Blood and Urine Biomarkers Predicting Worsening Kidney Function in Patients with Type 2 Diabetes Post-Acute Coronary Syndrome: An Analysis from the EXAMINE Trial

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Keywords

Kidney injury molecule 1 · Worsening kidney function ·
Type 2 diabetes · Acute coronary syndromes · Prognosis

Abstract

Introduction: Worsening kidney function (WKF) is frequent among patients with type 2 diabetes (T2D) and a recent acute coronary syndrome (ACS) and is associated with a poor prognosis. An accurate prediction of WKF is clinically important. **Aims:** Using data from the Cardiovascular Outcomes Study of Alogliptin in Patients with Type 2 Diabetes and Acute Coronary Syndrome trial including patients with T2D and a recent ACS, and a large biomarker panel incorporating proteins measured both in blood and urine, we aim to determine those with best performance for WKF prediction. **Methods:** WKF was defined as a $\geq 40\%$ estimated glomerular filtration rate (eGFR) drop from baseline, eGFR < 15 mL/min, or dialysis. Mixed-effects and time-updated Cox models were used. **Results:** 5,131 patients were included from whom 222 (4.3%) developed at least one WKF episode over a median follow-up of 18 months. Patients who developed WKF were more frequently women, had longer diabetes duration, a more frequent heart failure

history, higher anemia prevalence, and impaired kidney function. In multivariable models including all variables (clinical and biomarkers) independently associated with WKF with a p value ≤ 0.0001 , blood kidney injury molecule 1 (KIM-1) was (by far) the variable with strongest WKF association, followed by anemia. KIM-1 alone provided good discrimination for WKF prediction (area under the curve = 0.73). Patients in the high KIM-1-derived risk tertile had a 6.7-fold higher risk of any WKF than patients classified as low risk. In time-updated Cox models, the occurrence of WKF was independently associated with a higher risk of death: adjusted hazard ratio = 4.93 (3.06–7.96), p value < 0.0001 . **Conclusion:** Blood KIM-1 was the biomarker with the strongest association with WKF. The occurrence of WKF was independently associated with a higher risk of subsequent cardiovascular events and mortality.

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Introduction

Worsening kidney function (WKF) is frequent among patients with type 2 diabetes (T2D) and is associated with a poor prognosis [1]. The risk of WKF is particularly el-

evated in patients with T2D with a very high cardiovascular risk, such as those with a recent acute coronary syndrome (ACS) or myocardial infarction (MI) [2, 3].

Blood and urine biomarkers reflecting kidney damage have been shown to predict WKF and cardiovascular events in patients with and without T2D [4–8]. However, the identified biomarkers vary largely between studies, which poses difficulties in selecting biomarkers for clinical implementation [9].

The use of large biomarker panels incorporating both urinary and blood biomarkers may help in selecting the biomarkers with the best performance in predicting WKF. An accurate identification of patients at higher risk for WKF is important to select those who might experience a greater benefit from therapies that reduce kidney events and improve cardiovascular outcomes in patients with T2D [10–13]. Using data from the Cardiovascular Outcomes Study of Alogliptin in Patients with Type 2 Diabetes and Acute Coronary Syndrome (EXAMINE) trial [14], and a large biomarker panel incorporating proteins measured both in blood and urine, we aim to determine those with best performance for prediction of WKF.

Methods

Study Design

Details of the EXAMINE trial design have been previously published [14, 15]. In short, a total of 5,380 patients with T2D who had a recent ACS were randomly assigned to either alogliptin or placebo. In the overall population, alogliptin significantly reduced glycated hemoglobin without increasing the rates of major adverse cardiovascular events over a median follow-up of 18 months.

The steering committee, consisting of academic members and 3 nonvoting representatives of the sponsor (Takeda Development Center Americas), designed and oversaw the conduct of the trial. An independent data and safety monitoring committee monitored the trial and had access to the unblinded data. For the present analysis, we included 5,131 patients (95.4% of the overall population) who had biomarkers available.

Study Patients

Patients were eligible for enrollment if they had received a diagnosis of T2D, were receiving antidiabetic therapy (other than a DPP-4 inhibitor or GLP-1 analog), and had an ACS (MI and unstable angina requiring hospitalization) within 15–90 days prior to randomization. Major exclusion criteria were a diagnosis of type 1 diabetes, unstable cardiac disorders (e.g., advanced heart failure [HF], refractory angina, uncontrolled arrhythmias, critical valvular heart disease, or severe uncontrolled hypertension), and dialysis within 14 days before screening.

Institutional Review Board approval was obtained, and all patients provided informed consent to participate in the trial. The EXAMINE trial is registered with the clinicaltrials.gov number NCT00968708.

End Points

The primary endpoint in EXAMINE was a composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke, adjudicated by an independent committee. In the present analysis, we defined WKF as % of change in estimated glomerular filtration rate (eGFR) at each study visit (months 1, 3, 6, 9, 12, and every 4 months up to month 32; after month 32, eGFR had >90% of values missing) relative to the randomization visit. An eGFR drop $\geq 40\%$ from randomization or <15 mL/min/1.73 m² or progression to dialysis was considered WKF. A WKF that persisted in 2 or more consecutive visits was considered a sustained worsening kidney function. We used eGFR as calculated by the CKD-EPI formula [16]. Additionally, we studied the association of WKF with subsequent occurrence of the study the primary endpoint, and also the occurrence of the composite of HF hospitalization or cardiovascular death, plus all-cause mortality.

Clinical and Biomarker Measurements

Medical history and a physical examination were all recorded at randomization. A large protein biomarker panel with 92 biomarkers from a wide range of pathophysiological domains was measured (Olink® CVDII panel) at randomization. We selected this panel because it contains known human cardiovascular and inflammatory markers as well as some exploratory human proteins which may have potential as new markers of cardiovascular disease. These proteins are involved in multiple disease processes such as immune/inflammatory response, angiogenesis, coagulation, and cell adhesion. In short, the biomarkers were measured using a high-throughput technique using the Olink Proseek® Multiplex CVDII 96 × 96 kit, which simultaneously measures 92 proteins in 1 μ L of plasma. The kit uses a proximity extension assay technology, where 92 oligonucleotide-labeled antibody probe pairs bind to their respective target present in the sample. The platform provides log₂ normalized protein expression data wherein a high protein value corresponds to a high protein concentration, but not an absolute quantification. The full proteins names from the CVDII panel are described in the online supplementary Table 1 (see www.karger.com/doi/10.1159/000519436 for all online supplementary material). For further details, visit <https://www.olink.com/>.

In addition to the 92 Olink® biomarkers, high-sensitivity troponin I (troponin) was measured in plasma samples with the ARCHITECT i2000SR analyzer (Abbott Laboratories®); urinary neutrophil gelatinase-associated lipocalin was measured by enzyme immunoassay (R&D systems); and urinary kidney injury molecule-1 (uKIM-1) was measured by a microbead ELISA (R&D systems). Both urinary neutrophil gelatinase-associated lipocalin and uKIM-1 were indexed to urinary creatinine as recommended by the National Institute for Diabetes and Digestive and Kidney Diseases CKD biomarkers consortium [17].

Statistical Analyses

Baseline characteristics of the patients were compared between those who developed and those who did not develop WKF throughout the follow-up by means of χ^2 tests for categorical variables, *t* tests for continuous normally distributed variables, and Wilcoxon rank-sum tests for continuous non-normally distributed variables. Mixed-effects models were used to test the association between the biomarker levels and the occurrence of WKF (mixed-effects logistic regression) and the change in eGFR slope (mixed-effects linear regression). All mixed-effects models were

adjusted on age, sex, baseline eGFR, anemia, diabetes duration, smoking, hypertension, prior HF hospitalization, use of diuretics, insulin, metformin, statins, randomized treatment assignment (alogliptin or placebo), study visit, and randomized treatment by study visits interactions; random effects were assigned to patients in panel data with unstructured covariance matrix to allow for correlation between repeated measures. The associations between biomarker levels and WKF (or eGFR slope) were studied in multivariable models fully adjusted on the variables described in the previous step. To select the biomarker(s) with the strongest WKF predictive power while keeping the models parsimonious, we tested each individual biomarker while adjusting for the full list of covariates described in the previous step, and we retained only the biomarkers associated with WKF with a p value of 0.0001 (1/10,000) or less, which is a stricter selection than the conventionally used Bonferroni correction that would have given a p value of 0.0005 or less ($95/0.05 = 0.0005$). After this “pre-selection” process, all variables/biomarkers with a p value ≤ 0.0001 were entered in a multivariable stepwise forward selection model with a p value < 0.05 used to be retained in the model and we computed the area under the curve (AUC) of the model. After the stepwise selection, we then kept the variables with p value ≤ 0.0001 from the model while comparing the AUC until we reach the simplest and final model without much compromise of the model’s accuracy. Afterward, the linear predictor derived from the final model was divided in tertiles, and WKF events were plotted by tertiles of predicted risk. The association of WKF with subsequent cardiovascular outcomes was studied in time-updated Cox models, both crude and adjusted for the variables above described. All statistical analyses were performed with Stata® (StataCorp. 2019. Stata Statistical Software: Release 16.1. College Station, TX: StataCorp LLC).

Results

Baseline Patients’ Characteristics by WKF Status

Patients who developed at least one WKF episode during the follow-up ($n = 222$; 4.3%) were more frequently women (43 vs. 32%), had longer diabetes duration (10 vs. 7 years), were more frequently treated with insulin (41 vs. 30%), and less frequently treated with metformin (55 vs. 66%), smoked less (10 vs. 14%), had a more frequent history of HF (46 vs. 28%), higher prevalence of anemia (47 vs. 24%), more frequent kidney function impairment (eGFR < 60 : 46 vs. 28%), higher blood pressure (SBP > 140 : 26 vs. 20%), and were more frequently treated with diuretics (60 vs. 37%), and less frequently treated with statins (85 vs. 91%) (Table 1).

Associations with WKF and eGFR Slope Changes

Alogliptin (vs. placebo) had no statistically significant impact on eGFR slope of change during the follow-up: -1.11 (-2.55 to 0.33) mL/min, $p = 0.13$ (online suppl. Figure 1). In multivariable models, the strongest clinical variable associated with WKF was anemia: $\beta = 1.39$ (0.96 –

Table 1. Baseline patients’ characteristics by WKF status

Variable	No WKF	WKF	p
$N = 5,131$	4,909	222	
Age, years	60.9 $\pm$ 9.9	61.8 $\pm$ 10.1	0.19
Age > 65 yr, n (%)	1,735 (35.3)	88 (39.6)	0.19
Male, n (%)	3,359 (68.4)	127 (57.2)	< 0.001
Duration of T2D, years	7.0 (2.6, 13.5)	10.4 (4.0, 17.4)	< 0.001
HBA1c, %	8.0 $\pm$ 1.1	8.0 $\pm$ 1.0	0.66
Insulin, n (%)	1,451 (29.6)	90 (40.5)	< 0.001
Metformin, n (%)	3,265 (66.5)	122 (55.0)	< 0.001
Sulfonylureas, n (%)	2287 (46.6)	97 (43.7)	0.40
Thiazolidinediones, n (%)	117 (2.4)	9 (4.1)	0.12
BMI, kg/m ²	29.5 $\pm$ 5.5	29.8 $\pm$ 6.4	0.37
Race			0.33
White, n (%)	3,580 (72.9)	160 (72.1)	
Asian, n (%)	997 (20.3)	41 (18.5)	
Black, n (%)	187 (3.8)	10 (4.5)	
Other, n (%)	145 (3.0)	11 (5.0)	
Smoker (current), n (%)	683 (13.9)	21 (9.5)	0.059
MI (history), n (%)	4,320 (88.0)	191 (86.0)	0.38
HF (history), n (%)	1,369 (27.9)	103 (46.4)	< 0.001
Stroke (history), n (%)	344 (7.0)	20 (9.0)	0.26
PAD (history), n (%)	461 (9.4)	27 (12.2)	0.17
Atrial fibrillation, n (%)	343 (7.0)	17 (7.7)	0.70
Index event MI, n (%)	3,780 (77.2)	169 (76.5)	0.81
Index event ACS, n (%)	1,118 (22.8)	52 (23.5)	
Hemoglobin, g/dL	13.5 $\pm$ 1.6	12.6 $\pm$ 1.6	< 0.001
Anemia, n (%)	1,184 (24.2)	104 (46.8)	< 0.001
eGFR, mL/min/1.73 m ²	71.2 $\pm$ 21.1	63.9 $\pm$ 27.0	< 0.001
eGFR < 60 , n (%)	1,383 (28.2)	102 (45.9)	< 0.001
Heart rate, bpm	71.4 $\pm$ 10.8	72.3 $\pm$ 12.1	0.19
SBP, mm Hg	128.9 $\pm$ 16.6	132.3 $\pm$ 17.5	0.003
SBP > 140 , n (%)	983 (20.0)	58 (26.1)	0.027
Antiplatelet agents, n (%)	4,773 (97.2)	218 (98.2)	0.39
Beta-blockers, n (%)	4,034 (82.2)	183 (82.4)	0.92
ACEi or ARB, n (%)	4,054 (82.6)	179 (80.6)	0.45
Calcium channel blockers, n (%)	1,084 (22.1)	58 (26.1)	0.16
Diuretics, n (%)	1,792 (36.5)	133 (59.9)	< 0.001
Statins, n (%)	4,462 (90.9)	189 (85.1)	0.004
Randomized to alogliptin, n (%)	2456 (50.0)	126 (56.8)	0.050

WKF, worsening kidney function (first occurrence); T2D, type 2 diabetes; HBA1c, glycated hemoglobin; BMI, body mass index; MI, myocardial infarction; HF, heart failure; PAD, peripheral artery disease; ACS, acute coronary syndrome; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; ACEi or ARB, angiotensin converting enzyme inhibitors or angiotensin receptor blockers.

1.82), $Z = 6.4$ (online suppl. Table 2). In biomarkers (adjusted for clinical variables), the one with strongest association with WKF was blood KIM-1: $\beta = 0.84$ (0.66 – 1.03) per log2 increase, $Z = 9.1$; followed by platelet growth factor, $Z = 7.1$; and TRAIL receptor 2, $Z = 6.9$. A total of 18 biomarkers were independently associated with WKF

Table 2. Multivariable stepwise models predicting WKF

Biomarker	Beta coef. (95% CI)	Z-score	p value
<i>Model 1</i>			
KIM-1	0.50 (0.36–0.65)	6.6	<0.00001
Anemia	0.70 (0.36–1.04)	4.0	0.00005
VEGFD	0.76 (0.32–1.20)	3.4	0.001
IL4RA	0.50 (0.21–0.80)	3.3	0.001
uNGAL	0.11 (0.03–0.19)	2.8	0.006
SPON2	–0.88 (–1.64 to –0.13)	–2.3	0.022
AUC = 0.78	–	–	–
<i>Model 2</i>			
KIM-1	0.78 (0.63–0.92)	10.6	0.00001
Anemia	0.90 (0.54–1.26)	4.9	0.00001
AUC = 0.76	–	–	–
<i>Model 3*</i>			
KIM-1	0.78 (0.66–0.89)	12.9	0.00001
AUC = 0.73	–	–	–

KIM-1, kidney injury molecule 1; VEGFD, vascular endothelial growth factor-D; IL4RA, interleukin 4 receptor alpha subunit; uNGAL, urinary neutrophil gelatinase-associated lipocalin; SPON2, spondin 2; CI, confidence interval; AUC, area under the curve; WKF, worsening kidney function. The correlation coefficient of KIM-1 with the other proteins was not greater than 0.5. Model 1 shows the results of the stepwise forward model that started with all the variables with a *p* value ≤ 0.0001 shown in the online supplementary Tables 2 and 3 (light green); the retained variables with a *p* value of < 0.05 to stay in the model are shown in Model 1 of this table; Model 2 shows the results after keeping only the variables with a *p* value ≤ 0.0001 in Model 1; Model 3 is a simplest model retaining only KIM-1, the variable with strongest association with WKF. * Anemia alone gave an AUC = 0.65.

with a *p* value ≤ 0.0001 ($Z \leq 3.8$). uKIM-1 was associated with WKF but with a much weaker association than blood KIM-1, $Z = 2.9$ for uKIM-1. All biomarkers listed by descending order of strength of association with WKF are listed in the online supplementary Table 3. All the biomarkers associated with WKF were also associated with eGFR slope deterioration (online suppl. Table 4).

In multivariable models including all the variables (clinical and biomarkers) independently associated with WKF with a *p* value ≤ 0.0001 , blood KIM-1 was (by far) the variable with strongest association with WKF, followed by anemia. KIM-1 alone provided good discrimination for the prediction of WKF (AUC = 0.73), while anemia alone provided only moderate discrimination and was much lower than KIM-1 alone (AUC = 0.65). Table 2. The urinary albumin-to-creatinine ratio (UACR) variable contains 42% ($n = 2245$) missing values. As sensitivity analysis, we have adjusted our models to UACR

(plus age, sex, and eGFR) in complete cases ($n = 2999$) and after multiple imputation ($n = 5,380$), and KIM-1 remained the variable with the strongest association with the occurrence of WKF (online suppl. Table 5).

WKF Events by KIM-1 Levels

The predicted risk of WKF derived from KIM-1 alone was divided in tertiles (low, intermediate/medium, and high risk). Patients in the high-risk tertile had a 6.7-fold higher risk of any WKF than patients classified as low risk, and the risk of sustained worsening kidney function was 12.5-fold higher in high-risk than low-risk patients (Table 3 and Figure 1).

Events after WKF

In time-updated Cox models, the occurrence of WKF was independently associated with a higher risk of experiencing a subsequent primary outcome event: adjusted hazard ratio (HR) = 4.25 (2.83–6.39); cardiovascular death or HF hospitalization: adjusted HR = 6.19 (4.09–9.36); and all-cause mortality: adjusted HR = 4.93 (3.06–7.96) (all $p < 0.0001$) (Figure 2).

Discussion

The present study shows that in more than 5,000 patients with T2D and a recent ACS in whom 95 biomarkers (in both urine and blood) had been measured at baseline, blood KIM-1 was the biomarker with the strongest association with WKF. The occurrence of WKF was independently associated with a higher risk of subsequent cardiovascular events and mortality.

Identifying patients more likely to develop kidney dysfunction is important both for clinical practice and research. To date, the prediction of WKF is often performed by detecting rapid rises in serum creatinine or rapid decreases in eGFR, which is far from ideal, because it frequently represents overt WKF resulting in a late diagnosis, often at advanced stages of kidney injury where therapeutic options are limited and the prognosis is poor [18]. Therefore, more important is predicting the occurrence of WKF before its onset, so that preventive strategies can be implemented [19]. In this regard, several molecules, measured both in blood and urine, have been identified as potential markers for early detection of kidney damage before rises in serum creatinine or eGFR decline [20–23]. However, these markers are not routinely used in clinical practice nor for patient selection in clinical trials, due to limitations in accuracy and reproducibility [3, 6].

Table 3. WKF events by tertiles of risk predicted from blood KIM-1 levels

KIM-1 predicted risk	Low	Intermediate	High	Total
Total WKF (first and recurrent)				
No WKF	11,455	11,471	11,217	34,143
WKF	44 (0.4)	58 (0.5)	216 (1.9)	318
OR (95% CI)	Ref	1.40 (0.83–2.36)	6.68 (4.15–10.76)	–
AUC = 0.73	–	–	–	–
First WKF				
No WKF	1,675	1,662	1,572	4,909
WKF	36 (2.1)	48 (2.8)	138 (8.1)	222
HR (95% CI)	Ref	1.37 (0.89–2.11)	4.2 (2.91–6.06)	–
C-index = 0.69	–	–	–	–
sWKF				
No WKF	1,707	1,700	1,644	5,071
WKF	4 (0.2)	10 (0.6)	46 (2.7)	60
HR (95% CI)	Ref	2.55 (0.80–8.13)	12.46 (4.48–34.60)	–
C-index = 0.80	–	–	–	–

WKF, worsening kidney function; sWKF, sustained worsening kidney function; KIM-1, kidney injury molecule 1; OR, odds ratio; HR, hazard ratio; 95% CI, 95% confidence interval; AUC, area under the curve. Low, intermediate, and high represent the tertiles of predicted risk from KIM-1 levels. KIM-1 predicted the occurrence of WKF in an incremental manner, regardless of the WKF definition.

Fig. 1. WKF events by tertiles of risk predicted from blood KIM-1 levels. Caption: Higher KIM-1 levels predict WKF events defined by a deterioration in eGFR $\geq 40\%$ from baseline. WKF, worsening kidney function; KIM-1, kidney injury molecule 1; eGFR, estimated glomerular filtration rate.

Fig. 2. Death after a WKF event. WKF defined by a deterioration in eGFR $\geq 40\%$ from baseline. Caption: crude HR (95% CI) = 8.05 (5.08–12.76), $p < 0.0001$. WKF, worsening kidney function; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval.

In our study, blood KIM-1 was the biomarker with the strongest association with WKF and was also strongly associated with eGFR slope deterioration over time. KIM-1 is upregulated in the proximal tubular cells following kidney injury [24]. The disruption of renal endothelial cells,

with loss of cellular adhesion junctions and disruption of extracellular matrix, facilitates KIM-1 movement into the circulation and its blood detection, beyond its urinary excretion. In fact, raised levels of blood KIM-1 may represent a more severe kidney injury due to the disruption of

the endothelial barrier [25]. Higher levels of blood KIM-1 have been shown to predict acute and chronic kidney injury in patients with type 1 diabetes [4, 26], long-term deterioration of kidney function in the general population [27], and poorer renal function in HF [28]. In a study including patients with type 1 diabetes without proteinuria in whom both blood and uKIM-1 were measured, blood KIM-1 (but not uKIM-1) was the biomarker more strongly associated with kidney function decline [26]. In a previous analysis of the EXAMINE trial studying uKIM-1 and NGAL not measuring blood biomarkers, neither uKIM-1 nor urinary NGAL improved the prediction of eGFR decline [29]. These findings were concordant with the present analysis, where both blood and uKIM-1 were measured, but blood KIM-1 had a stronger association with WKF and renal function “slope” decline than uKIM-1, urinary NGAL, or any other measured biomarker. Our results suggest that damage to proximal tubules with disruption of the endothelial barrier plays an independent role in the development and progression of kidney dysfunction.

Important clinical and research implications can be drawn from these findings. Due to extensive replication and strong prediction capacity, blood KIM-1 could be implemented for the prediction of kidney function decline in the clinical setting, allowing to individualize preventive strategies to patients at higher risk of kidney dysfunction progression. These preventive strategies might include treatment with sodium glucose co-transporter 1/2 inhibitors and finerenone that have been shown to reduce WKF and prevent kidney function decline in patients with and without diabetes [10–13, 30, 31]. Interestingly, empagliflozin has been shown to reduce the urinary levels of KIM-1, suggesting that empagliflozin may reduce tubular injury and improve the function of the proximal tubule [32].

Blood KIM-1 can also be used in clinical trials for risk enrichment of kidney outcomes, allowing to increase the number of events and the study power, tailored to patients who might benefit the most from the treatment being studied [33]. Furthermore, along with brain natriuretic peptides and troponin, that strongly predict cardiovascular events [34], the addition of KIM-1 for WKF prediction may allow an optimal risk assessment of cardio-kidney endpoints [33].

Limitations

Some limitations should be acknowledged in this study. This is a post hoc analysis of a randomized controlled trial subject to biases inherent to observational

data. Blood KIM-1 and all the Olink[®] biomarkers represent normalized concentrations and cannot be translated into cut points ready for clinical use. Further studies using other laboratorial techniques for measuring blood KIM-1 (e.g., ELISA) are warranted to validate our findings. Despite extensive replication of blood KIM-1 as a biomarker strongly associated with WKF in several populations, further data are needed for patients with T2D and an ACS, where our study is unique. UACR has 42% of missing values in EXAMINE; still in sensitivity analysis adjusting for UACR (plus age, sex, and eGFR), KIM1 remained the variable with strongest association with WKF.

Conclusions

In patients with T2D and a recent ACS, blood KIM-1 was the biomarker with the strongest association with WKF. The occurrence of WKF was independently associated with a higher risk of subsequent cardiovascular events and mortality. Further studies are needed to confirm these hypothesis generating findings and assess whether KIM-1 could be implemented for early prediction of kidney outcomes in the clinical setting.

Acknowledgments

Cardiovascular Outcomes Study of Alogliptin in Patients with Type 2 Diabetes and Acute Coronary Syndrome (EXAMINE) is a clinical trial sponsored by Takeda Global Research and Development Center, Inc., Deerfield, IL. The authors are solely responsible for the design of the study, all study analyses, and the drafting and editing of the manuscript and its final contents. Clinical trials identifier: Clinicaltrials.gov-NCT00968708.

Statement of Ethics

The appropriate national and institutional regulatory authorities and ethics committees approved the study design, and all participants provided written informed consent.

Conflict of Interest Statement

Dr Ferreira is a consultant for Boehringer-Ingelheim and receives research support from AstraZeneca and Novartis. Dr Rossignol reports personal fees from Ablative Solutions, AstraZeneca, Bayer, Boehringer-Ingelheim, Corvidia, CVRx, Fresenius, G3P (stocks), Grunenthal, Idorsia, KBP, Novartis, Novo Nordisk, Relypsa, Sanofi, Sequana Medical, Servier, Stealth Peptides, Vifor, Vifor Fresenius Medical Care Renal Pharma, and Cofounder: CardioRenal, a company developing sensors for the home monitoring of

potassium and creatinine. Dr Zannad reports personal fees from Boehringer-Ingelheim during the conduct of the study; personal fees from Janssen, Novartis, Boston Scientific, Amgen, CVRx, AstraZeneca, Vifor Fresenius, Cardior, Cereno pharmaceutical, Applied Therapeutics, Merck, Bayer, and Cellprothera outside the submitted work; and other support from CVCT and CardioRenal, outside the submitted work. Dr Bakris has received personal fees from Takeda Development Center, is a consultant for Merck, Relypsa, and is on the steering committee for international renal/CV outcomes trials for Janssen, Bayer, and Vascular Dynamics. Dr White has received research support from the National Institute of Aging (NIH) and personal fees from Takeda Development Center (Deerfield, IL, USA) during the conduct of the EXAMINE trial until 2016 (Steering Committee Chair). All the other authors reported not having potential conflicts of interest relevant to this article.

Funding Sources

The Cardiovascular Outcomes Study of Alogliptin in Patients with Type 2 Diabetes and Acute Coronary Syndrome (EXAMINE) study was funded by Takeda, but the present analysis did not receive funding.

J.P.F., P.R., and F.Z. are supported by a public grant overseen by the French National Research Agency as part of the second “Investissements d’Avenir” programme (ANR-15-RHU-0004). All the other authors have nothing to disclose with regard to this manuscript.

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Author Contributions

J.P.F. performed statistical analysis and drafted the manuscript and its subsequent revisions. All authors provided critical input to the manuscript.

J.P.F. wrote the manuscript, performed the statistical analysis, and made critical revisions; C.M. contributed to the oversight of the EXAMINE trial, as a steering committee member and to discussion and reviewed/edited the manuscript including the revision of the statistical methods and analysis; G.B. contributed to the oversight of the EXAMINE trial, as a steering committee member and reviewed/edited the manuscript; P.R. reviewed/edited the manuscript; W.B.W. contributed to the oversight of the EXAMINE trial, as the principal investigator of the trial, and reviewed/edited the manuscript; F.Z. contributed to the oversight of the EXAMINE trial, as a steering committee member, discussion, and reviewed/edited the manuscript. Dr. Joao Pedro Ferreira is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data Availability Statement

The data and materials may be available upon reasonable request.

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