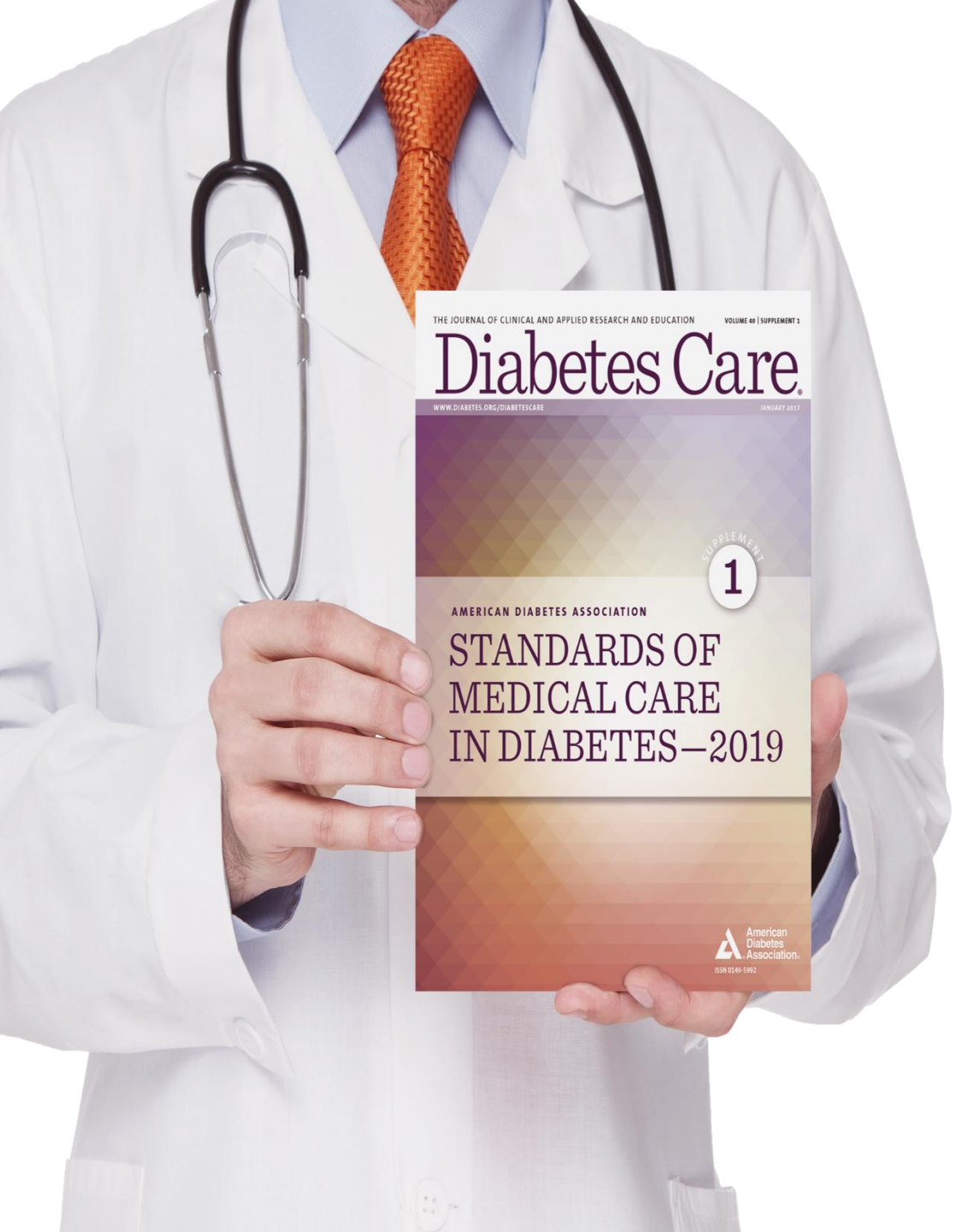
LABORATOIRE DE RECHERCHE SUR LE DIABETE
UNIVERSITE ABOUBEKR BELKAID
FACULTE DE MEDECINE BENAOUDA BENZERDJEB
CHU TIDJANI DAMERDJI

QUEL SULFAMIDE APRES LA METFORMINE EN 2019

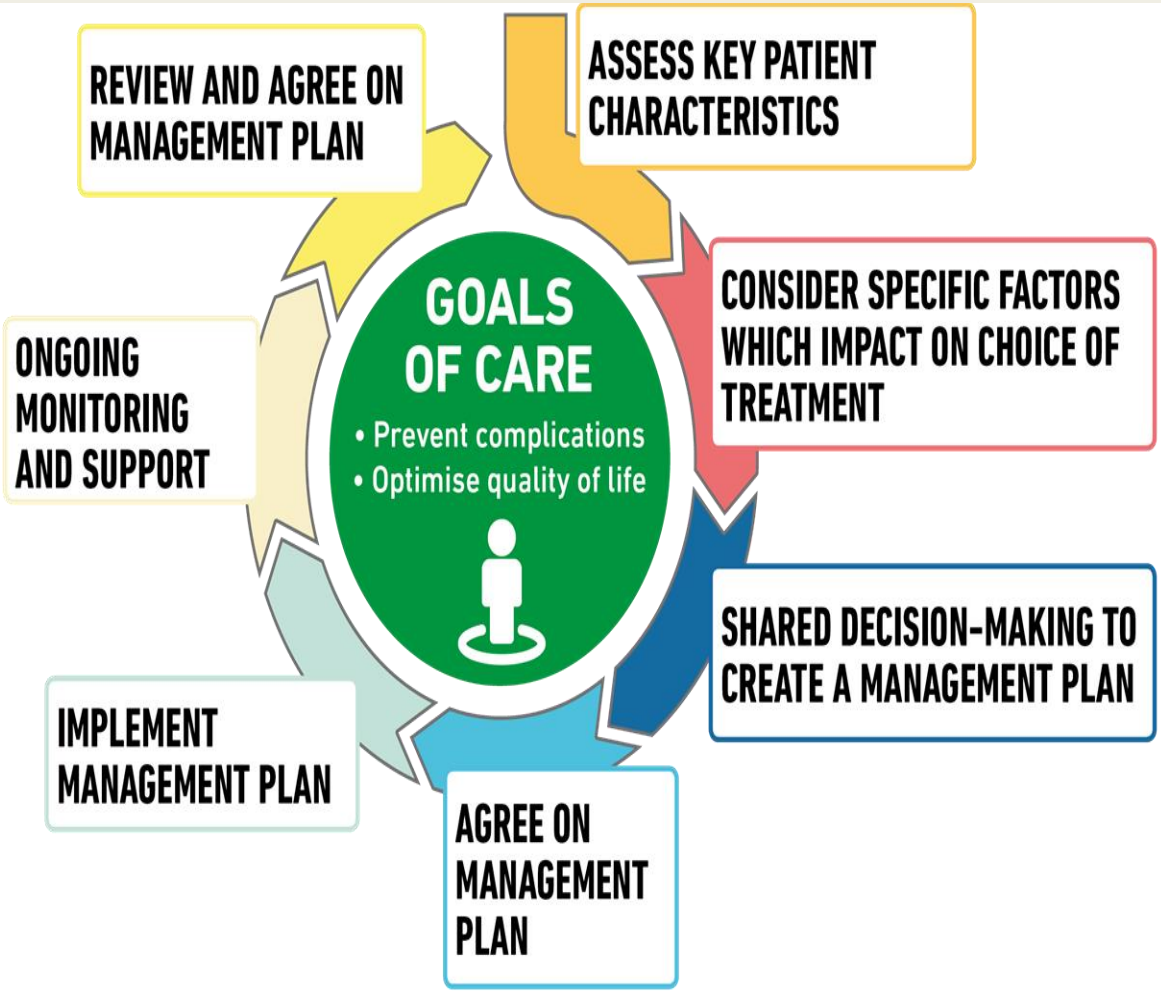
Ali Lounici

1er Séminaire du laboratoire de Recherche sur le Diabète
7émes Journée AMIWIT
Vendredi 29 & Samedi 30 Novembre 2019
Faculté SNVTU - Université de Tlemcen -

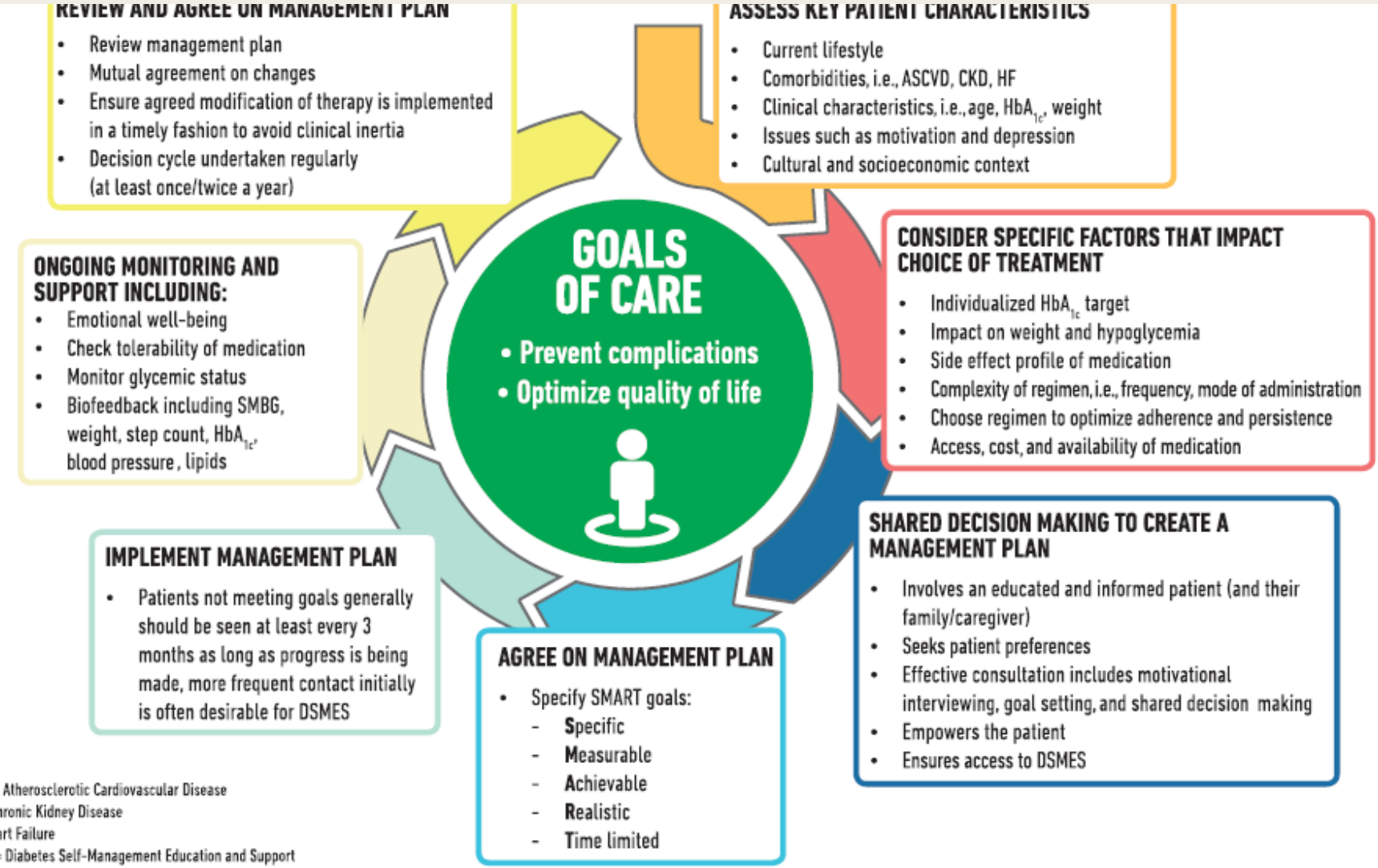


Standards of Medical Care in Diabetes – 2019

Decision Cycle for Patient-Centered Glycemic Management in Type 2 Diabetes



Decision Cycle for Patient-Centered Glycemic Management in Type 2 Diabetes



ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose

Standards of Medical Care in Diabetes - 2019. Diabetes Care 2019;42(Suppl. 1):S61-S70

Components of the Comprehensive Diabetes Medical Evaluation

Table 4.1 – Components of the comprehensive diabetes medical evaluation at initial, follow-up, and annual visits

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
PAST MEDICAL AND FAMILY HISTORY	**Diabetes history**			
	▪ Characteristics at onset (e.g., age, symptoms)	✓		
	▪ Review of previous treatment regimens and response	✓		
	▪ Assess frequency/cause/severity of past hospitalizations	✓		
	Family history			
	▪ Family history of diabetes in a first-degree relative	✓		
	▪ Family history of autoimmune disorder	✓		
	Personal history of complications and common comorbidities			
	▪ Macrovascular and microvascular	✓		✓
	▪ Common comorbidities (e.g., obesity, OSA)	✓		
	▪ Hypoglycemia: awareness/frequency/causes/timing of episodes	✓	✓	✓
	▪ Presence of hemoglobinopathies or anemias	✓		
	▪ High blood pressure or abnormal lipids	✓		✓
	▪ Last dental visit	✓		✓
	▪ Last dilated eye exam	✓		✓
	▪ Visits to specialists	✓	✓	✓
	Interval history			
	▪ Changes in medical/family history since last visit		✓	✓

Components of the Comprehensive Diabetes Medical Evaluation

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
LIFESTYLE FACTORS	▪ Eating patterns and weight history	✓	✓	✓
	▪ Physical activity and sleep behaviors	✓	✓	✓
	▪ Tobacco, alcohol, and substance use	✓		✓
MEDICATIONS AND VACCINATIONS	▪ Current medication regimen	✓	✓	✓
	▪ Medication-taking behavior	✓	✓	✓
	▪ Medication intolerance or side effects	✓	✓	✓
	▪ Complementary and alternative medicine use	✓	✓	✓
	▪ Vaccination history and needs	✓		✓
TECHNOLOGY USE	▪ Assess use of health apps, online education, patient portals, etc.	✓		✓
	▪ Glucose monitoring (meter/CGM): results and data use	✓	✓	✓
	▪ Review insulin pump settings and use	✓	✓	✓

Components of the Comprehensive Diabetes Medical Evaluation

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
BEHAVIORAL AND DIABETES SELF-MANAGEMENT SKILLS	**Psychosocial conditions**			
	▪ Screen for depression, anxiety, and disordered eating; refer for further assessment or intervention if warranted	✓		✓
	▪ Identify existing social supports	✓		
	▪ Consider assessment for cognitive impairment*	✓		✓
	Diabetes self-management education and support			
	▪ History of dietician/diabetes educator visits/classes	✓	✓	✓
	▪ Assess diabetes self-management skills and barriers	✓		✓
	▪ Assess familiarity with carbohydrate counting (type 1 diabetes)	✓		
	Pregnancy planning			
	▪ For women with childbearing capacity, review contraceptive needs and preconception planning	✓	✓	✓

Components of the Comprehensive Diabetes

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
PHYSICAL EXAMINATION	▪ Height, weight, and BMI; growth/pubertal development in children and adolescents	✓	✓	✓
	▪ Blood pressure determination	✓	✓	✓
	▪ Orthostatic blood pressure measures (when indicated)	✓		
	▪ Fundoscopic examination (refer to eye specialist)	✓		✓
	▪ Thyroid palpation	✓		✓
	▪ Skin examination (e.g., acanthosis nigricans, insulin injection or insertion sites, lipodystrophy)	✓	✓	✓
	▪ Comprehensive foot examination			
	• Visual inspection (e.g., skin integrity, callous formation, foot deformity or ulcer, toenails)**	✓		✓
	• Screen for PAD (pedal pulses–refer for ABI if diminished)	✓		✓
	• Determination of temperature, vibration or pinprick sensation, and 10-g monofilament exam	✓		✓
LABORATORY EVALUATION	▪ A1C, if the results are not available within the past 3 months	✓	✓	✓
	▪ If not performed/available within the past year	✓		✓
	• Lipid profile, including total, LDL, and HDL cholesterol and triglycerides#	✓		✓^
	• Liver function tests#	✓		✓
	• Spot urinary albumin–to–creatinine ratio	✓		✓
	• Serum creatinine and estimated glomerular filtration rate+	✓		✓
	• Thyroid-stimulating hormone in patients with type 1 diabetes#	✓		✓
	• Vitamin B12 if on metformin (when indicated)	✓		✓
	• Serum potassium levels in patients on ACE inhibitors, ARBs, or diuretics+	✓		✓

Table 4.2—Assessment and treatment plan*

Assess risk of diabetes complications

- ASCVD and heart failure history
- ASCVD risk factors (see **Table 10.2**) and 10-year ASCVD risk assessment
- Staging of chronic kidney disease (see **Table 11.1**)
- Hypoglycemia risk (**Table 4.3**)

Goal setting

- Set A1C/blood glucose target
- If hypertension present, establish blood pressure target
- Diabetes self-management goals (e.g., monitoring frequency)

Therapeutic treatment plan

- Lifestyle management
- Pharmacologic therapy (glucose lowering)
- Pharmacologic therapy (cardiovascular disease risk factors and renal)
- Use of glucose monitoring and insulin delivery devices
- Referral to diabetes education and medical specialists (as needed)

ASCVD, atherosclerotic cardiovascular disease. *Assessment and treatment planning is an essential component of initial and all follow-up visits.

Table 4.3—Assessment of hypoglycemia risk

Factors that increase risk of treatment-associated hypoglycemia

- Use of insulin or insulin secretagogues (i.e., sulfonylureas, meglitinides)
- Impaired kidney or hepatic function
- Longer duration of diabetes
- Frailty and older age
- Cognitive impairment
- Impaired counterregulatory response, hypoglycemia unawareness
- Physical or intellectual disability that may impair behavioral response to hypoglycemia
- Alcohol use
- Polypharmacy (especially ACE inhibitors, angiotensin receptor blockers, nonselective β-blockers)

See references 114–118.

Table 4.4—Referrals for initial care management

- Eye care professional for annual dilated eye exam
- Family planning for women of reproductive age
- Registered dietitian for medical nutrition therapy
- Diabetes self-management education and support
- Dentist for comprehensive dental and periodontal examination
- Mental health professional, if indicated

Common Comorbidities

- Autoimmune Diseases (T1D)
- Cancer
- Cognitive Impairment/ Dementia
- Fatty Liver Disease
- Pancreatitis
- Fractures
- Hearing Impairment
- HIV
- Low Testosterone (Men)
- Obstructive Sleep Apnea
- Periodontal Disease
- Psychosocial/Emotional Disorders

Section 6

Glycemic Targets

A1C Testing

6.1 Perform the A1C test *at least* two times a year in patients who are meeting treatment goals (and who have stable glycemic control). E

6.2 Perform the A1C test quarterly in patients whose therapy has changed or who are not meeting glycemic goals. E

6.3 Point-of-care testing for A1C provides the opportunity for more timely treatment changes. E

A1C Goals (1)

6.4 A reasonable A1C goal for many nonpregnant adults is <7% (53 mmol/mol). A

6.5 Providers might reasonably suggest more stringent A1C goals (such as <6.5% [48 mmol/mol]) for selected individual patients if this can be achieved without significant hypoglycemia or other adverse effects of treatment (i.e., polypharmacy). Appropriate patients might include those with short duration of diabetes, type 2 diabetes treated with lifestyle or metformin only, long life expectancy, or no significant cardiovascular disease C

Glycemic Targets:
Standards of Medical Care in Diabetes - 2019. *Diabetes Care* 2019;42(Suppl.

Table 6.2—Summary of glycemic recommendations for many nonpregnant adults with diabetes

A1C	<7.0% (53 mmol/mol)*
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

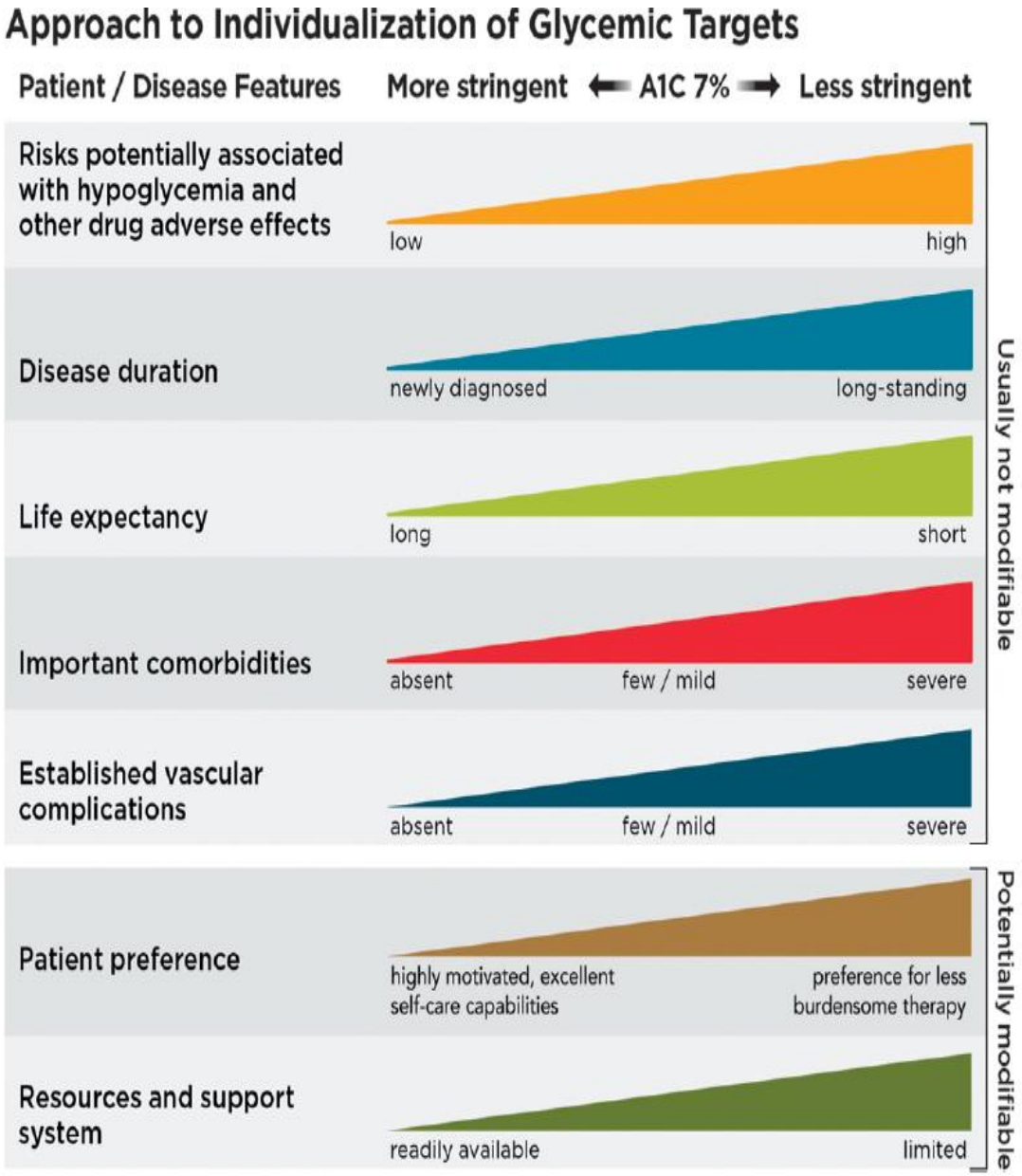
*More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations. †Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

A1C Goals (2)

6.6 Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes in whom the goal is difficult to achieve despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. B

6.7 Reassess glycemic targets over time based on the criteria in **Fig. 6.1** or, in older adults, **Table 12.1** E

Glycemic Targets:
Standards of Medical Care in Diabetes - 2019. *Diabetes Care* 2019;42(Suppl.



Glycemic Targets:
Standards of Medical Care in Diabetes - 2019. *Diabetes Care* 2019;42(Suppl

Hypoglycemia (1).

6.8 Individuals at risk for hypoglycemia should be asked about symptomatic and asymptomatic hypoglycemia at each encounter. C

6.9 Glucose (15-20 g) is the preferred treatment for the conscious individual with blood glucose <70 mg/dL (3.9 mmol/L), although any form of carbohydrate that contains glucose may be used. Fifteen minutes after treatment, if SMBG shows continued hypoglycemia, the treatment should be repeated. Once SMBG returns to normal, the individual should consume a meal or snack to prevent recurrence of hypoglycemia E

Glycemic Targets:
Standards of Medical Care in Diabetes - 2019. *Diabetes Care* 2019;42(Suppl.

Table 6.3—Classification of hypoglycemia (44)

Level	Glycemic criteria/description
Level 1	Glucose <70 mg/dL (3.9 mmol/L) and glucose ≥54 mg/dL (3.0 mmol/L)
Level 2	Glucose <54 mg/dL (3.0 mmol/L)
Level 3	A severe event characterized by altered mental and/or physical status requiring assistance

Glycemic Targets:
Standards of Medical Care in Diabetes - 2019. *Diabetes Care* 2019;42(Suppl. 1):S61-S70

Hypoglycemia (2).

6.10 Glucagon should be prescribed for all individuals at increased risk of level 2 hypoglycemia, defined as blood glucose <54 mg/dL (3.0 mmol/L), so it is available should it be needed. Caregivers, school personnel, or family members of these individuals should know where it is and when and how to administer it. Glucagon administration is not limited to health care professionals. E

6.11 Hypoglycemia unawareness or one or more episodes of level 3 hypoglycemia should trigger reevaluation of the treatment regimen E

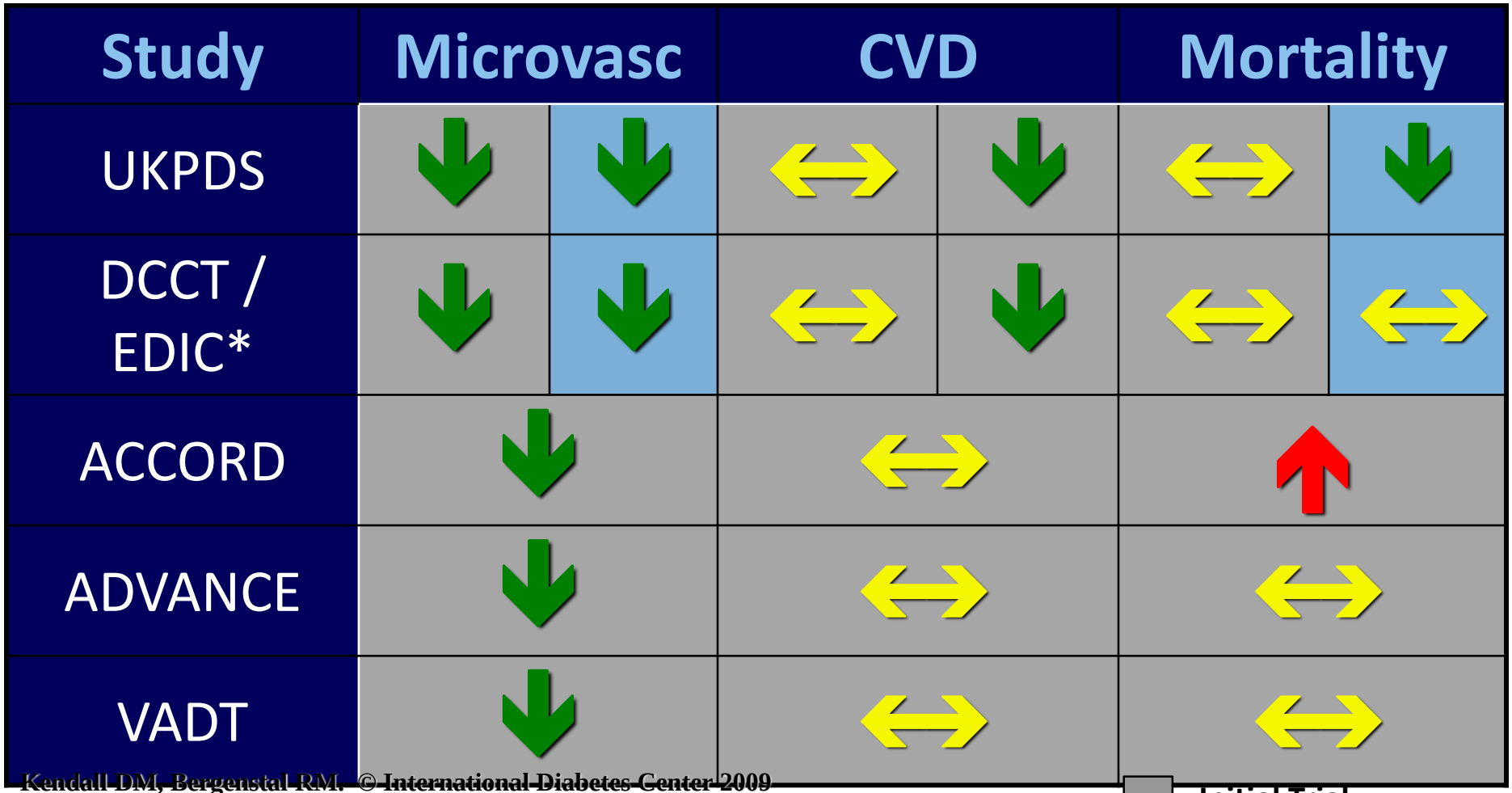
Glycemic Targets:
Standards of Medical Care in Diabetes - 2019. *Diabetes Care* 2019;42(Suppl. 1):S61-S70

Hypoglycemia (3).

6.12 Insulin-treated patients with hypoglycemia unawareness or an episode of level 2 hypoglycemia should be advised to raise their glycemic targets to strictly avoid hypoglycemia for at least several weeks in order to partially reverse hypoglycemia unawareness and reduce risk of future episodes. A

6.13 Ongoing assessment of cognitive function is suggested with increased vigilance for hypoglycemia by the clinician, patient, and caregivers if low cognition or declining cognition is found. B

Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials



Kendall DM, Bergenstal RM. © International Diabetes Center 2009

UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854.
Holman RR et al. *N Engl J Med*. 2008;359:1577. DCCT Research Group. N Engl J Med 1993;329;977.
Nathan DM et al. *N Engl J Med*. 2005;353:2643. Gerstein HC et al. *N Engl J Med.* 2008;358:2545.
Patel A et al. N Engl J Med 2008;358:2560. Duckworth W et al. N Engl J Med 2009;360:129. (erratum: Moritz T. *N Engl J Med* 2009;361:1024)

Initial Trial

Long Term Follow-up

* in T1DM

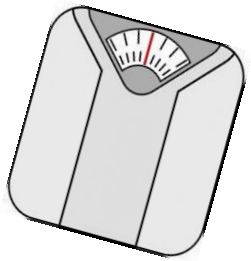
Section 9

Pharmacologic Approaches to Glycemic Treatment

3. ANTI-HYPERGLYCEMIC THERAPY

- **Therapeutic options: Lifestyle**

  - **Weight optimization**

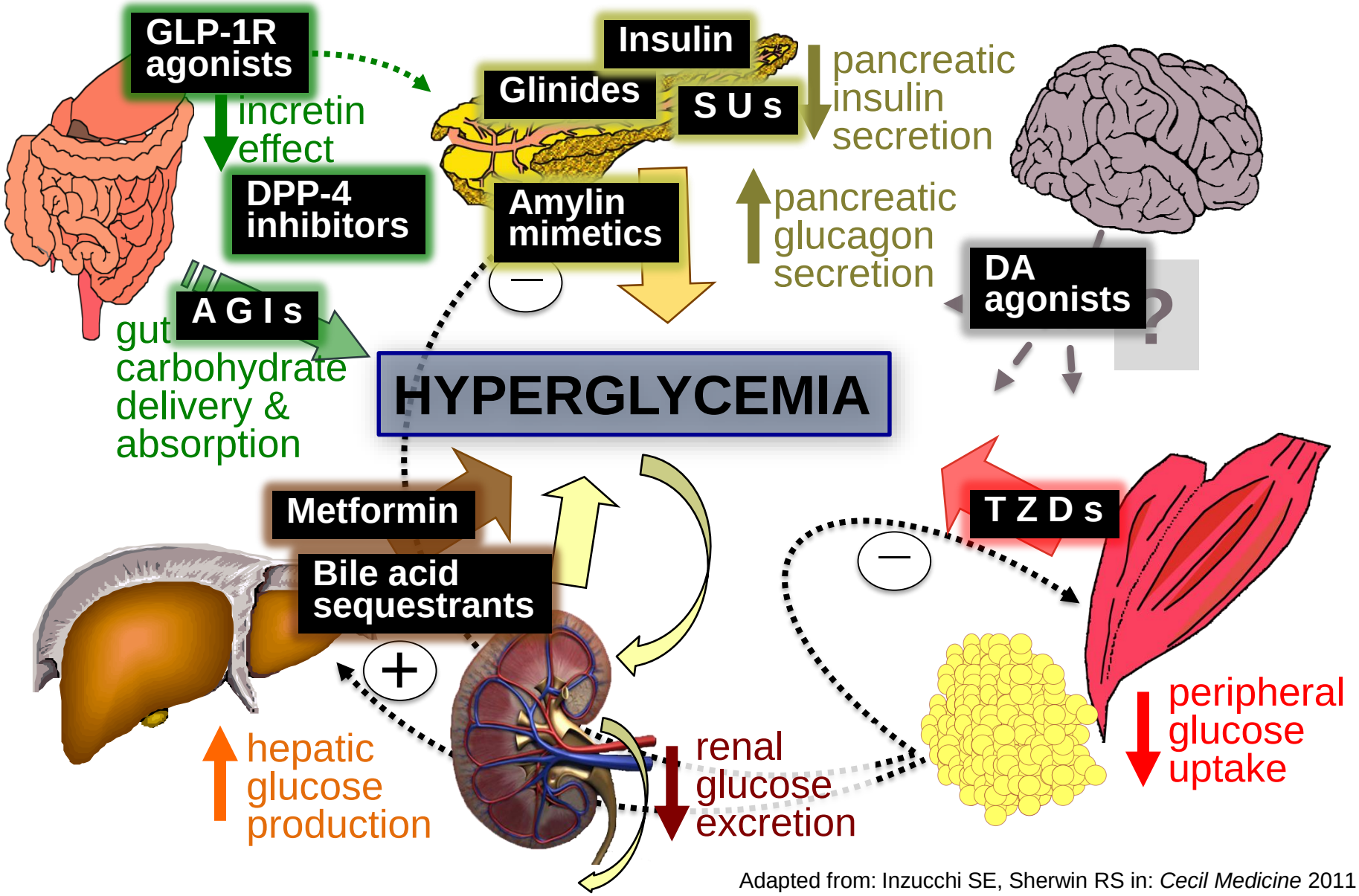


  - **Healthy diet**

  - **Increased activity level**

Diabetes Care 2012;35:1364–1379; *Diabetologia* 2012;55:1577–1596

Multiple, Complex Pathophysiological Abnormalities in T2DM



Adapted from: Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011

Oral Class	Mechanism	Advantages	Disadvantages	Cost
Biguanides	• Activates AMP-kinase (?other) • ↓ Hepatic glucose production	• Extensive experience • No hypoglycemia • Weight neutral • ? ↓ CVD	• Gastrointestinal • Lactic acidosis (rare) • B-12 deficiency • Contraindications	Low
Sulfonylureas	• Closes K_{ATP} channels • ↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk	• Hypoglycemia • ↑ Weight • Low durability • ? Blunts ischemic preconditioning	Low
Meglitinides	• Closes K_{ATP} channels • ↑ Insulin secretion	• ↓ Postprandial glucose • Dosing flexibility	• Hypoglycemia • ↑ Weight • ? Blunts ischemic preconditioning • Dosing frequency	Mod.
TZDs	• PPAR-γ activator • ↑ Insulin sensitivity	• No hypoglycemia • Durability • ↓ TGs (pio) • ↑ HDL-C • ? ↓ CVD events (pio)	• ↑ Weight • Edema/heart failure • Bone fractures • ↑ LDL-C (rosi) • ? ↑ MI (rosi)	Low

Table 1. Properties of anti-hyperglycemic agents

Diabetes Care 2015;38:140-149;
Diabetologia 2015;10.1077/s00125-014-3460-0

Oral Class	Mechanism	Advantages	Disadvantages	Cost
α-Glucosidase inhibitors	• Inhibits α-glucosidase • Slows carbohydrate digestion / absorption	• No hypoglycemia • Nonsystemic • ↓ Postprandial glucose • ? ↓ CVD events	• Gastrointestinal • Dosing frequency • Modest ↓ A1c	Mod.
DPP-4 inhibitors	• Inhibits DPP-4 • Increases incretin (GLP-1, GIP) levels	• No hypoglycemia • Well tolerated	• Angioedema / urticaria • ? Pancreatitis • ? ↑ Heart failure	High
Bile acid sequestrants	• Bind bile acids • ? ↓ Hepatic glucose production	• No hypoglycemia • ↓ LDL-C	• Gastrointestinal • Modest ↓ A1c • Dosing frequency	High
Dopamine-2 agonists	• Activates DA receptor • Alters hypothalamic control of metabolism • ↑ insulin sensitivity	• No hypoglyemia • **?** ↓ CVD events	• Modest ↓ A1c • Dizziness, fatigue • Nausea • Rhinitis	High
SGLT2 inhibitors	• Inhibits SGLT2 in proximal nephron • Increases glucosuria	•↓ Weight • No hypoglycemia • ↓ BP • Effective at all stages	• GU infections • Polyuria • Volume depletion • ↑ LDL-C • ↑Cr (transient)	High

Table 1. Properties of anti-hyperglycemic agents

Diabetes Care 2015;38:140-149;
Diabetologia 2015;10.1077/s00125-014-3460-0

Injectable Class	Mechanism	Advantages	Disadvantages	Cost
Amylin mimetics	• Activates amylin receptor • ↓ glucagon • ↓ gastric emptying • ↑ satiety	• ↓ Weight • ↓ Postprandial glucose	• Gastrointestinal • Modest ↓ A1c • Injectable • Hypo if insulin dose not reduced • Dosing frequency • Training requirements	High
GLP-1 receptor agonists	• Activates GLP-1 R • ↑ Insulin, ↓ glucagon • ↓ gastric emptying • ↑ satiety	• ↓ Weight • No hypoglycemia • ↓ Postprandial glucose • ↓ Some CV risk factors	• Gastrointestinal • ? Pancreatitis • ↑ Heart rate • Medullary ca (rodents) • Injectable • Training requirements	High
Insulin	• Activates insulin receptor • Myriad	• Universally effective • Unlimited efficacy • ↓ Microvascular risk	• Hypoglycemia • Weight gain • ? Mitogenicity • Injectable • Patient reluctance • Training requirements	Variable

Table 1. Properties of anti-hyperglycemic agents

Diabetes Care 2015;38:140-149;
Diabetologia 2015;10.1077/s00125-014-3460-0

Pharmacologic Therapy for Type 2 Diabetes

9.5 Metformin is the preferred initial pharmacologic agent for the treatment of type 2 diabetes. A

9.6 Once initiated, **metformin should be continued as long as it is tolerated and not contraindicated**; other agents, including insulin, should be added to metformin. A

9.7 Long-term use of metformin may be associated with biochemical vitamin B12 deficiency, and periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy. B

Pharmacologic Approaches to Glycemic Treatment:
Standards of Medical Care in Diabetes - 2019. *Diabetes Care* 2019;42(Suppl. 1):S90-S102

Pharmacologic Therapy for Type 2 Diabetes

9.8 The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels >10% or blood glucose levels ≥300 mg/dLare very high. E

9.9 Consider initiating dual therapy in patients with newly diagnosed type 2 diabetes who have A1C ≥1.5% above their glycemic target. E

9.10 A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include comorbidities (atherosclerotic cardiovascular disease, heart failure, chronic kidney disease), hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences. E

Pharmacologic Approaches to Glycemic Treatment:
Standards of Medical Care in Diabetes - 2019. *Diabetes Care* 2019;42(Suppl. 1):S90-S102

Pharmacologic Therapy for Type 2 Diabetes

9.11 Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease, sodium-glucose cotransporter 2 inhibitors, or glucagon-like peptide 1 receptor agonists with demonstrated cardiovascular disease benefit (**Table 9.1**) are recommended as part of the antihyperglycemic regimen. A

9.12 Among patients with atherosclerotic cardiovascular disease at high risk of heart failure or in whom heart failure coexists, sodium-glucose cotransporter 2 inhibitors are preferred. C

9.13 For patients with type 2 diabetes and chronic kidney disease, consider use of a sodium-glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist shown to reduce risk of chronic kidney disease progression, cardiovascular events, or both. C

Pharmacologic Approaches to Glycemic Treatment:
Standards of Medical Care in Diabetes - 2019. *Diabetes Care* 2019;42(Suppl. 1):S90-S102

Pharmacologic Therapy for Type 2 Diabetes

9.14 In most patients who need the greater glucose-lowering effect of an injectable medication, glucagon-like peptide 1 receptor agonists are preferred to insulin. B

9.15 Intensification of treatment for patients with type 2 diabetes not meeting treatment goals should not be delayed. B

9.16 The medication regimen should be reevaluated at regular intervals (every 3-6 months) and adjusted as needed to incorporate new patient factors (**Table 9.1**). E

Pharmacologic Approaches to Glycemic Treatment:
Standards of Medical Care in Diabetes - 2019. *Diabetes Care* 2019;42(Suppl. 1):S90-S102

Table 9.1—Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

	Efficacy	Hypoglycemia	Weight change	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
				ASCVD	CHF			Progression of DKD	Dosing/use considerations*	
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	• Contraindicated with eGFR <30	• Gastrointestinal side effects common (diarrhea, nausea) • Potential for B12 deficiency
SGLT-2 inhibitors	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	• Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	• **FDA Black Box:** Risk of amputation (**canagliflozin**) • Risk of bone fractures (canagliflozin) • DKA risk (all agents, rare in T2DM) • Genitourinary infections • Risk of volume depletion, hypotension • ↑LDL cholesterol • Risk of Fournier's gangrene
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide Benefit: liraglutide† > semaglutide > exenatide extended release	Neutral	High	SQ	Benefit: liraglutide	• Renal dose adjustment required (exenatide, lixisenatide) • Caution when initiating or increasing dose due to potential risk of acute kidney injury	• **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) • Gastrointestinal side effects common (nausea, vomiting, diarrhea) • Injection site reactions • ?Acute pancreatitis risk
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin, alogliptin	High	Oral	Neutral	• Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment • No dose adjustment required for linagliptin	• Potential risk of acute pancreatitis • Joint pain
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Low	Oral	Neutral	• No dose adjustment required • Generally not recommended in renal impairment due to potential for fluid retention	• **FDA Black Box:** Congestive heart failure (**pioglitazone, rosiglitazone**) • Fluid retention (edema; heart failure) • Benefit in NASH • Risk of bone fractures • Bladder cancer (pioglitazone) • ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	• Glyburide: not recommended • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	• FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin: Human insulin	Highest	Yes	Gain	Neutral	Neutral	Low	SQ	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin: Analogs						High	SQ			

*For agent-specific dosing recommendations, please refer to the manufacturers' prescribing information. †FDA approved for CVD benefit. CHF, congestive heart failure; CV, cardiovascular; DPP-4, dipeptidyl peptidase 4; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; NASH, nonalcoholic steatohepatitis; SGLT2, sodium–glucose cotransporter 2; SQ, subcutaneous; T2DM, type 2 diabetes.

Based on findings from The Dapagliflozin Effect on Cardiovascular Events-Thrombosis in Myocardial Infarction 58 (DECLARE-TIMI 58) Trial, which showed a reduction of hospitalization for heart failure with dapagliflozin treatment versus placebo (HR: 0.73; 95% CI: 0.61 to 0.88), the portion of the table highlighting benefit of SGLT-2 inhibitors for CHF is revised to read: "Benefit: empagliflozin†, canagliflozin, dapagliflozin"

Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy — Metformin — Lifestyle Management

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy — Metformin + — Lifestyle Management

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

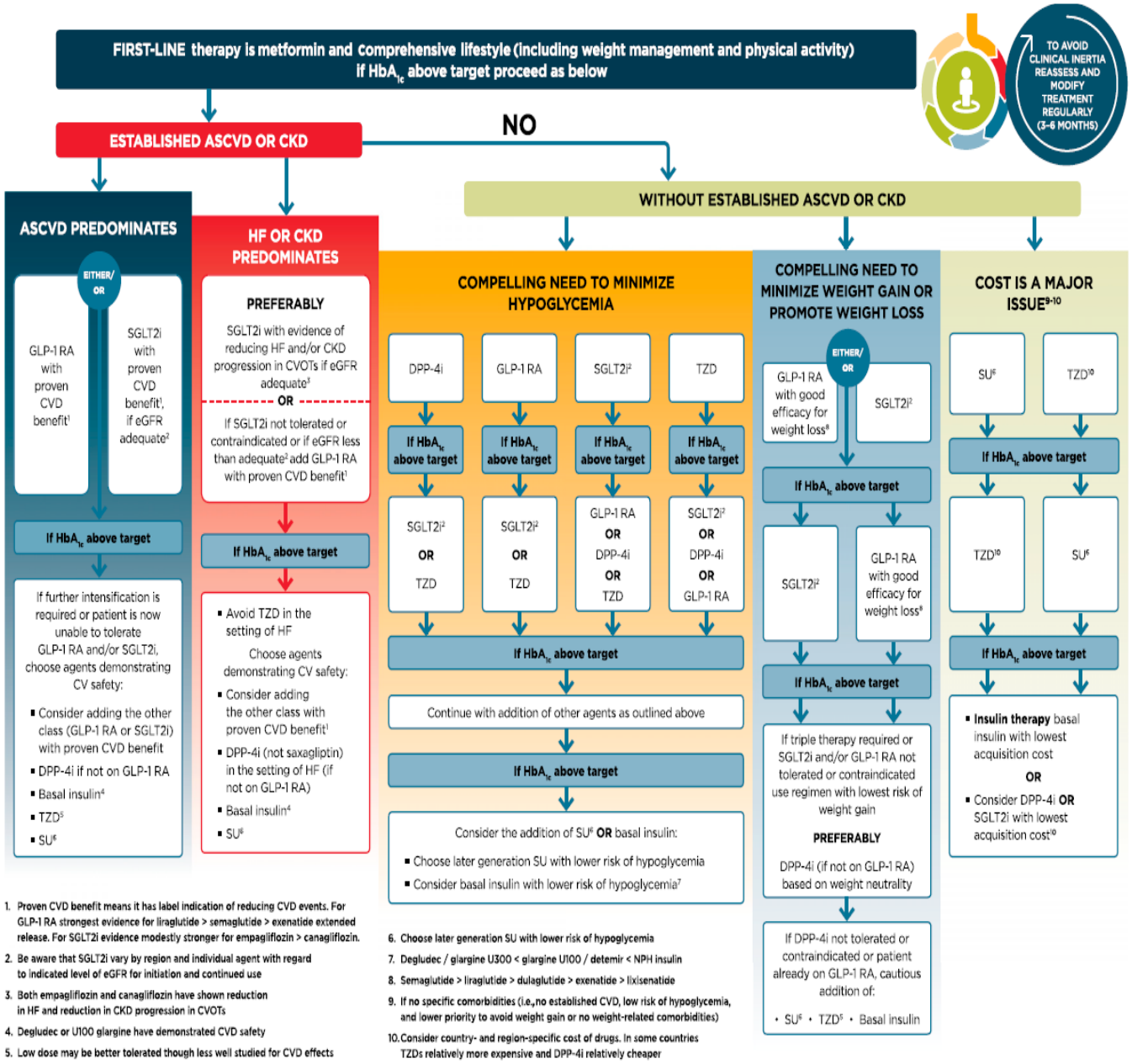
Triple Therapy — Metformin + — Lifestyle Management

Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin[§]	or GLP-1-RA	or Insulin[§]	or GLP-1-RA
or Insulin[§]	or Insulin[§]		or Insulin[§]		

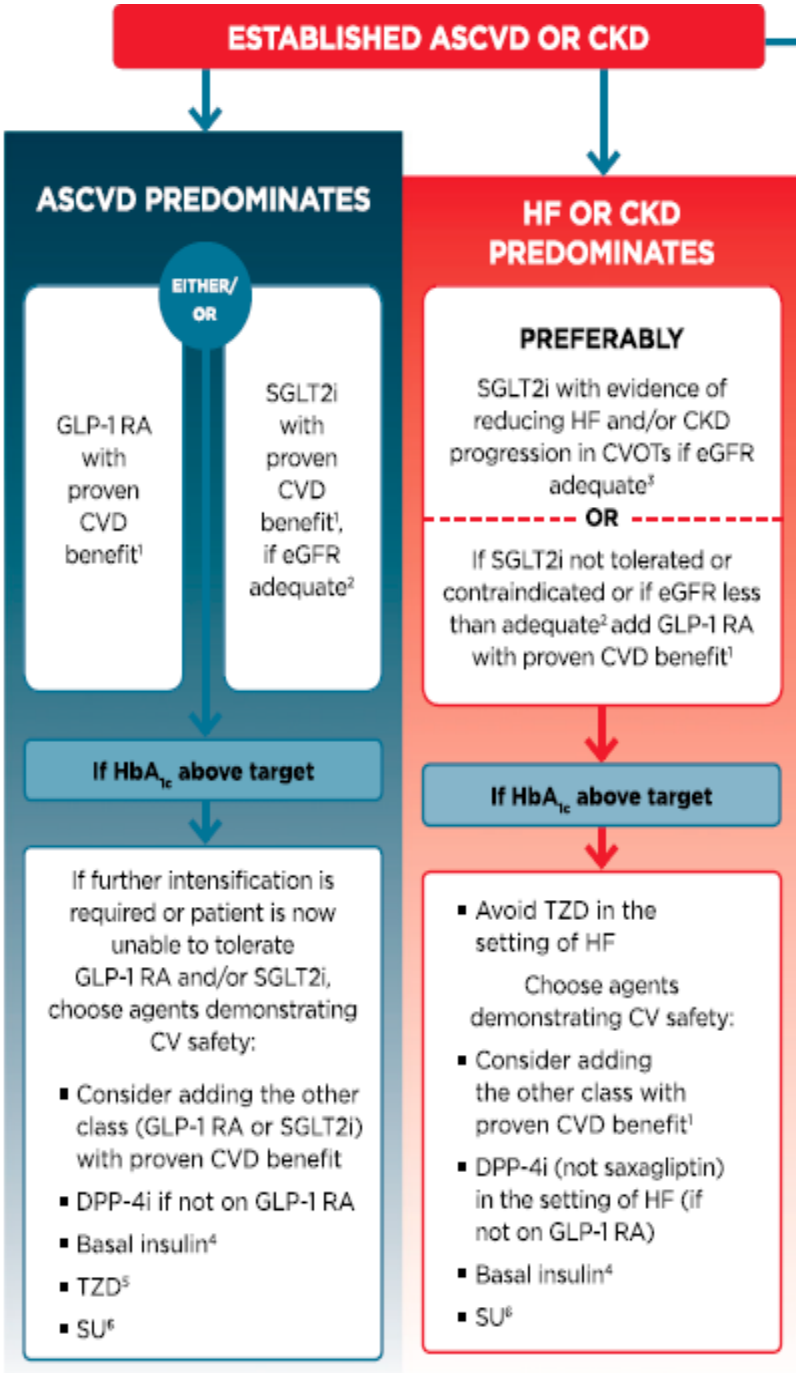
If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

Combination Injectable Therapy (See Figure 8.2)

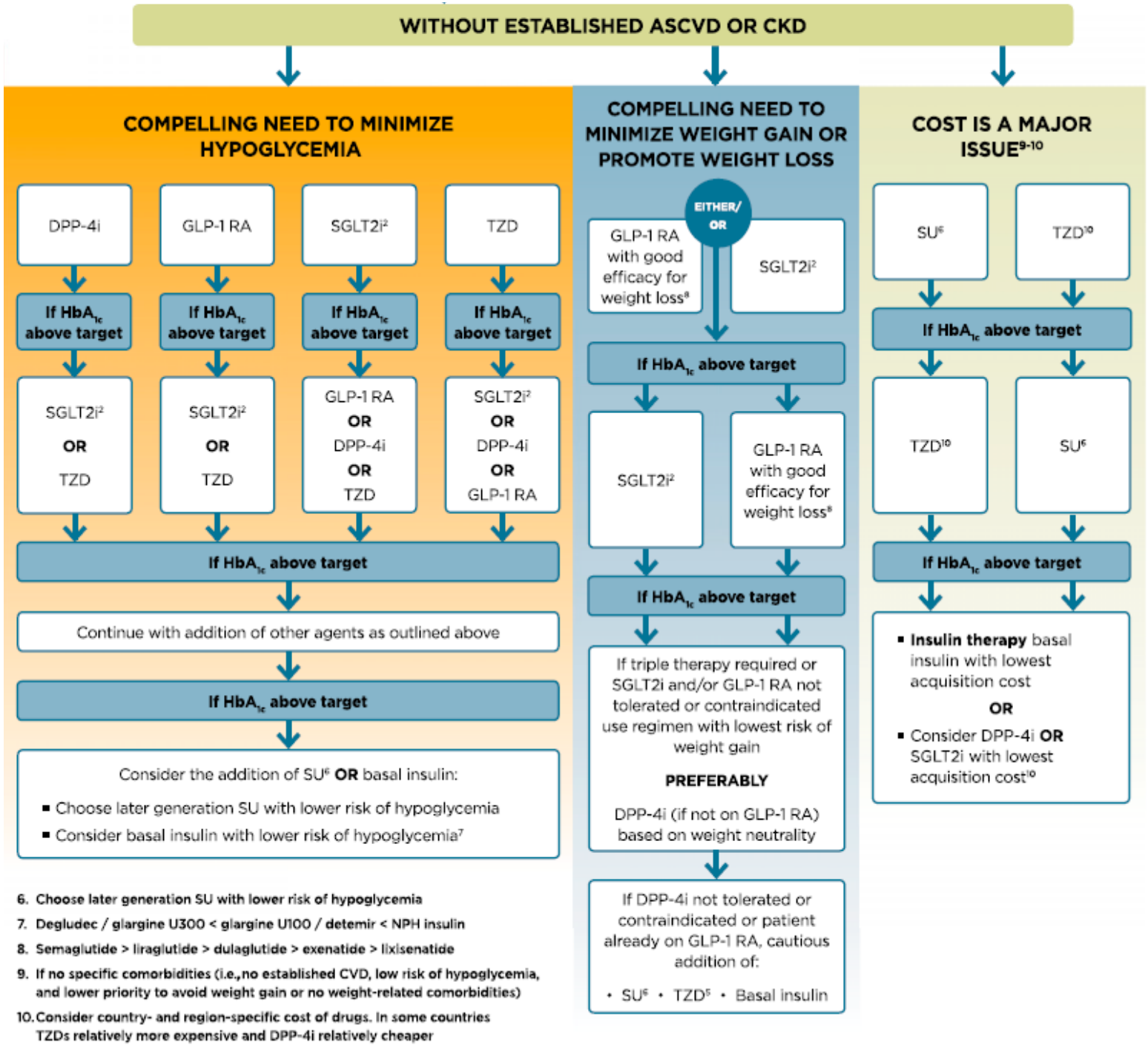
American Diabetes Association®



Based on findings from The Dapagliflozin Effect on Cardiovascular Events-Thrombosis in Myocardial Infarction 58 (DECLARE-TIMI 58) Trial, which showed a reduction of hospitalization for heart failure and a reduction in progression of CKD, footnote #3 within Figure 9.1 is revised to read: "Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs"

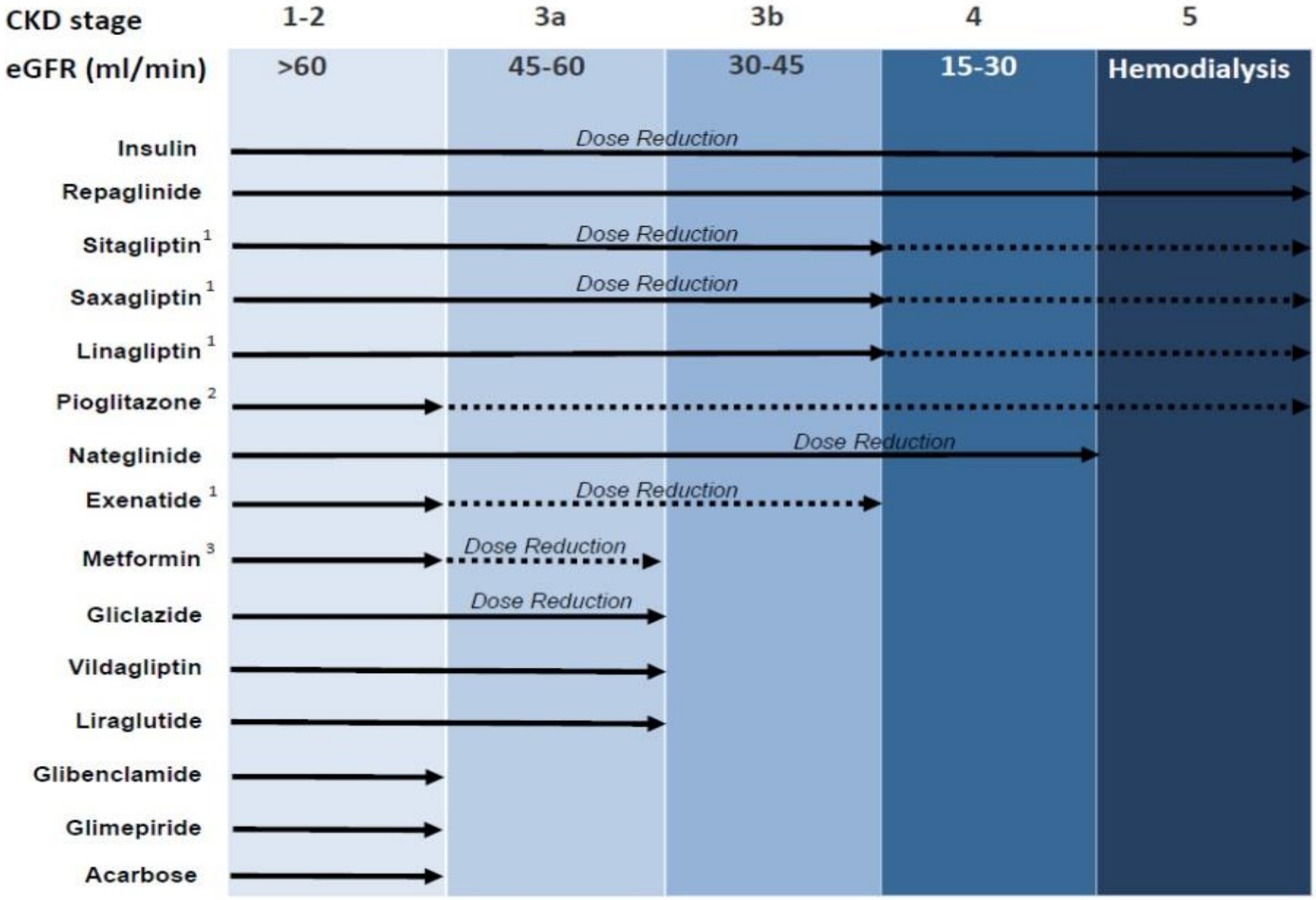


- If A1C is above target despite recommended first-line treatment and the patient has ASCVD or CKD:
  - **ASCVD Predominates:**
    - Add GLP-1 RA with proven CVD benefit, OR
    - Add SGLT-2 inhibitor with proven CVD benefit (if eGFR adequate)
  - **If HF or CKD Predominates:**
    - Add SGLT-2 inhibitor with evidence of benefit
    - If can't take an SGLT-2 inhibitor, use a GLP-1 RA with proven CVD benefit



6. **Choose later generation SU with lower risk of hypoglycemia**
7. **Degludec / glargine U300 < glargine U100 / detemir < NPH insulin**
8. **Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide**
9. **If no specific comorbidities (i.e.,no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)**
10. **Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper**

CHOIX DU SULFAMIDE FONCTION DES MARQUEURS BIO CLINIQUES


CKD stage
1-2
3a
3b
4
5
eGFR (ml/min)
>60
45-60
30-45
15-30
Hemodialysis
Insulin
Dose Reduction
Repaglinide
Sitagliptin 1
Dose Reduction
Saxagliptin 1
Dose Reduction
Linagliptin 1
Pioglitazone 2
Nateglinide
Dose Reduction
Exenatide 1
Dose Reduction
Metformin 3
Dose Reduction
Gliclazide
Dose Reduction
Vildagliptin
Liraglutide
Glibenclamide
Glimepiride
Acarbose

Sex and BMI Alter the Benefits and Risks of Sulfonylureas and Thiazolidinediones in Type 2 Diabetes: A Framework for Evaluating Stratification Using Routine Clinical and Individual Trial Data

John M. Dennis,[1] William E. Henley,[1] Michael N. Weedon,[2] Mike Lonergan,[3] Lauren R. Rodgers,[1] Angus G. Jones,[4,5] William T. Hamilton,[2] Naveed Sattar,[6] Salim Janmohamed,[7] Rury R. Holman,[8,9] Ewan R. Pearson,[3] Beverley M. Shields,[4] and Andrew T. Hattersley,[4,5] on behalf of the MASTERMIND Consortium*

Diabetes Care 2018;41:1844–1853 | https://doi.org/10.2337/dc18-0344

RESEARCH DESIGN AND METHODS

We studied 22,379 patients starting sulfonylurea or thiazolidinedione therapy in the U.K. CPRD to identify features associated with increased 1-year HbA1c fall with one therapy class and reduced fall with the second. We then assessed whether prespecified patient subgroups defined by the differential clinical factors showed differing 5-year glycemic response and side effects with sulfonylureas and thiazolidinediones using individual randomized trial data from ADOPT (first-line therapy, n = 2,725) and RECORD (second-line therapy, n = 2,222). Further replication was conducted using routine clinical data from GoDARTS (n = 1,977).

RESULTS

In CPRD, male sex and lower BMI were associated with greater glycemic response with sulfonylureas ($P < 0.001$).

In ADOPT and RECORD, non obese males had a greater overall HbA1c reduction with sulfonylureas than with thiazolidinediones ($P < 0.001$); in contrast, obese females had a greater HbA1c reduction with thiazolidinediones than with sulfonylureas ($P < 0.001$). Weight gain and edema risk with thiazolidinediones were greatest in obese females.

CONCLUSIONS

Patient subgroups defined by sex and BMI have different patterns of benefits and risks on thiazolidinedione and sulfonylurea therapy. Subgroup-specific estimates can inform discussion about the choice of therapy after metformin for an individual patient.

Diabetes Care 2018;41:1844–1853

SULFAMIDES ET SAFETY

Sulfamides hypoglycémiants
Registre Britannique

Diabetes Care

Pharmacologic Differences of Sulfonylureas and the Risk of Adverse Cardiovascular and Hypoglycemic Events

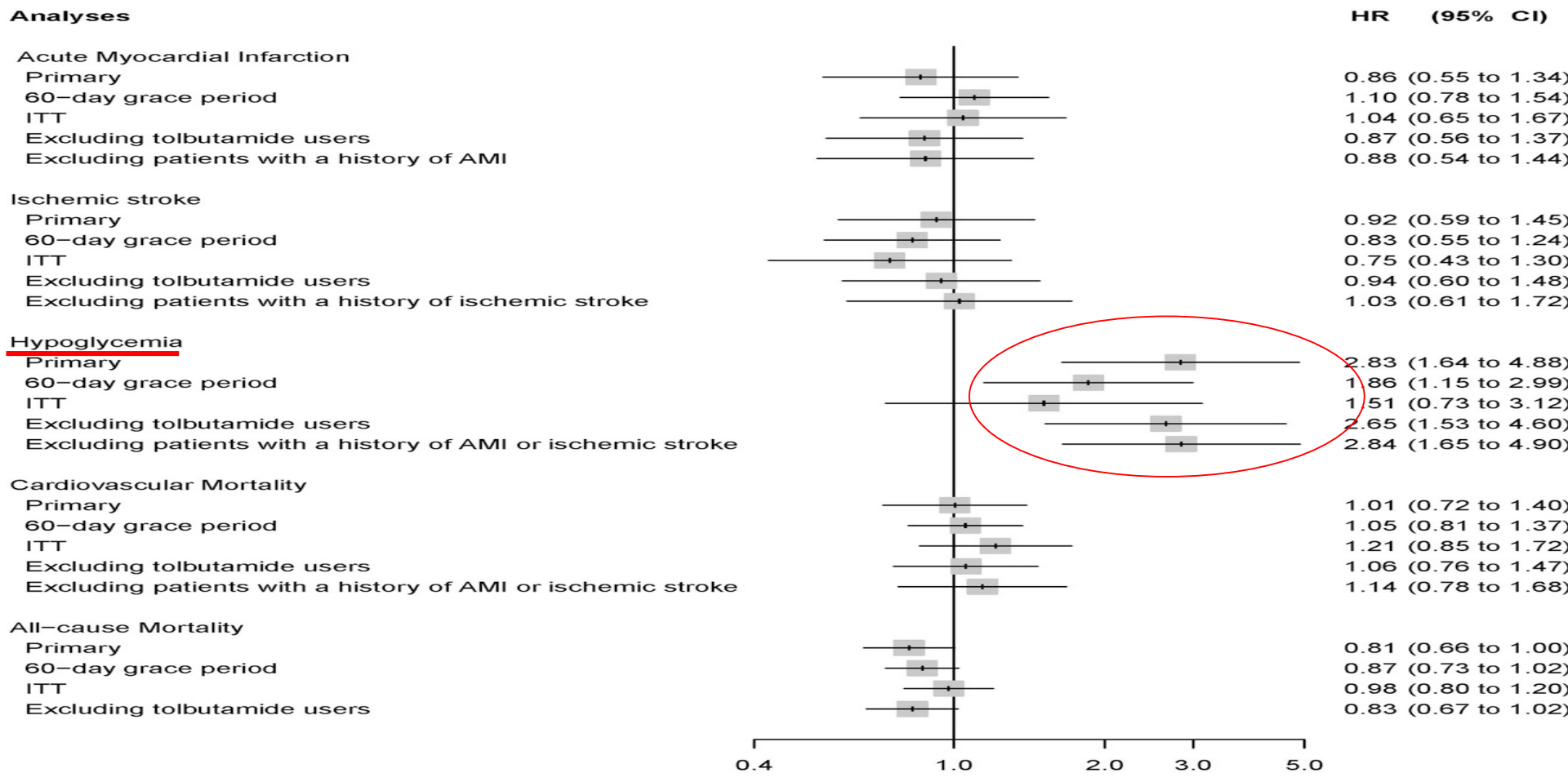
https://doi.org/10.2337/dc17-0595

Antonios Douros,[1,2,3] Hui Yin,[1] Oriana Hoi Yun Yu,[1,4] Kristian B. Filion,[1,2,5] Laurent Azoulay,[1,2,6] and Samy Suissa[1,2,5]

* Effet des sulfamides sur les **évènements CV** et l'**hypoglycémie**

* **DT2 nouveaux** (≥ 40ans) entre **1998 - 2013**
  * **SU à longue durée d'action avec action pancréatique non spécifique**
    Glyburide (50%) et **Glimépiride** (50%) : 1863
  * **SU à courte durée d'action avec action pancréatique plus spécifique**
    Gliclazide (92%), **Tobulamide** (3%) et **Glipizide** (5%) : 15741

Sulfamides hypoglycémiants



Pas de différence significative sur la Mortalité et évènements CV entre les 2 groupes

↑ Hypoglycémie avec SU à LDA
Glyburide et **Glimepiride**

Sulfonylureas as second line drugs in type 2 diabetes and the risk of cardiovascular and hypoglycaemic events: population based cohort study

the bmj | BMJ 2018;362:k2693 | doi: 10.1136/bmj.k2693

Antonios Douros,[1,2,3] Sophie Dell'Aniello,[1] Oriana Hoi Yun Yu,[1,4] Kristian B Filion,[1,2,5] Laurent Azoulay,[1,2,6] Samy Suissa[1,2,5]

[1]Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, 3755 Cote Ste-Catherine, H-461 Montréal, QC H3T 1E2, Canada

OBJECTIVE

To assess whether adding or switching to sulfonylureas is associated with an increased risk of myocardial infarction, ischaemic stroke, cardiovascular death, all cause mortality, severe hypoglycaemia, compared with remaining on metformin monotherapy in patients with type 2 diabetes.

DESIGN

Population based cohort study

SETTING

General practices contributing to the Clinical Practice Research Datalink

PARTICIPANTS

Patients with type 2 diabetes initiating metformin monotherapy between 1998 and 2013.

MAIN OUTCOME MEASURES

Using the prevalent new-user cohort design we matched 1:1 patients adding or switching to sulfonylureas with those remaining on metformin monotherapy on high-dimensional propensity score, haemoglobin A1c, and number of previous metformin prescriptions. The two groups were compared using Cox proportional hazards models to estimate adjusted hazard ratios and 95% confidence intervals for the study outcomes.

RESULTS

Among 77 138 metformin initiators, 25 699 added or switched to sulfonylureas during the study period. During a mean follow-up of 1.1 years, sulfonylureas were associated with an increased risk of myocardial infarction, all cause mortality, and severe hypoglycaemia, compared with remaining on metformin monotherapy. Continuing metformin when introducing sulfonylureas appears to be safer than switching.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Sulfonylureas are widely used second line oral antidiabetic drugs

Previous studies have assessed their cardiovascular and hypoglycaemic safety as first line drugs or in comparison with other second line antidiabetic drugs

WHAT THIS STUDY ADDS

Sulfonylureas as second line drugs are associated with an increased risk of myocardial infarction, all cause mortality, and severe hypoglycaemia, compared with remaining on metformin monotherapy

Continuation of metformin when introducing sulfonylureas is safer than switching

Analyses	Hazard ratio (95% CI)
Myocardial Infarction	
Primary	1.26 (1.01 to 1.56)
60 day grace period	1.12 (0.94 to 1.32)
Excluding patients with a history of the outcome	1.28 (1.02 to 1.60)
Adjusting for additional covariates	1.23 (1.00 to 1.53)
Ischaemic stroke	
Primary	1.24 (0.99 to 1.56)
60 day grace period	1.16 (0.96 to 1.40)
Excluding patients with a history of the outcome	1.22 (0.97 to 1.54)
Adjusting for additional covariates	1.24 (0.98 to 1.55)
Cardiovascular death	
Primary	1.18 (0.98 to 1.43)
60 day grace period	1.16 (1.00 to 1.34)
Excluding patients with a history of myocardial infarction or stroke	1.18 (0.97 to 1.44)
Adjusting for additional covariates	1.13 (0.93 to 1.37)
All cause mortality	
Primary	1.28 (1.15 to 1.44)
60 day grace period	1.22 (1.12 to 1.34)
Adjusting for additional covariates	1.25 (1.11 to 1.40)
Hypoglycemia	
Primary	7.60 (4.64 to 12.44)
60 day grace period	7.05 (4.75 to 10.47)
Excluding patients with a history of the outcome	7.58 (4.63 to 12.42)
Adjusting for additional covariates	7.10 (4.33 to 11.63)

JAMA Network | Open

Original Investigation | Diabetes and Endocrinology

Association of Second-line Antidiabetic Medications With Cardiovascular Events Among Insured Adults With Type 2 Diabetes

Corresponding Author: Matthew J. O'Brien, MD, MSc, Division of General Internal Medicine and Geriatrics, Department of Medicine, Northwestern University Feinberg School of Medicine, 750 N Lake Shore Dr, Sixth Floor, Chicago, IL 60611 (matthew.obrien1@northwestern.edu).

Matthew J. O'Brien, MD, MSc; Susan L. Karam, MD; Amisha Wallia, MD, MS; Raymond H. Kang, MA; Andrew J. Cooper, MSc; Nicola Lancki, MPH; Margaret R. Moran, MPH; David T. Liss, PhD; Theodore A. Prospect, FSA, MAAA; Ronald T. Ackermann, MD, MPH

OBJECTIVE To examine the association of second-line ADM classes with major adverse cardiovascular events.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study among 132 737 insured adults with type 2 diabetes who started therapy with a second-line ADM after taking either metformin alone or no prior ADM. This study used 2011-2015 US nationwide administrative claims data. Data analysis was performed from January 2017 to October 2018.

EXPOSURES Dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose cotransporter 2 (SGLT-2) inhibitors, thiazolidinediones (TZDs), basal insulin, and sulfonylureas or meglitinides (both referred to as sulfonylureas hereafter). The DPP-4 inhibitors served as the comparison group in all analyses.

MAIN OUTCOMES AND MEASURES The primary outcome was time to first cardiovascular event after starting the second-line ADM. This composite outcome was based on hospitalization for the following cardiovascular conditions: congestive heart failure, stroke, ischemic heart disease, or peripheral artery disease.

RESULTS Among 132 737 insured adult patients with type 2 diabetes (men, 55%; aged 45-64 years, 58%; white, 63%), there were 3480 incident cardiovascular events during 169 384 person-years of follow-up. Patients were censored after the first cardiovascular event, discontinuation of insurance coverage, transition from *International Classification of Diseases, Ninth Revision* (*ICD-9*) to end of *ICD-9* coding, or 2 years of follow-up. After adjusting for patient, prescriber, and health plan characteristics, the risk of composite cardiovascular events after starting GLP-1 receptor agonists was lower than DPP-4 inhibitors (hazard ratio [HR], 0.78; 95% CI, 0.63-0.96), but this finding was not significant in all sensitivity analyses. Cardiovascular event rates after starting treatment with SGLT-2 inhibitors (HR, 0.81; 95% CI, 0.57-1.53) and TZDs (HR, 0.92; 95% CI, 0.76-1.11) were not statistically different from DPP-4 inhibitors. The comparative risk of cardiovascular events was higher after starting treatment with sulfonylureas (HR, 1.36; 95% CI, 1.23-1.49) or basal insulin (HR, 2.03; 95% CI, 1.81-2.27) than DPP-4 inhibitors.

CONCLUSIONS AND RELEVANCE Among insured adult patients with type 2 diabetes initiating second-line ADM therapy, the short-term cardiovascular outcomes of GLP-1 receptor agonists, SGLT-2 inhibitors, and DPP-4 inhibitors were similar. Higher cardiovascular risk was associated with use of sulfonylureas or basal insulin compared with newer ADM classes. Clinicians may consider prescribing GLP-1 receptor agonists, SGLT-2 inhibitors, or DPP-4 inhibitors more routinely after metformin rather than sulfonylureas or basal insulin.

European Heart Journal (2011) **32**, 1900–1908
doi:10.1093/eurheartj/ehr077

CLINICAL RESEARCH
Prevention

Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study

Tina Ken Schramm[1]*, Gunnar Hilmar Gislason[2], Allan Vaag[3], Jeppe Nørgaard Rasmussen[4], Fredrik Folke[5], Morten Lock Hansen[2], Emil Loldrup Fosbøl[2], Lars Køber[1], Mette Lykke Norgaard[2], Mette Madsen[6], Peter Riis Hansen[2], and Christian Torp-Pedersen[2]

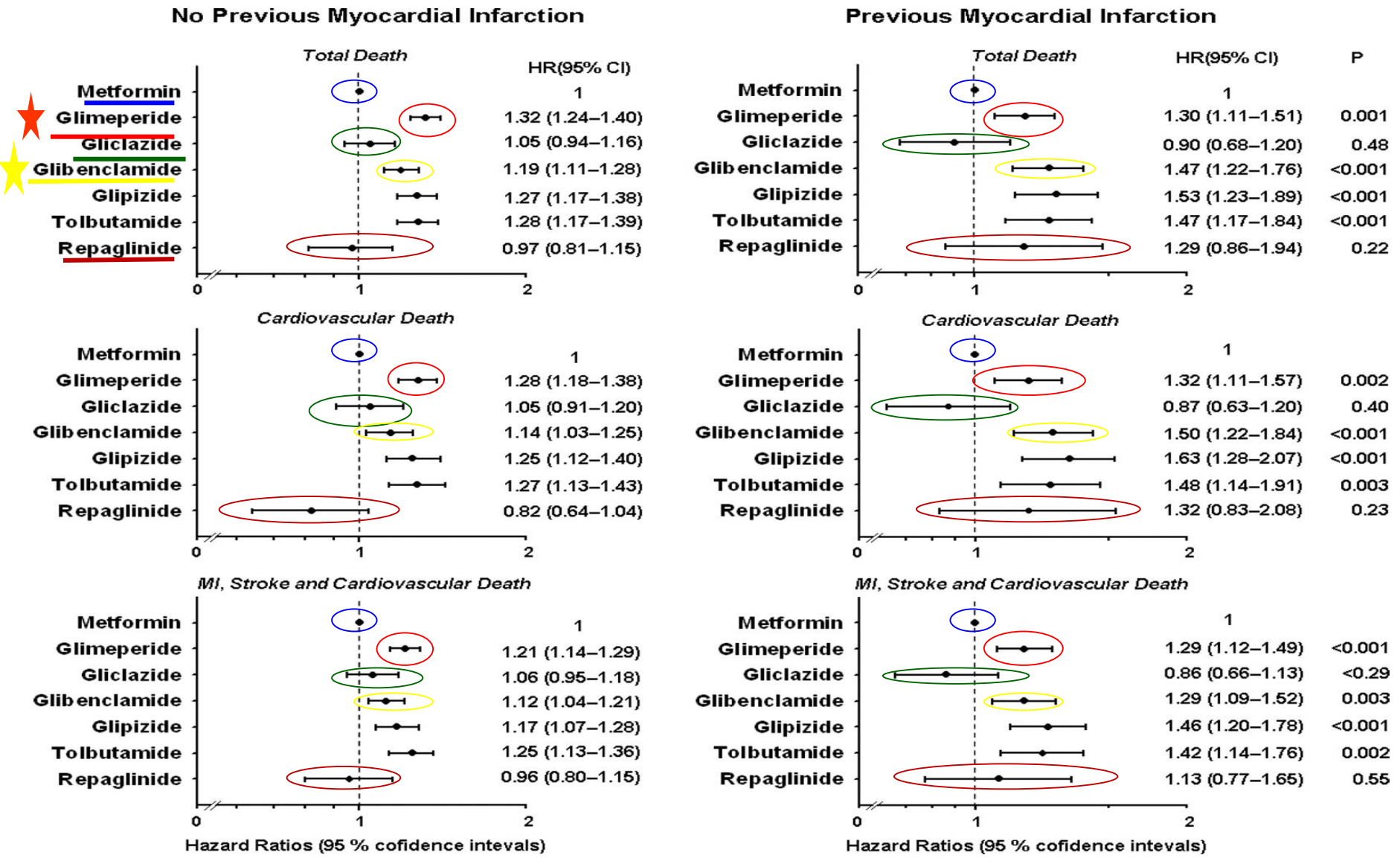
Aims The impact of insulin secretagogues (ISs) on long-term major clinical outcomes in type 2 diabetes remains unclear. We examined mortality and cardiovascular risk associated with all available ISs compared with metformin in a nationwide study.

Methods and results All Danish residents >20 years, initiating single-agent ISs or metformin between 1997 and 2006 were followed for up to 9 years (median 3.3 years) by individual-level linkage of nationwide registers. All-cause mortality, cardiovascular mortality, and the composite of myocardial infarction (MI), stroke, and cardiovascular mortality associated with individual ISs were investigated in patients with or without previous MI by multivariable Cox proportional-hazard analyses including propensity analyses. A total of 107 806 subjects were included, of whom 9607 had previous MI. Compared with metformin, glimepiride (hazard ratios and 95% confidence intervals): 1.32 (1.24–1.40), glibenclamide: 1.19 (1.11–1.28), glipizide: 1.27 (1.17–1.38), and tolbutamide: 1.28 (1.17–1.39) were associated with increased all-cause mortality in patients without previous MI. The corresponding results for patients with previous MI were as follows: glimepiride: 1.30 (1.11–1.44), glibenclamide: 1.47 (1.22–1.76), glipizide: 1.53 (1.23–1.89), and tolbutamide: 1.47 (1.17–1.84). Results for gliclazide [1.05 (0.94–1.16) and 0.90 (0.68–1.20)] and repaglinide and [0.97 (0.81–1.15) and 1.29 (0.86–1.94)] were not statistically different from metformin in both patients without and with previous MI, respectively. Results were similar for cardiovascular mortality and for the composite endpoint.

Conclusion Monotherapy with the most used ISs, including glimepiride, glibenclamide, glipizide, and tolbutamide, seems to be associated with increased mortality and cardiovascular risk compared with metformin. Gliclazide and repaglinide appear to be associated with a lower risk than other ISs.

Sulfamides hypoglycémiants

European Heart Journal



Antidiabétique Molécule	Risque Cardiovasculaire		
	↑	Neutre	↓
Metformine		X	±
Sulfamides / Glinides -Glibenclamide -Glimeperide -Gliclazide -Repaglinide	 X X 	 X X	
Acarbose		X	
Pioglitazone		X	
Inhibiteur DDP4		X	
Analogues GLP1 - Lixisenatide / Exenatide - Liraglutide / Semaglutide		X	 X
Inhibiteur SGLT2			X
Insuline	X **« Doses ↑ »**	X	

MESSAGE TO TAKE HOME

primum non nocere