Cardiovascular Risk Factors in DM

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The main cardiovascular risk factors in diabetes mellitus (DM) are hyperglycaemia, hypertension and dyslipidaemia; all of them share the same substrate: insulin-resistance. Primary prevention of cardiovascular events that compose the 3P-MACE (non-fatal acute coronary events, non-fatal stroke, cardiovascular-death) is the universal desiderate in DM patients. The modern management of cardiovascular risk factors includes: early identification, addressing all the cardiovascular risk factors, use of moderate to intensive therapy in order to ensure the safety of the patients and the adequate risk-benefit ratio, usage of therapeutic agents proven to decrease cardiovascular risk such as GLP-1 agonists, SGLT2-inhibitors, ACEI inhibitors or statins.

diabetes cardiovascular risk pathogenic mechanisms

DM itself represents a major CVR factor, the majority of diabetic patients' deaths being due to cardiovascular complications [1]. The risk is further increased by the frequent association between obesity, hypertension and dyslipidaemia.

There are several CVR factors classifications for diabetics. One of these distinguishes two categories: the glycaemic factors and non-glycaemic ones: arterial hypertension, dyslipidaemia, obesity, smoking, chronic inflammation and microalbuminuria. Another classification mentions traditional (old age, male gender, hypertension, DM, dyslipidaemia, smoking, sedentary lifestyle, and familial history of CVD) and non-traditional risk factors. The non-traditional risk factors have been the subject of increasing research, although their specific impact on CVR has been difficult to assess—some examples include: insulin resistance, endothelial dysfunction (due to excessive vasoconstriction and reduced vasodilation), inflammation (high C reactive protein levels, high leukocytes), microalbuminuria, intima-media thickness, and coronary calcium score [2][3].

Hyperglycaemia is another CVR factor and its control is being highly debated. The UKPDS has shown that for patients with excellent glycaemic control, with a mean HbA1c <7%, it was observed a 16% reduction in cardiovascular complications in comparison with patients with mean HbA1c values of 7.9%, although this reduction was not statistically significant [4]. Similarly, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study has highlighted the same statistically insignificant reduction of cardiovascular events in patients with more intensive glycaemic control; moreover, this group of patients experienced more frequent hypoglycaemic events and weight gains of over 10 kg. The study was discontinued due to significantly high mortality in this group of patients [5]. The ADVANCE study compared intensive treatment with standard treatment for patients, five years after therapy initiation. Mean HbA1c was 6.5% in the first group and 7.3% in the second one. The intensive treatment group presented a lower microvascular complications incidence than the standard group, especially nephropathy, but optimal glycaemic control did not have impact on macrovascular complications [6]. These results support the hypothesis that hyperglycaemia is not the only responsible for increased CVR in diabetic patients: high BP values, dyslipidaemia, and non-traditional risk factors also being responsible and requiring multiple target therapy to reduce CVR.

Other studies have shown that prompt intensive hyperglycaemia treatment reduces CVR in patients without other risk factors. DCCT study highlighted a 47% risk decrease for any CVD and a 57% reduction of MI, stroke or cardiovascular-related risks causing death [7]. The characteristic of this study was that more intensive therapy initiation was done for young patients with type 1 DM without any cardiovascular history. Another study, carried out for recently diagnosed T2DM patients who received more intensive treatment, showed 15% MI risk reduction in patients receiving sulphonylurea or insulin and a 33% reduction in those receiving metformin [8]. These data led to the conclusion that more intensive therapy in DM is effective in CVR reduction when there are patients with no or little CV risks [4]. As far as glycaemic control is concerned, ADA recommends an optimal HbA1c value <7% [5]. ADVANCE and ACCORD studies have proven that very intensive hyperglycaemia treatment does not offer cardiovascular benefits for patients with arterial or cardiac disease history, nor for those with long-standing DM history, however more recent studies have highlighted the existence of new oral antidiabetics which significantly reduce the CVR in patients with CVD history [4][9]. Therefore, the oral antidiabetic choice seems to be more important than glycaemic control; these are usually added to the metformin monotherapy. The EMPA-REG study has shown the efficiency of empagliflozin/metformin, a SGLT-2 inhibitor, in decreasing CV mortality for diabetic patients with CV history with up to 38% [10]. The CANVAS study has proven that canagliflozin was also efficient in reducing CVR [11][34]. Also, liraglutide, a GLP-1 analogue, has been shown to be effective in reducing CVD in patients with long-term DM [12]. Metformin has proven cardioprotective effects, reducing the risk of cardiovascular mortality by 33% [8]. Metformin improves lipid parameters, causes a slight weight loss or impedes weight gain, lowers TAS and reduces oxidative stress and chronic inflammation [13][14][15]. The American Diabetes Association (ADA) recommends for patients with metformin therapy and lifestyle modification, who have a cardiovascular history, the addition of an oral antidiabetic drug, strongly evidenced to provide cardiovascular protection [14].

Arterial hypertension is one of the most important CVR factors in diabetic patients. Indeed, 77–87% of these subjects suffered from it [13][16]. ADA recommendations include target values of <140/90 mmHg but stricter limits should be considered in high risk patients: <130/80 mmHg or <120/80 mmHg [14]. However, a meta-analysis has shown that systolic values under 140 significantly reduce CVR but further decreasing it under 130 does not offer additional benefits. All antihypertensive drugs are efficient in reducing CVR among both non-diabetic and diabetic patients, but the latter particularly benefit from angiotensin converting enzyme inhibitors and angiotensin receptors blockers [15].

ADA recommends lifestyle changes for diabetic patients with values >120/80 mm Hg as they can reduce blood pressure values as well as support glycaemic control [17]. These changes include as follows: low salt intake (<2.3 g/day), 8–10 portions of fruits and vegetables every day, 2–3 portions of low-fat dairy products consumption, smoking cessation, and increasing physical activity [18]. Diabetics with values <160/100 mm Hg should be prescribed one antihypertensive drug belonging to the following groups: angiotensin-converting-enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), diuretics (thiazide-like), dihydropyridine calcium channel blockers [18]. Naturally, these are added to the lifestyle changing measures. Patients with both diabetes and CKD should be treated with ACE inhibitors and ARBs [14]. However, these should never be given concomitantly due to risks of acute renal injury and hyperkalaemia. Patients who have values >160/100 mm Hg require the prescription of two different antihypertensive drugs. In cases of CKD, one of these drugs must be an ACE inhibitor or ARB. Regardless of hypertension values, if the target values of <140/80 mm Hg are not reached, one additional drug will be prescribed (ACE inhibitor/ARB/calcium channel blocker/diuretic). If the target is still not reached by using one diuretic, one calcium channel blocker, and one ACE inhibitor or ARB, the prescription of loop diuretics is recommended [14].

Another CVR factor in diabetic patients is dyslipidaemia. Decreasing LDL-cholesterol may reduce CVR by 20–50%. These patients mainly present small and dense LDL particles which easily traverse the arterial wall transforming into oxidized LDL due to the effects of oxygen reactive species [19]. The intake of statins may reduce LDL levels as well as CVR in diabetic patients. In primary prevention, it has been shown that even low doses of statins are effective in reducing cardiovascular events risk by 37% [20]. The importance of LDL-cholesterol reduction is proven by the findings that demonstrate that each mmol/L decreases CVR by 21% [21]. ADA recommends the use of medium-dose statins for diabetics without cardiovascular history and high-dose statins for those with cardiovascular history. The therapeutic target for the former is LDL <100 mg/dL and <70 mg/dL for the latter [21]. Recently, there has been interest in researching the effect of triglycerides increase and HDL-cholesterol decrease. Evidence suggests that hypertriglyceridemia leads to an increase in potential atherogenic triglyceride rich VLDL1 particles [22]. Fibrates are effective in reducing triglyceride levels and increasing HDL-cholesterol levels, thus reducing CVR [23]. The ACCORD-LIPID study has found a reduction of CVR by 7% in diabetic patients who were prescribed fibrates in addition to simvastatin, however not statistically significant [24]. The FIELD study indicated HDL-cholesterol growth by 5% and triglyceride reduction by 37% in diabetic patients on fibrate treatment. The non-fatal myocardial infarction was reduced by 24% and the cardiovascular mortality risk suffered an insignificant reduction [25]. Further research within the FIELD study has proven fibrates to be beneficial in significantly reducing CVR by 27% in patients who presented levels of triglycerides ≥240 mg/dL and HDL-cholesterol <40 mg/dL (men), <50 mg/dL (women) [25]. High triglycerides and low HDL-cholesterol are a frequent association in DM. The triglyceride/HDL ratio has proven to be a CVR predictive factor; when its value is >4 it represents an extremely high risk of cardiovascular events [26]. In addition, this ratio correlates with the LDL-cholesterol type, therefore a high ratio is associated with type B particles—small, dense and intensely thermogenic [27].

Recent literature data regarding T2DM patients considered that non-HDL cholesterol level measurements associated with LDL-C/HDL-C ratio could be used as markers of dyslipidaemia [28]. Non-HDL cholesterol is an equivalent of the total quantity of lipoprotein containing apolipoprotein B (apo B) [29]. This protein has a proatherogenic effect, therefore the determination of non-HDL cholesterol has been validated as a useful marker for the risk of cardiovascular disease in current guidelines [30]. Liu et al. demonstrated that an increase of non-HDL cholesterol by 1mg/dL is associated with an increase of cardiovascular mortality with 5% among patients with T2DM [31]. In their study [32], the value of non-HDL cholesterol was 1.5–2.5 higher among patients with diabetes compared with non-diabetic patients. Numerous studies promote the idea that non-HDL cholesterol has a better predicting accuracy for cardiovascular disease than other lipid fractions much more explored in studies, such as LDL-cholesterol and triglycerides [33][34]. Non-HDL cholesterol is also a strong predictor of metabolic syndrome, because non-HDL cholesterol is mostly the sum of VLDL particles with high triglyceride content and other apo B containing particles. Hypertriglyceridemia is a consequence of insulin resistance. Therefore, high triglyceride levels lead to high VLDL-synthesis, and a global increase in non-HDL cholesterol [35]. Non-HDL cholesterol determination is also simpler and more convenient than the determination of LDL-cholesterol and can be performed without fasting, from random serum sample [28]. In patients with DM that generally have numerous comorbidities, a target of non-HDL cholesterol <100mg/dL can be attained by an adequate therapy with statins, ezetimibe and, when needed, fenofibrate and omega 3 fatty-acids supplementation [36]. Data from NHANES study demonstrated that over a period of 17 years, among individuals with atherosclerotic disease, non-HDL cholesterol decreased by 21% as statin usage rose from 37% in the 1999–2000 period to 69% in 2015–2016 [37], confirming the efficacy of statin treatment in reducing non-HDL cholesterol. Recent data present the serum non-HDL cholesterol level as an efficient biomarker of coronary heart disease in patients with CKD. Regular evaluation of serum non-HDL-C levels may present clinical relevance for the efficient prophylaxis of cardiovascular incidence for patients with CKD that present increased risk of CVD [38][39].

DM leads to high activation and aggregation of thrombocytes that is a CVR factor. Primary prevention of cardiovascular disease with aspirin in diabetics remains controversial and is currently indicated only in secondary prevention [40]. The recommended dose is 75–162 mg/day [14]. Patients with a recent history of acute coronary syndrome must be prescribed double anti-aggregation therapy with aspirin and clopidogrel for one year.

Prediction of Cardiovascular Risk in the Diabetic Patient Based on Risk Equations

CVR prediction is important in patients with DM in identifying high-risk patients and choosing the therapeutic strategy. DM represents a CVD factor, considered by some authors to be a CVD equivalent and, in the diabetic patient, the presence of other CVD factors varies from one patient to another, thus leading to different categories of CVD. Each CVR factor present in the diabetic patient, such as hypertension or dyslipidaemia, influences the CVD and it is necessary to apply scores that provide data as close to reality as possible on the CVR by combining the impact that each factor has. There are several risk scores, some of them being specific for patients with diabetes because they take into account the glycaemic parameters while others are more suitable for the general population as they do not take glycaemic parameters into account.

Framingham and SCORE risk scores are some of the most commonly used CVR prediction scores in the general population. Within these scores DM is only a factor of CVD, the duration of the disease and the glycaemic control not being taken into account. The Framingham score predicts CVR over the next 10 years and includes the following variables: sex, age, total cholesterol and HDL-cholesterol, systolic blood pressure, blood pressure treatment, smoking status, and the presence of DM [25]. A score below 10% is considered low, a score between 10–20% is considered intermediate, a score above 20% is considered high. The SCORE project score considers the patient’s sex, age, SBP values, cholesterol value and smoking status as variables [41]. A score above 10% is considered very high, a score between 5% and 10% high, a score between 1% and 5% moderate, and a score below 1% is considered low.

The UKPDS risk engine predicts CVR in the diabetic patient, taking into account HbA1c values, DM duration and other CVR factors. Numerous studies have compared CVR scores in terms of risk prediction accuracy. The results are often contradictory. Some studies indicate that both the UKPDS and Framingham scores accurately identify patients with high CVR, but both scores overestimate the risk [42]. Comparing CVR predicted by UKPDS risk engine, Framingham score, and JALS-ACC, UKPDS risk engine had the highest accuracy in predicting CVR [43]. Other studies give different results, i.e., the Framingham score and the UKPDS score overestimate the CVR. However, both had the ability to identify patients with high CVR [44]. Data from the meta-analyses show that diabetes specific CVR scores, such as UKPDS or ADVANCE, appear to have a slight advantage over scores designed for the general population [45][46].

The assessment of CVR in the diabetic patient is particularly important for identifying patients in the high and moderate risk category and for initiating the multifactorial treatment of hyperglycaemia and other risk factors such as hypertension or dyslipidaemia. In newly diagnosed patients, by calculating CVR through the UKPDS risk engine, the category of high-risk subjects had the greatest benefit from reducing CVR, being prescribed drugs with cardioprotective effect. The lowest benefit was for patients registered at low risk category [46]. These data demonstrate the importance of scores in therapeutic decision making in patients newly diagnosed with DM; however, there remains the risk that less attention will be paid to multifactorial treatment in these subjects.

Different studies have identified risk categories for diabetic patients with low and high CVR. The categories of patients with high CVR were represented by the elderly, males, smokers and those with low socioeconomic status [47]. Some studies have determined CVR in patients newly diagnosed with DM by the UKPDS risk engine. The diagnosis of CVD in diabetic patients had an impact on the therapeutic decision. In a study on newly diagnosed diabetic patients, using a value of 20% to define high CVR, 20.9% of patients fell into this category by calculating the Framingham score and 21.7% fell into this category by using the UKPDS risk engine [48]. Statin treatment in patients over 45 years of age has proven to be cost effective in reducing CVD in newly diagnosed patients. It seems that in the newly diagnosed patients the intensive glycaemic control significantly reduces CVD. Thus, the risk of mortality through myocardial infarction was 15% lower in patients with sulphonyl urea or insulin treatment compared to those who were only recommended lifestyle changes and 39% lower in patients treated with metformin than those to whom only lifestyle changes were recommended [8][49].

Therefore, the evaluation of CVD in the diabetic patient is especially important at the time of diagnosis, as this is the best therapeutic window for long term reduction of CVD, numerous studies proving that after the onset of cardiovascular complications, glycaemic supervision no longer has a significant impact on primary prevention but having an important role in the control of the risk factors. The newly diagnosed diabetic patient, without cardiovascular complications, benefits the most from the multifactorial therapeutic intervention.

Modern Management of Cardiovascular Risk Factors in DM

Glycaemic Target and Managing Hyperglycaemia

As far as blood glucose levels recommendations go, ADA 2017 and ADA 2018 advise aiming for HbA1c <7%. This analysis should be done at least twice/year in patients reaching the target and every 3 months in those who have difficulties reaching it or with changes in their therapeutic regime. In newly diagnosed patients it should be aimed for fasting glucose between 80 and 130 mg/dL and post-prandial glucose <180 mg/dL [9][14].

The first therapeutic step in hyperglycaemia includes lifestyle changes and Metformin. This can be prescribed unless otherwise contraindicated and if HbA1c values are <9%. Patients with higher values than this should be promptly put on dual therapy and those with HbA1c ≥10% should benefit from insulin therapy [14].

Lifestyle changes include diet and increasing physical activity. Diabetics are recommended to consume whole grains, vegetables, fruits, low fat dairy products, lean meat, nuts and seeds. Obese patients should lose at least 5% body weight as this provides better glycaemic and risk factors control. At least 150 min of moderate-to-high intensity physical activity per week are recommended. Smoking cessation and psychosocial support are also very important for diabetic patients [14].

Metformin remains an extremely important antidiabetic in T2DM treatment because it has multiple advantages. Firstly, it is an oral drug which offers cardiovascular protection. One study has compared the effect of metformin vs. sulfonylureas or insulin treatments on a 10-year period; the first group reported a 33% decrease in acute myocardial infarction risk while the latter a 15% decrease [8]. Other studies confirmed these results by proving that patients undergoing coronarography while on metformin treatment had a 69% lower risk of acute myocardial infarction than those on insulin therapy [50]. Weight gain is not a side effect of metformin but, on the contrary, metformin provides a slight weight loss [51], has anti-inflammatory benefits [52][53], reduces oxidative stress [54][55]], lowers endothelial dysfunction [48], improves lipid parameters by reducing triglycerides and LDL-cholesterol [51], and reduces hypertension [56][57].

After three months of metformin treatment and lifestyle changes, for the patients who have not reached their glycaemic goals a second oral antidiabetic should be added. Studies have shown that any oral antidiabetic drug added to the initial treatment reduces HbA1c levels by almost 1% [58]. The main difference between ADA 2017 and 2018 guides is choosing the second antidiabetic in patients with atherosclerotic disease [9][14]. Thus, the patients without CVD can benefit from any of the following drug classes: sulfonylureas, DPP-4 inhibitors, GLP-1 agonists, thiazolidinediones and basal insulin. According to ADA 2018, atherosclerosis patients should benefit from drugs which offer cardiovascular protection: SGLT-2 inhibitors or GLP-1 agonists. In case the goal is not reached within 3 months, another drug belonging to a different class is added. Mixed injectable treatment is recommended if the goal could not be reached with three drugs after another three months [14].

Among the new categories of pharmaceutical formulations used in the therapy of diabetes, GLP-1RA and SGLT2-I are encouraging alternatives. In the treatment of T2DM, SGLT2 inhibitors represent the latest therapeutic category accepted. Their action is to supress, in the proximal convoluted tubule of the kidney, the SGLT2 transport proteins.

As these transporters represent almost 90% of the total resorption of filtered glucose in the body, they are valuable instruments in controlling the blood glucose. Being linked to decreases of 0.5–1% in HbA1c, SGLT2 inhibitors represent efficient alternative therapy choices for T2DM [59].

Besides their efficiency in treating diabetes, SGLT2 inhibitors are also helpful in weight loss as well as in the treatment of macrovascular and microvascular complications associated with T2DM [10][60][61]. Furthermore, SGLT2 inhibitors revealed favourable results in treating CV diseases. Moreover, SGLT-2 administration is correlated with renal protective effects; it is known that in patients with DM, CKD is highly prevalent mostly because of the association of hyper-glycemia, dyslipidaemia and high blood pressure [62]. The decrease in sodium reabsorption in the proximal renal tubule leads to a higher concentration of sodium at the level of macula densa, which leads to responsive dilatation of the proximal arteriole and therefore the glomerular filtration pressure is reduced, leading to a protection of renal glomerulus against hemodynamic stress [63]. A considerable improvement in lipid profile was observed after SGLT-2 administration: decreased triglycerides, decreased LDL-cholesterol, increased HDL-cholesterol, and suppression of generating small oxidized LDL-cholesterol molecules [64].

These data prove that the administration of SGLT-2 inhibitors has protective effects, opposed to almost all the pathophysiological mechanisms that insulin resistance generates in patients with T2DM [63], and serves as a useful therapy in clinical practice.

Numerous studies proved the efficacy of SGLT-2 inhibitors; probably the most cited being EMPAREG-OUTCOME that proved that empagliflozin administration, in T2DM patients and cardiovascular pathology, reduced the cardiovascular mortality by 38% (HR: 0.62; 95% CI: 0.49–0.77; $p < 0.001$) [65]. Also, the hospitalization of T2DM patients for heart failure was reduced by 35% [10]. CANVAS study demonstrated that canagliflozin administration reduced with 14% the incidence of 3Point-Major Advance Cardiovascular Events (3P-MACE) (nonfatal stroke, nonfatal myocardial infarction and cardiovascular death) [11].

ADA 2018 mentions that canagliflozin and empagliflozin (SGLT-2 inhibitors] as well as liraglutide (GLP-1 agonists] significantly reduce cardiovascular risk. The American Association of Endocrinologists recommends GLP-1 agonists as a first choice in initiating dual therapy, followed by SGLT-2 inhibitors [66].

GLP-1 receptor agonists (GLP-1 RA), such as exenatide or lixisenatide, act on post-prandial glycaemia, and as dulaglutide or long-acting release exenatide act on the fasting-glycemia [67]. Both types are efficient in reducing hyperglycaemia; various studies demonstrate that exenatide administrated twice daily in a dosage of 10 μg reduced HbA1c with an average of −0.78% statistically significantly higher than placebo [68]. Long acting GLP-1 RA proved superior to exenatide in improving HbA1c. Exenatide administration (twice a day), had a lower impact than long-acting exenatide administered weekly in DURATION-1 study [69], the first GLP-1 RA reduced HbA1c with −1.5% while the second reduced HbA1c with −1.9% ($p = 0.0023$). Exenatide administered twice a day was also inferior to liraglutide in LEAD-6 study, where liraglutide reduced HbA1c with −1.2% while exenatide reduced Hb1c with −0.79% [70]. GLP-1 RA acts by stimulating glucose-dependent insulin secretion, reducing gastric emptying and increasing satiety, reducing the appetite due to their central action on the hunger centre in the central nervous-system [67].

GLP-1 RA not only reduce hyper-glycemia, helping T2DM to achieve glycaemic targets, but they also have numerous effects on other CVR factors of these patients. GLP-1 RA generally reduce blood pressure; DURATION trials demonstrated a blood pressure reduction between −3 and −5 mmHg with exenatide administration, while in LEAD trials, patients treated with liraglutide benefited from a reduction of systolic blood pressure between −2.7 mmHg and −6.6 mmHg [71][72]. GLP-1 RA also act on blood lipids profile, DURATION studies demonstrating a reduction of total cholesterol between 4.64 and 34.8 mg/dL [73]. Another study revealed that exenatide administered twice-daily reduced LDL-cholesterol with −6% and triglycerides with −12% [74]. The reduction of blood pressure and improvement of lipid profile can be partially attributed to weight loss. Dulaglutide resulted in −1.4 to −3 kg weight loss in AWARD-3 study [75], while in LEAD trials liraglutide administration resulted in weight loss between −1 and −3.2kg. Other pleiotropic effects of GLP-1 RA are improvement of endothelial dysfunction by increasing nitric oxide (NO) production and decreasing the expression of vascular adhesion molecules (VAM) in human endothelial cells [76]. Further, they improve the left ventricle contractility and cardiac output [77] and, in animal models, they help in post-ischemia recovery and increase myocardial viability after ischemic events [78], having natriuretic effects and reducing albuminuria [79]. Receptors for GLP-1 are present in numerous tissues not only in the gut; they are also present in the vascular endothelium, cardiac myocytes, the smooth muscular cells of the arteries but also in the lungs, liver, kidneys, and central nervous system [12]. The LEADER trial, which included 9340 patients with T2DM, demonstrated that liraglutide administration resulted in a 13% reduction of 3-P MACE composite outcome (HR 0.87, 95% CI 0.78–0.97, $p < 0.001$) [12]. In SUSTAIN-6 study, that included 3297 patients with T2DM, administration of semaglutide (in a dose of 0.5 or 1.0 mg) resulted in a statistically significant reduction of 3-P MACE, with 26% (HR 0.74, 95% CI 0.58–0.95]) [80].

In case of T2DM patients with low risk of hypo-glycemia, SGLT2-I and GLP-1RA are efficient alternative therapies and may have positive effects on BP, weight and CV risk. GLP-1 agonists and SGLT-2 inhibitors are superior to current antidiabetic drugs such as sulfonylureas, thiazolidinediones, or DPP-4 inhibitors because of their low risk of hypo-glycemia, their beneficial roles in reducing body weight and reducing the grade of insulin resistance, their action on lowering blood lipids; therefore GLP-1 and SGLT-2 have been promoted as second-line therapeutic agents after metformin [81]. Their values come from their ability in reducing CVR [82] and the fact that therapies such as sulfonylureas, thiazolidinediones, and insulin generate weight gain [83], with all the negative consequences. Moreover, hypo-glycemia caused by sulfonylureas and insulin is associated with a significantly higher CVR because of the arrhythmogenic effect of hypo-glycemia caused by the activation of the sympathetic nervous system [84].

Other Cardiovascular Risk Factors Goals and Management

ADA 2017 and 2018 guides recommend target values of BP under 140/90 mmHg for most diabetic patients and mean values of 130/80 mmHg for patients with high CVR [9][24]. The American Association of Endocrinologists recommends target values of BP under 130/80 mmHg [16][21][53]. The ACCORD BP study has shown that reducing

SBP values under 120 mmHg does not offer any additional benefit in comparison to reducing it under 140 mmHg [85]. Multiple classes of anti-hypertensive drugs can be used, although the ideal ones would be ACE inhibitors and ARBs because they reduce the progression of CKD [82][86]. ADA 2017 and 2018 [9][14] guides recommend risk stratification as far as blood fat goals go; patients with atherosclerosis present high-risk respectively those without atherosclerosis present intermediate risk. Patients with high risk should be prescribed high dose statins and those with intermediate risk should be prescribed moderate dose statins, the lipid goals being LDL-cholesterol values of under 70 mg/dL for the former and under 100 mg/dL for the latter. ADA 2018 guide recommends that atherosclerotic patients who do not reach the goal with maximum tolerable statin dose should be added another drug which reduces LDL-cholesterol levels such as ezetimibe or a PCSK9 inhibitor [14]. Aspirin treatment is only recommended for atherosclerotic patients.

Data from multiple guides highlight the fact that the medical therapy should be very carefully chosen in diabetic patients, in such a way that CVR is reduced without any significant side effects. In recent years, there have been anti-diabetic drugs with pleiotropic effects which not only reduce glycaemic values, but also decrease the cardiovascular morbidity and mortality. It is very important to analyse the exact benefit of these drugs through their pleiotropic effect because there are often contraindications for the maximum reduction of the intensity of a CVR factor such as hypertension, thus the effect of the anti-diabetics which offer a cardiovascular benefit can be useful.

References

1. Alessandra Saldanha De Mattos Matheus; Lucianne Righeti Monteiro Tannus; Roberta Arnoldi Cobas; Catia C. Sousa Palma; Carlos Antonio Negrato; Marilia De Brito Gomes; Impact of Diabetes on Cardiovascular Disease: An Update. *International Journal of Hypertension* **2013**, *2013*, 653789, 10.1155/2013/653789.
2. Fonseca, V.; Desouza, C.; Asnani, S.; Jialal, I. Nontraditional risk factors for cardiovascular disease in diabetes. Endocr. Rev. 2004, 25, 153–175.
3. Vesa, C.M.; Popa, A.R.; Bungau, S.; Daina, L.G.; Buhas, C.; Judea-Pusta, C.T.; Pasca, B.; Dimulescu (Nica), I.A.; Zaha, D.C. Exploration of insulin sensitivity, insulin resistance, early insulin secretion and β-cell function, and their relationship with glycated hemoglobin level in normal weight patients with newly diagnosed type 2 diabetes mellitus. Rev. Chim. 2019, 70, 4217–4223.
4. Jay S. Skyler; Richard Bergenstal; Robert O. Bonow; John B. Buse; Prakash Deedwania; Edwin A.M. Gale; Barbara V. Howard; M. S. Kirkman; Mikhail Kosiborod; Peter Reaven; et al.Robert S. Sherwin Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials. *Diabetes Care* **2008**, *32*, 187-192, 10.2337/dc08-9026.
5. Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group; Gerstein, H.C.; Miller, M.E.; Byington, R.P.; Goff, D.C., Jr.; Bigger, J.T.; Buse, J.B.; Cushman, W.C.; Genuth, S.; Ismail-

Beigi, F.; et al.et al. Effects of intensive glucose lowering in type 2 diabetes. *N. Engl. J. Med.* **2008**, *358*, 2545–2559.

6. Anushka Patel; Stephen MacMahon; John Chalmers; Bruce Neal; Laurent Billot; Mark Woodward; Michel Marre; Mark Cooper; Paul Glasziou; Diederick Grobbee; et al.Pavel HametStephen B. HarrapS. R. HellerLisheng LiuGiuseppe ManciaCarl Erik MogensenChangyu PanNeil R PoulterAnthony RodgersBryan WilliamsSeverine BompointBastiaan E. De GalanRohina JoshiFlorence Travert Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. *New England Journal of Medicine* **2008**, *358*, 2560-2572, 10.1056/NEJMoa0802987.
7. Nathan, D.M.; Cleary, P.A.; Backlund, J.Y.; Genuth, S.M.; Lachin, J.M.; Orchard, T.J.; Raskin, P.; Zinman, B.; Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N. Engl. J. Med.* **2005**, *353*, 2643–2653.
8. Rury R. Holman; Sanjoy Paul; Mary Angelyn Bethel; David R. Matthews; H. Andrew W. Neil; 10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes. *New England Journal of Medicine* **2008**, *359*, 1577-1589, 10.1056/NEJMoa0806470.
9. American Diabetes Association. Standards of medical care in diabetes—2017. Diabetes Care 2017, 40 (Suppl. S1), S1–S2.
10. Bernard Zinman; John M. Lachin; Silvio E. Inzucchi; Pantelis Sarafidis; Apostolos Tsapas; Michael Fischereder; Ulf Schönermarck; Jonathan L Edwards; Robert Rosenstein; Augustus Hough; et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes.. *New England Journal of Medicine* **2015**, *373*, 2117–2128, 10.1056/NEJMc1600827.
11. Neal, B.; Perkovic, V.; Mahaffey, K.W.; de Zeeuw, D.; Fulcher, G.; Erondu, N.; Shaw, W.; Law, G.; Desai, M.; Matthews, D.R. for the CANVAS Program Collaborative Group.; et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N. Engl. J. Med.* **2017**, *377*, 644–657.
12. Marso, S.P.; Daniels, G.H.; Brown-Frandsen, K.; Kristensen, P.; Mann, J.F.E.; Nauck, M.A.; Nissen, S.E.; Pocock, S.; Poulter, N.R.; Ravn, L.S.; et al.et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N. Engl. J. Med.* **2016**, *375*, 311–322.
13. Lorber, D. Importance of cardiovascular disease risk management in patients with type 2 diabetes mellitus. Diabetes Metab. Syndr. Obes. 2014, 7, 169–183.
14. American Diabetes Association. Standards of medical care in diabetes—2018. Diabetes Care 2018, 41 (Suppl. S1), S3.
15. Wang, Y.W.; He, S.J.; Feng, X.; Cheng, J.; Luo, Y.T.; Tian, L.; Huang, Q. Metformin: A review of its potential indications. Drug. Des. Devel. Ther. 2017, 11, 2421–2429.
16. Manuela Stoicescu; C Csepento; Gabriela Muţiu; Simona Bungau; The role of increased plasmatic renin level in the pathogenesis of arterial hypertension in young adults.. *Romanian*

journal of morphology and embryology = Revue roumaine de morphologie et embryologie **2011**, *52*, 419–423.

17. Ian H. De Boer; Sripal Bangalore; Athanase Benetos; Andrew M. Davis; Erin D Michos; Paul Muntner; Peter Rossing; Sophia Zoungas; George Bakris; Diabetes and Hypertension: A Position Statement by the American Diabetes Association. *Diabetes Care* **2017**, *40*, 1273-1284, 10.2337/dci17-0026.
18. Thomopoulos, C.; Parati, G.; Zanchetti, A.; Effects of blood-pressure-lowering treatment on outcome incidence in hypertension: 10—Should blood pressure management differ in hypertensive patients with and without diabetes mellitus? Overview and meta-analyses of randomized trials. *J. Hypertens.* **2014**, *32*, 2285–2295.
19. Liang Chen; Jian-Hao Pei; Jian Kuang; Hong-Mei Chen; Zhong Chen; Zhong-Wen Li; Hua-Zhang Yang; Effect of lifestyle intervention in patients with type 2 diabetes: A meta-analysis. *Metabolism* **2015**, *64*, 338-347, 10.1016/j.metabol.2014.10.018.
20. Bruno Vergès; Lipid modification in type 2 diabetes: the role of LDL and HDL. *Fundamental and Clinical Pharmacology* **2009**, *23*, 681-685, 10.1111/j.1472-8206.2009.00739.x.
21. Colhoun, H.M.; Betteridge, D.J.; Durrington, P.N.; Hitman, G.A.; Neil, H.A.; Livingstone, S.J.; Thomason, M.J.; Mackness, M.I.; Charlton-Menys, V.; Fuller, J.H.; et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre randomised placebo-controlled trial. *Lancet* **2004**, *364*, 685–696.
22. Bruno Vergès; Pathophysiology of diabetic dyslipidaemia: where are we?. *Diabetologia* **2015**, *58*, 886-899, 10.1007/s00125-015-3525-8.
23. Cholesterol Treatment Trialists' (Ctt) Collaborators; Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *The Lancet* **2008**, *371*, 1670–1681, 10.1016/s0140-6736(08)60104-x.
24. ACCORD Study Group; Ginsberg, H.N.; Elam, M.B.; Lovato, L.C.; Crouse, J.R.; Leiter, L.A.; Linz, P.; Friedewald, W.T.; Buse, J.B.; Gerstein, H.C.; et al.et al. Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus. *New England Journal of Medicine* **2010**, *362*, 1563–1567, 10.1056/nejmx100016.
25. Keech, A.; Simes, R.J.; Barter, P.; Best, J.; Scott, R.; Taskinen, M.R.; Forder, P.; Pillai, A.; Davis, T.; Glasziou, P.; et al.et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): Randomised controlled trial. *Lancet* **2005**, *366*, 1849–1861.
26. Scott, R.; O'Brien, R.; Fulcher, G.; Pardy, C.; D'Emden, M.; Tse, D.; Taskinen, M.R.; Ehnholm, C.; Keech, A.; Effects of fenofibrate treatment on cardiovascular disease risk in 9,795 individuals with

type 2 diabetes and various components of the metabolic syndrome: The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Diabetes Care* **2009**, *32*, 493–498.

27. Protasio Lemos Da Luz; Desiderio Favarato; Jose Rocha Faria-Neto; Pedro Lemos; Antonio Carlos Palandri Chagas; High ratio of triglycerides to HDL-cholesterol predicts extensive coronary disease. *Clinics (Sao Paulo)* **2008**, *63*, 427–432.
28. Nanik Ram; Bilal Ahmed; Fauzan Hashmi; Abdul Jabbar; Importance of measuring non-HDL cholesterol in type 2 diabetes patients.. *Journal of the Pakistan Medical Association* **2014**, *64*, 124–128.
29. Emerging Risk Factors Collaboration; Emanuele Di Angelantonio; Nadeem Sarwar; Philip Perry; Stephen Kaptoge; Kausik K Ray; Alexander Thompson; Angela M Wood; Sarah Lewington; Naveed Sattar; et al.Chris J PackardRory CollinsSimon G ThompsonJohn DaneshThe Emerging Risk Factors Collaboration* Major Lipids, Apolipoproteins, and Risk of Vascular Disease. *JAMA* **2009**, *302*, 1993-2000, 10.1001/jama.2009.1619.
30. Mach, F.; Baigent, C.; Catapano, A.L.; Koskinas, K.C.; Casula, M.; Badimon, L.; Chapman, M.J.; De Backer, G.G.; Delgado, V.; Ference, B.A.; et al.et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *Eur. Heart J.* **2020**, *41*, 111–188.
31. Klaus G Parhofer; Pathophysiology of diabetic dyslipidemia: implications for atherogenesis and treatment. *Clinical Lipidology* **2011**, *6*, 401-411, 10.2217/clp.11.32.
32. Jian Liu; Christopher Sempos; Richard P. Donahue; Joan Dorn; Maurizio Trevisan; Scott M. Grundy; Joint distribution of non-HDL and LDL cholesterol and coronary heart disease risk prediction among individuals with and without diabetes.. *Diabetes Care* **2005**, *28*, 1916-1921, 10.2337/diacare.28.8.1916.
33. Robinson, J.G.; Wang, S.; Smith, B.J.; Jacobson, T.A. Meta-analysis of the relationship between non-high-density lipoprotein cholesterol reduction and coronary heart disease risk. J. Am. Coll. Cardiol. 2009, 53, 316–322.
34. Frontini, M.G.; Srinivasan, S.R.; Xu, J.; Tang, R.; Bond, M.G.; Berenson, G.S. Usefulness of childhood non-high density lipoprotein cholesterol levels versus other lipoprotein measures in predicting adult subclinical atherosclerosis: The Bogalusa Heart Study. Pediatrics 2008, 121, 924–929.
35. Saeed Ghodsi; Alipasha Meysamie; Mehrshad Abbasi; Reza Ghalehtaki; Alireza Esteghamati; Masoud M. Malekzadeh; Fereshteh Asgari; Mohammad M. Gouya; Non-high-density lipoprotein fractions are strongly associated with the presence of metabolic syndrome independent of obesity and diabetes: a population-based study among Iranian adults.. *Journal of Diabetes & Metabolic Disorders* **2017**, *16*, 25, 10.1186/s40200-017-0306-6.

36. Marie Russell; Angela Silverman; Jerome L. Fleg; Elisa T. Lee; Mihriye Mete; Matthew Weir; Charlton Wilson; Fawn Yeh; Barbara V. Howard; Wm. James Howard; et al. Achieving lipid targets in adults with type 2 diabetes: The Stop Atherosclerosis in Native Diabetics Study. *Journal of Clinical Lipidology* **2010**, *4*, 435-443, 10.1016/j.jacl.2010.07.007.
37. Gloria Lena Vega; Scott M. Grundy; Current trends in non-HDL cholesterol and LDL cholesterol levels in adults with atherosclerotic cardiovascular disease.. *Journal of Clinical Lipidology* **2019**, *13*, 563-567, 10.1016/j.jacl.2019.05.012.
38. Usui, T.; Nagata, M.; Hata, J.; Mukai, N.; Hirakawa, Y.; Yoshida, D.; Kishimoto, H.; Kitazono, T.; Kiyohara, Y.; Ninomiya, T. Serum Non-High-Density Lipoprotein Cholesterol and Risk of Cardiovascular Disease in Community Dwellers with Chronic Kidney Disease: The Hisayama Study. J. Atheroscler. Thromb. 2017, 24, 706–715.
39. Moisi, M.I.; Rus, M.; Bungau, S.; Zaha, C.D.; Uivarosan, D.; Fratila, O.; Tit, D.M.; Endres, L.; Nistor-Cseppento, D.C.; Popescu, M.I. Acute coronary syndromes in chronic kidney disease: Clinical and therapeutic characteristics. Medicina 2020, 56, 118.
40. Viktor Hanak; Julian Munoz; Joe Teague; Alfred Stanley; Vera Bittner; Accuracy of the triglyceride to high-density lipoprotein cholesterol ratio for prediction of the low-density lipoprotein phenotype B. *The American Journal of Cardiology* **2004**, *94*, 219-222, 10.1016/j.amjcard.2004.03.069.
41. R M Conroy; Kalevi Pyörälä; A P Fitzgerald; S Sans; A Menotti; G. De Backer; Dirk De Bacquer; P Ducimetière; P Jousilahti; U Keil; et al.I NjølstadR G OganovT ThomsenH Tunstall-PedoeA TverdalH WedelP WhincupLars WilhelmsenI.M. Graham Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *European Heart Journal* **2003**, *24*, 987–1003.
42. Kazuya Fujihara; Hiroaki Suzuki; Akira Sato; Tomoko Ishizu; Satoru Kodama; Yoriko Heianza; Kazumi Saito; Hitoshi Iwasaki; Kazuto Kobayashi; Shigeru Yatoh; et al.Akimitsu TakahashiNaoya YahagiHirohito SoneHitoshi Shimano Comparison of the Framingham Risk Score, UK Prospective Diabetes Study (UKPDS) Risk Engine, Japanese Atherosclerosis Longitudinal Study-Existing Cohorts Combine (JALS-ECC) and Maximum Carotid Intima-Media Thickness for Predicting Coronary Artery Stenosis in Patients with Asymptomatic Type 2 Diabetes. *Journal of Atherosclerosis and Thrombosis* **2014**, *21*, 799-815, 10.5551/jat.20487.
43. Ittaman, S.V.; VanWormer, J.J.; Rezkalla, S.H.; The role of aspirin in the prevention of cardiovascular disease. *Clin. Med. Res.* **2014**, *12*, 147–154.
44. Simmons, R.K.; Coleman, R.L.; Price, H.C.; Holman, R.R.; Khaw, K.T.; Wareham, N.J.; Griffin, S.J.; Performance of the UK prospective diabetes study risk engi ne and the framingham risk equations in estimating cardiovascular disease in the EPIC- Norfolk Cohort. *Diabetes Care* **2009**, *32*, 708–713.

45. Guzder, R.N.; Gatling, W.; Mullee, M.A.; Mehta, R.L.; Byrne, C.D. Prognostic value of the Framingham cardiovascular risk equation and the UKPDS risk engine for coronary heart disease in newly diagnosed Type 2 diabetes: Results from a United Kingdom study. Diabetes Med. 2005, 22, 554–562.

46. Echouffo-Tcheugui, J.B.; Kengne, A.P. Comparative performance of diabetes-specific and general population-based cardiovascular risk assessment models in people with diabetes mellitus. Diabetes Metab. 2013, 39, 389–396.

47. James Black; Stephen J Sharp; Nicholas J Wareham; Annelli Sandbæk; Guy E H M Rutten; Torsten Lauritzen; Kamlesh Khunti; Michael J. Davies; Knut Borch-Johnsen; S. J. Griffin; et al.Rebecca Simmons Change in cardiovascular risk factors following early diagnosis of type 2 diabetes: a cohort analysis of a cluster-randomised trial.. *British Journal of General Practice* **2014**, *64*, e208-e216, 10.3399/bjgp14X677833.

48. Maria Manea; Dragos Marcu; Anca Pantea Stoian; Mihnea Alexandru Gaman; Amelia Maria Gaman; Bogdan Socea; Tiberiu Paul Neagu; Ana Maria Alexandra Stanescu; Ovidiu Gabriel Bratu; Camelia Cristina Diaconu; et al. Heart Failure with Preserved Ejection Fraction and Atrial Fibrillation A review. *Revista de Chimie* **2018**, *69*, 3280-3284, 10.37358/rc.18.11.6730.

49. Dipika Bansal; Ramya S. R. Nayakallu; Kapil Gudala; Rajavikram Vyamasuni; Anil Bhansali; Agreement between Framingham Risk Score and United Kingdom Prospective Diabetes Study Risk Engine in Identifying High Coronary Heart Disease Risk in North Indian Population. *Diabetes & Metabolism Journal* **2015**, *39*, 321-327, 10.4093/dmj.2015.39.4.321.

50. John Kao; Jonathan Tobis; Robyn L McClelland; Melissa R Heaton; Barry R Davis; David R Holmes; Jesse W Currier; Relation of metformin treatment to clinical events in diabetic patients undergoing percutaneous intervention. *The American Journal of Cardiology* **2004**, *93*, 1347-1350, 10.1016/j.amjcard.2004.02.028.

51. Hauner, H.; Managing type 2 diabetes mellitus in patients with obesity. *Treat Endocrinol.* **2004**, *3*, 223–232.

52. Saisho, Y. Metformin and Inflammation: Its potential beyond glucose-lowering effect. Endocr. Metab. Immune Disord. Drug Targets 2015, 15, 196–205.

53. Popa, A.R.; Bungau, S.; Vesa, C.M.; Bondar, A.C.; Pantis, C.; Maghiar, O.; Dimulescu (Nica), I.A.; Nistor-Cseppento, D.C.; Rus, M. Evaluating the efficacy of the treatment with benfotiamine and alpha-lipoic acid in distal symmetric painful diabetic polyneuropathy. Rev. Chim. 2019, 70, 3108–3114.

54. Chakraborty, A.; Chowdhury, S.; Bhattacharyya, M. Effect of metformin on oxidative stress, nitrosative stress and inflammatory biomarkers in type 2 diabetes patients. Diabetes Res. Clin. Pract. 2011, 93, 56–62.

55. Abdel-Daim, M.M.; El-Tawil, O.S.; Bungau, S.G.; Atanasov, A.G. Applications of antioxidants in metabolic disorders and degenerative diseases: Mechanistic approach. Oxid. Med. Cell. Longev. 2019, 2019.

56. Landin-Wilhelmsen, K. Metformin and blood pressure. J. Clin. Pharm. Ther. 1992, 17, 75–79.

57. Gaman, M.A.; Dobrica, E.C.; Pascu, E.G.; Cozma, M.A.; Epingeac, M.E.; Gaman, A.M.; Pantea Stoian, A.; Bratu, O.G.; Diaconu, C.C. Cardiometabolic risk factors for atrial fibrillation in type 2 diabetes mellitus: Focus on hypertension, metabolic syndrome and obesity. J. Mind Med. Sci. 2019, 6, 157–161.

58. Wendy L. Bennett; Nisa M. Maruthur; Sonal Singh; Jodi B. Segal; Lisa M. Wilson; Ranee Chatterjee; Spyridon S. Marinopoulos; Milo A. Puhan; Padmini Ranasinghe; Lauren Block; et al.Wanda K. NicholsonSusan HutflessEric B. BassShari Bolen Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations.. *Annals of Internal Medicine* **2011**, *154*, 602-613, 10.7326/0003-4819-154-9-201105030-00336.

59. Daniel S. Hsia; Owen Grove; William T. Cefalu; An update on sodium-glucose co-transporter-2 inhibitors for the treatment of diabetes mellitus.. *Current Opinion in Endocrinology & Diabetes and Obesity* **2017**, *24*, 73-79, 10.1097/MED.0000000000000311.

60. Pereira, M.J.; Eriksson, J.W. Emerging role of SGLT-2 inhibitors for the treatment of obesity. Drugs 2019, 79, 219–230.

61. Davidson, J.A. SGLT2 inhibitors in patients with type 2 diabetes and renal disease: Overview of current evidence. Postgrad. Med. 2019, 131, 251–260.

62. Macaulay Amechi Chukwukadibia Onuigbo; Nneoma Agbasi; Diabetic Nephropathy and CKD—Analysis of Individual Patient Serum Creatinine Trajectories: A Forgotten Diagnostic Methodology for Diabetic CKD Prognostication and Prediction. *Journal of Clinical Medicine* **2015**, *4*, 1348-1368, 10.3390/jcm4071348.

63. Natalia De Albuquerque Rocha; Ian J Neeland; Peter A McCullough; Robert D Toto; Darren K McGuire; Effects of sodium glucose co-transporter 2 inhibitors on the kidney.. *Diabetes and Vascular Disease Research* **2018**, *15*, 375-386, 10.1177/1479164118783756.

64. Heidi Storgaard; Lise Lotte Gluud; Cathy Bennett; Magnus F. Grøndahl; Mikkel B. Christensen; Filip K. Knop; Tina Vilsbøll; Benefits and Harms of Sodium-Glucose Co-Transporter 2 Inhibitors in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. *PLOS ONE* **2016**, *11*, e0166125, 10.1371/journal.pone.0166125.

65. Nigro, J.; Osman, N.; Dart, A.M.; Little, P.J.; Insulin Resistance and Atherosclerosis. *Endocr. Rev.* **2006**, *27*, 242–259.

66. Garber, A.J.; Abrahamson, M.J.; Barzilay, J.I.; Blonde, L.; Bloomgarden, Z.T.; Bush, M.A.; Dagogo-Jack, S.; DeFronzo, R.A.; Einhorn, D.; Fonseca, V.A.; et al.et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm – 2018 Executive Summary. *Endocr. Pract.* **2018**, *24*, 91–120.

67. Del Olmo-Garcia, M.I.; Merino-Torres, J.F.; GLP-1 Receptor Agonists and Cardiovascular Disease in Patients with Type 2 Diabetes. *J. Diabetes Res.* **2018**, *2018*, 4020492.

68. Lalita Prasad-Reddy; Diana Isaacs; A clinical review of GLP-1 receptor agonists: efficacy and safety in diabetes and beyond. *Drugs in Context* **2015**, *4*, 212283, 10.7573/dic.212283.

69. John B. Buse; Daniel J. Drucker; Kristin L. Taylor; Terri Kim; Brandon Walsh; Hao Hu; Ken Wilhelm; Michael Trautmann; Larry Z. Shen; Lisa E. Porter; et al. DURATION-1: Exenatide Once Weekly Produces Sustained Glycemic Control and Weight Loss Over 52 Weeks. *Diabetes Care* **2010**, *33*, 1255-1261, 10.2337/dc09-1914.

70. Buse, J.B.; Rosenstock, J.; Sesti, G.; Schmidt, W.E.; Montanya, E.; Brett, J.H.; Zychma, M.; Blonde, L.; LEAD-6 Study Group.; Liraglutide once a day versus exenatide twice a day for type 2 diabetes: A 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet* **2009**, *374*, 39–47.

71. Sun, F.; Wu, S.; Guo, S.; Yu, K.; Yang, Z.; Li, L.; Zhang, Y.; Quan, X.; Ji, L.; Zhan, S. Impact of GLP-1 receptor agonists on blood pressure, heart rate and hypertension among patients with type 2 diabetes: A systematic review and network meta-analysis. Diabetes Res. Clin. Pract. 2015, 110, 26–37.

72. Okerson, T.; Yan, P.; Stonehouse, A.; Brodows, R. Effects of exenatide on systolic blood pressure in subjects with type 2 diabetes. Am. J. Hypertens. 2010, 23, 334–339.

73. Feng Sun; Shanshan Wu; Jing Wang; Shuxia Guo; Sanbao Chai; Zhirong Yang; Lishi Li; Yuan Zhang; Linong Ji; Siyan Zhan; et al. Effect of Glucagon-like Peptide-1 Receptor Agonists on Lipid Profiles Among Type 2 Diabetes: A Systematic Review and Network Meta-analysis. *Clinical Therapeutics* **2015**, *37*, 225-241.e8, 10.1016/j.clinthera.2014.11.008.

74. David C. Klonoff; John B. Buse; Loretta L. Nielsen; Xuesong Guan; Christopher L. Bowlus; John H. Holcombe; Matthew E. Wintle; D. G. Maggs; Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. *Current Medical Research and Opinion* **2008**, *24*, 275-286, 10.1185/030079907x253870.

75. Guillermo Umpierrez; Linda Shurzinske; Pechtner V; Santiago Tofé Povedano; Federico Pérez Manghi; Efficacy and Safety of Dulaglutide Monotherapy Versus Metformin in Type 2 Diabetes in a Randomized Controlled Trial (AWARD-3). *Diabetes Care* **2014**, *37*, 2168-2176, 10.2337/dc13-2759.

76. Tracey Gaspari; HongBin Liu; Iresha Welungoda; Yunshan Hu; Robert E. Widdop; Lotte Bjerre Knudsen; Richard W Simpson; Anthony E. Dear; A GLP-1 receptor agonist liraglutide inhibits endothelial cell dysfunction and vascular adhesion molecule expression in an ApoE-/- mouse model. *Diabetes and Vascular Disease Research* **2011**, *8*, 117-124, 10.1177/1479164111404257.

77. Yun Xie; Shao-Xin Wang; Wei-Wei Sha; Xue Zhou; Wei-Lin Wang; Li-Pin Han; Dai-Qing Li; De-Min Yu; Effects and mechanism of glucagon-like peptide-1 on injury of rats cardiomyocytes induced by hypoxia-reoxygenation. *Chinese Medical Journal* **2008**, *121*, 2134-2138, 10.1097/00029330-200811010-00005.

78. Ming Yu; Carol Moreno; Kimberly M Hoagland; Annette Dahly; Katie Ditter; Mahesh Mistry; R J Roman; Antihypertensive effect of glucagon-like peptide 1 in Dahl salt-sensitive rats. *Journal of Hypertension* **2003**, *21*, 1125-1135, 10.1097/00004872-200306000-00012.

79. Saraiva, F.K.; Sposito, A.C.; Cardiovascular effects of glucagon-like peptide 1 (GLP-1) receptor agonists. *Cardiovasc. Diabetol.* **2014**, *13*, 142.

80. Steven P Marso; Steve C Bain; Agostino Consoli; Freddy G. Eliaschewitz; Esteban Jódar; Lawrence A. Leiter; Ildiko Lingvay; Julio Rosenstock; Jochen Seufert; Mark L. Warren; et al.Vincent WooOluf HansenAnders G. HolstJonas PetterssonTina VilsbøllSUSTAIN-6 Investigators Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes.. *New England Journal of Medicine* **2016**, *375*, 1834-1844, 10.1056/NEJMoa1607141.

81. Bertoccini, L.; Baroni, M.G. GLP-1 Receptor Agonists and SGLT2 Inhibitors for the Treatment of Type 2 Diabetes: New Insights and Opportunities for Cardiovascular Protection. Adv. Exp. Med. Biol. 2020.

82. Moisi, M.; Vesa, C.M.; Bungau, S.; Tit, D.M.; Corb Aron, R.A.; Bratu, O.; Diaconu, C.C.; Rus, M.; Popescu, M.I.; Acute kidney injury incidence and models for mortality prediction in acute coronary syndromes. *Rom. J. Mil. Med.* **2020**, *123*, 133–140.

83. Vicky Cheng; Sangeeta R. Kashyap; Weight Considerations in Pharmacotherapy for Type 2 Diabetes. *Journal of Obesity* **2010**, *2011*, 984245, 10.1155/2011/984245.

84. Markolf Hanefeld; Brian M. Frier; Frank Pistrosch; Hypoglycemia and Cardiovascular Risk: Is There a Major Link?. *Diabetes Care* **2016**, *39*, S205-S209, 10.2337/dcs15-3014.

85. Cushman, W.C.; Evans, G.W.; Byington, R.P.; Goff, D.C., Jr.; Grimm, R.H., Jr.; Cutler, J.A.; Simons-Morton, D.G.; Basile, J.N.; Corson, M.A.; Probstfield, J.L.; et al.et al. Effects of intensive blood pressure control in type 2 diabetes mellitus. *N. Engl. J. Med.* **2010**, *362*, 1575–1585.

86. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO-HOPE substudy. Lancet 2000, 355, 253–259.