Diabetes Overview & Guidelines: New Recommendations

The Problem

Diabetes is prevalent,

It hurts,

It Kills.

But we have not been able to stop it to date!

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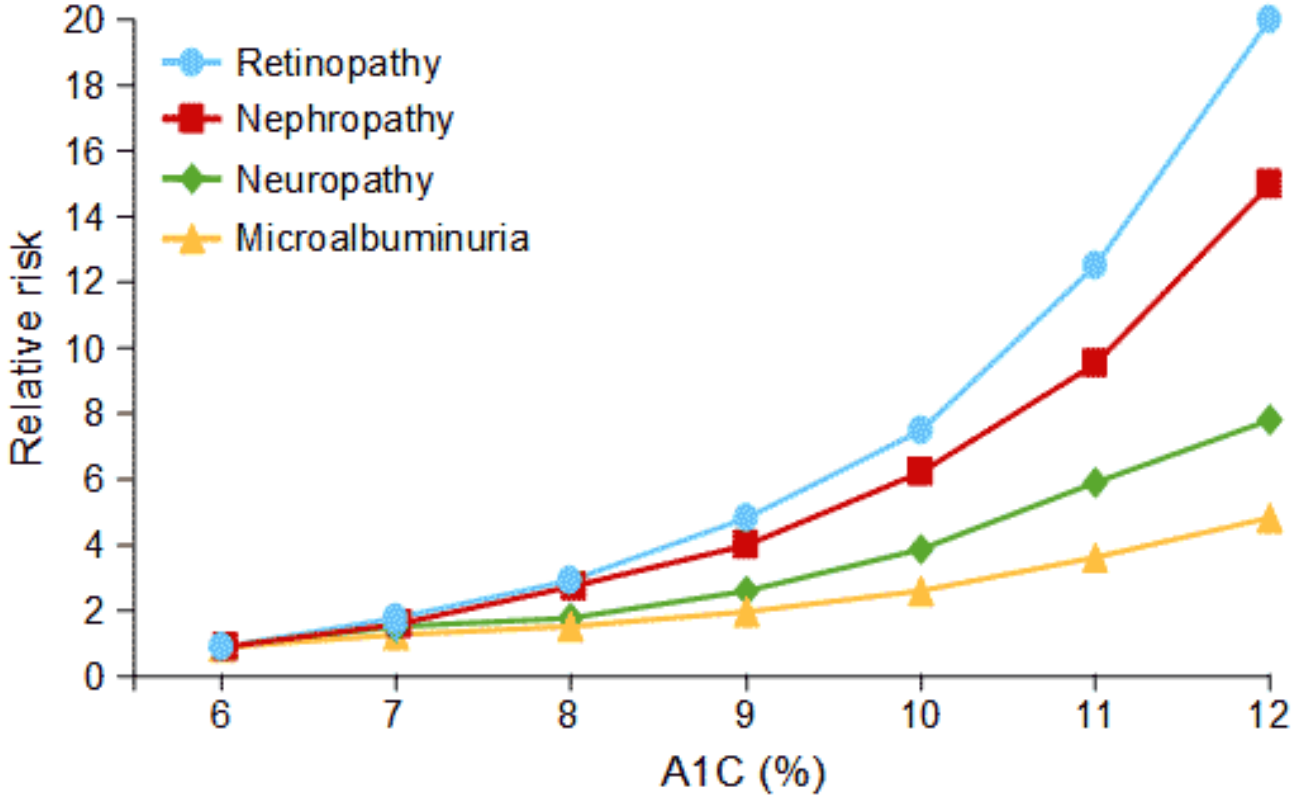
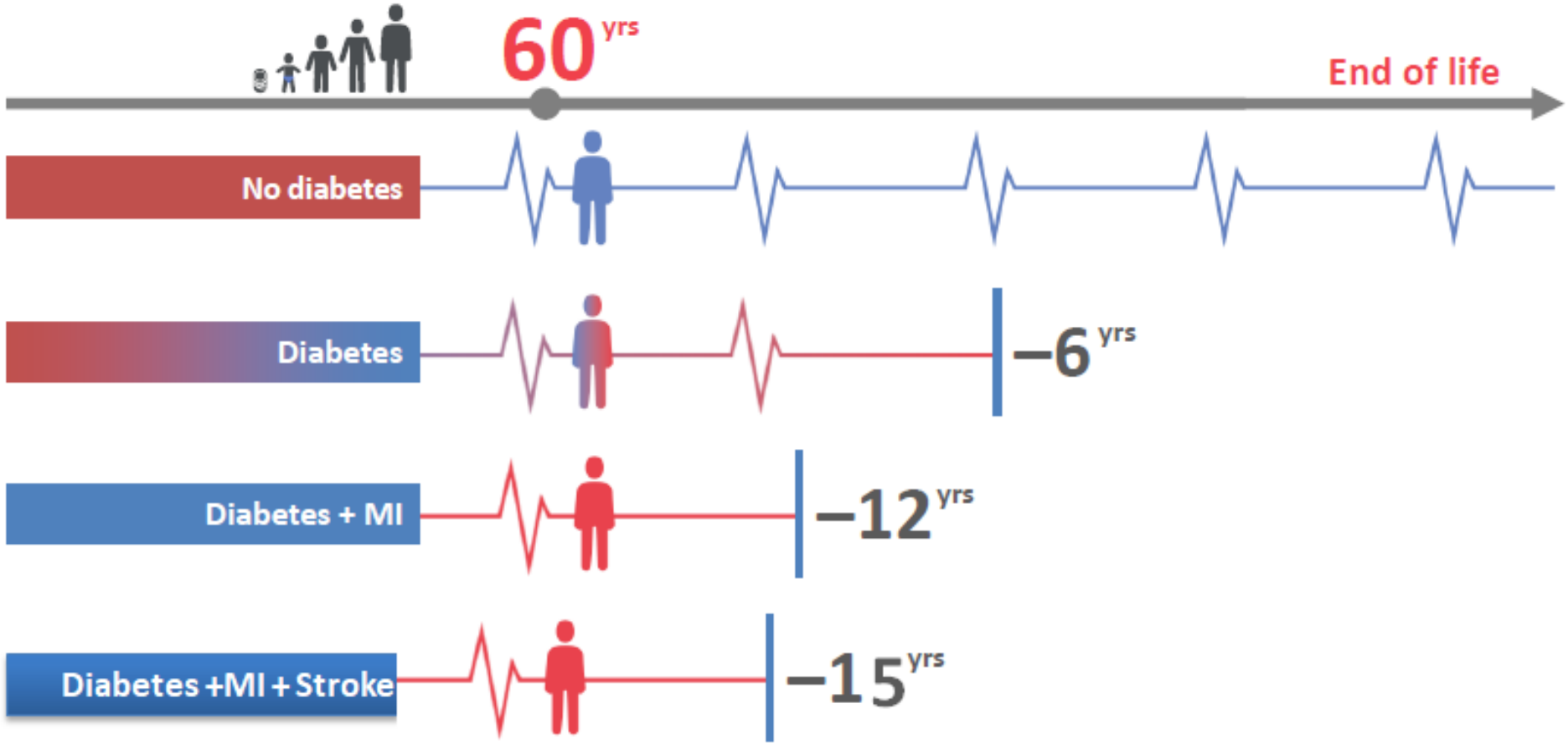
Relative Risk of Progression of Diabetic Complications



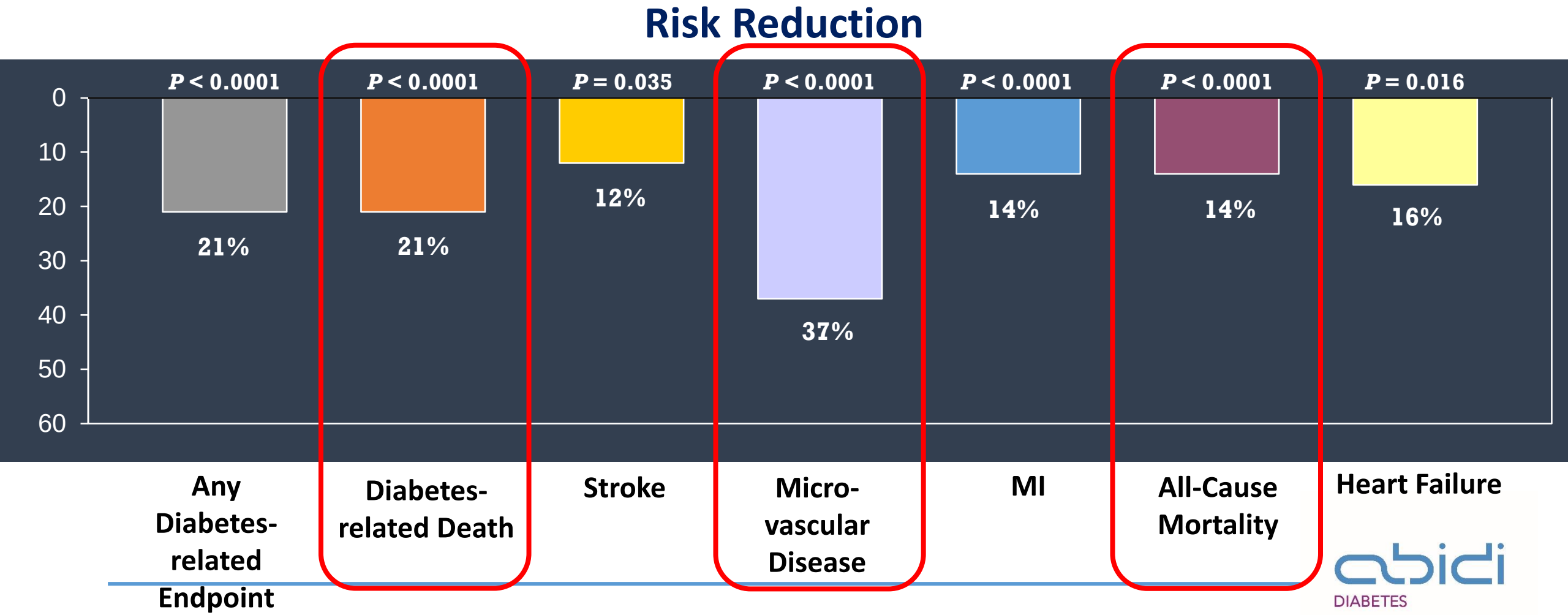
Adapted from DCCT. Diabetes 1995;44:968-43.

Life expectancy is reduced by ~ 15 years in diabetes patients with previous CVD



Di Angelantonio, E.(2015). *JAMA*, 314(1), 52-60

UKPDS 35
Each 1% Reduction in A1c Reduces the Complication Risk

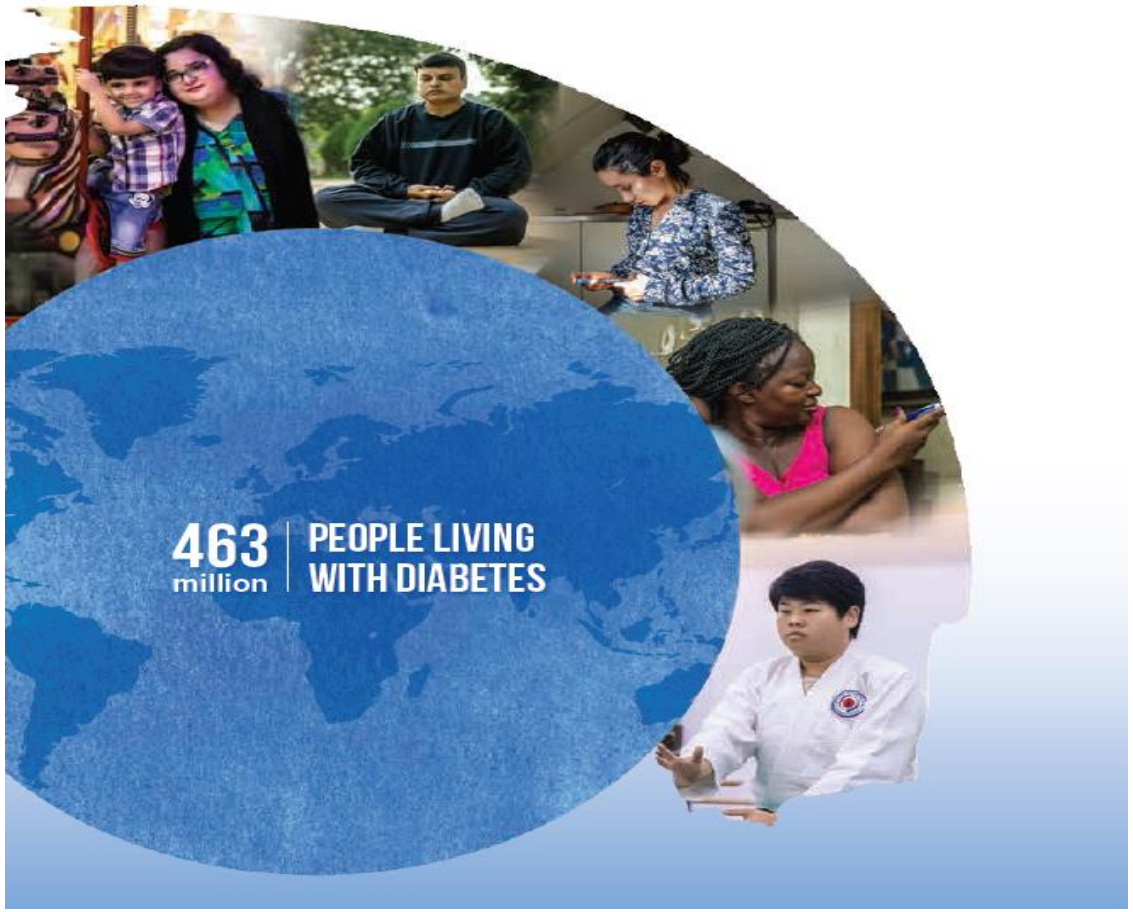


Stratton IM, et al. BMJ. 2000;321:405-412.

International Diabetes Federation

IDF **DIABETES ATLAS**

Ninth edition 2019



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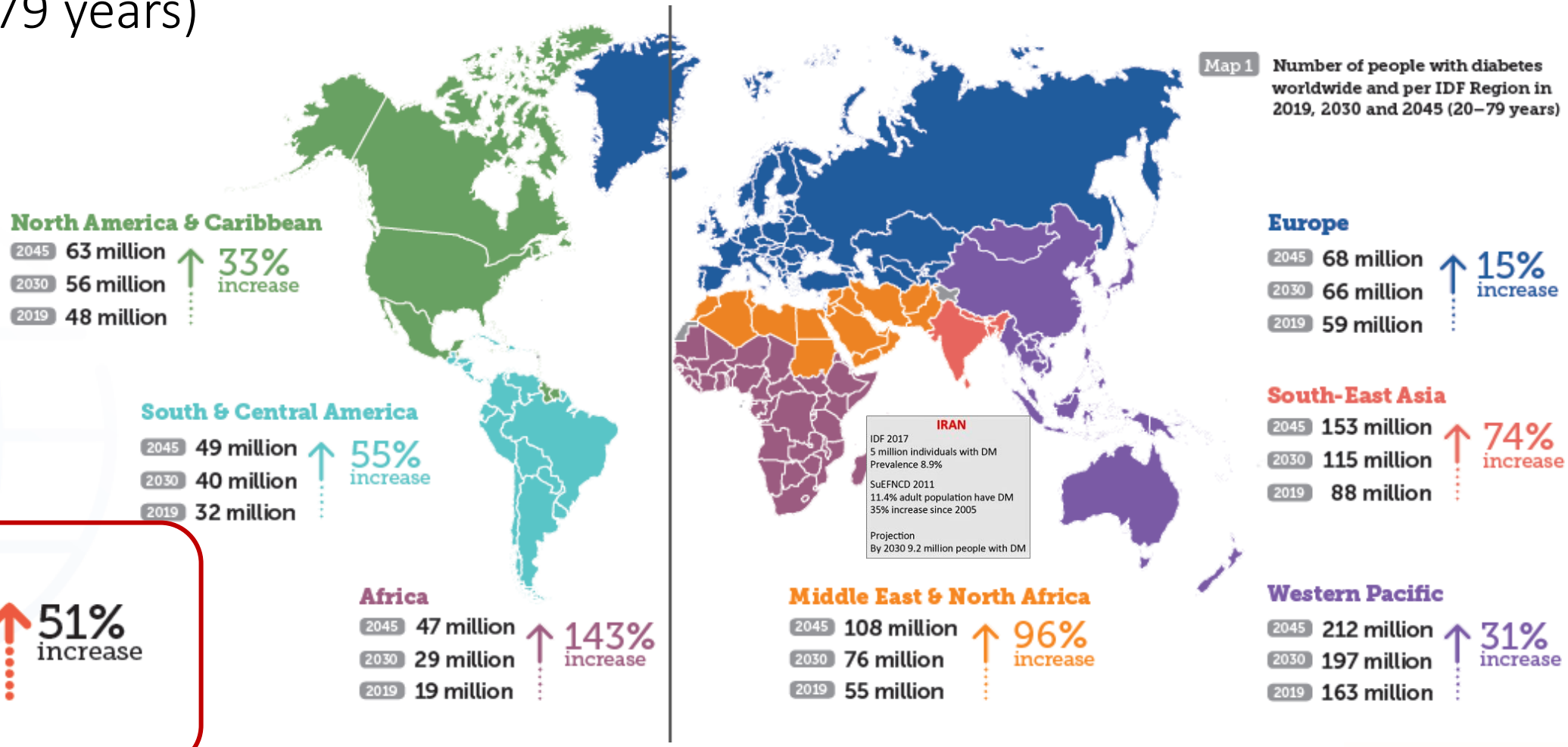
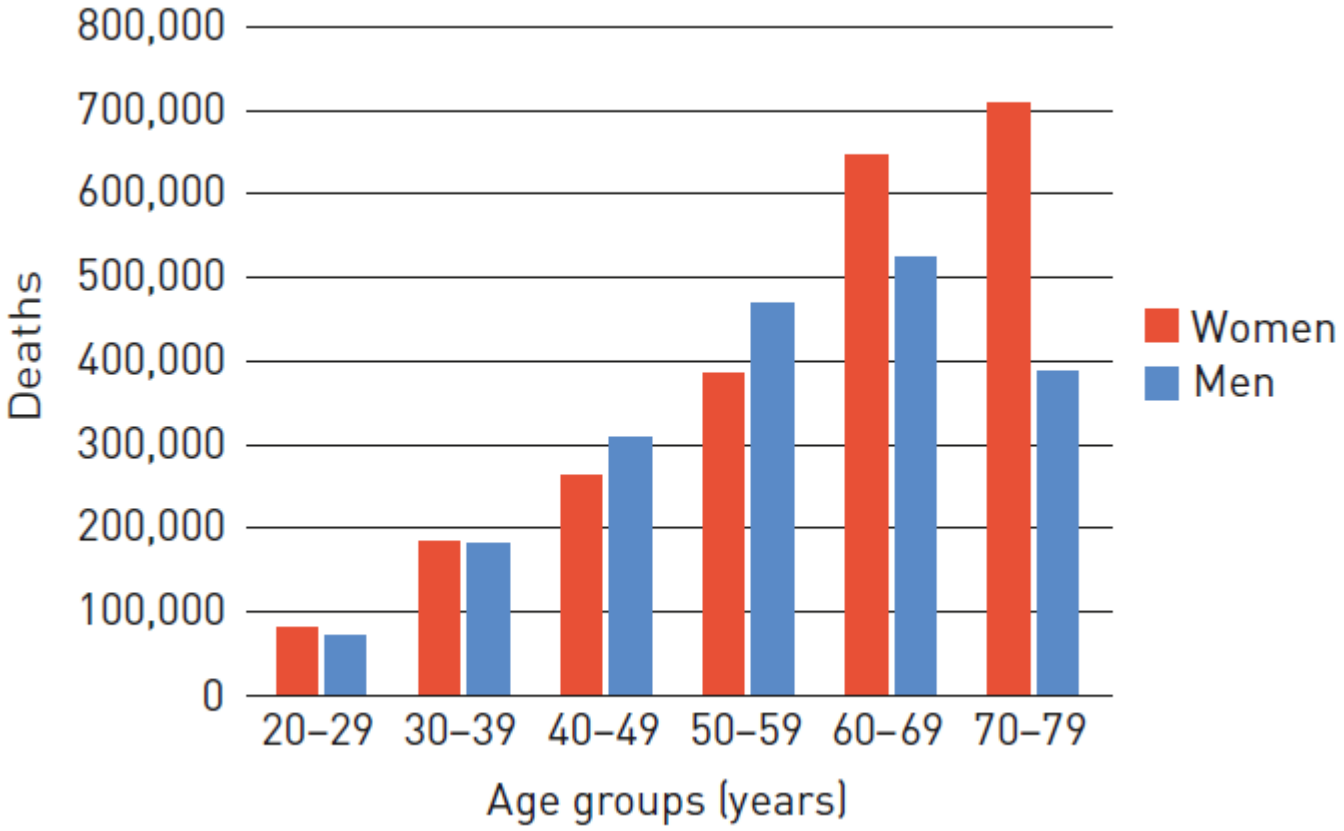
Diabetes: A global emergency

Number of people with diabetes worldwide and per region in 2019,2030 and 2045 (20-79 years)



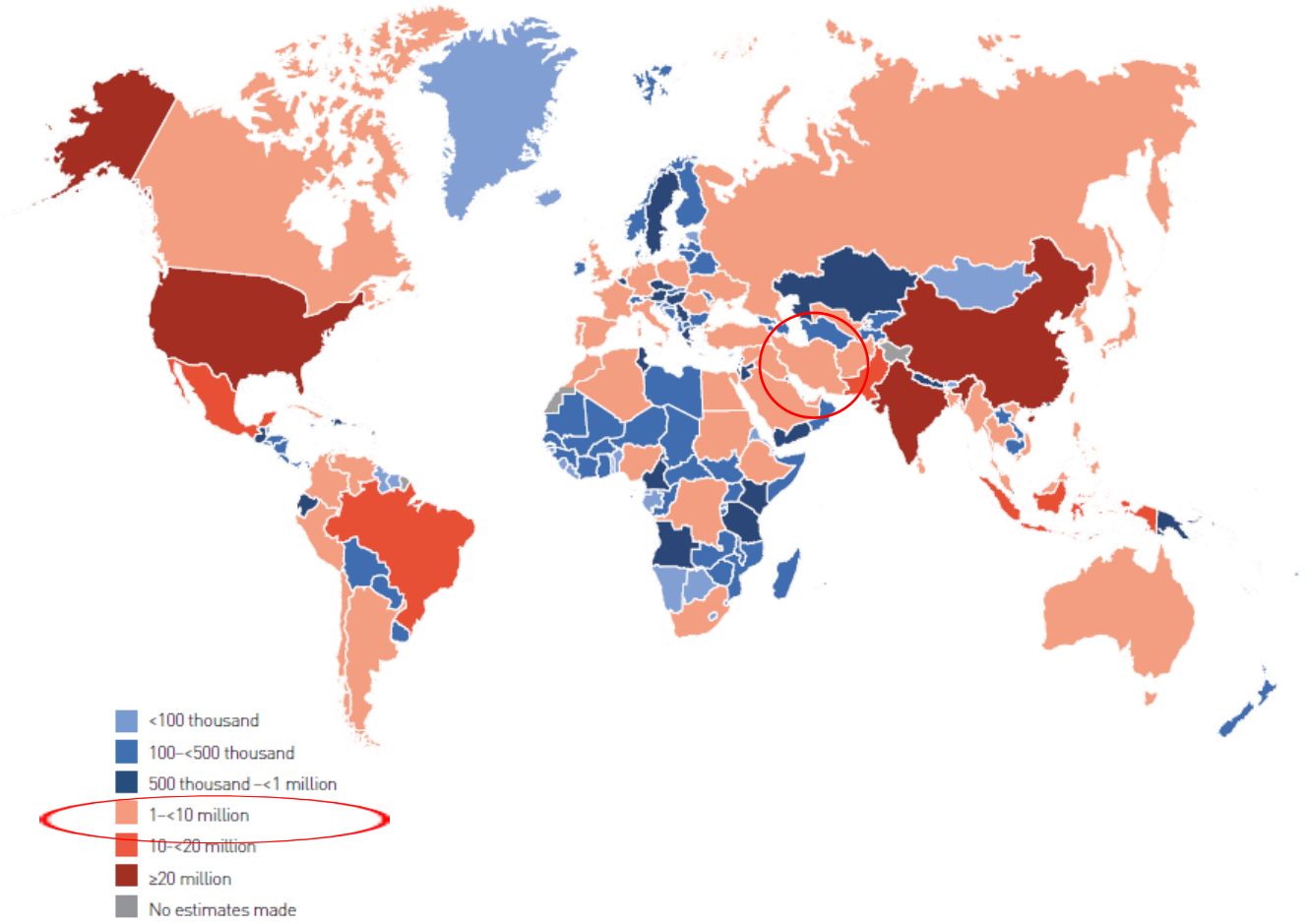
Number of deaths due to diabetes in adults (20–79 years) by age and sex in 2019



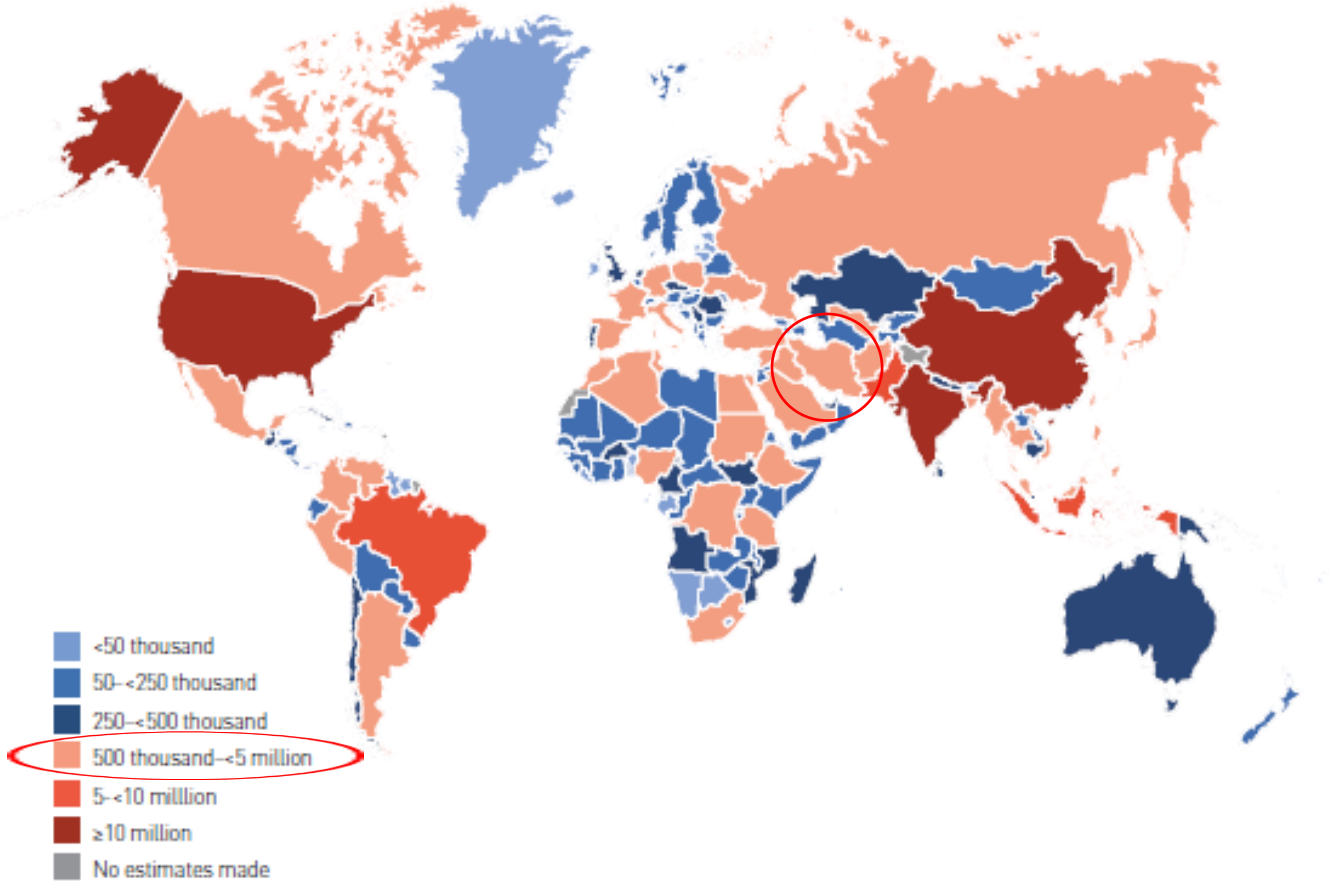
Every **8 seconds** a person dies from diabetes

(5 million annually)

Estimated total number of adults (20–79 years) with diabetes in 2019



Number of adults (20–79 years) with undiagnosed diabetes by country in 2019



Estimated total number of adults (20–79 years) with diabetes in 2019, 2030 and 2045

At a glance	2019	2030	2045
Total world population	7.7 billion	8.6 billion	9.5 billion
Adult population (20–79 years)	5.0 billion	5.7 billion	6.4 billion
Diabetes (20–79 years)			
Global Prevalence	9.3%	10.2%	10.9%
Number of people with diabetes	463.0 million	578.4 million	700.2 million
Number of deaths due to diabetes	4.2 million	-	-
Total health expenditures for diabetes[i]	USD 760.3 billion	USD 824.7 billion	USD 845.0 billion
Hyperglycaemia in pregnancy (20–49 years)			
Proportion of live births affected	15.8%	14.0%[ii]	13.3%[ii]
Number of live births affected	20.4 million	18.3 million	18.0 million
Impaired glucose tolerance (20–79 years)			
Global prevalence	7.5%	8.0%	8.6%
Number of people with impaired glucose tolerance	373.9 million	453.8 million	548.4 million
Type 1 diabetes (0–19 years)			
Number of children and adolescents with type 1 diabetes	1,110,100	-	-
Number of newly diagnosed cases each year	128,900	-	-

i Health expenditures for people with diabetes are assumed to be on average two-fold higher than people without diabetes.
ii Age-adjusted prevalence.

If current trends continue,
700 million adults will have diabetes by 2045.
The largest increases will take place where economies are moving from low- to middle-income status.

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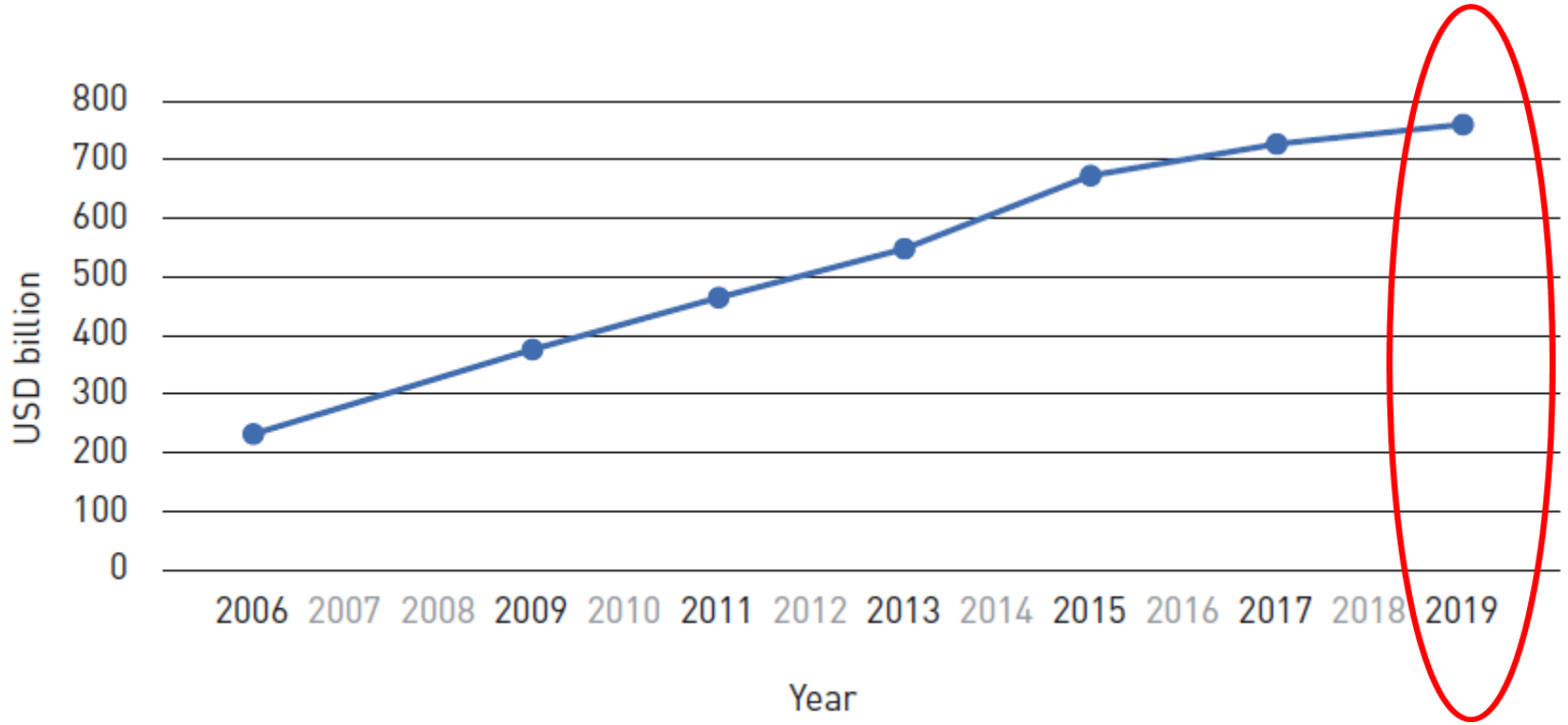
Total diabetes-related health expenditure for adults (20–79 years) with diabetes



DIABETES RESEARCH AND CLINICAL PRACTICE XXX (2014) XXX–XXX

Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Trends in the prevalence of diabetes and impaired fasting glucose in association with obesity in Iran: 2005–2011

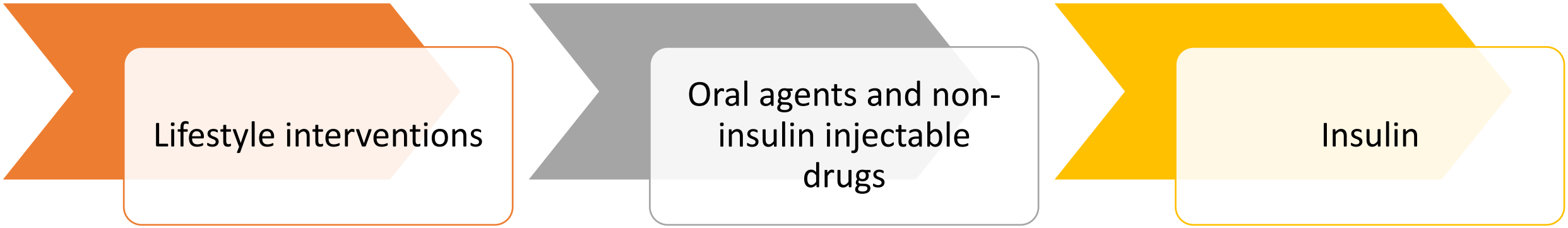
Alireza Esteghamati [a,*], *Koorosh Etemad* [b], *Jalil Koohpayehzadeh* [b], *Mehrshad Abbasi* [a], *Alipasha Meysamie* [c], *Sina Noshad* [a], *Fereshteh Asgari* [b], *Mostafa Mousavizadeh* [a], *Ali Rafei* [b], *Elias Khajeh* [a], *Mohamadreza Neishaboury* [a], *Sara Sheikhbahaei* [a], *Manouchehr Nakhjavani* [a]

- 11.4% (95% CI, 9.9-12.9) of Iranian adults aged 25-70 yrs had diabetes.
- In about one-fourth, diabetes, was undiagnosed.
- The prevalence of diabetes was higher in:
  - *Women (12.8%) than in men (9.9%)*
  - *Urban (12.6%) than in rural (7.6%) residents*
- 2005 to 2011: 35% increase in the diabetes prevalence rate
- The prevalence of IFG: 14.6 %

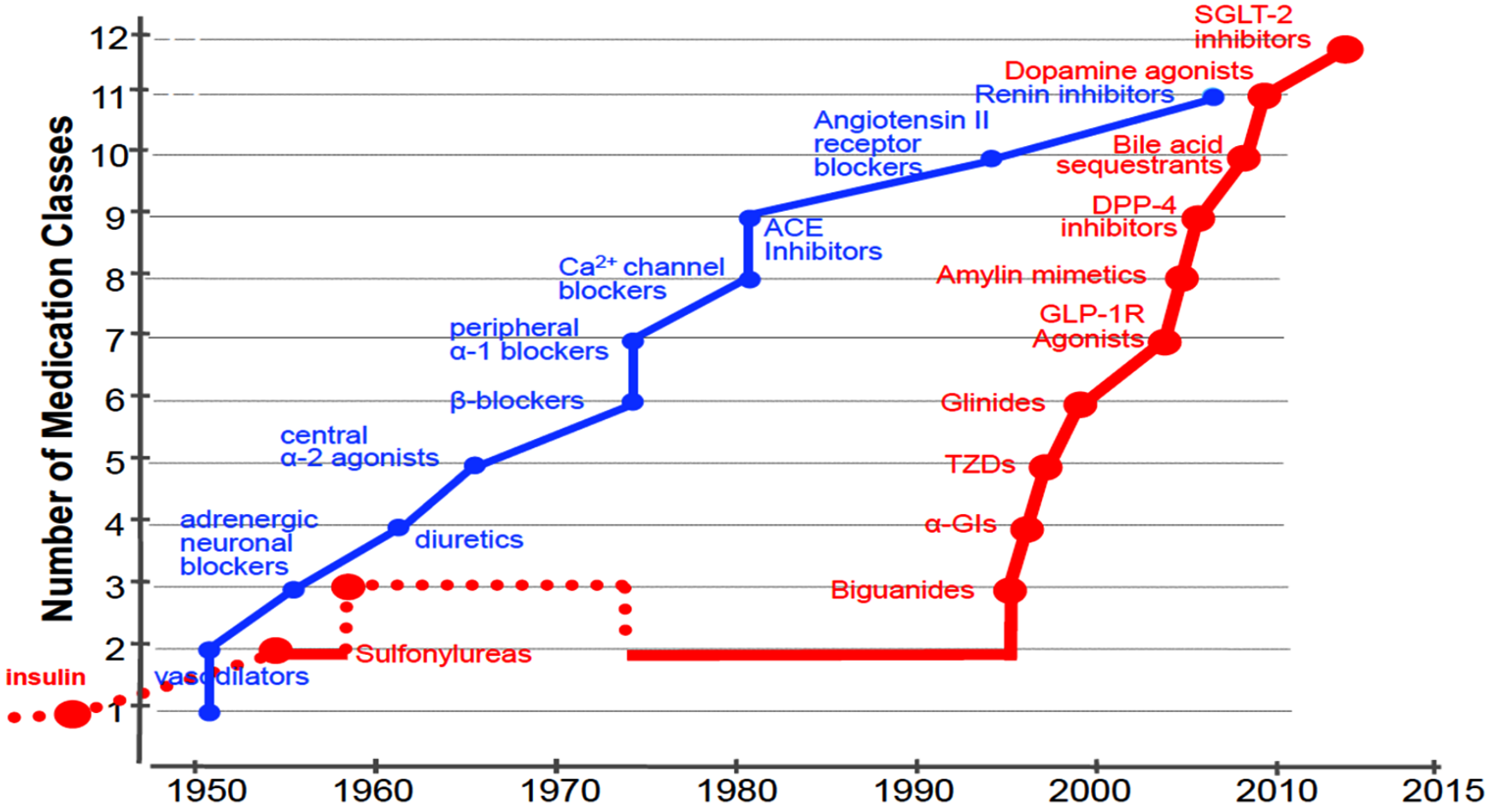
Esteghamati A, et al.*Diabetes Res Clin Pract* 2014;103:319-27.

What Do We Have for Treatment of T_2DM?

Sixty years of HTN and T2DM medications in USA

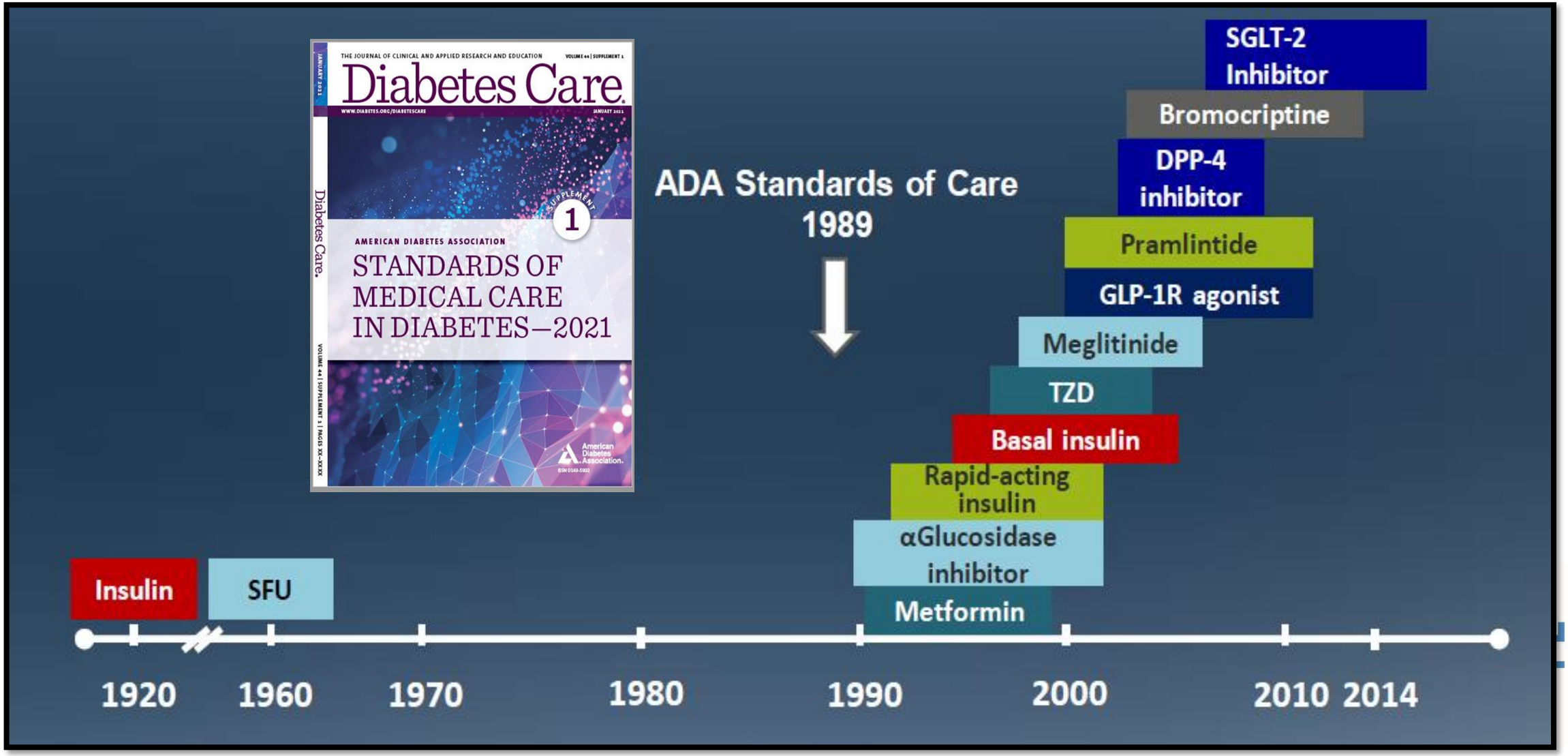


Sixty years of HTN and T2DM medications in USA

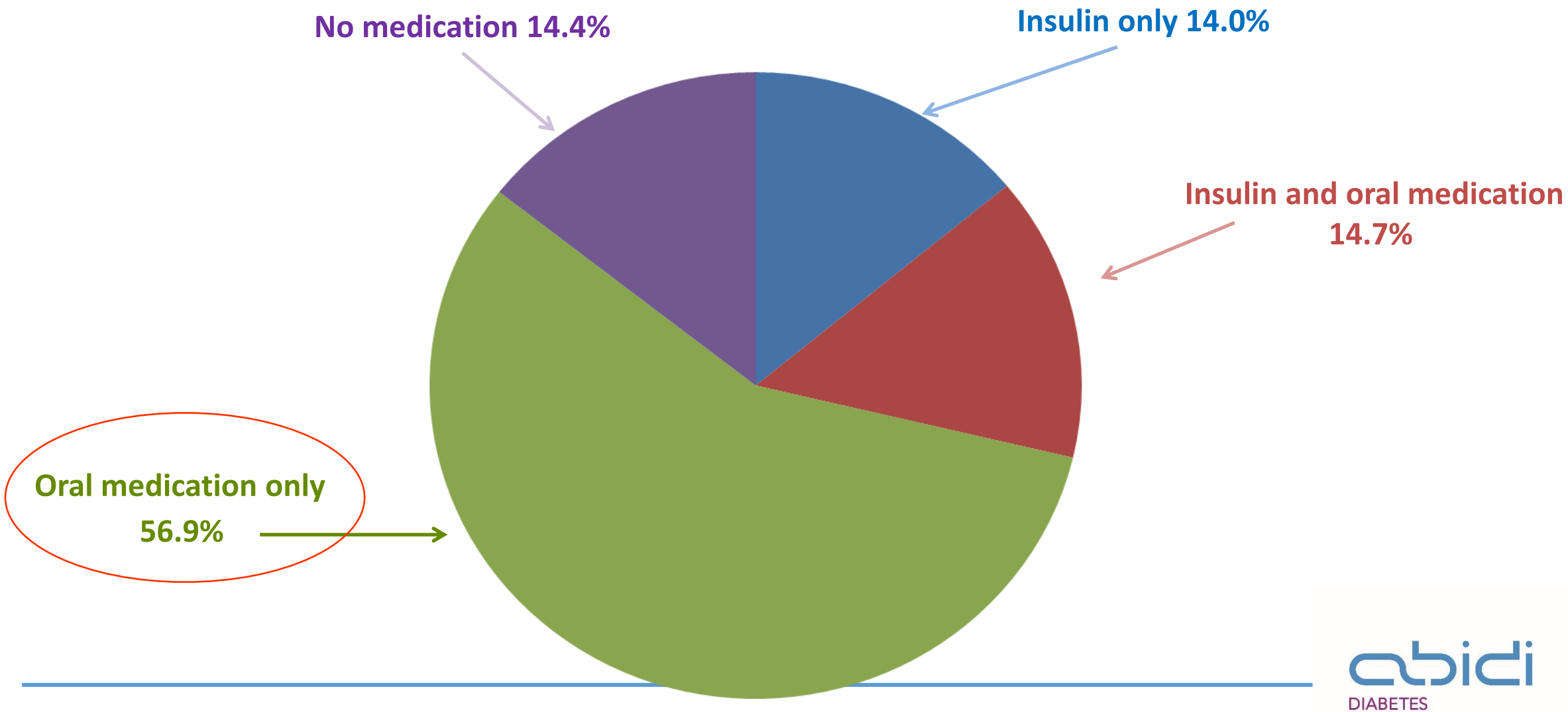


Courtesy of Silvio Inzucchi, MD, Yale University

Significant Therapeutic Advances in Diabetes Care Over Past 20 Years



Treatment of Diabetes



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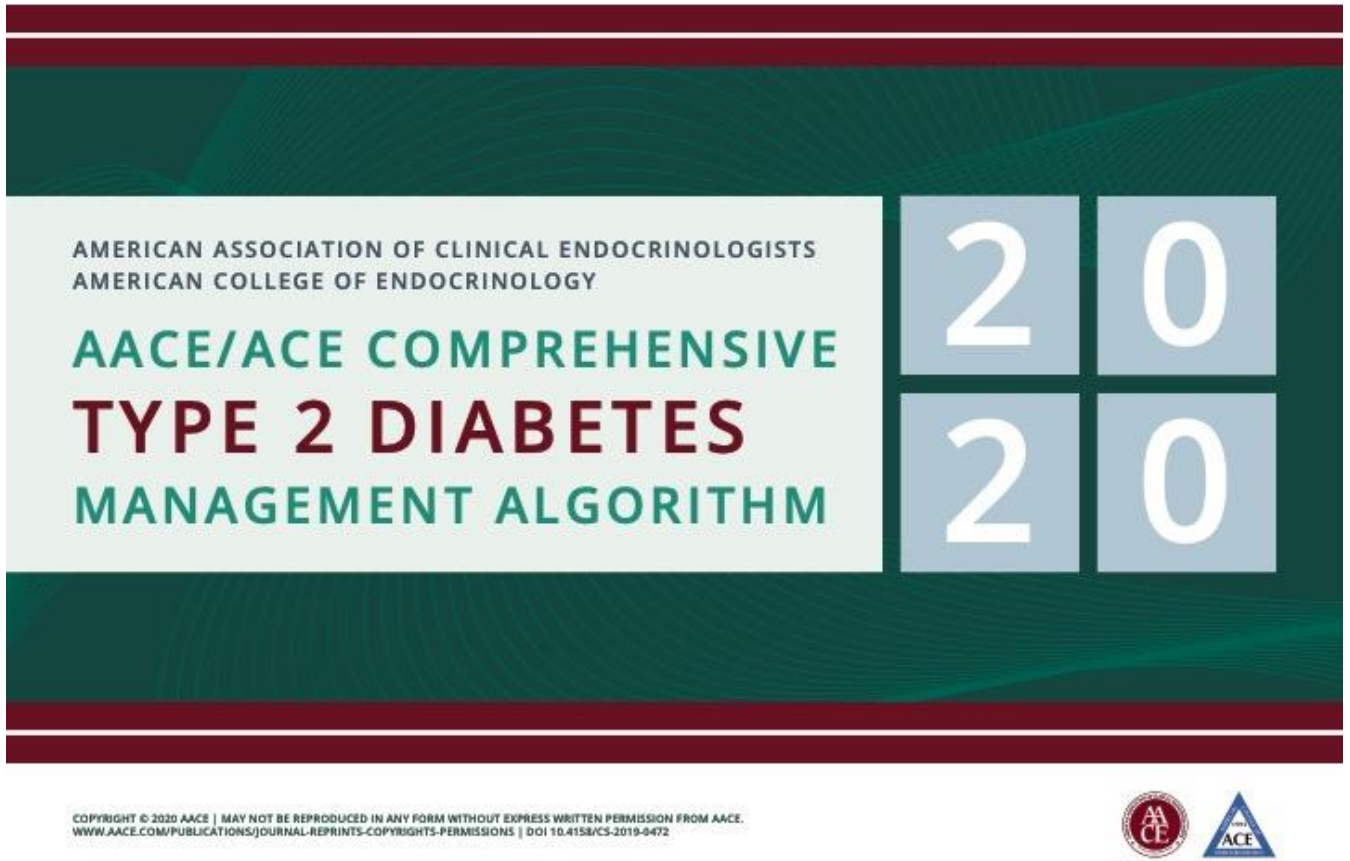
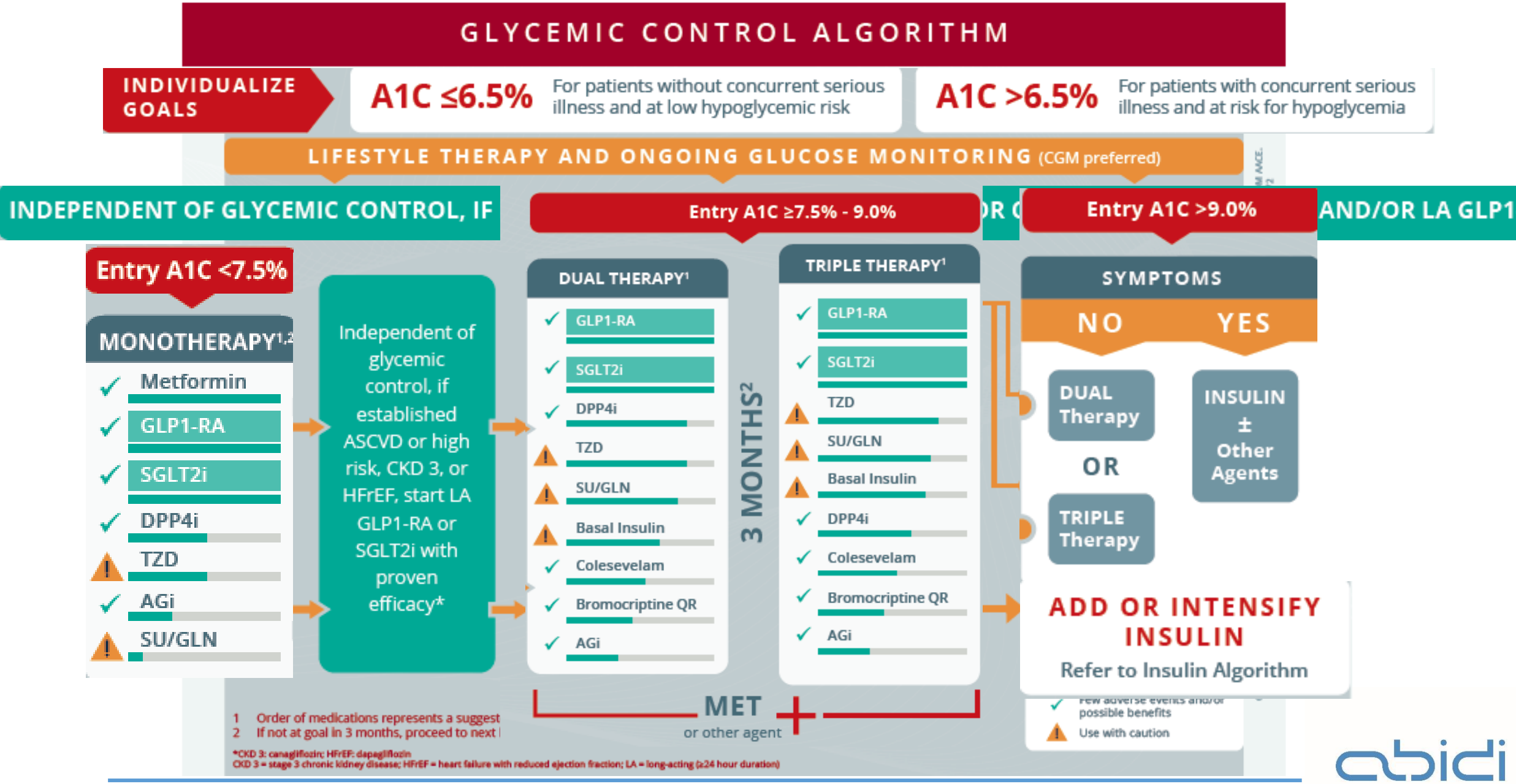
National Diabetes Information Clearinghouse. National Diabetes Statistics, 2014. Available at: http://diabetes.niddk.nih.gov/dm/pubs/statistics/

Pharmacologic Approaches to Glycemic Treatment



Diabetes Management Algorithm*, Endocr Pract*. 2020;26(No. 1)



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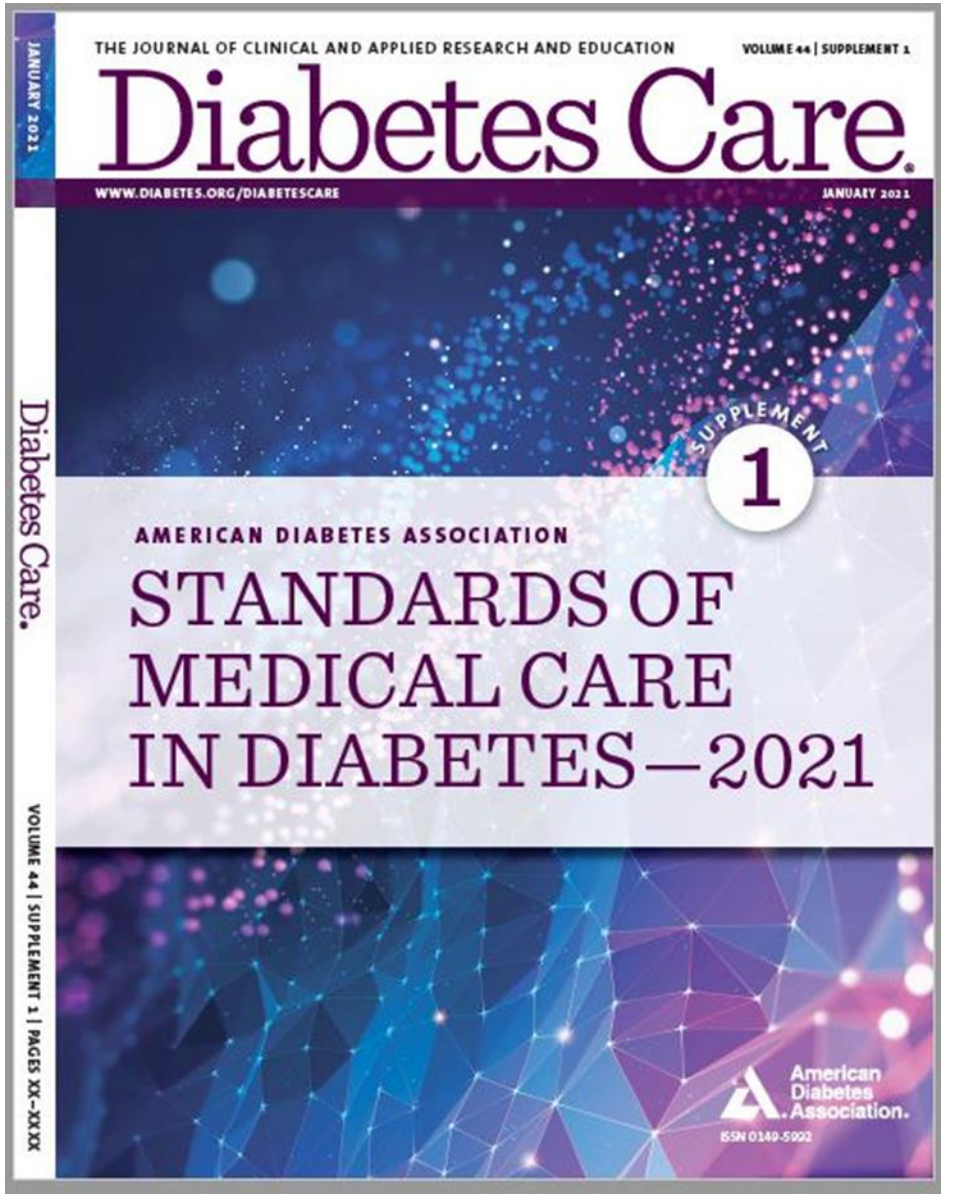
Diabetes Management Algorithm, *Endocr Pract*. 2020;26(No. 1)

Pharmacologic Approaches to Glycemic Treatment



Pharmacologic Approaches to Glycemic Management: *Diabetes Care* 2021;44(Suppl.1):S100-S110.

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CONSIDER INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE*

INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

+ASCVD/Indicators of High Risk

- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 years with coronary, carotid, or lower-extremity artery stenosis >50%, or LVH)

EITHER/OR

GLP-1 RA with proven CVD benefit[1]

SGLT2i with proven CVD benefit[1]

If A1C above target

If further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV benefit and/or safety:

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit and vice versa[1]
- TZD[2]
- DPP-4i if not on GLP-1 RA
- Basal insulin[3]
- SU[4]

+HF

Particularly HFrEF (LVEF <45%)

SGLT2i with proven benefit in this population[5,6,7]

+CKD

DKD and Albuminuria[8]

NO

PREFERABLY

SGLT2i with primary evidence of reducing CKD progression

OR

SGLT2i with evidence of reducing CKD progression in CVOTs[5,6,8]

OR

GLP-1 RA with

For patients with T2D and CKD[8] (e.g., eGFR <60 mL/min/1.73 m²) and thus at increased risk of cardiovascular events

EITHER/OR

GLP-1 RA with proven CVD benefit[1]

SGLT2i with proven CVD benefit[1,7]

COMPELLING NEED TO MINIMIZE HYPOGLYC

DPP-4i

GLP-1 RA

If A1C above target

If A1C above target

SGLT2i OR TZD

GLP-1 RA

SGLT2i

Continue with

Consider the addition of SU[4] **OR** basal insulin:

Choose later generation SU with lower risk of hypoglycemia

Consider basal insulin with lower risk of hypoglycemia[9]

If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain

PREFERABLY

DPP-4i (if not on GLP-1 RA) based on weight neutrality

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

• SU[4] • TZD[2] • Basal insulin

COST IS A MAJOR ISSUE[11,12]

SU[4]

TZD[12]

If A1C above target

SU[4]

1C above target

therapy basal insulin

est acquisition cost

OR

Consider other therapies based on cost

Indicators of high ASCVD risk (age≥55 years with coronary, carotid or lower extremity artery stenosis >50%, or LVH)

label indication of reducing CVD events

d though less well studied for CVD effects

demonstrated CVD safety

wer risk of hypoglycemia; safety to DPP-4i

aries by region and individual agent eGFR for initiation and continued use

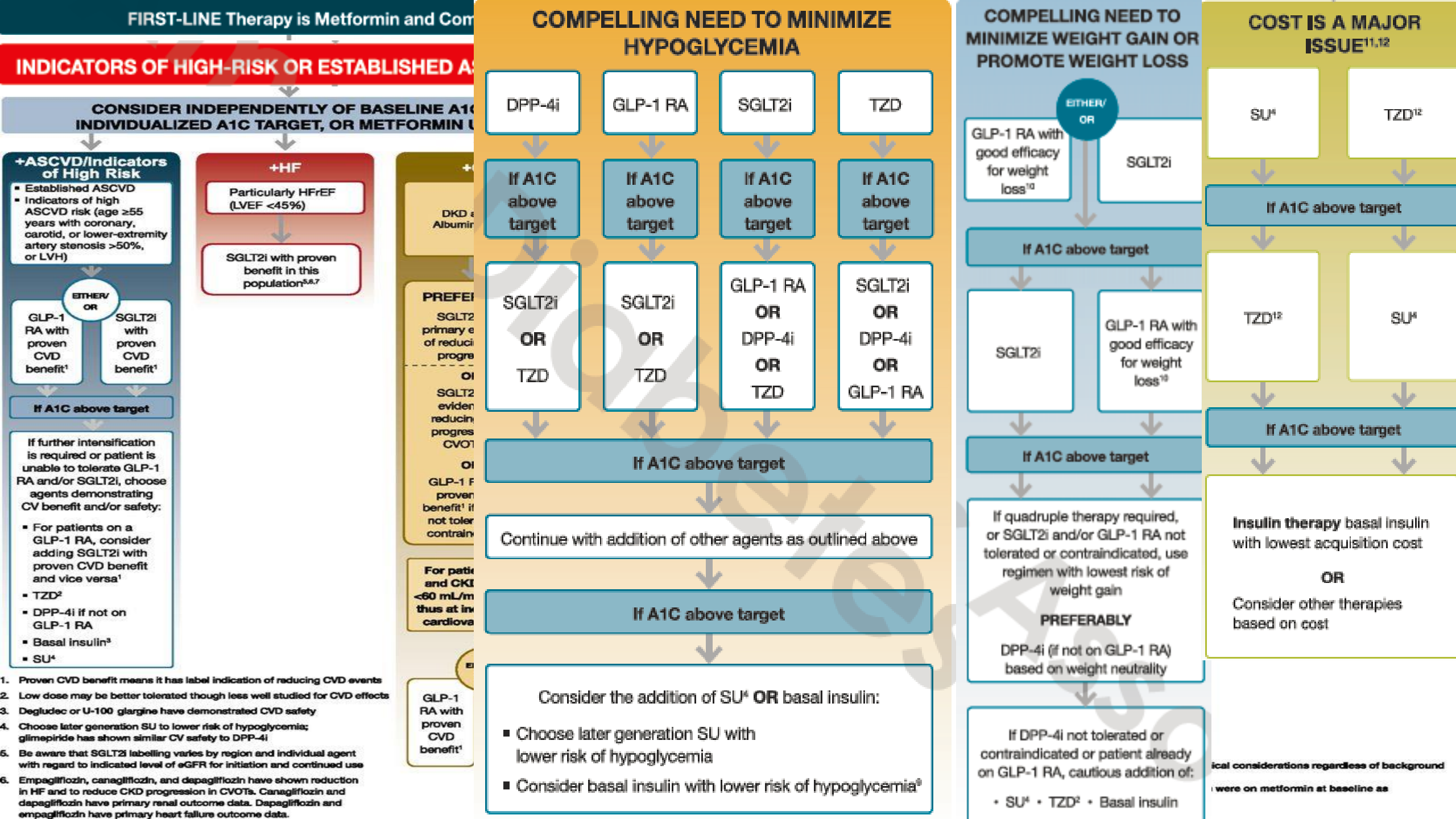
dapagliflozin have shown reduction ssion in CVOTs. Canagliflozin and outcome data. Dapagliflozin and failure outcome data.

oven benefit means it has label indication of reducing heart failure in this population

8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. 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)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.


FIRST-LINE Therapy is Metformin and Com
INDICATORS OF HIGH-RISK OR ESTABLISHED AS
CONSIDER INDEPENDENTLY OF BASELINE A1C
INDIVIDUALIZED A1C TARGET, OR METFORMIN U
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Established ASCVD
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SGLT2i with proven benefit in this population[5,6,7]
+
DKD
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PREFE
SGLT2
primary
of reduci
progre
OR
SGLT2
eviden
reducing
progres
CVOT
OR
GLP-1 R
proven
benefit[1] if
not toler
contrain
For patie
and CKD
<60 mL/m
thus at in
cardiova
GLP-1 RA with proven CVD benefit[1]
1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA
DPP-4i
GLP-1 RA
SGLT2i
TZD
If A1C above target
SGLT2i OR TZD
SGLT2i OR TZD
GLP-1 RA OR DPP-4i OR TZD
SGLT2i OR DPP-4i OR GLP-1 RA
If A1C above target
Continue with addition of other agents as outlined above
If A1C above target
Consider the addition of SU[4] OR basal insulin:
Choose later generation SU with lower risk of hypoglycemia
Consider basal insulin with lower risk of hypoglycemia[8]
COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS
EITHER/ OR
GLP-1 RA with good efficacy for weight loss[10]
SGLT2i
If A1C above target
SGLT2i
GLP-1 RA with good efficacy for weight loss[10]
If A1C above target
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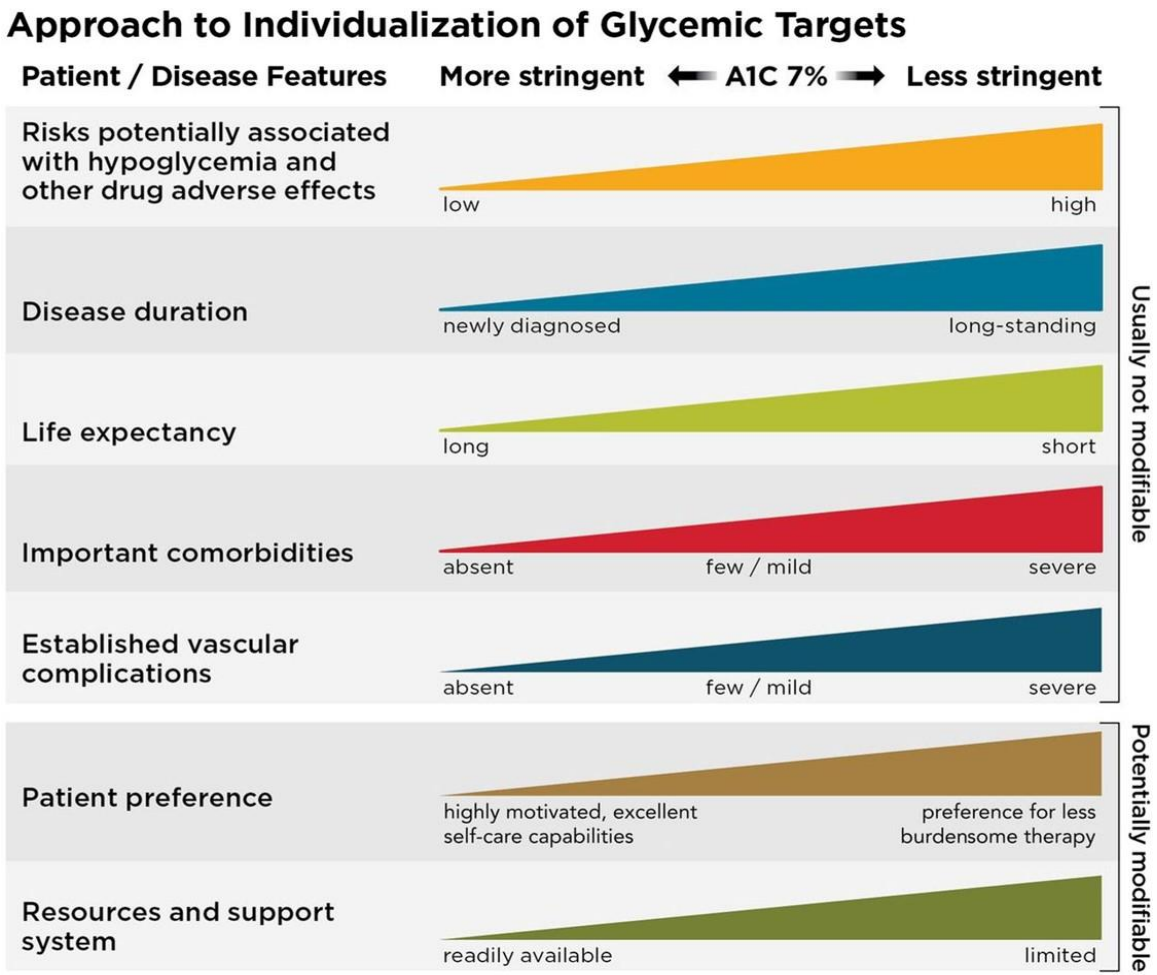
COST IS A MAJOR ISSUE[11,12]
SU[4]
TZD[12]
If A1C above target
TZD[12]
SU[4]
If A1C above target
Insulin therapy basal insulin with lowest acquisition cost
OR
Consider other therapies based on cost
ical considerations regardless of background
were on metformin at baseline as

Estimated average glucose

A1C (%)	mg/dL*	mmol/L
5	97 (76–120)	5.4 (4.2–6.7)
6	126 (100–152)	7.0 (5.5–8.5)
7	154 (123–185)	8.6 (6.8–10.3)
8	183 (147–217)	10.2 (8.1–12.1)
9	212 (170–249)	11.8 (9.4–13.9)
10	240 (193–282)	13.4 (10.7–15.7)
11	269 (217–314)	14.9 (12.0–17.5)
12	298 (240–347)	16.5 (13.3–19.3)

Data in parentheses are 95% CI. A calculator for converting A1C results into eAG, in either mg/dL or mmol/L, is available at professional.diabetes.org/eAG. *These estimates are based on ADAG data of ~2,700 glucose measurements over 3 months per A1C measurement in 507 adults with type 1, type 2, or no diabetes. The correlation between A1C and average glucose was 0.92 (6,7). Adapted from Nathan et al. (6).

Approach to individualization of glycemic target



Diabetes Care Volume 43, Supplement 1, January 2020

ESC European Society of Cardiology

European Heart Journal (2019) **00**, 1–69
doi:10.1093/eurheartj/ehz486

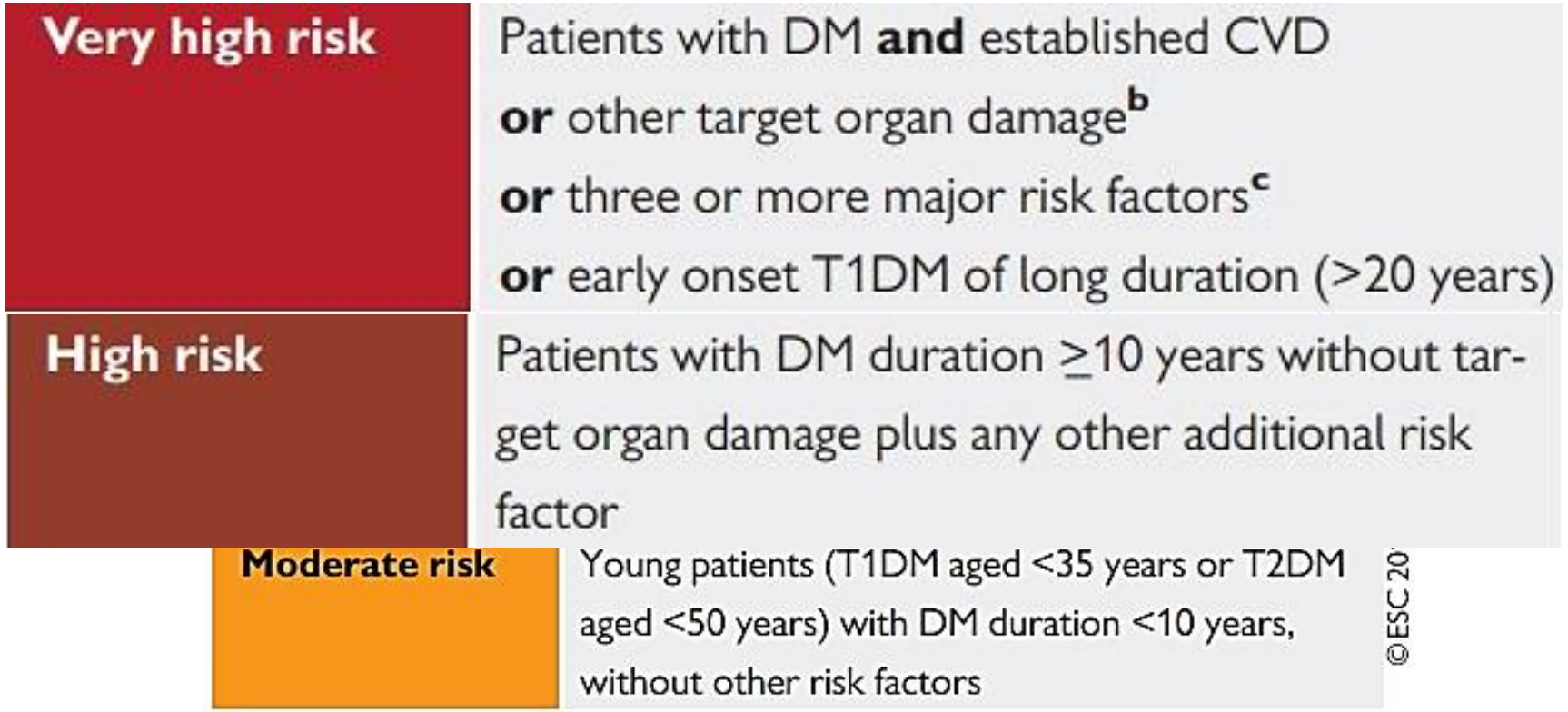
ESC GUIDELINES

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD)

European Heart Journal 2019; 00, 169

Cardiovascular risk categories in patients with diabetes[1]



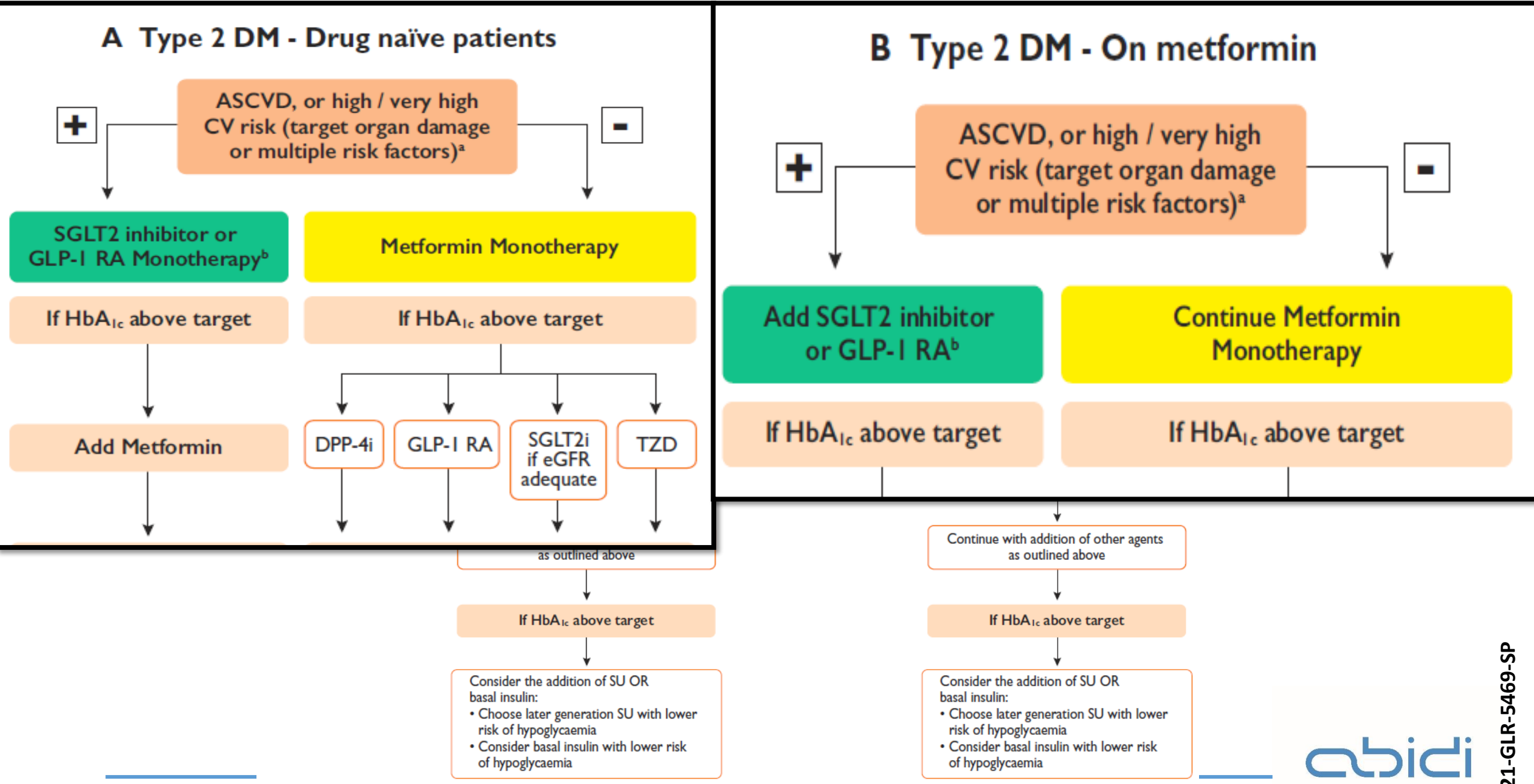
CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

[a]Modified from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.[27]

[b]Proteinuria, renal impairment defined as eGFR <30 mL/min/1.73 m^2, left ventricular hypertrophy, or retinopathy.

[c]Age, hypertension, dyslipidemia, smoking, obesity.

1-Piepoli, Massimo F., et al. "2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)." *European heart journal* 37.29 (2016): 2315-2381.



European Heart Journal 2019; 00, 169

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Heart failure and diabetes[1]

Key messages

- Patients with pre-DM and DM are at increased risk of developing HF.
- Patients with DM are at greater risk of HF with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction (HFpEF); conversely, HF increases the risk of DM.
- The coexistence of DM and HF imparts a higher risk of HF hospitalization, all-cause death, and CV death.
- Guideline-based medical and device therapies are equally effective in patients with and without DM; as renal dysfunction and hyperkalaemia are more prevalent in patients with DM, dose adjustments of some HF drugs (e.g. RAAS blockers) are advised.
- First-line treatment of DM in HF should include metformin and SGLT2 inhibitors; conversely, saxagliptin, pioglitazone, and rosiglitazone are not recommended for patients with DM and HF.

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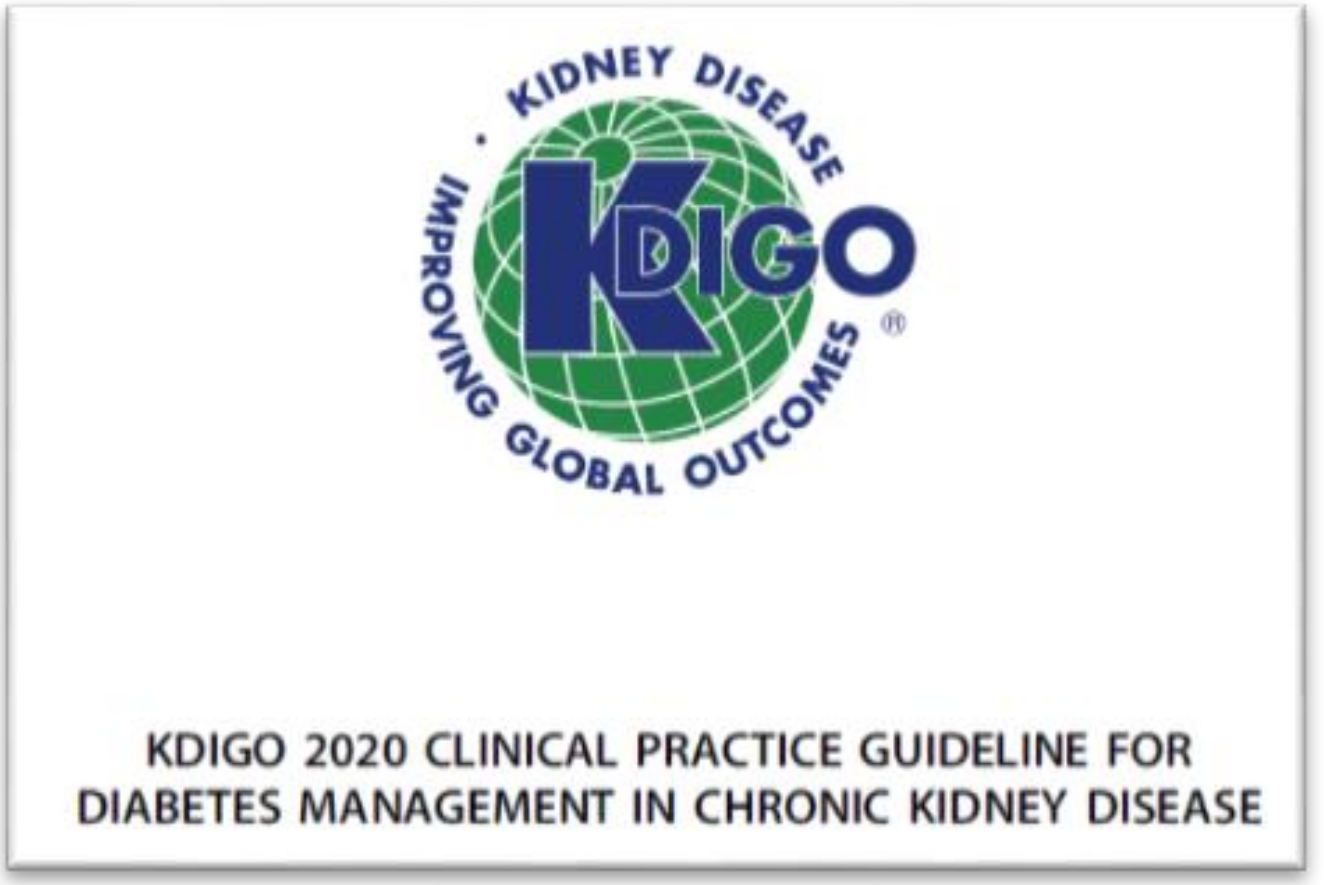
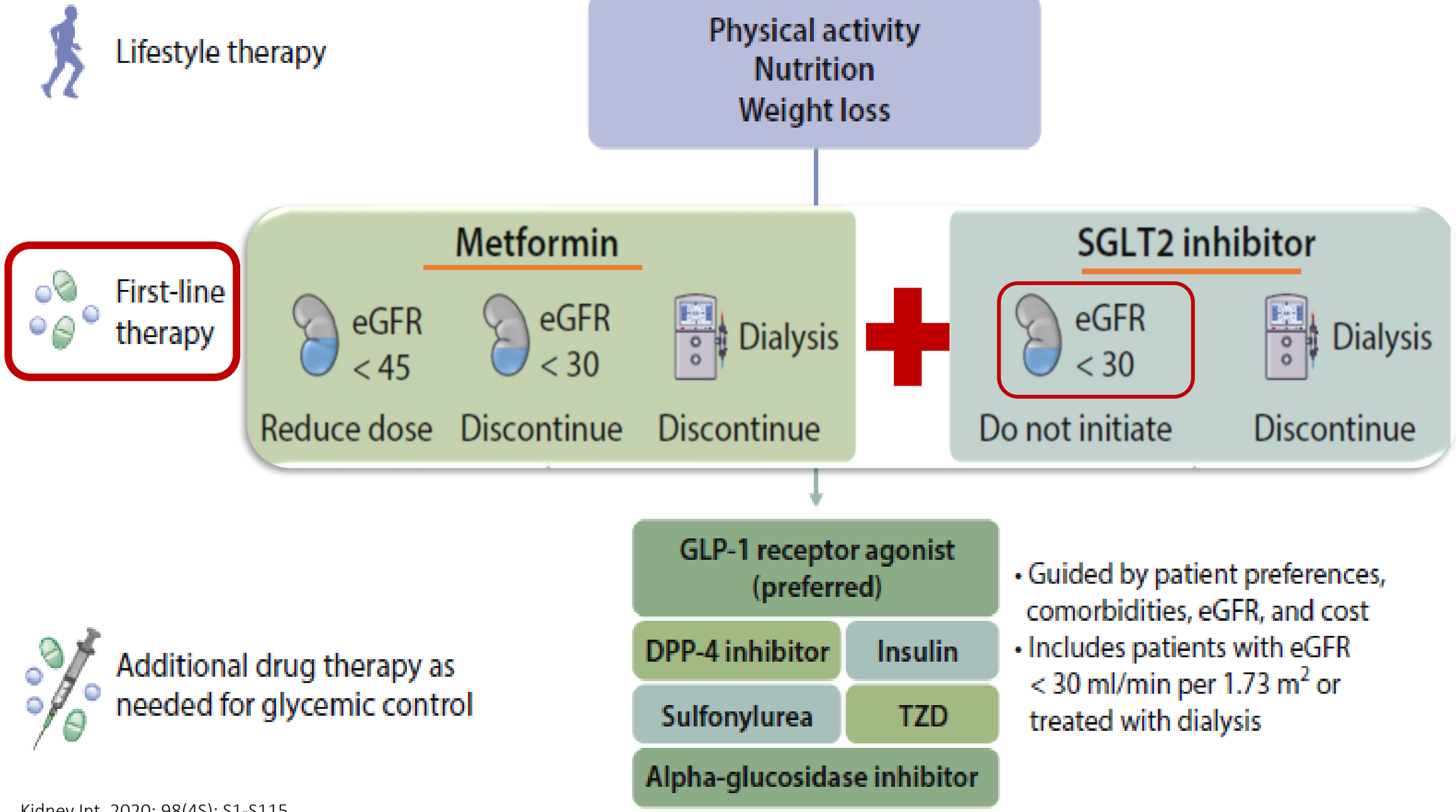
1-Lars R, Anker SD, Christian B, Francesco C, Nicolas D, Christi D, Javier E, Hammes HP, Heikki H, Michel M, Nikolaus M. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD.



Kidney Int. 2020; 98(4S): S1-S115



Kidney Int. 2020; 98(4S): S1-S115

KDIGO Guideline:
SGLT2 Inhibitors and Metformin Combination Are Recommended for T2D and CKD[1]

KDIGO Guideline Practical Recommendations[1]

- Most patients with T2DM, CKD, and eGFR ≥ 30ml/min per 1.73 m^2 would benefit from treatment with both metformin and an SGLT2i[1]
- Treating patients with T2DM, CKD, and an eGFR ≥ 30 ml/min per 1.73 m^2 with an SGLT2i[1]
- Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i **even if the eGFR falls below 30 ml/min per 1.73 m^2**, unless it is not tolerated or kidney replacement therapy is initiated[1]

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1- Kidney Int. 2020; 98(4S): S1-S115.
KDIGO: Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease;

In the era of growing number of diabetes medications and new data, we should consider the below factors to select the proper component for each individual patient:

- Effectiveness
- Safety profiles
- Side effects
- Extra-glycemic effects
- Cardiovascular effects
- Our experience in handling
- Availability
- Patient preference
- Cost

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Thank you