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Research Article

The Cardiovascular Events in Metabolic Surgery Compared to the New Classes of Glucose-Lowering Agents in Patients with T_2DM

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Abstract

Type 2 Diabetes Mellitus is a prevalent chronic disease with several macrovascular and microvascular complications. Cardiovascular diseases including coronary artery disease and stroke are common macrovascular complication that reduces the quality of life and lead to early mortality. Additionally, they pose enormous socioeconomic burden on the societies and the governments. Therefore, any intervention that reduces the cardiovascular events in patients with diabetes will have positive impact of the patients and the society. Thus, this systematic review aimed to evaluate the cardiovascular events after metabolic surgery in comparison with the new classes of glucose lowering agents in patients with type 2 diabetes mellitus.

The review included 11 randomized controlled trials to both GLP-1 RA and SGLT-2 i groups. It also included 7 metabolic surgery studies, 2 of these are randomized controlled trials and the other 5 are observational studies. These studies were the most relevant studies to the research question. The results revealed different baseline demographic and clinical characteristics between the medication trials and metabolic surgery studies. Moreover, it revealed significant reduction in cardiovascular events in metabolic surgery studies when compared to medication trials. It also showed significant HbA1c and weight reduction in the metabolic surgery group. The remission of diabetes was very high in the metabolic surgery group while none of medication trials accomplished diabetes recovery. However, both medication and surgery groups had adverse events.

In conclusion, the review is consistent with previous literature. It suggests that metabolic surgery is more effective than medical therapy in reducing cardiovascular events. Although this conclusion should be interpreted with caution due to the differences in baseline characteristics between studies. In general, the review recommends younger adult diabetic patients with obesity and history of established cardiovascular diseases to undergo metabolic surgery. Whereas, older patients with history of cardiovascular disease should be advised to take one of the medications that has been proved to reduce cardiovascular events. Future

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studies that compare metabolic surgery and the new classes of the glucose lowering agents is recommended to confirm the findings in this review.

Keywords: Cardiovascular events; Diabetes mellitus; Haemoglobin A1c; Glucose level.

Abbreviations: T2DM: Type 2 Diabetes Mellitus; NNT: Number needed to treat; GLP-1 RA: Glucagon like peptide-1 receptor agonist; YODA: Years of drug administration; SGLT-2 i: Sodium-glucose cotransporter-2 inhibitor; BMI Body Mass Index; RCT: Randomized controlled trials; HbA1c: Haemoglobin A1c/ Glycated hemoglobin; eGFR: Estimated Glomerular Filtration Rate; LGB: Laparoscopic gastric banding; CASP: Critical Appraisal Skills Program; VBG: Vertical banded gastroplasty; OR: Odds Ratio; GB: Gastric Bypass; RR: Relative Risk; RYGB: Roux-en-Y Gastric Bypass; HR: Hazard Ratio; SG: Sleeve Gastrectomy; ARR: Absolute risk reduction; DS: Duodenal Switch; RRR: Relative risk reduction; BPD: Biliopancreatic Diversion.

Introduction

Type 2 Diabetes Mellitus (T2DM) is a prevalent chronic non-communicable disease worldwide. The International Diabetes Federation (IDF) estimated that 463 million people were having diabetes mellitus in 2019 and the majority (90%) were having T2DM. IDF is also expecting a steep rise in the prevalence of diabetes over the coming years. The number of patients with diabetes might increase 51% reaching 700 million people with diabetes in 2045 [1]. Cardiovascular events, mainly ischemic heart disease and stroke, are the major macrovascular complications of diabetes. The risk of developing cardiovascular disease increases to more than 5-fold in patients with diabetes when compared to patients without diabetes. These cardiovascular diseases are the major causes of premature death and reduction in quality of life [2].

Moreover, cardiovascular diseases pose a socioeconomic burden on the families, societies and the governments. It was estimated that around £14 billion are spent by the National Health System (NHS) in UK to manage diabetes each year. It is worth noting that most of the financial costs are directed toward treating the chronic complications of the disease. This figure will keep rising with the rise in the disease prevalence [3]. Therefore, preventing the complications, particularly cardiovascular diseases, should be the main focus when treating diabetes mellitus.

Recently, the American Diabetes Association (ADA) and the European Association of the Study of Diabetes (EASD) clearly recommend focusing on providing cardiovascular protection together with providing glycaemic control and weight management while treating any diabetic patient [4]. These recommendations are based on several high quality randomized controlled trials published in 2019. Looking at these trials, the new classes of glucose lowering medications, particularly glucagon-like peptide 1 receptor agonists (GLP-1 RA) and sodium-glucose cotransporter-2 inhibitors (SGLT-2 i) proved to reduce major cardiovascular events in patients with diabetes. The effect of these agents is observed particularly in patients with established cardiovascular diseases [5, 6].

On the other hand, substantial amount of evidence in the literature proved the outstanding benefits of metabolic surgeries in remission of diabetes and weight reduction.

These surgeries previously known as bariatric surgeries were found to change the physiology of the gut to ultimately reduce weight as well as improve the metabolic function [7]. Although it is clear that metabolic surgery has its benefits in treating diabetes and reducing the microvascular and macrovascular complications [8], it is still unclear if the surgery will provide better cardiovascular protection in patients with T2DM when compared to the new classes of glucose lowering agents.

Therefore, the purpose of this systematic review is to compare the effectiveness of the new classes of glucose lowering agents with metabolic surgery in reducing the cardiovascular events in patients with T2DM. Moreover, identifying the patient's characteristics to recommend the suitability of each modality according to evidence to facilitate the adherence of the individualized treatment according to the patient's conditions and providing a holistic patient-centered approach based on informed decision.

Methodology

Data Sources and Searches

The systematic search was conducted in two main medical databases: MEDLINE/PubMed and Cochrane library. The publication date was not set from a specific date; however, the latest date was to April 2020. The purpose of the search is to identify English articles published from January 1, 2000 to April 30, 2020 relevant to the research objective. As far as the author's knowledge, no head-head trials had been conducted to compare the new classes of glucose lowering agents (GLP-1 RA and SGLT-2 i) and metabolic surgery. Therefore, the author considered a narrative synthesis of the available studies as a suitable approach to answer the research question. The comparison between these treatment modalities required three stages to search in each medical database.

The first stage, using the keywords of "glp-1 receptor agonist," "liraglutide," "semaglutide," "dulaglutide" or "exenatide" and "type 2 diabetes" and "cardiovascular diseases," "cardiovascular complications," "cardiovascular outcome," "cardiovascular events," "mortality," "myocardial infarction," "stroke" or "ischemic heart disease (Appendix 1-A). The search in MEDLINE medical database resulted in 109 abstracts and the search in Cochrane library resulted in 142 abstracts.

The second stage, using keywords of "Sodium-Glucose Transporter 2 Inhibitors," "dapagliflozin," "empagliflozin" or "canagliflozin" and "type 2 diabetes" and "cardiovascular diseases," "cardiovascular complications," "cardiovascular outcome," "cardiovascular events," "mortality," "myocardial infarction," "stroke" or "ischemic heart disease (Appendix 1-B). The search in MEDLINE medical database resulted in 73 abstracts and the search in Cochrane library resulted in 55 abstracts.

The third stage, using only "metabolic surgery" or "bariatric surgery" and "type 2 diabetes" as key terms to search for all the surgical relevant articles. Narrowing the search by adding cardiovascular outcomes as a key term in the search was not applicable due to the limited literature found during the scoping stage (Appendix 1-C). The search in

MEDLINE medical database resulted in 425 abstracts and the search in Cochrane library resulted in 75 abstracts.

Study Selection

The search was limited to randomized controlled trials to identify the articles studying the effectiveness of GLP-1 RA and SGLT-2 i in reducing the cardiovascular events in patients with T2DM. Nonetheless, the search for metabolic surgery studies was expanded to include both observational and interventional studies because limited randomized controlled trials were conducted to assess the effectiveness of metabolic surgery in reducing cardiovascular events in patients with T2DM. However, a quality assessment was done using CASP checklist on each study that was included in this review. These studies are either randomized controlled trials of metabolic surgery studying the effectiveness of surgical intervention in remission of diabetes and reducing cardiovascular events or observational studies directly assessing the effectiveness of metabolic surgery in reducing the cardiovascular events (Appendices 2 and 3).

The abstracts were screened to identify relevant studies. The findings were 7 main trials on GLP-1 RA and 4 main trials on SGLT-2 i. On the other hand, the findings related to the metabolic surgery studies were 28 articles in MEDLINE medical database and 3 articles in Cochrane medical database. After reviewing the full-articles, it was found that only 7 articles were relevant to the research question because they included cardiovascular outcomes Figure 1.

Data Extraction

The author extracted data from the original studies using the acronym of the studies for the GLP-1 RA and SGLT-2 I trials. Whereas the authors used the name of the authors and the years of publication to define the metabolic surgery studies. The data extracted were the baseline demographic and clinical characteristics of the study population including age, race, duration of diabetes, history of established cardiovascular disease (history of coronary artery disease, cerebrovascular accidents or peripheral artery disease), mean eGFR, history of heart failure, mean glycated haemoglobin, history of treatment with insulin, degree of obesity (measure by body mass index) an the use of cardioprotective agents (the use of statins, renin angiotensin aldosterone inhibitors and anti-thrombotic agents). Other data such as history of hypertension and dyslipidaemia were not included because it is beyond the scope of this review. Other data extracted were the number of the participants, duration of follow-up, the outcome measures and the adverse events. Although the trials on the new classes of glucose lowering agents were homogenous and were all designed to measure the 3-MACE (the first occurrence of death due to cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke) as the primary outcome, the metabolic surgery studies were heterogenous with different primary and secondary outcomes. Therefore, the author decided to identify 7 outcome measures and include them in the results. These outcome measures were the following:

1. Cardiovascular events,
2. cardiovascular mortality,

3. All-cause mortality,
4. the occurrence of coronary artery disease,
5. the occurrence of cerebrovascular accidents,
6. weight loss and
7. Remission of diabetes/HbA1c reduction.

The data to identify the association between the treatment and outcomes using OR, RR, or HR and 95% confidence interval were extracted. Moreover, this review calculated the absolute risk reduction, relative risk reduction, number needed to treat and years of drug administration as well as the cost of the outcome measures extracted from the medication trials (Appendix 4).

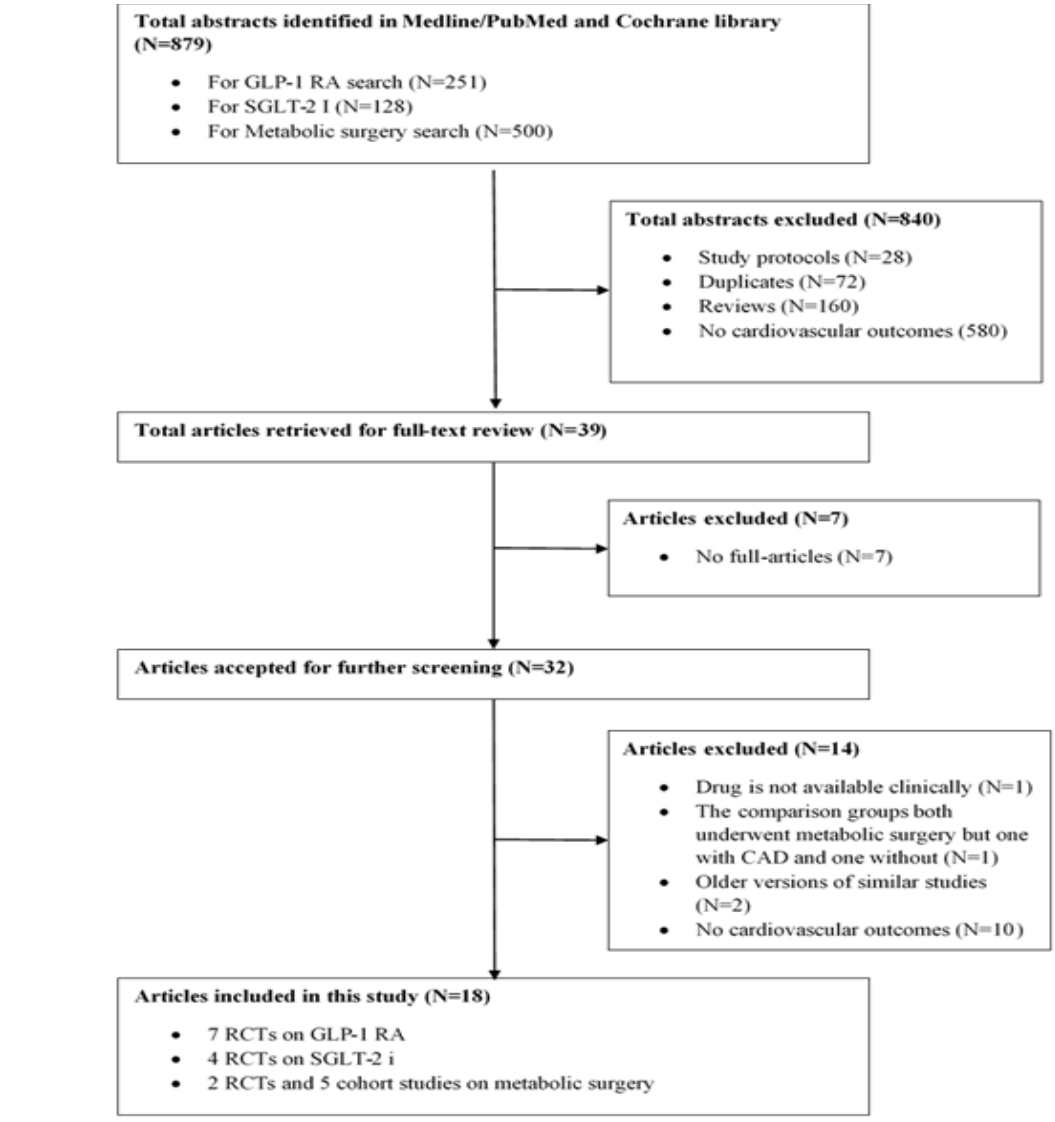

Fig. 1 PRISMA flow diagram

Figure 1: PRISMA flow Diagram.

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Data Synthesis and analysis

The data were synthesized descriptively. Firstly, the baseline characteristics were compared between the two treatment groups: Medications and metabolic surgery groups. Then, the studies were compared according to the treatment effect in reducing the cardiovascular events. Finally, other main outcome measures were analyzed in separate groups to identify the treatment effect of each modality.

Results

Study characteristics

Table 1 provides information about the type of study and the quality of the study. All the randomized controlled trials conducted on both the new classes of glucose lowering agents were of high quality based of CASP checklist (Appendix 2 and 3). On the other hand, the studies on metabolic surgery included two randomized controlled trials of moderate and high quality, one case-control study of low quality, 3 cohort studies of moderate and 1 of high quality. Tables (2,3 and 4) provide a summary of the main baseline demographic and clinical characteristics of the participants of the 18 studies included in this review. Tables (5,6 and 7) shows the findings of the studies included in this review. The sample sizes ranged from 50 to 20,235 participants, and follow-up time ranged from one year and half to 18 years. All studies included both men and women.

No.	Study Name	Type of study	Quality of study
1	**Leader**	RCT	High
2	**Sustain-6**		
3	**Pioneer-6**		
4	**Exscel**		
5	**Rewind**		
6	**Harmony**		
7	**Elixa**		
8	**Empa-Reg**		
9	**DECLARE-TIMI 58**		
10	**Credence**		
11	**Canvas**		
12	**Sjostrom, Peltonen [9]**	Cohort study	Moderate
13	**Fisher, Johnson [10]**	Cohort study	Moderate
14	**Aminian, Zajichek [11]**	Cohort study	High
15	**Mingrone, Panunzi [12]**	RCT	High
16	**Liakopoulos, Franzen [13]**	Cohort study	Moderate
17	**Iaconelli, Panunzi [14]**	Case-control study	Low
18	**Schauer, Bhatt [15]**	RCT	Moderate

Table 1: The type and quality of the studies included in the review.

Figure 2 illustrates a comparison between some of the baseline characteristics of each study population according to the two studied groups (the medications and the metabolic surgery groups).

Firstly, the medications trial included older adults with average age of 63.6-year-old, however, the metabolic surgery studies included younger population with average age of 48.6-year-old. Secondly, the patients who participate in the medication trials had a longer history of diabetes (12.8 years) than the patients who underwent metabolic surgery (5.4 years). Thirdly, the mean eGFR was higher in the metabolic surgery group. Fourthly, the patients who underwent surgery are more obese (BMI=43.61 kg/m2) than the patients who received the new classes of glucose lowering agents (BMI=31.8kg/m^2). Lastly, both groups were having similar mean glycated haemoglobin.

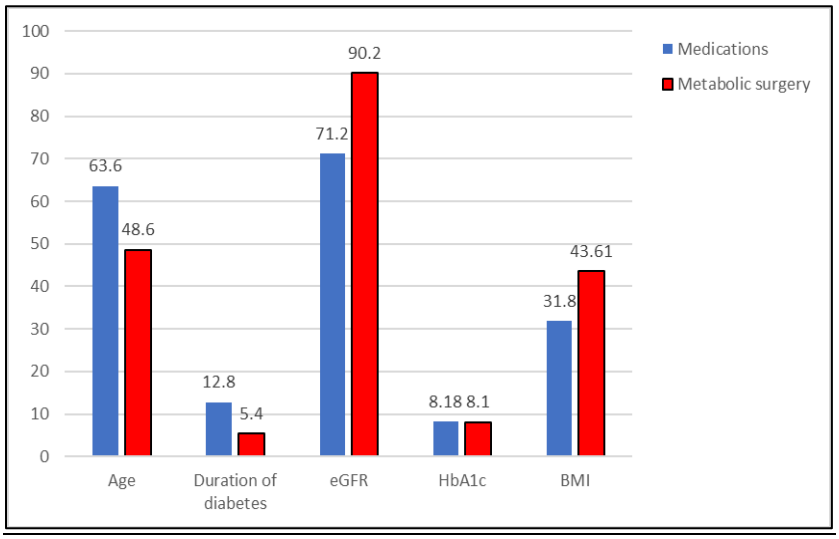

Figure 2: Comparison between the baseline characteristics of the studies involving the new classes of glucose lowering agents and the studies of the metabolic surgery. Age (the average of the mean age of the participants of each study by year). Duration of diabetes (the average of mean diabetes duration of the participants in each study by year). eGFR (the average of the mean estimated GFR of the participants of each study by mL/min/1.73m^2). HbA1c (the average of the mean glycated haemoglobin of the participants of each study by %). BMI (the average of the mean body mass index of the participants of each study by kg/m^2.

Figure 3 demonstrates comparison of other baseline characteristics of the participants involved in the 2 groups (medication and metabolic surgery groups) measured by percentages. The majority of the participants from both groups were of white race. It is noticeable that participants from the medication group are at higher risk to develop cardiovascular events due to the higher percentage of established cardiovascular diseases and heart failure when compared to the metabolic surgery group (69.3 vs. 9.9) and (14.9 vs. 6.5) respectively. However, the use of cardiovascular protective agents including aspirin, ACE inhibitors or ARBs and statins was higher among the medication group.

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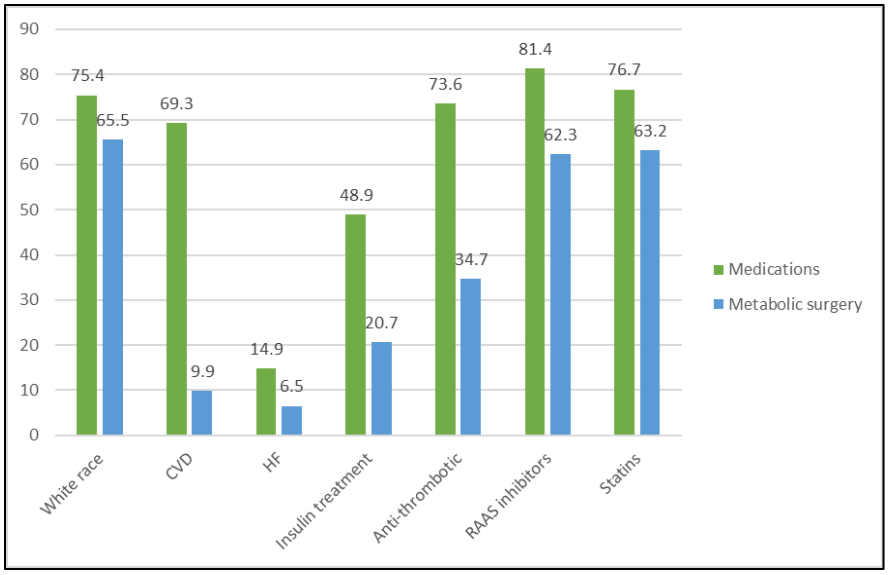

Figure 3: Comparison between other baseline characteristics of the participants of the 2 groups by percentage (%). 1. White race: the average percentage of white race involved in the studies. 2. CVD: the average percentage of participants with history of established cardiovascular diseases involved in the studies. 3. HF: the average percentage of participants with history of heart failure. 4. Insulin treatment: the average percentage of participants using insulin at baseline involved in the studies. 5. Anti-thrombotic: the average percentage of participants on aspirin or other anti-thrombotic agents. 6. RAAS inhibitors: the average percentage of participants on ACE inhibitors or ARBs. 7. Statins: the average percentage of participants on statins.

Cardiovascular Events

The primary composite outcome of all the 11 randomised controlled trials on the new classes of glucose lowering agents demonstrate non-inferiority of these agents in the occurrence of major cardiovascular events in patients with type 2 diabetes when compared to the usual care. However, 6 out of the 11 trials suggested a significant reduction in the number of cardiovascular event rates when compared to usual diabetes carrier.

On the other hand, 4 of the 7 studies on metabolic surgery confirmed significant reduction in cardiovascular events when compared to the medical care. Additionally, the other 3 studies didn't find higher cardiovascular event rate in the metabolic surgery group when compared to the medical care. Nonetheless, the 3 studies could not reach to a conclusion due to either small sample size or the cardiovascular events were identified as adverse events post-surgery, thus, the hazard ratio was not calculated.

Figure 4 is a forest plot illustrating the cardiovascular events' hazard ratios of all the studies included in this review. It is noticeable that the metabolic surgery studies have lower hazard ratios than the medication trials. CREDENCE trial on canagliflozin has the lowest hazard ratio within the medication trials [HR=0.7 and 95% CI (0.59-0.82)]. Whereas Sjostrom, Peltonen has the highest hazard ratios within the metabolic surgery studies [HR=0.68 and 95% CI (0.54-0.85)] [9].

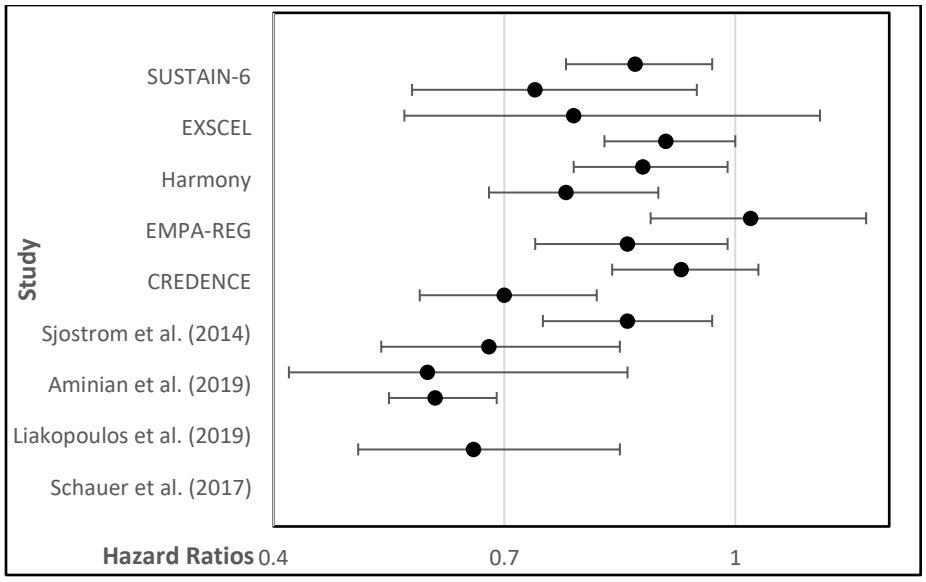

Figure 4: Forest plot of comparing cardiovascular events of all the studies included in the review.

All-cause mortality

LEADER and EMPA-REG outcome trials are the only 2 studies demonstrated significant reduction in all-cause mortality with p value of less than 0.05 among the medication trials. On the other hand, 3 of the 7 metabolic surgeries demonstrated a clear reduction in all-cause mortality when compared to the usual standard care. The other 4 studies could not confirm the reduction in all-cause mortality either because of small sample size or because it was not one of outcome measures. Figure 5 is forest plot of the hazard ratios of all-cause mortality of all the studies included in the review.

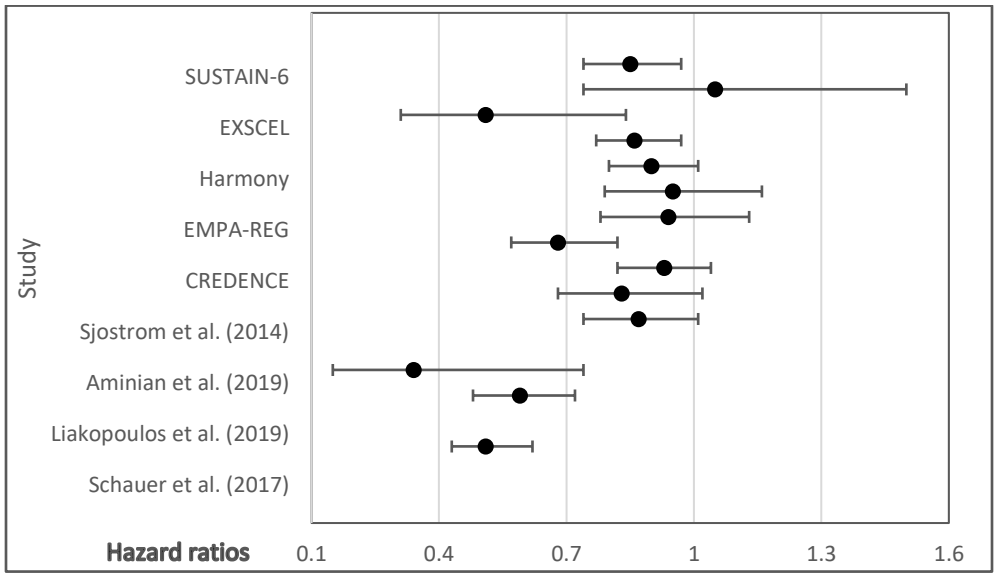

Figure 5: Forest plot all-cause mortality.

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HbA1c reduction/Remission of diabetes

Figure 6 illustrates the difference in HbA1c reduction between the intervention group and control group of each study included in the review. Firstly, the range of reduction in the trials assessing the medications is from (-0.11 to -0.9%). Secondly, none of the trials achieved remission of diabetes because of the continuous use of drugs to manage the disease. On the other hand, the surgery studies revealed a reduction in the glycated haemoglobin ranged from (-0.65 to -3.0%). Moreover, figure 7 illustrates high percentage of diabetes remission in the metabolic surgery group. Iaconelli, Panunzi found that all the patients who underwent metabolic surgery had normal blood glucose readings without glucose lowering agents [14]. However, the blood glucose level of 45% of the patients in the control group normalised without medications.

Mingrone, Panunzi and Schauer, Bhatt demonstrated diabetes remission in 50% and 18.6% respectively in the metabolic surgery group compared to none in the medical group [12,15]. Finally, Sjostrom, Peltonen revealed remission of diabetes in 38.1% in the metabolic surgery group compared to remission of diabetes in 10.4% of patients in the medical group [9].

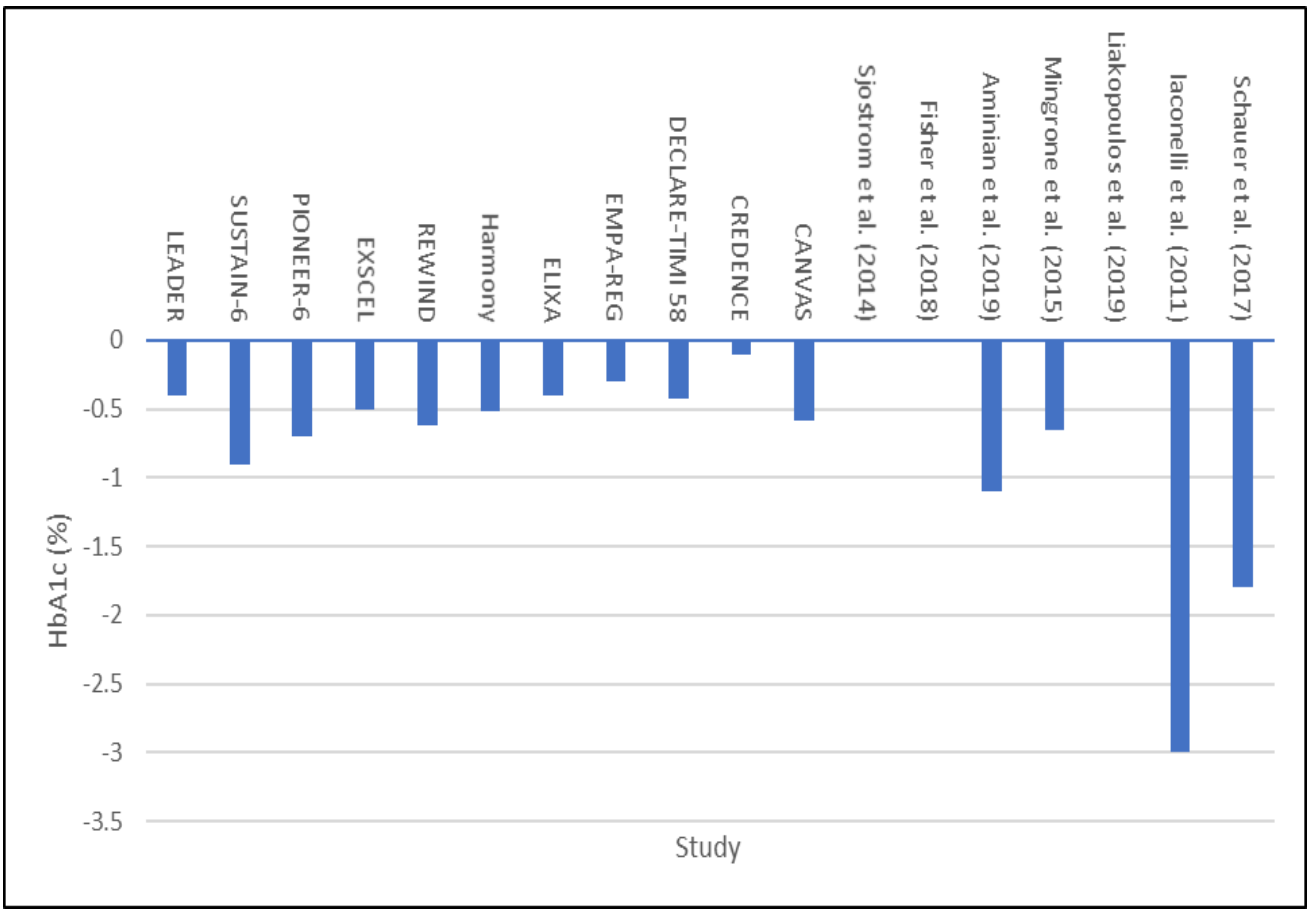

Figure 6: The difference in HbA1c reduction between intervention and control for each study included.

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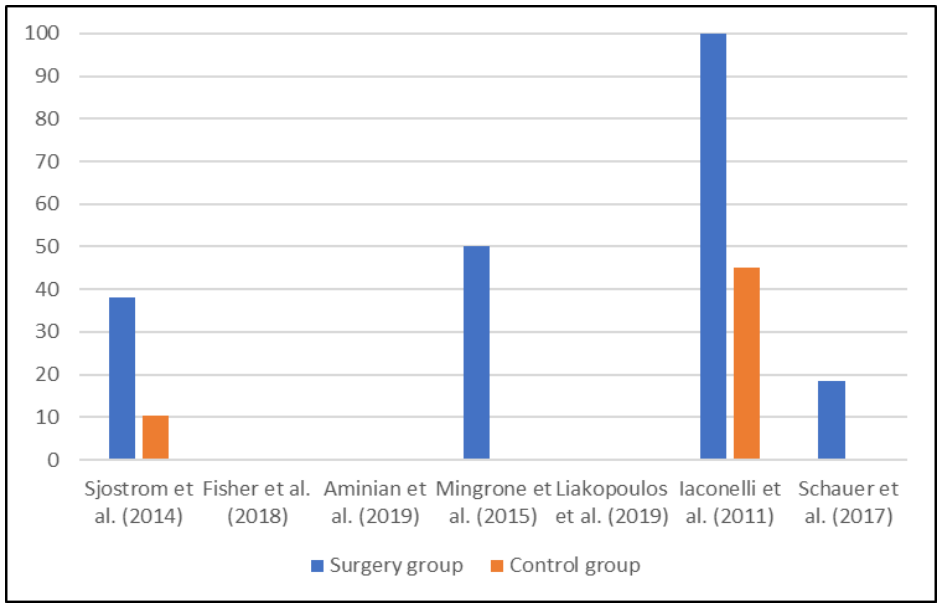

Figure 7: Comparison between percentage of diabetes remission in surgery group and control group.

Weight loss

Figure 8 illustrates the weight difference between the intervention and the control at the end of each study included in this review. The weight difference of the medication trials ranges from (-0.53 to -1.27Kg). Whereas, the weight difference of the metabolic surgery trial ranges from (-15.6 to -52Kg). However, Fisher, Johnson and Liakopoulos, Franzen studies didn't measure the weight loss [10,13].

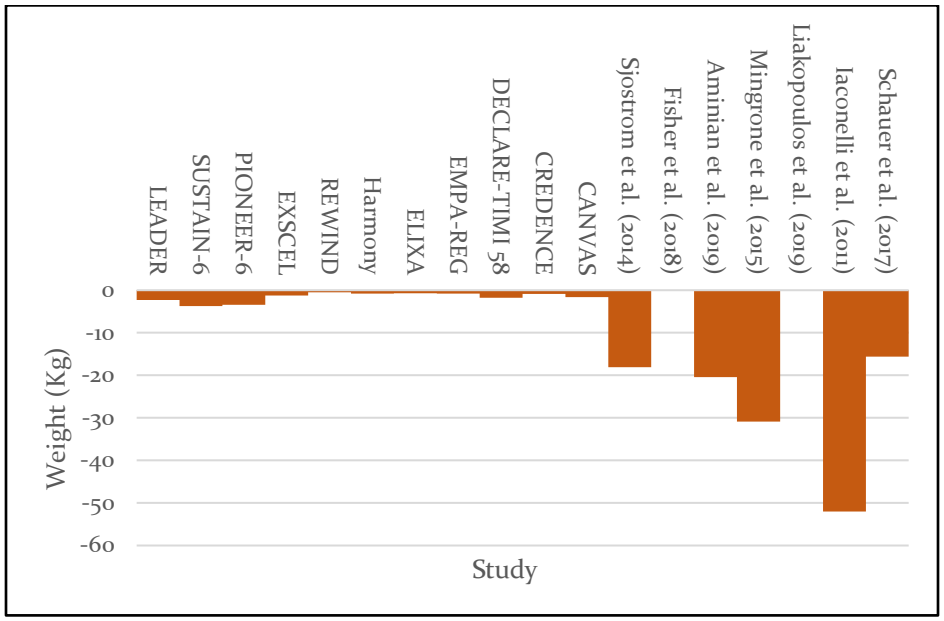

Figure 8: The weight loss difference between intervention and control at the end of each study.

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No	Trial	Age group (Mean)	White Race%	Duration of T2DM (years ± SD)	Established CVD % (CAD or CVA or PAD)	eGFR mean (SD) mL/min/1.73m2	Heart Failure (%)	Mean Glycated Haemoglobin (%) ± (SD)	Treatment with insulin (%)	Degree of obesity (BMI)	The use of cardioprotective agents (%)			
											Anti-thrombotic	RAAS inhibitors		Statins
												ACE-I	ARBs	
1	**LEADER(Liraglutide 1.8 mg SC inj daily)**	64	77.5	12.8 ± 8.0	82.1	-	14	8.7 ± 1.6	43.7	32.5 ± 6.3	68.7	51.8	31.9	72.9
	LEADER (Placebo)			12.9 ± 8.1	80.6	-		8.7 ± 1.5	45.6		66.8	50.3	31.8	71.4
2	**SUSTAIN-6 (Semaglutide 0.5-1 mg SC inj once weekly)**	64	84	14.2 ± 8.2	58.8	-	23.1	8.7 ± 1.5	58	32.8 ± 6.2	76	50.3	33.3	72.8
	SUSTAIN-6 (Placebo)		82	13.6 ± 7.98		-	24.1				76.5	49.3	34	72.8
3	**PIONEER-6 (Semaglutide 14 mg oral OD)**	66	72.2	14.7 ± 8.5	84.9‡	74 ± 21	11.8	8.2 ± 1.6	60.8	32.3 ± 6.5	78.4	N/A*		84
	PIONEER-6 (Placebo)		72.4	15.1 ± 8.5	84.5‡		12.6		60.4		80.3	N/A*		86.4
4	**EXSCEL (Exenatide-ER 2 mg SC inj once weekly)**	62	75.5	12	73.3	76.6	15.8	8	46.2	31.8	74.1	48.1	31.7	74.3

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	EXSCEL (Placebo)		76		72.8	76	16.6		46.5	31.7	73	49.3	30.7	72.7
5	**REWIND (Dulaglutide 1.5 mg SC inj once weekly)**	66.2	75.9	10.5	31.5	74.9	8.5	7.3	24	32.3	53.8	81		66.3
	REWIND (Placebo)		75.6		31.4		8.7	7.4	23.7		54.1	82		66
6	**Harmony (Albiglutide 30-50 mg SC inj once weekly)**	64.1	70	14.1	CAD=71% CVA=25% PAD=25%	79	20	8.7 ± 1.5	60	32.3	77	48	34	84
	Harmony (Placebo)		69						58			50	32	
7	**ELIXA (Lixisenatide 20 mcg SC inj OD)**	60	76.4	9.3	100%	76.7	22.3	7.6 ± 1.3	39	30.2	97.4	85		92.2
	ELIXA (Placebo)		74.4			75.2	22.5	74.4	39.2	30.1	97.6	84.9		93.3

Table 2: Baseline Demographic and Clinical Characteristics of GLP-1 RA trials.

ǂPIONEER-6 included established CVD or chronic kidney disease. *N/A: Not Available. However, more than 90% of patients in both groups were on Anti-hypertensive medications

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No.	Trial	Age group(mean)	White Race %	Duration of T2DM (years)	Established CVD % (CAD or CVA or PAD)	eGFR mean (SD) mL/min/1.73m2	Heart Failure (%)	Mean Glycated Haemoglobin (%) ± (SD)	Treatment with insulin (%)	Degree of obesity (BMI)	The use of cardioprotective agents (%)		
											Anti-thrombotic	RAAS inhibitors	Statins
												ACE-I / ARBs	
8	EMPA-REG (Empagliflozin 10 or 25 mg PO OD)	63	72.6	> 10 years = 57%*	98.9	74.2	9.9	8 ± 0.85	48	30.6	88.8	81	77.4
	EMPA-REG (Placebo)		71.9		99.4	73.8	10.5		48.6		89.6	80.1	76
9	DECLARE-TIMI 58 (Dapagliflozin 10 mg PO OD)	64	79.9	11	40.6	45**	9.9	8.3 ± 1.2	41.6	32	61.1	81.3	74.9^
	DECLARE-TIMI 58 (Placebo)		79.4				10.2		40.2				75^
10	CREDENCE (Canagliflozin 100 mg OD PO)	63	67.5	15.8	50.4	64.2***	14.9	8.3 ± 1.3	66	31.5	60.7	100	69.8
	CREDENCE (Placebo)		65.6				14.6		65.1		58.3	99.9	68
11	CANVAS (Canagliflozin 100 or 300 mg PO OD)	63.3	77.8	13.5	71.2	76.5^^	13.9	8.2 ± 0.9	50.2	32	73.6	80	74.9
	CANVAS (Placebo)		79		73.5		15.1						

Table 3: Baseline Demographic and Clinical Characteristics of SGLT-2 i trials.

*The duration of Type 2 diabetes was registered as percentage ≤ 1 year = 2.5%, 1 – 5 years 15.5%, > 5- 10 years = 25, > 10 years = 57%

**eGFR (ml/min/1.73m2) of less than 60 were excluded

^Statin or Ezetimibe

***The inclusion criteria are all the patients with chronic kidney disease of eGFR <90 ml/min/1.73m2 and the exclusion criteria is eGFR ≥30 ml/min/1.73m2

^^eGFR (ml/min/1.73m2) of less than 30 were excluded.

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No.	Study	Age group(mean)	White Race%	Duration of T2DM(years)	Established CVD %(CAD or CVA or PAD)	eGF Rmean (SD) mL/min/1.73 m2	Heart Failure (%)	Mean Glycated Haemoglobin (%) ± (SD)	Treatment with insulin (%)	Degree of obesity (BMI)	The use of cardioprotective agents (%)			
											Anti-thrombotic	RAAS inhibitors		Statins
												ACE-I	ARBs	
12	**Sjostrom, Peltonen (9) Surgery group**	48.7	-	2.9	21	-	-	Fasting blood glucose = 156 mg/dl*	12.2	42.1	-	-		-
	Sjostrom, Peltonen (9) Control group	50.4	-	3.3	15	-	-		13.1	40	-	-		-
13	**Fisher, Johnson (10) Surgery group**	49.5	48	5.65	3**	90.5 (23)	-	7.17 ± 1.24	24	44.7	-	56		55
	Fisher, Johnson (10) Control group	50.2	42	5.64	6**	87.6 (26.6)	-	7.2 ± 1.22	25	43.8	-	62		56
14	**Aminian, Zajichek (11) Surgery group**	52.5	75.8	-	CAD= 10.4 MI= 2.4 CVA= 1.8 Ischemic S= 1.5 PAD= 5.4	90	10.4	7.1	33.9	45.1	32	61		52.3
	Aminian, Zajichek (11) Matched Control group	54.8	69.9	-	CAD= 9.7 MI= 1.8 CVA= 3.1 Ischemic S= 2.6 PAD= 6.6	92	11.7	7.1	33.3	42.6	40.5	62.1		52.5
15	**Mingrone, Panunzi (12) Surgery group**	-	-	At least 5 years	-	-	-	8.8	10.5	44.4	-	-		-
	Mingrone, Panunzi (12) Control group	-	-		-	-	-	8.5	0	45.4	-	-		-
16	**Liakopoulos, Franzen (13) Surgery group**	49	-	-	5.1	-	2.6	-	-	42	-	-		-

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	Liakopoulos, Franzen (13) Control group	47.1	-	-	4.9	-	3.2	-	-	40.9	-	-	-
17	**Iaconelli, Panunzi (14) Surgery group**	43.77	-	Newly diagnosed	-	71.42 (17.54)	-	-	0	50.47	-	-	-
	Iaconelli, Panunzi (14) Matched Control group	43.71	-		-	69.5 (14.34)	-	-	0	51.53	-	-	-
18	**Schauer, Bhatt (15) Surgery group**	48.1	72.9	8.2	-	109	-	9.4 ± 1.5	43.8	36.5	37.4	69.7	82.2
	Schauer, Bhatt (15) Intensive medical care group	50.2	71.1	8.8	-	106	-	8.8 ± 1.1	44.7	36.4	55.3	63.2	84.2

Table 4: Baseline Demographic and Clinical Characteristics of Metabolic surgery studies.

*The study measure only fasting blood glucose and didn't measure the glycated haemoglobin level.

**This study excluded patients with established atherosclerotic cardiovascular disease prior to surgery except peripheral artery disease.

No.	Trial	No. of participants	Mean trial Duration (year)	Outcome measures								Adverse events of the intervention
				3-MACE* No. (%)	CAD No. (%)	CVA No. (%)	CV mortality No. (%)	All-cause mortality No. (%)	Expanded CV composite outcome** No. (%)	HbA1c reduction (%)	Weight loss (Kg)	
1	LEADER (Liraglutide 1.8 mg SC inj daily)	4,668/9,340	3.8	608/4,668 (13)	MI= 292 (6.3)	173(3.7)	219/4,668 (4.7)	381/4,668 (8.2)	948/4,668 (20.3)	-0.9	-2.4	1. Acute gallstone disease 2. Inj site reaction 3. Nausea 4. Vomiting 5. Diarrhoea 6. Decreased appetite 7. Abdominal discomfort

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												8. Not powered to exclude cancer risk
	LEADER (Placebo)	4,672/9,340		694/4,672 (14.9)	MI= 339 (7.3)	199 (4.3)	278/4,672 (6)	447/4,672 (9.6)	1,062/4,672 (22.7)	-0.5	-0.1	
2	SUSTAIN-6 (Semaglutide 0.5-1 mg SC inj once weekly)	1,648/3297	2.1	108/1,648 (6.6)	Non-fatal MI= 47 (2.9)	Non-fatal stroke = 27 (1.6)	44/1,648 (2.7)	62/1,648 (3.8)	199/1,648 (12.1)	-1.3	-4.3	1. Diabetic retinopathy complications 2. Diarrhoea 3. Nausea 4. Vomiting
	SUSTAIN-6 (Placebo)	1,649/3297		146/1,649 (8.9)	Non-fatal MI= 64 (3.9)	Non-fatal stroke = 44 (2.7)	46/1,649 (2.8)	60/1,649 (3.6)	264/1,649 (16)	-0.4	-0.6	
3	PIONEER-6 (Semaglutide 14 mg oral OD)	1591/3183		61/1,591 (3.8)	Non-fatal MI= 37 (2.3)	Non-fatal stroke = 12 (0.8)	15/1,591 (0.9)	23/1,591 (1.4)	83/1,591 (5.2)	-1	-4.2	1. Nausea 2. Vomiting 3. Diarrhoea 4. Retinopathy or related complications 5. Severe hypoglycaemia with insulin or SU
	PIONEER-6 (Placebo)	1592/3183	1.5	76/1,592 (4.8)	Non-fatal MI= 31 (1.9)	Non-fatal stroke = 16 (1)	30/1,592 (1.9)	45/1,592 (2.8)	100/1,592 (6.3)	-0.3	-0.8	
4	EXSCEL (Exenatide-ER 2 mg SC inj once weekly)	7,356/14,752		839/7,356 (11.4)	483 (6.6)	187 (2.5)	340/7,356 (4.6)	507/7,356 (6.9)				No difference between the groups in the incidence of adverse events
	EXSCEL (Placebo)	7,396/14,752	3.2	905/7,396 (12.2)	493 (6.7)	218 (2.9)	383/7,396 (5.2)	584/7,396(7.9)	N/A‡	-0.5^	-1.27^	
5	REWIND (Dulaglutide 1.5 mg SC inj once weekly)	4,949/9,901	5.4	594/4,949 (12)	223 (4.5)	158 (3.2)	317/4,949 (6.4)	536/4,949 (10.8)		-0.46	-1.08	1. Gastrointestinal adverse events 2. The incidence of other adverse events was similar in both groups
	REWIND (Placebo)	4,952/9,901		663/4,952 (13.4)	231 (4.7)	205 (4.1)	346/4,952 (7)	592/4,952 (12)	N/A‡	0.16	-0.55	
6	Harmony (Albiglutide 30-	4,731/9,463	1.6	338/4,731 (7.1)	181 (4)	94 (2)	122/4,731 (2.6)	196/4,731 (4.1)	373/4,731 (7.9)	-0.52^	-0.83^	1. Injection site reaction

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	50 mg SC inj once weekly)											2. The incidence of other adverse events was similar in both groups
	Harmony (Placebo)	4,732/9,463		428/4,732 (9)	240 (5)	108 (2)	130/4,732 (2.7)	205/4,732 (4.3)	468/4,732 (9.9)			
7	ELIXA (Lixisenatide 20 mcg SC inj OD)	3,034/6,068		406/3,034 *** (13.4)	270 (8.9)	67 (2.2)	156/3,034 (5.1)	211/3,034 (7)	661/3,034 (21.8)	-0.6		
	ELIXA(Placebo)	3,034/6,068	2.1	399/3,034** (13.2)	261 (8.6)	60 (2)	158/3,034 (5.2)	223/3,034 (7.4)	659/3,034 (21.7)	-0.2	-0.7^	1. Nausea 2. Vomiting

Table 5: GLP-1 RA Trials results.

*3-MACE: 3-point Major Adverse Cardiovascular Events (the first occurrence of death due to cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke). **Expanded CV composite outcome: death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, revascularization and hospitalization for unstable angina or heart failure.

‡N/A: Not Available. ^Overall least-squares mean difference between the intervention group and the control group.

***Primary end point in ELIXA trial: death from cardiovascular causes, non-fatal stroke, non-fatal stroke or unstable angina.

No.	Trial	No. of participants	Mean trial Duration (year)	Outcome measures								Adverse events of the intervention
				3-MACE* No. (%)	CAD No. (%)	CVA No. (%)	CV mortality No. (%)	All-cause mortality No. (%)	Expanded CV composite outcome** No. (%)	HbA1c reduction (%)	Weight loss (Kg)	
1	**EMPA-REG (Empagliflozin 10 or 25 mg PO OD)**	4,687/7,020	3.1	490/4,687 (10.5)	213 (4.5)	164 (3.5)	172/4,687 (3.7)	269/4,687 (5.7)	599/4,687 (12.8)	-0.3^	-1.9	1. Genital infection 2. Incidence of diabetic ketoacidosis, bone fracture and urinary tract infection were similar between groups
	EMPA-REG (Placebo)	2,333/7,020		282/2,333 (12.1)	121 (5.2)	69 (3)	137/2,333 (5.9)	194/2,333(8.3)	333/2,333 (14.3)		-1.1	
2	**DECLARE-TIMI 58 (Dapagliflozin 10 mg PO OD)**	8,582/17,160	4.2	756/8,582 (8.8)	393 (4.6)	235 (2.7)	245/8,582 (2.9)	529/8,582 (6.2)	Hospitalization for heart failure No. (%) 212/8,582 (2.5)	-0.42^^	-1.8^^	1. Diabetic ketoacidosis 2. Genital infection 3. Incidence of acute

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	DECLARE-TIMI 58 (Placebo)	8,578/17,160		803/8,578 (9.4)	441 (5.1)	231 (2.7)	249/8,578 (2.9)	570/8,578 (6.6)	286/8,578 (3.3)			kidney injury, bladder cancer, amputation, fracture, volume depletion and hypersensitivity were not higher in the intervention group when compared to the control group
3	**CREDENCE (Canagliflozin 100 mg OD PO)**	2,202/4,401	2.62	245/2,202 (11.1)	-	-	110/2,202 (5)	168/2,202 (7.6)	Hospitalization for heart failure No. (%) 89/2,202 (4)	-0.43	-1.99	1. Genital infections 2. Diabetic ketoacidosis 3. Urinary tract infections. 4. Volume depletion 5. No difference between groups for events of fractures, amputations and cancers
	CREDENCE (Placebo)	2,199/4,401		340/2,199 (15.5)	-	-	140/2,199 (6.4)	201/2,199 (9.1)	141/2,199 (6.4)	-0.32	-1.11	
4	**CANVAS (Canagliflozin 100 or 300 mg PO OD)**	5,795/10,142	3.6	26.9	MI= 11.2	7.9	11.6	17.3	5.5	-0.58+	-1.6++	1. Genital infection 2. Amputation 3. Fracture 4. Diabetic ketoacidosis, cancer, pancreatitis, urinary tract infection and acute
	CANVAS (Placebo)	4,347/10,142		31.5	MI= 12.6	9.6	12.8	19.5	8.7			

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												kidney injury events were not significant between groups

Table 6: SGLT-2 i Trials results.

*3-MACE: 3-point Major Adverse Cardiovascular Events (the first occurrence of death due to cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke).
**Expanded CV composite outcome: death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, revascularization and hospitalization for unstable angina or heart failure. ^The adjusted mean differences in HbA1c level between patients receiving empagliflozin (10 mg and 25 mg) and patients receiving placebo. ^^Overall least-squares mean difference between the intervention group and the control group +The mean difference in glycated level between the Canagliflozin group and the placebo group ++The mean difference in body weight between the Canagliflozin group and the placebo group.

No.	Trial	No. of participants	Mean trial Duration (year)	Procedure Type	Outcome measures							Post-op complications
					Cardiovascular events No. (%)	CAD No. (%)	CVA No. (%)	All-cause mortality No. (%)	Remission of Diabetes No. (%)	Weight loss Kg (SD)	HbA1c reduction (%)	
1	**Sjostrom, Peltonen (9) Surgery Group**	343/603	10* 18.1**	LGB= 61 VBG=227 GB=55	151/343*** (44)			2/343^ (0.58)	90/236 (38.1)	-22.5 (15.4)	-	-
	Sjostrom, Peltonen (9) Usual Care group	260/603	10* 17.6**	-	142/260*** (54.6)			1/260^ (0.38)	14/135 (10.4)	-4.4 (12.4)	-	
2	**Fisher, Johnson (10) Surgery group**	5,301/20,235	4.7	RYGB= 4,036 SG= 896 GB= 369	2.10%			1.30%	-	-	-	-
	Fisher, Johnson (10) Usual care group	14,934/20,23 (5)	4.6	-	4.30%			4.50%	-	-	-	
3	**Aminian, Zajichek (11) Surgical group**	2,287	3.9	RYGB= 1,443 SG= 730 LGB= 109 DS= 5	385/2,287 (30.8%^^)	7.90%	4.10%	10%	-	-29.1	-1.1	1. Blood transfusion (3%) 2. Pulmonary adverse events (2.5%) 3. venous thromboembolism (1%) 4. Cardiac events (0.7%) 5. Renal failure requiring dialysis (0.2%)

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	Aminian, Zajichek (11) Usual care group	11,435		-	3,243/11,435 (47.7%^^)	11.60%	5.60%	17.80%	-	-8.7		6. Abdominal surgical intervention (4.8%)
4	**Mingrone, Panunzi (12) Surgery Group**	40/60	5	RYGB= 20 BPD= 20	-	0/38	-	0/38	19/38 (50)	-40.9	-0.65	1. Intestinal occlusion (5%) 2. Incisional hernia (5%) 3. IDA (21%) 4. Hypoalbuminemia (16%)
	Mingrone, Panunzi (12) Usual Care group	20/60		-	-	15-Jan	-	15-Jan	0/15 (0)	-10		5. Osteopenia (16%) 6. Renal calculus (8%)
5	**Liakopoulos, Franzen (13) Surgery group**	5,321	4.5	GB	108 (43.54)+	309 (128.66)+	59 (23.7)+	183 (72.9)+	-	-	-	1. GI intervention 2. Abdominal pain 3. Gallstones 4. GI ulcers and reflux 5. Hernia 6. Bowel obstruction 7. GI leakage 8. Wound complications and bleeding 9. Psychiatric disorder 10. Malnutrition 11. Anaemia
	Liakopoulos, Franzen (13) Usual care group	5,321		-	150 (61.54)+	274 (114.28)+	71 (28.9)+	351 (142.06)+	-	-	-	
6	**Iaconelli, Panunzi (14) Surgical group**	22/50	10	BPD	0	0	0	0	100%	-52	-3	1. pulmonary complications (4.5%) 2. Wound infection (4.5%) 3. incisional hernias (13.6%) 4. peptic ulcer (9.1%)
	Iaconelli, Panunzi (14) Usual care group	28/50		-	4/28 (14%)	3/28 (10.5%)	1 (3.5%)	0	45%	0		

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7	**Schauer, Bhatt (15) Surgery group**	96/134	5	RYGB= 49 SG= 47	1/96 (1)	0/96	1/96 (1)	0/96 (0)	18/96	-20.9	-1.8	1. Anaemia 2. Wound infection 3. Pneumonia 4. GI bleeding, ulcer, leak, stricture.
	Schauer, Bhatt (15) Intensive medical treatment group	38/134		-	1/38 (2.6)	1/38 (2.6)	0/38	1/38 (2.6)	0	-5.3		4. Dumping syndrome

Table 7: Metabolic surgery studies results.

*The median follow-up period for weight and diabetes assessment **The median follow-up period for diabetes complications assessment ***Cardiovascular events in this study included coronary artery disease, heart failure, cerebrovascular accidents and peripheral artery disease. ^post-op mortality within 90 days. ^^The cumulative incidence of primary composite end point at 8-year follow-up (composite of 6 outcomes: first occurrence of all-cause mortality, coronary artery events, cerebrovascular events, heart failure, nephropathy and atrial fibrillation). +Events rates (%) per 10,000 person-years.

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Discussion

It is well established from a variety of studies that metabolic surgery is superior than the usual diabetes care in remission of diabetes. The results of this systematic review are consistent with the literature in suggesting that metabolic surgery is superior than the medical therapy and specifically new classes of glucose lowering agents (GLP-1 RA and SGLT-2 i) in reducing the cardiovascular events. It also suggests that metabolic surgery significantly reduce the glycated haemoglobin level and the weight among patients with type 2 diabetes when compared the medical therapy. Nonetheless, the findings should be interpreted with caution.

Cardiovascular events

The demographic and clinical characteristics play a role in recommending the preferred method in diabetes management. Older adults with a longer duration of diabetes and high cardiovascular risk especially history of established cardiovascular diseases and mild to moderate renal impairment would benefit more from the use of one of the medications that was proved to reduce cardiovascular events. The medications from GLP-1 RA group are Liraglutide, Dulaglutide and Albiglutide and the medications from SGLT-2 i are Empagliflozin and Canagliflozin. These patients may benefit from the mentioned medications even if they are obese and regardless of their glycated haemoglobin level.

Based on this review, no recommendations can be made to advice older diabetic adults with history of established cardiovascular diseases to undergo surgery in order to decrease their future risk of cardiovascular events. The reason is that most of the participants in the metabolic surgery studies had no previous history of cardiovascular disease. Moreover, a comparison of cardiovascular outcomes between patients with and without coronary artery disease after undergoing metabolic surgery revealed that the patients with coronary artery disease are at more risk of developing major adverse cardiovascular events than patients without the disease [16]. The findings of Pirlet, Biertho study should be confirmed by assessing the risk of developing cardiovascular disease in operated and non-operated patients who both have established cardiovascular disease [16].

Younger adult patients with short duration of T2DM exhibit significant reduction in developing cardiovascular events post-metabolic surgery. Nonetheless, it is worth noting that both restrictive and malabsorptive surgeries were included in this review. Although the evidence suggests that malabsorptive procedures are more favourable in improving T2DM and leading to remission of the disease, the studies included in this review was not design to confirm this (17). Firstly, Sjostrom, Peltonen included both restrictive (gastric banding and vertical banded gastroplasty) and malabsorptive (gastric bypass) procedures in their study [9]. However, the study was not power to assess the efficacy of the different types of procedures in decreasing the cardiovascular event rates. Secondly, more than three quarter of the participants in Fisher, Johnson study underwent Roux-en-Y gastric bypass procedure and the rest underwent either sleeve gastrectomy or adjustable gastric

banding. Therefore, the study didn't compare the effectiveness of different type of procedures [10]. Similarly, no comparison was made in Aminian, Zajichek study because most of the participants had RYGB [11]. The other metabolic surgery studies either included one type of procedure or had small sample size to confirm any difference in the effectiveness of the procedures.

All-cause mortality

The mortality rate in the medication trials were overall higher than the mortality in the metabolic surgery studies because the participants in the former group were older and have several chronic diseases. Nonetheless, the hazard ratios in the three studies that measured the mortality rate were significantly lower than the hazard rations of the mortality rate in the medication trials. This indicates that metabolic surgery reduces death from any cause significantly when compared to the non-surgical diabetes care. Moreover, the very low mortality rate post-operation indicates that metabolic surgery is a safe procedure.

HbA1c reduction/ Remission of diabetes

Remission of diabetes after metabolic surgery was higher significantly when compared to medical therapy. However, there are obvious differences between studies. Mingrone, Panunzi and Schauer, Bhatt demonstrated a high percentage of diabetes remission in the metabolic surgery group in oppose to no diabetes remission in the medical therapy group [12,15]. Whereas Iaconelli, Panunzi demonstrated remission of diabetes in both surgical and medical groups [14]. Although the remission rate was significantly higher in the surgical group, the medical group to demonstrates 45% recovery rate. The unusually high percentage of diabetes remission could be because the study included newly diagnosed diabetic patients and the intensive lifestyle modification provided to the medical group hindered this group from starting glucose lowering agents. On the other hand, the nature of the trials involved in providing the new classes of glucose lowering agents prevented diabetes recovery in any of the participants.

The reduction in the glycated haemoglobin was noticeably higher in the metabolic surgery studies when compared to the reduction in the medication trials. None of the medication trials exceeded 1% reduction in the HbA1c level after the completion. In contrast, Aminian, Zajichek, Iaconelli, Panunzi and Schauer, Bhatt demonstrated a significant reduction in HbA1c of more than 1% [11,14,15]. The glycated haemoglobin in these studies dropped by 1.1%, 3% and 1.8% respectively. Therefore, the findings suggest that metabolic surgery is a more powerful tool to control T2DM than the new classes of glucose lowering agents.

Weight loss

The new classes of glucose lowering agents provide modest weight reduction when compared to the metabolic surgery because the highest weight loss accomplished didn't reach 2kg. Whereas the minimal weight reduction noticed in metabolic surgery studies was 18.1kg, although there is a variation in weight reduction between studies. The reduction in weight might not help all the patients to reach to their ideal weight because the baseline BMI was higher

than 35 kg/m2 in most of the studies included. However, the weight loss was sustained over long period of time because most of the studies had 10 years or more follow-up duration. It is also worth noting that remission of diabetes was independent to weight loss. This might justify the theory of metabolic changes due to sodium-glucose transport modulation after gastric bypass surgery that assist in recovery from diabetes [17].

Adverse events

The most common side effects noticed in the trials involved GLP-1 RA is gastrointestinal adverse events and mainly nausea, vomiting and diarrhea. Other minor side effect was injection site reaction. Semaglutide was linked to increased number of diabetic retinopathy complications in patients with history of proliferative retinopathy. SGLT-2 i trials registered genital infections as the most common adverse event. Others were increase incidence of diabetic ketoacidosis, urinary tract infection, fractures and amputations. However, increase incidence of amputation and fractures were noticed only in CANVAS trial whereas the incidence was similar between the intervention group and control group in EMPA-REG outcome, DECLARE TIMI-58 and CREDENCE trials.

The adverse events post-metabolic surgery depended on whether the procedure was restrictive or malabsorptive. In general, the percentage of short-term complication was very low and involve similar complications to any other operation. This included pulmonary adverse events, wound infection and bleeding. Other complications involved gastrointestinal tract leading to surgical intervention were due to ulcer, leak, bowel obstruction and hernia. Malabsorptive procedures tend to lead to long-term complications such as malnutrition and anaemia especially if the patient was not adherent to the supplementation prescribed post-operatively.

Limitations

There are several limitations in this systematic review. Firstly, five out of the seven metabolic surgery studies were observational studies which might reduce the validity of the results. Secondly, not all the metabolic surgery studies measured cardiovascular events as the primary outcomes, therefore, no hazard ratio was measured in three of them. Thirdly, not all the studies measured other outcomes (HbA1c reduction and weight loss). Moreover, several baseline clinical characteristics were not identified in some of the studies including history of established cardiovascular disease, history of heart failure, measurement of mean glycated haemoglobin level and use of cardioprotective agent that may influence the cardiovascular outcomes.

In addition, the quality of Iaconelli, Panunzi study was low because they had very small sample size and the study was case-control with several confounding factors that were not recognised and matched such as race, history of established cardiovascular disease, heart failure, glycated haemoglobin and the use of cardioprotective agent [14]. Secondly, there is high drop-out rate and only 50 out of 95 recruited participants completed the study. Thirdly, the participants were newly diagnosed with diabetes and thus, were unlikely to have cardiovascular risk.

Therefore, all these factors reduce the accuracy of the results. Three other cohort studies were of moderate quality according to the CASP checklist (Appendix 3) which might also reduce the validity of the results.

Conclusion

In summary, this systematic review is consistent with the previous literature suggesting that metabolic surgery is more effective than the medical therapy in providing cardiovascular protection in patients with T2Dm. It also suggests that metabolic surgery increases the remission of diabetes and significantly reduce the glycated haemoglobin and weight when compared to the medical therapy. However, the comparison between the new classes of glucose lowering agents and metabolic surgery was indirect and several confounding factors may influence the results. Therefore, the findings of this systematic review should be interpreted with caution.

The recommendation is advising younger adult age group of patients with T2DM and obesity who have shorter duration of diabetes and no history of established cardiovascular diseases to undergo metabolic surgery. This medical advice should clarify the benefits of the surgery in reducing future cardiovascular events and high probability in achieving diabetes recovery and significant weight reduction. Similarly, the medical advice should clarify the possible post-op complications in order to make an informed decision making by the patients.

The other recommendation is advising older adult diabetic patients with history of cardiovascular diseases and mild to moderate renal impairment to start taking one of the medications that was proved to reduce future cardiovascular events. This should be done while explaining the side effects and considering the costs. Future studies that compare metabolic surgery and the new classes of the glucose lowering agents is recommended to confirm the findings of this review.

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