Research Article

Glucagon-Like Peptide-1 Receptor Agonists and Cardiovascular Events: A Meta-Analysis of Randomized Clinical Trials

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Objective. Data from randomized clinical trials with metabolic outcomes can be used to address concerns about potential issues of cardiovascular safety for newer drugs for type 2 diabetes. This meta-analysis was designed to assess cardiovascular safety of GLP-1 receptor agonists.

Design and Methods. MEDLINE, Embase, and Cochrane databases were searched for randomized trials of GLP-1 receptor agonists (versus placebo or other comparators) with a duration $\geq 12$ weeks, performed in type 2 diabetic patients. Mantel-Haenszel odds ratio with 95% confidence interval (MH-OR) was calculated for major cardiovascular events (MACE), on an intention-to-treat basis, excluding trials with zero events.

Results. Out of 36 trials, 20 reported at least one MACE. The MH-OR for all GLP-1 receptor agonists was 0.74 (0.50–1.08), $P = 0.12$ (0.85 (0.50–1.45), $P = 0.55$, and 0.69 (0.40–1.22), $P = 0.20$, for exenatide and liraglutide, resp.). Corresponding figures for placebo-controlled and active comparator studies were 0.46 (0.25–0.83), $P = 0.009$, and 1.05 (0.63–1.76), $P = 0.84$, respectively.

Conclusions. To date, results of randomized trials do not suggest any detrimental effect of GLP-1 receptor agonists on cardiovascular events. Specifically designed longer-term trials are needed to verify the possibility of a beneficial effect.

1. Introduction

Cardiovascular safety is a growing concern for drugs used for chronic conditions, such as diabetes. Among glucose-lowering agents, sulfonylureas [1, 2], insulin [3, 4], and thiazolidinediones [5–7], have been suspected of adverse cardiovascular effects, although some of those preoccupations have not been confirmed [8–11]. Following these concerns, the Food and Drug Administration issued a guidance for companies submitting new chemical entities as treatments for type 2 diabetes, requiring that, either in phase II–III trials, or in a subsequent phase IV specifically designed randomized clinical trial, a sufficient amount of information is collected so as to exclude a risk increase of over 30% (i.e., the upper limit—two-sided—of 95% confidence interval for major cardiovascular events, in comparison with placebo and/or other treatments, should not exceed 1.30; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071627.pdf).

Two GLP-1 receptor agonists (exenatide and liraglutide) have been approved for human use, and several others are currently under clinical development. It has been observed that chronic stimulation of GLP-1 receptors could produce beneficial effects on several cardiovascular risk factors [12]; furthermore, preliminary data on humans suggest that GLP-1 could have direct effects on myocardial function [13]. However, no major trial assessing the effects of GLP-1 receptor agonists on cardiovascular morbidity and mortality is available to date, nor will it be for a few years. In the meantime, the information on incident cases recorded as adverse
events during trials designed for metabolic endpoints could provide some hints on the possible cardiovascular profile of these drugs. This meta-analysis was designed to assess the effect of GLP-1 receptor agonists, compared with placebo or active hypoglycemic drugs, on major cardiovascular events in type 2 diabetic patients, as derived from randomized controlled trials.

2. Research Design and Methods

2.1. Data Sources and Searches. An extensive Medline, Embase, and Cochrane database search for “exenatide,” “liraglutide,” “albiglutide,” “taspglutide,” “lixisenatide,” and “semaglutide” was performed, collecting all randomized clinical trials on humans up to November 1th, 2010. The identification of relevant abstracts, the selection of studies based on the criteria described above, and the subsequent data extraction were performed independently by two of the authors (E. Mannucci and M. Monami), and conflicts resolved by the third investigator (N. Marchionni). Completed but still unpublished trials were identified through a search of http://www.clinicaltrials.gov/ website. Food and Drug Administration (FDA, http://www.fda.gov/) and European Medicines Agency (EMEA, http://www.ema.europa.eu/) reviews of approved drugs, as well as published information provided to FDA in response to queries during the approval process, were also searched for retrieval of unpublished trials.

2.2. Study Selection. A meta-analysis was performed including all randomized clinical trials with a duration of at least 12 weeks, either with a cross-over or a parallel series design, enrolling patients with type 2 diabetes, comparing glucagon-like peptide-1 (GLP-1) receptor agonists with placebo or active drugs (oral hypoglycemic agents and/or insulin) of other classes. Trials enrolling nondiabetic, or type 1 diabetic, subjects were also excluded. No review protocol was published elsewhere.

2.3. Data Extraction and Quality Assessment. Results of unpublished trials (characteristics of patients enrolled, treatments, and major cardiovascular events) were retrieved, if available, on http://www.clinicaltrials.gov/, http://www.novonordisk-trials.com/website/content/trial-results.aspx, http://www.lillytrials.com/results/results.html, or http://www.clinicalstudyresults.org/; Food and Drug Administration (FDA, http://www.fda.gov/) and European Medicines Agency (EMEA, http://www.ema.europa.eu/) reviews of approved drugs, as well as published information provided to FDA in
Table 1: Characteristics of the unpublished and undisclosed studies.

| Study         | Number of patients planned | Comparator Add-on to | Trial duration (wks) | Design | Study end date | Sponsor      |
|---------------|----------------------------|----------------------|----------------------|--------|----------------|--------------|
| Exenatide     | NCT00434954 488            | Aspart Metformin     | 26                   | PS, DB | August 2009   | Amylin       |
| Liraglutide   | NCT00696657 415            | Placebo None         | 12                   | PS, DB | February 2009 | Novo         |
| Taspropotide  | NCT00809705 60             | Placebo None         | 12                   | PS, DB | February 2010 | Hoff-Roche   |

PS: parallel series; DB: double blind; Hoff. Roche: Hoffman-La Roche; Novo: Novo Nordisk.

| Study name | Statistics for each study | MH odds ratio | P value |
|------------|---------------------------|---------------|---------|
| Nauck et al. [31] |                           | 1.833          | .24     |
| Heine et al. [34]  |                           | 1.588          | .529    |
| Russell-Jones et al. [44] |                     | 2.555          | .265    |
| NCT00360334 et al. [33] |                 | 0.983          | .986    |
| Diamant et al. [36] |                           | 3              | .502    |
| NCT00393718 et al. [33] |                | 0.652          | .579    |
| Pratley et al. [30]  |                           | 2.44           | .25     |
| Nauck et al. [47]  |                           | 0.497          | .396    |
| NCT00614120 et al. [33] |                 | 0.494          | .442    |
| Garber et al. [49]   |                           | 0.496          | .484    |
| Davis et al. [37]    |                           | 1.523          | .8      |

**Versus active comparators (overall)**

Nauck et al. [31] | 1.501 | 0.201
Heine et al. [34]  | 0.501 | 0.201
Russell-Jones et al. [44] | 0.822 | 0.791
Rosenstock et al. [17] | 0.500 | 0.791
Marre et al. [46]  | 0.25  | 0.25
Buse et al. [27]   | 0.25  | 0.25
DeFronzo et al. [26] | 0.25  | 0.25
Kaku et al. [43]   | 0.25  | 0.25
Gao et al. [21]    | 0.25  | 0.25
Nauck et al. [47]  | 2.017 | 0.123
Marre et al. [46]  | 0.243 | 0.123
Russell-Jones et al. [44] | 0.145 | 0.202
Kaku et al. [43]   | 0.497 | 0.623
Gao et al. [21]    | 0.145 | 0.623
Nauck et al. [47]  | 1.485 | 0.397
Zinner et al. [45] | 0.145 | 0.397
Bergenstal et al. [39] | 0.255 | 0.514
Marre et al. [46]  | 2.35  | 0.572
Bergenstal et al. [39] | 0.344 | 0.572
**Versus placebo (overall)**

Nauck et al. [31] | 0.459 | 0.009
Heine et al. [34]  | 0.459 | 0.009
Russell-Jones et al. [44] | 0.737 | 0.121
Marre et al. [46]  | 0.459 | 0.009

**Overall**

versus active comparators (overall)

GLP-1 RA: glucagon-like peptide-1 receptor agonists.

Figure 2: Effect of GLP-1 receptor agonists on fatal and nonfatal major cardiovascular events (MACE). Forest plot of individual studies. GLP-1 RA: glucagon-like peptide-1 receptor agonists. *Studies with multiple comparators.

2.4. Data Synthesis and Analysis. The principal outcome was the effect of GLP-1 receptor agonists, compared with other hypoglycemic agents or placebo, on major cardiovascular events (MACE) as defined in the list provided by FDA for this purpose (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Endocrinologic-andMetabolicDrugsAdvisoryCommittee/UCM148659.pdf), including cardiovascular death, nonfatal myocardial infarction and stroke, and hospitalizations due to acute coronary syndromes and/or heart failure.

Predefined separate analyses were performed for trials with different GLP-1 receptor agonists, whenever possible.

Mantel-Haenszel odds ratio with 95% confidence interval (MH-OR) was calculated for each of the events defined above, on an intention-to-treat basis, excluding trials with response to queries during the approval process, were also searched for retrieval of unpublished information. All those sources were also used to complete information on results of published trials, when not reported in publications. For all published trials, results reported in papers were used as the primary source of information, when available.

The quality of trials was assessed using some of the parameters proposed by Jadad et al. [14]. The score was not used as a criterion for the selection of trials whereas some items were used only for descriptive purposes.
Table 2: Characteristics of the studies included in the meta-analysis.

| Study (ref.) | NCT/FDA-reference | Add-on to | Description of randomization | Description of allocation | Description of blinding | Reporting of drop-out | Intention-to-treat |
|-------------|-------------------|-----------|------------------------------|----------------------------|-------------------------|------------------------|-------------------|
| **Albiglutide versus placebo** | | | | | | | |
| Rosenstock et al. [19] NCT00518115 | None/Metf. | NA | NA | A | A | Yes |
| **Exenatide versus placebo** | | | | | | | |
| Gill et al. [20] NCT00516074 | Metf./TZD | NA | NA | A | A | Yes |
| Kadowaki et al. [21] NCT00382239 | Sulfonylurea | A | NA | A | A | Yes |
| Zinman et al. [22] NCT00099320 | TZD | A | A | A | Yes |
| Gao et al. [23] NCT00324363 | SU + Metf. | A | NA | A | Yes |
| DeFronzo et al. [24] NCT00135330 | Rosiglitazone | A | NA | OL | A | Yes |
| Apovian et al. [25] NR | Multiple | A | A | A | Yes |
| Moretto et al. [26] NCT00381342 | None | A | A | A | Yes |
| Liutkus et al. [27] NR | Metf/TZD + Met | A | A | A | Yes |
| DeFronzo et al. [28] NCT0039013 | Metformin | A | NA | A | A | Yes |
| Buse et al. [29] NCT0039026 | Sulfonylurea | A | NA | A | Yes |
| Kendall et al. [30] NCT0035984 | SU + Metf. | NA | NA | A | Yes |
| **Exenatide versus rosiglitazone** | | | | | | | |
| DeFronzo# et al. [24] NCT00135330 | None | A | NA | OL | A | Yes |
| **Exenatide versus glibenclamide** | | | | | | | |
| Derosa et al. [31] NCT00135330 | None | A | NA | OL | A | Yes |
| **Exenatide versus BiAsp 30/70** | | | | | | | |
| Bergenstal et al. [32] NCT00097877 | SU + Metf. | A | A | OL | A | Yes |
| Nauck et al. [33] NCT00082407 | SU + Metf. | A | A | OL | A | Yes |
| **Exenatide versus glargine** | | | | | | | |
| Barnett et al. [34] NCT00099619 | SU + Metf. | A | A | OL | A | Yes |
| NCT00360334 [35] | OAD | NR | NR | OL | A | Yes |
| Heine et al. [36] NCT00082381 | SU + Metf. | A | A | OL | A | Yes |
| Bunck et al. [37] NCT00097500 | Metformin | A | NA | OL | A | Yes |
| Diamant et al. [38] NCT00641056 | SU + Metf./Metf | A | A | OL | A | Yes |
| **Exenatide versus insulin** | | | | | | | |
| Davis et al. [39] NCT00099333 | SU/Metf. | NA | NA | OL | A | Yes |
| **Exenatide LAR versus placebo** | | | | | | | |
| Kim et al. [40] NCT00103935 | Metf./None | A | A | A | A | Yes |
| **Exenatide LAR versus pioglitazone** | | | | | | | |
| Bergenstal et al. [41] NCT00637273 | None | A | A | A | A | Yes |
| **Exenatide LAR versus sitagliptin** | | | | | | | |
| Bergenstal et al. [41] NCT00637273 | None | A | A | A | A | Yes |
| **Liraglutide versus placebo** | | | | | | | |
| Madsbad et al. [42] FDA_1310 | None | NA | NA | A | A | Yes |
| Vilsbøll [43] NCT00154401 | None | NA | NA | A | A | Yes |
| Seino et al. [44] FDA_1334 | None | A | A | A | Yes |
| Kaku et al. [45] NCT00395746 | Sulfonylurea | NA | NA | NA | NA | Yes |
| Russell-Jones et al. [46] NCT00331851 | SU + Metf. | A | A | A | Yes |
| Zinman et al. [47] NCT00333151 | Metf. + TZD | A | A | A | Yes |
| Marre et al. [48] NCT00318422 | Sulfonylurea | NA | NA | A | Yes |
| Nauck et al. [49] NCT00318461 | Metformin | A | A | A | Yes |
### Table 2: Continued.

| Study (ref.) | NCT/FDA reference | Add-on to randomization | Description of randomization | Description of allocation | Description of blinding | Reporting of drop-out | Intention-to-treat |
|-------------|-------------------|-------------------------|-------------------------------|--------------------------|-------------------------|------------------------|-------------------|
| Liraglutide versus metformin | | | | | | | |
| Feinglos et al. [50] | N R | None | NA | NA | NA | A | No |
| | | | | | | | |
| Liraglutide versus rosiglitazone | | | | | | | |
| Marre et al. [48] | NCT00318422 | Sulfonylurea | NA | NA | A | A | Yes |
| | | | | | | | |
| Liraglutide versus glimepiride | | | | | | | |
| Madsbad et al. [42] | NR | None | NA | NA | OL | A | Yes |
| | | | | | | | |
| Nauck et al. [49] | NCT00318461 | Metformin | A | A | OL | A | Yes |
| | | | | | | | |
| Garber et al. [51] | NCT00294723 | None | A | A | OL | A | Yes |
| | | | | | | | |
| Liraglutide versus glibenclamide | | | | | | | |
| NCT00393718 [35] | NCT00393718 | None | NR | NR | OL | NR | NR |
| | | | | | | | |
| Liraglutide versus sitagliptin | | | | | | | |
| Pratley et al. [52] | NCT00700817 | None | A | A | OL | A | Yes |
| | | | | | | | |
| Liraglutide versus glargine | | | | | | | |
| Russell-Jones et al. [46] | NCT00331851 | SU + Metf. | A | A | A | A | Yes |

*All the studies are multicenter and designed as parallel series, with the exception of NCT00099619 which is a cross-over trial; #studies with multiple comparators. Metf.: metformin; NA: not adequate or not adequately reported; A: adequate; TZD: thiazolidinediones; TZD + Met.: thiazolidinediones + metformin; SU + Metf.: sulfonylureas and metformin; OL: open-label; OAD: oral antidiabetic drugs; NR: not reported; SU/Metf: sulfonylureas or metformin; LAR: long-acting release.

zero events. A random effect model was used because of the impossibility of a reliable assessment of heterogeneity, due to the small number of events in each trial [15]. Publication bias was not assessed, considering that the small number of adverse cardiovascular events in each study was irrelevant for the decision to publish trials with metabolic endpoints. The main expected bias is represented by the fact that the trials included were designed for noncardiovascular (metabolic) endpoint; this means that cardiovascular events were reported only as adverse events, without any systematic screening or predefined diagnostic criteria. The meta-analysis was reported following the PRISMA checklist [16]. All analyses were performed using Comprehensive Meta-analysis Version 2, Biostat (Englewood, NJ, USA) and SPSS 16.0.

This research was performed independently of any funding, as part of the institutional activity of the investigators.

### 3. Results

The trial flow is summarized in Figure 1. A total of 36 trials, 3 of which unpublished, were retrieved. Information on major cardiovascular events was reported in 33 trials, 20 of which with at least one event. The analysis on MACE was therefore performed on 20 trials, enrolling 6,490 and 3,995 patients (3.467 and 2.172 patient* years) in the GLP-1 receptor agonist and comparator groups, respectively. The characteristics of the retrieved trials, and of those which resulted to be complete but were undisclosed, or did not report information on MACE, are summarized in Tables 1, 2, and 3.

The total number of patients with events was 65 (0.01%) and 49 (0.01%) in the GLP-1 receptor agonists and comparator groups, respectively. Treatment with the experimental drugs was not associated with an increased incidence of MACE (MH-OR 0.74 (0.50–1.08); P = .12). A significant reduction of cardiovascular events with GLP-1 receptor agonists was observed in placebo-controlled trials but not in studies versus active comparators (Figure 2). No consistent pattern suggesting differences between exenatide and liraglutide emerged across analyses. In comparisons with insulin (5 trials with events) and sulfonylureas (4 trials with events), the MH-OR for GLP-1 receptor agonists was 1.77 (0.91–3.44), P = .09, and 0.49 (0.22–1.10), P = .085, respectively.

All-cause mortality was reported in 33 trials, 9 of which with at least one event (8 and 7) in GLP-1 receptor agonists and comparator, respectively; MH-OR for experimental drugs was 0.67 [0.26–1.78], P = .43.

### 4. Conclusions

The reduction of cardiovascular morbidity and mortality is one of the main aims of long-term treatment of hyperglycemia in type 2 diabetes. Therefore, the possibility of an increased cardiovascular risk associated with some hypoglycemic treatments [1, 3–7] is almost paradoxical. Although some data on adverse cardiovascular effects of specific drugs were not confirmed by subsequent investigations [8–11], the concerns of health authorities about the safety of new compounds appear to be justified (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071627.pdf).
| Study (ref.)                          | Number of patients (ID/C) | Trial duration (wks) | Age (ys) | Duration of DM (ys) | HbA1c/FPG baseline (%/mmol/L) | BMI baseline (Kg/m²) | MACE (n,ID/C) | All-cause mortality (n,ID/C) | Cardiovas. mortality (n,ID/C) |
|--------------------------------------|---------------------------|---------------------|----------|-------------------|-------------------------------|----------------------|--------------|-------------------------------|------------------------------|
| **Albiglutide versus placebo**       |                           |                     |          |                   |                               |                      |              |                               |                              |
| Rosenstock et al. [19]               | 128/50                    | 16                  | 54       | 5                 | 8.0/9.7                       | 32.0                 | 0/3          | NR/NR                         | NR/NR                        |
| **Exenatide versus placebo**         |                           |                     |          |                   |                               |                      |              |                               |                              |
| Gill et al. [20]                     | 27/25                     | 12                  | 55       | NR                | 7.3/NR                        | NR                   | 0/0          | 0/0                           | 0/0                          |
| Kadowaki et al. [21]                 | 115/40                    | 12                  | 59       | 11                | 8.0/9.1                       | 25.9                 | 0/0          | 0/0                           | 0/0                          |
| Zinman et al. [22]                   | 121/112                   | 16                  | 56       | 8                 | 7.9/8.9                       | 34.0                 | 0/0          | 0/0                           | 0/0                          |
| Gao et al. [23]                      | 234/232                   | 16                  | 55       | 8                 | 8.3/9.3                       | 26.2                 | 0/1          | 0/0                           | 0/0                          |
| DeFronzo et al. [24]                 | 47/45                     | 20                  | 56       | NR                | 7.9/NR                        | NR                   | 0/0          | 0/0                           | 0/0                          |
| Apovian et al. [25]                  | 96/98                     | 24                  | 55       | 5                 | 7.6/8.6                       | 33.7                 | 0/0          | 0/0                           | 0/0                          |
| Moretto et al. [26]                  | 155/77                    | 24                  | 54       | 1                 | 7.8/8.7                       | 31.5                 | 0/0          | 0/0                           | 0/0                          |
| Liutkus et al. [27]                  | 111/54                    | 26                  | 54       | 6                 | 8.2/9.1                       | 33.5                 | 0/0          | 0/0                           | 0/0                          |
| DeFronzo et al. [28]                 | 223/113                   | 30                  | 53       | 6                 | 8.2/9.4                       | 34.0                 | 1/2          | 0/0                           | 0/0                          |
| Buse et al. [29]                     | 248/123                   | 30                  | 55       | 6                 | 8.6/10.3                      | 33.5                 | 1/2          | 0/0                           | 0/0                          |
| Kendall et al. [30]                  | 486/247                   | 30                  | 55       | 9                 | 8.5/9.9                       | 34.0                 | 7/6          | 0/1                           | 0/1                          |
| **Exenatide versus rosiglitazone**   |                           |                     |          |                   |                               |                      |              |                               |                              |
| DeFronzo et al. [24]                 | 45/45                     | 20                  | 56       | NR                | 7.9/NR                        | NR                   | 0/0          | 0/0                           | 0/0                          |
| **Exenatide versus glibenclamide**   |                           |                     |          |                   |                               |                      |              |                               |                              |
| Derosa et al. [31]                   | 63/65                     | 52                  | 56       | NR                | 8.8/7.9                       | 28.6                 | NR/NR        | 0/0                           | 0/0                          |
| **Exenatide versus BiAsp 30/70**     |                           |                     |          |                   |                               |                      |              |                               |                              |
| Bergenstal et al. [32]               | 124/248                   | 24                  | 52       | NR                | 10.1/11.4                     | 33.8                 | NR/NR        | 0/1                           | 0/1                          |
| Nauck et al. [33]                    | 253/248                   | 52                  | 58       | 10                | 8.6/11.1                      | 30.4                 | 10/5         | 2/1                           | 1/1                          |
| **Exenatide versus glargine**        |                           |                     |          |                   |                               |                      |              |                               |                              |
| Barnett et al. [34]                  | 138/138                   | 16                  | 55       | 7                 | 8.9/12.0                      | 31.3                 | 0/0          | 0/0                           | 0/0                          |
| NCT00360334 [35]                     | 118/116                   | 26                  | 56       | NR                | 8.6/10.8                      | 34.1                 | 2/2          | NR/NR                         | NR/NR                        |
| Heine et al. [36]                    | 282/267                   | 26                  | 59       | 9                 | 8.2/10.2                      | 31.3                 | 5/3          | 0/0                           | 0/0                          |
| Bunck et al. [37]                    | 36/33                     | 52                  | 58       | 5                 | 7.5/9.1                       | 30.6                 | NR/NR        | NR/NR                         | NR/NR                        |
| Diamant et al. [38]                  | 233/232                   | 26                  | 58       | 8                 | 8.3/9.8                       | 32.0                 | 1/0          | 0/0                           | 0/0                          |
| **Exenatide versus insulin**         |                           |                     |          |                   |                               |                      |              |                               |                              |
| Davis et al. [39]                    | 33/16                     | 16                  | 53       | 11                | 8.1/8.7                       | 34.0                 | 1/0          | 0/0                           | 0/0                          |
| **Exenatide LAR versus placebo**     |                           |                     |          |                   |                               |                      |              |                               |                              |
| Kim et al. [40]                      | 30/14                     | 15                  | 53       | 4                 | 8.4/10.7                      | 36.0                 | 0/0          | 0/0                           | 0/0                          |
| **Exenatide LAR versus pioglitazone** |                           |                     |          |                   |                               |                      |              |                               |                              |
| Bergenstal et al. [41]               | 160/165                   | 26                  | 52       | 6                 | 8.5/9.1                       | 32.0                 | 0/3          | 0/0                           | 0/0                          |
| **Exenatide LAR versus sitagliptin** |                           |                     |          |                   |                               |                      |              |                               |                              |
| Bergenstal et al. [41]               | 160/166                   | 26                  | 52       | 6                 | 8.5/9.1                       | 32.0                 | 0/1          | 0/1                           | 0/0                          |
| **Liraglutide versus placebo**       |                           |                     |          |                   |                               |                      |              |                               |                              |
| Madsbad et al. [42]                  | 135/29                    | 12                  | 57       | 4                 | 7.5/NR                        | 30.4                 | 0/0          | 0/0                           | 0/0                          |
| Vilabell [43]                        | 123/40                    | 14                  | 56       | 4                 | 8.3/11.8                      | 30.1                 | 0/0          | 0/0                           | 0/0                          |
| Seino et al. [44]                    | 180/46                    | 14                  | 57       | 8                 | 8.3/NR                        | 23.9                 | 0/0          | 0/0                           | 0/0                          |
| Kaku et al. [45]                     | 176/88                    | 24                  | 60       | 10                | 8.4/NR                        | 24.9                 | 1/1          | 0/0                           | 0/0                          |
| Russell-Jones et al. [46]            | 232/115                   | 26                  | 57       | 9                 | 8.3/9.2                       | 30.6                 | 5/1          | 1/2                           | 0/2                          |
In order to reach definitive conclusions on cardiovascular safety of any drug, large-scale, long-term trials should be performed prior to marketing; unfortunately, this effort would be economically unfeasible for pharmaceutical companies. The FDA accepted a compromise, allowing the organization of such trials after drug approval, as a condition for the maintenance of marketing authorization. The limit of this approach is that cardiovascular safety of new drugs will be established only several years after their approval, leaving clinicians without reliable information on this critical point in the meantime.

Meta-analyses of cardiovascular events recorded as adverse events in randomized clinical trials designed for other purposes can represent an additional source of information. This approach has several limitations, most notably the lack of predefined diagnostic criteria and screening methods for incident cardiovascular disease, with the risk of misdiagnosis and underdiagnosis. It should also be recognized that in some of the trials included, cardiovascular events were reported only as adverse events, without being prospectively adjudicated. Moreover, the limited duration of trials designed for metabolic purposes can impair their ability to detect longer-term effects on atherogenesis. Furthermore, the meta-analysis of small trials with few events each poses some specific, and complex, statistical problems [17]. All these limitations affected the reliability of results of some meta-analyses [6, 7] on cardiovascular safety of hypoglycemic drugs [10, 17, 18].

Those considerations should be taken into account when interpreting the results of the present meta-analysis, which exclude, at least in the short term, any major adverse effect of GLP-1 receptor agonists on cardiovascular morbidity. Interestingly, those drugs, as a class, are below to the 1.3 threshold chosen by the FDA for the upper limit of 95% confidence interval to establish the cardiovascular safety of a new drug.

Interestingly, a significant reduction of cardiovascular morbidity with GLP-1 receptor agonists was observed in comparison with placebo. This result should be discussed with great caution, considering the limitations highlighted above; in fact, a meta-analysis of trials performed for different (noncardiovascular) endpoints provides reliable information on safety, but not on efficacy. Speculatively, several mechanisms could underlie a beneficial effect of GLP-1 receptor agonists on cardiovascular risk. Reduction of blood glucose, body weight, and blood pressure, as well as favorable effects on lipid profile, have all been reported. Direct myocardial effects of GLP-1 receptor stimulation could theoretically reduce the functional impact of myocardial ischemia [13], leading to clinical improvements. However, the possibility of a beneficial action of GLP-1 receptor agonists on cardiovascular events should be confirmed through specifically designed randomized clinical trials.

### Table 3: Continued.

| Study (ref.) | Number of patients (ID/C) | Trial duration (wks) | Age (ys) | Duration of DM (ys) | HbA1c/FPG baseline (%/mmol/L) | BMI baseline (Kg/m²) | MACE (n,ID/C) | All-cause mortality (n,ID/C) | Cardiovasc. mortality (n,ID/C) |
|-------------|---------------------------|----------------------|----------|---------------------|-----------------------------|---------------------|--------------|-----------------------------|-----------------------------|
| Zinman et al. [47] | 355/175 | 26 | 55 | 9 | 8.5/10.1 | 33.7 | 1/0 | 0/0 | 0/0 |
| Marre et al. [48] | 695/114 | 26 | 56 | 6 | 8.4/9.7 | 29.7 | 3/2 | 0/0 | 0/0 |
| Nauck et al. [49] | 724/121 | 26 | 57 | 7 | 8.4/10.0 | 31.2 | 6/0 | 1/0 | 0/0 |
| **Liraglutide versus metformin** | | | | | | | | | |
| Feinglos et al. [50] | 176/34 | 12 | 53 | 5 | 7.0/NR | 34.5 | 0/0 | 0/0 | 0/0 |
| **Liraglutide versus rosiglitazone** | | | | | | | | | |
| Marre et al. [48] | 695/232 | 26 | 56 | 6 | 8.4/9.7 | 29.7 | 3/0 | 0/0 | 0/0 |
| **Liraglutide versus glimepiride** | | | | | | | | | |
| Madsbad et al. [42] | 135/26 | 12 | 57 | 4 | 7.5/NR | 30.4 | 0/0 | 0/0 | 0/0 |
| NCT00614120 [35] | 698/231 | 16 | 53 | 7 | NR/NR | 25.5 | 3/2 | 0/0 | 0/0 |
| Nauck et al. [49] | 724/121 | 26 | 57 | 7 | 8.4/10.0 | 31.2 | 6/2 | 1/0 | 0/0 |
| Garber et al. [51] | 498/248 | 52 | 53 | 5 | 8.3/9.4 | 33.0 | 2/2 | 0/1 | 0/0 |
| **Liraglutide versus glimepiride** | | | | | | | | | |
| NCT00393718 [35] | 268/132 | 24 | 58 | 8 | 8.3/NR | 24.8 | 4/3 | 1/0 | 0/0 |
| **Liraglutide versus sitagliptin** | | | | | | | | | |
| Pratley et al. [52] | 446/219 | 26 | 55 | 6 | 8.4/10.0 | 32.8 | 1/1 | 1/1 | 0/1 |
| **Liraglutide versus glargine** | | | | | | | | | |
| Russell-Jones et al. [46] | 232/234 | 26 | 57 | 9 | 8.3/9.2 | 30.6 | 5/1 | 1/1 | 0/1 |

*Studies with multiple comparators; DM: diabetes mellitus; FPG: fasting plasma glucose; MACE: major cardiovascular events; cardiovasc.: cardiovascular; NR: not reported.*
In conclusion, GLP-1 receptor agonists do not appear to increase cardiovascular morbidity in comparison with placebo or other active drugs. Any possible beneficial action should be assessed in further trials.

**Author Contributions**

M. Monami organized the collection of clinical data, prepared and revised the paper, and performed data analysis. F. Cremasco collected clinical data and assisted in study design and data analysis. C. Lamanna collected clinical data and revised the paper. C. Colombi collected clinical data and assisted in study design. S. Zannoni collected clinical data. I. Iacomelli collected clinical data N. Marchionni reviewed/edited the paper. E. Mannucci designed the study, prepared and revised the paper, and took part in data analysis.

**Conflict of Interests**

The corresponding author confirms that he had full access to all the data in the study and had final responsibility for the decision to submit for publication. M. Monami has received speaking fees from Eli Lilly and Sanofi-Aventis. F. Cremasco is currently employed by Eli Lilly. N. Marchionni has received speaking fees from Eli Lilly, Novo Nordisk, and Sanofi-Aventis, and research grants from Eli Lilly, Novo Nordisk, and Sanofi-Aventis. E. Mannucci has received consultancy fees from Eli Lilly and Novo Nordisk, speaking fees from Eli Lilly, Novo Nordisk, and Sanofi-Aventis, and research grants from Eli Lilly, Novo Nordisk, and Sanofi-Aventis.

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