 25 to <30 or 30 kg/m^2), and as a sensitivity analysis, with the addition of BNP into the model. Spearman correlation coefficients were calculated between adiponectin concentration and other biomarker levels at baseline.

Assessment of the treatment effect of alogliptin was performed on an intention-to-treat basis. A 2-sided *P* value of .05 was taken to indicate statistical significance for all tests. All analyses were performed with SAS version 9.4 (SAS institute, Cary, North Carolina) and were performed by the Harvard Clinical Research Institute and the TIMI Study Group. The academic authors take full responsibility for the integrity of the database and the analyses.

3 | RESULTS

3.1 | Baseline characteristics

Adiponectin levels were available at baseline for 5213 patients with 523 primary endpoint events, including 184 deaths from CV causes, 315 MI events, and 58 strokes. There were 164 hospitalizations for HF in this cohort. The median (25th–75th percentile) adiponectin concentration was 5.2 (3.5–7.9) μg/mL. The mean age was 61 years, the mean HbA1c was 8.0% (64 mmol/mol), and the mean duration of diabetes was 9.2 years. The qualifying ACS was MI in 77% of patients (Table 1). The baseline distributions of BMI and HbA1c are provided in Figures S1 and S2, respectively, along with the mean adiponectin concentration for each BMI/HbA1c bin.

At baseline, patients with adiponectin levels in Q4 vs Q1 were older (mean age 65.3 ± 9.7 vs 56.3 ± 9.2 years; *P* < .001), had a lower BMI (median [25th–75th percentile] BMI 27.4 [24.4, 31.6] vs 29.0 [26.0, 32.6] kg/m^2), and had a higher BNP (median BNP 40.7 [16.5, 97.3] vs 13.4 [5.4, 31.0] pmol/L). They were also less likely to be current smokers or have a history of coronary revascularization and were more likely to have a history of hypertension or HF, with *P* < .001 for each (Table 1). There was no difference based on adiponectin quartile in the rate of dyslipidaemia.

3.2 | Adiponectin and other biomarkers

Spearman correlation coefficients were calculated with baseline cardiac and inflammatory biomarkers (Table 2). Continuous adiponectin concentration showed weak positive correlations with BNP (r = 0.34, *P* < .0001), hsTnI (r = 0.17, *P* < .0001), and cystatin C (r = 0.29, *P* < .0001) and weak negative correlations with HbA1c (r = −0.03, *P* = 0.019) and BMI

(r = −0.10, *P* < .0001). No significant correlation was observed with hsCRP (r = −0.01, *P* = 0.41; Table 2).

3.3 | Adiponectin and cardiovascular outcomes

In the unadjusted analysis, patients with adiponectin concentrations in Q4 had significantly higher rates of the primary endpoint (16.0% vs 8.8%; *P* < .0001), death from CV causes, all-cause mortality, hospitalization for HF, and death from CV causes or hospitalization for HF than did patients in Q1 (Figure 1). There was no significant difference in the rate of MI (7.7% vs 6.6%; *P* = 0.31) or stroke (1.7% vs 1.4%; *P* = 0.65).

After adjustment for potential confounders (age, sex, index event type, history of HF, eGFR, prior hypertension and randomized treatment), patients in Q4 had significantly higher risk of death from CV causes (HR 2.43 [95% CI 1.52, 3.88]), all-cause mortality (HR 2.45 [95% CI 1.65, 3.64]), hospitalization for HF (HR 2.44 [95% CI 1.47, 4.05]), and death from CV causes or hospitalization for HF (HR 2.40 [95% CI 1.68, 3.43]; Figure 2A).

Adiponectin remained significantly associated with risk within high and low BMI strata. After stratification by baseline BMI category (<25, 25 to <30, or 30 kg/m^2), patients with adiponectin concentrations in Q4 were still found to have a higher risk of death from CV causes (HR 2.34 [95% CI 1.46, 3.75]), all-cause mortality, hospitalization for HF, and death from CV causes or hospitalization for HF as compared with patients in Q1 (Figure 2B and Tables S1A–C).

After adjustment for BNP, patients with adiponectin concentrations in Q4 remained at higher risk of death from CV causes, all-cause mortality, hospitalization for HF, and death from CV causes or hospitalization for HF as compared with patients in Q1 (Figure 2C). The potential interaction between adiponectin and BNP was further explored in analyses stratified by BNP level < or the median. There was a homogeneous risk of death from CV causes or hospitalization for HF associated with elevated adiponectin concentration (Q4) across strata defined by BNP <median level (HR 2.20 [95% CI 0.50–10.08]) and BNP median (HR 2.27 [95% CI 1.39–3.71]) with *P*-interaction = 0.29.

Adjusted risk was calculated by adiponectin quartile after stratification by sex. Adiponectin concentration in the highest quartile continued to be associated with increased risk of death from CV causes or hospitalization for HF in the female (HR 2.25 [95% CI 1.36–3.72]) and male (HR 2.25 [95% CI 1.45–3.50]) strata (*P*-interaction = 0.31).

Among patients with highest CV risk identified by adiponectin levels in Q4, there was no difference in trial endpoints based on assignment to alogliptin or placebo. Relative to patients randomized to placebo, patients assigned to alogliptin had HRs of 0.94 (95% CI 0.71, 1.23) for the primary endpoint and 1.03 (95% CI 0.77, 1.37) for the combined outcome of CV death or hospitalization for HF. There was similarly no difference in the risk of hospitalization for HF based on treatment assignment (Table S2).

4 | DISCUSSION

In this contemporary trial population of adult patients with type 2 diabetes and recent ACS, we found baseline adiponectin concentration to be strongly directly, rather than inversely, associated with adverse cardiovascular events, including CV death, all-cause mortality, and hospitalization for HF. This association was independent of the patient's presentation and relevant clinical characteristics, including BMI. Adiponectin concentration showed only weak correlations with baseline biomarkers of inflammation, glycometabolic status, and myocardial stress.

4.1 | Adiponectin and cardiovascular disease

Previous studies have shown mixed associations between adiponectin and CV outcomes. Whereas a protective association has been observed in numerous cohorts of patients without manifest CV disease,[1,10,14,18,29] other samples of patients with HF,[21,25] stable coronary artery disease,[19,28] and advanced age[20,22,24,26] have found adiponectin to be directly correlated with adverse events. In the setting of ACS, adiponectin level has been positively correlated with adverse CV events at the time of percutaneous coronary intervention for STEMI (n = 735),[23] within 10 days of ACS (n = 3931),[30] and at 4 months after ACS (n = 3366).[30] By 18 months after ACS, however, this association was seen to reverse (n = 102).[1] Further complicating understanding of this relationship is the recent observation of a higher risk of CV events associated with high adiponectin concentrations in a cohort of relatively young, otherwise healthy patients.[27] Our study adds further evidence of increased risk with elevated adiponectin in the sub-acute post-ACS period in patients with diabetes irrespective of BMI.

Interpretation of the clinical and translational investigation of adiponectin to date has been difficult. Given the direct beneficial effects of adiponectin in animal and *in vitro* studies, one explanation offered for the association between elevated adiponectin and adverse outcomes in the acute setting is that adiponectin increases in response to cardiovascular derangement or systemic stress in a counter-regulatory manner, as most clearly evident in the setting of acute MI or HF.[19,23,30,34] In fact, increased adiponectin has been found to be a marker of poor prognosis in severe non-cardiovascular illness as well.[35] The mechanism for such a response is not well understood, although increased catecholamine production may be at least partly responsible.[36] Under this hypothesis, elevated adiponectin level would be expected to be associated with markers of disease severity such as NYHA class, reduced left ventricular ejection fraction, cardiac-specific troponin, and BNP, as some of the series described above have shown.[21,25,37–39]

In our analysis, patients with high adiponectin levels were more likely to have prior HF than patients with low adiponectin levels, perhaps supporting the counter-regulatory hypothesis. There was no association with NYHA class, however, and the correlations between continuous adiponectin and BNP and hsTnI were weak. Other biomarkers of inflammation, such as hsCRP, might be expected to provide a measure of systemic illness. Similar to findings in PROVE IT-TIMI 22,[31] adiponectin was not correlated with hsCRP in our sample and showed only weak correlations with the remainder of the biomarker panel.

Another possible mechanism is failure of a compensatory response by adiponectin, either by decreased responsiveness to or insufficient production of adiponectin following a systemic perturbation. It is conceivable that some patients with CV disease develop resistance to circulating adiponectin, analogous to insulin insensitivity. Given the assumed protective effects of adiponectin, these patients would be expected to face increased CV risk and would be identified by elevated adiponectin levels. While our data do not allow the direct examination of this hypothesis, the weak correlation between adiponectin and the measured inflammatory markers is of interest. Adiponectin has demonstrable anti-inflammatory effects, including reducing TNF-α,[2] and it is notable that the patients in the highest adiponectin quartile in the EXAMINE cohort were observed to have 1.5 times the adiponectin concentration of those in the lowest quartile yet a similar inflammatory state, as indicated by the biomarker panel.

While inappropriately low adiponectin production is an intriguing theoretical mechanism for adiponectin failure and may help explain the inverse association between adiponectin and adverse outcomes in stable patients, our finding of an overall positive association does not support this as being the dominant mechanism post-ACS in patients with diabetes.

4.2 | Relationship to BNP

Recent work has identified important relationships between adiponectin and BNP.[19,37,38] Observationally, BNP is known to be a strongly predictive biomarker in patients with HF, as has also been seen recently with adiponectin.[21,25,37] Furthermore, Tsukamoto et al.[38] have shown increased adiponectin messenger ribonucleic acid production in cultured human adipocytes in response to exposure to BNP or atrial natriuretic peptide. This finding may, in part, explain the association seen between natriuretic peptide levels and favourable adipose distribution.[37,40]

While we observed an increase in BNP from Q1 to Q4 of adiponectin concentration, the degree of correlation between adiponectin and BNP was only weak. Moreover, the association between adiponectin and adverse cardiovascular outcomes was consistent after adjusting for BNP and after stratifying by BNP level < or the median. Nonetheless, the possibility that an interrelation of natriuretic peptide release and adiponectin production may be tied to underlying mechanisms for poorer cardiovascular outcomes is intriguing and warrants continued investigation. Overall, the findings presented here are consistent with the trend in other reports of adiponectin as a stronger predictor of death and HF than of atherothrombotic events such as MI or stroke.

4.3 | Limitations

The present study has several limitations. While the EXAMINE trial provides a large, well-characterized study sample with adjudicated outcomes, the data reported result from an exploratory, observational analysis. Additionally, because one of the principal hypotheses connecting elevated adiponectin to adverse outcomes in the setting of CV disease is disease severity itself, and particularly severity of HF, it would be desirable to have left ventricular ejection fraction data. Similarly, it would have been ideal to have TNF-α measurements for the assessment of the inflammatory state, as TNF-α appears to be directly suppressed by

adiponectin,[2] as well as catecholamine levels. Finally, we only measured total adiponectin rather than specific subclasses, such as high-molecular-weight adiponectin. Data on the relevance of this distinction have been mixed.[22,25] There may be sex-based differences in the high-molecular-weight fraction[41] that are a consideration given the increased proportion of women among those with higher adiponectin concentration. Importantly, the sex-based difference in adiponectin concentration in our cohort was similar to that seen in other cohorts and sex was a covariate in all adjusted analyses in our report.[19,21,23,27,31,35] Additionally, results were consistent in female and male patients after stratification by sex.

4.4 | Conclusion

In conclusion, in this contemporary cohort of adult patients with diabetes and recent ACS, baseline adiponectin concentration was strongly associated with adverse cardiovascular events, adding to prior investigations of adiponectin in acute illness. This association is directionally opposite to that seen in patients at risk of CV disease. The role of adiponectin in manifest cardiovascular disease is complex and deserves further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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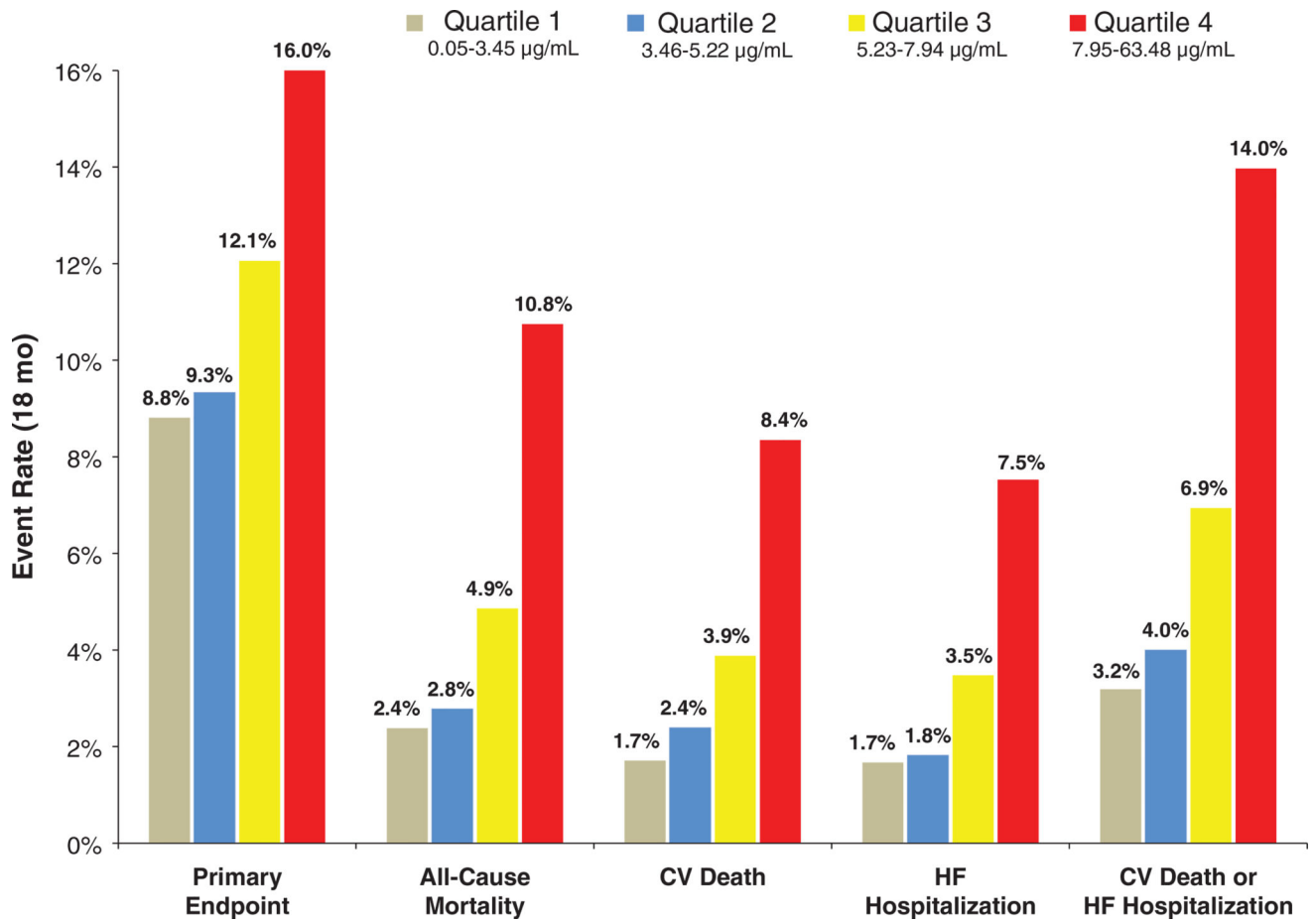
Figure 1.
Kaplan–Meier event rates at 18 months are shown by quartile of adiponectin concentration for the primary endpoint (death from CV causes, MI, or ischemic stroke), all-cause mortality, death from CV causes, HF hospitalization, and death from CV causes or HF hospitalization

Figure 2.
A–C, Adjusted hazard ratios are shown for Q4 vs Q1 adiponectin concentration for all-cause mortality, death from CV causes, HF hospitalization, and death from CV causes or HF hospitalization for the (A) primary analysis, (B) w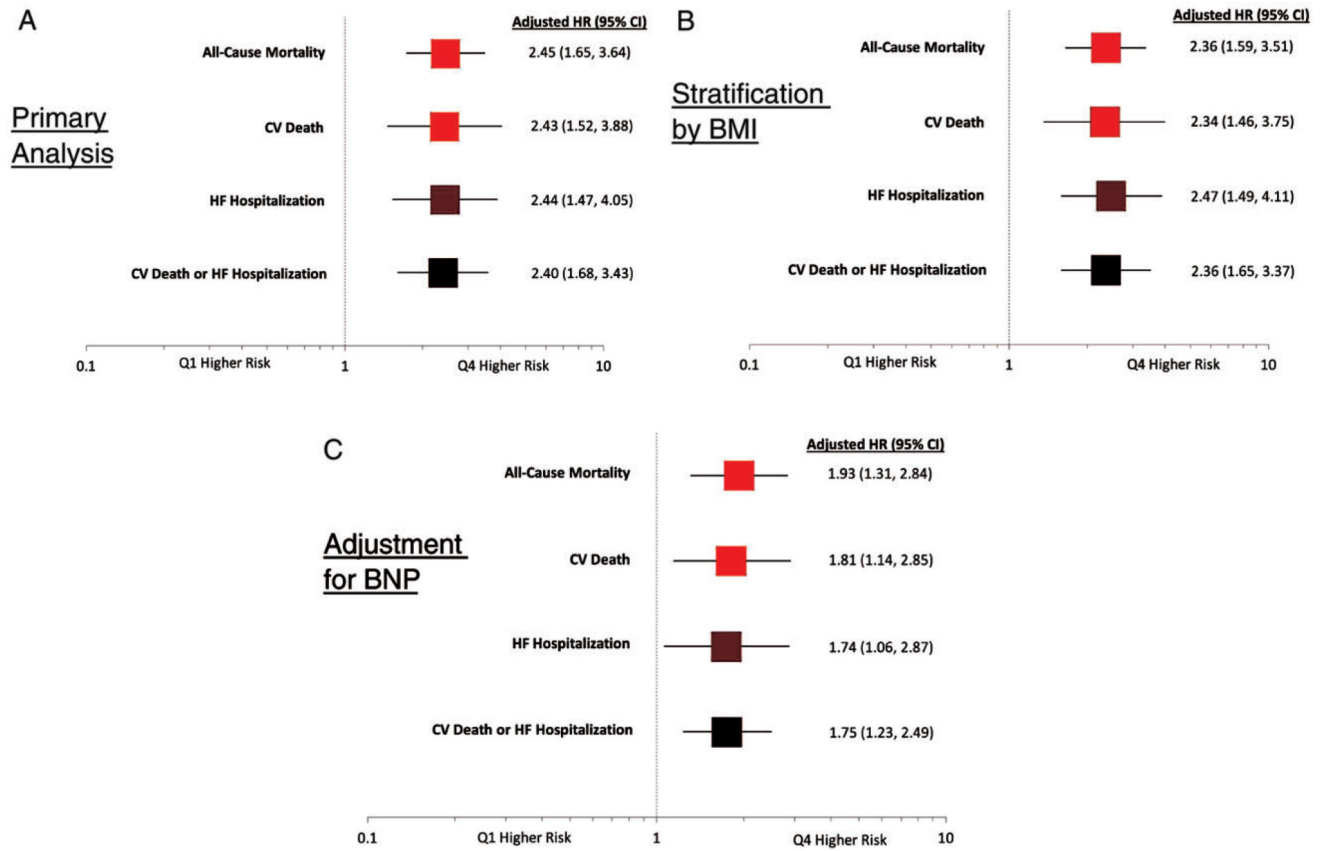ith stratification by BMI, and (C) with inclusion of BNP in the adjustment model. The covariates used for adjustment were age, sex, index event, prior heart failure, eGFR, HTN, treatment arm, and BNP (panel C only)

TABLE 1

Baseline patient characteristics by adiponectin quartile

Characteristics	Adiponectin, µg/mL				P
	Q1 (N = 1301)	Q2 (N = 1306)	Q3 (N = 1302)	Q4 (N = 1304)	
Age, years	56 (50, 63)	60 (53, 66)	62 (56, 69)	65 (59, 73)	<.001
Non-white, % (n/N)	33.5 (436/1301)	25.8 (337/1306)	23.1 (301/1302)	26.2 (341/1304)	<.001
Female, % (n/N)	14.1 (183/1301)	25.7 (336/1306)	38.3 (499/1302)	50.4 (657/1304)	<.001
BMI, kg/m²	29.0 (26.0, 32.6)	29.4 (26.1, 32.9)	29.3 (26.1, 33.0)	27.4 (24.4, 31.6)	<.001
Range (min, max)	(16.9, 55.9)	(16.9, 68.3)	(15.6, 65.9)	(15.7, 67.2)	
<25 kg/m²	25.0 (272/1086)	25.0 (272/1086)	24.9 (270/1086)	25.0 (272/1086)	
25 to <30 kg/m²	24.9 (493/1983)	25.1 (498/1983)	25.0 (496/1983)	25.0 (496/1983)	
30 kg/m²	24.8 (532/2143)	25.2% (541/2143)	25.0 (534/2143)	25.0 (536/2143)	
Duration of diabetes, years	5.3 (1.8, 10.3)	6.4 (2.3, 12.0)	7.8 (3.3, 14.7)	10.1 (4.2, 16.8)	<.001
Hypertension, % (n/N)	77.2 (1004/1301)	82.5 (1077/1306)	86.4 (1125/1302)	86.7 (1131/1304)	<.001
Dyslipidemia, % (n/N)	28.0 (364/1301)	25.4 (332/1306)	29.0 (378/1302)	26.8 (349/1304)	.188
Current smoker, % (n/N)	19.2 (250/1301)	14.9 (194/1306)	12.5 (163/1302)	8.2 (107/1304)	<.001
Prior MI, % (n/N)	88.2 (1148/1301)	87.8 (1147/1306)	87.8 (1143/1302)	88.2 (1150/1304)	.976
Prior percutaneous coronary intervention or CABG, % (n/N)	72.2 (939/1301)	71.0 (927/1306)	67.6 (880/1302)	61.6 (803/1304)	<.001
Prior HF, % (n/N)	18.1 (235/1301)	24.0 (314/1306)	30.3 (394/1302)	39.5 (515/1304)	<.001
NYHA classification at screening, % (n/N)					.260
I	27.2 (64/235)	22.0 (69/313)	20.6 (81/394)	20.0 (103/515)	
II	55.7 (131/235)	61.0 (191/313)	57.4 (226/394)	57.3 (295/515)	
III	15.3 (36/235)	15.7 (49/313)	20.6 (81/394)	21.6 (111/515)	
IV	1.7 (4/235)	1.3 (4/313)	1.5 (6/394)	1.2 (6/515)	
Systolic blood pressure, mm Hg	125 (116, 136)	130 (120, 140)	130 (120, 140)	130 (120, 140)	<.001
Heart rate, bpm	70 (64, 78)	70 (63, 77)	70 (64, 78)	72 (64, 80)	<.001
Estimated CrCl, mL/min	78 (65, 89)	74 (61, 86)	69 (56, 83)	62 (48, 77)	<.001
eGFR, mL/min/1.73 m²	77.0 (64.6, 89.0)	74.8 (61.2, 87.0)	68.8 (55.6, 83.4)	62.3 (47.2, 76.2)	<.001
Index inclusion ACS					.062

Characteristics	Adiponectin, µg/mL				
	Q1 (N = 1301)	Q2 (N = 1306)	Q3 (N = 1302)	Q4 (N = 1304)	P
Myocardial infarction, % (n/N)	79.6 (1034/1299)	77.5 (1011/1304)	75.2 (977/1299)	76.8 (998/1299)	
Time post-index ACS to randomization, days	43 (29, 61)	43 (30, 62)	44 (29, 66)	46 (30, 66)	.009
Percutaneous coronary intervention for index event, % (n/N)	8.7% (90/1035)	9.4% (95/1013)	7.1% (70/980)	5.4% (54/999)	.004
BNP, pmol/L	13.4 (5.4, 31.0)	16.8 (7.3, 36.9)	24.4 (10.7, 52.3)	40.7 (16.5, 97.3)	<.001

Abbreviations: bpm, beats per minute; CABG, coronary artery bypass graft; CrCl, creatinine clearance.

Values are median (interquartile range), unless otherwise indicated.

TABLE 2

Spearman correlation coefficients between baseline adiponectin and other biomarkers

Biomarker	|r|	P
hsTnI, ng/L	0.17	<.0001
BNP, pg/mL	0.31	<.0001
hsCRP, mg/L	−0.01	.40
MPO, ng/mL	0.06	<.0001
ST-2, ng/mL	0.11	<.0001
GDF-15, pg/mL	0.25	<.0001
Galectin-3, ng/mL	0.26	<.0001
Cystatin C, mg/L	0.29	<.0001
HbA1c, %	−0.03	.02
BMI, kg/m^2	−0.10	<.0001

Abbreviations: GDF-15, growth differentiation factor-15; MPO, myeloperoxidase.