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# **An review on epidemiology, biochemical characteristics, treatment suggestions, and continued studies on diabetes and cardiovascular disease**

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**Abstract**---Diabetes mellitus (DM) has become one of the very frequent and costliest chronic disease. Diabetes mellitus (DM) and cardiovascular disease (CVD), which is also the largest risk factor for mortality in diabetic individuals, have just a close relationship. Obesity, hypertension, and dyslipidemia all seem to be significant CV significant risk factor in people with diabetes, bringing them at greater risk for heart attacks and strokes. Also, several research have shown physiological processes linked to DM that enhance the risk of CVD in diabetic patients within their own. As a result, minimizing CV risk factors in diabetic individuals is essential to minimize the disease's long-term CV problems. This article investigates probable origins of disease progression, current treatment recommendations, and future studies prospects while discussing the relationship between diabetes and CVD.

**Keywords**---diabetes mellitus, cardiovascular disease, mechanism, treatment.

**Introduction**

The prevalence of diabetes mellitus (DM) is growing considerably global. Over the beyond 3 decades, the worldwide burden of DM has swelled from 30 million in 1985 to 382 million in 2014, with present day developments indicating that those charges will simplest preserve to rise[1]. The contemporary estimates through the global diabetes federation task that 592 million (1 in 10 persons) global could have DM through 2035[2]. While the charges of each kind 1 DM (T1DM) and T2DM are developing, T2DM has a disproportionately extra contribution to the growing incidence of DM globally as compared to T1DM[1]. One effect of the developing charges of DM is a tremendous financial burden each for the affected person and the healthcare device. In the United States, the entire value of DM

averages \$2108/affected person according to year, which is almost two times that of non-diabetic sufferers[3]. The financial burden related to DM is extensive each in phrases of the direct prices of hospital therapy in addition to oblique prices of dwindled productiveness tied to diabetes associated morbidity and mortality[4]. The direct prices of DM are usually attributed to each macrovascular and microvascular headaches inclusive of coronary artery disorder, myocardial infarction, high blood pressure, peripheral vascular disorder, retinopathy, end-level renal disorder and neuropathy[3,4]. A near hyperlink exists among DM and cardiovascular disorder (CVD). CVD is the maximum time-honored reason of mortality and morbidity in diabetic populations[5].

CVD dying charges withinside the United States are 1.7 instances better amongst adults (> 18 years) with DM than the ones with out recognized DM, in large part because of an accelerated chance of stroke and myocardial infarction (MI)[6]. This accelerated chance of CVD mortality in diabetic sufferers is discovered in each guys and ladies. The relative chance for CVD morbidity and mortality in adults with diabetes degrees from 1 to three in guys and from 2 to five in ladies as compared to the ones the ones with out DM[7]. Proper manipulate and remedy of DM is vital as each the superiority and financial burden of the disorder preserve to mount. As CVD is the maximum time-honored reason of mortality and morbidity in sufferers with DM, a number one intention of diabetes remedy ought to be to enhance the cardiovascular (CV) chance of diabetic sufferers. However, one project related to treating DM and lowering CV activities is the complicated and multifaceted nature of the connection linking DM to CVD. CV chance elements inclusive of obesity, high blood pressure and dyslipidemia are not unusualplace in sufferers with DM, specially people with T2DM. In addition, research have pronounced that numerous elements inclusive of accelerated oxidative stress, accelerated coagulability, endothelial disorder and autonomic neuropathy are regularly found in sufferers with DM and can at once make a contribution to the improvement of CVD[5]. Collectively, the excessive charges of CV chance elements and direct organic consequences of diabetes at the CV device area diabetic sufferers at accelerated chance of growing CVD, and make a contribution to the accelerated incidence of MI, revascularization, stroke and CHF[5,8]. Due to the complexity and severa mechanisms linking DM to CVD, it's far vital to recognition remedy to what's going to have the finest scientific effect on enhancing CV outcomes. This paper examines the mechanisms linking DM to CVD in addition to present day remedy suggestions and destiny studies in diabetes management.

## **CV risk factors and CVD**

### **Obesity**

Obesity is not unusualplace in sufferers with DM, specially T2DM, and is related to an expanded threat of CVD. One feasible mechanism linking DM and weight problems with next CVD is low-grade infection[9]. DM and insulin resistance are related to the overexpression of many cytokines through adipose tissue along with tumor necrosis factor- $\alpha$ , interleukin (IL)-1, IL-6, leptin, resistin MCP-1, PAI-1, fibrinogen and angiotensin[10].The overexpression of those cytokines contributes to expanded infection and lipid accumulation, that have a deleterious impact on blood vessels and might result in the improvement of endothelial disorder, MI and

cardiomyopathy (CMP)[5,11-14]. Diabetic sufferers additionally have expanded quantities of C-reactive protein (CRP), which might also additionally make contributions to endothelial disorder. Many research have confirmed that CRP impairs endothelial manufacturing of nitric oxide (NO) and prostacyclin, which might be important to vessel compliance. CRP has additionally been proven to growth the uptake of oxidized low-density lipoprotein (LDL) in coronary vasculature walls, that could make contributions to endothelial disorder in addition to the improvement of atherosclerotic plaques[14]. Patients with DM additionally have reduced adiponectin manufacturing, which might also additionally bring about faded endothelial function[10]. Adiponectin enables restrict endothelial disorder through growing NO manufacturing and lowering the expression of adhesion molecules. Adiponectin is likewise protecting withinside the atherosclerotic process through inhibiting LDL oxidation[15]. This growth in atherosclerotic plaque can area diabetic patients at a heightened threat of MI. In particular, expanded tiers withinside the inflammatory cytokine IL-1, as visible in sufferers with DM, can make contributions to the destabilization of atheromatous plaques and next MI[11]. Insulin resistance is likewise related to an elevation of plasma loose fatty acids, main to will increase in muscular triglycerides stores, hepatic glucose manufacturing, and expanded insulin manufacturing in sufferers with T2DM[16]. Insulin resistance has additionally been connected to CMP in diabetics through cardiomyocyte hypertrophy and contractile disorder[16,17].

### **Hypertension**

Hypertension may be very not unusual place amongst sufferers with T1DM and T2DM, with occurrence quotes of 30% and 60%, respectively[5]. Hypertension amongst diabetic sufferers is intently tied to the improvement of diabetic nephropathy (DN)[18]. With DN, renal cells are inspired through hyperglycemia, main to the manufacturing of humoral mediators, cytokines, and boom elements. The manufacturing of those elements is regularly answerable for structural changes visible withinside the glomeruli of diabetic sufferers along with hyaline arteriosclerosis (in general of the efferent arteriole), expanded collagen deposition of the extracellular matrix, and expanded permeability of the glomerular basement membrane[19]. These structural modifications growth filtration stress and regularly result in microalbuminemia with a compensatory activation of the renin-angiotensin system (RAAS). Chronic activation of the RAAS regularly progresses to hypertension, putting brought pressure at the glomeruli and inflicting extra harm to the nephrons of diabetic sufferers. If left untreated, DN can development to a nephrotic syndrome, characterised through proteinuria, a hypercoagulable state (because of lack of ATIII) and hyperlipidemia, which might also additionally make contributions to the expanded threat of CVD visible in diabetic sufferers with renal disorder[20,21].

### **Dyslipidemia**

Diabetic sufferers are at improved danger of growing dyslipidemia[22]. One mechanism underlying this connection is improved loose fatty-acid launch found in insulin-resistant fats cells. High degrees of loose-fatty acids sell triglyceride production, which in flip stimulates the secretion of apolipoprotein B (ApoB) and really LDL (VLDL) ldl cholesterol. High degrees of ApoB and VLDL have each been

tied to improved danger of CVD[23-26]. In addition to excessive ApoB and VLDL, hyperinsulinemia is related to low excessive-density lipoprotein (HDL) ldl cholesterol degrees[27]. Hyperglycemia might also negatively effect lipoproteins (specially LDL and VLDL) thru improved glycosylation and oxidation, reducing vascular compliance and facilitating the improvement of competitive atherosclerosis[28]. High circulating FFA's and triglycerides, improved stimulation of ApoB and VLDL ldl cholesterol, reduced HDL degrees and lipoprotein change have all been liked in sufferers with DM and probably contributes to the excessive incidence of CVD in diabetic sufferers.

### **Diabetic cardiomyopathy**

DM seems to make a contribution immediately to the improvement of CMP, in place of completely through coronary atherosclerosis and hypertension[29]. This diabetic CMP has been defined in lots of noninvasive research and consists of modifications that arise in LV shape and cardiac characteristic of diabetics. Specifically, diabetics have a tendency to have extra cardiac mass, specially LV mass, than the ones with out DM[30,31]. This can be associated with an improved adipocyte launch of cytokines which includes leptin and resistin that have hypertrophic results on cardiomyocytes[12,13]. One examine searching at a multi-ethnic populace discovered that the chance of getting LV mass that exceeds the seventy fifth percentile is extra in sufferers with T2DM, even after adjusting for covariates[32]. Patients with DM additionally have a tendency to have a barely dwindled diastolic characteristic evaluate to nondiabetics[33-35]. One viable mechanism will be that improved triglyceride synthesis in sufferers with DM ends in improved myocardial triglyceride content[36]. Increased cardiac triglyceride accumulation is related to lipotoxicity and adjusted calcium hemostasis in myocardium, each of which negatively effect diastolic characteristic[37-39]. This ought to assist give an explanation for the locating that 40%-75% of people with DM and no symptoms and symptoms of overt coronary artery disease (CAD) be afflicted by diastolic disorder[34,35]. Subtle abnormalities in systolic characteristic have additionally been located in sufferers with DM the usage of tissue Doppler imaging and Doppler pressure evaluation of top systolic velocity[40-44]. This systolic disorder can be associated with impaired myocardial sympathetic innervation and impaired contractile reserve[45]. In addition, interstitial fibrosis with improved collagen deposition has been located in sufferers with DM and might negatively make a contribution to the dwindled cardiac characteristic visible in diabetics[46]. It is probably that among the mechanisms that make a contribution to discounts in systolic and diastolic characteristic visible in diabetic sufferers additionally region them at an improved danger of coronary heart failure (HF)[47,48]. The incidence of HF, specially coronary heart failure and preserved ejection fraction, is better in diabetic sufferers (16%-31%) than the overall populace (4%-6%)[49]. While a number of the distinction can be accounted for with the aid of using conventional CV danger factors, DM might also additionally independently regulate cardiac shape and characteristic with the aid of using selling hypertrophy and fibrosis[50].

### **Cardiovascular Autonomic Neuropathy**

Cardiovascular autonomic neuropathy (CAN) is not unusual place amongst sufferers with DM and is correlated with an multiplied 5-yr mortality fee from CVD[51]. The scientific manifestations of CAN are resting tachycardia, hypotension, exercising intolerance, peculiar coronary vasomotor regulation, multiplied QT interval, and perioperative instability. Collectively, the scientific manifestations of CAN are associated with an multiplied chance of renal disease, stroke, CVD and unexpected death[52]. The improvement and development of CAN is probably associated with dysregulation of the autonomic anxious machine (ANS) with multiplied sympathetic pastime and improved inflammatory markers. As the ANS is liable for keeping the pastime of the sinus node, cease diastolic extent, cease systolic extent and systemic vascular resistance, ANS disorder can result in arterial stiffness, left ventricular hypertrophy and ventricular diastolic disorder[53]. Incidence of CAN will increase with age and insufficient glycemic control, which locations sufferers with DM at better chance of growing each CAN and CVD[54].

### **Myocardial infarction and DM**

Diabetes is a first-rate chance issue for the improvement of CAD with a better occurrence of MI in sufferers with DM than the ones with out[55,56]. In addition, following a MI, diabetic sufferers have better costs of morbidity, mortality and re-infarction than non-diabetics, with oneyear mortality costs of almost 50%[57]. Although the precise pathophysiology of CAD development in sufferers with DM has now no longer but been determined, the maximum latest research postulate that the underlying atherosclerotic technique is comparable among people with and with out DM. It is notion that the better occurrence of myocardial infarction in sufferers with DM is due to multiplied coagulability[58]. Many research have observed that diabetics have multiplied expression of glycoprotein IIb/IIIAreceptors and vWF, which can be liable for platelet activation[59,60]. Patients with DM additionally have multiplied plasminogen activator inhibitor kind 1 which could lower fibrinolysis, growth thrombus formation and boost up plaque formation[61]. Finally, diabetic sufferers additionally have a tendency to have reduced circulating anti-coagulants including protein c and antithrombin III due in a massive element to the proteinuria gift with DN[62]. Collectively, those elements area sufferers with DM in a prothrombotic and procoagulant state, which can also additionally account for the better costs of MI visible in diabetic sufferers. Silent myocardial ischemia may additionally make a contribution to the better costs of MI visible in diabetic sufferers. Ischemia and next angina frequently serves as an early caution machine to sufferers growing obstructive CAD[63]. However, people with silent ischemia are frequently asymptomatic and recognized later into the development of CAD, that is related to better costs of MI-associated mortality and morbidity[64]. Silent ischemia is some distance greater regular in sufferers with DM (10%-20%) than the ones with out DM (1%-4%). This disparity can be liable for the remark visible in a few angiographic research wherein CAD become generally greater superior on the time of prognosis in diabetic sufferers[65,66]. Diabetic neuropathy is one issue which could provide an explanation for the multiplied occurrence of silent ischemia in sufferers with DM[67,68].

## **Treatment**

As CVD is the maximum general reason of mortality and morbidity in sufferers with DM, powerful remedy is vital to decrease the following threat of CV events, especially MI, CAD, stroke and CHF in diabetics. Suboptimal glycemic manage, obesity, hypertension, dyslipidemia and autonomic disorder are not unusualplace CV threat elements amongst diabetic sufferers, putting them at heightened threat of CV complications. Therapy that istargeted to adjust those threat elements can enhance CV outcomes, however this will be a tough to achieve. The recommendations pertaining to those threat elements commonly range from the recommendations for non-diabetic sufferers and the hints regularly extrade or vary relying on what agency publishes them. In addition, the studies on how those distinct threat elements have an effect on the CV threat profile of diabetics may be unclear, and at times, contradictory. The motive of this segment is to offer the maximum current recommendations for the remedy of glycemic manage, hypertension, dyslipidemia and autonomic disorder in sufferers with DM, and additionally describe the studies that relates to every of those topics.

## **Glycemic Control**

As many research have connected bad glycemic manage to worse CV outcomes, modern-day remedy hints for sufferers with DM location a heavy emphasis on carefully tracking and controlling glycemic degrees which will enhance cardiac outcomes. The precise glycemic degree that have to be centered for diabetics, however, is debatable and varies relying on which agency is making the tenet. For example, the modern-day advice through the American Association of Clinical Endocrinologists Guidelines has a aim hemoglobin A1c (HbA1c) of much less than or identical to 6.5%, and encourages vendors to deal with sufferers with an A1c fee extra than 6.5% with a mixture of life-style modification, weight reduction and pharmacological agents[69].

The ACC/AHA have a barely extra comfortable A1c aim of much less than 7% for non-pregnant sufferers with T1DM or T2DM so that it will lessen the threat of microvascular or macrovascular complications. In addition, ACC/ AHA additionally qualifies their advice through which include a advice that an A1c aim of extra than 7 can be suitable for sufferers with a records of excessive hypoglycemia, constrained lifestyles expectancy, superior microvascular or macrovascular complications, great comorbidities, or for people with lengthy-status diabetes. The advice additionally states that an A1c aim decrease than the overall aim of much less than 7.0% can be useful for sure diabetic affected person populations which include people with a brief length of diabetes, lengthy lifestyles expectancy, and no CVD[70]. The VA/DoD recommendations use a extra individualized set of rules for figuring out the proper A1c aim for diabetic sufferers. This tenet variety from a goal A1c of < 7 to < nine relying at the affected person's modern-day fitness status, comorbid conditions, lifestyles expectancy, threat of hypoglycemia and length of diabetes status[71].

## CV outcomes

There had been many research which have investigated the impact of in depth remedy of hyperglycemia on CV consequences in sufferers with diabetes. The UKPDS trial changed into one of the first multi-middle, randomized manipulate trials to analyze the impact of in depth glycemic manipulate in sufferers with currently recognized T2DM. Patients have been both randomized to “traditional” or “in depth” glycemia-decreasing remedy and have been accompanied for 10 years. The in depth glycemic organization decreased HbA1c through 11% over 10 years (median 7.0%) in comparison to the organization handled with traditional remedy who did now no longer have a good sized alternate of their HbA1c (median 7.9%). The number one impact visible withinside the organization with tighter glycemic manipulate changed into a 12% discount in all diabetes-related endpoints and a 25% discount in microvascular disorder (often thru reduced retinopathy). In addition, the in depth remedy organization trended toward a lower in macrovascular disorder even though it changed into now no longer statistically good sized[72]. Another huge look at that investigated the impact of tight glycemic manipulate in sufferers with T2DM changed into the VADT trial. The populace for this look at consisted often of older (suggest age 60.four years) person guys with poorly managed T2DM (common HbA1c of 9.four%) and a median length of disorder of 11.five years. The topics have been randomized to both “in depth” or “traditional” glycemia-decreasing remedy and have been accompanied for five.6 years.

The organization with the tighter glycemic manipulate did have a drastically extra lower in A1c degrees over the direction of the look at (6.9% vs 8.four%), however there has been no good sized lower in MI or all reason mortality in the “in depth” remedy organization in comparison to the “traditional” remedy organization. The ADVANCE trial located a focal point at the vascular consequences of in depth glycemic remedy in adults with T2DM. This huge multi-middle randomized manipulate trial recruited T2DM sufferers with a records of main macrovascular or microvascular disorder from 215 collaboratin facilities in 20 countries. Subjects have been randomized together an “in depth” or “standard” glycemia-decreasing method and accompanied for five years. The in depth glycemic remedy organization changed into handled to an HbA1c of les than or same to 6.five%. The organization randomized to the tighter glycemic manipulate did have a drastically extra discount in HbA1c (6.five% vs 7.3%) and skilled a 23% discount in microvascular events (often nephropathy). However, there has been no distinction among the agencies in MI or all reason mortality and the organization with ‘in depth’ remedy had elevated charges of extreme hypoglycemia hospitalization[74]. The ACCORD trial become carried out simultaneously to the ADVANCE trial and centered frequently on whether or not in depth glycemic manipulate decreased to hazard of CV occasions. This multi-middle randomized manipulate trial investigated if very tight glycemic manipulate (much less than or same to an HbA1c of 6%) had decrease charges of nonfatal MI, nonfatal stroke and CV dying than trendy glycemic manipulate (HbA1c of 7%-7.9%) in older adults.

The topics have been accompanied for a median of 3.four years and the organization with the tighter glycemic manipulate did reap a appreciably decrease

HbA1c than people with trendy remedy (7.3% vs 6.5%). The in depth glycemic manipulate organization had barely decrease charges of nonfatal MI, however after 3.7 years the trial become stopped early due to the fact the in depth remedy organization had accelerated charges of all-cause and CV mortality. The organization with tight glycemic manipulate additionally had accelerated weight benefit, and hazard of hypoglycemia as visible withinside the ADVANCE trial. DCCT and the long-time period follow-up trial EDIC investigated how strict glycemic manipulate with in depth remedy effected CV consequences in sufferers with T1DM. These trials randomized young (a while 13-39 years) sufferers with T1DM to either “in depth” or “traditional” glycemic remedy with an HbA1c purpose of 7% withinside the organization for the ones withinside the “in depth” remedy organization. The number one locating of the DCCT trial become that when 10 years of follow-up, the organization with strict glycemic manipulate had a 70% decrease withinside the variety of microvascular complications, specially retinopathy.

In addition, the long-time period follow-up study, EDIC, located a 42% discount in CV occasions withinside the organization with in depth glycemic remedy in comparison to the traditional glycemic remedy. While it does seem that a hyperlink exists among glycemic manipulate and CV consequences in diabetic sufferers, the findings so far at the impact of tight glycemic manipulate on CVD are conflicting. Current research fail to expose that in depth glycemic manipulate (HbA1c  $\leq$  6.5%) has a good sized CV advantage as in comparison to conventional glycemic manipulate targets (HbA1c of 7%-7.9%) in sufferers with T2DM. While there can be a small discount withinside the variety of microvascular occasions in T2D sufferers with the tighter glycemic manipulate, there does now no longer appear to be a sizable advantage withinside the charges of all-cause and CV-particular mortality. Furthermore, very tight glycemic manipulate (HbA1c  $\leq$  6%), as visible withinside the ACCORD trial, may also location sufferers at extra hazard of hypoglycemia, weight benefit and all cause mortality. In sufferers with T1DM, tighter glycemic manipulate does look like beneficial. The DCCT and EDIC trials do advise that in depth glycemic remedy (intention HbA1c  $\geq$  7%) can assist lessen quotes of microvascular and macrovascular ailment in T1D.

One capacity interpretation of the research so far is that the concurrent CV hazard elements found in diabetics might also additionally weigh down any gain that in depth remedy of hyperglycemia can offer in decreasing hazard. Thus, diabetic sufferers who acquire tighter glycemic manage in advance at some stage in their ailment route and previous to the improvement of different CV hazard elements might also additionally see the best gain from greater in depth remedy in phrases of CV outcomes. For this reason, a number of the new hints appearance to tailor A1c dreams to the person affected person in preference to a unmarried A1c cutoff for all diabetic sufferers. The ACC/AHA and VA/DoD, for example, regulate their glycemic dreams primarily based totally on elements which includes age, years with the ailment and CV hazard. While in addition research are had to decide what the satisfactory glycemic remedy intention is for those distinctive affected person populations, adjusting the goal A1c relying at the person’s contemporary stage of CVD hazard might also additionally offer gain to diabetic sufferers.

## Obesity

Obesity is a not unusual place comorbidity of DM, specifically T2DM, and is related with better costs of CV morbidity and mortality. Thus, modern-day remedy guidelines inspire weight reduction in obese and overweight sufferers with DM to enhance their CV threat profile and reduce the threat of CVD. The advice is for 5% weight reduction over four years in diabetic sufferers which might be obese or overweight. A “moderate” quantity of proof shows that 5% weight reduction with the aid of using way of life intervention is related to an boom in HDL-c, a discount in triglycerides and a lower in newly prescribed lipid decreasing medicinal drugs in diabetic sufferers. In addition, there's a “high” degree of proof suggesting that orlistat outcomes in 2-three kg of weight reduction in obese and overweight diabetic sufferers at 1 and a couple of years, and is related to extra discounts in fasting blood glucose and HbA1c. These guidelines have been graded as high, moderate, or low on the idea of medical methodology, medical strength, and consistency of outcomes[77].

As weight problems is a prime threat element each for CVD and T2DM, many research have investigated the efficacy of weight reduction in lowering the improvement and severity of DM. Some research have targeted on frame weight loss in pre-diabetic sufferers so that it will lower the occurrence of next DM. Of note, the diabetes prevention program (DPP) and finnish diabetes prevention research evaluated the impact of conduct amendment on weight reduction and consequent threat of growing diabetes in pre-diabetic adults. Both research yielded comparable outcomes in that the ones randomized to the way of life intervention organization had considerably extra weight reduction and decreased threat of growing diabetes in comparison to the manage organization[78,79]. Other research have checked out techniques for accomplishing weight reduction and enhancing the CV threat profile of sufferers who're already diabetic. A style of strategies inclusive of in depth way of life intervention, weight reduction medicinal drugs and bariatric surgical operation have been powerful in accomplishing weight reduction and enhancing the CV threat profile of diabetic sufferers thru progressed glycemic manage, blood strain and ldl cholesterol levels[80-82].

Although many research have proven that weight reduction may be accomplished in diabetic sufferers, there's blended proof as to whether or not weight reduction in those sufferers genuinely reduces next CV morbidity and mortality. Thus far, there was blended proof if modest weight reduction in sufferers with DM does enhance their CV threat. While the SCOUT trial located that modest weight reduction should enhance 5-yr CV mortality costs amongst diabetic sufferers, the Look AHEAD trial did now no longer discover that weight reduction had any impact on CV mortality, MI, stroke, or angina hospitalization after 9.6 years of follow-up[83,84]. The modern-day advice for obese and overweight sufferers with DM is a purpose weight reduction of 5%[77]. Studies to this point have verified that this purpose is achievable each in pre-diabetic and diabetic sufferers via lots of strategies together with in depth behavioral change therapy, pharmacological dealers and bariatric surgery. In addition, all of those techniques of weight reduction seem to both lower the fees of incident DM in pre-diabetic sufferers, or enhance the CV chance profile of diabetic sufferers[78-82].

However, it's far uncertain whether or not modest weight reduction in diabetic sufferers interprets to a lower in CVD[83,84]. It is feasible that the CV chance profile is just too excessive in older adults with DM for modest weight reduction to make a big development in CV outcomes. It is probably extra high quality to attention weight problems remedy efforts on pre-diabetics earlier than they broaden DM. Programs inclusive of the DPP have verified that weight reduction can lower the fee of incident diabetes, however similarly studies is wanted to decide if modest weight reduction in pre-diabetic sufferers effects in stepped forward CV morbidity and mortality[78]. It is likewise feasible that even as modest weight reduction does appear to enhance the CV chance profile of sufferers with DM, even more weight reduction is essential to peer extra definitive upgrades withinside the fees of CV occasions. Further research into the consequences of weight reduction more than 5% on CVD in diabetic sufferers might also additionally assist become aware of the life of a dose impact with weight reduction and CV health.

### **Hypertension**

Since high blood pressure is a not unusualplace comorbidity of sufferers with DM and a chief chance component for CVD, the modern-day remedy hints strongly inspire vendors to decrease BP in hypertensive diabetics. There are many research which have investigated the impact of reducing blood strain in sufferers with diabetes on CV outcomes. The UKPDS 38 trial tested the impact of tight manage of blood strain manage (< 150/85) as compared to much less tight manage (< 180/105) on macrovascular and microvascular headaches in sufferers with T2DM. After nine years follow-up, imply blood strain become extensively decrease withinside the tightly managed BP organization (144/eighty two mmHg) as compared to the sufferers withinside the much less tightly managed organization (154/87 mmHg). In addition, the organization with tighter BP manage had a 34% discount in macrovascular sickness chance (myocardial infarction, surprising death, stroke, and peripheral vascular sickness) and a 37% discount in chance of microvascular sickness (retinopathy requiring photocoagulation, vitreous haemorrhage, and deadly or non-deadly renal failure) as compared with the much less tightly managed BP organization[85]. While many research have proven that reducing BP in diabetics does enhance CV outcomes, the ACCORD-BP trial investigated the impact of in depth BP manage (systolic BP < a hundred and twenty mmHg) as compared to conventional BP manage (systolic BP < one hundred forty mmHg) at the chance of deadly or nonfatal most important CV occasions in sufferers with T2DM.

After 4.7 years of follow-up, the organization with in depth BP manage did now no longer have a discount in deadly and nonfatal most important CV occasions as compared to the standard BP control group (1.87% vs 2.09% per year). In addition, the in depth BP organization had elevated unfavorable activities which include hypotension, syncope, bradycardia or arrhythmia, hyperkalemia, angioedema and renal failure[86]. Given the outcomes of those trials, latest remedy guidelines suggest that, pharmacologic remedy need to be initiated at a SBP of > one hundred forty mmHg or a DBP of > ninety mmHg for diabetic adults among 18 and 60 years of age. For sufferers older than 60, the edge to provoke remedy is a SBP of < one hundred fifty mmHg or a DBP of < ninety mmHg. The

advice at the kind of pharmacological remedy that need to be used varies withinside the trendy nonblack vs black population. For nonblack sufferers with DM and high blood pressure, preliminary remedy need to encompass a thiazide-kind diuretic, calcium channel blocker (CCB), angiotensin-changing enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). For black sufferers with DM and high blood pressure, the preliminary remedy need to encompass a thiazide-kind diuretic or a CCB. In addition, hypertensive sufferers with DM and CKD need to be handled with an ACE inhibitor or an ARB to enhance kidney outcomes[87].

While specific antihypertensive sellers used to deal with high blood pressure have various metabolic consequences, many research, which include the ALLHAT trail, discovered no enormous distinction withinside the danger of coronary coronary heart disease, nonfatal myocardial infarction, general mortality, or different medical headaches attributable to the preliminary antihypertensive drug remedy used to deal with diabetic sufferers[88,89]. This might advocate that metabolic variations among the numerous antihypertensive sellers do now no longer play a first-rate position withinside the next improvement of CVD in sufferers with DM. It need to be referred to that those guidelines were arguable and numerous authors have argued that the rule of thumb is just too comfortable withinside the remedy of positive at-danger organizations which include African Americans, ladies and the aged primarily based totally on preceding research comparing blood strain manage and next CVD in those populations[90]. There is in all likelihood a healing BP variety that offers diabetic sufferers with a decrease CV danger however additionally protects them from advers activities related to hypotension. Whether the brand new guidelines, specially with the elevated systolic BP threshold in adults over 60 years, suit this healing BP variety is but to be determined. There is likewise little proof as to what the right remedy variety need to be for specific age organizations. In addition, high blood pressure in specific racial subgroups might also additionally have specific consequences on CV health. Further studies is wanted to research the appropriate BP variety for adults of various age organizations in addition to specific racial organizations.

### **Dyslipidemia**

Dyslipidemia is each not unusualplace in sufferers with DM and related to elevated chance of CVD[91,92]. Healthm vendors are recommended to perceive and aggressively deal with sufferers with dyslipidemia to assist decrease their chance of next CV events. The present day advice for treating dyslipidemia in diabetic sufferers varies with the aid of using age and is in step with reputation that remedy with fixed-dose statins, as a substitute to particular LDL goal levels, is the confirmed technique from scientific trials. Accordingly, diabetic sufferers who're beneathneath the age of forty are encouraged to take a excessive-depth statin in the event that they have scientific proof of atherosclerotic CVD or a LDL-c more than 189 mg/dL. All diabetic sufferers over the age of forty are recommended to start statin remedy.

Patients over forty with an predicted 10-12 months ASCVD chance more than 7.5% are handled with a excessive-depth statin, and sufferers with a 10-12 months ASCVD chance much less than 7.5% are handled with a moderate-depth statin[93]. There had been many research carried out to decide the impact of

treating dyslipidemia in diabetic sufferers as a way to decrease CV chance. The CARDS look at turned into the primary multicenter randomized managed trial to assess statin remedy prospectively in sufferers with T2DM. Adult sufferers with T2DM had been randomized to both acquire a placebo or 10 mg/d of atorvastatin. The median follow-up time turned into 3.nine years and the institution handled with atorvastatin had a mean 26% discount in general ldl cholesterol and a forty% discount in LDL-c. In addition, the statin remedy institution had a 37% discount in CV events, a 27% discount in all-purpose mortality and a 48% discount in stroke compared to the institution handled with the placebo. The CARDS trial turned into stopped early to due the large gain verified with statin remedy[94].

After the CARDS trial determined that statin remedy supplied a large CV gain to diabetic sufferers, the TNT trial tested the impact of excessive-dose statins on CAD mortality, non-deadly MI, and deadly or nonfatal stroke in diabetic sufferers with T2DM. Adult sufferers with T2DM had been randomized to acquire both a excessive dose (eighty mg/d) or low dose (10 mg/d) statin and accompanied on common for 4.nine years. The excessive dose statin institution achieved more discount in LDL-c (seventy seven mg/dL vs one zero one mg/dL) and had a more discount in blended CAD mortality, non-deadly MI, or deadly or nonfatal stroke (8.7% vs 10.nine%) as in comparison to the decrease dose institution. However, it turned into cited that the better dose institution did have a better charge of unfavourable events (myalgia, continual elevation in alanine aminotransferase, aspartate aminotransferase, or rhabdomyolysis)[95]. As many research had verified that statins, specially excessive-dose statins, had CV gain in diabetic sufferers, the 4D look at tested the impact of statins in diabetic sufferers receiving hemodialysis. In the 4D trial, diabetic sufferers receiving hemodialysis have been randomly assigned both 20 mg of atorvastatin consistent with day or a placebo. The cause of the look at became to decide if a low-dose statin in diabetic sufferers with quit level renal sickness decreased the costs of demise from cardiac causes, nonfatal myocardial infarction, and stroke compared to the placebo institution.

The institution randomized the statin remedy did have a good sized discount of their LDL-c as in comparison to the placebo institution (-42.0% vs -1.3%), however there has been no good sized distinction among the corporations in CV consequences after 3.ninety six years of followup. In addition, there have been appreciably greater instances of deadly stroke withinside the statin remedy institution than the ones handled with a placebo[96]. While the preceding research had targeted on lowering ldl cholesterol in diabetic sufferers the usage of statin remedy, different studies corporations have investigated the impact of non-statin lipid-reducing treatment plans on CVD in diabetic sufferers. For example, the FIELD trial evaluated if reducing ldl cholesterol thru fenofibrate remedy should enhance CV consequences in sufferers with DM. In the FIELD trial, diabetic sufferers (imply age sixty two years; 63% men) have been randomized to both obtain a fenofibrate (2 hundred mg/d) or a placebo after which assessed for next costs of deadly coronary coronary heart sickness (CHD) or nonfatal MIs. While the institution randomized to the fenofibrate remedy did lessen their ldl cholesterol as in comparison to the placebo institution at four mo (general ldl cholesterol, LDL-ldl cholesterol, and triglycerides through 11%, 12%, and 29%, respectively), the variations reduced among the corporations because the trial endured due in a massive component to sufferers beginning extra ldl cholesterol

reducing treatment plans out of doors of the look at. After a mean of five years, the institution randomized to the fenofibrate institution had a mixed 11% discount in deadly CHD or nonfatal MIs, however this distinction became nonsignificant.

The fenofibrate institution did but have a statistically good sized discount (24% in nonfatal MI' as in comparison to the placebo institution[97]. In addition, for the reason that HDL has been diagnosed in lots of massive potential research to be related to advanced CV health, a few studies corporations have investigated whether or not elevating HDL thru pharmaceutical dealers reduces the chance of CV events. The HATS trial became the primary to research the impact of growing HDL with Niacin remedy and generated promising effects on enhancing CV consequences in person sufferers (16% with DM). After 38 mo of follow-up, the institution randomized to the niacin remedy did have a good sized boom in HDL and sufferers with T2DM had a 13% increase in absolute chance of CV sickness[98]. Recently however, the AIM-HIGH trial located no vast medical gain in including Niacin remedy to sufferers with atherosclerotic CVD compared to a placebo. The trial changed into stopped after three years because of loss of efficacy; the organization randomized to the niacin remedy (34% with DM) did now no longer have a vast discount in composite coronary coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for an acute coronary syndrome, or symptom-pushed coronary or cerebral revascularization (16.4% vs 16.2%) notwithstanding vast upgrades in HDL (25% vs 11.8%).

These findings had been comparable among diabetics and nondiabetics[99]. Dyslipidemia is customary amongst diabetic sufferers and a primary hazard aspect for CVD[91,92]. Current remedy pointers inspire carriers to decrease lipid degrees in diabetic sufferers, broadly speaking thru the usage of statins, with a dose depending on the patient's stage of hazard. Some trials have additionally investigated if extra CV gain may be completed in sufferers with DM via way of means of combining a statin with different lipid-reducing therapies. For example, the IMPROVE-IT trial located that the aggregate of ezetimibe (a ldl cholesterol absorption inhibitor) with simvastatin changed into advanced to simvastatin by myself in decreasing CV occasions for diabetic sufferers with acute coronary syndrome[100]. The proof to date indicates that statin remedy in sufferers with DM is positive for CV fitness and that better doses, in addition to blended lipid-reducing remedy, can offer extra CV protection[93]. While a few meta-analyses have advised that statin remedy can be related to improved occurrence of DM, absolutely the gain of the remedy in diabetic sufferers in large part outweighs the hazard[101]. Other lipid reducing retailers, including fenofibrates, have now no longer confirmed the equal stage of efficacy and discounts in CV occasions as statins[97]. Pharmacological retailers that boost HDL additionally seem to offer minimal, if any, CV gain[98,99]. Further research are essential to higher recognize the position of HDL in CV fitness.

## **CAN**

CAN is a now no longer unusualplace worry of diabetes and places patients with DM at elevated threat of CV related morbidity and mortality. The autonomic ailment typically decided in diabetic patients is associated with a immoderate

threat of cardiac arrhythmias and unexpected death, further to distinctive extreme CV sequelae collectively with silent myocardial ischemia, diabetic cardiomyopathy, stroke, and every intraoperative and perioperative CV instability. Some of the most now no longer unusual place scientific manifestations of CAN include coronary coronary heart fee variability (variability withinside the on the spotaneous beat-to-beat intervals), resting tachycardia, exercise intolerance, orthostatic hypotension and bizarre blood strain regulation[102]. Early treatment of autonomic ailment can sluggish the pathogenesis and complications of CAN[102].

Some studies have demonstrated that tight glycemic manipulate also can moreover play an crucial function in reducing the prevalence of CAN in patients with DM. For example, the DCCT demonstrated that patients with better glycemic manipulate, as measured thru Hba1c, had significantly lower threat of developing autonomic ailment regular with a CAN index[103]. While the effect of glycemic manipulate on CAN in patients with T2DM have been a good deal much less conclusive, some trials, collectively with the Steno-2 have a examine decided that improving glucose manipulate and distinctive CV threat factors reduced the prevalence of CAN in T2DM patients[104].

Lifestyle interventions that target improving exercise staying energy and promote weight loss have moreover improved autonomic ailment. Pharmacological treatment collectively with ACE inhibitors, angiotensin receptor blockers and aldose reductase inhibitors moreover appear to help sluggish the improvement of CAN[54]. In addition, IGF-1, ACE inhibitors and beta-blockers appear like beneficial withinside the treatment of diabetic cardiomyopathy thru slowing ventricular hypertrophy and normalizing the calcium homeostasis in diabetic cardiomyocytes[105-109]. Further studies are necessary, however, to validate what the nice pharmacological treatment is for diabetic patients with CAN.

### **Future directions in the treatment of DM**

While there have been many trials that have helped further the expertise of DM as it relates to CVD, further research is wanted to better find out and quantify CV threat in patients with DM. Determining ho glycemic manipulate relates to CVD is every different area wherein more research is wanted. There is some evidence that improved glycemic manipulate does in truth beautify CV outcomes patients with DM[72,73]. One have a examine even decided that HbA1c in non-diabetic patients is an independent predictor of coronary artery diseaseand its severity that may suggest that glycemic manipulate is critical to managing CV health in all affected man or woman populations[110]. While this observational trial shows an independent association also can moreover exist amongst glycemic degrees and CVD, massive randomized manipulate trials which incorporates ADVANCE and ACCORD have demonstrated that the effect of tight glycemic manipulate on subsequent CVD is modest and in massive element because of coexistent traditional threat factors[73-75,110]. One feasible purpose of the conflicting outcomes surrounding the relationship amongst glycemic control and CVD is due to terrible length tools. For example, fasting plasma glucose (FPG) is frequently used as a degree of glycemia, however research have observed a dayto- day within-man or woman variance of 12%-15% in FPG stages of diabetic

sufferers[111]. While the every day within-man or woman variance for HbA1c is a long way higher (< 2%), there may be proof that HbA1c does not anymore appropriately mirror glycemic manage because of organic versions and variations in RBC survival amongst sufferers [111-113].If glycemic manage does matter, nicely measuring glycemia and correlating it to CV danger is vital to be able to set clinically significant dreams for sufferers with DM.

The length and onset of advanced glycemic manage can also make contributions to the development and severity of CVD. The UKPDS verified that tight glycemic manage become related to discounts in CV effects in middle-elderly adults (median fifty four years) who had been these days identified with DM[72]. Conversely, the ADVANCE and ACCORD trials pronounced that tight glycemic manage won't offer any discount in next CVD and might surely be dangerous in sufferers that had been barely older and with an extended length of diabetes[74,75]. This would possibly monitor that treating hyperglycemia aggressively in highrisk sufferers with longer-status DM is just too overdue to have a clinically great impact, and that earlier, competitive remedy amongst sufferers rapidly after DM prognosis can be greater beneficial. More research are had to higher apprehend the connection among glycemic manage and the improvement of CVD and decide if the onset and length of remedy topics withinside the discount of CV occasions in sufferers with DM. Further studies is likewise essential to decide what the nice remedy is to lower the danger and severity of cardiomyopathy and CAN in sufferers with DM.

Many research have verified that autonomic disorder and diabetic cardiomyopathy are ailment strategies that aren't best not unusualplace in sufferers with DM, however additionally location them at accelerated danger of next CV complications [102]. Lifestyle modification, tighter glycemic manage and pharmacological marketers seem to offer a few advantage in slowing the development of CAN and diabetic cardiomyopathy [54,102-109]. However, few research have investigated what unique remedy is handiest in treating those conditions, in addition to what is probably completed to save you the improvement of those ailment strategies altogether. Additional studies is likewise had to higher apprehend how conventional CV danger elements along with dyslipidemia, weight problems and blood stress ought to be monitored and controlled in diabetic sufferers. For example, aggregate remedy can be the great manner to deal with dyslipidemia, opposite to the modern-day advice that focuses commonly on statin mono-remedy. More research like IMPROVE-IT may want to assist decide what remedy is simplest to manipulate dyslipidemia in diabetic sufferers[100].

In addition, the function of HDL on CV fitness is complicated, and similarly research is vital to decide if pharmacological dealers designed to boom HDL can offer scientific advantage in diabetic sufferers. The impact of weight reduction in sufferers with DM is likewise relatively doubtful as to if, and the way much, weight reduction is vital to acquire clinically great upgrades in CV consequences. Five percentage weight reduction might not be enough for diabetic sufferers with different CV threat elements and comorbidities. Further research are had to decide what quantity of weight reduction is wanted reap CV advantage, and what the great remedy approach is to attain that weight reduction goal. Finally, follow-

up concerning the brand new blood strain guidelines, specifically in adults over 60 years who now fall below the better systolic BP threshold, will want to be intently monitored transferring forward.

## Conclusion

As the superiority of DM maintains to rise, related CVD - via each conventional CV threat elements and the direct consequences of DM on CVD - also can be anticipated to rise. Accordingly, right manipulate and remedy of DM, in conjunction with competitive remedy of related CV threat elements is imperative to curtailing the developing incidence and development of DM and CVD. Additional studies is wanted to higher apprehend the sickness technique and its consequences on CV fitness so that it will enhance clinical control and CV consequences in diabetic sufferers.

## References

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; 27: 1047-1053 .
2. Aguiree F, Brown A, Cho NH, Dahlquist G, Dodd S, Dunning T, Hirst M, Hwang C, Magliano D, Patterson C. *IDF Diabetes Atlas*. 2013.
3. Bahia LR, Araujo DV, Schaan BD, Dib SA, Negrato CA, Leão MP, Ramos AJ, Forti AC, Gomes MB, Foss MC, Monteiro RA, Sartorelli D, Franco LJ. The costs of type 2 diabetes mellitus outpatient care in the Brazilian public health system. *Value Health* 2011; 14: S137-S140.
4. American Diabetes Association. Economic costs of diabetes in the U.S. In 2007. *Diabetes Care* 2008; 31: 596-615.
5. Matheus AS, Tannus LR, Cobas RA, Palma CC, Negrato CA, Gomes MB. Impact of diabetes on cardiovascular disease: an pdate. *Int J Hypertens* 2013; 2013: 653789 .
6. Centers for Disease Control and Prevention. National diabetes statistics report: Estimates of diabetes and its burden in the United States, 2014. Atlanta, GA: US Department of Health and Human Services, 2014
7. Rivelles AA, Riccardi G, Vaccaro O. Cardiovascular risk in women with diabetes. *Nutr Metab Cardiovasc Dis* 2010; 20: 474-480.
8. Li YW, Aronow WS. Diabetes mellitus and cardiovascular disease. *J Clinic Experiment Cardiol* 2011; 2: 2.
9. Duncan BB, Schmidt MI, Pankow JS, Ballantyne CM, Couper D, Vigo A, Hoogeveen R, Folsom AR, Heiss G; Atherosclerosis Risk in Communities Study. Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk communities study. *Diabetes* 2003; 52: 1799-1805 .
10. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. *J Clin Invest* 2006; 116: 1793-1801.
11. Vicenová B, Vopálenský V, Burýsek L, Pospíšek M. Emerging role of interleukin-1 in cardiovascular diseases. *Physiol Res* 2009; 58:481-498 .
12. Barouch LA, Berkowitz DE, Harrison RW, O'Donnell CP, Hare JM. Disruption of leptin signaling contributes to cardiac

- hypertrophy independently of body weight in mice. *Circulation* 2003; 108: 754-759.
13. Kim M, Oh JK, Sakata S, Liang I, Park W, Hajjar RJ, Lebeche D. Role of resistin in cardiac contractility and hypertrophy. *J Mol Cell Cardiol* 2008; 45: 270-280.
  14. Chait A, Han CY, Oram JF, Heinecke JW. Thematic review series: The immune system and atherogenesis. Lipoprotein-associated inflammatory proteins: markers or mediators of cardiovascular disease? *J Lipid Res* 2005; 46: 389-403 .
  15. Ferrarezi DA, Cheurfa N, Reis AF, Fumeron F, Velho G. Adiponectin gene and cardiovascular risk in type 2 diabetic patients: a review of evidences. *Arq Bras Endocrinol Metabol* 2007; 51:
    - a. 153-159.
  16. Leahy JL. Pathogenesis of type 2 diabetes mellitus. *Arch Med Res* 2005; 36: 197-209 .
  17. Belke DD, Betuing S, Tuttle MJ, Graveleau C, Young ME, Pham M, Zhang D, Cooksey RC, McClain DA, Litwin SE, Taegtmeier H, Severson D, Kahn CR, Abel ED. Insulin signaling coordinately regulates cardiac size, metabolism, and contractile protein isoform expression. *J Clin Invest* 2002; 109: 629-639.
  18. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993; 329: 977-986.
  19. Schena FP, Gesualdo L. Pathogenetic mechanisms of diabetic nephropathy. *J Am Soc Nephrol* 2005; 16 Suppl 1: S30-S33.
  20. Gesualdo L, Ranieri E, Monno R, Rossello MR, Colucci M, Semeraro N, Grandaliano G, Schena FP, Ursi M, Cerullo G. Angiotensin IV stimulates plasminogen activator inhibitor-1 expression in proximal tubular epithelial cells. *Kidney Int* 1999; 56: 461-470
  21. Wolf G, Ziyadeh FN. The role of angiotensin II in diabetic nephropathy: emphasis on nonhemodynamic mechanisms. *Am J Kidney Dis* 1997; 29: 153-163.
  22. Kannel WB. Lipids, diabetes, and coronary heart disease: insights from the Framingham Study. *Am Heart J* 1985; 110: 1100-1107
  23. Taskinen MR. Diabetic dyslipidaemia: from basic research to clinical practice. *Diabetologia* 2003; 46: 733-749.
  24. Krauss RM, Siri PW. Dyslipidemia in type 2 diabetes. *Med Clin North Am* 2004; 88: 897-909,
  25. Solano MP, Goldberg RB. Management of dyslipidemia in diabetes. *Cardiol Rev* 2006; 14: 125-135.
  26. Chahil TJ, Ginsberg HN. Diabetic dyslipidemia. *Endocrinol Metab Clin North Am* 2006; 35: 491-510.
  27. Mooradian AD, Albert SG, Haas MJ. Low serum high-density lipoprotein cholesterol in obese subjects with normal serum triglycerides: the role of insulin resistance and inflammatory cytokines. *Diabetes Obes Metab* 2007; 9: 441-443.
  28. Hamilton SJ, Watts GF. Endothelial dysfunction in diabetes: pathogenesis, significance, and treatment. *Rev Diabet Stud* 2013; 10: 133-156.

29. Asghar O, Al-Sunni A, Khavandi K, Khavandi A, Withers S, Greenstein A, Heagerty AM, Malik RA. Diabetic cardiomyopathy. *Clin Sci (Lond)* 2009; 116: 741-760.
30. Galderisi M, Anderson KM, Wilson PW, Levy D. Echocardiographic evidence for the existence of a distinct diabetic cardiomyopathy (the Framingham Heart Study). *Am J Cardiol* 1991; 68: 85-89.
31. Santra S, Basu AK, Roychowdhury P, Banerjee R, Singhania P, Singh S, Datta UK. Comparison of left ventricular mass in normotensive type 2 diabetes mellitus patients with that in the nondiabetic population. *J Cardiovasc Dis Res* 2011; 2: 50-56.
32. Eguchi K, Boden-Albala B, Jin Z, Rundek T, Sacco RL, Homma S, Di Tullio MR. Association between diabetes mellitus and left ventricular hypertrophy in a multiethnic population. *Am J Cardiol* 2008; 101: 1787-1791.
33. Patil VC, Patil HV, Shah KB, Vasani JD, Shetty P. Diastolic dysfunction in asymptomatic type 2 diabetes mellitus with normal systolic function. *J Cardiovasc Dis Res* 2011; 2: 213-222 .
34. Brooks BA, Franjic B, Ban CR, Swaraj K, Yue DK, Celermajer DS, Twigg SM. Diastolic dysfunction and abnormalities of the microcirculation in type 2 diabetes. *Diabetes Obes Metab* 2008; 10:739-746.
35. Shivalkar B, Dhondt D, Goovaerts I, Van Gaal L, Bartunek J, Van Crombrugge P, Vrints C. Flow mediated dilatation and cardiac function in type 1 diabetes mellitus. *Am J Cardiol* 2006; 97: 77-82.
36. Sharma S, Adroque JV, Golfman L, Uray I, Lemm J, Youker K, Noon GP, Frazier OH, Taegtmeyer H. Intramyocardial lipid accumulation in the failing human heart resembles the lipotoxic rat heart. *FASEB J* 2004; 18: 1692-1700.
37. McGavock JM, Lingvay I, Zib I, Tillery T, Salas N, Unger R, Levine BD, Raskin P, Victor RG, Szczepaniak LS. Cardiac steatosis in diabetes mellitus: a 1H-magnetic resonance spectroscopy study. *Circulation* 2007; 116: 1170-1175.
38. Rijzewijk LJ, van der Meer RW, Smit JW, Diamant M, Bax JJ, Hammer S, Romijn JA, de Roos A, Lamb HJ. Myocardial steatosis is an independent predictor of diastolic dysfunction in type diabetes mellitus. *J Am Coll Cardiol* 2008; 52: 1793-1799.
39. Aasum E, Hafstad AD, Severson DL, Larsen TS. Age-dependent changes in metabolism, contractile function, and ischemic sensitivity in hearts from db/db mice. *Diabetes* 2003; 52: 434-441.
40. Fang ZY, Schull-Meade R, Leano R, Mottram PM, Prins JB, Marwick TH. Screening for heart disease in diabetic subjects. *Am Heart J* 2005; 149: 349-354.
41. Yu CM, Chau E, Sanderson JE, Fan K, Tang MO, Fung WH, Lin H, Kong SL, Lam YM, Hill MR, Lau CP. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. *Circulation* 2002; 105:438-445 .
42. Ng AC, Delgado V, Bertini M, van der Meer RW, Rijzewijk LJ, Hooi Ewe S, Siebelink HM, Smit JW, Diamant M, Romijn JA, de Roos A, Leung DY, Lamb HJ, Bax JJ. Myocardial steatosis and biventricular strain and strain rate imaging in patients with type 2 diabetes mellitus. *Circulation* 2010; 122: 2538-2544.

43. Ng AC, Delgado V, Bertini M, van der Meer RW, Rijzewijk LJ, Shanks M, Nucifora G, Smit JW, Diamant M, Romijn JA, de Roo A, Leung DY, Lamb HJ, Bax JJ. Findings from left ventricular strain and strain rate imaging in asymptomatic patients with type 2 diabetes mellitus. *Am J Cardiol* 2009; 104: 1398-1401.
44. Ernande L, Rietzschel ER, Bergerot C, De Buyzere ML, Schnell F, Groisne L, Ovize M, Croisille P, Moulin P, Gillebert TC, Derumeaux G. Impaired myocardial radial function in asymptomatic patients with type 2 diabetes mellitus: a speckle-tracking imaging study *J Am Soc Echocardiogr* 2010; 23: 1266-1272.
45. Scognamiglio R, Avogaro A, Casara D, Crepaldi C, Marin M, Palisi M, Mingardi R, Erle G, Fasoli G, Dalla Volta S. Myocardial dysfunction and adrenergic cardiac innervation in patients with insulin-dependent diabetes mellitus. *J Am Coll Cardiol* 1998; 31: 404-412.
46. Regan TJ, Lyons MM, Ahmed SS, Levinson GE, Oldewurtel HA, Ahmad MR, Haider B. Evidence for cardiomyopathy in familial diabetes mellitus. *J Clin Invest* 1977; 60: 884-899.
47. Tribouilloy C, Rusinaru D, Mahjoub H, Tartièrre JM, Kesri-Tartièrre L, Godard S, Peltier M. Prognostic impact of diabetes mellitus in patients with heart failure and preserved ejection fraction: a prospective five-year study. *Heart* 2008; 94: 1450-1455.
48. Magri CJ, Cassar A, Fava S, Felice H. Heart failure with preserved ejection fraction and diabetes mellitus. *J Diab Res Clin Met* 2012; 1:2.
49. From AM, Leibson CL, Bursi F, Redfield MM, Weston SA, Jacobsen SJ, Rodeheffer RJ, Roger VL. Diabetes in heart failure: prevalence and impact on outcome in the population. *Am J Med* 2006; 119:591-599.
50. Dei Cas A, Khan SS, Butler J, Mentz RJ, Bonow RO, Avogaro A, Tschoepe D, Doehner W, Greene SJ, Senni M, Gheorghide M, Fonarow GC. Impact of diabetes on epidemiology, treatment, and outcomes of patients with heart failure. *JACC Heart Fail* 2015; 3: 136-145
51. Rolim LC, Sá JRd, Chacra AR, Dib SA. Neuropatia autonômica cardiovascular diabética: fatores de risco, impacto clínico diagnóstico precoce. *Arq Bras Cardiol* 2008; 90: e24-e32
52. Rolim LC, Sá JR, Chacra AR, Dib SA. Diabetic cardiovascular autonomic neuropathy: risk factors, clinical impact and early diagnosis. *Arq Bras Cardiol* 2008; 90: e24-e31.
53. Prince CT, Secrest AM, Mackey RH, Arena VC, Kingsley LA, Orchard TJ. Cardiovascular autonomic neuropathy, HDL cholesterol, and smoking correlate with arterial stiffness markers
54. determined 18 years later in type 1 diabetes. *Diabetes Care* 2010; 33: 652-657.
55. Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. *Circulation* 2007; 115: 387-397.
56. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA* 1979; 241: 2035-2038.
57. Fuller JH, Shipley MJ, Rose G, Jarrett RJ, Keen H. Mortality from coronary heart disease and stroke in relation to degree of glycaemia: the Whitehall study. *Br Med J (Clin Res Ed)* 1983; 287:867-870.
58. Haffner SM. Coronary heart disease in patients with diabetes. *N Engl J Med* 2000; 342: 1040-1042.

59. Williams IL, Noronha B, Zaman AG. Review: The management of acute myocardial infarction in patients with diabetes mellitus. *BJDVD* 2003; 3: 319-324.
60. Vinik AI, Erbas T, Park TS, Nolan R, Pittenger GL. Platelet dysfunction in type 2 diabetes. *Diabetes Care* 2001; 24: 1476-1485.
61. Vischer UM, Emeis JJ, Bilo HJ, Stehouwer CD, Thomsen C, Rasmussen O, Hermansen K, Wollheim CB, Ingerslev J. von Willebrand factor (vWf) as a plasma marker of endothelial activation in diabetes: improved reliability with parallel determination of the vWf propeptide (vWf: AgII). *Thromb Haemost* 1998; 80: 1002-1007.
62. Sobel BE, Woodcock-Mitchell J, Schneider DJ, Holt RE, Marutsuka K, Gold H. Increased plasminogen activator inhibitor type 1 in coronary artery atherectomy specimens from type 2
63. diabetic compared with nondiabetic patients: a potential factor predisposing to thrombosis and its persistence. *Circulation* 1998;97: 2213-2221.
64. Ceriello A, Giugliano D, Quatraro A, Marchi E, Barbanti M, Lefèbvre P. Evidence for a hyperglycaemia-dependent decrease of antithrombin III-thrombin complex formation in humans. *Diabetologia* 1990; 33: 163-167 .
65. Boras J, Brkljačić N, Ljubičić A, Ljubić S. Silent ischemia and diabetes mellitus. *Diabetologia Croatica* 2010; 39: 57-65.
66. Wackers FJ, Young LH, Inzucchi SE, Chyun DA, Davey JA, Barrett EJ, Taillefer R, Wittlin SD, Heller GV, Filipchuk N, Engel S, Ratner RE, Iskandrian AE. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. *Diabetes Care* 2004; 27: 1954-1961 .
67. Fazzini PF, Prati PL, Rovelli F, Antonucci D, Menghini F, Seccareccia F, Menotti A. Epidemiology of silent myocardial ischemia in asymptomatic middle-aged men (the ECCIS Project). *Am J Cardiol* 1993; 72: 1383-1388.
68. Koistinen MJ. Prevalence of asymptomatic myocardial ischaemia in diabetic subjects. *BMJ* 1990; 301: 92-95.
69. Ziegler D, Gries FA, Spüler M, Lessmann F. The epidemiology of diabetic neuropathy. *Diabetic Cardiovascular Autonomic Neuropathy Multicenter Study Group. J Diabetes Complication*
  - a. 1992; 6: 49-57.
  - b. O'Brien IA, O'Hare JP, Lewin IG, Corral RJ. The prevalence of autonomic neuropathy in insulin-dependent diabetes mellitus: a controlled study based on heart rate variability. *Q J Med* 1986; 61: 957-967.
70. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, Dagogo-Jack S, Davidson MB, Einhorn D, Garvey WT, Grunberger G, Handelsman Y, Hirsch IB, Jellinger PS, McGill JB, Mechanick JI, Rosenblit PD, Umpierrez GE, Davidson MH. American Association of Clinical Endocrinologists' comprehensive diabetes management algorithm 2013 consensus statement--executive summary. *Endocr Pract* 2013; 19: 536-557.
71. Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EA, Howard BV, Kirkman MS, Kosiborod M, Reaven P, Sherwin RS. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Circulation* 2009; 119: 351-357.

73. Pogach L, Conlin PR, Hobbs C, Vigersky RA. VA-DoD Update of Diabetes Guidelines: What Clinicians Need to Know About Absolute Risk of Benefits and Harms and A1c Laboratory Accuracy. Federal Practitioner, 2011
74. King P, Peacock I, Donnelly R. The UK prospective diabetes study (UKPDS): clinical and therapeutic implications for type 2 diabetes. *Br J Clin Pharmacol* 1999; 48: 643-648
75. Duckworth WC, McCarren M, Abraira C. Glucose control and cardiovascular complications: the VA Diabetes Trial. *Diabetes Care* 2001; 24: 942-945.
76. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; 358: 2560-2572.
77. Riddle MC. Effects of intensive glucose lowering in the management of patients with type 2 diabetes mellitus in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Circulation* 2010; 122: 844-846 .
78. Writing Team for the Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications Research Group. Sustained effect of intensive treatment of type diabetes mellitus on development and progression of diabetic
  - a. nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *JAMA* 2003; 290: 2159-2167 .
79. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, Hu FB, Hubbard VS, Jakicic JM, Kushner RF, Loria CM, Millen BE, Nonas CA, Pi-Sunyer FX, Stevens J, Stevens VJ, Wadden TA, Wolfe BM, Yanovski SZ, Jordan HS, Kendall KA,
  - a. Lux LJ, Mentor-Marcel R, Morgan LC, Trisolini MG, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC, Tomaselli GF. 2013.
80. AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation* 2014; 129: S102-S138
81. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF Lachin JM, Walker EA, Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; 346: 393-403.
82. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001; 344: 1343-1350.
83. Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. *Arch Intern Med* 2010; 170: 1566-1575 .
84. O'Neil PM, Smith SR, Weissman NJ, Fidler MC, Sanchez M, Zhang J, Raether B, Anderson CM, Shanahan WR. Randomized placebo-controlled

- clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. *Obesity (Silver Spring)* 2012; 20: 1426-1436 .
85. Sjöström L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, Dahlgren S, Larsson B, Narbro K, Sjöström CD, Sullivan M, Wedel H. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med* 2004; 351: 2683-2693.
  86. James WP, Caterson ID, Coutinho W, Finer N, Van Gaal LF, Maggioni AP, Torp-Pedersen C, Sharma AM, Shepherd GM, Rode RA, Renz CL. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N Engl J Med* 2010; 363: 905-917.
  87. Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, Crow RS, Curtis JM, Egan CM, Espeland MA, Evans M, Foreyt JP, Ghazarian S, Gregg EW, Harrison B, Hazuda HP, Hill JO, Horton ES, Hubbard VS, Jakicic JM, Jeffery RW, Johnson KC, Kahn SE, Kitabchi AE, Knowler WC, Lewis CE, Maschak-Carey BJ, Monte MG, Murillo A, Nathan DM, Patricio J, Peters A, Pi-Sunyer X, Pownall H, Reboussin D, Regensteiner JG, Rickman AD, Ryan DH, Safford M, Wadden TA, Wagenknecht LE, West DS, Williamson DF, Yanovski SZ. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013; 369:145-154 .
  88. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* 1998; 317: 703-713.
  89. Cushman WC, Evans GW, Byington RP, Goff DC, Grimm RH, Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, Katz L, Peterson KA, Friedewald WT, Buse JB, Bigger JT, Gerstein HC, Ismail-Beigi F. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010; 362:1575-1585 .
  90. James PA, Oparil S, Carter BL, Cushman WC, Dennison- Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC, Svetkey LP, Taler SJ, Townsend RR, Wright JT, Narva AS, Ortiz E. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; 311: 507-520 .
  91. Whelton PK, Barzilay J, Cushman WC, Davis BR, Iiamathi E, Kostis JB, Leenen FH, Louis GT, Margolis KL, Mathis DE, Moloo J, Nwachuku C, Panebianco D, Parish DC, Pressel S, Simmons DL, Thadani U. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med* 2005; 165: 1401-1409.
  92. Turnbull F, Neal B, Algert C, Chalmers J, Chapman N, Cutler J, Woodward M, MacMahon S. Effects of different blood pressure lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Arch Intern Med* 2005; 165: 1410-1419.
  93. Krakoff LR, Gillespie RL, Ferdinand KC, Fergus IV, Akinboboye O, Williams KA, Walsh MN, Bairey Merz CN, Pepine CJ. 2014 hypertension recommendations from the eighth joint national committee panel members raise concerns for elderly black and female populations. *J Am Coll Cardiol* 2014; 64: 394-402 .

94. Watts GF, Playford DA. Dyslipoproteinaemia and hyperoxidative stress in the pathogenesis of endothelial dysfunction in non-insulin dependent diabetes mellitus: an hypothesis. *Atherosclerosis* 1998; 141: 17-30.
95. Matheus AS, Cobas RA, Gomes MB. [Dyslipidemias in type 1 diabetes: a current approach]. *Arq Bras Endocrinol Metabol* 2008; 52: 334-339.
96. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC, Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC, Tomaselli GF. 2013.
97. ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014; 129: S1-45.
98. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Thomason MJ, Mackness MI, Charlton- Menys V, Fuller JH. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomized placebo-controlled trial. *Lancet* 2004; 364: 685-696 .
99. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005; 352: 1425-1435 .
100. Wanner C, Krane V, März W, Olschewski M, Mann JF, Ruf G, Ritz E. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005; 353: 238-248.
101. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesäniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M. 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.
102. Brown BG, Zhao XQ, Chait A, Fisher LD, Cheung MC, Morse JS, Dowdy AA, Marino EK, Bolson EL, Alaupovic P, Frohlich J, Albers JJ. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 2001; 345: 1583-1592 .
103. Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes- Nickens P, Koprowicz K, McBride R, Teo K, Weintraub W. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011; 365: 2255-2267 .
104. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med* 2015; 372: 2387-2397 .
105. Shah RV, Goldfine AB. Statins and risk of new-onset diabetes mellitus. *Circulation* 2012; 126: e282-e284 .

106. Pop-Busui R. Cardiac autonomic neuropathy in diabetes: a clinical perspective. *Diabetes Care* 2010; 33: 434-441.
107. The effect of intensive diabetes therapy on measures of autonomic nervous system function in the Diabetes Control and Complications Trial (DCCT). *Diabetologia* 1998; 41: 416-423 .
108. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003; 348: 383-393 .
109. Zhang X, Chen C. A new insight of mechanisms, diagnosis and treatment of diabetic cardiomyopathy. *Endocrine* 2012; 41: 398-409 .
110. Kajstura J, Fiordaliso F, Andreoli AM, Li B, Chimenti S, Medow MS, Limana F, Nadal-Ginard B, Leri A, Anversa P. IGF-1 overexpression inhibits the development of diabetic cardiomyopathy and angiotensin II-mediated oxidative stress. *Diabetes* 2001; 50:1414-1424.
111. Leri A, Liu Y, Wang X, Kajstura J, Malhotra A, Meggs LG, Anversa P. Overexpression of insulin-like growth factor-1 attenuates the myocyte renin-angiotensin system in transgenic mice. *Circ Res* 1999; 84: 752-762 .
112. Ren J, Samson WK, Sowers JR. Insulin-like growth factor I as a cardiac hormone: physiological and pathophysiological implications in heart disease. *J Mol Cell Cardiol* 1999; 31: 2049-2061 [PMID: 10591031 DOI: 10.1006/jmcc.1999.1036]
113. Norby FL, Wold LE, Duan J, Hintz KK, Ren J. IGF-I attenuates diabetes-induced cardiac contractile dysfunction in ventricular myocytes. *Am J Physiol Endocrinol Metab* 2002; 283.
114. Ashraf H, Boroumand MA, Amirzadegan A, Talesh SA, Davoodi G. Hemoglobin A1C in non-diabetic patients: an independent predictor of coronary artery disease and its severity. *Diabetes Res Clin Pract* 2013; 102: 225-232 .
115. Ollerton RL, Playle R, Ahmed K, Dunstan FD, Luzio SD, Owens DR. Day-to-day variability of fasting plasma glucose in newly diagnosed type 2 diabetic subjects. *Diabetes Care* 1999; 22:394-398 .
116. Sacks DB, Arnold M, Bakris GL, Bruns DE, Horvath AR, Kirkman MS, Lernmark A, Metzger BE, Nathan DM. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Diabetes Care* 2011; 34: e61-e99.
117. Petersen PH, Jørgensen LG, Brandslund I, De Fine Olivarius N Stahl M. Consequences of bias and imprecision in measurements of glucose and hba1c for the diagnosis and prognosis of diabetes mellitus. *Scand J Clin Lab Invest Suppl* 2005; 240: 51-60 .