



Adiponectin, Free Fatty Acids, and Cardiovascular Outcomes in Patients With Type 2 Diabetes and Acute Coronary Syndrome

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OBJECTIVE

In observational cohorts, adiponectin is inversely associated and free fatty acids (FFAs) are directly associated with incident coronary heart disease (CHD). Adiponectin tends to be reduced and FFAs elevated in type 2 diabetes. We investigated relationships of adiponectin and FFA and major adverse cardiovascular events (MACEs) and death in patients with acute coronary syndrome (ACS) and type 2 diabetes using data from the AleCardio (Effect of Alogliptazar on Cardiovascular Outcomes After Acute Coronary Syndrome in Patients With Type 2 Diabetes Mellitus) trial, which compared the PPAR- α/γ agonist alogliptazar with placebo.

RESEARCH DESIGN AND METHODS

Using Cox regression adjusted for demographic, laboratory, and treatment variables, we determined associations of baseline adiponectin and FFAs, or the change in adiponectin and FFAs from baseline, with MACEs (cardiovascular death, myocardial infarction, or stroke) and death.

RESULTS

A twofold higher baseline adiponectin ($n = 6,998$) was directly associated with risk of MACEs (hazard ratio [HR] 1.17 [95% CI 1.08–1.27]) and death (HR 1.53 [95% CI 1.35–1.73]). A doubling of adiponectin from baseline to month 3 ($n = 6,325$) was also associated with risk of death (HR 1.20 [95% CI 1.03–1.41]). Baseline FFAs ($n = 7,038$), but not change in FFAs from baseline ($n = 6,365$), were directly associated with greater risk of MACEs and death. There were no interactions with study treatment.

CONCLUSIONS

In contrast to prior observational data for incident CHD, adiponectin is prospectively associated with MACEs and death in patients with type 2 diabetes and ACS, and an increase in adiponectin from baseline is directly related to death. These findings raise the possibility that adiponectin has different effects in patients with type 2 diabetes and ACS than in populations without prevalent cardiovascular disease. Consistent with prior data, FFAs are directly associated with adverse outcomes.

Adiponectin and free fatty acids (FFAs) are markers of adipocyte function. Adiponectin is a hormone secreted by adipocytes and signals through specific receptors in target tissues, including myocardium and arterial wall. Adiponectin may modulate insulin action and sensitivity and has putative antiatherogenic and anti-inflammatory effects (1). Infusion of adiponectin in experimental animals may mitigate myocardial

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ischemia-reperfusion injury (2). Observational analyses show a strong and consistent association of higher adiponectin levels with lower risk of incident coronary heart disease (CHD) (3,4), but Mendelian randomization analysis does not support such an association (5). Studies in patients with established CHD have also yielded conflicting evidence, with some indicating favorable and others adverse associations of adiponectin with risk of future cardiovascular events (6–9). FFAs are an important energy substrate; although at elevated concentrations, FFAs may exert proinflammatory, proapoptotic, or proarrhythmic effects and impair endothelial function (10–12).

Adipocyte dysfunction is a hallmark of insulin-resistant states and is manifested by reduced adiponectin and elevated FFA levels. In fact, it has been postulated that low adiponectin and high FFAs may contribute to increased cardiovascular risk in type 2 diabetes (3,13). Agonists of the peroxisome proliferator-activated receptor γ (PPAR- γ) are among the most effective agents to raise adiponectin and lower FFA concentrations in circulation (14). The AleCardio (Effect of Alogliptazar on Cardiovascular Outcomes After Acute Coronary Syndrome in Patients With Type 2 Diabetes Mellitus) trial compared the effects of the dual PPAR- α/γ agonist alogliptazar with placebo on cardiovascular morbidity and mortality among patients with type 2 diabetes and acute coronary syndrome (ACS) (NCT01042769, www.clinicaltrials.gov). The AleCardio trial showed no effect of alogliptazar on cardiovascular outcomes. Using data from that trial, we evaluated the association of adiponectin and FFAs at baseline and on assigned study treatment with major adverse cardiovascular events (MACEs) and death.

RESEARCH DESIGN AND METHODS

Study Design and Patients

This study is a prespecified post hoc analysis of the AleCardio trial data. Study data and study materials are not publicly available for other researchers, but analytic methods can be requested from the corresponding author. The rationale, design, and primary results of the AleCardio trial have been published previously (15,16). The protocol was approved by institutional review boards,

and written informed consent was obtained from all participants. At 720 participating centers in 26 countries, 7,226 patients with established or newly diagnosed type 2 diabetes and recent ACS were randomly assigned to treatment with alogliptazar 150 μ g daily or placebo, added to standard of care. Randomization occurred during the interval spanning hospital discharge to 12 weeks after the index ACS event. The primary outcome measure was time to first occurrence of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke (defined as MACEs for this analysis). All-cause and cardiovascular deaths were secondary efficacy measures. After a median follow-up of 2 years, the trial was ended prematurely due to futility for efficacy and in response to a higher incidence of safety end points in the alogliptazar group.

Laboratory Assessments

All laboratory analyses were conducted by a central laboratory. Blood samples were collected after an overnight fast of at least 8 h at randomization and after 3 months of assigned study treatment. Plasma adiponectin was measured by a quantitative sandwich ELISA (Quantikine Adiponectin/Acrp30 Immunoassay; R&D Systems, Minneapolis, MN) with an intra-assay coefficient of variation of 2.5–4.7% and an interassay coefficient of variation of 5.8–6.9%. FFAs were measured by enzymatic colorimetry (NEFA HR2; Wako Chemicals, Richmond, VA) with an intra-assay coefficient of variation of 0.61–0.75% and an interassay coefficient of variation of 0.03–0.37%. Results were reported with a precision of 0.1 mmol/L. Testing was performed on Roche Modular Analyzers.

Statistical Methods

We compared baseline characteristics among quartiles of adiponectin and four categories of FFA concentrations using ANOVA or Kruskal-Wallis test for continuous variables, depending on the distribution, and χ^2 for categorical variables. Categories of FFAs were used instead of exact quartiles because the precision of measurement of FFA concentrations was 0.1 mmol/L, resulting in an unequal distribution of participants across quartiles. The distributions of adiponectin and FFA concentrations were checked, and log transformation

was conducted if required for further analysis.

Correlation between two variables was specified by the Pearson or Spearman correlation coefficient, as appropriate. Cox proportional hazards regression models were used to analyze the association between baseline adiponectin or FFA levels and time to event for MACE, all-cause death, and cardiovascular death. Additionally, we modeled the association between change in adiponectin or change in FFAs from baseline to month 3 of assigned study treatment with each of the three end points (occurring after month 3). We adjusted all models for covariates and treatment, and we stratified for the type of index ACS event (unstable angina, non-ST segment elevation MI, or ST segment elevation MI) and the need for reperfusion therapy for the index ACS event. We checked for a potential interaction with treatment and sex and stratified if necessary. The proportional hazards assumption and functional form of the covariates were evaluated using the ASSESS statement in SAS. Visual inspection of the cumulative Martingale residuals and the formal hypothesis based on simulation were assessed.

We included the following covariates in our model: age; sex; race; geographical region; prior history of MI, stroke or transient ischemic attack, heart failure, and hypertension; duration of diabetes; smoking history; BMI; time from ACS to randomization; systolic and diastolic blood pressure; use of antihyperglycemic agents (insulin, sulfonylureas, and biguanides); HbA_{1c}; fasting plasma glucose; LDL cholesterol; HDL cholesterol; triglycerides; hs-CRP; and estimated glomerular filtration rate (eGFR). Adiponectin or FFA concentration was added as a covariate, depending upon which of those was the variable of interest in the analysis. All covariates were selected a priori based on their relation with adiponectin, FFAs, or cardiovascular outcomes, as described in prior literature.

In the analysis on change in adiponectin or FFAs from baseline to month 3, additional adjustment was performed for concurrent changes in systolic and diastolic blood pressure, glucose, insulin, HbA_{1c}, LDL cholesterol, HDL cholesterol, triglycerides, eGFR, adiponectin (for analysis on change in FFAs), and FFAs (for analysis on change in adiponectin).

Two sensitivity analyses were performed. In the first, patients treated with exogenous insulin were excluded. In the second, N-terminal pro-B-type natriuretic peptide (NT-proBNP) was added as a covariate to the multivariable model because prior studies showed that NT-proBNP may be related to adiponectin concentrations (17,18).

Missing covariate data were replaced with use of multiple imputation (Markov chain Monte Carlo method). Results were considered significantly different at a P value of <0.05 . Statistical analyses were performed using SAS statistical software version 9.2 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics

Baseline adiponectin and FFAs were available for 6,998 and 7,038 patients, respectively. The distribution of baseline levels is tabulated in Supplementary Table 1 and illustrated in Supplementary Fig. 1. Adiponectin and FFA values both have a skewed distribution. The median (interquartile range [IQR]) of adiponectin was 4.0 $\mu\text{g}/\text{mL}$ (2.7–6.1). The four categories of FFAs were 0.1–0.3 mmol/L ($n = 1,878$), 0.4–0.5 mmol/L ($n = 2,308$), 0.6–0.7 mmol/L ($n = 1,683$), and 0.8–3.3 mmol/L ($n = 1,169$). As expected, baseline adiponectin and FFA concentrations did not differ between the aleglitazar and placebo groups. Paired baseline and month 3 measurements of adiponectin and FFAs were available for 6,325 and 6,365 patients, respectively. Tables 1 and 2 show baseline characteristics stratified according to adiponectin quartiles and FFA categories. Patients with higher adiponectin levels were older, more frequently women, and had a longer duration of type 2 diabetes. They had lower insulin, triglyceride, and eGFR but higher NT-proBNP, HDL cholesterol, and LDL cholesterol levels. Further, they were more likely to be treated with exogenous insulin but less likely to be treated with biguanides and diuretics.

Differences in baseline characteristics stratified according to FFA categories were less pronounced than those observed across quartiles of adiponectin. Nonetheless, patients with higher FFA levels were older, more frequently women, less frequently past/current smokers, and had a longer duration of type 2

diabetes. They had lower insulin, higher adiponectin, and higher NT-proBNP levels compared with patients with lower FFA levels.

In the aleglitazar arm, median (IQR) adiponectin concentration increased from baseline (4.0 $\mu\text{g}/\text{mL}$ [2.7–6.1]) to month 3 (11.9 $\mu\text{g}/\text{mL}$ [7.1–19.4]), an increase of 7.5 $\mu\text{g}/\text{mL}$ (3.7–13.7) ($P < 0.001$). In the placebo group, adiponectin at month 3 was 4.1 $\mu\text{g}/\text{mL}$ (2.6–6.0), a change of 0.0 $\mu\text{g}/\text{mL}$ (–0.9 to 0.9) from baseline (Supplementary Table 1 and Supplementary Figs. 2 and 3). FFAs decreased from 0.5 \pm 0.3 mmol/L at baseline to 0.4 \pm 0.2 mmol/L at month 3 in the aleglitazar arm (a decrease of -0.1 ± 0.3 mmol/L, $P < 0.001$). In the placebo group, FFAs at month 3 was 0.5 \pm 0.3 mmol/L, a change of 0.0 \pm 0.3 mmol/L from baseline.

Association Between Baseline Adiponectin and FFA Levels and Outcomes

A total of 684 (10%) and 688 (10%) MACEs, 276 (4%) and 281 (4%) all-cause deaths, and 202 (3%) and 206 (3%) cardiovascular deaths occurred in patients with baseline adiponectin and FFA data available, respectively. Median (IQR) follow-up time was 1.98 years (1.55–2.46). Figure 1 shows the Kaplan-Meier estimates of survival free of MACEs, all-cause death, and cardiovascular death according to adiponectin quartiles and FFA categories. The risk for each end point increased across quartiles of adiponectin ($P < 0.001$) and categories of FFAs ($P < 0.05$).

Table 3 shows the crude and adjusted risk for MACEs, all-cause death, and cardiovascular death according to baseline adiponectin and FFA concentrations. Baseline adiponectin that was two times higher was associated with higher risk for MACEs (hazard ratio [HR] 1.28 [95% CI 1.18–1.38], adjusted HR 1.17 [1.08–1.27]; $P < 0.001$), all-cause death (HR 1.75 [1.56–1.98], adjusted HR 1.53 [1.35–1.73]; $P < 0.001$), and cardiovascular death (HR 1.67 [1.45–1.92], adjusted HR 1.51 [1.30–1.76]; $P < 0.001$). No interaction existed between randomized treatment assignment and baseline adiponectin concentrations and the risk for any end point event (Table 3). Furthermore, no interaction was found for sex.

A baseline FFA level that was two times higher was associated with a higher risk

for MACEs (HR 1.15 [1.04–1.27], adjusted HR 1.12 [1.02–1.24]; $P = 0.019$), all-cause death (HR 1.31 [1.11–1.54], adjusted HR 1.20 [1.03–1.40]; $P = 0.018$), and cardiovascular death (HR 1.28 [1.06–1.54], adjusted HR 1.19 [0.99–1.42]; $P = 0.062$). As with adiponectin, the interaction between treatment and baseline FFA concentrations and end point events was not significant.

In the first sensitivity analysis, patients treated with exogenous insulin were excluded. The associations of baseline adiponectin with clinical outcomes remained significant with minimal effect on the point estimates of HRs (data not shown); however, the association of baseline FFAs with adverse outcomes was no longer significant. Adiponectin and NT-proBNP were weakly correlated with $r^2 = 0.09$ ($P < 0.001$). In the second sensitivity analysis with NT-proBNP added as a covariate to the regression model, a baseline adiponectin level that was two times higher remained significantly associated with MACEs (adjusted HR 1.14 [1.04–1.26], $P = 0.008$), all-cause death (adjusted HR 1.19 [1.02–1.39], $P = 0.025$), and cardiovascular death (adjusted HR 1.21 [1.01–1.44], $P = 0.040$), although the associations were attenuated (Table 3). With the addition of NT-proBNP as a covariate, the associations of baseline FFAs with death and cardiovascular death remained significant, but the association with MACEs was attenuated. A similar effect was seen for the separate end-point nonfatal MI (Supplementary Table 2).

Association Between Change in Adiponectin or FFAs and Outcomes

The associations between changes in adiponectin or FFAs from baseline to month 3 and outcomes are shown in Table 3. A doubling in adiponectin from baseline to month 3 was associated with a higher risk for all-cause death (HR 1.20 [1.03–1.41], $P = 0.022$) and cardiovascular death (HR 1.22 [1.02–1.46], $P = 0.029$) but not MACEs (HR 1.03 [0.93–1.15], $P = 0.540$) after multivariable adjustment. Because a change in adiponectin over time was identified only in the aleglitazar group (Supplementary Table 1, $P < 0.001$), we investigated interaction effects by treatment and conducted stratified analysis by treatment. No significant interaction effects were observed. In addition, interaction

Table 1—Baseline characteristics of A1eCardio participants by adiponectin quartiles and FFA categories

Variable	All n = 7,060	Adiponectin quartile				P value*	FFA category				P value*
		1 n = 1,749	2 n = 1,750	3 n = 1,750	4 n = 1,749		1 n = 1,878	2 n = 2,308	3 n = 1,683	4 n = 1,169	
Demographics											
Age, years (mean ± SD)	60.8 ± 9.9	57.2 ± 9.4	59.6 ± 9.7	61.9 ± 9.5	64.5 ± 9.6	<0.001	59.8 ± 9.7	60.3 ± 9.8	61.2 ± 10.1	62.7 ± 9.9	<0.001
Female sex [n (%)]	1,909 (27)	239 (14)	372 (21)	532 (30)	754 (43)	<0.001	364 (19)	510 (22)	526 (31)	499 (43)	<0.001
Race [n (%)]											
White	4,707 (67)	1,047 (60)	1,188 (68)	1,207 (69)	1,222 (70)	<0.001	1,312 (70)	1,511 (66)	1,117 (66)	749 (64)	<0.001
Asian	1,846 (26)	567 (32)	436 (25)	432 (25)	398 (23)		413 (22)	613 (27)	463 (28)	357 (31)	
Black	215 (3)	59 (3)	47 (3)	48 (3)	57 (3)		84 (4)	70 (3)	39 (2)	22 (2)	
Other	290 (4)	76 (4)	78 (4)	63 (4)	71 (4)		69 (4)	113 (5)	63 (4)	41 (4)	
Region [n (%)]											
Europe	2,485 (35)	592 (34)	641 (37)	643 (37)	584 (33)	<0.001	676 (36)	773 (34)	570 (34)	454 (39)	<0.001
Asia/Pacific	1,934 (27)	577 (33)	466 (27)	457 (26)	421 (24)		450 (24)	620 (27)	494 (29)	368 (31)	
North America	1,954 (28)	419 (24)	483 (28)	470 (27)	564 (32)		569 (30)	655 (28)	462 (27)	263 (23)	
South America	679 (10)	157 (9)	158 (9)	178 (10)	180 (10)		178 (10)	258 (11)	156 (9)	84 (7)	
Medical history											
Prior MI [n (%)]	1,613 (23)	374 (21)	387 (22)	403 (23)	439 (25)	0.053	429 (23)	515 (22)	396 (24)	268 (23)	0.844
Prior stroke or TIA [n (%)]	551 (8)	110 (6)	128 (7)	140 (8)	168 (10)	0.003	144 (8)	172 (7)	135 (8)	98 (8)	0.777
History of heart failure [n (%)]	746 (11)	155 (9)	167 (10)	176 (10)	239 (14)	<0.001	220 (12)	211 (9)	180 (11)	133 (11)	0.038
History of hypertension [n (%)]	5,498 (78)	1,286 (74)	1,355 (77)	1,380 (79)	1,431 (82)	<0.001	1,418 (76)	1,788 (77)	1,314 (78)	959 (82)	<0.001
Smoking, current or previous [n (%)]	4,332 (61)	1,207 (69)	1,118 (64)	1,014 (58)	953 (54)	<0.001	1,243 (66)	1,508 (65)	988 (59)	578 (50)	<0.001
Duration of diabetes, years [median (IQR)]	5.6 (1.8–11.1)	4.5 (1.1–9.8)	5.2 (1.6–10.5)	5.7 (1.8–10.9)	7.6 (2.6–14.6)	<0.001	5.8 (1.8–11.3)	5.2 (1.7–10.4)	5.5 (1.6–11.3)	6.6 (2.3–12.4)	<0.001
BMI, kg/m ² [median (IQR)]	29 (26–32)	29 (26–32)	29 (26–33)	29 (26–32)	28 (25–32)	<0.001	28 (25–32)	28 (26–32)	29 (26–33)	28 (25–33)	0.002
SBP, mmHg (mean ± SD)	128 ± 18	126 ± 16	128 ± 17	129 ± 18	130 ± 18	<0.001	126 ± 18	128 ± 17	129 ± 17	130 ± 18	<0.001
DBP, mmHg (mean ± SD)	76 ± 10	76 ± 9	76 ± 9	76 ± 10	76 ± 10	0.184	75 ± 10	76 ± 10	76 ± 10	77 ± 10	0.002
Index ACS event											
NSTEMI [n (%)]	2,575 (36)	627 (36)	624 (36)	628 (36)	676 (39)	<0.001	684 (36)	846 (37)	611 (36)	426 (36)	0.495
STEMI [n (%)]	2,775 (39)	742 (42)	713 (41)	652 (37)	643 (37)		746 (40)	932 (40)	642 (38)	446 (38)	
UA [n (%)]	1,709 (24)	379 (22)	413 (24)	470 (27)	430 (25)		448 (24)	529 (23)	430 (26)	297 (25)	

Continued on p. 1796

Table 1—Continued

	All n = 7,060	Adiponectin quartile 1 n = 1,749	Adiponectin quartile 2 n = 1,750	Adiponectin quartile 3 n = 1,750	Adiponectin quartile 4 n = 1,749	P value*	FFA category 1 n = 1,878	FFA category 2 n = 2,308	FFA category 3 n = 1,683	FFA category 4 n = 1,169	P value*
Time from ACS to randomization, days (mean ± SD)	29 ± 15	29 ± 15	28 ± 15	29 ± 14	29 ± 15	0.174	28 ± 15	29 ± 15	29 ± 15	28 ± 15	0.148
Reperfusion therapy for ACS event [n (%)]	5,654 (80)	1,465 (84)	1,423 (82)	1,404 (80)	1,313 (75)	<0.001	1,521 (81)	1,884 (82)	1,306 (78)	926 (79)	0.008
Assignment to alogliptazar [n (%)]	3,536 (50)	860 (49)	919 (53)	873 (50)	853 (49)	0.114	960 (51)	1,162 (50)	853 (51)	553 (47)	0.194
Medication [n (%)]	6,604 (94)	1,637 (94)	1,664 (95)	1,629 (93)	1,615 (92)	0.009	1,749 (93)	2,173 (94)	1,558 (93)	1,103 (94)	0.120
Aspirin	6,123 (87)	1,564 (89)	1,547 (88)	1,505 (86)	1,455 (83)	<0.001	1,638 (87)	1,993 (86)	1,451 (86)	1,020 (87)	0.720
Other antiplatelet agents	5,772 (82)	1,437 (82)	1,445 (83)	1,447 (83)	1,395 (80)	0.083	1,536 (82)	1,912 (83)	1,360 (81)	945 (81)	0.321
ACE inhibitors or ARB	6,587 (93)	1,648 (94)	1,655 (95)	1,638 (94)	1,590 (91)	<0.001	1,772 (94)	2,148 (93)	1,570 (93)	1,075 (92)	0.076
Statins	6,385 (90)	1,617 (92)	1,601 (91)	1,584 (91)	1,530 (87)	<0.001	1,710 (91)	2,114 (92)	1,493 (89)	1,047 (90)	0.011
β-Blockers	2,228 (32)	422 (24)	506 (29)	582 (33)	692 (40)	<0.001	579 (31)	679 (29)	526 (31)	435 (37)	<0.001
Diuretics	2,065 (29)	481 (28)	483 (28)	521 (30)	563 (32)	0.006	663 (35)	578 (25)	462 (27)	353 (30)	<0.001
Insulin	2,437 (35)	597 (34)	612 (35)	599 (34)	609 (35)	0.939	605 (32)	791 (34)	596 (35)	435 (37)	0.032
Sulfonyleureas	4,720 (67)	1,232 (70)	1,215 (69)	1,164 (67)	1,069 (61)	<0.001	1,189 (63)	1,548 (67)	1,176 (70)	794 (68)	<0.001
Biguanides											

Values are presented as mean ± SD, median (IQR), or n (%). ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; NSTEMI, non-ST segment elevation MI; SBP, systolic blood pressure; STEMI, ST segment elevation MI; TIA, transient ischemic attack; UA, unstable angina. *Two-sided P values for overall differences between adiponectin quartiles from ANOVA, Kruskal-Wallis, or χ^2 tests.

with sex was investigated and no interaction was found, with the exception for the association between change in adiponectin and MACEs ($P = 0.031$). Stratified analysis showed no association between change in adiponectin and MACEs in men (HR 0.99 [0.87–1.12], $P = 0.82$), whereas a borderline significant association for women existed (HR 1.19 [1.00–1.42], $P = 0.052$). The change in FFAs from baseline to month 3 was not associated with outcomes in crude or adjusted models.

When sensitivity analysis was performed by adding NT-proBNP as covariate to the model, associations between change in adiponectin (baseline to month 3) and outcomes were no longer significant (Table 3).

CONCLUSIONS

This study shows that both FFA and adiponectin levels are directly associated with the risk of MACEs and death in patients with type 2 diabetes and recent ACS. These findings extend the previously reported data on the relation between FFA levels and cardiovascular outcomes; although the observed relationships for adiponectin are opposite to conclusions from prior observational data in patients initially free of cardiovascular events.

In prior cohort studies without prevalent cardiovascular disease, higher adiponectin concentrations were related to a lower risk of incident cardiovascular disease and mortality (3,4). However, the current data are aligned with findings in patients with heart failure (19) or coronary artery disease (20), and in elderly people (21,22), that associated higher concentrations of adiponectin with greater risk of cardiovascular and all-cause death. Furthermore, an analysis of the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care in Patients With Type 2 Diabetes Mellitus and Acute Coronary Syndrome (EXAMINE) trial showed a positive association of adiponectin with cardiovascular and all-cause death (23). A post hoc analysis of the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) trial showed an adverse association of adiponectin with 2-year MACE outcomes but not death in 3,933 patients with recent ACS (24). Additionally, in patients without diabetes and a recent acute MI, higher

adiponectin levels have been associated with higher mortality but not cardiovascular mortality (25). The current data extend these findings by demonstrating associations between baseline adiponectin and death, as well as composite MACE outcomes. Furthermore, the current analysis indicates that a rise in adiponectin during the early period after ACS is associated with a greater risk of death, independent of treatment assignment in the clinical trial that provided the source data.

The underlying mechanisms for the adverse associations of adiponectin and FFAs with death and MACEs are unclear. Although most evidence supports the view of adiponectin as an anti-inflammatory mediator (26), a growing body of in vitro data indicates that adiponectin also has the potential to induce proinflammatory effects. Studies in a variety of cell types, including astrocytes (27), renal tubular cells (28), synovial cells (29), macrophages, and T cells (30), demonstrate stimulation of inflammatory signaling pathways by adiponectin. In clinical studies of patients with inflammatory or vascular disease, higher adiponectin levels correlated with greater severity of rheumatoid arthritis (31), higher likelihood of proliferative diabetic retinopathy (32), and greater aortic stiffness in patients with acute MI (33). Alternatively, higher circulating concentrations of adiponectin may reflect “adiponectin resistance” due to a decrease in adiponectin receptor expression or responsiveness in target tissues (34). Under this concept, an adverse association of adiponectin with outcomes might not reflect adverse actions of the adipokine but rather conditions that impair signaling of its favorable effects.

Prior studies have shown a consistent positive association between the circulating concentrations of adiponectin and natriuretic peptides (17,19,35), with evidence that natriuretic peptides stimulate the synthesis and release of adiponectin (18,36). Natriuretic peptides are increased in heart failure and predict poor outcomes. Therefore, we investigated the possibility that the adverse association of adiponectin with outcomes after ACS reflect an underlying adverse association of heart failure and elevated natriuretic peptides. In sensitivity analyses incorporating levels of NT-proBNP as a covariate in Cox regression models,

Table 2—Baseline laboratory values by adiponectin quartiles and FFA categories

Variable	Adiponectin quartiles				p value*	FFA categories				p value*
	All n = 7,060	quartile 1 n = 1,749	quartile 2 n = 1,750	quartile 3 n = 1,750		quartile 4 n = 1,749	category 1 n = 1,878	category 2 n = 2,308	category 3 n = 1,683	
FFAs (mmol/L)	0.5 (0.3–0.7)	0.4–2.7	2.7–4.0	4.0–6.1	6.1–50.0	0.1–0.3	0.4–0.5	0.6–0.7	0.8–3.3	n/a
Adiponectin (μg/mL)	4.0 (2.7–6.1)	n/a	n/a	n/a	n/a	3.9 (2.6–5.8)	3.7 (2.5–5.7)	4.1 (2.8–6.2)	4.6 (3.0–7.2)	<0.001
HbA _{1c} (%)	7.8 ± 1.6	7.9 ± 1.5	7.9 ± 1.7	7.7 ± 1.6	7.7 ± 1.8	7.9 ± 1.7	7.7 ± 1.6	7.8 ± 1.6	7.8 ± 1.6	0.053
HbA _{1c} (mmol/mol)	62 ± 18	63 ± 16	63 ± 19	61 ± 18	61 ± 20	63 ± 19	61 ± 18	62 ± 18	62 ± 18	0.053
FPG (mmol/L)	8.3 ± 3.2	8.3 ± 2.9	8.4 ± 3.1	8.3 ± 3.2	8.2 ± 3.6	8.4 ± 3.6	8.1 ± 2.8	8.2 ± 3.0	8.7 ± 3.6	<0.001
Insulin (pmol/L)	69 (44–117)	80 (50–135)	75 (49–124)	66 (44–112)	56 (34–96)	92 (51–185)	66 (42–107)	66 (42–105)	64 (41–95)	<0.001
HDL cholesterol (mg/dL)	1.08 ± 0.28	0.97 ± 0.21	1.04 ± 0.24	1.10 ± 0.25	1.22 ± 0.34	1.06 ± 0.27	1.06 ± 0.27	1.09 ± 0.27	1.16 ± 0.31	<0.001
LDL cholesterol (mg/dL)	2.05 ± 0.80	1.96 ± 0.74	2.03 ± 0.79	2.06 ± 0.80	2.15 ± 0.86	2.02 ± 0.76	2.05 ± 0.78	2.08 ± 0.84	2.07 ± 0.84	0.300
Triglycerides (mmol/L)	1.73 ± 1.08	1.93 ± 1.39	1.82 ± 1.17	1.66 ± 0.80	1.52 ± 0.77	1.69 ± 0.91	1.72 ± 0.91	1.75 ± 1.09	1.80 ± 1.53	0.123
hs-CRP (mmol/L)	64 ± 134	57 ± 115	64 ± 146	68 ± 136	66 ± 137	59 ± 120	66 ± 141	65 ± 134	65 ± 137	0.045
eGFR (mL/min/1.73 m ²)	78 ± 20	82 ± 19	80 ± 19	77 ± 20	73 ± 22	78 ± 20	79 ± 20	78 ± 20	76 ± 21	0.031
NT-proBNP (pg/mL)	832 ± 1,510	446 ± 609	595 ± 772	779 ± 995	1,490 ± 2,493	794 ± 1,222	741 ± 1,271	841 ± 1,634	1,054 ± 2,056	<0.001

Values are presented as mean ± SD or median (IQR). FPG, fasting plasma glucose; n/a, not applicable. *Two-sided P values for overall differences between adiponectin quartiles from ANOVA or Kruskal-Wallis tests.

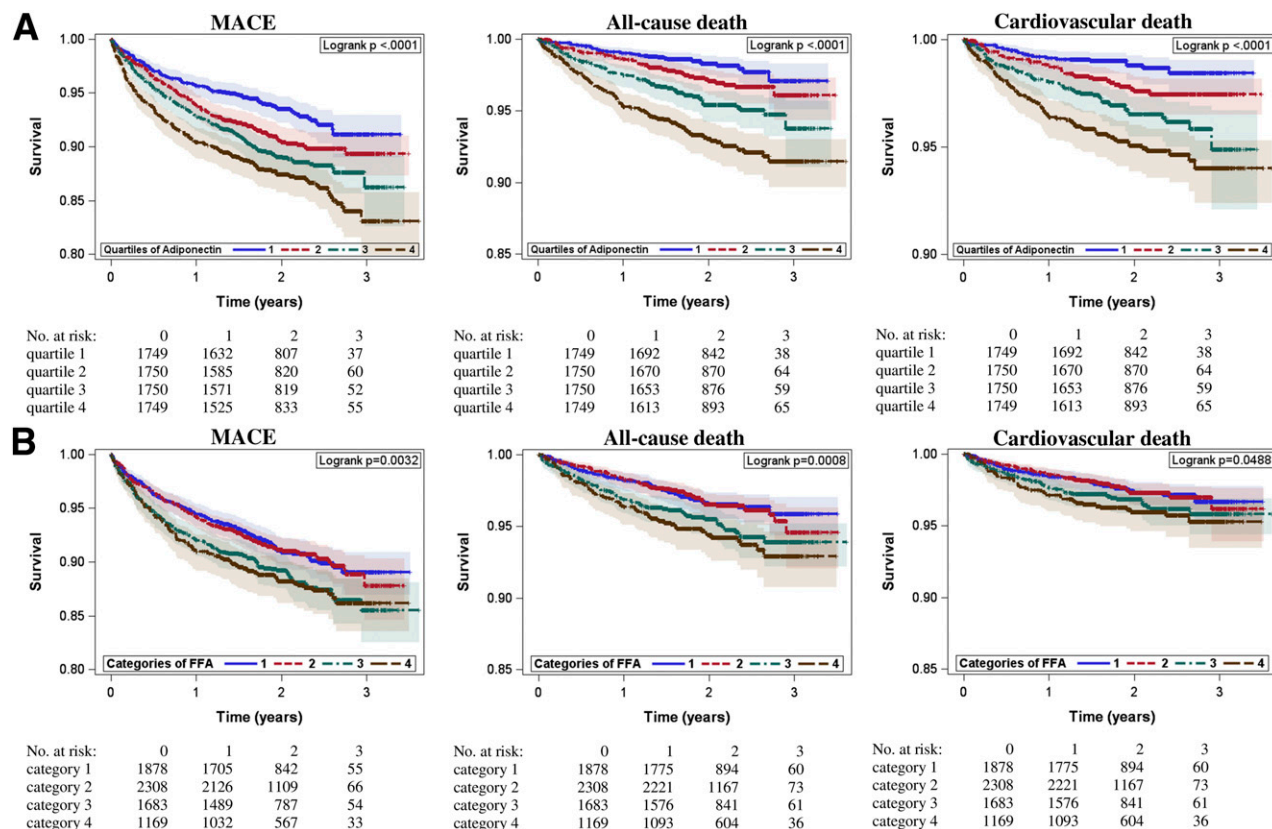


Figure 1—Kaplan-Meier curves of survival free of MACEs, all-cause death, and cardiovascular death by baseline adiponectin quartiles (A) and FFA categories (B) with 95% CI bands.

significant adverse associations persisted between baseline adiponectin and death and MACE outcomes, although the HRs were somewhat attenuated. Thus, higher levels of natriuretic peptides may explain part, but not all, of the paradoxical association of adiponectin with adverse outcomes in this study.

Elevated FFA levels in our study population are comparable to levels seen in obese patients and patients with type 2 diabetes (37,38). Elevated FFAs have been postulated to be a risk factor for arrhythmic and atherothrombotic events (9). In prior studies, higher FFA concentrations have been associated with greater risk of incident CHD (39), MACEs in patients with CHD (40), and sudden death (41). The current study extends those findings by demonstrating a strong association of FFAs with MACEs and death in patients with type 2 diabetes and ACS.

Study Limitations

The current study is a post hoc observational analysis of a randomized clinical trial. As such, it cannot determine the biological mechanisms responsible for

the adverse association of adiponectin or FFAs with outcomes. Second, unaccounted factors associated with adiponectin or FFAs may introduce an unknown degree of residual confounding. For example, we did not measure and therefore cannot account for relationships with other adipokines (e.g., leptin and ghrelin). Third, because of missing data in baseline or change in adiponectin and FFA concentrations, we had to exclude ~3% and 12% of the patients from our analyses, respectively. Fourth, analyses relating the change in adiponectin or FFAs from baseline to month 3 to outcomes have substantially less power than those relating baseline concentrations to outcomes. This is because there were fewer patients with data from both time points and because the analyses of the changes in biomarkers over time only consider events occurring after month 3. Moreover, the median change in FFAs from baseline was modest, further reducing power in that analysis. Fifth, the relationship of adiponectin and FFA concentrations with the qualifying (index) ACS event for the AleCardio study is unknown. Therefore, we cannot exclude

index event bias as an explanation for the current findings (42). Sixth, adiponectin and FFAs were measured only once at each time point. Intraindividual variability in these measures may have weakened the apparent associations with outcomes. By analogy, intraindividual variability in NT-proBNP may have weakened the effects of adjustment for that variable. Furthermore, a total of 452 patients in AleCardio either withdrew consent or were lost to follow-up prior to the common study end date. We cannot exclude the possibility of resulting bias in our reported results. Finally, the reported adiponectin concentrations represent total adiponectin levels, without discriminating between the low- and more metabolically active high-molecular-weight fractions. However, Kizer et al. (43) found a similar direct positive relation for total and high-molecular-weight adiponectin with cardiovascular and all-cause mortality in older people from the Cardiovascular Health Study.

Conclusion

In patients with type 2 diabetes and recent ACS, both baseline adiponectin and FFA

Table 3—HRs and point estimates of end points per doubling of adiponectin and FFA concentrations at baseline and from baseline to month 3

		n	Events (%)	Crude model	Multivariable model	Interaction of treatment assignment	Multivariable model + NT-proBNP
				HR (95% CI)	HR (95% CI)	Point estimate (95% CI)*	HR (95% CI)
Baseline adiponectin	MACEs	6,998	684 (10%)	1.28 (1.18–1.38)†	1.17 (1.08–1.27)†	1.12 (0.96–1.31)	1.14 (1.04–1.26)†
	All-cause death	6,998	276 (4%)	1.75 (1.56–1.98)†	1.53 (1.35–1.73)†	1.07 (0.85–1.36)	1.19 (1.02–1.39)‡
	CV death	6,998	202 (3%)	1.67 (1.45–1.92)†	1.51 (1.30–1.76)†	1.02 (0.77–1.35)	1.21 (1.01–1.44)‡
Baseline FFAs	MACEs	7,038	688 (10%)	1.15 (1.04–1.27)†	1.12 (1.02–1.24)‡	0.94 (0.78–1.14)	1.02 (0.93–1.11)
	All-cause death	7,038	281 (4%)	1.31 (1.11–1.54)†	1.20 (1.03–1.40)‡	1.07 (0.79–1.44)	1.22 (1.07–1.40)†
	CV death	7,038	206 (3%)	1.28 (1.06–1.54)‡	1.19 (0.99–1.42)	1.05 (0.74–1.51)	1.14 (0.97–1.33)
Change in adiponectin	MACEs	6,212	443 (7%)	0.92 (0.84–1.01)	1.03 (0.93–1.15)	0.95 (0.73–1.25)	1.00 (0.90–1.10)
	All-cause death	6,325	188 (3%)	1.00 (0.87–1.14)	1.20 (1.03–1.41)‡	0.84 (0.56–1.28)	1.06 (0.90–1.24)
	CV death	6,325	130 (2%)	1.03 (0.87–1.21)	1.22 (1.02–1.46)‡	0.91 (0.55–1.49)	1.06 (0.89–1.26)
Change in FFAs	MACEs	6,253	448 (7%)	0.96 (0.87–1.06)	0.92 (0.84–1.02)	1.12 (0.92–1.36)	0.93 (0.85–1.03)
	All-cause death	6,365	191 (3%)	0.88 (0.73–1.06)	0.93 (0.80–1.08)	1.01 (0.75–1.35)	0.93 (0.80–1.08)
	CV death	6,365	131 (2%)	0.90 (0.77–1.04)	0.90 (0.75–1.08)	1.12 (0.79–1.59)	0.89 (0.74–1.07)

The multivariable model was adjusted for treatment; baseline \log_2 (FFA) or \log_2 (adiponectin); age; sex; race; region; prior history of MI, stroke or transient ischemic attack, heart failure, and hypertension; duration of diabetes; smoking history; BMI; time from ACS to randomization; systolic and diastolic blood pressure; use of antihyperglycemic agents (insulin, sulfonylureas, biguanides); HbA_{1c}; fasting plasma glucose; LDL; HDL; triglycerides; hs-CRP; and eGFR. The model was stratified by ACS index event and reperfusion therapy for ACS. The multivariable model + NT-proBNP was the multivariable model with additional adjustment for \log (NT-proBNP). Change models were additionally adjusted for change in \log_2 (FFA) or \log_2 (adiponectin) and change in systolic and diastolic blood pressure, HbA_{1c}, fasting plasma glucose, LDL, HDL, triglycerides, hs-CRP, and eGFR from baseline to month 3. The interaction model was the multivariable model with extra adjustment for interaction with treatment. CV, cardiovascular. *Point estimate shown is the ratio by which the HR of the multivariable model changes when going from aleglitazar to placebo. † $P < 0.01$. ‡ $P < 0.05$.

levels are directly associated with the risk of MACEs and death. These relationships persist after multivariable adjustment. Additional adjustment for NT-proBNP attenuates, but does not abrogate, these associations. Moreover, an increase in adiponectin during the 3 months after the ACS event is associated with higher risk for all-cause and cardiovascular death after multivariable adjustment. The neutral results of the AleCardio trial may reflect a balance between beneficial and adverse effects of aleglitazar. Beneficial effects may include reduced FFAs, as well as reduced glycemic indices and triglycerides and increased HDL cholesterol. Adverse effects of aleglitazar may include increased adiponectin, as well as increased LDL cholesterol and creatinine levels, as previously described (16). The present results suggest that interventions that are specifically intended to increase adiponectin are unlikely to be useful in patients with CHD.

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Author Contributions. I.C.S. designed the study and wrote the manuscript. A.N. conducted statistical analysis and reviewed and edited the manuscript. B.E.S., J.B.B., R.R.H., K.M., B.N., S.J.N., L.R., L.M., A.S., H.W., A.W., A.M.L., J.-C.T., and D.E.G. reviewed and edited the manuscript. G.G.S. designed the study and wrote and edited the manuscript. I.C.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the

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