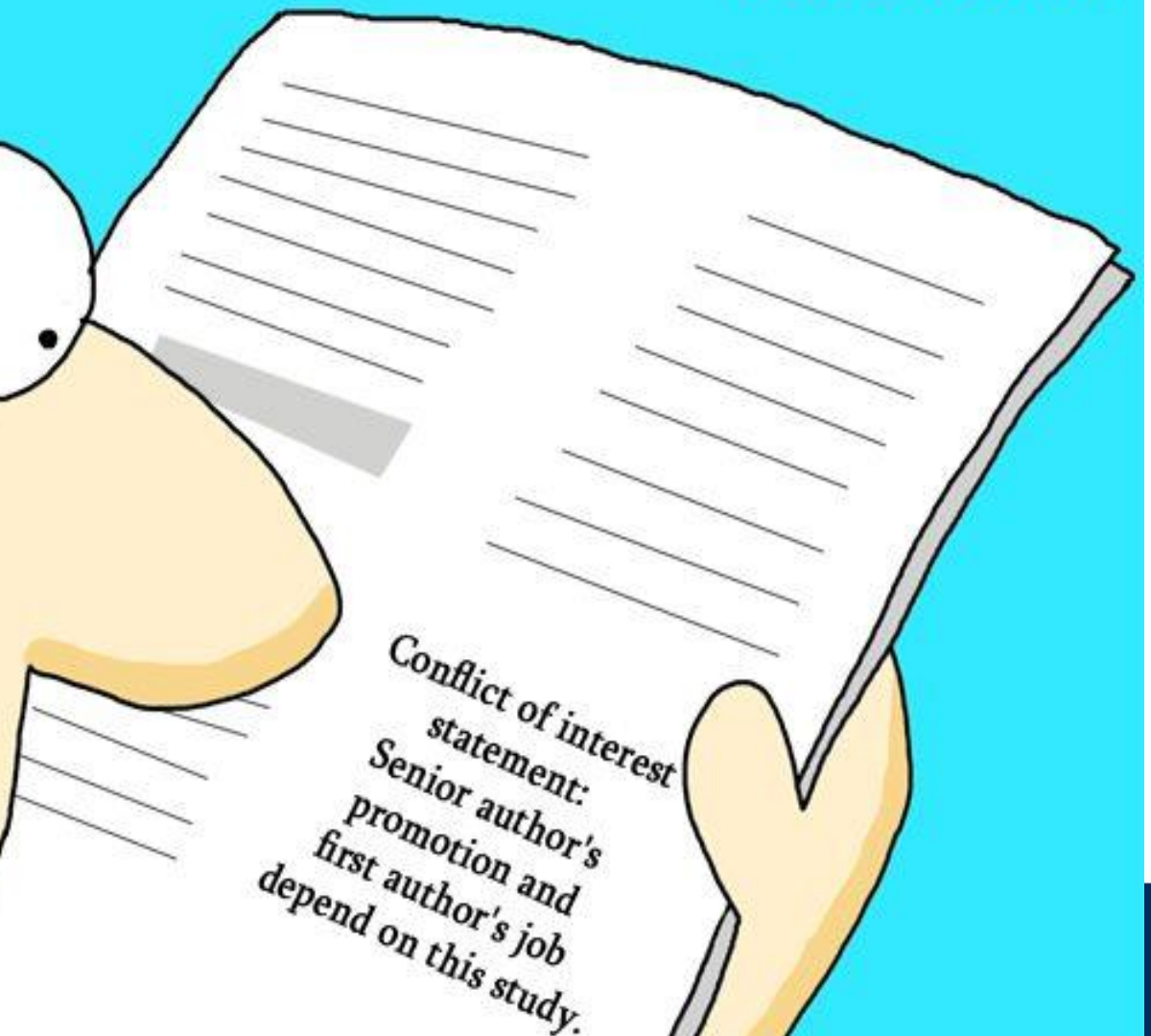
ACC Middle East Conference 2018

In partnership with:

جمعية القلب السعودية
Saudi Heart Association

OLD AND NEW DRUGS FOR CONTROLING DIABETES – THERAPEUTIC CLASSES AND MECHANISM OF ACTION

Biljana Parapid, MD, PhD, FESC
Belgrade University School of Medicine, Belgrade (Serbia)
@biljana_parapid


Conflict of interest statement:
Senior author's promotion and first author's job depend on this study.

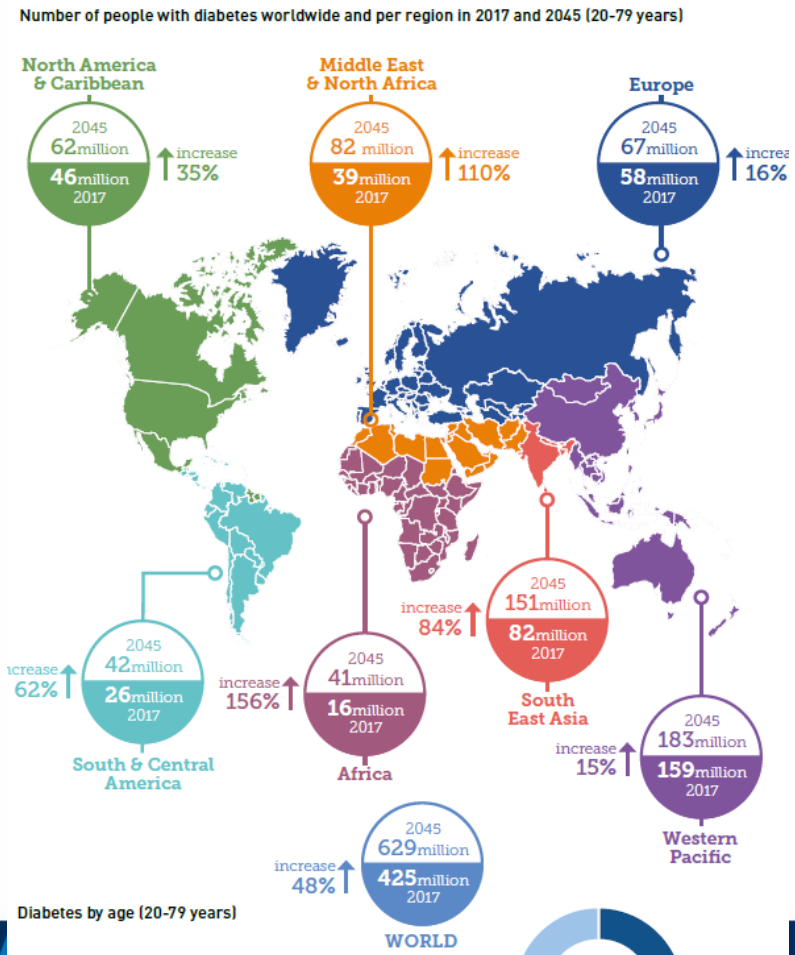
COI

DIABETES should be diagnosed if **ONE OR MORE** of the following criteria are met	**IMPAIRED GLUCOSE TORELANCE** (IGT) should be diagnosed if **BOTH** of the following criteria are met	**IMPAIRED FASTING GLUCOSE** (IFG) should be diagnosed if **BOTH** of the following criteria are met
Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL)	Fasting plasma glucose <7.0 mmol/L (126 mg/dL)	Fasting plasma glucose 6.1-6.9 mmol/L (110 to 125 mg/ dL)
or	and	and
Two-hour plasma glucose ≥11.1 mmol/L (200 mg/dL) following a 75g oral glucose load	Two-hour plasma glucose ≥7.8 <11.1mmol/L (≥140 to <200 mg/dL) following a 75g oral glucose load	Two-hour plasma glucose <7.8mmol/L (140mg/dL) following a 75g oral glucose load
or		
A random glucose > 11.1 mmol/L (200 mg/ dL) or HbA1c ≥ 48 mmol/mol (equivalent to 6.5%)		

International Diabetes Federation, 2017

IDF

2017



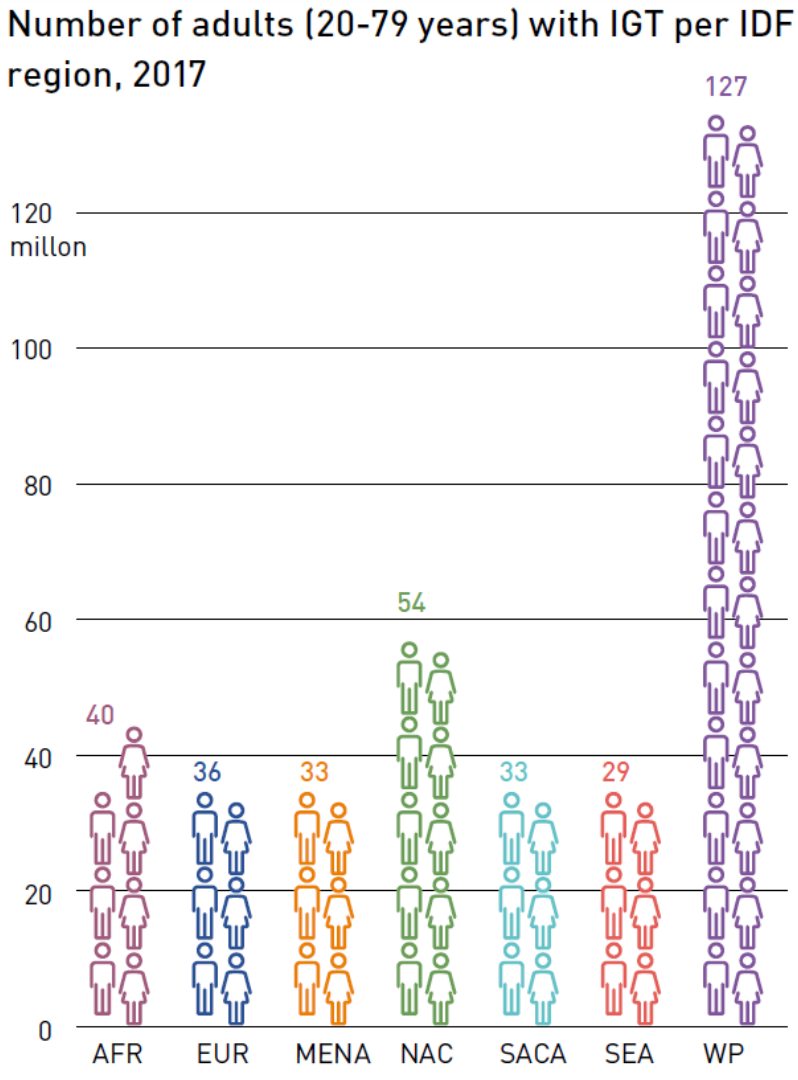
Choi et al, Diabetes Research and Clinical Practice Volume 138, April 2018, Pages 271-281

ACC Middle East Conference 2018

In partnership with:

IDF

2017



Choi et al, Diabetes Research and Clinical Practice Volume 138, April 2018, Pages 271-281

ACC Middle East Conference 2018

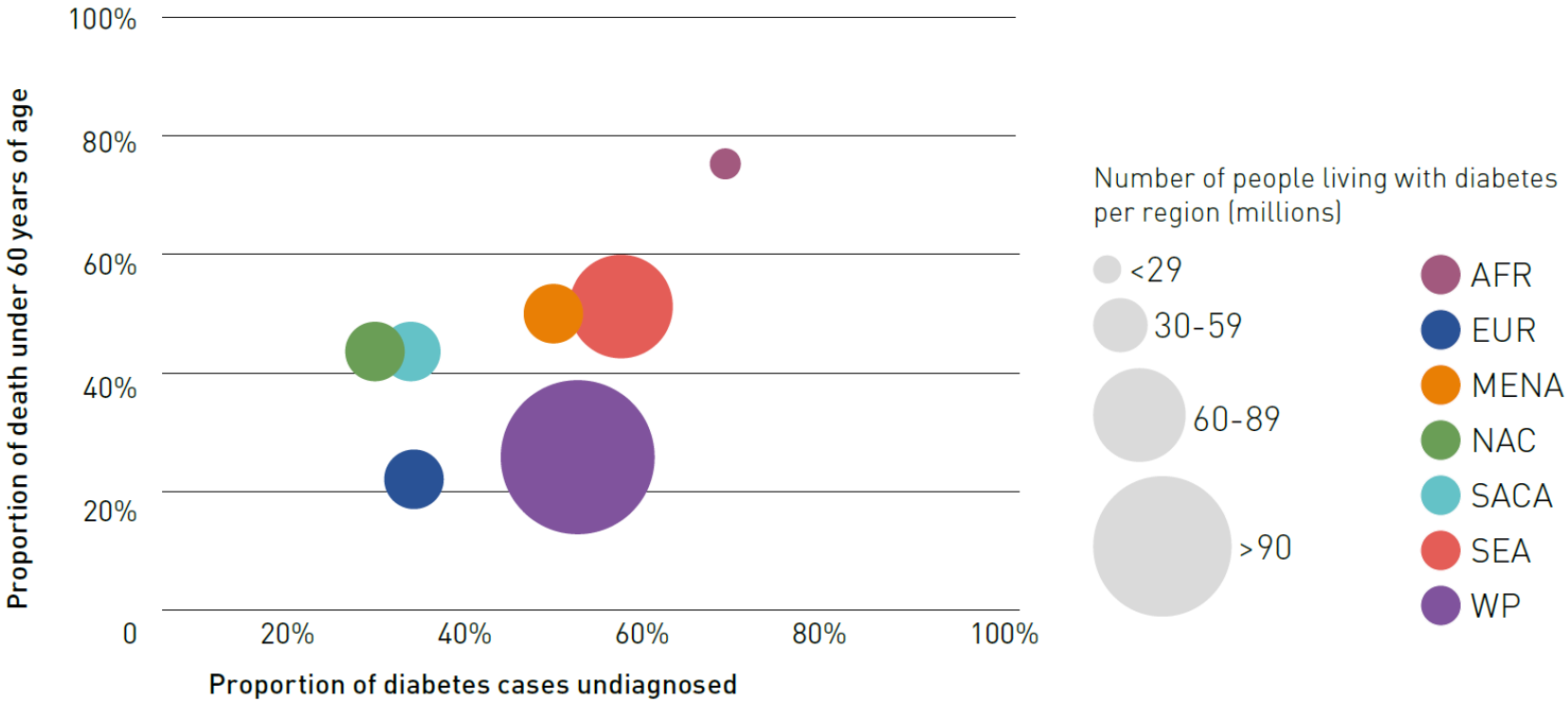
In partnership with:

IDF

2017

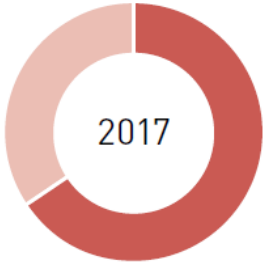
The hidden diabetes epidemic

Proportion of early deaths, undiagnosed diabetes and number of diabetes per region.



IDF

2017



146 million people with diabetes living in rural areas

279 million people with diabetes living in urban areas

Diabetes Prevalence in Middle East and North Africa region (Estimates for 2017 and 2045)

International Diabetes Federation

Yadi Huang[1], Joao da Rocha Fernandes[1], Suvi Karuranga[1], Belma Malanda[1], Nam Han Cho[2]
[1]International Diabetes Federation, Brussels,Belgium [2] Ajou Univeristy School of Medicine, Suwan , Korea

At a glance	2017	2045
Adult population (18-99 years)	435.1 million	728.5 million
Regional prevalence (18-99 years)	9.2% (6.4 – 12.3%)	11.8% (8.2 – 15.7%)
Age-adjusted comparative prevalence (18-99 years)	10.5% (7.2 – 13.9%)	10.4% (7.1 – 14%)
Number of people with diabetes (18-99 years)	39.9 million (27.9 – 53.3 million)	85.9 million (59.5 – 114.2million)
Number of deaths due to diabetes (20-99 years)	373,556 (256,544 -501,539)	

- ✓ 33 population-based data sources from 16/21 MENA countries
- ✓ Only Kuwait had a nationwide study conducted in 2014
- ✓ Algeria, Jordan, Oman, Pakistan, Saudi Arabia, Palestine, Sudan & United Arab Emirates have estimates partly based on OGTT

Presented at the IDF Congress 2017 in the category of Epidemiology and Public Health, poster number p-0749

Diabetes Prevalence in Middle East and North Africa region (Estimates for 2017 and 2045)

Yadi Huang[1], Joao da Rocha Fernandes[1], Suvi Karuranga[1], Belma Malanda[1], Nam Han Cho[2]
[1]International Diabetes Federation, Brussels,Belgium [2] Ajou Univeristy School of Medicine, Suwan , Korea

International Diabetes Federation

Figure 2 Age-adjusted diabetes prevalence ranked by countries and the number of people with diabetes in each country

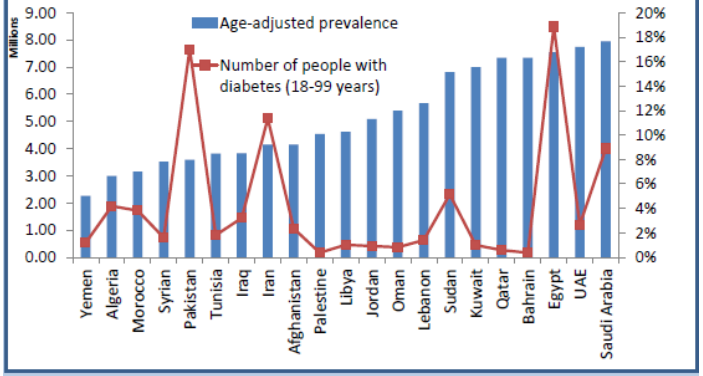
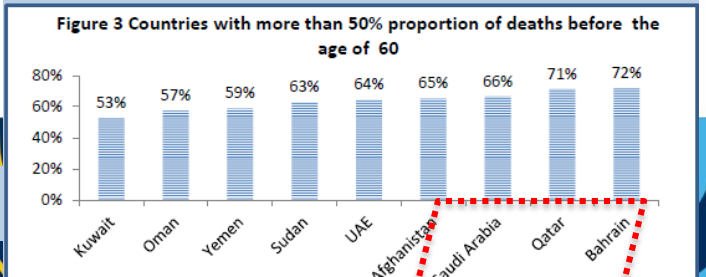


Figure 3 Countries with more than 50% proportion of deaths before the age of 60



25% women

Figure 1 Diabetes estimates by different age groups in women and men

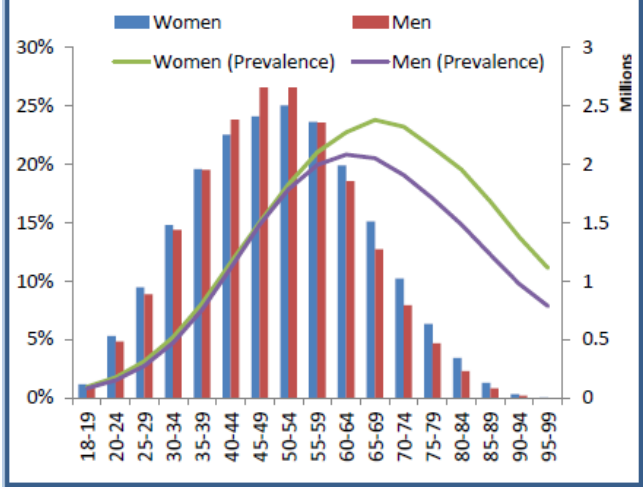


Table 2 Top 5 countries with highest age adjusted diabetes prevalence

Rank	Country	Age adjusted prevalence
1	Saudi Arabia	17.7%
2	UAE	17.2%
3	Egypt	16.8%
4	Bahrain	16.3%
5	Qatar	16.3%

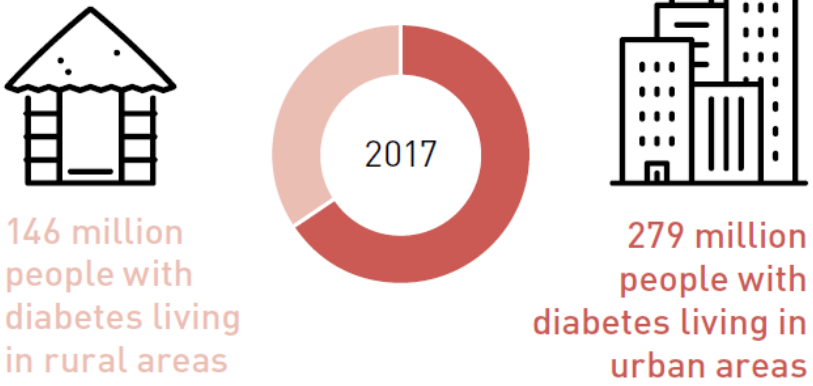
- Bahrain, Qatar (14.9%) & UAE highest age-adjusted prev
- Egypt, Pakistan & Iran highest DM population

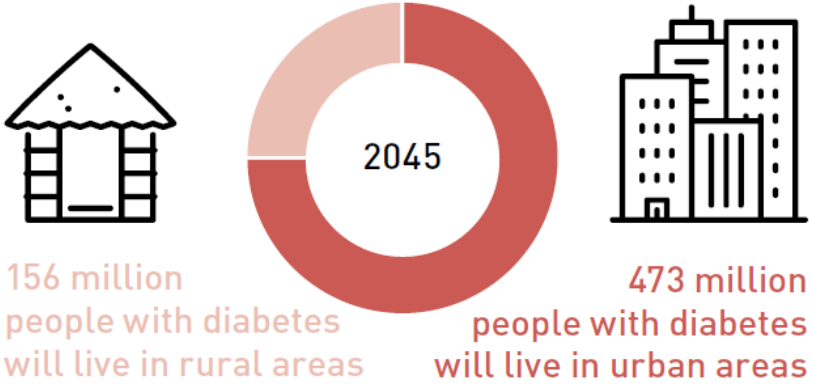
ACC Middle East Conference 2018

In partnership with: Saudi Heart Association

IDF

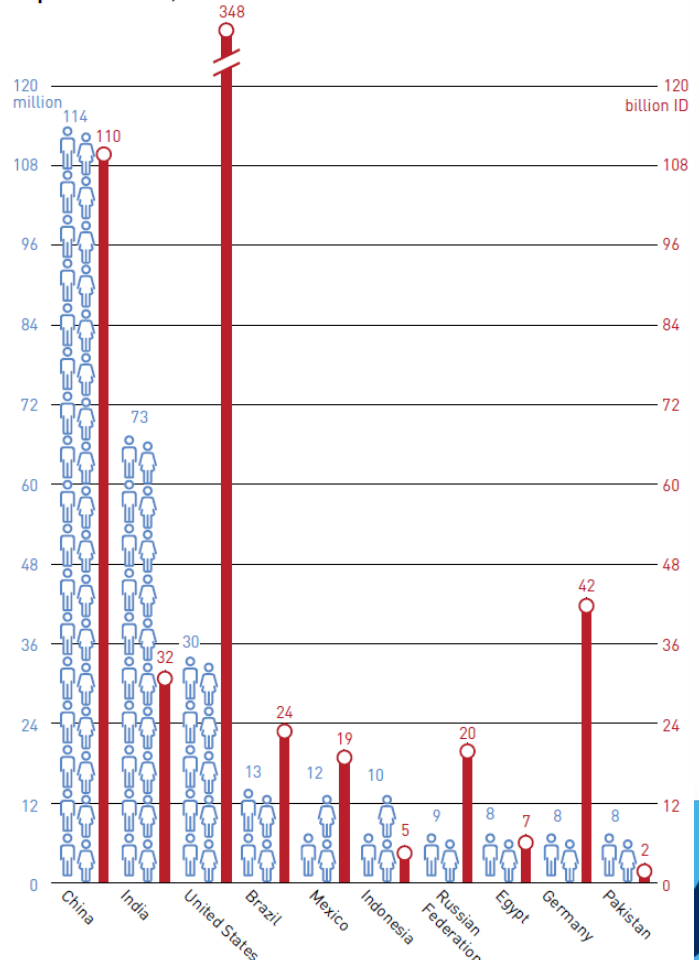
2017


2017
146 million people with diabetes living in rural areas
279 million people with diabetes living in urban areas

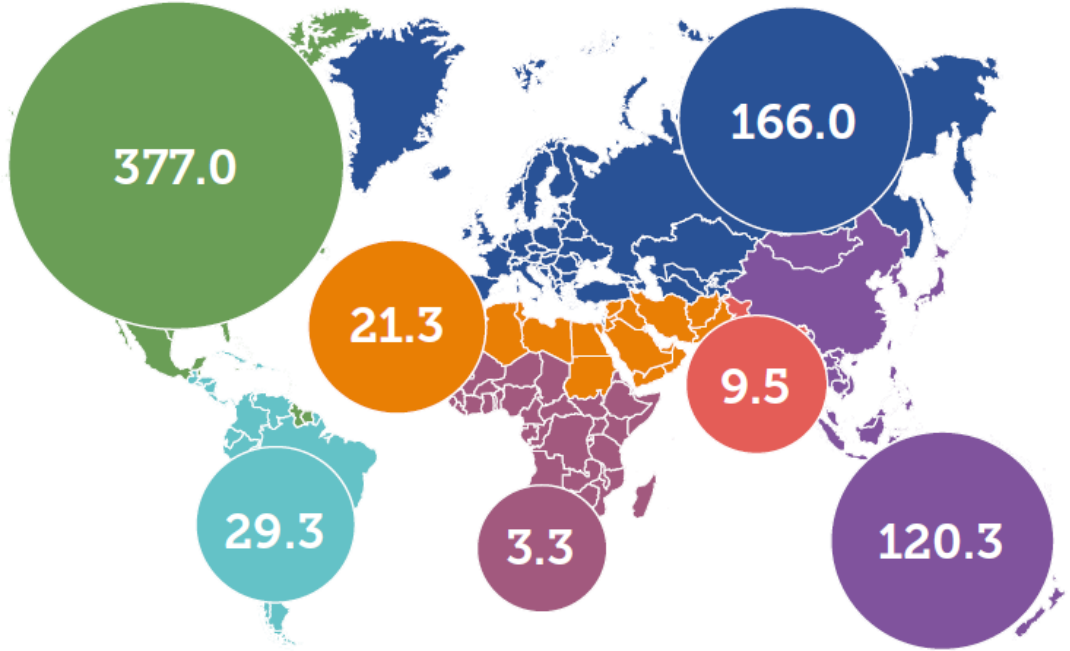

2045
156 million people with diabetes will live in rural areas
473 million people with diabetes will live in urban areas

IDF, 2017

Top 10 countries for number of adults with diabetes (20-79 years) and their healthcare expenditure, 2017



Diabetes-related healthcare expenditure in adults (20-79 years) in 2017 USD in billions



Choi et al, Diabetes Research and Clinical Practice Volume 138, April 2018, Pages 271-281

ACC Middle East Conference 2018

In partnership with:

ANTIDIABETIC DRUGS (September 2018)

Class	Generic name (brand name)	Mechanism of action	When to take it	Adverse effects
Sulfonylureas	*Gliclazide* (Diamicron®) *Gliclazide* (Diamicron® MR) *Glimepiride* (Amaryl®) *Glyburide* (DiaBeta®)	Stimulate the pancreas to produce more insulin	Before meals (≤ 30 minutes); Do not take at bedtime For Diamicron® MR ONLY : Take at breakfast	Hypoglycemia (low blood sugar)
Meglitinides	*Repaglinide* (GlucoNorm®)	Stimulate the pancreas to produce more insulin	Before meals (≤ 15 minutes); Do not take at bedtime	Hypoglycemia (low blood sugar)
Biguanides	*Metformine* (Glucophage®)	Reduce the production of glucose by the liver	During meals	Diarrhea, metallic aftertaste, nausea
	Metformine extended-release (Glumetza®)		At dinner	
Thiazolidinediones (TZD)	*Pioglitazone* (Actos®) *Rosiglitazone* (Avandia®)	Increase insulin sensitivity of the body cells and reduce the production of glucose by the liver	With or without food, at the same time each day	• Swelling due to water retention, weight gain • Pioglitazone : inscreased risk of bladder cancer (Health Canada restriction) • Rosiglitazone : increased risk of non-fatal heart attack (Health Canada restriction)
Alpha-glucosidases inhibitor	*Acarbose* (Glucobay®)	Slow the absorption of carbohydrates (sugar) ingested	With the first mouthful of a meal	Bloating and flatulence (gaz)
Dipeptidyl-peptidase-4 (DPP-4) inhibitors	*Linagliptine* (Trajenta®) *Saxagliptine* (Onglyza™) *Sitagliptine* (Januvia®) *Alogliptine* (Nesina®)	Intensify the effect of intestinal hormones (incretines) involved in the control of blood sugar	With or without food, at the same time each day	Pharyngitis, headache
Glucagon-like peptide-1 (GLP-1) agonist	*Exenatide* (Byetta®)	Mimic the effect of certain intestinal hormones (incretines) involved in the control of blood sugar	Injection to take 0 to 60 minutes before breakfast or dinner	Nausea, diarrhea, vomiting
	Exenatide extended-release (Bydureon®)		Injection once a week, the same day, any hour of the day, with or without food	
	Liraglutide (Victoza®)		Injection to take with or without food, at the same time each day	
	Dulaglutide (Trulicity®)		Injection once a week, the same day, any hour of the day, with or without food	
	Lixisenatide (Adlyxine™)		Injection once daily within the hour prior to any meal of the day	
	Semaglutide (Ozempic®)		Injection once a week, same day each week, at any time of the day, with or without food	
Sodium glucose cotransporter 2 (SGLT2) inhibitors	*Canagliflozine* (Invokana®)	Help eliminate glucose in the urine	Before the first meal of the day	Genital and urinary infections, more frequent urination
	Dapagliflozine (Forxiga®) *Empagliflozine* (Jardiance®)		Any time of day, with or without food	
	Ertugliflozine (Steglatro™)		Once a day, in the morning, with or without food	

The following pills combine 2 classes of antidiabetic drugs:

- Thiazolidinedione + biguanide (Avandamet®)
- DPP-4 inhibitors + biguanide (Janumet®, Janumet®XR, Jentadueto™ Komboglyze™)
- SGLT2 inhibitor + biguanide (Xigduo®, Invokamet®, Synjardy®, Steglumet™)
- DPP-4 inhibitor + SGLT2 inhibitor (Glyxambi™, QTERN®, Steglujan™)
- GLP-1 agonist + degludec insulin (Xultophy®)
- GLP-1 agonist + glargine insulin (Soliqua™)

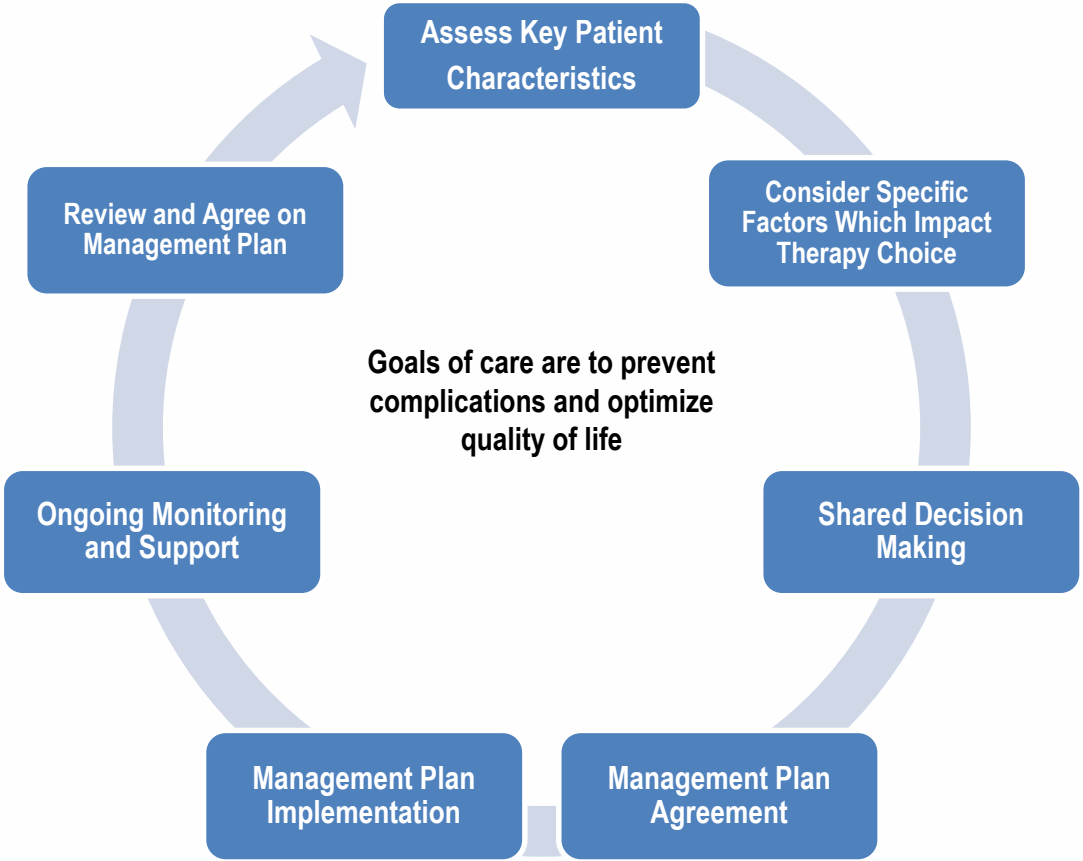
Diabetes Québec
www.diabete.qc.ca

Management of Hyperglycemia in Type 2 Diabetes: 2018 ADA/EASD Consensus Report

- 2018 ADA/EASD Consensus Report Overview
  - Patient-centered Glycemic Management
  - Key Highlights
  - Treatment of Patients without ASCVD, HF, or CKD
  - Treatment of Patients with ASCVD, HF, or CKD
  - Intensifying to Injectable Therapy
- Summary

Individualized Patient Care Approach

Decision Cycle for Patient-Centered Glycemic Management

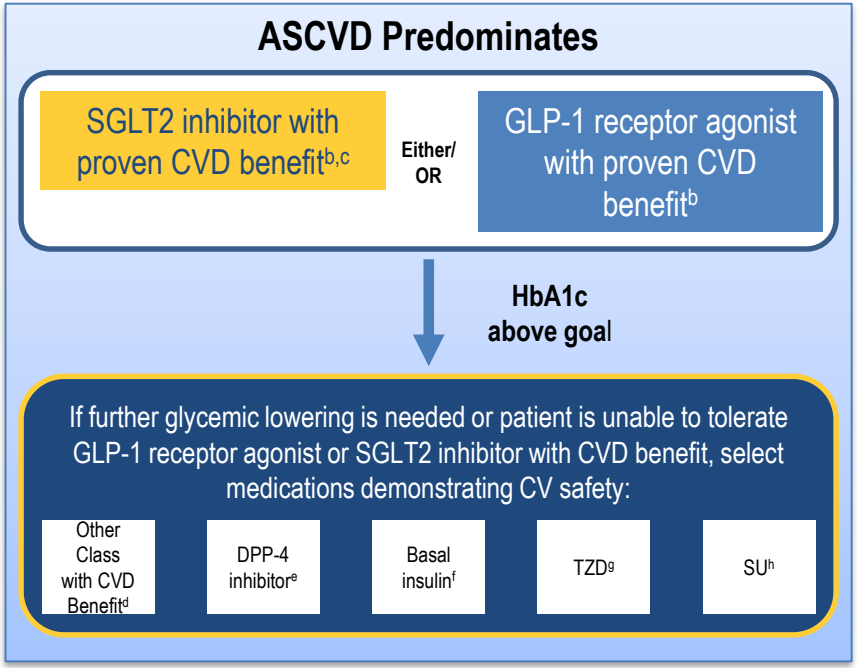


Diabetes Self-Management Education and Support: Key Components

- ✓ Evidence-based
- ✓ Individualized to the patient's needs (language, culture)
- ✓ Structured theory-driven written curriculum with supporting materials
- ✓ Delivered by trained and competent educators
- ✓ Delivered in group or individual settings
- ✓ Aligns with the local population needs
- ✓ Supports patient/family in developing attitudes, beliefs, knowledge, and skills
- ✓ Includes comprehensive core content (including pathophysiology/treatment options, medication use, etc.)
- ✓ Available to patients at critical times (diagnosis, annually, when complications arise, etc.)
- ✓ Includes monitoring of patient progress
- ✓ Quality audited regularly

Treatment of Patients in Whom ASCVD Predominates

If not at HbA1c goal with metformin, continue metformin[a] and
add either
SGLT2 inhibitor or GLP-1 receptor agonist with proven CVD benefit[b]



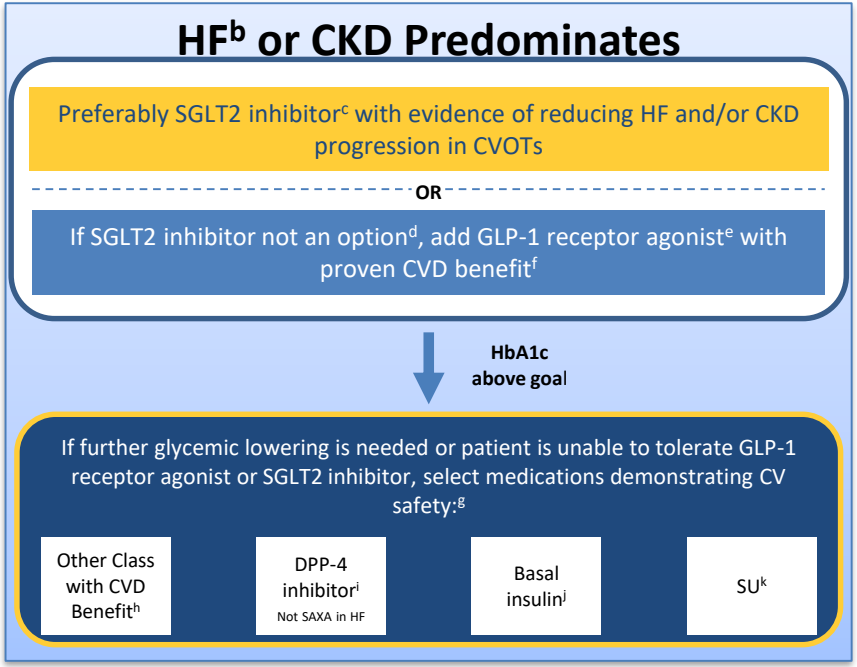
[a]Unless contraindicated or intolerable. Adjust dose or stop metformin with declining eGFR; [b]Proven CVD benefit refers to a label indication of reducing CVD events. Hierarchy of evidence for CVD benefits: modestly stronger for EMPA > CANA for SGLT2 inhibitors and LIRA > SEMA > EQW for GLP-1 receptor agonists; [c]If renal function is adequate; [d]If on SGLT2 inhibitor with CVD benefit, then consider GLP-1 receptor agonist with CVD benefit (or vice versa); [e]If not currently on GLP-1 receptor agonist; [f]CVD safety demonstrated with Degludec or U100 Glargine; [g]Low dose less studied for CVD effects but may be better tolerated; [h]Select later generation SU with lower risk of hypoglycemia. ASCVD = atherosclerotic cardiovascular disease; CANA = canagliflozin; CKD = chronic kidney disease; CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; EMPA = empagliflozin; EQW = exenatide once-weekly; GLP-1 = glucagon-like peptide-1; HbA1c = glycated hemoglobin; HF = heart failure; LIRA = liraglutide; SEMA = semaglutide; SGLT2 = sodium-glucose cotransporter 2; SU = sulfonylurea; TZD = thiazolidinedione.
Davies MJ et al. Online ahead of print. *Diabetologia*. 2018. https://doi.org/10.1007/s00125-018-4729-5. Accessed October 5, 2018.9

Treatment of Patients in Whom HF or CKD Predominates

If not at HbA1c goal with metformin, continue metformin[a] and preferably add an SGLT2 with evidence of reducing HF and /or CKD progression in CVOTs

Consensus Recommendation:
In patients with ASCVD in whom HF coexists or is of special concern, recommended therapy after metformin is an SGLT2 inhibitor with evidence of reducing HF in CVOTs.

Consensus Recommendation:
In patients with CKD (**with or without ASCVD**), consider an SGLT2 inhibitor (assuming adequate renal function) with evidence of reducing CKD progression in CVOTs, or if contraindicated or not preferred, a GLP-1 receptor agonist shown to reduce CKD progression. Note caution with GLP-1 receptor agonists in ESRD.



[a]Unless contraindicated or intolerable. Adjust dose or stop metformin with declining eGFR; [b]Proven CVD benefit refers to a label indication of reducing CVD events. Hierarchy of evidence for CVD benefits: modestly stronger for EMPA > CANA for SGLT2 inhibitors and LIRA > SEMA > EQW for GLP-1 receptor agonists; [c]If renal function is adequate; [d]If on SGLT2 inhibitor with CVD benefit, then consider GLP-1 receptor agonist with CVD benefit (or vice versa); [e]If not currently on GLP-1 receptor agonist; [f]CVD safety demonstrated with Degludec or U100 Glargine; [g]Low dose less studied for CVD effects but may be better tolerated; [h]Select later generation SU with lower risk of hypoglycemia. ASCVD = atherosclerotic cardiovascular disease; CANA = canagliflozin; CKD = chronic kidney disease; CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; EMPA = empagliflozin; EQW = exenatide once-weekly; GLP-1 = glucagon-like peptide-1; HbA1c = glycated hemoglobin; HF = heart failure; LIRA = liraglutide; SEMA = semaglutide; SGLT2 = sodium-glucose cotransporter 2; SU = sulfonylurea; TZD = thiazolidinedione.

Davies MJ et al. Online ahead of print. *Diabetologia*. 2018. https://doi.org/10.1007/s00125-018-4729-5. Accessed October 5, 2018.9

Treatment in Patients with ASCVD, HF, or CKD

If at HbA1c goal:

If on dual therapy which does not include an SGLT2 inhibitor or GLP-1 receptor agonist, consider the following

- Switching to one of the agents within these drug classes with CVD benefit[a], or
- Lower HbA1c goal and initiate an SGLT2 inhibitor or GLP-1 receptor agonist, or
- Reevaluating HbA1c at 3 month intervals and add an SGLT2 inhibitor or GLP-1 receptor agonist if above target

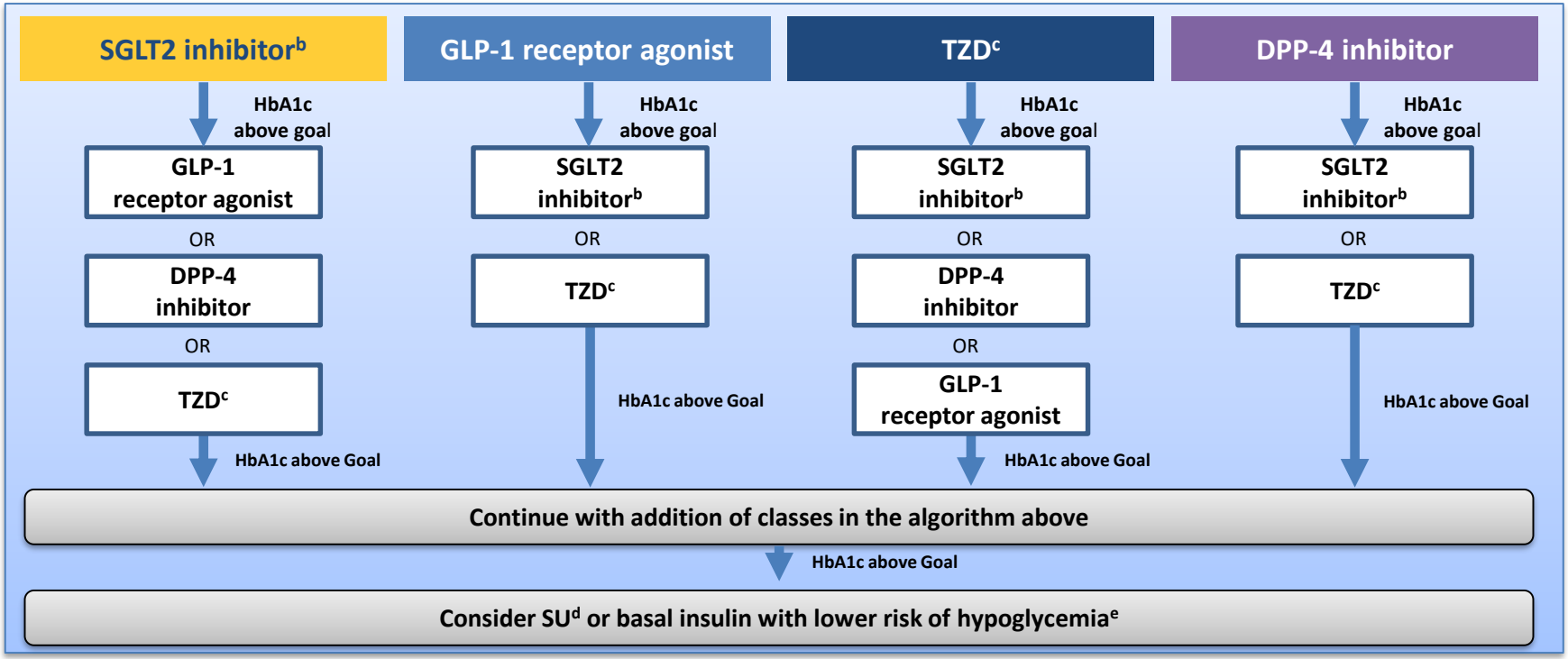
The use of an SGLT2 inhibitor or GLP-1 receptor agonist should follow the previous algorithms based on comorbidities.

- [a]Proven CVD benefit refers to a label indication of reducing CVD events. Hierarchy of evidence for CVD benefits: modestly stronger for EMPA > CANA for SGLT2 inhibitors and LIRA > SEMA > EQW for GLP-1 receptor agonists.
- ASCVD = atherosclerotic cardiovascular disease; CANA = canagliflozin; CVD = cardiovascular disease; EMPA = empagliflozin; EQW = exenatide once-weekly; GLP-1 = glucagon-like peptide-1; HbA1c = glycated hemoglobin; HF = heart failure; LIRA = liraglutide; SEMA = semaglutide; SGLT2 = sodium-glucose cotransporter 2.

Davies MJ et al. Online ahead of print. *Diabetologia*. 2018. https://doi.org/10.1007/s00125-018-4729-5. Accessed October 5, 2018.9

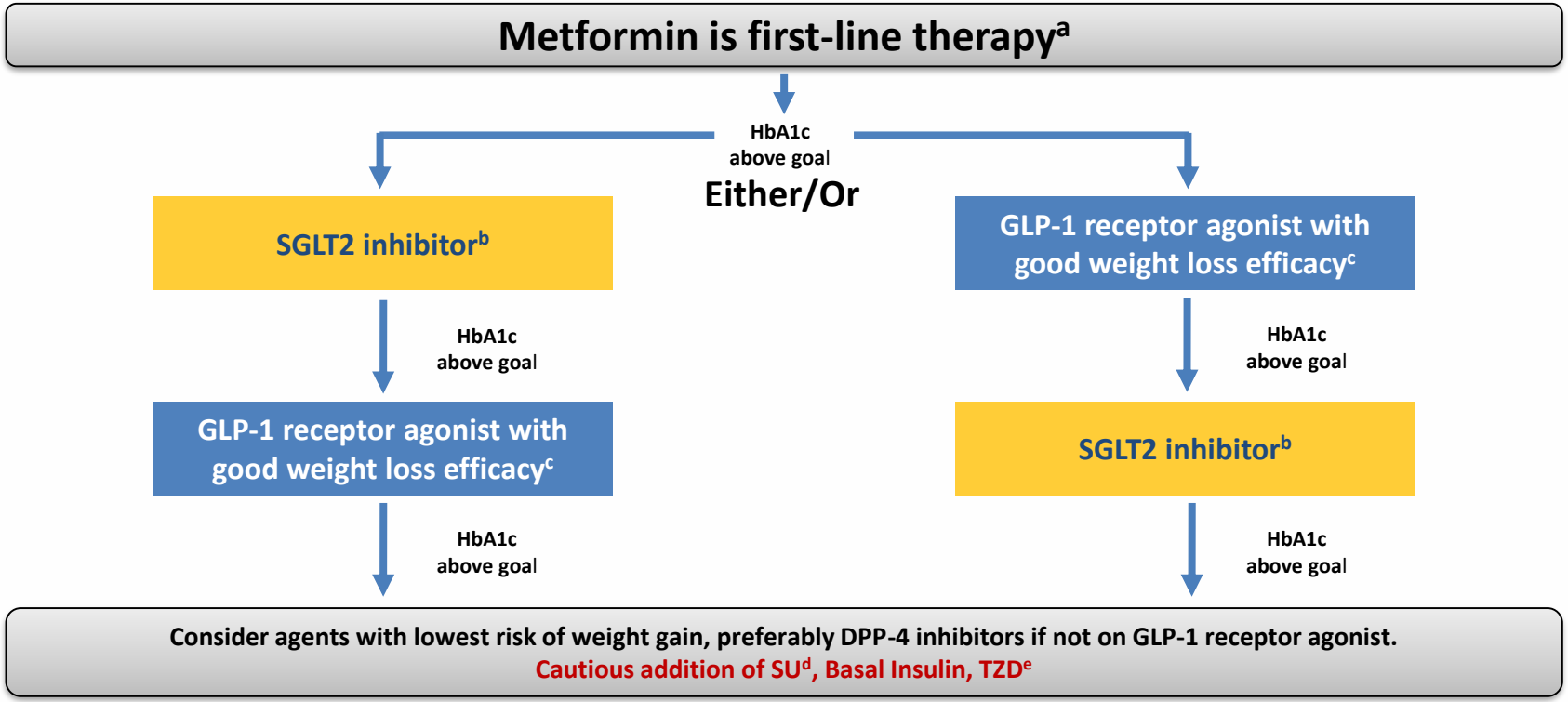
Patients Without ASCVD or CKD: Need to Minimize Hypoglycemia

If not at HbA1c goal with metformin, continue metformin[a] and consider the drug classes below



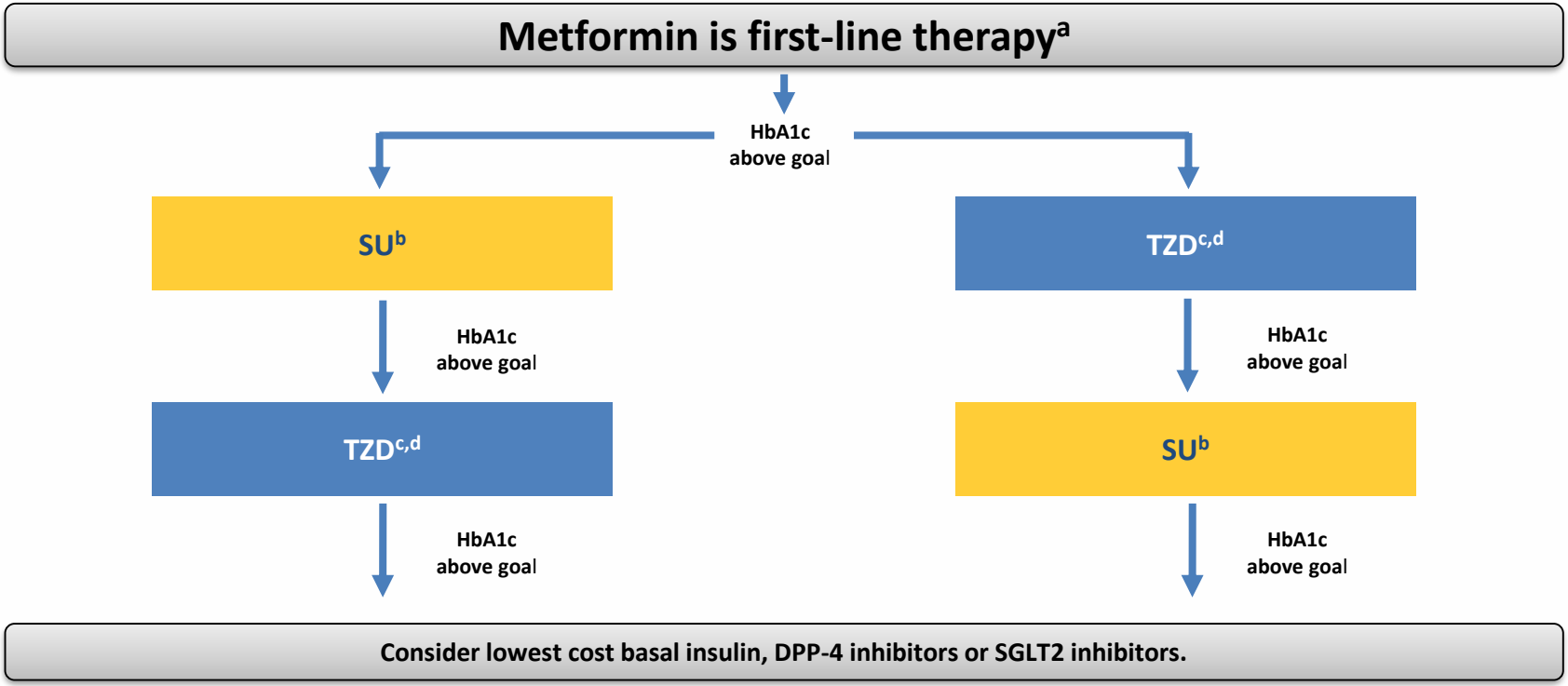
Davies MJ et al. Online ahead of print. *Diabetologia*. 2018. https://doi.org/10.1007/s00125-018-4729-5. Accessed October 5, 2018.9

Patients Without ASCVD or CKD:
Need to Promote Weight Loss or Minimize Weight Gain



Davies MJ et al. Online ahead of print. *Diabetologia*. 2018. https://doi.org/10.1007/s00125-018-4729-5. Accessed October 5, 2018.9

Patients Without ASCVD or CKD: Cost Issues



Intensifying to Injectable Therapy

GLP-1 receptor agonists are preferred to insulin-

HbA1c above target goal with dual/triple oral therapy

↓

GLP-1 receptor agonist for most patients prior to insulin[a,b]

HbA1c above goal ↓

Add basal insulin

HbA1c above goal despite adequate titration of basal insulin ↓

Add prandial insulin

In patients with HbA1c >10% or 2% above individual goal, consider initial injectable combination (ie, GLP-1 receptor agonist with basal insulin or basal/prandial combination)

Concomitant Drug or Class	Recommended Action When Initiating Injectable Therapy
Metformin	Continue treatment.
SGLT2 inhibitor	Continue treatment but beware of euglycemic DKA. • Instruct patients on sick day rules. • Do not aggressively down titrate insulin.
DPP-4 inhibitor	Discontinue if GLP-1 receptor agonist initiated.
TZD	Discontinue TZD when initiating insulin or decrease dose[c]
SU	Discontinue SU or reduce dose by 50% when initiating basal insulin. Discontinue SU if prandial insulin initiated.

Davies MJ et al. Online ahead of print. *Diabetologia*. 2018. https://doi.org/10.1007/s00125-018-4729-5. Accessed October 5, 2018.9

Summary of the 2018 ADA/EASD Consensus Report

- ✓ Focus on patient-centered glycemic management.
- ✓ To avoid clinical inertia, the statement emphasizes regular assessment and modification of treatment (every 3-6 months).
- ✓ Metformin & comprehensive lifestyle management remain the foundational therapy recommendations
- ✓ If HbA1c is ≥1.5% is above individualized target, consider early combination with metformin & an additional agent.
- ✓ After metformin:
  - ✓ The treatment approach is to consider presence or absence of ASCVD, HF, or CKD.
  - ✓ For patients **with ASCVD**, HF, or CKD **add** either an **SGLT2** inhibitor or **GLP-1** receptor agonist with proven CVD benefit. Specific algorithms apply based on comorbidity.
  - ✓ For patients **without ASCVD**, HF, or CKD, treatment should focus on **individual patient's needs and preferences, including weight, hypoglycemia & cost concerns**
- ✓ GLP-1 receptor agonists are preferred as the 1st injectable treatment over insulin in most clinical situations.

Davies MJ et al. Online ahead of print. *Diabetologia*. 2018. https://doi.org/10.1007/s00125-018-4729-5. Accessed October 5, 2018.9

More news soon…

DECLARE-TIMI58

Brief Title ICMJE	Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events
Official Title ICMJE	Dapagliflozin Effect on Cardiovascular Events A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10 mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients With Type 2 Diabetes
Brief Summary	This study is being carried out to determine the effect of dapagliflozin on cardiovacular outcomes when added to current background therapy in patients with type 2 diabetes with either established cardiovacular disease or cardiovascular risk factors.

EMPA-HEART

Brief Title ICMJE	Effects of Empagliflozin on Cardiac Structure in Patients With Type 2 Diabetes
Official Title ICMJE	Effects of Empagliflozin on Cardiac Structure, Function, and Circulating Biomarkers in Patients With Type 2 Diabetes
Brief Summary	The purpose of this study is to evaluate the effects of Empagliflozin on cardiac structure, function and circulating biomarkers in patients with Type II diabetes. Empagliflozin (anti-hyperglycemic agent), approved by Health Canada and the FDA for the treatment of Type II diabetes, demonstrated a reduction in cardiovascular deaths and heart failure from a previous post-marketing clinical trial. The use of empagliflozin to treat patients with diabetes and heart disease has been approved by Health Canada. However, the process by which it may give this beneficial effect remains unclear and needs further investigation. Therefore, the aim of this study is to provide a fundamental understanding of the mechanistic basis by which Empagliflozin could provide its potential cardio-protective effects by employing the use of Cardiac Magnetic Resonance Imaging (CMRI).

ACC Middle East Conference 2018

In partnership with:

جمعية القلب السعودية
Saudi Heart Association

CASE 1

Biljana Parapid, MD, PhD, FESC
Belgrade University School of Medicine, Belgrade (Serbia)
@biljana_parapid

Ms Jane Doe, 55y

- ✓ Reffered to Cardiologist for newly discovered HTN
- ✓ Current Tx: Metformin 500mg bid
- ✓ HbA1c 9.0%, not obese
- ✓ My advice:
  - ✓ Metformin 1000mg bid
  - ✓ lifestyle management
  - ✓ ACEI if ABPM shows it needed

ACC Middle East Conference 2018

In partnership with:

جمعية القلب السعودية
Saudi Heart Association

CASE 2

Biljana Parapid, MD, PhD, FESC
Belgrade University School of Medicine, Belgrade (Serbia)
@biljana_parapid

Mr John Doe, 60y

- ✓ Reffered to Cardiologist for a FU visit, known prior pPCI, HTN, dislypidemia
- ✓ Current Tx: Metformin 1000mg bid, ACEI, ASA, Statin
- ✓ HbA1c 10.0%, borderline obese, EF% 40% w episodes of CHF
- ✓ My advice:
  - ✓ Metformin 1000mg bid + SGLT-2
  - ✓ More FU with Endocrinologist

Thank you...