Thieme

Therapy of Type 2 Diabetes

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The Clinical Practice Guidelines of the German Diabetes Society/Deutsche Diabetes Gesellschaft (DDG) together with the German Society for Internal Medicine/Deutschen Gesellschaft für Innere Medizin (DGIM) are based on the contents of the National Treatment Guideline (Nationale Versorgungsleitlinie (NVL)) "Type 2 Diabetes" [1]. The modifications in therapy and their justifications made in the present Clinical Practice Guidelines were updated on the basis of new randomized controlled trials (RCTs) and meta-analyses.

In order to improve the work with the extensive practice guideline in practice, the authors have decided to move the individual glucose-lowering pharmaceuticals and some algorithms in the current practice guideline to a detailed appendix. The corresponding bibliography can also be found in the appendix.

Definition of type 2 diabetes

Type 2 diabetes is a chronic, very heterogeneous, multi-factorial, progressive disease characterized by inherited and acquired insulin resistance and qualitative and quantitative insulin secretion disturbances.

Influenceable and uninfluenceable risk factors for type 2 diabetes are listed in the "Risk factors for type 2 diabetes" info box.

CAUTION

RISK FACTORS FOR CARDIOVASCULAR DISEASES AND TYPE 2 DIABETES

Uninfluenceable

Higher age
- Sex (Male > Female)
- Ethnicity
- Diabetes in the family
- Gestational diabetes (in the history)
- Intrauterine development (foetal programming)

Influenceable
- Visceral obesity
- Fatty liver
- Depression
- Obstructive sleep apnoea (OSA)
- Physical inactivity
- High-energy, low-fibre food
- High sugar consumption (soft drinks etc.)
- Excessive alcohol consumption (fatty liver)
- Smoking
- Diabetogenic drugs
- Diabetogenic environment (e. g., deprivation) = disadvantage due to lack of resources, exposure to excessive chronic noise and air pollution)

Metabolic syndrome [2]

At least 3 out of 5 criteria must be fulfilled:
- Abdominal obesity (waist circumference): male *> 94 cm; female ** > 80 cm
- Triglycerides *** : ≥ 150 mg/dl or ≥ 1.7 mmol/l
- HDL cholesterol *** : male < 40 mg/dl or < 1.03 mmol/l; female: < 50 mg/dl or < 1.29 mmol/l
- Elevated blood pressure *** : ≥ 130/ ≥ 85 mmHg
- Fasting plasma glucose *** : ≥ 100 mg/dl or ≥ 5 mmol/l or pre-existing diabetes

* / ** People from: Southeast Asia or China: 90/80 cm; Japan: 90/85 cm

*** Pharmacological intervention is an alternative criterion

Therapy goals

In the present guidelines, target corridors are specified which, with varying degrees of evidence, inform the doctor and the patient which target corridor/target value (e. g., HbA1c, blood pressure, LDL cholesterol values) should normally be aimed for according to the current state of medical knowledge and on the basis of evidence and consensus. This does not affect the superordinate goal of setting personal therapy goals (both superordinate and secondary) primarily together with the patient and possibly together with relatives, and agreeing on them in writing on a quarterly basis (e. g., in the Diabetes Health Pass). According to Elwyn and Vermunt [3], the 3 categories of goals: superordinate goals (e. g., maintaining quality of life or independence), function-related goals (e. g., maintaining eyesight and job) and disease-related goals (e. g., eliminating pain, improving metabolism) should be discussed and prioritised in terms of shared decision-making.

General and specific therapy goals

The therapeutic goals of people with type 2 diabetes depend on patient preference, comorbidity, age and life expectancy, quality of life, cultural conditions, psychosocial circumstances and possibilities as well as abilities of the persons concerned. The diagnosis of type 2 diabetes, which is often experienced by those affected as a severe life restriction, requires a strategy of acceptance and gradual intensification of therapy (exception: severe metabolic decompensation).

In the Type 2 Diabetes [1] guideline, a chapter was created on shared decision-making (SDM) and participation in all relevant areas of life. The following recommendations with a high degree of recommendation [1] should be implemented in the care of people with diabetes:

1. People with type 2 diabetes and their doctor should jointly agree on and prioritise individual therapy goals at the beginning and frequently during the course of the disease.
2. Therapy goals should be agreed upon individually with the patient should be evaluated regularly and as needed during the course of treatment and followed up, or adjusted, according to the results.
3. The doctor should document and make available the individual therapy goals and, if necessary, the reasons for not having achieved the goals in a way that is comprehensible for the patient and the professional care groups. This also applies to the evaluation of achieving therapy goals.
4. When providing information on the diagnosis and treatment options for type 2 diabetes, the different options with their advantages and disadvantages should be presented comprehensively and in an understandable form.
5. When health-related decisions regarding type 2 diabetes are to be made, the discussion should be conducted in accordance with the concept of shared decision-making.
6. When agreeing on and prioritising treatment options for type 2 diabetes, the discussion should be conducted in accordance with the concept of shared decision-making.
7. Personal and environmental contextual factors should be taken into account when agreeing and prioritising individual treatment goals and evaluating the treatment strategy. The effects on participation in all relevant areas of life should be taken into account.
8. If individual therapy goals agreed according to the concept of shared decision-making are not achieved, a structured approach should be taken [1, 3]. A detailed discussion of shared decision-making is presented in the section “Fundamentals of Diabetes Management” in this Supplement.

CAUTION

GENERAL TREATMENT AND CARE GOALS

- Preservation or restoration of quality of life
- Empowerment of those affected in dealing with the disease and its complications
- Reduction of stigma associated with the disease
- Treatment satisfaction
- Promotion of therapy adherence
- Reduction of risk for cardiac, cerebrovascular and other macrovascular complications
- Avoidance and treatment of microvascular and neurological complications
- Avoidance and treatment of diabetic foot syndrome
- Treatment and improvement of comorbidities
- Minimization of side effects of therapy (e. g., severe hypoglycaemia, weight gain)
- Reduction of the burden of complex therapies (polypharmacy, drug interactions)
- Reduction of morbidity
- Normalisation of shortened life expectancy with good quality of life

In people with type 2 diabetes, individualized therapy goals should be agreed for the following **vascular risk parameters** (info box "General treatment and care goals"; ▶ **Tab. 1**):

- Lifestyle
- Blood pressure
- Glucose metabolism
- Lipid status
- Body weight

Prioritisation of the therapy goal on the basis of the personal risk profile

The guiding factors for the selection of the appropriate therapy strategy are the jointly prioritised therapy goals and the probability of benefiting from a certain therapy due to individual disease factors. On the basis of the evidence currently available, there are 2 basic, possible approaches:

- Reduction of diabetes complications mainly by controlling the HbA1c value as an indicator for metabolic control;
- Primary reduction of the probability of a specific cardiovascular and renal event by administering drugs that reduce these endpoints.

It is worth noting that the above approaches are not mutually exclusive, but ideally complementary.

Diagnosis

Medical history and clinical examinations as well as monitoring of people with type 2 diabetes are compiled in the annex to this practical guideline.

Diagnosis is ensured by standardized and quality-assured laboratory tests for both plasma glucose and HbA1c. Devices for self-measurement (POCT systems) must successfully pass external quality assurance otherwise they are unsuitable for the diagnosis. Since a large number of preanalytical, analytical and interpretational problems are present in the diagnosis of diabetes, the updated and detailed practical recommendations for diabetes diagnosis should be referred to in addition to other sources of information [8–11].

In the differential diagnosis of the heterogeneous disease type 2 diabetes, subtypes of diabetes are increasingly defined and clinically considered in practice [12–14].

Therapy

Basic therapy

Adapting to a healthy lifestyle is crucial not only to prevent type 2 diabetes, but also to reduce the complex pharmacotherapy and the development and progression of diabetic complications of type 2 diabetes. In this context, it makes sense to address not only one, but as many risk factors as possible through lifestyle modification [15].

Education and training

As an indispensable part of diabetes treatment, all persons affected by diabetes mellitus and, if applicable, their family members should be offered structured, evaluated and target group- and topic-specific training and treatment programmes as well as, if necessary, problem-oriented follow-up training [16].

Plasma glucose self-monitoring

In the case of an indication for plasma glucose self-monitoring, the situations listed in ▶ **Tab. 2** should be taken into account in people with type 2 diabetes. However, the measurements should result in behavioural and therapeutic adjustments.

Urine glucose analyses

These are not standard in the diagnosis, therapy decision-making and monitoring, because urine glucose is only positive in the case of high blood glucose values (renal glucose transport capacity is very different between individuals, it is age-dependent, it is not systematically examined at reduced kidney function, it lowers with certain diseases and is not useful in pregnancy or with the use of drugs such as Sodium-glucose Cotransporter-2 (SGLT2) inhibitors). However, in the assessment of hyperglycaemic metabolic derailment, however, the measurement of ketonuria is decisive for therapy.

Nutritional therapy and consultation

Nutritional recommendations for people with type 2 diabetes should include the following key points. These are just a few recommendations:

- Motivation to maintain a healthy, well-balanced diet considering the patient's previous nutrition routine. At the same time, the joy of eating should be preserved.
- As far as possible, the use of industrially-processed food should be avoided, and the intake of sucrose should be limited (World Health Organization [WHO] recommendation < 25 g/day). The German Nutrition Society (DGE) recommends limiting mono- and disaccharide consumption to < 10 % of daily energy intake.

▶ **Tab. 1** Orientation parameters for therapeutical goals.

Indicator	**Orientation parameters for therapeutic goals**	
	mg/dl	mmol/l
Fasting/preprandial plasma glucose (venous)	100–125	5.6–6.9
Postprandial plasma glucose (venous) 1–2 h postprandial	140–199	7.8–11.0
Indicator	Individualization of the therapeutic goals	
HbA1c	HbA1c target range of 6.5–7.5 % (48–58 mmol/mol Hb) to prevent complications and severe hypoglycaemia.	
	In elderly people with multimorbidity and people with severely reduced life expectancy HbA1c < 8.0 % (< 64 mmol/mol Hb), sometimes < 8.5 % (< 69 mmol/mol Hb). If only antidiabetic medications without intrinsic hypoglycaemia risk are used, lower HbA1c targets may also be defined.	
Uric acid	Serum levels ≤ 6.0 mg/dl (357 µmol/l) [4]	
Lipids	LDL cholesterol reduction: Very high risk in primary and secondary prevention: ≥ 50 % LDL-C reduction from baseline before lipid-lowering therapy and an LDL-C target < 1.4 mmol/l (< 55 mg/dl)	
	High risk: ≥ 50 % LDL-C reduction from baseline and an LDL-C < 1.8 mmol/l (< 70 mg/dl).	
	Moderate risk: < 2.6 mmol/l (< 100 mg/dl) [5, 6].	
Weight loss for excess weight	For BMI from 27–35 kg/m^2: > 5 % weight reduction; for BMI > 35 kg/m^2: > 10 % weight reduction	
Blood pressure	Systolic blood pressure: 120–140 mmHg (≥ 65 years 130–140 mmHg;	
	≤ 65 years 120–129 mmHg); diastolic blood pressure: < 80 mmHg (not < 70 mmHg); if the therapy has no relevant side effects [7]	

LDL = Low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; BMI = body mass index

▶ **Tab. 2** Situations in which plasma glucose self-monitoring is necessary or may be temporarily necessary in people with type 2 diabetes[1].

	Clinically defined situations
Diabetes stage	Newly diagnosed, adjustment phase
Diabetes along its course	▪ Unstable with frequent hypoglycaemia (at this point, measure before all meals until the therapy goal is achieved, then return to targeted situational measurements) ▪ Therapy intensification ▪ Temporarily after switching from insulin to oral antidiabetic therapy
Additional illnesses/ interventions	▪ Serious infections ▪ Planned operations ▪ Mental illnesses with unreliable intake of medication ▪ During sport/exercise and blood glucose-lowering substances, which may be associated with hypoglycaemia, and corresponding symptoms occur ▪ Acute changes in diet due to illness (e. g., diarrhoea/vomiting)
Diabetes therapy	▪ Oral antidiabetics (OAD) with hypoglycaemia potential (sulfonylureas, glinides, then occasional measurements) ▪ Insulin therapy and necessity of insulin dose self-adjustment ▪ Intensified conventional insulin therapy (before all meals, occasionally at night) ▪ Insulin pump therapy (before all meals, occasionally at night)[1] ▪ Situations with special hazards (e. g. shift work, driving lorries, buses, cranes, etc.)

[1] G-BA decision of June 16, 2016 (BAnz AT 06.09.2016 B3): Continuous interstitial glucose measurements with real-time measuring devices (rtCGM) for therapy control in patients with insulin-dependent diabetes mellitus can be provided under special conditions as contracted medical services at the expense of the health insurance funds. The costs for **FGM** ("flash glucose monitoring"), also known as "intermittent-scanning continuous glucose monitoring" (iscCGM), are now also covered by insurance companies.

- No generalized ban on sugar, but avoidance of large amounts of regular sugar, fructose, sugar alcohols (e. g., sorbitol, xylitol) or drinks containing these substances.
- The estimation of type and amount of carbohydrates of each meal should be used as an essential metabolic control strategy for people with type 2 diabetes who inject insulin.
- People with type 2 diabetes without insulin therapy should be able to recognize foods which increase blood glucose.
- For people with type 2 diabetes and renal insufficiency, a daily protein intake of 0.8 g/kg is recommended. At the dialysis therapy stage, the protein intake should be increased to 1.2–1.3 g/kg.
- People with type 2 diabetes should be advised how to deal with alcohol in a differentiated manner as part of the individual consultation.
- Practical recommendations for a healthy and balanced diet, a Mediterranean diet at best [17–21].

- Avoidance of large portions and frequent consumption of fatty foods, e. g., fatty meat, fatty sausages, fatty cheese, fatty baked goods, fatty ready-made products, fatty fast food, cream, chocolate, chips, etc.
- Choosing vegetable fats, e. g., oils, nuts, seeds.
- Enriching meals with dietary fibres, e. g., vegetables, fresh fruit, whole grain cereals.

The effectiveness of weight loss and improvement of the vascular risk profile always depends on how the diet is designed: low-carb, vegan or Mediterranean - how well the acceptance and adherence as well as the long-term management of the dietary change succeed [21, 22].

Weight reduction

Weight reduction in overweight and obese people with type 2 diabetes supports the reduction of vascular risks, increases self-esteem, quality of life and can lead to remission in the early stages of type 2 diabetes [20, 23–26].

Physical activity (see ▶ **Fig. 1**)

Increased physical activity and sport are essential therapeutic interventions for all forms of diabetes. Physical activity is particularly beneficial for people with type 2 diabetes for a number of reasons [27–29]. The structured approach is outlined in the step-by-step programme [see Appendix] of the guideline. Extensive practical recommendations can be found in this supplement [30].

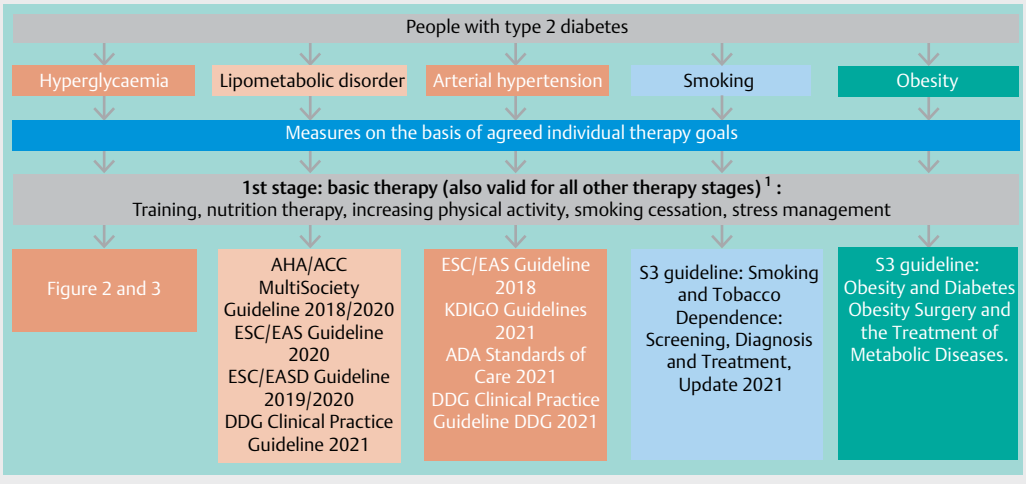
In brief:

- People with type 2 diabetes should be motivated to increase their physical activity.
- It should be decided which types of exercise or sports are suitable for people with type 2 diabetes on an individual basis.
- Aerobic endurance training and strength training to build and maintain musculature should be offered as structured movement programmes.
- At least 150 min of moderate intensity exercise are recommended per week [31].
- Lower intensity training shows lower drop-out rates and seems to be more successful in the long run than high intensity exercise training, either intermittently or continuously [32]. In particular, it is recommended for people with type 2 diabetes in the second half of their life to train dexterity, reactions, coordination, flexibility and mobility.

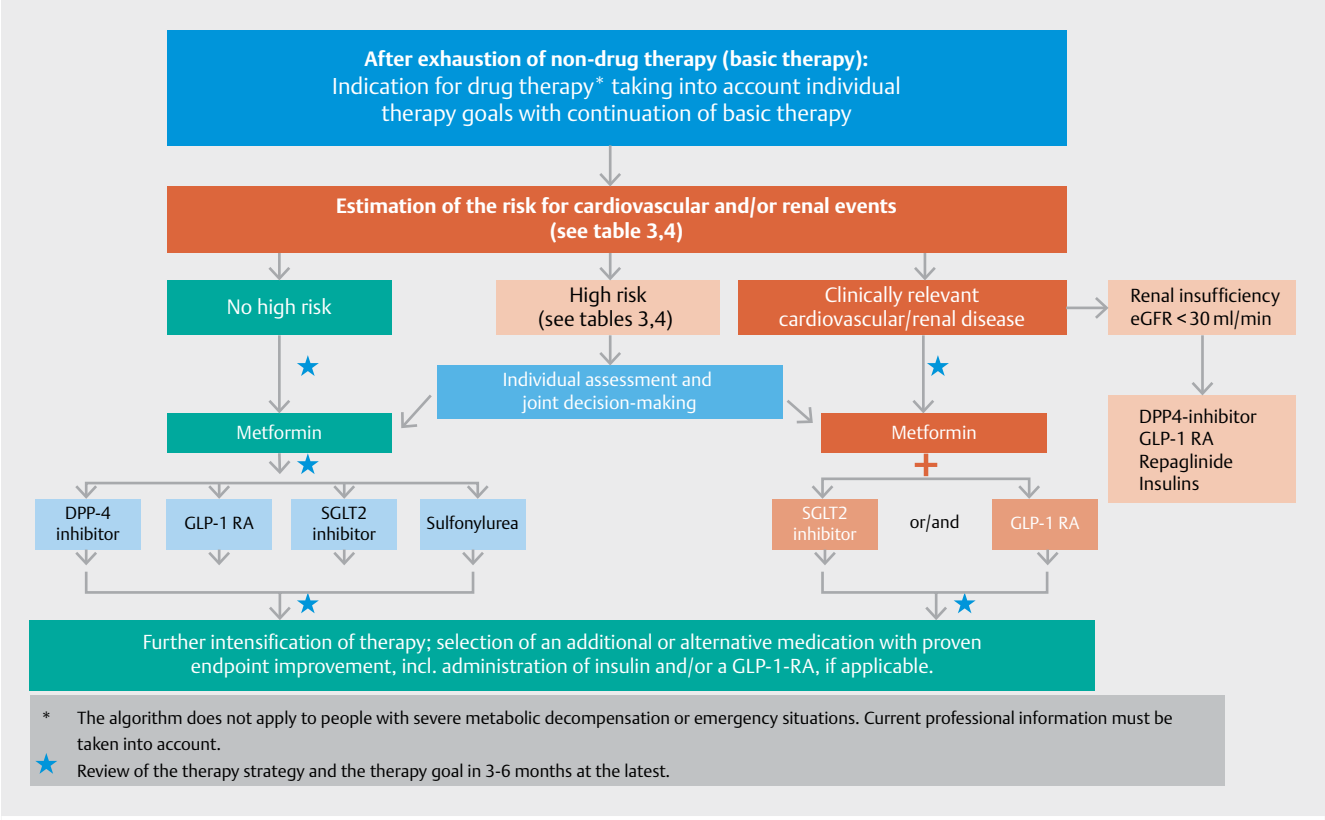
Cessation of smoking

Active and passive smoking, in addition to being a preventable cause of significantly increased morbidity and mortality, are also significant risk factors for type 2 diabetes (Pan A, Wang Y, Talaei M et al. Relation of active, passive, and quitting smoking with incident diabetes: a meta-analysis and systematic review. Lancet Diabetes Endocrinol 2015;3 (12): 958–996). In a recently published meta-analysis, smoking was shown to be an independent risk factor for the progression of albuminuria [33]. Albuminuria is one of the strongest predictors for the development and progression of cardiovascular complications. When appropriate to the situation, smokers should therefore always be educated and specifically counselled about the particular risks of smoking for type 2 diabetes, microvascular and macrovascular sequelae and pulmonary disease. They should be strongly advised to stop smoking tobacco.

Further information on tobacco cessation and support for quitting smoking can be found in the S3 guideline “Smoking and Tobacco Dependence: Screening, Diagnosis and Treatment”, Update 2021 [34] and in the Tobacco Atlas Germany [35].



▶ **Fig. 1** Therapy algorithm for type 2 diabetes. [1] Lifestyle-modifying, non-drug therapy measures are the basic therapy at every therapy level. AHA/ACC = American Heart Association / American College of Cardiology; ESC/EAS = European Society of Cardiology / European Atherosclerosis Society (EAS); DDG = German Diabetes Association; KDIGO = Kidney Disease: Improving Global Outcomes; ADA = American Diabetes Association



▶ **Fig. 2** Algorithm for drug therapy in type 2 diabetes. eGFR = Estimated Glomerular Filtration Rate; DPP4-inhibitor = Dipeptidyl peptidase-4 inhibitor; GLP-1 RA = Glucagon-like peptide-1 receptor agonist; SGLT2 = Sodium-glucose cotransporter-2

Smokers who are willing to change should receive regular counselling regarding possible tobacco cessation procedures (see Appendix; ▶ **Fig. 2**).

The basic therapy at every therapy level comprises lifestyle-modifying, non-drug therapy measures, but these are often not sufficient on their own. In patients for whom lifestyle-modifying measures are not expected to be sufficiently successful (due to severity of metabolic derailment, adherence problems, multimorbidity), these measures should be combined with metformin and, if contraindicated or intolerant, with another antidiabetic drug. Most people with type 2 diabetes have multimorbidity and thus, depending on the individual therapy goal, there is a need for polypharmacy with prioritisation according to the severity of vascular risks (▶ **Fig. 1**).

Pharmacotherapy

The step-by-step procedure provided in the therapy algorithm (▶ **Figs. 1, 2**) refers to the time of clinical diagnosis of type 2 diabetes in the stage of relative metabolic compensation. Newly-diagnosed patients with metabolic decompensation should receive basic therapy and pharmacotherapy (e. g., even insulin) at the same time.

Risk assessment

Before starting drug treatment, a detailed risk assessment is absolutely necessary, because this determines the choice and possible combination of antidiabetic and organ-protective drugs. In ▶ **Tab. 3**, important risk factors are listed in accordance with the National Care Guideline:

▶ **Tab. 3** Risk factors for which early use of organ-protective drugs is indicated. Data source: [1]

▪ Duration of diabetes (> 10 years)
▪ (Biological) age
▪ Gender (male > female)
▪ Lifestyle: unbalanced diet/physical inactivity
▪ Family history of early cardiovascular disease (Men < 55 years; women < 60 years)
▪ Hypertension or antihypertensive therapy
▪ Dyslipidaemia or lipid-lowering therapy
▪ Obesity (> 30 kg/m2)
▪ Renal insufficiency (eGFR < 60 ml/min.)
▪ Albuminuria (> 30 mg/g U creat.)
▪ Smokers and ex-smokers
▪ Subclinical arteriosclerosis or cardiovascular disease
▪ Left ventricular hypertrophy
▪ Obstructive sleep apnoea syndrome

Due to the complexity and the large number of risk factors (▶ **Tab. 3**), which have not been evaluated in their entirety, the risk assessment cannot be depicted in the form of scores. The analysis of important RCTs impressively shows how heterogeneous the inclusion criteria for the study participants were (▶ **Tab. 4**). In addition, most RCTs (strict inclusion and exclusion criteria) only represent a maximum of 4–50 % of real-world patients. In order to assess the effectiveness of interventions in Randomised controlled trials

▶ **Tab. 4** Criteria used to diagnose high cardiovascular risk (in patients without manifest atherosclerotic heart disease) in 12 published cardiovascular "Outcome" studies on the effect of GLP-1 receptor agonists or SGLT2 inhibitors: EMPA-REG, CANVAS-Program, DECLARE TIMI-58, VERTIS CV, ELIXA, LEADER, SUSTAIN-6, EXSCEL, REWIND, HARMONY Trials, PIONEER-6, AMPLITUDE-O.

Criteria	Frequency (n)	Frequency (%)	Comment
Age ≥ 50, 55, or 60 years	**6**	**100**	**Basic criterion, requires additional risk factors**
Plus reduced renal function (eGFR 25–59.9 ml/min.)	1	17	Also occurs as CHD-equivalent
Plus ≥ 1 (n = 4) or ≥ 2 (n = 2) further risk factors (see below)	**6**	**100**	**Further risk factors (see below)**
Diabetes duration ≥ 10 years	1	17	Main criterion according to ESC
Arterial hypertension (> 140 and > 90 mmHg or antihypertensive medication)	**3**	**50**	**Surprisingly low rated**
Smoking/tobacco use	**3**	**50**	**Surprisingly low rated**
Micro- or macroalbuminuria	**5**	**83**	**Central and meaningful criterion**
HDL cholesterol low (e. g., < 1 mmol/l or 42.5 mg/dl)	2	33	Surprisingly low rated
LDL cholesterol elevated (e. g., > 3.36 mmol/l/or 130 mg/dl)	2	33	Surprisingly low rated
Lipid-modifying therapy	1	17	Surprisingly low rated
Left ventricular hypertrophy (in arterial hypertension)	**3**	**50**	**Hypertension with end organ damage**
Left ventricular systolic or diastolic dysfunction	**3**	**50**	**Heart failure**
Ankle-brachial index < 0.9 (≥ 1 leg affected)	**3**	**50**	**Is also used for already manifested PAD**
Obesity	1	17	Surprisingly low rated
First-degree relative(s) with coronary heart disease with manifestation ≤ 55 years (men) or ≤ 65 years (women)	1	17	Seldom mentioned

6 of 12 cardiovascular "outcome" studies recruited patients without manifest disease due to risk factors. The percentages refer to this total number (6 studies). Criteria that were used consistently often (≥ 50 %) are highlighted in bold. All other criteria were suggested in a maximum of 33 % of the studies.

(RCTs) in real-world settings, pragmatic and register studies with the same patient characteristics as in corresponding RCTs are therefore necessary. Thus, only an individual careful assessment of the risk for cardiovascular and renal diseases before implementation of the corresponding therapy algorithm is helpful at present (▶ **Fig. 2** and **3**).

Overview with regard to metabolic effects and clinical endpoints

▶ **Tab. 5** allows a quick, orientating overview with regard to metabolic effects and clinical endpoints of the pharmaceuticals discussed in this Clinical Practice Guideline - apart from oral semaglutide, which was not inferior to subcutaneous semaglutide in terms of clinical endpoints. The table is a careful interpretation of the available evidence from randomised controlled trials and meta-analyses, which was compiled and consulted by the Medical Centre for Quality in Medicine and the National Care Guidelines working group (www.leitlinien.de/nvl/diabetes; AWMF Register No. 001; [1] and supplemented by the author group of this Clinical Practice Guideline because of new study results.

Reasons for the therapy level non-drug basic therapy

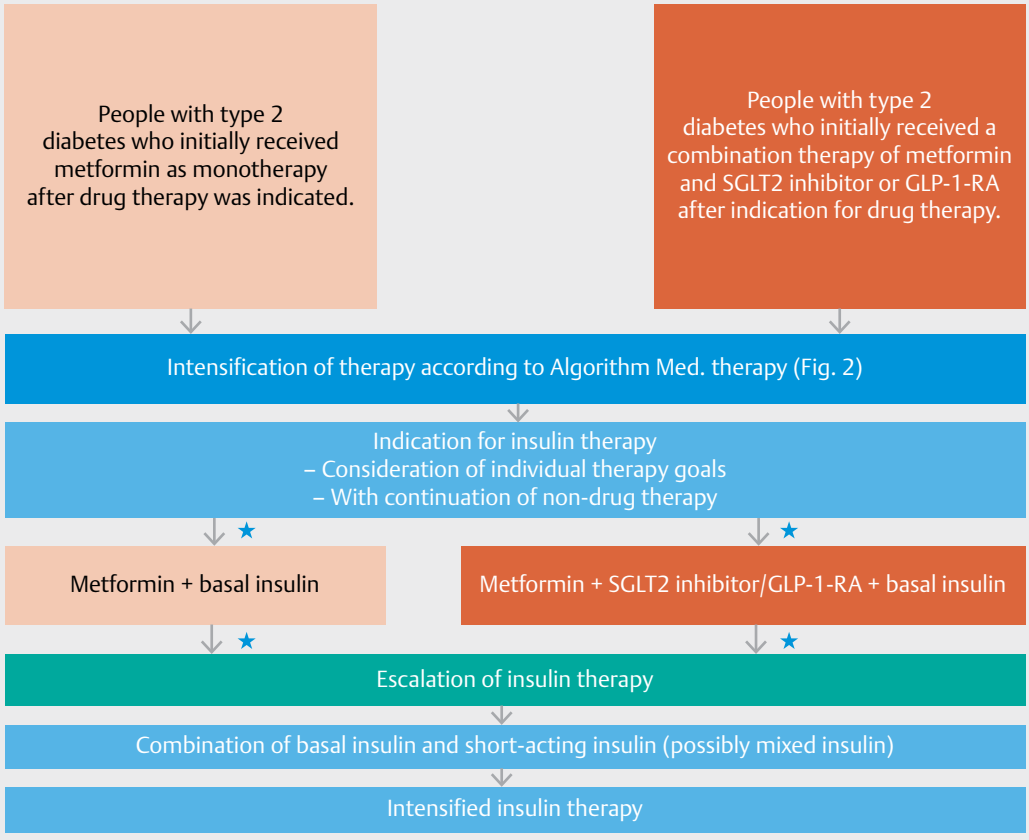
Basic therapy includes all lifestyle-modifying, non-drug measures. These include education and training of the patient, nutritional therapy, increasing physical activity and smoking cessation, as well as stress management strategies. An important goal is to strengthen the will to lead a healthy lifestyle (refraining from smoking, maintaining a diabetes-appropriate diet, increased physical activity, limiting alcohol consumption) (▶ **Fig. 2** and **3**). Digital tools and telemedical support are becoming increasingly important for the implementation of a personalised basic therapy [36].

Since many people with type 2 diabetes have a variety of other vascular risk factors in addition to chronic hyperglycaemia or already have cardiovascular, renal and other diseases, the treatment of these people is complex and should take into account all vascular risk factors and manifested clinical diseases individually. To emphasise this more clearly, the previous treatment algorithm has been expanded to address major cardiovascular risks in more detail.

Reasons for pharmacotherapy therapy level

The basic therapy plays an important role in every further level of therapy modification. Pharmacotherapy is indicated to achieve the individual therapy goals if these lifestyle-modifying measures cannot be implemented or cannot be implemented adequately by the person with diabetes and are therefore not successful or do not make sense in the foreseeable future (2–3 months). Whenever possible, the advantages of metformin (see appendix) should be used and doses should start gradually and increase slowly (e. g., starting with 500 mg with the main meal and increasing by another 500 mg each week up to a total dose of 2 × 1000 mg per day).

In case of contraindications (eGFR!) or poor tolerability of metformin (mainly dose-dependent gastrointestinal complaints), other options for monotherapy are available and should be used according to the patient risk profile (cardiorenal risks and morbidity) and the other patient-relevant benefits (influence on body weight, risk of hypoglycaemia, metabolic effects, side effect profile and clinical endpoints). It is essential that patient preferences are taken into



▶ **Fig. 3** Algorithm for insulin therapy [1] in addition to ▶ **Fig. 2**. The algorithm does not refer to people with severe metabolic decompensation or emergency situations. Current specialist information must be taken into account. Review the therapy strategy and the therapy goal in 3–6 months at the latest. GLP-1 RA = Glucagon-like peptide-1 receptor agonist; SGLT2 = Sodium-glucose cotransporter-2

account, as this is the only way to ensure good treatment adherence.

In patients with cardiovascular or renal diseases or a very high cardiovascular risk (▶ **Tab. 3**), substances that reduce evidence-based cardiovascular and renal diseases as well as mortality (SGLT2 inhibitors, GLP-1 receptor agonists) should be used primarily in combination with metformin (eGFR > 30 ml/min.!). For people with type 2 diabetes with HbA1c levels significantly outside the individual glucose target range (e. g., > 1.5 % above the target range) at diagnosis, initial pharmacotherapy, including the use of multiple combinations including insulin, if necessary, is warranted. After reaching the HbA1c target value, the therapy should be adjusted at individually agreed intervals.

Reason for combination therapies

A dual combination is necessary for many patients for metabolic reasons and is more favourable with regard to side effects of the individual substances, since in some cases lower doses can be used in the combination.

An early combination therapy should be aimed for in order to avoid derailing the metabolic parameters far from the agreed target range [37, 38]. The target values should usually be checked at 3-month intervals. There is now a large number of publications with good evidence for the selection of combinations. Patient preferences, individual therapy goals, simplicity of treatment, existing cardiovascular diseases and possible contraindications also play an important role. If the number of oral medications becomes too complex due to the complexity of the therapy, vascular risk factors or comorbidities (including COPD, depression, chronic pain conditions, etc.), fixed combinations should be used wherever possible. Parenteral blood glucose-lowering principles (GLP-1 RAs, insulins) can also be useful and helpful for these patients and significantly increase therapy adherence. The higher the HbA1c level, the more likely the use of insulin, but this does not mean that initial insulin therapy must be continued after metabolic recompensation. De-escalation strategies should be considered for each patient.

The administration of more than 2 oral antidiabetic agents may be individually-appropriate if therapy with a GLP-1-RA or insulin is not yet indicated (▶ **Fig. 3**), the patient is not yet comfortable with injection therapy, or this therapy should be delayed for other reasons.

Oral triple therapy in the combination of metformin, a DPP4 inhibitor and an SGLT2 inhibitor is a safe, effective and simple therapy. Potentiation of side effects has not been observed with oral triple combination; they are essentially the same as those observed with monotherapy for the respective substance.

In case of non-response to therapy, the patient's compliance with therapy should always be discussed before increasing the dose or changing the treatment.

▶ **Tab. 5** Informative, comparative consideration of the substance classes (supplement to the algorithm (▶ **Fig. 2**)). This table is a summary interpretation of the evidence. For a detailed presentation of the evidence, see Type 2 Diabetes. Long version. 2nd edition, 2020. consultation version. AWMF Register No.: nvl-001 [rerif].

Medicine	Total mortality	Cardiovascular endpoints	Microvascular endpoints 1	Renal endpoints	Hypoglycaemias	HbA1c Weight	Comments/selected safety information
Metformin	0	0	0	0	↔ ↑	HbA1c ↓ ↓ Weight: ↔ ↓	Risk of lactic acidosis, taking a break in form of sick days when unwell
SGLT2 inhibitors						HbA1c ↓ ↓ Weight: ↓	Risk of genital infections, atypical ketoacidosis, Fournier gangrene Taking a break in form of sick days when unwell Weight reduction (undesired in cases of frailty)
Dapagliflozin	0 * sinks with patients with HF	MACE: 0 CV death: 0 heart failure-related hospitalization: ↓ sinks	Not specified: retinopathy, neuropathy, amputations: 0	↓ sinks	↔	HbA1c ↓ ↓ Weight: ↓	
Empagliflozin	↓ sinks *	MACE: ↓ sinks CV death: ↓ sinks heart failure-related hospitalization: ↓ sinks	Not specified	↓ sinks	↔	HbA1c ↓ ↓ Weight: ↓	
Ertugliflozin		MACE: 0 CV death: 0 heart failure-related hospitalization: ↓ sinks		0 (eGFR decrease is reduced)			
GLP-1-RA							Gastrointestinal side effects, gallstones Low risk of pancreatitis Injections necessary Weight reduction (undesired in cases of frailty)
Dulaglutide	0	MACE: ↓ sinks CV death: 0 heart failure-related hospitalization: 0	Retinopathy: 0 Not specified: neuropathy, amputations	↓ sinks	↔	HbA1c ↓ ↓ Weight: ↓	
Exenatide	↓ sinks *	MACE: 0 CV death: 0 heart failure-related hospitalization: 0	Amputations: 0	Not specified	↔	HbA1c ↓ ↓ Weight: ↓	
Liraglutide	↓ sinks *	MACE: ↓ sinks CV death: ↓ sinks heart failure-related hospitalization: 0	Retinopathy: 0 Not specified: neuropathy, amputations	↓ sinks	↔	HbA1c ↓ ↓ Weight: ↓	
Lixisenatide	0 *	MACE: 0 CV death: 0 heart failure-related hospitalization: 0	Not specified: retinopathy, neuropathy, amputations	Not specified	↔	HbA1c ↓ ↓ Weight: ↓	

▶ **Tab. 5** Continued.

Medicine	Total mortality	Cardiovascular endpoints	Microvascular endpoints 1	Renal endpoints	Hypoglycaemias	HbA1c Weight	Comments/selected safety information
Semaglutide	0 *	MACE: ↓ sinks CV death: 0 heart failure-related hospitalization: 0 For ORAL semaglutide: MACE: 0 CV death: ↓ sinks heart failure-related hospitalization: 0	Retinopathy: ↑ Not specified: neuropathy, amputations	↓ sinks	↔	HbA1c ↓ ↓ Weight: ↓	Caution in case of pre-existing retinopathy
Sulfonylureas	(0)	MACE: (0)* CV death: (0) heart failure-related hospitalization: (0)	(0 to ↓)	(0 to ↓)	↑ ↑	HbA1c ↓ ↓ Weight: ↑	-Risk of severe, prolonged hypoglycaemias -CVOT study: no difference in the primary CV endpoint in direct comparison to CV-neutral linagliptin
DPP-4 inhibitors	(0)	MACE: (0) certain CV death: (0) heart failure-related hospitalization: (0)	(0)	(0)	↔	HbA1c ↓ ↓ Weight: ↔	Very rare: pancreatitis, inflammation bowel diseases CVOT present for sitagliptin, saxagliptin, linagliptin Vildagliptin has NO CVOT Saxagliptin is not recommender with pre-existing heart failure
Possibly as of stage 3 of the algorithm							
Insulin	(0)	(0)	(↓)	(0)	↑ ↑	HbA1c ↓ ↓ (depending on the dose) Weight: ↑ ↑	▪ Risk of hypoglycaemias, especially at the start of therapy ▪ Lipohypertrophy

Effects on endpoints: ↓: positive effect (endpoint was reached less frequently in the studies), ↑: negative effect (endpoint was reached more frequently in the studies); 0: endpoint was not affected in the studies considered, assumptions in parentheses () are from studies with low methodological quality, or there was insufficient evidence to assess.; All-cause mortality endpoint*: The study was not laid out for the endpoint all-cause mortality.; MACE: cardiovascular death, stroke, myocardial infarction (for exact definition, see cardiovascular endpoint studies); CV death: cardiovascular death, HHI: hospitalization for heart failure.; CVOT: cardiovascular outcome studies. n.s.: not specified (effect sizes were not reported or were reported without confidence interval in the main publication).; Hypoglycaemia: ↑ increased risk, ↔ low risk; HbA1c: ↓: decrease; weight: ↑: weight gain, ↓: weight loss.; Compared with linagliptin in CVOT, dapagliflozin and ertugliflozin are approved for the treatment of chronic heart failure. This applies to patients with impaired left ventricular function (HFrEF). Then dapagliflozin can be given up to an eGFR of 30 ml/min. and empagliflozin up to an eGFR of 20 ml/min.; Safety aspects and effects listed represent the state of discussion of the available evidence in the expert group and should not be considered a comprehensive presentation.; [1] microvascular endpoints: retinopathy, neuropathy, amputations.

Reasons for injection therapy

Due to lower hypoglycaemia rates and a favourable body weight progression (compared to intensified insulin therapy), starting with GLP-1 RA-assisted therapy or basal insulin in combination with oral antidiabetics is recommended for most cases (▶ **Fig. 3**).

Insulin dose reduction should absolutely be considered in case of worsening renal function in order to avoid severe hypoglycaemia.

A combination of GLP-1-RA with oral antidiabetic drugs (except DPP4 inhibitors) is an effective treatment if the individual therapy goal was not achieved with the previous oral antidiabetic drugs in mono- or multiple combinations or if side effects make a new therapy strategy absolutely necessary. In principle, the use of GLP-1-RA should be considered before starting a therapy with insulin, especially because of the very low hypoglycaemia risk of the substance class, the favourable weight progression and the favourable cardiovascular and renal outcome data of these substances.

Combinations of a GLP-1-RA with a basal insulin lead to a significant delay in the intensification of antidiabetic therapy (e. g., escalation of the basal insulin dose or additional administration of prandial insulin), to significantly better metabolic control without a significant increase in the risk of hypoglycaemia and to favourable weight effects [39–43].

Only when these combination therapies are no longer sufficiently effective or indicated will a further intensification of insulin therapy with prandial insulin be required in a next step.

Flexibility of therapy decisions due to the heterogeneity of type 2 diabetes and individual therapy goals is necessary at every stage of treatment. In most cases, persuasion to accept injection treatment and extensive education/training of the patient are necessary. In individual cases, a Continuous Subcutaneous Insulin Infusion (CSII) is indicated if the therapy goals are not achieved sufficiently under intensified conventional therapy (ICT).

Treatment of dyslipidaemia

Dyslipidaemia is common in people with type 2 diabetes and is an important vascular risk factor. Detailed information on the treatment of dyslipidaemia can be found in the ESC/EAS guideline [6] and in the practice recommendation of this supplement [44].

Treatment of arterial hypertension

Arterial hypertension is an important cardiovascular and renal risk factor that should be treated early and consistently. Structured training on hypertension, including practical training of patients to self-monitor their blood pressure, is helpful [45]. Detailed information on the treatment of hypertension has been discussed in guidelines [7, 46–48] and other publications [49, 50].

Conflict of Interest

The authors declare that they have no conflict of interest.

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Appendix

Medical history and clinical examinations

▶ **Tab. 1** Medical history and clinical examinations in people with type 2 diabetes.

History and examination	
It should be noted that type 2 diabetes is frequently poor in symptoms or asymptomatic and that the symptoms are often overlooked.	▪ Excess weight/obesity ▪ High blood pressure ▪ Lipid metabolism disorders ▪ Thirst ▪ Frequent urination ▪ Involuntary weight loss ▪ Tendency to infection – especially infections of the skin or mucous membranes ▪ Exhaustion, fatigue, weakness ▪ Physical inactivity ▪ Drug intake (e. g., glucocorticoids, psychotherapeutics) ▪ Alcohol consumption ▪ Smoking ▪ Depression ▪ Exertional dyspnea ▪ NYHA Class ▪ Angina symptoms ▪ Intermittent claudication (walking distance) ▪ Memory deficits, cognitive dysfunction ▪ Visual disturbances, retinopathy ▪ Periodontitis ▪ Erectile dysfunction ▪ Birth of children > 4000 g
Family history	▪ Diabetes ▪ Excess weight ▪ High blood pressure ▪ Lipid metabolism disorders ▪ Retinopathy ▪ Myocardial infarction ▪ Stroke ▪ Kidney disease ▪ Amputation
Physical examination	▪ Height ▪ Weight (BMI) ▪ Waist circumference (in the middle between lower rib-bone and upper iliac crest right after exhaling normally) ▪ Cardiovascular system ▪ Blood pressure ▪ Peripheral arteries, pulse status [1] ▪ Peripheral nervous system [2] ▪ Skin ▪ Oral hygiene (periodontitis) [230] ▪ Eye examinations [3] ▪ Foot examinations [4]
Laboratory values Optional GAD: antibodies test for the sometimes-difficult differentiation to type 1 diabetes or LADA and insulin or better C-peptide (with HOMA2-B and HOMA2-IR) in cases of unclear differential diagnosis or for subtyping if this results in a therapeutic consequence (see also the Clinical Practice Guideline “Definition, classification and diagnosis of diabetes mellitus’ in this supplement)	▪ Plasma glucose ▪ Blood count ▪ HbA1c ▪ Creatinine ▪ eGFR ▪ Potassium ▪ Lipid profile ▪ Gamma GT ▪ AST ▪ ALT [5] ▪ Uric acid [6] ▪ Urinalysis incl. albuminuria or UACR (albumin mg/g creatinine), ketones in urine or blood (only for high glucose values; for SGLT-2 inhibitor therapy, also at plasma glucose values < 250 mg/dl [13.9 mmol/l])

▶ **Tab. 1** Continued.

History and examination	
Technical examinations	▪ Resting and exercise ECG [7, 7] ▪ Echocardiography with or without pharmacological stress as an alternative to a stress ECG; ask about (HFpEF/HFrEF) ▪ Abdominal sonography (fatty liver and others) ▪ Eye examination ▪ Ankle-brachial index for weak or not palpable pulses in the feet (consider: media sclerosis)

NYHA class = New York Heart Association; BMI = Boy Mass Index; GAD = glutamic acid decarboxylase; LADA = Latent Autoimmune Diabetes in Adults; HOMA2-B = Homeostatic Model Assessment2-beta cell function; HOMA2-IR = Homeostatic Model Assessment2-Insulin resistance; HbA1c = Haemoglobin A1c; eGFR = Estimated Glomerular Filtration Rate; Gamma GT = Gamma Glucose Tolerance; AST = Aspartate transaminase; ALT = Alanine transaminase; UACR = Urinary Albumin-to-Creatinine Ratio; SGLT-2 = Sodium Glucose CoTransporter 2; ECG = Echocardiography; HFpEF = Heart Failure with Preserved Ejection Fraction; HFrEF = Heart Failure with Reduced Ejection Fraction

▶ **Tab. 2** Monitoring of people with type 2 diabetes.

History/Examination/ Screening	
History	▪ Diabetes duration ▪ Weight/BMI, waist-height ratio if applicable (weight progression, excess weight) ▪ Blood pressure ▪ Foot status ▪ Previous therapy (complete medication plan if possible) ▪ Physical activity ▪ Eating habits ▪ Smoking ▪ Diabetes education and training programme carried out, blood glucose self-monitoring ▪ Hypoglycaemia (frequency and severity) ▪ Anxiety ▪ Depression ▪ Erectile dysfunction
Physical examination	▪ Weight ▪ Blood pressure ▪ Cardiovascular system ▪ Lungs ▪ Examination of injection sites in diabetes patients treated with insulin and/or GLP-1-RA ▪ Examination of the FGM/CGM puncture or implant sites
Laboratory values Screening for oral hygiene	▪ HbA1c ▪ Creatinine clearance rate (eGFR) ▪ Lipid profile including LDL-, HDL-cholestrol ▪ Urinalysis incl. albuminuria or UACR (albumin mg/g creatinine), ketones in urine or blood (only for high glucose values; for SGLT-2 inhibitor therapy) ▪ People with type 2 diabetes should be regularly checked for periodontitis
Screening for diabetic neuropathy [2]	People with type 2 diabetes neuropathy should be screened once per year from the moment of diagnosis for sensorimotor and autonomic neuropathy.
Screening for foot lesions [4]	People with type 2 diabetes also with no clinical findings of sensorimotor neuropathy should be examined for foot lesions at least once a year. If clinical findings of sensorimotor neuropathy are already present, regular examinations for foot lesions should be carried out every 3–6 months.
Screening for nephropathy [9]	People with type 2 diabetes should be examined for albuminuria at least once a year, as this allows a significant additional risk assessment for cardiovascular and renal complications. In addition, the eGFR should be determined, whereby the frequency of the measurement varies depending on the stage of the renal disease and possible renal complications (nephrotoxic substances, contrast agents, hypovolemia).
Screening for retinal complications [3]	An ophthalmic screening should be performed:– For type 2 diabetes upon diagnosis (initial examination). If no diabetic retinal change is detected, the screening interval should be ▪ 2 years in case of known low risk (= no ophthalmological risk and no general risk), ▪ 1 year for all other risk constellations.
	If the ophthalmologist does not know the general risk factors, he/she should treat the patient as with an unfavourable general risk profile. Patients with diabetic retinopathy changes (= ophthalmic risk) should be examined annually or more frequently, depending on the findings. In the case of newly-occurring symptoms such as deterioration of vision, distorted vision, blurred vision and/or floaters, an examination should be carried out promptly at the ophthalmologist.

▶ **Tab. 2** Continued.

History/Examination/ Screening	
Assessment of macro- and microvascular overall risk	People with type 2 diabetes should be examined for vascular risks (hypertension) at least once a year and they should be asked whether they smoke. In addition, HbA1c, lipids, uric acid and circulatory parameters (blood pressure measurement and pulse measurement at different sites) should be controlled and a micro-/macroalbuminuria should be measured quantitatively. Looking for symptoms of heart insufficiency should be done at least twice a year.

BMI = Body Mass Index; GLP-1-RA =Glucagon-like Peptide-1 Receptor Agonists; FGM = Flash Glucose Monitoring; CGM = Continuous Glucose Monitoring; HbA1c = Hemoglobin A1c; eGFR = Estimated Glomerular Filtration Rate; LDL-cholestrol = Low Density Lipoprotein-cholestrol; HDL-cholestrol = High Density Lipoprotein-cholestrol; UACR = Urinary Albumin-to-Creatinine Ratio; SGLT-2 = Sodium Glucose CoTransporter 2

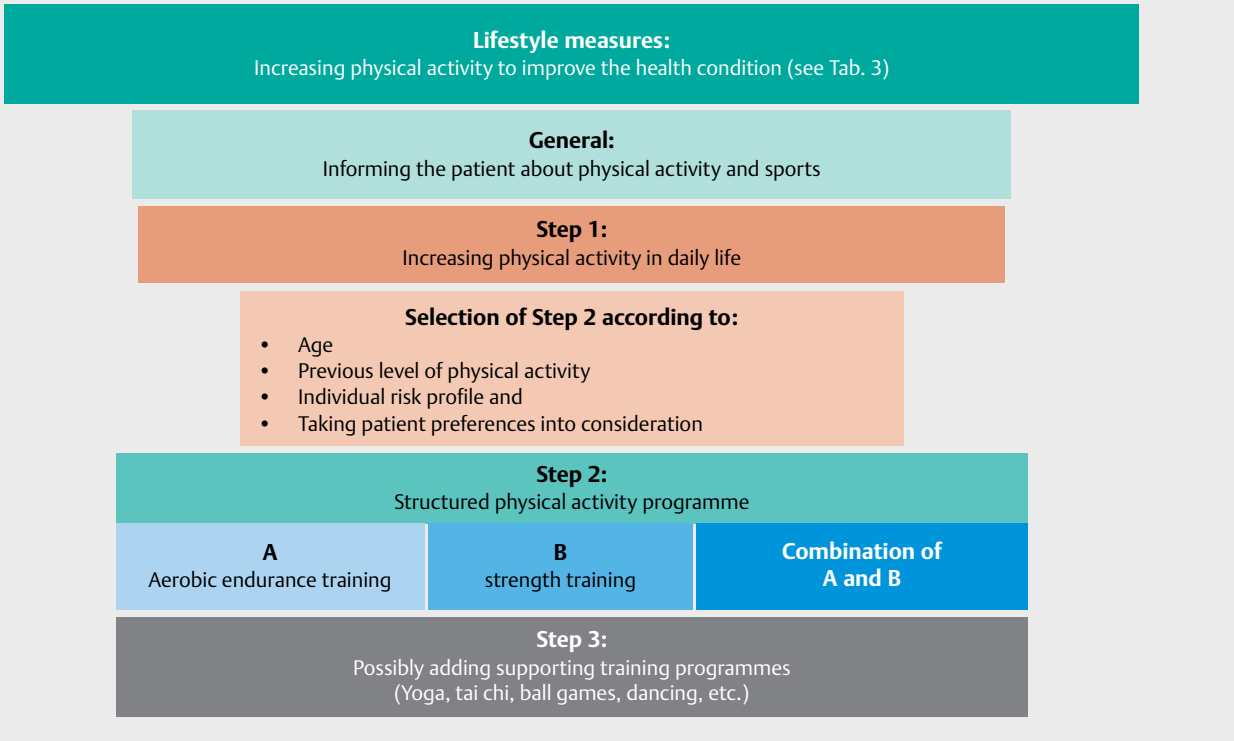
Physical exercise

Regular exercise is particularly important for people with type 2 diabetes [10–17].

▶ **Tab. 3** Benefits of regular physical activity

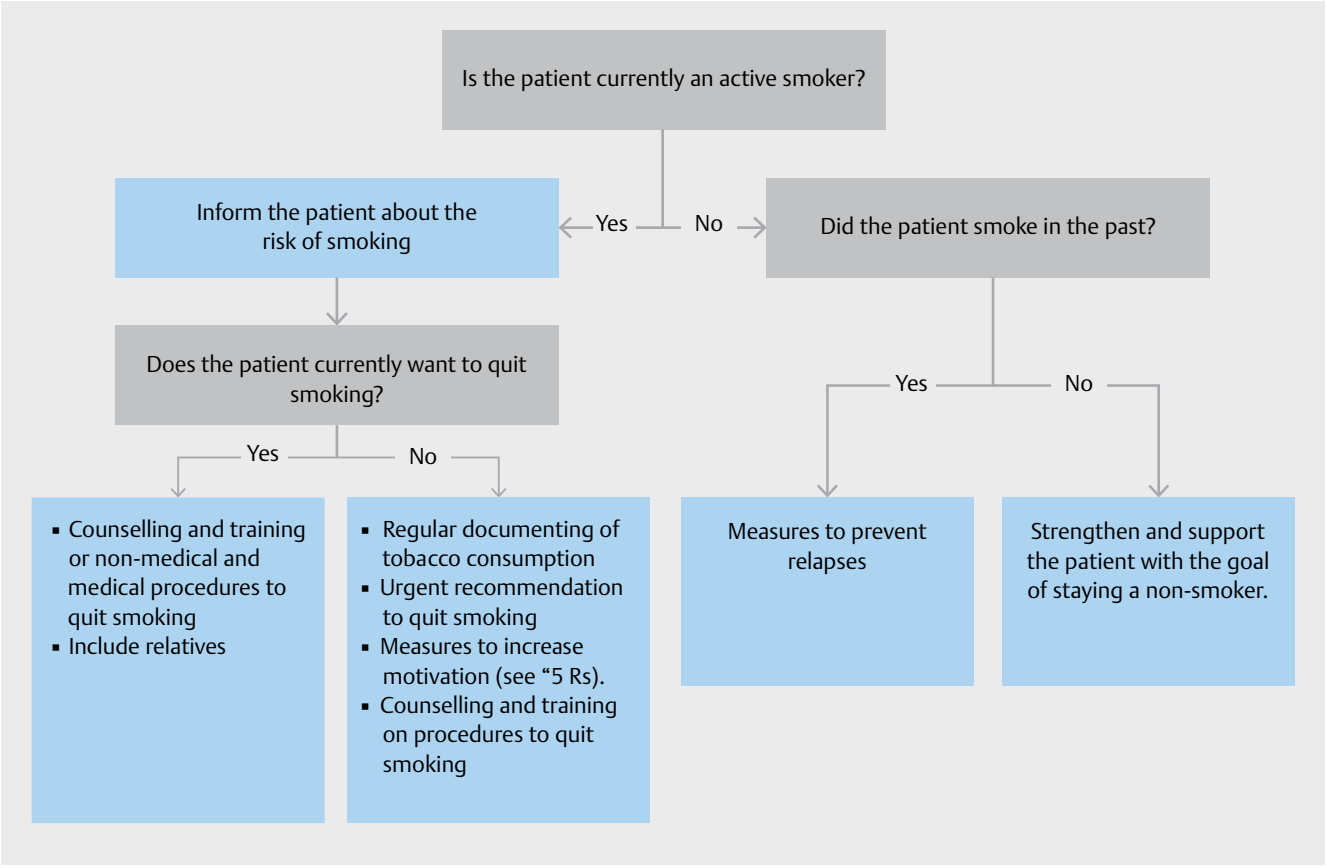
- Lowers blood pressure
- Reduces heart rate at rest and under stress
- Improves dyslipidaemia
- Reduces cardiovascular risk
- Reduces insulin resistance
- Supports weight loss
- Improves the flow of blood and thus the supply of muscles and organs
- Reduces the risk of thrombosis
- Relieves chronic pain
- Prevents certain types of cancer
- Strengthens the immune system
- Strengthens confidence in one's own ability and thus self-esteem
- Lifts the mood and reduces stress
- Promotes mobility and coordination, especially in older people
- Promotes general well-being

Lifestyle measures – Figure



▶ **Fig. 1** Step programme for physical activity. Data source: [231].

Smoking cessation



▶ **Fig. 2** Algorithm for the approach to smoking. Source: German Medical Association (BÄK), National Association of Statutory Health Insurance Physicians (KBV), Association of the Scientific Medical Societies (AWMF). National Health Care Guideline Therapy of Type 2 Diabetes - Long version, 1st edition. Version 4. 2013, last modified: November 2014. Available from: www.dm-therapie.versorgungsleitlinien.de; [cited: 15.08.2018]; DOI: 10.6101/AZQ/000 213 [rerif].

Critical presentation of the individual antidiabetic pharmaceuticals

Metformin

Thanks to its effectiveness in lowering the HbA1c value, its well-known safety profile, the approval conditions of other substances with positive effects in CVOTs, extensive experience with it and its' low costs, metformin continues to be the antidiabetic drug of first choice for the treatment of type 2 diabetes. The low risk of hypoglycaemia (caveat: simultaneous alcohol consumption) and the beneficial effect of slightly reducing weight are also advantageous. The indication as monotherapy and in combination therapy with metformin was expanded in February 2017 [18]:

- Patients with a renal insufficiency up to degree 3b (> eGFR 30 ml/min) can be treated with metformin if there are no other contraindications.
- Maximum daily dose is 1000 mg (500–0–500 mg) for an eGFR of 30–44 ml/min. At this eGFR, a metformin therapy should not be started.
- Maximum daily dose is 2000 mg for an eGFR of 45–59 ml/min.
- To be on the safe side, a dose reduction to 500 mg per day can be carried out at an eGFR of 30–44 ml/min, because the eGFR can worsen acutely at this level, particularly in elderly people with exsiccosis or due to kidney toxic drugs.

The pros and cons of metformin therapy at an eGFR of 30–44 ml/min must be explained to the patient.

In the population-based large study involving 75 413 patients of the Geisinger Health System, an analysis of all patients with regard to hospitalisation due to acidosis was carried out. 2335 hospitalizations due to acidosis were found in the period from 2004 to 2017 (mean follow-up time of 5.7 years). In this clinical real-world setting and compared to other antidiabetic drugs (excluding insulin), metformin was only associated with lactate acidosis if the eGFR was lower than < 30 ml/min. [19]

As far as clinical endpoints are concerned, despite the frequent use of metformin, the data are inconclusive. Positive data from the UKPDS can be found in a relatively small number of overweight patients and from several small studies. In a recent meta-analysis, neither significant positive nor negative effects of metformin on

cardiovascular endpoints were found [20]; however, the authors admit that the numbers are too small for a meta-analysis and a large controlled study would be necessary to clarify the question. Correspondingly, there is no evidence of an advantage of metformin for a given combination therapy with respect to cardiovascular endpoints and all-cause mortality [21,22]. The European Society of Cardiology Guidelines have replaced primary therapy with metformin with SGLT2 inhibitors and GLP-1-RA in patients with newly-diagnosed type 2 diabetes and atherosclerotic cardiovascular disease, as there is no cardiovascular outcome study for metformin in this population. In addition, further analyses of endpoint studies with GLP-1-RA or SGLT2 inhibitors show that metformin use had no modulating effect on the cardioprotective effect of these agents [22a]. However, there is no definitive evidence to support the benefit of this recommendation as there have been no controlled trials to date [23]. Strictly observing the contraindications for metformin, one should therefore continue to start with metformin as primary therapy and, if clinically indicated (manifest cardiovascular and renal diseases or patients with a high cardiorenal risk (Part 1; Tab. 3, 4), start combination therapy with SGLT2 inhibitors and/or GLP1-RA early (within 1–2 months).

Metformin is currently gaining great interest due to interesting pleiotropic effects that influence changes at the epigenetic level and gene expression and are thus potentially protective against carcinomas [24–32].

Metformin and COVID-19

A number of observational studies have shown that hospitalised COVID-19 infections in people with diabetes on pre-hospital metformin therapy, are associated with significantly lower mortality [33,34]. This was confirmed in a recent meta-analysis, which found a significant reduction in the odds ratio for mortality in COVID-19 patients with diabetes treated with metformin compared to those not treated with metformin: OR 0.62; 95 %-CI: 0.43–0.89 [35]. In some of the studies, the confounding variables were not or only insufficiently taken into account. As long as no controlled studies are available, metformin should be maintained [36,37] or used with great caution in seriously-ill inpatients infected with COVID-19 because of the risk of lactic acidosis.

Summary of the therapy with metformin:

- Kidney function must be checked regularly (every 3–6 months). Caveat: metformin must be discontinued immediately if eGFR drops to < 30 ml/min.
- Beware of diseases which increase the risk of lactic acidosis (e. g., acute deterioration of kidney function due to gastroenteritis, respiratory insufficiency, acute diseases and infections or non-steroidal anti-inflammatory drugs).
- Caution when initiating therapy with ACE inhibitors or AT-1 receptor blockers, diuretics, at the beginning of therapy with non-steroidal anti-inflammatory drugs.
- When administering x-ray contrast media, prior to interventional or major surgical procedures, the patient should discontinue the use of metformin and only restart taking it after 48 h, and only if the eGFR has not deteriorated significantly postoperatively and the patient can eat again.
- In cardiovascular and renal high-risk individuals or people with manifest cardiorenal disease, extreme caution is advised.

Sulfonylureas

Sulfonylureas have been used for decades because they effectively lower blood glucose, are well tolerated and are inexpensive.

Due to their ability to increase insulin secretion by inhibiting the potassium channels of the β-cells independently of glucose, they have the highest hypoglycaemic potential of all oral antidiabetics, with the risk of sometimes severe and prolonged hypoglycaemia, especially in older people with impaired renal function and polypharmacy. Sulfonylureas are largely contraindicated with decreasing renal function (eGFR < 30 ml/min) with the exception of gliclazide and gliquidone. Due to the high risk of severe hypoglycaemia in patients with cardiovascular and renal complications, sulfonylureas should not be used in these people. Sulfonylureas usually lead to moderate weight gain.

Favourable effects on microvascular endpoints were found in the UKPDS more than 6 years after treatment initiation for chlorpropramide and glibenclamide (mainly reduced rate of photocoagulation). In the ADVANCE trial, gliclazide was found to have positive effects on microvascular complications, mainly by reducing nephropathy [38,39].

In the prospective, randomised, controlled CAROLINA study (mean observation time 6.3 years, approx. 3000 patients in each study arm; in both study arms 42 % of the participants already suffered from clinically manifest cardiovascular complications at baseline), a comparison was made between linagliptin (5 mg/d) and glimepiride (1–4 mg/d) with regard to cardiovascular endpoints, hypoglycaemia and weight progression. There was no difference when comparing the two study arms for 3P-MACE, 4P-MACE, all-cause and cardiovascular death, and mortality with overall comparable HbA1c levels [40]. Weight progression was more favourable with linagliptin compared with glimepiride (− 1.54 kg), and rates of all, moderate and severe hypoglycemic events requiring hospitalization were significantly lower with linagliptin compared with glimepiride at all doses between 1 and 4 mg (1 mg: HR 0.23; 95 % CI 0.21–0.26; p < 0.0001, 2 mg: HR 0.18; 95 % CI 0.15–0.21; p < 0.0001, 3 mg: HR 0.15; 95 % CI 0.08–0.29; p < 0.0001, 4 mg: HR 0.07; 95 % CI 0.02–0.31; p = 0.0004). The authors concluded from the CAROLINA trial data that there are no reasons, other than the lower cost of glimepiride, to use glimepiride more preferentially than linagliptin in antidiabetic therapy [40].

In several retrospective observational studies, in a large randomised pragmatic trial, analyses from registry data and their meta-analyses, and Cochrane reviews, sulfonylureas were shown to have no benefits in terms of macrovascular endpoints, either in monotherapy or in combination therapy. Rather, increased cardiovascular morbidity and mortality were described [24,41–49].

Repaglinide

Due to a decision of the Federal Joint Committee (G-BA), a comprehensive prescription restriction for glinides was implemented as of 01.07.2016. The prescription restriction reads: "The treatment of patients with renal insufficiency and a creatinine clearance < 25 ml/min with repaglinide is excluded if no other oral antidiabetic agents are suitable and insulin therapy is not indicated. Despite a detailed evidence-based statement (see also http://www.deutsche-diabetes-gesellschaft.de/stellungnahmen) to the G-BA and Federal Ministry of Health (BMG), the G-BA decision still stands.

DPP-4 inhibitors

DPP-4 inhibitors are increasingly replacing therapy with sulfonylureas for reasons of a favourable safety profile, even in progressive renal insufficiency and a good tolerability, which is particularly important for elderly people. Therapy adherence and persistence with DDP-4 inhibitors (in 594,138 patients) were suboptimal despite good tolerability: after 1 year of therapy, adherence was 56.9 % (95 % CI 49.3–64.4) and after 2 years, 44.2 % (95 % CI 36.4–52.1) [50].

With the exception of linagliptin, the dosage of all DPP-4 inhibitors on the market must be adjusted to the kidney function. In addition, DPP-4 inhibitors show largely weight-neutral effects with similar antihyperglycaemic effects and low hypoglycaemic rates. DPP-4 inhibitors seem to exert better metabolic control for longer than sulfonylureas (observation period 104 weeks) [51].

The results of the CAROLINA study [40] (see section on sulfonylureas) were examined in a real-world study with inclusion criteria as in the CAROLINA study in a propensity score matching (PSM) [52]. There were 24 131 study pairs for linagliptin and glimepiride to be analysed. As in the CAROLINA study, no differences were found with regard to cardiovascular safety.

The results of the RCTs SAVOR TIMI 53® (saxagliptin [53]), EXAMINE® (alogliptin [54]), TECOS® (sitagliptin [55]), CARMELINA® (linagliptin [56,57]) on the effect of DPP-4 inhibitors on cardiovascular and renal endpoints each show cardiovascular safety across all eGFR ranges (< 30 ml/min.- > 60 ml/min.) of the investigated DPP-4 inhibitor in their primary endpoint, which was also confirmed in extensive meta-analyses [58–64]. In a large US database, a 3-year follow-up showed that DDP-4 inhibitors reduced the risk of the composite clinical endpoint (eGFR decline > 50 %, end-stage renal failure or all-cause mortality) more significantly compared with sulfonylureas but were less effective than GLP-1-RA and SGLT2 inhibitors [65].

DPP-4 inhibitors are therefore effective antidiabetics with few side effects and can be used very well as mono- and combination therapy if contraindications to the use of metformin are present and there is a corresponding patient preference. Another advantage is that DPP-4 inhibitors act largely weight-neutrally, hardly induce hypoglycaemia and the use of linagliptin is not contraindicated even in (pre)terminal renal insufficiency.

Hospitalisation for heart failure was not increased with the use of DPP-4 inhibitors, except for saxagliptin (SAVOR TIMI 53). In a large meta-analysis on the risk of DPP-4 inhibitors with regard to heart failure or hospitalisation for heart failure including RCTs and observational studies, the authors concluded that the effect of DPP-4 inhibitors on heart failure remains uncertain (due to relatively short observation periods and overall weak data) [60]. A recent meta-analysis of alogliptin, linagliptin, saxagliptin and sitagliptin showed a neutral effect on myocardial infarction, stroke, heart failure (OR 1.06; 95 % CI 0.96–1.18) and cardiovascular death [66].

Based on NAFLD and NASH studies with imaging and liver histology, DPP-4 inhibitors showed no significant benefit in people with type 2 diabetes and NAFLD, in contrast to GLP-1 RAs or SGLT2 inhibitors [67].

DPP-4 inhibitors in hospitalised patients

The use of DPP-4 inhibitors in people with type 2 diabetes and moderate, relatively stable hyperglycaemia has been shown in a number of RCTs to have a good safety profile, effective blood glucose-lowering and insulin savings with insulin co-medication [68].

DPP-4 inhibitors may be able to slow down the over-activated immune system in people with Sars-CoV-2 infection and thus contribute to a more favourable cardiovascular outcome [69]. However, in the absence of randomised trials, the observational studies available to date do not provide robust evidence to use DPP-4 inhibitors in COVID-19 infection [70].

Safety aspects

In the meta-analysis of the 3 RCTs on DPP-4 inhibitors (SAVOR TIMI 53, EXAMINE and TECOS), an increased incidence of **acute pancreatitis** was found compared with corresponding controls (odds ratio 1.79; 95 % CI 1.13–2.82; p = 0.013), although the absolute risk of acute pancreatitis was low overall and only 0.13 % higher in absolute terms under DPP-4 inhibitors [71]. A newer meta-analysis found an association between DPP-4 inhibitors and the risk of acute pancreatitis (OR 1.72; 95 % CI 1.18–2.53). However, the authors stated that the number of cases was too small to make a definite statement [72]. Therefore, great caution should be exercised when using DPP-4 inhibitors in people with type 2 diabetes and a history or risk of pancreatitis.

A clear association between DPP-4 inhibitor therapy and **bullous pemphigoid** has been seen in a number of cases [73].

It has also been shown that DPP-4 inhibitors are not associated with a higher rate of **carcinoma** [74].

DPP-4 inhibitors were associated with a significantly higher incidence of **inflammatory bowel disease** in type 2 diabetes in a large population-based study (HR 1.75; 95 %- CI 1.22–2.49) [75]. This association was highest 3–4 years after DPP-4 inhibitor therapy but became significantly lower thereafter. The association started 2–4 years after the start of therapy. However, in a recent meta-analysis of 13 studies, no association was found between DPP-4 inhibitors and inflammatory bowel disease [76].

In combination with metformin, sitagliptin was certified by the G-BA as having a low added benefit (BAnz AT 29.04.2019). However, neither in monotherapy nor in combination therapy was saxagliptin granted an added benefit (BAnz AT 18.01.2017, BAnz AT 13.03.2018 B2). The combination of linagliptin and empagliflozin was also not considered to be of additional benefit (BAnz AT 24.12.2019 B3).

SGLT-2 inhibitors

SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin) are effective antihyperglycaemic substances in the treatment of type 2 diabetes in both mono- and combination therapy with all other glucose-lowering drugs.

Their efficacy profile is favourable, also because the risk of hypoglycaemia is low, patients lose weight and there is a clinically-relevant reduction in systolic blood pressure [77–87].

Approved in Germany: Dapagliflozin, empagliflozin and ertugliflozin.

Not approved in Germany: Canagliflozin and sotagliflozin.

Safety aspects

However, there is a significantly increased risk of **genital infections** with SGLT-2 inhibitors in RCTs [88,89]. The relative risk of SGLT-2 inhibitors for genital infections was more than 3 times higher than placebo (RR 3.37; 95 % CI 2.89–3.93) and almost 4 times higher than an active comparator (RR 3.89; 95 % CI 3.14–4.82). By contrast, the risk of urinary tract infections was not significantly increased by SGLT-2 inhibitors compared to placebo (RR 1.03; 95 % CI 0.96–1.11) or an active comparator therapy (RR 1.08; 95 % CI 0.93–1.25). In a large retrospective cohort study of a US database, an approximately 3-fold higher risk of genital infection was found with SGLT2 inhibitors compared to DPP-4 inhibitors, starting in the first 4 weeks of therapy and as long as therapy was continued [90]. Comparable results were also seen in the real-world analysis of people with diabetes at a relatively advanced age (71.8 ± 5 years) [91]. Patients with a history of genital infections were particularly at risk of infection when taking SGLT2 inhibitors [92].

A **necrotizing fasciitis of the perineum and genitals (Fournier gangrene)** is a very rare, severe infection with the need for immediate antibiotic and usually surgical intervention. Diabetes is one of the risk factors. With the introduction of SGLT-2 inhibitor therapy, a few cases of Fournier gangrene under SGLT-2 inhibitor therapy were described. A Red Hand letter was published in consultation with the European Medicines Agency (EMA) and the Federal Institute for Drugs and Medical Products/Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) to clarify the 'Risk of a Fournier gangrene (necrotizing fasciitis of the perineum) when using SGLT-2 inhibitors (sodium glucose cotransporter-2 inhibitors)".

A recently published real-world study investigated the incidence of Fournier gangrene in patients after starting therapy with SGLT2 inhibitors (n = 93,197) or with DPP-4 inhibitors. No increased risk of this gangrene was found with SGLT2 inhibitor therapy compared with persons with DPP-4 inhibitor treatment [93].

In a recent meta-analysis of all randomised controlled trials of SGLT2 inhibitors (n = 84) in patients with type 2 diabetes, no differences were found in the risk of Fournier gangrene, abscess, cellulitis or erysipelas with SGLT2 inhibitors vs. comparators or placebo. The rate of Fournier gangrene was very low at 3.53 per 100 000 patient-years [94].

The European Medicines Agency (EMA) has started a review process to investigate whether canagliflozin therapy leads to an increased **rate of amputations** (mostly toes): In 2016, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) extended the review to include dapagliflozin and empagliflozin [95].

The canagliflozin CANVAS programme [96] trials confirmed the suggestion of a higher risk of amputations (predominantly toe and metatarsal areas) with canagliflozin compared with placebo (event rate 6.3 vs. 3.4 persons per 1000 patient-years; HR 1.97; 95 % CI 1.41–2.75; p < 0.001). For SGLT2 inhibitors, higher rates of amputations are also found in RCTs in pharmacovigilance reports [97]. In contrast, current studies and searches did not find higher amputation rates with dapagliflozin [98] and empagliflozin [99]. The large CREDENCE study with canagliflozin also found no signal for an increased amputation rate [100]. The meta-analysis by Huang et al. [101] also found no evidence that SGLT2 inhibitors were associated with an increased risk of amputation.

The FDA has also issued a warning about an **increased fracture risk** due to reduced bone density under canagliflozin (http://www.fda.gov/Drugs/DrugSafety/ucm461449.htm). Indeed, the fracture event rate was significantly higher with canagliflozin compared with placebo: 15.4 vs. 11.9 per 1000 patient-years (p = 0.02) [102]. However, careful elaboration of the CANVAS and CANVAS-R data showed significant heterogeneity of fracture risk in both studies: in the CANVAS study (n = 4330: HR 1.55; 95 % CI 1.21–1.97) the risk was significantly increased, whereas this could not be demonstrated in the CANVAS-R study (n = 5812: HR 0.86; 95 % CI 0.62–1.19) [103]. In the recently published large RCT (CREDENCE study) with canagliflozin, there was also no signal for an increased fracture risk [104].

A recent fracture analysis of people with type 2 diabetes (n ≥ 12 000) treated with empagliflozin (pooled data from placebo-controlled trials and a head-to-head trial vs. glimepiride) found no significantly increased rate of fractures [105]. Numerous meta-analyses also showed no significant increase in fracture rates with SGLT2 inhibitor therapy [106–108].

Real-world studies and analyses of health care data also showed no increased fracture rate with SGLT2 inhibitor therapy [109].

When SGLT2 inhibitors were used, **ketoacidosis** was occasionally observed in people with type 2 diabetes [110, 111]. The SGLT2 inhibitor manufacturers in Germany already informed physicians and pharmacists about the situation in 2015.

A comprehensive analysis of all reports of ketoacidosis cases with a possible connection to SGLT2 inhibitors that were listed in the US Food and Drug Administration Adverse Event Reporting System (FAERS) between January 2014 and October 2016 has been published [112]. They found a Proportional Reporting Ratio (PPR) of 7.9 (95 % CI 7.5–8.4). The PPR is the ratio of spontaneous reports for a specific drug (in this case SGLT2 inhibitors) associated with a specific adverse event (= ketoacidosis) divided by the corresponding ratio for all or some other drugs with this adverse event. However, the PPR does not describe a relative risk, i. e., the real risk for ketoacidosis. Detailed analysis of 2397 reports of ketoacidosis in FAERS showed a predominance in people with type 1 diabetes, in women, across a wide age and body weight range, and high variability in the duration of SGLT2 inhibitor therapy. 37 people (1.54 %) died from ketoacidosis. In the large randomised controlled trials of SGLT2 inhibitors, the risk of ketoacidosis was significantly increased with SGLT2 inhibitors in type 2 diabetes but was less than 1 %. The meta-analysis published last year (39 RCTs with 60 580 patients) again confirmed a statistically significant increased rate of ketoacidosis with SGLT2 inhibitors (0.18 %) compared to controls (0.09 %) with an OR of 2.13 (95 % CI 1.38–3.27). Older age and longer use of SGLT2 inhibitors played a role [113].

Normoglycaemia or mild hyperglycaemia does not exclude a ketoacidosis with SGLT-2 inhibitors. Risk factors for the development of a (euglycaemic) ketoacidosis with SGLT-2 inhibitors included a rapid and significant reduction of the insulin dose, severe dehydration, and alcohol consumption; almost all patients with ketoacidosis were in a catabolic state (operations, myocardial infarction, severe infections, long fasting, excessive physical strain).

Therefore, the German Diabetes Association (DDG) recommends that the following be considered when dealing with SGLT-2 inhibitors:

- Discontinuation of SGLT2 inhibitors at least 3 days (= about 5 half-life times equivalent to 11–13 hours) before major elective surgery [114, 115], immediate pause of SGLT2 inhibitor therapy in emergencies and acute illness,
- Caution during ongoing insulin therapy (avoid significant reduction or discontinuation of insulin therapy),
- Avoidance of prolonged periods of fasting, ketogenic/ extremely low-carbohydrate diets and excessive alcohol consumption.
- The combination of SGLT-2 inhibitors with metformin increases the risk of ketoacidosis [116] and
- If symptoms are present, consider the possibility of euglycaemic ketoacidosis and initiate the appropriate diagnostic procedures (plasma glucose and ketones in blood, possibly also necessary venous blood gas).

Effects on cardiovascular and renal endpoints

Dapagliflozin

The DECLARE-TIMI 58 study with dapagliflozin [117] included 6974 patients (40.6 %) with known cardiovascular diseases and 10 186 (59.4 %) with multiple risk factors for arteriosclerotic cardiovascular diseases. The mean follow-up of the patients was 4.2 years. A total of 3962 patients stopped the study prematurely (= 5.7 % per year): 1811 of the 8574 patients (21.1 %) on dapagliflozin and 2151 of 8569 (25.1 %) in the control group. Dapagliflozin resulted in a significantly lower hospitalization rate for heart failure compared to placebo (HR 0.73; 95 % CI 0.61–0.88). There was no difference between the dapagliflozin group and the placebo group in the rate of 3P-MACE (8.8 vs. 9.4 %; HR 0.93; 95 % CI 0.84–1.03; p = 0.17), cardiovascular morality (HR 0.98, 95 % CI 0.82–1.17) and all-cause mortality (HR 0.93, 95 % CI 0.82–1.04). In the renal composite secondary endpoint (≥ 40 % reduction in eGFR, newly-developed terminal renal failure or death of renal or cardiac genesis), dapagliflozin led to a significant reduction in renal endpoints (HR 0.76; 95 % CI 0.67–0.87).

Extensive sub-analyses of the DECLARE-TIMI 58 population confirmed the beneficial effects of dapagliflozin on the development and progression of renal [118] and cardiovascular endpoints [119, 120].

In the DAPA-HF study, at a median follow-up of 18.2 months of 2373 study participants, the primary composite endpoint of worsening heart failure (hospitalisation or intravenous therapy for heart failure) or cardiovascular death was met in 386 (16.3 %) in the dapagliflozin group and 502 (21.2 %) in the placebo group: HR 0.74, 95 % CI 0.65–0.85; p < 0.001. The primary endpoints were comparable between people with (42 % of the study population) and without diabetes (HR 0.75, 95 % CI 0.63–0.90 vs HR 0.73, 95 % CI 0.60–0.88). Dapagliflozin reduced numerous secondary endpoints such as total number of hospitalisations for heart failure (first and recurrent), reduction in all-cause mortality and improvement in quality of life [121].

In the recently-published multicentre RCT DAPA-CKD [122], patients (n = 4304; 68 % of patients had type 2 diabetes) with an albumin:creatinine ratio of 200–5000 mg/g and an eGFR of 25–75 mL/min were randomised 1:1 to dapagliflozin (10 mg/d) or placebo. The median follow-up was 2.4 years. The primary endpoint was composed of a decrease in eGFR of more than 50 %, ESRD, renal or cardiovascular death. Secondary endpoints were the primary endpoint other than cardiovascular death, a composite endpoint of cardiovascular death or hospitalisation for heart failure and all-cause mortality. The relative risk reduction of the primary endpoint was consistent with dapagliflozin between patients with diabetes (HR 0.64, 95 % CI 0.52–0.79) and patients without diabetes (HR 0.50, 0.35–0.72). Comparable results were seen for the renal secondary endpoint (0.57 [0.45–0.73] vs 0.51 [0.34–0.75]), cardiovascular death or hospitalisation for heart failure (0.70 [0.53–0.92] vs 0.79 [0.40–1.55]) and all-cause mortality (0.74 [0.56–0.98] vs 0.52 [0.29–0.93]).

The 3 SGLT2 inhibitors empagliflozin (EMPA-REG OUTCOME), canagliflozin (CANVAS programme and CREDENCE trial) and dapagliflozin (DECLARE-TIMI 58) with a total of 38 723 study participants resulted in the meta-analysis by Neuen et al. [123] resulted in a significant risk reduction for dialysis, kidney transplantation or mortality due to renal failure (RR 0.67, 95 % CI 0.52–0.86, p = 0.0019). SGLT2 inhibitors also reduced the risk of end-stage renal failure (RR 0.65, 95 % CI 0.53–0.81, p < 0.0001) and acute renal failure (RR 0.75, 95 % CI 0.66–0.85, p < 0.0001) across all trials. There was a clear advantage of all 3 SGLT2 inhibitors across all eGFR subgroups and also independent of the degree of albuminuria at baseline. A recent meta-analysis of 11 trials involving 93 502 patients showed similar beneficial effects of SGLT2 inhibitors in older people with type 2 diabetes (> 65 years) on MACE (HR 0.90; 95 % CI 0.83–0.98), hospitalisation for heart failure (HR 0.62; 95 % CI 0.51–0.76) and composite renal endpoint (HR 0.57; 95 % CI 0.43–0.77) [124]. In the meta-analysis by Bae et al. [125] of 17 trials involving 87 263 patients, SGLT2 inhibitors significantly reduced renal risks such as microalbuminuria (OR 0.64; 95 % CI 0.41–0.93), macroalbuminuria (OR 0.48; 95 % CI 0.24–0.72), worsening renal function (OR 0.65; 95 % CI 0.44–0.91) and end-stage renal failure (OR 0.65; 95 % CI 0.46–0.98) compared with placebo. In the most comprehensive meta-analysis of 736 trials with a total of 421 346 patients, SGLT inhibitors led to robust significant reductions in all-cause and cardiovascular mortality, non-fatal myocardial infarctions, and renal failure, but also, as expected, increased genital infections. SGLT2 inhibitors had less robust evidence on weight reduction. Weak or no evidence was found for positive effects of SGLT1 inhibitors on amputations, retinopathy or loss of sight, neuropathic pain, and health-related quality of life. The absolute benefit of SGLT2 inhibitors was found across a broad spectrum in patients with low and high cardiovascular and renal outcomes [126].

Empagliflozin

The effects of SGLT-2 inhibitor therapy on clinical endpoints were investigated for empagliflozin in a large RCT published in 2015 (EMPA-REG OUTCOME study [127]). Patients with type 2 diabetes and already manifested cardiovascular diseases showed fewer cardiovascular events (10.5 vs. 12.1 %; HR 0.86; 95 % CI 0.74–0.99; p < 0.04 for superiority) during an observation period of 3.1 years on average with empagliflozin compared to placebo. There was no difference in the rate of myocardial infarction and stroke, but a significantly lower event rate for cardiovascular mortality (3.7 vs. 4.1 %; HR 0.62; 95 % CI 0.49–0.77; HR 0.49-p < 0.001); for all-cause mortality (5.7 vs. 8.3 %; HR 0.68; 95 % CI 0.57–0.82; p < 0.001) and

hospitalization for heart failure (2.7 vs. 4.1 %; HR 0.65; 95 % CI 0.50–0.85; p = 0.002). The risk of cardiovascular events was greater when cardiovascular risk factors were less well controlled at baseline. However, the cardioprotective effect of empagliflozin was significantly associated, independent of the degree of risk factor control [128]. Analysis of recurrent events (including outcome of coronary events, hospitalisation for heart failure, hospitalisation for other reasons) and cardiovascular mortality showed significant reductions with empagliflozin compared to placebo [129].

Further analyses of the EMPA-REG OUTCOME study [130] showed that empagliflozin slows the development and progression of nephropathy in patients with an eGFR initial of ≥ 30 ml/min: beginning or progression of nephropathy with empagliflozin compared to standard therapy (12.7 vs. 18.8 %; HR 0.61; 95 % CI 0.53–0.70; p < 0.001).

The post-hoc renal endpoint (doubling of S-creatinine, renal replacement therapy, or death from kidney disease) was significantly lower for empagliflozin compared to placebo (HR 0.54; 95 % CI 0.40–0.75; p < 0.001). In an analysis of the short-term and long-term effects (164 weeks) of empagliflozin on albumin excretion, a significant reduction of 22 % on average in the microalbuminuria group and 29 % in the macroalbuminuria cohort was observed [131], irrespective of the level of initial albuminuria. Based on 1738 participants in the EMPA-REG-OUTCOME trial with a history of coronary artery bypass grafting at baseline, empagliflozin reduced the risk of all-cause mortality by 43 %, cardiovascular mortality by 48 %, hospitalisation rate for heart failure by 50 % and nephropathy (onset or worsening) by 35 % [132].

The EMPEROR-REDUCED study [133] included 3730 patients (50 % with diabetes) with functional class II, III or IV heart failure and an ejection fraction ≤ 40 % were treated with either empagliflozin (10 mg/d) or placebo (1:1) in addition to guideline-guided heart failure therapy. The median duration of the study was 16 months. With empagliflozin, the primary composite endpoint (cardiovascular death or hospitalisation for worsening of heart failure) occurred in 19.4 % of patients versus 24.7 % with placebo. The hazard ratio was 0.75; 95 % CI 0.65–0.86; p < 0.001). The effect of empagliflozin on the primary endpoint was independent of whether patients had diabetes or not. The total number of hospitalisations was lower in the empagliflozin compared with the placebo group (HR 0.70; 95 % CI 0.58–0.85; p < 0.001). The annual decline in eGFR was lower in the empagliflozin vs. placebo group (− 0.55 vs. − 2.28 ml/min./year; p < 0.001). The rate of serious renal complications was also lower with empagliflozin: HR 0.50 (0.32–0.77).

For the SGLT2 inhibitor empagliflozin - as well as for the other gliflozines - clinically very relevant effects on all-cause mortality as well as on cardiovascular and renal endpoints in appropriate risk populations have been documented and confirmed in meta-analyses [134–137].

The underlying mechanisms of cardiac and renal protection of SGLT2 inhibitors are the subject of extensive studies [138–142].

In the 2016 benefit assessment by the Federal Joint Committee (Gemeinsamen Bundesausschuss - G-BA), empagliflozin was certified as having evidence of considerable additional benefit in patients with type 2 diabetes with manifest cardiovascular disease in combination therapy with metformin (https://www.g-ba.de/downloads/39–2612 %20694/2016–09–01_AM-RL-XII_Empagliflozin_D-214_BAnz.pdf). Accordingly, this additional benefit was included in the new edition of the disease management programme for type 2 diabetes in 2017 [143].

Ertugliflozin

The cardiovascular safety of ertugliflozin was investigated in the VERTIS-CV study. The study design and also the characteristics of the study population at baseline were similar to those of the EMPA-REG-OUTCOME study, particularly in relation to pre-existing cardiovascular disease [144]. Approximately 2750 patients were included in each of the 3 study arms (standard therapy/placebo; 5 mg ertugliflozin, 15 mg ertugliflozin daily) and were followed for approximately 3.5 years. MACE was slightly lower in ertugliflozin groups compared with the placebo group (HR 0.97; 95 % CI 0.85–1.11; p < 0.001 for non-inferiority). Data on cardiovascular death or hospitalisation for heart failure (ertugliflozin vs. placebo: 8.1 vs. 9.1 % (HR 0.88; 95 % CI 0.75–1.03; p = 0.11 for superiority), the analyses for cardiovascular death (HR 0.92; 95% CI 0.77–1.11), death from renal causes, renal replacement therapy or doubling of serum creatinine (HR 0.81; CI 0.63–1.04) were not significant. Amputations were reported in 2 % with ertugliflozin (5 mg) therapy and in 1.6 % with 15 mg dose. The amputation rate with placebo was also 1.6 % [145]. In a post-hoc analysis of the VERTIS MET [146] and VERTIS SU [147] trials, ertugliflozin reduced eGFR in the first 6 weeks but returned to baseline after 104 weeks and therefore resulted in preservation of renal function. The eGFR was slightly higher at both ertugliflozin doses (5 and 15 mg) than in patients who did not receive ertugliflozin. Ertugliflozin significantly reduced albumin excretion rates by 30 and 38 % in people who had albuminuria at baseline (21 %) [148]. Another analysis of the VERTIS-CV trial showed that at a mean follow-up of 3.5 years, the exploratory composite endpoint (time to doubling of serum creatinine, dialysis (kidney transplantation or renal death) was significantly reduced with ertugliflozin compared with placebo (HR 0.66; 95 % CI 0.50–0.88). Renal function and albumin excretion rates were stabilised [149].

In the VERTIS programme, a number of studies with ertugliflozin were published that analysed combination therapies with metformin, metformin plus sitagliptin, insulin or sulfonylureas, which were recently summarised in a review [150].

Ertugliflozin is only approved in Germany in a fixed combination with sitagliptin (VERTIS-Factorial study). According to the decision of the G-BA of 01.11.2018, there is no additional benefit of this fixed combination. The G-BA also certified no additional benefit for the combination of linagliptin and empagliflozin (BAnz AT 24.12.2019 B3).

Canagliflozin

Recent outcome RCT data on canagliflozin [96] (CANVAS programme) show a significant reduction in composite endpoint (cardiovascular death, non-fatal myocardial infarction and stroke) with canagliflozin compared with placebo of 14 % (HR 0.86; 95 % CI 0.75–0.97), decrease in hospitalisation rate due to heart failure of 33 % (HR 0.67; 95 % CI 0.52–0.87) and renal outcome data with a reduction in the progression of albuminuria by 27 % (HR 0.73; 95 % CI

0.67–0.79) and composite endpoint (40 % reduction in eGFR, renal replacement therapy, renal death) by 40 % (HR 0.60; 95 % CI 0.47–0.77) [100]. Another large RCT (CREDENCE trial) was conducted with canagliflozin in relation to a primary combined renal endpoint [104]. Patients already had renal insufficiency at randomisation, significant proteinuria and had to be already treated with an ACE inhibitor or AT blocker. Canagliflozin (100 mg per day) was shown to significantly reduce the relative risk of the composite endpoint (dialysis, transplantation or sustained eGFR < 15 ml/min), doubling of serum creatinine, death from renal or cardiovascular causes (HR 0.70, 95 % CI 0.59–0.82; p = 0.00 001).

In the recently published post hoc analysis of the CANVAS programme and the CREDENCE trial, canagliflozin was not associated with a reduction in myocardial infarction in the study populations [151].

Canagliflozin is currently not available on the German market despite positive patient-relevant endpoints.

Sotagliflozin

Sotagliflozin is a dual SGLT1 and SGLT2 inhibitor. Two large studies have been published so far for the treatment of type 2 diabetes. In the SOLOIST-WHF trial, people with type 2 diabetes and decompensated heart failure were studied with sotagliflozin (n = 608) or placebo (n = 614) for a median of 9 months. Mean ejection fraction (EF) was 35 % and baseline heart failure therapy was the same in both groups. There was a significant reduction in the composite primary endpoint (cardiovascular death and hospitalisation or acute hospitalisation for heart failure) with sotagliflozin compared with placebo: hazard ratio (HR) 0.67, 95 % CI 0.52–0.85, p < 0.001). As the study had to be discontinued due to COVID-19 and a lack of financial support, the calculated event rates were not achieved, so that the data of this study are not sufficiently robust overall [152].

In the randomised controlled SCORED trial [153], 10 584 patients with type 2 diabetes and renal insufficiency (eGFR 25–60 ml/min.) and cardiovascular risk factors were randomised 1:1 (sotagliflozin:placebo). The median follow-up was 16 months. The primary endpoint was changed during the study to a composite endpoint (all-cause cardiovascular mortality, hospitalisation for or acute care for heart failure). The primary endpoint was significantly lower with sotagliflozin compared to placebo: hazard ratio 0.74; 95 % CI 0.63–0.88; p < 0.001). This study also had to be stopped early for financial reasons. Sotagliflozin is currently only approved for combination therapy with insulin in people with type 1 diabetes.

GLP-1 receptor agonists (RAs)

GLP-1-RAs are antidiabetic drugs for the subcutaneous or oral therapy of type 2 diabetes. They can on average lower plasma glucose more than classic oral antidiabetics and also have blood pressure-lowering (slight), weight-reducing [154] and specific cardio- and renal protective (see below) effects. If the individual therapeutic objective is not achieved, GLP-1-RAs are useful combination partners to metformin, other OADs (except DPP-4 inhibitors) and/or basal insulin. GLP-1-RAs themselves have a low hypoglycaemic risk.

Human GLP-1-RAs

Available in Germany: dulaglutide, liraglutide, semaglutide

Not available in Germany: albiglutide

Exendin-based GLP-1 RAs

Approved in Germany: exenatide, lixisenatide (only in fixed combination with insulin glargine).

Not available in Germany: efpeglenatide

Dulaglutide

In the AWARD trial programme, dulaglutide was shown to be effective in lowering blood glucose and weight, and for a low incidence of hypoglycaemia when used as monotherapy and in combination with prandial and basal insulin. Patients with various degrees of chronic renal insufficiency were also included [155]. The multi-centre (371 study centres in 24 countries), randomized, double-blind placebo-controlled study on the cardiorenal effects of dulaglutide therapy (REWIND study; 1.5 mg s.c. weekly) was recently published [156, 157]. Included were 9901 patients with type 2 diabetes (mean age 66 years, average HbA1c 55,2 mmol/mol; 7,2 %). This study differs from the previously published studies on the cardiovascular and renal outcome under GLP-1-RA in the following important points: Longer observational period (mean 5.4 years), 69 % of the study participants had cardiovascular risk factors, but no clinically manifested cardiovascular pre-illnesses and the ratio between women and men was fairly balanced (46 % women). Compared to placebo, dulaglutide was able to reduce the mean HbA1c baseline value of 7.2 % over the entire study (HbA1c: –0.46 % for dulaglutide, + 0.16 % for placebo; body weight: –2.95 kg dulaglutide, –1.49 kg placebo). In addition, dulaglutide showed a reduction of the secondary combined microvascular endpoint (HR 0.87; 95 % CI 0.79–0.95), with this reduction predominantly affecting the renal outcome (HR 0.85; 95 % CI 0.77–0.93; p = 0.0004). The primary endpoint 3P-MACE was significantly lower with dulaglutide (HR 0.88; 95 % CI 0.79–0.99; p = 0.026), as was the risk of non-fatal stroke (HR 0.76; 95 % CI 0.61–0.95; p = 0.017). No risk reductions were found for the following endpoints: non-fatal and fatal myocardial infarction, fatal stroke, cardiovascular death, all-cause mortality, and hospitalization for heart failure. Compared to placebo, dulaglutide did not show any differences with regard to relevant side effects: Cancer (pancreatic, medullary thyroid carcinoma, other thyroid carcinomas), acute pancreatitis or pancreatic enzyme elevations, liver diseases, cardiac arrhythmias and hypoglycaemic rate.

In an explorative analysis of the REWIND data [157] renal outcome data concerning dulaglutide, a significant risk reduction for the summarized renal endpoint (new macroalbuminuria, eGFR reduction of ≥ 30 % or chronic renal replacement therapy; HR 0.85; 95 % CI 0.77–0.93; p = 0.0004) was determined with the clearest effect with respect to the macroalbuminuria component (HR 0.77; 95 % CI 0.68–0.87; p < 0.0001).

In a post-hoc analysis of the REWIND trial, the incidence of MACE (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) or non-cardiovascular death was 35.8 per 1000 person-years in the dulaglutide group and 40.3 per 1000 person years in the placebo group (HR 0.90, 95 % CI 0.82–0.98, p = 0.020). The incidence data on more complex MACE (MACE plus heart failure, un-

stable angina or revascularisation) were more impressive: dulaglutide vs. placebo 67.1 vs. 74.7 per 1000 person years: HR 0.93 (95 % CI 0.87–0.99) p = 0.023 [158]. In the G-BA decision of 16.07.2020, dulaglutide was assigned an indication for a small additional benefit in people with type 2 diabetes in whom diet and exercise and treatment with insulin (with or without another antidiabetic drug) do not sufficiently control blood glucose, both in patients without renal insufficiency and in patients with moderate or severe renal insufficiency (CKD stages 3 and 4).

Liraglutide

In a randomised trial in obese patients, liraglutide (3 mg/d) resulted in greater weight loss than placebo in all intensively treated patients compared to physical activity alone: 8 weeks after a low-calorie diet resulted in a weight loss of 13.1 kg. At the end of the study (after one year), weight loss with increased physical activity was − 4.1 kg (95 % CI − 7.8 to − 0.4; p = 0.03); in the liraglutide group − 6.8 kg (95 % CI − 10.4 to − 3.1; p < 0.001); in the combination physical activity plus liraglutide − 9.5 kg (95 % CI − 13.1 to − 5.9; p < 0.001). The combination therapy also resulted in a 3.9 % reduction in body fat mass, which was approximately 2-fold higher than in the physical activity group (− 1.7 %; 95 % CI − 3.2 to − 0.2; p = 0.02) and in the liraglutide group alone (− 1.9 %; 95 % CI − 3.3 to − 0.5; p = 0.009) [159]. For the GLP-1 receptor agonist (RA) liraglutide, the RCT (LEADER trial) showed positive effects on clinically-relevant endpoints [160]. The median follow-up of the 9340 patients was 3.8 years. The composite primary endpoint (first event for cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) was significantly lower with liraglutide compared with placebo (13 vs. 14.9 %; HR 0.87; 95 % CI 0.78–0.97; p < 0.001 for non-inferiority and p = 0.01 for superiority). Fewer patients died from cardiovascular causes (4.7 vs. 6.0 %; HR 0.78; 95 % CI 0.66–0.93; p = 0.007). All-cause mortality was also lower with liraglutide (8.2 vs. 9.6 %; HR 0.85; 95 % CI 0.74–0.97; p = 0.02). Thus, for the first time, a positive effect on patient-relevant outcomes could also be demonstrated for a GLP-1 RA in an RCT.

A sub-analysis of the LEADER study population showed that 72 % of patients had vascular disease at baseline. 23 % of this subpopulation had polyvascular disease and 77 % had monovascular disease. Liraglutide led to a reduction in MACE at 54-month follow-up: in polyvascular disease (HR 0.82; 95 % CI 0.66–1.02) and in monovascular disease (HR 0.82; 95 % CI 0.71–0.95) compared with placebo. No positive effects of liraglutide were found in patients without vascular complications [161]. The analysis by Marso et al. [162], which demonstrated a reduction in myocardial infarctions with liraglutide in patients at high vascular risk, points in the same direction. In the meta-analysis published by Duan et al. in 2019 [163], patients in the liraglutide group compared with controls were found to have lower risks of: MACE (RR 0.89, 95 % CI 0.82–0.96, p = 0.002), acute myocardial infarction (RR = 0.85, 95 % CI 0.74–0.99, p = 0.036), all-cause mortality (RR 0.84, 95 % CI 0.74–0.96, p = 0.009) and cardiovascular death (RR 0.77, 95 % CI 0.65–0.91, p = 0.002). However, the incidence of stroke was not reduced in the liraglutide group (RR 0.86, 95 % CI 0.70–1.04, p = 0.124).

In the analysis of secondary renal endpoints in the LEADER study, liraglutide was associated with a lower rate of development and progression of the renal composite endpoint (HR 0.78; 95 % CI 0.67–0.92; p = 0.003) and persistence of macroalbuminuria (HR 0.74; 95 % CI 0.60–0.91; p = 0.004) compared with placebo [164].

In its decision of 17.01.2019 (BAnz AT 22.03.2019 B5), the G-BA granted liraglutide an added benefit and included it in the structured treatment programmes for type 2 diabetes.

The meta-analysis by Kristensen et al. [165] showed a significant reduction in MACE of 12 % (HR 0.88; 95 % CI 0.82–0.94; p < 0.0001) with GLP-1-RA. The hazard ratios were 0.88 (95 % CI 0.81–0.96; p = 0.003) for death from cardiovascular events, 0.84 (95 % CI 0.76–0.93; p < 0.0001) for fatal and non-fatal stroke, and 0.91 (95 % CI 0.84–1.00; p = 0.043) for non-fatal and fatal myocardial infarction. GLP- 1-RA resulted in a 12 % reduction in all-cause mortality (HR 0.88; 95 % CI 0.83–0.95; p = 0.001) and a 9 % reduction in hospitalisation for heart failure (HR 0.91; 95 % CI 0.83–0.99; p = 0.028). The composite renal endpoint (development of new macroalbuminuria, reduction in eGFR, progression to ESRD) decreased by 17 % (HR 0.83; 95 % CI 0.78–0.89; p < 0.0001), mainly due to the reduction in albuminuria. No increased risk of hypoglycaemia, pancreatitis or pancreatic cancer was reported with GLP-1 RA.

The very detailed and critical meta-analysis by Liu et al. [166] also came to a comparable conclusion. All-cause mortality was slightly lower under GLP-1 RAs compared to control therapies: OR 0.89 (95 %-KI 0.80–0.98).

The association of GLP-2 RAs with renal events under real-world conditions was analysed in a large Scandinavian study [167]. 38 731 users of GLP-1 RAs (liraglutide 92.5 %, exenatide 6.2 %, lixisenatide 0.7 %, dulaglutide 0.6 %) were studied 1:1 in a propensity-matched control group taking DPP-4 inhibitors. The primary composite endpoint (renal replacement therapy, renal-related death and hospitalisation for renal complications) was significantly lower with GLP-1-RA than with DPP-4 inhibitor therapy: HR 0.76 (95 % CI 0.68–0.85). In particular, renal replacement therapy (HR 0.73, 95 % CI 0.62–0.87) and hospitalisation rates (HR 0.73, 95 % CI 0.65–0.83) were significantly lower with GLP-1-RA [167].

Semaglutide

Semaglutide s. c.

Semaglutide 1 × weekly s. c. showed a greater HbA1c reduction (− 0.4 %) and weight loss (− 2.5 kg) compared to other GLP-1 RAs [168].

In the STEP-1 study with semaglutide (1 × weekly s. c.), a mean weight loss of − 14.9 % was observed in the observation period of 68 weeks compared to placebo of only − 2.4 %. The difference in weight loss of − 12.4 % was highly significant. More patients in the semaglutide group than in the placebo group achieved weight losses of ≥ 5 % (86.4 vs. 31.5 %), ≥ 10 % (69.1 vs. 12.0 %) and ≥ 15 % (50.5 vs. 4.9 %), all of which were highly significant with a p = 0.001 [169]. The STEP 3 and STEP 4 trials showed similar favourable effects of semaglutide on weight progression [170, 171].

In the SUSTAIN-6 trial, cardiovascular benefit was demonstrated by significant reduction in the primary endpoint 3P-MACE compared to the control group. In patients with a high cardiovascular risk, there was a significant risk reduction (HR 0.74; 95 % CI 0.58–0.95) for the primary endpoint (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in the semaglutide group

compared to placebo [172]. In the recently published post-hoc analysis of the SUSTAIN-6 study, semaglutide 1 × weekly s.c. vs. placebo was found to reduce the risk of MACE in all study participants regardless of sex, age or cardiovascular risk profile at baseline [173].

Oral semaglutide

In the PIONEER-6 trial of oral semaglutide 1 × daily (n = 3183 patients, 84.7 % > 50 years with cardiovascular or chronic renal complications; mean observation time 15.9 months) the following results were found: MACE was found in 3.8 % in the oral semaglutide and 4.8 % in the placebo group (HR 0.79; 95 % CI 0.57–1.11; p < 0.001 for non-inferiority); cardiovascular death (HR 0.49; 95 % CI 0.27–0.92); non-fatal myocardial infarction (HR 1.18; 95 % CI 0.73–1.90); non-fatal stroke (HR 0.74; 95 % CI 0.35–1.57); all-cause mortality (HR 0.51; 95 % CI 0.31–0.84) [174]. In the meta-analysis published in 2020, oral semaglutide was shown to reduce the risk of all-cause mortality (OR 0.58; 95 % CI 0.37–0.92) and cardiovascular mortality (OR 0.55; 95 % CI 0.31–0.98) compared with placebo. However, it showed a neutral effect with regard to myocardial infarction, stroke and severe hypoglycaemia [175].

In a combined post-hoc analysis of the two cardiovascular outcome trials SUSTAIN 6 and PIONEER 6, the effect of semaglutide was analysed in patients with a continuum of initial cardiovascular risk. Thereby, semaglutide showed a significant absolute and relative risk reduction of MACE (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) across the spectrum of cardiovascular risk compared to comparator therapies. This was also found for the individual components of MACE [176].

However, in the recent re-analysis of the SUSTAIN 6 and PIONEER 6 studies [177], the authors placed the analyses in a broader context to the results of the other studies SUSTAIN 1–5 and PIONEER 1–5, 7–8. The hazard ratio for MACE was 0.85 with a wide confidence interval (95 % CI: 0.55–1.33) because of the low event rates in most studies.

Treatment with GLP-1 RAs or SGLT2 inhibitors was associated with significantly lower all-cause mortality compared with DPP-4 inhibitors or other antidiabetic drugs or no therapy in the meta-analysis by Zheng SL et al. (HR 0.88; 95 % CI 0.81–0.94 and/or HR 0.80; 95 % CI 0.71–0.89, respectively). Similar data were also found for cardiovascular mortality as well as myocardial infarction and heart failure compared to the control groups [178].

In the meta-analysis of the GLP-1 RAs exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide and semaglutide published in 2017, there was a significant reduction in the incidence of nephropathy compared with other antidiabetic drugs (OR 0.74; 95 % CI 0.60–0.92; p = 0.005) [179]. Mann et al.'s [180] post-hoc analysis of the SUSTAIN 1–7 trials showed that semaglutide initially led to a reduction in eGFR in normal and mildly impaired renal function (in the SUSTAIN 6 trial with 1.0 mg semaglutide). From week 30 onwards, there was no difference in eGFR between the semaglutide vs. placebo groups in the SUSTAIN 1–5 and SUSTAIN 7 trials and at week 104 for SUSTAIN 6. In the SUSTAIN 1–6 trials, albuminuria decreased in patients with microalbuminuria and macroalbuminuria. In patients with normoalbuminuria, there was no difference in albuminuria from the beginning to the end of the study.

Semaglutide and G-BA

In a detailed statement by the German Diabetes Society (DDG), the German Society of Cardiology (DGK), the German Society for Atherosclerosis Research (DGAF), the German Ophthalmological Society (DOG), the Retinological Society (RG), the Professional Association of Ophthalmologists (BVA), the Research Group Diabetes e.V. at Helmholtz Zentrum München, and the Federal Association of Registered Diabetologists (BVND) on the dossier assessment (A20–93, version 1. 0, status 28.1.2021) of the Institute for Quality and Efficiency in Health Care (IQWiG) on the benefit assessment of semaglutide in the form of a subcutaneous application as well as in an oral dosage form for the treatment of patients with type 2 diabetes mellitus, the experts of the professional societies came to the conclusion that the negative assessment of semaglutide (oral and s. c.) by IQWiG is unjustified [www.deutsche-diabetes-gesellschaft.de/politik/stellungnahmen/]. Nevertheless, with the decision of the Federal Joint Committee of 15.04.2021, no additional benefit was granted to semaglutide (BAnz AT 02.06.2021 B5).

Albiglutide

Safety and cardiorenal outcome data have been published for albiglutide [181, 182]. Cardiovascular outcome data on albiglutide (HARMONY outcomes trial [183]) were analysed and published in 2018. At that time, albiglutide had already been withdrawn from the market worldwide (July 2017). The HARMONY trial enrolled and randomised 9463 patients (albiglutide 30–50 mg, n = 4731; placebo n = 4732). The median observation period was only 1.6 years. There was no evidence of a difference in major adverse events between the two study arms. In the 3P-MACE, a significant risk reduction with albiglutide (HR 0.78; 95 % CI 0.68–0.90; non-inferiority p = 0.0001, superiority p = 0.0006) was already evident after this short study duration.

In a recent publication, the authors reported that albiglutide was able to completely replace prandial insulin in 54 % of study participants in patients with type 2 diabetes on baseline bolus insulin therapy, with concomitant improvement in metabolic control, reduction in hypoglycaemia and body weight [184].

Exendin-based GLP-1 RAs

Exenatide

In the EXSCEL study 14 752 patients (73.1 % with cardiovascular disease) were treated at a mean of 3,2 years with 2.0 mg exenatide once a week. Patients with or without cardiovascular disease showed no significant difference in the incidence of MACE between those who received exenatide or a placebo. Critical for the evaluation of the effects in the EXSCEL study is the very high dropout rate of over 40 %. Compared to the control group, there were no differences in cardiovascular mortality, non-fatal or fatal myocardial infarction or stroke, hospitalization for heart failure and incidence of acute pancreatitis, pancreatic carcinoma, medullary thyroid carcinoma or other serious side effects [185].

In the EXSCEL study, the benefits of exenatide, namely risk reduction in all-cause mortality (− 14 %) and first hospitalisation for heart failure (− 11 %), could only be seen in study participants who did not have heart failure at baseline [186]. The risk reduction for all-cause mortality was confirmed in a recent meta-analysis [187].

The combination of exenatide (1 × weekly) plus dapagliflozin resulted in a significant reduction in HbA1c (− 1.7 vs. − 1.29 %) compared to exenatide plus placebo; dapagliflozin plus placebo decreased HbA1c by − 1.06 % over the same 104-week period. There were also clinically-relevant positive changes for fasting glucose, 2-h postprandial glucose, body weight and systolic blood pressure. Severe hypoglycaemia was not observed in any of the treatment arms [188].

In the meta-analysis by Bethel et al. [189], the 4 large RCTs ELIXA (lixisenatide), LEADER (liraglutide), EXSCEL (exenatide 1 × weekly) and SUSTAIN 6 (semaglutide) were evaluated. Compared with placebo, GLP-1 RAs showed a significant risk reduction (HR 0.90; 95 % CI 0.82–0.99; p = 0.033) in the primary endpoint (cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke), a relative risk reduction (RRR) of 13 % for cardiovascular mortality (HR 0.87; 95 % CI 0.79–0.96; p = 0.007) and for all-cause mortality of 12 % (HR 0.88; 95 % CI 0.81–0.95; p = 0.002). However, the statistical heterogeneity between the studies was large. No significant reductions were found by GLP-1 RAs for non-fatal or fatal myocardial infarction, stroke, hospitalisation for unstable angina or heart failure.

Exenatide 1 × weekly resulted in a significant reduction in albumin excretion of 26 rel. % (95 % CI − 39.5 to − 10) compared with a comparison group. Compared with oral antidiabetics, the reduction in albuminuria was − 29.6 % (95 % CI − 47.6 to − 5.3); with insulin therapy, the value was − 23.8 rel. % (95 % CI − 41.8 to − 0.2) [190].

Lixisenatide

After this GLP-1 RA showed only non-inferior effects on cardiovascular endpoints in the ELIXA study [191] and was thus inferior to other GLP-1 RAs, the combination of insulin glargine with lixisenatide (iGlarLixi) was then investigated [192]. In a meta-analysis, 8 studies (study duration: 24–30 weeks) with 3538 participants were evaluated. In this analysis, iGlarLixi was superior to therapy with combination insulin: − 0.50 %- units (95 % CI − 0.93 to − 0.06), basal bolus therapy − 0.35 % (− 0.89 to + 0.13) and basal plus therapy − 0.68 % (− 1.18 to − 0.17). When compared with combi-insulin therapy, there were fewer symptomatic hypoglycaemias and less weight gain. Analyses of cardiovascular or renal endpoints were not reported.

Efpeglenatide

Efpeglenatide is an exendin-based GLP-1 RA that has recently been studied in large RCTs (multicentre and international) in 4076 patients with type 2 diabetes and a history of cardiovascular disease or renal insufficiency (eGFR 25.0 to 59.9 ml/min) plus another cardiovascular risk factor. Patients were randomised 1:1:1 (efpeglenatide 4 mg: efpeglenatide 6 mg: placebo) and analysed after a median observation period of 1.8 years. The primary endpoint was MACE. This was found in 7.0 % with efpeglenatide and 9.2 % with placebo: HR 0.73; 95 % CI 0.58–0.92; p < 0.001 for non-inferiority; p = 0.007 for superiority. The composite renal endpoint (reduction in eGFR or macroalbuminuria) was found in 13 % in the efpeglenatide group and 18.4 % in the placebo group: HR 0.68; 95 % CI 0.57–0.79; p < 0.001) [193].

Combination peptides in the near future

Tirzepatide

Tirzepatide is a dual receptor agonist (RA) based on glucose-dependent insulinotropic peptide (GIP) and dulaglutide administered 1 × weekly. It combines the effects of both substances in a new molecule [194, 195]. In the recently published results of the RCT study SURPASS 1, tirzepatide was superior at all doses (5 mg, n = 121; 10 mg, n = 121; 15 mg, n = 121) compared with placebo (n = 115) at the end of the study (40 weeks): Mean HbA1c decreased from baseline by 1.87 % (20 mmol/mol), 1.89 % (21 mmol/mol) and 2.07 % (23 mmol/mol Hb), respectively. There was no increased risk of hypoglycaemia. With placebo, the value increased by 0.04 % (+ 0.4 mmol/mol Hb). Tirzepatide resulted in a dose-dependent weight loss of 7.0 to 9.5 kg [196]. When comparing metabolic effects, tirzepatide was not inferior to semaglutide, but superior in terms of reduction of HbA1c and body weight [197]. As the first peptide of a new substance class, another therapy option will soon be available for the treatment of type 2 diabetes, obesity and fatty liver [198, 199].

A review discusses the potential advantages - SURPASS studies - of this combined peptide over dulaglutide [200].

Safety aspects of GLP-1 RAs

Retinopathy remained unchanged among GLP-1-RAs except for semaglutide, which had a negative effect on changes in the ocular fundus (OR 1.75; 95 % CI 1.10–2.78; p = 0.018) [179]. Whether this is related to the rapid optimisation of the metabolism is being discussed [201]. In addition, only patients with pre-existing retinopathy were affected. A corresponding study was initiated to clarify the retinopathy risk when using semaglutide (Clinical-Trials.gov number, NCT03 811 561). However, the meta-analysis by Avgerinos et al. on oral semaglutide showed no evidence of a higher rate of retinopathy [175].

Pancreatitis and cholecystolithiasis as well as neoplasms: Of 113 studies included in the analysis by Monami et al., 13 found no data on pancreatitis. No pancreatitis or pancreatic cancer events were reported in 72 studies. In the remaining studies (n = 28), the incidence of pancreatitis and pancreatic carcinomas with GLP-1-RAs was comparable with the comparative drugs (pancreatitis OR 0.93; 95 % CI 0.65–1.34; p = 0.71; pancreatic carcinomas OR 0.94; 95 % CI 0.52–1.70; p = 0.84). However, the risk for gallstones was increased (OR 1.30; 95 % CI 1.01–1.68; p = 0.041) [126]. In the comprehensive analysis of RCTs published in 2020 with incretin-based therapies (SAVOR-TIMI 53 (saxagliptin), EXAMINE (alogliptin), TECOS (sitagiptin), ELIXA (lixisenatide), and with liraglutide in LEADER and semaglutide in SUSTAIN-6) no significant risk increase for pancreatitis and pancreatic carcinoma for GLP-1-RA could be found in contrast to therapies with DPP-4 inhibitors [203]. In the meta-analysis by Cao et al. there was also no evidence for an increased cancer risk under therapy with GLP-1 RAs [204]. In the meta-analysis published in 2018 by Bethel et al. [189], there were no differences in pancreatitis, pancreatic carcinoma and medullary thyroid carcinoma in patients treated with GLP-1-RA therapy compared to participants treated with placebo. In addition, the large multinational population-based cohort study with 1 532 513 patients included in the period from January 1, 2007 to June 30, 2013,

and followed up until June 30, 2014, showed no association of a higher risk for pancreatitis among incretin-based therapies compared to OADs [128]. These data are consistent with the results of a meta-analysis of real-world data, which also found no evidence of a higher risk for pancreatitis among incretin-based therapies [205]. These data fit with the results of a further meta-analysis of real-world data, which also found no evidence for a higher risk of pancreatitis with incretin-based therapies [206].

The rate of cholangiocarcinoma was not increased with incretin-based therapy in a large recent cohort study [207]. A recent meta-analysis also found no evidence for a higher risk of breast neoplasia with GLP-1 RA therapy [208].

Incretin-based therapies and fatty liver

Non-alcoholic fatty liver (NASH) is a risk factor for the manifestation of type 2 diabetes, is commonly present in people with type 2 diabetes and is associated with higher morbidity and mortality. In a recent study with an observation period of 72 weeks, 380 patients with NASH and fibrosis F2 and F3 were randomised to receive semaglutide s. c. (0.1 mg; n = 80 or 0.2 mg; n = 78 or 0.4 mg; n = 82) or placebo (n = 80). In contrast to placebo, regression of fatty liver without progression of fibrosis was found with semaglutide: 40 % in the 0.1 mg group, 36 % in the 0.2 mg group and 59 % in the 0.4 mg group. In the placebo group, the improvement was only 17 % ($p < 0.001$ for semaglutide 0.4 mg vs. placebo). However, neoplasia (benign, malignant or unspecified) was found in 15 % of patients in the semaglutide group and 8 % in the placebo group, with no specific organ manifestations observed [209].

Combination of GLP-1 receptor agonists and SGLT2 inhibitors

Compared with GLP-1 RA monotherapy, HbA1c was 0.61 % (95 % CI − 1.09 to − 0.14 %, 4 trials) lower, body weight reduction was (− 2.59 kg, − 3.68 to − 1.51 kg, 3 trials) and systolic blood pressure reduction was (− 4.13 mmHg, − 7.28 to − 0.99 mmHg, 4 trials) in 7 trials analysed (n = 1913 patients). Monotherapy with SGLT2 inhibitors reduced HbA1c by 0.85 %, − 1.19 to − 0.52 %, 6 trials) and systolic blood pressure (− 2.66 mmHg, − 5.26 to − 0.06 mmHg, 6 trials). Body weight was unchanged in 5 analysable studies (− 1.46 kg, − 2.94 to 0.03 kg). Combination therapy did not lead to increased severe hypoglycaemia. Data on clinical endpoints were insufficient [210].

Insulins

With the manifold possibilities of oral antidiabetic therapy with or without combination with GLP-1-RAs, insulin therapy can in many cases be postponed to later stages of the disease. However, a necessary insulin administration should not then be delayed by years, as can sometimes be observed [211]. Insulin therapy can be easily combined with other antidiabetics, and the large number of insulins and injection aids facilitates individualisation of the therapy.

An extensive discussion on new insulins, however, would go far beyond the scope of this Clinical Practice Guideline but a comprehensive review was recently published as a contribution to 100 years of insulin [212].

Therefore, the authors have concentrated on a few aspects of new insulin preparations in the Clinical Practice Guidelines.

Basal insulin analogues

Insulin degludec (n = 3818) is not inferior to insulin glargin 100 (n = 3819) in the therapy of people with type 2 diabetes and a high risk of cardiovascular events in terms of MACE. The HbA1c values were identical in both groups over the observational period of 2 years (7.5 ± 1.2 %), but the fasting plasma glucose values were significantly lower under insulin degludec. The hazard ratio was 0.91 (95 % CI 0.78–1.06) for the primary endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke). By contrast, the rate of severe hypoglycaemia (secondary endpoint) was significantly lower for insulin degludec (4.9 %) than for insulin glargin 100 (6.6 %) (hazard ratio 0.60; 95 % CI 0.48–0.76; $p < 0.001$). The rate of severe side effects such as benign and malignant neoplasia was comparable (DEVOTE study [213]). In the DEVOTE study, it was shown once again that confirmed severe hypoglycaemia was associated with an increased rate of all-cause mortality in a period of 15–365 days before the clinical endpoint [214].

Pharmacokinetic and pharmacodynamic studies have shown that insulin glargin 300 has a flatter efficacy profile, lasts slightly longer and has a lower day-to-day variability than insulin glargin 100. Metabolic control was comparable for both insulin types, while the rate of nocturnal hypoglycaemia was significantly lower for insulin glargin 300 than for insulin glargin 100 [215–217].

Biosimilar insulin glargin 100: Pharmacokinetics and -dynamics are comparable for insulin glargin 100 and biosimilar insulin glargin 100 in people without and with type 2 diabetes [218, 219]. In the meta-analysis by Yamada et al. [220] there were no differences between biosimilar insulins and the original insulins in relation to: HbA1c, fasting plasma glucose, hypoglycaemia, injection site reactions, insulin antibodies, allergic reactions and mortality.

When comparing different insulin analogues (insulin glargin and insulin degludec) with human insulin, a large cohort study from Denmark, Finland, Norway, Sweden and Great Britain found no evidence of an increased carcinoma risk, neither for insulin glargin nor for insulin degludec compared to human insulin for the 10 examined carcinomas in a mean observational period of 4.6 years [221].

Combination of long-acting insulin plus GLP-1-RA

The fixed combination of long-acting insulin plus GLP-1-RA or free simultaneous or consecutive combinations have advantages over intensive insulin therapy with prandial and basal insulin in terms of therapy adherence, rate of hypoglycaemia, weight progression and insulin usage. Compared to intensive insulin therapy, however, gastrointestinal side effects were more frequent with GLP-1-RA [222–224]. In a recent meta-analysis, the authors concluded that combinations of basal insulin with long-acting GLP-1-RA were superior to combinations of basal insulin with short-acting GLP-1-RA in terms of weight reduction, HbA1c value reduction, lower fasting glucose values and benefits in terms of gastrointestinal side effects [225].

The first fixed combination approved in Germany is insulin glargine (100 I.U./ml) and lixisenatide (see above).

Fast-acting insulin analogues

Insulin lispro 200 shows potential advantages for a higher concentrated insulin especially in cases of severe insulin resistance (e. g.,

obesity), as less volume has to be injected with the same amount of insulin and economic advantages for the patient. Compared to insulin lispro 100, insulin lispro 200 showed also significant improvements in variability of fasting glucose, HbA1c, hypoglycaemic rate and satisfaction with therapy. At the same time, a reduction of 20 % insulin was possible [226].

Ultra-fast insulin aspart is absorbed by the blood twice as fast and thus has an approximately 50 % higher insulin effect with significantly lower postprandial blood glucose values, especially in the first 30 min after injection. The faster onset of action means that glucose is even better controllable, especially in people with type 1 diabetes and those on insulin pump therapy [227]. Ultra-fast insulin aspart showed a similar reduction of HbA1c compared to insulin aspart in people with type 2 diabetes (observation time 26 weeks); the 1-hour postprandial glucose values were significantly lower after injection of fast insulin aspart, but not 2–4 h after a test meal. The total rates of severe hypoglycaemia were not different between the two insulins. However, the relative risk of hypoglycaemia 0–2 h postprandially was significantly higher with fast insulin aspart (RR 1.60; 95 % CI 1.13–2.27) [228].

Ultra-rapid insulin lispro (URLI = Ultra Rapid Lispro Insulin) showed a 6.4-fold faster onset in the first 15 min after injection compared to insulin lispro ($p < 0.0001$). The insulin effect of URLi was 13 min significantly faster and 4.2-fold greater in the first 30 min than that of insulin lispro [229].

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