UPDATES IN CARDIOLOGY:

LIPID AND DIABETIC MANAGEMENT

Clint Allred, MD, FACC

HEALTH
UNIVERSITY OF UTAH

DISCLOSURES

- None

2018

Retraction and Republication diovascular Disease with a Mediter 1279-90.

Andrew Sharp, Rob
Justin E Davies, Dar

Summary

Background Syn
is commonly ol
show its efficac

391: 31–40
line
2017
org/10.1016/

Figure 2. An atrial view of the MitraClip device (Abbott Vascular) grasping both leaflets of the mitral valve.

FILE Barber Eric Muhammad (left) a

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 72, NO. 8, 2018

PUBLISHED BY ELSEVIER

JACC CV HEALTH PROMOTION SERIES

JACC FOCUS SEMINAR

Reprint of: Positive Psychological Well-Being and Cardiovascular Disease

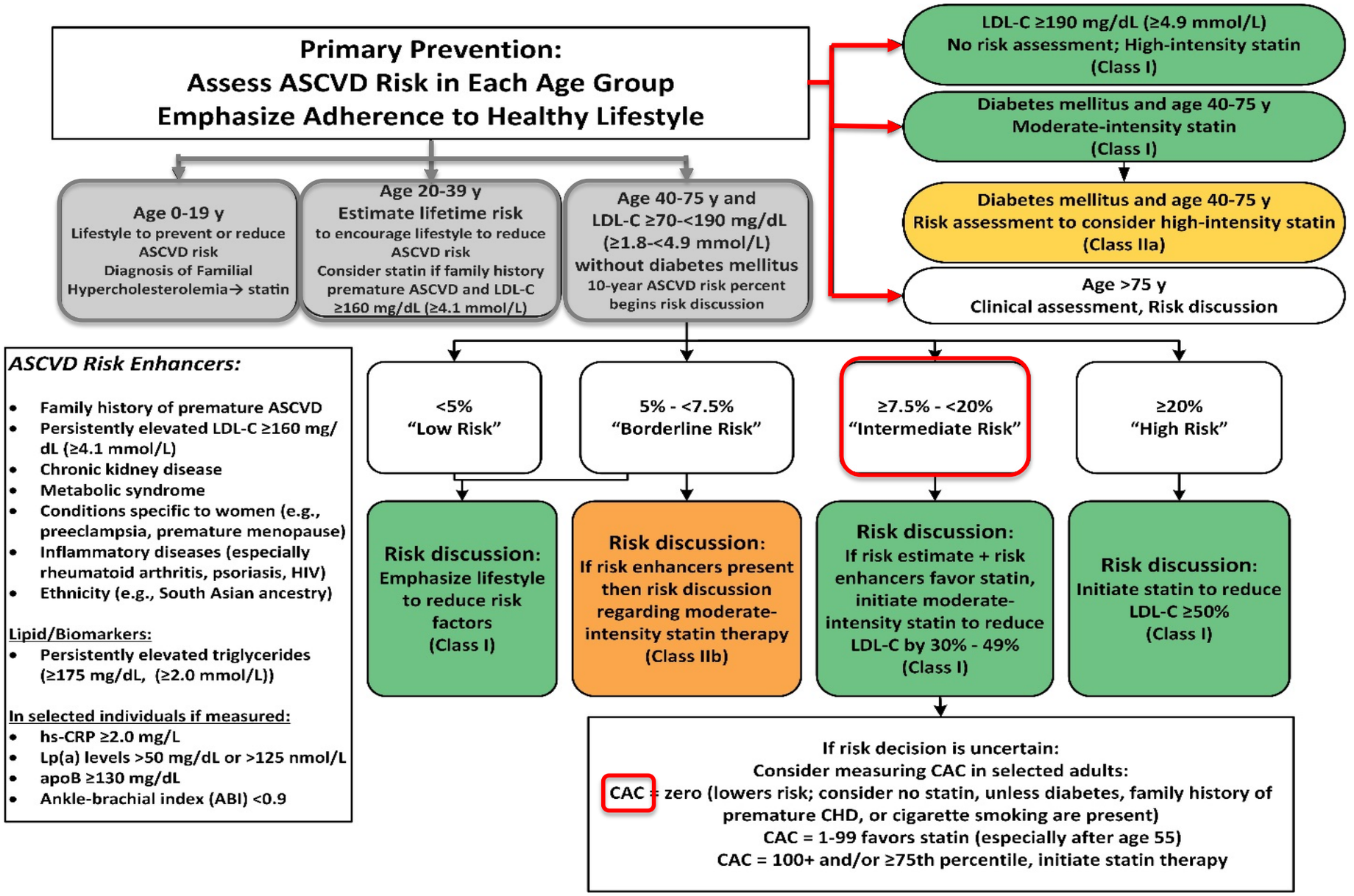
JACC Health Promotion Series

Laura D. Kubzansky, PhD,[a,*] Jeff C. Huffman, MD,[b,c,*] Julia K. Boehm, PhD,[d] Rosalba Hernandez, PhD,[e] Eric S. Kim, PhD,[a] Hayami K. Koga, MD, MPH,[a] Emily H. Feig, PhD,[b,c] Donald M. Lloyd-Jones, MD, MSc,[f] Martin E.P. Seligman, PhD,[g] Darwin R. Labarthe, MD, MPH, PhD[f]

LEARNING OBJECTIVES

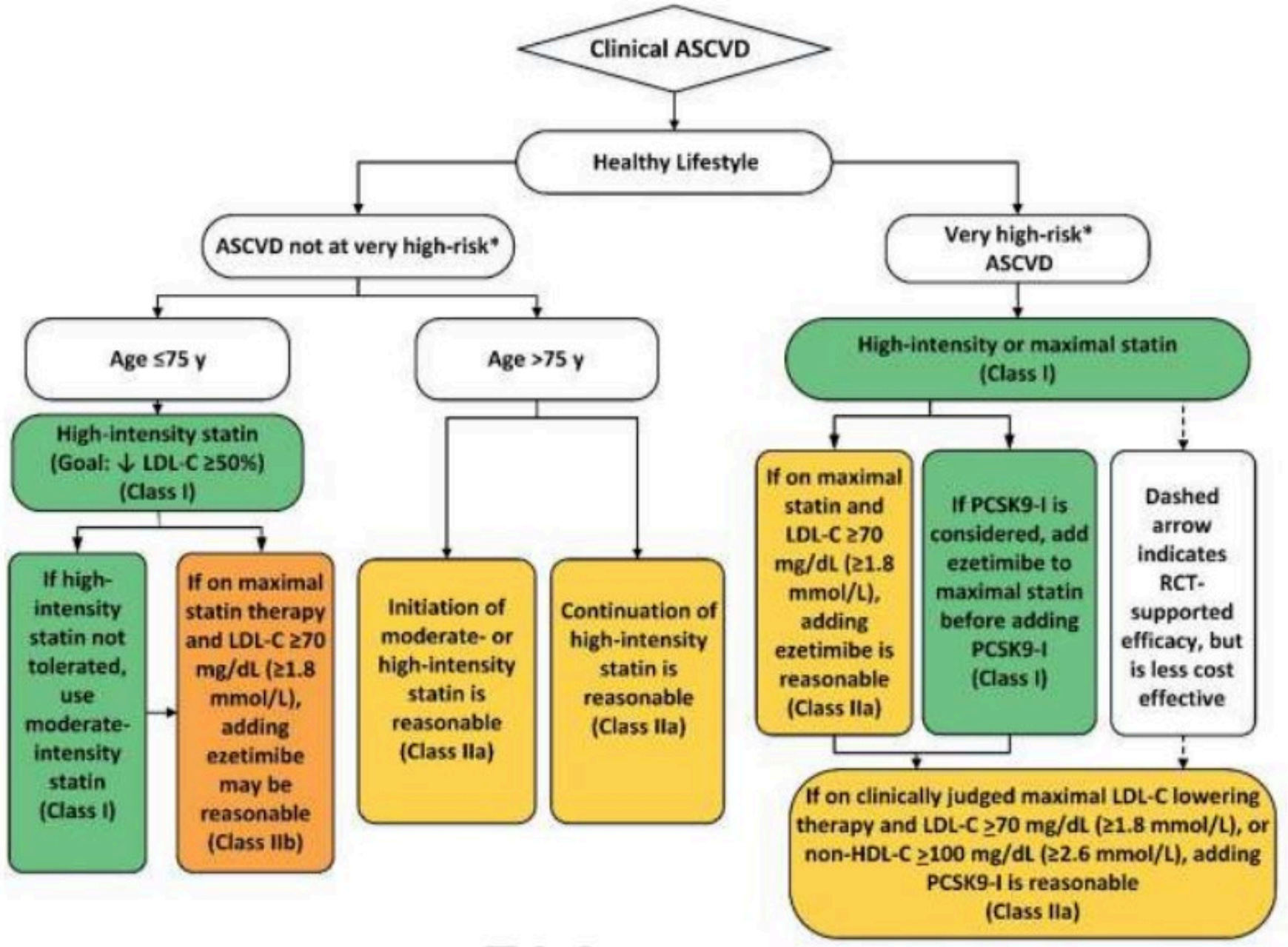
1. Review updated Lipid Guideline including the role of non-statin means to treat hyperlipidemia

1. Review diabetic management strategies for the cardiac patient



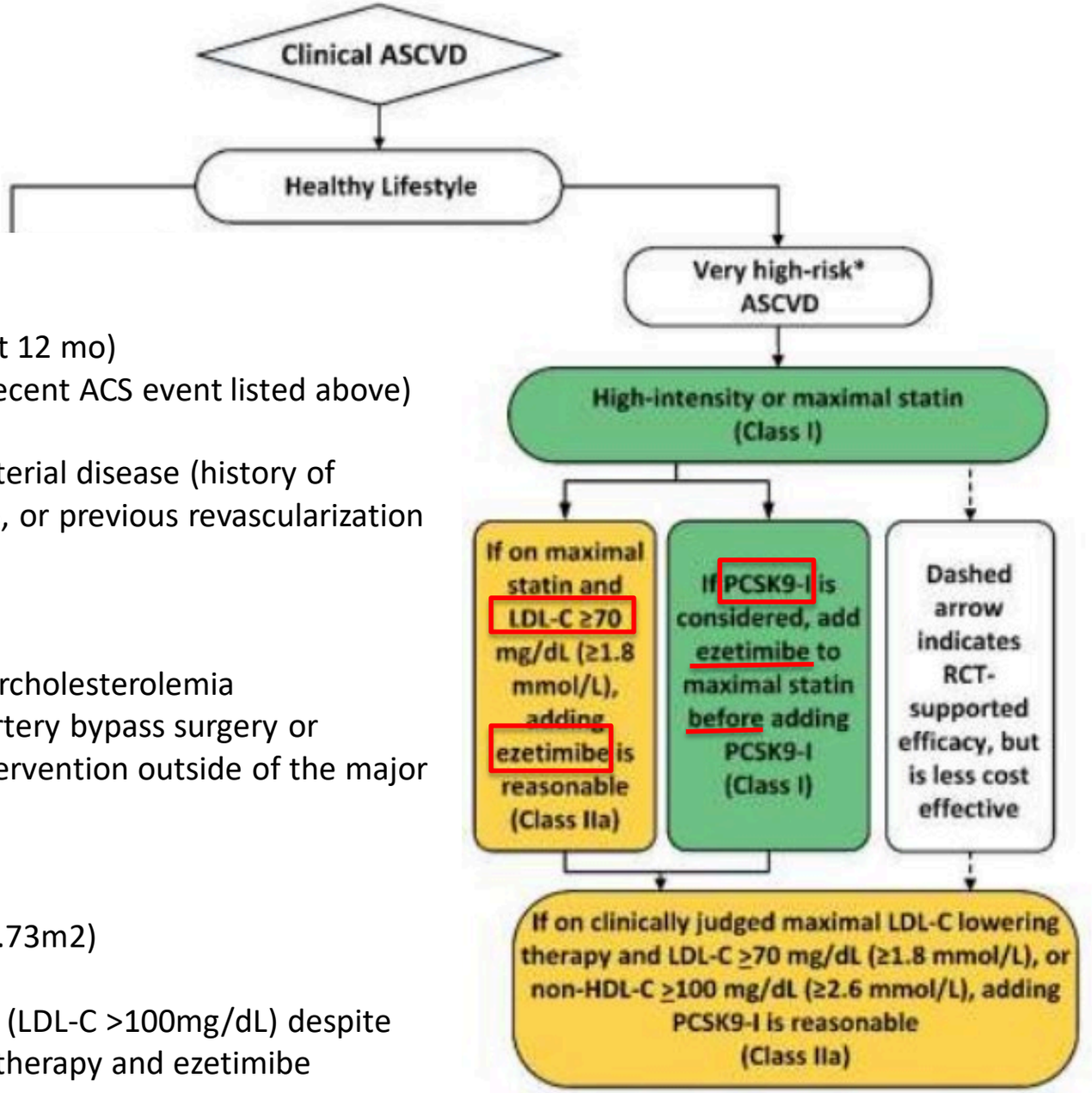
Grundy et al 2018 JACC

Figure 1. Secondary Prevention in Patients With Clinical ASCVD



Grundy et al 2018

Figure 1. Secondary Prevention in Patients With Clinical ASCVD

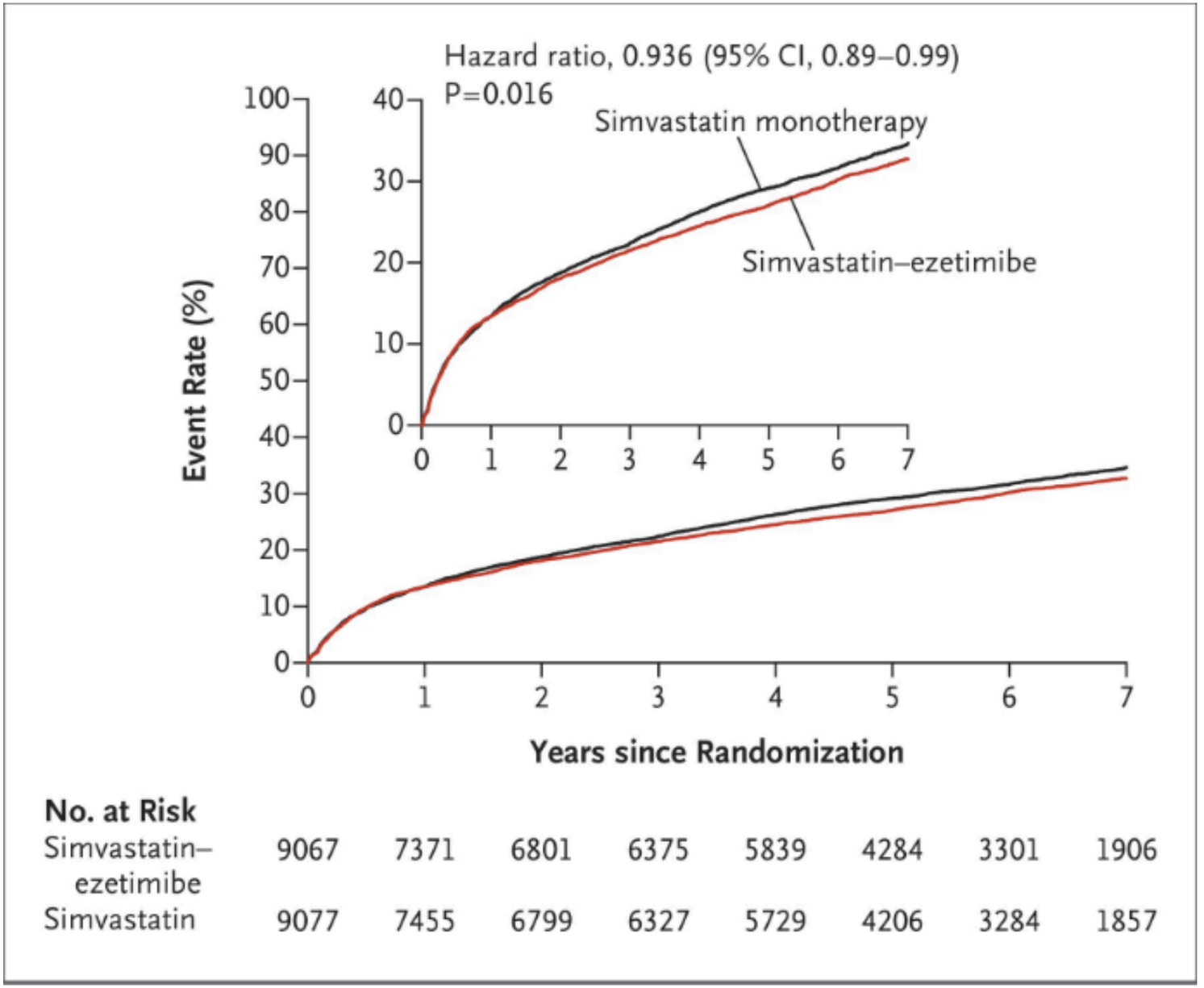


Very high risk of future ASCVD events

- Major ASCVD Events
  - Recent ACS (within the past 12 mo)
  - History of MI (other than recent ACS event listed above)
  - History of ischemic stroke
  - Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation)
- High-Risk Conditions
  - Age >65 y
  - Heterozygous familial hypercholesterolemia
  - History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
  - Diabetes mellitus
  - Hypertension
  - CKD (eGFR 15-59mL/min/1.73m2)
  - Current smoking
  - Persistently elevated LDL-C (LDL-C >100mg/dL) despite maximally tolerated statin therapy and ezetimibe
  - History of congestive HF

Grundy et al 2018

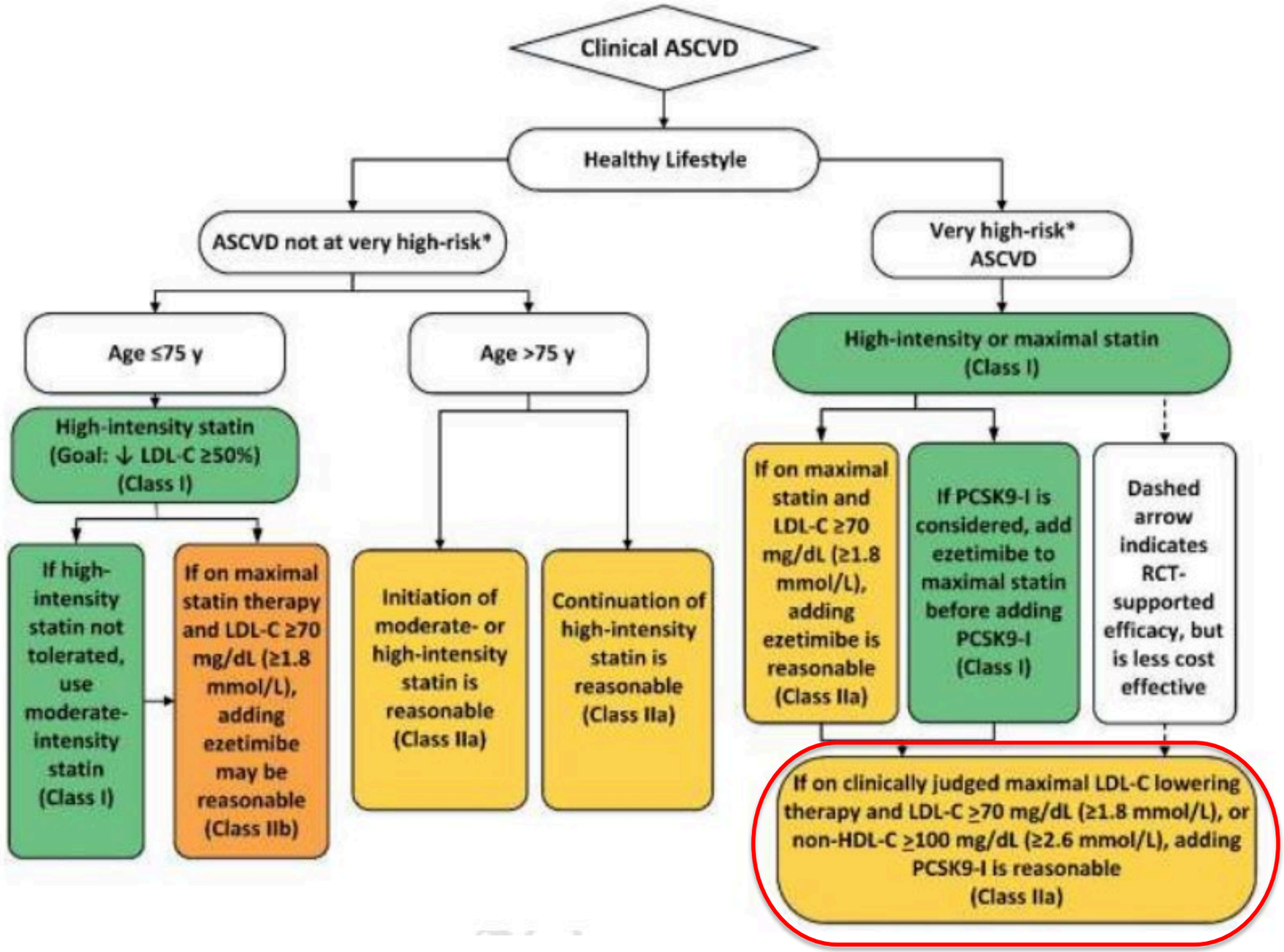
IMPROVE-IT



ARR: 2%
RRR: 5.7%
NNT 50

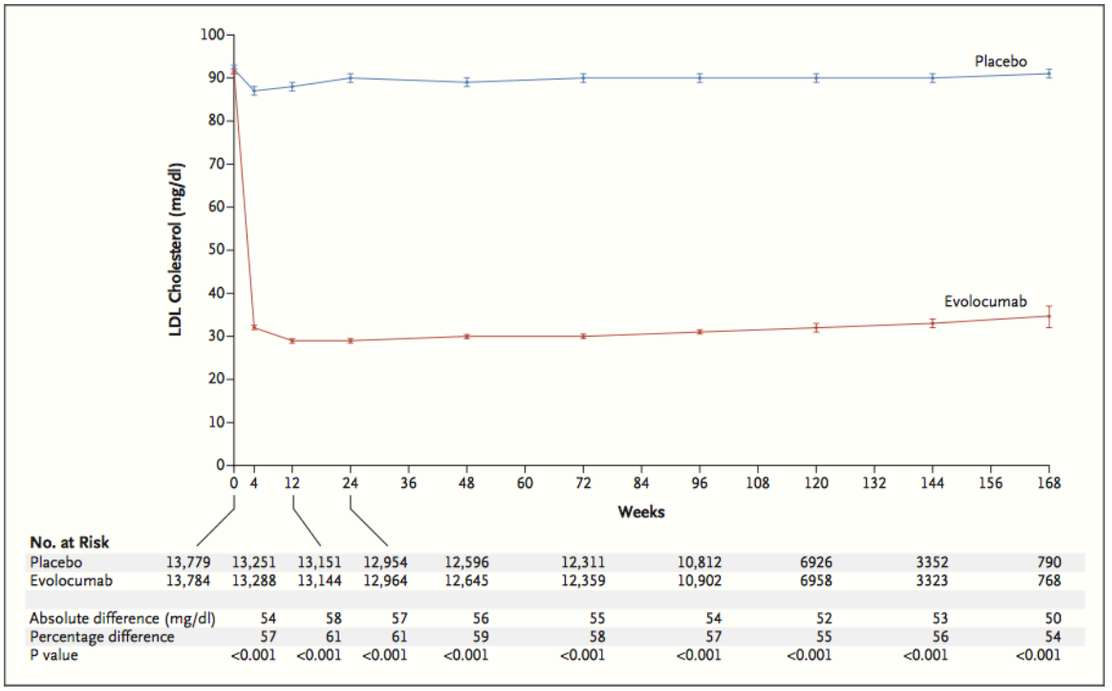
Cannon et al. NEJM 2015

Figure 1. Secondary Prevention in Patients With Clinical ASCVD



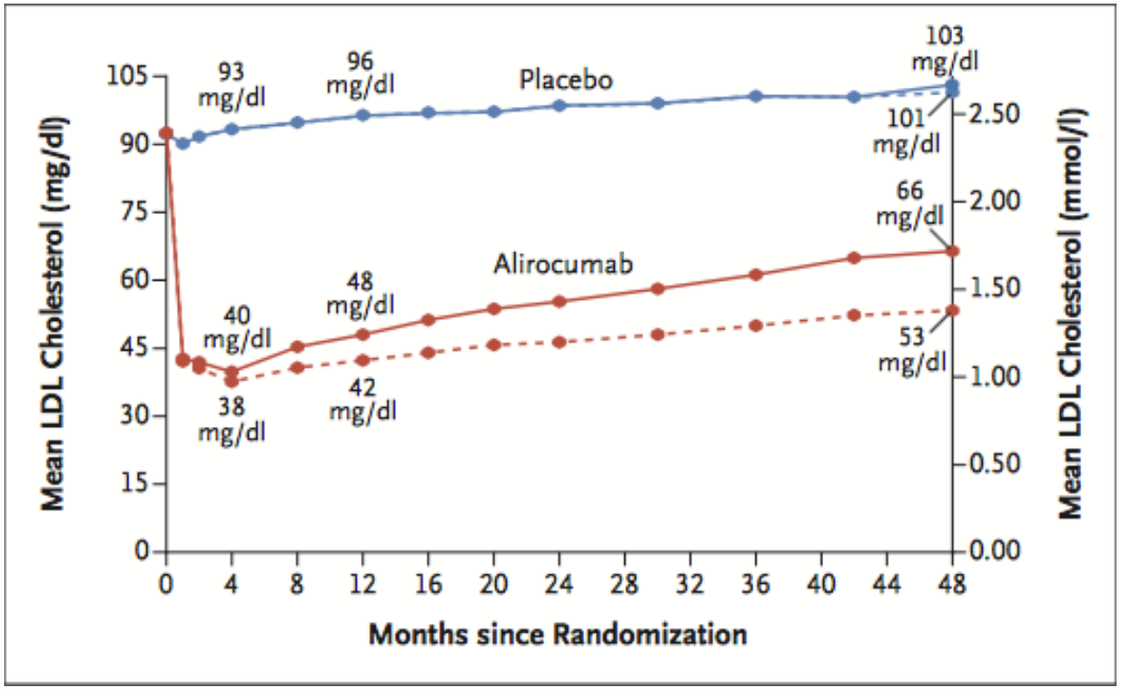
Grundy et al 2018

EVOLOCUMAB – (REPATHA)



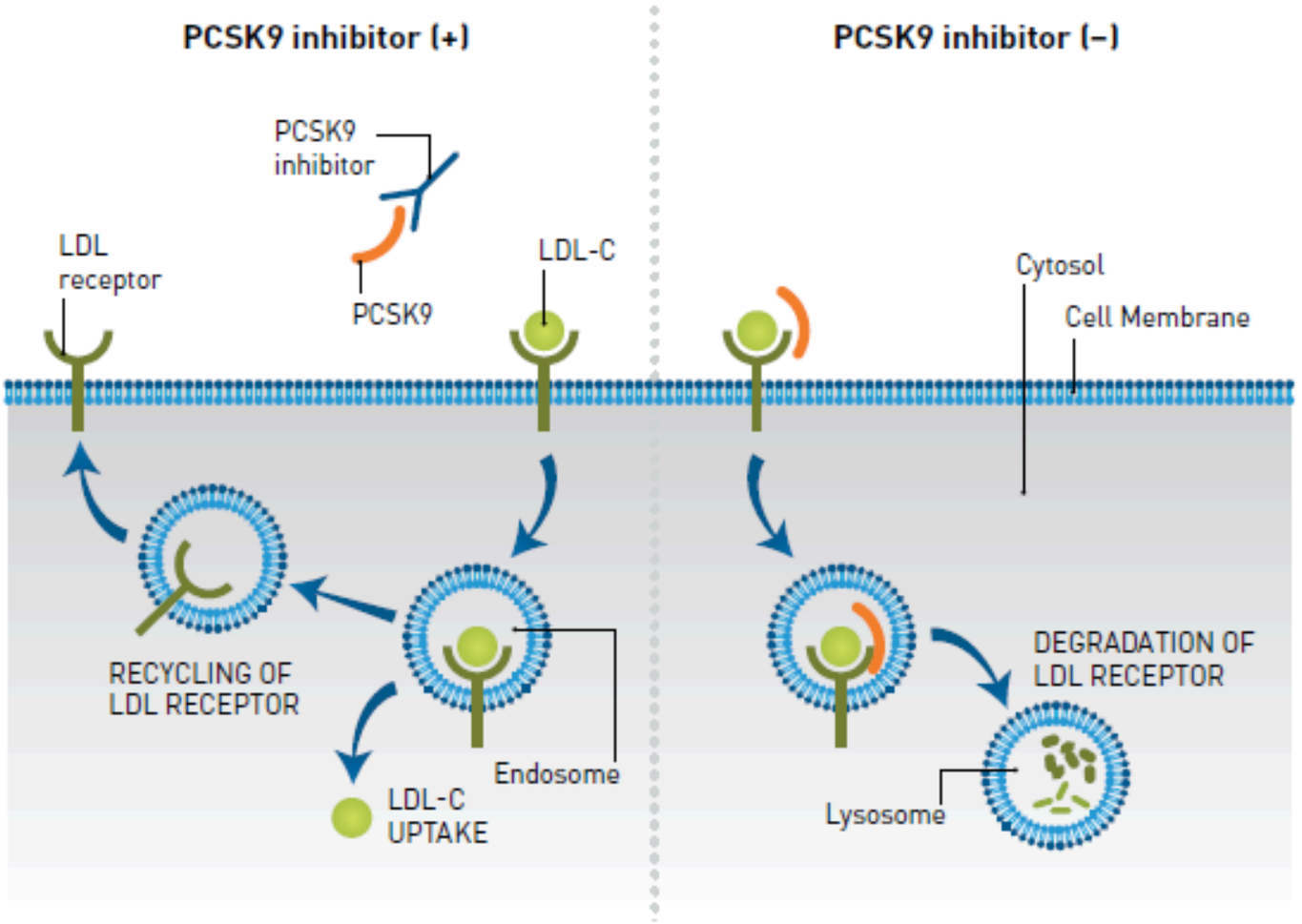
Sabatine et al. NEJM 2017

Alirocumab (Praluent)

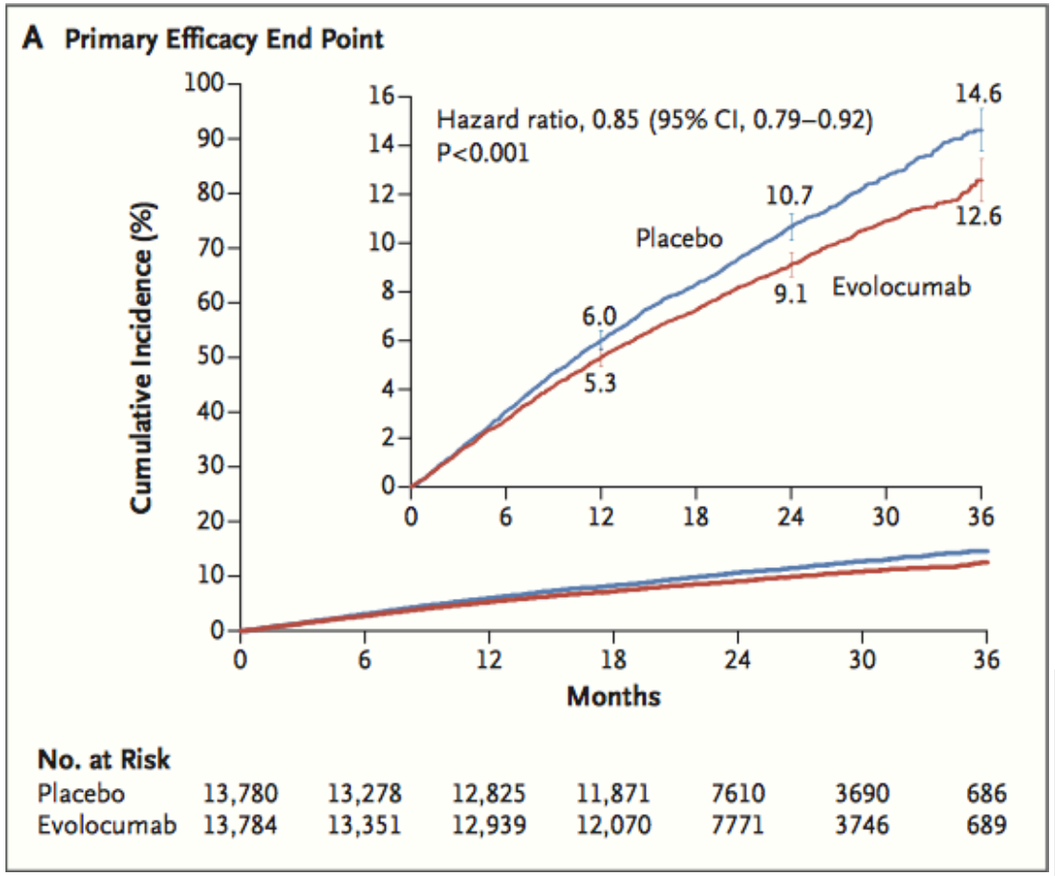


Schwartz et al NEJM 2018

FIGURE. Mechanism of LDL-C Reduction via PCSK9 Inhibition[4,a]



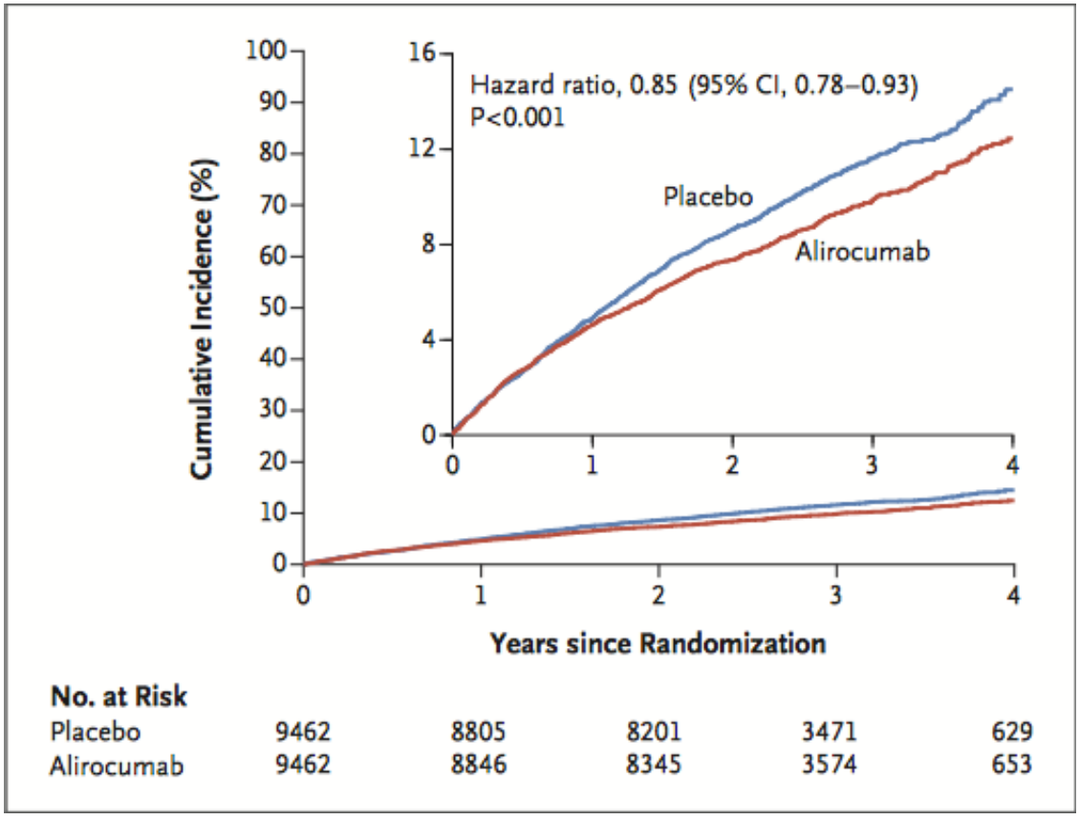
[a]Without a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, PCSK9 binds to the low-density lipoprotein (LDL) receptor (LDLR) leading to lysosomal degradation of LDLRs. With PCSK9 inhibition (eg, via monoclonal antibodies [mAb] binding), the binding of PCSK9 to LDLRs is blocked, which stimulates recycling of the LDLR and leads to increased LDLR expression at the cell membrane. The increase in LDL receptor expression then leads to an increase in low-density lipoprotein cholesterol (LDL-C) binding and catabolism.



Sabatine et al. NEJM 2017

ARR: 1.5%

NNT: 67

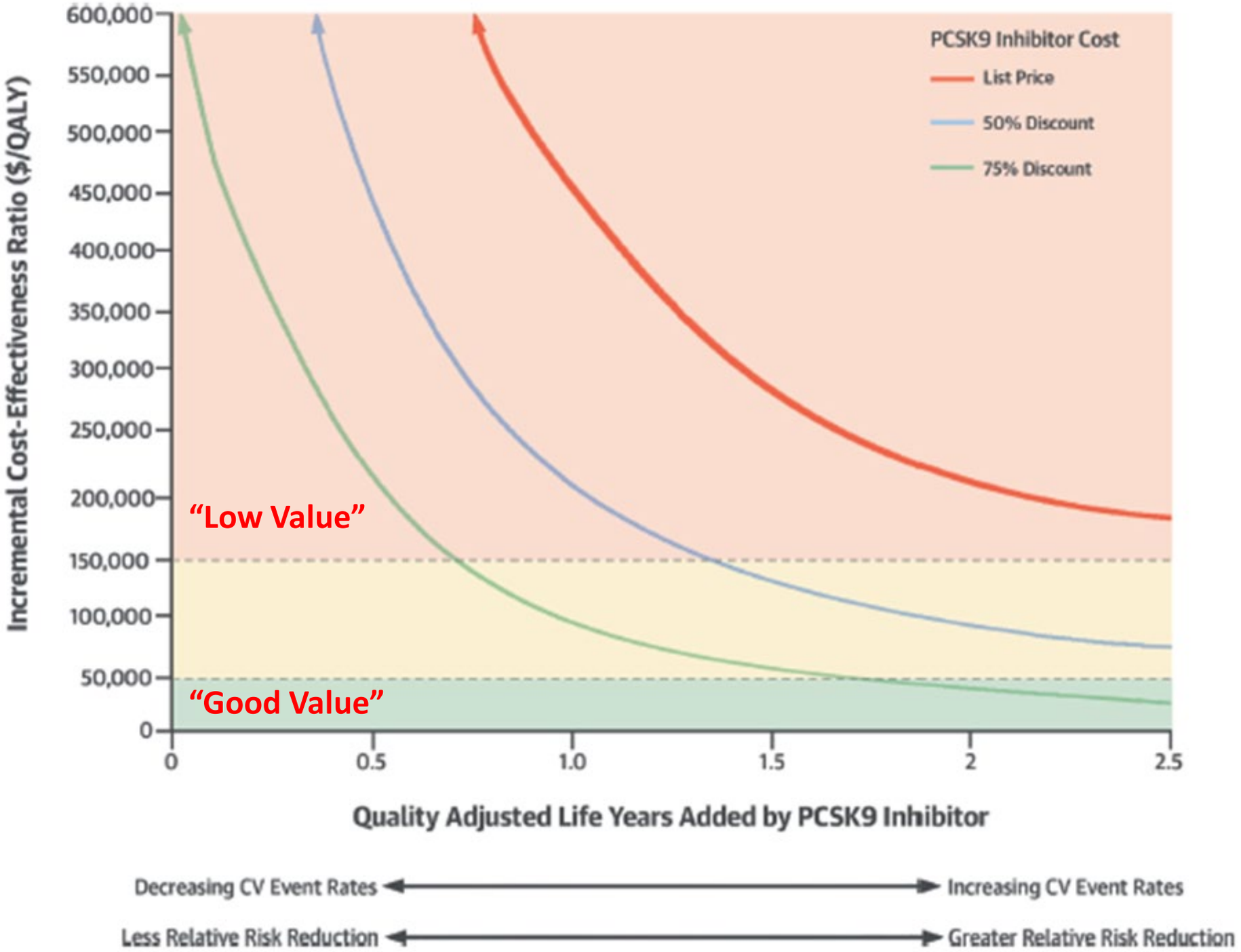


ARR: 1.6%

NNT: 62

Schwartz et al NEJM 2018

PCSK9I COST EFFECTIVENESS (MID 2018 $)



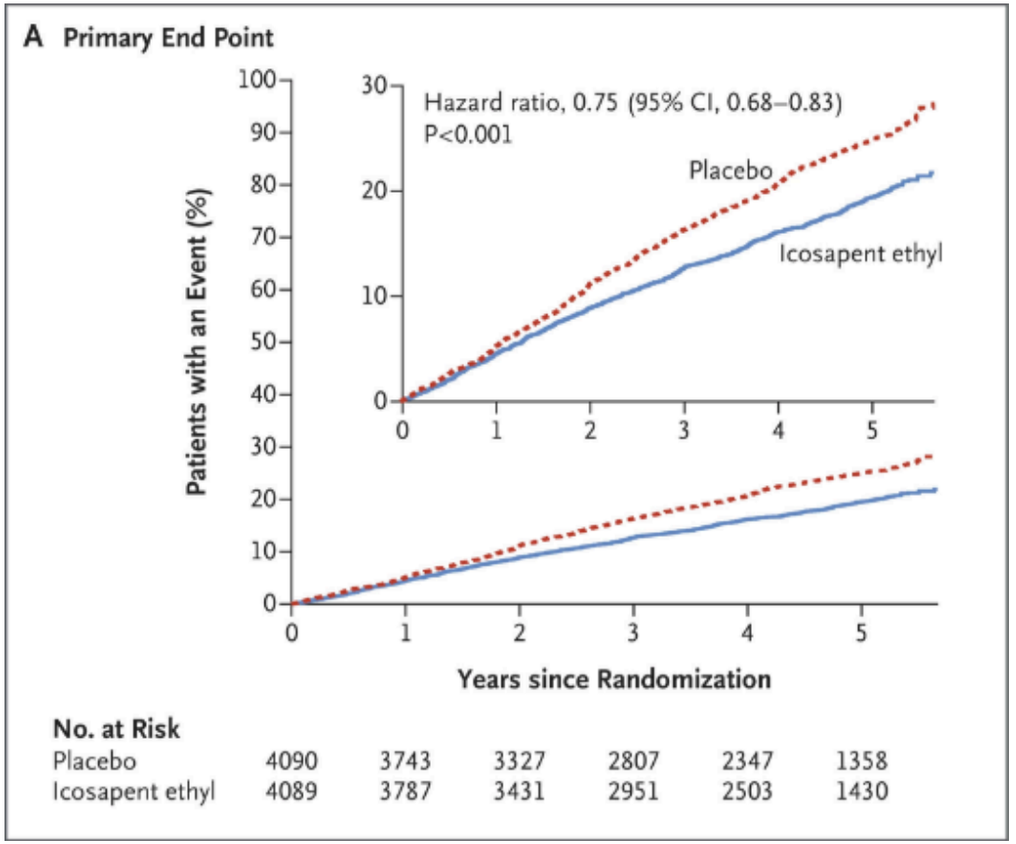
Hlatky et al. *JACC*. 2017;70:2677-87

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

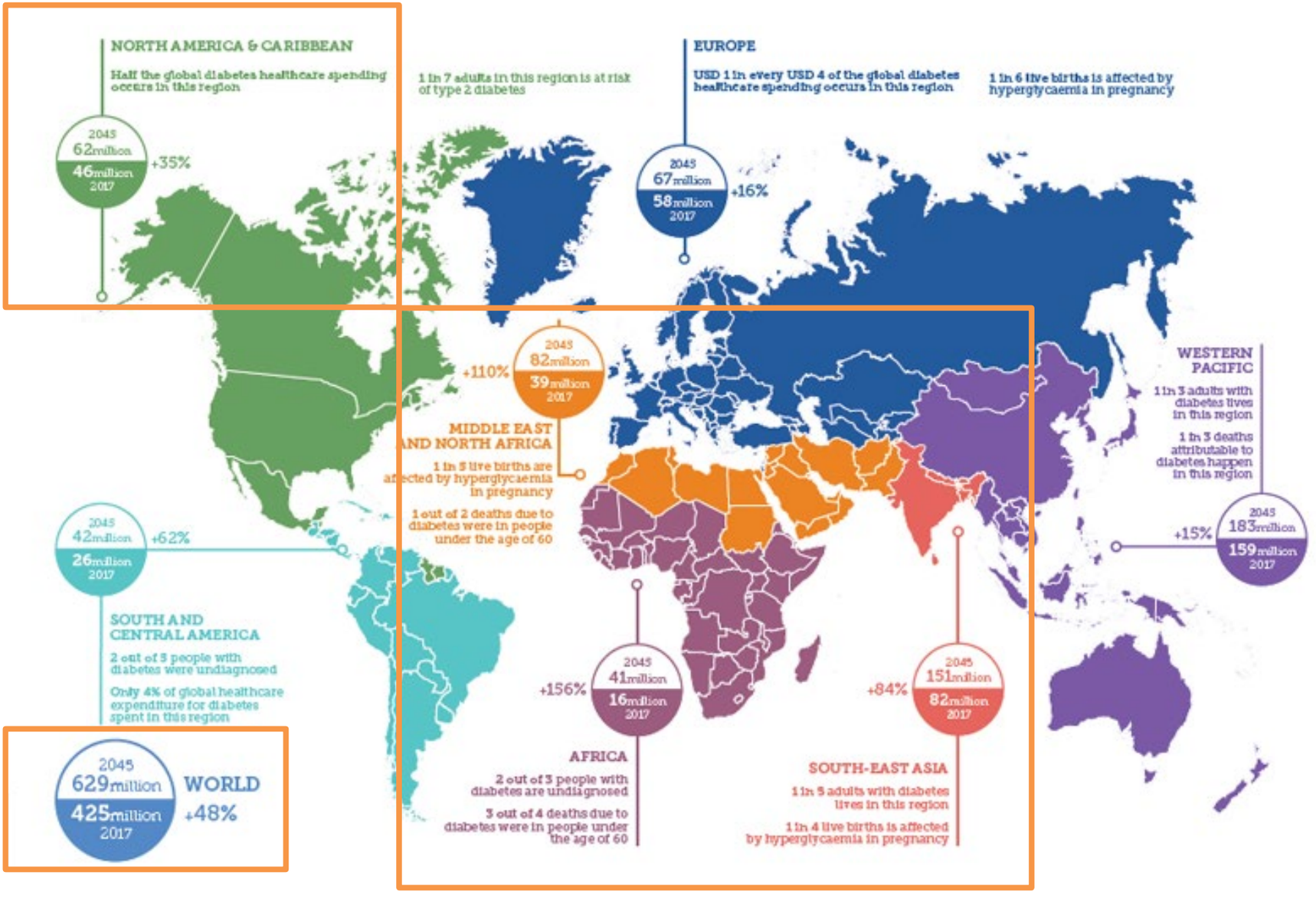


ARR: 4.8%
NNT: 21

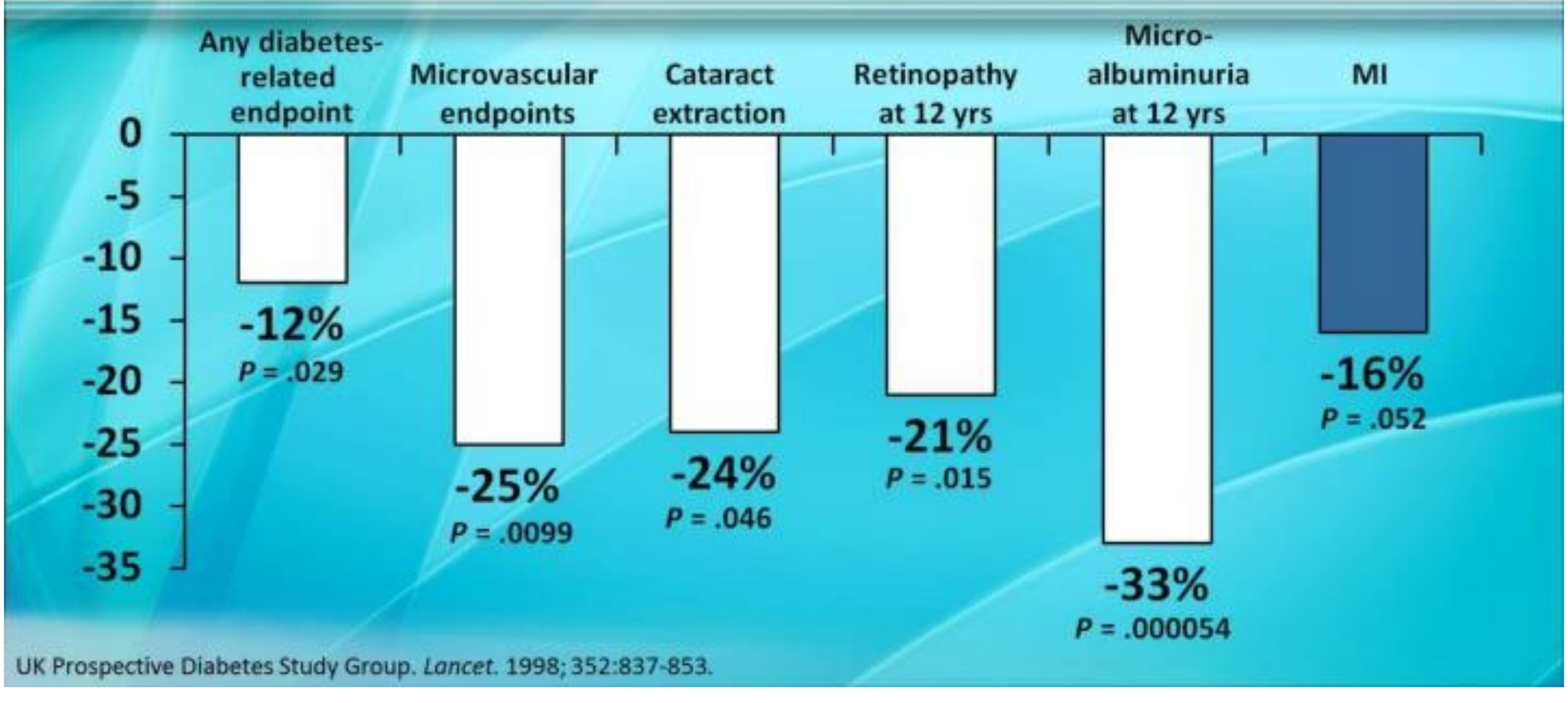
Bhatt et al. NEJM Jan 2019

CARDIOVASCULAR RISK REDUCTION AND TYPE 2 DIABETES MELLITUS

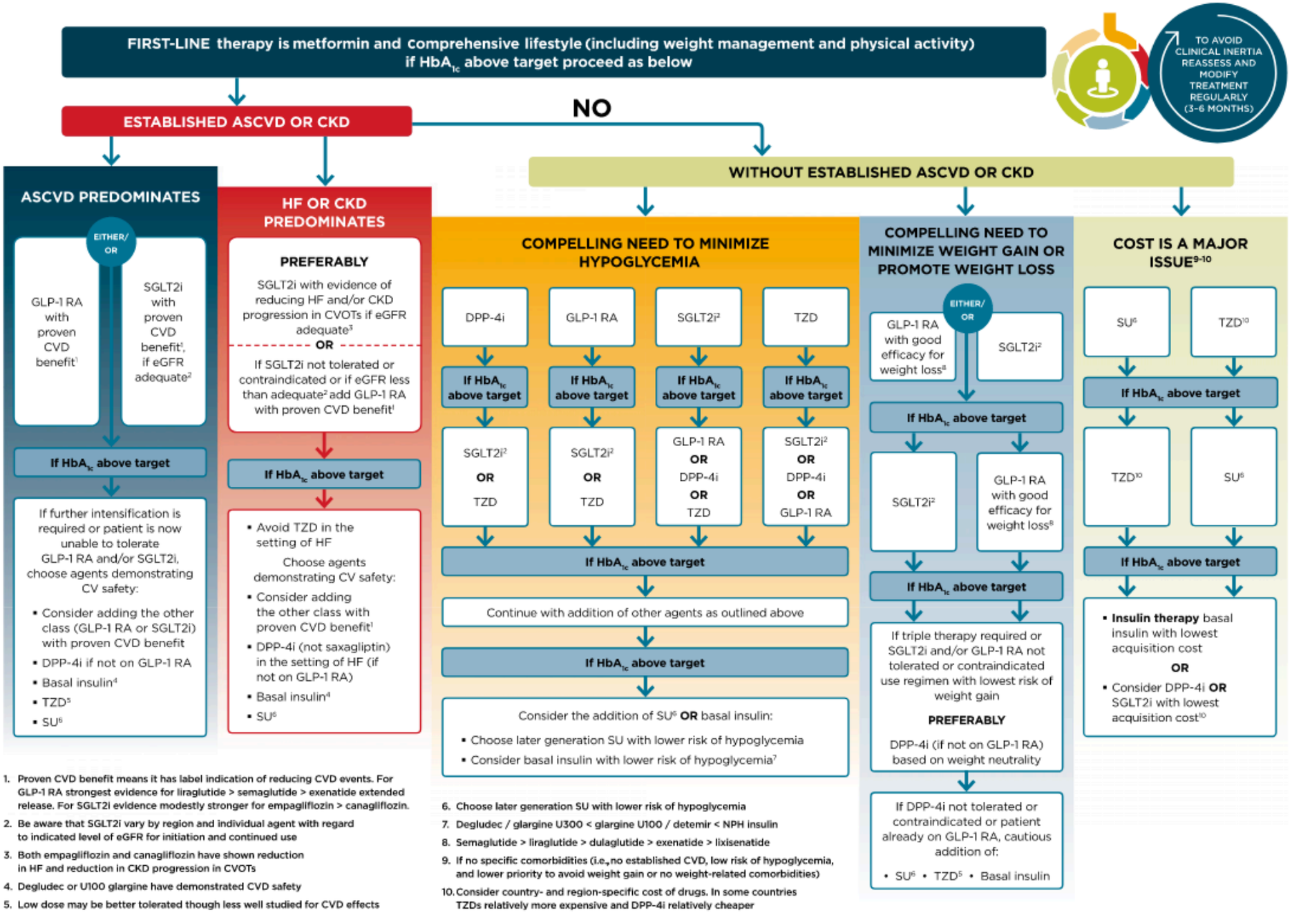
EPIDEMIOLOGY



UKPDS 33: Intensive Glycemic Control Significantly Reduces Microvascular Complications



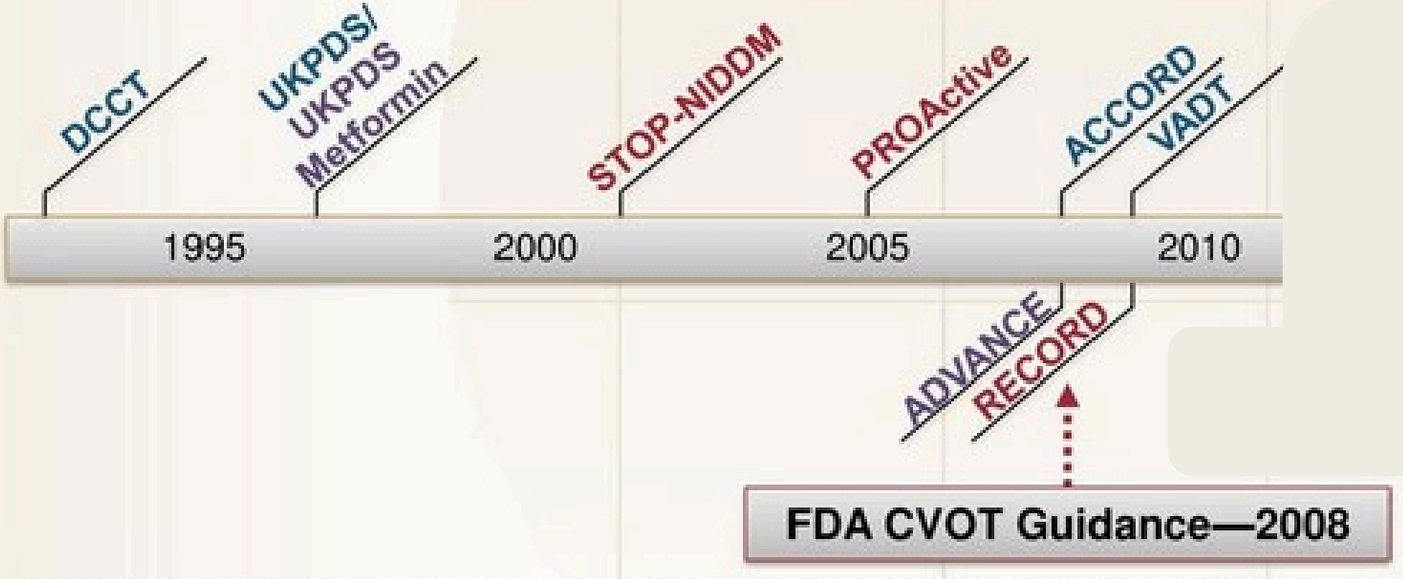
UK Prospective Diabetes Study Group. *Lancet*. 1998; 352:837-853.



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

Figure 9.1—Glucose-lowering medication in type 2 diabetes: overall approach. For appropriate context, see **Fig. 4.1**. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOTs, cardiovascular outcomes trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione. Adapted from Davies et al. (39).

Timeline of Major Diabetes Outcomes Trials



Blue = Intensive vs standard control using same set of glucose-lowering agent(s)
Purple = Intensive control with a specific agent vs standard care
Red = Placebo- or active-controlled study
* = FDA-mandated cardiovascular safety trial

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; CANVAS, Canagliflozin Cardiovascular Assessment Study; DCCT, Diabetes Control and Complications Trial; DEVOTE, Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; EMPA-REG, EMPA-REG OUTCOME trial; Exenatide Study of Cardiovascular Event Lowering; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; ORIGIN, Outcome Reduction with an Initial Glargine Intervention; PROActive, Prospective Pioglitazone Clinical Trial in Macrovascular Events; RECORD, Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction; STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus; SUSTAIN, Trial to Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34)

*UK Prospective Diabetes Study (UKPDS) Group**

Metformin v Diet

1° outcomes:

- Composite of "any DM endpoint"
  - 32% RRR (p=0.002)
- DM related death
  - 42% risk reduction (p=0.002)
- All cause mortality
  - 36% risk reduction (p=0.01)

2° Analysis Metformin v SU/Insulin

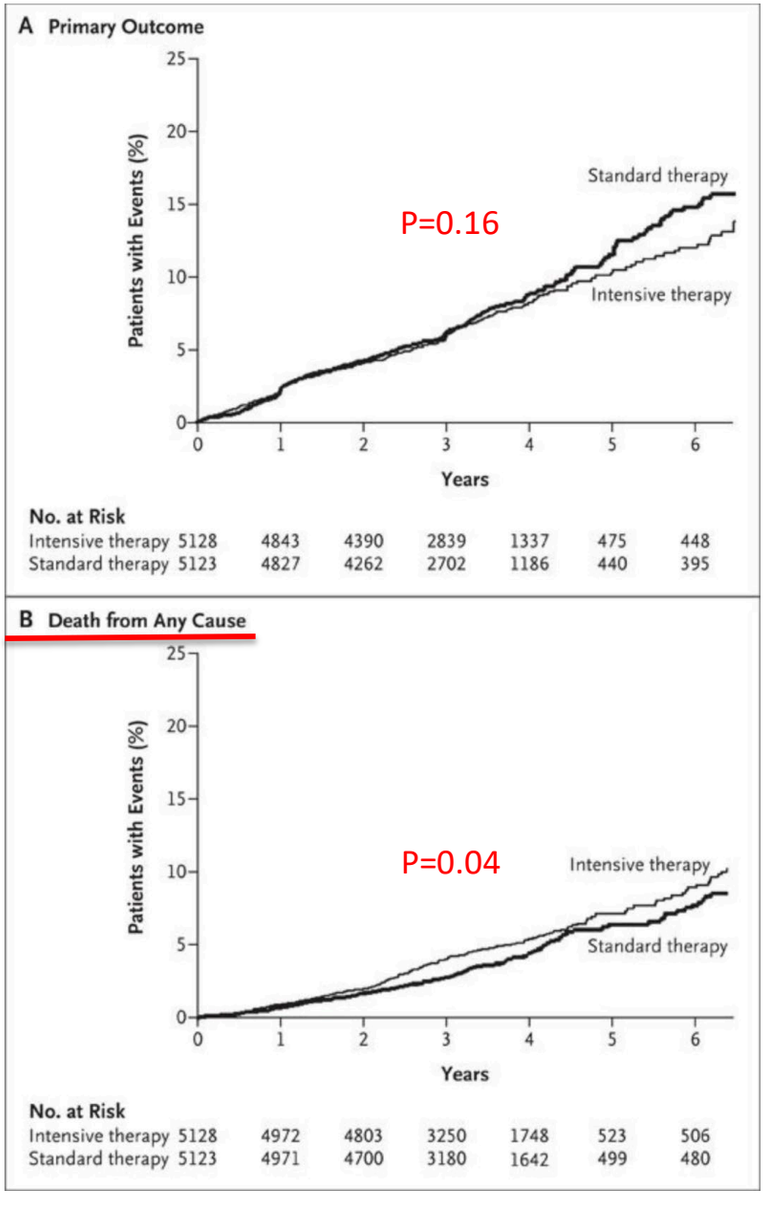
- Composite of "any DM endpoint"
  - 26% RRR (p=0.003)
- DM related death
  - NS (p=0.11)
- All-Cause Mortality
  - 29% RRR (p=0.02)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 12, 2008 VOL. 358 NO. 24

Effects of Intensive Glucose Lowering in Type 2 Diabetes

The Action to Control Cardiovascular Risk in Diabetes Study Group*



Primary Outcome:
Annual rate of nonfatal MI, nonfatal stroke or CV death

The NEW ENGLAND JOURNAL of MEDICINE

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Effects of Intensive Glucose Lowering in Type 2 Diabetes

The Action to Control Cardiovascular Risk in Diabetes Study Group*

Table 3. Adverse Events, Clinical Measures, Tobacco Use, and Use of Nonglycemic Medication after Randomization.*

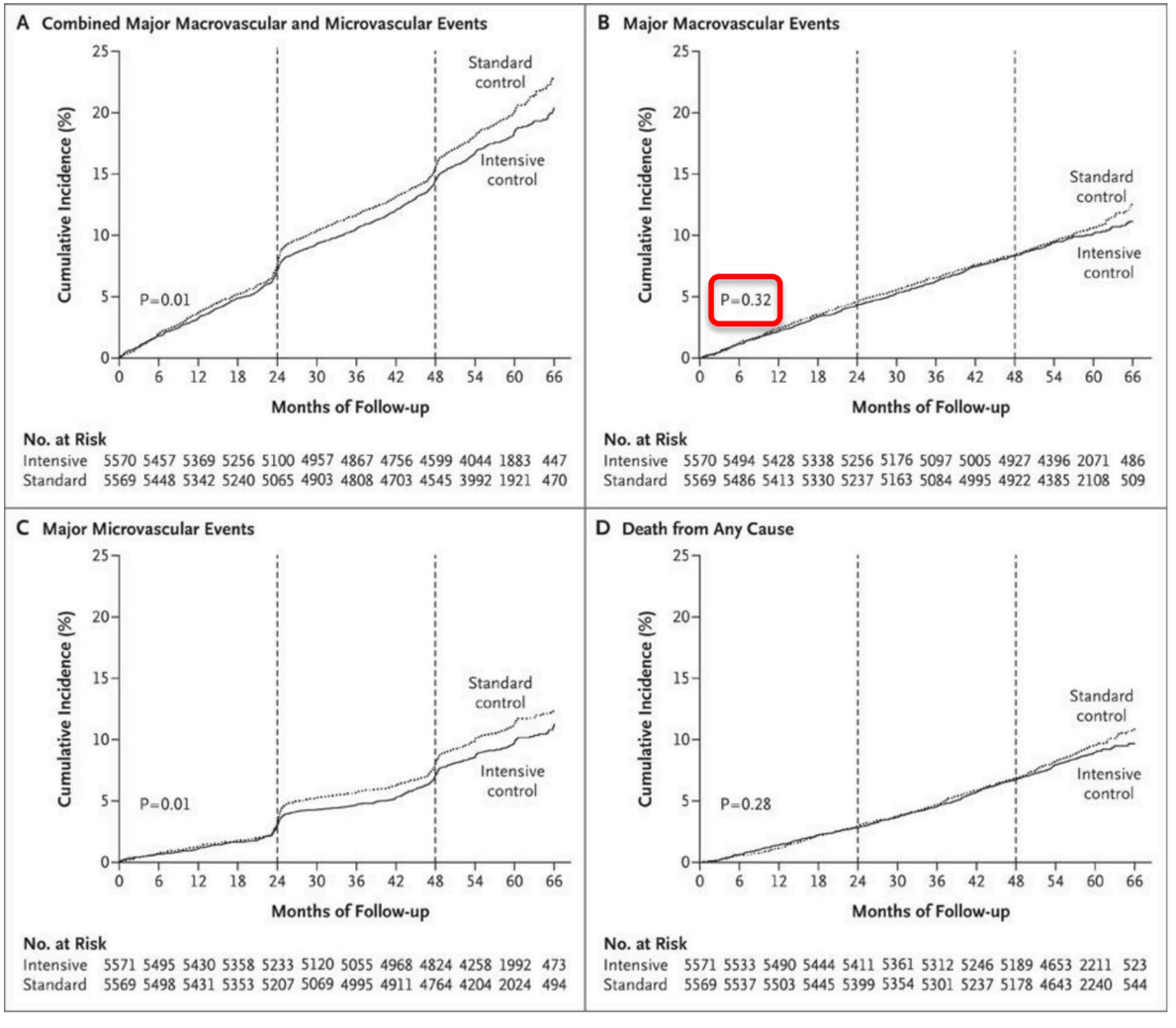
Variable	Intensive Therapy (N=5128)	Standard Therapy (N=5123)	P Value†
Adverse events			
Hypoglycemia — no. (%)			
Requiring medical assistance	538 (10.5)	179 (3.5)	<0.001
Requiring any assistance	830 (16.2)	261 (5.1)	<0.001
Fatal or nonfatal heart failure — no. (%)	152 (3.0)	124(2.4)	0.10
Motor vehicle accident in which patient was driver — no./total no. (%)	9/5033 (0.2)	14/5036 (0.3)	0.40
Any nonhypoglycemic serious adverse event — no. (%)	113 (2.2)	82 (1.6)	0.03
Fluid retention — no./total no. (%)‡	3541/5053 (70.1)	3378/5054 (66.8)	<0.001
Clinical measures			
Weight gain >10 kg since baseline — no./total no. (%)	1399/5036 (27.8)	713/5042 (14.1)	<0.001
Alanine aminotransferase >3 times ULN — no./total no. (%)§	51/5065 (1.0)	77/5061 (1.5)	0.02
Low-density lipoprotein cholesterol — mg/dl¶	90.8±33.5	90.6±34.0	0.74
Blood pressure — mm Hg¶			
Systolic	126.4±16.7	127.4±17.2	0.002
Diastolic	66.9±10.5	67.7±10.6	<0.001
Cigarette-smoking status — no. (%)‖			0.54
Current (previous 30 days)	505 (9.8)	508 (9.9)	
Former	2524 (49.2)	2467 (48.2)	
Never	2093 (40.9)	2143 (41.8)	
Missing data	6 (0.1)	5 (0.1)	
Use of nonglycemic medication — no./total no. (%)			
Antihypertensive	4664/5127 (91.0)	4714/5123 (92.0)	0.06
Angiotensin-converting–enzyme inhibitor	3512/5038 (69.7)	3621/5037 (71.9)	0.02
Aspirin	3736/4950 (75.5)	3753/4970 (75.5)	0.98
Beta-blocker	2395/5038 (47.5)	2450/5037 (48.6)	0.27
Statin	4432/5039 (88.0)	4425/5054 (87.6)	0.54

The NEW ENGLAND JOURNAL of MEDICINE

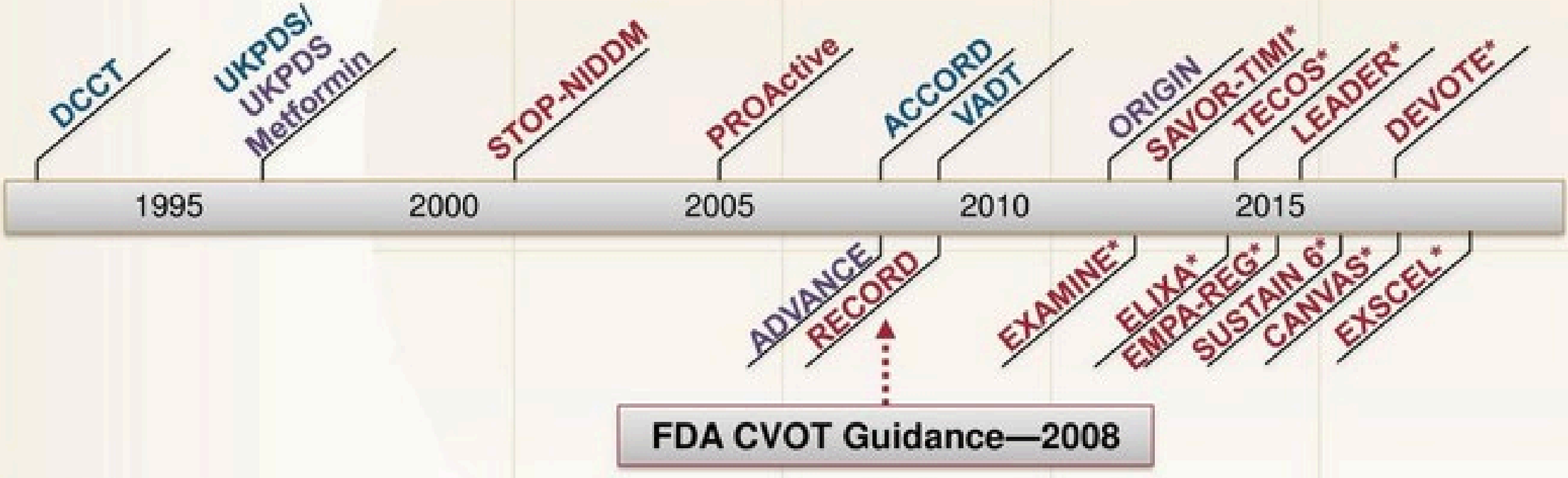
ORIGINAL ARTICLE

Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

The ADVANCE Collaborative Group*



Timeline of Major Diabetes Outcomes Trials



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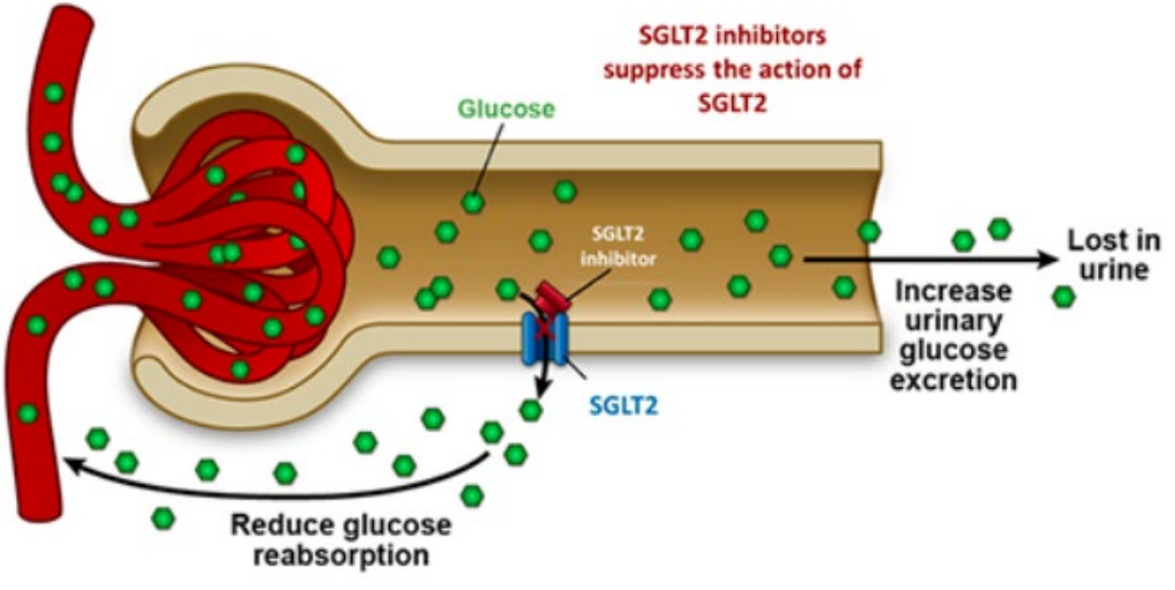
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators



EMPA-REG OUTCOMES TRIAL – *NEJM* 2015

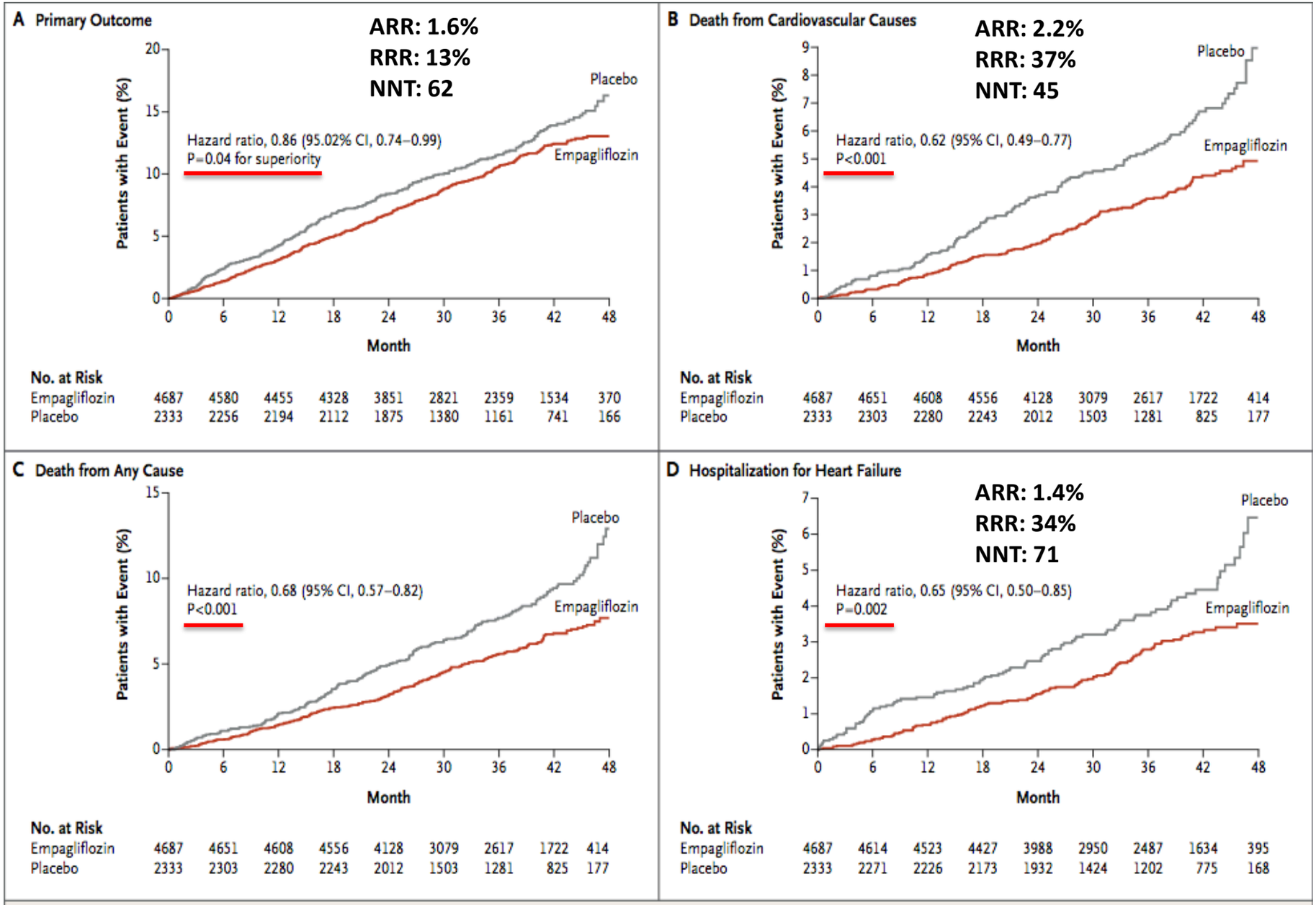


Figure 1. Cardiovascular Outcomes and Death from Any Cause.

Shown are the cumulative incidence of the primary outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) (Panel A), cumulative incidence of death from cardiovascular causes (Panel B), the Kaplan–Meier estimate for death from any cause (Panel C), and the cumulative incidence of hospitalization for heart failure (Panel D) in the pooled empagliflozin group and the placebo group among patients who received at least one dose of a study drug. Hazard ratios are based on Cox regression analyses.

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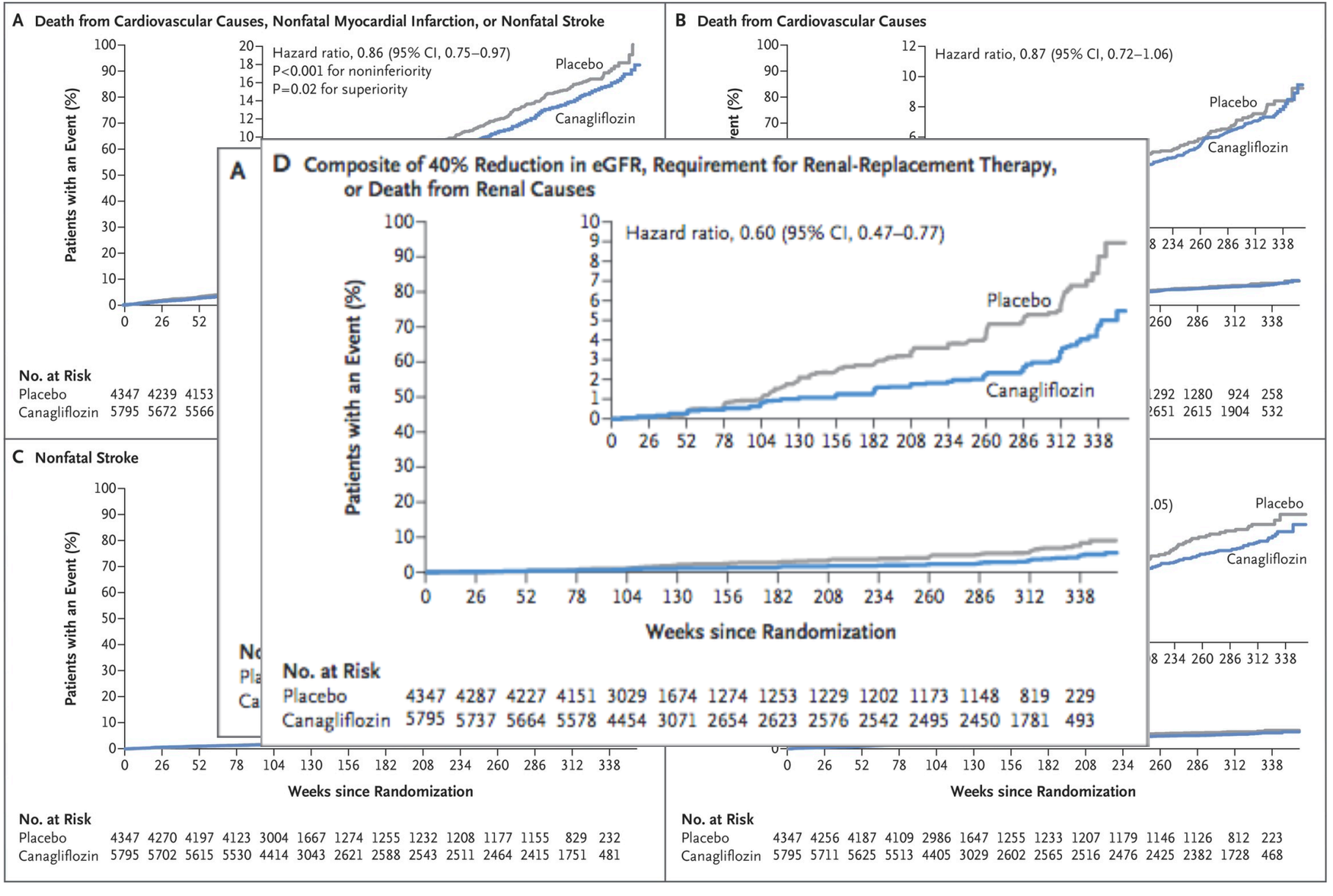
Cardiovascular Outcomes – Canagliflozin 2017

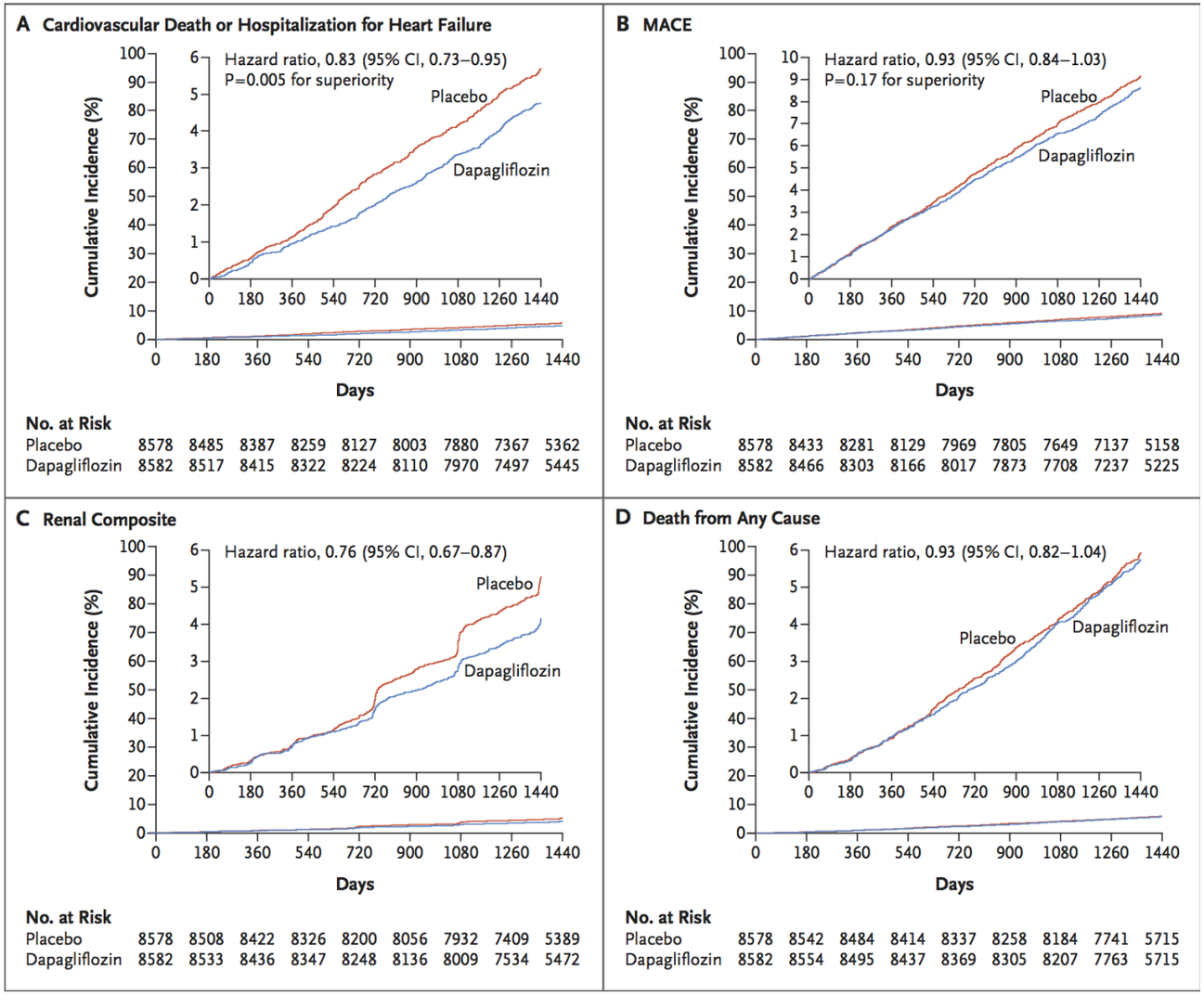


The NEW ENGLAND JOURNAL of MEDICINE

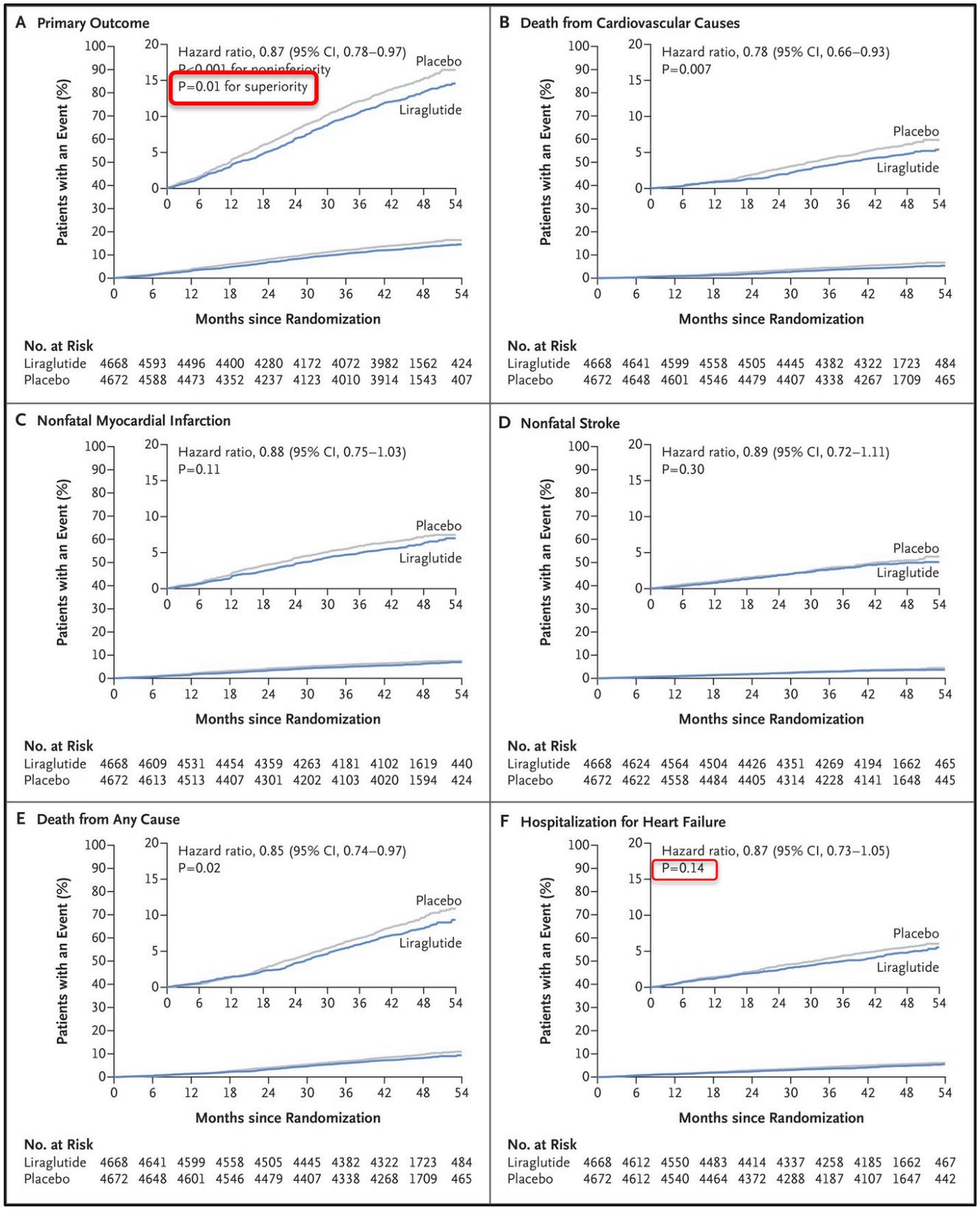
ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

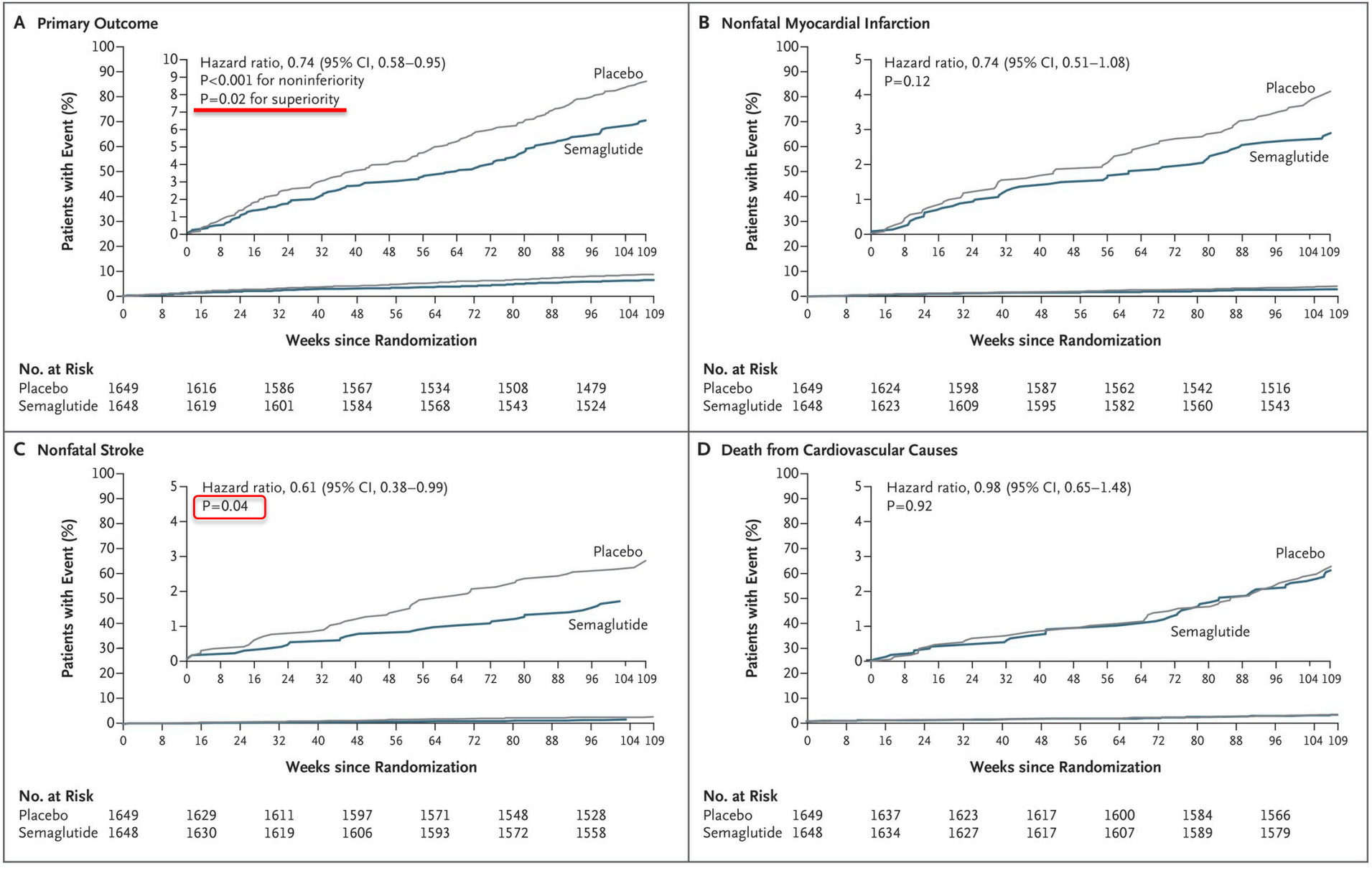
S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, and M.S. Sabatine, for the DECLARE–TIMI 58 Investigators*



Liraglutide LEADER 2016 NEJM



Semaglutide Cardiovascular Outcomes
SUSTAIN-6 (2016)



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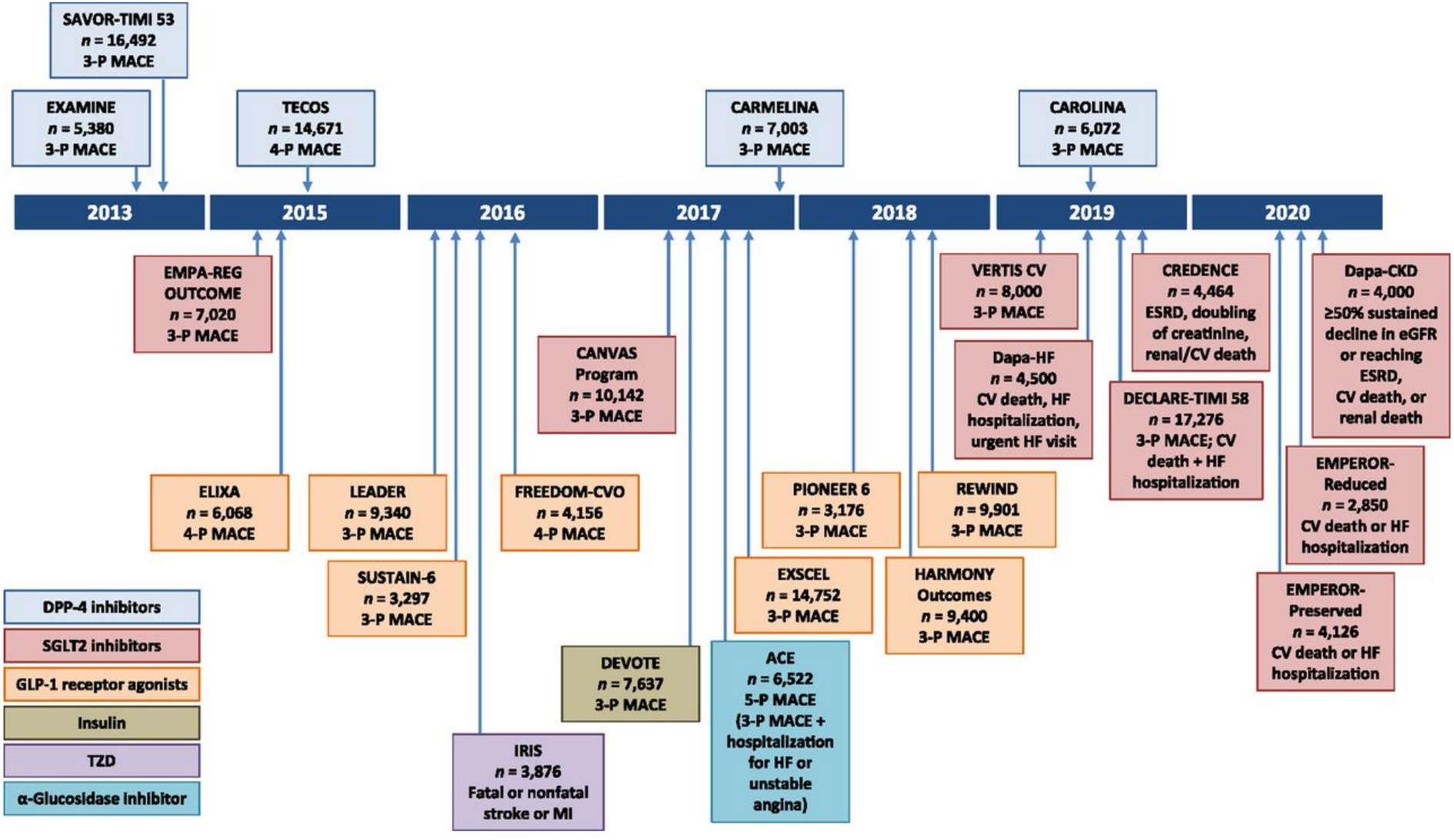
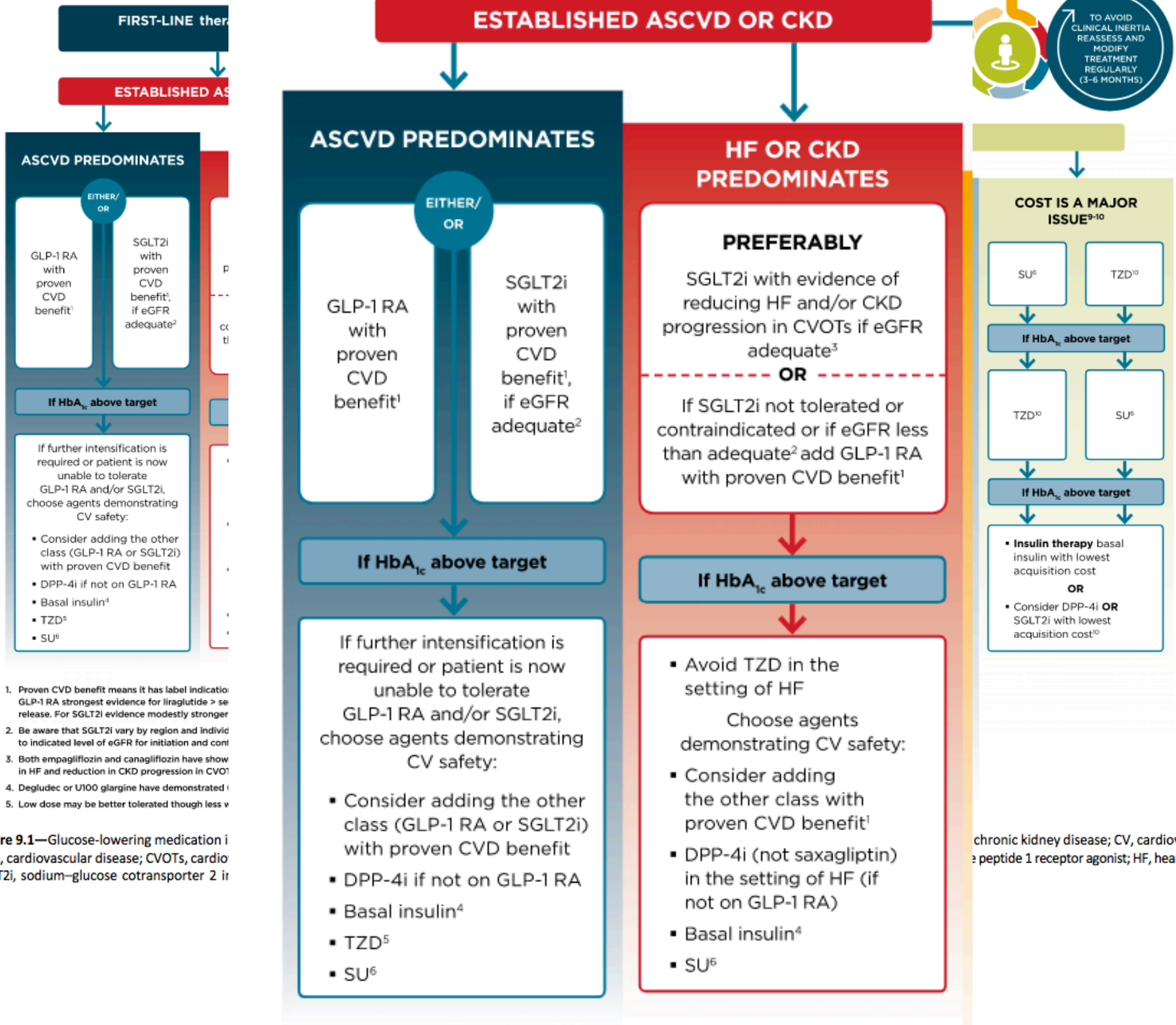
Completed and ongoing CVOTs (6–14,39,44–58). 3-P, 3-point; 4-P, 4-point; 5-P, 5-point.



William T. Cefalu et al. Dia Care 2018;41:14-31

American Diabetes Association.



1. Proven CVD benefit means it has label indicatio
GLP-1 RA strongest evidence for liraglutide > se
release. For SGLT2i evidence modestly stronger
2. Be aware that SGLT2i vary by region and individ
to indicated level of eGFR for initiation and cont
3. Both empagliflozin and canagliflozin have show
in HF and reduction in CKD progression in CVO
4. Degludec or U100 glargine have demonstrated
5. Low dose may be better tolerated though less v

Figure 9.1—Glucose-lowering medication i
CVD, cardiovascular disease; CVOTs, cardio
SGLT2i, sodium–glucose cotransporter 2 i
chronic kidney disease; CV, cardiovascular;
e peptide 1 receptor agonist; HF, heart failure;

A CARDIOLOGIST'S PRACTICAL GUIDE TO USING SGLT2I

Patients with T2DM with or at High Risk for CV Disease, Already on Metformin

Below Individualized HbA1c Target:

Switch non-metformin oral therapies (e.g. sulfonylureas) to a SGLT2i

Above Individualized HbA1c Target:

Consider SGLT2i initiation

Drug Type

Canagliflozin, dapagliflozin, & empagliflozin with similar efficacy profile in reducing HF events

Starting Dose (once daily in AM)

- Canagliflozin (100mg)
- Dapagliflozin (5mg)
- Empagliflozin (10mg)
- Ertugliflozin (5mg)

Metformin+SGLT2i Combination Therapies

Consider to limit non-adherence and pill burden

Stable Hemodynamic and Clinical Status

Pre-Initiation eGFR must be above:

- 60 mL/min/1.73 m^2 (dapagliflozin, ertugliflozin)
- 45 mL/min/1.73 m^2 (canagliflozin, empagliflozin)

Anticipatory Guidance

Consider diuretic dose reduction

Patient Counseling

- Genital/perineal hygiene
- Orthostatic hypotension
- Regular foot exams
- Symptoms of DKA
- Avoid excessive alcohol

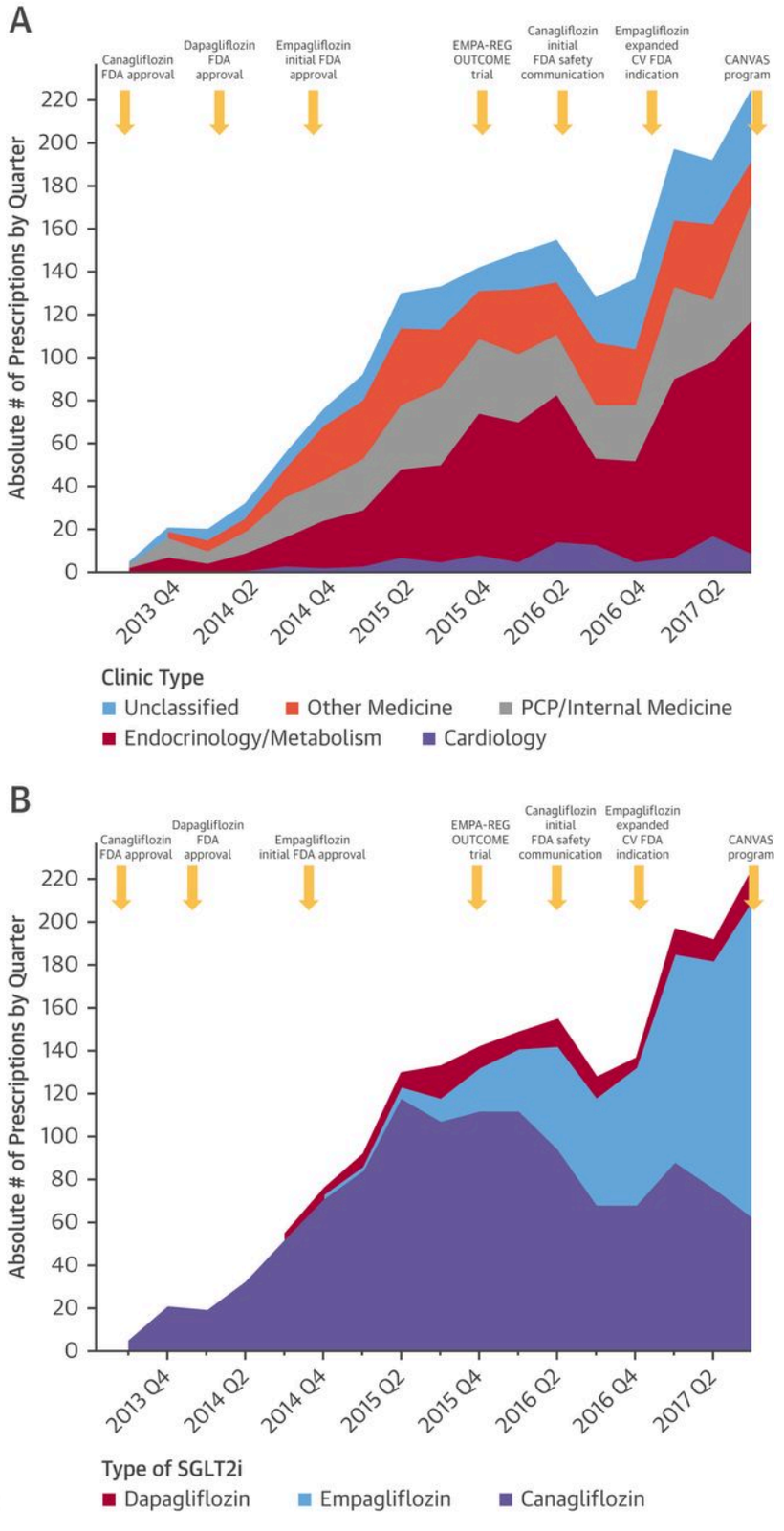
Multidisciplinary Care

Close communication with other providers, including PCPs and endocrinologists

Follow-up and Monitoring

- Serial assessment of renal function, body weights, blood pressure, and symptoms
- Dose uptitration guided by need for glycemic control
- Ensure adherence to SGLT2i, other therapies, and therapeutic lifestyle
- Multidisciplinary care team follow-up

Vardeny et al JACC HF 2019:169-172



- Estimated that ~5% of eligible DM-CV patients are prescribed SGLT2-I
- <5% of current prescriptions generated by cardiologists

Muthiah Vaduganathan et al. JACC 2018;72:3370-3372

JACC

BOTTOM LINE

- Statins first line for lipid lowering therapy
  - Ezetimibe is second line agent.
  - PCSK9 inhibitors should be reserved for very high risk patients with careful consideration to cost

- Significant CV event reduction has been established with SGLT2-I and GLP1-RA

QUESTION

- 65 yo F history of coronary artery disease (10 mo ago w NSTEMI presentation – mid LAD 90%), HLD, obesity HTN,
- At time of NSTEMI placed on atorvastatin 40
- 3 weeks after statin initiation she develops petechial rash.
- PCP transitions to simvastatin with recurrence of rash, no further statin challenge given
- Diet – bad (McD weekly, Pepsi, Coke, chips, candy, lots of red meat)
- Physical activity – sedentary (BMI 41)

	NSTEMI	RASH	Off Statin
Component	8/2017	10/2017	3/2018
Total Cholesterol	169	109	183
LDL Calculated	110	53	77
HDL	25	22	30
Triglyceride	168	169	381
Non-HDL	144	87	153

Agrees to try rosuvastatin 10mg

QUESTION

	NSTEMI	Atorva 40 Rash	Off Statin	Rosuva 10
Component	8/2017	10/2017	3/2018	6/2018
Total Cholesterol	169	109	183	124
LDL Calculated	110	53	77	64
HDL	25	22	30	31
Triglyceride	168	169	381	144
Non-HDL	144	87	153	93

What do you recommend in light of the patient's "on-therapy" lipid profile?

a) No change to therapy
b) Addition of PCSK9 inhibitor Evolocumab
c) Addition of ezetimibe 10mg daily
d) Increase dose of Rosuvastatin to 20mg daily

REFERENCES

- Grundy et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol. *J Am Col Card*. Nov 2018 [Epub ahead of print]
- Cannon et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Eng J Med*. 2015;Jun 18;372(25):2387-97)
- Sabatine et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Eng J Med*. 2017 May 4;376(18):1713-1722
- Schwartz et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Eng J Med*. 2018 Nov 29;379(22):2097-2107
- Cannon et al. Simulation of lipid-lowering therapy intensification in a population with atherosclerotic cardiovascular disease. *JAMA Cardiol*. 2017 Sep 1;2(9):959-966
- Hlatky et al. PCSK9 inhibitors; economics and policy. *J Am Col Card*. 2017;70:2677-87
- Bhatt et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Eng J Med*. Nov 10;2018 [Epub ahead of print]
- Association AD. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2019. *Diabetes Care*. 2019;42(Supplement 1):S90-S102.
- Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *New England Journal of Medicine*. 2017;377(7):644-657.
- Vardeny O, Vaduganathan M. Practical Guide to Prescribing Sodium-Glucose Cotransporter 2 Inhibitors for Cardiologists. *JACC: Heart Failure*. 2019;7(2):169-172.
- Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *New England Journal of Medicine*. 2019;380(4):347-357.
- Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *New England Journal of Medicine*. 2015;373(22):2117-2128.
- Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *The Lancet*. 1998;352(9131):837-853.
- Effects of Intensive Glucose Lowering in Type 2 Diabetes. *New England Journal of Medicine*. 2008;358(24):2545-2559.
- Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. *New England Journal of Medicine*. 2008;358(24):2560-2572.
- Marso et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Eng J Med* 2016;375:1834-1844
- Marso et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Eng J Med* 2016;375:311-322
- Hong J, et al. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. *Diabetes care* 2013;36:1304-1311
- Cefalu W, et al. Cardiovascular outcomes trials in type 2 diabetes: where do we go from here? Reflections from a Diabetes care editors' expert forum. Diab Care 2018 Jan; 41(1):14-31