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Summary: Swiss Recommendations of the Society for Endocrinology and Diabetes (SGED/SSED) for the Treatment of Type 2 Diabetes Mellitus (2023)

Working group of the SGED/SSED
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Introduction

With the announcement of the Federal Drug Administration (FDA) in the USA that each new antidiabetic drug has to prove its cardiovascular safety in a cardiovascular outcome trial in the year 2008 **a revolution in diabetes treatment** took place. The initial trials with DPP-4 inhibitors proved their cardiovascular safety, but no additional short-term benefits were seen in these trials [1-4].

The year 2015 was the beginning of a success story of all SGLT-2 inhibitors (SGLT-2i) and GLP-1 Receptor Agonists (GLP-1RA). What was newly discovered by these trials was the benefit of all SGLT-2i for a reduction in hospitalisation due to heart failure (both reduced and preserved ejection fraction) [5] and the reduction of stroke in all GLP-1 RA trials [6]. All these trials [7-15] resulted in the updated SGED/SSED recommendations as illustrated in figure 1.

Step by step algorithm

Figure 1 summarizes the new Swiss recommendations for the treatment of Type 2 diabetes mellitus. As a first step we emphasize lifestyle changes and a multifactorial treatment as detailed in the next chapter. The initial medical treatment should always be a combination treatment with metformin and a SGLT-2i or metformin and a GLP-1 RA. Metformin is maintained as a first line treatment, because all cardiovascular outcome trials were performed on the base of metformin treatment, and because no other antidiabetic drug has an explicit effect of reducing the hepatic glucose production. Therefore, this initial combination treatment is like the guidelines in hypertension, where the initial treatment should be the inhibition of the Renin-Angiotensin-Aldosteron-System (RAAS) with an ACE-inhibitor or a sartan and a secondary drug in a lower dosage is added. In persons with type 2 diabetes, if the initial double combination is not sufficient, a triple combination (SGLT-2 inhibitor, GLP-1 RA, and metformin) is recommended. This triple combination has not been officially tested in the above mentioned cardiovascular outcome trials but there is more and more real world experience in Europe and in the USA [16, 17] that prove that the triple combination with metformin, SGLT-2 inhibitor and GLP-1 RA is the best treatment to reduce 3-Point MACE, total mortality and heart failure as compared to other combinations. If the triple combination is not sufficient to reduce the HbA1c to the desired target, insulin treatment is necessary. It is important to keep in mind that a quarter of all patients with type 2 diabetes (sometimes misdiagnosed) requires insulin treatment. If insulin deficiency is the predominant factor at the outset of T2D the order of medications has to be reversed (figure 1: arrows in blue). Insulin first and then cardio-renal protective medications (SGLT-2 inhibitors, GLP-1 RA, and metformin (figure 1).

Lifestyle changes, prevention of diabetes, and multifactorial treatment in T2D

Lifestyle intervention is recommended as the first-line treatment of pre-diabetes and diabetes at all ages. Healthy nutrition, weight control and physical activity are essential. Ideally, they should be carried out concomitantly (figure 3). With these measures and with GLP-1RA and SGLT-2i diabetes prevention can be achieved [18-22].

The main targets are to improve:

- Glucose control, blood pressure and cholesterol levels based on individual targets
- Achieve and maintain body weight goals
- Delay or prevent diabetes complications (micro- and macrovascular disease)

Multifactorial treatment

The Steno-2 trial [23] has well demonstrated the role of a multifactorial treatment

in the care of type 2 diabetes mellitus, including hyperglycemia management, blood pressure control, lowering LDL-cholesterol, and stop smoking.

For the control of high LDL-cholesterol a high potency statin (rosuvastatin, atorvastatin) is the first choice and if targets cannot be achieved ezetimibe is added, and if still not at target PCSK-9 inhibitors might be given [24], depending on the respective limitations in a specific country.

The target for blood pressure is also individualized [24] and should be between 120-130/70-80 mm Hg, whereas in a person above the age of 65 years the recommended systolic blood pressure is between 130-139 mm Hg. The choice of drugs is usually an early combination of ACE-inhibitor and calcium antagonist if the ACE-inhibitor is not tolerated an ARB (angiotensin II receptor blocker or sartan) can be given [24]. The platelet aggregation inhibition by aspirin or by other drugs is accepted in patients with established cardiovascular disease, but it is generally not recommended in primary prevention [24].

Adherence and SGED/SSED Score

Considering that non-adherence to diabetes medical standards (< 2 x HbA1c, Lipid profile at target, nephropathy status and ophthalmologist visit per year) in diabetes care is associated with an increased probability of future hospitalization among patients with diabetes [25, 26] (Table 2). The suggested target is ≥70 out of 100 points among all patients with T2D in a practice [26].

Chronic kidney disease (CKD) and decreasing glomerular filtration rate

In patients with CKD (impaired GFR and/or albuminuria) antidiabetic treatment should include SGLT-2i independent of glucose control because SGLT-2i have shown particularly beneficial cardiorenal effects in patients with and even without diabetes [27]. SGLT-2i reduce not only renal and cardiovascular endpoints but also mortality in patients with CKD [27]. Although the glucose-lowering efficacy of SGLT-2i is reduced or even absent when GFR is markedly decreased, the nephroprotective effects remain preserved and, therefore, we recommend continuing SGLT-2i, even if the GFR falls below 30 ml/min. GLP-1 RA also do have nephroprotective effects although not to the same extent as SGLT-2i. GLP-1 RA (in patients with BMI >28 kg/m^2) can be used without dose adjustment even in patients with severely decreased GFR or dialysis. DPP-4i do not have short-term nephroprotective effects [1-4], but can be used as an alternative to GLP-1 RA (e.g. in patients with BMI <28 kg/m^2 or intolerance of GLP-1RA). DPP-4i are safe to use in patients with decreased GFR, but dose needs adjustment to kidney function (except linagliptin). Sulfonylureas including gliclazide should not be used in patients with eGFR <30 ml/min because of the increased risk of hypoglycemia. In patients treated with insulin, insulin requirement is reduced, and risk of hypoglycemia is increased, when kidney function declines. Therefore, insulin regimens and insulin preparations with the lowest risk for hypoglycemia are preferred in patients with a decreased GFR. A non-steroidal mineralocorticoid receptor antagonist, finerenone, has shown to decrease the decline in chronic kidney disease in patients with type 2 diabetes mellitus by 22% and reduced the combined cardiovascular outcome by 14% [28-30].

Heart failure and diabetes (HFrEF and HFpEF)

Heart failure (HF) is a common complication of diabetes (figure 2), with a prevalence of up to 30% in individuals with diabetes above the age of 65 years, even in patients without other cardiovascular risk factors [31, 32]. Typical symptoms of HF are breathlessness, orthopnea, reduced exercise tolerance, fatigue, tiredness and ankle swelling. If clinical suspicion exists and EKG abnormalities are present, the

measurement of the following markers are recommended: natriuretic peptides (B-type natriuretic peptide [BNP] or N-terminal pro-BNP [NT-proBNP]) on at least a yearly basis [33]. If NT-proBNP is > 125 pg/ml or BNP > 35 pg/ml, a transthoracic echocardiography will result in the diagnosis of HF. It is, however, not recommended as routine screening for all patients with diabetes [34]. SGLT-2i are beneficial for prevention or treatment of all forms of HF (HFpEF, HFmEF, HFrEF) with and without diabetes mellitus [5, 35-38]. A meta-analysis with GLP-1 RA suggests that this group does not only decrease stroke, 3-Point MACE, and mortality, but also significantly improve the HF outcome [39].
Taken all cardiovascular outcome trials together, SGLT2i are clinically proven to be an effective treatment for HF, independently of the HbA1c value and if diabetes is present or not. Therefore, they should be introduced as soon as possible for treatment or prevention of HF. If additional glycemic control is needed, use of GLP-1 RA, metformin is recommended. Insulin should be added, if a triple treatment of SGLT-2i, GLP-1 RA and metformin is not sufficient to reach individual glycemic targets.

Weight management in Type 2 Diabetes and Obesity

60-90% of all people with T2D are obese [40]. Besides prevention of micro- and macrovascular complications, a main target of diabetes treatment is, therefore, to reduce the weight [41]. Therefore, losing weight and keep an active lifestyle with physical activity and resistance training is of utmost importance. With a BMI of >28kg/m² the use of GLP-1 receptor agonists in the therapy of T2D is reimbursed by health insurance in combination with metformin or as monotherapy in the case of metformin intolerance. It has to be mentioned, however, that this group of medication reduce glucose even if the BMI is below 28, but in Switzerland it will not be reimbursed by health insurance.

Potency of GLP-1 RA and GLP-1/GIP RA

The potency of GLP-1 RA and GLP-1/GIP RA varies between different GLP-1 RA and dosages with regard to weight loss. GLP-1 RA with a high potency are semaglutide or in higher dosages liraglutide and dulaglutide. So far, the best results with weight loss have been achieved with 2.4 mg semaglutide and the new GLP-1/GIP RA tirzepatide (close to market introduction in Switzerland). However, the cardiovascular outcome trials of these treatments are still ongoing [20, 21, 41, 42]. GLP-1 receptor agonists in lower dosages with proven evidence for reducing cardiovascular outcomes (semaglutide, liraglutide, or dulaglutide) are, therefore, at present, the preferred treatment option in the vast majority of T2D cases.
In contrast to SGLT-2 inhibitors, GLP-1 receptor agonists lead to a more substantial weight loss and should therefore be given priority over SGLT-2 inhibitors in obese patients with T2D [7-15]. The main limitation of GLP-1 receptor agonists is their side effects, such as nausea and vomiting. These side effects occur mainly in the first days to weeks of therapy. Conscious nutrition and the avoidance of large portions can sometimes positively influence the symptoms of nausea. Although GLP-1 receptor agonists can also be used in higher-grade renal failure, increased nausea is sometimes a limitation of use, particularly in end-stage renal failure. SGLT-2 inhibitors also have a weight-reducing effect, but to a lesser extent. The extended indication of SGLT-2 inhibitors in heart failure and nephroprotection also allows the combination of these drugs in different indications in patients with and without T2D [27, 37, 38].

Non-Alcoholic Fatty Liver Disease and Steatohepatitis (NAFLD, NASH)

NAFLD is the most common liver disease world-wide [43]. In diabetes the prevalence is even higher 50-70%, and of NASH 30-40% [44].The management of T2D in people with NAFLD/NASH should include lifestyle modification with a goal of weight loss,

including strong consideration of medical and/or surgical approaches to weight loss in those at higher risk of hepatic fibrosis. GLP-1 RA have evidence of a benefit. SGLT2i have been shown to reduce elevated levels of liver enzymes and hepatic fat content in people with NAFLD, at this time there is less evidence for SGLT-2i as treatment for NASH. NAFLD, and NASH, is also associated with an increased risk of cardiovascular complications (figure 3) [41].
In addition to drug therapy, bariatric surgery should be evaluated and is considered to be therapeutically effective in difficult-to-control T2D with HbA1c >8% and a BMI of >30kg/m². However, the gap with regard to weight loss between bariatric surgery and high dose semaglutide or tirzepatide is shrinking [20, 21, 41, 42].

Differential Diagnosis of Different Diabetes Subtypes and Insulin Deficiency

In specific circumstances, insulin may be the preferred agent for glucose lowering, specifically in the setting of severe hyperglycemia (HbA1c >10%]), particularly when associated with the typical signs of insulin deficiency like weight loss or ketonuria/ketosis and with acute glycemic dysregulation (e.g., during hospitalization, surgery, or acute illness), in underweight people, or when the diagnosis of type 1 diabetes is suspected [41]. In these circumstances, giving insulin is never wrong and after euglycemia is restored, it might be possible to stop insulin treatment in certain people with type 2 diabetes.
T2D is not a uniform disease [45]. The general rule is that two pathogenetic factors are prominent such as insulin resistance and relative insulin deficiency. Either of the two can be dominant and appear before the other. Insulin resistance is generally linked to visceral obesity and physical inactivity. In the face of extreme insulin resistance, even if insulin and C-peptide are in the normal range, the insulin produced may not be sufficient to achieve a normal glucose homeostasis.
Whenever treating a patient with T2D, the physician should be aware that 25% of patients have an insulin deficiency and sometimes are wrongly diagnosed as type 2 diabetes (type 1 diabetes, monogenic form of diabetes and mitochondrial diabetes, or pancreatic diabetes (chronic pancreatitis) [45, 46]. The contribution of type 1 diabetes and specific forms of diabetes is about 5% each.

Glucose target range, HbA1c goal and how to reduce risk of hypoglycemia

The main goal of diabetes control is to maintain the HbA1c as close to normal as possible with avoidance of hypoglycemia. In most patients this level will be a HbA1c of 7.0%. In younger people with a short history of diabetes and/or patients with microvascular complications this goal should be reduced to 6.5 %, if this can be reached without significant and repetitive hypoglycemia. An HbA1c level < 6.5% is not dangerous regarding hypoglycemia or cardiovascular complications if no insulin or no sulfonylurea are used.
For older patients, patients with a history of severe hypoglycemia, patients with co-morbidities (vision trouble, osteoporosis, neurologic disease such as autonomic neuropathy) or patients with restricted life expectancy a higher HbA1c target of 7-8% is reasonable. In all instances a HbA1c level >8.0% should be avoided because the associated complications outweigh the possible benefits of a higher HbA1c.
It has been shown that hypoglycemia is associated with worse outcomes and higher mortality. As GLP-1 RA and SGLT-2 inhibitors, as previously mentioned are not associated with a risk of hypoglycemia and are efficient to reduce blood glucose, they represent the first choice of medication with concomitant metformin use.
While the use of sulfonylureas - which are associated with hypoglycemia - has dropped dramatically in the last years in favor the newer medications, they are still used in selected cases (e.g. Maturity-onset Diabetes of the Young (MODY) 1 and 3). The

highest risk exists in long-acting sulfonylureas with active metabolites (glibenclamide, glimepiride). At the present time we recommend only gliclazide as the risk of hypoglycemia with this specific molecule is very low, due to the shorter half-live and no active metabolites. We prefer a basal insulin over a sulfonylurea when the HbA1 target is not reached after GLP-1 RA, SGLT-2 inhibitor and metformin. The increased risk of hypoglycemia with the newer ultra-long-acting insulins (degludec and glargine300) is low, if used in monotherapy. The risk of hypoglycemia will increase, if an intensive therapy (basal -bolus regimen) is used. Under these circumstances, the prescription of the nasal spray of glucagon (Baqsimi®) is recommended and might help to apply glucagon much easier to a patient with severe hypoglycemia. It has been shown, that the use of a twice daily co-formulated insulin for the main meals achieves the same HbA1c as a basal-bolus regimen but with much lower hypoglycemia rates (daytime and during the night) [47]. If insulin is started the concomitant use of SGLT-2, GLP-1 RA and metformin should be continued (figure 1).

Special Considerations in the Elderly

The ADA cutoff to define older adults with diabetes has been set at 65 years [48]. Older adults with diabetes represent nearly half of all individuals with diabetes mellitus worldwide and the prevalence of diabetes above 65 years in western countries varies between 16 to 30% [48, 49]. Longer life expectancy, and lifelong exposure to cardiometabolic risk factors are the main factors explaining such increase in diabetes prevalence among elderly [50].

Older patients with diabetes have a higher risk of common geriatric syndromes, including frailty, cognitive impairment and dementia, urinary incontinence, traumatic falls and fractures, disability, side effects of polypharmacy, which have an important impact on quality of life and may interfere with anti-diabetic treatment. Malnutrition is a common symptom, even if the patient is obese. Because of all these factors, clinical management of type 2 diabetes in elderly patients currently represents a real challenge for the physician [51].

If elderly people have no appetite, medications with minimal side effects (avoid loss of appetite and hypoglycemia) and maximal benefit are preferred. SGLT-2 inhibitors for cardio-renal protection are undisputed. Particularly the prevention or treatment of all forms of heart-failure, which is becoming more frequent with advancing age and comorbidities (>25% in the age group above 65 years) and carries a high mortality rate is extremely important. In some elderly men with hypertrophy of the prostrate SGLT-2i cause some more nycturia and are, therefore, not appreciated by the patients. If there is insulin deficiency, an ultra-long acting basal insulin or a co-formulated insulin is required before the use of SGLT-2 inhibitors (figure 1). In malnourished patients, GLP-1 RA are not the preferred group, because you would like to prevent loss of appetite. The alternative would be DPP-4 inhibitors since they lower HbA1c in each category of chronic kidney disease and have no side-effects. The preferred drug is linagliptin, because it does not have to adapted to eGFR (in contrast to sitagliptin).

The glycemic target depends on the use of medications that might cause hypoglycemia (insulin and sulfonylurea). If none of these agents are used, the HbA1c should be 6.5-7.0%. If insulin or sulfonylurea are used the HbA1c target should always be <8.0%.

Limitations for the use of anti-diabetic medication and forbidden combinations

The use of different preparations from the same class of drugs (e.g. two different SGLTi or two different DPP-4i) is not reasonable and is therefore a forbidden combination.

GLP-1 RA do not need cost approval before treatment is started, but GLP-1 RA are reimbursed only in patients with BMI >28 kg/m2 at the start of the therapy. If the BMI

falls below 28 kg/m2 during therapy with GLP-1 RA, GLP-1 RA can be continued. The combination of GLP-1 RA and DPP-4i makes pharmacologically no sense and is, therefore, a useless combination. Unfortunately, the combination of GLP-1 RA and SGLT-2i is still not always reimbursed by general health insurance. For the favorable combination of GLP-1 RA and SGLT-2i, a cost approval is still required. Because of the increased risk for hypoglycemia, insulin and sulfonylureas should not be combined whenever possible.
In situations resulting in dehydration (diarrhea, fever, vomiting) or if food intake is not guaranteed (nausea, vomiting, perioperatively), some antidiabetic medications must be temporarily stopped. It is important to inform patients which medications need to be stopped in these situations (figure 4, table 3). Metformin needs to be temporarily stopped in all situations leading to relevant dehydration, acute kidney injury or hypoxemia because of the risk for lactic acidosis. SGLT-2i should be temporarily stopped in situation when intake of carbohydrates is not possible (vomiting, prolonged fasting, perioperatively, before gastric or colon endoscopy) due to the risk of ketoacidosis. Medication with risk for hypoglycemia (insulin and sulfonylureas) need to be temporarily stopped or adjusted in dose in all situations in which intake of carbohydrates is not guaranteed. Insulin therapy needs dose adjustment during acute illness but should never be stopped completely.

Cost of antidiabetic medications and cost-effectiveness-analysis

Clinical outcomes studies demonstrated effectiveness and benefits of the new drugs, especially of SGLT2iand GLP1-RA in populations with ASCVD or high risk for ASCVD, heart failure and CKD. However, it is important to assess whether these additional clinical benefits offset the relatively high cost of these drugs. As first-line agents, SGLT2-I and GLP1-RA would improve type 2 diabetes outcomes, but they are probably not cost-effective compared to metformin due to their high medication costs [52]. However, several studies showed that SGLT2i and GLP1-RA as an add-on therapy to metformin are cost-effective and maybe cost-saving compared to other antidiabetic drugs [53-58].

Concluding remarks and summary of Swiss recommendations

The view how to treat type 2 diabetes has completely changed over the last years. Cardiovascular outcome trials, however, proved that GLP-1 RA and SGLT-2 inhibitors have some direct effects on cardio-renal protection **independent of glucose control** [7-15]. This led to a change in paradigm that in persons with type 2 diabetes and a high to very high cardiovascular risk (basically all patients with type 2 diabetes) [24] the primary choice of treatment is either a SGLT-2 inhibitor or a GLP-1 RA. In order to facilitate the use of antidiabetic treatment and combinations we summarized in table 4 the current available medications with generic and trade names. The cumulative glycemic exposure is tightly linked to development of microvascular complications. Metformin is used in early combination treatment with GLP-1RA or SGLT-2i, to reduce hepatic glucose production and because it was the basic treatment to which SGLT-2 inhibitors and GLP-1 RA were added [7-15]. If this initial dual treatment regimen does not lower HbA1c to the individual desired level, then the third medication is added, either GLP-1 RA or SGLT-2 inhibitors (figure 1). As seen in figure 2 the multifactorial approach is essential to reduce all cardiovascular risk factors and permanent lifestyle changes contribute markedly to reduce all complications of diabetes mellitus. It is, however, obvious that the adherence level in general practioners to monitor these risk factors and complications is very low and has to be improved in order to reduce hospitalizations for complications [25, 26]. When taking a holistic view on how to treat diabetes mellitus, a new player entered the field. When applying these new, updated

recommendations, some caution must be applied when to apply the sick day rules and how to treat elderly people with many comorbidities. If physicians have a focus on weight management particularly in younger patients to reduce obesity early, many diseases associated with obesity, including diabetes, could be prevented [20, 21, 27]. For weight management treatments with high potency are recommended such as GLP-1 RA in higher dosages and the new dual agonists GLP-1/GIP RA. The costs of new medications are the topic of many deliberations in modern health care. Therefore, a cost-effectiveness analysis of these updated recommendations was added, because nowadays it is very important, if a treatment is cost-saving or cost-effective. In most of these analyses only the direct costs are evaluated and not the sum of direct and indirect costs, which would make almost all our current treatment recommendations cost-saving. The newest trials with SGLT-2 inhibitors that also included patients without diabetes [35-38, 59], lead to new indications to treat chronic kidney disease and heart failure without concomitant diabetes mellitus.

The fact that SGLT-2 inhibitors are indicated for people with chronic kidney disease and heart failure with and without diabetes, and that GLP-1 RA and GLP-1/GIP RA are given in obesity represent, in our opinion, **the second revolution in medical treatment.**

Declaration of possible conflicts of interests

Giacomo Gastaldi: Giacomo Gastaldi: Advisory Boards and Lectures for Abbott, Asencia, Astra Zeneca, Boehringer Ingelheim, Dexcom, Insulet, E. Lilly, Medtronic, Novo-Nordisk, OM Pharma, Roche, and Sanofi, Research conflicts: none

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Peter Wiesli: Advisory Boards and Lectures for Abbott, Amgen, Astra Zeneca, Boehringer Ingelheim, Daiichi Sankyo, E. Lilly, Novo-Nordisk, and Sanofi, Research conflicts: none

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Figures

Figure 1: Flow chart of the updated recommendations 2023 at a glance

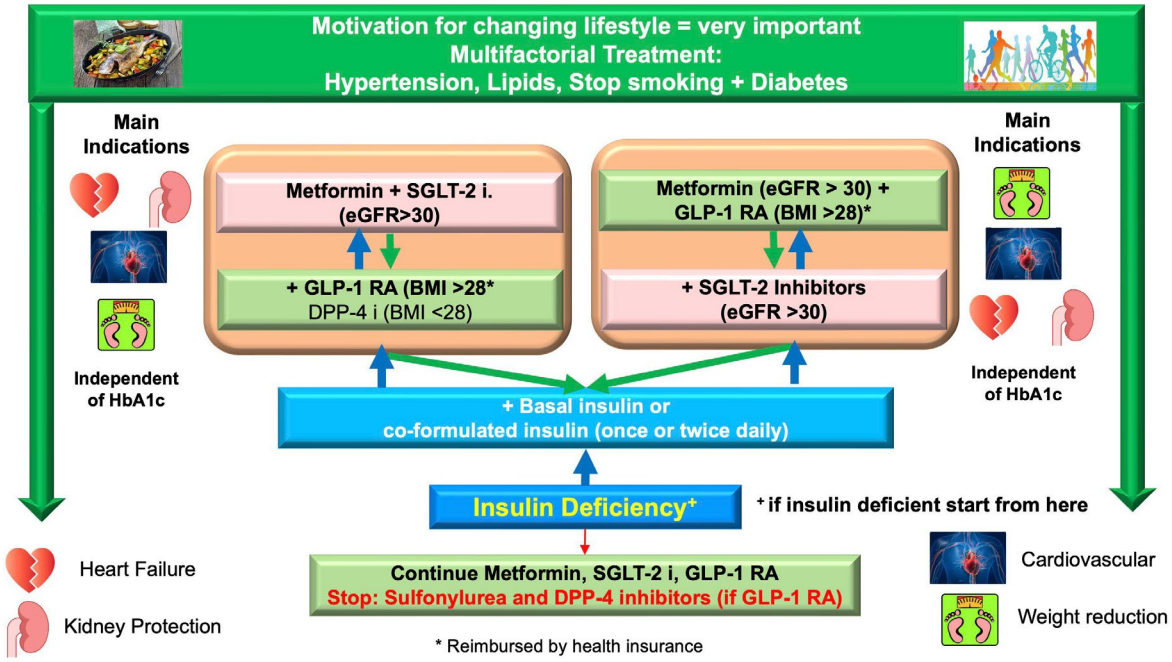


Figure 2: Important Factors in Diabetes Treatment

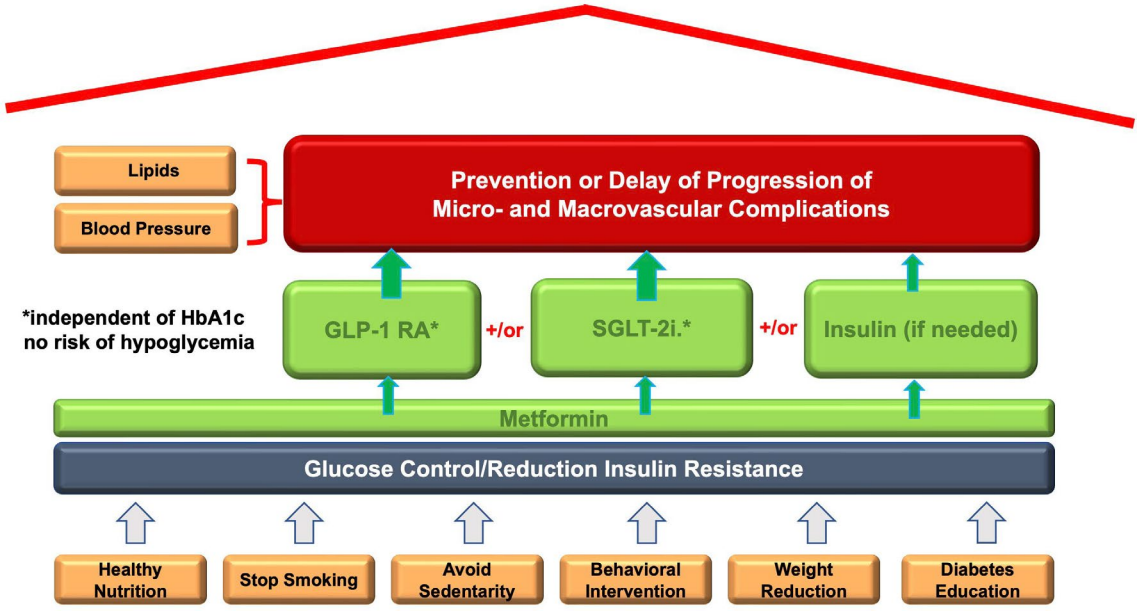


Figure 3: Comorbidities in Type 2 Diabetes mellitus

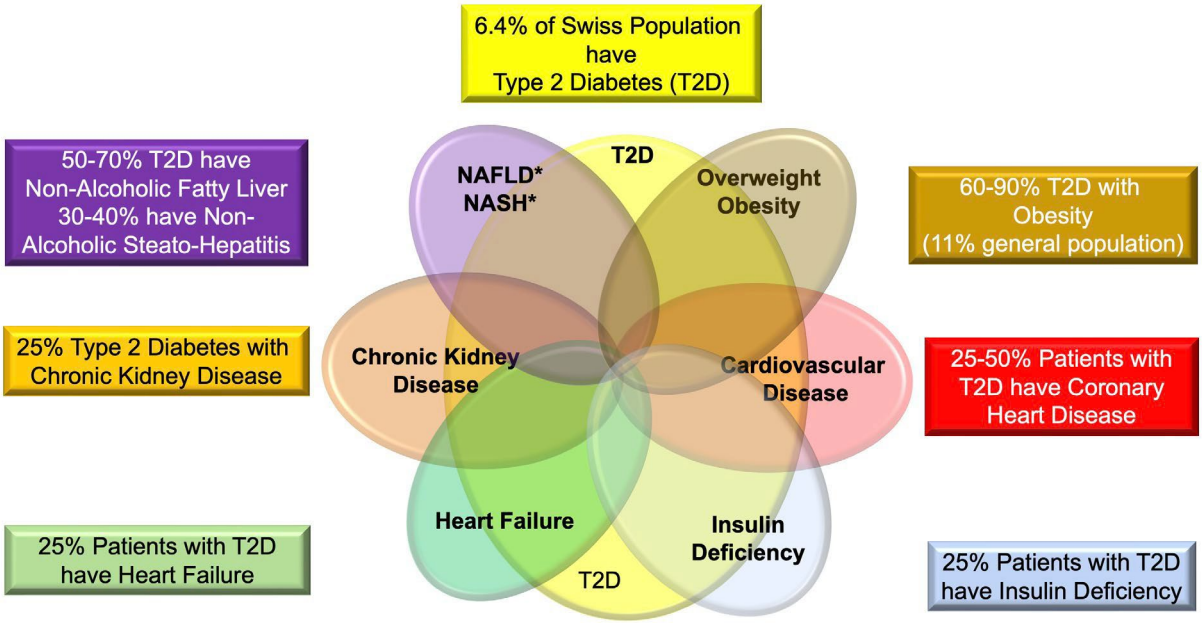
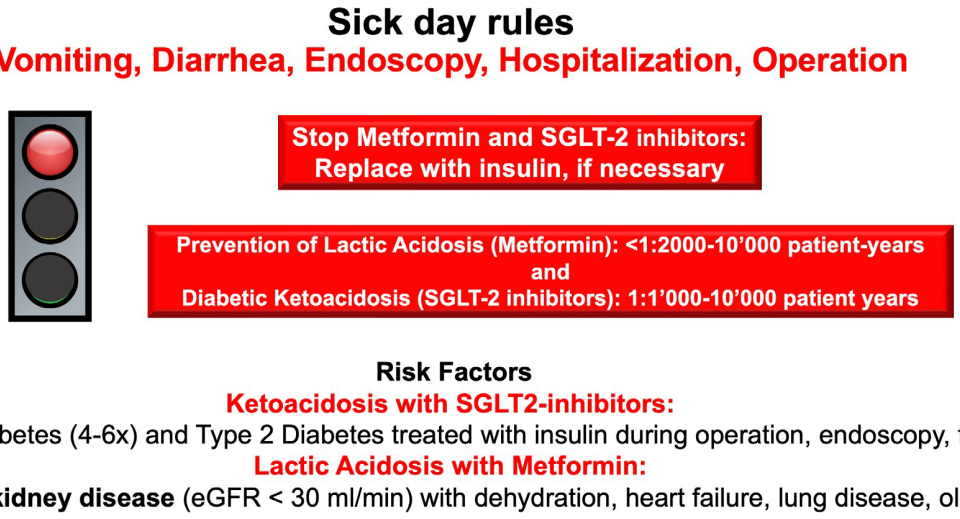


Figure 4: Sick day rules [60-62]



Tables

Table 1: Cardiovascular Risks in Diabetes (ESC 2021)[24]

Patient category	Subgroups	Risk categories	CVD risk and therapy benefit estimation
Patients with type 2 diabetes mellitus			
Patients with type 1 DM above 40 years of age may also be classified according to these criteria	Patients with well controlled short-standing DM (e.g. <10 years), no evidence of TOD and no additional ASCVD risk factors	Moderate-risk	N/A
	Patients with DM without ASCVD and/or severe TOD, and not fulfilling the moderate risk criteria.	High-risk	Residual 10-year CVD risk estimation after general prevention goals (e.g. with the ADVANCE risk score or DIAL model). Consider lifetime CVD risk and benefit estimation of risk factor treatment (e.g. DIAL model).
	Patients with DM with established ASCVD and/or severe TOD:[87, 93-95] • eGFR <45 mL/min/1.73 m^2 irrespective of albuminuria • eGFR 45-59 mL/min/1.73 m^2 and microalbuminuria (ACR 30 -300 mg/g) • Proteinuria (ACR >300 mg/g) • Presence of microvascular disease in at least 3 different sites (e.g. microalbuminuria plus retinopathy plus neuropathy)	Very high-risk	Residual 10-year CVD risk estimation after general prevention goals (e.g. with the SMART risk score for established CVD or with the ADVANCE risk score or with the DIAL model). Consider lifetime CVD risk and benefit estimation of risk factor treatment (e.g. DIAL model).

TOD: Target Organ Damage

Table 2: SGED Score [25, 26]: suggested target: ≥70/100 points

Criteria	Intervention	Aim (on a yearly basis)	Points
Regular visits	General diabetes control	>80% of patients with ≥3 visits	10
Lifestyle measures	a) BMI >25 kg/m^2: physical exercise and nutrition counselling	>80% of patients have BMI ≤25 kg/m^2 or if BMI >25 kg/m^2 received counselling ≥1/year	5
	b) Nicotin abuse: smoking cessation counselling	>80% of patients none smokers or if active smokers received counselling ≥1/year	5
Glycemic control	HbA1c measurement (DCCT traceable)	Annual mean, min. 2 measurements*:	
		≥85% of patients <9.0%	12
		≥60% of patients <8.0%	+8
		≥40% of patients <7.0%	+5
Blood pressure	Blood pressure measurement (mmHg)	Annual mean, min. 2 measurements*: ≥65% of patients <140/90 mmHg	15
LDL-C if <75 years of age	LDL-C measurement	Annual mean*: ≥63% of patients <2.6 mmol/L	10
Nephropathy screening	Measurement of serum creatinine + microalbuminuria	≥80% of patients screened	10
Retinopathy screening	Ophthalmological consultation	≥80% of patients examined min.every second year	10
Foot examination	Pulses (Arteria dorsalis pedis, Arteria tibialis posterior), mono-filament, and vibration sensation	≥80% of patients examined	10

BMI: body mass index; DCCT: Diabetes Control and Complications Trial; HbA1c: haemoglobin A1c; LDL-C: low-density lipoprotein cholesterol; min.: minimum.

* The annual average of all available measurements for each patient

Table 3: When to discontinue or change antidiabetic drugs

Medication	Situations when to temporarily stop
Metformin	Dehydration Acute kidney injury Hypoxemia
SGLT-2 inhibitor	Dehydration Prolonged fasting Perioperatively Before endoscopy
Sulfonylurea (Gliclazide)	Stop when fasting Acute kidney injury
Insulin	Adjust dose when fasting

Table 4 a: **Oral** Antidiabetic Medications with/without Cardiovascular Outcome Trials

Class and Substance	Trade Name	Combinations
Biguanide		
Metformin	Glucophage® or Generics	
SGLT-2 inhibitors		
Canagliflozin	Invokana®	Vokanamet®
Dapagliflozin	Forxiga®	Xigduo® XR*, Qtern (Dapagliflozin/Saxagliptin)
Empagliflozin	Jardiance®	Jardiance Met® Glyxambi (Empaglifozin/Linagliptin)
Ertugliflozin	Steglatro®	Segluromet®, Steglujan (+Sitagliptin)
GLP-1 Receptor Agonists		
Semaglutide	Rybelsus®	
DPP-4-inhibitors		
Alogliptin	Vipidia® (Heart failure possible)	Vipdomet®
Linagliptin	Trajenta®	Jentadueto®
Saxagliptin	Onglyza® (Heart failure)	Kombiglyze® XR*
Sitagliptin	Januvia®, Xelevia®	Janumet®, -XR*, Velmetia®
Vildagliptin	Galvus®	Galvumet®
Sulfonylurea		
Gliclazide	Diamicron® or Generics	
Glibenclamide	Daonil®/Semi-Daonil®	Glucovance®/- mite
Glimepiride	Amaryl® or Generics	

Drug classes in yellow have cardiovascular outcome trials

Table 4 b: **Injectable** Antidiabetic Medications with/without Cardiovascular Outcome Trials

Drug classes and substances	Trade names	combinations
GLP-1 Receptor Agonists (Glucagon-Like Peptide 1) and GLP-1/GIP RA		
Lixisenatide	Lyxumia®	+ Glargin: Suliqua®100/50;33
Exenatide long-acting	Bydureon® Pen (once weekly)	
Liraglutide (1.8/3.0 mg)	Victoza® (qd)/Saxenda®	+Degludec: Xultophy®
Semaglutide (1.0/2.4 mg)	Ozempic® /Wegovy® (once weekly)	
Dulaglutide (1.0/3.0/4.5 mg)	Trulicity® (once weekly)	
Tirzepatide (GLP-1/GIP RA) (5.0, 10, 15 mg)	Mounjaro® (once weekly)	
Insulin analogues, long-acting		
Degludec	Tresiba®	+ Liraglutid: Xultophy®
Detemir	Levemir®	
Glargin 100	Lantus®	
- Glargin 300	Toujeo®	
- Glargin Biosimilar	Abasaglar®	
Human insulin, intermediate action		
NPH	Huminsulin, Insulatard	
Insulin analogues, short-acting		
Lispro	Humalog®, Lyumjev® (jultra-fast)	
Aspart	NovoRapid®, Fiasp® jultra-fast)	
Glulisin	Apidra®	
Premixed or co-formulated insulins		
Lispro	Humalog®	Humalog® Mix (NPH-Insulin)
Aspart	NovoRapid®	NovoMix® (NPH Insulin)
Degludec/Aspart	NovoRapid®	Ryzodeg® (Degludec/Aspart)

Drug classes in yellow have cardiovascular outcome trials