

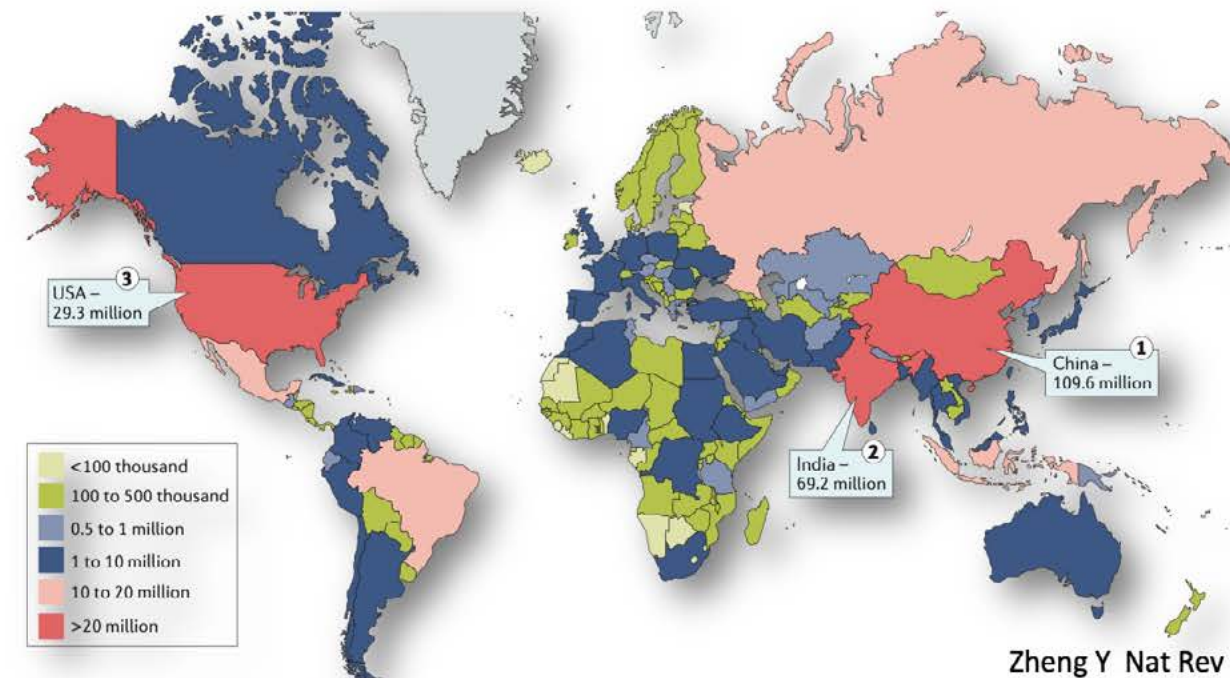
DIABETE E MALATTIE CARDIOVASCOLARI

LE NUOVE LINEE GUIDA ESC 2023
TRATTAMENTO DELLE MALATTIE CARDIOVASCOLARI NEL PAZIENTE DIABETICO

IL PUNTO DI VISTA DEL CARDIOLOGO

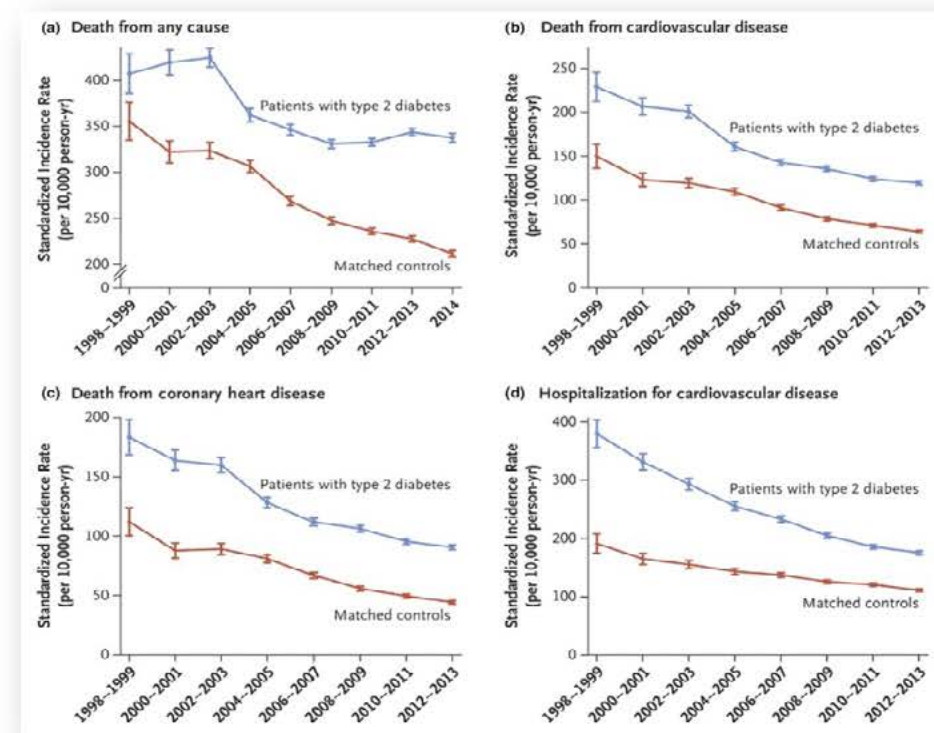
ALESSANDRA SABINI
UOC CARDIOLOGIA - OSPEDALE S. DONATO AREZZO
DIPARTIMENTO CARDIONEUROTORACOVASCOLARE – AZIENDA TOSCANA SUD EST

Estimated total number of adults living with diabetes mellitus, highlighting the top three countries or territories for number of adults with diabetes mellitus in 2015



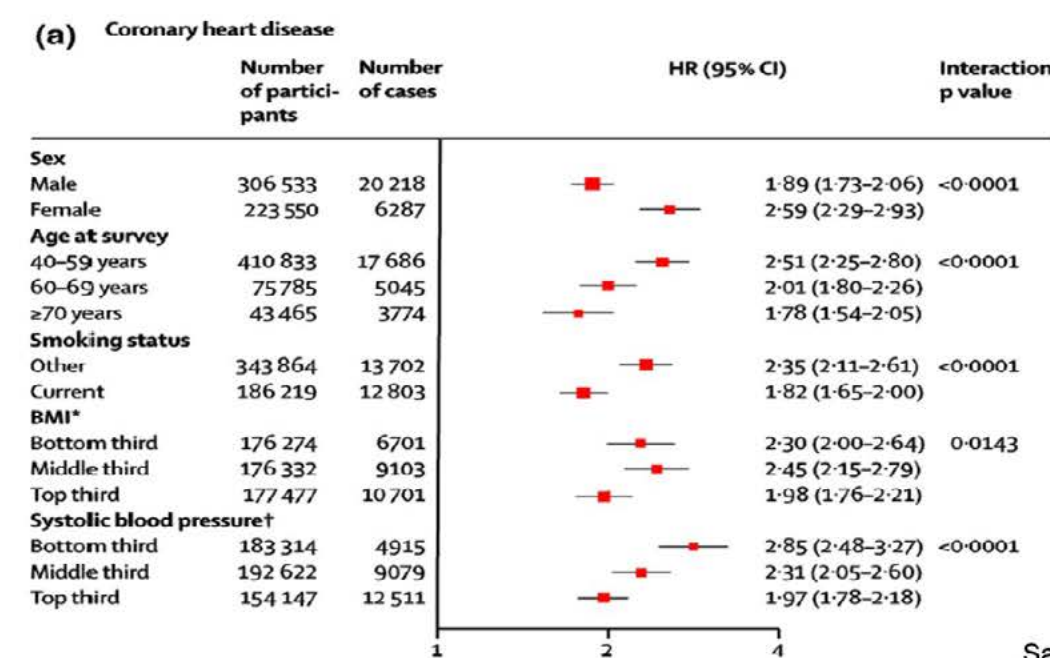
Zheng Y Nat Rev Endocrinol 2018 Feb;14(2):88-98.

Major cardiovascular outcomes in patients with type 2 diabetes



Rosengren A Journal of Internal Medicine, 2018, 284; 240–253

Hazard ratios (HRs) for coronary heart disease in people with versus those without diabetes at baseline, by individual characteristics



Sarwar N et al. Lancet 2010; 375: 2215-22.

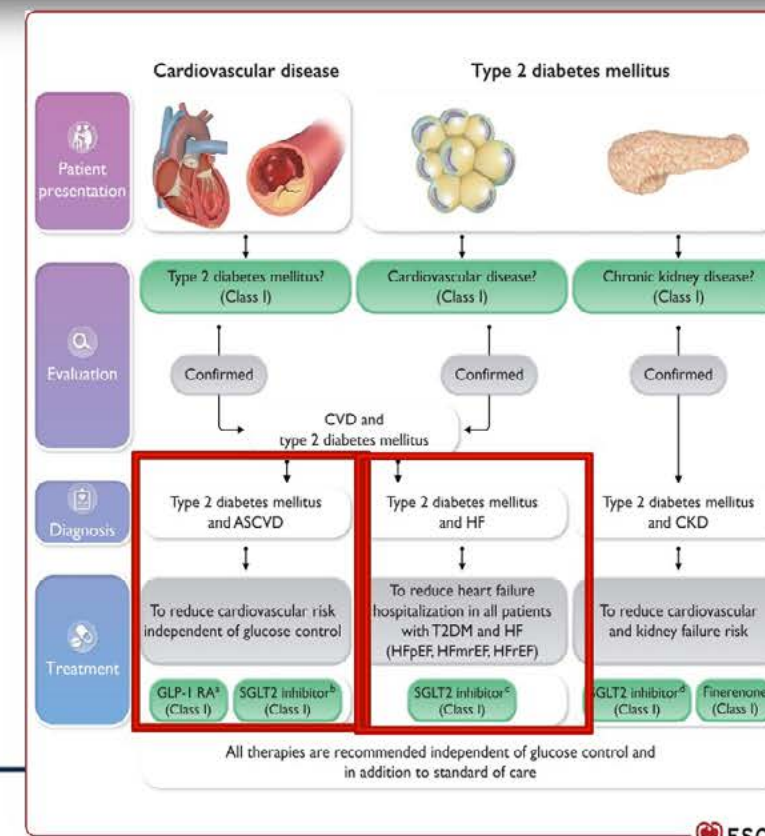


ESC European Society of Cardiology
 European Heart Journal (2023) 44, 4043–4140
<https://doi.org/10.1093/eurheartj/ehad192>

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2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes



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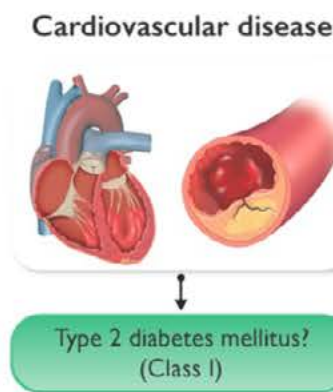


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**MANAGEMENT OF
ATHEROSCLEROTIC
CARDIOVASCULAR DISEASE**

Recommendation for screening for diabetes in individuals with cardiovascular disease



Recommendation	Class	Level
Screening for diabetes is recommended in all individuals with CVD, using fasting glucose and/or HbA1c.	I	A

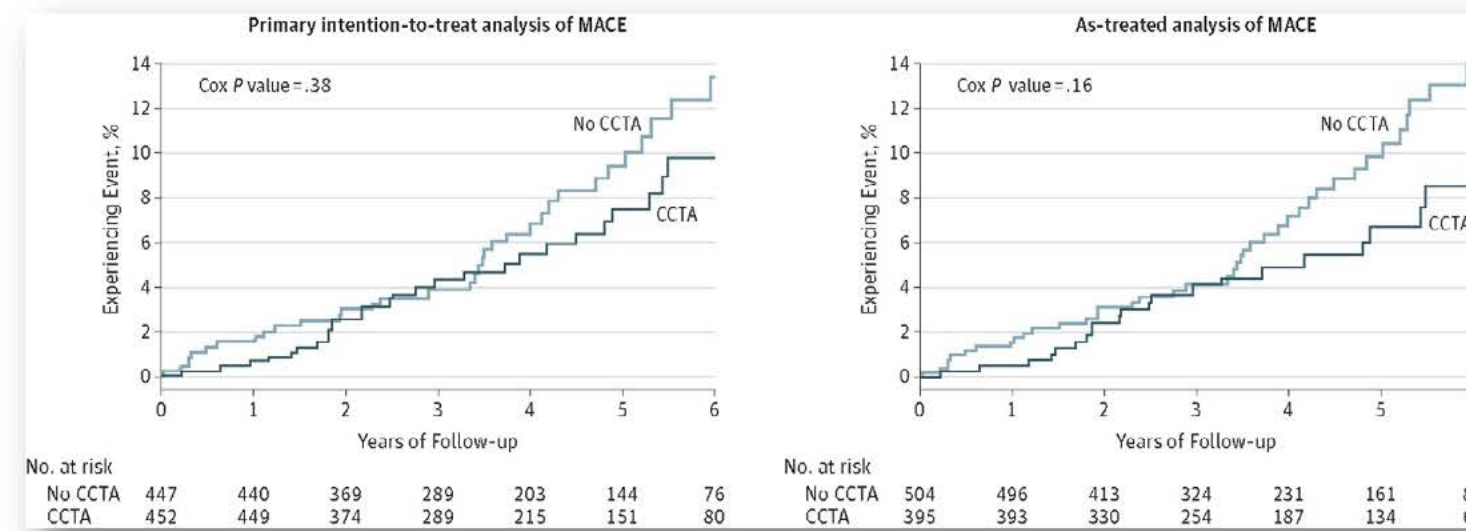
MANAGEMENT OF CORONARY ARTERY DISEASE IN PATIENTS WITH DM

- 1 SCREENING FOR CARDIOVASCULAR DISEASE IN ASYMPTOMATIC PATIENTS
- 2 ANTITHROMBOTIC THERAPY IN PRIMARY PREVENTION
- 3 PHARMACOLOGICAL TREATMENT

MANAGEMENT OF CORONARY ARTERY DISEASE IN PATIENTS WITH DM

1 SCREENING FOR CARDIOVASCULAR DISEASE IN ASYMPTOMATIC PATIENTS

Effect of Screening for Coronary Artery Disease Using CT Angiography on Mortality and Cardiac Events in High-Risk Patients With Diabetes: The FACTOR-64 Randomized Clinical Trial



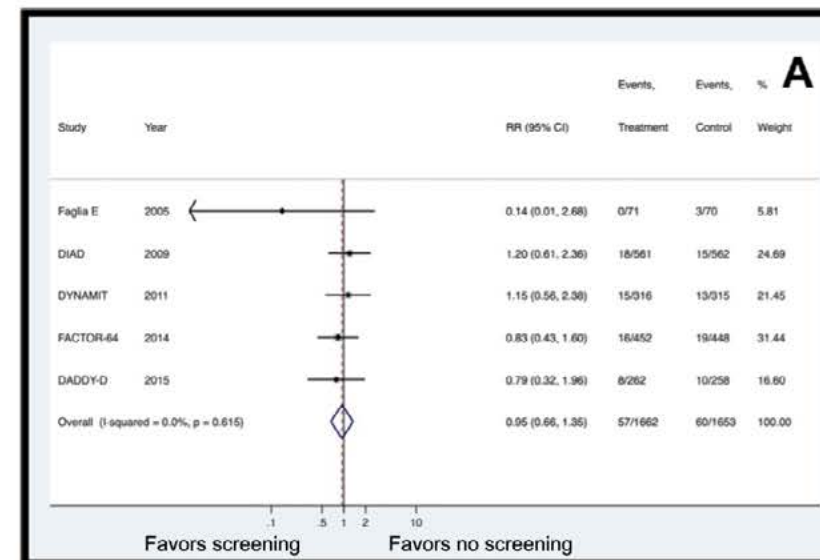
(MACE; Death, Nonfatal Myocardial Infarction, or Hospitalization for Unstable Angina)

JAMA. 2014;312(21):2234-2243. doi:10.1001/jama.2014.15825

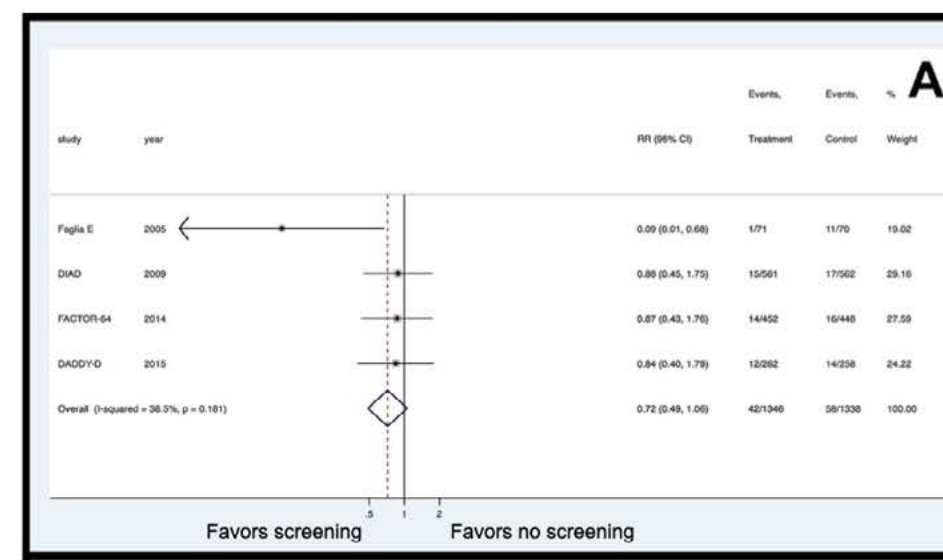
Screening for coronary artery disease in patients with type 2 diabetes: a meta-analysis and trial sequential analysis

Dimitris V Rados, Lana C Pinto, Cristiane B Leitão, Jorge L Gross

All-cause mortality outcome



Cardiac events outcome



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Rados DV, et al. BMJ Open 2017



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THE NEW ENGLAND JOURNAL OF MEDICINE


RESEARCH SUMMARY

Five-Year Outcomes of the Danish Cardiovascular Screening (DANCAVAS) Trial

Lindholt JS et al. DOI: 10.1056/NEJMoa2208681

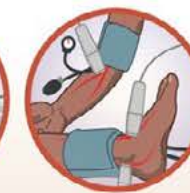
46,611 men
age 65-74 yrs

Screening Methods




Noncontrast ECG-Gated CT

- Coronary-artery calcium score
- Aneurysms
- Atrial fibrillation



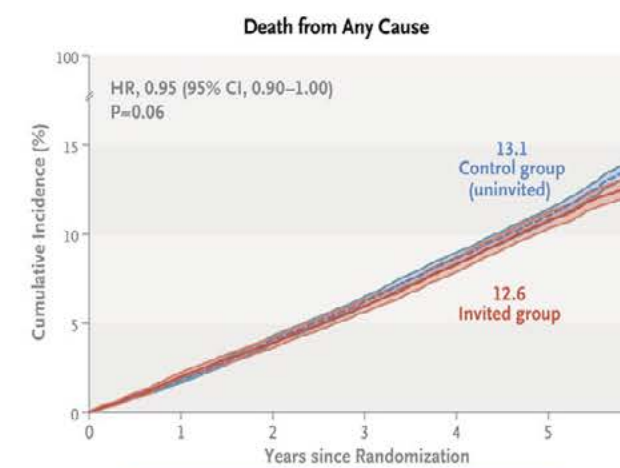
Ankle-Brachial Blood-Pressure Measurements

- Peripheral artery disease
- Hypertension



Blood Sample

- Diabetes mellitus
- Hypercholesterolemia



CONCLUSIONS
Among older men, an invitation to undergo comprehensive cardiovascular screening did not significantly reduce the incidence of death at 5.6 years' follow-up.

Subgroup	Screened Invited Participants	Unscreened Invited Participants	Hazard Ratio (95% CI)
Age			
<70 yr	18.75	20.90	0.87 (0.63-1.26)
≥70 yr	30.71	30.33	1.01 (0.74-1.39)
Cardiovascular disease			
No	20.17	21.40	0.95 (0.89-1.01)
Yes	47.50	47.33	0.99 (0.89-1.10)
Smoke			
No	22.64	23.65	0.96 (0.90-1.03)
Yes	42.37	44.19	0.97 (0.86-1.17)
Ischemic heart disease			
No	21.05	24.26	0.91 (0.80-1.09)
Yes	35.30	34.63	1.03 (0.82-1.29)
Heart failure			
No	22.31	23.44	0.95 (0.90-1.00)
Yes	39.61	39.07	0.99 (0.81-1.21)
Peripheral occlusive arterial disease			
No	22.35	23.72	0.94 (0.89-0.99)
Yes	41.96	42.74	1.11 (0.81-1.46)
Aortic aneurysm			
No	23.09	24.25	0.95 (0.90-1.00)
Yes	48.37	53.89	0.90 (0.66-1.23)
Hypertension at baseline			
No	18.95	18.66	0.96 (0.88-1.05)
Yes	27.71	29.29	0.95 (0.89-1.01)
Diabetes mellitus at baseline			
No	21.65	22.24	0.96 (0.90-1.03)
Yes	38.41	39.91	0.91 (0.81-1.03)
Lipid-lowering therapy at baseline			
No	22.21	22.27	1.00 (0.93-1.07)
Yes	45.63	48.24	0.90 (0.83-0.97)

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N Engl J Med 2022; 387:1385-1394



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«Screening for asymptomatic CAD in diabetes remains controversial.

Various RCTs evaluating the impact of routine screening for CAD in asymptomatic patients with diabetes and no history of CAD showed no differences in CV outcomes at follow-up in those who underwent routine screening compared with standard recommendations.»



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 European Heart Journal (2023) 44, 4043–4140
<https://doi.org/10.1093/eurheartj/ehad192>

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«When assessing CV risk in individuals with T2DM, it is important to consider medical and family history, symptoms, findings from examination, laboratory and other diagnostic test results, and the presence of ASCVD or severe TOD.

There is not enough robust evidence to suggest that assessment of coronary artery calcium (CAC) or intima media thickness help reclassify CV risk in people with T2DM».



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MANAGEMENT OF CORONARY ARTERY DISEASE IN PATIENTS WITH DM

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- 2 ANTITHROMBOTIC THERAPY IN PRIMARY PREVENTION
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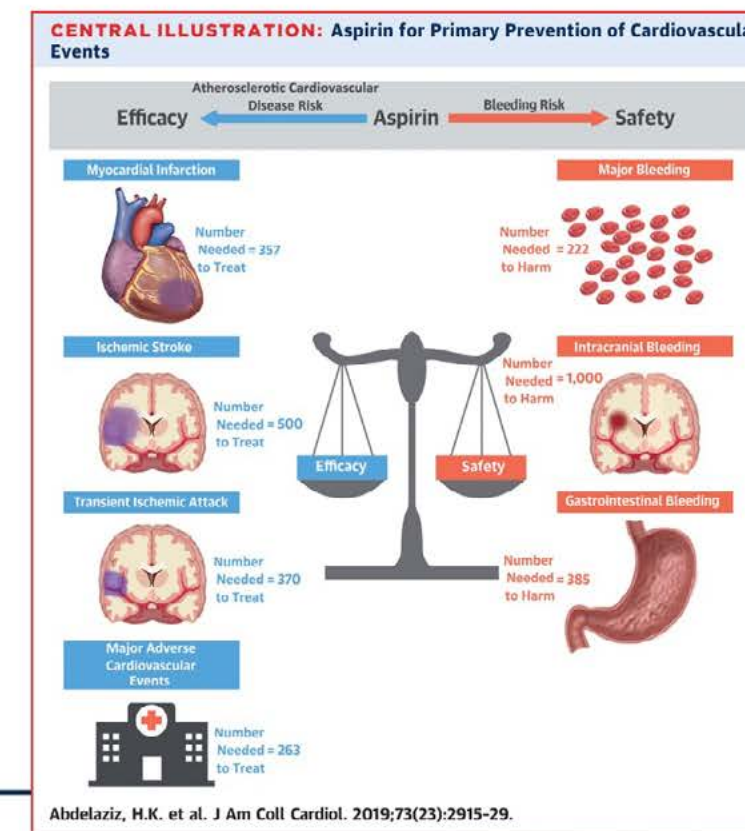
MANAGEMENT OF CORONARY ARTERY DISEASE IN PATIENTS WITH DM

2 ANTITHROMBOTIC THERAPY IN PRIMARY PREVENTION

Aspirin for Primary Prevention of Cardiovascular Events

Aspirin was associated with similar all-cause death, CV death, and non-CV death, but a lower risk of nonfatal MI, ischemic stroke and TIA.

Aspirin was associated with a higher risk of major bleeding, intracranial bleeding, and major GI bleeding

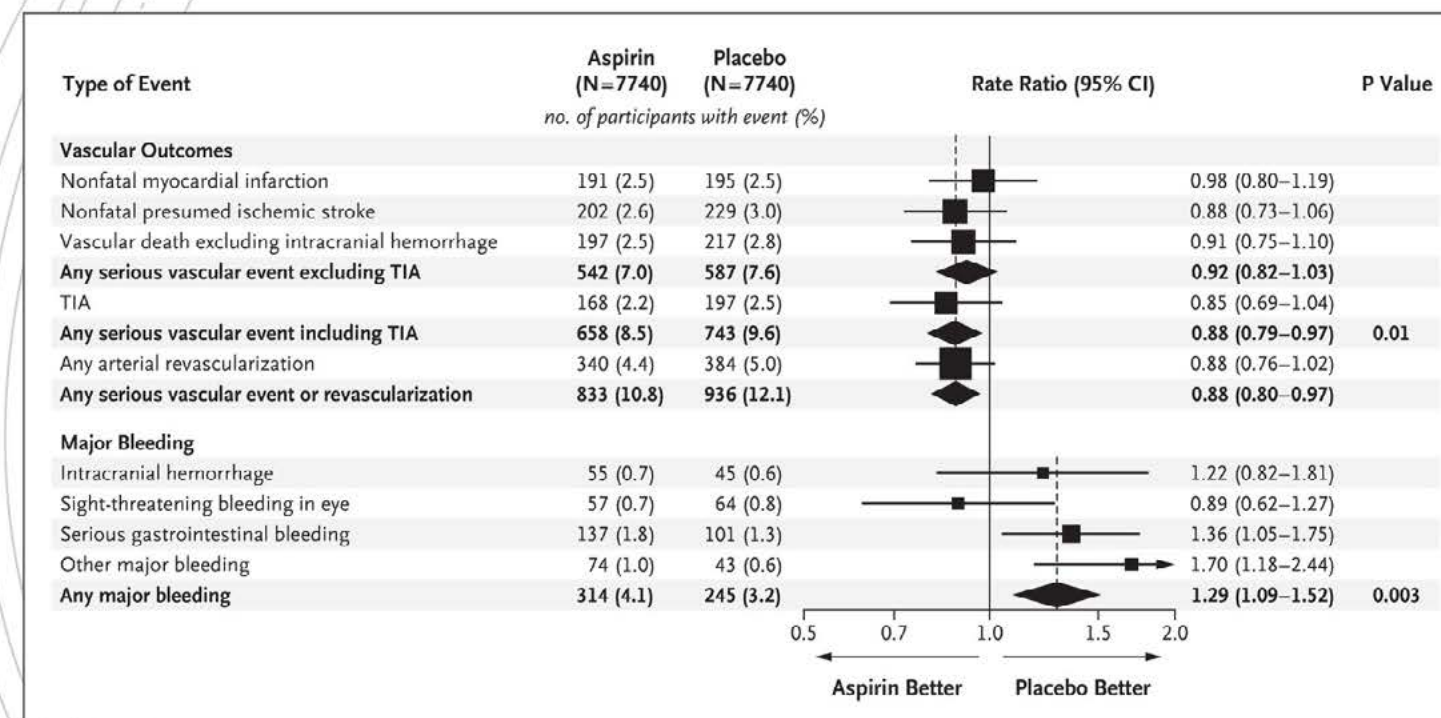


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Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus
The ASCEND Study Collaborative Group

15,480 pts
7,4 yrs fu





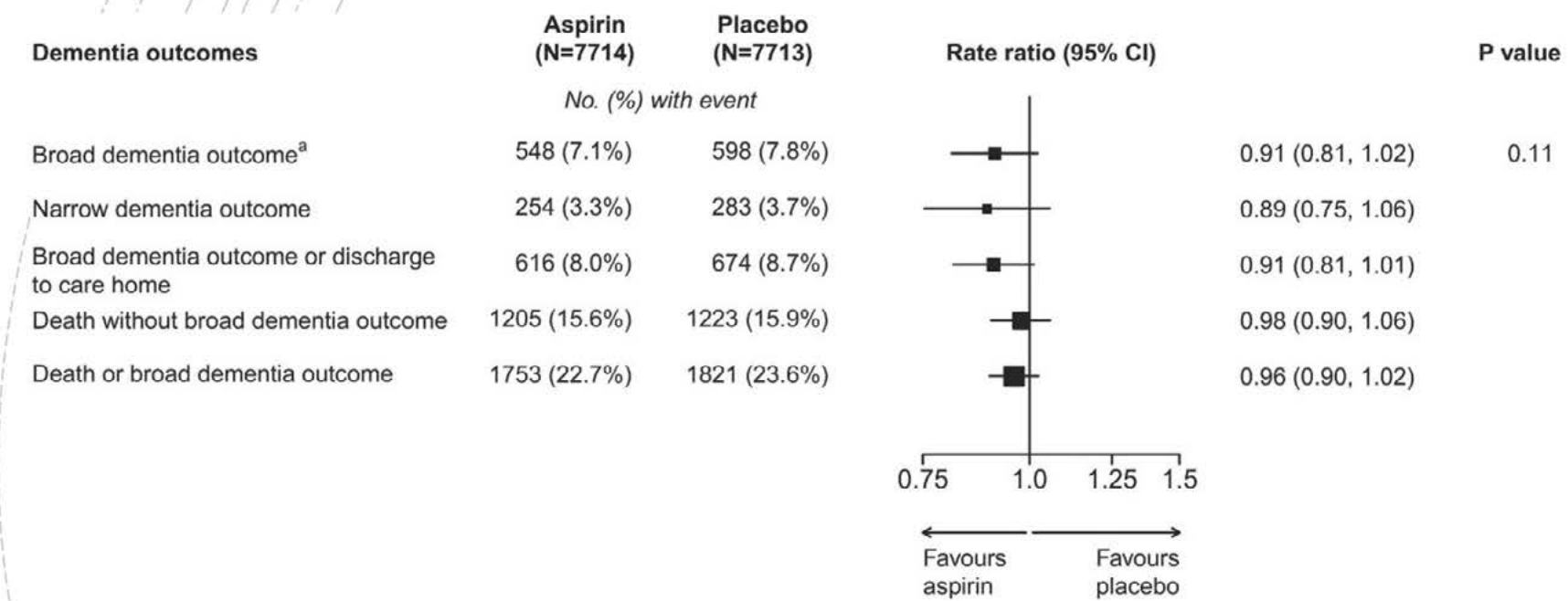
ESC
 European Society of Cardiology
 European Heart Journal (2022) 43, 2010–2019
<https://doi.org/10.1093/eurheartj/ehac179>

FASTTRACK CLINICAL RESEARCH
 Clinical trials

NOVEMBRE 2023
CONGRESSI



Effects of aspirin on dementia and cognitive function in diabetic patients: the ASCEND trial



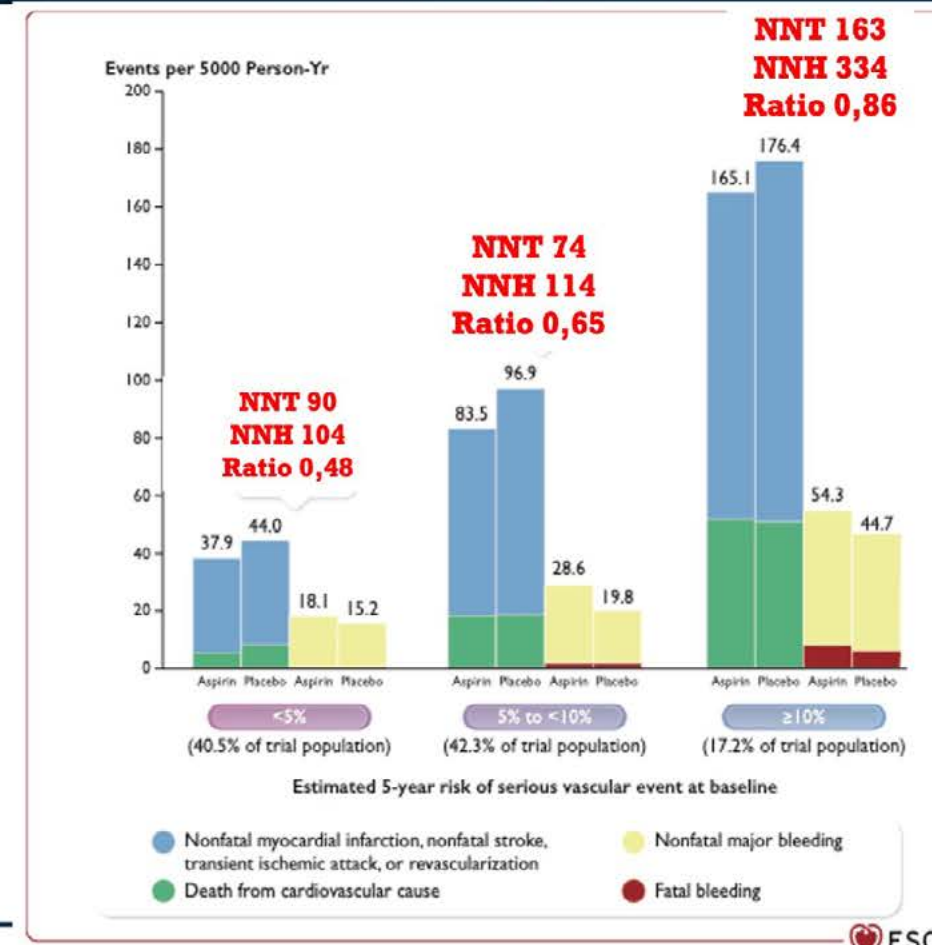
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Parish et al, European heart Journal 2022



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Observed absolute effect in aspirin and placebo groups for serious vascular events, including major bleeding or revascularization.



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N Engl J Med. 2018 Oct 18;379(16):1529-1539

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Recommendations for patients with diabetes without a history of symptomatic atherosclerotic cardiovascular disease or revascularization



Recommendation	Class	Level
In adults with T2DM without a history of symptomatic ASCVD or revascularization, ASA (75–100 mg o.d.) may be considered to prevent the first severe vascular event, in the absence of clear contraindications*.	IIb	A

* High risk of bleeding due to gastrointestinal haemorrhage or peptic ulcer within the previous 6 months, active hepatic disease (such as cirrhosis, active hepatitis), or history of ASA allergy.

www.escardio.org/guidelines

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes (European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

MANAGEMENT OF CORONARY ARTERY DISEASE IN PATIENTS WITH DM

- 1 SCREENING FOR CARDIOVASCULAR DISEASE IN ASYMPTOMATIC PATIENTS
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MANAGEMENT OF CORONARY ARTERY DISEASE IN PATIENTS WITH DM

3 PHARMACOLOGICAL TREATMENT

Benefits of GLP-1 RA and SGLT2i in cardiovascular disease

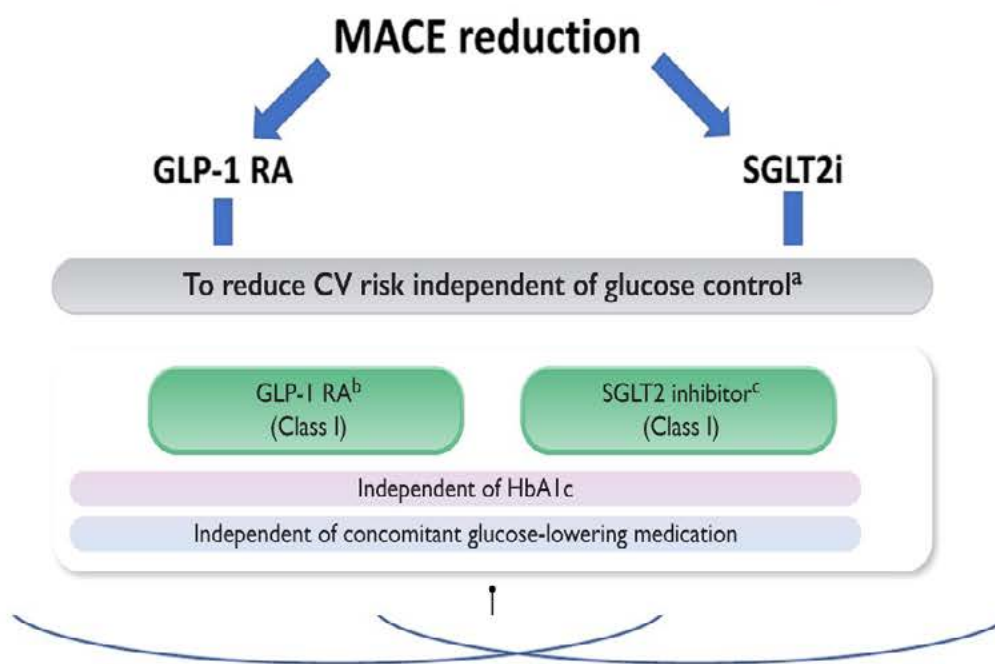
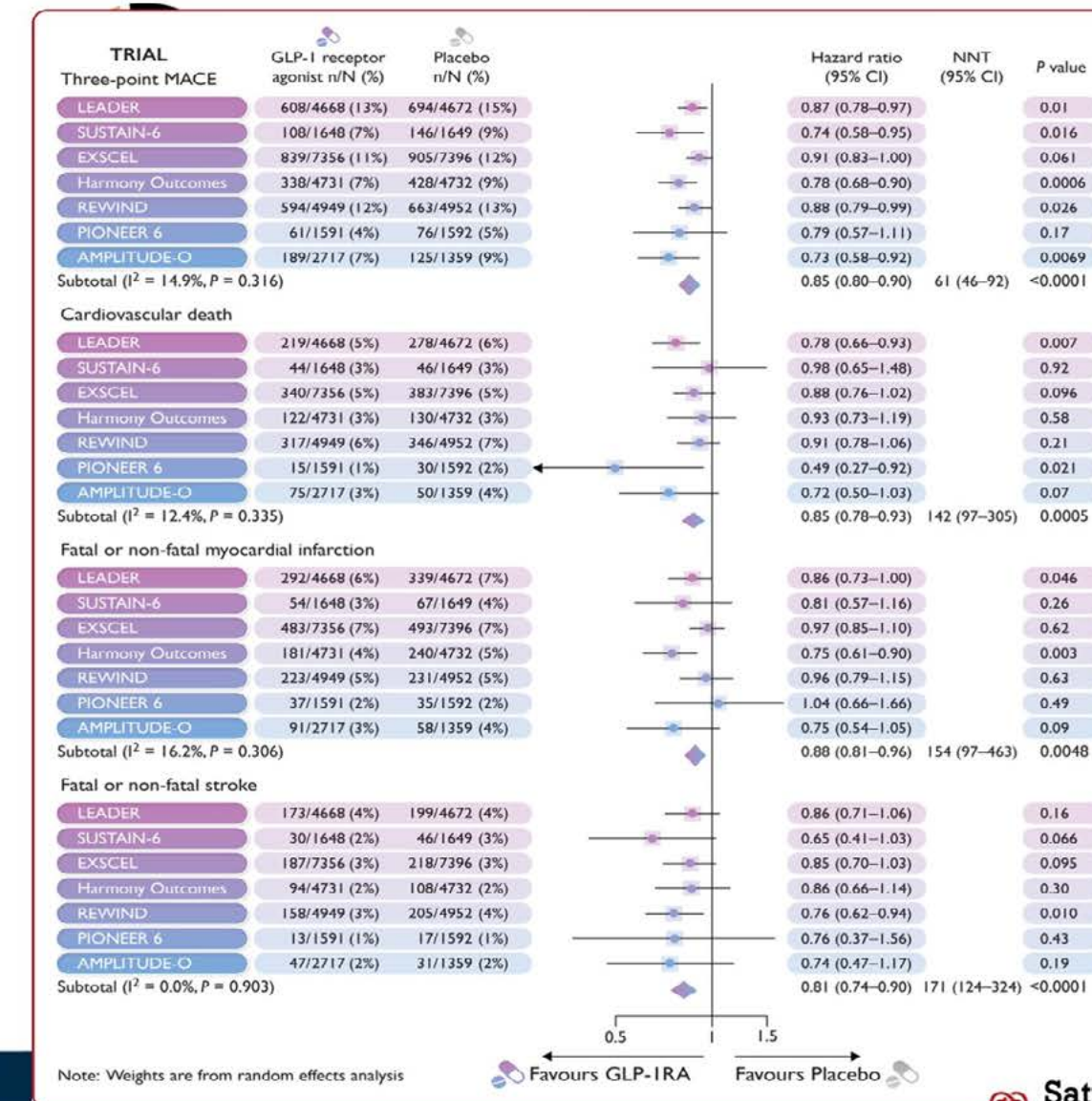
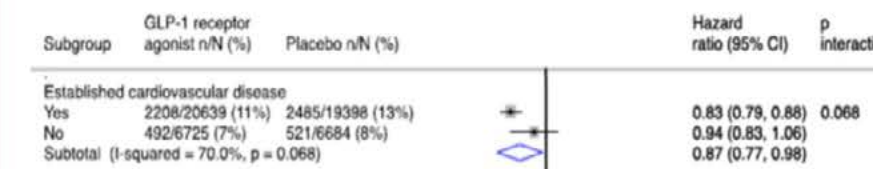


Fig. 1 Benefits of GLP-1 RA and SGLT2i in cardiovascular disease. *CKD* chronic kidney disease, *GLP-1 RA* glucagon-like peptide 1 receptor agonists, *HF* heart failure, *MACE* major adverse cardiovascular events, *SGLT2i* sodium-glucose co-transporter 2 inhibitors



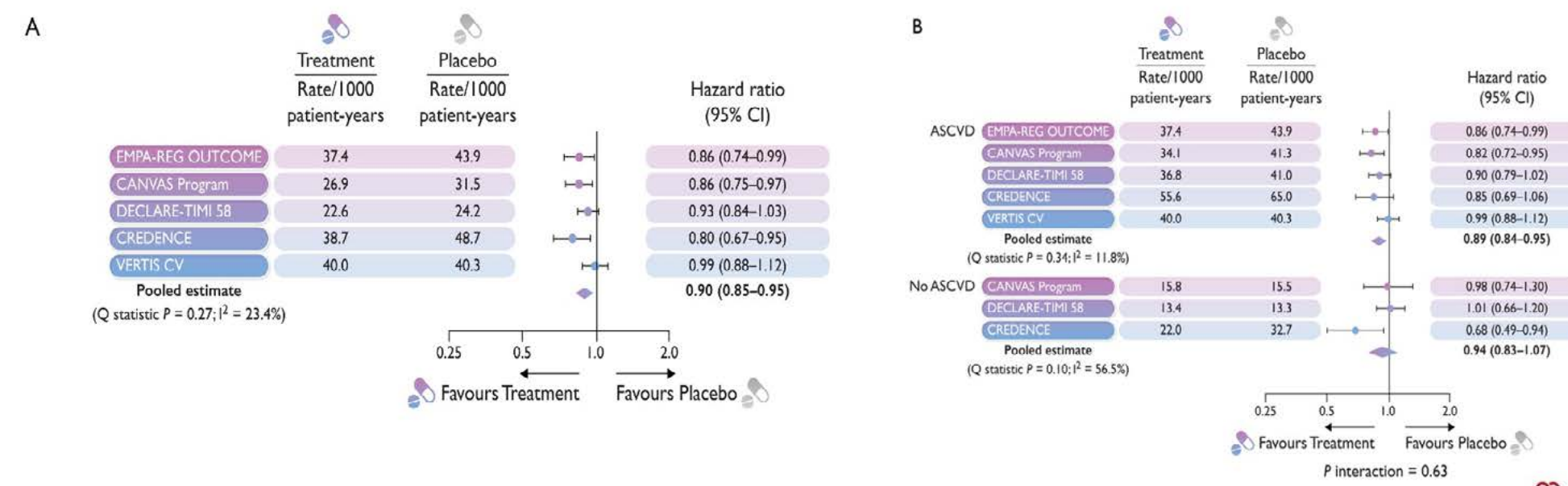
Meta-analysis of cardiovascular outcomes trials with glucagon-like peptide-1 receptor agonists in pts with type 2 diabetes with or at high risk for ASCVD

Subgroup analyses for risk of three-point MACE in patients with and without ASCVD



Sattar N et al, The Lancet Diabetes & Endocrinology 2021

Meta-analysis of cardiovascular outcomes trial
 results of SGLT2i among patients with type 2 diabetes with or at high risk for ASCVD



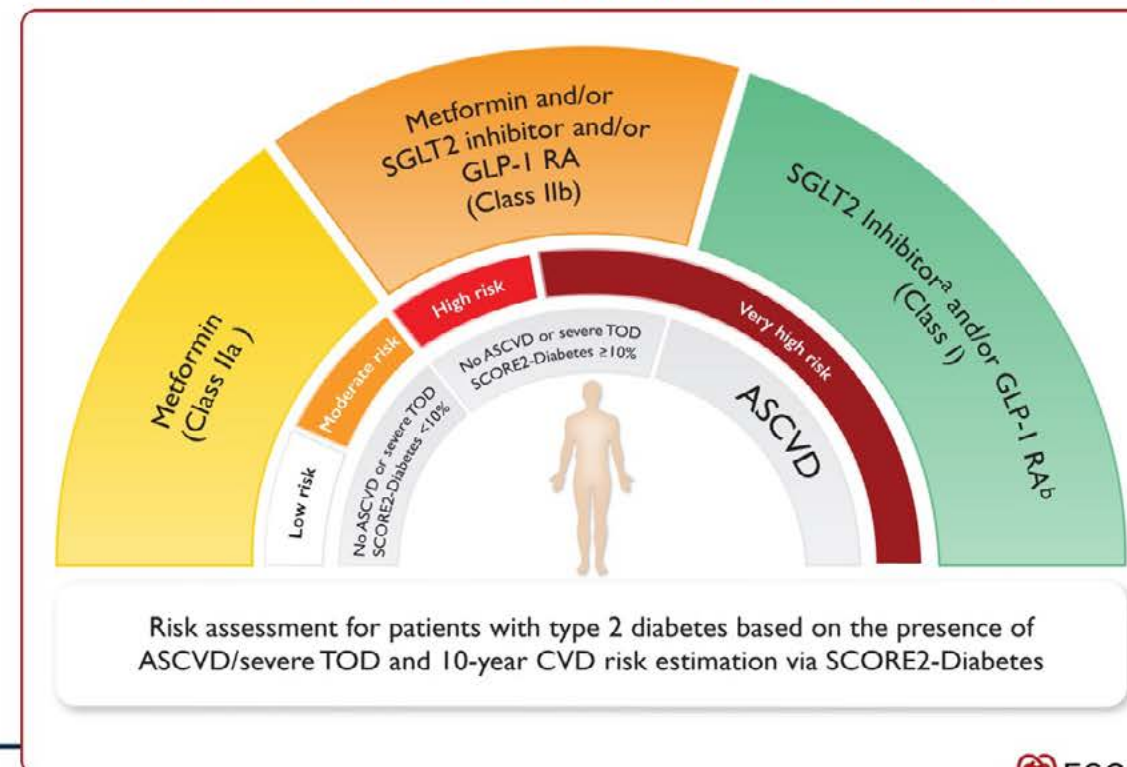
Recommendations for glucose-lowering treatment for patients with type 2 diabetes and ASCVD to reduce cardiovascular risk (1) 

	Recommendations	Class	Level
	It is recommended to prioritize the use of glucose-lowering agents with proven CV benefits followed by agents with proven CV safety over agents without proven CV benefit or proven CV safety.	I	C
SGLT-2 i	Sodium-glucose co-transporter-2 inhibitors SGLT2 inhibitors with proven CV benefit are recommended in patients with T2DM and ASCVD to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.	I	A
GLP-1 ra	Glucagon-like peptide-1 receptor agonists GLP-1 RAs with proven CV benefit are recommended in patients with T2DM and ASCVD to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.	I	A

www.escardio.org/guidelines

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes (European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

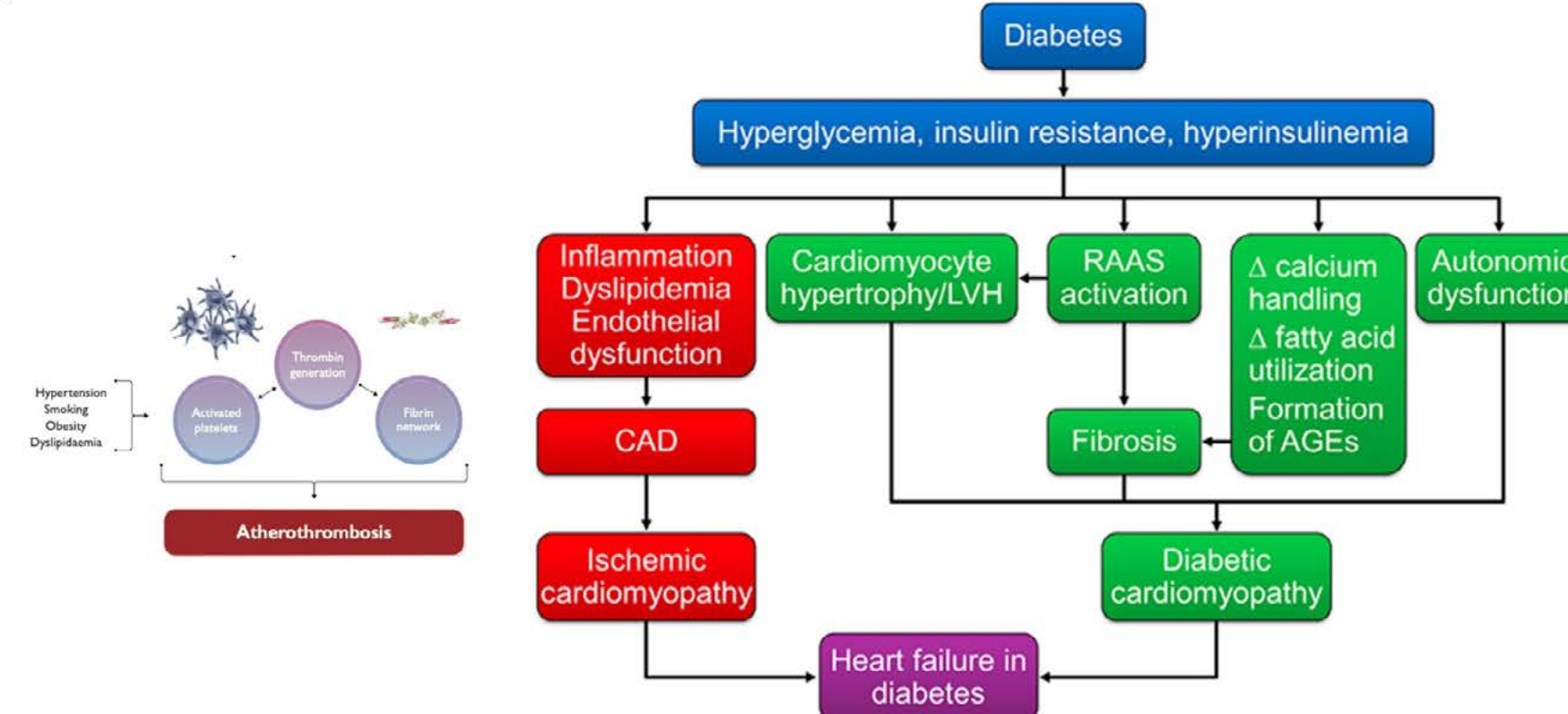
Glucose-lowering treatment for patients with type 2 diabetes and ASCVD to reduce cardiovascular risk



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MANAGEMENT OF HEART FAILURE IN PATIENTS WITH DM



Shannon M. Dunlay. Circulation. Volume: 140, Issue: 7, Pages: e294-e324

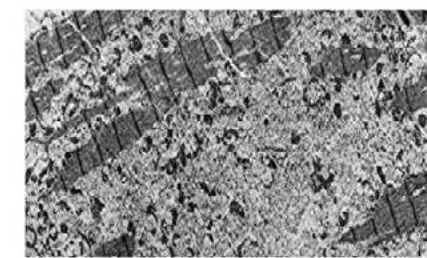
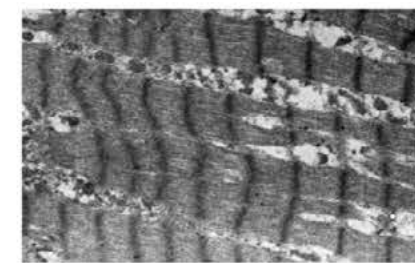
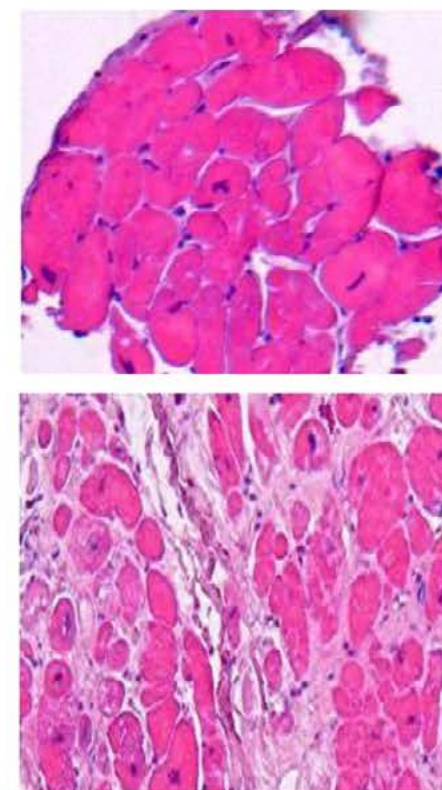
Two distinct phenotypes of diabetes-related cardiomyopathy exist

HFpEF (earliest)	HFrEF
<ul style="list-style-type: none"> ▪ Cardiomyocyte hypertrophy ▪ Cardiomyocyte fibrosis ▪ Increased cardiomyocyte stiffness 	<ul style="list-style-type: none"> ▪ Cardiomyocyte apoptosis ▪ Cardiomyocyte necrosis ▪ Decreased cardiomyocyte shortening

This suggests the earliest defect in the diabetic heart is that of diastolic dysfunction not atherothrombosis

HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricular; LVD = LV dysfunction; T2D = type 2 diabetes.
 Seferović PM et al. *Eur Heart J*. 2015;36:1718-1727..

Myocardial structure in restrictive/HFPEF and dilated/HFREF



HF p EF



HF r EF

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Seferović PM et al. *Eur Heart J*. 2015;36:1718-1727



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European Society
of Cardiology

European Heart Journal (2021) 00, 1–2
doi:10.1093/eurheartj/ehab765



Braunwald's Corner

SGLT2 inhibitors: the statins of the 21st century

Eugene Braunwald  ^{1,2*}

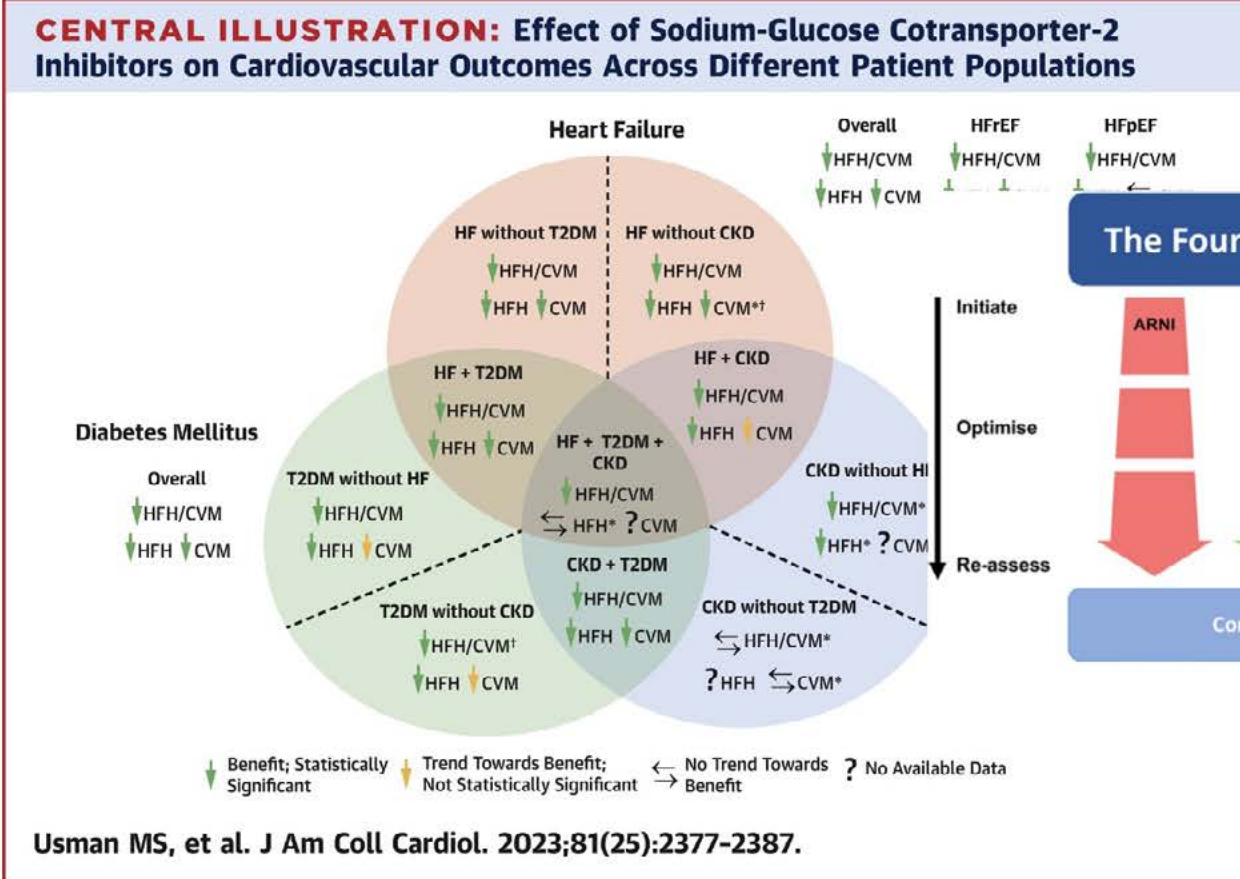
¹TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Hale Building for Translational Medicine, Suite 7022, 60 Fenwood Road, Boston, MA 02115, USA; and ²Department of Medicine, Harvard Medical School, Boston, MA, USA

A relatively small number of drugs have been responsible for major advances in medical practice. The discovery, development, and elucidation of the mechanisms of action of aspirin, penicillin, and statins are remarkable success stories, each with some surprises and each crowned by a Nobel Prize. The sodium glucose co-transporter inhibitors have been proven effective in the treatment of type 2 diabetes mellitus, various forms of heart failure, and kidney failure and represent the, or one of the, major pharmacological advances in cardiovascular medicine in the 21st century.

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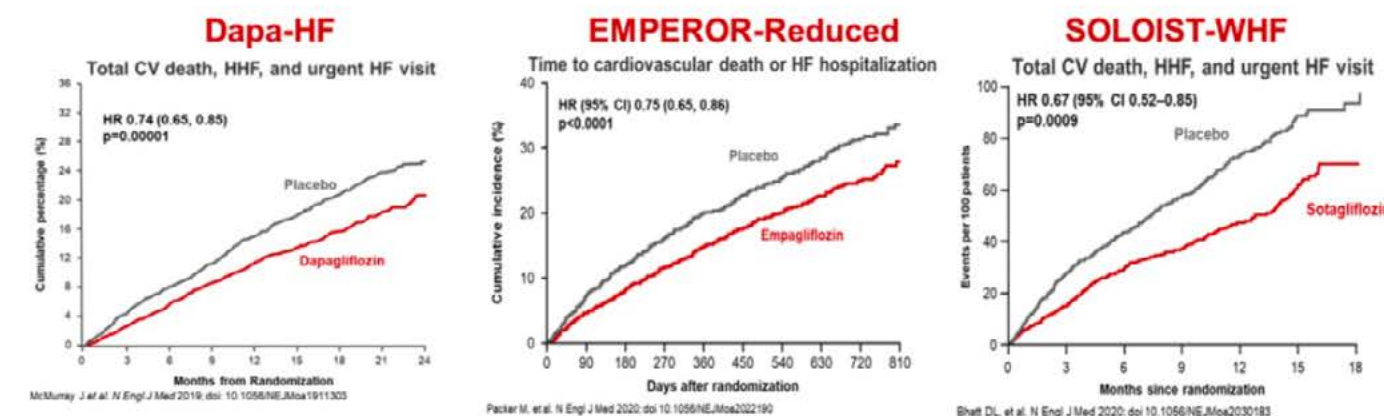




Recommendations for heart failure treatments in patients with heart failure with reduced ejection fraction and diabetes (1)



Recommendations	Class	Level
Recommendations for the pharmacological treatment indicated in patients with HFrEF (NYHA class II–IV) and diabetes		
SGLT2 inhibitors (dapagliflozin, empagliflozin, or sotagliflozin) are recommended in all patients with HFrEF and T2DM to reduce the risk of HF hospitalization and CV death.	I	A



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2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes (European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

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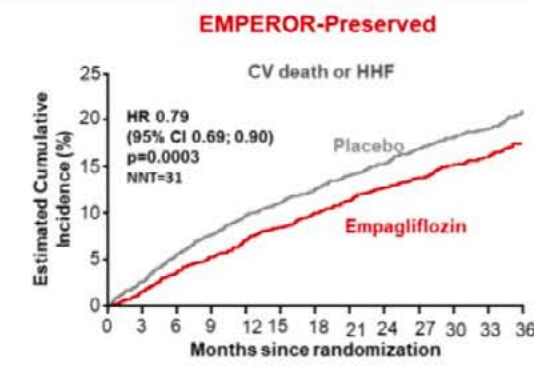




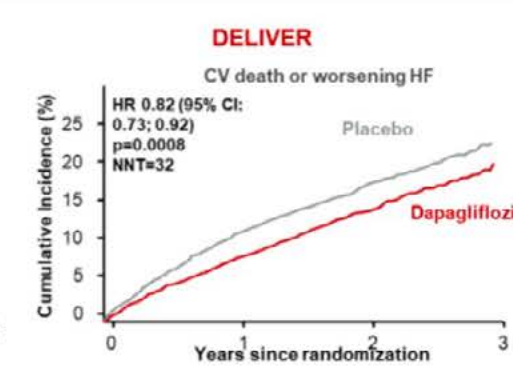
Recommendations for heart failure treatments in patients with diabetes and left ventricular ejection fraction over 40%



Recommendations	Class	Level
Empagliflozin or dapagliflozin are recommended in patients with T2DM and LVEF >40% (HFmrEF and HFpEF) to reduce the risk of HF hospitalization or CV death.	I	A



Anker SD, et al. N Engl J Med 2021; doi:10.1056/NEJMoa2107038



Solomon SD, et al. N Engl J Med 2022; doi:10.1056/NEJMoa2206286
 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes (European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

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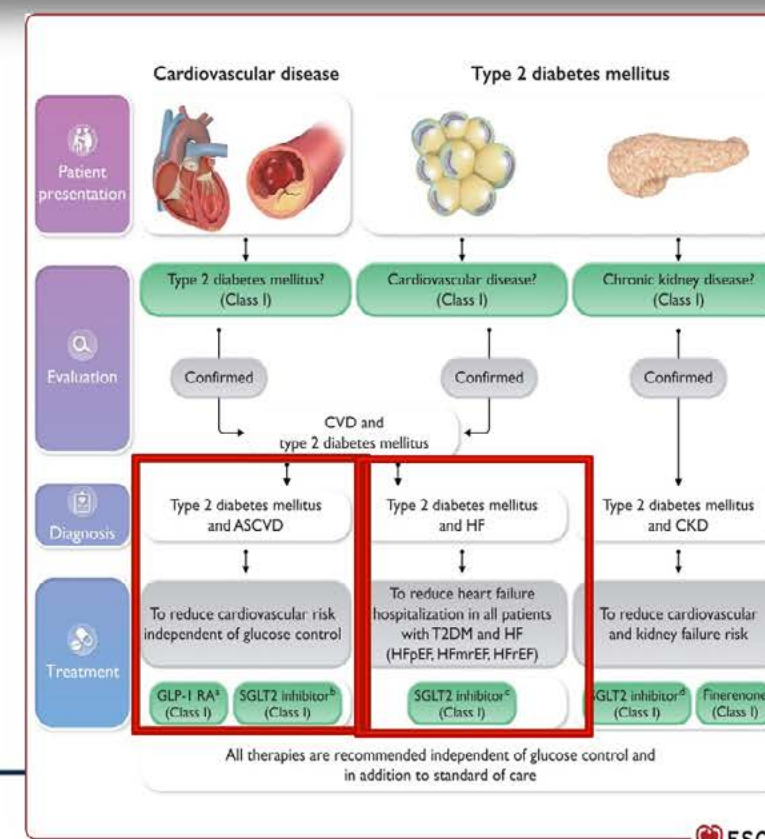
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2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes



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Thank you for
your attention

For additional glucose control

Other glucose-lowering agents with neutral effects on HF in CVOTs should be considered

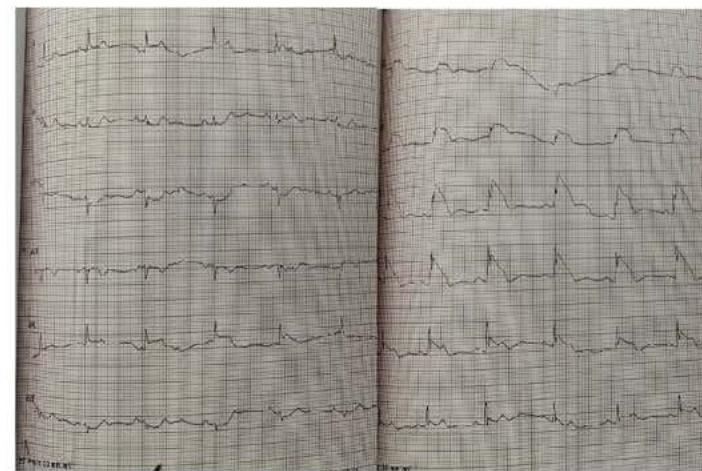
GLP-1 RA ^c (Class IIa)	Sitagliptin Linagliptin (Class IIa)	Metformin (Class IIa)	Insulin glargine Insulin degludec (Class IIa)
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Other glucose-lowering agents with increased risk for HF hospitalization in CVOTs are not recommended

Pioglitazone (Class III)	Saxagliptin (Class III)
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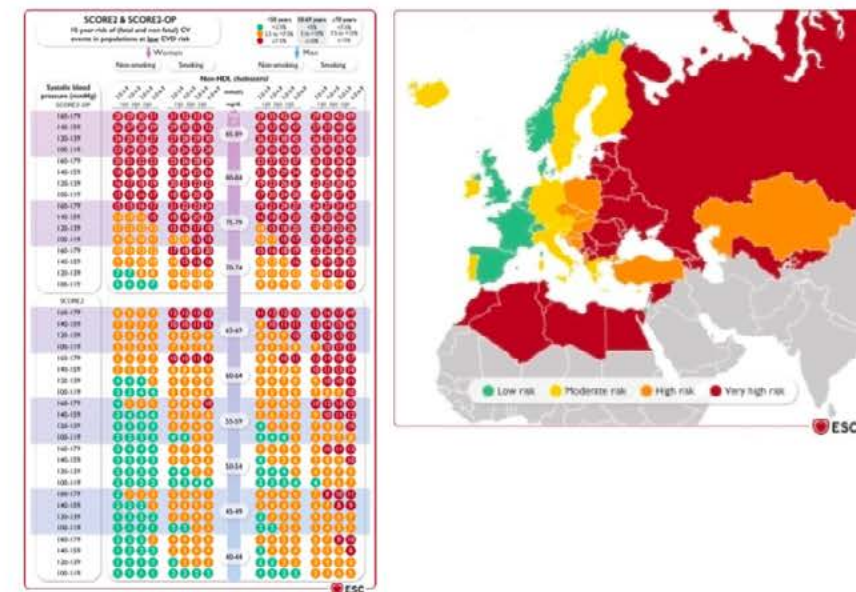
SCENARIO 1

STEMI



SCORE 2

SCORE2
 10-year risk of (fatal and non-fatal) CV events

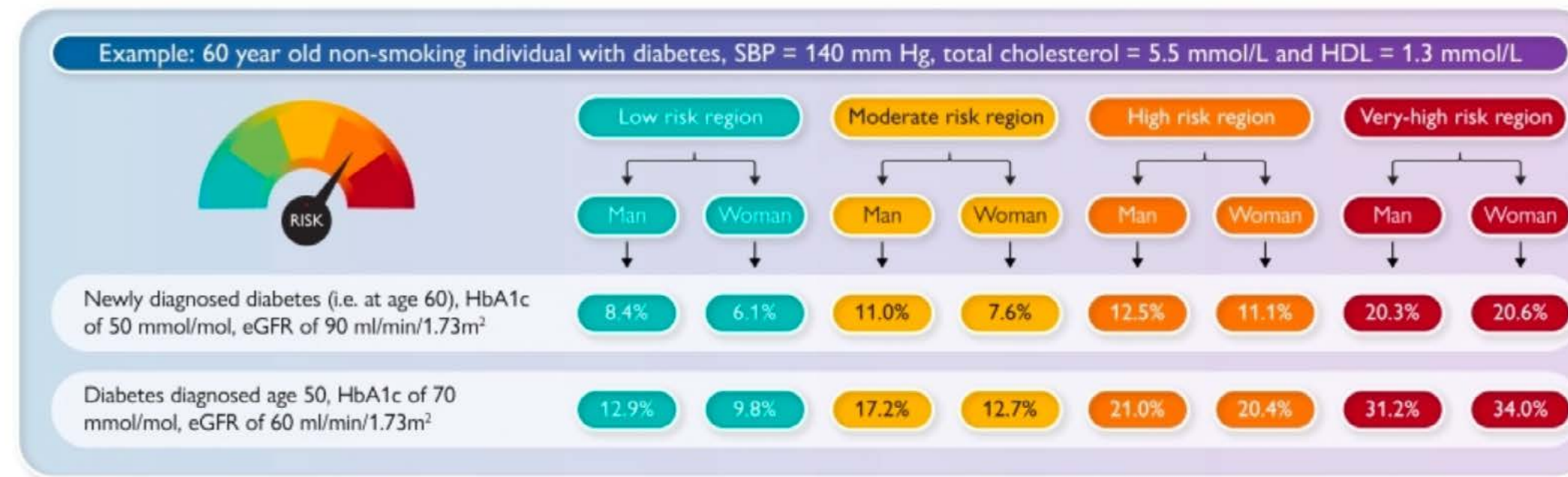


Hageman S et al, *Eur Heart J* 2021

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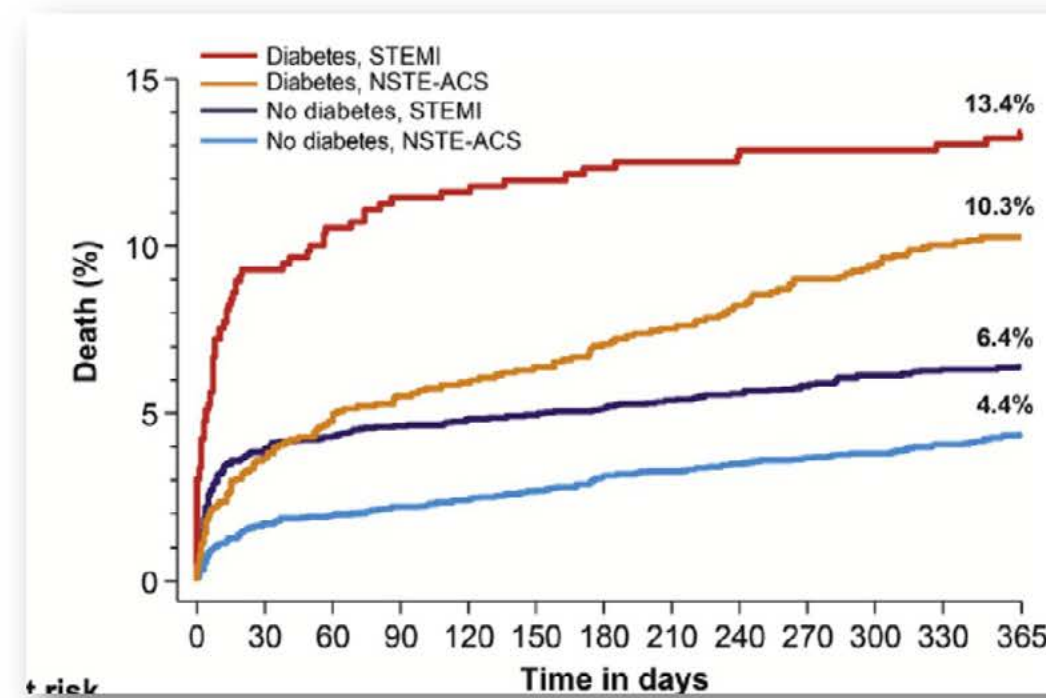


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Effect of Diabetes Mellitus on Frequency of Adverse Events in Patients With ACS Undergoing PCI



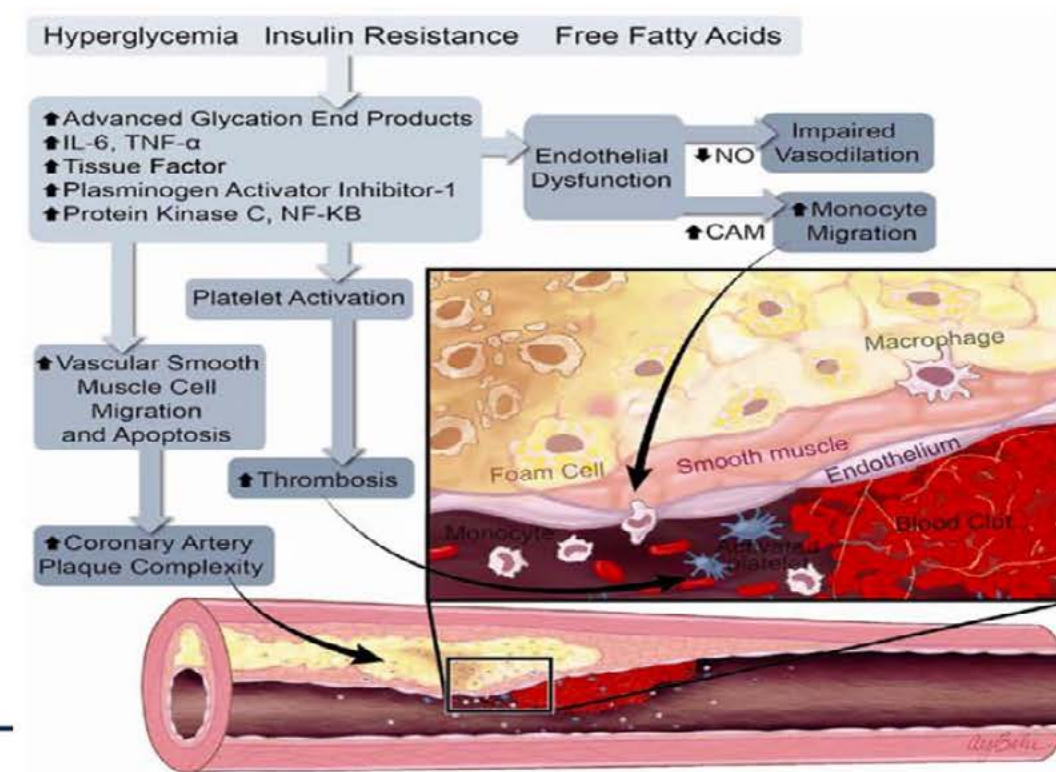
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Piccolo R et al. Am J Cardiol 2016;118:345e-352



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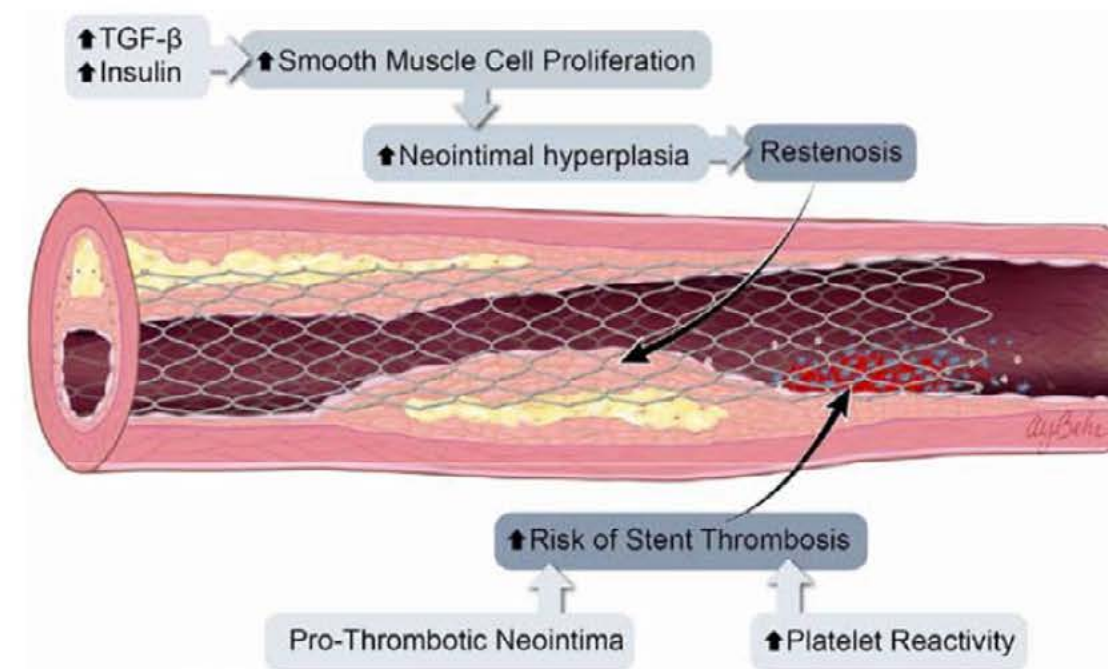
Mechanisms Linking DM, Atherosclerosis, and Outcomes After Percutaneous Coronary Revascularization



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Restenosis and Stent Thrombosis



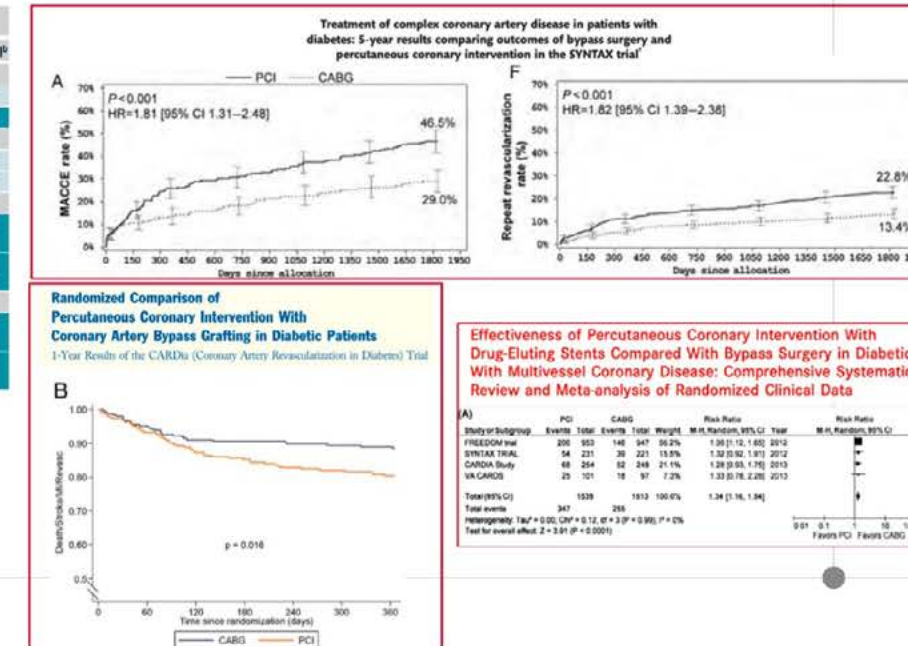
Coronary revascularization in diabetes: guideline recommendations



Recommendations according to the extent of CAD	CABG		PCI	
	Class*	Level†	Class* Level†	Class* Level†
Single-vessel CAD				
Without proximal LAD stenosis	IIb	C	I	C
With proximal LAD stenosis ⁴¹⁰⁻⁴¹³	I	A	I	A
Two-vessel CAD				
Without proximal LAD stenosis	IIb	C	I	C
With proximal LAD stenosis ⁴¹⁰⁻⁴¹²	I	B	I	C
Three-vessel CAD				
With low disease complexity (SYNTAX score 0-22) ^{380-383, 413-415}	I	A	IIb	A
With intermediate or high disease complexity (SYNTAX score > 22) ^{386-391, 413-415}	I	A	III	A
Left-main CAD				
With low disease complexity (SYNTAX score 0-22) ^{391, 413, 423-425}	I	A	I	A
With intermediate disease complexity (SYNTAX score 23-32) ^{391, 413, 423-425}	I	A	Bx	A

Marx N et al, EHI 2023
Kappetein AP et al, Eur J Cardiothorac Surg 2013
Kapur A et al, J Am Coll Cardiol 2010
Hakeem A et al, J Am Heart Assoc 2013

www.escardio.org/guidelines

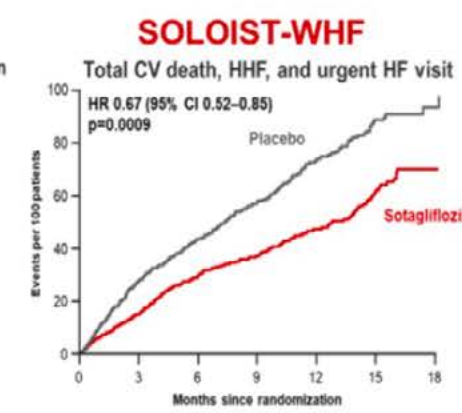
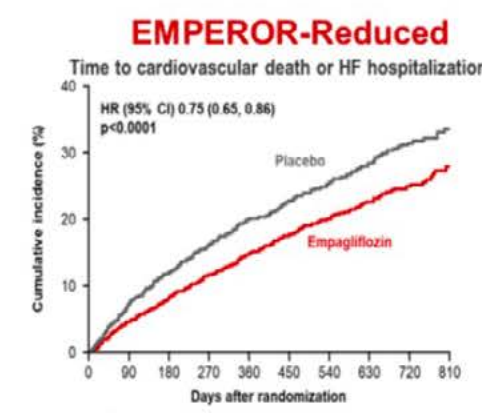
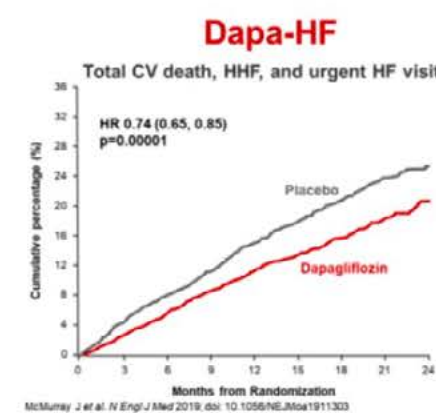




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SGLT2 inhibitors (dapagliflozin, empagliflozin, or sotagliflozin) are recommended in all patients with HFrEF and T2DM to reduce the risk of HF hospitalization and CV death.	I	A



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2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes (European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

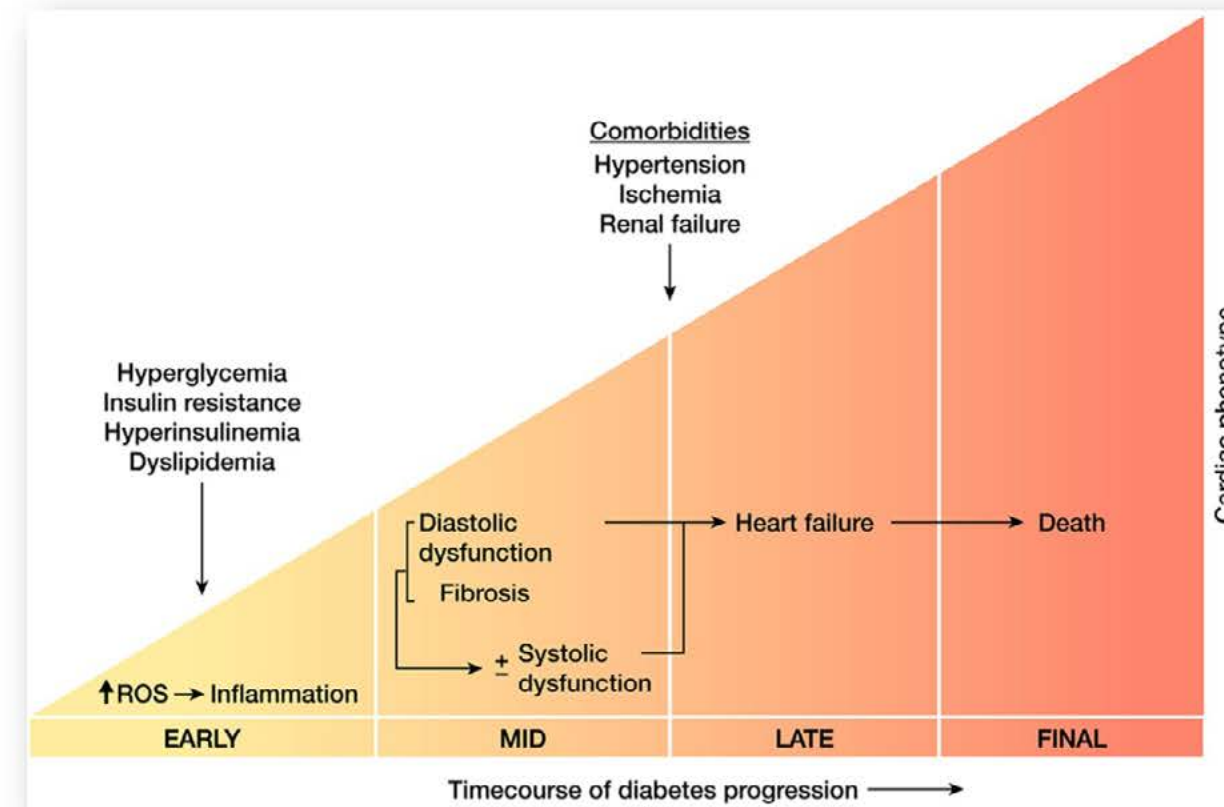
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Current understanding of diabetes progression and CV effects



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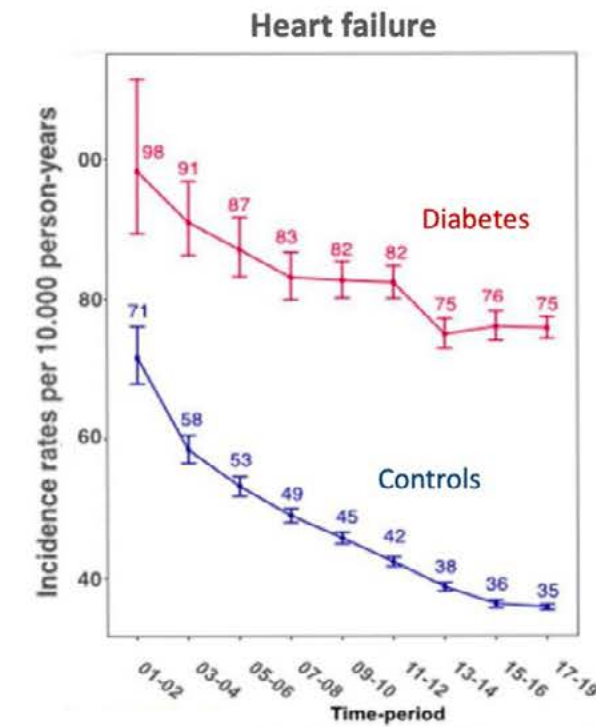
Ritchie RH, Abel ED. Basic Mechanisms of Diabetic Heart Disease. *Circ Res.* 2020;126(11):1501-1525.



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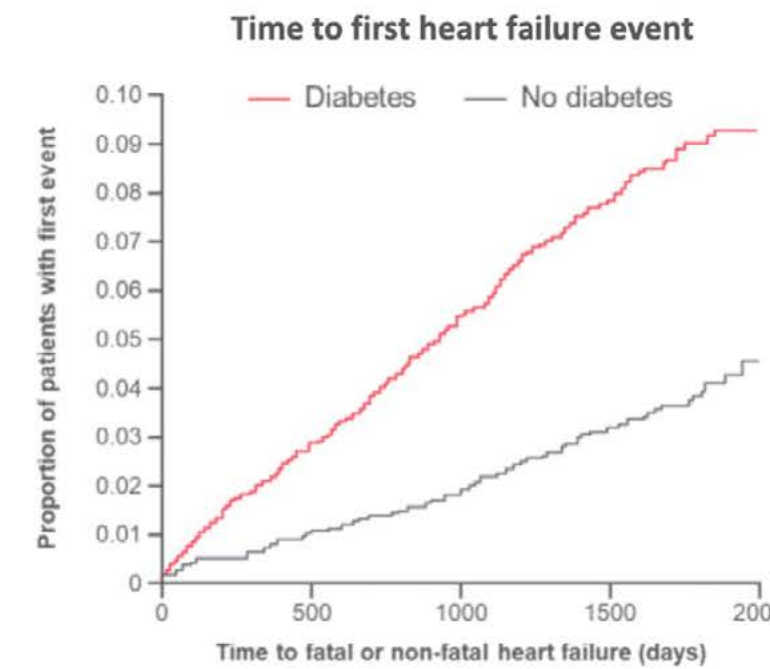


Patients with DM have a higher incidence rate of HF and DM accelerates the time to first CV event



Naveed Sattar et al. Circulation 2023;147:00-00

www.escardio.org/guidelines



McMurray JJV et al. Lancet Diabetes Endocrinol 2014;2:843

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes (European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

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Severe TOD is defined as:

- Estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m² irrespective of albuminuria, or
- eGFR 45–59 mL/min/1.73 m² and microalbuminuria (urinary albumin-to-creatinine ratio [UACR] 30–300 mg/g; stage A2), or
- Proteinuria (UACR >300 mg/g; stage A3), or
- Presence of microvascular disease in at least three different sites (e.g. microalbuminuria (stage A2) plus retinopathy plus neuropathy"

Delitti in materia di violazione del diritto d'autore (Art. 25-novies, D.Lgs. n. 231/2001) [articolo aggiunto dalla L. n. 99/2009]

- Messa a disposizione del pubblico, in un sistema di reti telematiche, mediante connessioni di qualsiasi genere, di un'opera dell'ingegno protetta, o di parte di essa (art. 171, legge n.633/1941 comma 1 lett. a) bis)
- Reati di cui al punto precedente commessi su opere altrui non destinate alla pubblicazione qualora ne risulti offeso l'onore o la reputazione (art. 171, legge n.633/1941 comma 3)
- Abusiva duplicazione, per trarne profitto, di programmi per elaboratore; importazione, distribuzione, vendita o detenzione a scopo commerciale o imprenditoriale o concessione in locazione di programmi contenuti in supporti non contrassegnati dalla SIAE; predisposizione di mezzi per rimuovere o eludere i dispositivi di protezione di programmi per elaboratori (art. 171-bis legge n.633/1941 comma 1)
- Riproduzione, trasferimento su altro supporto, distribuzione, comunicazione, presentazione o dimostrazione in pubblico, del contenuto di una banca dati; estrazione o reimpiego della banca dati; distribuzione, vendita o concessione in locazione di banche di dati (art. 171-bis legge n.633/1941 comma 2)
- Abusiva duplicazione, riproduzione, trasmissione o diffusione in pubblico con qualsiasi procedimento, in tutto o in parte, di opere dell'ingegno destinate al circuito televisivo, cinematografico, della vendita o del noleggio di dischi, nastri o supporti analoghi o ogni altro supporto contenente fonogrammi o videogrammi di opere musicali, cinematografiche o audiovisive assimilate o sequenze di immagini in movimento; opere letterarie, drammatiche, scientifiche o didattiche, musicali o drammatico musicali, multimediali, anche se inserite in opere collettive o composite o banche dati; riproduzione, duplicazione, trasmissione o diffusione abusiva, vendita o commercio, cessione a qualsiasi titolo o importazione abusiva di oltre cinquanta copie o esemplari di opere tutelate dal diritto d'autore e da diritti connessi; immissione in un sistema di reti telematiche, mediante connessioni di qualsiasi genere, di un'opera dell'ingegno protetta dal diritto d'autore, o parte di essa (art. 171-ter legge n.633/1941)
- Mancata comunicazione alla SIAE dei dati di identificazione dei supporti non soggetti al contrassegno o falsa dichiarazione (art. 171-septies legge n.633/1941)
- Fraudolenta produzione, vendita, importazione, promozione, installazione, modifica, utilizzo per uso pubblico e privato di apparati o parti di apparati atti alla decodificazione di trasmissioni audiovisive ad accesso condizionato effettuate via etere, via satellite, via cavo, in forma sia analogica sia digitale (art. 171-octies legge n.633/1941).

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