

# Régi és új szempontok a 2-es típusú diabétesz kezelésében

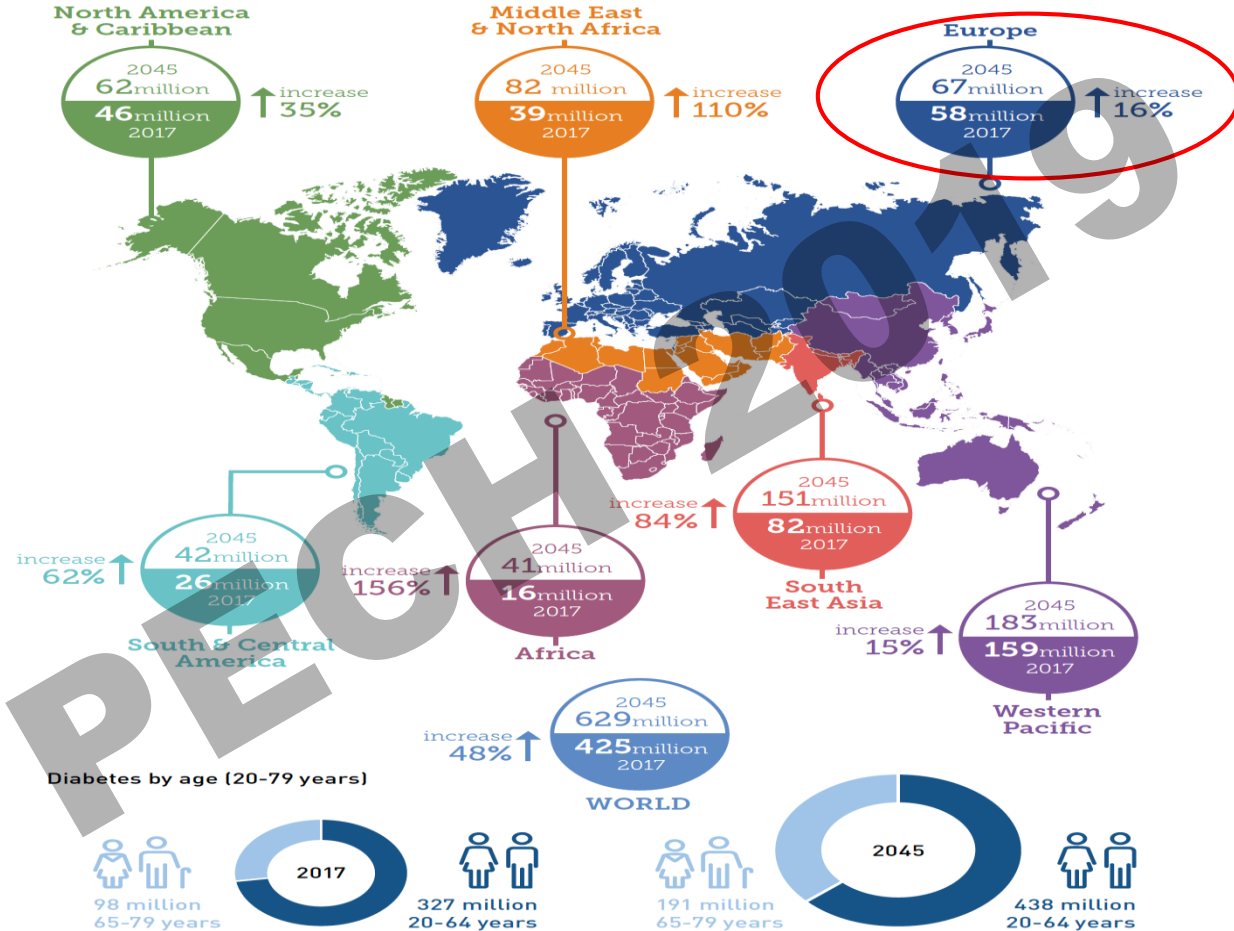
Új korszak tanúi vagyunk...

*dr. Kocsis Győző*

**Péterfy Kórház és Manninger Jenő Országos Traumatológiai Intézet  
(PMJOTI)**

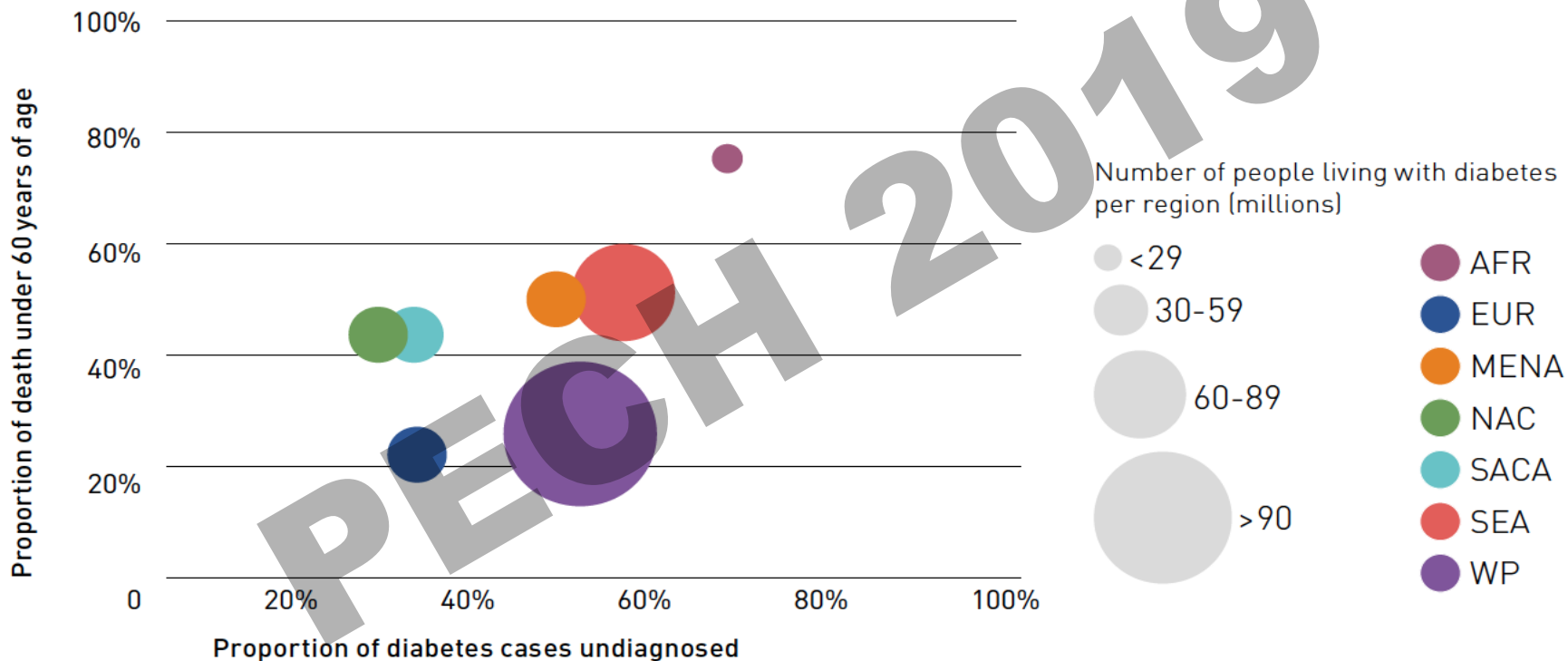
II. Kardiovaszkuláris Belgyógyászat és Diabetes Szakrendelő

Number of people with diabetes worldwide and per region in 2017 and 2045 (20-79 years)



## The hidden diabetes epidemic

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



People with diabetes are at **higher risk** of developing periodontal disease

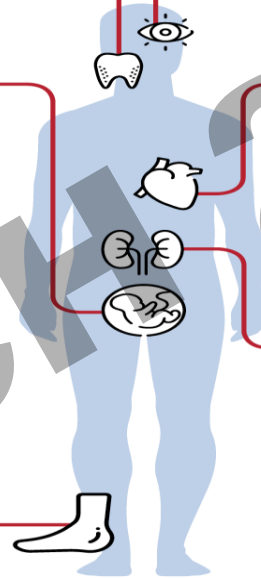
Diabetic retinopathy affects over **one-third** of all people with diabetes and is the leading cause of vision loss in working-age adults.

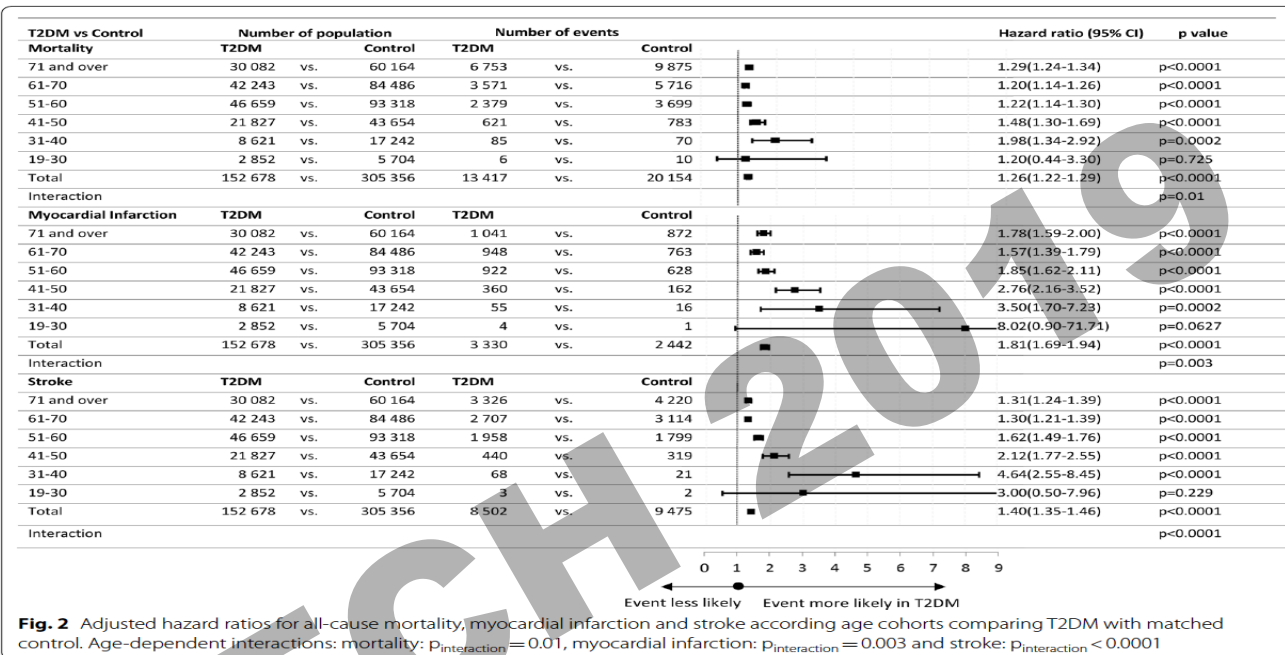
Pregnant woman with diabetes or at high risk for GDM should manage their glycaemia throughout their pregnancy to avoid long-term consequences for themselves and their children, and **transgenerational effects** (higher risk of obesity, diabetes, hypertension and kidney disease in the offspring)

People with diabetes are **2 to 3 times** more likely to have cardiovascular disease (CVD)

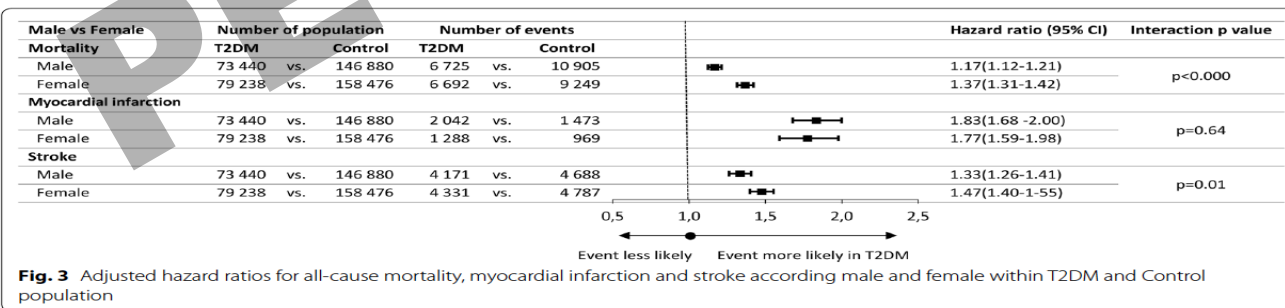
The prevalence of end-stage renal disease (ESRD) is up to **10 times higher** in people with diabetes

Every **30 seconds** a lower limb or part of a lower limb is lost to amputation somewhere in the world as a consequence of diabetes





**Fig. 2** Adjusted hazard ratios for all-cause mortality, myocardial infarction and stroke according age cohorts comparing T2DM with matched control. Age-dependent interactions: mortality:  $p_{\text{interaction}} = 0.01$ , myocardial infarction:  $p_{\text{interaction}} = 0.003$  and stroke:  $p_{\text{interaction}} < 0.0001$



**Fig. 3** Adjusted hazard ratios for all-cause mortality, myocardial infarction and stroke according male and female within T2DM and Control population

# Vezérfonal...

Távolabbról kell elindulni, ha akarunk tenni valamit....

A 2-es típusú diabétesz pathofiziológiája

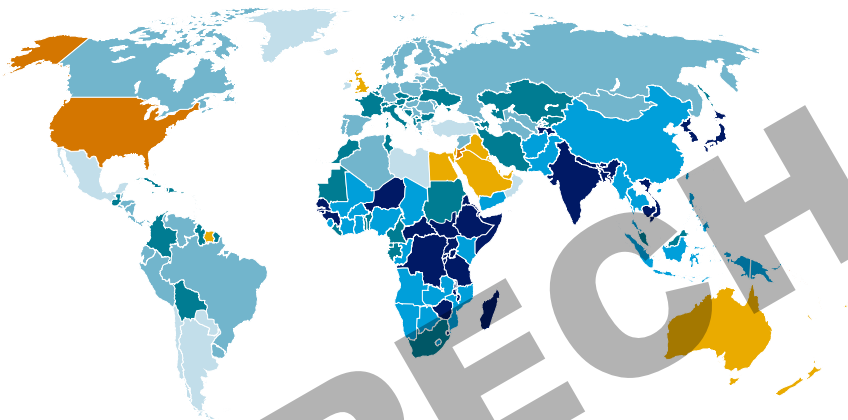
Az eddig publikált CVOT vizsgálatok adatai megváltoztatják a gondolkodásunkat...?!

Hogyan illesszük a jelen kezelési ajánlásaiba az új szemléletet?

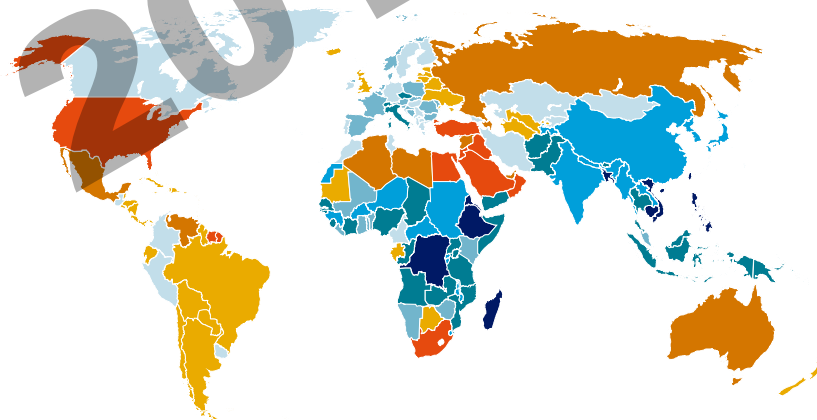
# The Obesity Pandemic

Age-standardised prevalence of obesity: 2015

Men



Women



Prevalence of obesity, %

■ <5

■ 5-10

■ 10-15

■ 15-20

■ 20-25

■ 25-30

■ 30-35

■ ≥35

# Obesity is

Metabolic, Mechanical

Metabolic

Mechanical

Mental

Cancers\*

Physical functioning

# Comorbidities

diseases

a  
ery disease  
heart failure

mbolism

ain

es



NAFLD, non-alcoholic fatty liver disease

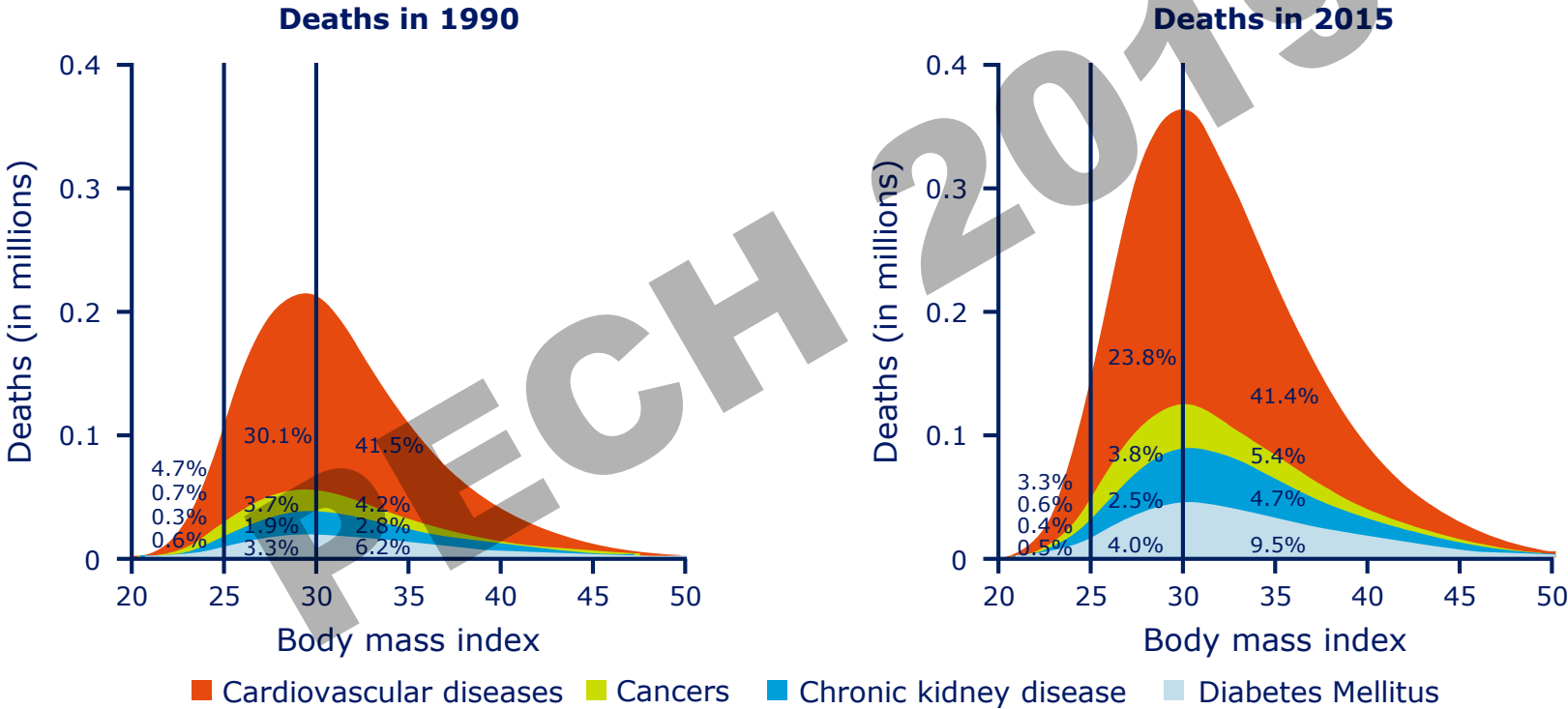
\*Including breast, colorectal

Adapted from Sharma AM. *Obes Rev* 2006;7:103-113; Sharma AM, Goldstein SA, Kushner M, et al. *Gen Psychiatry* 2006;63:824-30; C

;67:220-9; Simon et al. *Arch Chronic Dis* 2009;6:A48



# CV death contributes to the majority of deaths associated with high BMI



# Vezérfonal...

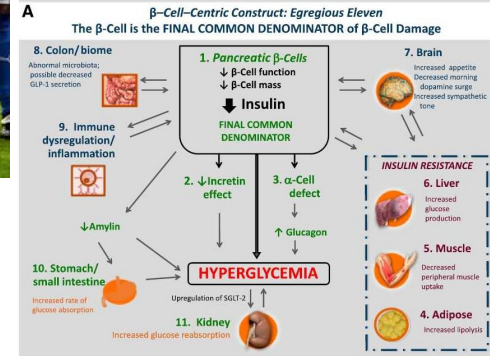
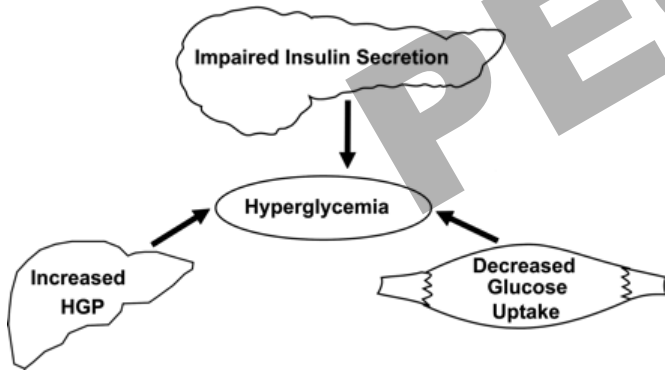
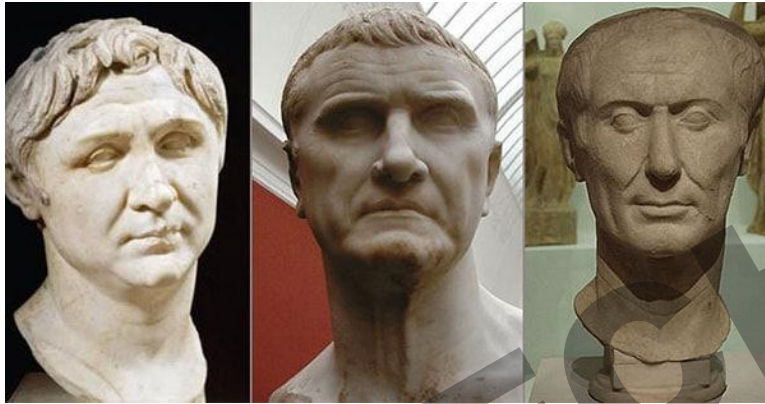
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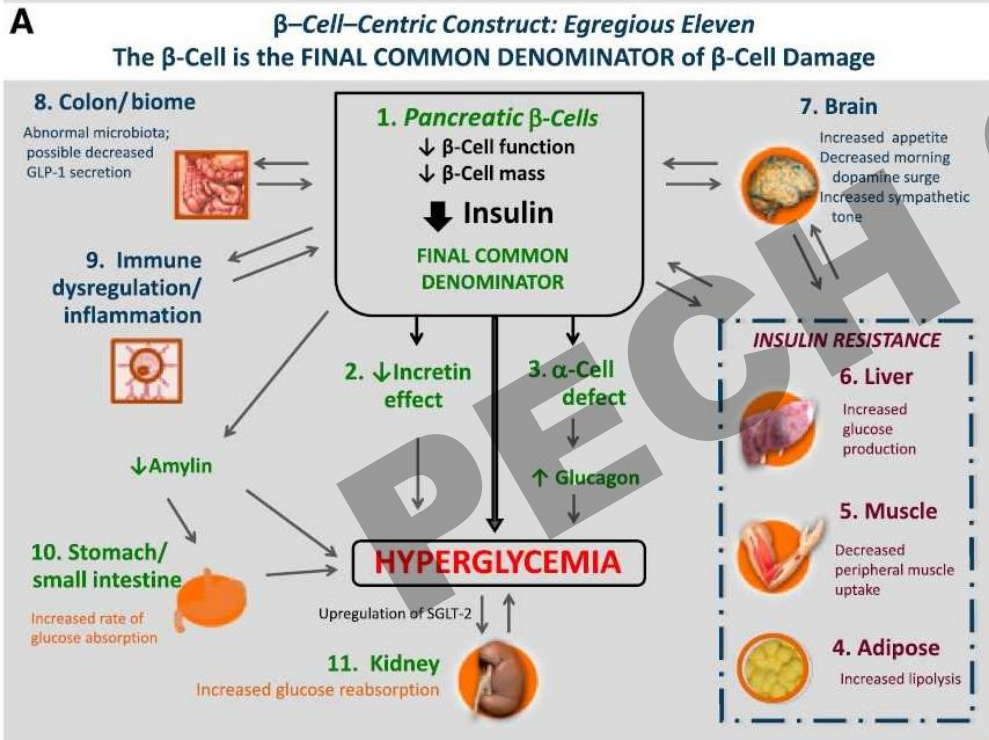
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# 2-es típusú diabétesz régen és ma: a triumvirátustól a baljós 11-ig



# 2018: árnyaltabb a kép...



2019

Béta-sejt  
 Alfa-sejt  
 Inkretin tengely  
 Inszulin rezisztencia (máj, izom, zsírszövet)  
 Vese  
 Agy  
 Immunrendszer  
 Gyomor -és vékonybél  
 Vastagbél flóra

# 2-es típusú diabétesz: Nagyon erős genetikai faktorok, környezeti faktorokkal kiegészülve





# Prevalence Rates of CV Comorbidities in Persons With T2DM: Results of a Systematic Literature Review

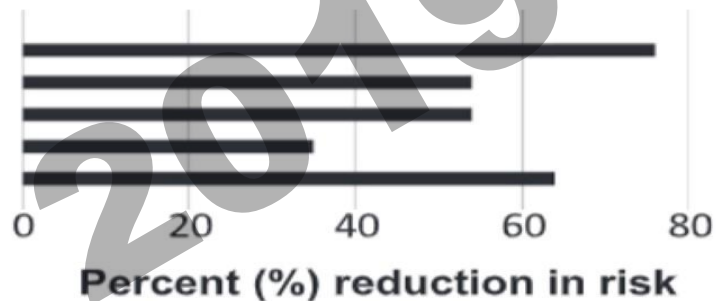
Sex	CV Outcome	Studies	N	Rate (%)	95% Confidence Interval (%)
Both	Stroke	39	3,901,505	7.6	6.6, 8.6
	MI	13	3,518,833	10.0	7.5, 12.5
	Angina pectoris	4	354,743	14.6	12.0, 17.3
	Heart failure	14	601,154	14.9	13.0, 16.7
	Atherosclerosis	4	1153	29.1	21.7, 36.4
	Coronary artery disease	42	3,833,200	21.2	20.3, 22.2
	CVD (any)	53	4,289,140	32.2	30.0, 34.4

Globally, more than 30% of persons with T2DM have some form of CV disorder.  
CVD is a major cause of mortality in patients with T2DM.

# Controlling Glycemia Reduces Microvascular Complications: DCCT

DCCT  
1983-93

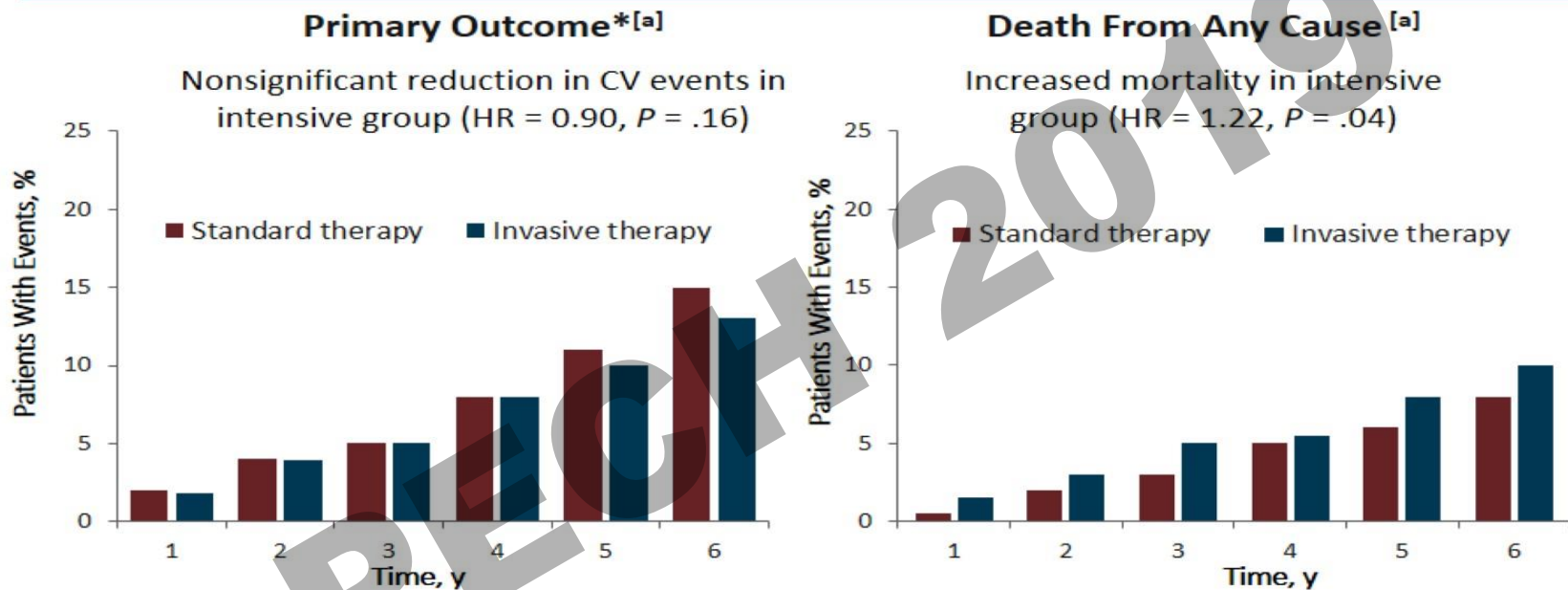
3+step devel, Prim  
3+step progression, Scnd  
Microalb  
Macroalb  
Neuropathy



3+step devel, Prim: three-step or more development of retinopathy based on Early Treatment of Diabetic Retinopathy scale in the primary prevention group. Scnd: secondary intervention group. Microalb: microalbuminuria defined as albumin excretion  $\geq 40$  mg/24 h. Macroalb: macroalbuminuria defined as albumin excretion  $> 300$  mg/24 h.

- In the Diabetes Control and Complications Trial (DCCT), intensive therapy, which featured 3 or more daily insulin injections or insulin pump therapy, and which achieved a median HbA1c of 7.0%, reduced the early stages of microvascular complications by 35% to 76% compared with conventional therapy, with which the median HbA1c was 9.0%

# Intensive Glycemic Control Increased All-Cause Mortality (ACCORD)



Mortality did not increase in other outcome trials  
(eg, VADT and ADVANCE)<sup>[b,c]</sup>

\*MACE: nonfatal MI, nonfatal stroke, or CV death

a. ACCORD Study Group. *N Engl J Med.* 2008;358:2545-2559; b. Duckworth W, et al. *N Engl J Med.* 2009;360:129-139; c. ADVANCE Collaborative Group. *N Engl J Med.* 2008;358:2560-2572.



# Vezérfonal...

Távolabbról kell elindulni, ha akarunk tenni valamit....

A 2-es típusú diabétesz pathofiziológiája

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Hogy illesszük a jelen kezelési ajánlásaiba az új szemléletet?

# Experience with rosiglitazone: Are diabetes medications associated with increased CV risk?

CVOTs in T2D



*"Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance"*

# Addressing the need for CVOTs in T2D

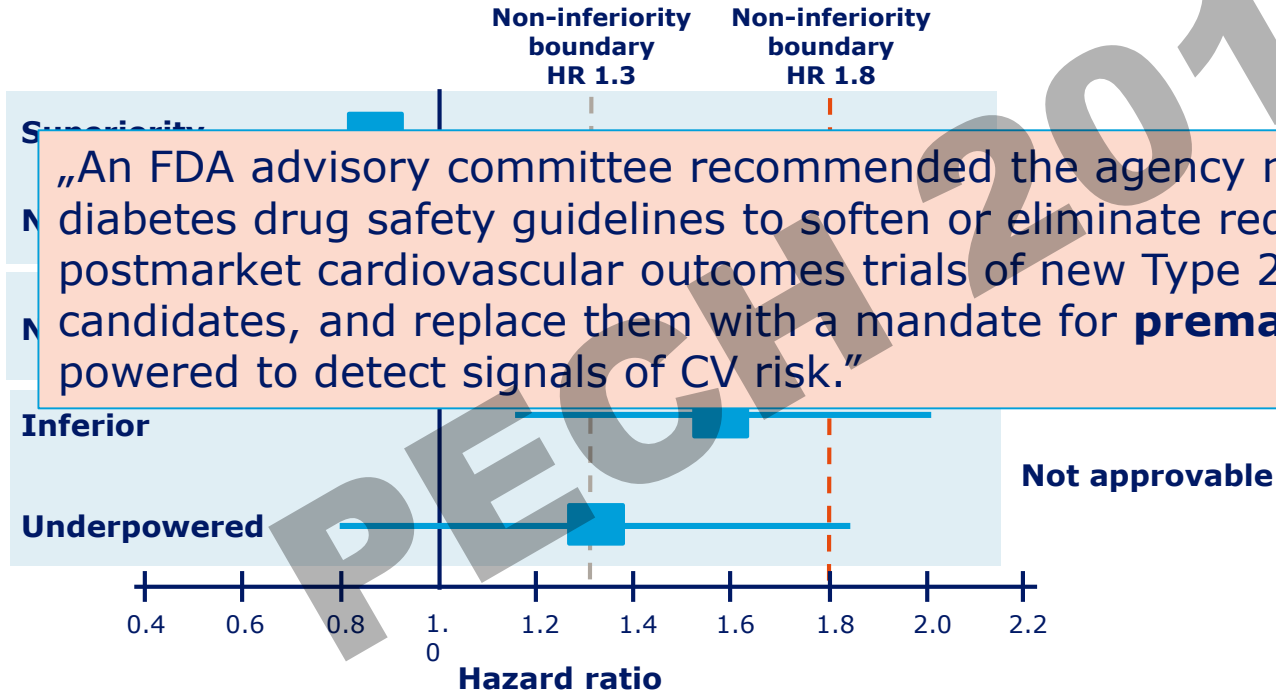
CVOTs in T2D

- Meta-analyses have raised the question of increased CV risk
- To date, clinical trial designs have not included CV outcomes assessments
- Need to assess non-inferiority versus placebo and versus standard of care

“Demonstrate that a new anti-diabetic therapy is not associated with **unacceptable increase** in cardiovascular risk”



# FDA criteria for requirement of a postmarketing CV outcomes trial

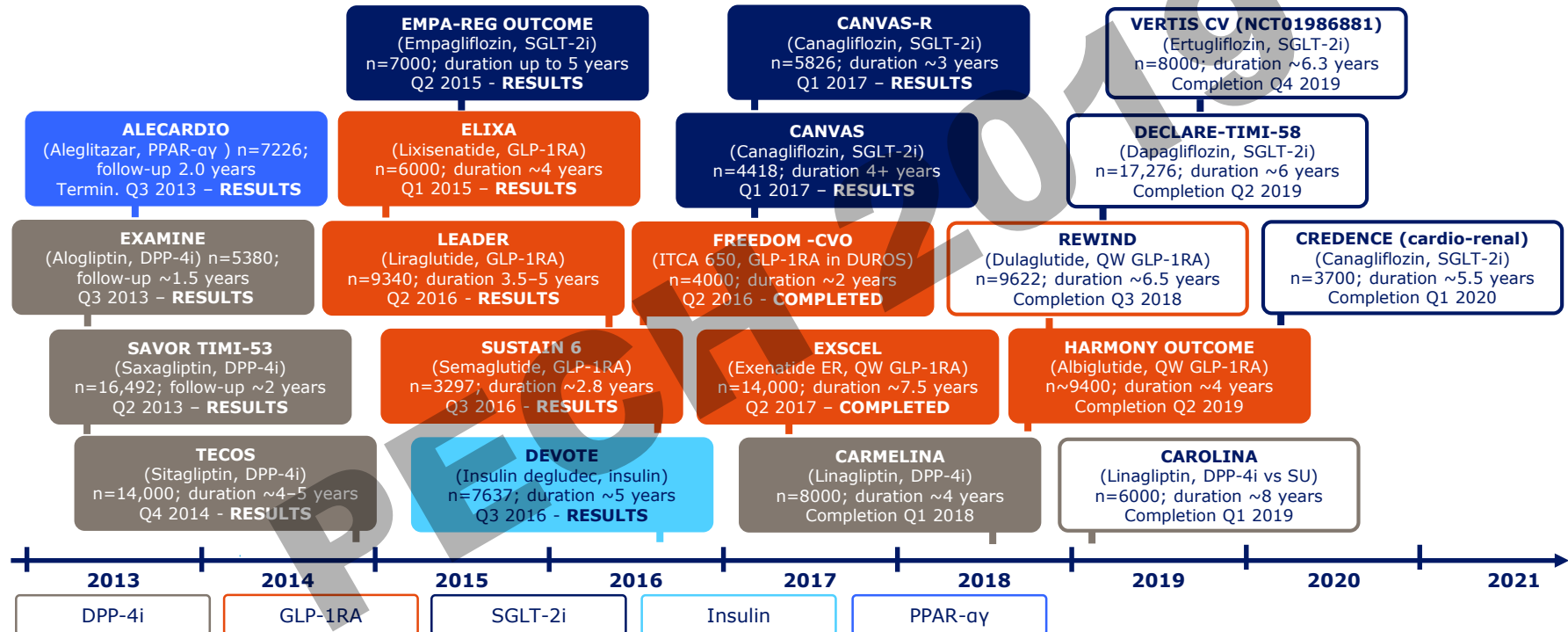


All phase 2 and 3 studies should include a prospective identification of events

A minimum of 2 years' CV safety data must be provided

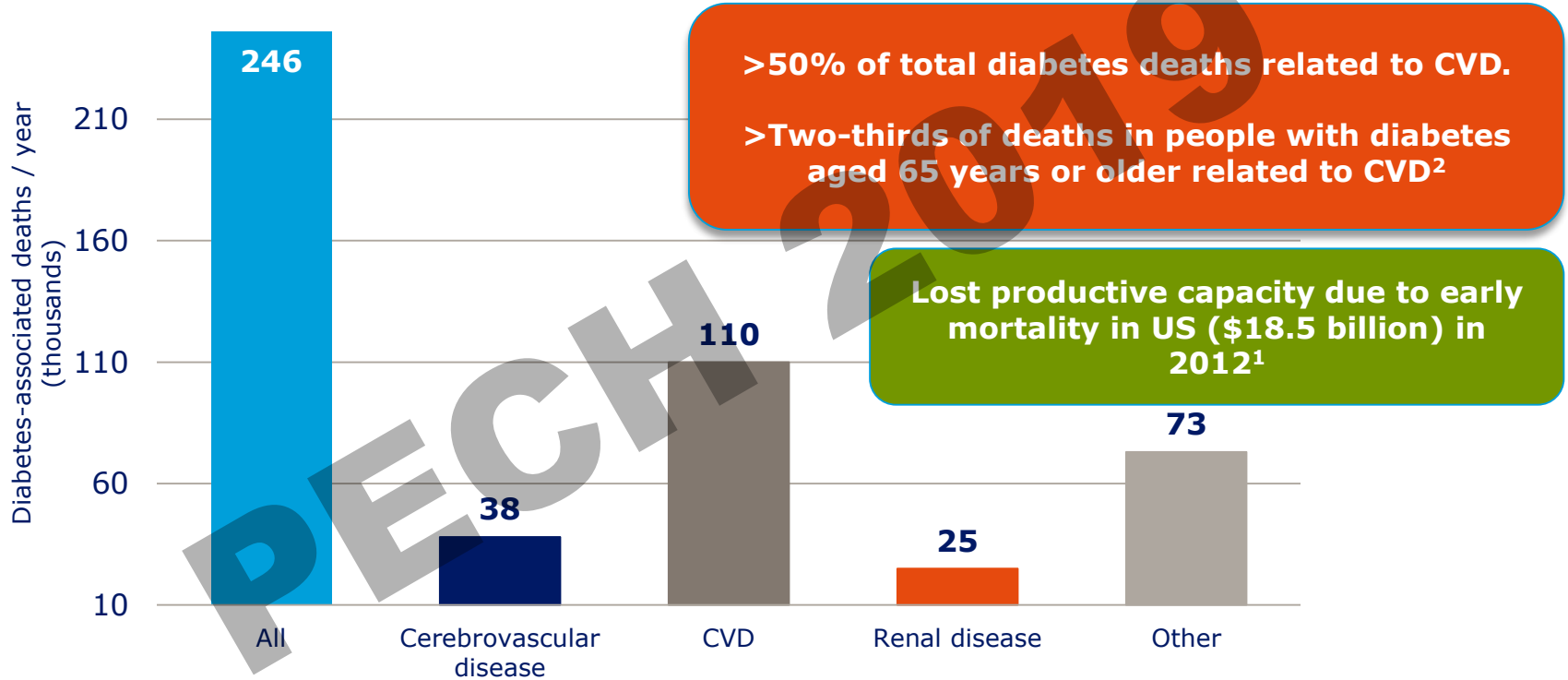
„An FDA advisory committee recommended the agency modify diabetes drug safety guidelines to soften or eliminate requirements for postmarket cardiovascular outcomes trials of new Type 2 diabetes drug candidates, and replace them with a mandate for **premarket** studies powered to detect signals of CV risk.”

## CVOTs in T2D



CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase-4 inhibitor; ER, extended release; GLP-1RA, glucagon-like peptide-1 receptor agonist; ITCA 650, continuous subcutaneous delivery of exenatide; PPAR- receptors-αγ, peroxisome proliferator-activated receptors-α and γ; QW, once weekly; SGLT-2i, sodium-glucose cotransporter 2 inhibitor; SU, sulphonylurea; T2D, type 2 diabetes  
 ClinicalTrials.gov. Accessed June 2017

# CVD remains the leading cause of diabetes-associated death 1,2



**Data source:** USA Centers for Disease Control and Prevention National Vital Statistics Reports for total deaths in 2009 by primary cause of death, scaled to 2012 using the annual diabetes population growth rate from 2009 to 2012 for each age, sex, and race/ethnicity group  
CVD, cardiovascular disease

1. ADA. *Diabetes Care* 2013;36:1033–1046; 2. Centers for Disease Control and Prevention. National Diabetes Fact Sheet 2011. Available at: [http://www.cdc.gov/diabetes/pubs/pdf/ndfs\\_2011.pdf](http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf)

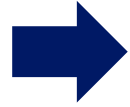
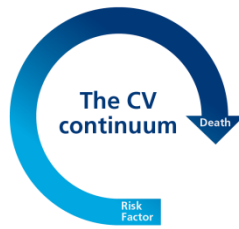
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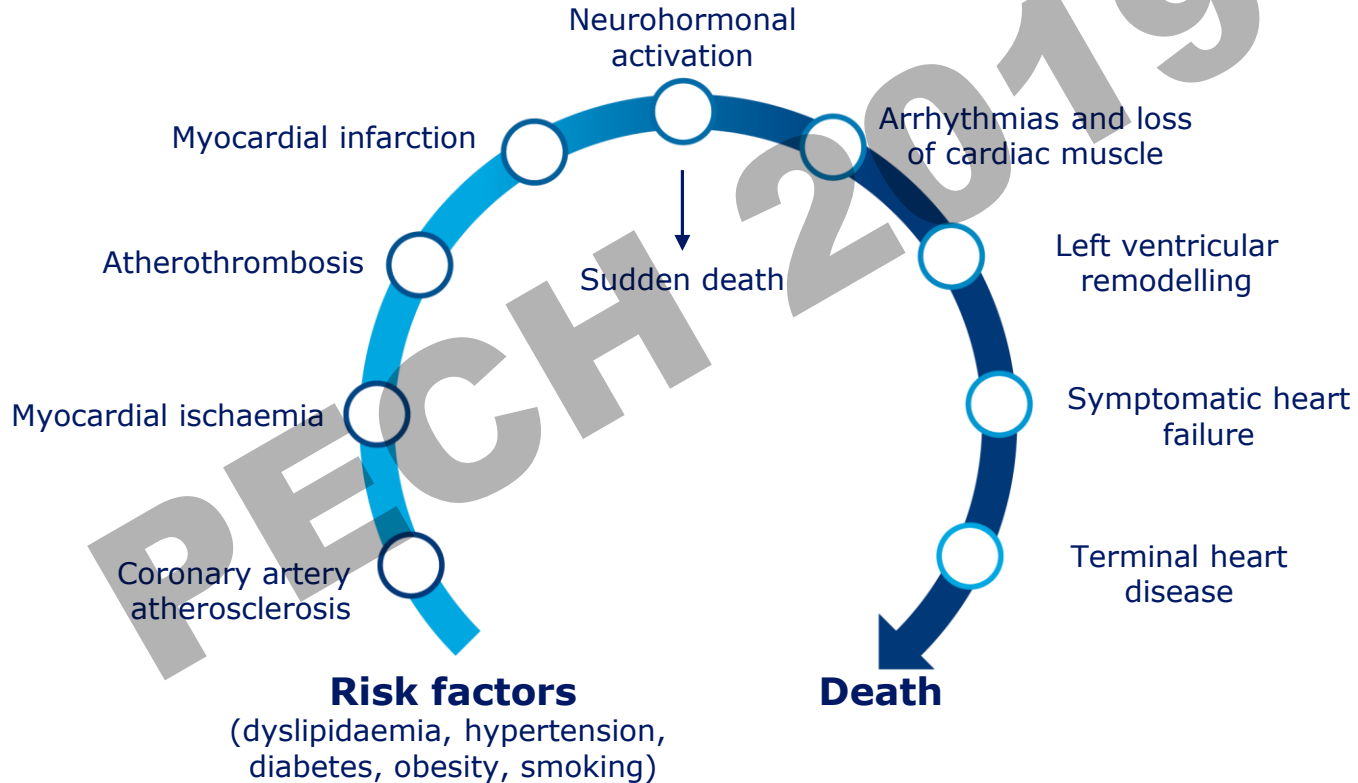
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Hogyan illesszük a jelen kezelési ajánlásaiba az új szemléletet?



*Loose definition*

A chain of events originating from risk factors, which ultimately leads to end-stage CV disease<sup>1</sup>







# Key points to consider

Update informed by **evidence** generated in the past two years\*

## GOALS OF CARE

- Prevent complications
- Optimise quality of life



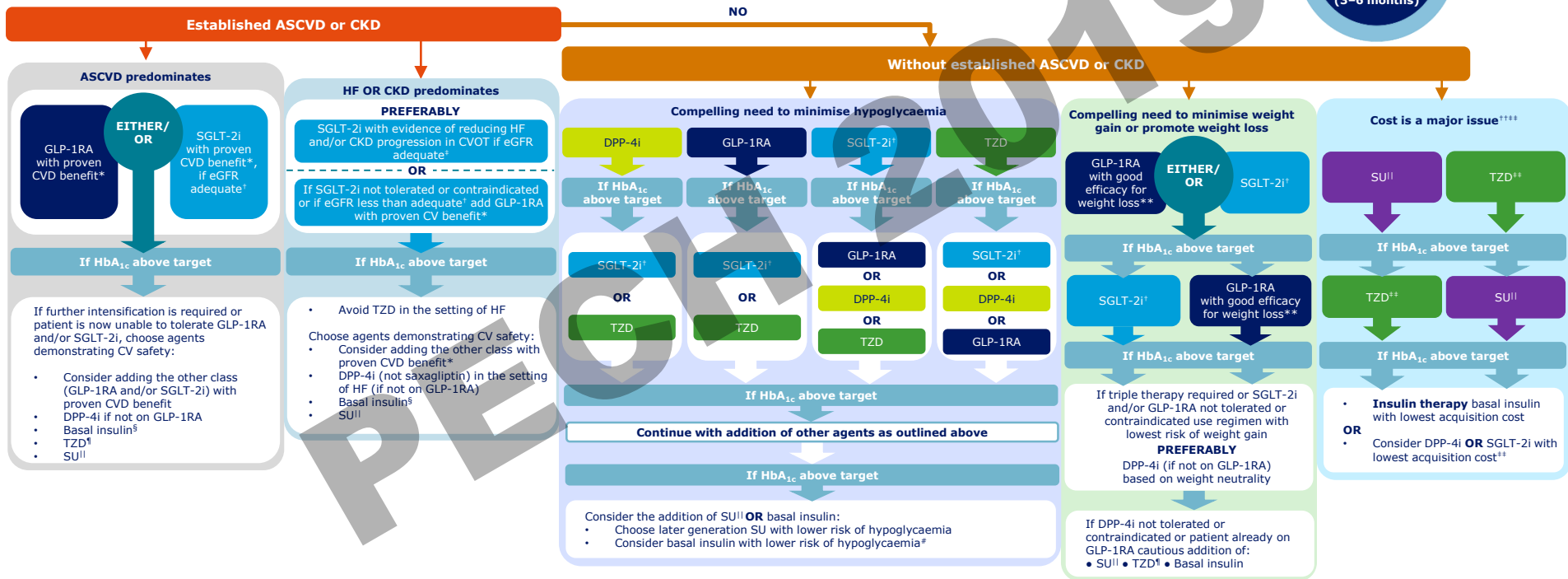
Preferred choices of glucose-lowering agents driven by the **new evidence from CVOTs** and consideration of major clinical need

\*Between 1 January 2014 and 28 February 2018

ADA, American Diabetes Association; CVOT, cardiovascular outcomes trial; EASD, European Association for the Study of Diabetes

**FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)  
IF HbA<sub>1c</sub> ABOVE TARGET PROCEED AS BELOW**

To avoid clinical inertia reassess and modify treatment regularly (3-6 months)

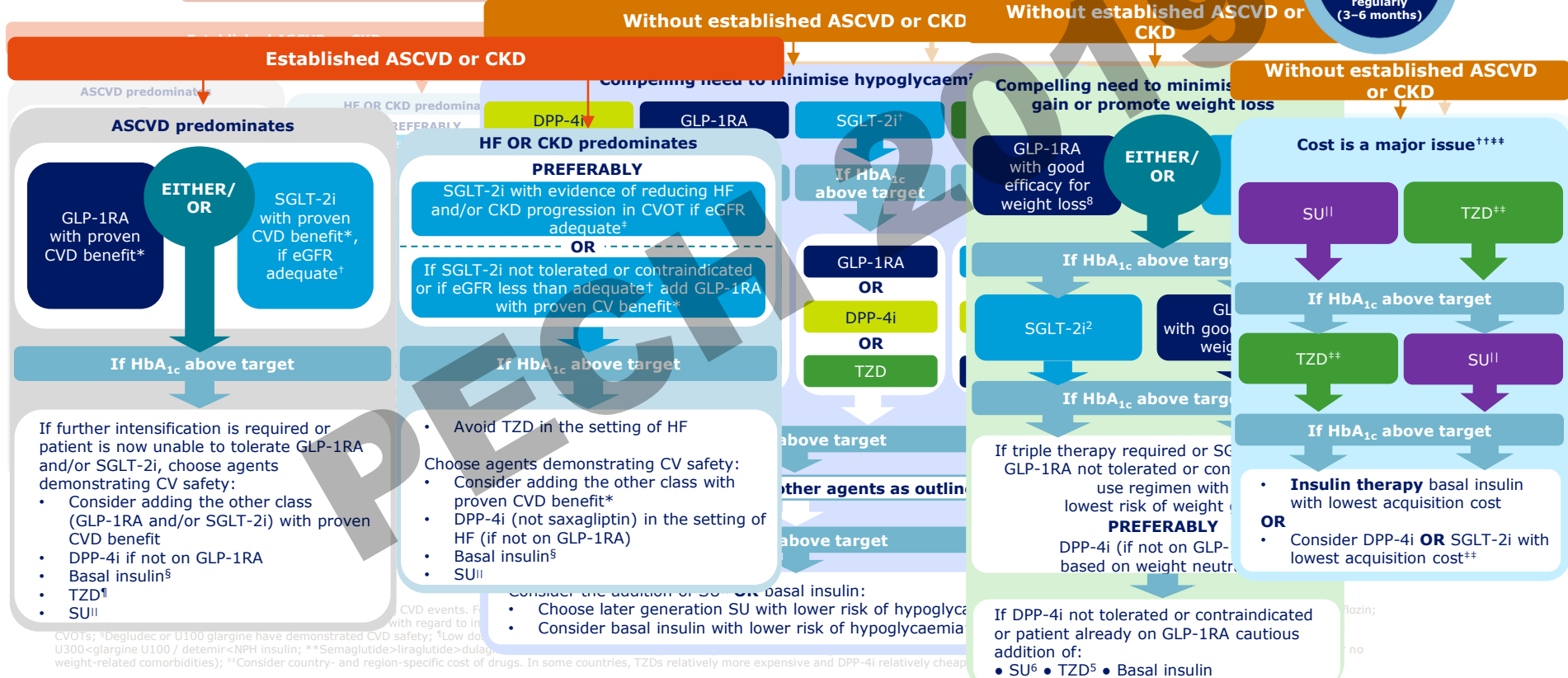


\*Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1RA strongest evidence for liraglutide>semaglutide>exenatide extended release. For SGLT-2i evidence modestly stronger for empagliflozin>canagliflozin;  
 †Be aware that SGLT-2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use; ‡Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs; §Degludec or U100 glargine have demonstrated CVD safety; ¶Low dose may be better tolerated though less well studied for CVD effects; ||Choose later generation SU with lower risk of hypoglycaemia; ††Degludec / glargine U300<glargine U100 / detemir<NPH insulin; \*\*Semaglutide>liraglutide>dulaglutide>exenatide>lixisenatide; †††If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities); ††††Consider country- and region-specific cost of drugs. In some countries, TZDs relatively more expensive and DPP-4i relatively cheaper

# Glucose-lowering medication in type 2 diabetes: Overall approach

FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)  
IF HbA<sub>1c</sub> ABOVE TARGET PROCEED AS BELOW

To avoid clinical inertia reassess and modify treatment regularly (3-6 months)



CVOTs; <sup>†</sup>Degludec or U100 glargine have demonstrated CVD safety; <sup>‡</sup>Low dose U300-cglargine U100 / detemir<NPH insulin; <sup>§</sup>Low dose weight-related comorbidities); <sup>¶</sup>Consider country- and region-specific cost of drugs. In some countries, TZDs relatively more expensive and DPP-4i relatively cheap



## 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)

**Authors/Task Force Members:** Francesco Cosentino<sup>\*</sup> (ESC Chairperson) (Sweden), Peter J. Grant<sup>\*</sup> (EASD Chairperson) (United Kingdom), Victor Aboyans (France), Clifford J. Bailey<sup>†</sup> (United Kingdom), Antonio Ceriello<sup>‡</sup> (Italy), Victoria Delgado (Netherlands), Massimo Federici<sup>§</sup> (Italy), Gerasimos Filippatos (Greece), Diederick E. Grobbee (Netherlands), Tina Birgitte Hansen (Denmark), Heikki V. Huikuri (Finland), Isabelle Johansson (Sweden), Peter Jüni (Canada), Maddalena Lettino (Italy), Nikolaus Marx (Germany), Linda G. Mellbin (Sweden), Carl J. Ostgren (Sweden), Bianca Rocca (Italy), Marco Roffi (Switzerland), Naveed Sattar<sup>¶</sup> (United Kingdom), Petar M. Seferovic (Serbia), Miguel Sousa-Uva (Portugal), Paul Valensi (France), David C. Wheeler<sup>||</sup> (United Kingdom)

<sup>\*</sup>Corresponding authors: Francesco Cosentino, Cardiology Unit, Department of Medicine, Karolinska Institute and Karolinska University Hospital, Solna, 171 76 Stockholm, Sweden. Tel: +46 8 507 72 203; Fax: +46 8 30 49 46; Email: francesco.cosentino@ki.se; Peter J. Grant, Leeds Institute of Cardiovascular and Medical Research, University of Leeds, Leeds, LS2 9JT, UK. Tel: +44 113 343 7271; Email: p.j.grant@leeds.ac.uk

<sup>†</sup>Authors/Task Force Member Affiliations listed in the Appendix.

ESC Committee for Practice Guidelines (CPG) and National Cardiac Societies document reviewers listed in the Appendix.

<sup>‡</sup>Representing the EASD.

ESC entities being participated in the development of this document

Associations: Acute Cardiovascular Care Association (ACCA), Association of Cardiovascular Nursing & Allied Professions (ACNAP), European Association of Cardiovascular Imaging (EACVI), European Association of Preventive Cardiology (EAPC), European Association of Percutaneous Cardiovascular Intervention (EAPCI), European Heart Rhythm Association (EHRA), Heart Failure Association (HFA).

Councils: Council on Cardiovascular Primary Care, Council on Hypertension.

Working Groups: Aorta and Peripheral Vascular Disease, Cardiovascular Surgery, Thrombosis.

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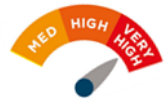
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# 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

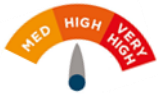
# CV risk categories in patients with diabetes in the new 2019 ESC guidelines

The 2019 ESC guidelines<sup>1a</sup> build upon the SCORE risk from the 2016 European Guidelines on CVD prevention in clinical practice<sup>2</sup> to stratify CV risk in patients with diabetes and pre-diabetes



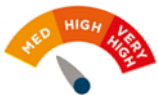
**Very high risk**

Patients with DM **and** established CVD **or** other target organ damage<sup>b</sup> **or** three or more major risk factors<sup>c</sup> **or** early onset T1D of long duration (>20 years)



**High risk**

Patients with DM duration  $\geq 10$  years without target organ damage plus any other additional risk factor



**Moderate risk**

Young patients (T1D aged <35 years or T2D aged <50 years) with DM duration <10 years, without other risk factors

<sup>a</sup>Modified from the 2016 European guidelines on cardiovascular disease prevention in clinical practice<sup>2</sup>

<sup>b</sup>Proteinuria, renal impairment defined as eGFR  $\geq 30$  mL/min/1.73 m<sup>2</sup>, left ventricular hypertrophy or retinopathy

<sup>c</sup>Age, hypertension, dyslipidaemia, smoking, obesity

CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; SCORE, Systematic Coronary Risk Estimation; T1D, type 1 diabetes; T2D, type 2 diabetes

1. Cosentino F et al. *Eur Heart J* 2019;00:1–69; 2. Piepoli MF et al. *Eur Heart J* 2016;37:2315–2381

# Targeted preventions strategies to reduce CVD in patients with diabetes and pre-diabetes

## Lifestyle changes



- Reduced calorie intake is recommended to lowering excessive body weight (**IA**)
- Moderate-to-vigorous physical activity for  $\geq 150$  min/week is recommended for the prevention and control of DM (**IA**)

## Glucose



- Apply tight glucose control, targeting a near-normal HbA<sub>1c</sub> ( $< 7.0\%$  or  $< 53$  mmol/mol), to decrease microvascular complications (**IA**)

## Blood pressure



- Target SBP to 130 mmHg and  $< 130$  mmHg if tolerated, but not  $< 120$  mmHg. In older people (aged  $> 65$  years), the SBP goal is to a range of 130–139 mmHg (**IA**)

## Lipids



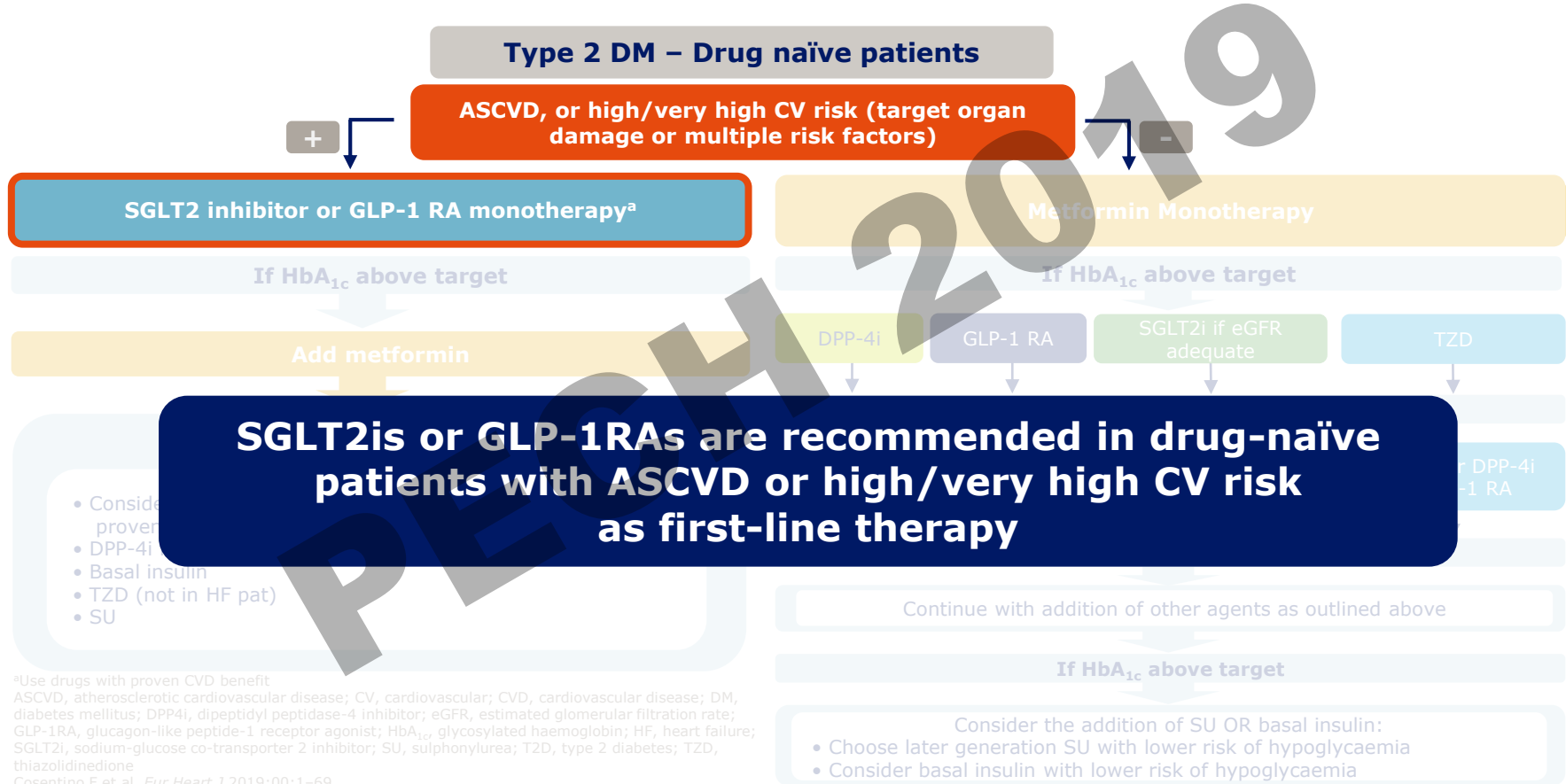
- Very high CV risk, target LDL-C to  $< 1.4$  mmol/L ( $< 55$  mg/dL) or LDL-C reduction  $\geq 50\%$  (**IB**)
- High CV risk, target LDL-C of  $< 1.8$  mmol/L ( $< 70$  mg/dL) or LDL-C reduction  $\geq 50\%$  (**IA**)
- Moderate CV risk, an LDL-C target of  $< 2.5$  mmol/L ( $< 100$  mg/dL) (**IA**)

## Platelets



- In patients with DM at:
- High/very high risk, aspirin may be considered in primary prevention (**IIbA**)
  - Moderate CV risk, aspirin for primary prevention is not recommended (**IIIB**)

# Recommended treatment pathway in drug-naïve patients

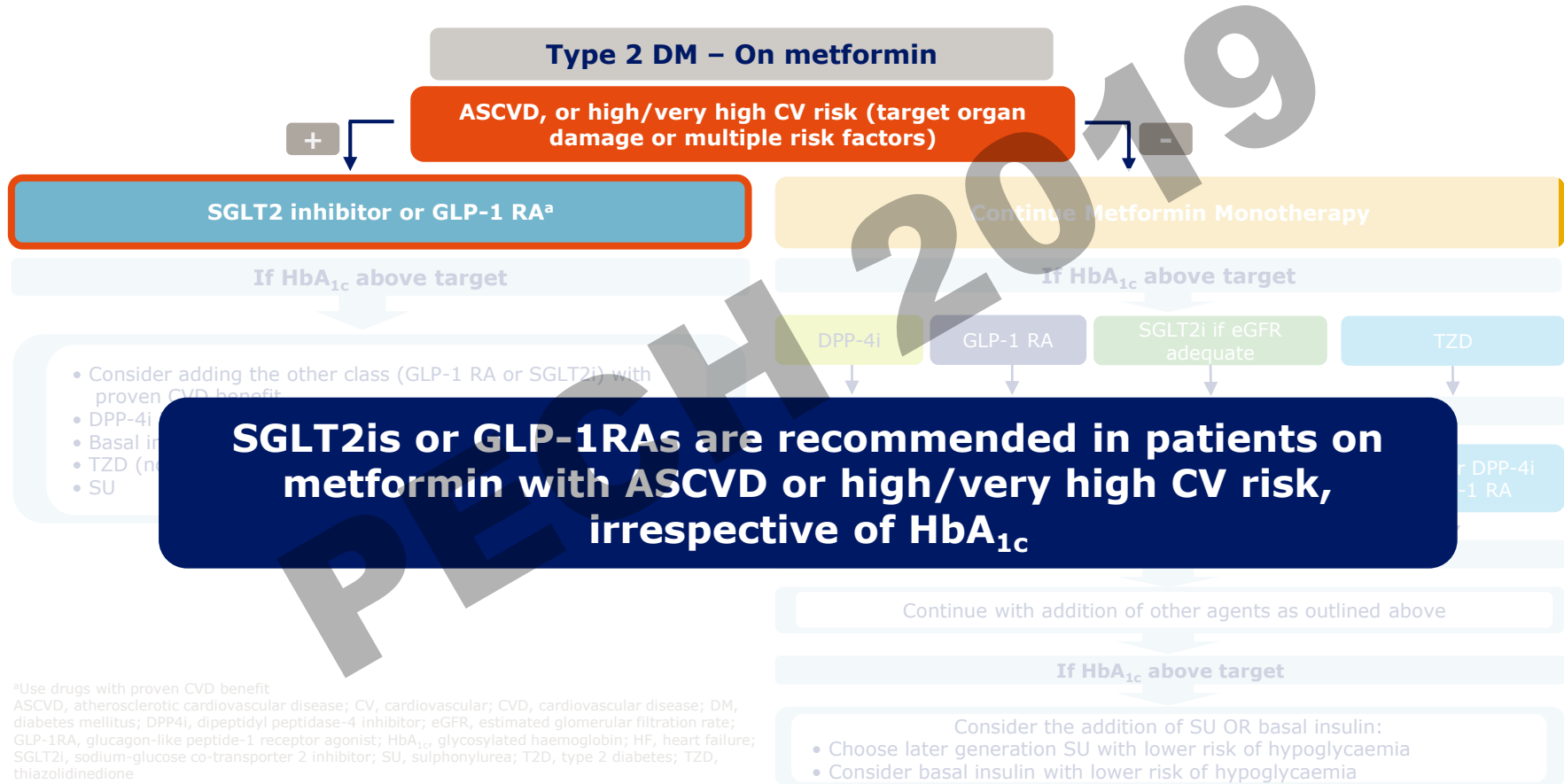


- Consider drugs with proven CVD benefit
- DPP-4i
- Basal insulin
- TZD (not in HF pat)
- SU

<sup>a</sup>Use drugs with proven CVD benefit  
 ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA<sub>1c</sub>, glycosylated haemoglobin; HF, heart failure; SGLT2i, sodium-glucose co-transporter 2 inhibitor; SU, sulphonylurea; TZD, type 2 diabetes; TZD, thiazolidinedione  
 Cosentino F et al. *Eur Heart J* 2019;00:1–69

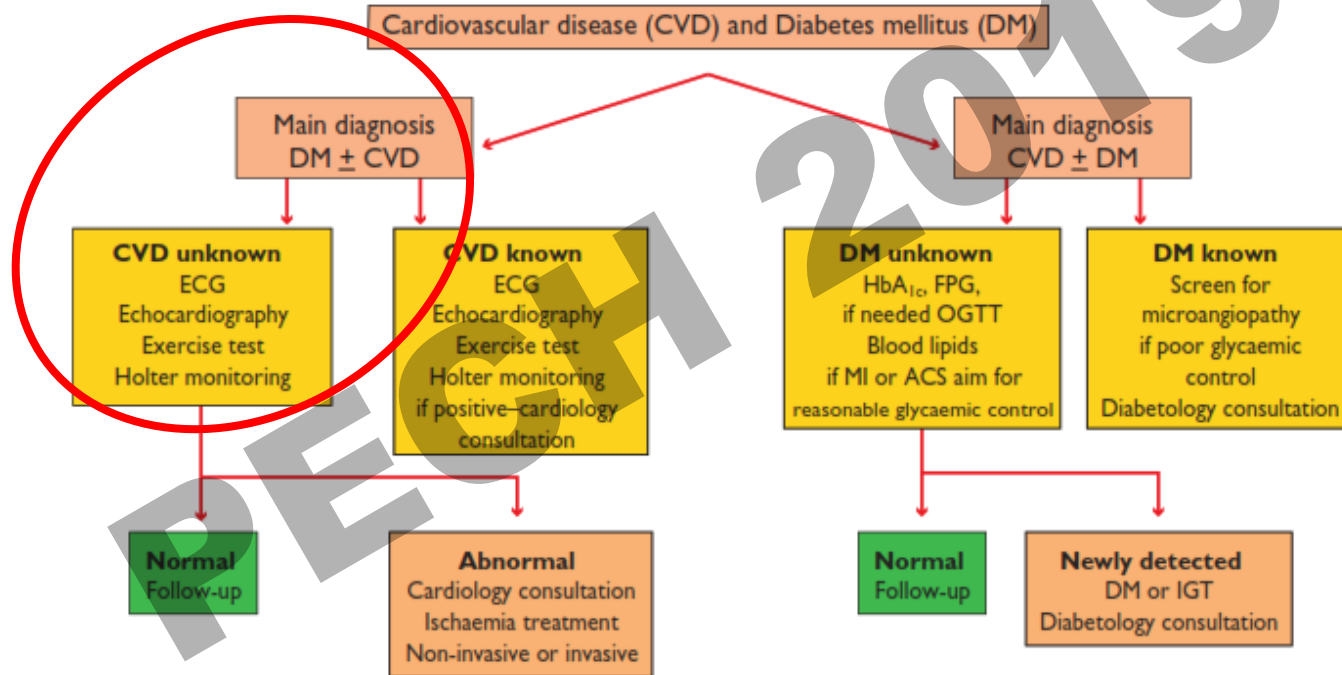


# Recommended treatment pathway in patients on metformin



<sup>a</sup>Use drugs with proven CVD benefit  
 ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA<sub>1c</sub>, glycosylated haemoglobin; HF, heart failure; SGLT2i, sodium-glucose co-transporter 2 inhibitor; SU, sulphonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione  
 Cosentino F et al. *Eur Heart J* 2019;00:1–69

# Miért küldjük kardiológira betegünket?



# Kit irányítsunk kardiológiára?

## Tünetes betegek

- Típusos angina
- Fulladás (szívelégtelenség vs. angina ekvivalens)
- Megszédülés, eszméletvesztés
- Palpitatio



**KARDIOLÓGIA**

# Ami fontos...

Izgalmas időket élünk a T2DM kutatásában és kezelésében

Számos új gyógyszercsoport egyes képviselői anyagcsere és direkt kardiovaszkuláris hatással is rendelkeznek

Kiemelkedően fontos, hogy ezeket az új készítményeket olyan betegeknél használjuk, akik a legtöbbet profitálnak belőle

Az inzulin 1921-es felfedezése óta ezek a legfontosabb új eredmények a diabetes kezelésében.

# Abbreviations

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ADA = American Diabetes Association  
ASCVD = atherosclerotic cardiovascular disease  
BP = blood pressure  
CI = confidence interval  
CV = cardiovascular  
CVD = cardiovascular disease  
CVOT = cardiovascular outcomes trial  
DPP-4 = dipeptidyl peptidase-4  
DPP-4i = dipeptidyl peptidase-4 inhibitor  
FPG = fasting plasma glucose  
GLP-1 RA = glucagon-like peptide-1 receptor agonist  
HbA1c = glycated hemoglobin  
HR = hazard ratio  
LDL-C = low-density lipoprotein cholesterol  
MACE = major adverse cardiovascular events  
MET = metformin  
MI = myocardial infarction  
N/A = not available  
PK = pharmacokinetics

# Abbreviations (cont)

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PPG = postprandial glucose

RA = receptor agonist

SD = standard deviation

SU = sulphonylurea

SGLT2 = sodium glucose co-transporter2

$t_{1/2}$  = half-life

T2DM = type 2 diabetes mellitus

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