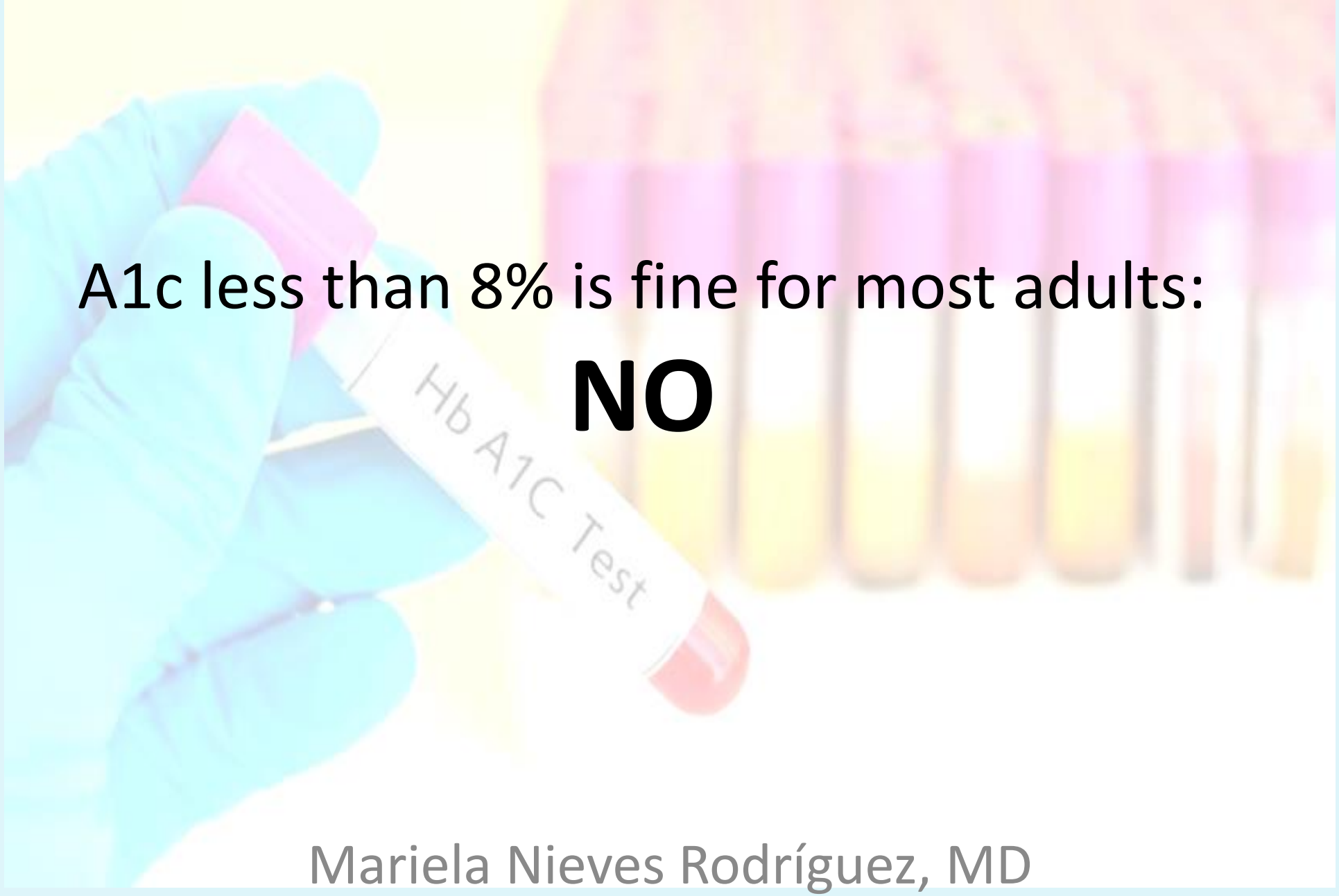


A1c less than 8% is fine for most adults:

NO

Mariela Nieves Rodríguez, MD

Disclosure

- I do not have any actual or potential financial conflict of interest in relation to this presentation to disclose.
- I am not promoting any service or product.

When this topic became an issue?

- April 17, 2018 ACP published a clinical guidelines for a nonpregnant adults with type 2 diabetes where they stated:
  - Personalization of goals for glycemic control
  - **Levels of A1c between 7%-8% for most patients with type 2 diabetes should be aim**
  - Deintensification of pharmacological therapy in patients with A1c less than 6.5%
  - To treat patient with type 2 diabetes to minimize symptoms and avoid targeting A1c in patients with life expectancy less than 10 years.

The issue…

- ACP is an association that reunite a very large number of Primary Care Physicians
- These recommendations about the care of most type 2 diabetic patients could prevent many of them to received the benefit of long term glucose control.

Where we agree?

AACE Comprehensive Diabetes Care: Glucose Goals

Parameter	Treatment Goal
A1C (%)	**≤6.5 if it can be achieved without substantial hypoglycemia or other unacceptable consequences** >6.5% to 8% for those at risk*
FPG (mg/dL)	<110
2- hour PPG (mg/dL)	<140

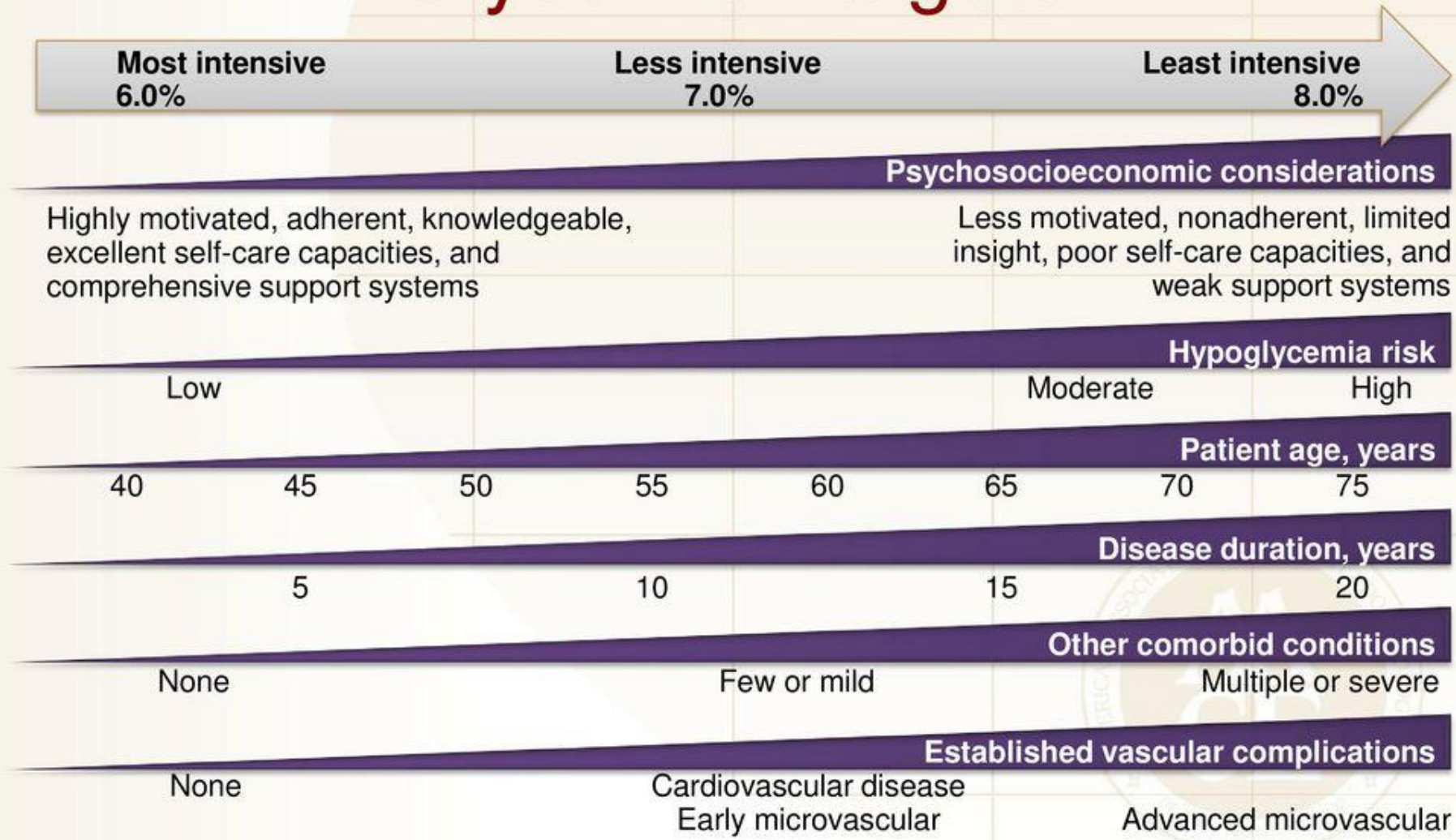
ADA-Recommended Glucose Goals

Parameter	Treatment Goal
A1C (%)	<7.0% for most adults **<6.5 if it can be achieved without significant hypoglycemia or other adverse effects of treatment*** <8% for those at risk*
Preprandial glucose (mg/dL)	80-130
Peak postprandial glucose (mg/dL)	<180

Those at risk…

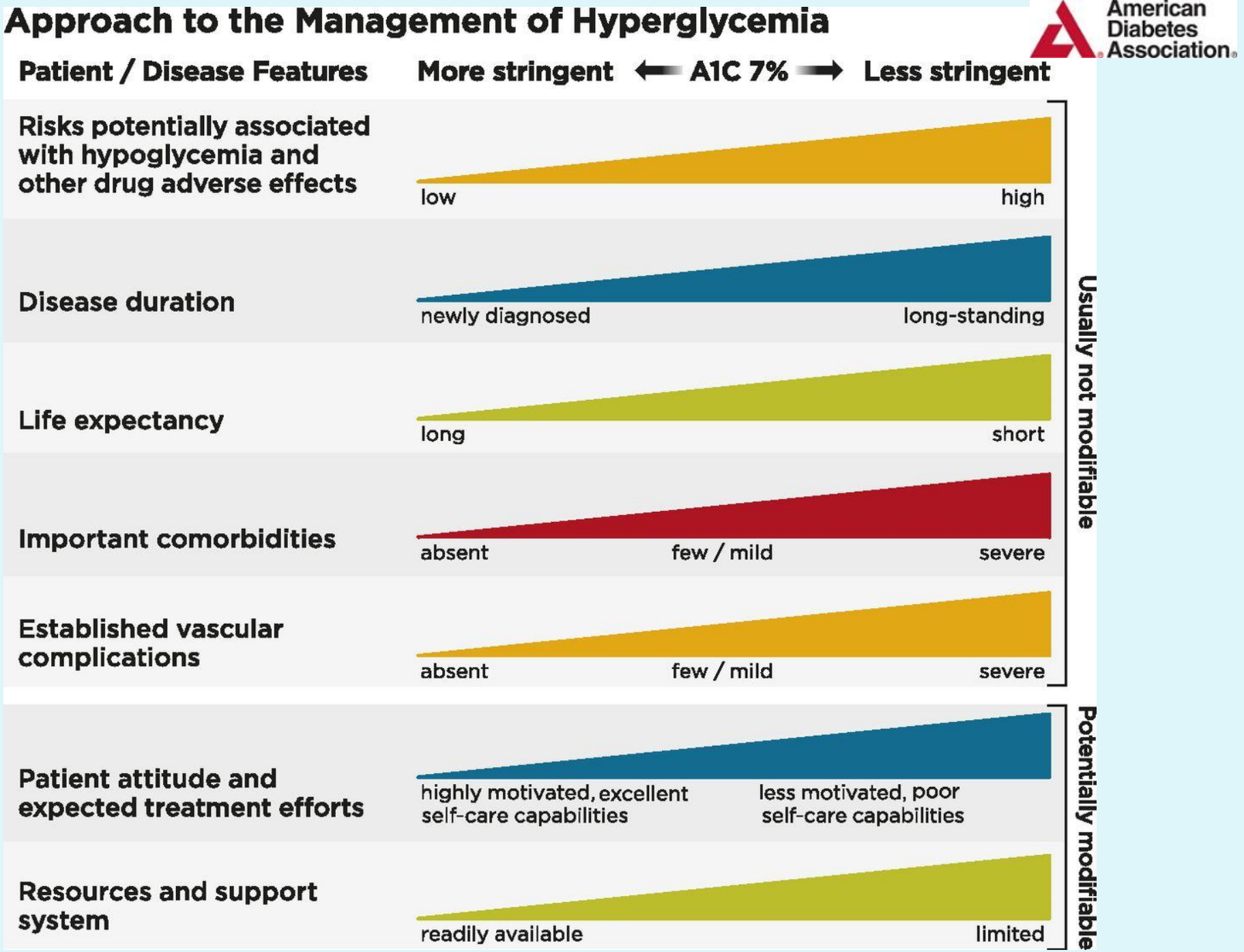
- Factors for a higher A1C target include
  - Risk for hypoglycemia
  - History of severe hypoglycemia
  - Limited life expectancy
  - Long-standing T2D in which the A1C goal has been difficult to attain despite intensive efforts
  - Advanced micro- or macrovascular complications
  - Extensive comorbid conditions

Algorithm for Individualizing Glycemic Targets



Ismail-Beigi F, Moghissi E, et al. *Ann Intern Med.* 2011;154:554-559.

Approach to the Management of Hyperglycemia



ADA. *Diabetes Care*. 2018;41:S55-S64.

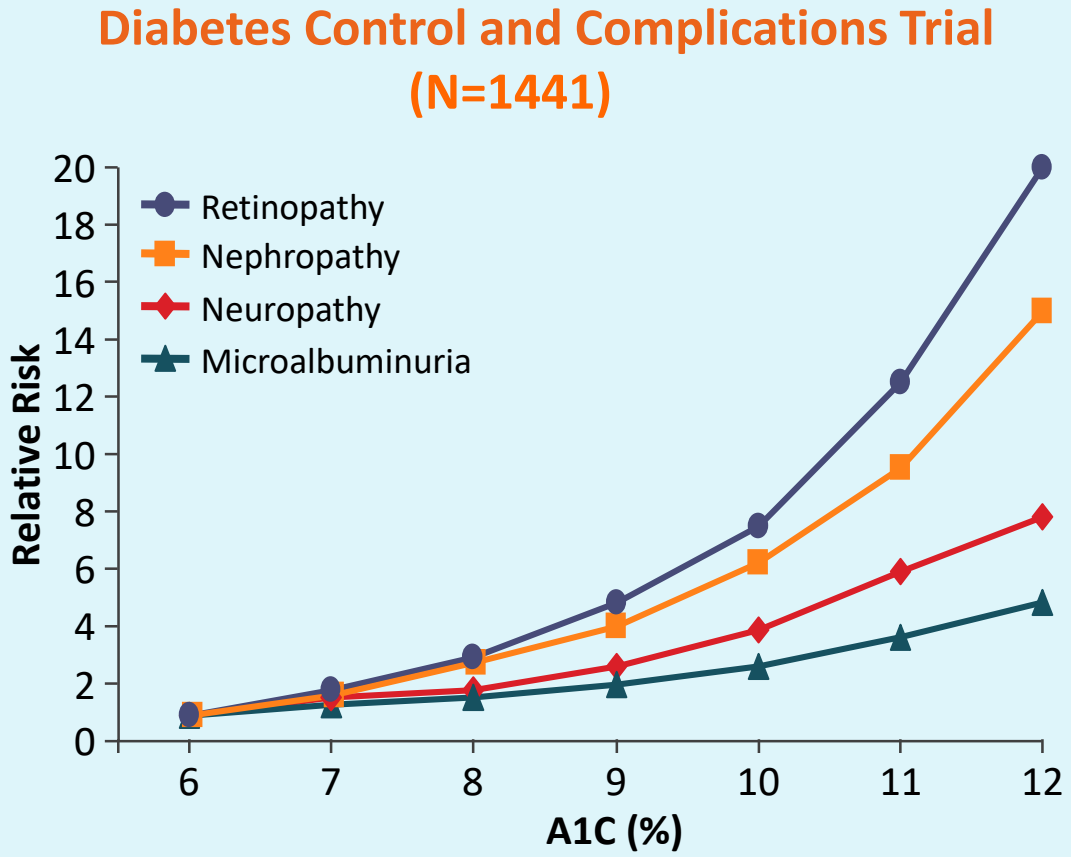
Where we disagree?

- Deintensification of pharmacological therapy in patients with A1c less than 6.5%

- **Levels of A1c between 7%-8% for most patients with type 2 diabetes**
  - ACP analyzed the same international studies that we used for patients with DM
    - **UKPDS-1998**
    - **ADVANCE-2008**
    - **ACCORD-2008/2011**
    - **VADT-2009/2015**
  - “Trials did not show substantial reductions in clinical microvascular events”
  - “Studies have not consistently shown that intensive glycemic control to A1c < 7% reduces microvascular events or reduces macrovascular events or death”

What do we know?

Microvascular Complications Increase With Increasing A1C



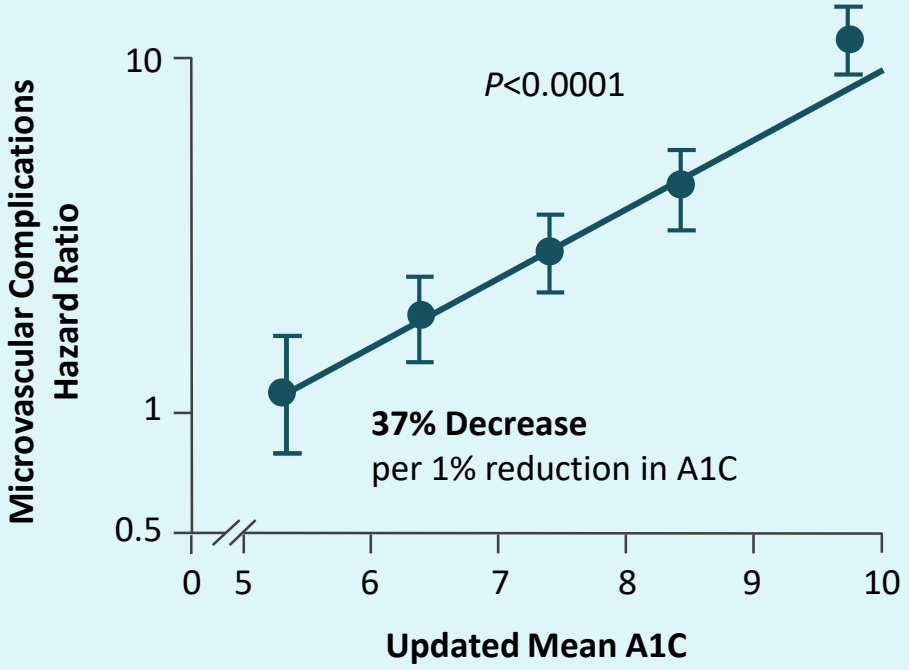
- Long term randomized prospective study with type 1 diabetic patients reported that lowering of blood glucose levels with intensive insulin therapy delayed the onset and slowed progression of microvascular complications.
- **EDIC**-follow up observational study documented that even though the difference between A1C were lost, the intensive therapy group had reduced risk of microvascular complications

Skyler JS. *Endocrinol Metab Clin North Am*. 1996;25:243-254.

Reducing A1C Reduces Microvascular Risk

United Kingdom Prospective Diabetes Study

(N=4209)



- Randomized, multicentric trial with patients with newly diagnosed type 2 diabetes documented that Intensive glucose lowering therapy reduced the risk for microvascular complications.

- In the 10 year F/U of intensive glucose control group the reduced risk for microvascular complications continued to be observed despite an early loss of glycemic differences, **"legacy effect"**

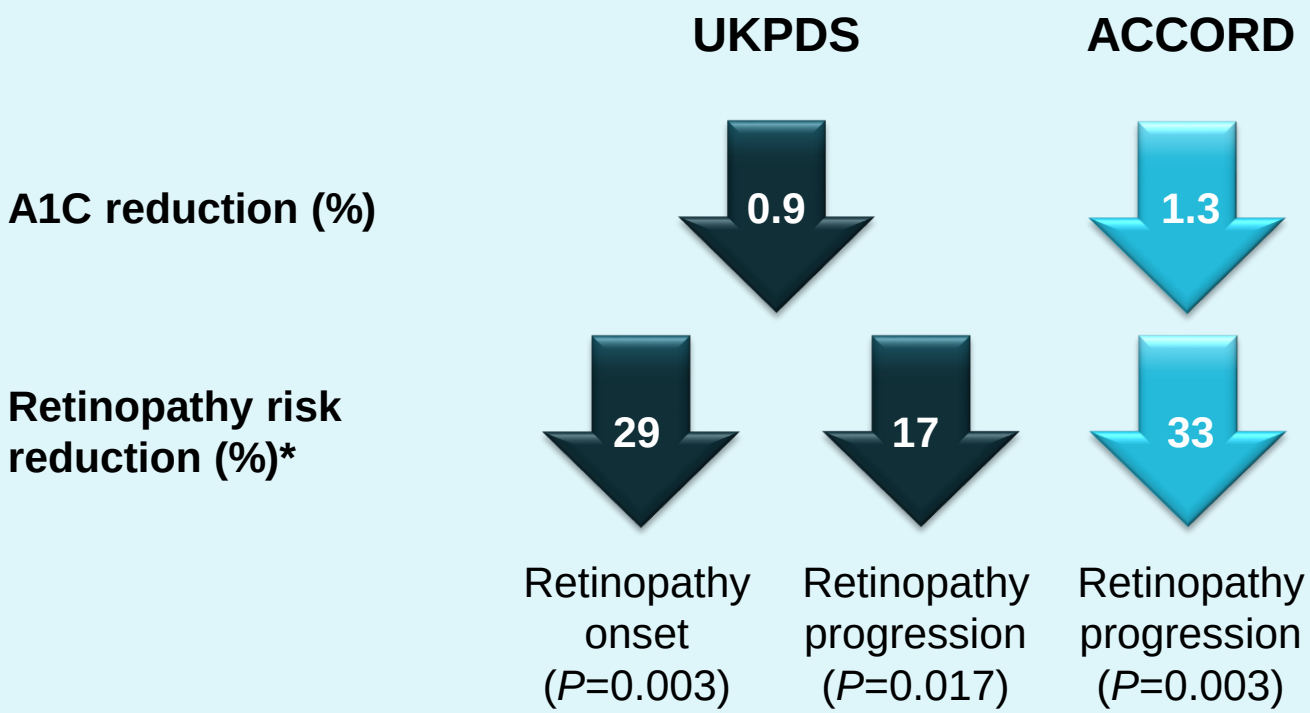
Stratton IM, et al. *BMJ*. 2000;321:405-412.

Characteristics of Major Type 2 Diabetes Trials

Study	Age at baseline(y)	Diabetes Duration (y)	A1c (%)		Anti diabetic Medications
			baseline	Achieved	
UKPDS-1998 N=4209	54	Newly diagnosed	9.1	7.0 vs 7.9	Sulfonylureas/ Insulin
	Overweight newly diagnosed patients				Metformin
ACCORD-2008 N=10,251	62.2	10	8.1	6.4 vs 7.6	Insulin, metformin, TZD's, sulfonylureas
ADVANCE-2008 N=11,140	66	7.9	7.2	6.4 vs 7.0	Sulfonylureas, metformin, TZD's, acarbose, insulin
VADT-2009 N=1791	60.4	11.5	9.4	6.9 vs 8.4	Metformin, TZD's, sulfonylureas, Insulin

*Patient populations differed between studies: Duration of disease, comorbilities
**Medications used includes Insulin and sulfonylureas which are associated with hypoglycemia and weight gain

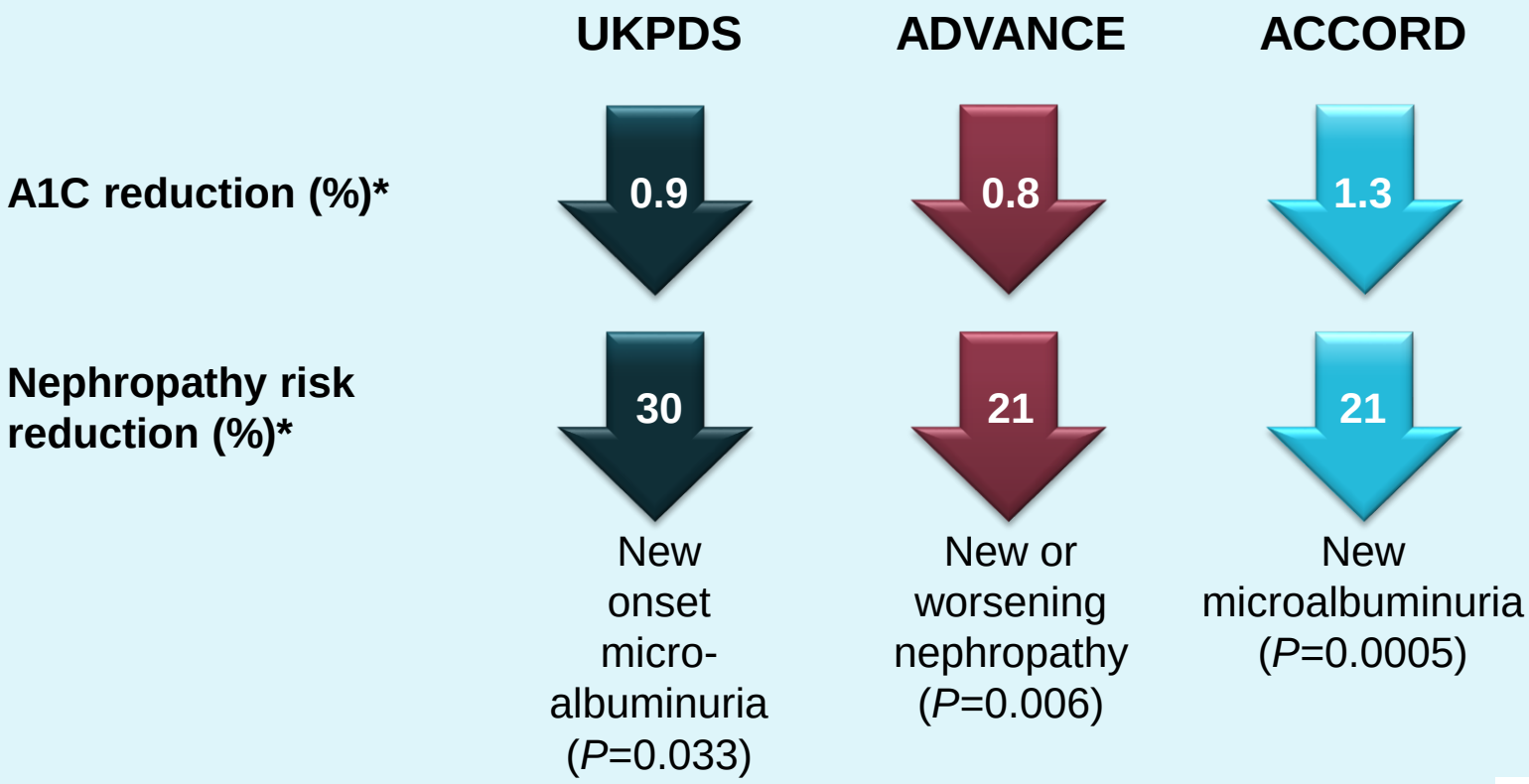
Reducing A1C Reduces Retinopathy Progression in T2D



*Intensive vs standard glucose control.

UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:837-853.
Ismail-Beigi F, et al. *Lancet*. 2010;376:419-430.
Chew EY, et al. *N Engl J Med*. 2010;363:233-244.

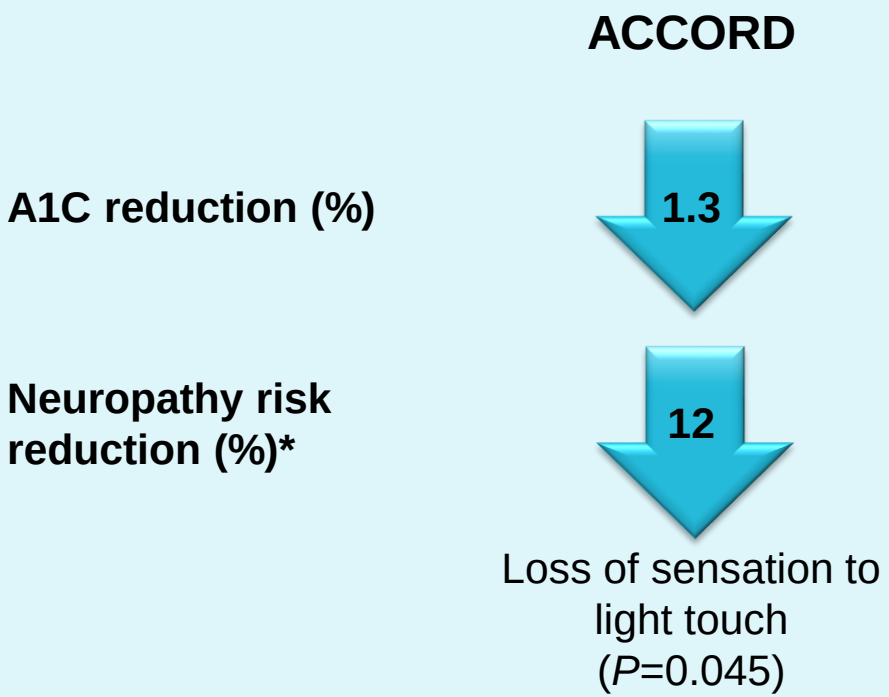
Reducing A1C Reduces Nephropathy Risk in T2D



*Intensive vs standard glucose control.

UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:837-853.
ADVANCE Collaborative Group. *N Engl J Med*. 2008;358:2560-2572.
Ismail-Beigi F, et al. *Lancet*. 2010;376:419-430.

Reducing A1C Reduces Neuropathy Risk in T2D



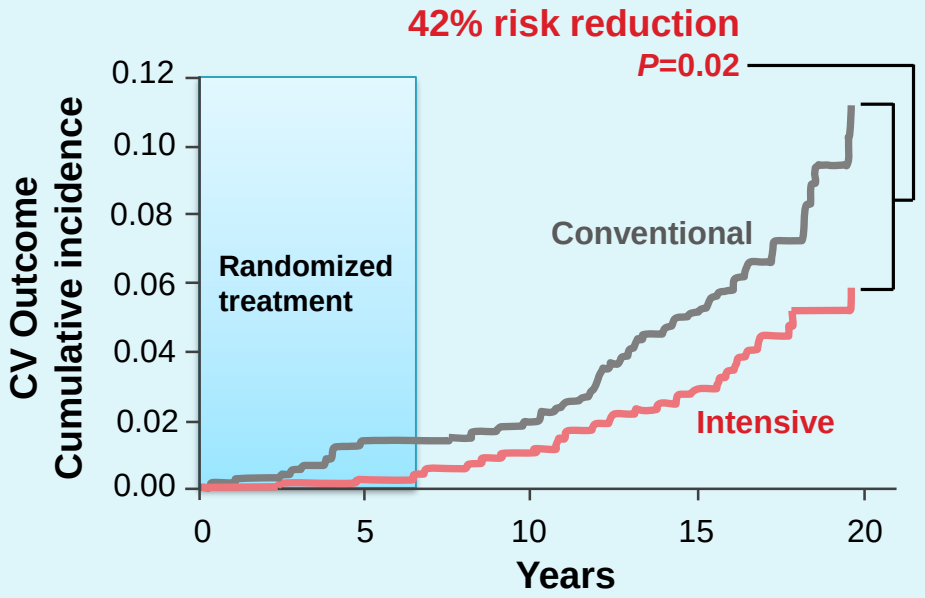
*Intensive vs standard glucose control.

Ismail-Beigi F, et al. *Lancet*. 2010;376:419-430.

Intensive Glycemic Control Reduces Long-term Macrovascular Risk

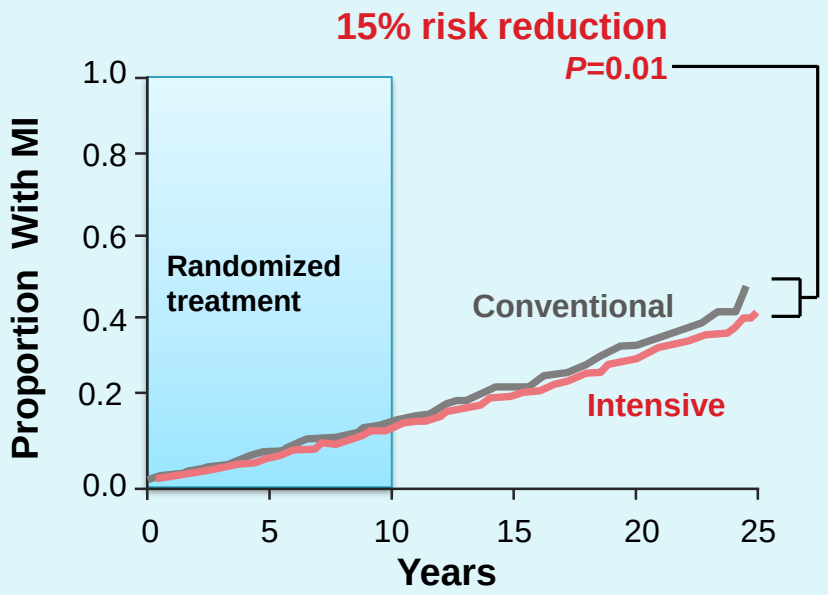
DCCT
T1D, 5-6 years duration

EDIC



UKPDS
T2D, newly diagnosed

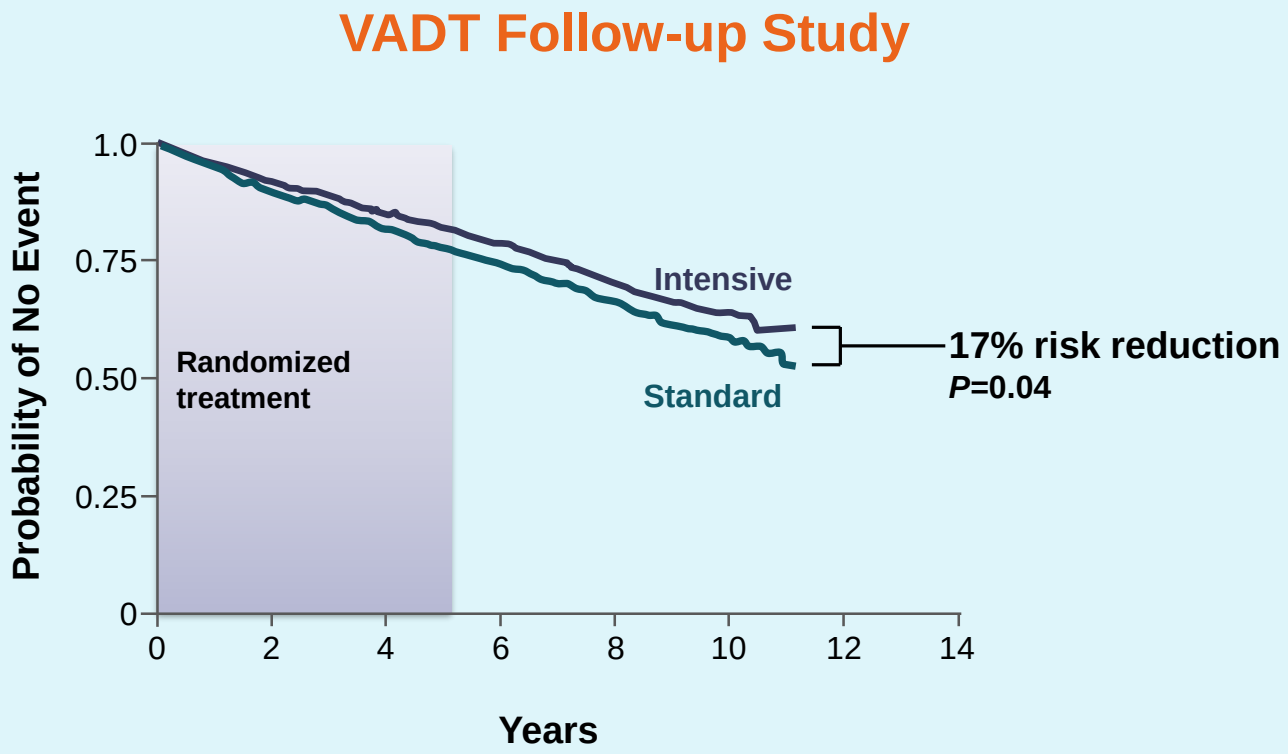
UKPDS 10-year F/U



CV, cardiovascular; DCCT, Diabetes Control and Complications Trial; MI, myocardial infarction; T1D, type 1 diabetes; T2D, type 2 diabetes; UKPDS, United Kingdom Prospective Diabetes Study.

Nathan DM, et al. *N Engl J Med*. 2005;353:2643-2653. Holman RR, et al. *N Engl J Med*. 2008;359:1577-1589.

Long-Term Effect of Intensive Glycemic Control on Macrovascular Risk



VADT, Veterans Affairs Diabetes Trial.

Hayward RA, et al. *N Engl J Med*. 2015;372:2197-2206.

Early major trials evaluating the effects of intensive glycemic control of diabetes

Study	Diabetes type	CV composite		MI		CV mortality		All-cause mortality	
DCCT/EDIC (17,26,27)	Type 1	↔	↓	—	—	—	—	↔	↓
UKPDS	Type 2								
Main randomization (SU or insulin vs. conventional therapy) (18,28)		—	—	↔	↓	—	—	↔	↓
Additional randomization of overweight patients (metformin vs. SU vs. conventional therapy) (19,28)		—	—	↓*	↓*	—	—	↓*	↓*
ACCORD (20,30)	Type 2	↔	↔	↓	↔	↑	↑	↑	↔
ADVANCE (21)	Type 2	↔†		↔		↔		↔	
VADT (22,29)	Type 2	↔	↓	↔	↔	↔	↔	↔	↔

Left columns show initial results; right columns show long-term follow-up. ↔, Neutral effect; ↓, decrease; ↑, increase; — not assessed/reported; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; SU, sulfonylurea. Adapted from Bergenstal et al. (97).

↵*Metformin group only.

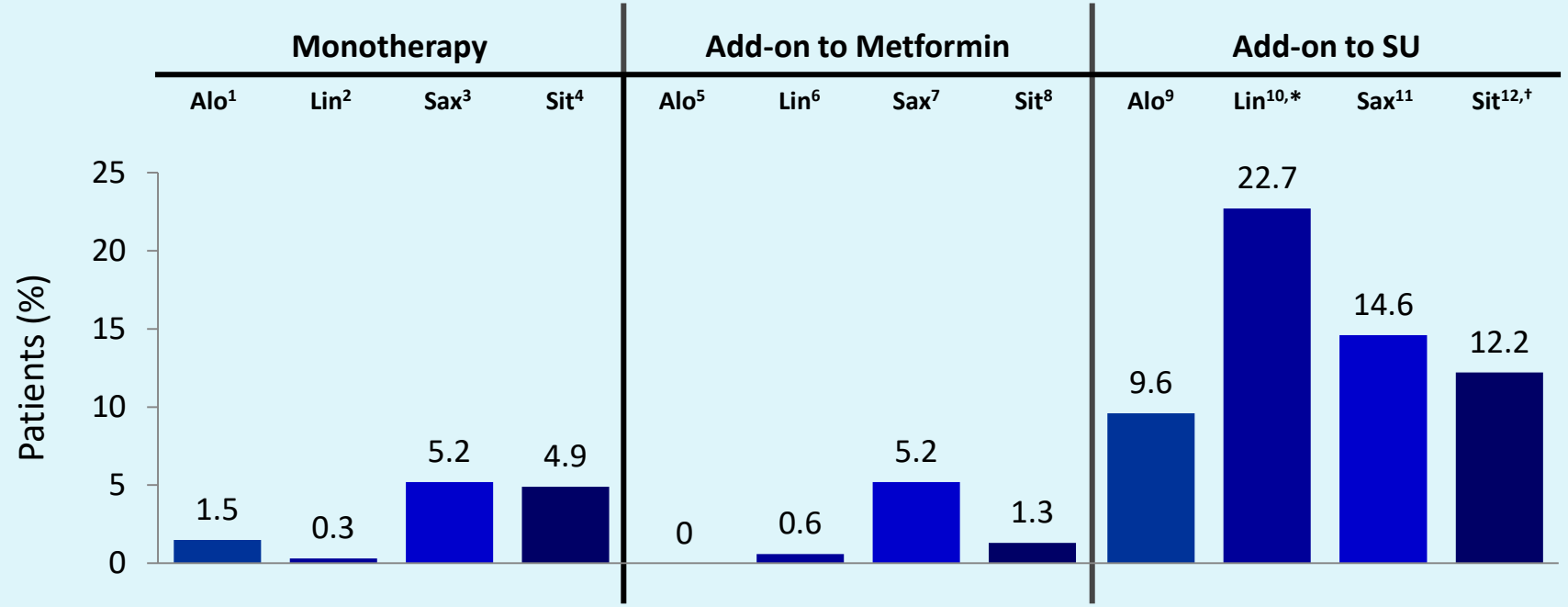
↵†A decrease was reported in a combined CV/microvascular composite but was found to be mostly attributable to nephropathy.

What is missing in the ACP guidelines?

- ACP have not consider the medications with low profile of hypoglycemia (DDP4i's, GLP1 agonists and SGLT-2i's) and with evidence to improve morbidity and mortality in patient with type 2 Diabetes (GLP1 agonists and SGLT-2i's)
- Was forgotten the concept of "**Legacy effect**"; positive effect of intensive blood glucose control and lower A1c target on diabetic patients newly diagnosed and its long term benefit.

Hypoglycemia with DPP4 Inhibitors

Percentage of Patients Reporting Hypoglycemia (Not Head-to-Head Trials)



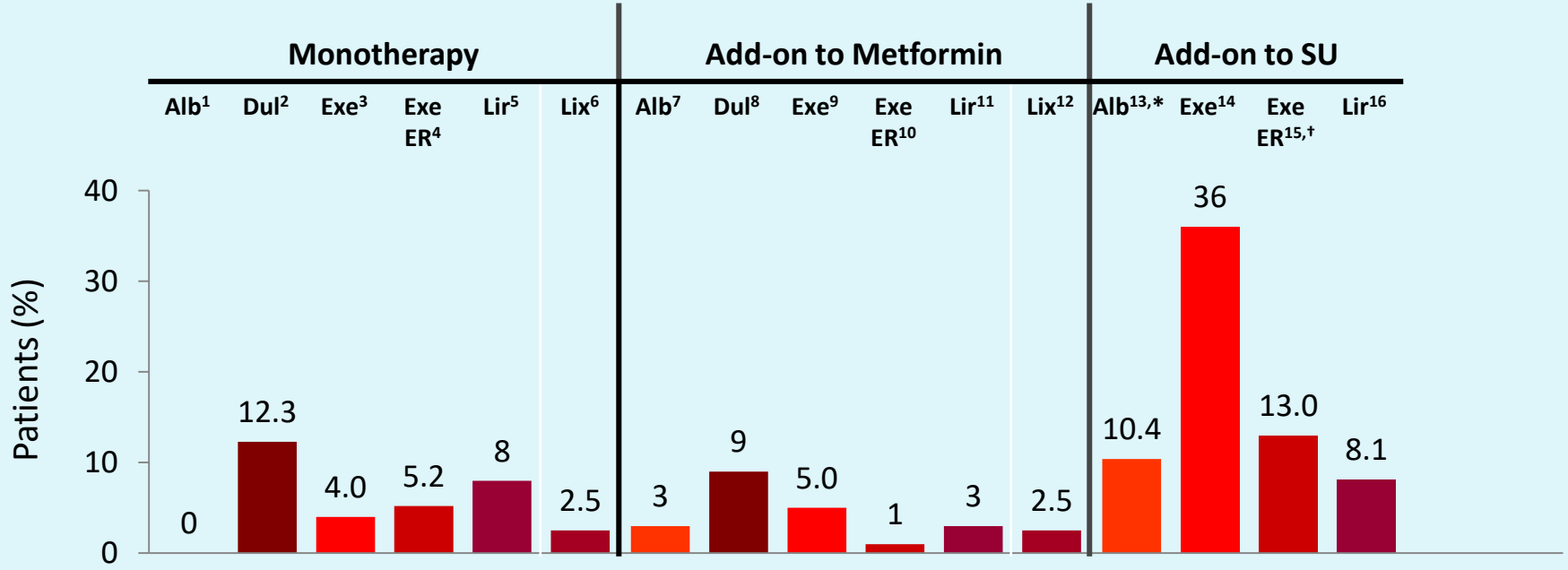
NR, value not reported.

*SU + metformin. †With or without metformin.

1. DeFronzo RA, et al. *Diabetes Care*. 2008;31:2315–2317. 2. Del Prato S, et al. *Diabetes Obes Metab*. 2011;13:258-267.
3. Rosenstock J, et al. *Curr Med Res Opin*. 2009;25:2401-2411. 4. Nauck MA, et al. *Diabetes Obes Metab*. 2007;9:194-205. 5. Nauck MA, et al. *Int J Clin Pract*. 2009;63:46-55. 6. Taskinen MR, et al. *Diabetes Obes Metab*. 2011;13:65-74. 7. DeFronzo RA, et al. *Diabetes Care*. 2009;32:1649-1655. 8. Charbonnel B, et al. *Diabetes Care*. 2006;29:2638-2643. 9. Pratley RE, et al. *Diabetes Obes Metab*. 2009;11:167-176. 10. Owens DR, et al. *Diabet Med*. 2011;28:1352-61. 11. Chacra AR, et al. *Int J Clin Pract*. 2009;63:1395-1406. 12. Hermansen K, et al. *Diabetes Obes Metab*. 2007;9:733-745.

Hypoglycemia with GLP1 Receptor Agonists

Percentage of Patients Reporting Hypoglycemia (Not Head-to-Head Trials)

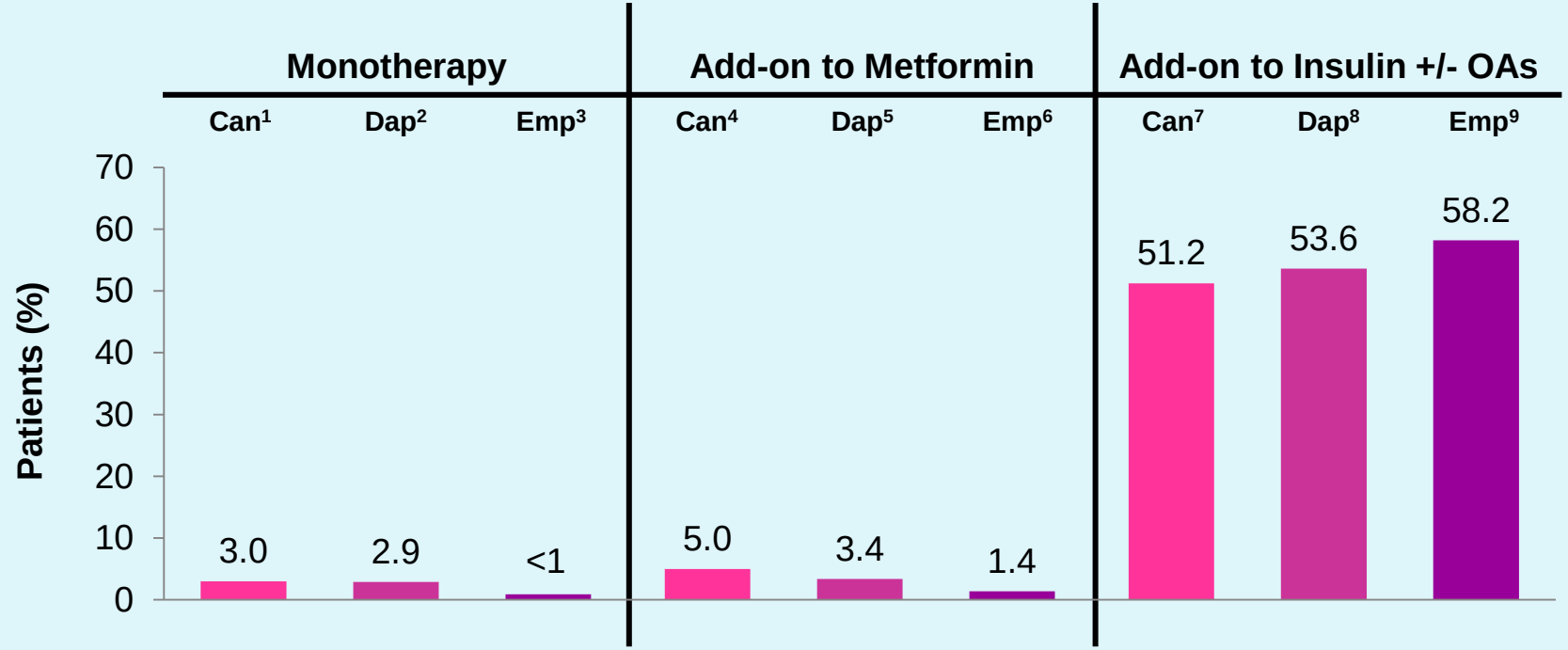


*Metformin with or without SU or TZD. †Metformin with or without SU.

1. Nauck M, et al. *Diabetes*. 2013;62(suppl 2): Abstr. 55-LB. 2. Umpierrez G, et al. *Diabetes Care*. 2014;37:2168-2176. 3. Moretto TJ, et al. *Clin Ther*. 2008;30:1448-1460. 4. Russell-Jones D, et al. *Diabetes Care*. 2012;35:252-258. 5. Garber A, et al. *Lancet*. 2009;373:473-481. 6. Fonseca VA, et al. *Diabetes Care*. 2012;35:1225-1231. 7. Ahrén B, et al. *Diabetes Care*. 2014;37:2141-2148. 8. Dungan KM, et al. *Lancet*. 2014;384:1349-1357. 9. DeFronzo RA et al. *Diabetes Care*. 2005;28:1092-1100. 10. Bergenstal RM, et al. *Lancet*. 2010;376:431-439. 11. Pratley RE, et al. *Lancet*. 2010;375:1447-1456. 12. Rosenstock J, et al. *Diabetes Care*. 2013;36:2945-2951. 13. Pratley RE, et al. *Lancet Diabetes Endocrinol*. 2014;2:289-297. 14. Buse JB, et al. *Diabetes Care*. 2004;27:2628-2635. 15. Diamant M, et al. *Lancet*. 2010;375:2234-2243. 16. Marre M, et al. *Diabet Med*. 2009;26:268-278.

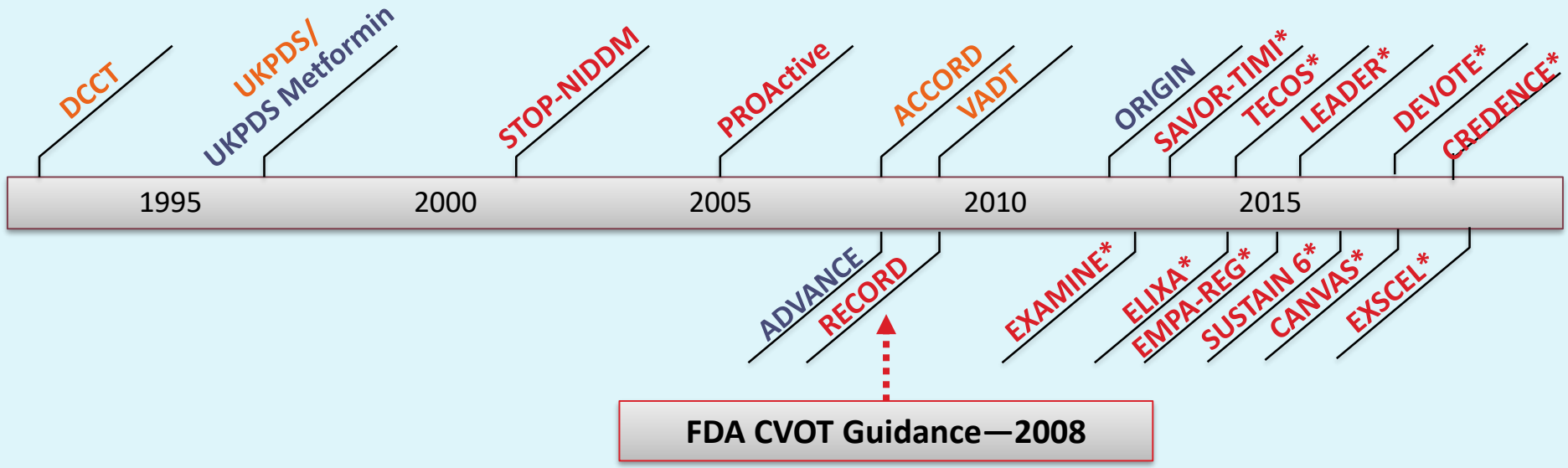
Hypoglycemia with SGLT2 Inhibitors

Percentage of Patients Reporting Hypoglycemia (Not Head-to-Head Trials)



1. Stenlof K, et al. *Diabetes Obes Metab*. 2013;15:372-382. 2. Ferrannini E, et al. *Diabetes Care*. 2010;33:2217-2224. 3. Roden M, et al. *Lancet Diabetes Endocrinol*. 2013;1:208-219. 4. Cefalu WT, et al. *Lancet*. 2013;382:941-950. 5. Nauck MA, et al. *Diabetes Care*. 2011;34:2015-2022. 6. Haring HU, et al. *Diabetes Care*. 2014;37:1650-1659. 7. Yale J-F, et al. *Diabetes Obes Metab*. 2013;15:463-473. 8. Wilding JPH, et al. *Ann Intern Med*. 2012;156:405-415. 9. Rosenstock J, et al. *Diabetes Care*. 2014;37:1815-1823.

Timeline of Major Diabetes Outcomes Trials



Blue = Intensive vs standard control using same set of glucose-lowering agent(s)

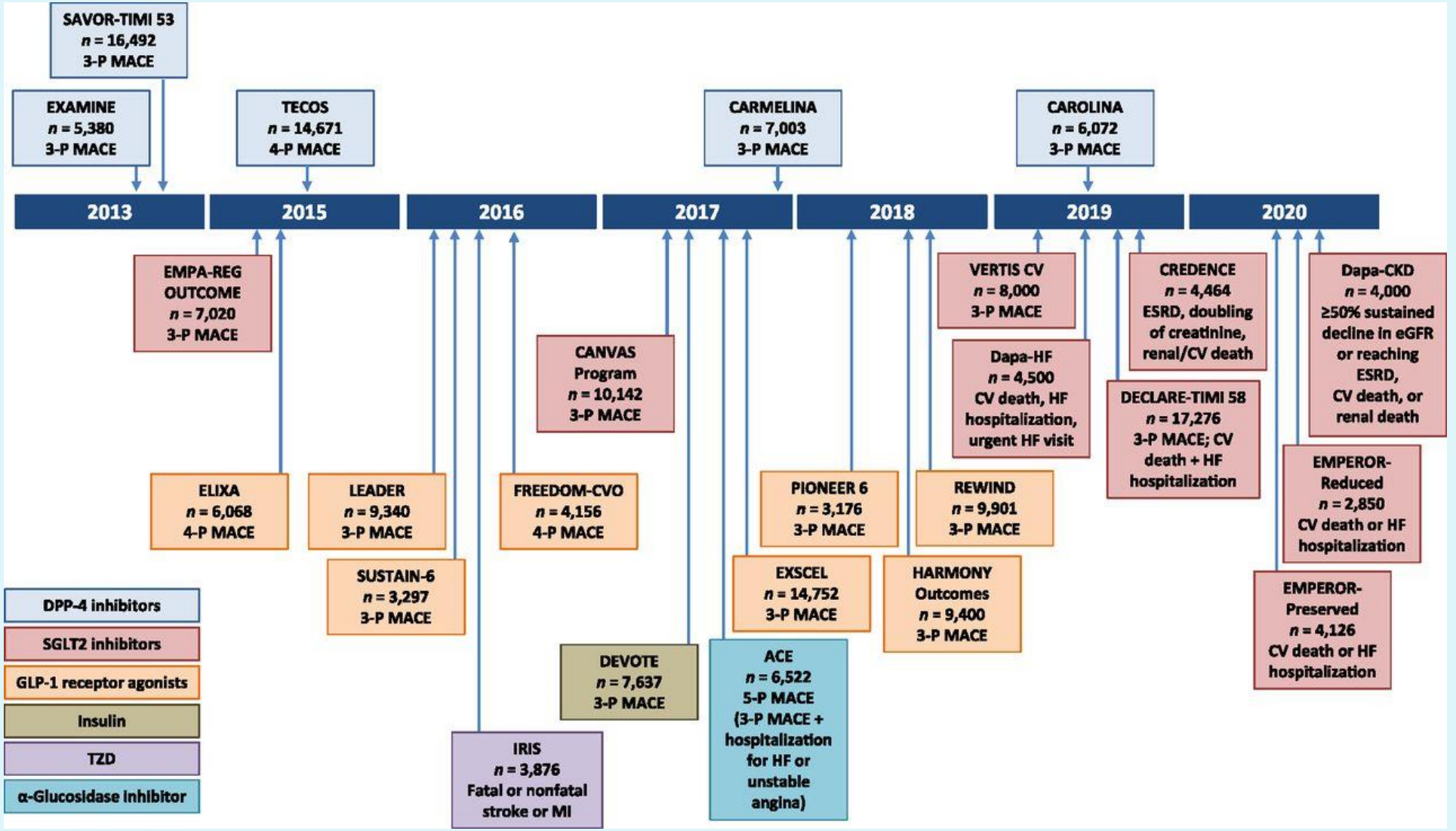
Purple = Intensive control with a specific agent vs standard care

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.

Completed and ongoing CVOTs



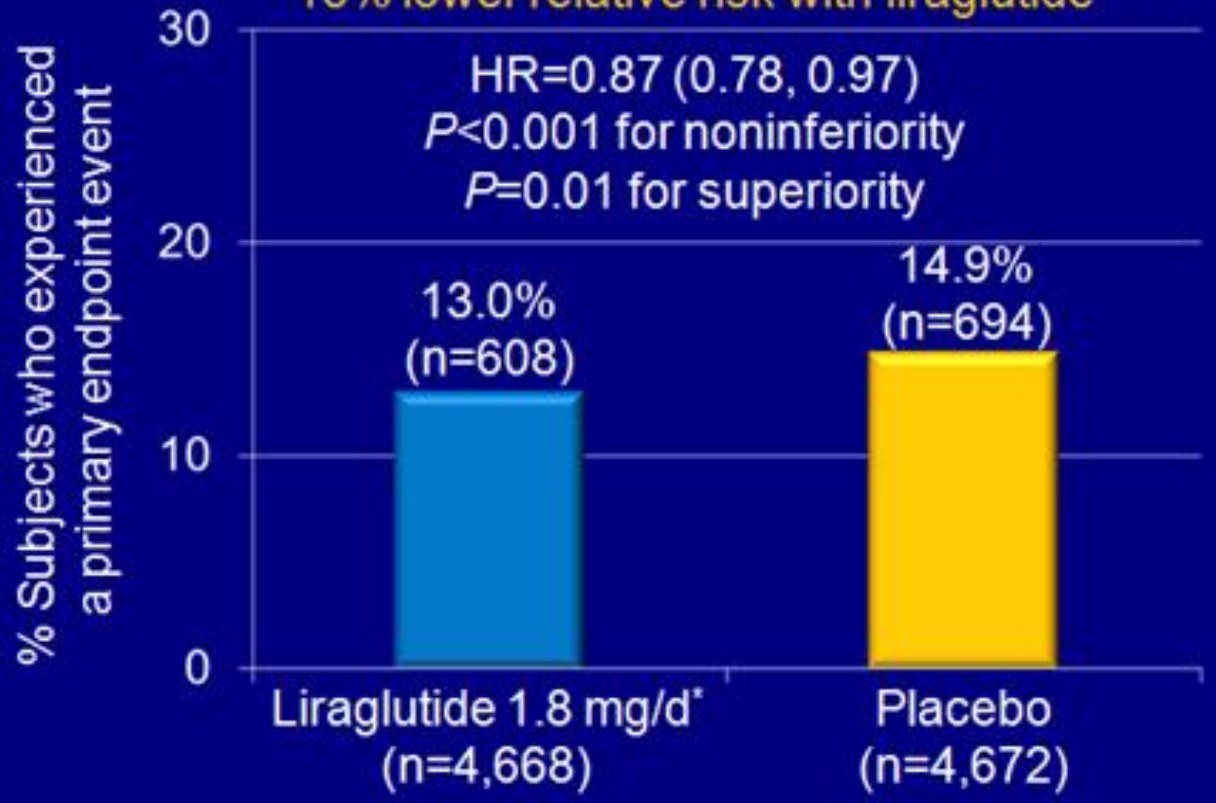
William T. Cefalu et al. Dia Care 2018;41:14-31

American Diabetes Association.

LEADER: Fewer CV Events With Liraglutide Vs Placebo in High-Risk Patients

Primary composite endpoint: first occurrence of CV death, nonfatal (including silent) MI, or nonfatal stroke

13% lower relative risk with liraglutide

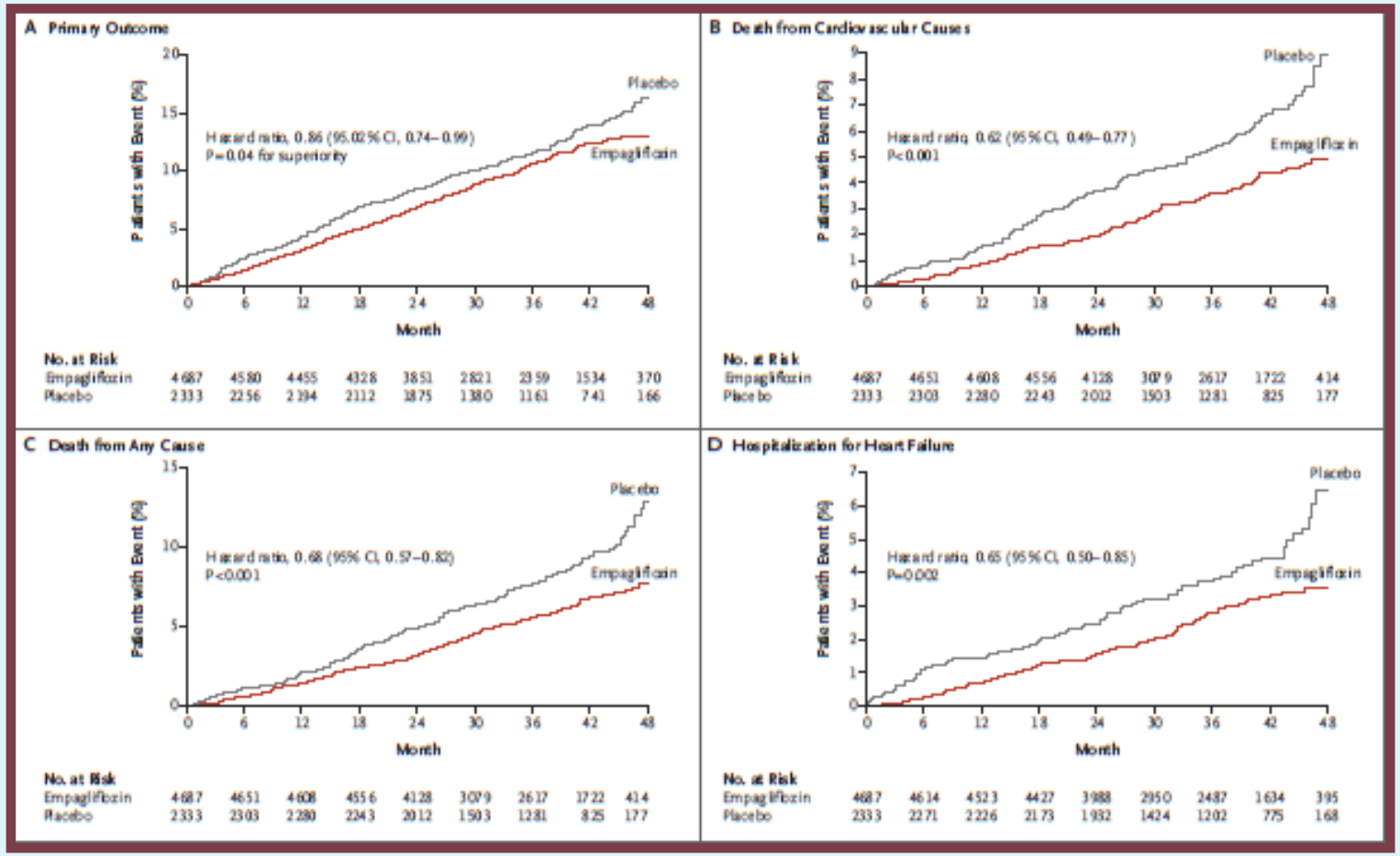


*Or max tolerated dose
MI=myocardial infarction

Marso SP, et al; for the LEADER Trial Investigators. *N Engl J Med*. 2016. DOI:10.1056/NEJMoa1603827.

Clinical Outcomes with Empagliflozin

EMPA-REG OUTCOME Pooled Analysis (N=7020)



*CV death, nonfatal MI (excluding silent MI), or nonfatal stroke; †CV death, nonfatal MI (excluding silent MI), nonfatal stroke, and hospitalization for unstable angina.

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

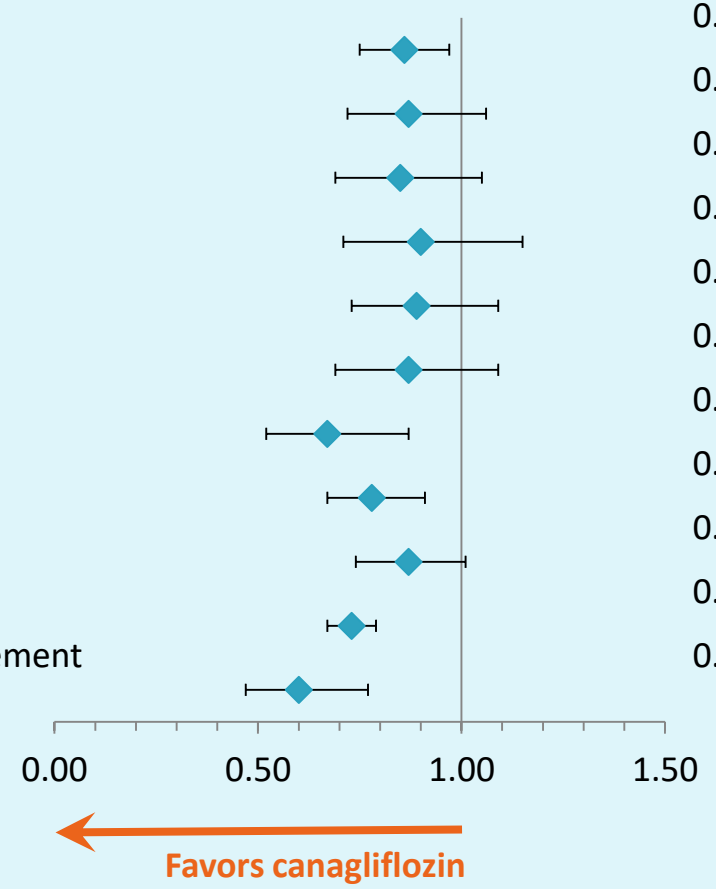
Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128.

Clinical Outcomes with Canagliflozin

CANVAS Program (N=10,142)

Median follow-up: 2.4 years

	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	0.86 (0.75-0.97)	0.02†
CV death	0.87 (0.72-1.06)	
Nonfatal MI	0.85 (0.69-1.05)	
Nonfatal stroke	0.90 (0.71-1.15)	
Fatal or nonfatal MI	0.89 (0.73-1.09)	
Fatal or nonfatal stroke	0.87 (0.69-1.09)	
HF hospitalization	0.67 (0.52-0.87)	
CV death or HF hospitalization	0.78 (0.67-0.91)	
All-cause death	0.87 (0.74-1.01)	
Progression of albuminuria	0.73 (0.67-0.79)	
40% reduction in eGFR, renal replacement therapy, or renal death	0.60 (0.47-0.77)	



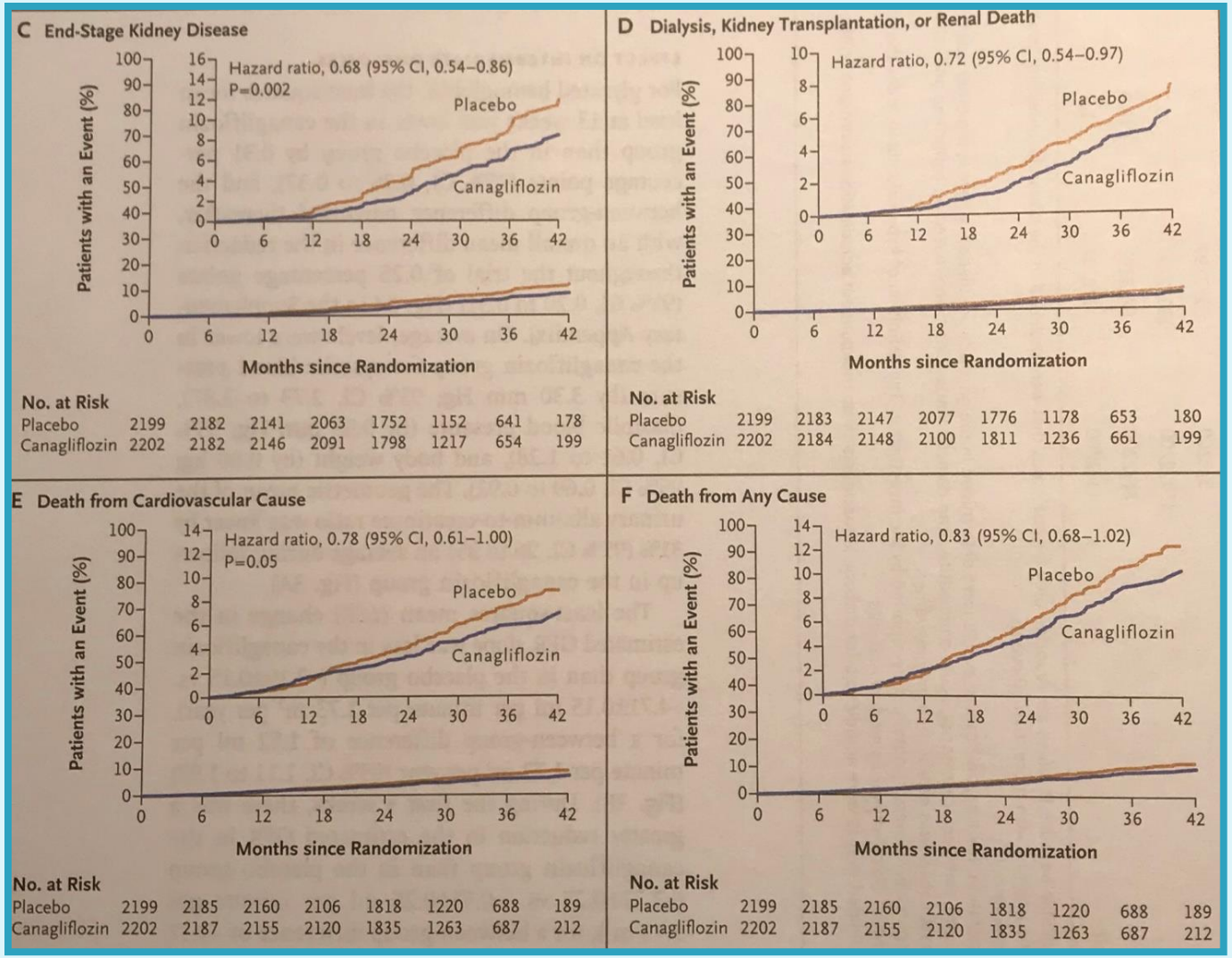
*CV death, nonfatal MI, or nonfatal stroke. †Superiority.
CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.
Neal B, et al. *N Engl J Med*. 2017 Jun 12 [epub ahead of print].

Canagliflozin and Renal Events in Diabetes with Establish Nephropathy Clinical Evaluation

- CREDENCE-April 14, 2019 N=4401
  - Randomized, double-blinded study with diabetic patients with renal manifestations and GFR between 30 to 90 ml/min already receiving ARB's.
  - They received canagliflozin 100mg vs placebo and were F/U for 2.62 years
  - Primary outcome: ESRD, doubling of creatinine level or death from renal or CV causes.
  - RR for primary outcome was 30% lower with canagliflozin (P=0.00001), lower risk for CV death, MI or stroke (P=0.01) in patients receiving canagliflozin 100mg

Canagliflozin and Renal Events in Diabetes with Establish Nephropathy Clinical Evaluation

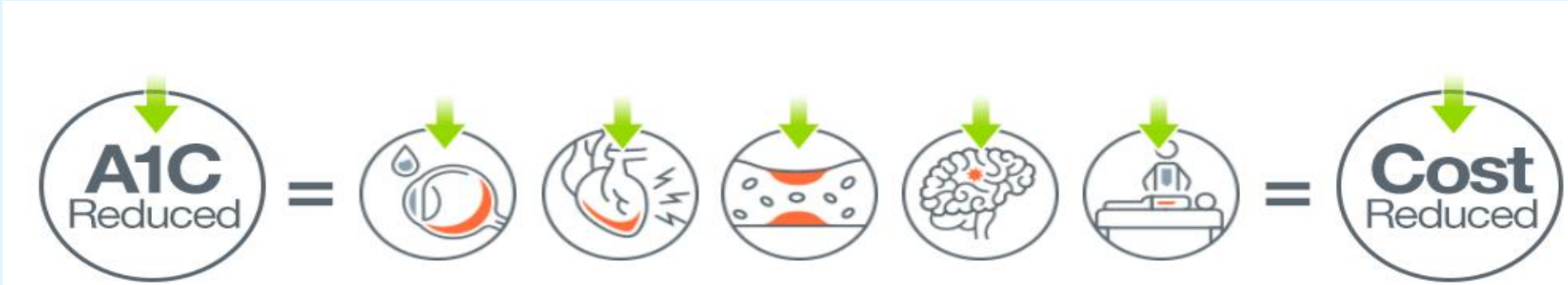
CREDENCE (N=4401)



Perkovic V., et al. *N Engl J Med*. April 14,2019.

Conclusions

- The recommendation of increase 1% of A1c
  - has the potential to do harm in newly diagnosed patients
  - may prevent patients to benefits of long term glucose control
- We agree to individualized patients treatment to improve their lives and reduce risk of complications




Thanks