Major Adverse Cardiovascular Events and Mortality Prediction by Circulating GDF-15 in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis

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Abstract: Background: Growth differentiation factor 15 (GDF-15) is a homeostatic cytokine that regulates neural and cardio-metabolic functions, and its release is increased in response to stress, injury, and inflammation. In patients with coronary artery disease and heart failure (HF), three separate meta-analyses have found that elevated circulating GDF-15 was predictive of major adverse cardiovascular events (MACE), but none has evaluated its effects on incident MACE including HF and mortality hazard in type 2 diabetes. Methods: MEDLINE, EMBASE, and Scopus databases were queried. Articles that met the predefined eligibility criteria, including prospective studies that reported adjusted hazard ratios (aHRs), were selected according to the Cochrane Handbook and PRISMA guidelines. Study endpoints were (1) MACE including HF, and (2) all-cause mortality. Different GDF-15 concentration measurements were harmonized using a validated mathematical approach to express log-transformed values in per standard deviation (SD). Study heterogeneity (I²), quality, and bias were assessed. Results: 19354 patients in 8 prospective studies were included. In 7 studies that reported 4247 MACE among 19200 participants, the incident rate was 22.1% during a median follow-up of 5.6 years. It was found that four of eight studies included HF decompensation or hospitalization as a component of MACE. In 5 studies that reported all-cause mortality, 1893 of 3223 patients died, at an incidence rate of 15.1% over 5.0 years. Of note, each 1 SD increase of [GDF-15] was associated with aHRs of 1.12 (1.09–1.15, I² = 5%, p < 0.000001) and 1.27 (1.11–1.46, p < 0.000001).
\( I^2 = 86\%, \ p = 0.00062 \) and for MACE and all-cause mortality, respectively. Conclusion: Elevated circulating level of GDF-15 was robustly predictive of MACE in patients with T2D but its prognostic significance in the prediction of mortality requires further studies.

Keywords: growth differentiation factor 15; adverse cardiovascular outcomes; coronary artery disease; heart failure; type 2 diabetes; mortality

1. Introduction

Growth differentiation factor 15 (GDF-15), or macrophage inhibitory cytokine 1 (MIC-1), is a 308-amino acid protein encoded by a 1.2-kilobase transcript of the GDF15 gene located on chromosome 19p13.11. Following post-translational processing, GDF-15 is released as a 25-kDa dimer consisting of 224 amino acids that signals through its receptor, glial-derived neurotrophic factor receptor alpha-like (GFRAL), and co-receptor, Ret [1]. Whereas GFRAL is prominently expressed in the brain (particularly, in the area postrema and the nucleus tractus solitarius for appetite regulation) and at lower levels in other tissues including adipose tissue in the human, Ret is widely expressed and may signal in complex with cell-surface or soluble GDF-15/GFRAL [1]. GDF-15 originates from a wide range of cells (e.g. adipocytes, cardiomyocytes, vascular smooth muscle cells, endothelial cells) and tissue types, and is released in response to tissue injury, cellular stress, and inflammation [2]. In addition to playing important regulatory roles in energy metabolism, body weight, appetite, and immune response, GDF-15 is elevated in cardiometabolic diseases, including hypertension [3,4], diabetes mellitus [5,6], coronary heart disease [7], and heart failure (HF) [8,9]. While GDF-15 has antihypertrophic effects on cardiac remodeling and counter-regulates inflammation, studies have shown that chronic elevation of GDF-15 can result in anorexia, inhibition of muscle growth, weight loss, and cachexia [1].

Previously, GDF-15 has been examined as a biomarker to indicate CVD risk and all-cause mortality in three meta-analyses of patients with HF and/or acute coronary syndrome, irrespective of diabetes status [10–12]. However, those meta-analyses were limited by a lack of clarity on the definition of study endpoints, harmonization of GDF-15 levels, confounder adjustment, and/or characteristics of the study population [10–12]. In view of conflicting findings from separate studies [13,14], and a knowledge gap in an important patient population of type 2 diabetes that has not been closely examined, we performed a time-to-event meta-analysis to determine the impact of elevated GDF-15 levels on incident major adverse cardiovascular events (MACE) [15] including HF, and all-cause mortality, and demonstrated the successful application of a validated mathematical approach to harmonize HRs for the different measurements of GDF-15 concentration.

2. Materials and Methods

2.1. Data Sources and Search Strategy

Articles were searched on MEDLINE, EMBASE, and Scopus from inception of the databases until December 2021. Guidance and recommendations provided in the Cochrane Handbook of Systematic Reviews (http://handbook.cochrane.org (accessed on 1 May 2022)) and the Preferred Reporting Items for Systematic reviews and Meta-Analyses Statement (PRISMA) were followed. The PRISMA checklist was used in carrying out this study.

2.2. Eligibility Criteria

The following search terms were used: (GDF-15 OR MIC-1) AND (diabetes mellitus OR diabetes OR prediabetes OR hyperglycemia OR glucose OR insulin resistance). Two reviewers (S.X., Q.L.) independently evaluated the studies’ eligibility by screening literature titles and abstracts. Original research articles meeting the eligibility criteria were retrieved and reviewed. The inclusion criteria were: (i) type 2 diabetes; (ii) investigations into how circulating GDF-15 predicted risks of cardiovascular disease or mortality; (iii) human
individuals, (iv) subjects aged 18 years or above, and (v) articles published in English.
The exclusion criteria were: (i) basic science or animal research, (ii) subjects younger
than 18 years old, (iii) type 1 diabetes, (iv) pregnant women, and (v) not primary and
original research articles including reviews, commentaries, editorials, conference abstracts,
or letters.

2.3. Definition of Study Endpoints

The study endpoints were (1) MACE, a composite of non-fatal MI, stroke, CV death,
and/or HF events (hospitalizations, initiation of loop diuretics, or NT-proBNP elevation)
and/or revascularization and/or worsening arrhythmia, critical limb ischemia, or venous
thromboembolism; and (2) all-cause mortality.

2.4. Data Extraction

The characteristics, outcomes definitions, and adjusted confounders of the included
studies were documented by two independent reviewers for descriptive analysis. Disagree-
ment was resolved through discussion with and adjudication by a third reviewer. Data
on the most fully adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were
extracted. We extracted HRs from the most fully adjusted models in the respective study,
or the models that consisted of the most common covariates among the included studies.

2.5. Data Harmonization and Statistical Analysis

Median or mean values of blood GDF-15 concentrations were extracted from stud-
ies, in respect of the distribution of the study populations. All included studies used
log-transformed concentrations, log(GDF-15) or log₂(GDF-15), in the respective Cox re-
gression models. We standardized the HRs in the same units and pooled the HRs in
per SD of log₂(GDF-15). Studies that reported HRs in the unit of per IQR log(GDF-15),
per log(GDF-15), per log₂(GDF-15), or per SD log(GDF-15) were converted to per SD
of log₂(GDF-15) according to sample sizes and the dispersion characteristics of GDF-15
levels [16–19] (Tables S1 and S2).

HRs were converted using three equations as shown below. Fixed ratio between log(x)
and log₂(x):

\[
\frac{\log(x)}{\log_2(x)} = \frac{\log_e(x)}{\log_e(2)} = \log_k^2 = \log_{e2}
\]  

(1)

Estimating HR(x) for n unit change of x:

\[
\exp(coef(x) \times n) = \exp(log(HR) \times n)
\]  

(2)

Estimating SD from quantiles by the method of Wan et al. [17]:

\[
SD_{est} \approx \frac{q_3 - q_1}{2\Phi^{-1}(((0.75n - 0.125)/n + 0.25))}
\]  

(3)

where SD_{est} was defined as the estimated standard deviation; n, number; q, quantile; \( \Phi^{-1}(z) \)
was the upper zth percentile of the standard normal distribution.

Results from eligible studies were pooled and meta-analyzed using the random-effects
model with inverse-variance weighting and visually displayed by forest plots. Potential
covariates were analyzed for effects on GDF-15 levels in predicting the composite CVD
outcomes. The presence (Figure 2A and Figure 3A) or absence (Figure 2B and Figure 3B) of
canagliflozin treatment in the study of Sen et al. [20] and its effects on the overall pooled
estimates were assessed. A 2-tailed p-value of < 0.05 was considered statistically significant.

Study heterogeneity was assessed by the total heterogeneity/total variability (I²).
I² threshold values of 25%, 50%, and 75% were regarded as low, moderate, and high,
respectively. Review Manager 5.3 (The Cochrane Collaboration) and R 4.0.3 (R Foundation,
Vienna, Austria) software packages were used.
2.6. Assessment of Publication Bias and Study Quality

Funnel plot analysis and Duval-Tweedie’s trim and fill test were used to assess publication bias [21]. Quality of studies was individually assessed using the Newcastle-Ottawa scale [22], and verified (Table S3).

3. Results

3.1. Characteristics of the Included Prospective Studies

The workflow of our search strategy and selection of articles was summarized (Figure 1). A total of 19543 patients with type 2 diabetes from prospective studies that reported hazard ratios [13,14,20,23–27], including one study with 1561 individuals who had undiagnosed diabetes and confirmed dysglycemia [24], were entered into the meta-analysis (Table 1). The median duration of type 2 diabetes was 8.7 years, as reported in 4 of 8 studies only. Hypertension was present in 66.9% to 83.3% of patients. Other comorbidities are shown in Table 1. The median duration of follow-up in eight studies was 5.0 years. Table 2 summarized the definitions of MACE and adjusted confounders in each included study.

![Figure 1. PRISMA flow diagram showing the literature search and article selection strategy.](image-url)
Table 1. Summary of prospective studies in this meta-analysis.

| Country      | Sample size, n | Study type          | Statistical adjustment (Cox) | Median follow-up time, y | Age, y | Male, n (%) | BMI, kg/m² | Smoking, n (%) | Hypertension, n (%) | Heart failure, n (%) | Atrial fibrillation, n (%) | Coronary artery disease, n (%) | Myocardial infarction, n (%) | Duration of diabetes, y | HbA1c, % | eGFR, mL/min/1.73 m² | hsTnT †, ng/L | NT-proBNP †, pg/mL | GDF-15 †, pg/mL | Medications:                                                                 |
|--------------|----------------|---------------------|-----------------------------|--------------------------|--------|-------------|------------|----------------|---------------------|--------------------------|-----------------------------|-----------------------------|--------------------------|-----------|---------------------|----------------|----------------|----------------|-----------------------------------------------------------------------------|
| Sweden       | 231            | Prospective         | Multivariate                | 7.9                      | 68     | 169 (73.0)  | 30         | 123 (15.0)     | –                   | –                        | –                          | –                           | –                        | –                       | –         | 70.0                | –              | –               | –              | Aspirin, n (%)                                                            |
| USA          | 154            | Prospective         | Multivariate                | 5.0                      | –      | –           | –          | –              | 54 (35.1)           | 14.7                     | 7 (4.5)                   | –                           | –                        | –                       | –         | 70.0                | –              | –               | –              | Statin, n (%)                                                             |
| Denmark      | 200            | Prospective         | Multivariate                | 6.1                      | 59     | 152 (76.0)  | 159        | –              | –                   | –                        | –                          | –                           | –                       | –         | 91.1                | –              | –               | –              | ACEI/ARB, n (%)                                                            |
| Canada       | 8401           | Prospective         | Multivariate                | 6.2                      | 63.2   | 5928 (70.6) | 1050       | –              | 123 (15.0)          | 1050 (12.5)              | –                          | –                           | –                       | –         | 70.0                | –              | –               | –              | Beta-blocker, n (%)                                                       |
| Austria      | 919            | Multivariate        | Univariate                  | 5.0                      | 62     | 511 (55.6)  | 358        | 132 (15.0)     | –                   | 0 (0)                    | –                          | –                           | –                       | –         | 73.3                | –              | –               | –              | Any OHA, n (%)                                                            |
| USA          | 746            | Prospective         | Multivariate                | 5.0                      | –      | –           | –          | –              | –                   | –                        | –                          | –                           | –                       | –         | 7.1                | –              | –               | –              | Metformin, n (%)                                                           |
| Denmark      | 420 (56.3)     | Prospective         | Multivariate                | 5.0                      | –      | –           | –          | –              | –                   | –                        | –                          | –                           | –                       | –         | 72.7                | –              | –               | –              | Sulfonylurea, n (%)                                                       |
| Austria      | 2374 (66.9)    | Prospective         | Multivariate                | 6.1                      | –      | –           | –          | –              | –                   | –                        | –                          | –                           | –                       | –         | 7.0                | –              | –               | –              | Insulin, n (%)                                                            |
| Int’l        | 3491 (67.7)    | Prospective         | Multivariate                | 1.5                      | –      | –           | –          | –              | –                   | –                        | –                          | –                           | –                       | –         | 8.2                | –              | –               | –              | –                                                             |
| Int’l        | 3491 (67.7)    | Prospective         | Multivariate                | 2.9                      | –      | –           | –          | –              | –                   | –                        | –                          | –                           | –                       | –         | 7.7                | –              | –               | –              | –                                                             |
| Int’l        | 5154           | Prospective         | Multivariate                | 1.5                      | –      | –           | –          | –              | –                   | –                        | –                          | –                           | –                       | –         | –                  | –              | –               | –              | –                                                             |

† Continuous variables are reported as mean or median. ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker; BMI: body mass index; eGFR: estimated glomerular filtration rate; GDF-15: growth differentiation factor-15; hsTnT: high-sensitivity troponin T; Int’l: international; NT-proBNP: N-terminal prohormone of B-type natriuretic peptide; OHA: oral hypoglycemic agent; –: not applicable.
### Table 2. Definition of study endpoints, MACE, and adjusted confounders in the included studies.

| Study (Year)               | Endpoint | Definition of MACE | Adjusted Confounders                                                                 | Reference |
|----------------------------|----------|--------------------|--------------------------------------------------------------------------------------|-----------|
| Carlsson et al. (2020)     | MACE     | (1) Fatal or nonfatal MI or stroke | Age, sex, frailty, microalbuminuria, renal function, CVD at baseline, smoking, LDL, and SBP | [14]      |
|                            |          |                    | All-cause death                                                                     |           |
| Cavusoglu et al. (2015)    | MACE     | –                  | Age, HF or MI at presentation, extent of angiographic CAD, eGFR, metformin use, TZD use, and ST2 | [23]      |
|                            |          |                    | All-cause death                                                                     |           |
| Frimodt-Møller et al. (2018)| MACE   | (1) Incidence of CV death, nonfatal MI, stroke, ischemic CVD, and HF | Age, sex, smoking status, systolic BP, LDL, HbA1c, plasma creatinine, and urinary albumin excretion rate | [13]      |
|                            |          |                    | All-cause death                                                                     |           |
| Gerstein et al. (2015)     | MACE     | (1) Composite of MI, stroke, or CV death Outcome 1 plus HHF or revascularization | Age, sex, smoking status, prior DM, HT and CV events, LDL/HDL, albuminuria, and levels of serum creatinine, NT-proBNP, chromogranin A, Ang-2, GSTA, apolipoprotein B and tissue inhibitor of metalloproteinase 1 | [24]      |
|                            |          |                    | All-cause death                                                                 |           |
| Pavo et al. (2016)         | MACE     | (1) CV death        | Age, sex, and log-transformed duration of DM, BP, eGFR, LDL, total cholesterol, HbA1c, urinary albumin excretion and NT-proBNP | [25]      |
|                            |          |                    | All-cause death                                                                     |           |
| Resl et al. (2016)         | MACE     | (1) Composite endpoint of unplanned hospitalization for CV events or CV death secondary to MI, decompensated HF, worsening arrhythmia, critical limb ischemia or venous thromboembolism | Age, sex, race, and randomized treatment assignment (canagliflozin or placebo) *, history of CVD, HbA1c, systolic and diastolic BP, BMI, LDL cholesterol, eGFR and UACR | [26]      |
|                            |          |                    | All-cause death                                                                     |           |
| Sen et al. (2021)          | MACE     | (1) Nonfatal MI, nonfatal stroke, or CV death | Age, sex, smoking status, systolic BP, history of HF, duration of DM, prior MI, HT, hyperlipidemia, and eGFR | [20]      |
|                            |          |                    | All-cause death                                                                     |           |
| Sharma et al. (2020)       | MACE     | (1) Composite of CV death, HHF, initiation of loop diuretics, or NT-proBNP elevation | Age, sex, smoking status, systolic BP, history of HF, duration of DM, prior MI, HT, hyperlipidemia, and eGFR | [27]      |
|                            |          |                    | All-cause death                                                                     |           |

Ang-2: angiopoietin-2; BMI: body mass index; BP: blood pressure; DM: diabetes mellitus; CAD: coronary artery disease; CVD: cardiovascular disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; GSTA: glutathione-S-transferase A; HDL: high-density lipoprotein; HF: heart failure; HHF: hospitalization for heart failure; HT: hypertension; IGF: insulin-like growth factor; LDL: low-density lipoprotein; MACE: major adverse cardiovascular event; MI: myocardial infarction; Ref.: reference number; ST2: suppression of tumorigenicity 2; TZD: thiazolidinedione; UACR: urine albumin-to-creatinine ratio; –: not applicable. * Note the absence of treatment effect on GDF-15 levels reported in the randomized controlled trial, CANVAS.3.2. Elevated GDF-15 and Risks of Future MACE.
3.2. Elevated GDF-15 and Risks of Future MACE

Seven prospective studies including 19200 participants and 4247 composite endpoints were analyzed for MACE. For each SD increase in log₂(GDF-15), the hazard for MACE was significantly increased (pooled adjusted HR 1.21, 95% CI 1.11–1.33, \(p < 0.0001\), \(I^2 = 87\%\)) (Figure 2A). Sensitivity analysis identified Pavo et al. [26] and study subjects who received canagliflozin in the study of Sen et al. [20] as major sources of study heterogeneity. When both groups were removed, the study heterogeneity markedly improved (\(I^2 = 5\%\)), while the hazard estimate remained statistically significant (pooled adjusted HR 1.12, 95% CI 1.09–1.15, \(p < 0.00001\)) (Figure 2B).

![Figure 2](image-url)

3.3. Elevated GDF-15 and Hazard of All-Cause Mortality

In the five prospective studies reporting mortality that were included, 1893 all-cause deaths occurred in 13223 patients with type 2 diabetes. For each 1 SD increase in log₂(GDF-15), the hazard estimate was significantly increased (pooled adjusted HR 1.47, 95% CI 1.23–1.75, \(p < 0.0001\), \(I^2 = 95\%\)) (Figure 3A). When both Pavo et al. [25] and study subjects who received canagliflozin in the study of Sen et al. [20] were excluded, the pooled adjusted HR decreased (1.27, 95% CI 1.11–1.46, \(p = 0.0006\)), while study heterogeneity marginally improved (\(I^2 = 86\%\)) (Figure 3B).
Figure 2. Elevated circulating GDF-15 levels are significantly associated with future MACE (HR 1.12, 95% CI 1.09–1.15) among patients with type 2 diabetes. The funnel plot of GDF-15 in predicting incident MACE including HF, and all-cause mortality, during a median follow-up of 5.6 years. Prior to this, no meta-analysis has specifically focused on this important patient population. Our meta-analysis has applied previously validated mathematical equations [17–19] to harmonize GDF-15 metrics across different studies to derive hazard estimates (see Methods). Our main findings were that each 1 SD increment of GDF-15 level was associated with a 13% increased risk for future MACE in individuals with diabetes [28].

3.4. Ascertainment of Quality of Study and Publication Bias

The relatively high quality of the included studies were ascertained (Table S3). Initially, the funnel plot of GDF-15 in predicting MACE appeared asymmetric and indicated potential publication bias (Figure S1). However, regardless of the presence or absence of three studies identified as potential causes of asymmetry in the trim-and-fill analysis, the resulting effect size was similar (1.11, 95% CI 1.06–1.16) as the pooled effect size in our meta-analysis (Figure 2). Both Begg’s test (p = 0.19) and Eggers’ test (p = 0.15) did not detect the presence of statistically significant asymmetry, suggesting that the pooled effect size of GDF-15 in predicting MACE was reliable.

4. Discussion

To our knowledge, this was the first time-to-event meta-analysis on prospective studies that summarized in patients with type 2 diabetes the effects (hazards) of elevated GDF-15 in predicting incident MACE including HF, and all-cause mortality, during a median follow-up of 5.6 years. Prior to this, no meta-analysis has specifically focused on this important patient population. Our meta-analysis has applied previously validated mathematical equations [17–19] to harmonize GDF-15 metrics across different studies to derive hazard estimates (see Methods). Our main findings were that each 1 SD increment in log2-transformed GDF-15 concentration was associated with (1) a 12–21% increase in the risks for future MACE (Figure 2), and (2) a 27–47% increase in the hazard of all-cause mortality (Figure 3), depending on stringency of study inclusion and heterogeneity. These findings were similar to those reported in the Framingham Heart Study that each SD increment of GDF-15 level was associated with a 13% increased risk for future MACE in individuals with diabetes [28].

The effects of circulating GDF-15 on adverse outcomes in patients with HF or coronary artery disease have been meta-analyzed in three studies previously [10–12], but diabetic
patients were a minority in each of those studies and none has specifically summarized the effects of elevated GDF-15 in patients with diabetes. Given that GDF-15 level is increased in not only patients with vascular inflammation, coronary artery disease, and heart failure \[11,12\], it has been unclear if the totality of evidence in the literature concur that patients with type 2 diabetes were similarly affected.

The recent discoveries and reinterpretations of the complex functional roles of GDF-15 beyond coronary artery disease and HF [1], particularly diabetes [29–31] and cardiometabolic conditions [29–31], have led us to conduct this meta-analysis focusing on patients with type 2 diabetes. Although increased circulating GDF-15 levels have been closely associated with cardiometabolic disorder and cardiovascular disease [1,32,33], its elevation may also reflect insulin responsiveness [34] and the therapeutic effects of antidiabetic medications [35,36]. As such, GDF-15 serves not only as an indicator of dysmetabolism but exerts also functional cardiometabolic effects. In this study, we also attempted to clarify the effects of canagliflozin, an SGLT2 inhibitor, on GDF-15 levels and the study outcomes [20]. We compared the inclusion (Figures 2A and 3A) and removal of patients who had received canagliflozin in CANVAS (Figures 2B and 3B), a placebo-controlled randomized clinical trial, but observed no significant difference in the adjusted HRs for MACE (1.21 [1.11–1.33] and 1.22 [1.11–1.34], respectively), or all-cause mortality (1.47 [1.23–1.75] and 1.49 [1.22–1.81], respectively). Future prospective studies are needed to ascertain the effects of this important cardiometabolic drug class on incident MACE including HF, and mortality.

Apart from its role as a biomarker, the genetic and quantitative association of GDF-15 with the etiology of atherosclerotic and metabolic CVD is complex and controversial. GDF-15 levels are determined by genetic and other complex lifestyle-related factors (e.g., smoking, diet, physical activity) [37]. Although data on this topic are scarce, several studies have found that single nucleotide polymorphisms (SNPs) in the GDF15 gene could partly explain circulating levels of GDF-15 [37,38]. Indeed, a meta-analysis summarized that nine SNPs in GDF15 explained approximately 21% of the variance in blood GDF-15 concentration [38]. However, a recent Mendelian randomization study in 2.6 million individuals from 5 genome-wide association studies found no evidence of causality between GDF15 SNPs and the incidence of stroke, HF, or nonischemic cardiomyopathy [39]. Further mechanistic studies are needed to fully characterize how the potent functionalities of GDF-15 could be harnessed, if possible, for improving cardiometabolic and vascular health.

There are several limitations in our study. First, we could not obtain individual-level data from authors of the original articles to examine the effects of variables including antidiabetic drugs. An individual-level meta-analysis could further improve the precision of our estimates by analyzing effects of individual variables or potential confounders, and potentially allow for an in-depth analysis of the effects of antidiabetic medications. Second, the study of Gerstein et al. included 1561 individuals without “previous diabetes mellitus” but had impaired glucose tolerance, impaired fasting glycemia and evidence of prediabetes. These individuals were included along with 6840 patients with established type 2 diabetes [24] and accounted for approximately 8.1 % [1561 of 19200] and 11.8% [1561 of 13223] of patients in the meta-analysis for incident MACE and all-cause mortality, respectively. It is possible that that might have potentially reduced the magnitude of the effect size and precision of our estimates. Third, while the removal of two major sources of heterogeneity [20,25] led to an significant improvement in the outcome of incident MACE (Figure 2), we were unable to identify the source of high study heterogeneity for all-cause mortality (Figure 3).

5. Conclusions

This meta-analysis found compelling evidence that elevated circulating GDF-15 level is associated with increased risk for incident MACE including HF in patients with type 2 diabetes. While there is suggestive evidence that elevated GDF-15 is indicative of increased mortality hazard, the quality of those data are insufficient for a conclusive interpretation.
Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/biom12070934/s1, Figure S1: Funnel plots assessing publication bias in the meta-analysis of A) MACE. Effect corrected by small-study bias by Duval and Tweedie’s trim and fill test B) shared similar size as pooled effect size A); Table S1: Format and details of source data from the 8 studies included in the meta-analysis; Table S2: Summary table of included studies with harmonized hazard ratios and the harmonization methodology used; Table S3: Assessment of quality of studies using the Newcastle-Ottawa scale.

Author Contributions: E.F. conceived the study. E.F., S.X., and Q.L. contributed to study design. S.X. and Q.L. performed literature search and review. S.X. and Q.L. completed the systematic review and meta-analysis under the supervision of E.F. E.F. and S.X. wrote the manuscript text and prepared the tables and figures. A.O.Y.L., H.-Y.L., P.K.S.C., A.B.-G., and F.K.L.C. edited the manuscript, and E.F. and S.X. prepared it for submission. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: Data collected for this study are available upon request. Queries should be directed to the corresponding author: e.fung@cuhk.edu.hk.

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