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Effects of GLP-1 Agonists on mortality and arrhythmias in patients with Type II diabetes

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ABSTRACT

Background: Glucagon-like Peptide-1 Receptor Agonists (GLP-1 RA) are frequently used for the management of diabetes. The impact of GLP-1 RA on cardiovascular outcomes is unclear. We aim to assess the effect of GLP-1 RA on mortality, atrial and ventricular arrhythmias, and sudden cardiac death in patients with type II diabetes.

Methods: We searched databases including Ovid MEDLINE, EMBASE, Scopus, Web of Science, Google Scholar and CINAHL, from inception to May 2022, for randomized controlled trials reporting the relationship between GLP-1 RA (including albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, and semaglutide) and mortality, atrial arrhythmias, and the combined incidence of ventricular arrhythmias and sudden cardiac death. The search was not restricted to time or publication status.

Results: A total of 464 studies resulted from literature search, of which 44 studies, including 78,702 patients (41,800 GLP-1 agonists vs 36,902 control), were included. Follow up ranged from 52 to 208 weeks. GLP-1 RA were associated with lower risk of all-cause mortality (odds ratio 0.891, 95% confidence interval 0.837–0.949; P < 0.01) and reduced cardiovascular mortality (odds ratio 0.88, 95% confidence interval 0.881–0.954; P < 0.01). GLP-1 RA were not associated with increased risk of atrial (odds ratio 0.963, 95% confidence interval 0.869–1.066; P 0.46) or ventricular arrhythmias and sudden cardiac death (odds ratio 0.895, 95% confidence interval 0.706–1.135; P 0.36).

Conclusion: GLP-1 RA are associated with decreased all-cause and cardiovascular mortality, and no increased risk of atrial and ventricular arrhythmias and sudden cardiac death.

1. Introduction

Type II Diabetes Mellitus (DM2) is a global disease with a continuously growing incidence and prevalence. Those affected are at higher risk for morbidity and mortality as compared to the general population, with complications affecting a broad range of organ systems. [1] With regard to cardiovascular health, DM2 is an important risk factor for diastolic dysfunction, coronary artery disease, and arrhythmic events. Myocardial infarction is the leading cause of premature death in patients with DM2. [2] DM2 has also been associated with development of atrial fibrillation (AF) and thromboembolic events. [1,2] Therefore, prevention of cardiovascular complications and reduction of cardiovascular events should be a primary goal in the management of DM2.

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have been shown to reduce the risk of heart failure hospitalization, cardiovascular death, and all-cause mortality in heart failure patients with either reduced ejection fraction (EF) or preserved EF, independent of the presence of DM2. [3–5].

These findings have led to interest regarding whether other classes of medications used in DM2 may be associated with similar reductions in cardiovascular outcomes. Glucagon-like Peptide-1 Receptor Agonists (GLP-1 RAs) have been associated with improvement in patients' lipid profiles, making this class of agents a promising avenue for further investigation. [6] However, GLP-1 RAs have been associated with increase in patient heart rate, eliciting concern for arrhythmias. [6,17,18] Studies assessing for improvement in cardiovascular outcomes have also been limited to small trials with few clinical events. [7] The goal of this meta-analysis and systematic review was to synthesize the data regarding the association of GLP-1 RAs with all-cause mortality, cardiovascular mortality, sudden cardiac death, and atrial and ventricular

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arrhythmias in patients with DM2.

2. Methods

2.1. Data search

This systematic review and meta-analysis was performed with a protocol in accordance with the Preferred Reporting of Items for Systematic reviews and Meta-Analyses (PRISMA) statement. Searches were conducted in May 2022 using the following databases: Embase, Ovid Medline, CINAHL, Cochrane Central Register of Controlled Trials, Web of Science: Science Citation Index Expanded, Latin American and Caribbean Health Sciences Literature (LILACS), and Google Scholar. Rayyan systematic review software was used as screening tool aid after removal of duplicates. [8].

2.2. Study selection

Studies were selected using the PICO (patient/population, intervention, comparison and outcomes) format to include those that studied patients with DM2 (Population), comparing those on one of GLP-1 Ras: Dulaglutide (Trulicity), Exenatide extended release (Bydureon), Exenatide (Byetta), Semaglutide (Ozempic), Semaglutide (Rybelsus), Liraglutide (Victoza), or Lixisenatide (Adlyxin) (Intervention) to patients not on GLP-1 RAs (Comparison), and assessing for all-cause mortality, cardiovascular mortality, and composite endpoint of ventricular and atrial arrhythmias and sudden cardiac death (Outcomes). Two investigators (MA and FA) independently screened titles and abstracts using the following search words:

Keywords: "Dulaglutide", "Trulicity", "Exenatide", "Bydureon", "Byetta", "Semaglutide", "Ozempic", "Rybelsus", "Liraglutide", Victoza", "Lixisenatide", "Adlyxin", "Diabetes", "randomized controlled trail". The inclusion criteria was randomized controlled trials comparing GLP-1 RA medications and reporting one or more of the following outcomes: all-cause mortality, cardiovascular mortality, ventricular and atrial arrhythmias, and sudden cardiac death. Ventricular arrhythmias included: non-sustained ventricular tachycardia, sustained ventricular tachycardia, or ventricular fibrillation. Atrial arrhythmias included atrial tachycardia, atrial flutter, and atrial fibrillation. We excluded review articles, case reports, case series, non-randomized controlled trials, systematic reviews, letters to editors, abstracts, and publication in languages other than English. Any discrepancy was resolved by the author

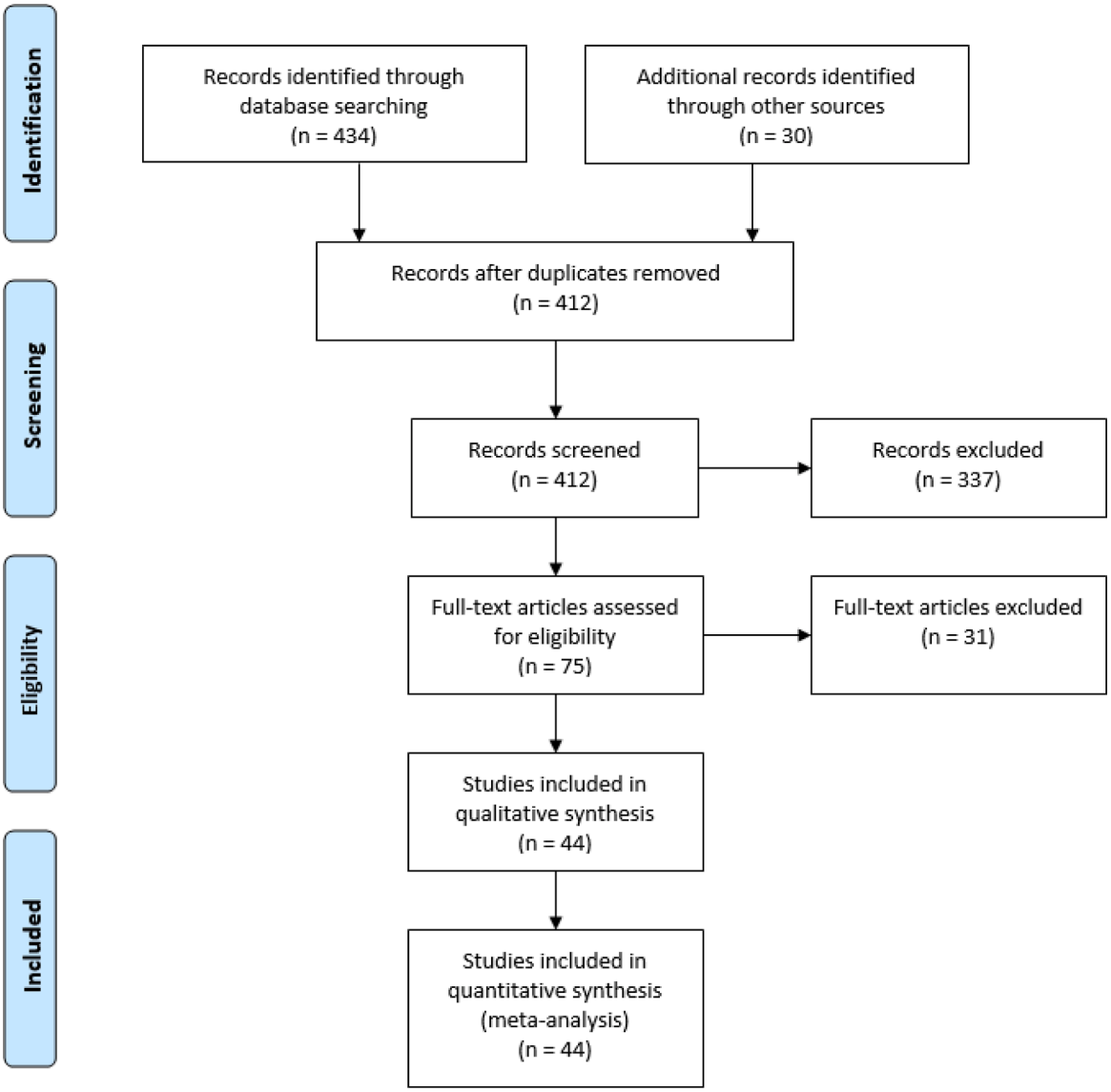

Fig. 1. PRISMA Flow Chart. Flow diagram depicts study selection for inclusion in the meta-analysis according to the PRISMA statement for reporting systematic reviews and meta-analyses.

(MT). The numbers of participants, year of publication, odd ratio (OR) were collected for included studies.

2.3. Statistical analysis

Meta-analysis was performed using Comprehensive Meta-Analysis software, version 3. [9] A random-effects model was used to examine the association between GLP-1 RA and outcomes, which were presented an odd ratio (OR) with upper and lower limits and Z-value. The extent of heterogeneity was determined by I2 (ranging from 0% to 100%). Statistical significance was considered with a *P*-value < 0.05 and all tests were 2-sided. The included trials were assessed using Cochrane risk-of-bias tool for randomized trials (RoB 2).

3. Results

3.1. Literature search and study selection

The first stage of the search identified 464 eligible studies. The process of study inclusion is described in detail in (Fig. 1). 44 studies including 78,702 patients were included in the final analysis. Follow up ranged from 52 to 208 weeks.

3.2. Study, Patient, and procedural characteristics

41,800 patients in GLP-1 RA group and 36,902 patients in control group were included with a mean follow up of 21 months (12–48 months). Table 1 summarizes the basic characteristics of the included studies. The studies did not stratify the results based on age, sex or race.

3.3. Association between GLP-1 RA and all-cause mortality

GLP-1 RA therapy in patients with DM2 was associated with lower all-cause mortality (odds ratio 0.891, 95% confidence interval 0.837–0.949; P < 0.01). Heterogeneity was low: df = 37 (P 0.697), I2 = 0; Test for overall effect: Z = -3.61 (P < 0.001). (Fig. 2).

3.4. Association between GLP-1 RA and cardiovascular mortality

GLP-1 RA therapy in patients with DM2 was associated with lower cardiovascular mortality (odds ratio 0.88, 95% confidence interval 0.881–0.954; P < 0.01). Heterogeneity was low: df = 21 (P 0.776), I2 = 0; Test for overall effect: Z = -3.11 (P = 0.002). (Fig. 3).

Table 1
Demographic data of the included studies: GLP-1 RA: Glucagon-like Peptide-1 Receptor Agonists; **meds**: diabetes mellitus medications other than GLP-1 RA.

Name	Year	GLP-1 RA	Control	Duration (weeks)	Number in GLP-1 RA group	Number in Control group
HARMONY 1 [23]	2014	albiglutide	Placebo	156	150	151
HARMONY 2 [24]	2015	albiglutide	Placebo	52	200	101
HARMONY 3 [25]	2014	albiglutide	placebo/meds	104	302	710
HARMONY 4 [26]	2014	albiglutide	glargine	52	504	241
HARMONY 5 [27]	2015	albiglutide	Placebo	52	271	115
Harmony Outcomes [28]	2018	albiglutide	Placebo	83	4731	4732
Leiter [29]	2014	albiglutide	sitagliptin	52	249	246
AWARD-2 [30]	2015	dulaglutide	glargine	78	275	262
AWARD-3 [31]	2014	dulaglutide	metformin	52	269	268
AWARD-4 [32]	2015	dulaglutide	glargine	52	588	296
AWARD-5 [33]	2015	dulaglutide	sitagliptin	104	606	177
AWARD-7 [34]	2018	dulaglutide	glargine	52	382	194
AWARD-10 [35]	2018	dulaglutide	Placebo	24	272	137
REWIND [36]	2019	dulaglutide	Placebo	281	4949	4952
Miyagawa [37]	2015	dulaglutide	Placebo	52	281	70
DURATION-3 [38]	2014	exenatide	glargine	156	233	234
DURATION-7 [39]	2018	exenatide	Placebo	28	231	230
DURATION-8 [40]	2018	exenatide	Placebo	52	231	233
EXSCEL [41]	2017	exenatide	Placebo	166	7356	7396
Derosa [42]	2011	exenatide	glimepiride	52	490	487
Gallwitz [43]	2011	exenatide	glimepiride	208	22	24
Inagaki [44]	2012	exenatide	glargine	52	215	212
Jaiswal [45]	2015	exenatide	glargine	78	19	24
Nauck [46]	2007	exenatide	Insulin	52	253	248
ELEGANT [47]	2014	liraglutide	glargine	52	26	24
LEAD-2 [48]	2009	liraglutide	Placebo	104	482	363
LEAD-3 [49]	2008	liraglutide	glimepiride	104	498	248
LEADER [50]	2016	liraglutide	Placebo	198	4668	4672
Lira-1 [51]	2016	liraglutide	Placebo	24	50	50
SCALE Diabetes [52]	2015	liraglutide	Placebo	56	211	212
Pratley [53]	2011	liraglutide	sitagliptin	52	439	219
ELIXA [54]	2015	lixisenatide	placebo	109	3034	3034
PIONEER 1 [55]	2019	semaglutide	Placebo	26	350	178
PIONEER 2 [56]	2019	semaglutide	empagliflozin	52	410	409
PIONEER 3 [57]	2019	semaglutide	sitagliptin	78	1397	467
PIONEER 5 [58]	2019	semaglutide	Placebo	26	163	161
PIONEER-6 [59]	2019	semaglutide	Placebo	68	1591	1591
PIONEER 7 [60]	2019	semaglutide	sitagliptin	52	253	250
PIONEER 8 [61]	2019	semaglutide	Placebo	52	362	184
STEP 1 [62]	2021	semaglutide	Placebo	68	1306	655
STEP 4 [63]	2021	semaglutide	Placebo	68	535	268
SUSTAIN 2 [64]	2017	semaglutide	sitagliptin	56	818	407
SUSTAIN 6 [65]	2016	semaglutide	Placebo	109	1648	1649
Kaku [66]	2018	semaglutide	none	56	480	121

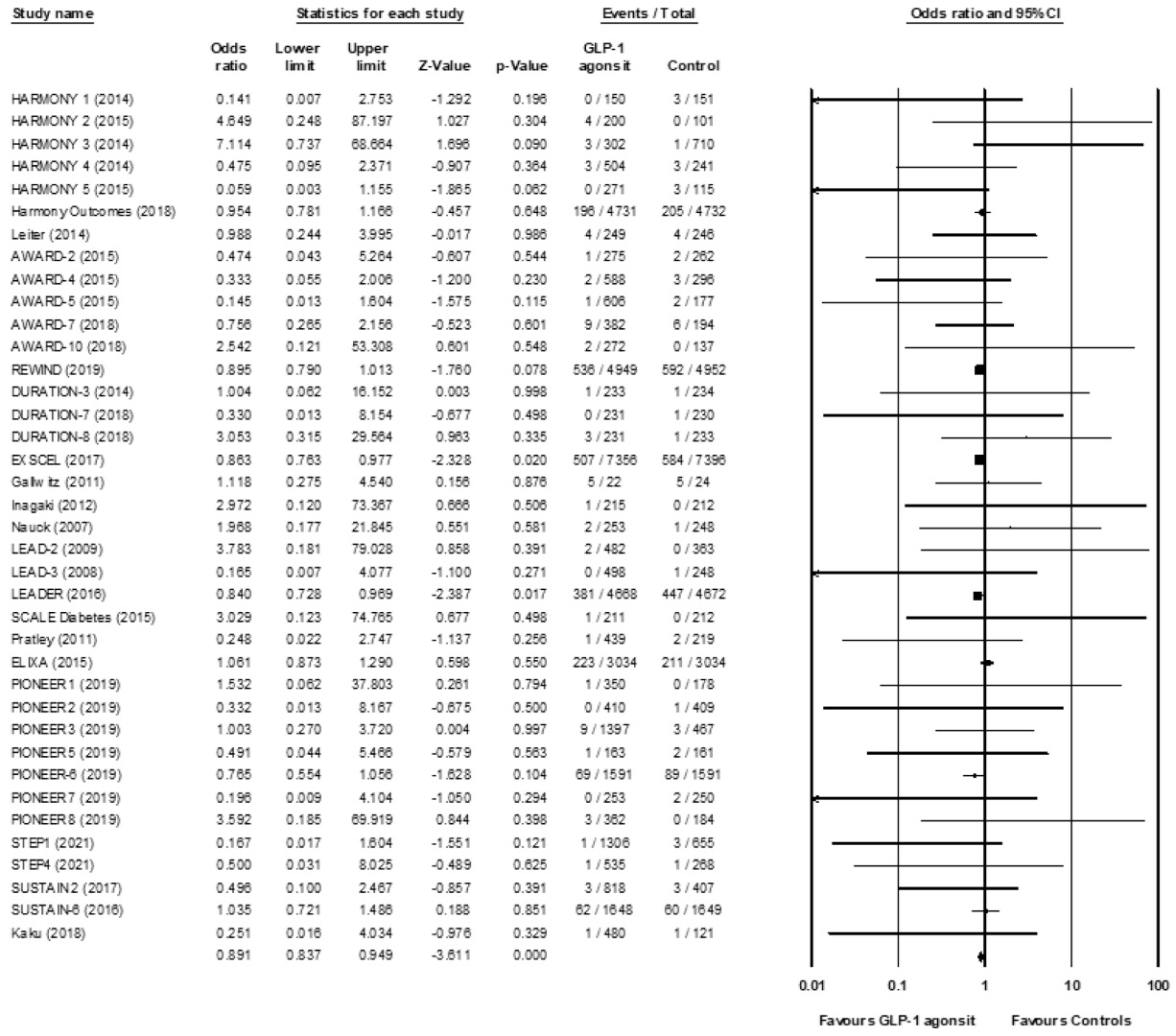

Fig. 2. Forest plot showing Association between GLP-1 RA and all-cause mortality: Using GLP-1 RA therapy in patients with DM2 was associated with lower all-cause mortality (odds ratio 0.891, 95% confidence interval 0.837–0.949; P < 0.01) compared to controls. Heterogeneity is low: df = 37 (P 0.697), I2 = 0; Test for overall effect: Z = -3.61 (P < 0.001).

3.5. Association between GLP-1 RA and composite ventricular arrhythmias and/or sudden cardiac death

GLP-1 RA therapy in patients with DM2 was not associated with increased risk of ventricular arrhythmias and/or sudden cardiac death (odds ratio 0.895, 95% confidence interval 0.706–1.135; P 0.36). Heterogeneity was low: df = 5 (P 0.479), I2 = 0; Test for overall effect: Z = −0.913 (P = 0.36). (Fig. 4).

3.6. Association between GLP-1 RA and atrial arrhythmias

GLP-1 RA therapy in patients with DM2 was not associated with increased risk of atrial arrhythmias (odds ratio 0.963, 95% confidence interval 0.869–1.066; P 0.46). Heterogeneity was low: df = 24 (P 0.72), I2 = 0; Test for overall effect: Z = −0.69 (P = 0.49). (Fig. 5).

4. Discussion

The major findings of this study are two-fold. Firstly, GLP-1 RA therapy was associated with a significant reduction in all-cause mortality and cardiovascular mortality. Secondly, GLP-1 RA use was not associated with increased risk for atrial or ventricular arrhythmias. These findings provide a strong rationale for the use of GLP-1 RA therapy in diabetic patients with the goal of reducing the risk of adverse cardiovascular outcomes.

Patients with DM2 have been shown to be at 35 to 60% higher risk of developing atrial fibrillation, which is subsequently associated with a significant risk for all-cause mortality, cardiovascular death, and development of heart failure [2] Patients with DM2 have been noted to be at three to four times higher risk of mortality compared to the general population. [10] Thus, it is imperative to identify therapeutic agents for the reduction of cardiovascular events. The results of our study demonstrate that GLP-1 RAs may be an effective class of medications for the reduction of all-cause and cardiovascular mortality.

Several different mechanisms of action have been proposed to explain why GLP-1 RA reduce cardiovascular events. One of the theories about the mechanism of which GLP-1 Ras reduces cardiovascular mortality is due to direct and indirect anti-atherosclerotic effects. GLP-1 RAs have been demonstrated to result in modest reductions in blood pressure through a mechanism of action that remains to be further elucidated. In one study, GLP-1 RAs have been reported to result in a 1 mm to 5 mm Hg reduction in blood pressure, which appears to be independent of its effects on weight loss, as the reduction occurs prior to weight reduction. [11] Additionally, GLP-1 RAs have been associated with improvements in lipid profiles and inflammatory markers after extended use. The use of either once weekly or twice-daily exenatide for 30 weeks was associated

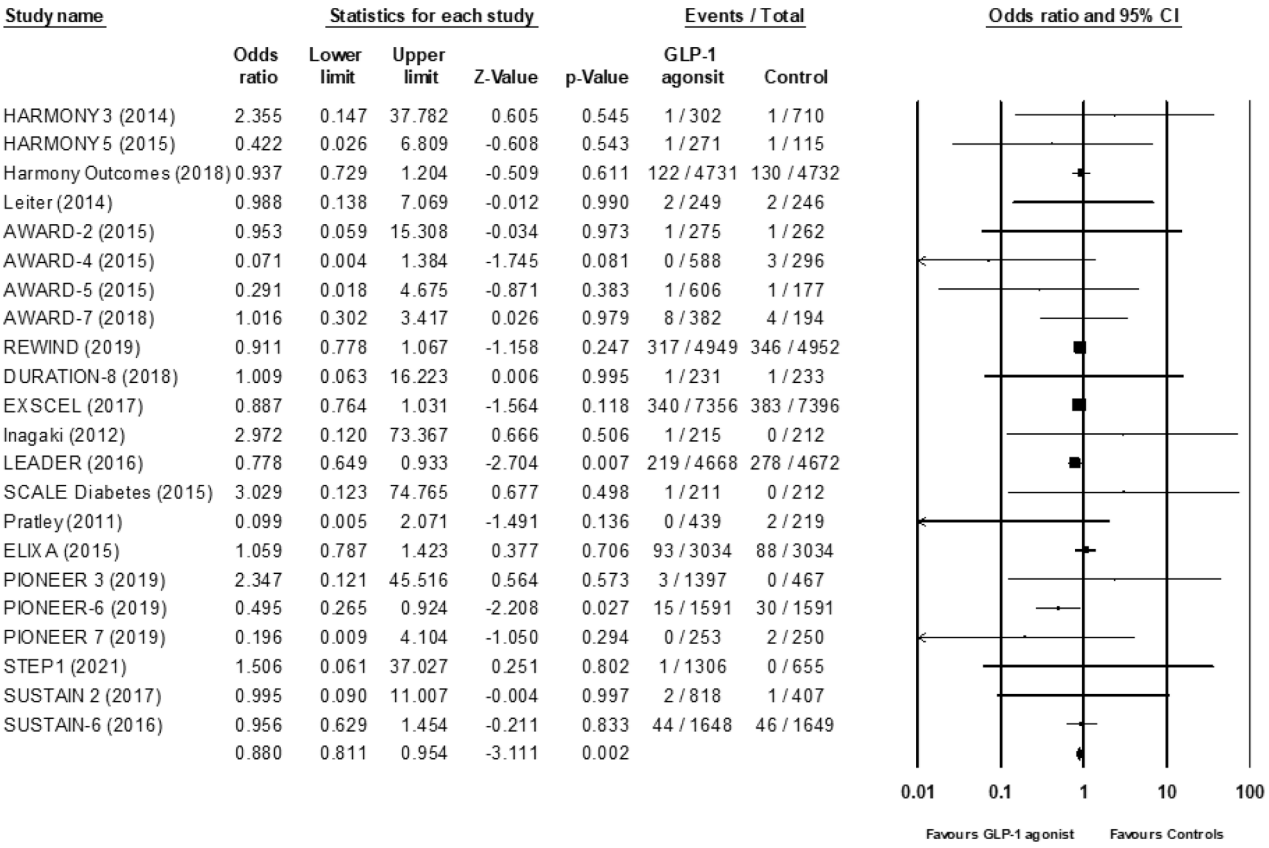

Fig. 3. Forest plot showing Association between GLP-1 RA and cardiovascular mortality: Using GLP-1 RA therapy in patients with DM2 was associated with lower cardiovascular mortality (odds ratio 0.88, 95% confidence interval 0.881–0.954; P < 0.01) compared to controls. Heterogeneity is low: df = 21 (P 0.776), I2 = 0; Test for overall effect: Z = -3.11 (P = 0.002).

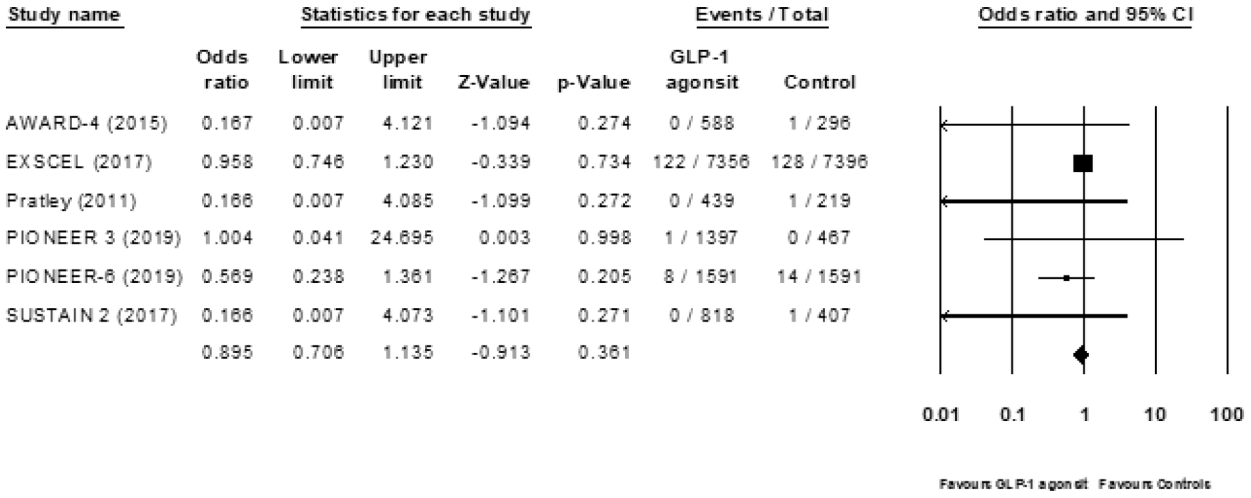

Fig. 4. Forest plot showing Association between GLP-1 RA and ventricular arrhythmias and/or sudden cardiac death: Using GLP-1 RA therapy in patients with DM2 was not associated with increased risk of ventricular arrhythmias and/or sudden cardiac death (odds ratio 0.895, 95% confidence interval 0.706–1.135; P 0.36) compared to controls. Heterogeneity is low: df = 5 (P 0.479), I2 = 0; Test for overall effect: Z = −0.913 (P = 0.36).

with a reduction in apolipoprotein B, high-sensitivity C-reactive protein, low-density lipoprotein, and triglyceride levels. [12] Lastly, GLP-1 RAs have been proposed to have direct beneficial effects on both the endothelium and myocardium. Through direct action on cardiac myocytes along with activation of antioxidant genes, this medication class has been implicated in preventing development of fibrosis, preventing left ventricular remodeling after ischemic injury, and facilitating left ventricular reverse remodeling. [13–15] Similarly, in one study on endothelial function, GLP-1 RAs were shown to improve arterial vasodilation, which may explain their association with modest reductions in blood pressure. [16] Direct anti-atherosclerotic effects is postulated through reduction of inflammatory response, decrease lipid deposition in plaques and plaque stabilization. [67] They are ongoing studies trying to elucidate the effect of GLP-1 RAs on CV outcomes and their mechanism like “A Heart Disease Study of Semaglutide in Patients With Type 2 Diabetes (SOUL)” (NCT03914326).

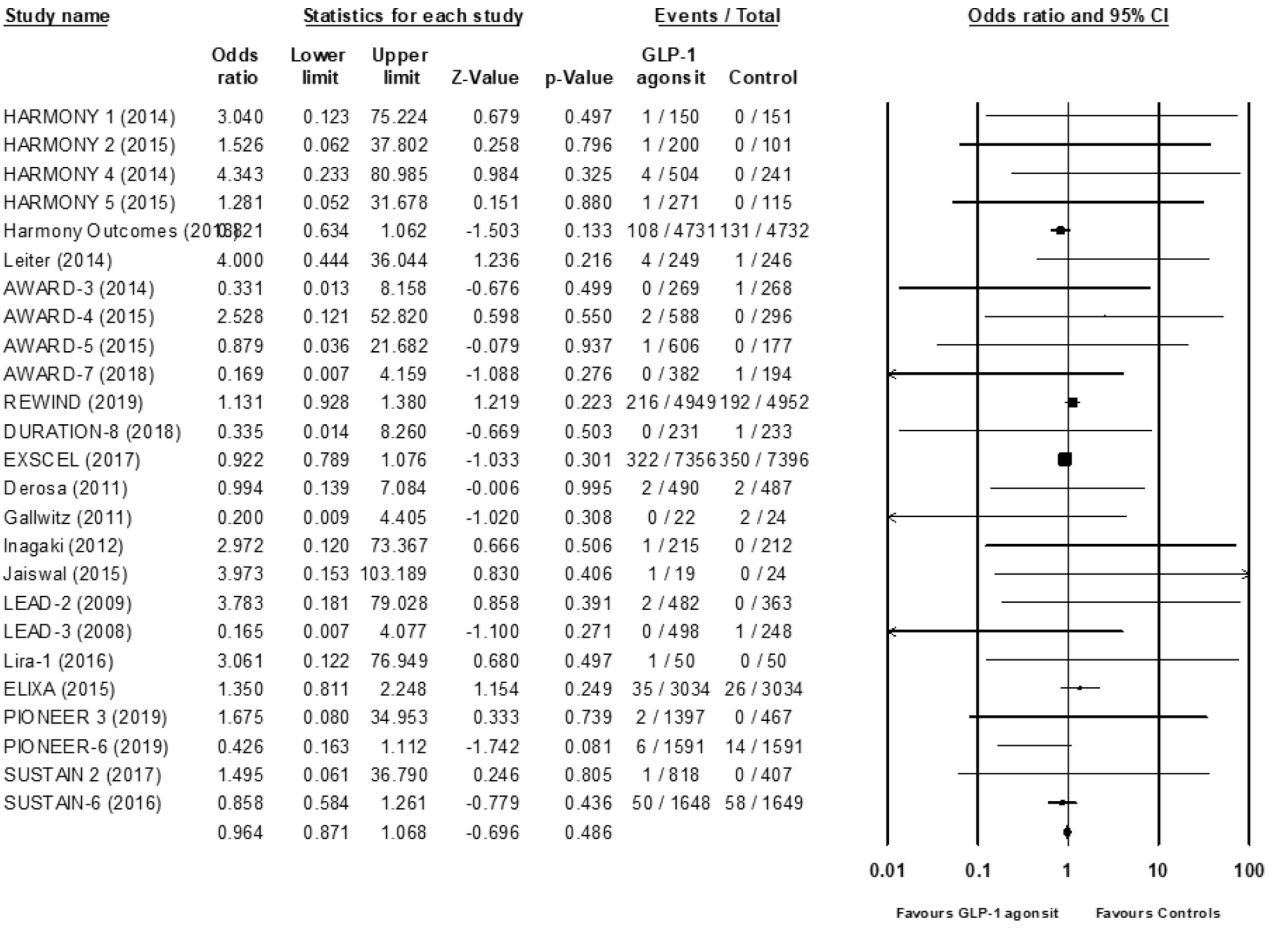

Fig. 5. Forest plot showing Association between GLP-1 RA and atrial arrhythmias: Using GLP-1 RA therapy in patients with DM2 was not associated with increased risk of atrial arrhythmias (odds ratio 0.963, 95% confidence interval 0.869–1.066; P 0.46) compared to controls. Heterogeneity is low: df = 24 (P 0.72), I2 = 0; Test for overall effect: Z = −0.69 (P = 0.49).

There have been multiple studies that have reported an increase in heart rate associated with GLP-1 RA use. [6,17,18] This has been a primary area of concern as this increase in heart rate has been suggested to possibly result from stimulation of the sympathetic nervous system, which places patients at higher risk for the development of arrhythmias and sudden cardiac death. Since patients with DM2 are already at increased risk for the development of arrhythmias, particularly atrial fibrillation, it is important to minimize therapies that will increase this risk. Increased heart rate by itself has been associated with increased risk for major cardiovascular arrhythmias and mortality. [19–21] The combination of atrial fibrillation and DM2 has also been shown to place patients at a 79% higher risk of having thromboembolic events. [2] For these reasons, an important objective of this study was to assess whether GLP-1 RA use was associated with an increased risk for arrhythmic events. Our results provide strong evidence that GLP-1 RAs are not associated with increased risk for atrial or ventricular arrhythmias, or sudden cardiac death.

5. Study limitations

There are some limitations to our current study that need to be taken into consideration. The most important limitation is the fact that GLP-1 RAs come in different doses and frequencies of administration, which was not included as a study selection criteria. Varying dosing schedules and potencies of GLP-1 RAs have been implicated to have differing associations with improvements in cardiovascular outcomes. Several studies have suggested weekly exenatide to be associated with a larger reduction in blood pressure and a more substantial effect on lipid profiles compared to twice-daily exenatide. [22] Similar findings have been reported with 1.8 mg liraglutide dosing as compared to 1.2 mg dosing. [6] Additionally, several studies have suggested that the cardiovascular associations of GLP-1 RAs may not be a class effect, with specifically liraglutide and exenatide being reported as the most effective medications in this class in improving cardiovascular outcomes. [6,11,12] Furthermore, although the results of this meta-analysis suggest that GLP-1 RAs are associated with a lower risk of all-cause mortality and cardiovascular mortality, the underlying mechanism remains to be further elucidated. There is much that remains unknown regarding the interlaced relationship between insulin resistance, glycemic control, and effects on the cardiovascular system.

6. Conclusion

GLP-1 RA therapy in patients with DM2 was associated with decreased all-cause mortality and cardiovascular mortality. Importantly, GLP-1 RA therapy was not associated with increased atrial or ventricular arrhythmias, or sudden cardiac death. These findings provide additional support for practice guidelines that recommend the use of GLP-1 RA therapy in patients with DM2 and cardiac disease.

Funding

None.

Guidelines Statement

The systematic review was conducted with a protocol in accordance with the Preferred Reporting of Items for Systematic reviews and Meta-Analyses (PRISMA) statement.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

None

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