The Dangerous Intersection of Diabetes and Heart Disease

Darren K. McGuire, MD, MHSc
Distiinguished Teaching Professor of Medicine
University of Texas Southwestern Medical Center

UT Southwestern Medical Center

Conflicts of Interest/Disclosures

- Clinical trials leadership:
  - Merck & Co
  - Pfizer
  - AstraZeneca
  - Janssen
  - Lilly USA
  - Boehringer Ingelheim
  - Novo Nordisk
  - Lexicon
  - Eisai
  - GlaxoSmithKline
  - Sanofi-Aventis
- Consultancy:
  - Novo Nordisk
  - Sanofi-Aventis
  - Boehringer Ingelheim
  - Lilly USA
  - Merck & Co
  - AstraZeneca
  - Metavant
  - Applied Therapeutics

UT Southwestern Medical Center

Secular trends in cause of death among US adults with diabetes

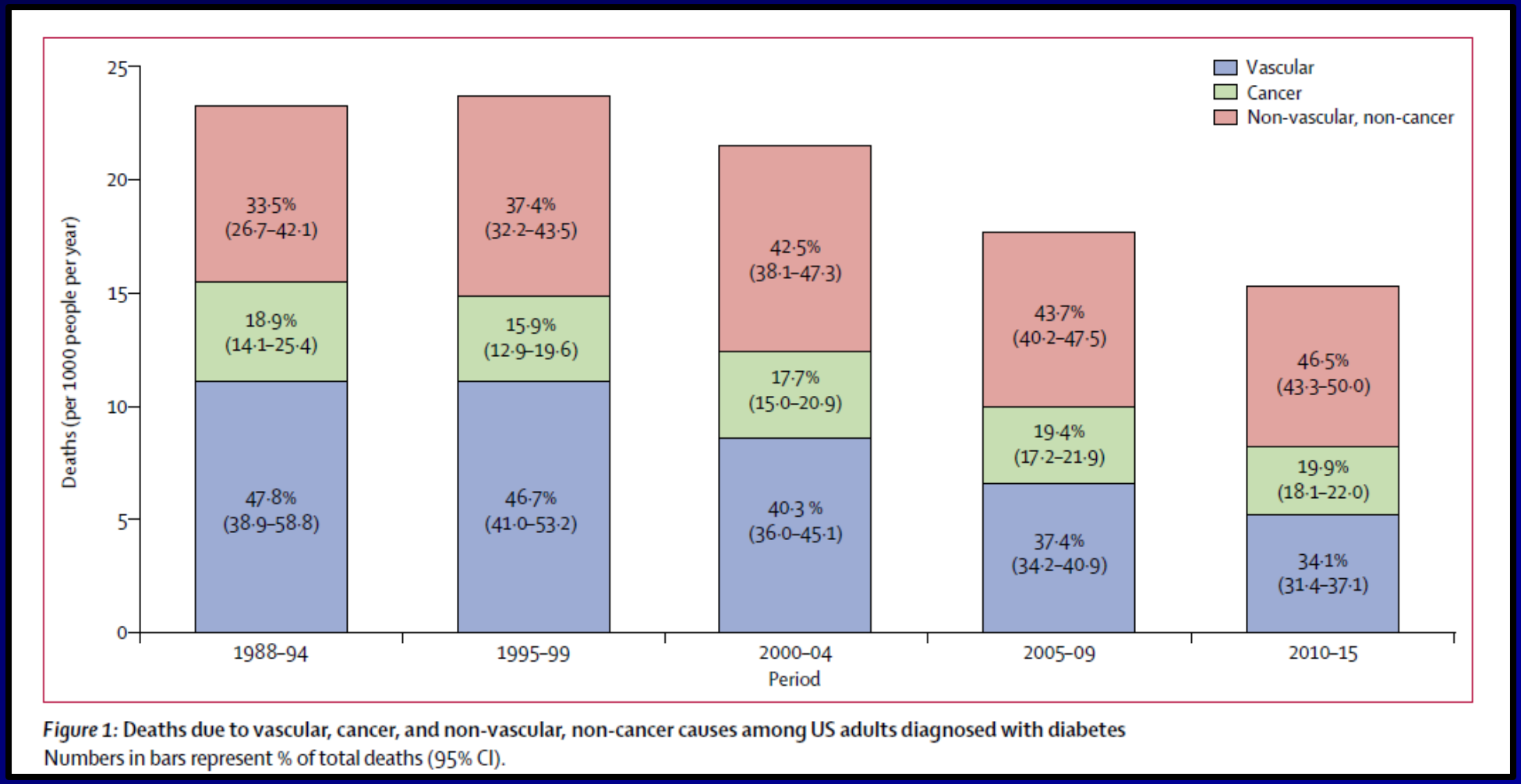


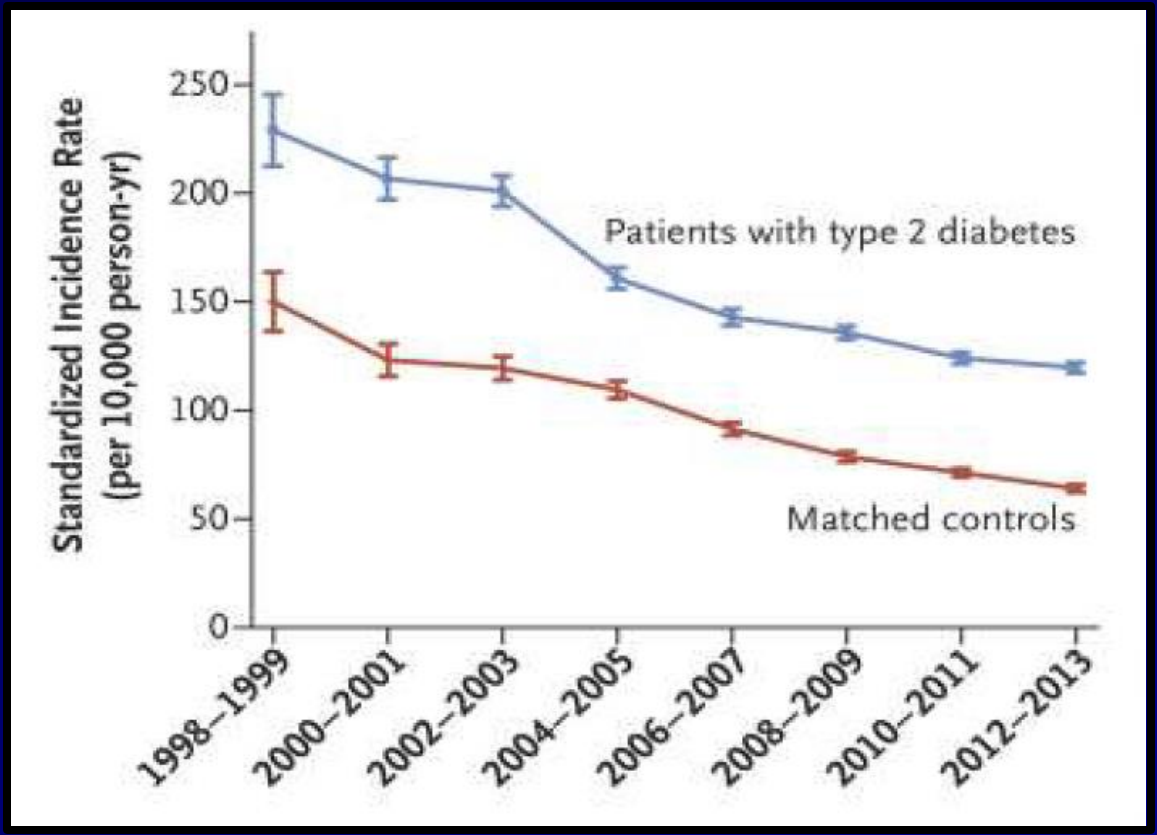
Figure 1: Deaths due to vascular, cancer, and non-vascular, non-cancer causes among US adults diagnosed with diabetes
Numbers in bars represent % of total deaths (95% CI).

UT Southwestern Medical Center

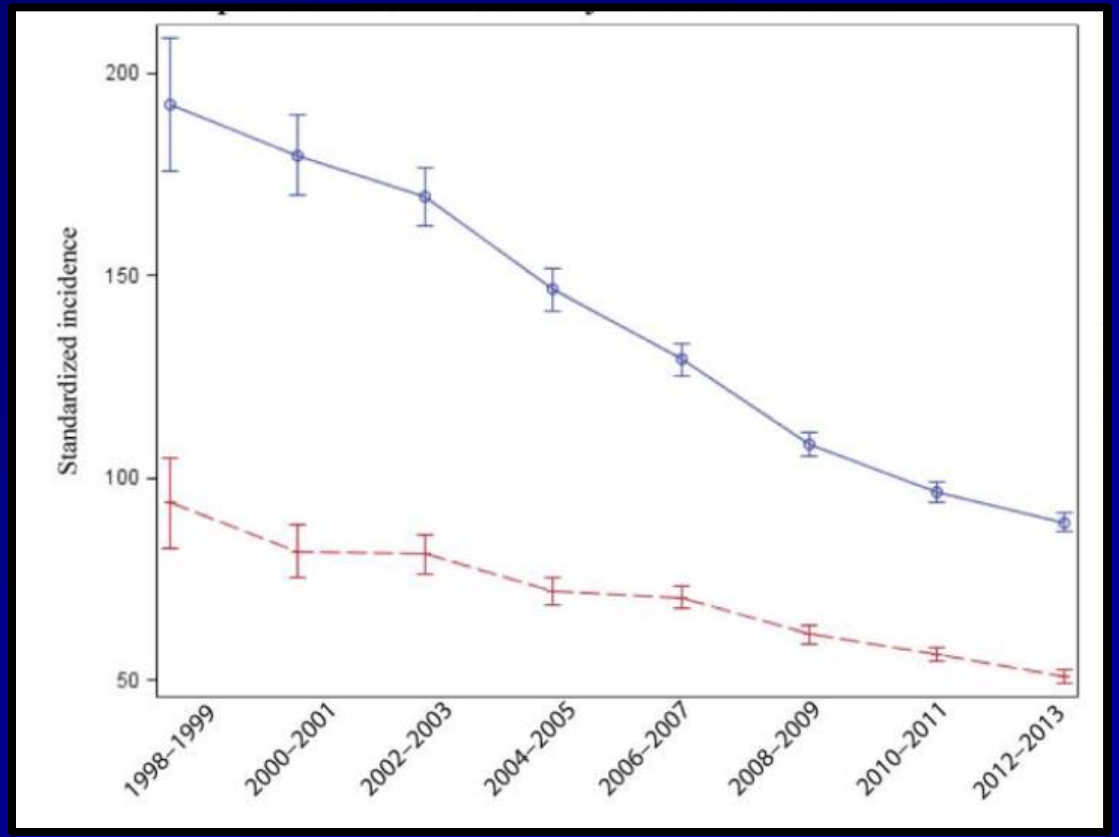
Gregg, E. W., et al. Lancet 2018; 391: 2430-2440

ASCVD Risk Associated with T2DM: Swedish National Registry Data 1998-2013

CV Death

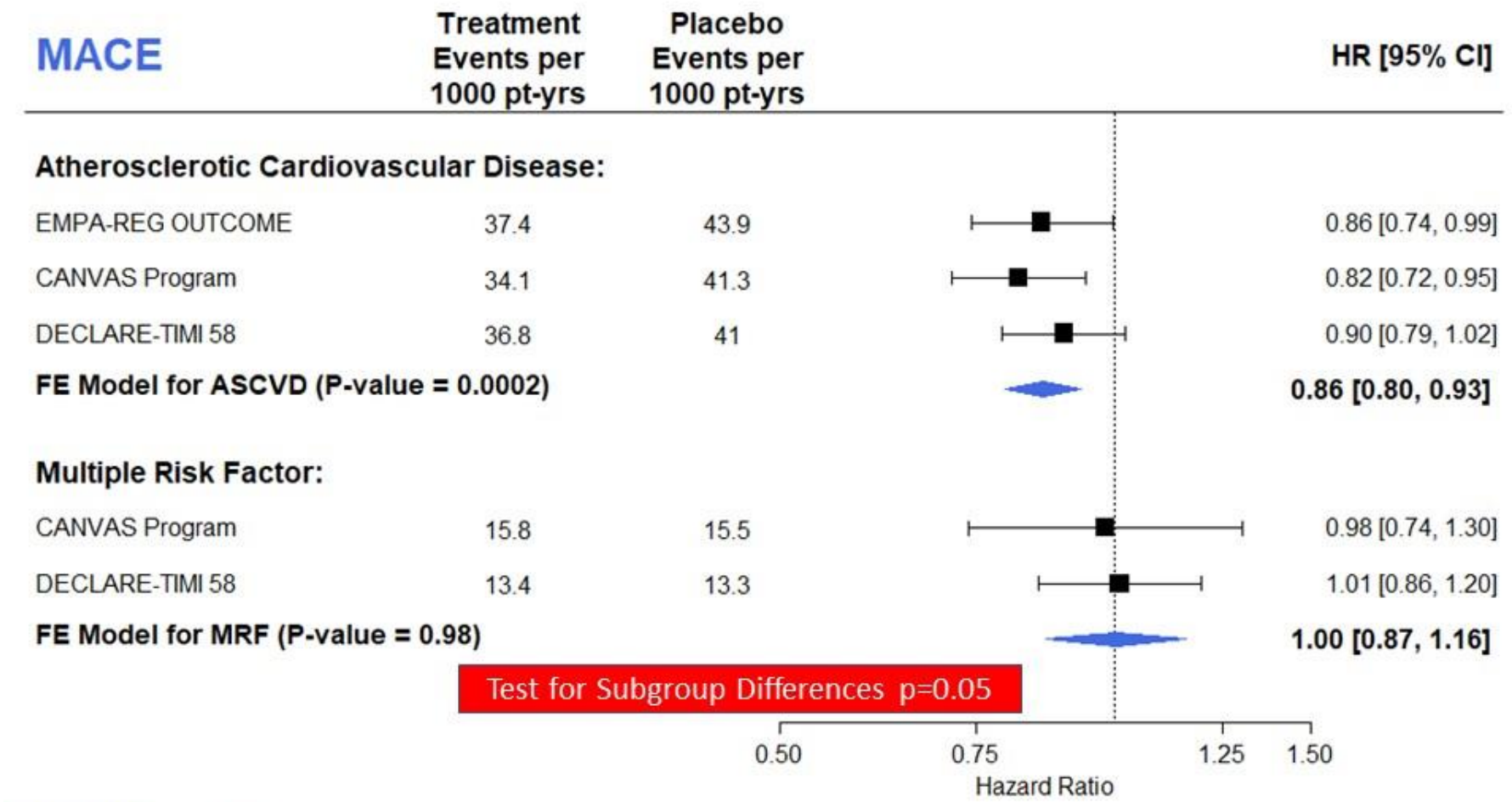


Myocardial Infarction



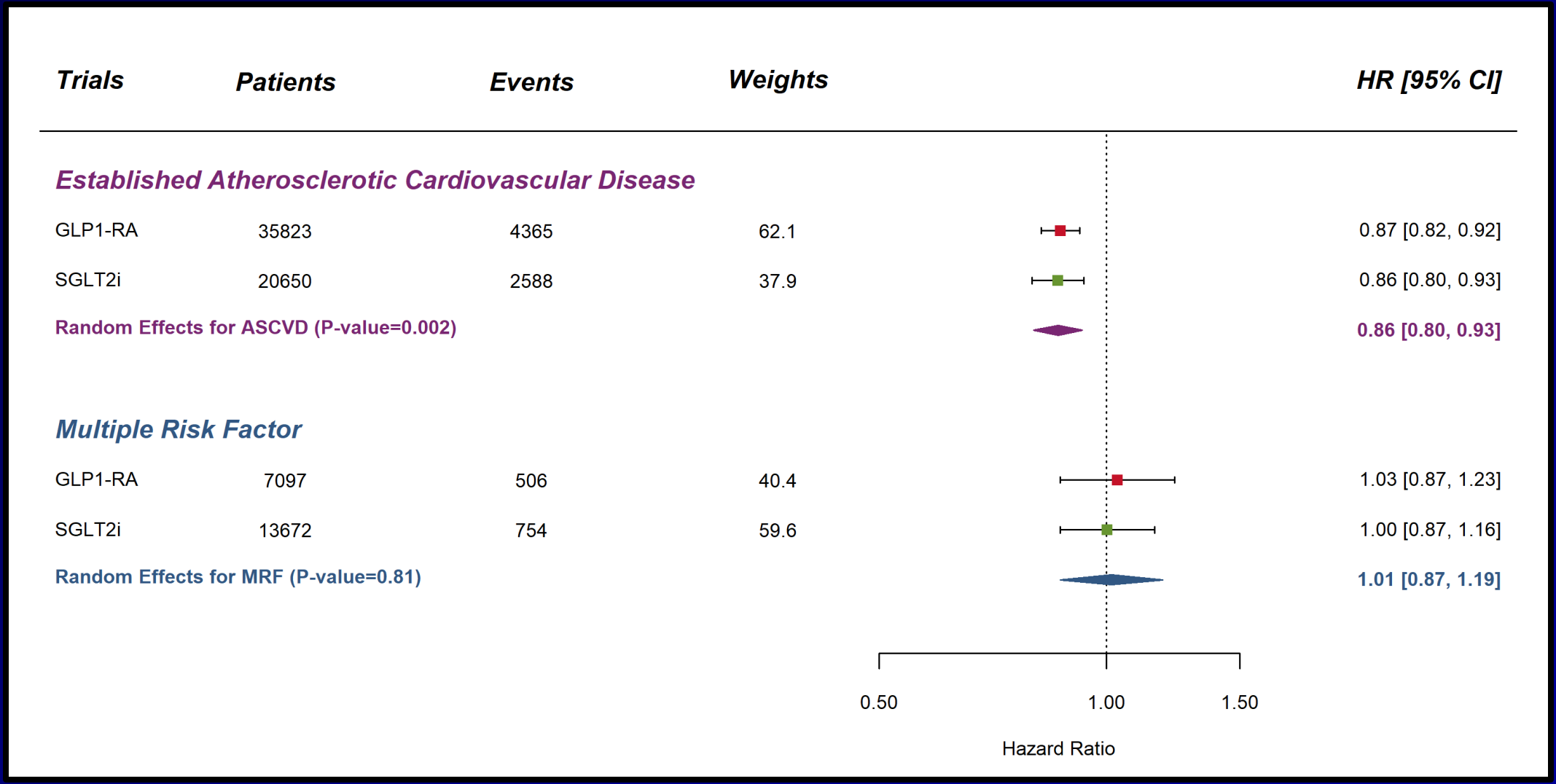
Rawshani, A., et al. N Engl J Med 2017; 376: 1407-1418.

Meta-Analysis of CVOTs: MACE by Presence of ASCVD



Zelniker TA et al. Lancet 2018; DOI 10.1016/S0140-6736(18)32590-X

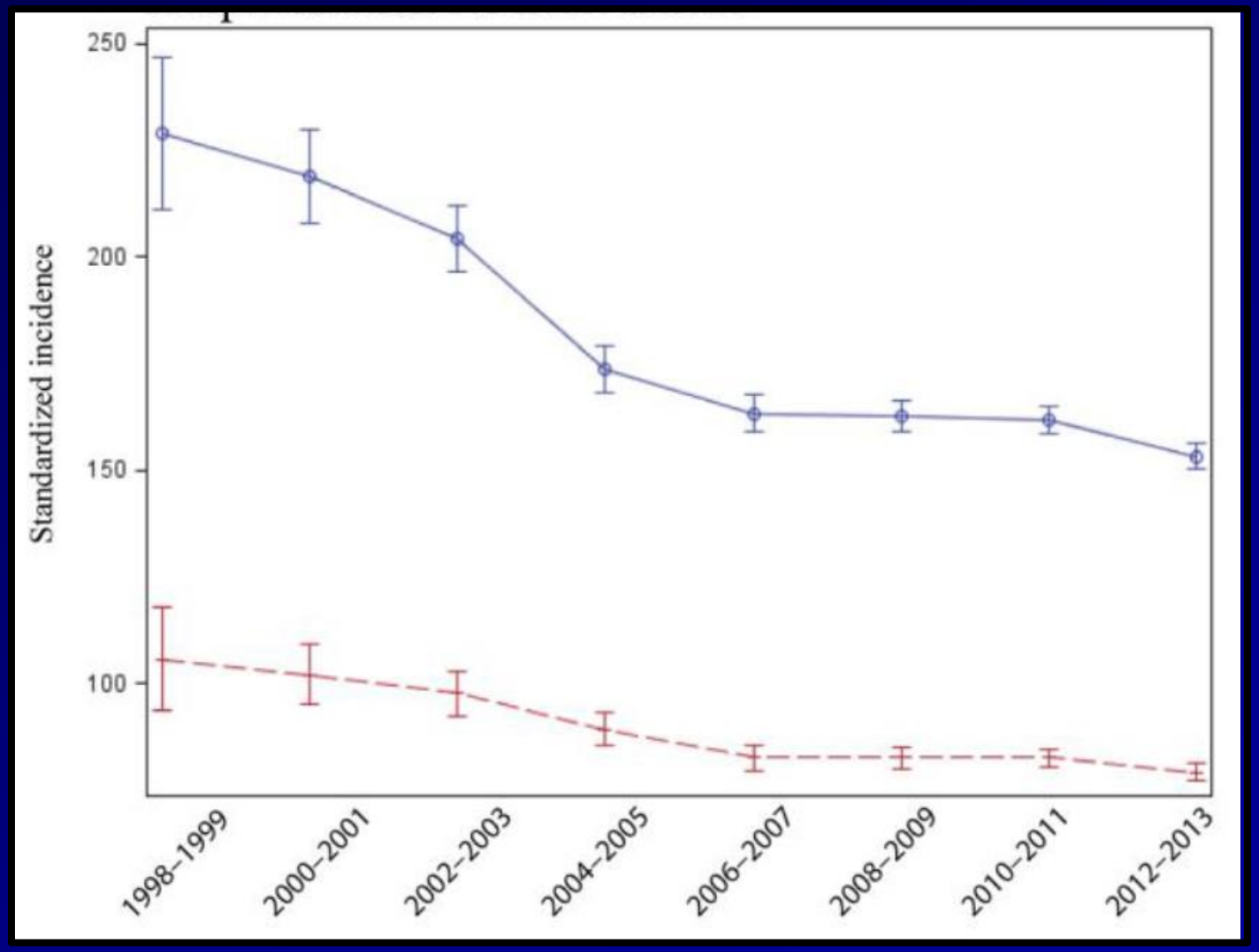
Effects of GLP1 RA and SGLTi on CV death/MI/stroke outcomes



UT Southwestern Medical Center

Zelniker TA, et al. Circulation. 2019 Feb 21. doi: 10.1161/CIRCULATIONAHA.118.038868.

HF Hospitalization Risk Associated with T2DM: Swedish National Registry Data 1998-2013

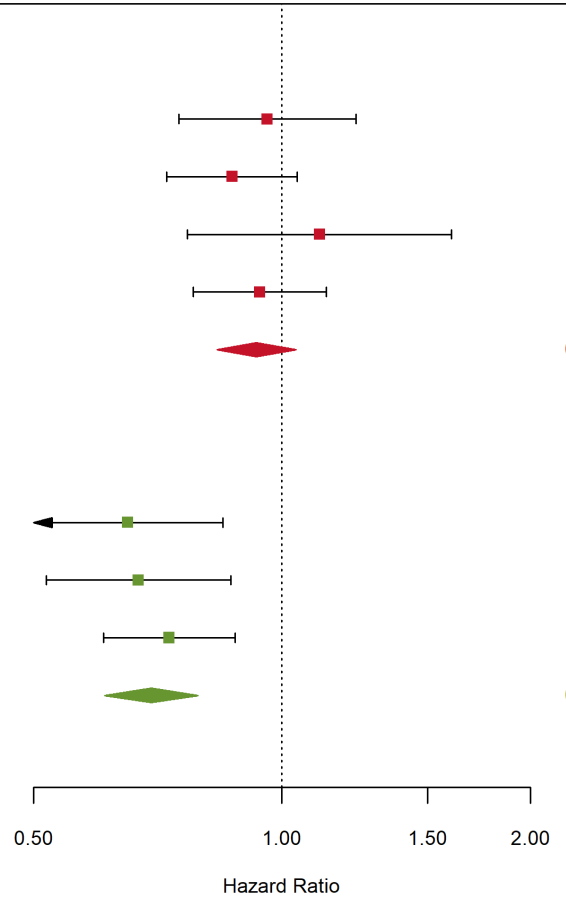


UT Southwestern Medical Center

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

Effects of GLP1 RA and SGLTi on HF Hospitalization

Trials	Patients	Events	Treatment Events per 100 ptyrs	Placebo Events per 100 ptyrs	Weights	HR [95% CI]
GLP1-RA						
ELIXA	6068	249	1.8	1.9	19.7	0.96 [0.75, 1.23]
LEADER	9340	466	1.2	1.4	36.4	0.87 [0.73, 1.05]
SUSTAIN-6	3297	113	1.8	1.6	8.8	1.11 [0.77, 1.61]
EXSCEL	14752	450	0.9	1.0	35.0	0.94 [0.78, 1.13]
Fixed Effects for HHF (P-value=0.20)						**0.93 [0.83, 1.04]**
SGLT2i						
EMPA-REG OUTCOME	7020	221	0.9	1.4	24.0	0.65 [0.50, 0.85]
CANVAS Program	10142	243	0.6	0.9	25.6	0.67 [0.52, 0.87]
DECLARE-TIMI 58	17160	498	0.6	0.8	50.4	0.73 [0.61, 0.88]
Fixed Effects for HHF (P-value<0.001)						**0.69 [0.61, 0.79]**



UT Southwestern Medical Center

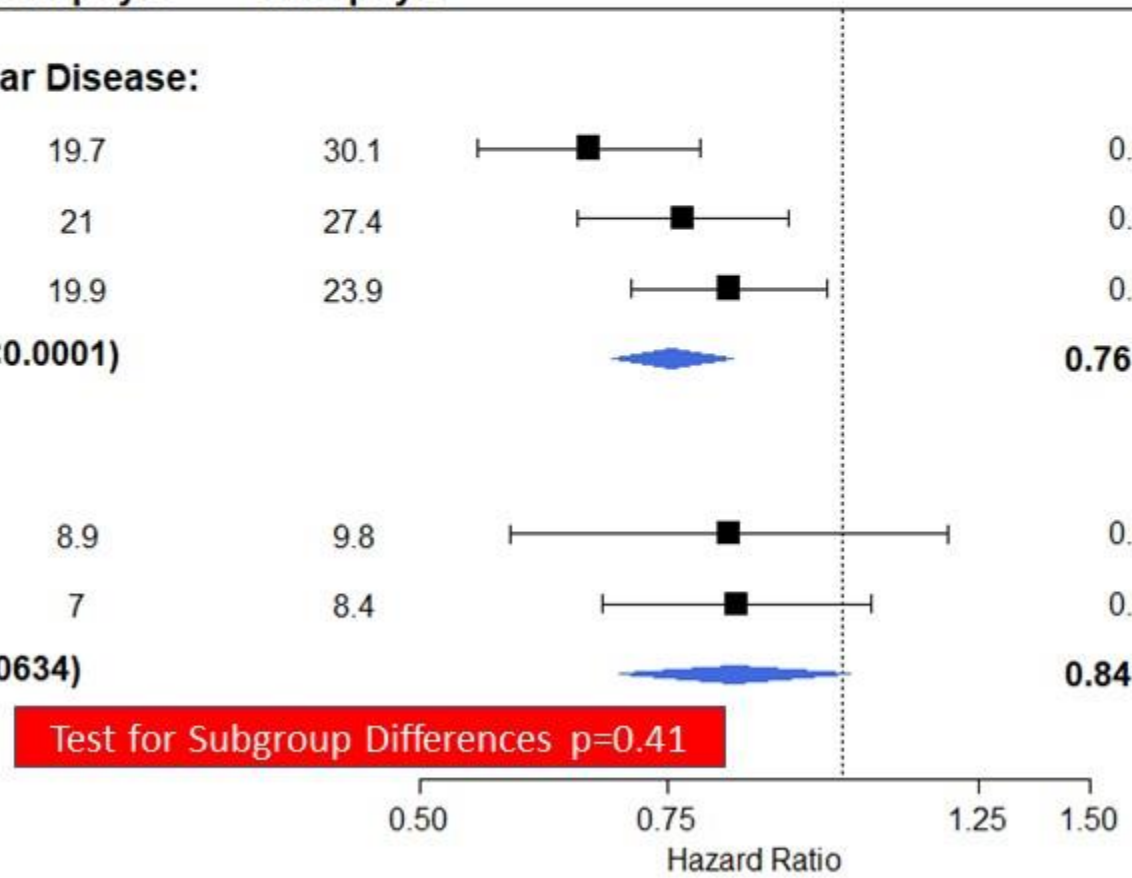
Zelniker TA, et al. Circulation. 2019 Feb 21. doi: 10.1161/CIRCULATIONAHA.118.038868.

Meta-Analysis of CVOTs: CVD/HHF by Presence of ASCVD

DECLARE TIMI-58 Dapagliflozin Effect on Cardiovascular Events

TIMI

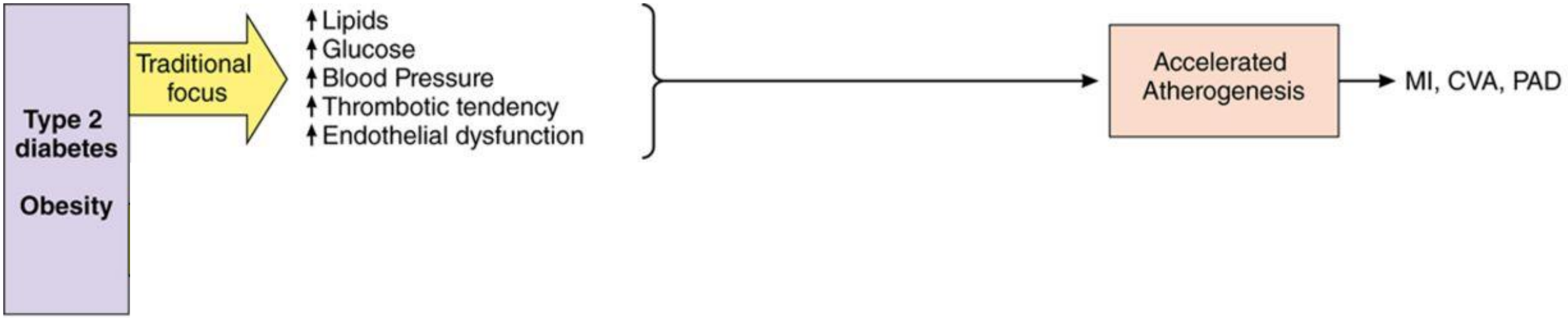
CVD/HHF	Treatment Events per 1000 pt-yrs	Placebo Events per 1000 pt-yrs	HR [95% CI]
Atherosclerotic Cardiovascular Disease:			
EMPA-REG OUTCOME	19.7	30.1	0.66 [0.55, 0.79]
CANVAS Program	21	27.4	0.77 [0.65, 0.92]
DECLARE-TIMI 58	19.9	23.9	0.83 [0.71, 0.98]
FE Model for ASCVD (P-value <0.0001)			**0.76 [0.69, 0.84]**
Multiple Risk Factor:			
CANVAS Program	8.9	9.8	0.83 [0.58, 1.19]
DECLARE-TIMI 58	7	8.4	0.84 [0.67, 1.04]
FE Model for MRF (P-value = 0.0634)			**0.84 [0.69, 1.01]**



BRIGHAM HEALTH
BRIGHAM AND WOMEN'S HOSPITAL
HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Zelniker TA et al. Lancet 2018; DOI 10.1016/S0140-6736(18)32590-X

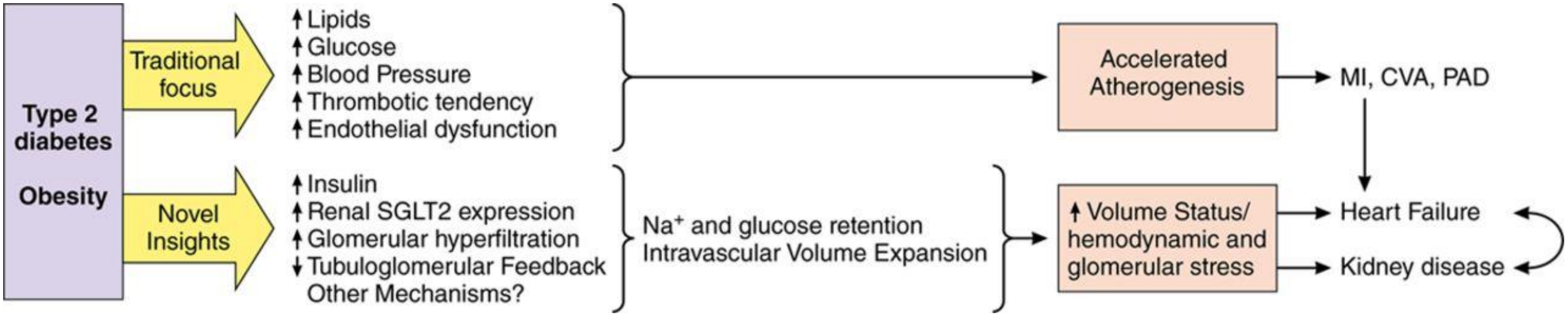
Redefining pathways to cardiorenal complications of type 2 diabetes mellitus.



Sattar N & McGuire DK. Circulation 2018; 138:7-9

Copyright © American Heart Association, Inc. All rights reserved.

Redefining pathways to heart failure and kidney disease in patients with type 2 diabetes mellitus.

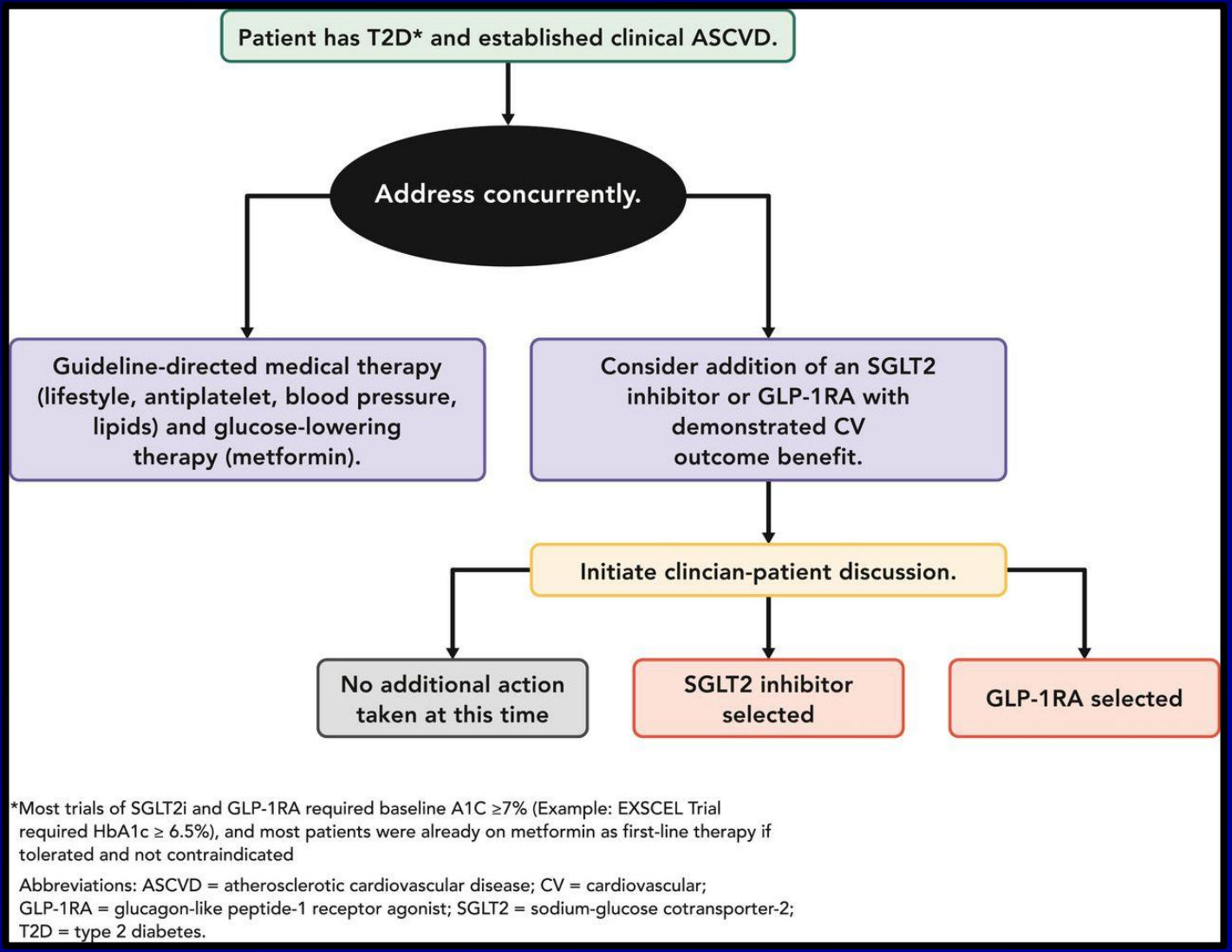


American Heart Association.

Sattar N & McGuire DK. Circulation 2018; 138:7-9

Copyright © American Heart Association, Inc. All rights reserved.

ACC Decision Pathway



Das SR et al. https://doi.org/10.1016/j.jacc.2018.09.020

PERSPECTIVE

Use of Sodium Glucose Cotransporter 2 Inhibitors in the Hands of Cardiologists

With Great Power Comes Great Responsibility

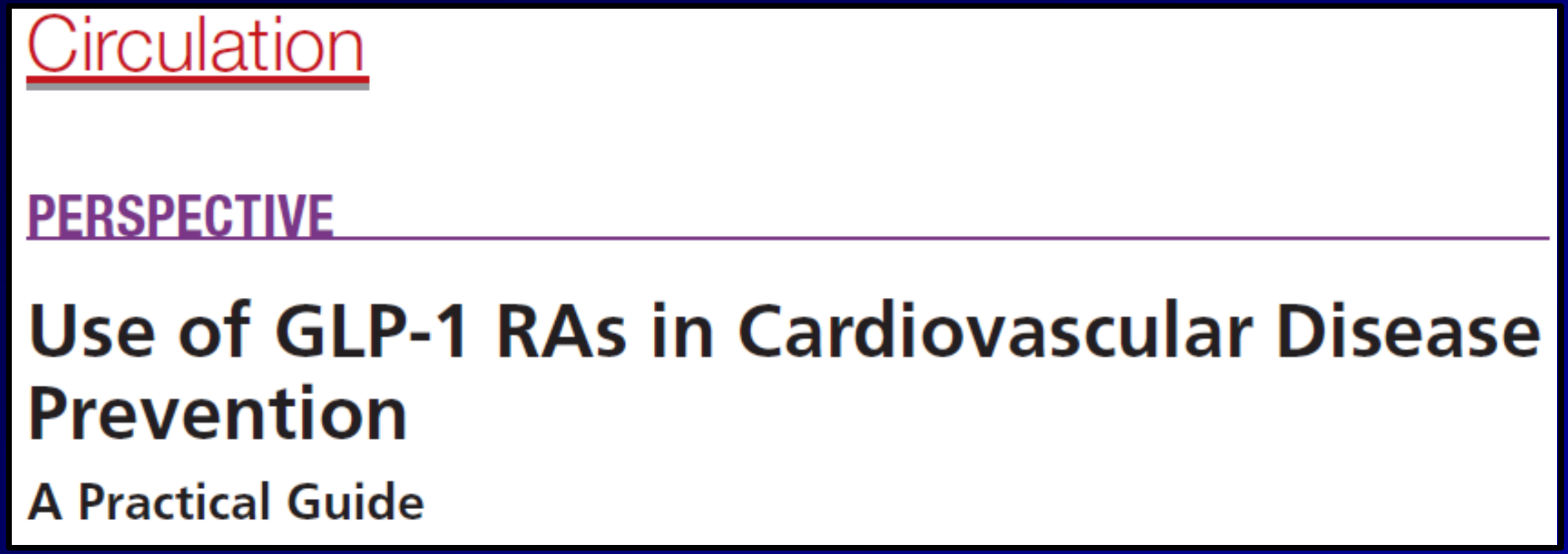
FRAME OF REFERENCE

- Consider altering background blood pressure medications if intensively controlled
- Consider stopping/reducing background diuretics
- If on insulin and/or sulfonylurea, consider dose reducing each of those

- Counsel re: urinary hygiene
- “Sick Day” medication concept-hold on days with reduced PO intake

UT Southwestern Medical Center

Cherney DZ and Udell JA. Circulation 134: 1915-1917



- Start lowest dose and increase at 1-2 week intervals
- Counsel patients to expect some nausea initially that almost always resolves in a week or 2 and uncommonly prohibitive
- Encourage eating small portions and to stop eating when satisfied instead of when full

Lingvay I and Leiter LA. Circulation 2018; 137: 2200-2202

Conclusions

- Regulatory requirements have dramatically altered the trial landscape of drug development for T2DM
  - > 300,000 patients enrolled/planned in CV outcomes trials
- Trial results have directly impacted contemporary care for T2DM
- 6 completed trials demonstrating CV safety
  - DPP4i: saxagliptin, alogliptin, sitagliptin, linagliptin
    - Labeled caution for HF for all DPP4i's based on alogliptin and saxagliptin data
  - GLP1 RA: lixisenatide, exenatide ER
- 7 trials/programs have reported CV benefit
  - SGLTi: empagliflozin, canagliflozin, dapagliflozin
  - GLP1 RA: liraglutide, semaglutide, albiglutide, dulaglutide