Behandeling van patienten met ASCVD en diabetes: trials and guidelines

September 2020

Prof. Dr. J.W. Jukema

LUMC

HEARTLUNG CENTER LEIDEN

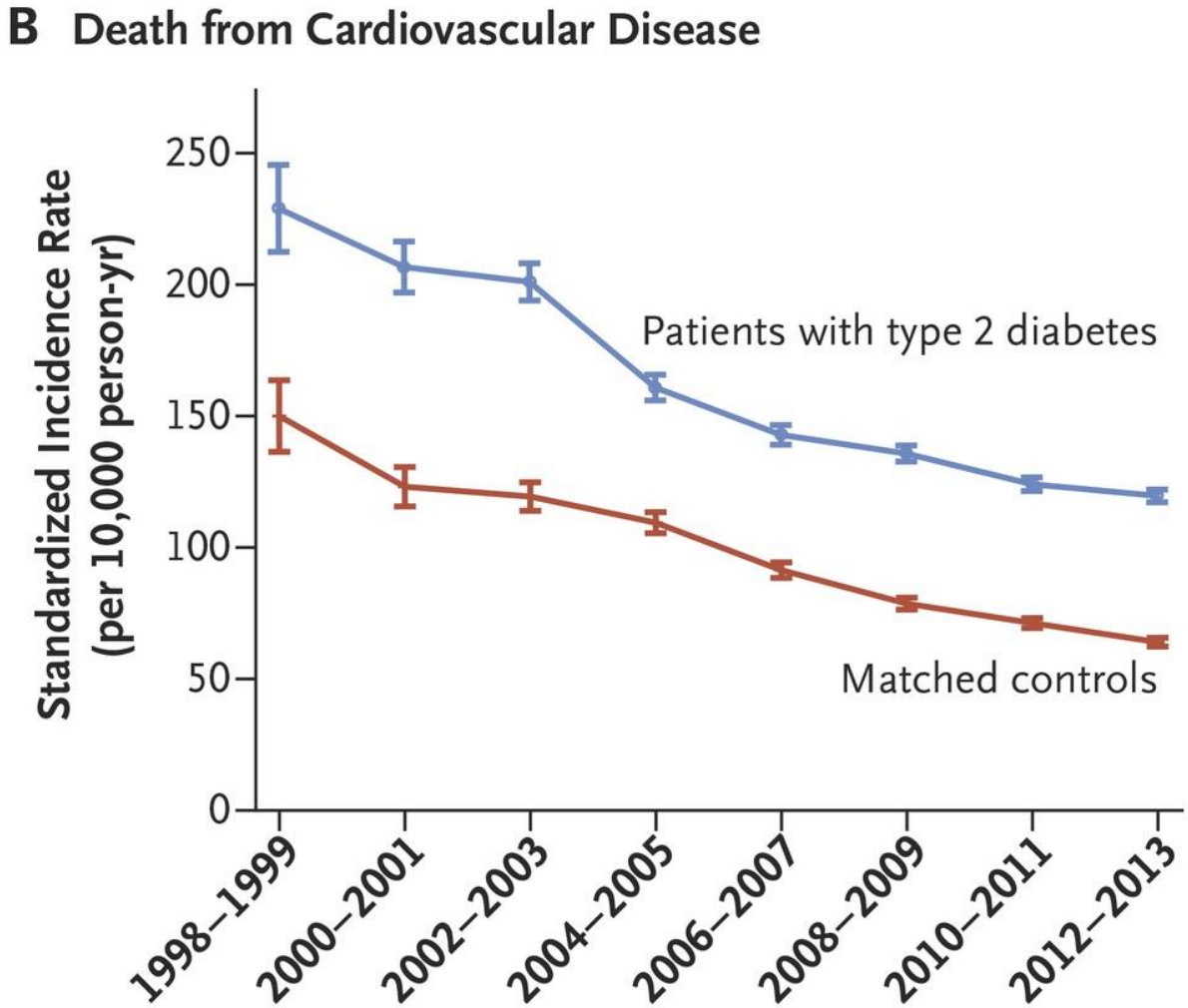
ESC European Society of Cardiology

EAS

Disclosure potential conflicts of interest J.W. Jukema

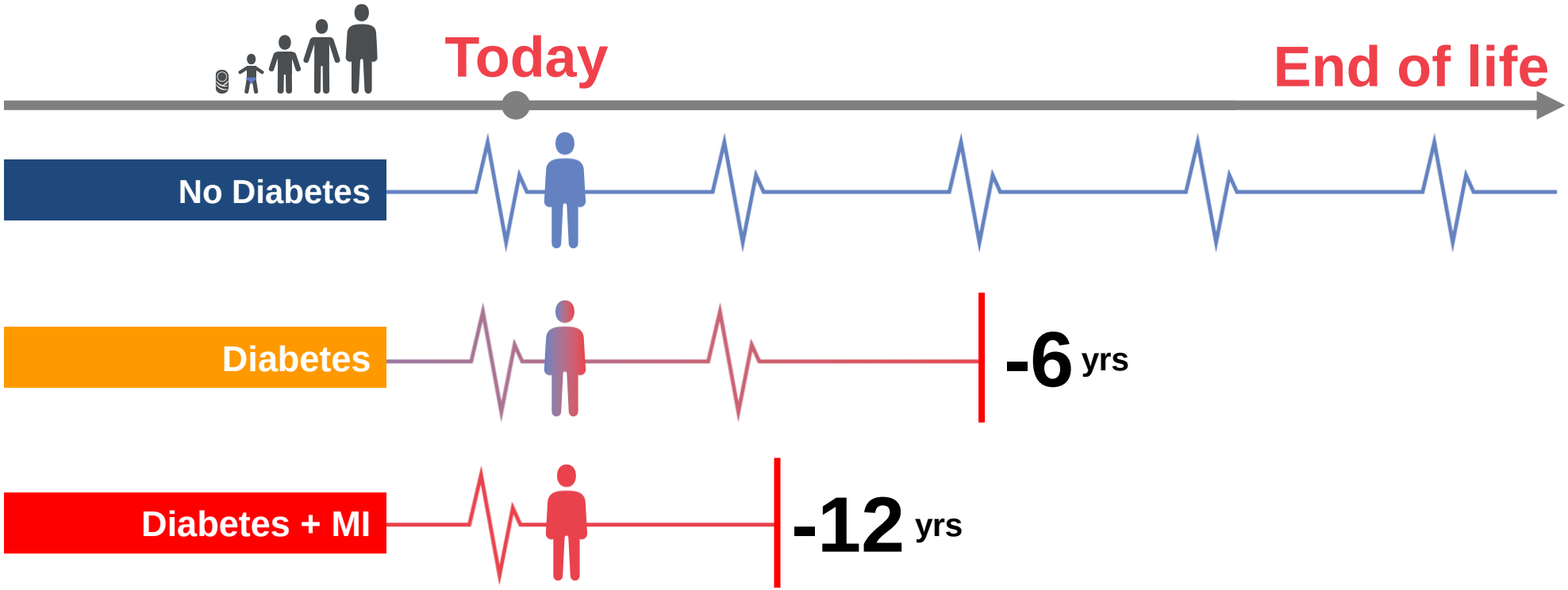
Geen (potentiële) belangenverstrengeling	
Voor bijeenkomst mogelijk relevante relaties:	**Bedrijfsnamen**
• Sponsoring/ Honorarium/Vergoeding of onderzoeksgeld	JW Jukema/his department has received research grants from and/or was speaker (with or without lecture fees) on a.o.(CME accredited) meetings sponsored by Amgen, Athera, Astra-Zeneca, Biotronik, Boston Scientific, Dalcor, Daiichi Sankyo, Lilly, Medtronic, Merck-Schering-Plough, Pfizer, Roche, Sanofi Aventis, The Medicine Company, the Netherlands Heart Foundation, CardioVascular Research the Netherlands (CVON), the Netherlands Heart Institute and the European Community Framework KP7 Programme.
• **Aandeelhouders**	•

CV death in type 2 diabetes



Rawshani A et al. N Engl J Med 2017;376:1407-1418

Life expectancy of a 60 year old man



Adapted from Danesh et al. for ERFC JAMA 2015;314:52–60.

Diabetes type 2

Dyslipidaemic problem:
DM2 dyslipidemia represents a cluster of lipid and lipoprotein abnormalities, including elevation of both fasting and post-prandial TG, ApoB, and small dense LDL, and low HDL-C and ApoA1 levels.
Atherogenic dyslipidaemia is one of the major risk factors for CVD in people with type 2 diabetes, and in people with abdominal obesity and insulin resistance or impaired glucose tolerance.

Glucose problem:
Microvascular and Macrovasculair ASCVD / Heart failure

Interaction between the problems

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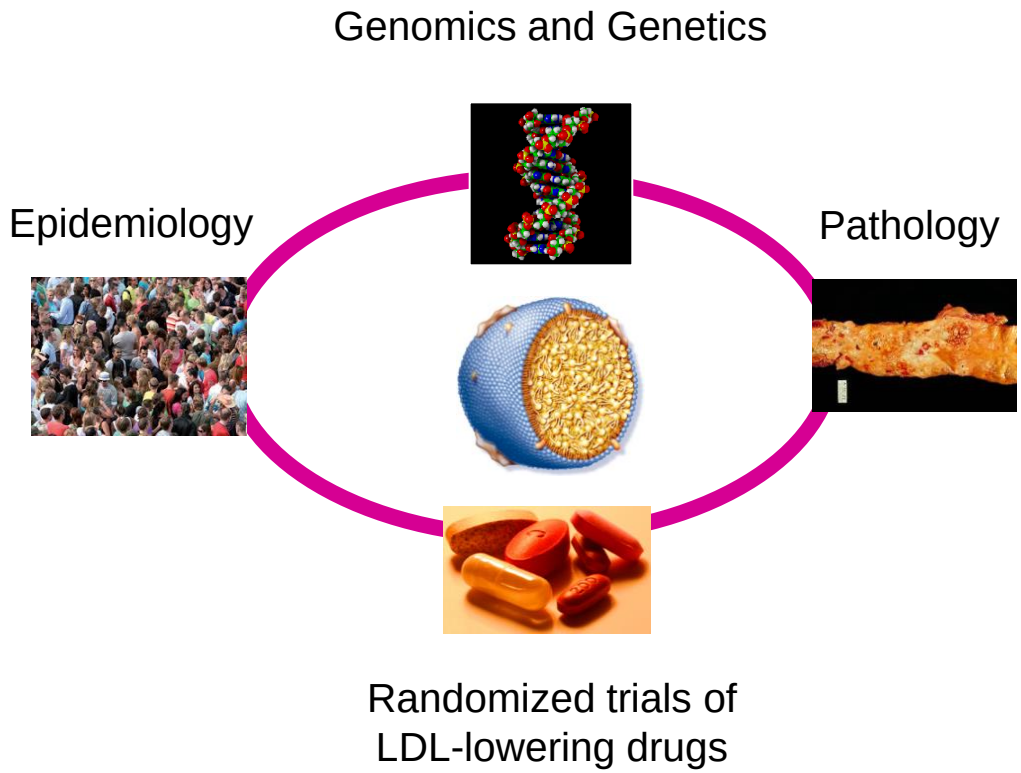
LDL and atherosclerosis: a coalescence of evidence



2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (1)

Task Force Members:

François Mach (ESC Chairperson) (Switzerland), Colin Baigent (ESC Chaiperson) (United Kingdom), Alberico L. Catapano (EAS Chairperson) (Italy), Konstantinos C. Koskinas (Switzerland), Manuela Casula[1] (Italy), Lina Badimon (Spain), M. John Chapman[1] (France), Guy G. De Backer (Belgium), Victoria Delgado (Netherlands), Brian A. Ference (United Kingdom), Ian M. Graham (Ireland), Alison Halliday (United Kingdom), Ulf Landmesser (Germany), Borislava Mihaylova (United Kingdom), Terje R. Pedersen (Norway), Gabriele Riccardi[1] (Italy), Dimitrios J. Richter (Greece), Marc S. Sabatine (United States of America), Marja-Riitta Taskinen[1] (Finland), Lale Tokgozoglu[1] (Turkey), Olov Wiklund[1] (Sweden).

[1]Representing the European Atherosclerosis Society (EAS)

Main principles for LDL-lowering therapy

- Genetic, epidemiological and trial evidence indicates that LDL cholesterol is a CAUSE of atherosclerotic vascular disease
- Trials of LDL-lowering indicate RELATIVE RISK reduction is proportional to the ABSOLUTE REDUCTION in LDL-C
- Lower is better: lowering LDL-C with statins, ezetimibe, or PCSK9-inhibitors safe and effective to <1.4 mmol/L (55 mg/dL)
  - Cholesterol Treatment Trialists' Collaboration
  - Data on ezetimibe from the IMPROVE-IT trial
  - Data from large randomized trials of PCSK9 inhibitors
- Intensity of LDL-lowering should be based on risk, irrespective of cause(s) of the risk (e.g., primary or secondary prevention, diabetes, or chronic kidney disease)

ESC European Society of Cardiology

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Cardiovascular risk categories (1)

Very-high-risk	People with any of the following: Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularisation (PCI, CABG and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis) or on carotid ultrasound. DM with target organ damage, ≥3 major risk factors or early onset of T1DM of long duration (>20 years). Severe CKD (eGFR <30 mL/min/1.73 m^2). A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Cardiovascular risk categories (2)

High-risk	People with: Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg. Patients with FH without other major risk factors. Patients with DM without target organ damage*, with DM duration ≥10 years or another additional risk factors. Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1% and <5% for 10-year risk of fatal CVD.
Low-risk	Calculated SCORE <1% for 10-year risk of fatal CVD.

*Target organ damage is defined as microalbuminuria, retinopathy or neuropathy

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

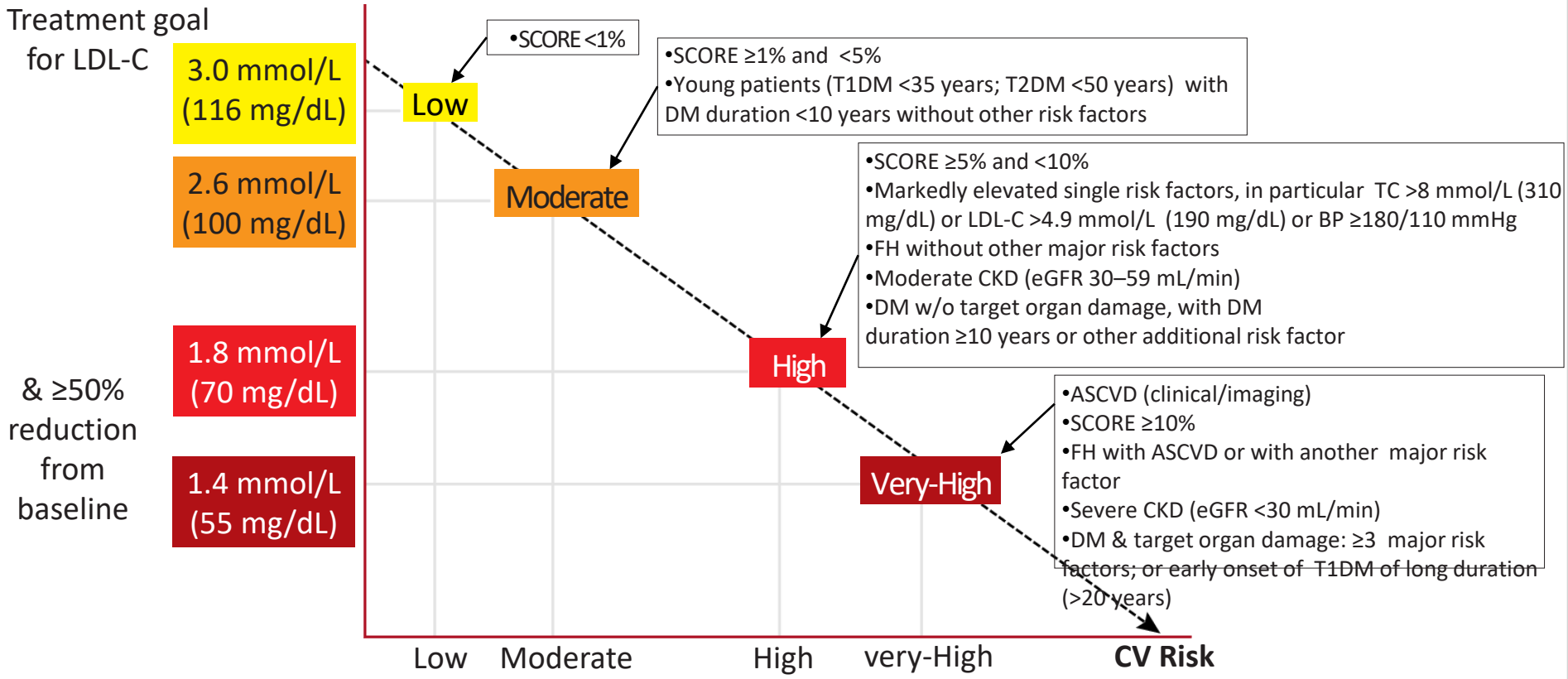
EAS ESC
European Society of Cardiology

Recommended treatment goals for LDL-lowering therapy: main changes from 2016 to 2019

Risk category	LDL goals (starting with untreated LDL-C)	
	2016	2019
Very-high-risk	<1.8 mmol/L (70 mg/dL) or >50% ↓ if LDL-C 1.8-3.5 (70 - 135 mg/dL)	<1.4 mmol/L (55 mg/dL) and >50% ↓
High-risk	<2.6 mmol/L (100mg/dL) or >50% ↓ if LDL-C 2.6-5.2 (100 - 200 mg/dL)	<1.8 mmol/L (70 mg/dL) and >50% ↓
Moderate-risk	<3.0 mmol/L (115 mg/dL)	< 2.6 mmol/L (100 mg/dL)
Low-risk	<3.0 mmol/L (115 mg/dL)	<3.0 mmol/L (115 mg/dL)

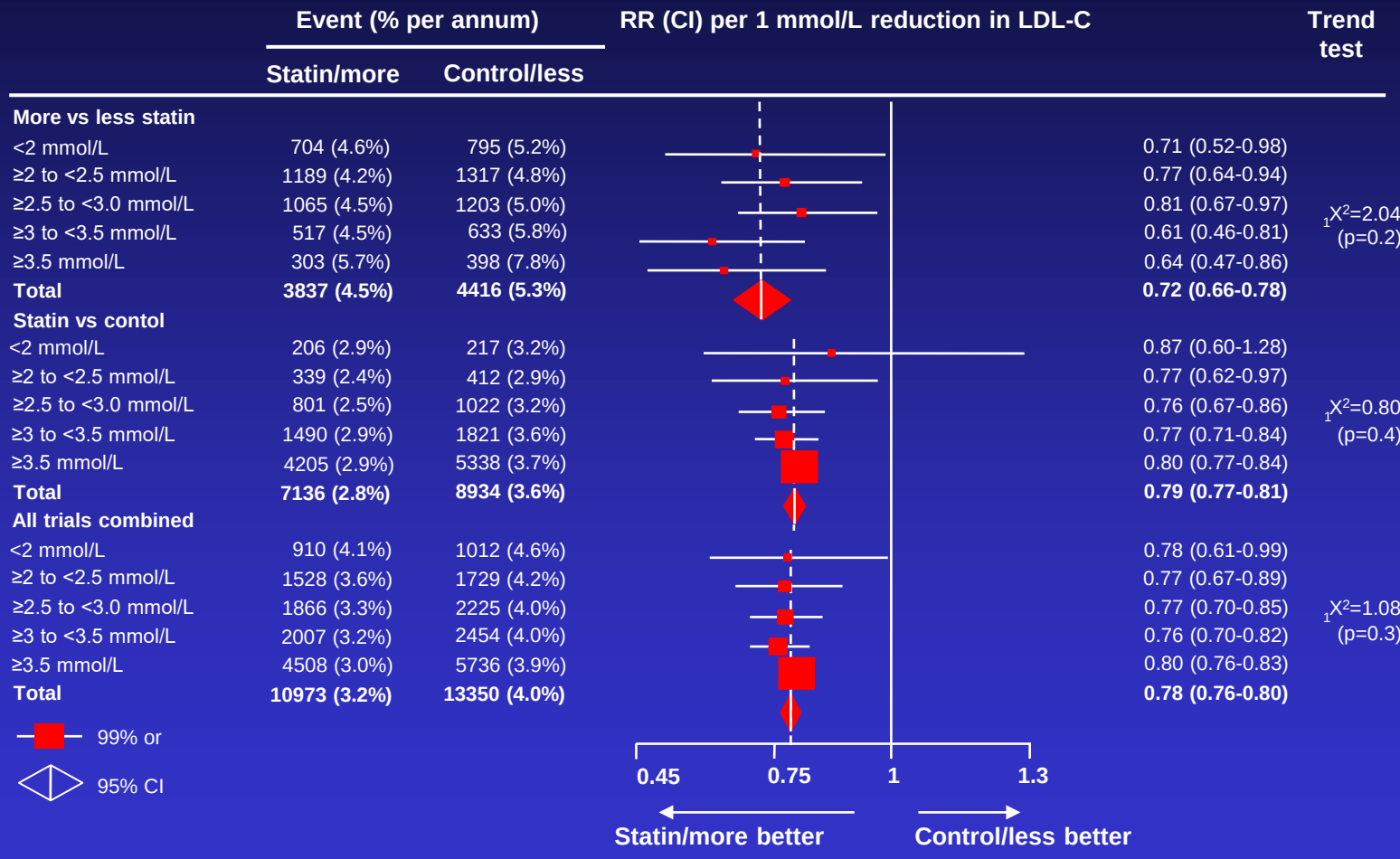
2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Treatment goals for low-density lipoprotein cholesterol (LDL-C) across categories of total cardiovascular disease risk



2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

CTT: more intensive LDL lowering can decrease CV events by 40-50%



Cholesterol Treatment Trialists' (CTT) Collaboration. Lancet. 2010;376:1670-1681

Recommendations for the treatment of dyslipidaemias in diabetes (1)

Recommendations	Class	Level
In patients with T2DM at very-high risk[c], an LDL-C reduction of at least 50% from baseline and LDL-C goal of <1.4 mmol/L (<55 mg/dL) is recommended.	I	A
In patients with T2DM at high risk[c] an LDL-C reduction of at least 50% from baseline and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) is recommended.	I	A
Statins are recommended in patients with T1DM who are at high or very-high-risk[c].	I	A

[c] See Table in Full Text.

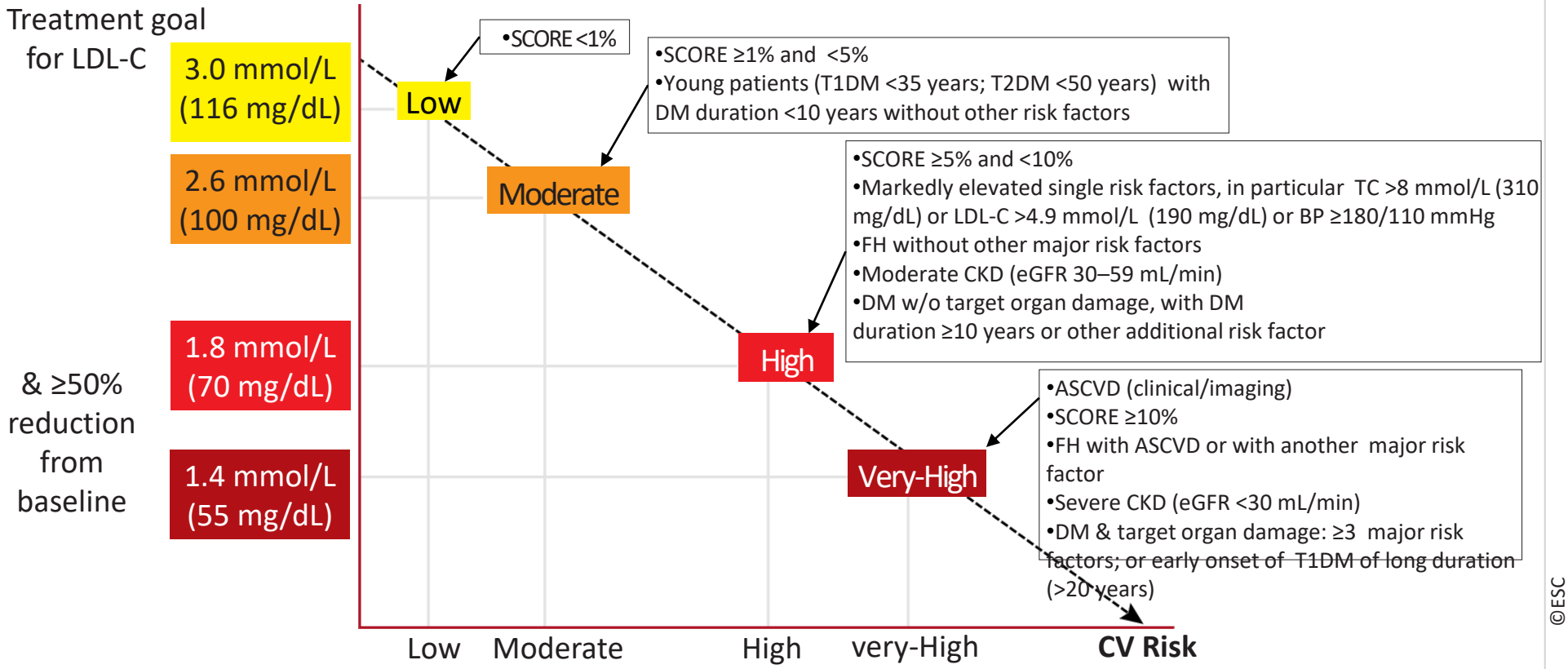
2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Recommendations for the treatment of dyslipidaemias in diabetes (2)

Recommendations	Class	Level
Intensification of statin therapy should be considered before the introduction of combination therapy.	IIa	C
If the goal is not reached, statin combination with ezetimibe should be considered.	IIa	B
Statin therapy is not recommended in pre-menopausal patients with diabetes who are considering pregnancy or not using adequate contraception.	III	C
Statin therapy may be considered in both T1DM and T2DM patients aged ≤30 years with evidence of end organ damage and/or LDL-C >2.5 mmol/L as long as pregnancy is not being planned.	IIb	C

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Treatment goals for low-density lipoprotein cholesterol (LDL-C) across categories of total cardiovascular disease risk (with statins, ezetimibe, PCSK-9 inhibitors)



www.escardio.org/guidelines

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Glucose problem:
Microvascular and Macrovasculair ASCVD / Heart failure

Interaction between the problems

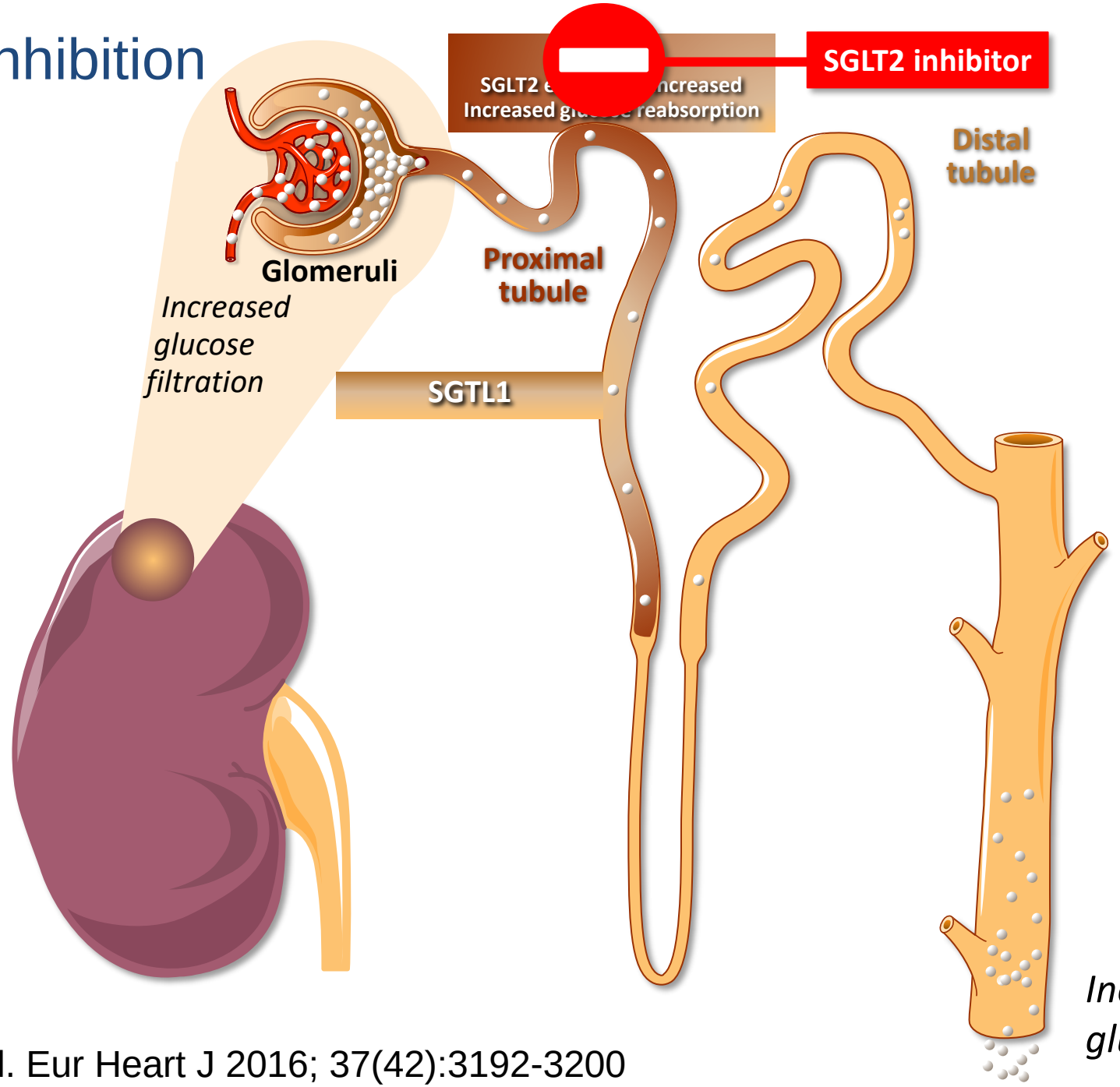
Cardiovascular safety trials with newer glucose-lowering agents

16 CVOTs published between 2013 and 2019

	SGLT2 inhibitors				GLP1-RAs							DPP4 inhibitors				
Trial	**EMPA-REG OUTCOME**[306]	**CANVAS**[309]	**DECLARE–TIMI 58**[311]	**CREDENCE**[313]	**ELIXA**[297]	**LEADER**[176]	**SUSTAIN-6**[299]	**EXSCEL**[158]	**Harmony Outcomes**[301]	**REWIND**[303]	**PIONEER 6**[300]	**SAVOR–TIMI 53**[291]	**EXAMINE**[292]	**TECOS**[293]	**CARMELINA**[294]	**CAROLINA**[277]
Baseline	**Empagliflozin vs. placebo**	**Canagliflozin vs. placebo**	**Dapagliflozin vs. placebo**	**Canaglifozin vs. placebo**	**Lixisenatide vs. placebo**	**Liraglutide vs. placebo**	**Semaglutide vs. placebo**	**Exenatide vs. placebo**	**Albiglutide vs. placebo**	**Dulaglutide vs. placebo**	**Oral Semaglutide vs. placebo**	**Saxagliptin vs. placebo**	**Alogliptin vs. placebo**	**Sitagliptin vs. placebo**	**Linagliptin vs. placebo**	**Linagliptin vs. glimiperide**
n	7020	10 142	17160	4401	6068	9340	3297	14 752	9463	9901	3182	16 492	5400	14 671	6979	6033
Age (years)	63	63	63	63	60	64	64	62	64	66	66	65	61	66	65	64
DM (years)	57% >10	13.5	11.8	15.8	9.3	12.8	13.9	12.0	14.1	10.5	14.9	10	7.2	9.4	14.7	6.2
Body mass index (kg/m^2)	30.6	32.0	32.1	31.3	30.1	32.5	32.8	31.8	32	32.3	32.3	31	29	30	31.3	30.1
Insulin (%)	48	50	~40	65	39	44	58	46	60	24	61	41	30	23	58	0
HbA1c (%)	8.1	8.2	8.3	8.3	7.7	8.7	8.7	8.0	8.7	7.2	8.2	8.0	8.0	7.3	7.9	7.2
Previous CVD (%)	99	65	40	50.4	100	~81	~83	73	100	31	35	78	100	100	57	42
CV risk inclusion criteria	**MI, CHD, CVD, or PVD**	**MI, CHD, CVD, or PVD**	**CVD or at least one CVRF**	**CKD**	**ACS <180 days**	**Age ≥50 years and CVD,[b] or CKD, or age ≥60 years and at least one CVRF**		**CHD, CVD, or PVD27% no previous CV event**	**MI, CHD, CVD, or PVD**	**Age ≥50 years and CVD or CVRFs**	**Age ≥50 years and CVD, or CKD, or age ≥60 years and CVRFs**	**Age ≥40 years and CVD (CHD, CVD, or PVD), or age ≥55 years and at least one CVRF**	**ACS <90 days**	**CHD, CVD, or PVD**	**CVD and/or CKD**	**CVD or evidence of vascular-related end-organ damage, or age ≥70 years, or at least two CVRFs**
Hypertension (%)	94	89	89	96.8	76	92	92	90	86	93	94	81	83	86	95	90
Follow-up (years)	3.1	2.4	4.5	2.6	2.1	3.8	2.1	3.2	1.6	5.4	1.3	2.1	1.5	2.8	2.2	6.3

Adapted from Bailey and Marx, Diabetes Obes Metab. 2019; 21:3-18

SGLT2-Inhibition



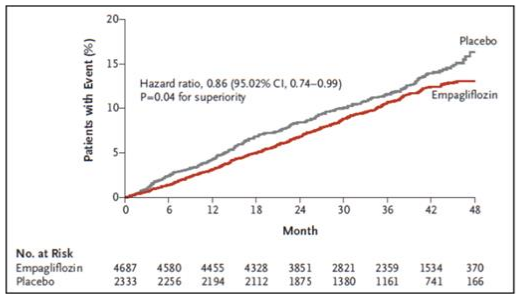
Increased urinary glucose excretion

Marx et al. Eur Heart J 2016; 37(42):3192-3200

CVOTs with SGLT2 inhibitors I

3-P MACE endpoint

EMPA-REG OUTCOME[1]



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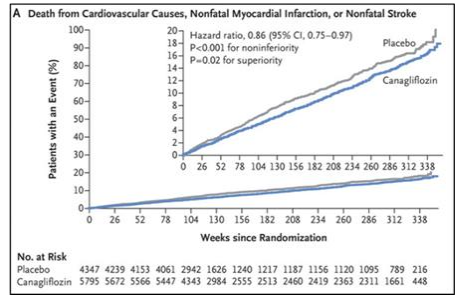

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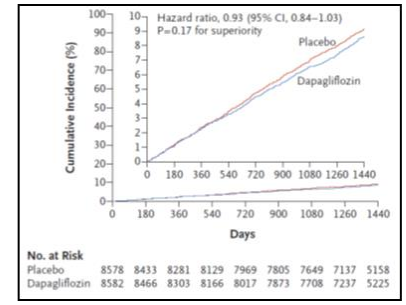

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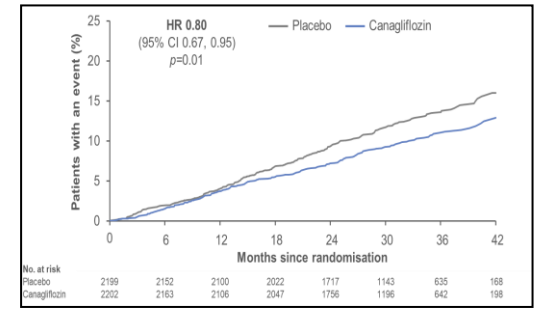

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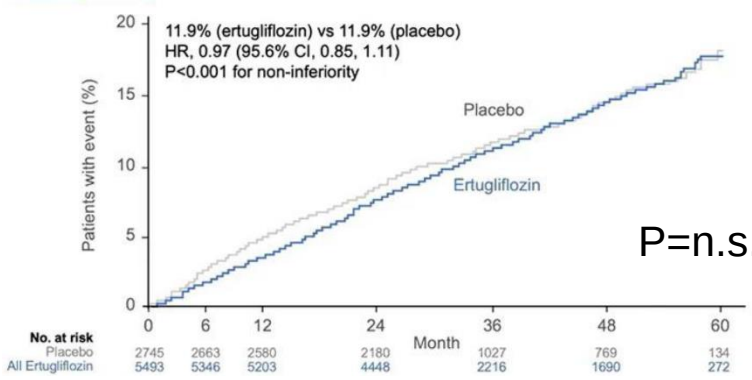


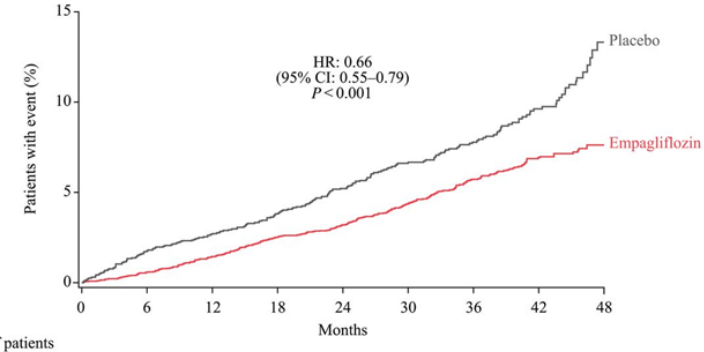
P=n.s.

1. Zinman B et al. N Engl J Med. 2015; 373:2117-2128
2. Neal B et al. N Engl J Med 2017; 377:644-656
3. Wiviott SD et al. N Engl J Med 2019;380:347-357
4. Perkovic V et al. N Engl J Med 2019;380:2295-2306
5. Cannon C. Presentation ADA 2020; 16.06.2020

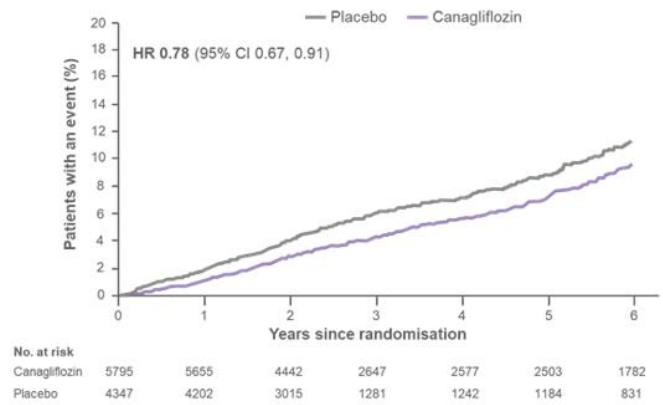
CVOTs with SGLT2 inhibitors II

Heart failure hospitalisation or CV death

EMPA-REG Outcome[1]



Canvas program[2]



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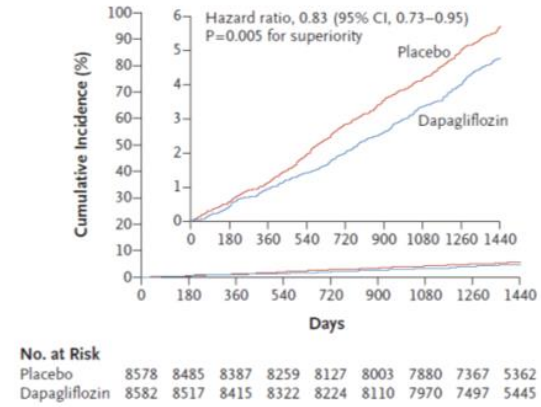

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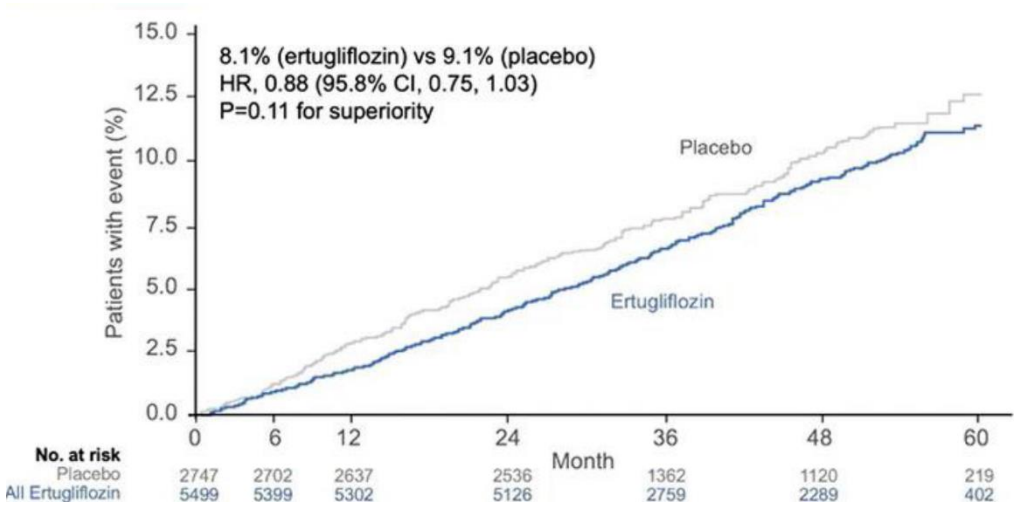
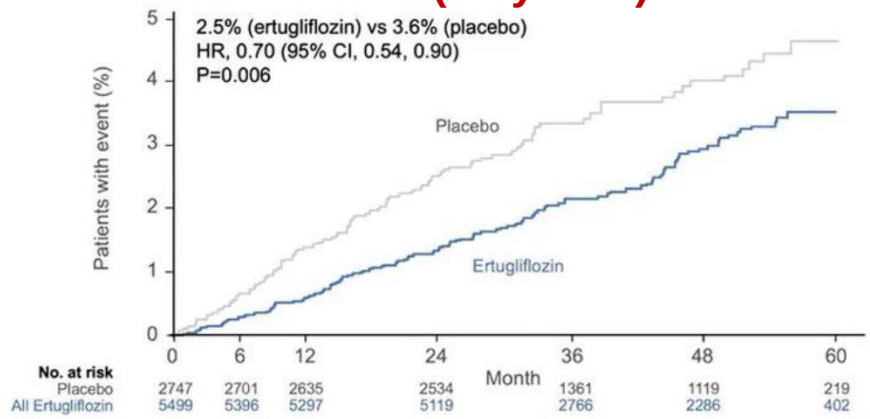


VERTIS[4] (only HHF)



1. Zinman B et al. N Engl J Med. 2015; 373:2117-2128
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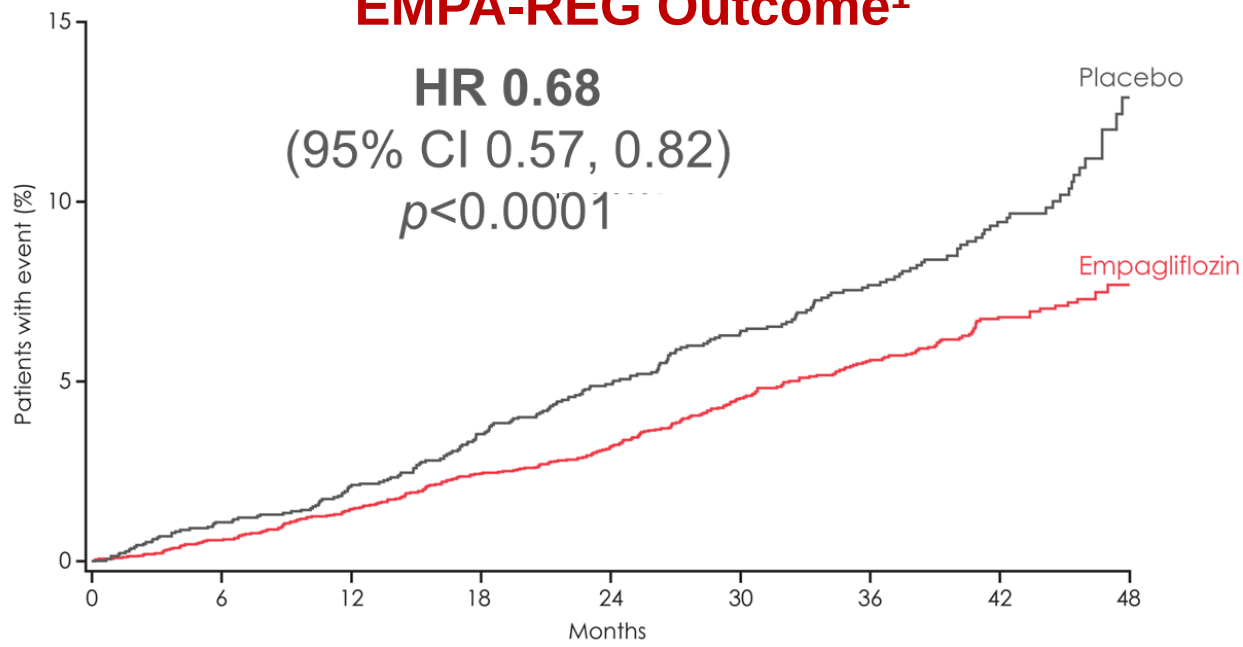
4. Cannon C. Presentation ADA 2020; 16.06.2020

CVOTs with SGLT2 inhibitors III

All-cause mortality

EMPA-REG Outcome[1]



No. of patients									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Kaplan-Meier estimate. HR, hazard ratio

1. Zinman B et al. N Engl J Med. 2015; 373:2117-2128

ESC European Society of Cardiology

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

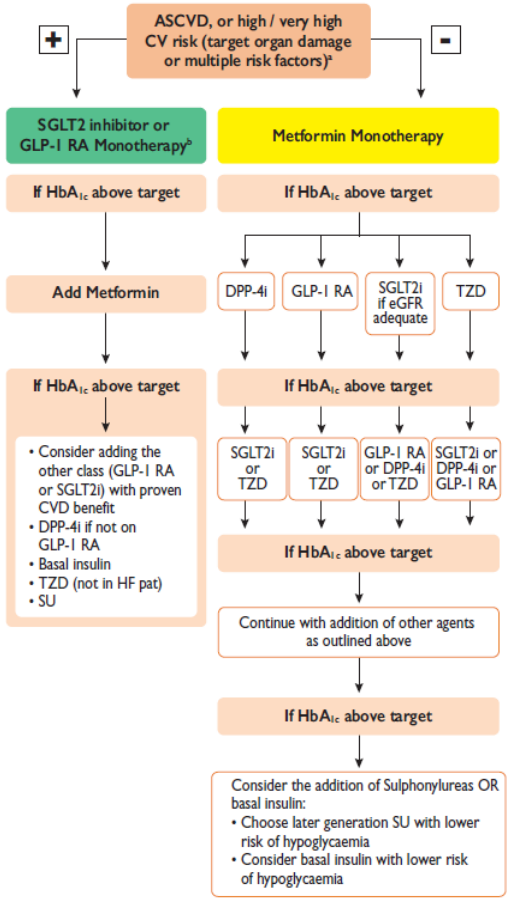
ESC GUIDELINES

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)

Authors/Task Force Members: Francesco Cosentino* (ESC Chairperson) (Sweden), Peter J. Grant* (EASD Chairperson) (United Kingdom), Victor Aboyans (France), Clifford J. Bailey[1] (United Kingdom), Antonio Ceriello[1] (Italy), Victoria Delgado (Netherlands), Massimo Federici[1] (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. Östgren (Sweden), Bianca Rocca (Italy), Marco Roffi (Switzerland), Naveed Sattar[1] (United Kingdom), Petar M. Seferović (Serbia), Miguel Sousa-Uva (Portugal), Paul Valensi (France), David C. Wheeler[1] (United Kingdom)

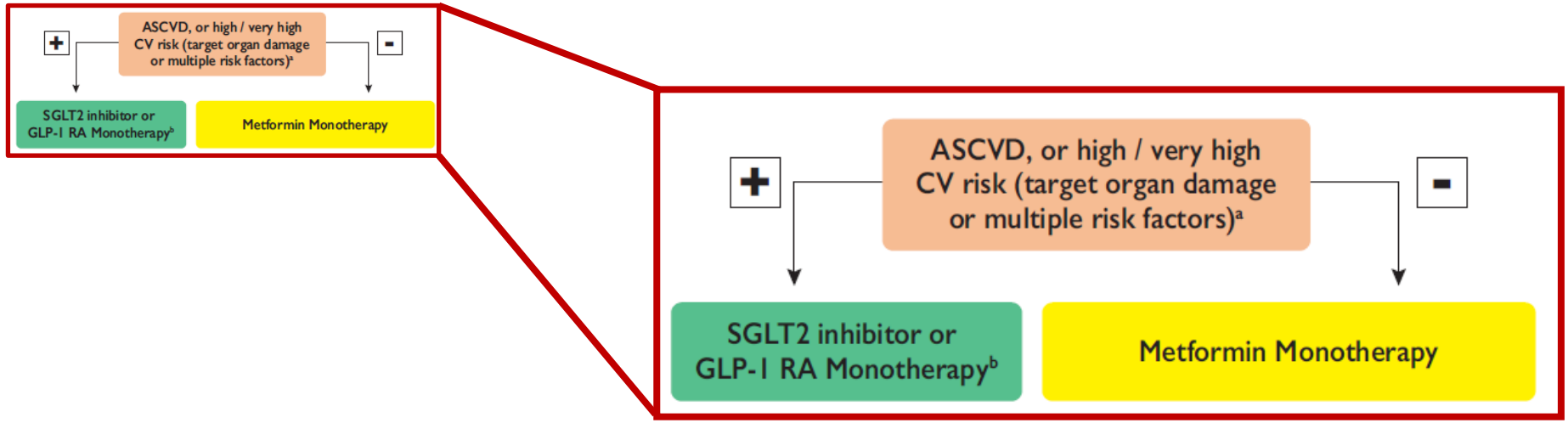
Treatment algorithm in patients Type 2 Diabetes (T2DM)

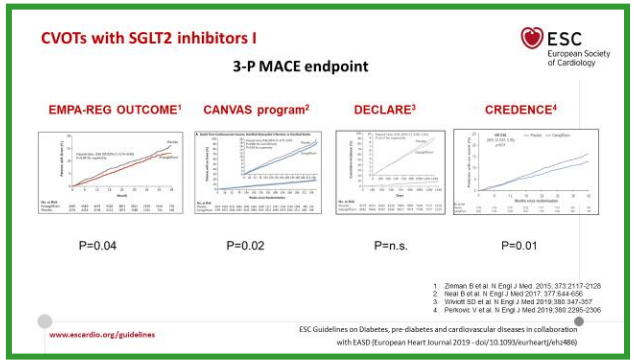


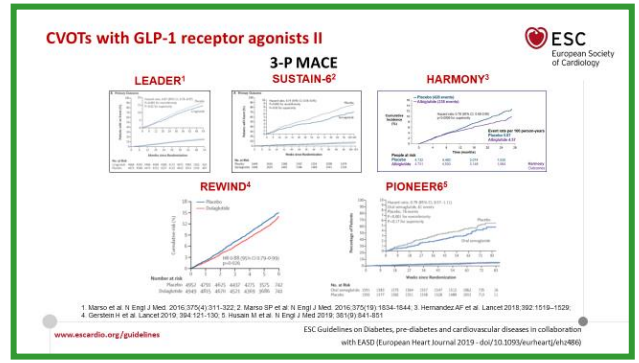
Class I recommendation

Class IIa recommendation

Treatment algorithm in patients Type 2 Diabetes (T2DM)







Class I recommendation

Class IIa recommendation

Diabetes type 2 and ASCVD guidelines

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>> Lifestyle – statins - ezetimibe – PCSK-9 inhibitors

Glucose problem:
Microvascular and Macrovasculair ASCVD / Heart failure
>> Lifestyle – SGLT2 inhibitors – GLP1-RA - Methformin

>> Combination therapy

uce
55)