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Heart failure : News on pathophysiology and innovative treatments to prevent it in diabetic patients. A study based on literature

Insuffisance cardiaque : Actualités sur la physiopathologie et les traitements innovants pour la prévenir chez les patients diabétiques. Une étude basée sur la littérature

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Summary

Background : The treatment of heart failure in diabetic patients is a major clinical challenge worldwide.

It is crucial to prevent the synergy of diabetes mellitus and heart failure, especially as heart failure is the main cardiovascular complication of diabetic patients, and current projections point to high proportions of diabetics in the future. This should also increase the incidence of heart failure among diabetics.

This review of the literature has brought together several documents that can help clinicians prevent diabetics from developing heart failure through knowledge of the existing relationship between diabetes mellitus and heart failure (pathophysiology), as well as the preventive treatment of heart failure in diabetic patients justifies the implementation of this highly fruitful literature for all healthcare personnel.

Key words : Pathophysiology, Prevention, Heart failure, Diabetes mellitus.

Résumé

Contexte : Le traitement de l'insuffisance cardiaque chez les patients diabétiques est un défi clinique majeur dans le monde entier.

Il est crucial de prévenir cette synergie du diabète sucré et l'insuffisance cardiaque ; d'autant plus que l'insuffisance cardiaque est la principale complication cardiovasculaire des patients diabétiques et les projections actuelles annoncent de fortes proportions de diabétiques à l'avenir. Ceci devra également croitre la fréquence de l'insuffisance cardiaque chez les diabétiques.

Cette revue de la littérature vient de rassembler plusieurs documents qui peuvent aider les cliniciens à éviter aux diabétiques de développer une insuffisance cardiaque via la connaissance des relations existantes entre le diabète sucré et l'insuffisance cardiaque (physiopathologie), ainsi que le traitement préventif de l'insuffisance cardiaque chez les patients diabétiques justifie la mise en place de cette littérature très fructueuse pour l'ensemble du personnel de santé.

Mots clés : Physiopathologie, Prévention, Insuffisance cardiaque, Diabète sucré**.**

I. Introduction

Heart failure (HF) is symmetrically related to diabetes mellitus ; its onset in the setting of type 1 or type 2 diabetes mellitus remains a first major complication, leading to a more fragile life for the diabetic patient **[1]** than for a patient with heart failure not associated with diabetes. In this review of the literature, we look at the mechanisms by which heart failure occurs in diabetic patients.

I.1 Definitions

Heart failure can be defined according to pathophysiology, clinical and paraclinical criteria. According to Pathophysiology, Heart failure is the inability of the heart to pump sufficient cardiac output to meet the body's metabolic needs during exercise or at rest [2,3]. Clinically, we define Heart failure according to New York Heart Association (NYHA) I, II, III, IV respectively, depending on whether the patient has dyspnoea beyond usual exertion, dyspnoea at usual exertion, dyspnoea at least exertion and dyspnoea at rest or orthopnoea [4]. The echographic definition is based on the left ventricular ejection fraction (LVEF) in three stages : heart failure with preserved LVEF (HFpEF) for a LVEF ≥ 50%, heart failure with moderately reduced LVEF (HFmrEF) : LVEF ranges from 41 to 49% and IC with reduced LVEF (HFrEF): LVEF ≤ 40% [5]

The current revised definition of heart failure includes an asymptomatic individual associated with the presence of at least one of the following :1) evidence of structural heart disease, 2) abnormal heart function,3) elevated cardiac natriuretic peptide levels or elevated cardiac troponin levels [6].

Diabetes is defined by the presence of a chronically elevated fasting plasma glucose (FPG) level ≥ 126mg/dl(≥7.0mmol/L) 8hours after a low-calorie meal, linked to a deficit, a relative or absolute deficiency of insulin or a defect in its action, or a combination of these mechanisms; a glycated hemoglobin (HbA1c) level ≥6.5%(48mmol/mol) or presence of signs of diabetes associated with a blood glucose level ≥200mg/dl(11.1mol/l) or oral glucose tolerance test (OGTT) ≥200mg/dl(11.1mmol/L) 2 hours after injection of 75g glucose dissolved in water [1,7, 8].

OGTT is used to diagnose postprandial hyperglycemia, which is a risk marker for cardiovascular disease (CVD) [10].

I.2 Epidemiology of heart failure risk in diabetics

I.2.1. Worldwide epidemiology

Heart failure is the first major cardiovascular feature to appear in diabetics [11].

The Framingham study showed that the cardiovascular risk of diabetics differs by 2.4 times in men and 5 times in women with diabetes compared to the non-diabetic population, irrespective of the coexistence of hypertension or ischemia [1, 12,13].

Men have a twofold increased risk of cardiovascular death compared with non-diabetic men, while this risk was fourfold in women compared with non-diabetic women [1, 14].

In relation to gender, the risk of heart failure and other MACE (Major cardiovascular events) in diabetics does not appear to differ in men RH 0.90 [0.83-0.97] and women RH 0.88 [0.79-0.99] respectively [10].

The relative risk (RR) of developing heart failure is 2.36 in diabetic men compared with non-diabetic men, and the RR of developing heart failure is 5.14 in diabetic women compared with non-diabetic women [1,15].

In 2019 two large studies had without distinguishing between heart failure (HF) with preserved (HFpEF) or reduced (HFrEF) ejection fraction showed data from 13 prospective studies from 47 cohorts of 11925 128 type 2 diabetic patients with an RR of heart failure of 1.95(1.70-2.22) in diabetic women compared to non-diabetic

women, while this RR was 1.74(1.55-1.95) in diabetic men and the male-female difference was significant. In type 1 diabetics, there were two cohorts with 3284,123 participants, the RR of heart failure was 5.15(3.43-7.74) in type 1 diabetic women compared with non-diabetic women, whereas this RR was 3.47(2.57-4.69) in diabetic men, and the male/female difference was significant [16].
The prevalence of HFpEF is the same in men and women with diabetes [17]. Hypertension, chronic renal failure, obesity and diabetes are predictive factors for heart failure [18, 19].
In a cohort of patients with HFPEF, the prevalence was 40% at Cliniques Universitaires Saint Luc [20].

I.2.2. Epidemiology of heart failure risk in Africa, the Democratic Republic of Congo and Goma.
No study has been found in the literature in Africa, in the Democratic Republic of Congo as in Goma, on the risk of heart failure in diabetics.

I.3. Pathophysiology of heart failure in diabetics
The relationship between diabetes and heart failure has long been described as a two-way relationship (diabetes mellitus towards heart failure and heart failure towards diabetes mellitus). We will give the pathophysiology of diabetes mellitus leading to heart failure (Figure 1)

I.3.1. Abnormal systolic function (left ventricular systolic dysfunction)
Abnormal systolic function results from myocardial injury, such as infarction, leading to progressive myocardial destruction following inflammation, myocardial remodeling and eccentric hypertrophy characterized by increased myocyte length [21-23].
The persistent inflammatory process results in abundant fibrotic tissue production, leading to impaired myocardial contractility, systolic dysfunction and acute heart failure [10,18,22].

I.3.2. Relaxation anomaly (diastolic dysfunction)
Incomplete or slow return to rest of the myocardial fiber after stretch often leads to concentric hypertrophy, increased intraventricular pressure, poor left ventricular filling ; increased left atrial pressures and heart failure with preserved ejection fraction [4,18,22-24].

II.3.3. Diabetic cardiomyopathy
This is myocardial dysfunction associated with myocardial hypertrophy in the absence of valvulopathy, hypertension or ischemic heart disease [24-26].
Apolipoprotein B (APOB) is a new clue to the understanding of diabetic cardiomyopathy, causing massive lipid penetration of the myocardium, leading to lipid accumulation in the myocardium, resulting in inflammation, myocardial hypertrophy and myocardial energy depletion. However, contractility is impaired, left ventricular filling is impaired and heart failure sets in [24,25].

I.3.4. Hyperglycemia, hyperinsulinemia, insulin resistance
Chronic hyperinsulinism appears to reduce sympathetic activity as a result of impaired insulin transport across the blood-brain barrier, leading to poor heart rate (HR) variability [26-29].

I.3.5. Alteration of calcium transporter
The activity of the sarcoplasmic reticulum calcium pump (SERCa2) is diminished by a drop in intracellular glucose concentration. This results in reduced uptake of intracellular calcium by the sarcoplasmic reticulum and, finally, an increase in intracellular calcium, leading to impaired cardiomyocyte contractility and relaxation, which is also impaired by the maintenance of relatively high intracellular calcium concentrations [30,31,32].

I.3.6. Alteration of the metabolic reserve
In healthy subjects, the main energy substrates of cardiomyocytes at rest are free fatty acids (FFA) (60-90%) and glucose (10-40%). During stress or physical activity, glucose utilization doubles, while that of FFA remains stable ; this is known as the metabolic reserve. In diabetics, this reserve is altered in favor of GLA during stress, instead of glucose [20,32].
Insulin resistance (IR) in the myocardium leads to impaired glucose uptake, associated with a reduction in Type 1 glucose transporters (GLUT1), especially Type 4 in the myocardium (GLUT4), and excess free fatty acids (FFA) linked to reduced lipolysis, with increased bioavailability of FFA in the myocardium compared with glucose [30,31,33,34].
The myocardium of diabetic patients oxidizes glucose less, and metabolizes more of the free fatty acids available through beta-oxidation, leading to deficient production of the ATP required for myocardial contractility. The result is an energy deficit in the myocardium, mitochondrial dysfunction due to pyruvate deficiency, production of toxins such as oxygen free radicals by lipid oxidation, leading to oxidative stress, mitochondrial dysfunction, reduced myocardial contractility and heart failure [30,31,33,34-37].

I.3.7. Increased oxidative stress and atherosclerosis
Insulin resistance(IR), chronic hyperglycemia triggers low-grade inflammation, chronic oxidative stress, endothelial dysfunction leading to atherosclerosis [38]. In this inflammation, we have the production of interleukin (IL) beta (ILβ), IL-6, Tumor Necrosis Factor alpha (TNFα), Protein-C-Reactive (CRP), which today are biomarkers for evaluating diabetic patients [38,39]

The antioxidant superoxide dismutase (SOD)2 fights free radicals. Women with diabetes have a genetic variant in SOD2 called Ala16Val (rs4880), which increases their risk of developing CVD [40].

Oxidative stress is further accentuated by the reduced availability of the vasodilator nitric oxide (NO). Coronary NO synthetase is dependent on circulating insulin levels, and its activity is therefore reduced in diabetics, leading to cardiomyocyte apoptosis and coronary suffering [32].

I.3.8. Actions of glycation products

Hyperglycemia accelerates the intensity of non-enzymatic glycation, characterized by the binding of glucose or their derivatives to the amine groups of proteins ; these include glycated hemoglobin(HbA1c), glycated albumin and advanced glycation products (AGEs) [41].

Advanced glycation products, when bound to their receptors, activate the Janus kinase (JAK) and Mitogen-activated protein kinase (MAPK) signalling pathways, resulting in a pro-inflammatory response in the myocardium with an increase in extracellular matrix and interstitial fibrosis [32,41].

A high HbA1c level is associated with a high affinity for oxygen, resulting in reduced tissue oxygen extraction, oxidative stress and the onset of CV diseases, for which aerobic exercise would be cost-effective in improving tissue oxygen extraction [42].

I.3.9. Diabetic autonomic neuropathy

Cardiac autonomic dysfunction (CAD) in diabetics is the result of diabetes itself, as well as co-morbidities associated with diabetes mellitus. Insulin, hyperglycemia, hypoglycemia, insulin resistance, free fatty acids, oxidative stress, and other hormonal and nutritional signals lead to activation of the autonomic nervous system, reduced vagal activity and sympathetic predominance [26].

This increase in sympathetic activity leads on the one hand to an increase in heart rate (HR), and on the other to an increase in cardiac output (CI) and peripheral vascular resistance, leading to an increase in blood pressure (BP) and then to heart failure [26].

On the other hand, sympathetic hyperactivity will lead to a disturbance in myocardial energy metabolism and QT prolongation, together resulting in arrhythmia, hypo-contractility and eventual IC [26].

Cardiac autonomic neuropathy (CAN) is a risk marker not only for heart failure, but also for cardiac mortality, stroke, myocardial ischemia, reduced coronary reserve, arterial stiffness and altered tissue uptake of norepinephrine, altered nycthemeral blood pressure profile leading to suppression of nocturnal dipping and reverse dipping, orthostatic hypotension, postprandial hypotension, chronotropic incompetence and progression to nephropathy [26,27, 42,43].

I.3.10. Ischemic heart disease

It has been clearly demonstrated that diabetes mellitus is accompanied by atherosclerosis, platelet hyperactivity and haemostasis, exposing diabetics to ischaemic and thromboembolic complications [38,44].

I.3.11. Activation of the renin-angiotensin-aldosterone system

Hyperglycemia and multiple myocardial changes lead to stimulation of the local renin angiotensin system (RAAS) and sympathetic stimulation [30,31,32].

Activation of the RAAS produces aldosterone, which accentuates systemic and cardiac insulin resistance. Inflammation accentuates the increased expression of pro-inflammatory AT-1R receptors (angiotensin type 1 receptors) and the decreased expression of anti-inflammatory AT-2R receptors in diabetics [32].

I.3.12. Genetics and Epigenetics

The presence today of the common variant of the high mobility group A1 (HMGA1), non-coding RNAs and epigenetics are the regulators leading to cardiometabolic diseases such as diabetes mellitus and myocardial infarction [38,45,46]. This lends credence to Stern's view that diabetes and CVD derive from a common ancestor [38,47].

I.3.13. Obesity

Today, obesity is considered by the World Health Organization (WHO) to be an epidemic, affecting more than 200 million men and 300 million women, with a risk of heart failure of 5% to 7% when the body mass index (BMI) increases by 1 kg/m. [2]

Adipocytes secrete inflammatory substances such as pro-inflammatory adipokines in excess and a decrease in anti-inflammatory adipokines, TNFα, interleukin 6, plasminogen inhibitor, insulin-like growth factor leading to systemic inflammation, IR then endothelial dysfunction, prothrombotic state exposing to thrombosis [48,49].

The inflammatory state associated with obstructive sleep apnea syndrome (OSAS) (sleep fragmentation leads to stimulation of the sympathetic and hypothalamic-pituitary axis, resulting in the release of adeno-cortico-trophin-hormone (ACTH)) leads to dyslipidemia, hypertension and increased total blood volume, however, the onset of heart failure via exacerbation of the heart's workload, altering early diastolic and late systolic function, atrial rhythm disorders followed by atrial and ventricular dilatation linked to left hypertrophy and myocardial fibrosis; with the onset of hypertension, stimulation of the angiotensin aldosterone system (RAAS)

accentuates the deleterious effects on cardiac function [50-53].

Angiotensin 2 thus produced leads to systemic vasoconstriction, leading to diffuse hypoperfusion, especially of the pancreatic islets of Langerhans (reduced insulin secretion), sympathetic stimulation aggravating vasoconstriction via catecholamines, hepatic glycolysis and lipolysis, aldosterone release by the adrenal gland leading to hypokalemia, hypertension ; and inhibition of insulin signalling pathways, while bradykinin plays a facilitating role.

Excess GLA is deposited in the pericardium and along the coronary arteries between the myocardium and epicardium (TAE). On the other hand, FFAs synthesize pro-inflammatory cytokines leading to endothelial dysfunction, the onset of fibrosis with transforming grawth factor β as a marker, and myocardial stiffness resulting in CI [54,55,56].

Abdominal obesity, the metabolic syndrome, is the main source of altered HR variability, especially high sympathetic activity and hypoxia [26]. These alterations will lead to increased HR, cardiac output, increased BP, myocardial hypertrophy, diastolic dysfunction and, ultimately, heart failure [26].

I.3.13. Hypertension

The hyperinsulinism present and the excess of GLA lead to arterial hypertension via sympathetic stimulation, increased renal tubular reabsorption of sodium and reduced vasodilatory effect of insulin [26, 57,58,].

Arterial hypertension chronically increases afterload by Laplace's law, resulting in left ventricular hypertrophy, followed by diastolic dysfunction and other myocardial changes leading to heart failure [57,68].

I.3.14. Diabetes-renal impairment-heart failure

The sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) are activated in diabetic patients with impaired renal function and IC (cardio-renal syndrome). The common marker for assessing vascular dysfunction in diabetic patients is microalbuminuria, which points to the risk of major cardiovascular events (MACE), in this case heart attack and mortality. The prevalence of microalbuminuria is 20% to 30% in type 2 diabetic patients [59,60].

Estimated glomerular filtration rate (eGFR) is a second marker for predicting the occurrence of major cardiovascular events (MACE) such as heart failure in type 1 and 2 diabetics [60], and a reduction in eGFR is a marker of unfavorable heart failure progression [60,61].

In type 1 diabetic patients, the risk of heart failure is twice as high for an eGFR of 45-60ml/min /1.73m² and ≥three times higher for an eGFR below 30ml/min/1.73m² compared with a normal eGFR [62]. For type 2 diabetic patients, reduced eGFR is also associated with an approximately twofold increase in the risk of CI [10].

An observational study analyzing survival and the risk of new-onset heart failure in type 2 diabetic patients showed a decrease in survival with increasing eGFR [63]. Survival of 2.8 years was observed in type 2 diabetic patients with eGFR of 45 to 59ml/min/1.73m² and 0.7 years for eGFR below 15ml/min/1.73m² [63].

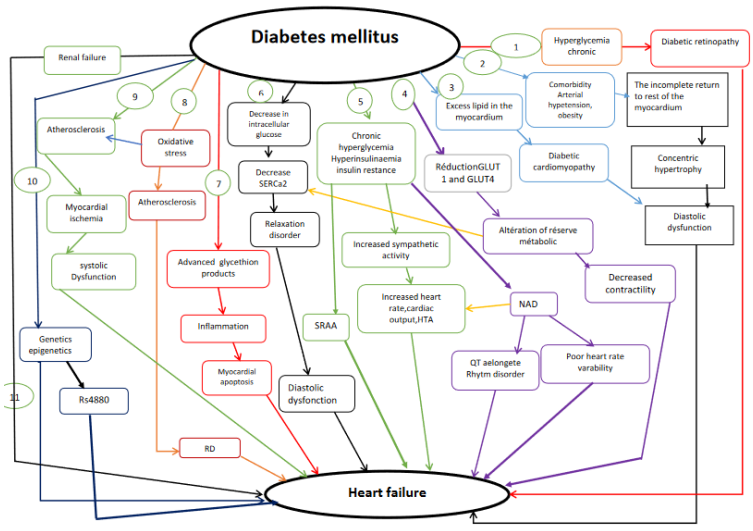
Ultimately, the risk ratio for the occurrence of major cardiovascular events is estimated at 2.2 for each halving of baseline eGFR in type 2 diabetic patients [64].

I.3.15. Diabetes, retinopathy and heart failure

Chronic hyperglycemia leads to biochemical changes (aldose reductase pathway, non-enzymatic glycation, activation of protein kinase C, hexosamine pathway), resulting in hypoxia, inflammatory reaction, oxidative stress, endothelial dysfunction; resulting in tissue damage (reduced pericyte numbers, loss of endothelial cells), thickening of the basement membrane, neuronal apoptosis, activation of glial cells, leukostasis, capillary occlusion, rupture of the blood-retinal barrier (BHR), onset of macular edema (MD) and diabetic retinopathy (DR) [65,66].

Chronic inflammation is at the root of multi-organ damage in diabetic patients, such as non-alcoholic steatosishepatitis (NASH), diabetic nephropathy, polyneuropathy, diabetic retinopathy, macular edema and many other inflammatory diseases [67,69-71]. Testosterone is also low in relation to this chronic inflammation [72].

Retinopathy, an eye condition affecting the blood vessels of the retina, can potentially lead to heart failure because of its implications for blood flow and oxygen delivery to tissues [73].



RD: diabetic retinopathy, NAD: Neuropathy Autonome Diabetique, *SRAA: Systems Renine Angiotensine Aldosterone*

Figure 1. Pathophysiological mechanisms of diabetes mellitus leading to heart failure

I.4. Diagnostics

Heart failure is currently diagnosed by the presence of current or previous symptoms and/or signs caused by structural and/or functional abnormalities of the Heart [74]. The presumption must be affirmed by at least one of the following : elevated natriuretic peptide levels, objective evidence of cardiogenic pulmonary or systemic congestions by diagnostic modalities or hemodynamic measurements [5,6,74].

I.4.1. Clinical

The asymptomatic presentation of CI in the early stages is a diagnostic challenge [10], which today is driving the use of scores to diagnose it without reaching the presence of signs.

The similar clinical features of heart failure, also found in a number of conditions such as obesity and respiratory diseases, justify its under- or delayed diagnosis or misdiagnosis [75].

I.4.2. Paraclinical

I.4.2.1. Blood glucose and glycated haemoglobin

High HbA1C levels are associated with vascular impairment and a high risk of cardiac events **[76].** Poor glycemic control characterized by an HbA1C level ≥7% within one year of hospital discharge is associated with a risk of major cardiovascular events up to and including death, whereas good glycemic control with an HbA1C level below 7% spares MACE patients **[77**].

An interesting study evaluated the level of glycemic control in diabetic patients with heart failure, and a high mortality rate was found in patients with an HbA1C level below 7%, with better glycemic control on insulin than those taking oral antidiabetics ; this clearly shows the negative effects of insulin **[78].**

I.4.2.2. Biomarkers

I.4.2.2.1.BNP and NT-proBNP

Today, biomarkers are increasingly used to predict the risk of major cardiovascular events, and to diagnose and monitor cardiometabolic diseases [10].

Myocardial stress leads to the synthesis of a 108-amino acid precursor peptide, proBNP in myocytes, which splits into an active BNP fragment and an inactive NT-proBNP fragment. NT-proBNP is a powerful predictor of CI risk in type 2 diabetics [79]. Both NT-ProBNP and BNP are crucial in predicting short- and medium-term MACE risk in diabetic patients. NT-ProBNP levels correlate with NYHA classification and give the prognosis of CHF patients [7,79].

I.4.2.2.2. Troponins

Troponin TnT, a protein involved in myocardial contractility, is a cardiac marker par excellence for diagnosing myocardial lesions, especially in the case of rupture of the myocyte membrane **[5].**

In diabetic patients, chronic hyperglycemia leads to myocardial damage and is associated with dramatic troponin elevations. Ultrasensitive troponin plays an important role in the diagnosis of CHF, prediction of MACE risk and cardiovascular mortality**.** Of the three forms of troponin, two - troponin T (TnT) and troponin I (TnI) - are highly sensitive to cardiomyocyte injury.

In general, despite the high prevalences of troponin levels encountered in practice, manufacturers must be taken into account and the prognosis is no different in heart failure patients with or without diabetes **[5].**

I.4.2.2.3. Markers of inflammation and angiogenesis

Inflammation markers such as tumor necrosis factor receptor superfamily 1a (TNFR 1a), periostin, ultrasensitive c-reactive protein and angiogenesis markers such as vascular endothelial growth factor receptor (VGEFR) and angiogenin show that inflammation and fibrosis are perfectly associated in diabetic patients with heart failure**.** High levels of plasma reactive protein-c (CRP) are associated with a high percentage of cardiovascular events **[67,80].**

I.4.2.3. MAPA

Ambulatory blood pressure measurement (ABPM) is a crucial investigation in the evaluation of diabetic patients. ABPM provides information on orthostatic hypotension, which is common in diabetic patients with NAC as postprandial hypotension, and allows us to diagnose nocturnal hypertension **[26].**

I.4.2.4. Electrocardiography

The electrocardiogram (ECG) is currently recommended for diagnosing CI by the ESC 2021 guidelines **[5].** The Electrocardiogram (ECG) enables us to diagnose NAC in good time, pointing to the risk of IC via arrhythmias, QT abnormalities, ventricular hypertrophy and myocardial ischemia **[26].** The absence of abnormal cardiac damage on ECG greatly reduces the probability of CI **[5].**

I.4.2.5. Holter-ECG

The 24-hour recording allows us to diagnose NAC disorders, notably QT interval prolongation at night with daytime reduction for a given heart rate, poor sinus variability of HR as markers of risk of death ; severe arrhythmias **[26].**

I.4.2.6. Exercise stress test (EGC d'effort)

NAC simultaneously alters hemodynamic response and exercise tolerance, often with chronotropic incompetence and post-exercise recovery FC. Exercise ECG is recommended in asymptomatic diabetics over 10 years of age to detect myocardial ischemia [26].

I.4.2.7. Cardiac Doppler ultrasound and Myocardial Train

Ultrasound is the easiest way to diagnose CI, given the structural and functional alterations in the myocardium [10]. Impaired left ventricular diastolic and systolic function is common in NAC [26,81].

I.5. Cardiovascular risks

A cardiovascular risk factor (CRF) is a physiological or non-physiological element capable of causing a major cardiovascular event after 5 to 10 years of exposure to it.

Cardiovascular risk assessment is recommended for all patients with ≥1 major CVD factor, i.e. family history of CVD, diabetes mellitus, smoking, hypertension, dyslipidemia, obesity or any CVD comorbidity. There are several tools for estimating cardiovascular risk including the Biomarker score, which will be used in this doctoral work, scores such as the Systematic Coronary Risk Estimation (SCORE2), Systematic Coronary Risk Estimation 2-Older Persons (SCORE2-0P), which will not be the focus of this work, is not yet validated for Africans [5,82].

Patients with established atherosclerotic disease, diabetes, moderate to severe chronic kidney disease (CKD), hypertension or genetic dyslipidemia are considered at high or very high cardiovascular risk.

Systematic assessment of SVR may be considered in men >40 years and women >50 years with no known FRCV. This systematic observation is not recommended for men under 40 and women under 50. For both sexes, the current age of onset of diabetes mellitus is 35 years [5,7].

FRCV management is recommended for healthy patients without CV co-morbidities (diabetes, IC, CKD, familial dyslipidemia, hypertension).

The acceptable blood pressure level is to lower the BP below 140/90mmHg in general, but depending on the patient's age, it is desirable to lower the PAS from 120 to 130mmHg in patients aged 18 to 69, and below 140mmHg to 130mmHg if tolerated in patients over 70, and the PAD in treated patients should be 80mmHg [5].

I.6. Treatment

At present, the treatment of diabetes must be individually focused, especially on the cardiovascular risk in place [1].

Treatment of heart failure risk in diabetic patients should meet the following three objectives :

1) Good glycemic control, with individual glycemic limits to avoid hypoglycemia
2) The HbA1c level recommended to reduce the risk of heart failure is 6.4 to 7.0%, i.e. 7 to 8%, because beyond 8% there is the onset of MACE.
3) The use of hygienic-dietary measures, drugs to reduce the risk of heart failure and other cardiovascular diseases [5,9,13,83-86].

I.5.1. Prevention of heart failure

Current heart failure prevention must be a major concern, including the following CV risk reduction measures on an individual basis :

- Communicating with patients about their CV risk and involving them in risk reduction,
- An optimal doctor-patient relationship,
- Physical activity adapted to the patient's condition (a weekly aerobic activity of 150 to 300 minutes of moderate intensity and 75 to 150 minutes of greater intensity, i.e. endurance exercise, is recommended at least twice a week),
- Avoid a sedentary lifestyle.
- Replace saturated fatty acids (animal products and their derivatives such as milk, cheese, butter and deli meats) with unsaturated fatty acids (Omega-3, Omega-9 (vegetable oils including olive oil, avocados and oilseeds).
- Moderate salt consumption to reduce hypertension (in hypertensive patients 5.8mmHg and 1.9mmHg in normotensive patients) and cardiovascular disease,
- Regular consumption of fiber-rich vegetables and fruit without adding salt (consumption of 30g of fruit a day reduces the RCV by 30%),
- Eat fish at least once a week, and reduce your consumption of meat and sweets,
- Alcohol consumption should be limited to 100g per week.
- Smoking cessation may involve prescribing Veranicline or bupropion alone or in combination.

Withdrawal from e-smoking is easier than nicotine-based smoking and is associated with a 5kg weight gain, but the withdrawal is more beneficial than the weight gain.

Hygienic dietary measures aimed at reducing weight and increasing physical activity establish the vagosympathetic balance, thus improving and reducing complications associated with NAC impairment [5,26].

For reducing the risk of MACE, death from cardiovascular etiologies and hospitalization for heart failure, the iSGLT-2 class is the most recommended, led by dapagliflozin, Empagliflozin, and the others are also recommended [10,22,87, 88- 94,]. SGLT2 inhibitors have cardioprotective effects not only in patients with diabetes and established CVD, but also in patients at risk of MACE ; they significantly reduce NT-proBNP [10].

Potential mechanisms of SGT2 action include reduced sodium retention and plasma volume, reduced insulin levels, modulation of the RAAS, reduced weight and blood pressure without increasing sympathetic nerve activity [4].

I.5.2. Treatment of acute heart failure

The following drugs are recommended for the treatment of acute failure: ACE inhibitors (ACE inhibitors:

Enalapril) or angiotensin II receptor blockers (ARBs: Candesartan),neprilysin receptor blockers (NRBs: sacubitril-valsartan),beta-blockers recommended for diabetics with heart failure (Metoprolol succinate, Carvedilol, Bisoprolol) and beta-blockers recommended for diabetics with heart failure (Metoprolol succinate, Carvedilol, Bisoprolol):sacubitril-valsartan),beta-blockers recommended for diabetics with heart failure (Metoprolol succinate, Carvedilol, Bisoprolol) [95] and nebivol is also used, mineralocorticoid receptor antagonists (MRA: Spironolactone, Eplerenone) and type 2 sodium-glucose cotransporter inhibitors (iSGLT2) [10].

Empagliflozione reduces the risk of cardiovascular death in diabetic patients with IC and hypertension [10].

Metformin monotherapy is the treatment of diabetic patients without MACE, with moderate CVR and should be continued in heart failure patients with eGFR > 30ml/min/1.73 m^2 according to ADA and ESC because metformin is associated with a reduced risk of MACE and death in diabetic patients with CV risk defined by an NT-proBNP level above 300pg/mL [10,95]. Metformin treatment should be stopped if the IC patient is unstable or hospitalized [96].

Diamicron is the best drug for treating heart failure patients, thanks to its potential antioxidant action [10,7].

I.5.3. Treatment of heart failure with preserved ejection fraction. There is no consensus on the treatment of HFpEF, but it is always necessary to combat the symptoms and the factors that lead to them [9]. A major study showed the importance of using spironolactone and sacubitril/Valsartan even in patients with LVEF up to 57% [97]. The use of SGLT2 inhibitors is also recommended in HFpEF [95].

I.5.4. Treatment of heart failure with moderately reduced or reduced ejection fraction

The treatment of HFrEF or collapsed heart failure is the same as that of acute heart failure, but the major differences lie in dosage and monitoring **[5,9].**

Vericiguat is a recently studied soluble guanylate cyclase stimulator indicated for the treatment of patients with chronic heart failure and ejection fraction (EF) below 45% and recent hospitalization for CHF **[98]** after optimization of the Medical Treatment Guidelines (MTG) **[95].**

Patients resistant to loop or lasix diuretics should be given a thiazide diuretic to boost the diuretic effect, involving electrolyte and renal function monitoring **[95].**

I.5.5. Thiazolidinediones

Several authors and evidence from meta-analyses and randomized trials have shown that the use of Thiazolidinediones (TZDs) increases the risk of CHF, hospitalization for heart failure, or death, via weight gain, edema, especially worsening of lower limb edema, and hence increased risk of failure, especially in combination with insulin **[99,100].**

I.5.6. Dyslipidemia

Atherogenic dyslipidemia, especially LDL-cholesterol and apolipoprotein B, while at the same time eliminating situations that favor an increase in lipids : alcohol intake, hypothyroidism, cushing's syndrome, chronic renal failure, cholestatic liver disease, certain drugs (thiazides, beta-blockers, cyclosporine, antiretrovirals, tacrolimus and hormone therapy).

Dyslipidemia should be treated with statins in diabetics aged 40 and over at high CV risk, and with MACE in young diabetics aged 20 to 39. The use of statins in diabetic patients over 75 years of age remains more ambiguous [101].

However, it remains to be seen whether lowering LDL cholesterol (LDL-C) will prevent heart attack per se in 600 type 2 diabetic patients. High-intensity statin use versus low-intensity statin use or no statin use was associated with a lower incidence of heart attack over the 6-year follow-up independent of lower LDL levels **[7,101,102].**

When maximum-dose statins fail to achieve the target, the addition of ezetimibe in combination is recommended. LDL-C<0.55g/L and a reduction of at least 50% in initial LDL-C class I recommendation in patients with atherosclerotic disease, and in the event of recurrence of a CV event within 2 years despite optimal lipid-lowering therapy, a target of LDL-C<1.0mmol/L(0.55g/L) may be considered.

In secondary prevention, if patients fail to reach their targets despite a high-intensity statin at maximum tolerated dose combined with ezetimibe, treatment with a PCSK9 inhibitor is recommended, even in patients with a very high SVR and no familial hypercholesterolemia whose target has not been reached **[5].**

I.5.7. Aspirin Junior and the prevention of major cardiovascular events

As a reminder, acetylsalicylic acid (ASA) prevents platelet aggregation by permanently inhibiting the enzymes cyclooxygenases 1 and 2 (COX-1 and COX-2), i.e. ASA irreversibly inhibits COX-1 by acetylation. This action blocks the formation of thromboxaneA2, a powerful vasoconstrictor that also ensures platelet aggregation [103]. The absolute benefit of primary prevention with aspirin 75 to 160mg is recommended for all diabetics with intermediate or high CV risk in the absence of bleeding risk, even for patients with asymptomatic carotid stenosis at high cardiovascular risk [104]. Bleeding is often encountered in patients with insulin resistance, which can be explained by aspirin resistance in diabetics and less platelet rejuvenation ; hence, control of hypertension, dyslipidemia and glycemia remains a priority [105]. The

presence of diabetes alone should not lead to the systematic prescription of aspirin 100mg ; the association of diabetes and other cardiometabolic risk factors and the existence of MACE must be taken into account [104].

Conclusion

This literature review is the fruit of a long reading resembling several works related to diabetes and heart failure. Readers and clinicians alike will find here the right literature to properly care for patients with this combination of failure and diabetes mellitus.

Interest conflicts : None

References

1. Abdallah A, EL BOUZEGAOUI N, SARAVAL-GROSS M. DIABÈTE ET RISQUE CARDIOVASCULAIRE CHEZ LES HOMMES ET LES FEMMES. Paris, 19-20 novembre 2021.
2. Van Mieghem W. La physiopathologie de l'insuffisance cardiaque chronique. VCP. 2009;226:6-12.
3. Jondeau G. Insuffisance cardiaque et cardiomyopathies. ARCHIVES DES MALADIES DU CŒUR ET DES VAISSEAUX. 2006;99(2).
4. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200.
5. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. European heart journal. 2021;42(36):3599-726.
6. Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, et al. Universal definition and classification of heart failure: a report of the heart failure society of America, heart failure association of the European society of cardiology, Japanese heart failure society and writing committee of the universal definition of heart failure. Journal of cardiac failure. 2021;27(4):387-413.
7. American Diabetes Association Professional Practice Committee.2. Classification and diagnosis of diabetes : Standard of medical care in Diabetes-2022 Diabetes care 2022 ; 45(Suppl.1) : S17-S38.
8. Stumvoll M, Goldstein BJ, Van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. The Lancet. 2005;365(9467):1333-46.
9. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020;41(2):255-323.
10. Ceriello A, Catrinoiu D, Chandramouli C, Cosentino F, Dombrowsky AC, Itzhak B, et al. Heart failure in type 2 diabetes: current perspectives on screening, diagnosis and management. Cardiovascular diabetology. 2021;20(1):218.
11. Birkeland KI, Bodegard J, Eriksson JW, Norhammar A, Haller H, Linssen GCM, et al. Heart failure and chronic kidney disease manifestation and mortality risk associations in type 2 diabetes: A large multinational cohort study. Diabetes, obesity & metabolism. 2020;22(9):1607-18.
12. De Flines J, Scheen A. Insuffisance cardiaque et diabete de type 2: une relation a double sens. Revue Médicale de Liège. 2007;62(2).
13. Udelson JE, Stevenson LW. The future of heart failure diagnosis, therapy, and management. Circulation. 2016;133(25):2671-86.
14. Garcia MJ, McNamara PM, Gordon T, Kannel WB. Morbidity and mortality in diabetics in the Framingham population. Sixteen year follow-up study. Diabetes. 1974;23(2):105-11.
15. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol. 1974;34(1):29-34.
16. Ohkuma T, Komorita Y, Peters SAE, Woodward M. Diabetes as a risk factor for heart failure in women and men: a systematic review and meta-analysis of 47 cohorts including 12 million individuals. Diabetologia. 2019;62(9):1550-60.
17. Bouthoorn S, Valstar GB, Gohar A, den Ruijter HM, Reitsma HB, Hoes AW, et al. The prevalence of left ventricular diastolic dysfunction and heart failure with preserved ejection fraction in men and women with type 2 diabetes: A systematic review and meta-analysis. Diabetes and Vascular Disease Research. 2018;15(6):477-93.
18. Simmonds SJ, Cuijpers I, Heymans S, Jones EA. Cellular and molecular differences between HFpEF and HFrEF: a step ahead in an improved pathological understanding. Cells. 2020;9(1):242.
19. Ho JE, Lyass A, Lee DS, Vasan RS, Kannel WB, Larson MG, et al. Predictors of new-onset heart failure: differences in preserved versus reduced ejection fraction. Circulation: heart failure. 2013;6(2):279-86.

20. Hermans MP. Traitement du diabète de type 2 en 2019: un même rapport coût-bénéfices? Le point de vue du diabétologue. Louvain médical. 2019;138:157.
21. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. European journal of heart failure. 2020;22(8):1342-56.
22. Martin AC, Bories MC, Tence N, Baudinaud P, Pechmajou L, Puscas T, et al. Epidemiology, Pathophysiology, and Management of Native Atrioventricular Valve Regurgitation in Heart Failure Patients. Frontiers in cardiovascular medicine. 2021;8:713658.
23. Yoon S, Eom GH. Heart failure with preserved ejection fraction: present status and future directions. Experimental & Molecular Medicine. 2019;51(12):1-9.
24. Nirengi S, da Silva CPV, Stanford KI. Disruption of energy utilization in diabetic cardiomyopathy; a mini review. Current opinion in pharmacology. 2020;54:82-90.
25. Jia G, Hill MA, Sowers JR. Diabetic cardiomyopathy: an update of mechanisms contributing to this clinical entity. Circulation research. 2018;122(4):624-38.
26. Valensi P. Autonomic nervous system activity changes in patients with hypertension and overweight: role and therapeutic implications. Cardiovascular diabetology. 2021;20(1):1-12.
27. Straznicky NE, Grima MT, Sari CI, Eikelis N, Lambert EA, Nestel PJ, et al. Neuroadrenergic dysfunction along the diabetes continuum: a comparative study in obese metabolic syndrome subjects. Diabetes. 2012;61(10):2506-16.
28. Tentolouris N, Tsigos C, Perea D, Koukou E, Kyriaki D, Kitsou E, et al. Differential effects of high-fat and high-carbohydrate isoenergetic meals on cardiac autonomic nervous system activity in lean and obese women. Metabolism: clinical and experimental. 2003;52(11):1426-32.
29. Kaiyala KJ, Prigeon RL, Kahn SE, Woods SC, Schwartz MW. Obesity induced by a high-fat diet is associated with reduced brain insulin transport in dogs. Diabetes. 2000;49(9):1525-33.
30. Nagoshi T, Yoshimura M, Rosano GM, Lopaschuk GD, Mochizuki S. Optimization of cardiac metabolism in heart failure. Current pharmaceutical design. 2011;17(35):3846-53.
31. Rosano GM, Fini M, Caminiti G, Barbaro G. Cardiac metabolism in myocardial ischemia. Current pharmaceutical design. 2008;14(25):2551-62.
32. Lacout M, Demiralp A, Donal E. Insuffisance cardiaque chez le patient diabetique : Faut-il dépister ? 2022.
33. Field BC, Gordillo R, Scherer PE. The role of ceramides in diabetes and cardiovascular disease regulation of ceramides by adipokines. Frontiers in endocrinology. 2020;11:569250.
34. Park T-S, Goldberg IJ. Sphingolipids, lipotoxic cardiomyopathy, and cardiac failure. Heart failure clinics. 2012;8(4):633-41.
35. Zheng H, Zhu H, Liu X, Huang X, Huang A, Huang Y. Mitophagy in diabetic cardiomyopathy: roles and mechanisms. Frontiers in Cell and Developmental Biology. 2021;9:750382.
36. Grundy SM. Does a diagnosis of metabolic syndrome have value in clinical practice? The American journal of clinical nutrition. 2006;83(6):1248-51.
37. Gaddam KK, Ventura HO, Lavie CJ. Metabolic syndrome and heart failure—the risk, paradox, and treatment. Current hypertension reports. 2011;13(2):142-8.
38. De Rosa S, Arcidiacono B, Chiefari E, Brunetti A, Indolfi C, Foti DP. Type 2 Diabetes Mellitus and Cardiovascular Disease: Genetic and Epigenetic Links. Front Endocrinol (Lausanne). 2018;9:2.
39. Carr ME. Diabetes mellitus: a hypercoagulable state. Journal of Diabetes and its Complications. 2001;15(1):44-54.
40. Jones D, Prior S, Tang T, Bain S, Hurel S, Humphries S, et al. Association between the rs4880 superoxide dismutase 2 (C> T) gene variant and coronary heart disease in diabetes mellitus. Diabetes research and clinical practice. 2010;90(2):196-201.
41. Tagougui S. Impact du diabète de type 1 et des niveaux élevés d'hémoglobine glyquée sur l'oxygénation musculaire et cérébrale à l'exercice: répercutions sur l'aptitude physique aérobie: Université du Droit et de la Santé-Lille II; 2014.
42. Spallone V, Ziegler D, Freeman R, Bernardi L, Frontoni S, Pop-Busui R, et al. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. Diabetes/metabolism research and reviews. 2011;27(7):639-53.
43. Pop-Busui R, Evans GW, Gerstein HC, Fonseca V, Fleg JL, Hoogwerf BJ, et al. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes care. 2010;33(7):1578-84.
44. Ross, R., *Atherosclerosis—an inflammatory disease.* New England journal of medicine, 1999. 340(2): p. 115-126.
45. Iaconetti C, Gareri C, Polimeni A, Indolfi C. Non-coding RNAs: the "dark matter" of cardiovascular pathophysiology. International Journal of Molecular Sciences. 2013;14(10):19987-20018.
46. De Rosa S, Curcio A, Indolfi C. Emerging role of microRNAs in cardiovascular diseases. Circulation Journal. 2014;78(3):567-75.

47. Stern MP. Stern MP. Diabetes and cardiovascular disease: the "common soil" hypothesis. Diabetes. 1995;44(4):369-74.
48. Arena R, Lavie CJ. The obesity paradox and outcome in heart failure: is excess bodyweight truly protective? Future Cardiology. 2010;6(1):1-6.
49. Bays HE. Adiposopathy: is "sick fat" a cardiovascular disease? Journal of the American College of Cardiology. 2011;57(25):2461-73.
50. Roche J. Le sommeil, ses troubles et la santé cardio-métabolique d'adolescents obèses: effets d'une prise en charge associant exercice physique et modification des habitudes alimentaires: Université Bourgogne Franche-Comté; 2018.
51. Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K, et al. General and abdominal adiposity and risk of death in Europe. New England Journal of Medicine. 2008;359(20):2105-20.
52. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation. 2006;113(6):898-918.
53. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. J Am Coll Cardiol. 2009;53(21):1925-32.
54. Mazur A, Ostański M, Telega G, Malecka-Tendera E. Is epicardial fat tissue a marker of metabolic syndrome in obese children? Atherosclerosis. 2010;211(2):596-600.
55. Li Y, Liu B, Li Y, Jing X, Deng S, Yan Y, et al. Epicardial fat tissue in patients with diabetes mellitus: a systematic review and meta-analysis. Cardiovascular diabetology. 2019;18(1):3.
56. Packer M. Epicardial adipose tissue may mediate deleterious effects of obesity and inflammation on the myocardium. Journal of the American College of Cardiology. 2018;71(20):2360-72.
57. da Silva AA, do Carmo JM, Li X, Wang Z, Mouton AJ, Hall JE. Role of hyperinsulinemia and insulin resistance in hypertension: metabolic syndrome revisited. Canadian Journal of Cardiology. 2020;36(5):671-82.
58. Kirk EP, Klein S. Pathogenesis and pathophysiology of the cardiometabolic syndrome. The Journal of Clinical Hypertension. 2009;11(12):761-5.
59. Van de Wal RM, Asselbergs FW, Plokker HT, Smilde TD, Lok D, van Veldhuisen DJ, et al. High prevalence of microalbuminuria in chronic heart failure patients. Journal of cardiac failure. 2005;11(8):602-6.
60. Stehouwer CD, Smulders YM. Microalbuminuria and risk for cardiovascular disease: analysis of potential mechanisms. Journal of the American Society of Nephrology. 2006;17(8):2106-11.
61. Mullens W, Damman K, Testani JM, Martens P, Mueller C, Lassus J, et al. Evaluation of kidney function throughout the heart failure trajectory - a position statement from the Heart Failure Association of the European Society of Cardiology. European journal of heart failure. 2020;22(4):584-603.
62. Vestberg D, Rosengren A, Olsson M, Gudbjörnsdottir S, Haraldsson B, Svensson A-M, et al. Decreased eGFR as a risk factor for heart failure in 13 781 individuals with type 1 diabetes. Journal of diabetes science and technology. 2016;10(1):131-6.
63. Lawson CA, Seidu S, Zaccardi F, McCann G, Kadam UT, Davies MJ, et al. Outcome trends in people with heart failure, type 2 diabetes mellitus and chronic kidney disease in the UK over twenty years. EClinicalMedicine. 2021;32:100739.
64. Ninomiya T, Perkovic V, De Galan BE, Zoungas S, Pillai A, Jardine M, et al. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. Journal of the American Society of Nephrology: JASN. 2009;20(8):1813.
65. Varma R, Bressler NM, Doan QV, Gleeson M, Danese M, Bower JK, et al. Prevalence of and risk factors for diabetic macular edema in the United States. JAMA ophthalmology. 2014;132(11):1334-40.
66. Delcourt C, Delyfer MN. Epidémiologie de l'œdème maculaire diabétique, facteur de risque Société Française d'ophtalmologie,2016.
67. Marc Y, Danath. L. Inflammation dans la physiopathologie et le traitement du diabète de type 2 et de ses complications. Med. Mal. Metab.2021 ;15 :661-668.
68. De Flines J, Scheen A. Insuffisance cardiaque et diabete de type 2: une relation a double sens. Revue Médicale de Liège. 2007;62(2).
69. Tesch GH. Diabetic nephropathy–is this an immune disorder? Clinical science. 2017;131(16):2183-99.
70. Mesquida M, Leszczynska A, Llorenç V, Adán A. Interleukin-6 blockade in ocular inflammatory diseases. Clinical & Experimental Immunology. 2014;176(3):301-9.
71. Stahel M, Becker M, Graf N, Michels S. Systemic interleukin 1β inhibition in proliferative diabetic retinopathy: a prospective open-label study using canakinumab. Retina (Philadelphia, Pa). 2016;36(2):385.
72. Urwyler SA, Schuetz P, Ebrahimi F, Donath MY, Christ-Crain M. Interleukin-1 antagonism decreases

cortisol levels in obese individuals. The Journal of Clinical Endocrinology & Metabolism. 2017;102(5):1712-8.
73. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. Circulation. 2014;129(3):e28-e292.
74. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Journal of the American College of Cardiology. 2022;79(17):e263-e421.
75. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. European journal of heart failure. 2020;22(8):1342-56.
76. Seferovic JP, Tesic M, Seferovic PM, Lalic K, Jotic A, Biering-Sørensen T, et al. Increased left ventricular mass index is present in patients with type 2 diabetes without ischemic heart disease. Scientific reports. 2018;8(1):926.
77. Kong MG, Jang SY, Jang J, Cho H-J, Lee S, Lee SE, et al. Impact of diabetes mellitus on mortality in patients with acute heart failure: a prospective cohort study. Cardiovascular diabetology. 2020;19:1-10.
78. Jang SY, Jang J, Yang DH, Cho H-J, Lim S, Jeon E-S, et al. Impact of insulin therapy on the mortality of acute heart failure patients with diabetes mellitus. Cardiovascular diabetology. 2021;20:1-11.
79. Ohkuma T, Komorita Y, Peters SA, Woodward M. Diabetes as a risk factor for heart failure in women and men: a systematic review and meta-analysis of 47 cohorts including 12 million individuals. Diabetologia. 2019;62:1550-60.
80. Bays HE. Adiposopathy: is "sick fat" a cardiovascular disease? Journal of the American College of Cardiology. 2011;57(25):2461-73.
81. Dinh W, Füth R, Lankisch M, Bansemir L, Nickl W, Scheffold T, et al. Cardiovascular autonomic neuropathy contributes to left ventricular diastolic dysfunction in subjects with type 2 diabetes and impaired glucose tolerance undergoing coronary angiography. Diabetic Medicine. 2011;28(3):311-8.
82. Pandey A, Patel KV, Vongpatanasin W, Ayers C, Berry JD, Mentz RJ, et al. Incorporation of biomarkers into risk assessment for allocation of antihypertensive medication according to the 2017 ACC/AHA high blood pressure guideline: a pooled cohort analysis. Circulation. 2019;140(25):2076-88.
83. Dunlay SM, Givertz MM, Aguilar D, Allen LA, Chan M, Desai AS, et al. Type 2 Diabetes Mellitus and Heart Failure: A Scientific Statement From the American Heart Association and the Heart Failure Society of America: This statement does not represent an update of the 2017 ACC/AHA/HFSA heart failure guideline update. Circulation. 2019;140(7):e294-e324.
84. Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EA, et al. 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(2):351-7.
85. Lind M, Olsson M, Rosengren A, Svensson A-M, Bounias I, Gudbjörnsdottir S. The relationship between glycaemic control and heart failure in 83,021 patients with type 2 diabetes. Diabetologia. 2012;55:2946-53.
86. Castagno D, Baird-Gunning J, Jhund PS, Biondi-Zoccai G, MacDonald MR, Petrie MC, et al. Intensive glycemic control has no impact on the risk of heart failure in type 2 diabetic patients: evidence from a 37,229 patient meta-analysis. American heart journal. 2011;162(5):938-48.e2.
87. O'Donoghue ML, Kato ET, Mosenzon O, Murphy SA, Cahn A, Herrera M, et al. The efficacy and safety of dapagliflozin in women and men with type 2 diabetes mellitus. Diabetologia. 2021;64(6):1226-34.
88. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. The New England journal of medicine. 2020;383(15):1413-24.
89. Bhatt DL, Szarek M, Pitt B, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. The New England journal of medicine. 2021;384(2):129-39.
90. Heerspink HJ, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou F-F, et al. Dapagliflozin in patients with chronic kidney disease. New England Journal of Medicine. 2020;383(15):1436-46.
91. McMurray JJ, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. New England Journal of Medicine. 2019;381(21):1995-2008.
92. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. The New England journal of medicine. 2019;380(24):2295-306.
93. Zinman B, Inzucchi SE, Wanner C, Hehnke U, George JT, Johansen OE, et al. Empagliflozin in women with type 2 diabetes and cardiovascular disease - an

analysis of EMPA-REG OUTCOME®. Diabetologia. 2018;61(7):1522-7.

94. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. The New England journal of medicine. 2017;377(7):644-57.
95. Pop-Busui R, Januzzi JL, Bruemmer D, Butalia S, Green JB, Horton WB, et al. Heart Failure: An Underappreciated Complication of Diabetes. A Consensus Report of the American Diabetes Association. Diabetes care. 2022;45(7):1670-90.
96. Association A. 10. Cardiovascular disease and risk management: standards of medical care in diabetes—2021. Diabetes care. 2021;44(Supplement 1):S125-S50.
97. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, et al. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. European heart journal. 2016;37(5):455-62.
98. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, et al. Vericiguat in patients with heart failure and reduced ejection fraction. New England Journal of Medicine. 2020;382(20):1883-93.
99. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. New England Journal of Medicine. 2007;356(24):2457-71.
100. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet (London, England). 2005;366(9493):1279-89.
101. Kishimoto I, Makino H, Ohata Y, Tamanaha T, Tochiya M, Anzai T, et al. Intensity of statin therapy and new hospitalizations for heart failure in patients with type 2 diabetes. BMJ Open Diabetes Research and Care. 2015;3(1):e000137.
102. Kjekshus J, Apetrei E, Barrios V, Böhm M, Cleland JG, Cornel JH, et al. Rosuvastatin in older patients with systolic heart failure. New England Journal of Medicine. 2007;357(22):2248-61.
103. Fumeaux D, Becerra M, Philippe J, Louis-Simonet M. L'aspirineen prévention primaire. Rev Med Suisse. 2010;6:244-8.
104. Kani C, Franco JM, Marmion N, Forecourt. La prescription d'aspirine en prevention primaire des évenements cardiovasculaires: la fin d'un cassa-tete.2019.
105. Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, Barton J, et al. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. The New England journal of medicine. 2018;379(16):1529-3