Review of updated guidelines on managing diabetic patients with cardiovascular diseases

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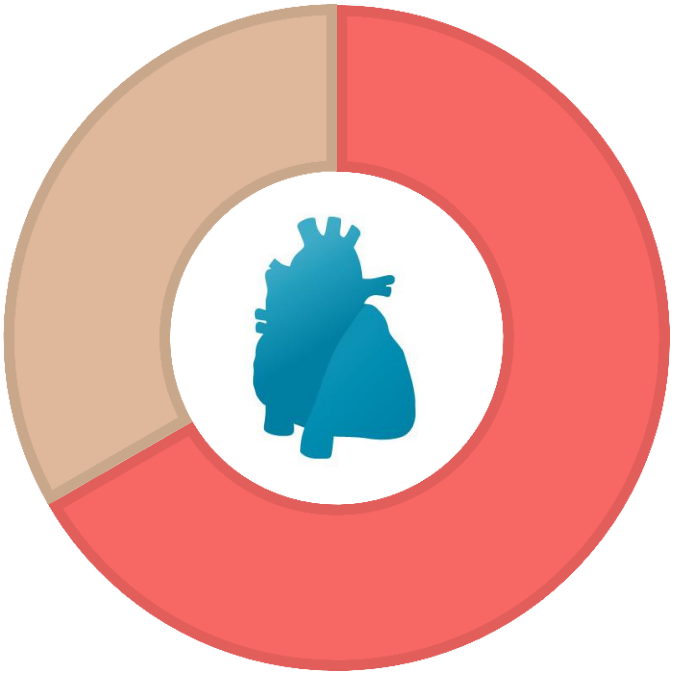
Diabetes and cardiovascular disease



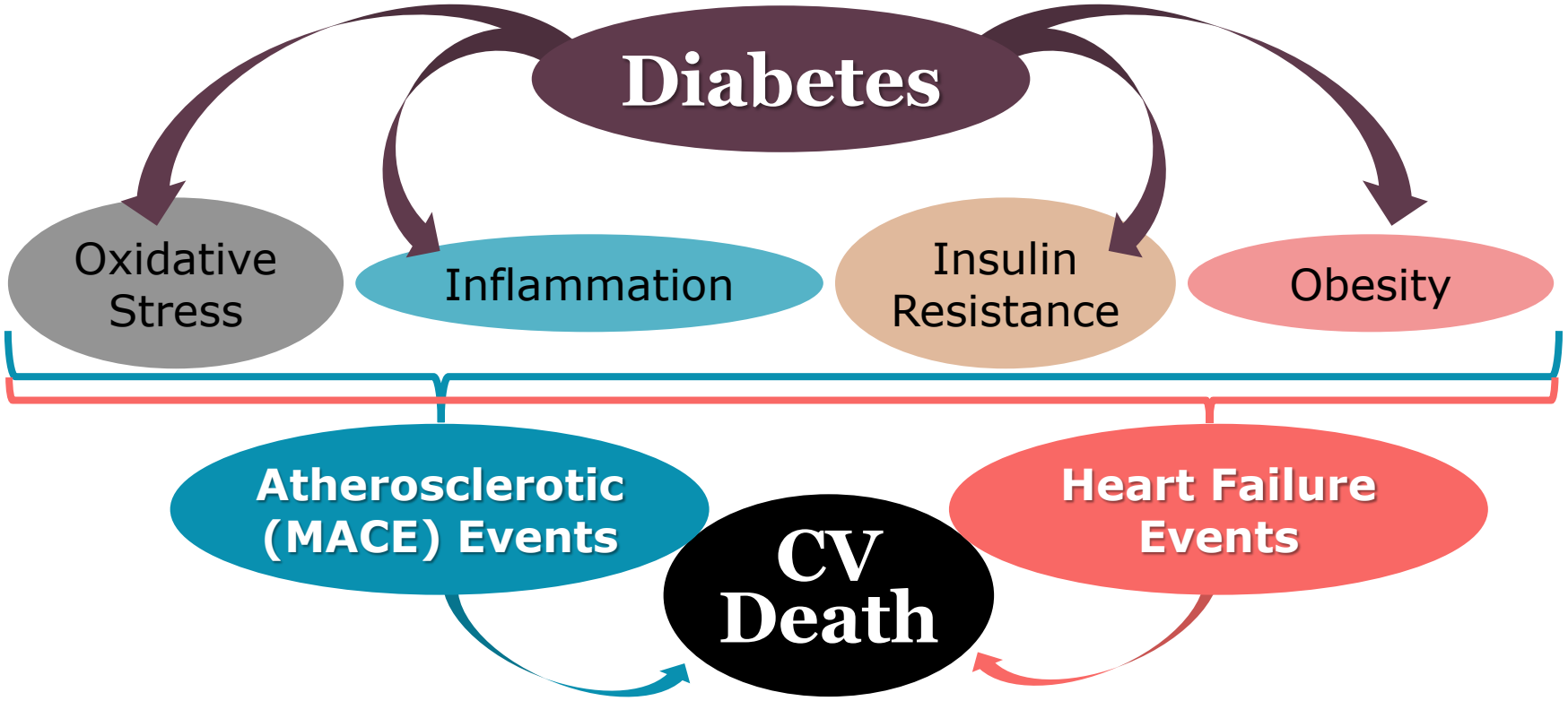
2/3 of deaths

in diabetes are attributable to cardiovascular disease

(coronary artery disease, cerebrovascular disease, peripheral arterial disease, congestive heart failure, sudden death)

Low Wang CC et al. Circulation. 2016;133(24):2459-502.

Pathophysiology of CVD in diabetes

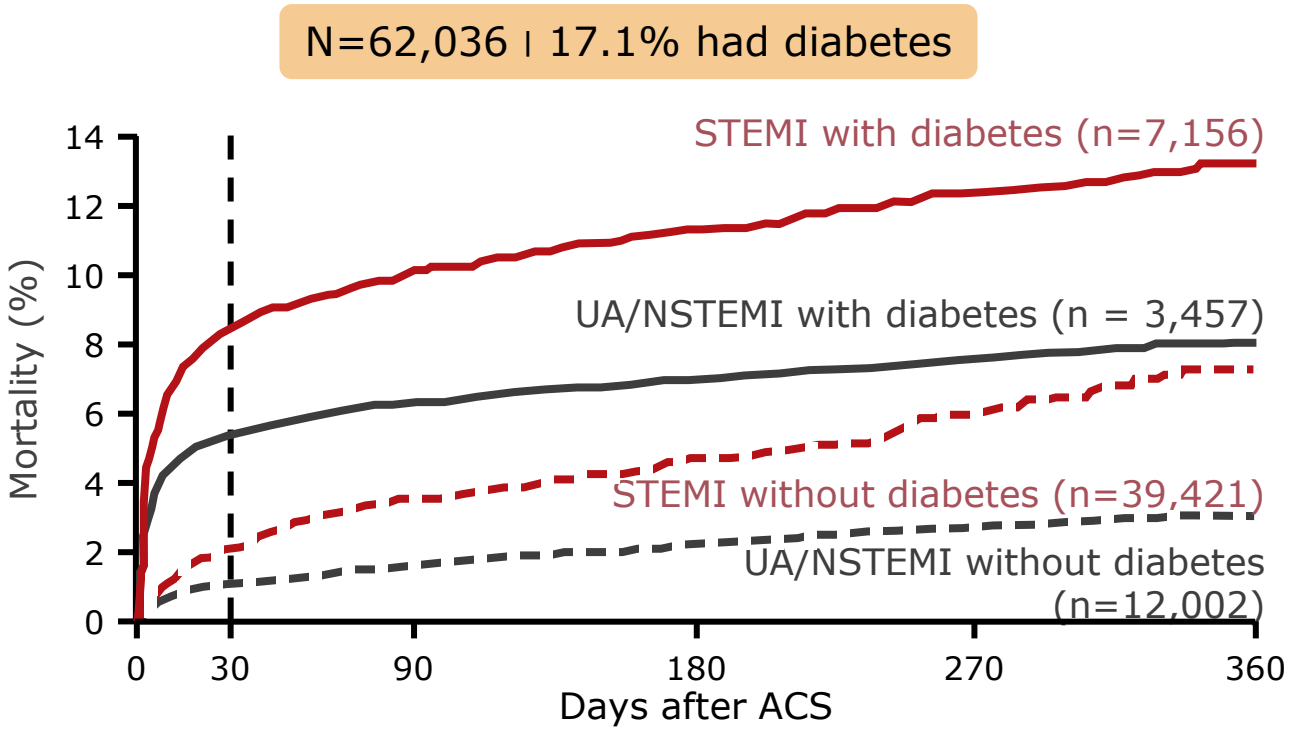


CV, cardiovascular; CVD, cardiovascular disase; MACE, major adverse cardiovascular events.

DM and CVD
Worse combination and outcome

- Diabetes increases the risk of CVD by two- to fourfold
- DM is present in 25–30% of patients admitted with ACS and in up to 40% of patients undergoing CABG.
- Presence of DM in CVD is one of the most powerful predictors of adverse clinical outcome.
- worse prognosis after MI, particularly those requiring treatment with insulin,
- more likely to have
  - LM disease and multivessel CD
  - more diffuse disease involving smaller vessels
  - greater atherosclerotic burden
  - increased number of lipid-rich plaques,
- unstable angina: more fissured plaques and intracoronary thrombi
- Worse outcome and at greater risk of kidney injury undergoing revascularization, either with CABG or PCI

11 TIMI Group Studies: Post-MI mortality is higher in diabetes



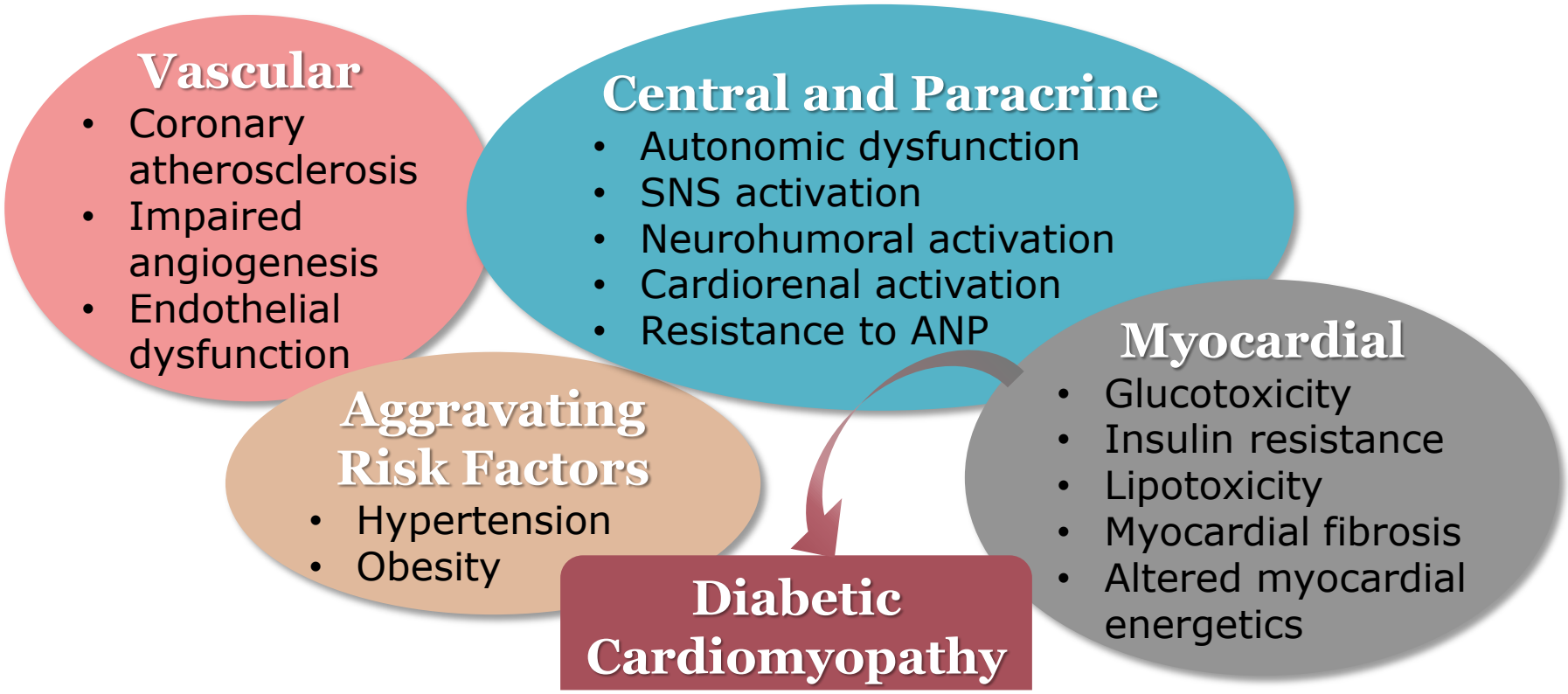
UA/NSTEMI, unstable angina/non-STEMI; MI, myocardial infarction; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.
Donahoe SM et al. JAMA. 2007;298(7):765-75.

Diabetes and Heart Failure

- Although ischemic heart disease remains the most important risk factor for HF, other major risks factors contribute to the development of HF including age, male sex, hypertension, LV hypertrophy, myocardial infarction, valvular heart disease, obesity and **diabetes**.
  - Diabetes as well as insulin resistance are linked to HF development, with diabetes increasing the risk of HF by approximately twofold in men, and up to fivefold in women
- Diabetes and HF:
  - In a survey from 1999 to 2010 among US adults with type 2 diabetes, **11%** of the patients had **prevalent HF**
- As many as 50% of patients with type 2 diabetes may develop heart failure

National Diabetes Statistics Report, 2014
Nature Reviews Cardiology 8, 30-41 January 2011
Wong et all Diab Vasc Dis Res. 2013

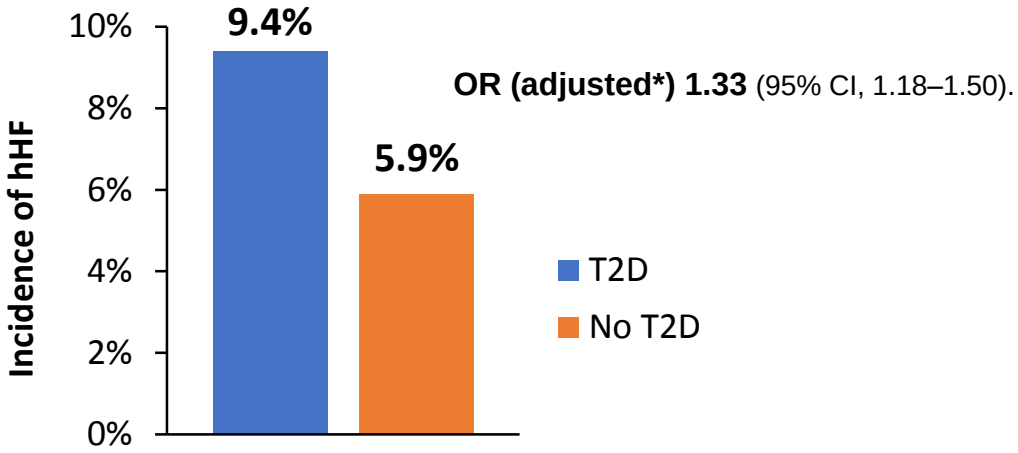
Mechanisms for diabetic heart failure



Abdul-Ghani MA et al. Am J Physiol Renal Physiol. 2015;309(11):F889-900; Heerspink HJ et al. Circulation. 2016;134(10):752-72;
Sattar N et al. Diabetologia. 2016;59(7):1333-1339.

Type 2 diabetes is a potent, independent risk factor for heart failure

Four year follow up of a cohort with and without T2D (n=45,227) and either established CVD or CV risk factors



OR (adjusted*) 1.33 (95% CI, 1.18–1.50).

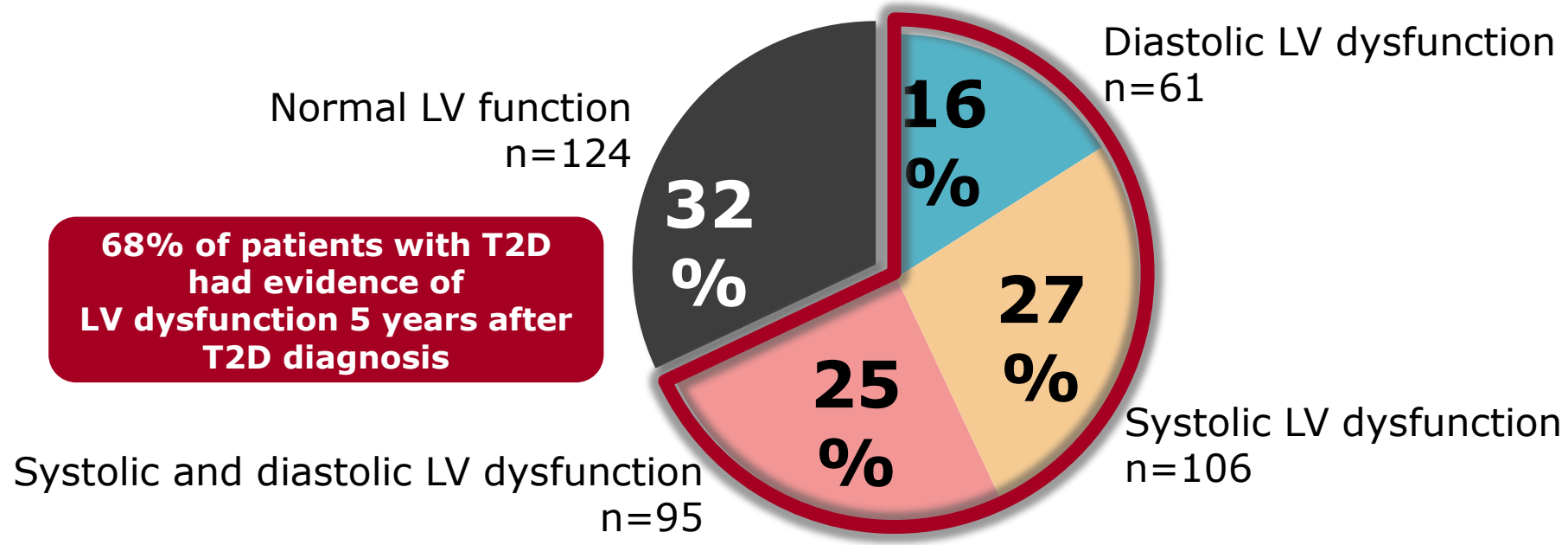
Diabetes mellitus was associated with a 33% greater risk of hospitalization for heart failure

- hHF, hospitalization for heart failure
- Cavender *Circulation*. 2015;132:923-931.

* sex, age, geographic region , cardiovascular risk factors; ischemic event, renal dysfunction, known vascular disease, congestive heart failure, atrial fibrillation, and medications (statins, aspirin, blood pressure treatment, antihyperglycemic agent).

SHORTWAVE: Asymptomatic LV dysfunction is detectable in individuals without overt cardiac disease 5 years after T2D diagnosis

N=386 with T2D and no evidence of inducible ischemia by stress testing at baseline

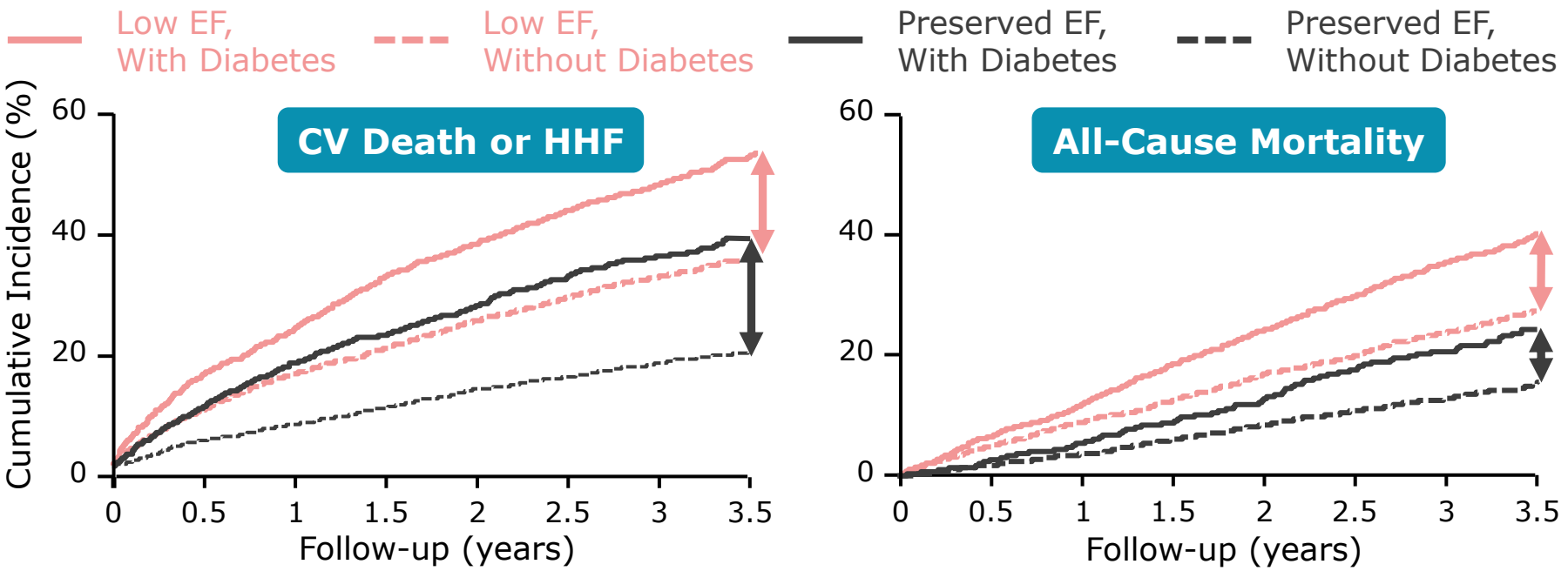


LV, left ventricular; T2D, type 2 diabetes.

Faden G et al. Diabetes Res Clin Pract. 2013;101(3):309-16.

CHARM Programme: DM worsens CV death and HHF in both HFrEF and HFpEF

N=7,599 with symptomatic HF and a broad range of EF



CHARM, Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity; CV, cardiovascular; DM, diabetes; EF, ejection fraction; HF, heart failure; HHF, hospitalization due to heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

DM with CVD
Comprehensive therapeutic strategy

- Therapeutic lifestyle modification
- Comprehensive and aggressive CV risk reduction
- Aggressive management of
  - glycemic status?
  - blood pressure
  - Lipids
- Use of antiplatelet agents
- Use of antihyperglycemic agents with proven CV benefit
- Appropriate coronary revascularization strategy

Review of Guidelines
DM with CVD

- Glycemic Targets
- Use of anti-platelet agent (DAPT duration)
- Lipid management (new LDL target, non-statin therapy)
- Choice of Antihyperglycemic agents in ASCVD
- Antihyperglycemic agents and Heart Failure
- Coronary revascularization (PCI vs CABG)

Case 1

- Executive Health Assessment
- M/45
- Father had MI at age 50
- Smoker
- Hba1c 7.8 (newly diagnosed)
- LDL 4.0. HDL 1. TG 2
- BP 140/90
- BMI 32
- CT coronary calcium score: Ca score 120; calcified plaque at proximal LAD and RCA , <50% stenosis

Case 2

- F/75
- Type 2DM for 25 years. Metformin and gliclazide
- A1c: 8.4, BP 130/60;
- LDL 3.2 (atorvastatin 10mg)
- BMI 28
- NSTEMI, CHF.
- Diffuse 3 vessel disease (Syntax score :22)
- Mild DM nephropathy

Question

- HbA1c Target

Impact of Intensive vs Conventional Glycemic-Lowering Strategies on Risk of CV Outcomes Is Unclear

- **Lowering HbA_{1c} may prevent macrovascular disease if started early, but the effects may not be apparent until for a very long time**

Study	Diabetes Duration (mean)	Antihyperglycemic Medication[a]	Follow-up (median)	HbA_{1c}: Baseline, Between-arm Difference	Microvascular	CVD	Mortality
UKPDS[1]	Newly diagnosed	SU/insulin or metformin[a] vs dietary restriction	10 years	7.1% (all patients), –0.9%	↓	↔	↔
UKPDS Long-term follow-up[2]			10 years post intervention	No difference in HbA_{1c} between treatment arms	↓	↓	↓
ADVANCE[3]	8 years	Intensive glucose control including gliclazide vs standard treatment	5 years	7.5% (both arms), –0.8%	↓	↔	↔
ACCORD[4,5]	10 years	Multiple drugs in both arms	3.4 years	8.1% (both arms), –1.1%	↓	↔	↑
VADT[6]	11.5 years	Multiple drugs in both arms	5.6 years	9.4% (both arms), –1.5%	↔	↔	↔

1. UKPDS Group. *Lancet*. 1998;352:837–853. **2.** Holman RR et al. *N Engl J Med*. 2008;359:1577–1589. **3.** ADVANCE Collaborative Group et al. *N Engl J Med*. 2008;358:2560–2572. **4.** Gerstein HC et al. *N Engl J Med*. 2008;358:2545–2559.. **6.** Duckworth W et al. *N Engl J Med*. 2009;360:129–139.

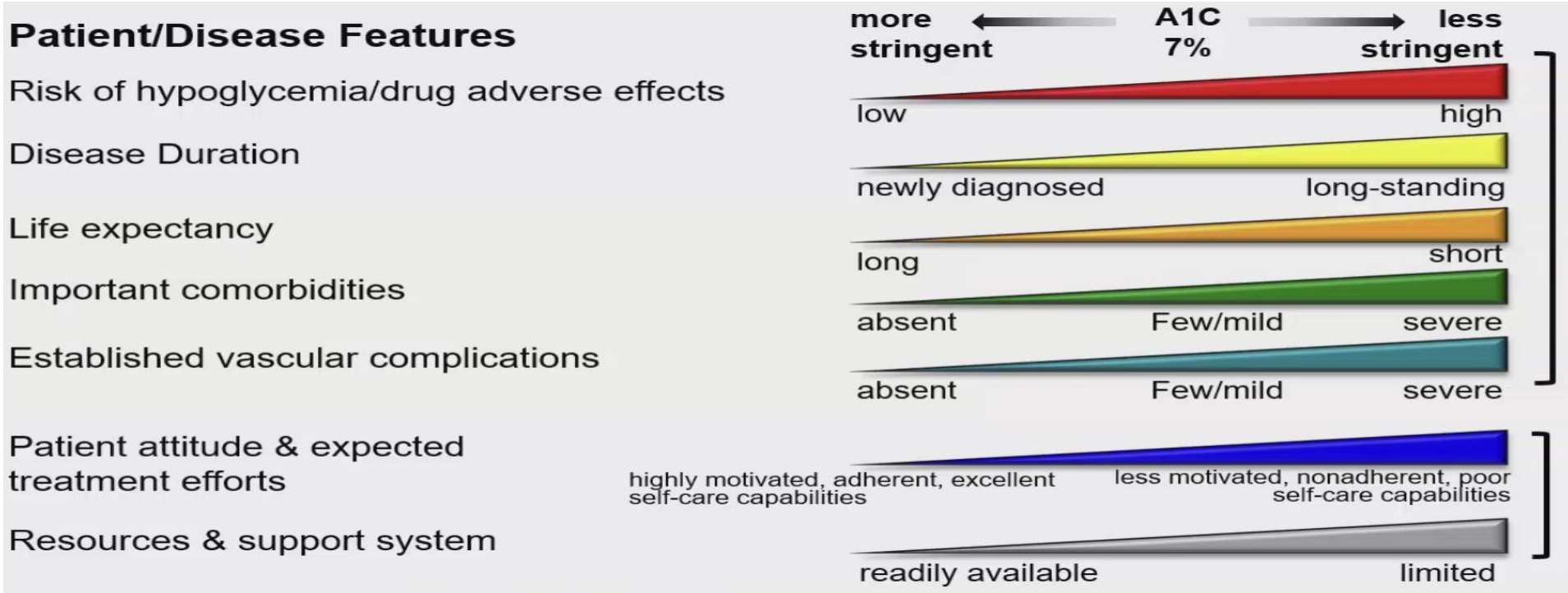
More Intensive Glycemic Control has no Effect on HF Outcomes

Trials	Number of events (annual event rate, %)		ΔHbA1c (%)	Overall HR (95% CI)
	More intensive	Less intensive		
Major cardiovascular events*				
ACCORD	352 (2.11)	371 (2.29)	-1.01	0.90 (0.78, 1.04)
ADVANCE	557 (2.15)	590 (2.28)	-0.72	0.94 (0.84, 1.06)
UKPDS	169 (1.30)	87 (1.60)	-0.66	0.80 (0.62, 1.04)
VADT	116 (2.68)	128 (2.98)	-1.16	0.90 (0.70, 1.16)
Overall	1194	1176	-0.88	0.91 (0.84, 0.99)
Stroke				
Overall	378	370	-0.88	0.96 (0.83, 1.10)
Myocardial infarction				
Overall	730	745	-0.88	0.85 (0.76, 0.94)
Hospitalized/fatal heart failure				
Overall	459	446	-0.88	1.00 (0.86, 1.16)

*Major CV events defined as CV death, non-fatal stroke, or non-fatal myocardial infarction

ADA Standards of Diabetes Care 2019

- A reasonable HbA1c target for adults with diabetes is < 7%
- Target of < 6.5% may be considered if can be done without undue side effects or adverse events
- A less stringent target of 8% may be appropriate for those with hx of advanced microvascular or macrovascular complications or severe hypoglycemia



Questions

- Case 1
- Should I take aspirin ?

- Case 2
- What is the duration of DAPT?

Use of aspirin is controversial in primary prevention

- aspirin is not recommended in European guidelines for primary ASCVD prevention
- recommended in prior U.S. guidelines for selected primary prevention for adults who have elevated risk of ASCVD based on traditional risk factors
- recently conducted primary-prevention trials that, in contrast to older trials have shown less overall benefit of prophylactic aspirin alongside coadministration of contemporary ASCVD preventive treatments, such as evidence-based hypertension and cholesterol therapies

2010, position statement of the ADA, the American Heart Association, and the American College of Cardiology Foundation

- In patients with T2DM
- Aspirin for primary prevention is reasonable for aged ≥50 years with diabetes and at least one additional major risk factor
  - family history of premature ASCVD
  - hypertension
  - dyslipidemia,
  - smoking
  - chronic kidney disease/albuminuria
  - no increased risk of bleeding (e.g., older age, anemia, renal disease)

AHA/ADA Scientific Statement

Update on Prevention of Cardiovascular Disease in Adults With Type 2 Diabetes Mellitus in Light of Recent Evidence

A Scientific Statement From the American Heart Association and the American Diabetes Association

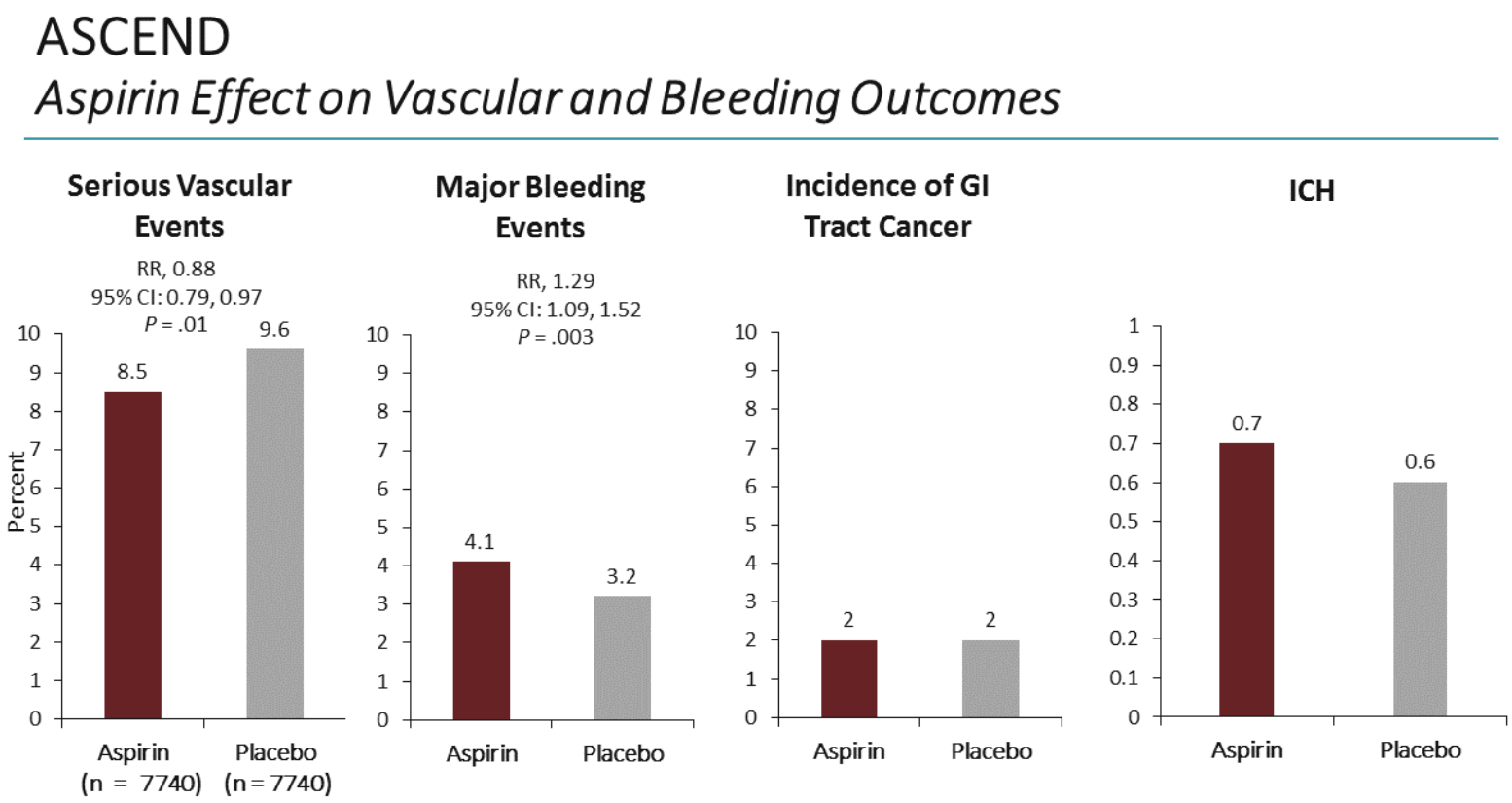
- Whether to use aspirin for the primary prevention of CVD events in patients with diabetes mellitus remains controversial
- Specific recommendations based on current clinical guidelines for aspirin administration in adults with diabetes mellitus and no pre-existing CVD are summarized

Recommendations

1. **Low-dose aspirin (75–162 mg/d) is reasonable among those with a 10-year CVD risk of at least 10% and without an increased risk of bleeding (*ACC/AHA Class IIa; Level of Evidence B*) (*ADA Level of Evidence C*).**
2. **Low-dose aspirin is reasonable in adults with diabetes mellitus at intermediate risk (10-year CVD risk, 5%–10%) (*ACC/AHA Class IIb; Level of Evidence C*) (*ADA Level of Evidence E*).**

Fox et al. *Circulation*. 2015;132:691-718.

ASCEND
Aspirin Effect on Vascular and Bleeding Outcome



ASCEND Study Collaborative Group. *N Engl J Med*. 2018;379:1529-1539.

ANTIPLATELET AGENTS Recommendations

- Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of atherosclerotic cardiovascular disease. **A**

- For patients with atherosclerotic cardiovascular disease and documented aspirin allergy, clopidogrel (75 mg/day) should be used. **B**

- Aspirin therapy (75–162 mg/day) may be considered as a primary prevention strategy in those with diabetes who are at increased cardiovascular risk, **after a discussion with the patient on the benefits versus increased risk of bleeding**. **C**

Cardiovascular Disease and Risk Management:
ADA *Standards of Medical Care in Diabetes—2019*

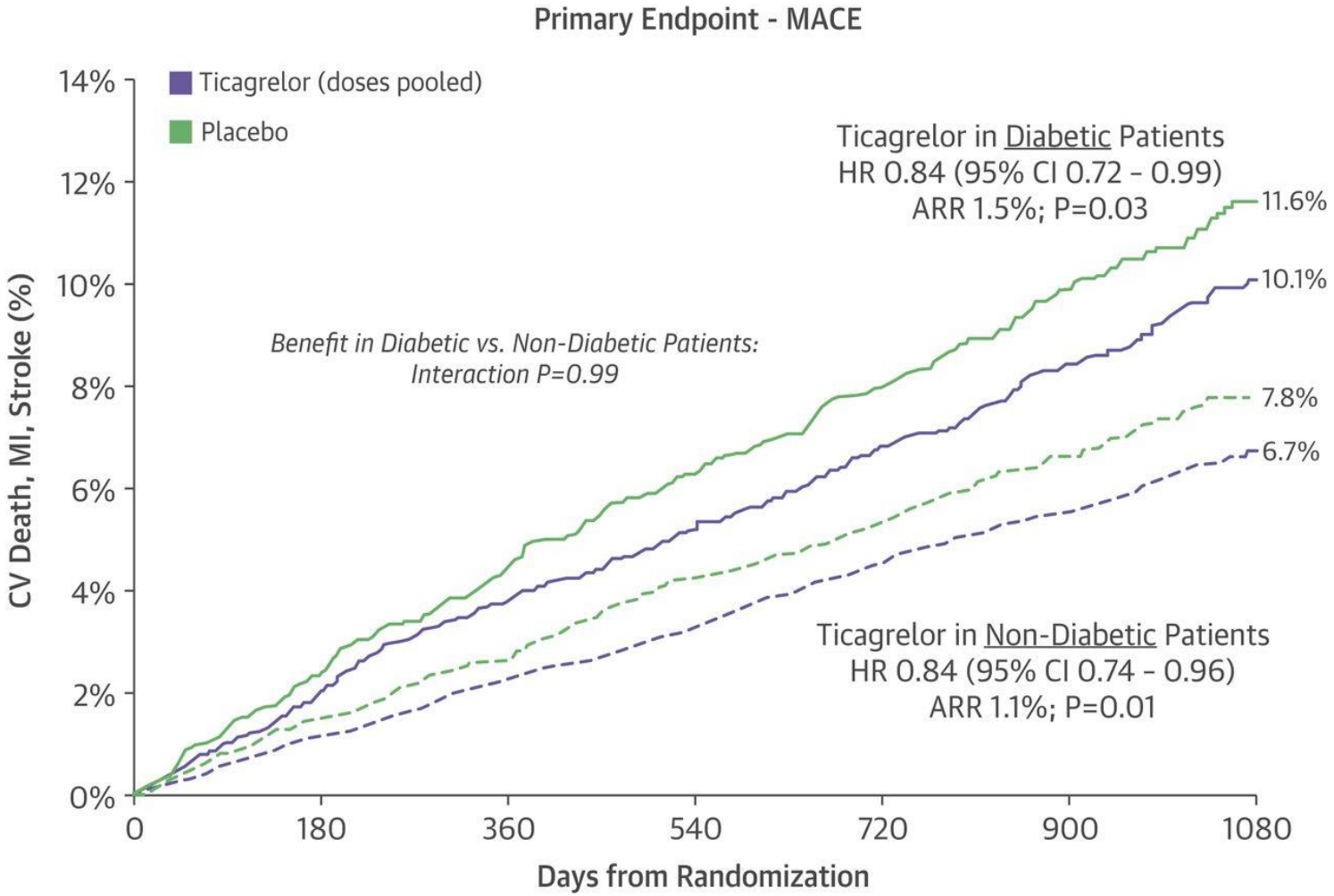
Cardiovascular Disease and Risk Management: ADA *Standards of Medical Care in Diabetes—2019*

- Noninvasive imaging techniques such as coronary computed tomography angiography may potentially help further tailor aspirin therapy, particularly in those at low risk , but are not generally recommended

Anti-platelet agent
DM and post MI

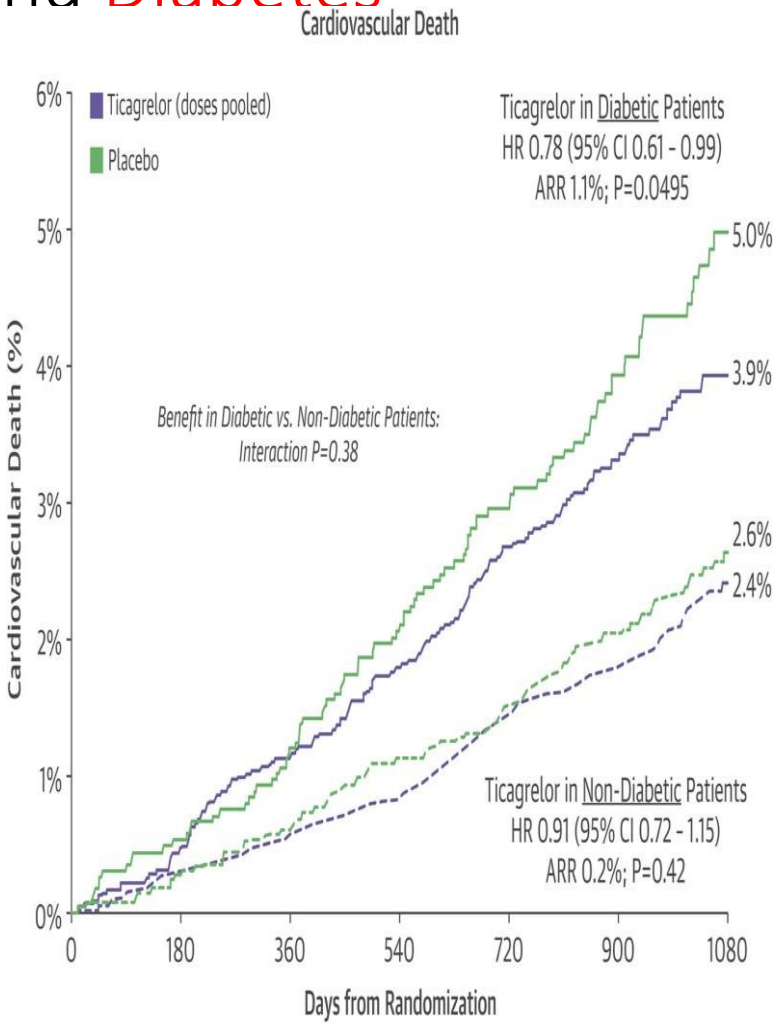
- Duration of DAPT

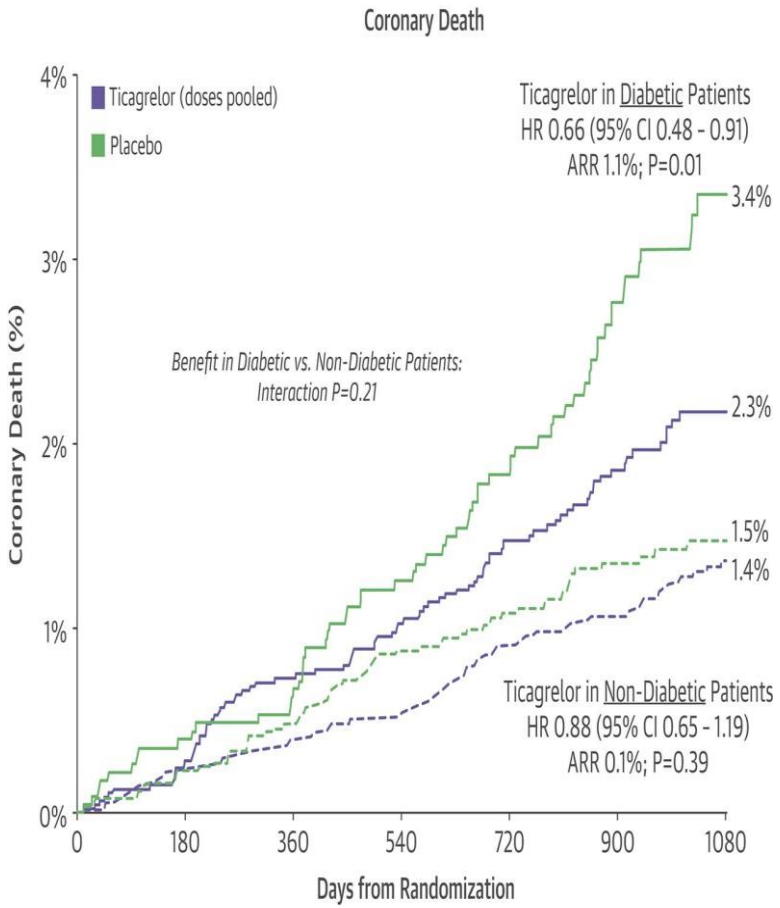
PEGASUS-TIMI 54: Efficacy in Patients with Prior MI



PEGASUS-TIMI 54. J Am Coll Cardiol 2016;**67**:2732–2740

PEGASUS-TIMI 54: Efficacy in Patients with Prior MI and Diabetes





PEGASUS-TIMI 54. J Am Coll Cardiol 2016;**67**:2732–2740

Anti-platelet agent
ASCVD and post MI

- Dual antiplatelet therapy (with low-dose aspirin and a P2Y12 inhibitor) is reasonable for a year after an acute coronary syndrome **A** and may have benefits beyond this period. **B**

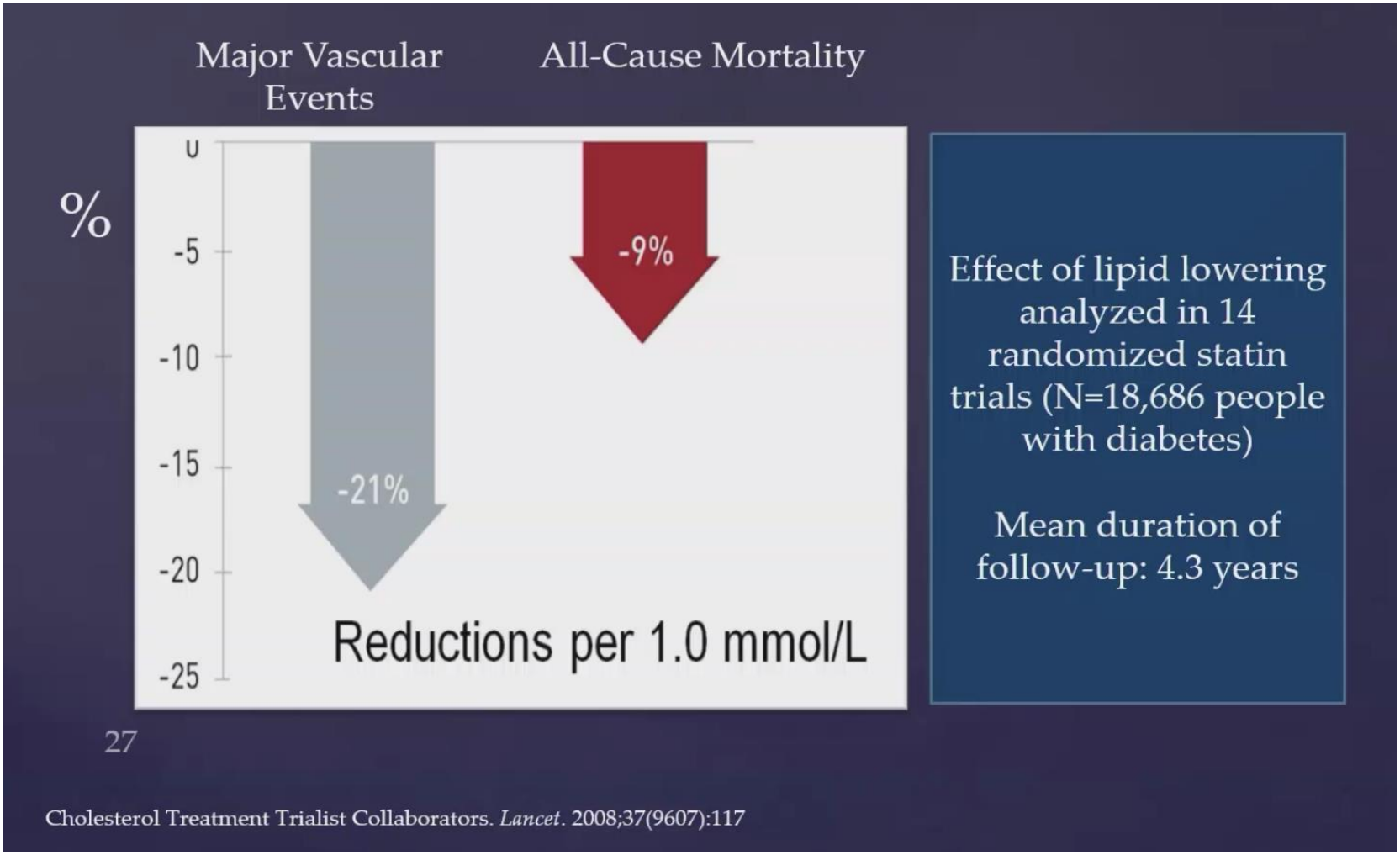
- In patients with diabetes and prior MI (1–3 years before), adding ticagrelor to aspirin significantly reduces the risk of recurrent ischemic events including cardiovascular and CHD death

Cardiovascular Disease and Risk Management:
ADA Standards of Medical Care in Diabetes—2019

Questions

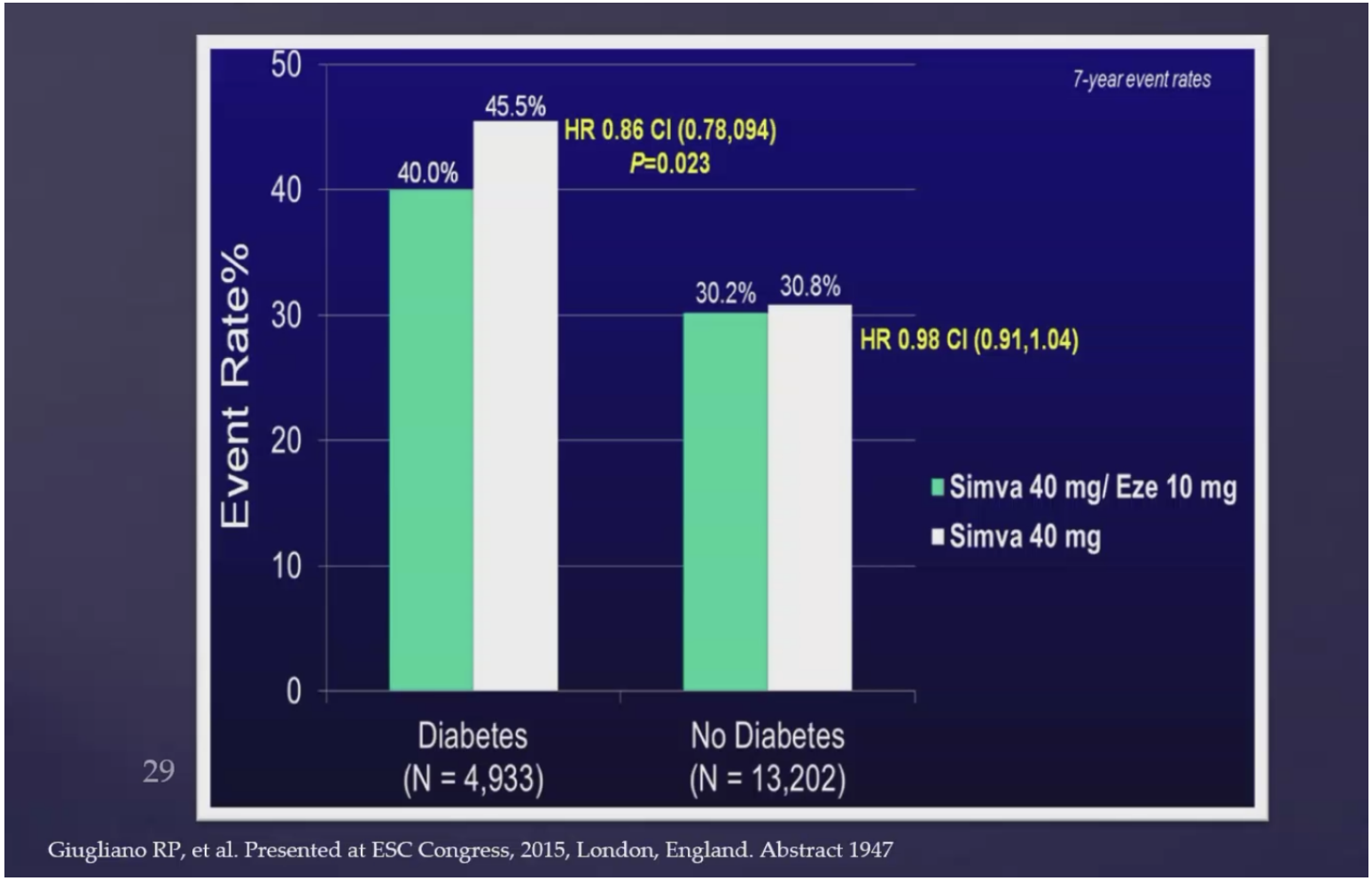
- Lipid management
- Target LDL ?
- Statin
- Role of Non-statin agent

Statins in Type 2 Diabetes



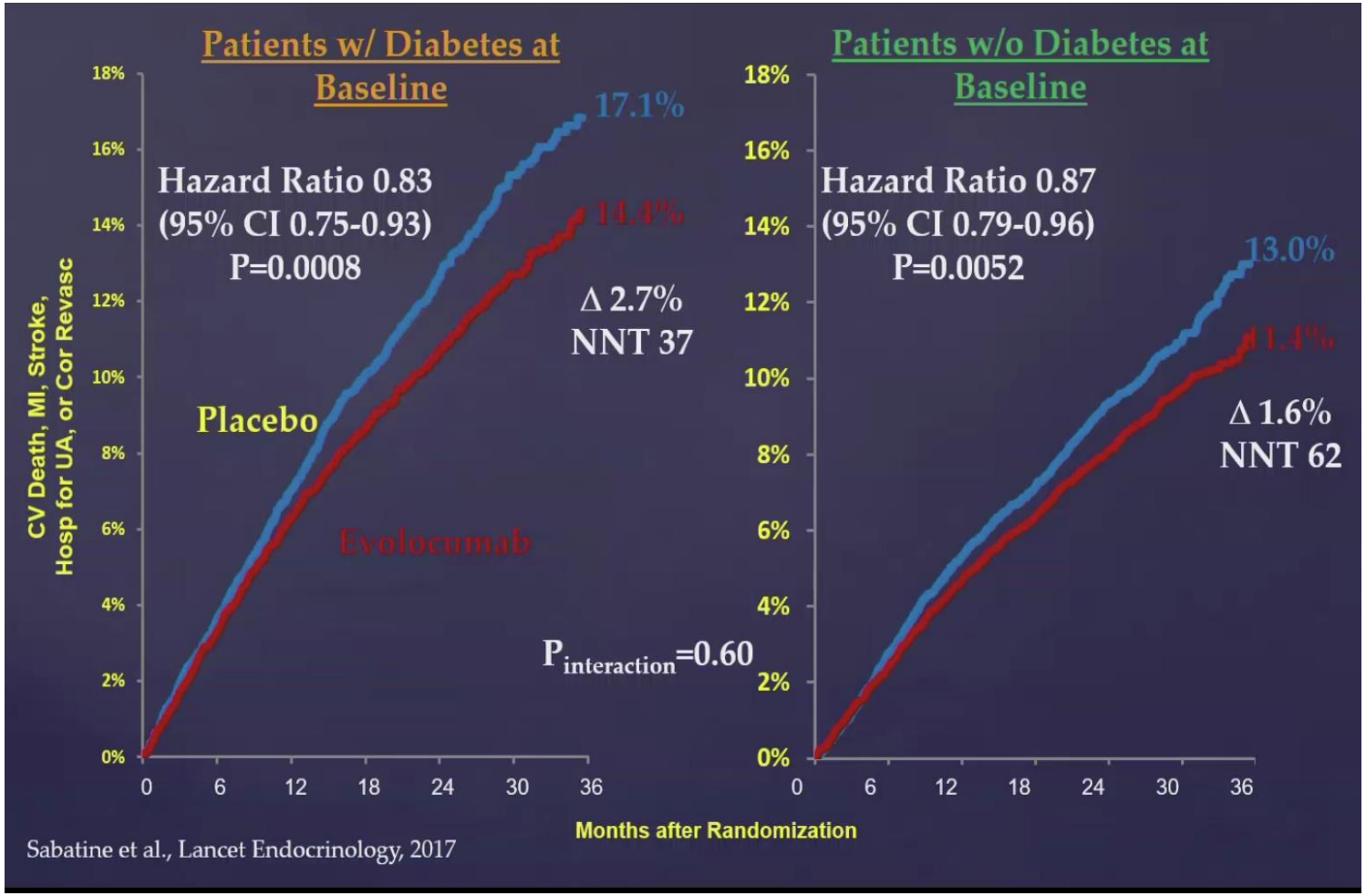
Cholesterol Treatment Trialist Collaborators. *Lancet*. 2008;37(9607):117

IMPROVE-IT Diabetes Subgroup Analyses



Giugliano RP, et al. Presented at ESC Congress, 2015, London, England. Abstract 1947

PCSK 9 Inhibitor (Fourier study)
Effect of Evolocumab on Primary Endpoint



Statin Treatment Recommendations

- For patients of all ages with diabetes and atherosclerotic cardiovascular disease or 10-year atherosclerotic cardiovascular disease risk >20%, high-intensity statin therapy should be added to lifestyle therapy. **A**
- For patients with diabetes aged <40 years with additional atherosclerotic cardiovascular disease risk factors, the patient and provider should consider using moderate-intensity statin in addition to lifestyle therapy. **C**
- For patients with diabetes aged 40–75 years **A** and >75 years **B** without atherosclerotic cardiovascular disease, use moderate-intensity statin in addition to lifestyle therapy.
- In patients with diabetes who have multiple atherosclerotic cardiovascular disease risk factors, it is reasonable to consider high-intensity statin therapy. **C**
- For patients who do not tolerate the intended intensity, the maximally tolerated statin dose should be used. **E**
- **For patients with diabetes and atherosclerotic cardiovascular disease, if LDL cholesterol is ≥70 mg/dL (1.8 mmol/l) on maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor). A Ezetimibe may be preferred due to lower cost.**

Cardiovascular Disease and Risk Management:
Standards of Medical Care in Diabetes—2019

AACE Lipid Targets for Patients with Type 2 Diabetes 2017

Risk Category	Risk Factors[a] / 10-Year Risk[b]	Treatment Goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme Risk	– Progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dL – Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH – History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very High Risk	– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease – Diabetes or CKD 3/4 with 1 or more risk factor(s) – HeFH	<70	<100	<80
High Risk	≥2 risk factors and 10-year risk >10% or CHD risk equivalents[c], including diabetes or CKD 3, 4 with no other risk factors	<100	<130	<90

[a] Major independent risk factors are high LDL-C, polycystic ovary syndrome, cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or on hypertensive medication), low HDL-C (<40 mg/dL), family history of coronary artery disease (in male, first-degree relative younger than 55 years; in female, first-degree relative younger than 65 years), chronic renal disease (CKD) stage 3/4 , evidence of coronary artery calcification and age (men≥45; women≥55 years years). Subtract 1 risk factor if the person has high HDL-C.

[b] Framingham risk scoring is applied to determine 10-year risk.

Abbreviations: ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; MESA = Multi-Ethnic Study of Atherosclerosis; NR = not recommended; UKPDS = United Kingdom Prospective Diabetes Study.

Jellinger, P. S., Handelsman, Y., Rosenblit, P. D., Bloomgarden, Z. T., Fonseca, V. A., Garber, A. J., ... & Pessah-Pollack, R. (2017). AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE. *Endocrine Practice*, *23*(s2), 1-87.

Question

- Choice of anti-hyperglycemic regimen

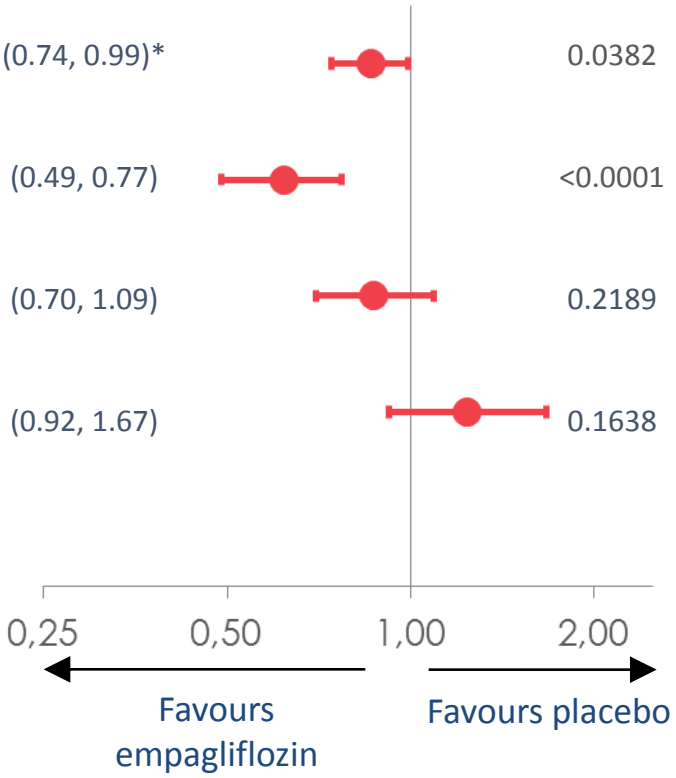
Established CVD Treatment Recommendations

- In patients with known atherosclerotic cardiovascular disease, consider ACE inhibitor or angiotensin receptor blocker therapy to reduce the risk of cardiovascular events. **B**
- In patients with prior myocardial infarction, β-blockers should be continued for at least 2 years after the event. **B**
- In patients with type 2 diabetes with stable congestive heart failure, metformin may be used if estimated glomerular filtration rate remains >30 mL/min but should be avoided in unstable or hospitalized patients with congestive heart failure. **B**
- Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease, **sodium–glucose cotransporter 2 inhibitors or glucagon-like peptide 1 receptor agonists with demonstrated cardiovascular disease benefit** are recommended as part of the antihyperglycemic regimen. **A**
- Among patients with atherosclerotic cardiovascular disease at high risk of heart failure or in whom heart failure coexists, **sodium–glucose cotransporter 2 inhibitors** are preferred. **C**

Cardiovascular Disease and Risk Management: ADA *Standards of Medical Care in Diabetes—2019*

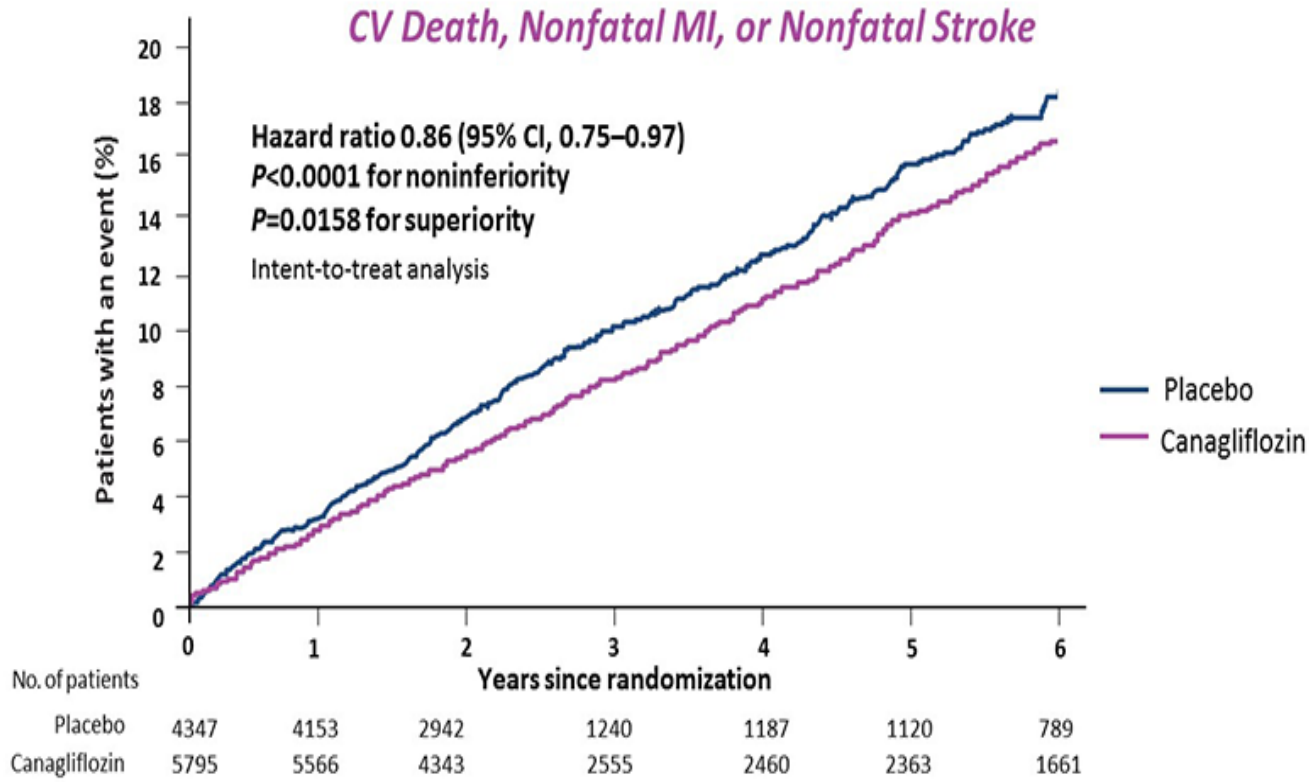
EMPA-REG: CV death, MI and stroke with empagliflozin vs. placebo

	Patients with event/analysed Empagliflozin	Placebo	HR	(95% CI)	*p*-value
3-point MACE	490/4687	282/2333	0.86	(0.74, 0.99)*	0.0382
CV death	172/4687	137/2333	0.62	(0.49, 0.77)	<0.0001
Non-fatal MI	213/4687	121/2333	0.87	(0.70, 1.09)	0.2189
Non-fatal stroke	150/4687	60/2333	1.24	(0.92, 1.67)	0.1638



- Zinman B, et al. *New Engl J Med* 2015; Sep 17

CANVAS
Primary MACE Outocme



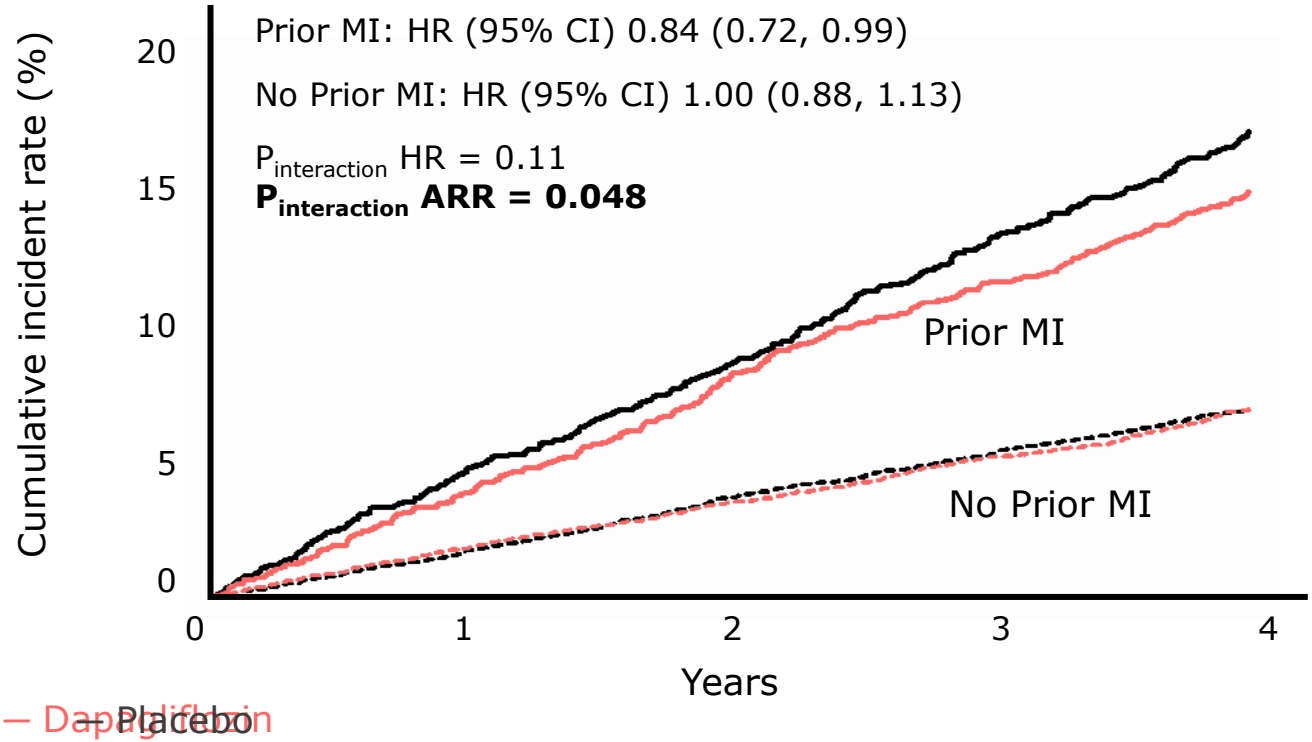
Neal B, et al. *N Engl J Med*. 2017.

DECLARE-TIMI 58

Dapagliflozin reduced the risk of MACE in patients with prior MI

59%	41%
1º Prevention (MRF)	2º Prevention (ECVD)

MACE



ARR, absolute risk reduction; CV, cardiovascular; MACE, major adverse cardiovascular events; MI, myocardial infarction; MRF, multiple risk factors.

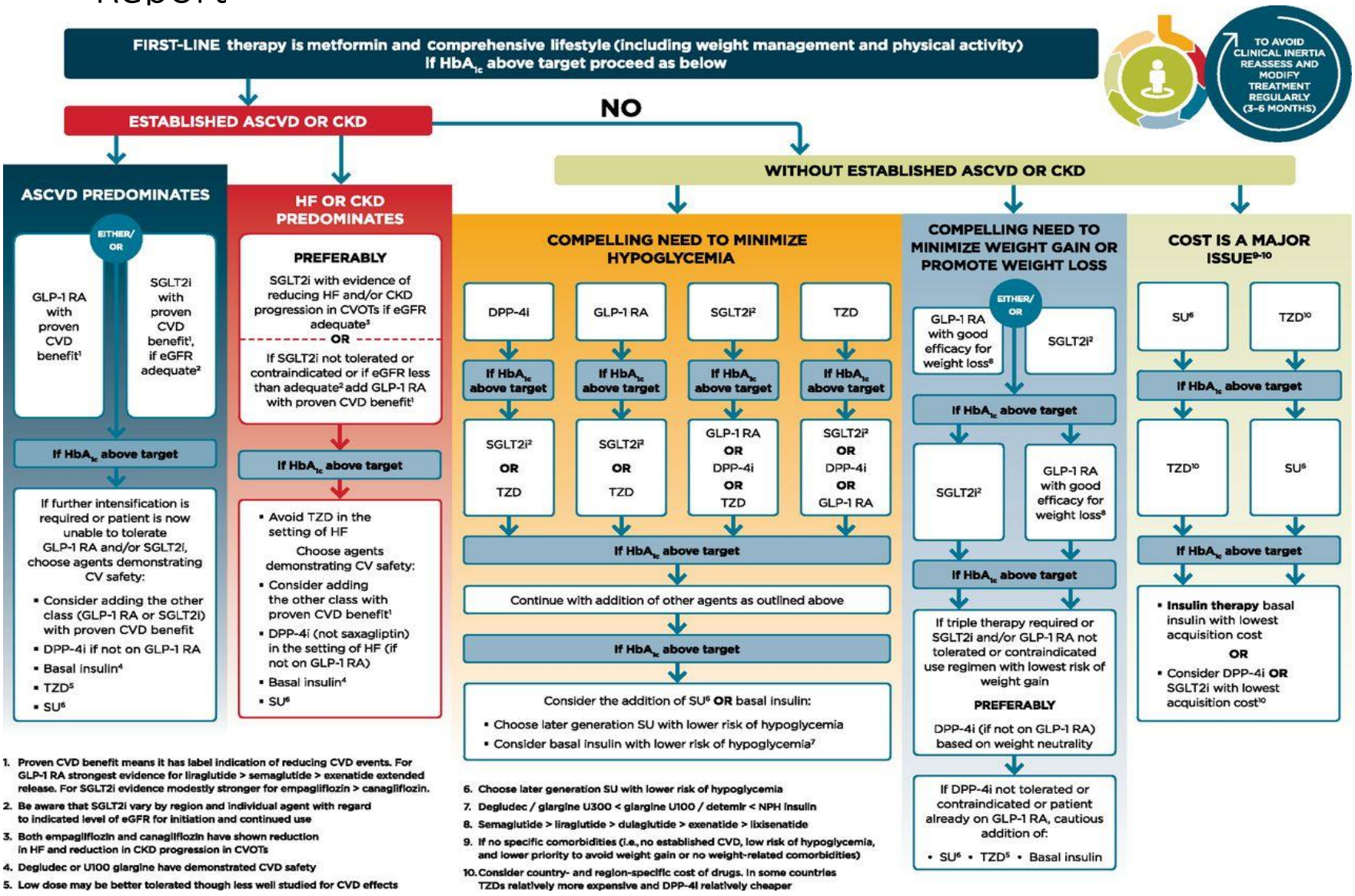
Adapted from Furtado RHM et al. Circulation. 2019 Mar 18. doi: 10.1161/CIRCULATIONAHA.119.039996.

GLP1 RA Cardiovascular Outcome Study

(2 GLP1 CVOT shown positive)

CV outcome study	GLP1 RA	Patient size	Patient Type	Major Result	Status
ELIXA	Lixisenatide	6,068	T2DM, ACS within 180 days	Show non-inferior to placebo arm for primary composite end point of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina	Completed & Published in 2015
LEADER	Liraglutide	9,340	T2DM with established CVD or CHF	Show superiority to placebo in reducing first occurrence of primary composite endpoint :death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Reduce CV mortality and all cause mortality	Completed & Published in 2016
SUSTAIN-6** (Semaglutide not available in market)	Semaglutide	3,297	T2DM with established CVD or CHF or CKD	Show superiority to placebo in reducing first occurrence of primary composite endpoint :death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.	Completed & Published in 2016
EXSCEL	Exenatide QW	~14,000	T2DM, with or without additional cardiovascular risk factors or prior cardiovascular events	noninferior to placebo for the primary outcome (MACE),	Completed & Published in 2017

2018 American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) Consensus Report



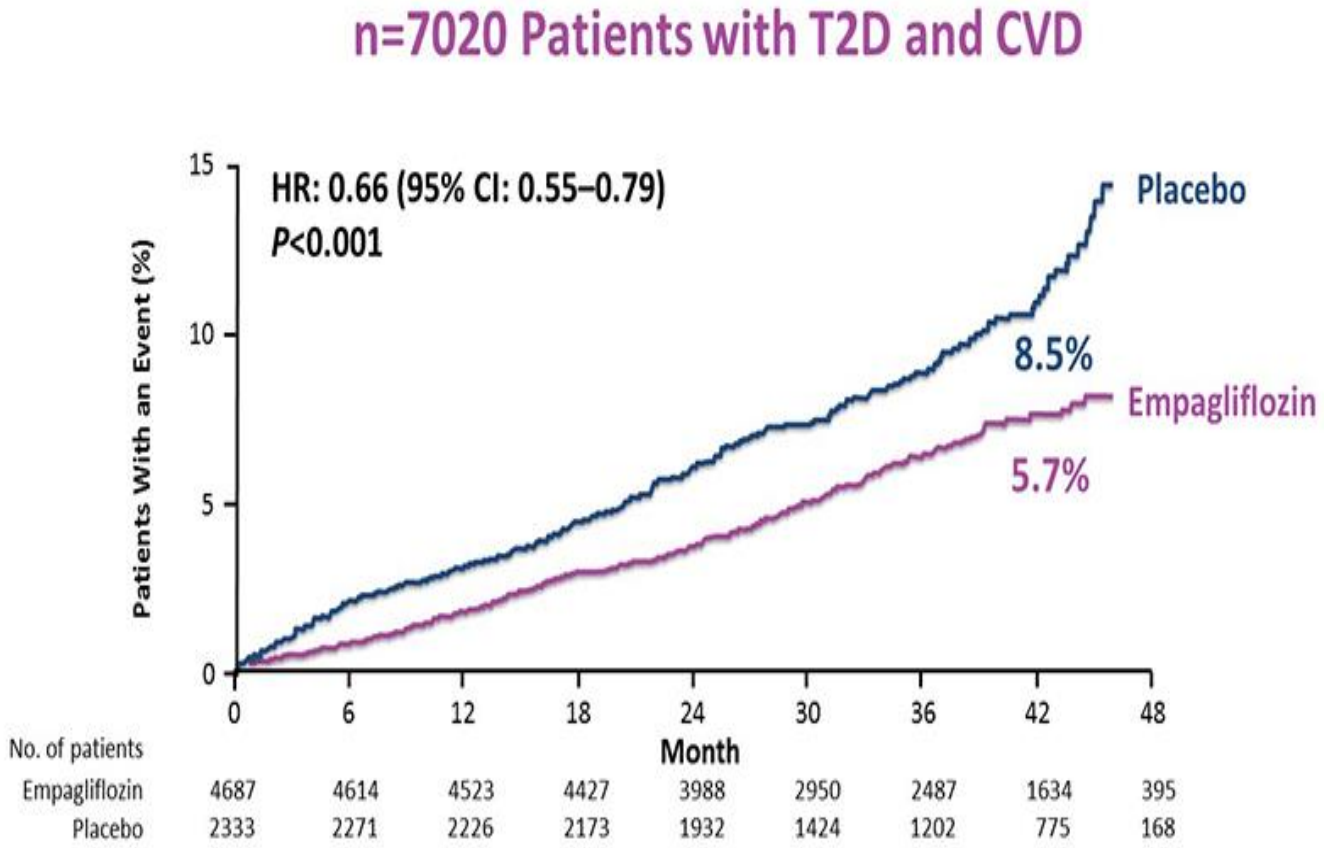
1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. 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)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

Proven CVD benefit

- Proven CVD benefit means it has label indication for reducing CV events.
- Strongest evidence for liraglutide > semaglutide> exenatide extended release
- Evidence modest stronger for empagliflozin >canagliflozin

2018 American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) Consensus Report

EMPA-REG Outcome
CV Death/ HHF

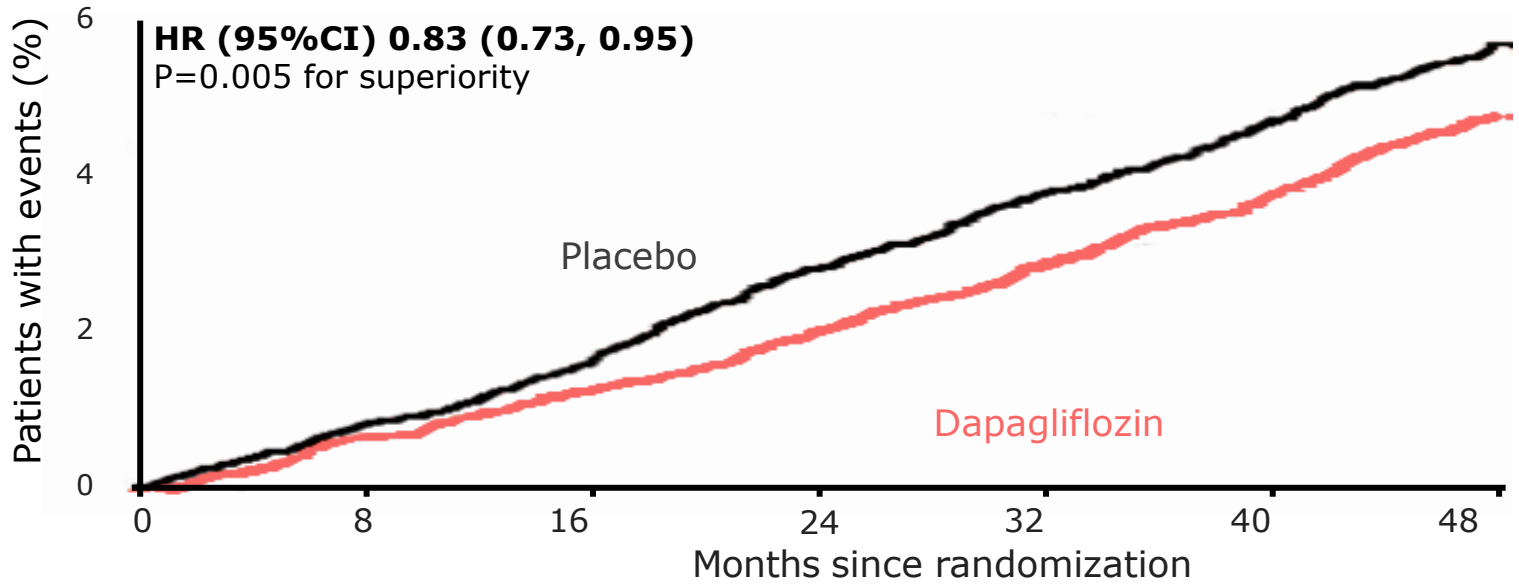


Fitchett D, et al. *Eur Heart J.* 2016.

DECLARE-TIMI 58

Dapagliflozin significantly lowered CV death/hospitalization for heart failure

59%	41%
1º Prevention (MRF)	2º Prevention (ECVD)



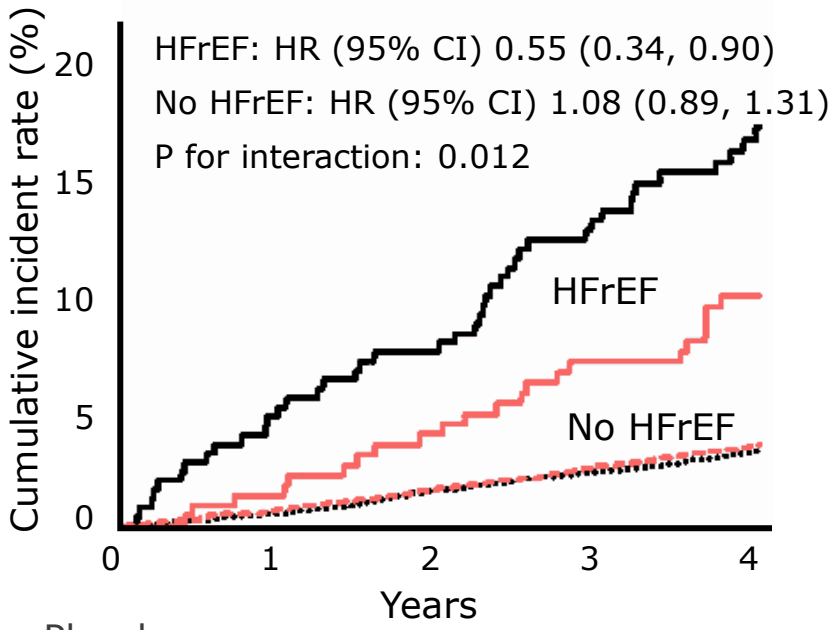
Wiviott SD et al. N Engl J Med. 2018. DOI: 10.1056/NEJMoa1812389.

DECLARE-TIMI 58

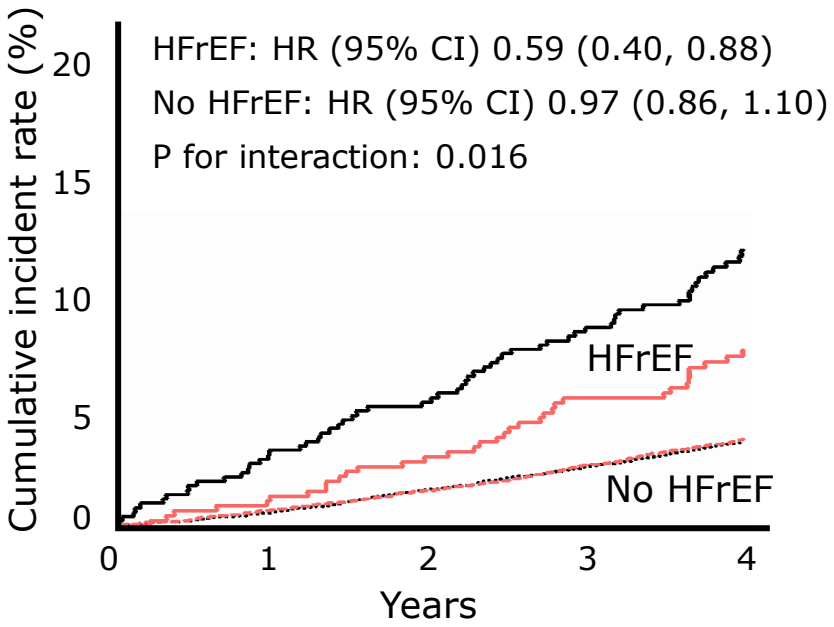
59% 1° Prevention (MRF) | 41% 2° Prevention (ECVD)

Dapagliflozin reduced CV death and all-cause mortality in people with HFrEF

CV Death



All-cause Mortality



— Placebo
— Dapagliflozin

HFrEF, heart failure with reduced ejection fraction.
Adapted from Kato ET et al. Circulation. 2019 Mar 18. doi: 10.1161/CIRCULATIONAHA.119.040130.

Antihyperglycemic Therapies and Heart Failure

- Data on the effects of glucose-lowering agents on heart failure outcomes have demonstrated that thiazolidinediones have a strong and consistent relationship with increased risk of heart failure TZD use should be avoided in patients with symptomatic heart failure

Cardiovascular Disease and Risk Management: ADA *Standards of Medical Care in Diabetes—2019*

EXAMINE and SAVOR-TIMI: Hospitalization for Heart Failure (HHF)

SAVOR-TIMI[3]

	Saxagliptin n=8,280	Placebo n=8,212	HR (95% CI)
HHF	3.5%	2.8%	**1.27** (1.07–1.51)

SAVOR-TIMI: Hospitalization for HF was significantly increased with saxagliptin compared with placebo[3]

– Mortality due to HF was not significantly different between saxagliptin and placebo (0.5% for both)[3]

EXAMINE[1,2]

	Alogliptin n=2,701	Placebo n=2,679	HR (95% CI)
HHF[a]	3.9%	3.3%	**1.19** (0.89–1.58)

EXAMINE: In a post-hoc analysis, No increased risk of the composite endpoint of cardiovascular death and hospital admission for heart failure for alogliptin versus placebo

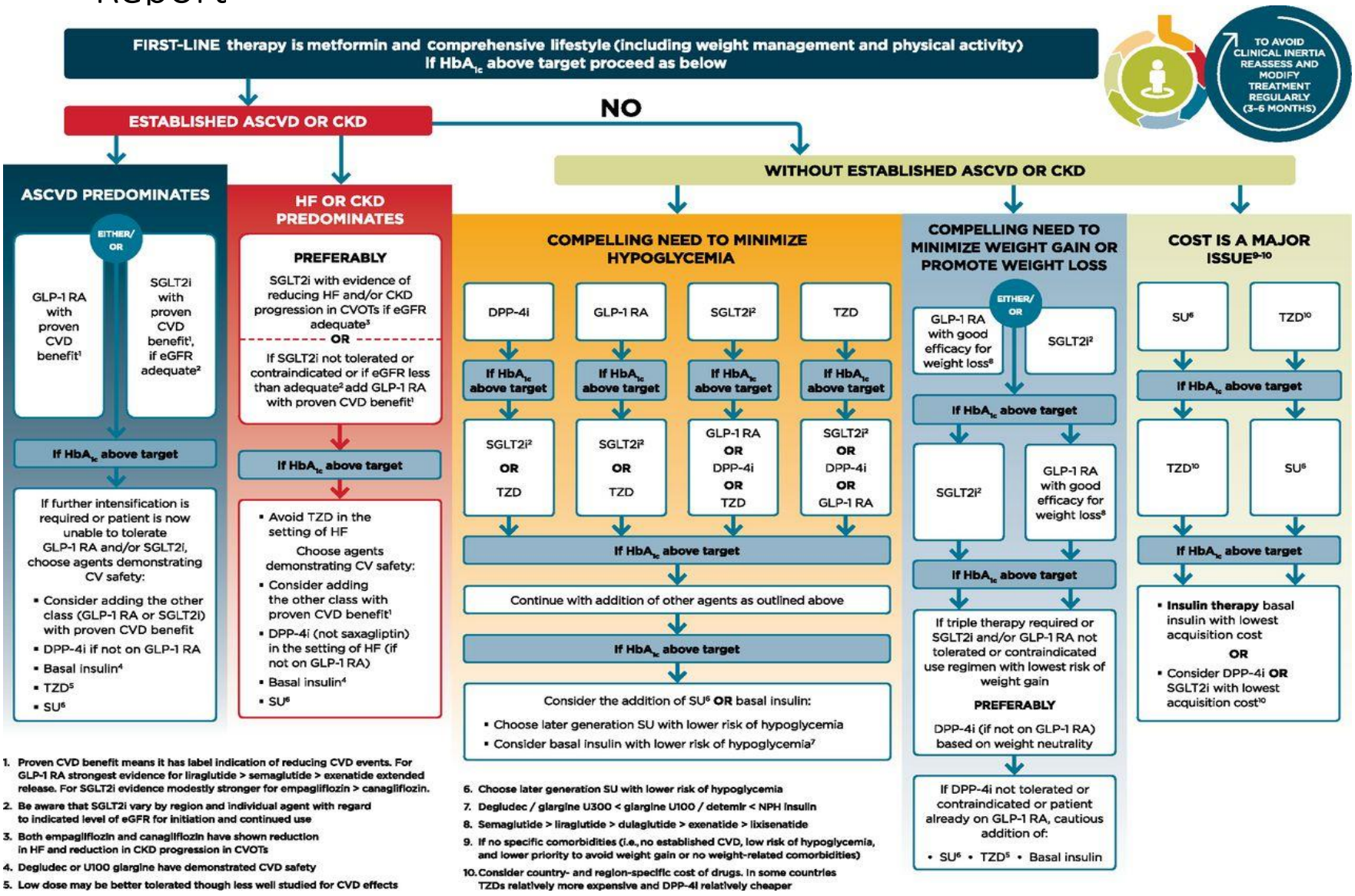
[a]Post-hoc analysis.

1. Reproduced with permission from White WB et al. *N Engl J Med* 2013;369:1327–1335. **2.** Sanon VP et al. *Clin Diabetes.* 2014;32:121–126. **3.** Reproduced with permission from Scirica BM et al. *N Engl J Med* 2013;369:1317–1326.

Antihyperglycemic Therapies and Heart Failure

- In four cardiovascular outcome trials of GLP-1 receptor agonists, no evidence for an increased risk of heart failure was found and the agents had a neutral effect on hospitalization for heart failure

2018 American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) Consensus Report



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. 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)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

Question

- Choice of revascularization strategy

Revascularization for coronary artery disease in diabetes mellitus

- Diabetes mellitus is present in 25–30% of patients admitted with ACS and in up to 40% of patients undergoing CABG.
- more likely to have LM disease and multivessel CD,
- with more diffuse disease involving smaller vessels
- greater atherosclerotic burden
- increased number of lipid-rich plaques,
- unstable angina have more fissured plaques and intracoronary thrombi
- Higher outcome post PCI /CABG
- undergoing revascularization, either with CABG or PCI, are at greater risk of kidney injury

Freedom

Compared PCI Vs CABG in1900 patients with diabetes with multivessel disease but without LM stenosis

Outcome	2 Years after Randomization		5 Years after Randomization		Patients with Event		P Value*
	PCI	CABG	PCI	CABG	PCI	CABG	
	number (percent)				*number*		
Primary composite†	121 (13.0)	108 (11.9)	200 (26.6)	146 (18.7)	205	147	0.005‡
Death from any cause	62 (6.7)	57 (6.3)	114 (16.3)	83 (10.9)	118	86	0.049
Myocardial infarction	62 (6.7)	42 (4.7)	98 (13.9)	48 (6.0)	99	48	<0.001
Stroke	14 (1.5)	24 (2.7)	20 (2.4)	37 (5.2)	22	37	0.03§
Cardiovascular death	9 (0.9)	12 (1.3)	73 (10.9)	52 (6.8)	75	55	0.12

* P values were calculated with the use of the log-rank test on the basis of all available follow-up data (i.e., more than 5 years).
† The primary composite outcome was the rate of death from any cause, myocardial infarction, or stroke.
‡ P=0.006 in the as-treated (non–intention-to-treat) analysis.
§ P=0.16 by the Wald test of the Cox regression estimate for study-group assignment in 1712 patients after adjustment for the average glucose level after the procedure.

N Engl J Med. 2012;367:2375–2384

Conclusion

- Outcomes for patients with CVD and DM are less favorable post both PCI and CABG
- CABG results in significantly better outcomes compare with PCI with multivessel in DM patients CAD, although stroke was slightly increased.
- Improvement in stent technology have not eliminated advantage of CABG

Mortality after CABG versus PCI with stenting for coronary artery disease: a pooled analysis of individual patient data.

- 11 518 patients assigned to PCI (n=5753) or to CABG (n=5765) from 11 randomized trials
- 5 year all-cause mortality was 11·2% after PCI and 9·2% after CABG (hazard ratio [HR] 1·20, 95% CI 1·06-1·37; p=0·0038)
- 5 year all-cause mortality was significantly different between the interventions in patients with multivessel disease (11·5% after PCI vs 8·9% after CABG; HR 1·28, 95% CI 1·09-1·49; p=0·0019), including in those with diabetes (15·5% vs 10·0%; 1·48, 1·19-1·84; p=0·0004), but not in those without diabetes (8·7% vs 8·0%; 1·08, 0·86-1·36; p=0·49).
- SYNTAX score had a significant effect on the difference between the interventions in multivessel disease.
- 5 year all-cause mortality was similar between the interventions in patients with left main disease (10·7% after PCI vs 10·5% after CABG; 1·07, 0·87-1·33; p=0·52), regardless of diabetes status and SYNTAX score
- CABG had a mortality benefit over PCI in patients with multivessel disease, particularly those with diabetes and higher coronary complexity. No benefit for CABG over PCI was seen in patients with left main disease.

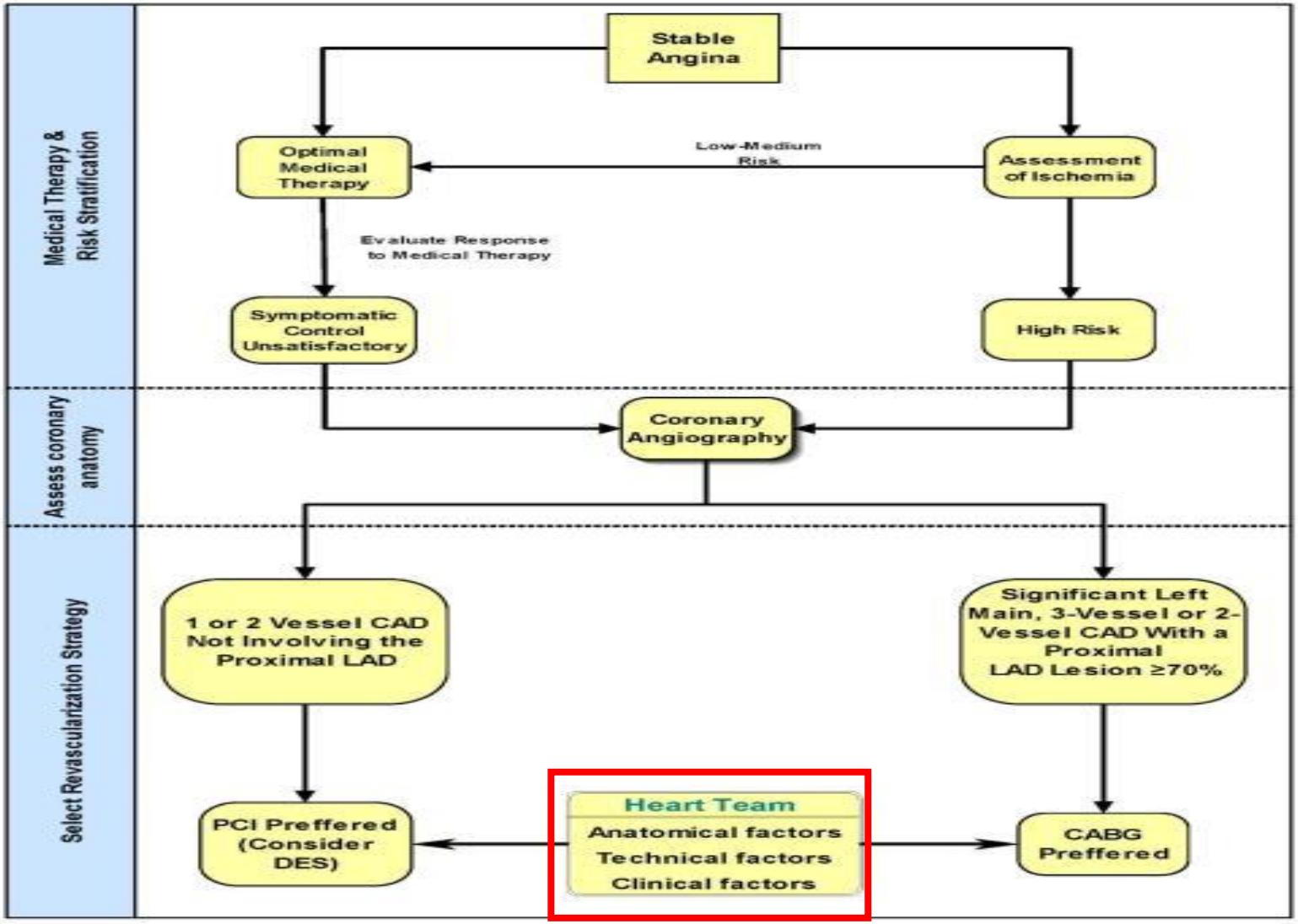
Lancet. 2018 Mar 10;391(10124):939-948

2018 ESC/EACTS Guidelines on myocardial revascularization

Recommendation for the type of revascularization in patients with stable coronary artery disease with suitable coronary anatomy for both procedures and low predicted surgical mortality

Recommendations according to extent of CAD	CABG		PCI	
	Class[a]	Level[b]	Class[a]	Level[b]
One-vessel CAD				
Without proximal LAD stenosis.	IIb	C	I	C
With proximal LAD stenosis.[68,101,139–144]	I	A	I	A
Two-vessel CAD				
Without proximal LAD stenosis.	IIb	C	I	C
With proximal LAD stenosis.[68,70,73]	I	B	I	C
Left main CAD				
Left main disease with low SYNTAX score (0 - 22).[69,121,122,124,145–148]	I	A	I	A
Left main disease with intermediate SYNTAX score (23 - 32).[69,121,122,124,145–148]	I	A	IIa	A
Left main disease with high SYNTAX score (≥33).[c] [69,121,122,124,146–148]	I	A	III	B
Three-vessel CAD without diabetes mellitus				
Three-vessel disease with low SYNTAX score (0 - 22).[102,105,121,123,124,135,149]	I	A	I	A
Three-vessel disease with intermediate or high SYNTAX score (>22).[c] [102,105,121,123,124,135,149]	I	A	III	A
Three-vessel CAD with diabetes mellitus				
Three-vessel disease with low SYNTAX score 0–22.[102,105,121,123,124,135,150–157]	I	A	IIb	A
Three-vessel disease with intermediate or high SYNTAX score (>22).[c] [102,105,121,123,124,135,150–157]	I	A	III	A

Revascularization strategy in patients with diabetes with stable angina



Summary
Coronary revascularization

- overall current evidence continues to favour CABG as the revascularization modality of choice for patients with diabetes and multivessel disease.
- When patients present with a comorbidity that increases surgical risk, the choice of revascularization method is best decided by multidisciplinary individualized risk assessment.

- selection of the optimal myocardial revascularization strategy must take into account multiple factors and requires a multidisciplinary team approach (‘heart team’).

Case 1

- Exacutive Health check
- M/45
- Father had MI at age 50
- Smoker
- FBS 8. Hba1c 7.8
- LDL 4.0. HDL 1. TG 2
- BP 145/90
- BMI 32
- CT coronary angiogram: Ca score 120.; calcified plaque at proximal LAD and RCA ; <50% stenosis

- Therapeutic Lifestyle intervention
- HbA1c : 6.5
  - Metformin
  - SGLT2 inhibitor
- Bp 125/78
  - ARB
- LDL 1.8
  - High-intensity Statin
- Aspirin

Case 2

- F/75
- Type 2DM for 25 years. Metformin and gliclazide
- A1c: 8.4, BP 140/60; LDL 3.2 (atorvastatin 20mg)
- BMI 28
- NSTEMI, CHF.
- Diffuse 3 vessel disease (Syntax score :22)
- Mild DM nephropathy

- Multiple vessel PCI (refused CABG)
- Hba1c: 7.4
  - Metformin
  - SGLT2 inhibitor
  - GLP 1RA
- Aspirin , ticagrelor
- ACEI, Betablocker
- LDL 1.2 (Statin, PCSK 9 inhibitor)

Shared decision making

- Applying clinical trials results into clinical practice
- Clinical judgment
- Adjustments for individual preferences, comorbidities, and other patient factors
- Ethnic groups

- **Shared decision making**

Thank you