Schweizerische Gesellschaft für Endokrinologie und Diabetologie
Société Suisse d'Endocrinologie et de Diabétologie
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Societad Svizra d'Endocrinologia e Diabetologia

Swiss Recommendations of the Society for Endocrinology and Diabetes (SGED/SSED) for the Treatment of Type 2 Diabetes Mellitus (2020)

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Contents

The committee of the SSED approved this original version 2020 in English on January 23rd 2020.

Figure 1: Flow chart of the updated recommendations 2019 - at a glance

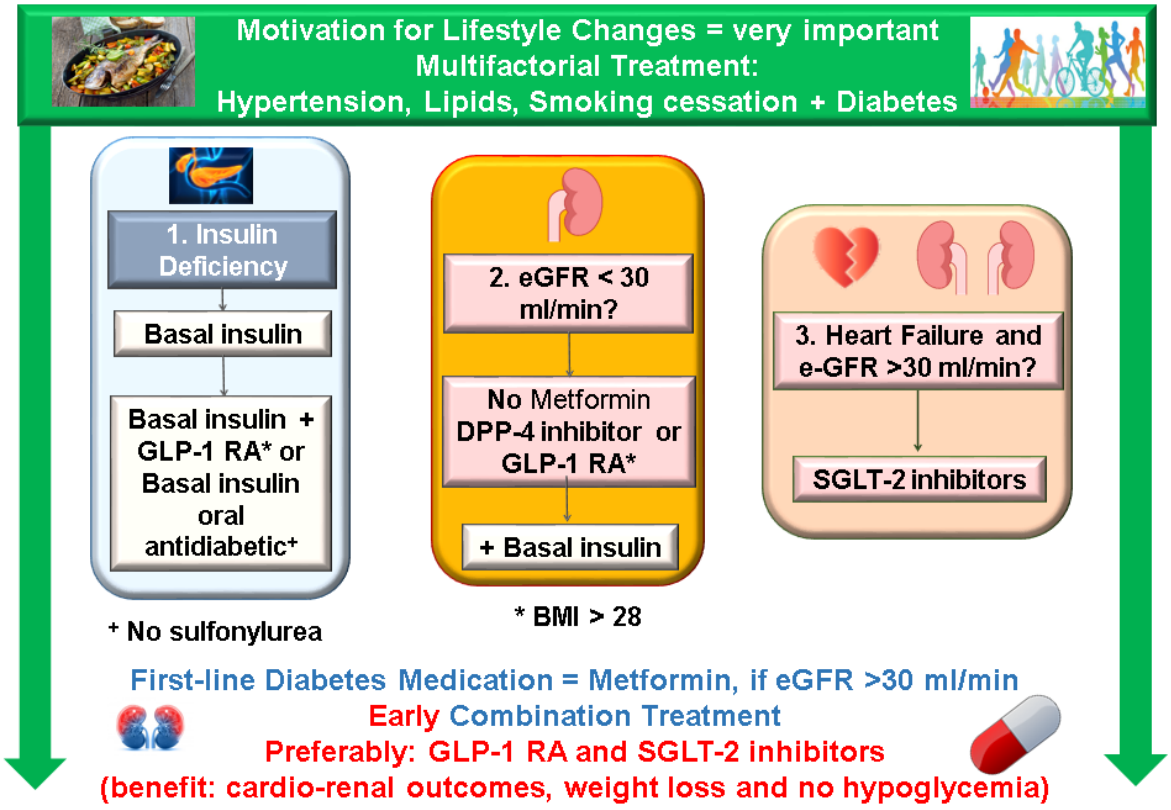
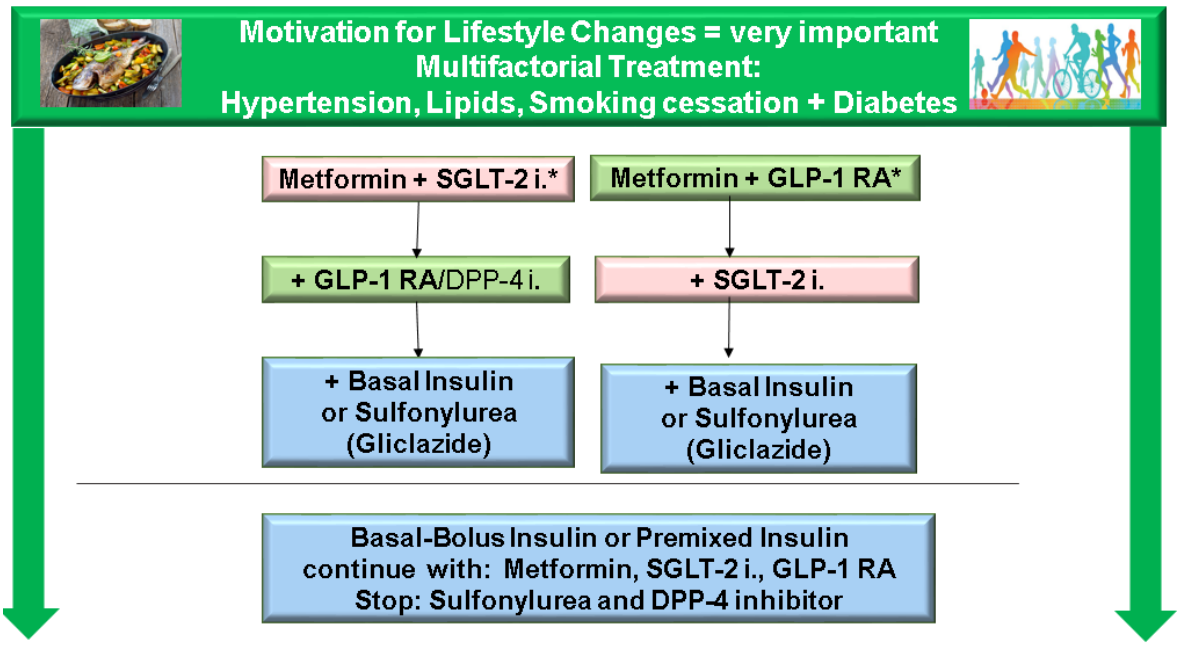


Figure 2: Essential recommendations for general practitioners - at a glace



*In patients with low to moderate cardiovascular or no risk factors, you might consider the use of DPP-4 inhibitors or sulfonylureas (gliclazide preferred)

Ref. SGED/SSED 2019

Table 1: Cardiovascular Risk evaluation table (adapted from Mach et al., 2019[4] and Cosentino et al. 2019[5])

Very high risk	Patients with diabetes **and** established cardiovascular disease **or** other target organ damage (microalbuminuria, renal impairment with eGFR ≤ 30 ml/min, retino- or neuropathy, left ventricular hypertrophy) **or** three or more risk factors (age >65 years, smoking, high blood pressure, raised lipid levels, obesity) **or** early onset type 1 diabetes mellitus of long duration (>20 years)
High-risk	Patients with diabetes duration ≥ 10 years without organ damage **plus** any other additional risk factor or chronic kidney disease (eGFR 30-59 ml/min)
Moderate-risk	Young patients (T1DM < 35 years; T2DM < 50 years) with diabetes duration < 10 years without other risk factors

Introduction

These Swiss recommendations for type 2 diabetes (T2D) treatment intend to guide general practitioners through the prescription process. The selection of the most appropriate T2D treatment for the individual patient can be complex due to T2D heterogeneity and the presence of complicating factors or comorbidities.

Since 2008, the Federal Drug administration (FDA) requires a post-market cardiovascular outcome trial (CVOT) for each new diabetes drug to prove its cardiovascular safety. All drugs belonging to the classes of DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists (GLP-1 RA) were tested for cardiovascular neutrality. The CVOTs results have provided a significant amount of data and positively, unexpected results.

The 2019 updates of the Swiss recommendations for T2D treatment consider these new developments.

New insights emerging from CVOTs

The CVOTs in the diabetes field were not designed to test for primary prevention and hence show cardiovascular benefit or reduction of mortality in a setting of secondary or primary and secondary prevention. Such trials would have had to have a much longer follow-up than two to four years. The current CVOTs were designed to demonstrate the safety of antidiabetic drugs in a high-risk population with an established cardiovascular disease with or without a chronic kidney disease.

For these reasons, the present recommendations are mainly based on opinions of experts in the field who have taken these results into consideration and who focus on a practical approach even though clear evidences are not yet available (eg. the combinations of GLP-1 RA and SGLT-2 inhibitors in primary prevention). Moreover, in the latest ESC/EASD guidelines "high-risk" was not only reserved for patients with established cardiovascular disease but also for patients with three or more additional risk factors, as it is common in most patients with

type 2 diabetes (T2D) or when T2D is associated with microvascular complications (nephropathy, retinopathy or neuropathy)[4,5].

There are currently two classes of drugs, which have shown reduction of cardiovascular events, cardiovascular mortality, total mortality, nephron protection (SGLT-2 inhibitors (6-9) and GLP-1 RA (10-13)), and mainly secondary cardiovascular prevention (with weaker evidence for primary prevention) or treatment of heart failure (SGLT-2 inhibitors) (6-9). There are some differences in these two classes: Whereas GLP-1 RA seem to have an effect on the occurrence of micro- and macro-albuminuria, SGLT-2 inhibitors have also demonstrated evidence on hard endpoints such as reduction of eGFR by 40 or 50%, a delay of the progression of kidney disease, renal replacement therapy or renal death. No head-to-head comparison of the two classes was done. Empagliflozin (6) and liraglutide (12) show a reduction of cardiovascular and total mortality. SGLT-2 inhibitors (6-9) do not seem to have an effect on stroke, whereas GLP-1 RA have shown reduction of stroke (10-14). It is now generally agreed upon that SGLT-2 inhibitors and GLP-1 RA have significant beneficial effects on cardiovascular disease, cardiovascular mortality, and total mortality. Furthermore, they postpone the development of chronic kidney disease and heart failure in patients with diabetes. There is no cardiovascular outcome trial, which tested the combined use of these two drug classes. Data exist, however, that the combination of these two drug classes have additive effects on lowering HbA1c, weight, and blood pressure (1-3), as a post hoc analysis of the EXSCEL trial (n=14'529) (3) showed where a SGLT-2 inhibitor was added to exenatide LAR in 645 patients. A propensity-matched analysis of 575 patients with the combination of SGLT-2 inhibitors and GLP-1 RA compared to 575 patients with GLP-1 RA alone vs. 572 patients with neither of the two drugs showed a significant reduction of 79% in cardiovascular mortality and 59% in total mortality with regard to exenatide LAR alone over a follow-up of 30 months. 3-Point MACE (major adverse cardiovascular events) was not significantly reduced by 15% [38].
Based on the evidence of all known results of cardiovascular endpoint trials, DPP-4 inhibitors are safe, easy to use, but do not show any positive effect on cardiovascular events [9, 15, 16].
With the exception of the ADVANCE (gliclazide)[17] and the CAROLINA trial (DPP-4 inhibitor linagliptin vs. the sulfonylurea glimepiride) [16] there are no cardiovascular trials with sulfonylurea. A meta-analysis of all trials with sulfonylurea clearly show more events of hypoglycemia and weight gain, implicated with the use of this class [18]. Here, gliclazide is somewhat an exception, showing minimal risk of hypoglycemia and no or minimal weight gain. It seems to be the best sulfonylurea in its class.
With the exception of the UK Prospective Diabetes Study (UKPDS) [19], there are no trials with metformin showing a clear advantage of this class [20], but all modern cardiovascular outcome trials were performed based on metformin treatment.
Therefore, we recommend the **use of metformin** as long as the eGFR is > 30 ml/min in an **early combination treatment**, considering the patient preferences of no hypoglycemia and a possible weight loss (Figure 2). However, for GLP-1 RA injection has to be accepted by the patient. The two classes of drugs fulfilling these preferences, preventing cardiovascular events and even reducing mortality are SGLT-2 inhibitors[6-9] and GLP-1 RA[10-14]. SGLT-2 inhibitors on the other hand can have significant side effects such as ketoacidosis and genital infections. Some rarer side-effects were shown in some trials but not confirmed by others. We therefore recommend the use of one of these drug classes in an early combination with metformin, and, if a reduction of HbA1c to the desired level is not sufficiently achieved, to combine it with the other class (figure 1). This recommendation is in line with the ADA-EASD

consensus [21] in high-risk individuals as well as with the new ESC guidelines (4, 5) to reduce cardiovascular risk in people with high or very high risk for cardiovascular disease, considering that the vast majority of people with type 2 diabetes mellitus belongs to the high-risk category.

Lifestyle changes and multifactorial treatment in type 2 diabetes mellitus

Lifestyle changes should be promoted regularly and independently of diabetes duration. Nutrition therapy (NT) and regular physical activity (150 minutes per week) play key roles in diabetes management. The goals of NT are to improve glycemic control and help weight management. Overweight or obese patients with T2D willing to lose weight, benefit from the reduction of calorie intake and a behavioral therapy designed to achieve and maintain 5% weight loss. The focus of such interventions is to achieve a sustainable daily energy deficit (500–750 kcal/day). NT should be individualized, associated to comprehensive weight maintenance programs, regular body weight monitoring (weekly), and regular physical activity. The promotion of healthy food choices, such as limited amounts of ultra-transformed food, carbohydrate sources that are high in fiber, select monounsaturated and polyunsaturated fats, as well as the avoidance of sugar-sweetened beverages, is crucial. There is limited evidence to promote one specific diet out of the different types of diet [22-24]. In addition, the duration of these trials is limited to one or two years, rather than during the entire life span of a patient. There are no recommendations to favor any specific percentage of macronutrients (carbohydrate, lipids and proteins) intake. The adherence rate to a particular diet is the most important predictor for weight loss [26, 27].

A multifactorial approach, based on the data of the Steno-2-trial and focusing on the control of glycemia, blood pressure, lipid profile and tobacco cessation is recommended [28]. The treating physician has to guide each patient individually through the possible interventions. The order of the interventions must comply with the patient's preferences (Figure 3). Most patients fear hypoglycemia and weight gain as well-known side effects of certain interventions (Figure 2). Therefore, drug choices with none of these sides-effects are preferred. Furthermore, new recommendations of guidelines for LDL-cholesterol and blood pressure targets in the T2D population have to be taken into consideration[5]. The guidelines for the control of LDL-cholesterol are ambitious, and cannot be achieved in all patients since the limitations for PCSK9i are above the ESC targets (<1.4 mmol/l) for patients with very high cardiovascular risk. The Federal Office of Public Health (FOPH) has recently updated its limitations for both PCSK9i (LDL>2.6 mmol/l on maximum tolerated statin therapy in patients with prevalent clinical cardiovascular disease). First choice is a statin with high efficacy and, if targets cannot be achieved, Ezetimibe should be added. Is the target still not met, PCSK-9 inhibitors might be given [5].

The target for blood pressure is also individualized and should be in general 130/<80 mmHg, but at the same time, the diastolic blood pressure should be >70 mmHg in a high-risk individual. In a younger patient, the systolic blood pressure can be in the range of 130 mmHg and 120 mm Hg, whereas in a person above the age of 65 years, the recommended systolic blood pressure is between 130-139 mmHg. The usual choice of drugs is an early combination of ACE-inhibitor and calcium antagonist, if the ACE-inhibitor is not tolerated, an ARB (angiotensin II receptor blocker) can be prescribed[4].

People with diabetes have a higher platelet reactivity and turnover, resulting in a pro-thrombotic status[28]. The platelet aggregation inhibition by aspirin or by other drugs is acceptable in patients with established cardiovascular disease, but is controversial in high-risk and especially in moderate risk patients[30]. The addition of Rivoraxaban to aspirin twice daily in a high-risk group showed a significant reduction in 3-point MACE, stroke and total mortality[31].

Figure 3: Patient preferences have to be verified by the physician

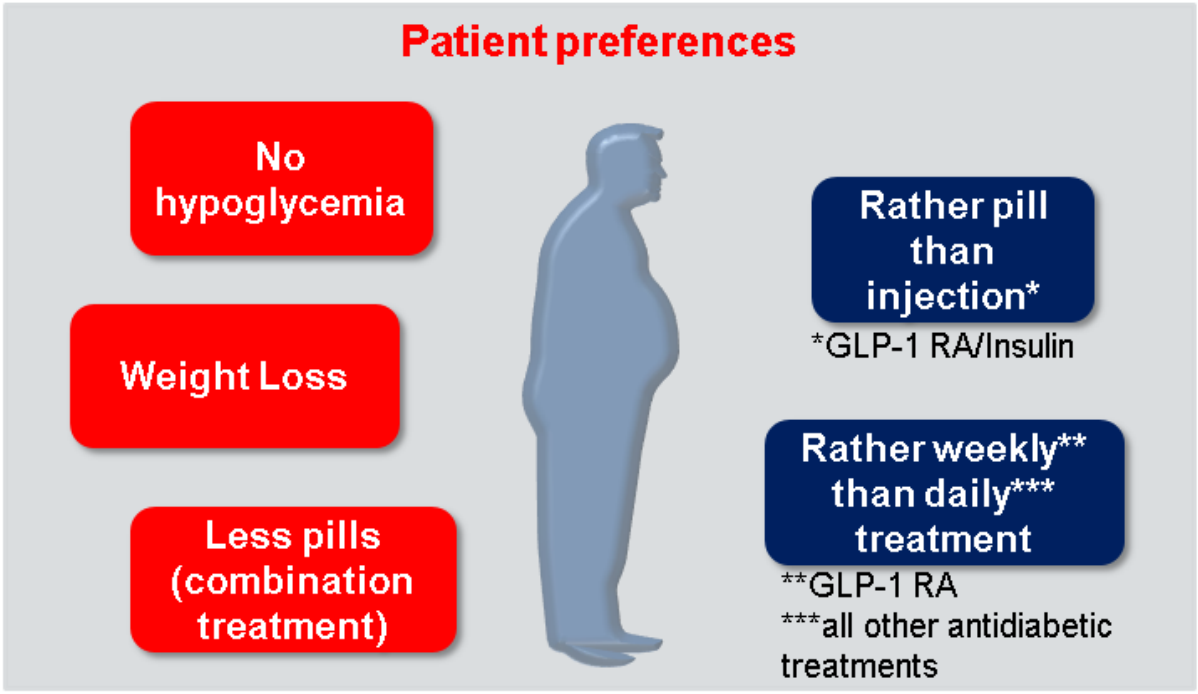


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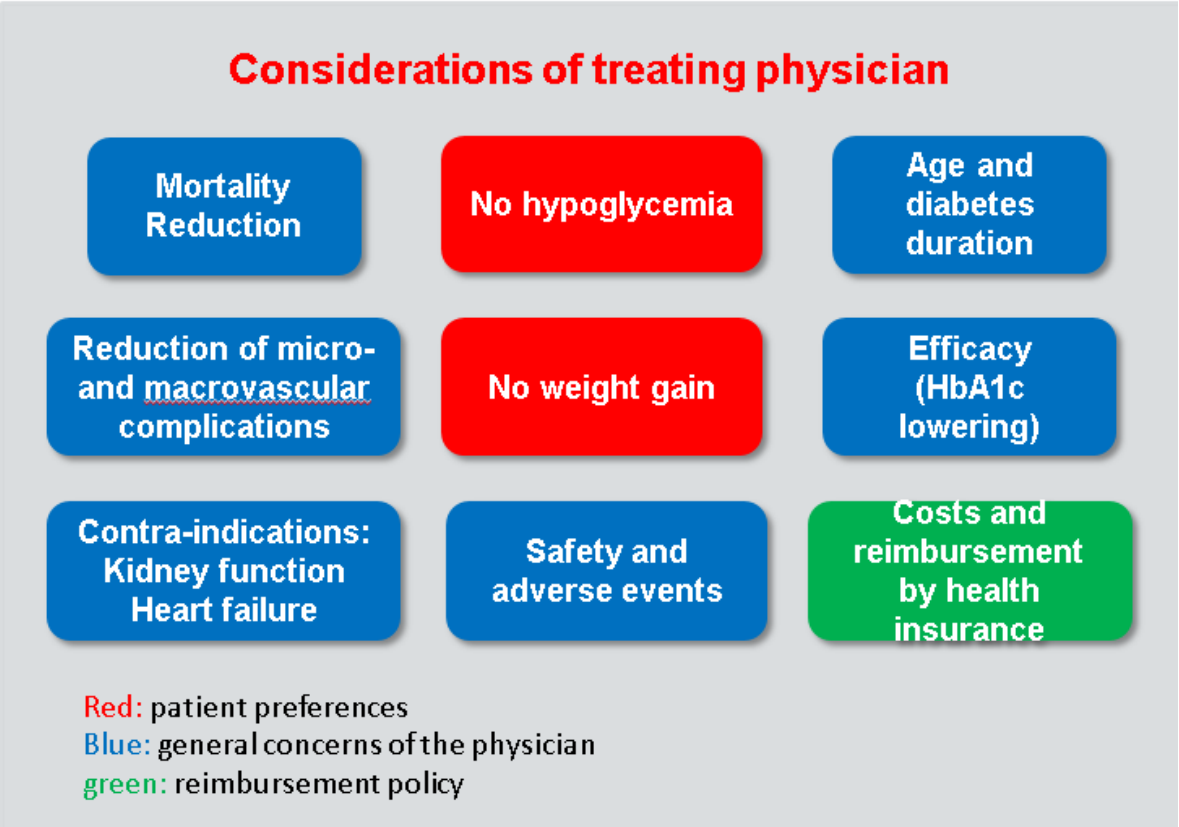
Figure 4: Considerations of treating physician



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Antidiabetic Medications and cardio-renal prevention

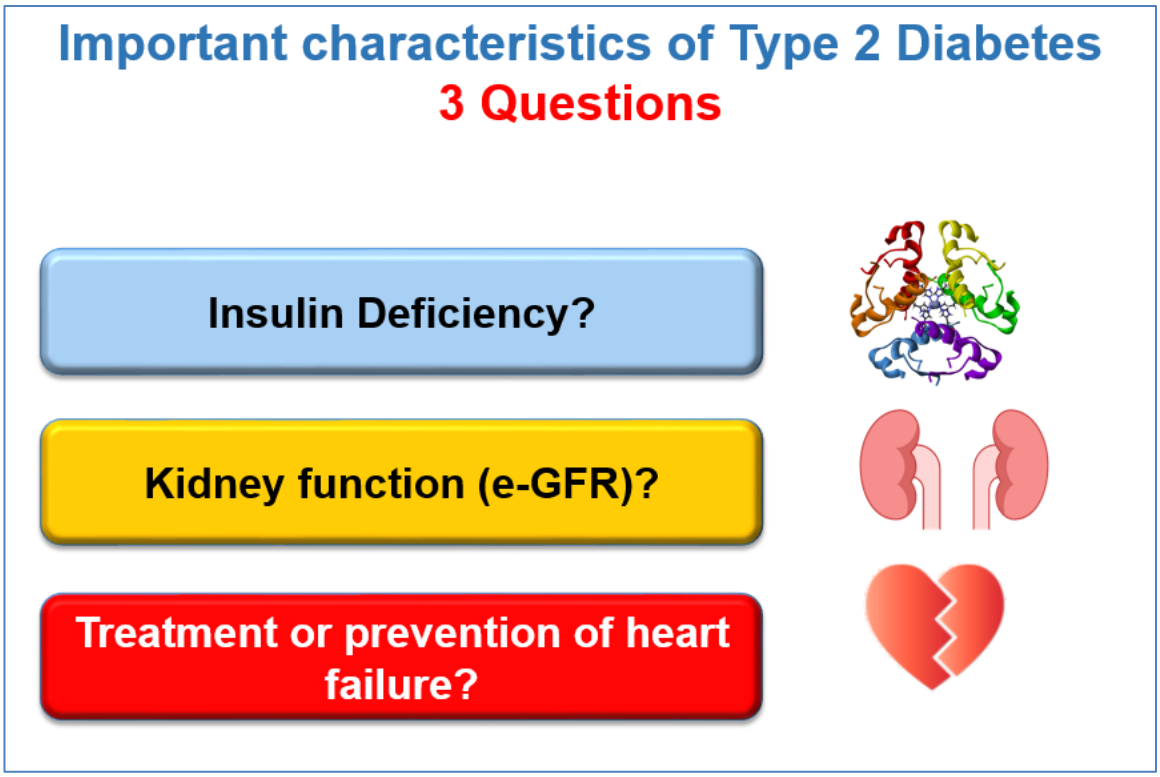
The goal in every diabetes patient is to treat atherosclerotic cardiovascular disease (ASCVD) and avoid microvascular disease. Therefore, we recommend GLP-1 RA and SGLT-2 inhibitors. When choosing glucose-lowering medications for a patient with T2D apart from this, there are three key questions to consider always (figure 4).

To guide the physician, we recommend the following steps:

1.	**Exclude insulin deficiency** a. Evidence of ongoing catabolism (weight loss, **RED FLAG : chronic pancreatitis or ketonuria +++** b. History suggesting insulin deficiency (type 1 diabetes, pancreatectomy, long duration type 2 diabetes, etc.) c. Symptoms of hyperglycemia : polyuria, nocturia, thirst, asthenia d. HbA1c levels > 10% or blood glucose levels >16.7mmol/l → If any of this answers is yes : the introduction of insulin has to be considered and is never a wrong choice. → **if any RED FLAG** : the **introduction of insulin** should not be delayed

2.	**Define the HbA1c goal** In young adults with recently diagnosed diabetes and no cardiovascular disease, a reasonable goal of Hba1c is < 7% (more stringent HbA1c < 6.5% can be targeted in selected individuals without significant risks of hypoglycemia. In elderly patients with a long duration of diabetes and patients with a history of severe hypoglycemia, limited life expectancy, advanced micro- and/or macro-vascular complications or extensive comorbid conditions), which are treated with sulfonylurea or insulin, less stringent goals of < 8.0% are applied. HbA1c should be reassessed at least 2x per year if at target, and quarterly if otherwise.
3.	**Metformin is the preferred initial pharmacologic agent for the treatment of type 2 diabetes if well tolerated and not contraindicated**. All other agents should be added to metformin, **unless**: 1) eGFR < 45ml/min → do not introduce metformin or, in case metformin is already prescribed, decrease daily dosage (1000 mg, as low as 500/day), follow eGFR 2-3 times / year 2) eGFR < 30 ml/min → metformin must be stopped 3) Vitamin B12-deficiency and polyneuropathy → in addition, start vitamin B12 substitution and periodic measurements of vit. B12 levels (metformin reduces the resorption of vitamin B12)
4.	**Patients with chronic kidney disease** and eGFR < 30-45 ml/min. SGLT-2 inhibitors can be given until an eGFR of 45 ml/min (Compendium), except ertugliflozin until eGFR above 60ml/min. Recent data of empagliflozin and canagliflozin in cardiovascular outcome studies show that they can be safely used until an eGFR of 30 ml/min. GLP-1 RA or DPP-4 inhibitor are the preferred agents if eGFR< 30ml/min (GLP-1 RA can only be given if BMI >28kg/m^2)
5.	**Patients with T2D and established atherosclerotic cardiovascular disease or at high cardiovascular risk**: consider early combination with second-line therapy (SGLT2 or GLP-1 RA) with a proven cardiovascular benefit or a combination of the two classes (get insurance approval beforehand)
6.	In patients with T2D and a history of heart failure consider early combination of SGLT2 and metformin.
7.	Do not delay intensifying the treatment for **patients with type 2 diabetes and unmet treatment goal (HbA1c target)!**
8.	**Lifestyle changes and medication** for T2D should be re-evaluated in regular intervals and adherence to medication and lifestyle change should be encouraged regularly every 3-6 months.

Figure 5: Questions to be asked, when choosing an antidiabetic treatment



Ref. SGED/SSED 2019

In order to prevent adverse events and to reduce the burden of cardio-renal complications, the three questions have to be asked (figure 4) before prescribing or adding antidiabetic drugs.

1. **The first and foremost question always concerns insulin: Does the patient require insulin?**

If the patient's HbA1c is >10% in absence of key features of the metabolic syndrome such as visceral obesity and the typical dyslipidemia (low HDL-cholesterol and high triglycerides) and he/she has clinical symptoms of insulin deficiency (weight loss, polyuria and polydipsia), administering insulin is never wrong. After normalizing the metabolic situation, the physician can decide to continue or discontinue the use of insulin. In a small percentage of patients, diabetes can be due to type 1 diabetes/LADA or a pancreatic disease (chronic pancreatitis).

2. **The second question concerns the kidney function (KF) which determines the antidiabetic choice.**

Most drugs cannot be prescribed if the eGFR is below 30 ml/min.

3. **The third question concerns heart failure:**

The physician needs to consider the patient preferences (Figure 2), but also the treatment targets that include a reduction of mortality and cardiovascular events (figure 3). Sulfonylureas[18] and DPP-4 inhibitors have no effect with respect to these hard outcome measures[9, 15, 16].

Two forms of heart failure exist: Heart failure with preserved ejection fraction (HFPEF; 3/4 of heart failure in patients with type 2 diabetes) and a left-ventricular ejection

fraction > 40% and heart failure with reduced ejection fraction (HFREF; ¼ of patients with heart failure) [37]. SGLT-2 inhibitors are the preferred drug class in this indication [6-9]. Trials including patients with HFREF and HFPEF with and without diabetes are ongoing. In case of heart failure, glitazones (pioglitazone) should be avoided [21].

In patients with a history of a cardiovascular disease and/or reduced kidney function or advanced age, it is important to avoid hypoglycemia, as they have a higher risk of hypoglycemia and an increased risk of cardiac arrhythmias. Therefore, the combination of sulfonylurea and insulin should be avoided as this combination significantly increases the risk for hypoglycemia by 9 to 40x [25]. The newer basal insulins such as degludec[32] and glargine-U300[33] have a lower incidence of hypoglycemia, particularly of nighttime hypoglycemia, when compared to the first generation analogues (detemir, glargine-U100) and NPH insulin. The combination of basal insulin and GLP-1 RA reduces the risk of hypoglycemia even more and eliminates the insulin side effect of gaining weight[34, 35]. With drugs that do not cause any hypoglycemia, no lower target for HbA1c is necessary even in patients with advanced kidney or cardiovascular disease. When using medications that do not cause hypoglycemia, the HbA1c should be as close to normal as possible (6.0-7.0%). In regards to a reduction of cardiovascular events and mortality, metformin shows a reduction of macrovascular events in the UKPDS, but a meta-analysis shows no significant effect for metformin in regards to hard cardiovascular and renal outcomes [20]. Therefore, the only two drug classes with a proven cardiovascular benefit in secondary prevention are SGLT-2 inhibitors and GLP-1 receptor agonists (GLP-1 RA) such as liraglutide, semaglutide or dulaglutide (albiglutide).
Their effect on 3-Point MACE are very similar. SGLT-2 inhibitors delay the loss of renal function and progression to end-stage kidney disease (ESKD) and consequently have more pronounced hard renal endpoints[6-9]. GLP-1 RA[10-14] have the most pronounced effects in reducing the progression to macro-albuminuria in the setting of an eGFR between 30-60 ml/min.
SGLT-2 inhibitors seem to have a lesser effect on stroke incidence [6-9], whereas the PIONEER 6[14], SUSTAIN-6[11] and REWIND[39] trials show a reduction of stroke incidence for long-acting GLP-1 RA (liraglutide, semaglutide und dulaglutide). Only empagliflozin and liraglutide have been associated with a significant reduction in mortality.

Regarding the treatment of heart failure or its prevention, the effects of SGLT-2 inhibitors are very convincing[6-9]. This effect has not been seen with GLP-1 RA.

These observations provided a rational for a new direction of investigation.
The DAPA-HF trial showed that Dapagliflozin caused a significant reduction of 3-Point MACE and cardiovascular deaths in people with and without diabetes and heart failure with reduced ejection fraction[38]. A pre-specified subgroup analysis showed the same effect on this combined outcome in people with and without diabetes.
Even though there is no cardiovascular outcome trial looking at the effects of the combination of these two drug classes, it seems logical to combine these two classes, since the effects on weight, hypoglycemia, blood pressure and HbA1c are additive. Therefore, the ADA/EASD consensus and the new ESC/EASD guidelines [4, 5] recommend their combined use for best protective effects on kidneys, cardiovascular events, heart failure and total mortality. The indication for the combination of these two drug classes exists for many substances already, but currently, reimbursement issues exist with the Swiss health insurance, so that the prescribing doctor needs to obtain a clearance from

the patient's insurance before prescribing a combination of a SGLT-2 inhibitor and a GLP-1 RA.

Limitations for the use of anti-diabetic medication

The major limiting factor for the use of anti-diabetic medication is renal function. No long-acting sulfonylureas with active metabolites should be used (glibenclamide, glimepiride)[35]. The preferred drug in this class is gliclazide, as it shows the lowest incidence of hypoglycemia, cardiovascular events, and total mortality [36], and its safety was shown in the ADVANCE trial[17].
The indication for all SGLT-2 inhibitors is eGFR ≥45 ml/min, but evidence exists that Canagliflozin (CREDENCE trial)[9] and empagliflozin (EMPA-REG trial, with less patients) (6) can be safely used down to an eGFR of 30 ml/min. Whereas the glucose-lowering effect decreases with lower eGFRs, the nephro- and cardioprotective effects are preserved even at low eGFR[6, 9].
If the eGFR is below 30 ml/min, treatment options are very limited. If GLP-1 RA are tolerated, they can be given down to eGFR 15ml/min, usually with a reduced dosage. Data for liraglutide and semaglutide exists showing that this class is safe even with a low eGFR[10]. As an alternative, in case of poor tolerance or other reasons for not being able to use GLP-1 RA, DPP-4 inhibitors are preferred.
Most of the time, though, insulin is required in patients with a CKD class 4 or 5. A basal insulin with ultra-long duration (insulin degludec or insulin glargine U300) is preferred, because of its reduced hypoglycemia rate[32, 33].
In the class of the DPP-4 inhibitors, sitagliptin and linagliptin show the best results (saxagliptin should not be used in heart failure)[15]. Whereas the dosage of sitagliptin has to be adjusted to the kidney function, no adjustment is necessary for linagliptin.

Concluding remarks and summary of Swiss recommendations

1. Does the patient require insulin? If the HbA1c is high (>10%) and if it is not a typical patient with metabolic syndrome, visceral obesity and the typical dyslipidemia (low HDL-cholesterol and high triglycerides) and he/she has clinical symptoms of insulin deficiency (weight loss, polyuria and polydipsia), insulin is never wrong. After normalization of the metabolic situation, the physician can decide to continue or discontinue the use of insulin. In a small percentage of patients, diabetes can be due to type 1 diabetes or pancreatic disease (chronic pancreatitis).
2. Reducing the cardiovascular burden is of prime importance. Therefore, we recommend SGLT-2 inhibitors and GLP-1 RA in early combination with metformin, as shown in the cardiovascular outcome trials with SGLT-2 inhibitors and GLP-1 RA in which >70% of patients used metformin.
3. SGLT-2 inhibitors and GLP-1 RA have different modes of action, of which still many are poorly understood. Both classes have shown to reduce cardiovascular events, mortality and the progression of nephropathy. Therefore, we recommend the combination of these two drug classes, but costs' acceptance by the insurer or self-payment by the patient needs to be clarified prior to prescribing
4. Reducing HbA1c to the usual target of >7.0 (if no reduction of life expectancy, etc.) is of importance to reduce micro- and macro-vascular complications. If no drug classes are

used which can cause hypoglycemia (insulin and/or sulfonylurea), no lower limit for HbA1c is necessary. In this situation, an HbA1c as close to normal should be the target (HbA1c 6-7%).

5. Patient preferences have to be considered (Figure 2). The efficacy, benefits and adverse effects of the available antidiabetic drugs should be discussed with the patient in order to allow a shared decision-making.
6. The indication for the use of a GLP-1 RA is a BMI >28. GLP-1 RA can be used together with insulin, preferably in a fixed combination.
7. The patient needs instructions about sick day rules. If the patient vomits, has diarrhea, is acutely ill, has to go to the hospital or has an operation planned, the use of SGLT-2 inhibitors and metformin should be stopped, and, if necessary, replaced by insulin. By this simple measure, the rare cases of diabetic ketoacidosis and lactic acidosis can be prevented.
8. When choosing a basal insulin current evidence suggest that insulin degludec and glargine U300 are superior to avoid hypoglycemia, particularly night-time hypoglycemia, followed by insulin glargine U100 and detemir, followed by NPH-insulin.

List of antidiabetic drugs

Drug classes in yellow have cardiovascular outcome trials or cardiovascular safety data

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)
DPP-4-inhibitors		
Alogliptin	Vipidia® (Heart failure possible)	Vipdomet®
Linagliptin	Trajenta®	Jentadueto®
Saxagliptin	Onglyza® (Heart failure)	Kombiglyze® XR*
Sitagliptin	Januvia®	Janumet®, -XR*
Vildagliptin	Galvus®	Galvumet®
Sulfonylurea*		
Gliclazide	Diamicron® or Generics	
Glibenclamide	Daonil®/Semi-Daonil®	Glucovance®/- mite
Glimepiride	Amaryl® or Generics	
GLP-1 Receptor Agonists (Glucagon-Like Peptide 1)		
Lixisenatide	Lyxumia®	+ Glargin: Suliqua®100/50;33

Exenatide long-acting	Bydureon® Pen (once weekly)	
Liraglutide	Victoza® (qd)	+Degludec: Xultophy®
Semaglutide	Ozempic® (once weekly)	
Dulaglutide	Trulicity® (once weekly)	
Insulin analogues, long-acting		
Degludec	Tresiba®	+ Liraglutide: Xultophy®
Detemir	Levemir®	
Glargin 100	Lantus®	+Lixisentatide: Suliqua®100/50;33
- Glargin 300	Toujeo®	
- Glargin Biosimilar	Abasaglar®	
Human insulin, intermediate action		
NPH	Huminsulin, Insulatard	
Insulin analogues, short-acting		
Lispro	Humalog®	
Aspart	NovoRapid®, Fiasp®	
Glulisin	Apidra®	
Premixed or co-formulated insulins		
Lispro	Humalog®	Humalog® Mix (NPH-Insulin)
Aspart	NovoRapid®	NovoMix® (NPH Insulin)
Degludec/Aspart	NovoRapid®	Ryzodeg® (Degludec/Aspart)

* Glinides like repaglinide have a very low market share in Switzerland; therefore, they are not included here and in the recommendations of 2016, like the glitazones.

Declaration of possible conflicts of interests

The members of the working group declare the following:
Roger Lehmann receives honoraria for lectures and talks about diabetes Amgen, Astra Zeneca, Boehringer Ingelheim, Eli-Lilly, MSD, Medtronic, Mundipharma, Novo Nordisk, Roche, and Sanofi. *Giacomo Gastaldi* receives educational grants from Eli-Lilly, Novo Nordisk, Sanofi, Medtronic, Roche, Abbott, Dexcom, Insulet, Ypsomed, her receives honoraria for serving on advisory boards of Medtronic and Vifor, as well as research support from private foundations. *Astrid Czock* holds stocks from Axapharm and Vifor. *Marc Egli* speaking fees, travel grants or honoraria for serving on advisory board from Merck, Novo Nordisk, Eli Lilly, Boehringer Ingelheim, Sanofi, Astra Zeneca and Medtronic. *Doris Fischer-Taeschler* declared no possible conflicts. *Markus Laimer* receives research support from Novo Nordisk and receives honoraria or serves on advisory boards of Roche, Medtronic, MSD, Eli Lilly and Sanofi-Aventis. All unrestricted grants, honoraria, and fees are transferred to an independent scientific and educational account of the department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism of the Inselspital University Hospital and University Bern. *Barbara Lucchini* declared holding stock, receiving honoraria or serving on advisory board of Novo Nordisk, Sanofi and Astra Zeneca. *Sebastien Thalmann* served on advisory board of Astra Zeneca and Novo Nordisk in 2017 as well as received travel grants from Novo Nordisk and Eli Lilly. *Peter Wiesli* received speaking fees, travel grants and honoraria serving on the advisory boards of Novo Nordisk, Sanofi, AstraZeneca; he received speaking fees and honoraria serving on the advisory boards of Eli-Lilly, Boehringer Ingelheim, MSD, Bayer, Abbott. Furthermore, he receives speaking fees from Dexcom, Medtronic, Roche, Servier, Mundipharma and Amgen.

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