Presenter Disclosures

Dr. David Fitchett

The changing landscape of secondary prevention

Focus on Patients with Prior MI

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- **Other:** Member of Empa Reg Outcomes Steering committee, Chair of DSMBs Novo Nordisk

Educational Goals

1. To understand that classical risk factor management improves outcomes but leaves a large residual risk
2. To learn about more recent approaches to risk management with
   - New agents
   - New therapeutic targets
   - New uses of existing drugs
3. To develop a strategy to apply the new therapeutic approaches to the individual patient

A Personal Experience
Management of Patients with Myocardial Infarction in 1960s

Acute management:

Bed rest 2-6 weeks

Open ward / no monitoring

Long-term ma

Lifestyle

No medical treatment

No revascularisation

No ASA

No beta-blocker

No ACE inhibitor

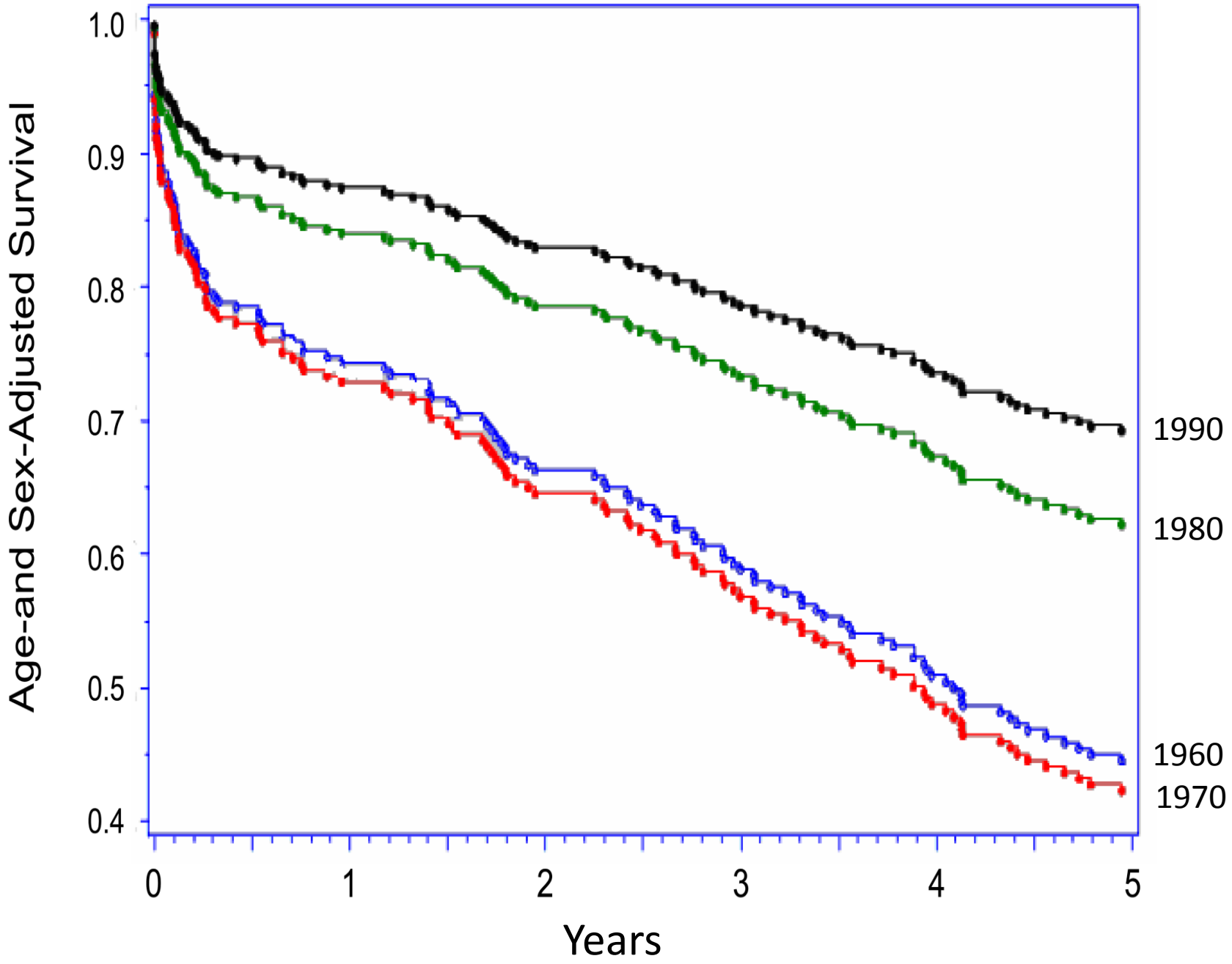
In hospital mortality	25%
5 year mortality	55%

5 Year Age adjusted Survival after Acute Myocardial Infarction 1960-1990

Improved survival

- Acute management
- Long-term management

But changing diagnostic criteria



Parikh et al Circulation. 2009;119:1203

Classical Secondary Prevention of ASCVD

	Goals	Impact on mortality
Smoking Cessation	No exposure	Persistent smoking 20% increase Smoking cessation NNT 13 (5yrs)
Diet	Low saturated fat	
Physical Activity	3.5-7 hrs/ week	
Weight	BMI 20--25	
BP	<140/90	
LDL-C	< 2.0, > 50% reduction	Life expectancy + 2.5yrs
Diabetes	A1C < 7.0	None
ASA	Low dose	Life expectancy + 1yr
Beta blocker	Post MI	Life expectancy + 2 yrs
ACE inhibitor	LV dysfunction post MI	Life expectancy + 1.5 yrs

Changing Landscape of Cardiovascular Prevention

- New public health measures
- New treatments
- New applications
- New targets
- Personalized approach
- Improved uptake of recommendations

Lifestyle Modifications

- Stop smoking
- Weight reduction
- Increased physical activity
- Stress management
- Depression counselling
- Healthy diet

Impact of smoking cessation / advice

In hospital counselling 0.5 yrs ↑ life expectancy

Persistent smoking 17 year mortality ↑ 20%

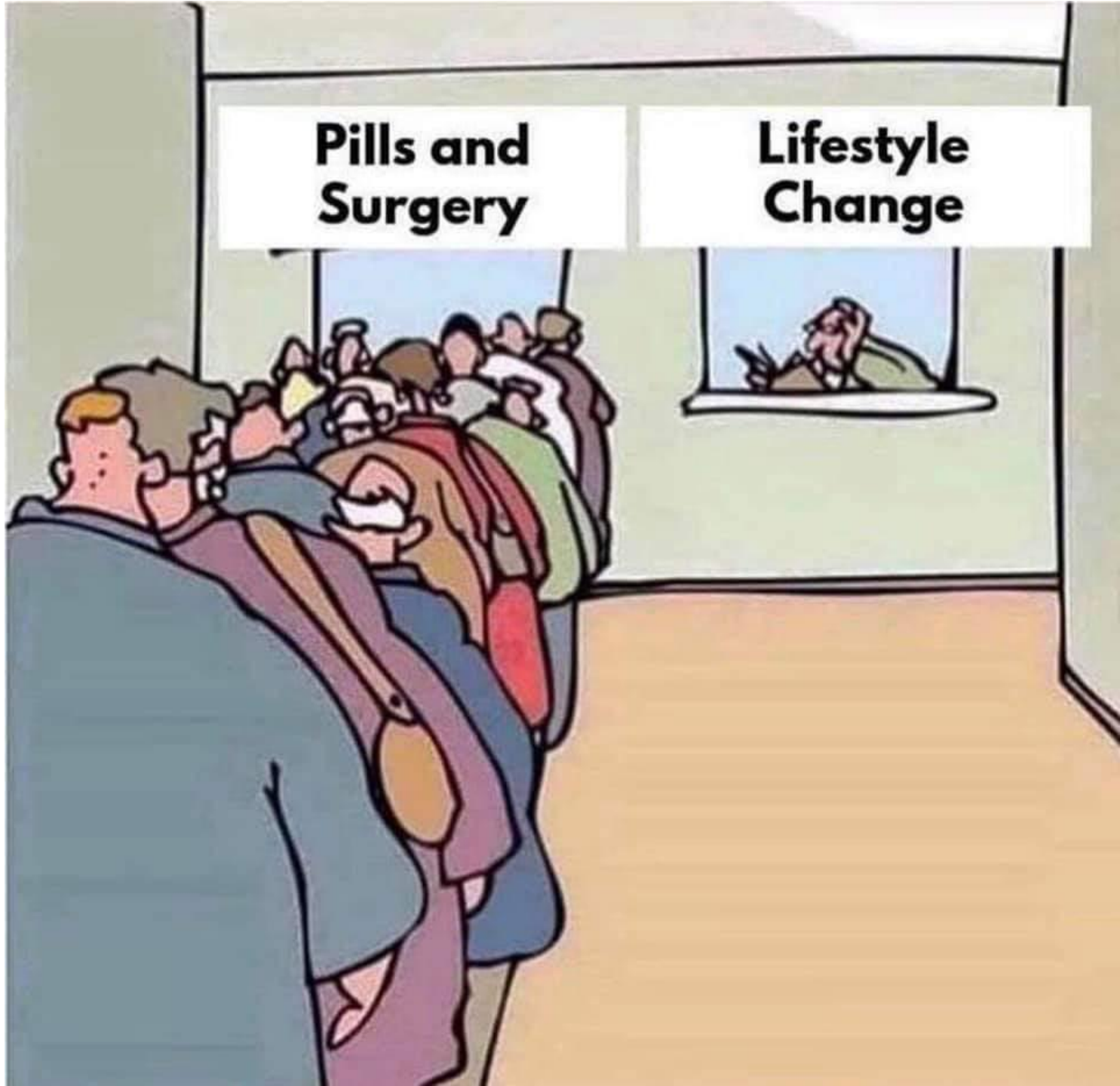
Yudi et al BMJ Open 2017

NNT to save 1 life 13

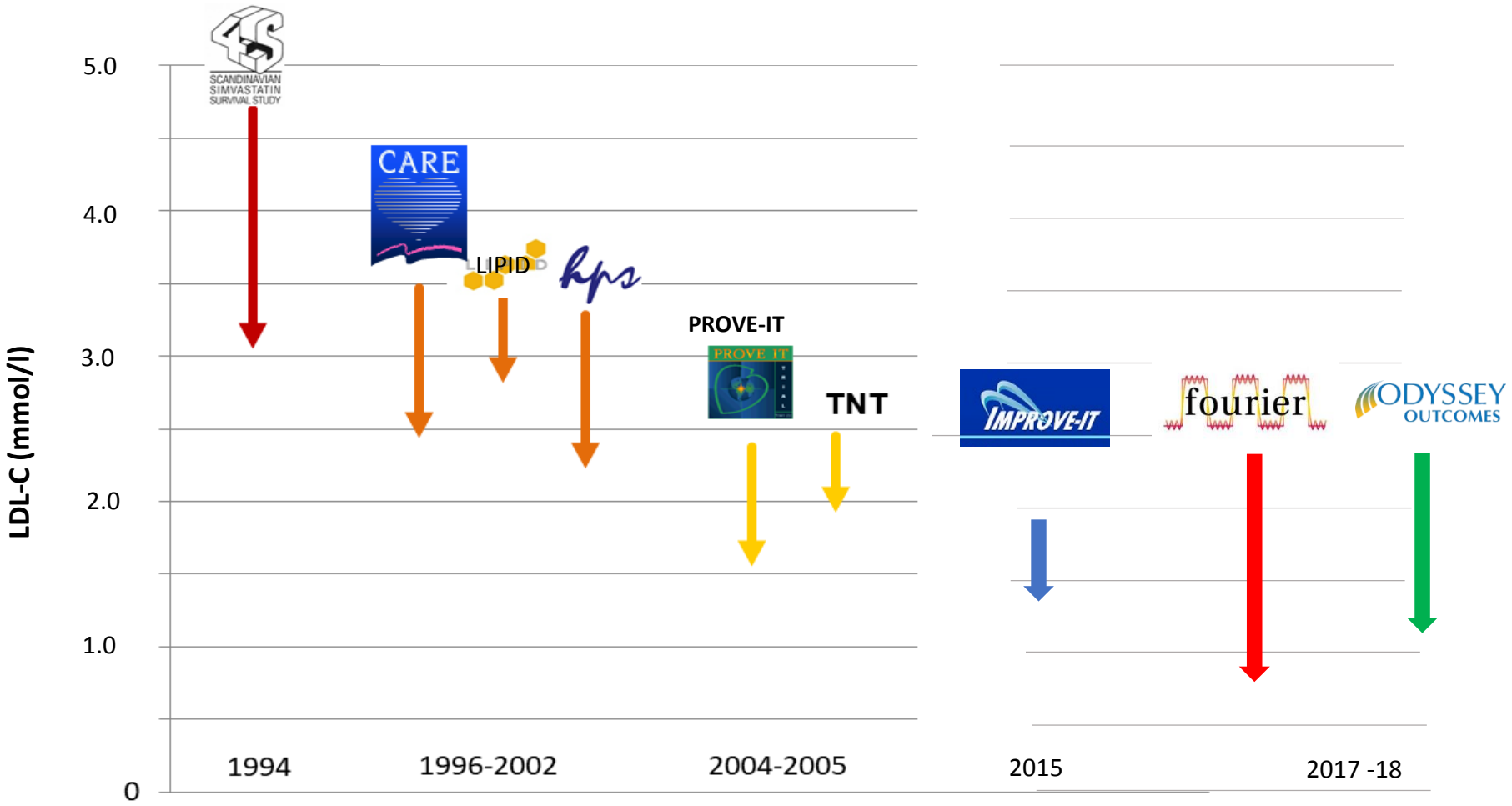
Wilson et al Arch Int Med 2000;160:939

Importance of smoking restrictions

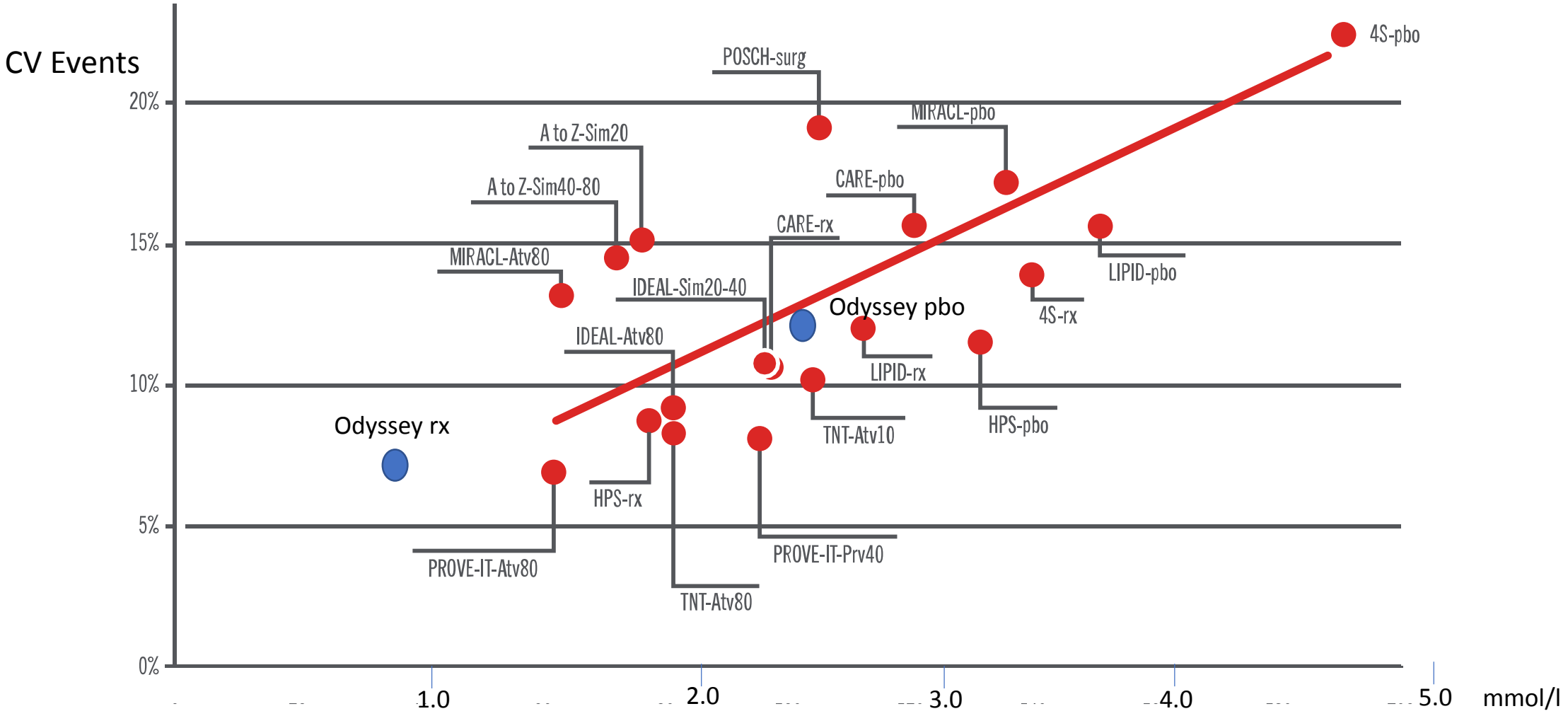
Lifestyle Change is tough



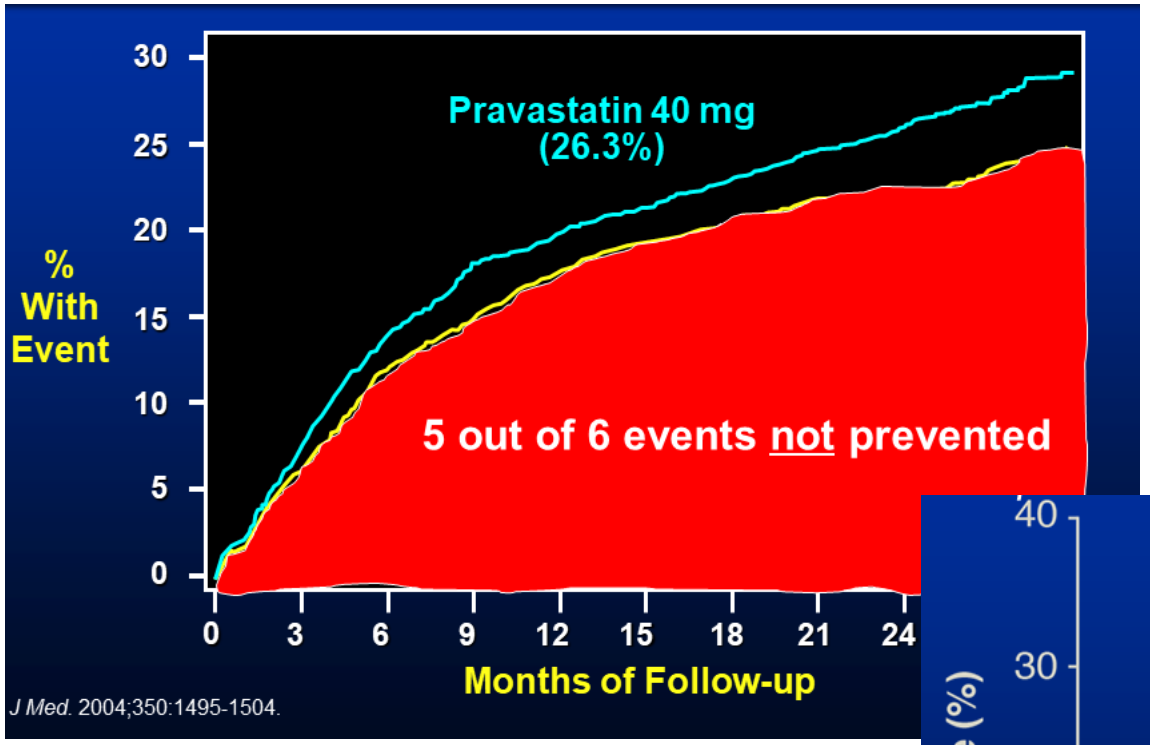
LDL Cholesterol Reduction 1994-2020



Reduced CV Events with Lower Achieved LDL-C

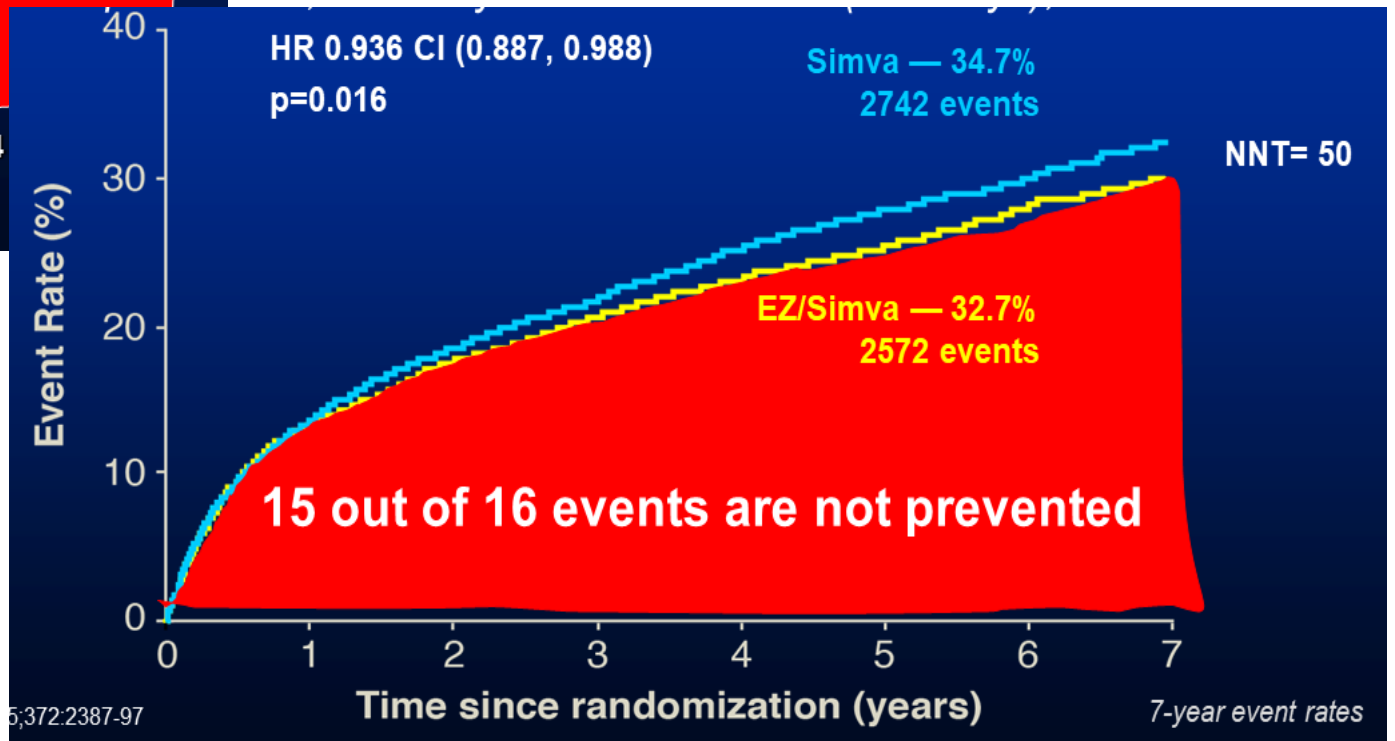


Large Residual Risk Despite further LDL Reduction

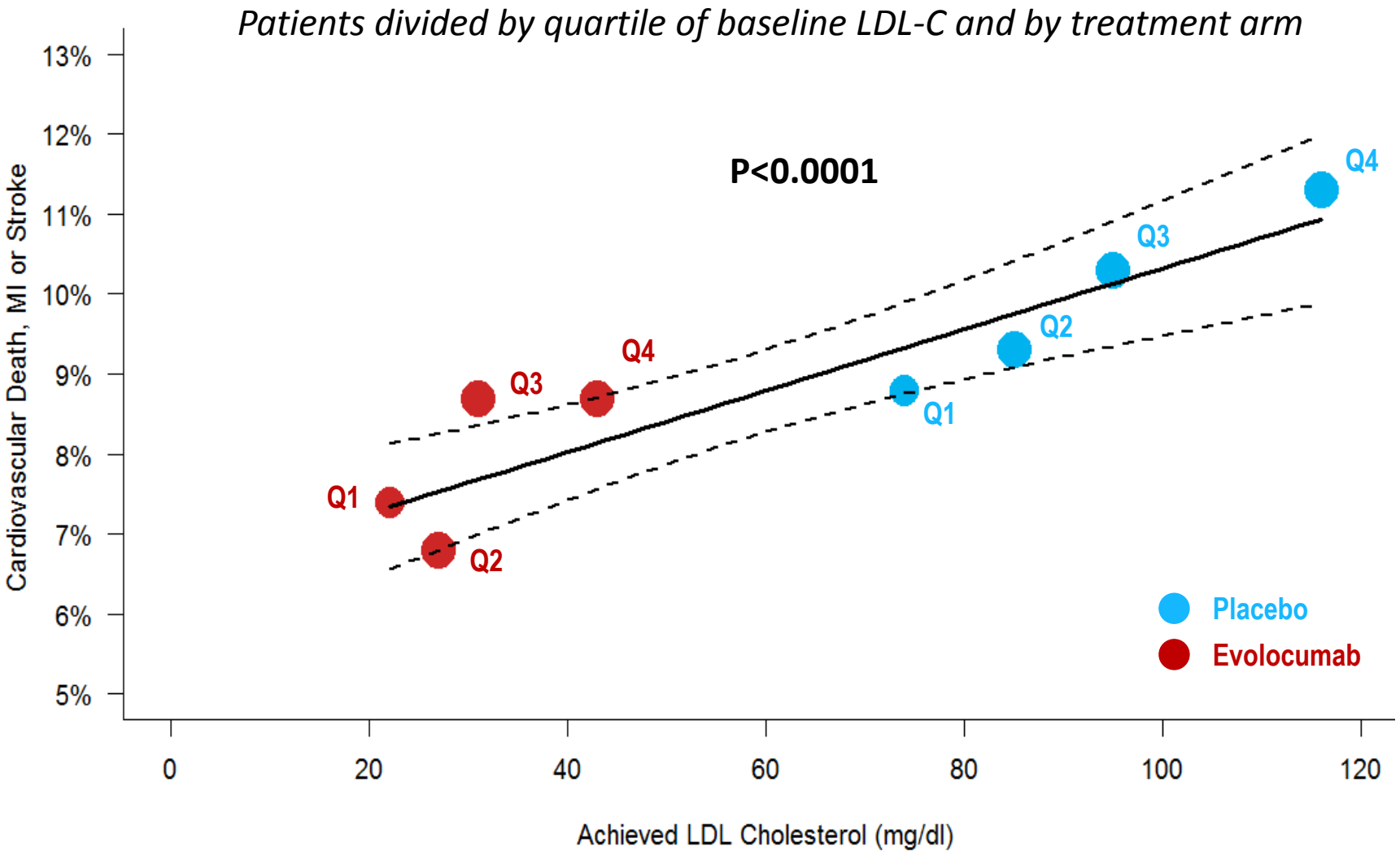


PROVE-IT

IMPROVE-IT



Lower LDL-C Is Better



Recent MI Subgroup in FOURIER

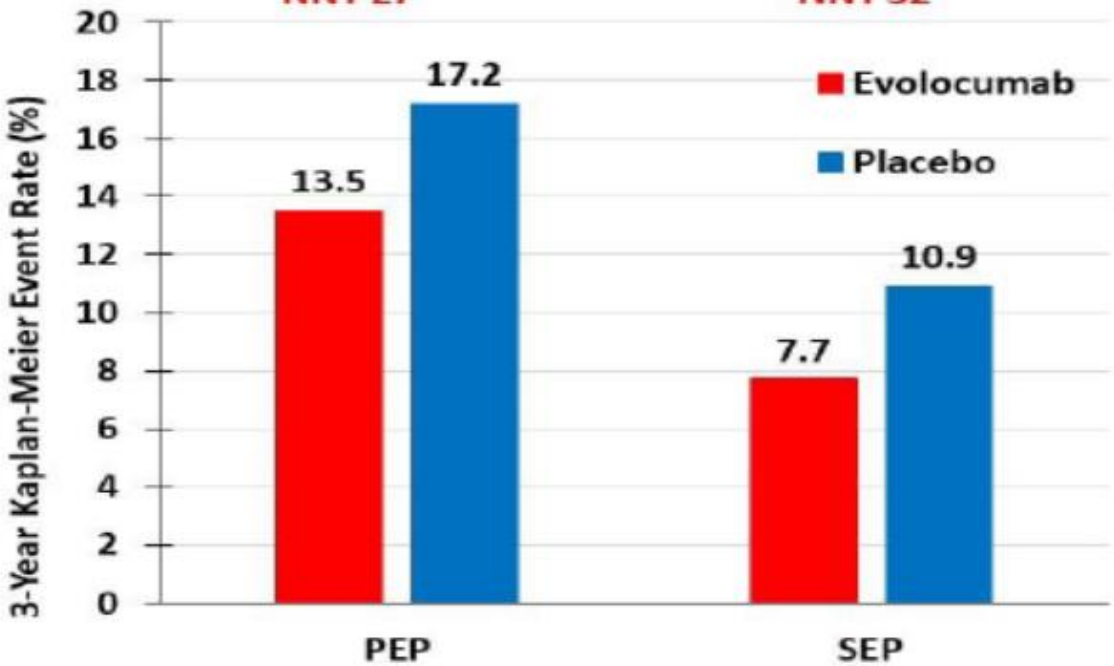
Recent MI ≤ 12 months (N=5711)

19% RRR
HR 0.81 (0.70-0.93)
P=0.004

3.7% ARR over 3 years
NNT 27

25% RRR
HR 0.75 (0.62-0.91)
P=0.003

3.2% ARR over 3 years
NNT 32



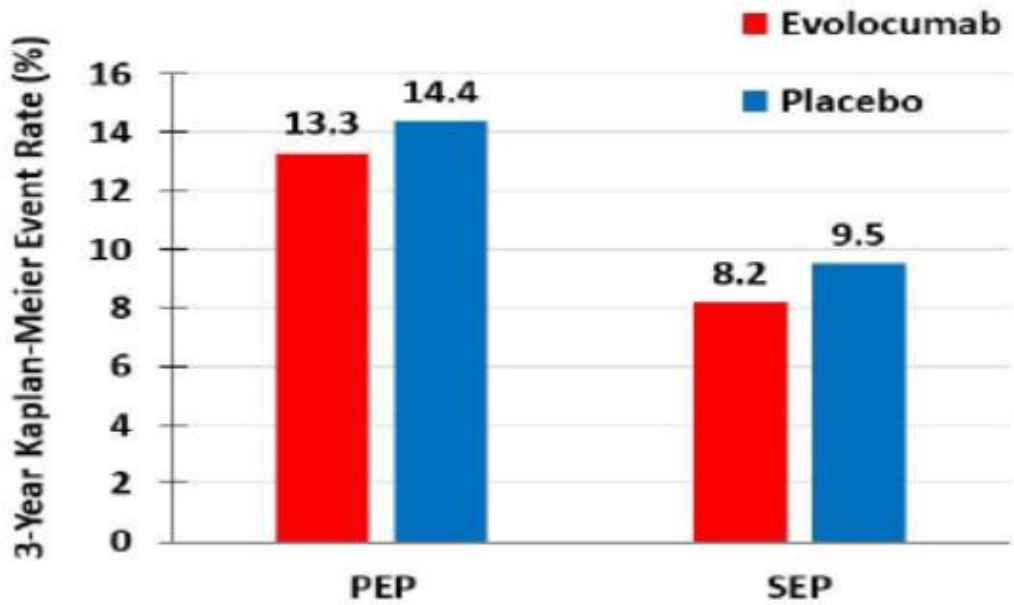
Remote MI > 12 months (N=16,609)

8% RRR
HR 0.92 (0.84-1.01)
P=0.075

1.1% ARR over 3 years
NNT 95

15% RRR
HR 0.85 (0.76-0.96)
P=0.009

1.3% ARR over 3 years
NNT 79



PEP: CV death, MI, stroke, unstable angina or coronary revascularization. SEP: CV death, MI or stroke.

Indications for Consideration of PCSK9 Inhibitor

- Very high risk (including post ACS) failing to achieve LDL C <1.4mmo/l
  After 4-6 weeks treatment with maximally tolerated statin with ezetimibe
- Recent ACS
- Residual multivessel CAD
- Polyvascular disease
- Diabetes

Secondary Prevention Guideline Updates

CCS 2016 Guidelines update recommendations

Thanassoulis et al Can J Cardiol 2019;35:558

- Treatment intensification (with ezetimibe followed by PCSK9i to achieve LDL C goal < 2.0 (or < 1.8 if recent ACS)
- Use PCSK9 i in ASCVD when LDL not at target despite statin and ezetimibe

ESC 2019 Guidelines

European Heart Journal (2019) 00, 178

Recommendations		Class[a]	Level[b]
Very high risk patients:	LDL-C reduction > 50% and LDL-C goal < 1.4mmol/l	I	A
ASCVD with second event within 2 years on maximal statin:	LDL-C goal < 1.0mmol/l	IIb	B

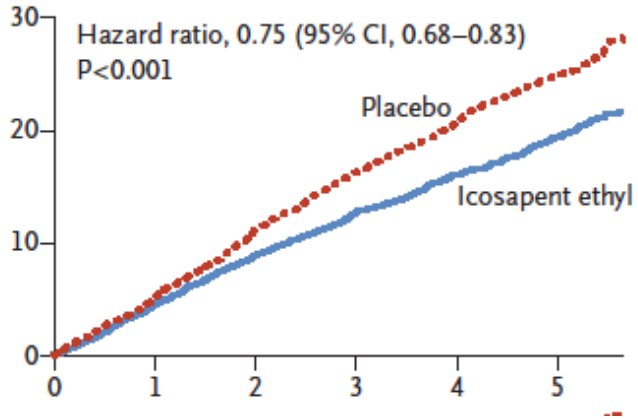
Very High Risk includes
- Documented ASCVD
- Prior ACS

Triglycerides as a Target for CV Risk Reduction Benefit of Icosapent ethyl

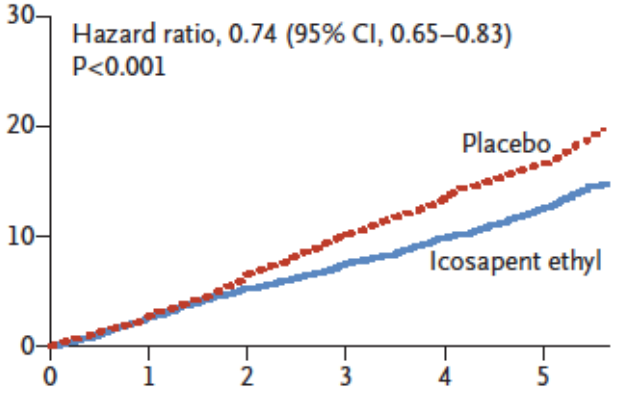
REDUCE IT

- 8179 patients
  - Established CVD (71%) or > 50yrs with DM and other CV risk factor (29%)
  - Triglycerides 1.52-5.63 mmol/l LDL-C 1.06-2.5 mmol/l
  - On stable statin dose for 4 weeks
  - Randomised to Icosapent ethyl 2G bid

Primary EP (CVD, MI,Stroke, revasc, UA)



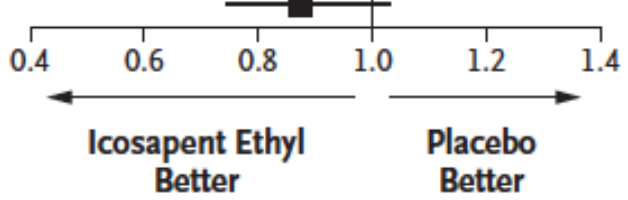
Secondary EP (CVD, MI, stroke)



Bhatt et al N Engl J Med 2019;380:11-22

REDUCE IT
Cardiovascular Outcomes

End Point	Icosapent Ethyl (N=4089)	Placebo (N=4090)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)			
Primary composite	705 (17.2)	901 (22.0)	0.75 (0.68–0.83)	<0.001
Key secondary composite	459 (11.2)	606 (14.8)	0.74 (0.65–0.83)	<0.001
Death from any cause, nonfatal myocardial infarction, or nonfatal stroke	549 (13.4)	690 (16.9)	0.77 (0.69–0.86)	<0.001
Death from any cause	274 (6.7)	310 (7.6)	0.87 (0.74–1.02)	—



- Icosapent Ethyl reduced CV outcomes including CV mortality
- Effective over wide range of TG levels
- Benefit did not relate to achieved TG levels (> 1.69 or < 1.69 at 1 year)

Adverse outcomes

Hospitalisation for AF	3.2 vs 2.1%	p=0.004
Serious bleeding	2.7 vs 2.1%	p=0.06

Bhatt et al N Engl J Med 2019;380:11-22

Anti-Platelet Therapy : Long-term Management of CAD

ASA
Post MI
Chronic CAD

ISIS 2
ATC metanalysis

Clopidogrel
Superior to ASA
Chronic CAD

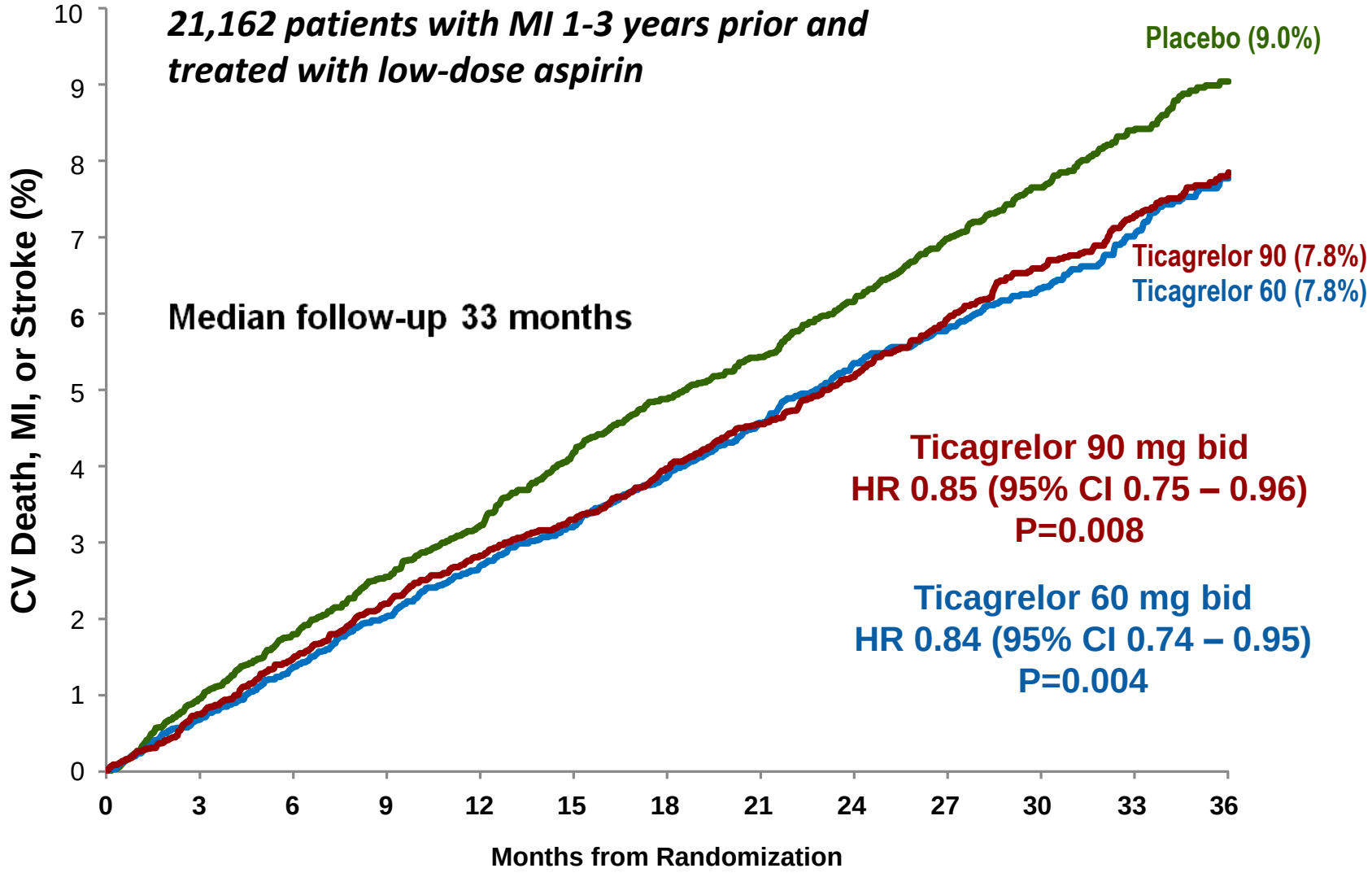
CURE

Ticagrelor / Prasugrel + ASA
Superior to Clopidogrel
Post ACS

PLATO
TRITON

1. DAPT for 1 year post ACS in most patients
2. Ticagrelor preferable to clopidogrel post ACS
3. For patients with higher bleeding risk
   - Shorter DAPT
   - Single APT
   - Use of PPI
4. Consider longer term (>1 year) DAPT

Continued use of Ticagrelor beyond 1 year

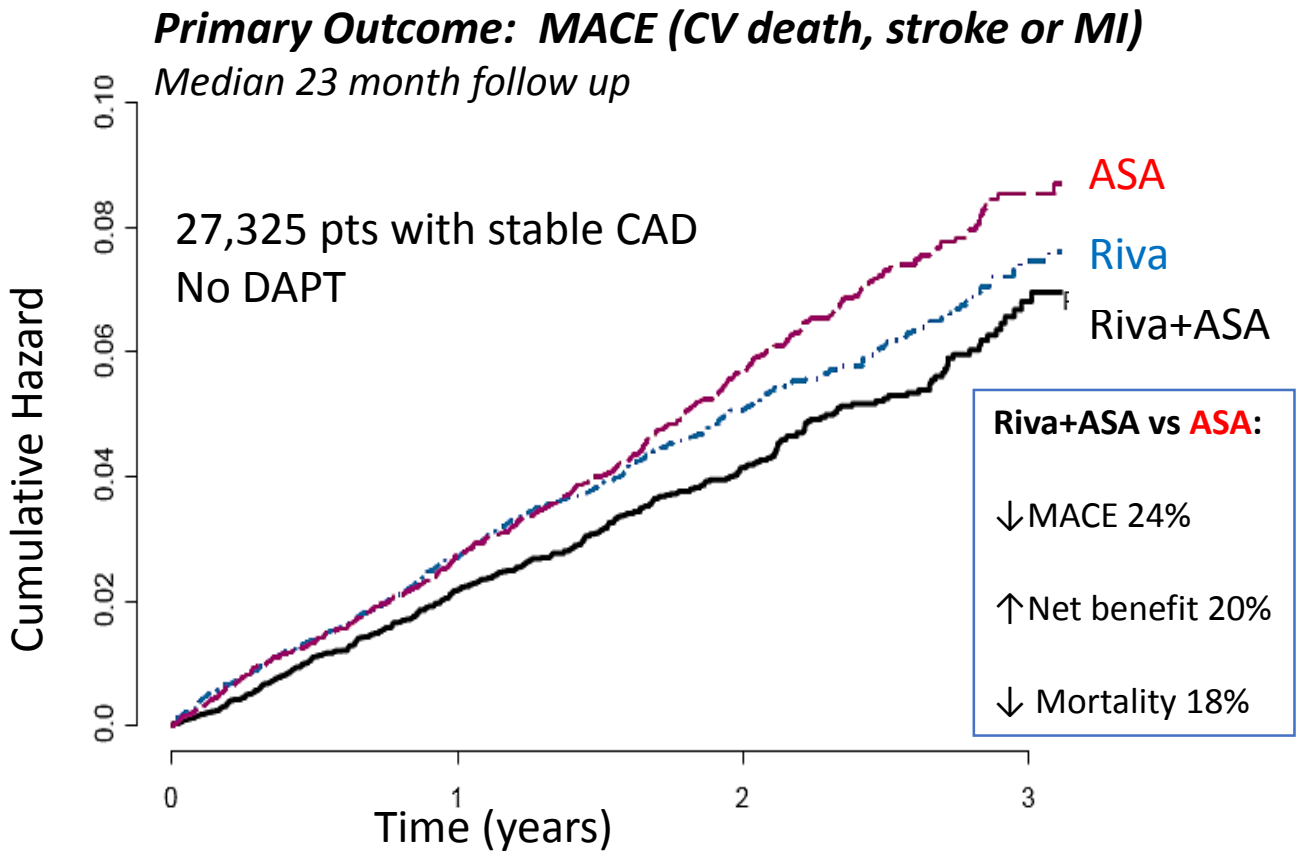


Larger net benefit

- Chronic kidney disease
- Peripheral arterial disease
- Mulivessel CAD
- Diabetes

PEGASUS Bonaca MP et al. . *NEJM* 2015;372:1791-800

Rivaroxaban in Chronic CAD

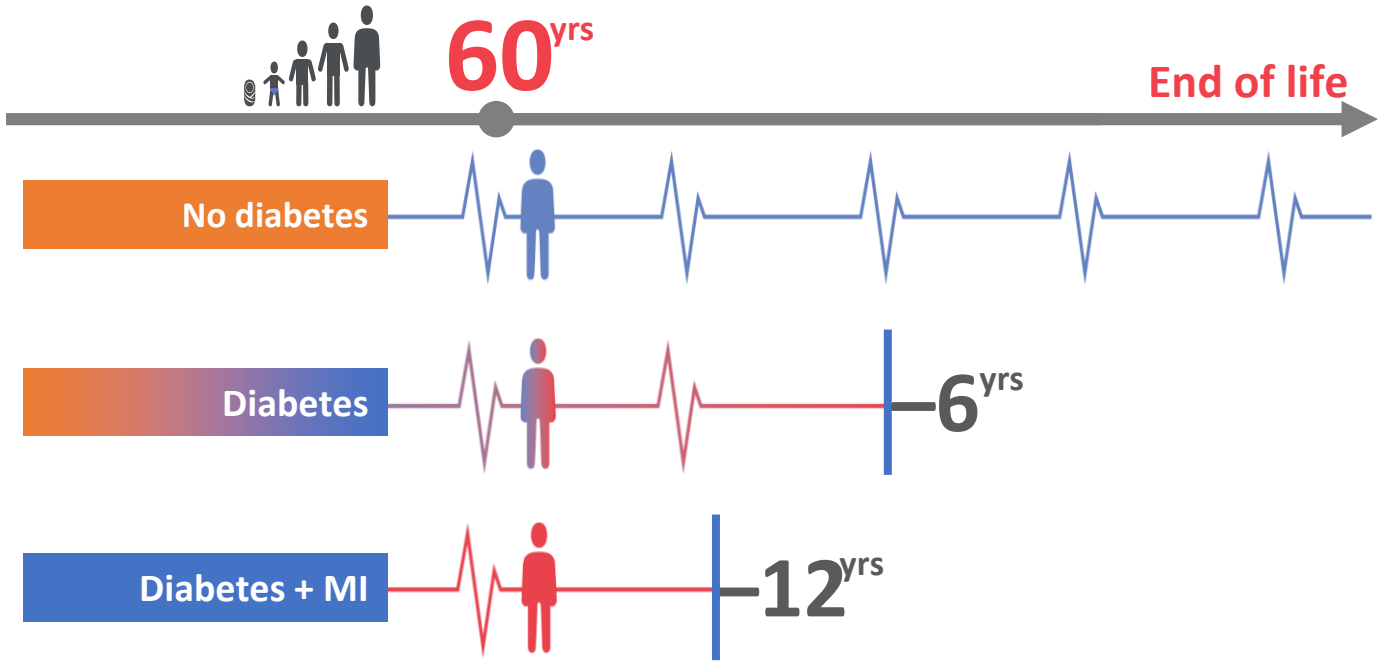


Consider adding Rivaroxaban

- High / Very high risk Chronic CAD
- Not high bleeding risk

COMPASS Eikelboom JW, et al. NEJM 2017;377:1319-1330.

Life Expectancy Is Reduced by ~12 Years in Diabetes Patients with Previous CVD



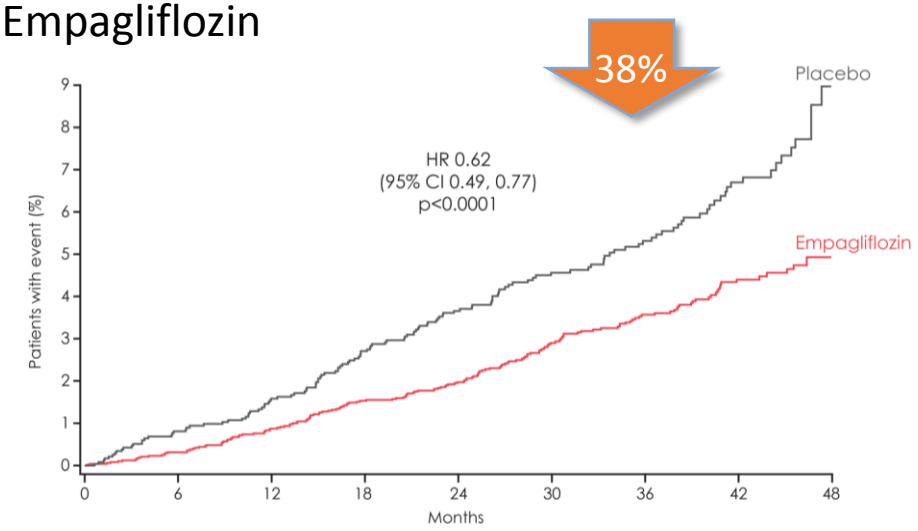
The Emerging Risk Factors Collaboration. *JAMA* 2015;314:52

Diabetes: Prevention of CV Events

- Glycemic control: No impact on CV mortality,
  but reduces microvascular complications
- Choice of glycemic agent more important.

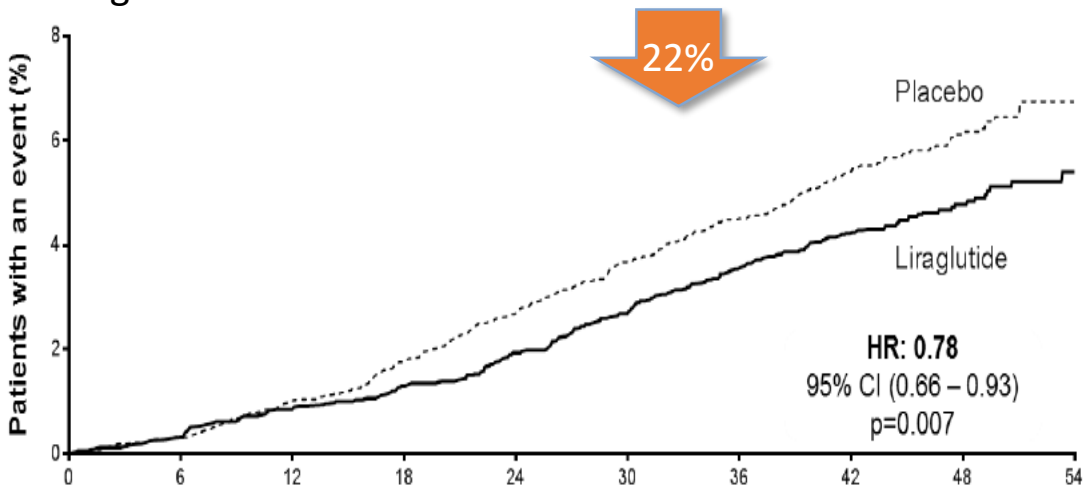
CV Mortality

Empagliflozin



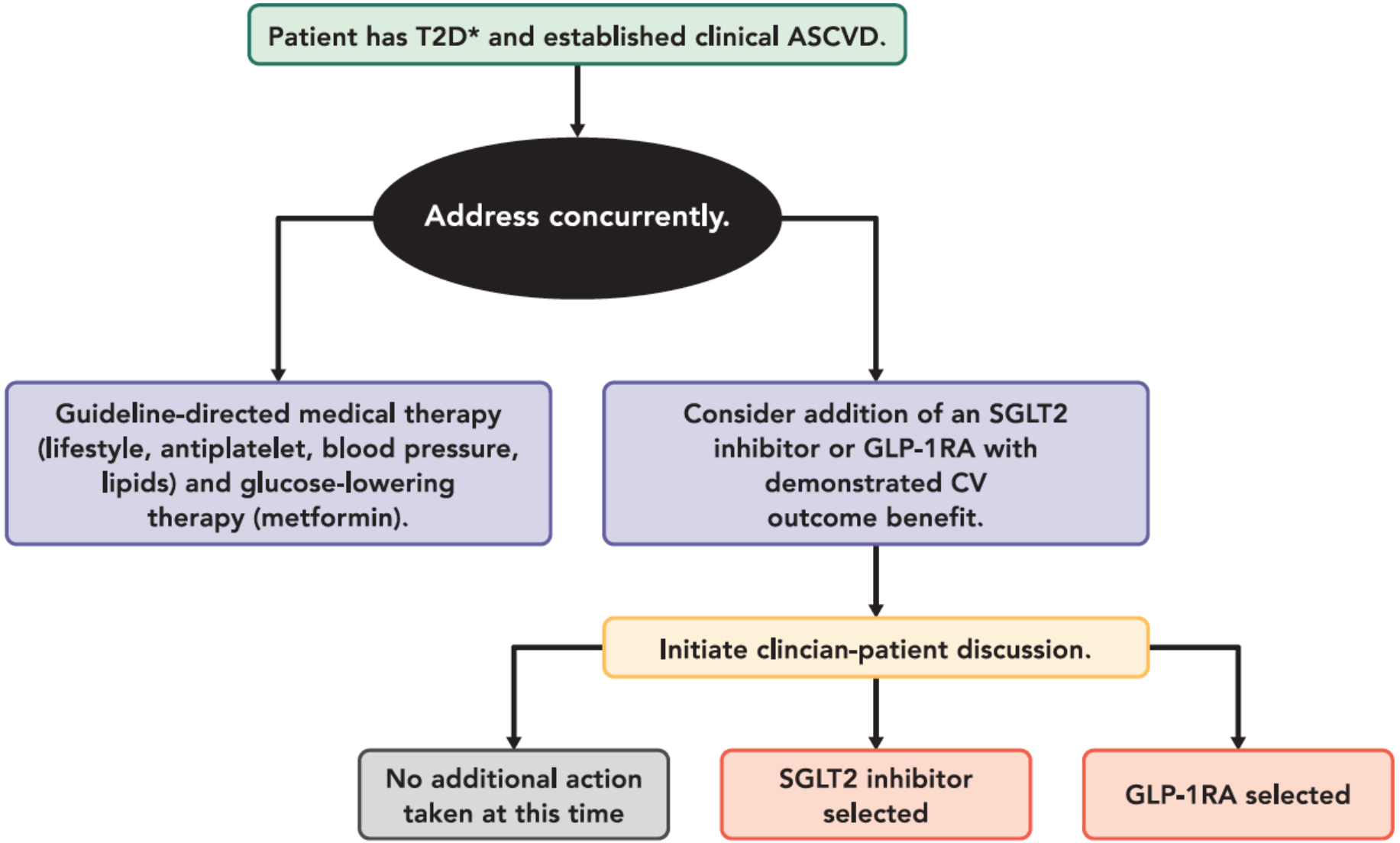
EMPA REG Outcome

Liraglutide



LEADER

Use of Glucose Lowering Agent with CV Benefit



2018 ACC Expert Consensus CVD Risk Reduction in T2DM J Am Coll Cardiol 2018;72:3200

SECONDARY PREVENTION POST ACS AND BEYOND

Lifestyle Recommendations
- Stop smoking
- Weight reduction
- Increased physical activity
- Stress management
- Depression counselling
- Healthy diet

Refer to Cardiac Rehabilitation

Recommended		Comments	Considerations
• Dual APT	→ *ASA 81 mg daily + Ticagrelor 90 mg BID x 1 yr*	• Extended DAPT or Dual pathway therapy should be considered ~1 year post-ACS	
or Extended APT	→ *ASA 81 mg daily + Ticagrelor 60 mg BID* or *clopidogrel 75 mg daily*		
or ASA + rivaroxaban	*ASA 81 mg daily + Rivaroxaban 2.5 mg BID*		
• Lipid lowering	→ *Atorvastatin 80 mg daily or equivalent with LDL target < 1.8 mmol/L (2016 Canadian guidelines), <1.4 mmol/L (2019 ESC/EAS guidelines)*	• LDL not at target • Statin intolerance • Very high risk*	Ezetimibe 10 mg daily and/or Alicuromab 75-150 mg Q2 weeks Evolocumab 140 mg Q2 weeks (or 420 mg Q4 weeks)
		• TG 1.5-5.6mmol/l + LDL < 2.6	Icosapent ethyl 2 g BID
• ACE inhibition /ARB	→ *Ramipril 10 mg daily or perindopril 8 mg daily or Telmisartan 80mg*		
• Beta-blocker	→ *Metoprolol 50 mg BID or Carvedilol 25 mg BID Atenolol 50 mg daily or Bisoprolol 10mg daily*		
• BP Control	→ *CHEP based algorithm*	As needed	DHP CCB + ACEi or ARB ± Chlorthalidone or indapamide
• CV protection and glycemic control in diabetes	→ *Diabetes Canada based algorithm*	Add agent with CV benefit	Empagliflozin Canagliflozin Dapagliflozin and/or Liraglutide Semaglutide Dulaglutide

Secondary Prevention After MI

1. Fitchett D et al Secondary prevention beyond hospital discharge for acute coronary syndrome. Canadian Journal of Cardiology 2016; S15-S34
2. Fitchett D et al Update to evidence based secondary prevention strategies post acute coronary syndrome. CJC Open 2020 (in press)