Thieme

Therapy of Type 2 Diabetes

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The practical recommendations 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) "Therapy of Type 2 Diabetes" [1]. The modifications in therapy and their justifications made in the present DDG practical recommendations were updated on the basis of new randomized controlled trials (RCTs) and meta-analyses and were consented by the DDG and the DGIM.

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" infobox.

Therapeutic goals

In the present recommendations, target ranges are identified which - with varying levels of strengths of evidence - inform the physician and the patient on which target range/target value should be aimed for according to current medical knowledge based on evidence and consensus. The main objective remains to set individual therapy goals primarily together with the patient and possibly his or her relatives and agreeing them optimally in writing on a quarterly basis (e. g. in the Health Passport Diabetes).

General and specific therapeutic goals

The therapeutic goals of people with type 2 diabetes depend on patient preference, comorbidity, duration of the disease, age and life expectancy, quality of life, cultural conditions, psychosocial circumstances and possibilities as well as abilities of the persons

RISK FACTORS FOR CARDIOVASCULAR DISEASES AND TYPE 2 DIABETES

Uninfluenceable

- Higher age
- Sex
- Ethnicity
- Positive family history
- Gestational diabetes (in the history)
- Intrauterine development (foetal programming)

Influenceable

- Visceral obesity
- Fatty liver
- Depression
- Poor sleep (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, excessive chronic noise and air pollution)

Metabolic syndrome [2]

at least 3 out of 5 criteria must be fulfilled:

- Abdominal obesity (waist circumference): men * > 94 cm; women ** > 80 cm
- Triglycerides: ≥ 150 mg/dl or ≥ 1.7 mmol/l
- HDL cholesterol *** : Men < 40 mg/dl or < 1.03 mmol/l; women: < 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: 85/90 cm

*** Pharmacological intervention is an alternative criterion

concerned. The diagnosis of type 2 diabetes, which is often experienced by those affected as a severe life restriction, requires a strategy of consent and gradual intensification of therapy (exception: severe metabolic decompensation). In people with type 2 diabetes, individualized therapy goals should be agreed for the following vascular risk parameters (infobox "General treatment and care goals"; ▶ **Table 1**):

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

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 comorbidity
- 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

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

Indicator	Orientation 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	140–199	7.8–11.0
postprandial	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) [7]	
Lipids	LDL cholesterol reduction to target values < 100 mg/dl (< 2.6 mmol/l); for CHD or other risk factors < 70 mg/dl (< 1.8 mmol/l) and at least a 50 % reduction [8].	
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 130–139 mmHg; ≤ 65 years 120–129 mmHg); diastolic blood pressure: < 80 mmHg (not < 70 mmHg); if the therapy has no relevant side effects [9]	

Diagnosis

Medical history and clinical examinations are listed in ▶ **Table 2** and monitoring of people with type 2 diabetes are depicted in ▶ **Table 3**.

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 [3–5].

Therapy

Non-pharmacological therapy

Education and training

A structured, evaluated, target group-specific and topic-specific training and treatment programme should be offered to all patients with diabetes and, where appropriate, their relatives as an indispensable component of the treatment [6].

Plasma glucose self-monitoring

In the case of an indication for plasma glucose self-monitoring, the situations listed in ▶ **Table 4** should be taken into account in people with type 2 diabetes. The glucose self-monitoring should result in eventually necessary therapeutic adjustments.

Urine glucose analyses are not standard in the diagnosis, therapy decision making and monitoring, because urine glucose becomes only positive in the case of high blood glucose values (renal glucose transport capacity is very different intra- and inter-individually, 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 SGLT-2 inhibitors).

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 for healthy, well-balanced diet considering the patient's previous nutrition routine.
- As far as possible, the use of industrial food processing equipment should be avoided, and the intake of sucrose should be limited (WHO recommendation < 25 g/day).
- 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. In endstage renal disease, the protein intake should be increased to 1.2–1.3 g/kg.
- People with type 2 diabetes should be 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 [10–13].
- No complete ban of sugar, but the avoidance of large quantities of glucose, fructose, sucrose and sugar alcohols (e. g. sorbitol, xylitol) or beverages containing these substances.
- 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.

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

History and examination	
History It should be noted that type 2 diabetes is frequently poor in symptoms or asymptomatic and that the symptoms are often overlooked.	▪ Overweight/obesity ▪ High blood pressure ▪ Dyslipidemia ▪ Thirst ▪ Frequent urination ▪ Involuntary weight loss ▪ Tendency to infection - especially infections of the skin or mucous membranes ▪ Exhaustion, fatigue, weakness ▪ Physical activity ▪ 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 ▪ Erectile dysfunction ▪ Birth of children > 4000 g
Family history	▪ Diabetes ▪ Overweight ▪ High blood pressure ▪ Dyslipidemia ▪ 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 [17] ▪ Peripheral nervous system [18] ▪ Skin ▪ Eye examinations [19] ▪ Foot examinations [20]

▶ **Table 2** Continued

History and examination	
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 of type 2 diabetes if a therapeutic consequence results (see also the practical recommendation "Definition, classification and diagnosis of diabetes mellitus' in this supplement)	▪ Plasma glucose ▪ Blood count ▪ HbA1c ▪ Creatinine ▪ eGFR ▪ Potassium ▪ Lipid profile ▪ Gamma GT ▪ AST ▪ ALT [21] ▪ Uric acid [7] ▪ Urine analysis including determination of quantitative albuminuria [22], 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])
Technical examinations	▪ Resting and exercise ECG [23–24] ▪ 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 palpapabler pulses in the feet (consider: media sclerosis)

- Choose vegetable fats, e. g. oils, nuts, seeds.
- Enrich your meals with dietary fibres, e.g. vegetables, fresh fruit, whole grain cereals.

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 [13–15]. See also [16]: S3 guideline Prevention and treatment of obesity/Prävention und Therapie der Adipositas" (www.awmf.org/leitlinien/detail/ll/050–001.html).

Physical activity (▶ **Fig. 1**)

- 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 [25].
- 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.

▶ **Table 3** Monitoring of people with type 2 diabetes.

History/Investigation/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 patients treated with insulin and/or GLP-1-RA ▪ Examination of the FGM/CGM puncture or implant sites
Laboratory values	▪ HbA1c ▪ Creatinine clearance rate (eGFR) ▪ Lipid profile ▪ Urine analyses incl. albuminuria [22], ketones in urine or blood (only for high blood glucose levels; if applicable with SGLT-2 inhibitor therapy)
Screening for diabetic neuropathy [18]	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 [20]	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 there are already clinical findings of sensorimotor neuropathy, regular examinations for foot lesions should be carried out every 3–6 months.
Screening for nephropathy [22]	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 renal disease and possible renal complications (nephrotoxic substances, contrast agents, hypovolemia).

▶ **Table 3** Continued

History/Investigation/Screening	
Screening for retinal complications [19]	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 ▪ in case of known low risk (= no ophthalmological risk and no general risk) 2 years, ▪ for all other risk constellations 1 year. If the ophthalmologist does not know the general risk factors, he should treat the patient as if he had 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's.
Estimation 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.

▶ **Table 4** 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 ▪ Temporarliy 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.

Intensive lifestyle intervention, including an extensive sports and exercise programme, did not lead to better cardiovascular endpoints in the large mean RCT of 9.6 years [26]. The difference between the intensive lifestyle intervention group and the control group at the end of the study was only 2.5 % of body weight. Nevertheless, the study participants profited from a significantly improved vascular risk profile, better physical fitness and mobility, improvement of depression, sleep apnoea and quality of life. In the long term, better physical fitness and weight reduction or stabilization can be better maintained [27]. In a post-hoc analysis of the Look-AHEAD study, participants in the intensified lifestyle intervention who lost ≥ 10 % or more of their body weight had a 20 % lower risk for the primary endpoint (cardiovascular death, non-fatal heart attack, non-fatal stroke, hospitalization for angina pectoris); adjusted HR 0.80; 95 % CI 0.65–0.99; p = 0.039) and a 2 % risk reduction for the secondary endpoint (all-cause mortality, coronary bypass, percutaneous coronary intervention, carotid endarterectomy, hospitalization for cardiac insufficiency; adjusted HR 0.79; 95 % CI 0.66–0.95; p = 0.011) [28]. The disability-free, but not the total life expectancy was extended in the Look-AHEAD intervention [29].

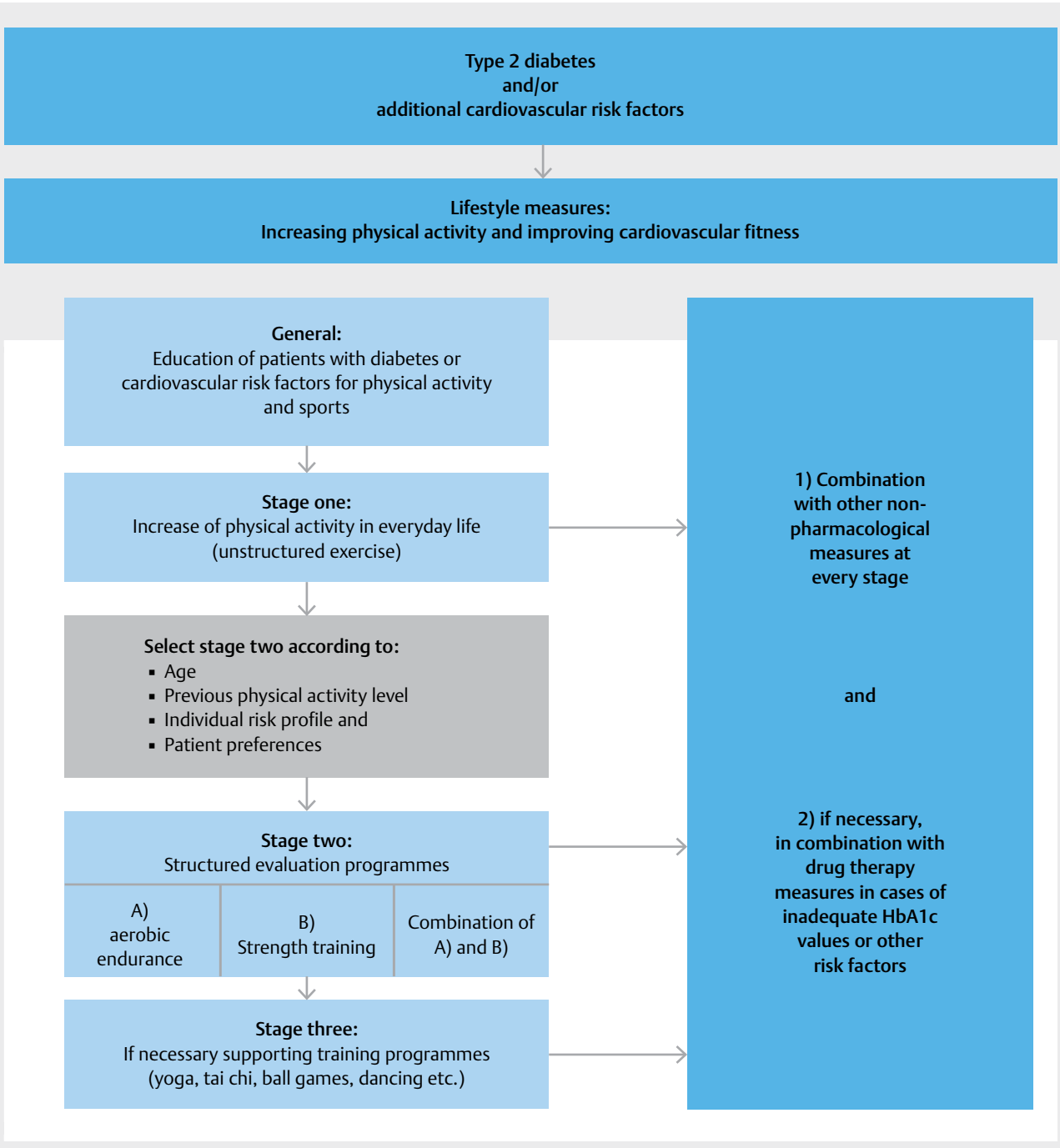
Physical activity is especially beneficial for people with type 2 diabetes for a number of reasons [30–32].

Cessation of smoking

Active and passive smoking is not only an avoidable cause of significantly increased morbidity and mortality, it is also a significant risk factor for type 2 diabetes [33].

Smokers should therefore always be informed about the particular risks of smoking for type 2 diabetes, microvascular and macrovascular complications and lung diseases and should be given specific advice whenever this appears appropriate to the situation. They should be urged to give up tobacco smoking.

Smokers wishing to change their smoking habits should be given regular advice on possible methods of cessation (▶ **Fig. 2**).

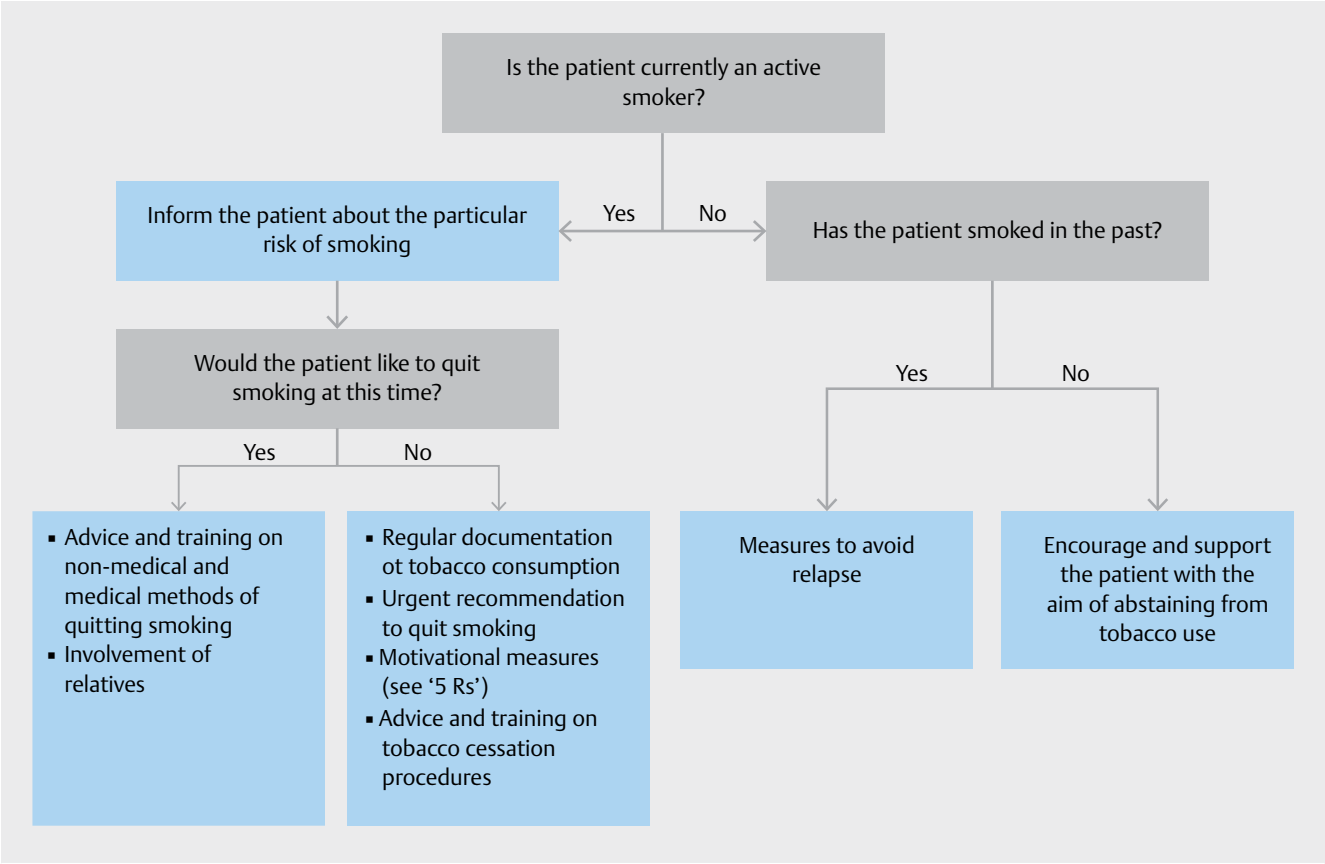


▶ **Fig. 1** Step-by-step programme of physical activity. Source: German Medical Association/Bundesärztekammer (BÄK), National Association of Statutory Health Insurance Physicians/Kassenärztliche Bundesvereinigung (KBV), German Association of the Scientific Medical Professional Societies/Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). National Treatment Guideline for Type 2 Diabetes, long version/Nationale Versorgungsleitlinie Therapie des Typ-2-Diabetes – Langfassung, first edition. Version 4. 2013, last modified: November 2014. Available from: www.dm-therapie.versorgungsleitlinien.de; [cited: 05.09.2019]. doi:10.6101/AZQ/000 213 [rerif].

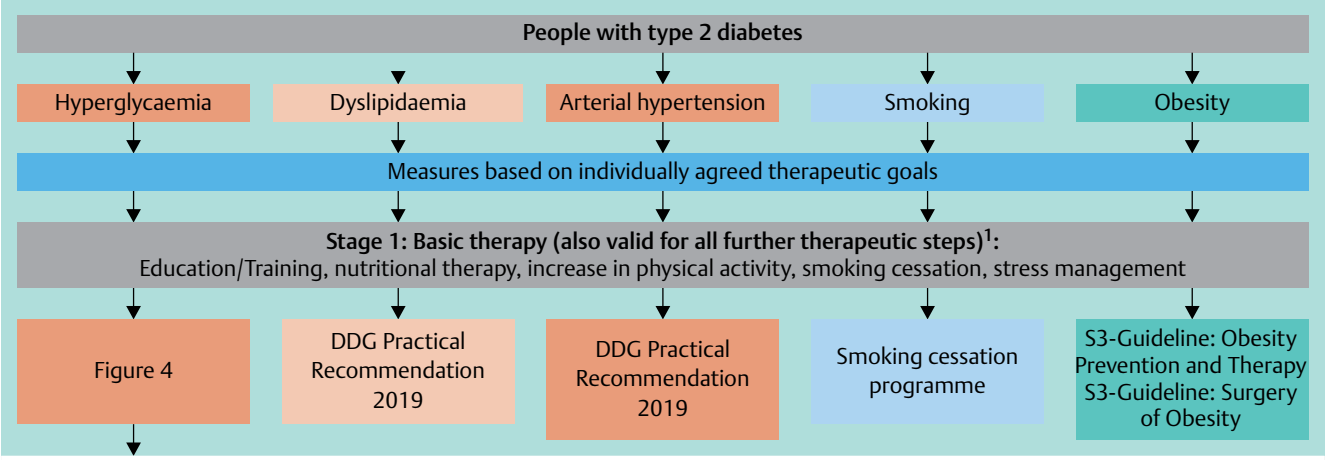
Pharmacotherapy

The step-by-step procedure provided in the therapy algorithm (▶ **Figs. 3,4**) 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 at the same time.

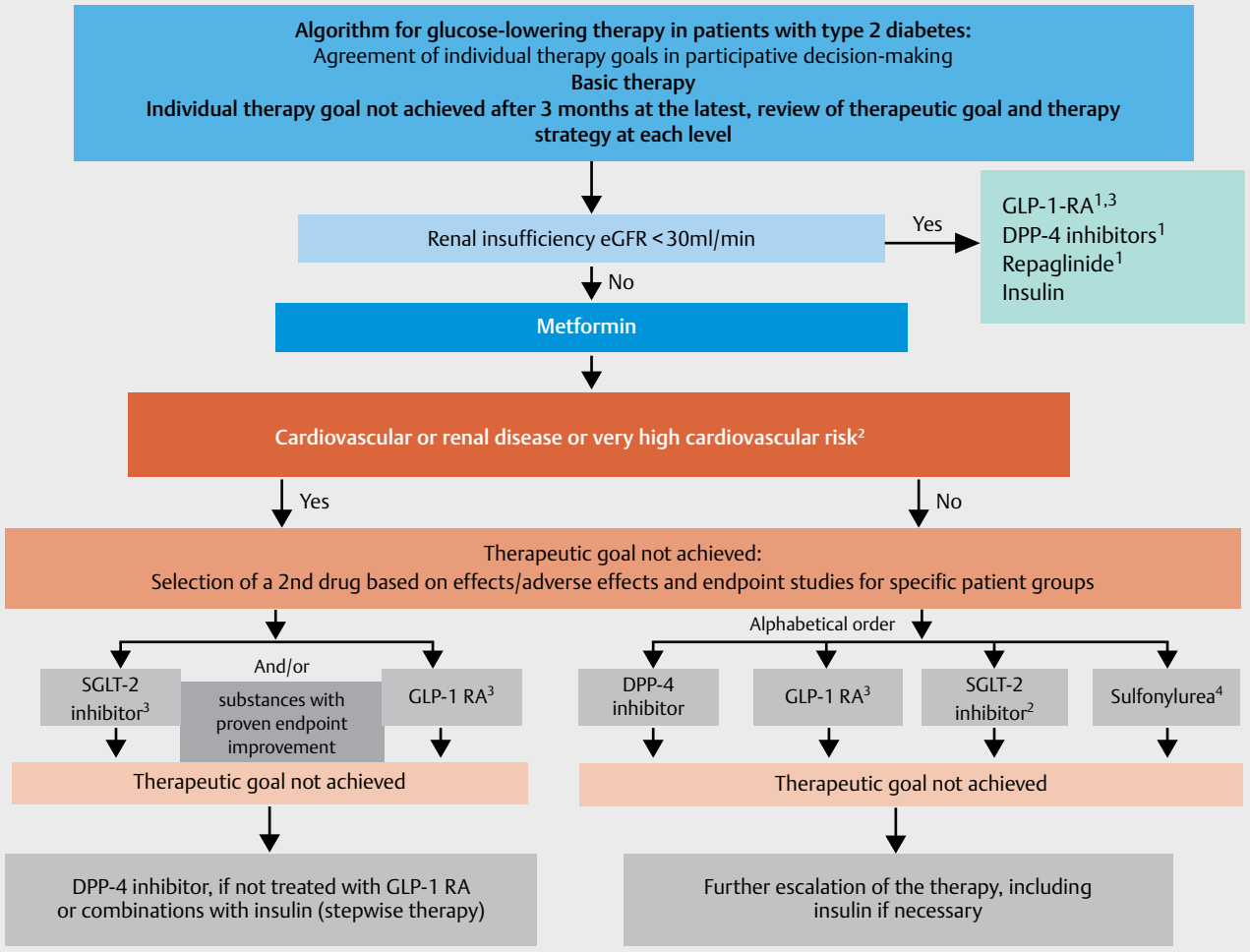
The alphabetical listing of oral antidiabetic drugs after metformin was deliberately chosen because all drugs have advantages and disadvantages which depending on the multimorbidity and patient preferences have to be discussed with each patient with type 2 diabetes.



▶ **Fig. 2** Algorithm for the procedure of tobacco cessation. Source: German Medical Association/Bundesärztekammer (BÄK), National Association of Statutory Health Insurance Physicians/Kassenärztliche Bundesvereinigung (KBV), German Association of the Scientific Medical Professional Societies/Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). National Treatment Guideline for Type 2 Diabetes, long version/Nationale Versorgungsleitlinie Therapie des Typ-2-Diabetes – Langfassung, first edition. [cited: 15.08.2018]. doi:10.6101/AZQ/000 213 [rerif].



▶ **Fig. 3** Therapy algorithm for type 2 diabetes. 1 Lifestyle modifying, non-pharmacological therapy measures represent the basic therapy at all therapeutic steps levels but are often insufficient on their own. For patients who do not exhibit signs of success using lifestyle modification measures (due to the degree of severity of the metabolic derangement, adherence problems, multimorbidity), these measures should be combined with metformin and if contraindications or side effects exist with another antidiabetic drug [rerif].



▶ **Fig. 4** Algorithm for glucose-lowering therapy in type 2 diabetes. For the therapeutic significance of the individual individual drug/drug groups, see background information in these practical recommendations. 1 According to the product inserts. 2 according to the current ESC definition: very high risk (ESC definition): persons with one or more of the following factors: CVD documented either clinically or with clear findings documented in imaging. Documented clinical CVD includes patient history of AMI, ACS, coronary revascularization as well as other arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD. CVD unequivocally documented in imaging procedures includes significant plaque in coronary angiography or ultrasound examination of the carotid artery; diabetes mellitus with organ damage, findings in imaging, documented CVD. Documented clinical CVD includes patient history of AMI, ACS, coronary revascularization; severe CKD (GFR < 30 ml/min/1.73 m2). Calculated SCORE 30. 3 evidence-based renal protection. 4 Only in patients who are not known to have severe hypoglycaemia. In the group of sulfonylureas, it can be assumed that not all active substances benefit equally [rerif].

At the same time, all antidiabetics show varying degrees of evidence for patient-relevant endpoints. This means that there are primary or secondary classifications of glucose-lowering drugs which have a significant influence on the treatment decision based on the patient's characteristics (very high vascular risk profile or manifested cardiovascular and/or renal complications, tendency to hypoglycaemia, severely overweight and evidence-based studies).

Metformin

Thanks to its good efficacy in reducing HbA1c, known safety profile, long experience and low cost, metformin is currently the first-choice antidiabetic for the treatment of type 2 diabetes. Other advantages are the low risk of hypoglycaemia (warning: when consuming alcohol at the same time) and the advantageous effect of slightly reducing weight.

The indication of mono- and combination therapy with metformin was extended in February 2017 due to extensive publications [34]:

- Patients up to a renal insufficiency CKD 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 newly.
- 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 be worsen acutely at this level, patricularly in elderly people with exsiccosis or due to kidney toxic drugs.

The pros and cons of metformin therapy at this eGFR 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 [35].

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 [36]; however, the authors admit that the numbers are too small 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 [37, 38].

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 [39–44].

Summary of the therapy with metformin:

- Kidney function must be checked regularly (every 3–6 months). Warning: 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.

Sulphonylureas

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 independently of glucose, they have the highest hypoglycaemia potential of all oral antidiabetics with the risk of severe and prolonged hypoglycaemia, especially in elderly people with impaired kidney 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). The ADVANCE study found positive effects for gliclazide on microvascular complications [43].

In the recently published CAROLINA study, a prospective, randomized, controlled study (observation period approx. 5 years, in each study arm approx. 3000 patients) linagliptin (5 mg/d) and glimepiride (1–4 mg/d) were compared with regard to cardiovascular endpoints, hypoglycaemia and body weight [45]. There was no difference in the comparison of the two study arms for 3P-MACE, 4P-MACE, total and cardiovascular morbidity and mortality with comparable HbA1c [46]. Weight was more favourable under linagliptin compared to glimepiride (–1.5 kg) and rates of all, moderate, severe and hospitalization for hypoglycemia were significantly lower under linagliptin compared to glimepiride (HR 0.23; 95 % CI 0.21–0.26; p < 0.0001, HR 0.18; 95 % CI 0.15–0.21; p < 0.0001), HR 0.15; 95 % CI 0.08-0.29; p < 0.0001, HR 0.07; 95 % CI 0.02– 0.31; p = 0.0004; resp.). The authors concluded from the data of the CAROLINA study that there are no other reasons than cost reasons to use glimepiride more preferentially than linagliptin in antidiabetic therapy.

In several retrospective observational studies, analyses from register data and their meta-analyses as well as Cochrane reviews it was shown that sulfonylureas have no benefit on macrovascular endpoints, neither in mono- nor in combination therapy. Rather, increased cardiovascular morbidity and mortality were described [38, 47–54].

Repaglinide

Based on a Federal Joint Committee (G-BA) decision, a comprehensive limitation of the prescribability of glinides was introduced as of July 1, 2016. The prescribability restriction is as follows:

> "*Repaglinide therapy is only allowed for patients with renal insufficiency (< 25 ml/min) unless other oral antidiabetics und insulin therapy are not indicated.*"

Despite a detailed evidence-based statement (see also http://www.deutsche-diabetes-gesellschaft.de/stellungnahmen) to the G-BA and BMG, the G-BA decision remains valid.

DPP-4 inhibitors

DPP-4 inhibitors are increasingly replacing the therapy with sulfonylureas. The reasons are a favourable safety profile even in progressive renal insufficiency and a good tolerability, which is particularly important for elderly people. With the exception of linagliptin, the dosage of all DPP-4 inhibitors on the market must be adapted 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) [55]. However, a longer beta-cell reserve under linagliptin cannot be clearly proven in the CAROLINA study [55].

The results of the RCTs SAVOR TIMI 53® (saxagliptin [56]), EXAMINE® (alogliptin [57]), TECOS® (sitagliptin [58]), CARMELINA® (linagliptin [59]) on the effect of DPP-4 inhibitors on cardiovascular and renal endpoints each show cardiovascular safety of the investigated DPP-4 inhibitor in their primary endpoints, which was also confirmed in extensive meta-analyses [60–66]. 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.

Hospitalization for heart failure was not increased with DPP-4 inhibitors except for saxagliptin (SAVOR TIMI 53). In an extensive meta-analysis of the risk of DPP-4 inhibitors for heart failure or hospitalization due to 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 times and overall weak database).

The meta-analysis of the 3 RCTs with DPP-4 inhibitors (SAVOR TIMI 53, EXAMINE and TECOS) showed an increased incidence of acute pancreatitis compared to corresponding controls (Odds ratio 1.79; 95 % CI 1.13-2.82; p = 0.013), whereby the absolute risk of acute pancreatitis was low overall and only 0.13 % higher in absolute terms among DPP-4 inhibitors [67]. Yet DPP-4 inhibitors should avoided in patients with a history of or risks for pancreatitis.

In an extensive population-based study, DPP-4 inhibitors were associated with a significantly higher incidence of inflammatory bowel disease in type 2 diabetes (HR 1.75; 95 % CI 1.22–2.49) [68]. This association was highest 3-4 years after therapy with DPP-4 inhibitors but was significantly lower thereafter. The association started 2–4 years after the beginning of the therapy. In a recent meta-analysis of 13 studies, however, no association was found between DPP-4 inhibitors and inflammatory bowel diseases [69].

In combination with metformin, sitagliptin was certified by the G-BA as having a low additional benefit (BAnz AT 29.04.2019). Saxagliptin however neither in the mono- nor in a combination therapy showed an additioan benefit (BAnz AT 18.01.2017, BAnz AT 13.03.2018 B2).

SGLT-2 inhibitors

SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozine, 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 [70–77]. They also significantly reduce cardiovascular and renal endpoints (see below).

However, there is a significantly increased risk of genital infections with SGLT-2 inhibitors in RCTs [78, 79]. 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).

Ertugliflozine (VERTIS mono study [80]) is approved in Germany only in a fixed combination with sitagliptin (VERTIS Factorial Study [81]). According to the decision of the G-BA of November 01, 2018, there is no additional benefit of this fixed combination.

In the use of SGLT-2 inhibitors, ketoacidosis was occasionally observed in people with type 2 diabetes [82, 83]. The SGLT-2 inhibitor manufacturers in Germany informed physicians and pharmacists about this issue on July 9, 2015.

An extensive analysis of all reports on ketoacidosis with a possible association of SGLT-2 inhibitors with ketacidosis listed in the US Food and Drug Administration Adverse Event Reporting System (FAERS) between January 2014 and October 2016 has been published [84]. A PPR of 7.9 (95 % CI 7.5–8.4) was found. The proportional reporting ratio (PRR) is the ratio of spontaneous reports for a given drug (in this case SGLT-2 inhibitors) associated with a specific side effect (here, ketoacidosis) divided by the corresponding ratio for all or some other drugs with this side effect. However, PPR does not describe a relative risk, i. e. the real risk for ketoacidosis, and therefore cannot be used in clinical practice. The detailed analysis of 2397 reports of ketoacidosis in FAERS showed a dominance in people with type 1 diabetes, in women, in a wide age and body weight range and a high variability in the duration of SGLT-2 inhibitor therapy. 37 people (1.54 %) died of ketoacidosis. In the large randomized controlled trials with SGLT-2 inhibitors, the risk of ketoacidosis among SGLT-2 inhibitors was significantly increased in type 2 diabetes, but below 1 %.

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 DDG recommends, as does the ADA, that the following be considered when dealing with SGLT-2 inhibitors:

- SGLT-2 inhibitors must be discontinued 24 h prior to a major elective surgery,
- Immediate interruption of SGLT-2 inhibitor therapy in emergency cases and acute diseases,
- Caution during ongoing insulin therapy (avoid significant reduction or discontinuation of insulin therapy),
- Avoidance of ketogenic/extremely low carbohydrate foods and excessive alcohol consumption,
- The combination of SGLT-2 inhibitors with metformin increases the risk of ketoacidosis [85] and
- If symptoms are present, consider the possibility of ketoacidosis and initiate the appropriate diagnostic procedure (at least plasma glucose and ketones in the urine, possibly also necessary blood gas analysis).

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 [86]). 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).

Further analyses of the EMPA-REG OUTCOME study [87] 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 [88], irrespective of the level of initial albuminuria.

Thus, the positive effect of the SGLT-2 inhibitor empagliflozin on cardiovascular and renal endpoints in a corresponding risk population has been convincingly demonstrated. The underlying mechanisms of cardiac and renal production of empagliflozin are the subject of extensive studies [89, 90].

In 2016, the G-BA certified empagliflozin in the benefit assessment in combination therapy with metformin a considerable additional benefit in patients with type 2 diabetes with manifested cardiovascular disease (https://www.g-ba.de/downloads/39-2612694/2016-09-01_AM-RL-XII_Empagliflozin_D-214_BAnz.pdf). Accordingly, this additional benefit was included in the relaunches of the disease management programme for type 2 diabetes in April 2017 [91].

Current outcome RCT data on canagliflozin [92] (CANVAS programme) show the same tendency, namely a significant reduction in the composite endpoint (cardiovascular death, non-fatal myocardial infarction, and stroke) by 14% (HR 0.86; 95 %-KI 0.75–0.97) compared to placebo, decrease of the hospitalization rate due to heart failure by 33 % (HR 0.67; 95 % CI 0.52–0.87) and renal outcome data with a reduction of the progression of albuminuria by 27 % (HR 0.73; 95 % CI 0.67–0.79) and the composite endpoint (40 % reduction of eGFR, renal replacement therapy, renal death) by 40 % (HR 0.60; 95 % CI 0.47–0.77). Another large RCT was performed with canagliflozin in relation to a primary combined renal endpoint [93]. The patients already had renal insufficiency, a significant proteinuria at randomisation and had to be treated with an ACE-inhibitor or AT_1-antagonist. Canagliflozin (100 mg per day) significantly reduce clinically relevant endpoints compared to the control group.

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

The DECLARE-TIMI 58 study with dapagliflozin [94] 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 [95] and cardiovascular endpoints [96, 97].

The European Medicines Agency (EMA) has launched a review process to investigate whether treatment with canagliflozin leads to an increased rate of amputations (usually toes):

On July 8, 2016, the Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA extended the review to dapagliflozin and empagliflozin [98].

The canagliflozin studies CANVAS programme [92] confirms the assumption of a higher risk of amputations (mainly in the toe and metatarsal area) with canagliflozin compared to 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). The data on SGLT- inhibitors with respect to an increased rate of amputations in RCTs, higher amputation rates are also found in pharmacovigilance reports [99]. However, current studies and research did not find higher amputation rates under dapagliflozin [100] and empagliflozin [101], and the large CREDENCE study with canagliflozin also found no sign of an increased amputation rate.

The FDA has also issued a warning of an increased fracture risk due to reduced bone density under canagliflozin (www.fda.gov/Drugs/DrugSafety/ucm461 449.htm). Indeed, the fracture event rate was significantly higher under canagliflozin compared to placebo: 15.4 vs. 11.9 per 1000 patient years (p = 0.02) [92]. In the recently published large RCT (CREDENCE study) with canagliflozin, however, no sign of an increased risk for fractures was found [93]. The careful elaboration of the CANVAS and CANVAS-R data showed a significant heterogeneity of the 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 proven in the CANVAS-R study (n = 5812: HR 0.86; 95 % CI 0.62–1.19) [102].

A recent fracture analysis of people with type 2 diabetes (n ≥ 12 000) treated with empagliflozin (pooled data from placebo-controlled studies and a head-to-head study vs. glimepiride) did not reveal a significantly increased rate of fractures [103]. Two meta-analyses also showed no significant increase in fracture rates under therapy with SGLT-2 inhibitors, although the time of oberservation and follow-up were relatively short and the incidence rates for fractures were very low [104, 105].

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 empagliflozin therapy were described. On January 21, 2019, 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")". Patients should be informed about this rare complication and adverse drug reactions should be reported (www.bfarm.de – Arzneimittel-Pharmakovigilanz– Risiken).

GLP-1 receptor agonists

GLP-1-RAs are antidiabetic drugs for the subcutaneous therapy of type 2 diabetes. Soon also an oral GLP-1 RA becomes available.

They can lower plasma glucose more on average than oral antidiabetics and also have blood pressure-lowering (slight), weight-reducing [106] 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 hypoglycemic risk.

For the GLP-1 receptor agonist (RA) liraglutide, the RCT (LEADER study) showed positive effects on clinically relevant endpoints [107]. The follow-up of 9340 patients averaged 3.8 years. The combined primary endpoint (first event for cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) was significantly lower for liraglutide compared to 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 of cardiovascular reasons (4.7 vs. 6.0 %; HR 0.78; 95 % CI 0.66–0.93; p = 0.007). All-cause mortality under liraglutide was also lower (8.2 vs. 9.6 %; HR 0.85; 95 % CI 0.74–0.97; p = 0.02). For the first time, this made it possible to demonstrate a positive effect on patient-relevant endpoints with a GLP-1-RA in an RCT.

A sub-analysis of the LEADER study population showed that 72.5 % of patients had a vascular disease at the beginning of the study. 23 % of this subpopulation had polyvascular disease and 77 % had monovascular disease. In a 54-month follow-up, liraglutide led to a reduction of MACE: in patients with polyvascular disease (HR 0.82; 95 % CI 0.66–1.02) and monovascular disease (HR 0.82; 95 % CI 0.71–0.95) compared to placebo. No positive effects of liraglutide were found in patients without vascular complications [108]. The same was found in an analysis by Marso et al. [109], which demonstrated a reduction of myocardial infarctions in patients with a high vascular risk using liraglutide.

The analysis of secondary renal endpoints in the LEADER study showed that 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 to placebo [110].

In its decision of January 17, 2019 (BAnz AT 22.03.2019 B5), the G-BA recognised an additional benefit of liraglutide and included it in the structured treatment programmes for type 2 diabetes.

The current meta-analysis by Kristensen et al. [111] found a significant reduction of MACE of 12 % (HR 0.88; 95 % CI 0.82–0.94; p < 0.0001) using GLP-1-RAs. Hazard ratios were 0.88 (95 % CI 0.81–0.96; p = 0.003) for cardiovascular death and 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 led to a 12 % reduction in all-cause mortality (HR 0.88; 95 % CI 0.83–0.95; p = 0.001) and a 9 % reduction in hospitalization for heart failure (HR 0.91; 95 % CI 0.83–0.99; p = 0.028). The composite renal endpoint (development of a new macroalbuminuria, reduction of eGFR, progression to terminal renal failure) decreased by 17 % (HR 0.83; 95 % CI 0.78–0.89; p < 0.0001), which was mainly due to the reduction of albuminuria.

GLP-1-RA was not reported to increase the risk of hypoglycaemia, pancreatitis or pancreatic cancer.

The very detailed and critical meta-analysis by Liu et al. [112] also came to a comparable result. All-cause mortality was slightly lower among GLP-1-RAs compared to control therapies: OR 0.89 (95 % CI 0.80–0.98).

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 [113]. Included were 9901 patients with type 2 diabetes (mean age 66 years, average HbA1c 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 hypoglycemic rate.

In an explorative analysis of the REWIND data [114] 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).

Safety and cardiorenal outcome data have been published for albiglutide [115, 116]. The cardiovascular endpoint data on albiglutide (HARMONY outcomes trial [117]) were analysed and published in 2018. At that time albiglutide had already been taken off the market worldwide (July 2017). In the HARMONY study, 9463 patients were included and randomized (albiglutide 30-50 mg, n = 4731; placebo n = 4732). The mean observation period was only 1.6 years. There was no evidence for a difference in the two study

arms with regard to important side effects.In 3P-MACE, a significant risk reduction using albiglutide (HR 0.78; 95 % CI 0.68–0.90; non-inferiority p = 0.0001, superiority p = 0.0006) was already observed after this short study period.

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 [118].

In the recently published meta-analysis by Bethel et al. [119], the 4 large RCTs ELIXA (lixisenatide), LEADER (liraglutide), EXSCEL (exenatide once a week) and SUSTAIN 6 (semaglutide) were evaluated. Compared to placebo, GLP-1 RAs showed a significant risk reduction (HR 0.90; 95 % CI 0.82–0.99; p = 0.033) for the primary endpoint (cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke), a relative risk reduction (RRR) of 13 % for cardiovascular mortality (0.87; 95 % CI 0.79–0.96; p = 0.007), and an RRR of 12 % (0.88; 95 % CI 0.81–0.95; p = 0.002) for all-cause mortality. However, the statistical heterogeneity between the studies was large. There were no significant reductions by GLP-1-RAs for non-fatal or fatal myocardial infarction, stroke, hospitalization due to unstable angina or heart failure. Semaglutide s.c. is now also available in Germany. The SUSTAIN-6 study demonstrated cardiovascular benefit by significantly reducing the primary endpoint 3P-MACE compared to the control group. In patients with high cardiovascular risk, a significant reduction (HR 0.74; 95 % CI 0.58–0.95) was found in the semaglutide group compared to placebo for the primary endpoint (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) [120].

In the recently published post-hoc analysis of the SUSTAIN-6 study, a risk reduction of MACE was found for semaglutide once a week s.c. versus placebo in all study participants regardless of gender, age or cardiovascular risk profile at the start of the study [121]. In the PIONEER-6 study, there was a significant reduction in cardiovascular death (HR 0.49; 95 % CI 0.27–0.92) and all-cause mortality (HR 0.51; 95 % CI 0.31– 0.84) with oral semaglutide versus placebo [122]. In a recent meta-analysis, treatment with GLP-1-RAs or SGLT-2 inhibitors was associated with significantly lower all-cause mortality compared to DPP-4 inhibitors or other antidiabetics or no therapy (HR 0.88; 95 % CI 0.81–0.94 or HR 0.80; 95 % CI 0.71–0.89).

Similar data were found for cardiovascular mortality, myocardial infarction and heart failure in comparison to the control groups [123].

The meta-analysis of GLP-1-RAs exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide and semaglutide published in 2017 showed a significant reduction in the incidence of nephropathy compared to other antidiabetics (OR 0.74; 95 % CI 0.60–0.92; p = 0.005). 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) [124]. Whether this is related to the rapid optimisation of the metabolism is being discussed [125]. In addition, only patients with pre-existing retinopathy were affected. A corresponding study was initiated to clarify the retinopathy risk when using semaglutide (ClinicalTrials.gov number, NCT03 811 561).

GLP-1 receptor agonists: pancreatitis, pancreatic carcinoma and cholecystolithiasis

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 with incretin-based therapies (SAVOR-TIMI 53 (saxagliptin), EXAMINE (alogliptin), TECOS (sitagiptin), which also took place in 2017, 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 [127].

In the meta-analysis published in 2018 by Bethel et al. [119], 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 up to 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 [129].

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 [130]. 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 these practical recommendations. Therefore, the authors have concentrated on a few aspects of new insulin preparations.

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 [131]). 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 [132].

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 [133–135].

Biosimilar insulin glargin 100: Pharmacokinetics and -dynamics are comparable for insulin glargin 100 and biosimilar insulin glargin 100 in humans without and with type 2 diabetes [136, 137]. In the meta-analysis by Yamada et al. [138] 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 [139].

Combination of long-acting insulin plus GLP-1-RA: The fixed combination of long-acting insulin plus GLP-1-RA (currently not available in Germany) 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, gastrointestinal side effects were more frequent with GLP-1-RA [140–142].

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, hypoglycemic rate and satisfaction with therapy. At the same time, 20 % insulin could be saved [143].

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 [144]. 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) [145].

Arguments for therapy stage 1

The basic therapy comprises all lifestyle-modifying, non-pharmacological measures. These include patient training and education, nutrition therapy, increasing physical activity and cessation of smoking (National Treatment Guideline (Nationale Versorgungsleitlinie NVL)) type 2 diabetes mellitus), as well as stress management strategies. One important goal is to strengthen the willpower to lead a healthy lifestyle (giving up smoking, a diet appropriate to diabetes, exercise, reducing alcohol consumption) (▶ **Figs. 3,4**). Digital aids and telemedical support are becoming increasingly important for the implementation of personalised basic therapy. As many people with type 2 diabetes have a variety of other vascular risk factors in addition to chronic hyperglycaemia, the treatment of these people is complex and should consider all vascular risk factors individually. In order to emphasize this more clearly, the previous therapy algorithm was extended to address essential cardiovascular risks in more detail (see also the separate section on lipid metabolism disorders in these practical recommendations). Arterial hypertension is also an important cardiovascular and renal risk factor. Detailed information on the treatment of hypertension was provided in the National Treatment Guideline (Nationale Versorgungsleitlinie NVL) on renal disease in diabetes in adulthood [22].

Arguments for therapy stage 2

The basic therapy plays an important role in every further step of the therapy. If people with diabetes are not able to implement these lifestyle modification measures in full or in part, even in the foreseeable future within a maximum of three months, pharmacotherapy is indicated to achieve the individual therapeutic goal. When ever possible metformin is first choice, which should be started and increased slowly by increments of 500 mg (e. g. starting with 500 mg at the main meal and increasing by 500 mg per week up to a total dose of 2 × 1000 mg per day).

In the case of contraindications (eGFR!) or poor tolerance of Metformin (mainly dose-dependent gastrointestinal complaints), other options for monotherapy are available, the use of which should be based on patient-relevant benefit (influence on body weight, hypoglycaemia risk, metabolic effects, side effect profile and clinical endpoints). Patient preferences should also be taken into account.

In people with type 2 diabetes with HbA1c values clearly outside the individual target range (e. g. > 1.5 % above the target range) at diagnosis, initial pharmacotherapy is justified, potentially also using combination therapy. After HbA1c target value is achieved, the therapy should be adjusted at individually set intervals.

Arguments for therapy stage 3

A dual combination is necessary for many patients for metabolic reasons and is more favourable with regard to side effects of individual substances, since doses can sometimes be lower when dosed in combination with other substances.

In patients with pre-existing cardiovascular or renal diseases or with a very high cardiovascular risk, substances should mostly be used in combination with metformin (eGFR > 30 ml/min!) primar-

ily to reduce evidence-based cardiovascular and renal diseases and mortality (SGLT-2 inhibitors, GLP-1 receptor agonists).

Early combination therapy should be aimed for keeping metabolic parameters close to the agreed target range [149]. A review of the target values should take place at approximately 3-month intervals. A large number of publications providing good evidence are now available for the selection of combinations. Patient preferences, individual therapeutic goals, simplicity of treatment, existing cardiovascular diseases, possible contraindications and the considerations mentioned in stage 2 also play an important role. If the number of oral drugs becomes too high due to the complexity of the therapy, the vascular risk factors or comorbidities (e. g. COPD, depression, chronic pain, etc.), fixed combinations should be used wherever possible. Parenteral blood glucose-lowering principles can also be useful and helpful for these patients and significantly increase therapy adherence. The higher the HbA1c, the more likely the use of insulin, but this does not mean that the initial insulin therapy must be continued after metabolic recompensation.

The administration of more than 2 oral antidiabetic drugs may be valuable in some cases if the therapy with a GLP-1-RA or insulin is not yet indicated (▶ **Fig. 4**), if the patient is not yet ready for an injection therapy or if this therapy needs to be postponed for another reason.

A triple oral therapy as a combination of metformin, a DPP-4 inhibitor and an SGLT-2 inhibitor is a safe, effective and simple therapy. A potentiation of side effects was not observed under oral triple combination; they essentially corresponded to those that were observed with monotherapy for the respective substance.

A detailed medication plan and its analysis is very helpful.

If a therapy shows no effectiveness, the patient must always be consulted about therapy adherence before increasing the dosage or otherwise changing the treatment.

Arguments for therapy stage 4

Due to a lower risk for hypoglycemia and a more favorable body weight (in comparison with an intensified insulin treatment) in most patients it is recommended to start with a long-acting insulin mostly in combination with an OAD (socalled basal insulin supported oral therapy (BOT). A good alternative is to support an OAD therapy with a GLP-1-RA therapy.

Insulin dose reduction should be considered when kidney function deteriorates in order to avoid severe hypoglycaemia.

A combination of GLP-1-RA with oral antidiabetic drugs (except DPP-4 inhibitors) is an effective treatment if the individual therapeutic goal has not been achieved with the existing oral antidiabetic drugs in mono- or combination therapy or if side effects make a new therapeutic strategy necessary. In principle, the use of GLP-1-RA should be considered before starting insulin therapy, especially due to the very low hypoglycaemia risk of the substance class and the advantageous cardiovascular and renal outcome data of some of these substances (which should then be preferred).

Combining a GLP-1-RA with a basal insulin results in a significant delay in the intensification of antidiabetic therapy (e. g. escalation of the basal insulin dose or additional administration of prandial insulin), in significantly better metabolic control without a significant increase in the risk of hypoglycaemia and in favourable weight effects [150–154].

Only when these combination therapies are no longer sufficiently effective or indicated, the next step is to further intensify insulin therapy with prandial insulin.

Flexibility in therapy decisions based on the heterogeneity of type 2 diabetes and individual therapy goals is necessary at every stage of treatment. In most cases, it takes time, empathy and comprehension to convince the patient to accept injection treatment and a detailed patient training is necessary. In individual cases, CSII is indicated if the therapeutic goal is not achieved adequately using ICT.

Therapy of dyslipidaemia

Here we refer to:

- ESC/EAS Guidelines for the Management of Dyslipidemia [155]
- DDG position paper on lipid therapy in patients with diabetes [156]
- Position paper on lipid therapy in patients with diabetes mellitus in these practical recommendations [Diabetologie und Stoffwechsel 2019; 14 (Suppl 2): S226–S231]

Therapy of arterial hypertension

Here we refer to:

- 2018-ESC/ESH Guidelines for the Management of Arterial Hypertension [9]
- NVL kidney disease in adult diabetes [22]

German Diabetes Association: Clinical Practice Guidelines

This is a translation of the DDG clinical practice guideline published in Diabetologie 2019; 14 (Suppl 2): S111–S118.

Conflict of Interest

R. Landgraf is the lead author and declares the following potential conflicts of interest: Advisory Boards: Lilly Deutschland, Novo Nordisk Pharma; has received lecture fees from: AstraZeneca, Berlin Chemie, Lilly Deutschland, Novo Nordisk Pharma. Other activities: Representative of the Executive Board of the German Diabetes Foundation, Steering committee for the development and updating of the National Treatment Guidelines/Nationalen Versorgungsleitlinien Diabetes.

J. Aberle is a member of advisory boards and has received lecture fees from: Astra Zeneca, Berlin-Chemie, Boehringer-Ingelheim, Eli Lilly & Co, Novo Nordisk, Roche Diabetes Care. Institutional research funding: Astra Zeneca.

A. L. Birkenfeld is member of Advisory Boards and has received lecture fees from: Amgen, Astra Zeneca, Boehringer-Ingelheim, Eli Lilly & Co, Merck Sharp & Dohme, Novo Nordisk, Sanofi. Institutional research funding: Boehringer Ingelheim.

B. Gallwitz declares the following potential conflicts of interest over the last 3 years: Advisory Boards/Consultancy: Amgen, AstraZeneca, Bayer Vital, Boehringer Ingelheim, Eli Lilly & Co., Merck Sharp & Dohme, Mylan, Novo Nordisk; Lecturing activities: Amgen, AstraZeneca, Bristol Myers Squibb, Boehringer-Ingelheim, Eli Lilly & Co., Merck Sharp & Dohme, Novartis, Novo Nordisk, Sanofi; Company shares: none.

M. Kellerer is a co-author and declares the following potential conflicts of interest: Research support: GlaxoSmithKline, AstraZeneca; Consultancy: Abbott, AstraZeneca, Boehringer Ingelheim, Lilly, MSD, Novo

Nordisk; Lecturing activities: AstraZeneca, Boehringer Ingelheim, Lilly, MSD, Novo Nordisk, Novartis, Janssen-Cilag, Sanofi.

H. Klein declares the following potential conflicts of interest: Advisory Board: AstraZeneca, Janssen Cilag, Boehringer Ingelheim; Lecture fees: Berlin-Chemie.

D. Müller-Wieland declares the following potential conflicts of interest: Member of the Advisory Board and lecture fees in the last 3 years from the following companies: Amgen, MSD, AstraZeneca, Novartis, Boehringer Ingelheim, Lilly, Novo Nordisk, Roche Diabetes Care, Sanofi.

M. A. Nauck declares the following potential conflicts of interest: Member of the Advisory Board: Berlin Chemie, Boehringer Ingelheim, Fractyl, Eli Lilly & Co., GlaxoSmithKline, MSD, Novo Nordisk, Intarcia Therapeutics; Consultancy fees: AstraZeneca, Berlin Chemie, Boehringer Ingelheim, Eli Lilly & Co., GlaxoSmithKline, Intarcia Therapeutics, MSD, Novo Nordisk; Fees: AstraZeneca, Berlin Chemie, Boehringer Ingelheim, Eli Lilly & Co., Medscape, MSD, Novo Nordisk, Research Support: AstraZeneca, Eli Lilly & Co., GSK, MSD, Novo Nordisk, Novartis.

H.-M. Reuter declares that he has served on Advisory Boards for Lilly Germany, Berlin-Chemie, MSD, Novo Nordisk, BMS and AstraZeneca over the past 3 years and has received lecture fees from Lilly, MSD, Berlin-Chemie, BMS, Amgen, Bayer, Boehringer Ingelheim, Sanofi and AstraZeneca.

E. Siegel declares that he had no economic or personal conflicts of interest concerning this manuscript.

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