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The revolution of the anti-diabetic drugs in cardiology

Paolo Verdecchia[1]*, Fabio Angeli[2], Claudio Cavallini[1], Adolfo Aita[1], Dario Turturiello[2], and Gianpaolo Reboldi[3]

[1]*Fondazione Umbra Cuore e Ipertensione-ONLUS, Struttura Complessa di Cardiologia, Ospedale S. Maria della Misericordia, Perugia, Italy*
[2]*Struttura Complessa di Cardiologia e Fisiopatologia Cardiovascolare, Ospedale S. Maria della Misericordia, Perugia, Italy*
[3]*Dipartimento di Medicina, Università di Perugia, Perugia, Italy*

Beginning in December 2008, under the auspices of Food and Drug Administration, numerous controlled clinical trial were planned, and in part completed, concerning the cardiovascular (CV) effects of hypoglycaemic drug in patients with Type 2 diabetes mellitus. At least 9 studies have been concluded, 13 are still open, and 4 have been initiated and closed ahead of time. Of the nine completed studies, three concerned inhibitor of the dipeptidyl peptidase 4 (inhibitors of DPP-4), four the glucagon-like peptide 1 agonist (GLP-1 agonist), and two the inhibitor of sodium-glucose co-transporter-2 (inhibitors of SGLT-2). Only four studies demonstrated the superiority, and not the mere 'non-inferiority', of the anti-diabetic drugs compared to placebo, in addition to standard treatment, in terms of reduction of the primary endpoint (CV death, non-fatal myocardial infarction, and non-fatal stroke). Two of the four studies regarded GLP-1 analogues (liraglutide and semaglutide), and two inhibitors of SGLT-2 (empaglifozin and canaglifozin). As a whole, these studies provided solid data supporting major beneficial CV effects of anti-diabetic drugs. During the next 3–4 years, an equal number of studies will be completed and published, so we will soon have the 'final word' on this issue. In the meantime, the clinical cardiologist should become familiar with these drugs, selecting the patients able to gain the best clinical advantage from this treatment, also by establishing a close relationship with the diabetologist.

Introduction

To understand the importance of recent trials that have shown the effectiveness of some anti-diabetic drugs on major cardiovascular (CV) complications in patients with Type 2 diabetes mellitus (DM2), it is appropriate to start from three premises. (i) The incidence and prevalence of DM2 are constantly growing all over the world. It is estimated that in 2035 we will have over 600 million diabetic patients.[1] (ii) Cardiovascular diseases represent the leading cause of death in diabetic patients.[1,2] (iii) Until a few years ago, commonly used anti-diabetic drugs (oral hypoglycaemic agents, insulin) had been shown to reduce 'microangiopathic' complications of diabetes (retinopathy, nephropathy, and neuropathy), but not 'macroangiopathic' complications (myocardial infarction, stroke, heart failure, etc.).[1,2]

In this context, the Food and Drug Administration (FDA) entered the scene on December 2008. Following the finding of some undesirable CV effects (heart failure, etc.) induced by rosiglitazone, the FDA has arranged that, to maintain the commercialization of the new anti-diabetic drugs, the Pharmaceutical Companies would have had to perform some randomized phase 2 and 3 studies in patients with DM2, possibly complicated by CV diseases, concurrent risk factors or renal failure. These studies should have had the

*Corresponding author. Email: verdecchiapaolo@gmail.com

following characteristics: (i) major 'hard' CV events (MACE) as primary endpoint (i.e. CV death, myocardial infarction, stroke, hospitalization for acute coronary syndrome, revascularization or heart failure, etc.); (ii) non-inferiority studies (with upper margin of the 95% confidence interval for MACE not higher than 1.80 in phase 3 studies and 1.30 for phase 4 studies to prove non-inferiority); (iii) independent event award committees; and (iv) pre-defined protocols and predefined meta-analysis proposals.[2]

In practice, the FDA requested companies to demonstrate that, 'on top' of classical anti-diabetic therapy (diet, traditional oral hypoglycaemic agents, and insulin), the 'new' anti-diabetic drug added to the therapeutic regimen, would NOT have increased incidence of CV events compared to placebo higher than a certain limit, thus demonstrating 'non-inferiority' compared to placebo. It goes without saying that some or all of these studies could also have demonstrated 'superiority' over placebo, however not formally requested by the FDA. Following these directives, in the years following 2008, there was a veritable 'explosion' of controlled and randomized high-quality studies (*Figure 1*): at least 9 studies have been completed, 13 studies are still in progress, and 4 studies have been started but closed in advance. Of the nine studies completed, three concerned drugs that inhibited dipeptidyl peptidase-4 (DPP-4 inhibitors), four concerned agonists of the glucagon-like peptide 1 (GLP-1 agonists), two concerned drug inhibitors of Na-glucose transport in the proximal renal tubule (SGLT-2 inhibitors).

This is not the place to expose, in detail, the complex mechanisms of action of these drugs. In order to understand better their CV effects, it is useful to summarize some essential points.

GLP-1 analogues and DPP-4 inhibitors

The main hormones belonging to the group of 'incretins' are GLP-1, produced by entero-endocrine cells 'L' of ileum and colon, and GIP (glucose-dependent insulin-tropic peptide), produced by K cells of the duodenum. GLP-1 secretion is immediate after food ingestion, and independent of physical contact between food and intestinal L cells. It is therefore a secretion mediated by neurogenic effects, not entirely known. GLP-1 stimulates insulin secretion and simultaneously inhibits pancreatic glucagon secretion. Since the release of GLP-1 occurs after a meal, when the blood sugar level increases due to the carbohydrates introduced, GLP-1 does not induce hypoglycaemia. Through an action on the centres of hunger regulation in the central nervous system, GLP-1 also slows gastric emptying, increasing the sense of satiety and decreasing appetite in response to food intake. At the level of the muscular and adipose tissue, GLP-1 increases the uptake and deposition of glucose. At cardiac level, an improvement in cardiac function has been described, with reduction of microvascular thrombosis and oxidative stress and inflammation phenomena.[1,3]

Unfortunately, these are short-acting hormones that, after release, are rapidly degraded by a specific enzyme, DPP-4. For this reason, the therapeutic use of GLP-1 is feasible only by continuous infusion. To overcome this problem, some similar drugs (GLP-1 agonists) have been developed, which despite having a structure formula similar to GLP-1, can resist the degradation effect exerted by DPP-4. The exenatide, the first of these drugs to be developed, was extracted from a reptile, the Gila Monster, which lives in the Arizona desert. There are six FDA approved GLP-1 agonist drugs: three of these have a half-life <24 h (exenitide, liraglutide, and lixisenatide) and three have a half-life >24 h (long-acting exenitide, dulaglutide, and abiglutide). The latter can be administered once a week. Another long-acting GLP-1 agonist drug, semaglutide, has not yet been approved by the FDA. Some of these drugs (liraglutide and lixisenatide) are also available in a pre-established combination in fixed doses with insulin (degludec and glargine, respectively).

The main side effects of these drugs are gastrointestinal disorders and itching at the injection site.[1,3] GLP-1 agonists should be avoided in patients with: (i) history of medullary thyroid carcinoma (since liraglutide has been associated with thyroid C cell hyperplasia),[4] although this has not been confirmed in other studies;[5] (ii) history of multiple endocrine neoplasia 2A and 2B; and (iii) history of pancreatitis.

Drugs that inhibit DPP-4, or gliptins, through the inhibition of DPP-4, increase the circulating levels of incretins GLP-1 and GIP, favouring their multiple actions (see above). The drugs of this class currently on the market are sitagliptin, saxagliptin, vildagliptin, linagliptin, and alogliptin. All DPP-4 inhibitory drugs exert a competitive and reversible inhibitory effect on this enzyme, albeit with differences in terms of chemical binding to the enzyme. These chemical differences affect the half-life and dosage. The half-life of DPP-4 inhibitor drugs varies between 1.5 and 40 h. All drugs are administered once a day with the exception of vildagliptin, which requires twice daily dosing. Sitagliptin, saxagliptin, and vildagliptin reach the steady-state phase within 3 days, linagliptin within 4-6 days.

SGLT-2 inhibitor drugs

The SGLT-2 inhibitor drugs increase the urinary excretion of glucose by acting on the renal tubule.[6] As is known, the normal kidney filters about 180 L of plasma and 180 g of glucose into the proximal tubule every day.[6] Ninety percent of the filtered glucose is reabsorbed at the level of the first segment of the proximal tubule by a high-capacity, low-affinity receptor system (SGLT-2 receptors), the remaining 10% at a more distal level of the proximal tubule by a low-capacity system and high affinity (SGLT-1 receptors).[6,7] On the luminal side of the tubular cells, at the level of the SGLT-2 receptors, the glucose is actively re-absorbed, against concentration gradient, together with the sodium, using the energy produced by a Na/K/ATP-asi system. Once penetrated into the cell, glucose is expelled towards the blood, through the basement membrane, via the GLUT-2 channels along a concentration gradient.[7] The SGLT-1 receptors are also located in the intestine (intestinal villi) and in the heart, and the SGLT-2 receptors also in pancreatic cells. It should be noted that in diabetic patients,
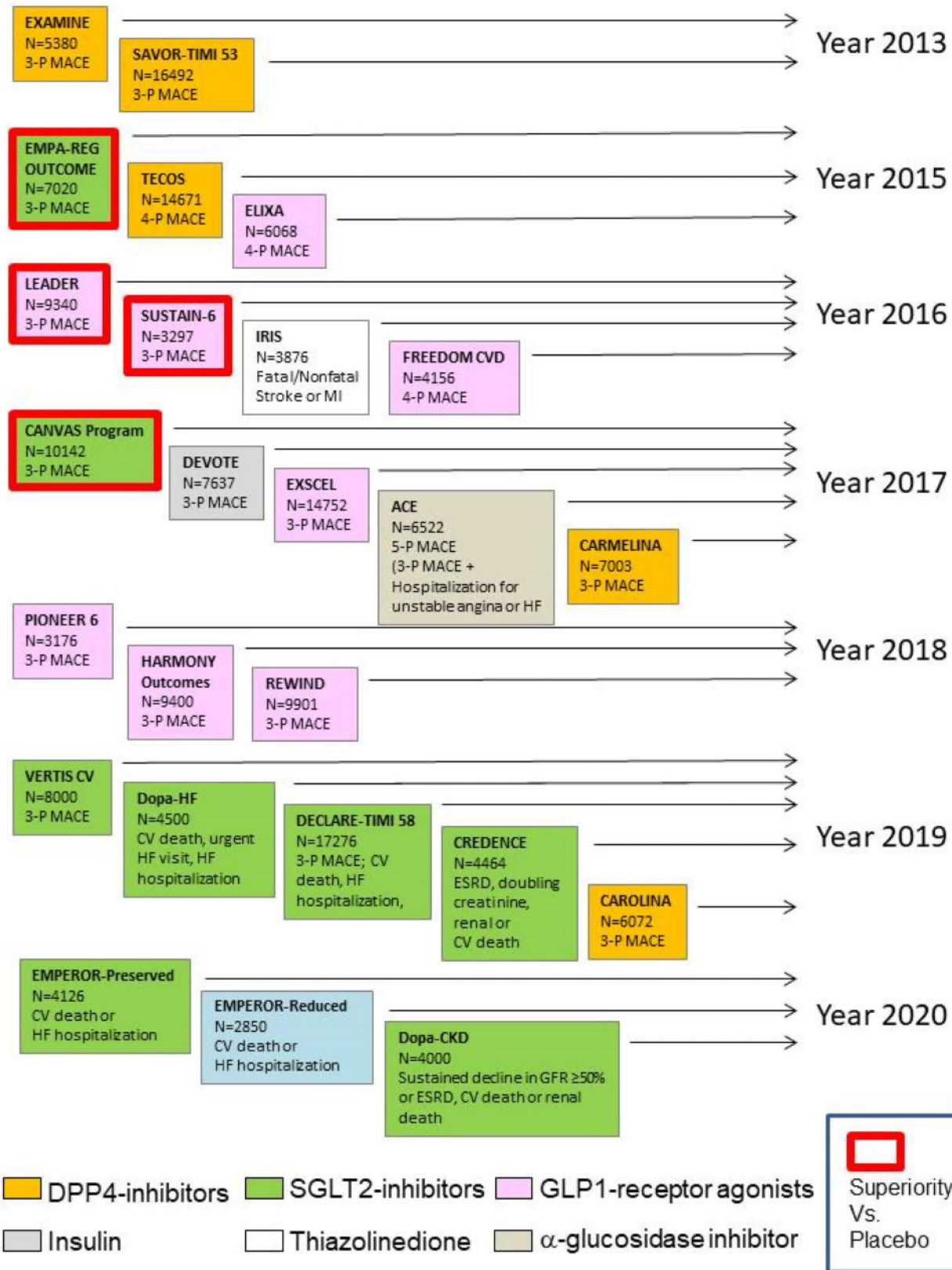
Figure 1 Summary of randomized and controlled clinical trials performed with anti-diabetic drugs in compliance with the 2008 FDA recommendations. Further details in the text.

SGLT-2 receptors and GLUT-2 channels may be hyper-expressed, a phenomenon that can contribute to raising blood glucose levels.[8]

Florizine, the first drug inhibitor of these receptors, was abandoned because, acting not selectively on the SGLT-1 and SGLT-2 receptors, it caused important undesirable effects at the gastrointestinal level. Furthermore, ironically, it was also accused of favouring diabetes by increasing glycosuria.[6]

There are currently three FDA approved selective SGLT-2 inhibitor drugs (empaglifozin, canaglifozin, and dapaglifozin). Only for empaglifozin[9] and canaglifozin,[10] there are post-marketing controlled studies conducted according to the FDA criteria (see above).[2]

SGLT-2 inhibitor drugs increase the elimination of glucose with urine at 60-80 mg per day. In other words, they reduce glucose reabsorption by about a third, despite some compensatory increase in glucose reabsorption by SGLT-1.6 receptors. It is evident that the effect of SGLT-2 inhibitor drugs requires the integrity of renal tissue. These drugs are contraindicated in patients with estimated glomerular filtrate <60 mL/min/1.73 m^2 or with creatinine clearance <60 mL/min. The increased urinary elimination of glucose leads to a negative caloric balance, with an average weight loss of 2-3 kg (about two-thirds of the weight loss is secondary to fat loss). The diuretic effect seems to be linked both to the reduction of sodium reabsorption in the proximal tubule, and to the osmotic diuresis, with a final reduction of the extracellular volume (about 5-10%).

The reduction in blood pressure, estimated at around 4-5/2 mmHg (EMPA-REG OUTCOME study), and 3.93/1.39 mmHg (CANVAS PROGRAM), appears to be due both to the diuretic effect and to weight loss. This effect was also confirmed by the use of ambulatory blood pressure monitoring for 24 h.[11] The decrease in HbA1C is about 0.3% with empaglifozin and 0.58% with canaglifozin. There is also a minimal increase in HDL and LDL cholesterol with both empaglifozin and canaglifozin.

At myocardial level, SGLT-2 inhibitors could lead to increased use of ketone bodies. As it is known, the ketone bodies are a sort of 'super-fuel' for the myocardium, where they serve to produce ATP more efficiently than the exploitation of glucose and free fatty acids.[12] The myocardium is a large consumer of ketone bodies (whose consumption decreases in the presence of insulin, which blocks lipolysis and therefore reduces its formation).[12] Blocking of SGLT2 receptors induces a slight increase in ketone bodies, which can increase myocardial energy efficiency.[12]

Among the undesirable effects of SGLT-2 inhibitor drugs, urinary tract infections should be considered, probably secondary to high glucose elimination and hypotension secondary to hypovolaemia (more frequent in elderly patients). It should also be considered the rare occurrence of non-hyperglycaemic diabetic ketoacidosis (generally associated with blood sugar <250 mg/dL), characterized by non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, fatigue, or unusual drowsiness, which requires immediate suspension of treatment.

The main results of the megatrials

As can be seen in *Figure 1*, only four trials demonstrated the superiority of antidiabetic drugs compared to placebo, obviously in addition to standard pre-existing antidiabetic therapy (metformin, sulfonylureas, and insulin). *Figure 2* shows, in more detail, the characteristics of these four trials. As can be seen, two trials were conducted with GLP-1 analogues (liraglutide[13] and semaglutide[14]), and two trials with SGLT-2 inhibitors (empaglifozin[9] and canaglifozin[10]).

The inclusion criteria in these trials are quite similar, but with some differences. EMPA-REG OUTCOME enrolled only diabetic patients with a history of previous CV events (secondary prevention),[9] while the other three studies also enrolled diabetic patients in primary prevention, albeit at high risk of CV events.[10,13,14] The average duration of follow-up fluctuated between 2.05 years (semaglutide) and 3.8 years (liraglutide).

As shown in *Figure 2*, all four trials showed a significant reduction in the risk of a pre-defined primary endpoint (death from CV causes, non-fatal myocardial infarction, and non-fatal stroke).

In the EMPA-REG OUTCOME study,[9] the reduction in the primary endpoint was 'driven' by a reduction in CV mortality of 38%, but not by a reduction in myocardial infarction nor by stroke. Note, in the EMPA-REG OUTCOME study, a significant reduction in hospitalizations for heart failure (-35%), of similar magnitude also in the CANVAS PROGRAM with canaglifozin (-33%),[10] and of all-cause mortality (-32%). Based on the results of the EMPA-REG OUTCOME study, in December 2016, the FDA approved the empaglifozin 'in order to reduce the risk of CV death in patients with DM2 and coexisting CV diseases', despite the fact that CV mortality was not a primary endpoint of the study. This, however, in considering the 'robust' results on the primary endpoint, total mortality, and heart failure.[2]

Analysing the two studies conducted with GLP-1 agonist drugs, in the LEADER study (with liraglutide), the reduction of the primary endpoint was 'guided' by the reduction of CV mortality and mortality from all causes, but not from myocardial infarction neither from the stroke.[13] In the SUSTAIN[6] study (with semaglutide), instead from a reduction of stroke alone.[14] Based on the results of the LEADER study, in August 2017, the FDA approved the liraglutide 'to reduce the risk of major CV events in adult patients with Type 2 diabetes and history of CV disease'. The semaglutide has not yet been approved by the FDA for CV risk reduction.

An interesting fact of the LEADER study with liraglutide is the apparent late separation of the Kaplan-Meier curves (over 12 months for CV death and over 18 months for death from all causes), which suggest a probably late onset benefit, perhaps secondary to a reduction in the phenomena linked to the progression of atherosclerosis.[2] On the contrary, in the EMPA-REG OUTCOME study, the Kaplan-Meier curves showed a tendency to early separation (within the first 3 months), especially on the endpoint heart failure. Despite some methodological reservations, this has been interpreted as a possible 'early' effect of haemodynamic type (secondary pressure decrease to diuresis and hypovolaemia).[2]

Trial	LEADER (N= 9 340)	SUSTAIN-6 (N = 3 297)	CANVAS (N=10 142)	EMPAREG-OUTCOME (N= 7 020)
Farmaco	Liraglutide (GLP-1 agonista)	Semaglutide (GLP-1 agonista)	Canaglifozin (SGLT2-inibitore)	Empaglifozin (SGLT2-inibitore)
Criteri di inclusione	T2D + età>50 + CVD, o età>60 e ≥1 fatt. rischio CV; HbA$_{1c}$>7%	T2D + age>50 + CVD, o età>60 e ≥1 fatt. rischio CV; HbA$_{1c}$>7%	T2D + età>30 + CVD, o età>50 e ≥1 fatt. rischio CV; HbA$_{1c}$ 7.0-10.5%	T2D + CVD HbA$_{1c}$ 7-10%
Durata del trial	3,8 anni	2,05 anni	3,6 anni	3,1 anni
HbA$_{1c}$ basale	8,7%	8,7%	8,2%	8,1%
End-point primario	↓ 13% (3% - 22%)	↓ 26% (5% - 42%)	↓ 14% (3% - 25%)	↓ 14% (1% - 26%)
Morte CV	↓ 22% (7% - 34%)	↓ 2% (-48% - +35%)	↓ 13% (-28% - 6%)	↓ 38% (23% - 51%)
Infarto miocardio	↓ 2% (-3% - +25%)	↓ 26% (-8% - +49%)	↓ 11% (-27% - 9%)	↓ 13% (-30% - +9%)
Ictus cerebrale	↓ 14% (-29% - +6%)	↓ 39% (1% - 62%)	↓ 13% (-31% - 9%)	↑18% (-11% - +56%)
Ospedalizzazione per scompenso cardiaco	↓ 13% (-5% - +27%)	↑ 11% (-23% - +61%)	↓ 33% (13 % - 48%)	↓ 35% (15% - 50%)
Morte	↓ 15% (3% - 26%)	↑ 5% (-24% - 50%)	↓ 13% (-24% - +1%)	↓ 32% (18 % - 43%)
Effetti indesiderati maggiori	Calcolosi biliare, Effetti gastrointestinali	Retinopatia	Infezioni genitourinarie Amputazioni, fratture, Ipovolemia	Infezioni genitourinarie
Possibili meccanismi del beneficio	Beneficio ad insorgenza relativamente lenta→ minore aterotrombosi; minore ipoglicemia	Beneficio ad insorgenza relativamente lenta→ minore aterotrombosi; minore ipoglicemia	Beneficio ad insorgenza relativamente rapida→ effetti emodinamici, metabolici, vascolari	Beneficio ad insorgenza relativamente rapida→effetti emodinamici, metabolici, vascolari

Figure 2 The only four randomized and controlled clinical trials performed with anti-diabetic drugs, in compliance with the 2008 FDA recommendations, which showed a superiority of the drug tested compared to placebo. The significant components of the primary endpoint are framed. More details in the text.

Conclusions

A recent 'Expert Forum' published in the journal *Diabetes Care* concludes that, taken together, the trials published in recent years have brought solid demonstrations on the major CV benefits of anti-diabetic drugs.[2] These trials have also brought important reassurance on the tolerability of these drugs.[2] In the next 3-4 years, as many trials will be published that will certainly give a 'final verdict' on the subject. Meanwhile, it is beyond doubt that the cardiologist should become more familiar with these drugs, identifying the patients who can benefit most from these preparations in a context of collaboration, where necessary, with diabetologist.

Conflict of interest: none declared.

References

1. Ahmed HM, Khraishah H, Cho L. Cardioprotective anti-hyperglycaemic medications: a review of clinical trials. *Eur Heart J* 2018;**39**:2368-2375.
2. Cefalu WT, Kaul S, Gerstein HC, Holman RR, Zinman B, Skyler JS, Green JB, Buse JB, Inzucchi SE, Leiter LA, Raz I, Rosenstock J, Riddle MC. Cardiovascular outcomes trials in type 2 diabetes: where do we go from here? Reflections from a diabetes care editors' expert forum. *Diabetes Care* 2018;**41**:14-31.
3. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology* 2007;**132**:2131-2157.
4. Drucker DJ, Sherman SI, Bergenstal RM, Buse JB. The safety of incretin-based therapies—review of the scientific evidence. *J Clin Endocrinol Metab* 2011;**96**:2027-2031.
5. Lunati ME, Grancini V, Colombo C, Palmieri E, Resi V, Perrino M, Orsi E, Fugazzola L. Basal and stimulated calcitonin levels in patients with type 2 diabetes did not change during 1 year of Liraglutide treatment. *Metabolism* 2016;**65**:1-6.
6. Tahrani AA, Barnett AH, Bailey CJ. SGLT inhibitors in management of diabetes. *Lancet Diabetes Endocrinol* 2013;**1**:140-151.
7. Lee YJ, Lee YJ, Han HJ. Regulatory mechanisms of Na(+)/glucose cotransporters in renal proximal tubule cells. *Kidney Int Suppl* 2007;**72**:S27-S35.
8. Rahmoune H, Thompson PW, Ward JM, Smith CD, Hong G, Brown J. Glucose transporters in human renal proximal tubular cells isolated from the urine of patients with non-insulin-dependent diabetes. *Diabetes* 2005;**54**:3427-3434.
9. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**:2117-2128.
10. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;**377**:644-657.
11. Tikkanen I, Narko K, Zeller C, Green A, Salsali A, Broedl UC, Woerle HJ. Empagliflozin reduces blood pressure in patients with type 2 diabetes and hypertension. *Diabetes Care* 2015;**38**:420-428.
12. Ferrannini E, Mark M, Mayoux E. CV protection in the EMPA-REG OUTCOME trial: a "thrifty substrate" hypothesis. *Diabetes Care* 2016;**39**:1108-1114.
13. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;**375**:311-322.
14. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;**375**:1834-1844.