Thieme

Diabetes Mellitus and the Heart

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Cardiovascular risk

Patients with diabetes mellitus (DM) have a significantly increased risk of developing cardiovascular diseases with their sequelae of acute myocardial infarction, stroke and cardiovascular death. For example, even today a 60-year-old male patient with diabetes has 6 years less life expectancy compared to a metabolically healthy male of the same age, and a 60-year-old patient with diabetes and a previous history of a heart attack has 12 years less [1]. These data highlight the need for targeted risk stratification of patients with diabetes and the consistent treatment of diabetes, associated risk factors and cardiovascular disease.

Patients with diabetes mellitus should be categorized according to their cardiovascular risk into those with very high cardiovascular risk, high cardiovascular risk and moderate cardiovascular risk [2].

Very high cardiovascular risk

DM and existing cardiovascular disease, or end organ damage, or ≥ 3 risk factors or diabetes duration > 20 years.

High cardiovascular risk

DM with a diabetes duration > 10 years without end organ damage, but with an additional risk factor.

Moderate cardiovascular risk

Young patients (type 1 diabetes < 35 years; type 2 diabetes < 50 years) with a diabetes duration < 10 years without other risk factors.

Further risk stratification

In addition to diagnostics for the above-mentioned risk stratification, patients with diabetes and hypertension or clinical suspicion of cardiovascular disease should receive a resting ECG. At present, no convincing data exist to use additional imaging techniques such as echocardiography, stress echocardiography, scintigraphy or MRI in asymptomatic patients with diabetes mellitus. As part of clinical routines, no determination of circulating biomarkers should be carried out as part of risk stratification.

Cardiovascular risk reduction

For the recommendations on the reduction of cardiovascular risk in diabetes treatment, refer to the DDG practice recommendations on the therapy of type 2 diabetes (see p. 65–92) and on the treatment of lipid metabolic disorders (see p. 160–165). Therefore, only the basic statements are listed here:

- Patients with diabetes should receive structured advice on how to stop smoking. For patients with diabetes, a Mediterranean diet enriched with polyunsaturated and monounsaturat-

ed fatty acids is recommended. Patients with diabetes should perform moderate to strenuous physical activity for at least 150 min/week.

- In patients with type 2 diabetes and very high cardiovascular risk, a target value for LDL cholesterol of < 55 mg/dL and a minimum of 50 % reduction in LDL cholesterol is recommended. For patients with a high cardiovascular risk, a target value of 70 mg/dL and a minimum of 50 % reduction in LDL cholesterol is recommended. For patients with a moderate risk, a reduction in LDL cholesterol to < 100 mg/dL is recommended.
- The administration of aspirin (100 mg/day) is recommended for secondary prevention in patients with diabetes mellitus. In the context of primary prevention, patients with diabetes should not receive antiplatelet therapy. Platelet aggregation inhibition after acute coronary syndrome and/or coronary intervention (duration of dual antiplatelet therapy, etc.) should be coordinated with the treating cardiologist.
- In accordance with the new guideline of the European Society of Cardiology, patients with diabetes mellitus should have a target systolic blood pressure of 130 mmHg. If possible, systolic values < 130 mmHg should be targeted. The diastolic blood pressure target is < 80 mmHg. A blood pressure setting < 120/70 mmHg should be avoided.
- When adjusting blood glucose levels, patients without a cardiovascular pre-existing condition should be treated according to the recommendations for type 2 diabetes; in patients with a pre-existing cardiovascular condition, hypoglycaemia should be avoided and proven therapy strategies in reducing cardiovascular risk should be used. Therefore, GLP-1 receptor agonists and/or SGLT-2 inhibitors with proven event reduction should be used for reducing cardiovascular events and mortality based on the results of large cardiovascular endpoint studies in cases of type 2 diabetes and cardiovascular diseases or a high/very high cardiovascular risk.

Diabetes and coronary heart disease

All patients with coronary heart disease should be examined for the presence of diabetes mellitus (see Diagnostics and Classification of Diabetes Mellitus). For prognostic factors, patients with diabetes mellitus and coronary heart disease should receive platelet aggregation inhibitors, ACE inhibitor therapy and lipid-lowering therapy with statins.

The first year after myocardial infarction the administration of a beta-blocker additionally leads to an improvement of the prognosis, whereby this effect decreases over the course of time. With respect to antidiabetic therapy, for patients with type 2 diabetes at high cardiovascular risk, empagliflozin [3] or canagliflozin [4] versus placebo. In addition, empagliflozin significantly reduced all-cause mortality [3]. In DECLARE, there was no significant effect for dapagliflozin vs. placebo [5]. However, it seems that the individual substance is less important for the different results in the studies than the patient population. Similarly, in LEADER with liraglutide [6], in SUSTAIN-6 semaglutide [7], in HARMONY with albiglutide [8], in REWIND with dulaglutide [9], and in PIONEER-6 [10] with oral semaglutide vs. placebo showed a significant reduction in the 3-point MACE endpoint. In addition, liraglutide and oral semaglutide vs. placebo reduced all-cause mortality in the LEADER trial and PIONEER 6 trial, respectively. Administration of semaglutide resulted in significant reduction of cardiovascular events [11]. Against the background of these data, therapy with one of these substances should be an integral part of blood glucose-lowering therapy in patients with diabetes and cardiovascular disease.

In the presence of coronary artery disease requiring intervention or surgery, the therapy of coronary revascularization in patients with diabetes does not differ from the therapy in patients without diabetes. In complex coronary findings with multi-vascular disease and low perioperative mortality, bypass surgery appears to be superior to coronary intervention. The decision on the revascularization procedure to be performed (coronary intervention or bypass surgery) should always be made by the interdisciplinary cardiac team in the case of complex coronary heart disease.

Diabetes and heart failure

Epidemiological and clinical data of recent years have shown that patients with diabetes mellitus have a significantly increased risk of developing heart failure and that the prognosis of patients with diabetes and heart failure is significantly worse than that of patients with heart failure without diabetes [12], [13]. Heart failure with a reduced ejection fraction (HFrEF), Heart failure with preserved ejection fraction (HFpEF) and Heart failure with mildly reduced ejection fraction (HFmrEF) are categorized according to the recommendation of the European Society of Cardiology guideline (▶ **Tab. 1**) [14]. In principle, it can be said that half of patients with heart failure and diabetes have impaired left ventricular function.

At present, clinical data only exist for patients with HFrEF that suggest an improvement in prognosis. The therapy for HFrEF in patients with diabetes does not differ from the therapy of non-diabetic patients in terms of both drug therapy and device therapy (Implantable cardioverter defibrillator [ICD], Cardiac Resynchronization Therapy [CRT]). For HFpEF and HFmrEF there are no data available that reliably prove an improvement in the prognosis of the patients, so that symptomatic therapy options -e. g. the administration of diuretics – and a treatment of comorbidity -e. g. adjustment of the arterial hypertension – are in the foreground.

With regard to blood glucose-lowering therapy, the studies with empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin showed a significant reduction in hospitalization for heart failure, so that these substances should be used in patients at high risk for heart failure and in patients with heart failure for blood glucose lowering and reduction of cardiovascular morbidity and mortality. For patients with HFrEF, the DAPA-HF and EMPEROR-Reduced trials are also available, both conducted in patients with and without diabetes. Administration of dapagliflozin or empagliflozin significantly reduced worsening heart failure, cardiovascular death, or all-cause mortality regardless of the presence of diabetes mellitus [15], [17]. Dapagliflozin is the first SGLT-2 inhibitor since the end of 2020 to be approved for the treatment of heart failure with an ejection fraction < 40 % (HFrEF), regardless of the presence of diabetes mellitus. Important to note in this regard is the Estimated Glomerular Filtration Rate (eGFR) limit, which is important for use. While dapagliflo-

▶ **Tab. 1** Definition of heart failure with preserved (HFpEF), moderately restricted (HFmrEF) and reduced ejection fraction (HFrEF).

HF type		HFrEF	HFmrEF	HFpEF
Criteria	1	Symptoms ± sign[1]	Symptoms ± sign[1]	Symptoms ± sign[1]
	2	LVEF < 40 %	LVEF 40-49 %	LVEF ≥ 50 %
	3	–	1. Increased serum concentrations of natriuretic peptides[2] 2. At least 1 additional criterion: a. Relevant structural heart disease (LVH and/or LAE) b. Diastolic dysfunction[3]	1. Increased serum concentrations of natriuretic peptides[2] 2. At least 1 additional criterion: a. Relevant structural heart disease (LVH and/or LAE) b. Diastolic dysfunction[3]

LAE Left atrial enlargement (left atrial volume index [LAVI] > 34 ml/m^2); LVH left ventricular hypertrophy (left ventricular muscle mass index [LVMI] ≥ 115 g/m^2 for men and ≥ 95 g/m^2 for women).; [1] Signs may be absent in early stages of heart failure (especially HFpEF) and in patients on diuretic treatment. [2] BNP > 35 pg/ml and/or NT-proBNP > 125 pg/ml. [3] E/A ratio ≥ 13, mean (septal and lateral) "E" velocity < 9 cm/s (for details see section 4.3.2 in [1]). LAE = Left atrial enlargement, LVEF = left ventricular ejection fraction, LVH = Left ventricular hypertrophy.

▶ **Tab. 2** Approach based on risk factors, expressed as point system with the acronym CHA_2DS_2 -VASc score.

Risk factor	Score
Chronic heart failure or left ventricular dysfunction	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Vascular disease history[1]	1
Age 65-74 years	1
Female	1
Maximum score	9

Note: As the age can be evaluated with 0, 1 or 2 points, the maximum score is 9. [1] Condition after myocardial infarction, peripheral arterial occlusive disease, or plaque in the aorta. TIA = Transient ischemic attack.

zin may be started at an eGFR > 60 ml/min and continued up to an eGFR of 45 ml/min for the treatment of diabetes mellitus, therapy may be started and continued in patients with heart failure up to an eGFR of 30 ml/min. In addition, on May 20, 2021, the Committee for Medicinal Products for Human Use (CHMP) gave a positive evaluation to empagliflozin for the treatment of heart failure with reduced ejection fraction. European approval was granted on June 21, 2021, making two SGLT-2 inhibitors currently available for the treatment of heart failure with reduced ejection fraction. Due to the increased risk of hospitalization for heart failure, glitazones and the DPP4 inhibitor saxagliptin are contraindicated in patients with heart failure.

Diabetes and atrial fibrillation

The presence of diabetes mellitus is a separate risk factor for thromboembolic events in patients with atrial fibrillation. All patients with atrial fibrillation should be risk stratified for their risk of thromboembolism using the CHADS-VASC score (▶ **Tab. 2**) and accordingly receive anticoagulation with vitamin K antagonists and Non-vitamin K antagonist oral anticoagulants (NOACs) [16]. At this stage, no data exists that show a prognostic advantage of a rhythm restoration (cardioversion in the sinus rhythm) or frequency control in atrial fibrillation. In this respect, the procedure is comparable for patients with and without diabetes.

Conflict of Interest

KS has lectured for Amgen, AstraZeneca, Bayer, OmniaMed, Lilly, Boehringer Ingelheim, Novartis, NovoNordisc and MSD and acted as consultant to AstraZeneca, Amgen, Böhringer Ingelheim and Lilly. KS also carried out a research project supported by Boehringer Ingelheim.; DMW has lectured and advised Amgen, AstraZeneca, Boehringer Ingelheim, MSD, NovoNordisk and Sanofi-Aventis. NM has lectured for Amgen, Boehringer Ingelheim, Sanofi-Aventis, MSD, BMS, AstraZeneca, Lilly, NovoNordisk; NM has conducted research projects supported by Boehringer Ingelheim and MSD and has acted as consultant to Amgen, Boehringer Ingelheim, Sanofi-Aventis, MSD, BMS, AstraZeneca, NovoNordisk, Lilly and Bayer.; ALB has lectured for Amgen, AstraZeneca, Lilly, Boehringer Ingelheim, NovoNordisc, and MSD, and served as a consultant for Böhringer Ingelheim, AstraZeneca, and NovoNordisk.; AZ has acted as consultant for: Bayer Health Care; Boehringer Ingelheim; Rigel; Cardiorentis; Medscape; Stealth Peptides; Sanofi Aventis; Medtronic; Novartis. He received honoraria from: Bayer Health Care; Astra-Zeneca; Medtronic; ResMed; Boehringer Ingelheim; Rigel; Sanofi Aventis; Pfizer; Janssen-Cilag; Novartis; Bristol Myers Squib; Thoratec; Abiomed; Daiichi Sankyo; Abbott; Cardiac Dimensions.; TF has the following conflicts of interest: Speaker Panel: Abbott; Astra Zeneca; Böhringer Ingelheim, Berlin Chemie; Cipla, Eli Lilly; Fortbildungskolleg; MSD; Novartis, Novo Nordisk; Sanofi. Advisory Panel: Astra Zeneca; Bayer; Cipla, Eli Lilly; Fortbildungskolleg; Novo Nordisk; Pfizer; Sanofi; Bayer; Roche; Eyesense.

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