How Has Diabetes Management Changed in 2019: A Review of the ADA Standards of Care

Matt Bouchonville, MD, CDE
Family Medicine Resident School
September 18, 2019

Conflicts of Interest

None

Join us for Endo ECHO!

- Wednesdays 12-2pm
- No cost CME
- Complex diabetes, thyroid, adrenal, pituitary, transgender care, metabolic bone disease

Objectives

1. To recognize that patients with diabetes are at increased risk for cardiovascular morbidity and mortality
2. To be familiar with clinical practice guidelines directed at targeting individual cardiovascular risk factors in patients with diabetes
3. To understand the impact of a multifactorial risk reduction strategy on outcomes in patients with diabetes

ADA *Standards of Care in Diabetes*

- Published every year in Diabetes Care; continuously updated to incorporate new evidence, best practices
- Funded out of the ADA's general revenues; *does not use* industry support
- Not the only guidelines available for diabetes management (i.e. AACE, IHS, ACP, etc)
- Numerous updates to the 2019 ADA Standards of Care which will be beyond the scope of this presentation

Diabetes Care 2019;42(S1).

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ACC Endorses New ADA 2019 Standards of Medical Care in Diabetes

Dec 17, 2018

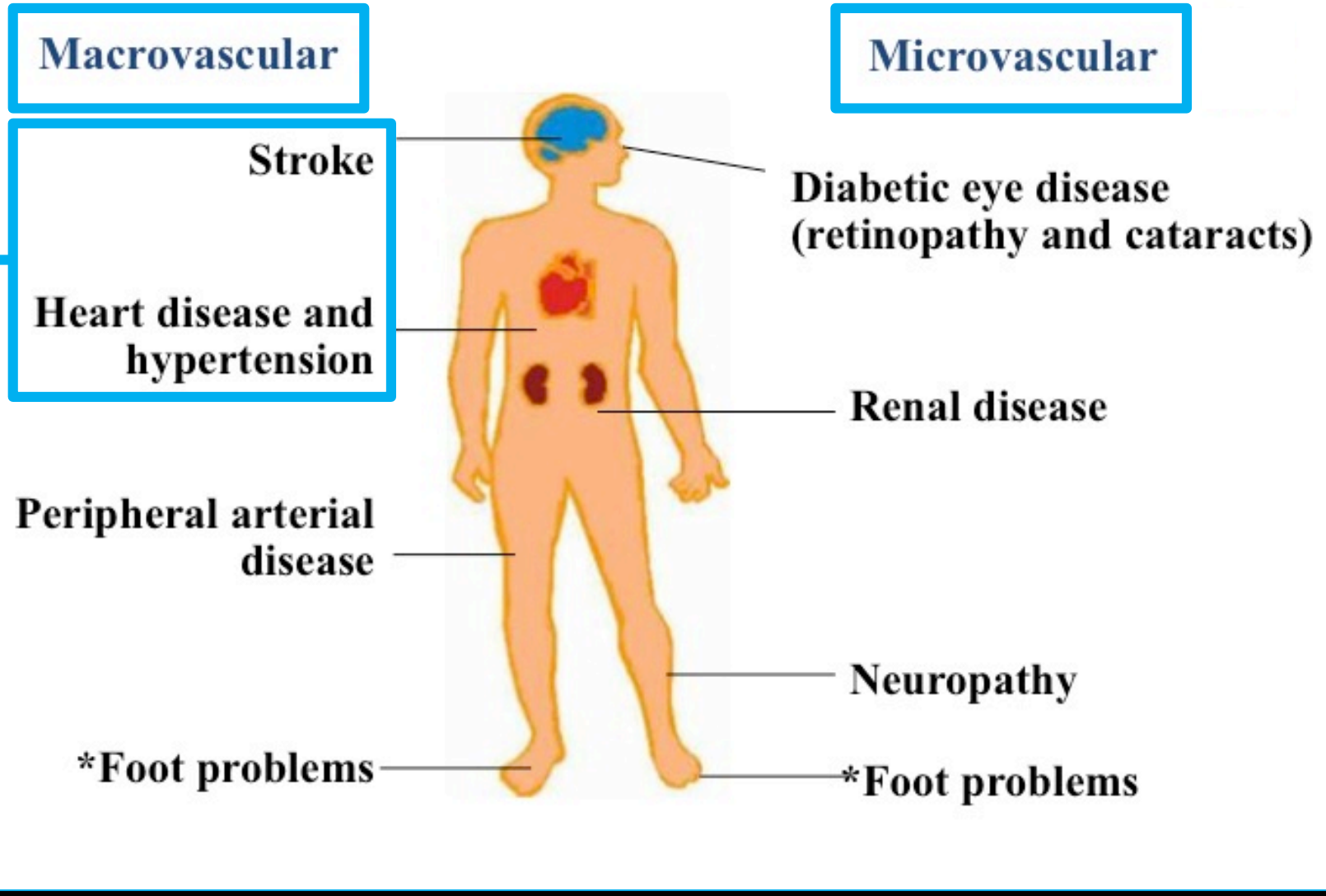
ACC News Story

Dr. Richard Kovacs, ACC Vice President:

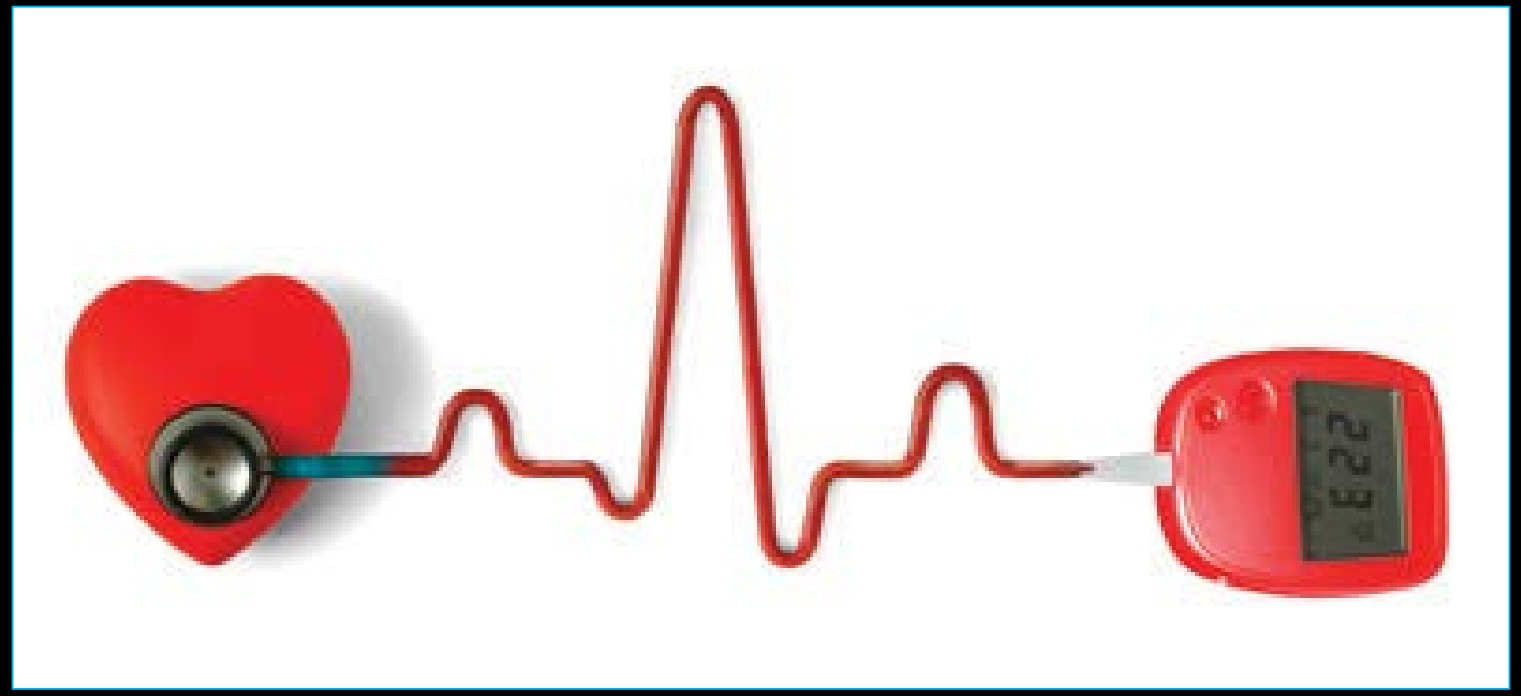
"The American College of Cardiology and the American Diabetes Association share a goal to reduce the burden of cardiovascular disease that too often follows a diabetes diagnosis. ACC is proud to stand behind this important document that will provide a roadmap for clinicians to effectively assess and manage cardiovascular disease in patients with diabetes and, in turn, save lives."

Overview of Diabetic Complications

Leading cause of death in people with diabetes

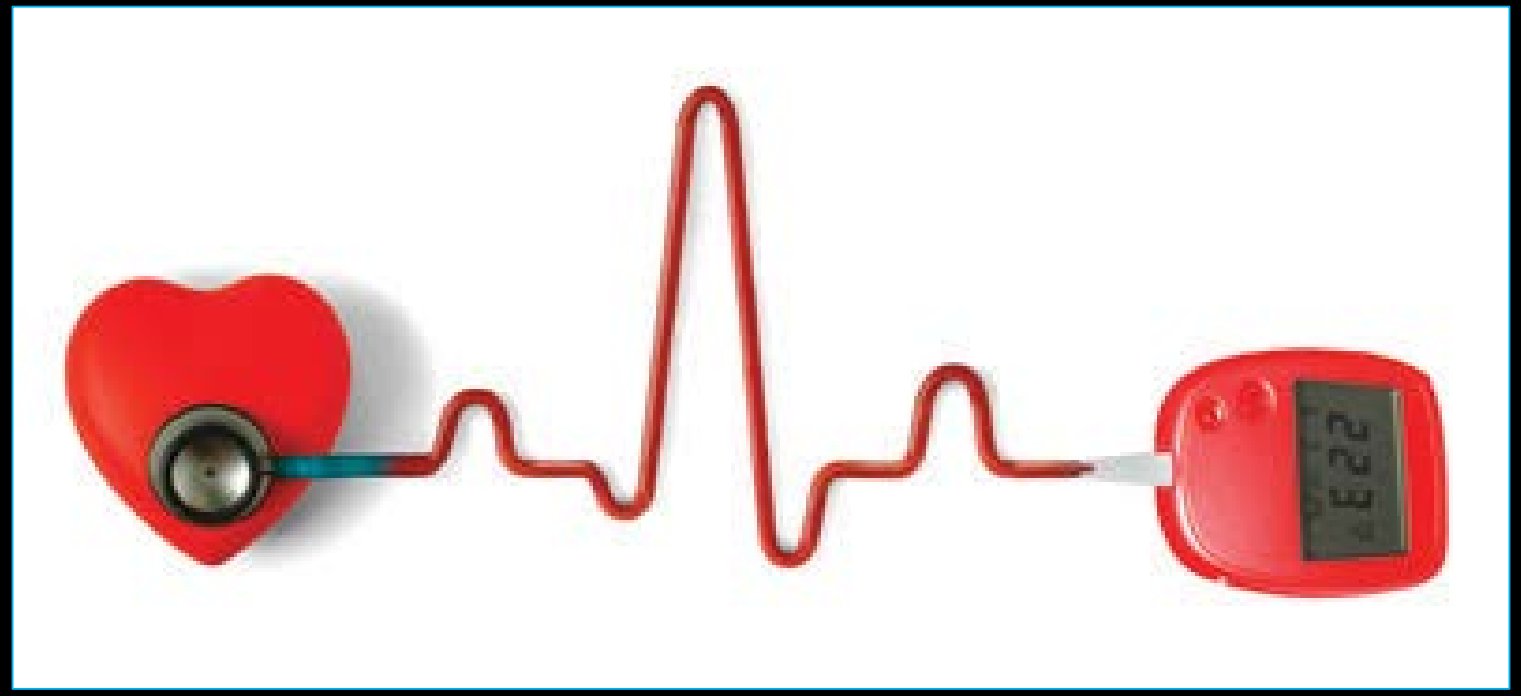


According to the American Heart Association, more than 80% of older people with diabetes will die of heart disease or stroke



http://www.heart.org

According to the Centers for Disease Control and Prevention (CDC), more than 200,000 cardiovascular deaths per year are preventable



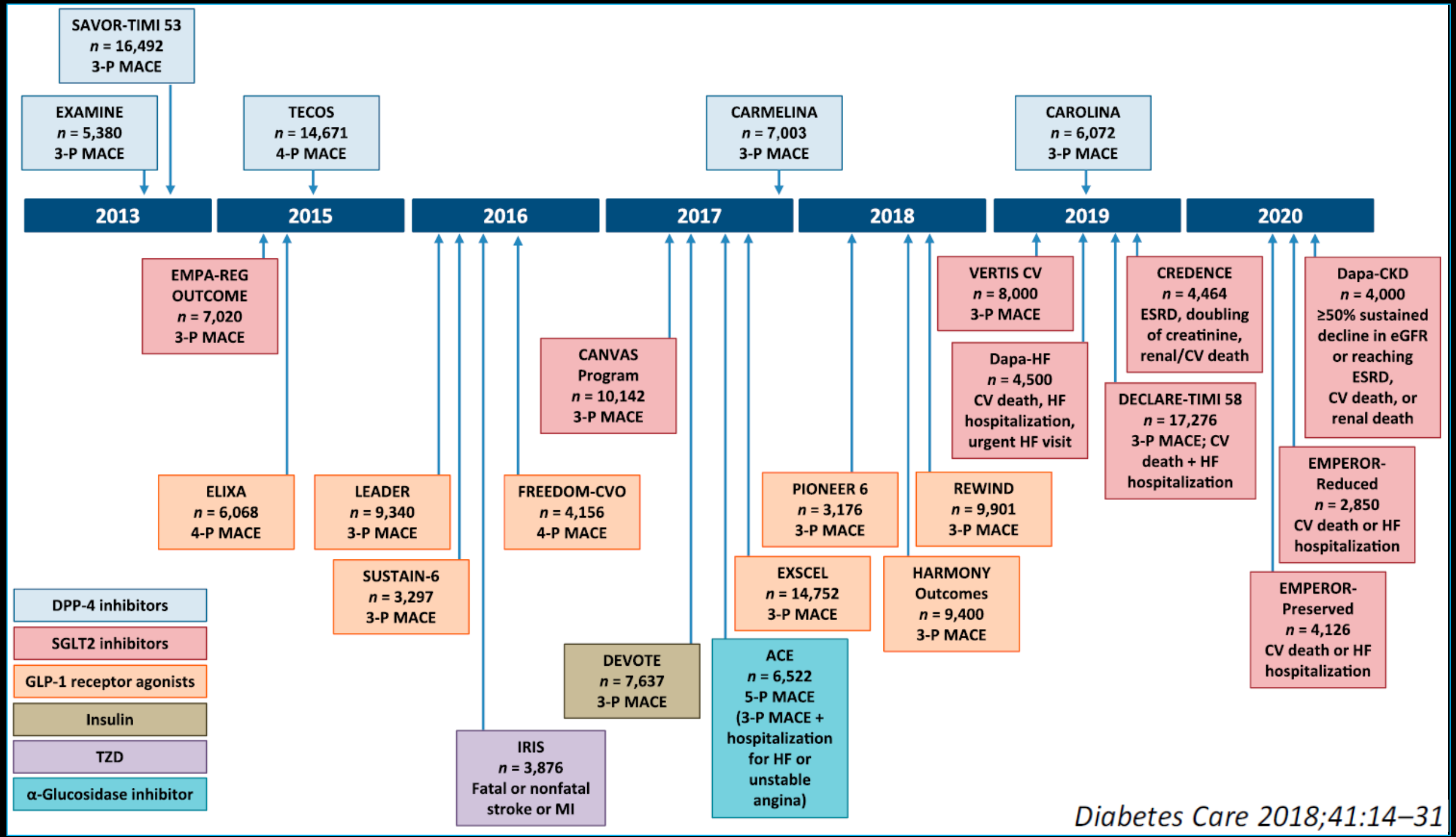
http://www.cdc.gov

A1c target: < 7-8%

Blood pressure management

Cholesterol lowering therapy

Diabetes Care 2019;42(S1).



Diabetes Care 2018;41:14–31

My patient with T2D and CAD remains hyperglycemic on metformin and I am considering adding a second agent. Which of the following antihyperglycemic therapies has NOT been linked to a reduction in cardiovascular events or mortality?

A. Liraglutide
B. Pioglitazone
C. Empagliflozin
D. Sitagliptin

See Table 9.1 for a helpful comparison of CV/renal effects of available hyperglycemic agents

Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ	Renal Effects	
			ASCVD	CHF			Progression of DKD	Dosing/Use considerations

Diabetes Care 2019;42(S1).

	CV Effects	
	ASCVD	CHF
Metformin	Potential Benefit	Neutral
SGLT-2 Inhibitors	Benefit: canagliflozin, empagliflozin†	Benefit: canagliflozin, empagliflozin

HOME

CANVAS

EMPA-REG

DECLARE TIMI 58 (Dapagliflozin)

Diabetes Care 2019;42(S1).

SGLT2 inhibitors

EMPA-REG: 38% reduction in CV death, 32% reduction in all cause mortality, 35% reduction in CHF hospitalization, NO cardiovascular event benefit

CANVAS: 33% reduction in CHF hospitalization, NO mortality or cardiovascular event benefit

DECLARE TIMI 58: 27% reduction in CHF hospitalization, NO mortality or cardiovascular event benefit

	CV Effects	
	ASCVD	CHF
GLP-1 RAs	**Neutral:** lixisenatide	**Neutral**
	Benefit: liraglutide† > semaglutide > exenatide extended release	
DPP-4 Inhibitors	**Neutral**	**Potential risk:** saxagliptin, alogliptin

ELIXA

EXSCEL

LEADER

SUSTAIN-6

?REWIND (Dulaglutide)

Diabetes Care 2019;42(S1).

GLP-1 agonists

ELIXA: NO cardiovascular event, CHF, or mortality benefit

LEADER: + benefit in primary combined outcome; 22% reduction in CV death, 14% reduction in MI (p=0.046), NO CHF benefit

SUSTAIN-6: + benefit in primary combined outcome; 39% reduction in nonfatal stroke, NO MI (p=0.12), mortality, or CHF benefit

EXSCEL: NO cardiovascular event or CHF benefit. Primary combined outcome just missed significance (p=0.06). Small benefit in all cause mortality?

	CV Effects	
	ASCVD	CHF
GLP-1 RAs	Neutral: lixisenatide	Neutral
	Benefit: liraglutide† > semaglutide > exenatide extended release	
DPP-4 Inhibitors	Neutral	Potential risk: saxagliptin, alogliptin

ELIXA

EXSCEL

LEADER

SUSTAIN-6

Diabetes Care 2019;42(S1).

	CV Effects	
	ASCVD	CHF
Thiazolidinediones	Potential Benefit: pioglitazone	Increased Risk
Sulfonylureas (2nd Generation)	Neutral	Neutral

PROactive

IRIS

Diabetes Care 2019;42(S1).

FIRST-LINE therapy is metformin and comprehensive lifestyle (including weight management and physical activity) if HbA_{1c} above target proceed as below

ESTABLISHED ASCVD OR CKD

GLP-1 RA with proven CVD benefit[1]

SGLT2i with proven CVD benefit[1], if eGFR adequate[2]

If HbA_{1c} above target

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:

- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin[4]
- TZD[5]
- SU[6]

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1]

If HbA_{1c} above target

- Avoid TZD in the setting of HF

Choose agents demonstrating CV safety:

- Consider adding the other class with proven CVD benefit[1]
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin[4]
- SU[6]

NO

WITHOUT ESTABLISHED ASCVD OR CKD

DPP-4i → If HbA_{1c} above target → SGLT2i[2] **OR** TZD

GLP-1 RA → If HbA_{1c} above target → SGLT2i[2] **OR** TZD

SGLT2i[2] → If HbA_{1c} above target → GLP-1 RA **OR** DPP-4i **OR** TZD

TZD → If HbA_{1c} above target → SGLT2i[2] **OR** DPP-4i **OR** GLP-1 RA

If HbA_{1c} above target

Continue with addition of other agents as outlined above

If HbA_{1c} above target

Consider the addition of SU[6] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycemia
- Consider basal insulin with lower risk of hypoglycemia[7]

EITHER/OR

GLP-1 RA with good efficacy for weight loss[8] → If HbA_{1c} above target → SGLT2i[2]

SGLT2i[2] → If HbA_{1c} above target → GLP-1 RA with good efficacy for weight loss[8]

If HbA_{1c} above target

If triple therapy required or SGLT2i and/or GLP-1 RA not tolerated or contraindicated use regimen with lowest risk of weight gain

PREFERABLY

DPP-4i (if not on GLP-1 RA) based on weight neutrality

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

• SU[6] • TZD[5] • Basal insulin

SU[6] → If HbA_{1c} above target → TZD[10]

TZD[10] → If HbA_{1c} above target → SU[6]

If HbA_{1c} above target

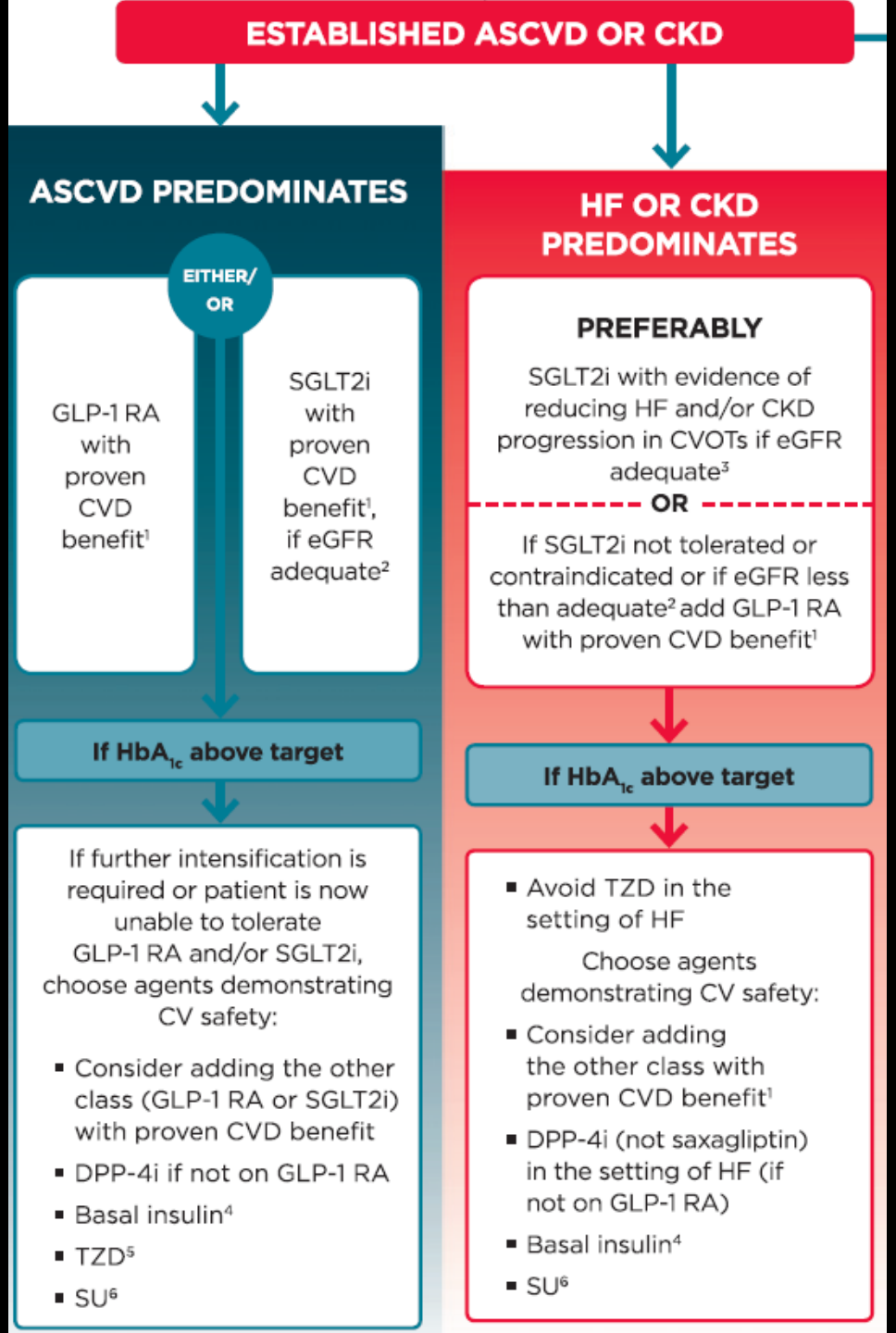
- **Insulin therapy** basal insulin with lowest acquisition cost

OR

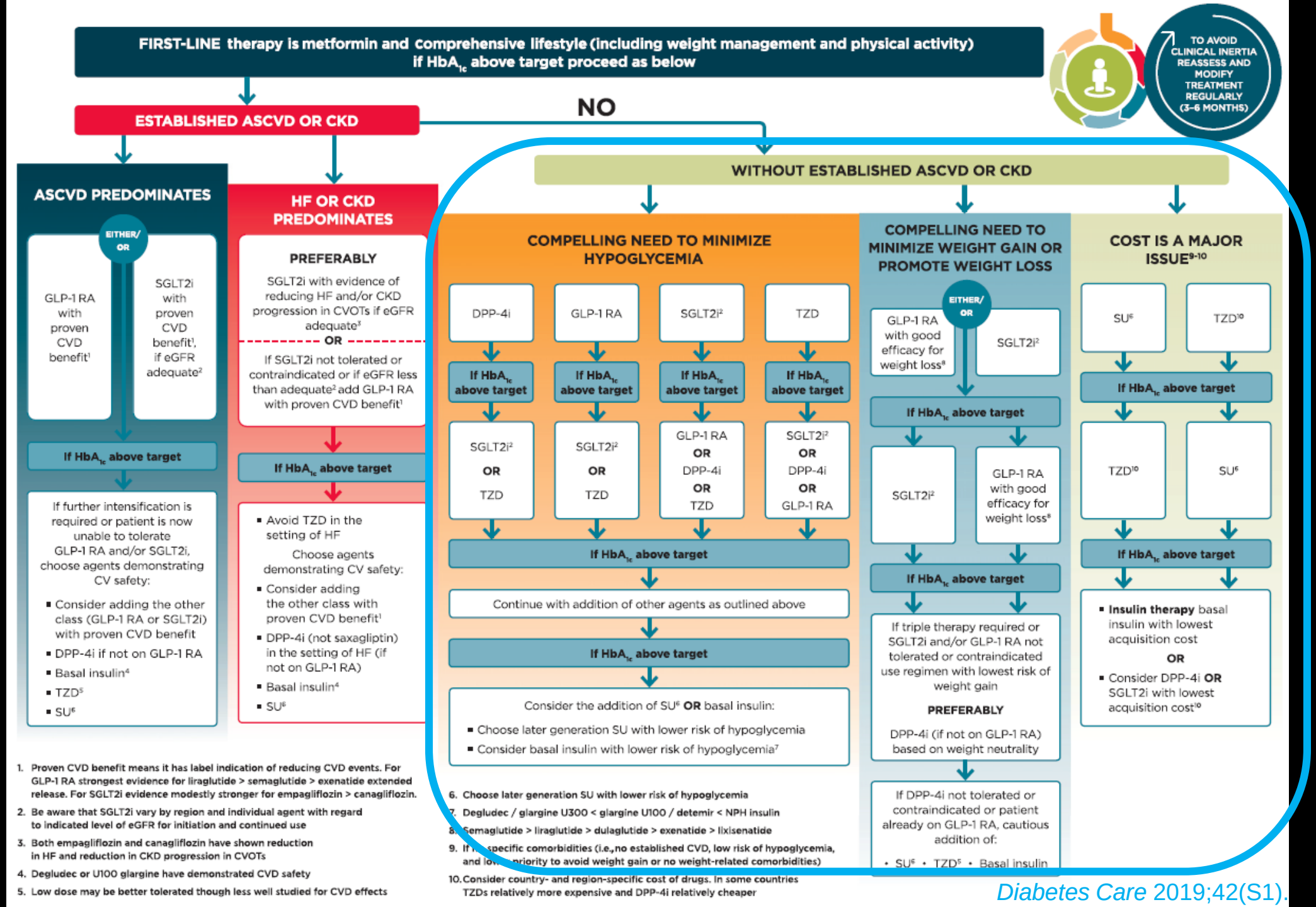
- Consider DPP-4i **OR** SGLT2i with lowest acquisition cost[10]

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

Diabetes Care 2019;42(S1).



Diabetes Care 2019;42(S1).



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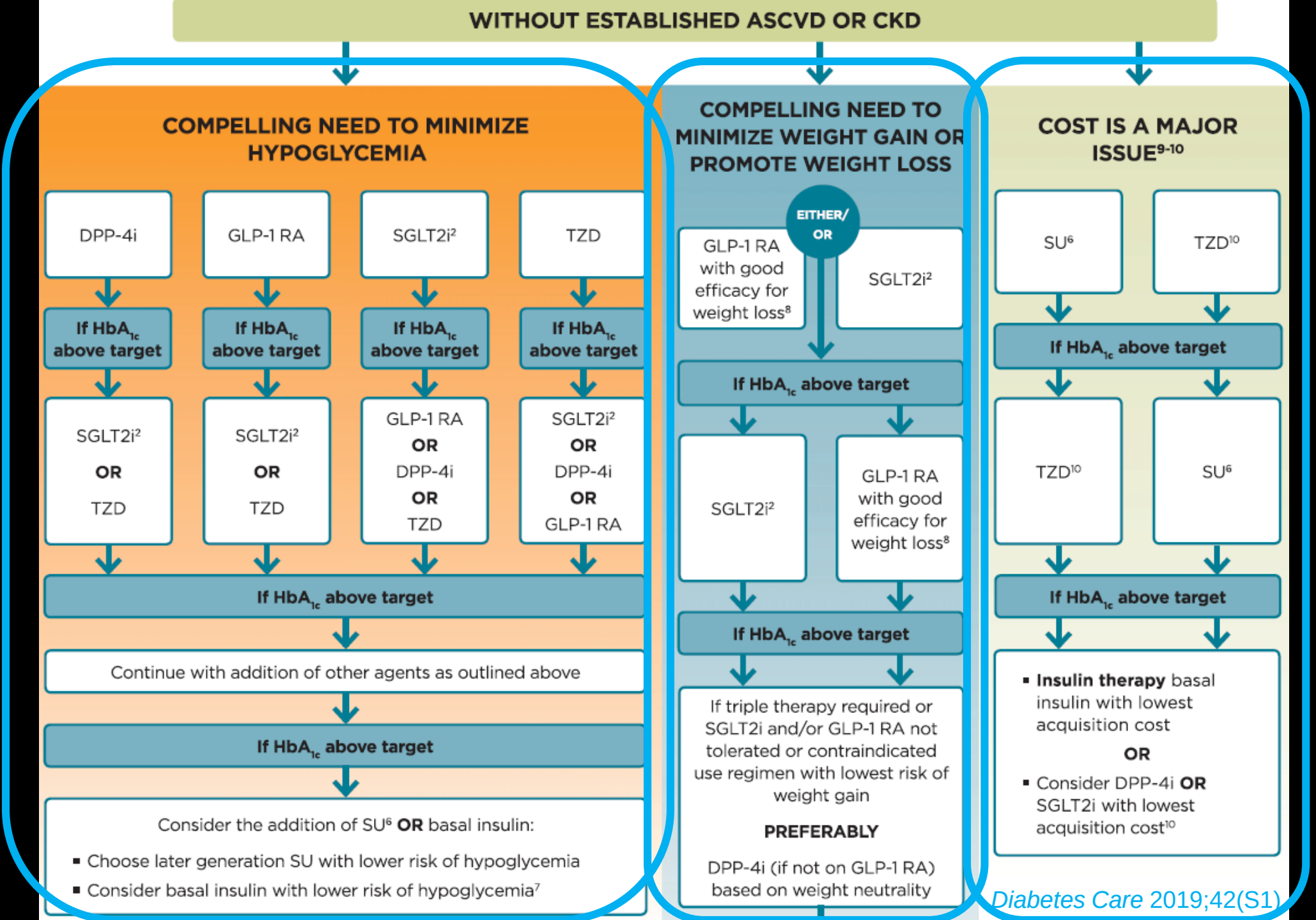
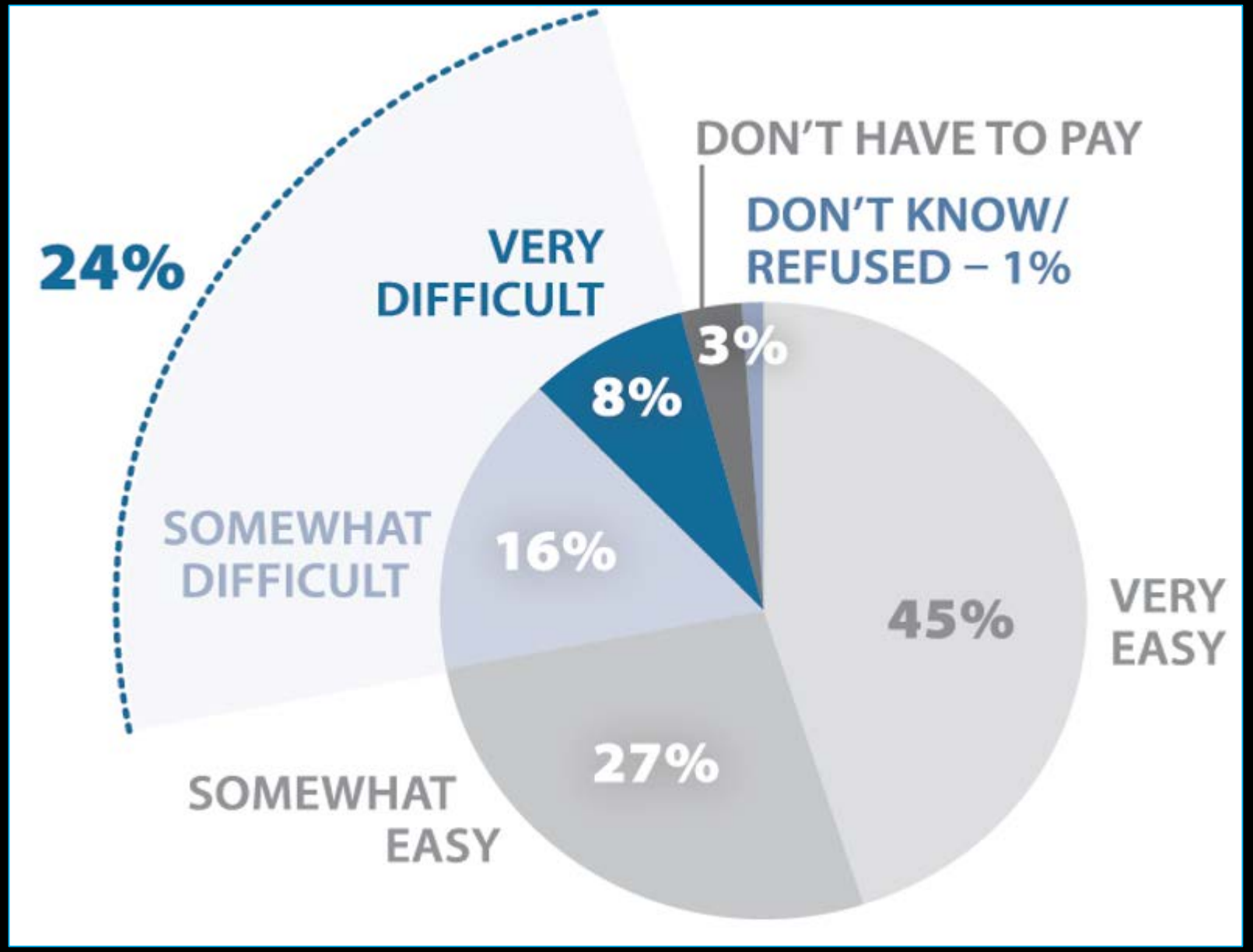
Diabetes Care 2019;42(S1).



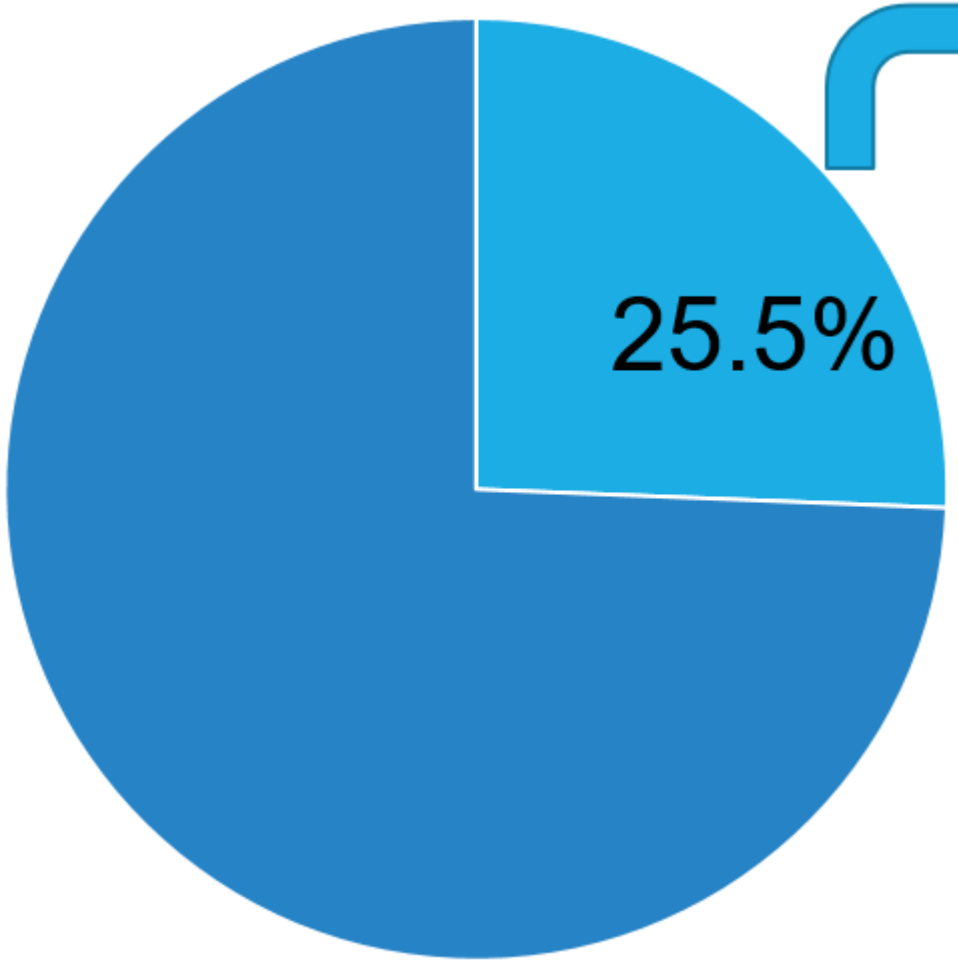
Diabetes Care 2019;42(S1)

Nearly 1 in 4 people in the US taking prescription drugs report difficulty affording them



JAMA 2016;315(13):1326. (adapted from Dr. Kasia Lipska)

Yale Diabetes Center Survey



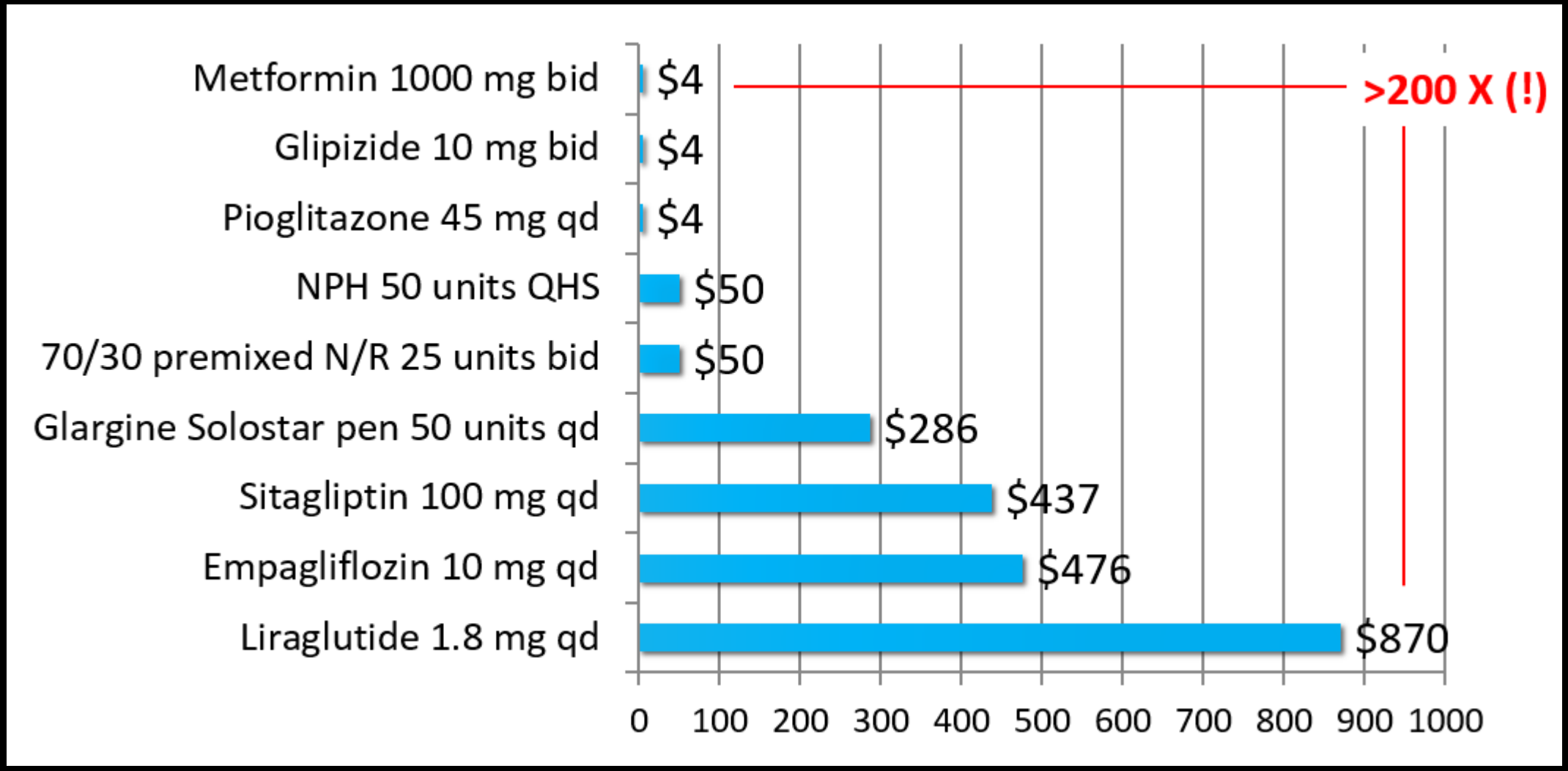
Responded YES:

Over the past 12 months, did you:

1. *Use less insulin than prescribed*
2. *Try to stretch out your insulin*
3. *Take smaller doses of insulin than prescribed*
4. *Stop insulin*
5. *Not fill an insulin prescription*
6. *Not start insulin …* ***because of cost****?*

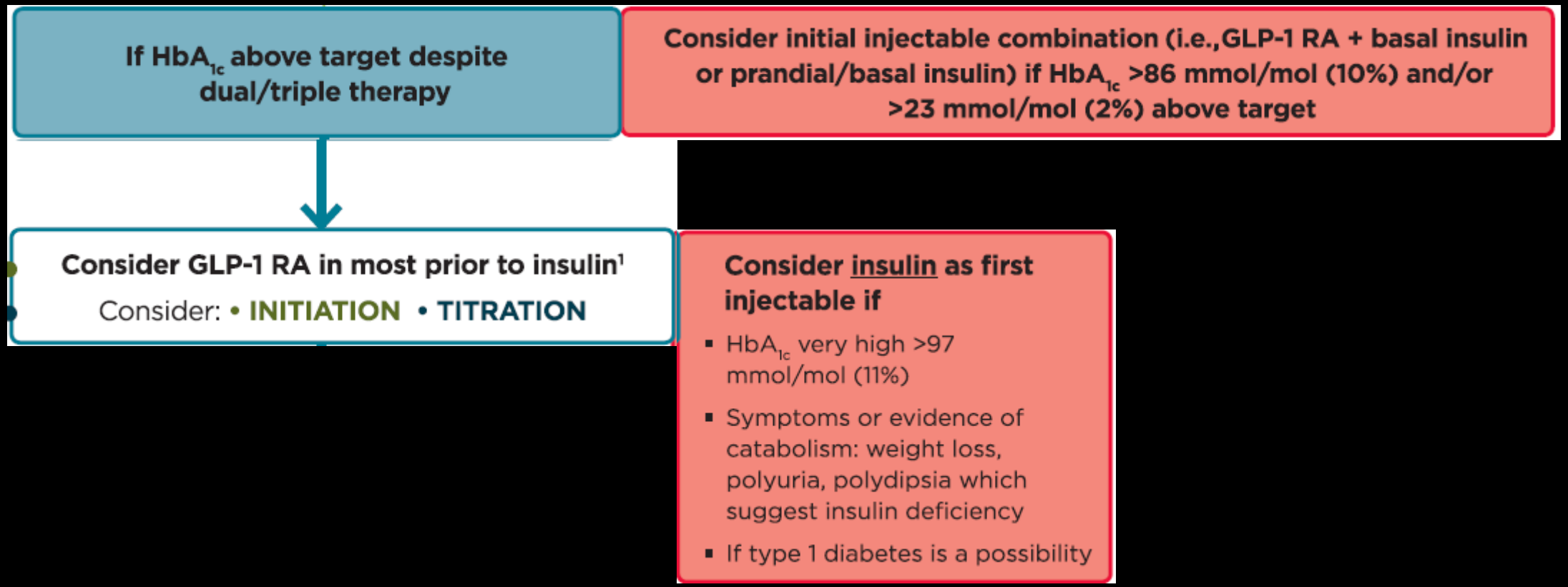
JAMA Intern Med 2019;179(1):112-114. (adapted from Dr. Kasia Lipska)

Cost of 30-day supply of meds



www.GoodRx.com, accessed January 14, 2019 (adapted from Dr. Kasia Lipska)

What if A1c remains above goal despite dual/triple therapy? Time for insulin?



Diabetes Care 2019;42(S1).

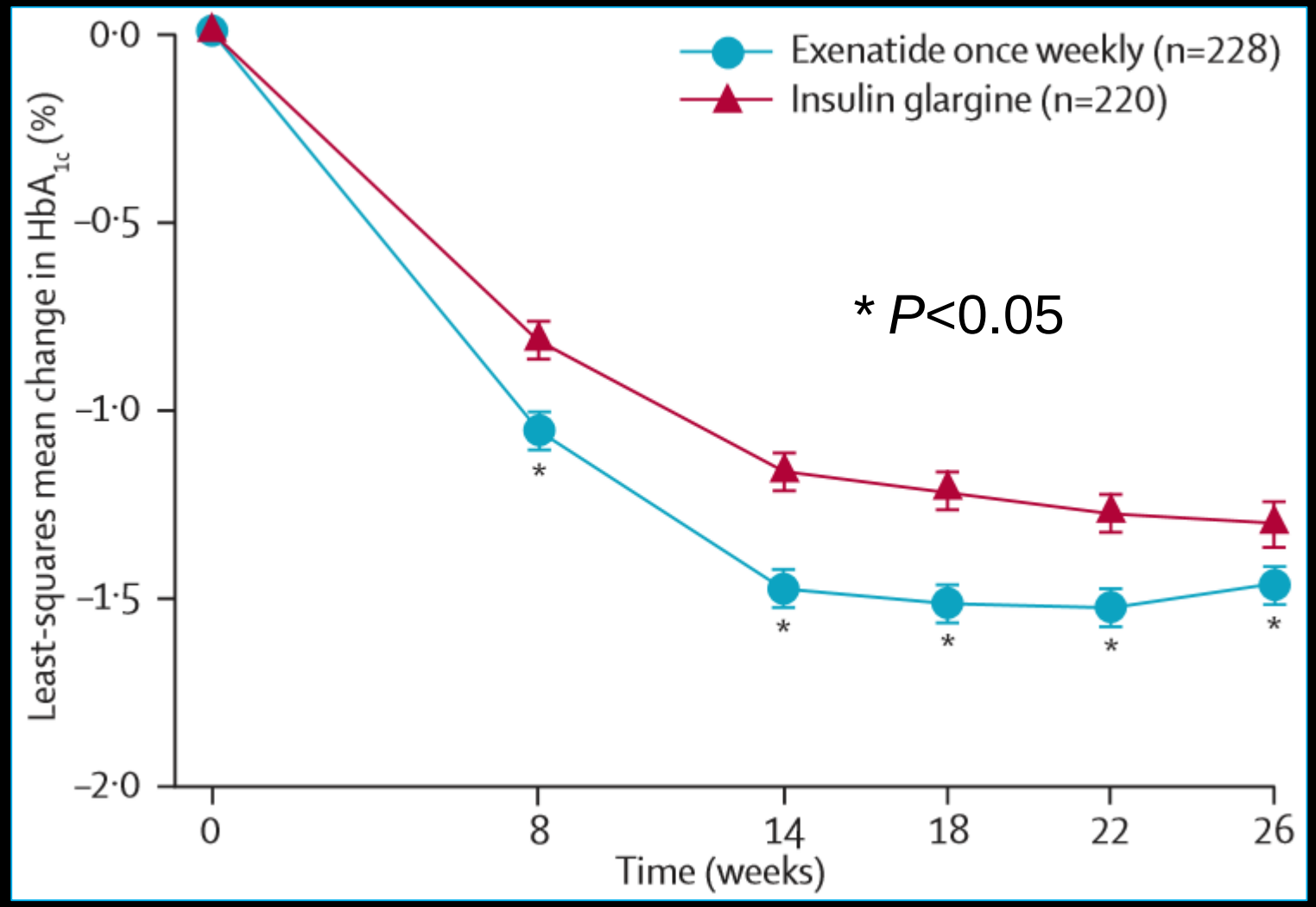
Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial

Michaela Diamant, Luc Van Gaal, Stephen Stranks, Justin Northrup, Dachuang Cao, Kristin Taylor, Michael Trautmann

- 26 week, multicenter, open-label, randomized, two-arm, parallel trial
- T2D (n=456) with suboptimal glycemic control on metformin +/- sulfonylurea
- Baseline mean A1c 8.3%, BMI 32
- Randomized to weekly exenatide vs insulin glargine (titrated to target fasting glucose)

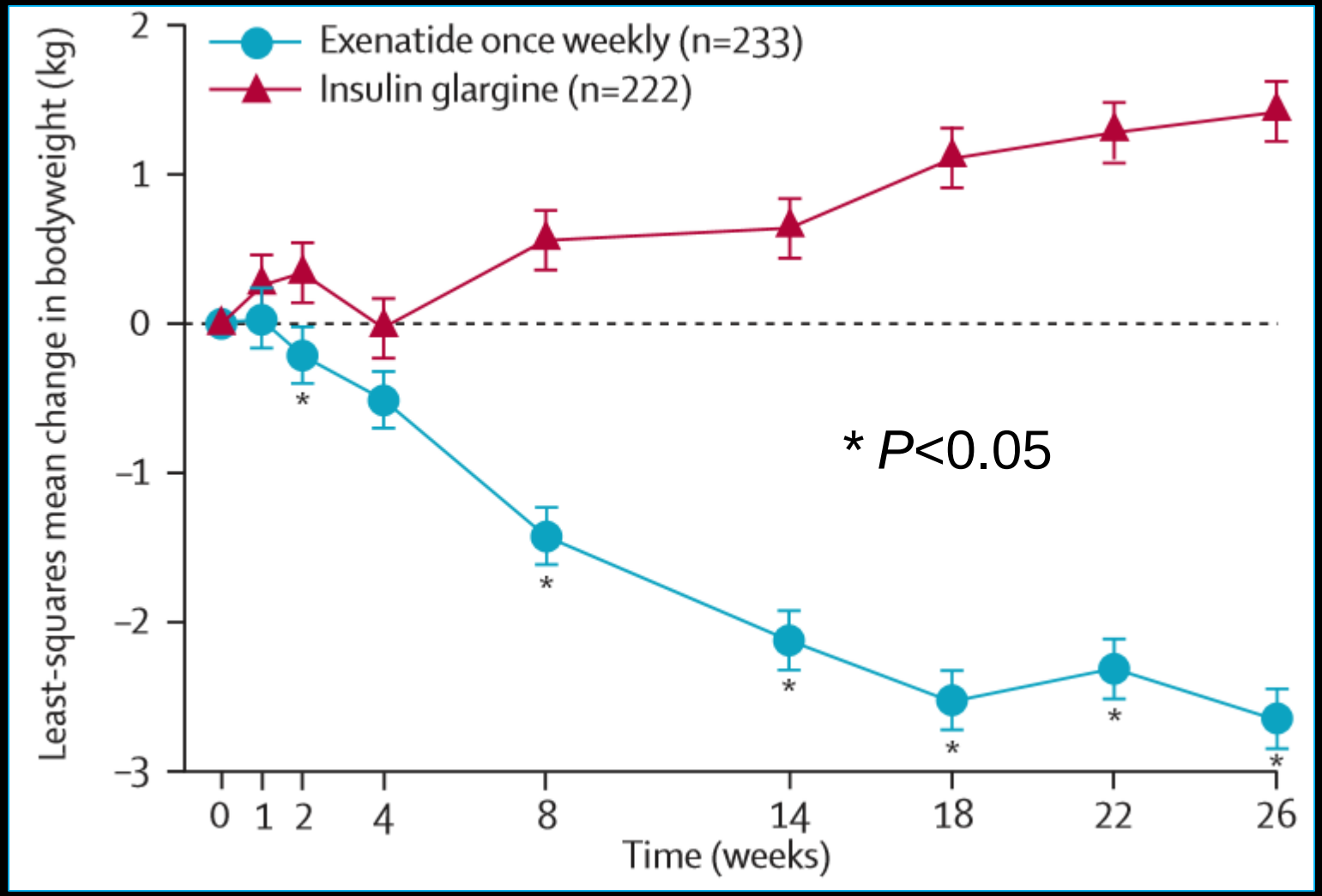
Lancet 2010;375:2234-43.

Greater A1c reduction with once weekly GLP-1 agonist



Lancet 2010;375:2234-43.

Weight loss with once weekly GLP-1 agonist only



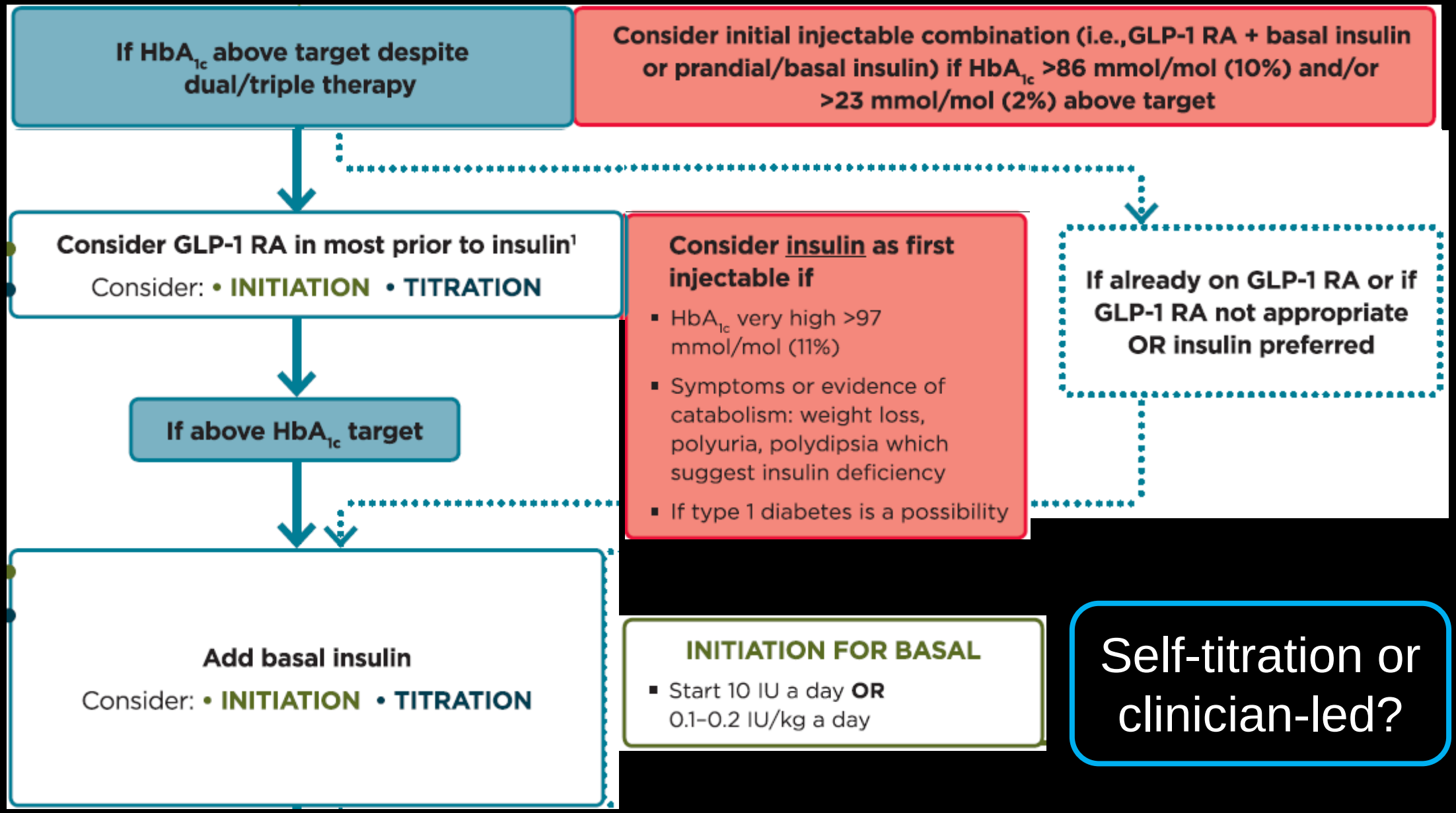
Lancet 2010;375:2234-43.

Other findings from DURATION-3

- Exenatide associated with:
  - Higher risk of nausea
  - Increased heart rate
  - Lower risk of hypoglycemia
  - Reduced postprandial glucose excursions

- Insulin glargine associated with:
  - Lower fasting glucose

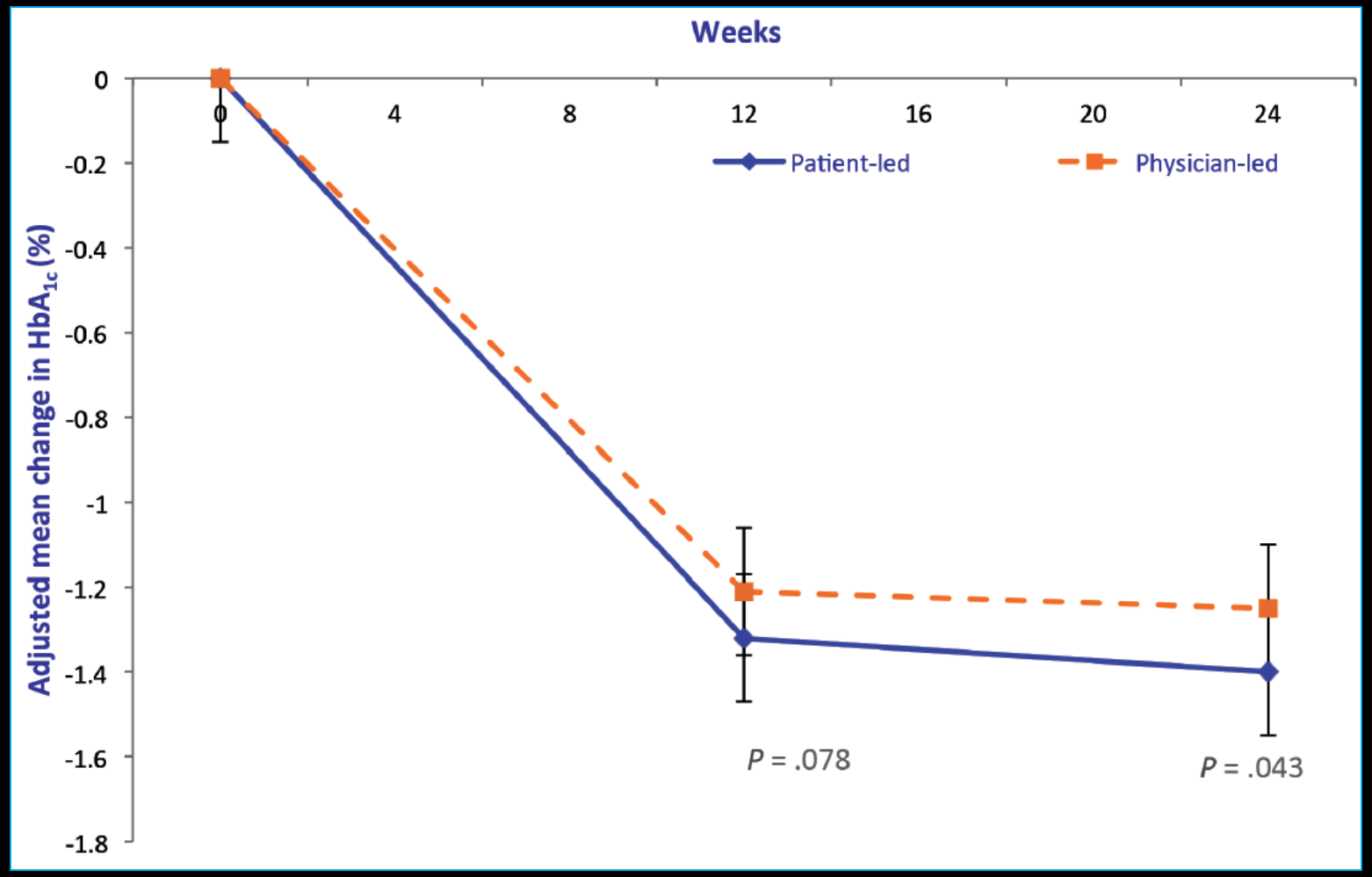
Lancet 2010;375:2234-43.

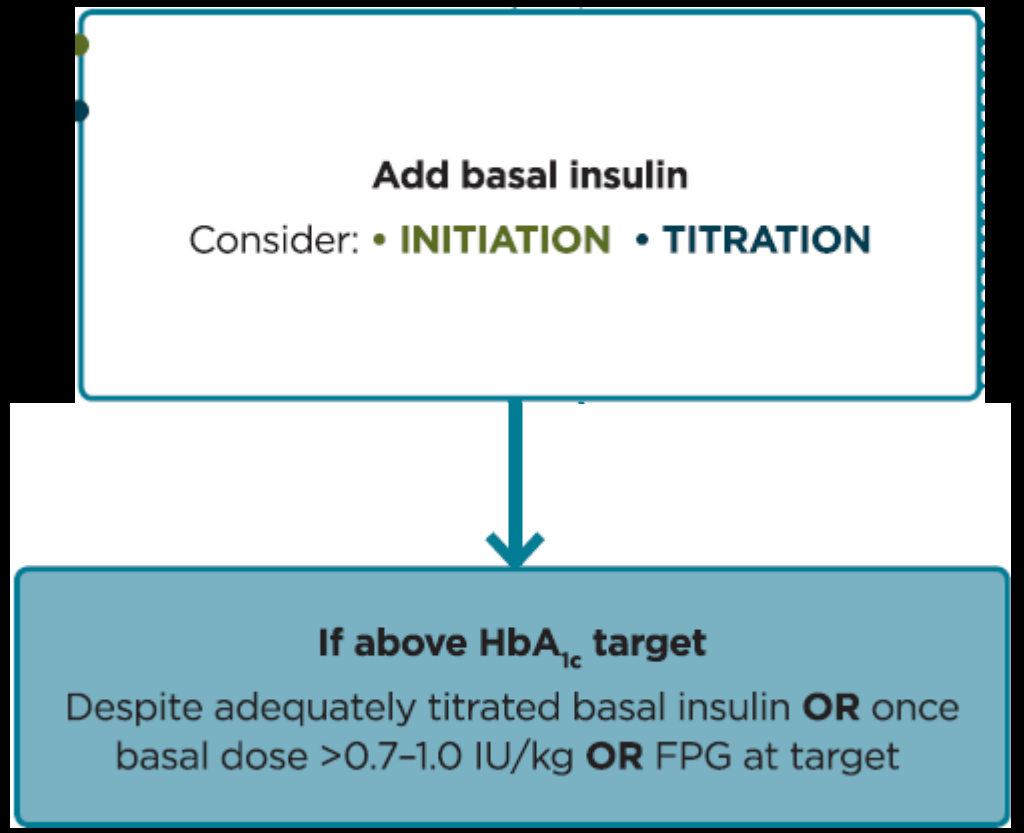


Self-titration or clinician-led?

Diabetes Care 2019;42(S1).

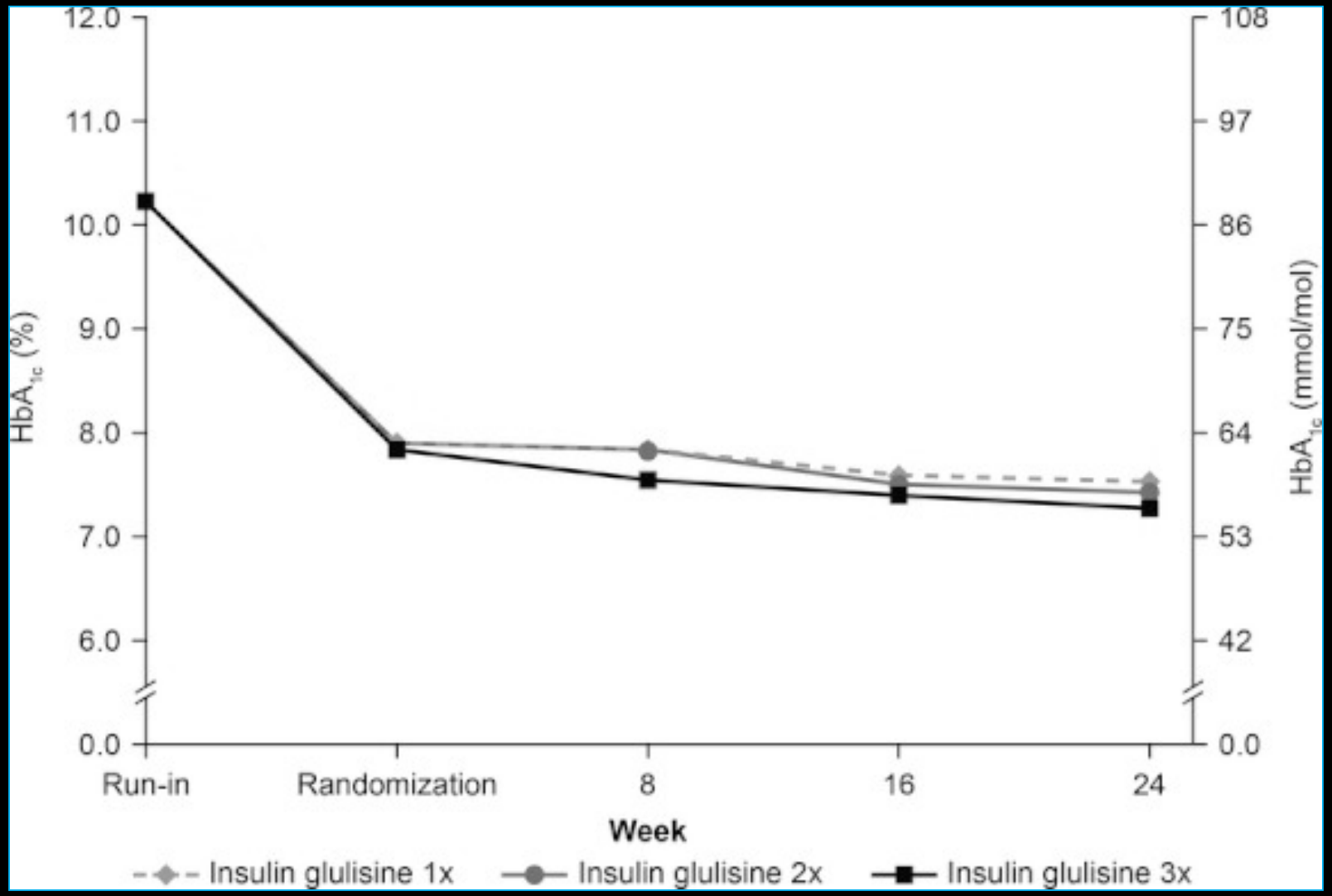
PATIENT-LED VERSUS PHYSICIAN-LED TITRATION OF INSULIN GLARGINE IN PATIENTS WITH UNCONTROLLED TYPE 2 DIABETES: A RANDOMIZED MULTINATIONAL ATLAS STUDY



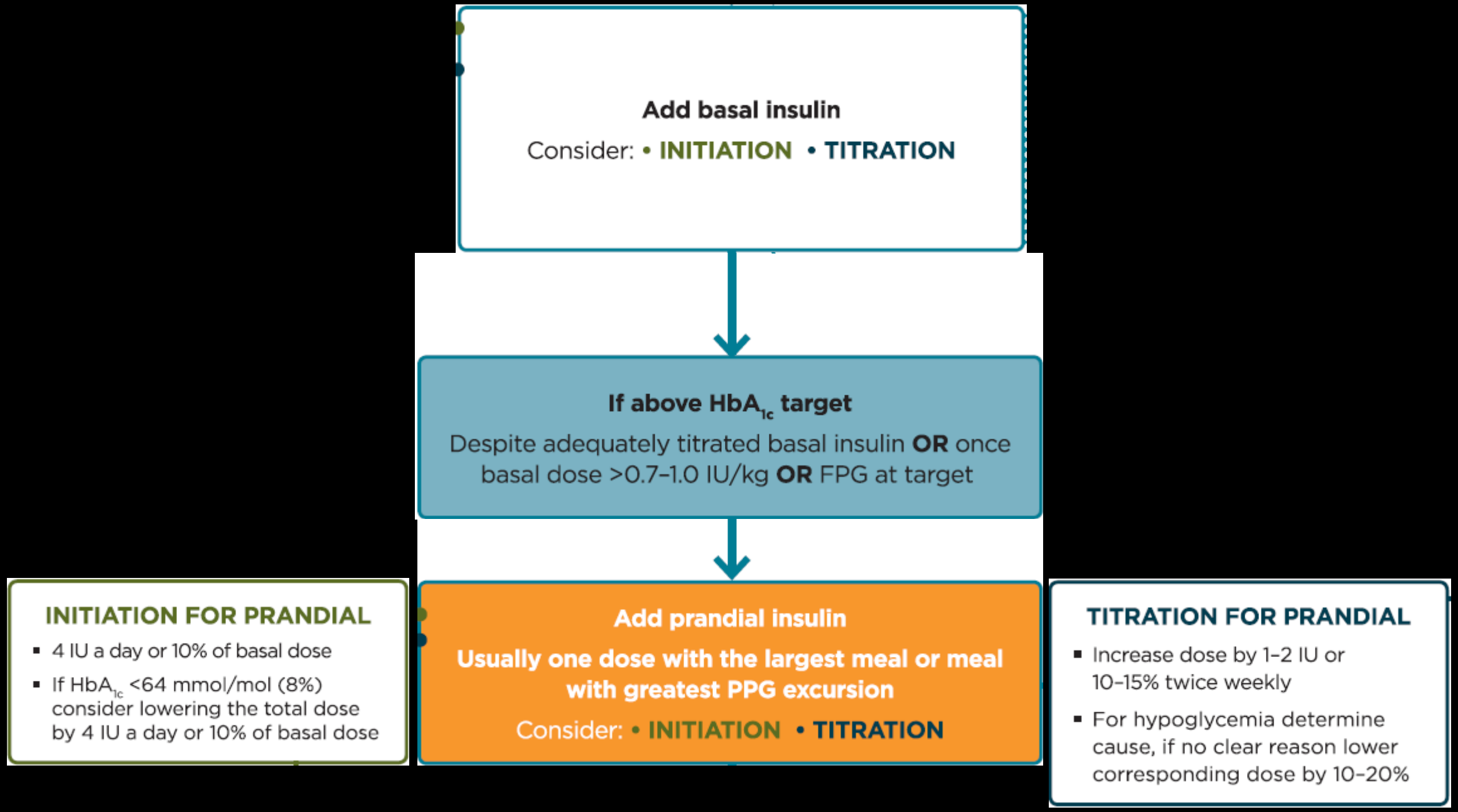


Diabetes Care 2019;42(S1).

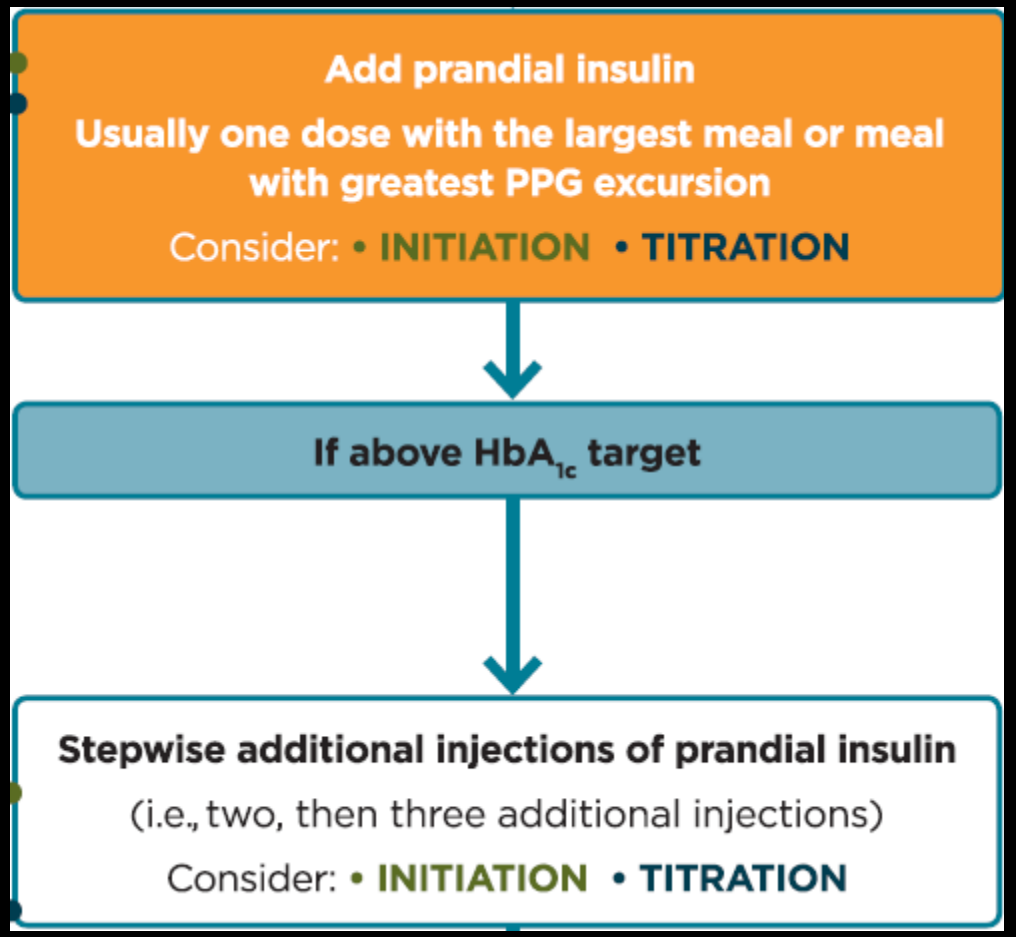
Adding rapid-acting insulin to basal insulin: One meal? Two? All meals?



Endocr Pract 2011;17(3):395.



Diabetes Care 2019;42(S1).



IF HbA_{1c} DOES NOT IMPROVE REVIEW ONGOING NEED FOR BASAL-BOLUS REGIMEN. CONSIDER ADDITIONAL DSMES

Diabetes Care 2019;42(S1).

A1c target: < 7-8%

Blood pressure management

Cholesterol lowering therapy

019;42(S1).

What is considered a normal BP by the ADA?

What is recommended for BP>120/80 but <140/90?

- Weight loss (if overweight)
- Exercise
- DASH diet
- Decrease sodium intake
- Increase potassium intake
- Moderate alcohol intake

42 year-old woman with type 2 diabetes returns to clinic with BP 148/92 mmHg. She has no microvascular complications. Which of the following medications should be started for hypertension?

A. Lisinopril
B. Losartan
C. Hydrochlorothiazide
D. Amlodipine
E. Any of the above are appropriate

Recommendations for the Treatment of Confirmed Hypertension in People With Diabetes

Initial BP between 140/90 mmHg and 160/100 mmHg

Initial BP ≥ 160/100 mmHg

Diabetes Care 2019;42(S1).

2016 ADA Guidelines

- Pharmacological therapy for patients with diabetes and hypertension should comprise a regimen that includes either an ACE inhibitor or an angiotensin receptor blocker but not both. **B**

2019 ADA Guidelines

Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes (ACE inhibitors, angiotensin receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers). **A**

Diabetes mellitus as a compelling indication for use of renin angiotensin system blockers: systematic review and meta-analysis of randomized trials

Sripal Bangalore,[1] Robert Fakheri,[1] Bora Toklu,[2] Franz H Messerli[3]

BMJ 2016;352:i438

- Designed to evaluate ADA Guidelines for BP treatment
- ACE/ARBs renoprotective in setting of albuminuria
- Less clear why ACE/ARB recommendation extended to all hypertensive patients with DM
- Review of CV outcomes in 19 RCTs (25K patients with DM) comparing ACE/ARB with other BP agent
- Excluded heart failure RCTs
- Included 3 RCTs with albuminuria

RAS blocker vs CCB

Outcomes	No of studies	No of events/ No of participants: RAS blockers	Calcium channel blockers	I^2	Relative risk (95% CI)	Relative risk (95% CI): Random	Fixed
All cause mortality	13	985/7174	986/7255	0.0		1.01 (0.92 to 1.10)	1.01 (0.92 to 1.10)
Cardiovascular mortality	10	132/3068	112/3103	0.0		1.17 (0.90 to 1.50)	1.17 (0.90 to 1.50)
Myocardial infarction	9	111/2478	129/2501	54.6		0.84 (0.54 to 1.30)	0.86 (0.66 to 1.13)
Angina	4	22/1149	35/1185	25.3		0.69 (0.33 to 1.42)	0.70 (0.40 to 1.20)
Stroke	13	467/7226	432/7324	15.2		1.08 (0.90 to 1.28)	1.10 (0.96 to 1.25)
Heart failure	8	499/5528	643/5594	0.0		0.78 (0.70 to 0.88)	0.78 (0.70 to 0.88)

1.39)

08)
46)
74)
12)
22)
24)

Conclusion:

In patients with diabetes, RAS blockers are not superior to calcium channel blockers, diuretics, or beta blockers at reducing hard cardiovascular outcomes

RAS blocker vs β blocker

Outcomes	No of studies	RAS blockers	β blockers	I^2	Relative risk (95% CI)	Random	Fixed
All cause mortality	2	138/986	163/967	84.1		0.84 (0.47 to 1.51)	0.83 (0.66 to 1.04)
Cardiovascular mortality	2	77/986	90/967	73.3		0.87 (0.47 to 1.60)	0.84 (0.61 to 1.14)
Myocardial infarction	2	102/986	96/967	24.8		1.02 (0.73 to 1.40)	1.02 (0.77 to 1.35)
Angina	2	50/986	55/967	0.0		0.89 (0.60 to 1.30)	0.89 (0.60 to 1.30)
Stroke	2	72/986	82/967	0.0		0.88 (0.64 to 1.21)	0.88 (0.64 to 1.21)
Heart failure	1	12/400	9/358	NA		1.19 (0.50 to 2.83)	1.19 (0.50 to 2.83)
Revascularization	1	62/586	70/609	NA		0.92 (0.65 to 1.30)	0.92 (0.65 to 1.30)

What should our treatment target be once we've started antihypertensive therapy?

AMERICAN COLLEGE of CARDIOLOGY

ASCVD Risk Estimator Plus

Current Age ⓘ *

Age must be between 20-79

Sex *

Male | Female

Race *

White | African American | Other

Systolic Blood Pressure (mm Hg) *

Value must be between 90-200

Diastolic Blood Pressure (mm Hg) ○

Value must be between 60-130

Total Cholesterol (mg/dL) *

Value must be between 130 - 320

HDL Cholesterol (mg/dL) *

Value must be between 20 - 100

LDL Cholesterol (mg/dL) ⓘ ○

Value must be between 30-300

History of Diabetes? *

Yes | No

Smoker: ⓘ *

Yes | Former | No

On Hypertension Treatment? *

Yes | No

On a Statin? ⓘ ○

Yes | No

On Aspirin Therapy? ⓘ ○

Yes | No

Lower CV risk (<15%)

10.5 For individuals with diabetes and hypertension at lower risk for cardiovascular disease (10-year atherosclerotic cardiovascular disease risk <15%), treat to a blood pressure target of <140/90 mmHg. **A**

Higher CV risk (>15%)

10.4 For individuals with diabetes and hypertension at higher cardiovascular risk (existing atherosclerotic cardiovascular disease or 10-year atherosclerotic cardiovascular disease risk >15%), a blood pressure target of <130/80 mmHg may be appropriate, if it can be safely attained. **C**

Diabetes Care 2019;42(S1).

Combination therapy: should I add a thiazide or calcium channel blocker to my ACE or ARB if BP remains elevated?

A. Thiazide
B. Calcium channel blocker

The NEW ENGLAND JOURNAL of MEDICINE

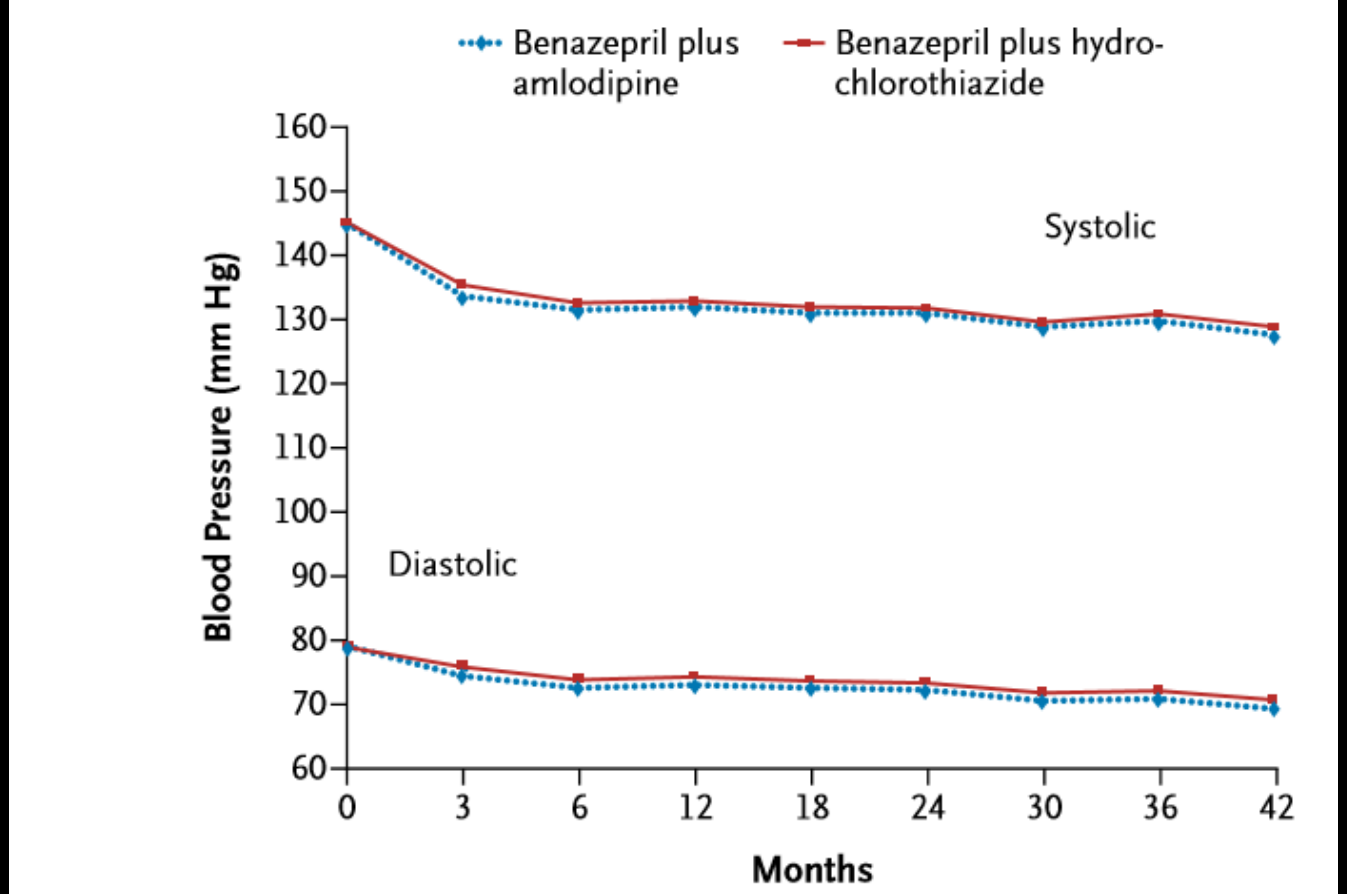
ESTABLISHED IN 1812 DECEMBER 4, 2008 VOL. 359 NO. 23

Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients

Kenneth Jamerson, M.D., Michael A. Weber, M.D., George L. Bakris, M.D., Björn Dahlöf, M.D., Bertram Pitt, M.D., Victor Shi, M.D., Allen Hester, Ph.D., Jitendra Gupte, M.S., Marjorie Gatlin, M.D., and Eric J. Velazquez, M.D., for the ACCOMPLISH trial investigators*

- RCT: ~11K high risk patients (60% with DM)
- ACE plus amlodipine vs ACE plus HCTZ
- Primary outcome: composite of CV death/events

Minimal differences in BP between groups



No. at Risk

Benazepril plus amlodipine	5740	5517	5404	5178	5010	4866	4298	2804	1074
Benazepril plus hydrochlorothiazide	5757	5537	5408	5222	5033	4825	4299	2529	1042

Figure 1. Effects of Treatment on Systolic and Diastolic Blood Pressure over Time.

N Engl J Med 2008;359(23):2417.

- 20% reduction in CV outcome with combination of ACE plus amlodipine
- 22% reduction in MI with combination of ACE plus amlodipine
- Subgroup analysis: benefit still present when assessing only those with/without DM

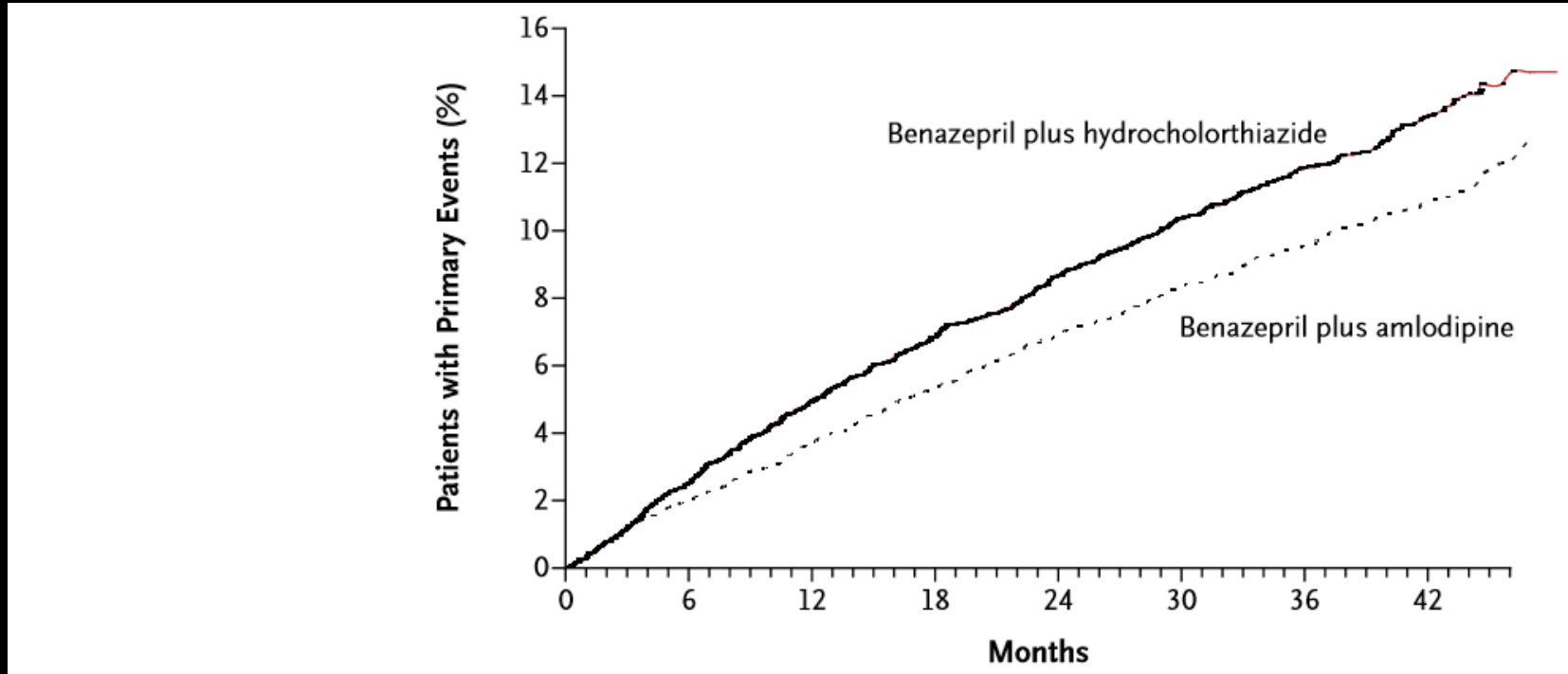
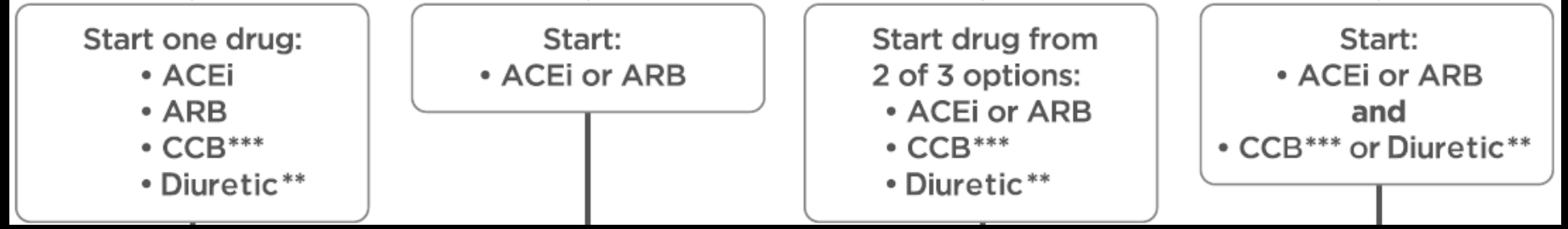


Figure 2. Kaplan–Meier Curves for Time to First Primary Composite End Point.

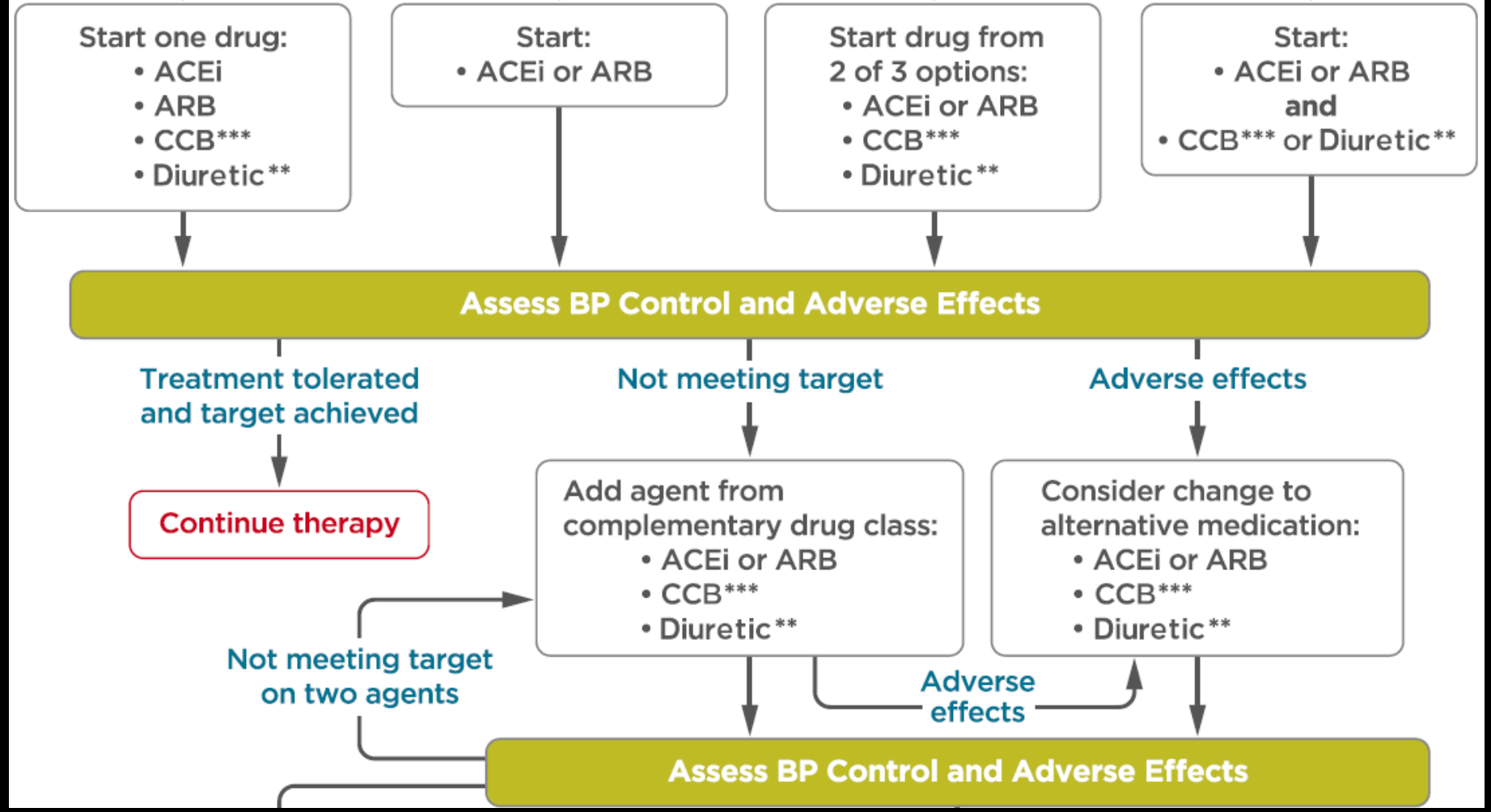
N Engl J Med 2008;359(23):2417.



Diabetes Care 2018;41(S1).

Which of the following agents are recommended as a 4th antihypertensive agent in a patient with diabetes not meeting BP goals on an ACE/ARB, CCB, and diuretic?

A) Beta blocker
B) Alpha blocker
C) Mineralocorticoid receptor antagonist



Diabetes Care 2018;41(S1).

Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial

*Bryan Williams, Thomas M MacDonald, Steve Morant, David J Webb, Peter Sever, Gordon McInnes, Ian Ford, J Kennedy Cruickshank, Mark J Caulfield, Jackie Salsbury, Isla Mackenzie, Sandosh Padmanabhan, Morris J Brown, for The British Hypertension Society's PATHWAY Studies Group**

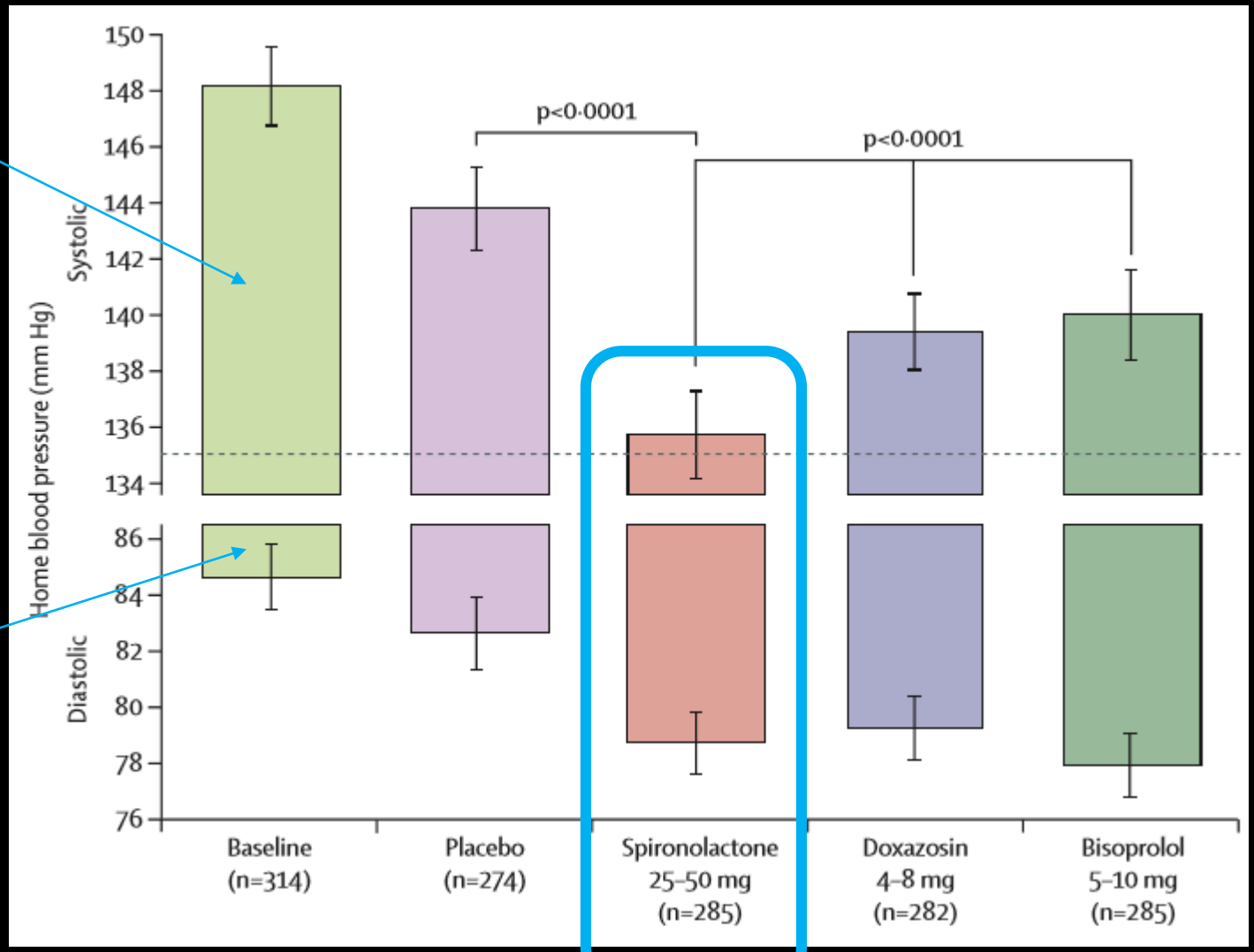
- Double-blind, placebo controlled, crossover trial
- 335 adults (14% with DM) with 3-drug (ACE/ARB, CCB, thiazide) resistant hypertension
- Randomly assigned to placebo, spironolactone, bisoprolol, or doxazosin (12 weeks per cycle)

Lancet 2015;386:2059-68.

Superior BP lowering with addition of spironolactone as 4th agent

systolic

diastolic



Lancet 2015;386:2059-68.

Any impact of timing of BP medications?

Influence of Time of Day of Blood Pressure–Lowering Treatment on Cardiovascular Risk in Hypertensive Patients With Type 2 Diabetes

RAMÓN C. HERMIDA, PHD
DIANA E. AYALA, MD, MPH, PHD
ARTEMIO MOJÓN, PHD
JOSÉ R. FERNÁNDEZ, PHD

- Randomized controlled trial x 5 yrs
- 448 hypertensive patients withT2D; average age 63 yrs
- After 5 yrs, taking ≥ 1 BP meds at bedtime vs all meds in am:
  - Lower sleep time BP
  - Lower risk of CV death, cardiovascular events, strokes, heart failure

Diabetes Care 2011;34:1270-1276.

A1c target: < 7-8%

Blood pressure management

Cholesterol lowering therapy

019;42(S1).

Lifestyle Interventions

- Lifestyle modification focusing on weight loss (if indicated); application of a Mediterranean diet or Dietary Approaches to Stop Hypertension (DASH) dietary pattern; reduction of saturated fat and trans fat; increase of dietary n-3 fatty acids, viscous fiber, and plant sterols/sterols intake; and increased physical activity should be recommended to improve the lipid profile and reduce the risk of developing atherosclerotic cardiovascular disease in patients with diabetes. A

Diabetes Care 2019;42(S1).

Monitoring

10.17 In adults not taking statins or other lipid-lowering therapy, it is reasonable to obtain a lipid profile at the time of diabetes diagnosis, at an initial medical evaluation, and every 5 years thereafter if under the age of 40 years, or more frequently if indicated. **E**

Diabetes Care 2019;42(S1).

Monitoring

10.18 Obtain a lipid profile at initiation of statins or other lipid-lowering therapy, 4–12 weeks after initiation or a change in dose, and annually thereafter as it may help to monitor the response to therapy and inform medication adherence. **E**

Diabetes Care 2019;42(S1).

Pharmacotherapy

Table 10.2—Recommendations for statin and combination treatment in adults with diabetes

Age	ASCVD or 10-year ASCVD risk >20%	Recommended statin intensity^ and combination treatment*
<40 years	No	None†
	Yes	High • In patients with ASCVD, if LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)#
≥40 years	No	Moderate‡
	Yes	High • In patients with ASCVD, if LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)

Diabetes Care 2019;42(S1).

Why consider the addition of ezetimibe?

Ezetimibe inhibits cholesterol absorption and lowers LDL by ~10-20%

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 18, 2015 VOL. 372 NO. 25

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes (IMPROVE-IT)

Christopher P. Cannon, M.D., Michael A. Blazing, M.D., Robert P. Giugliano, M.D., Amy McCagg, B.S.,

- Double blind RCT
- 18,000 patients (mean age 64 yrs, BMI ~28) within 10 days of ACS
- LDL 50-125 mg/dL at enrollment
- Simvastatin 40 mg plus either ezetimibe 10 mg or placebo
- Primary outcome: composite of CV outcomes
- Median follow up 6 yrs

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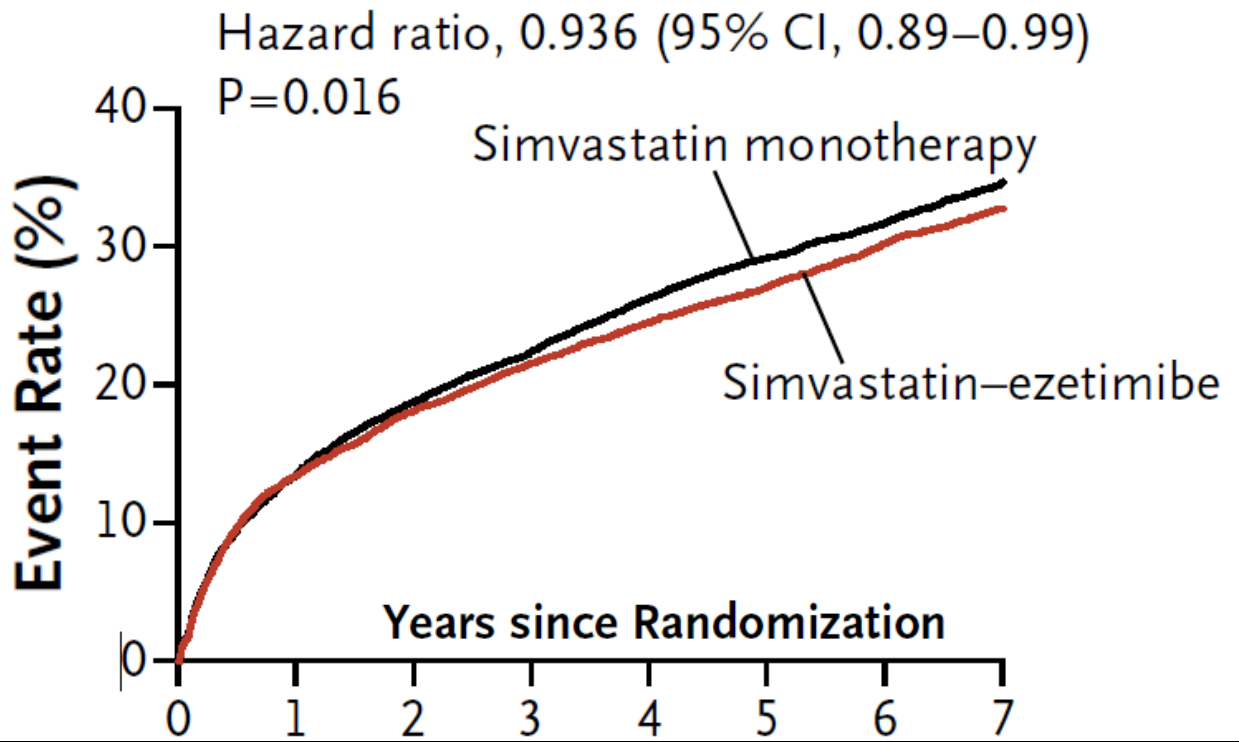
ESTABLISHED IN 1812 JUNE 18, 2015 VOL. 372 NO. 25

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes (IMPROVE-IT)

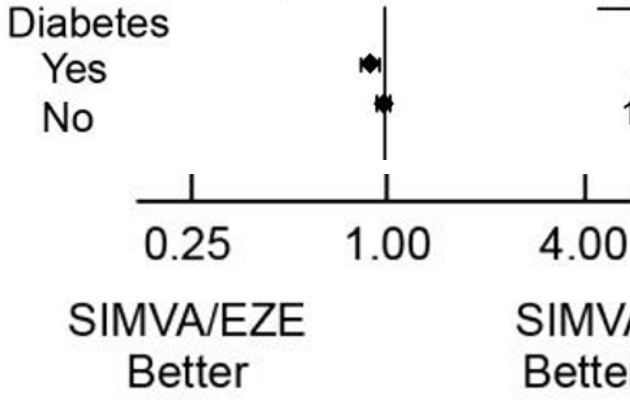
Christopher P. Cannon, M.D., Michael A. Blazing, M.D., Robert P. Giugliano, M.D., Amy McCagg, B.S.,

Small reduction in composite CV outcome with addition of ezetimibe to statin post-ACS

No impact on mortality (6 yrs)



What about the 27% of patients with diabetes in the IMPROVE-IT trial?



Characteristic	Total Patients	KM % at 7 years SIMVA/EZE	KM % at 7 years SIMVA	Hazard Ratio (95% CI)	Interaction *P*-Value
Diabetes					
Yes	4933	40.04	45.51	0.856 (0.779, 0.939)	0.023
No	13202	30.16	30.84	0.977 (0.915, 1.044)	

14% relative risk reduction in subjects with diabetes

5% absolute risk reduction in subjects with diabetes

Treating 20 patients would reduce 1 cardiovascular event

N Engl J Med 2015;372:2387 [Supplementary Material].

Do PCSK9 inhibitors reduce cardiovascular events?

Yes – by 15% in the FOURIER study (evolocumab) and by 15% in the ODYSSEY study (alirocumab)

All cause mortality benefit also observed in ODYSSEY study (15% reduction)

N Engl J Med 2017;376:1713-1722.

N Engl J Med 2018;379:2097-2107.

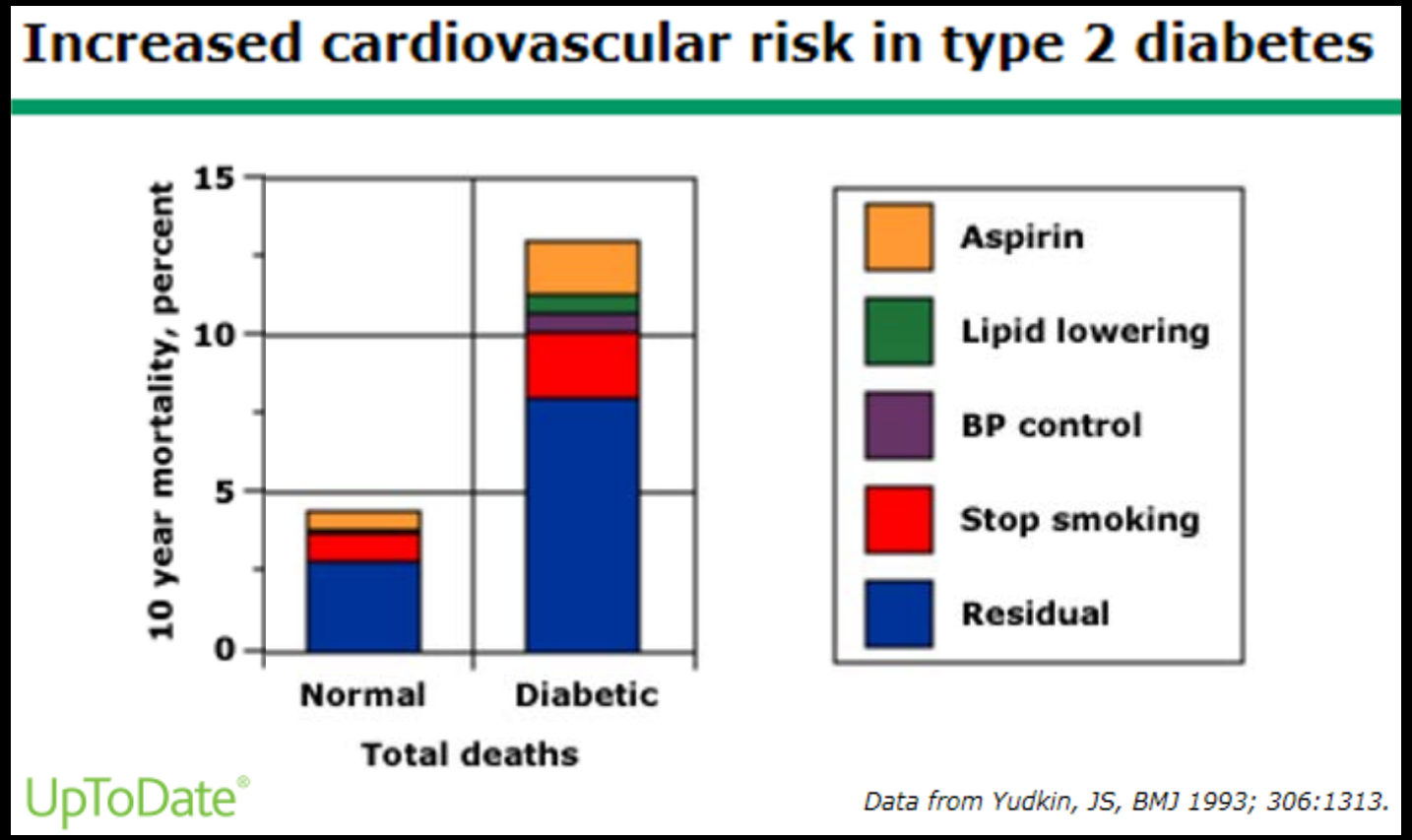
Beyond the ABCs…

How about other interventions besides blood glucose, blood pressure, and cholesterol lowering?

Which of the following interventions has the greatest impact on survival in patients with diabetes?

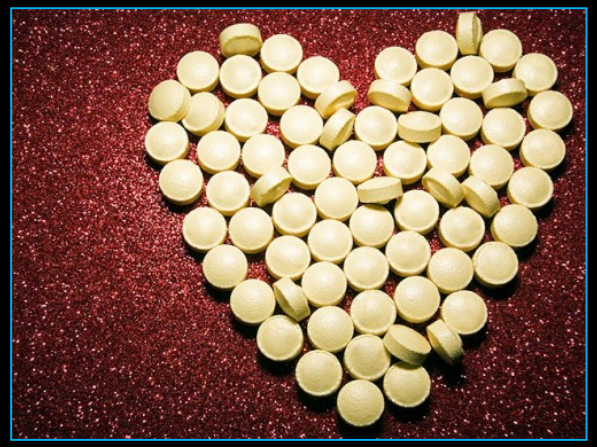
A. Blood pressure control
B. Lipid lowering
C. Aspirin
D. Smoking cessation

Smoking cessation



Meta-analysis: Smoking cessation has greater impact on survival than several other interventions

Aspirin



Secondary prevention

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

Primary prevention

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**

Diabetes Care 2019;42(S1).

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

The ASCEND Study Collaborative Group*

- ~15K adults with T2D, no CVD
- Mean age 63 yrs
- Randomized to ASA 100 mg/day vs placebo
- Mean follow up 7.4 yrs
- Vascular events reduced by 12%
- Major bleeding increased by 29%
- NNT and NNH similar (~100)

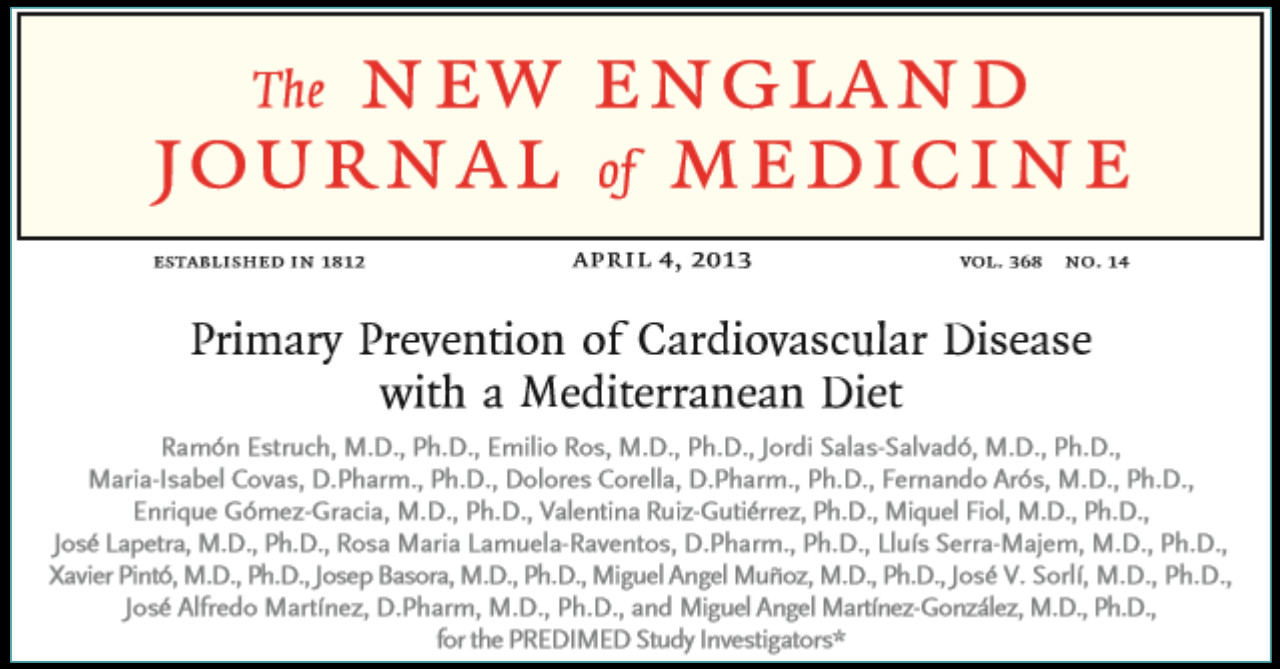
N Engl J Med 2018;379:1529-39.

Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly

J.J. McNeil, R. Wolfe, R.L. Woods, A.M. Tonkin, G.A. Donnan, M.R. Nelson, C.M. Reid, J.E. Lockery, B. Kirpach, E. Storey, R.C. Shah, J.D. Williamson, K.L. Margolis, M.E. Ernst, W.P. Abhayaratna, N. Stocks, S.M. Fitzgerald, S.G. Orchard, R.E. Trevaks, L.J. Beilin, C.I. Johnston, J. Ryan, B. Radziszewska, M. Jelinek, M. Malik, C.B. Eaton, D. Brauer, G. Cloud, E.M. Wood, S.E. Mahady, S. Satterfield,* R. Grimm, and A.M. Murray, for the ASPREE Investigator Group†

- ~19K adults age ≥70 yrs (11% with diabetes)
- Randomized to ASA 100 mg/day vs placebo
- Median follow up 4.7 yrs
- NO impact on cardiovascular events
- Major bleeding increased by 38%

N Engl J Med 2018;379:1509-18.



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 4, 2013 VOL. 368 NO. 14

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

Ramón Estruch, M.D., Ph.D., Emilio Ros, M.D., Ph.D., Jordi Salas-Salvadó, M.D., Ph.D., Maria-Isabel Covas, D.Pharm., Ph.D., Dolores Corella, D.Pharm., Ph.D., Fernando Arós, M.D., Ph.D., Enrique Gómez-Gracia, M.D., Ph.D., Valentina Ruiz-Gutiérrez, Ph.D., Miquel Fiol, M.D., Ph.D., José Lapetra, M.D., Ph.D., Rosa Maria Lamuela-Raventos, D.Pharm., Ph.D., Lluís Serra-Majem, M.D., Ph.D., Xavier Pintó, M.D., Ph.D., Josep Basora, M.D., Ph.D., Miguel Angel Muñoz, M.D., Ph.D., José V. Sorlí, M.D., Ph.D., José Alfredo Martínez, D.Pharm, M.D., Ph.D., and Miguel Angel Martínez-González, M.D., Ph.D., for the PREDIMED Study Investigators*

(PREDIMED Study)

- ~7500 participants with high CV risk but NO known CVD (~50% with diabetes)
- Mediterranean diet vs low fat diet; no caloric restriction

Mediterranean diet	
Recommended	
Olive oil*	≥4 tbsp/day
Tree nuts and peanuts†	≥3 servings/wk
Fresh fruits	≥3 servings/day
Vegetables	≥2 servings/day
Fish (especially fatty fish), seafood	≥3 servings/wk
Legumes	≥3 servings/wk
Sofrito‡	≥2 servings/wk
White meat	Instead of red meat
Wine with meals (optionally, only for habitual drinkers)	≥7 glasses/wk
Discouraged	
Soda drinks	<1 drink/day
Commercial bakery goods, sweets, and pastries§	<3 servings/wk
Spread fats	<1 serving/day
Red and processed meats	<1 serving/day

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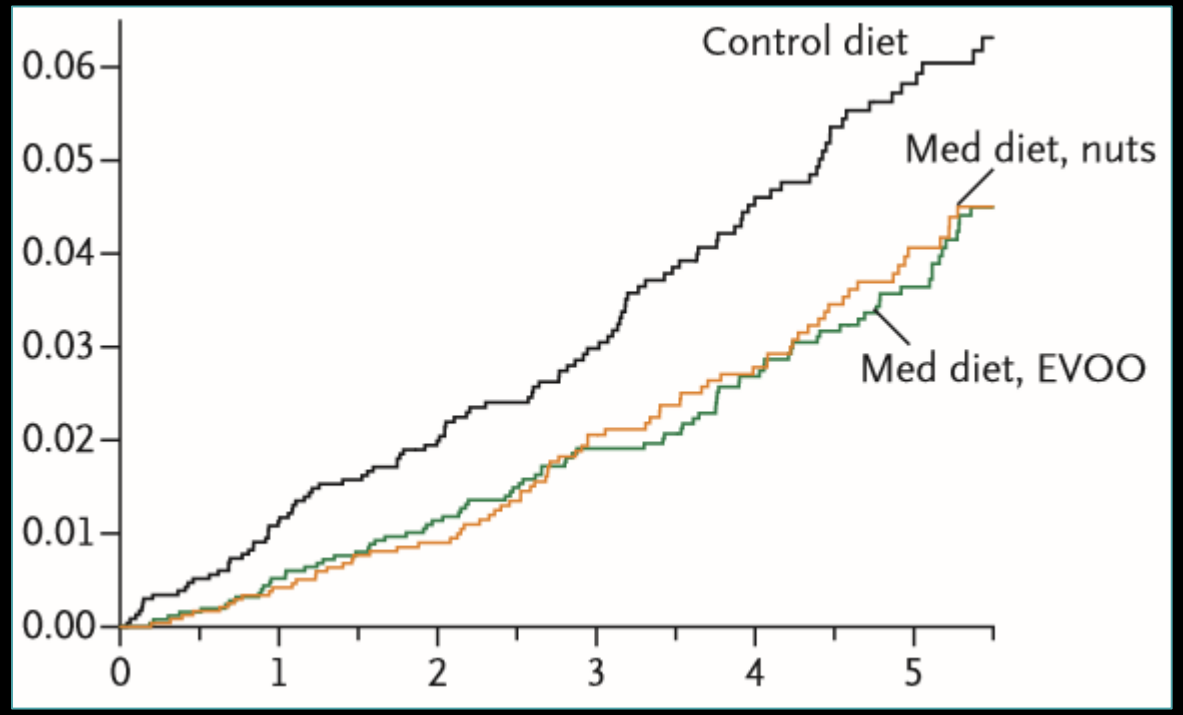
Trial stopped early at median of 4.8 yrs based on interim analysis

- Cardiovascular events cut by 30%
- NNT: 61 patients
- No adverse effects



What about in patients who have already had a heart attack?

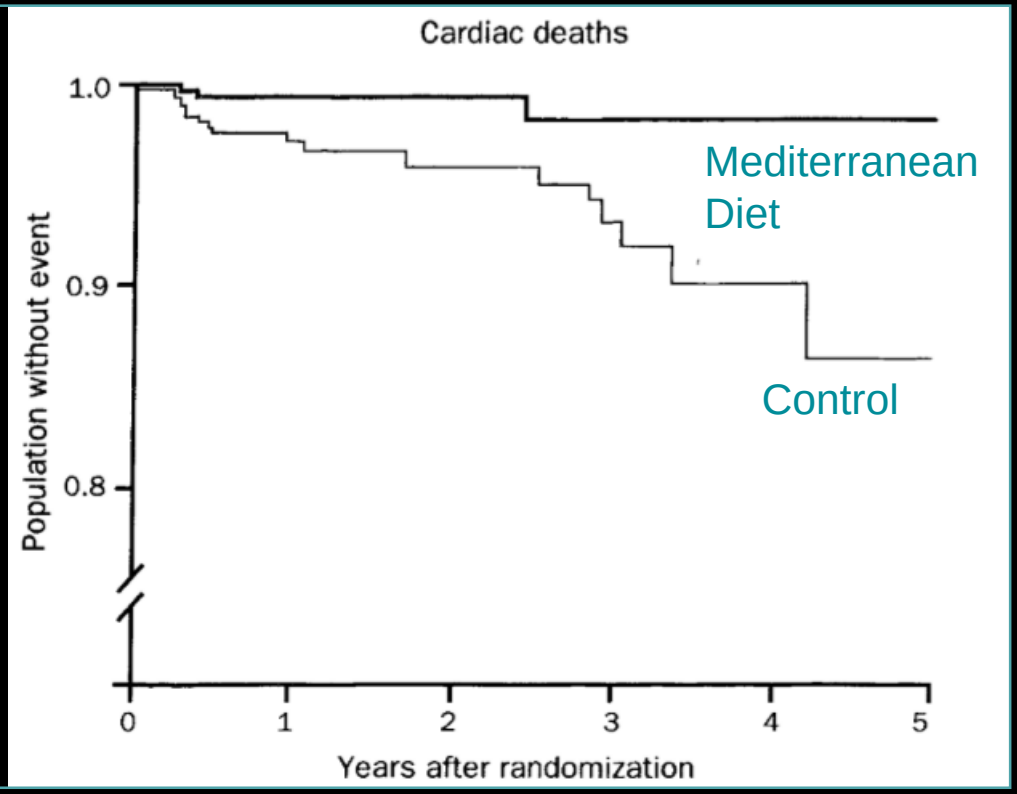
Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease

Michel de Lorgeril, Serge Renaud, Nicole Mamelle, Patricia Salen, Jean-Louis Martin, Isabelle Monjaud, Jeannine Guidollet, Paul Touboul, Jacques Delaye

Lancet 1994; **343:** 1454–59

(Lyon Heart Study)

- Mean follow up 27 months; n=605
- LDL, weight, BP similar in both groups throughout study
- Cardiovascular death cut by **76%**
- NNT: 9 patients



What happens when we combine all of these interventions?

The NEW ENGLAND JOURNAL of MEDICINE

Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes

Peter Gæde, M.D., D.M.Sc., Henrik Lund-Andersen, M.D., D.M.Sc., Hans-Henrik Parving, M.D., D.M.Sc., and Oluf Pedersen, M.D., D.M.Sc.

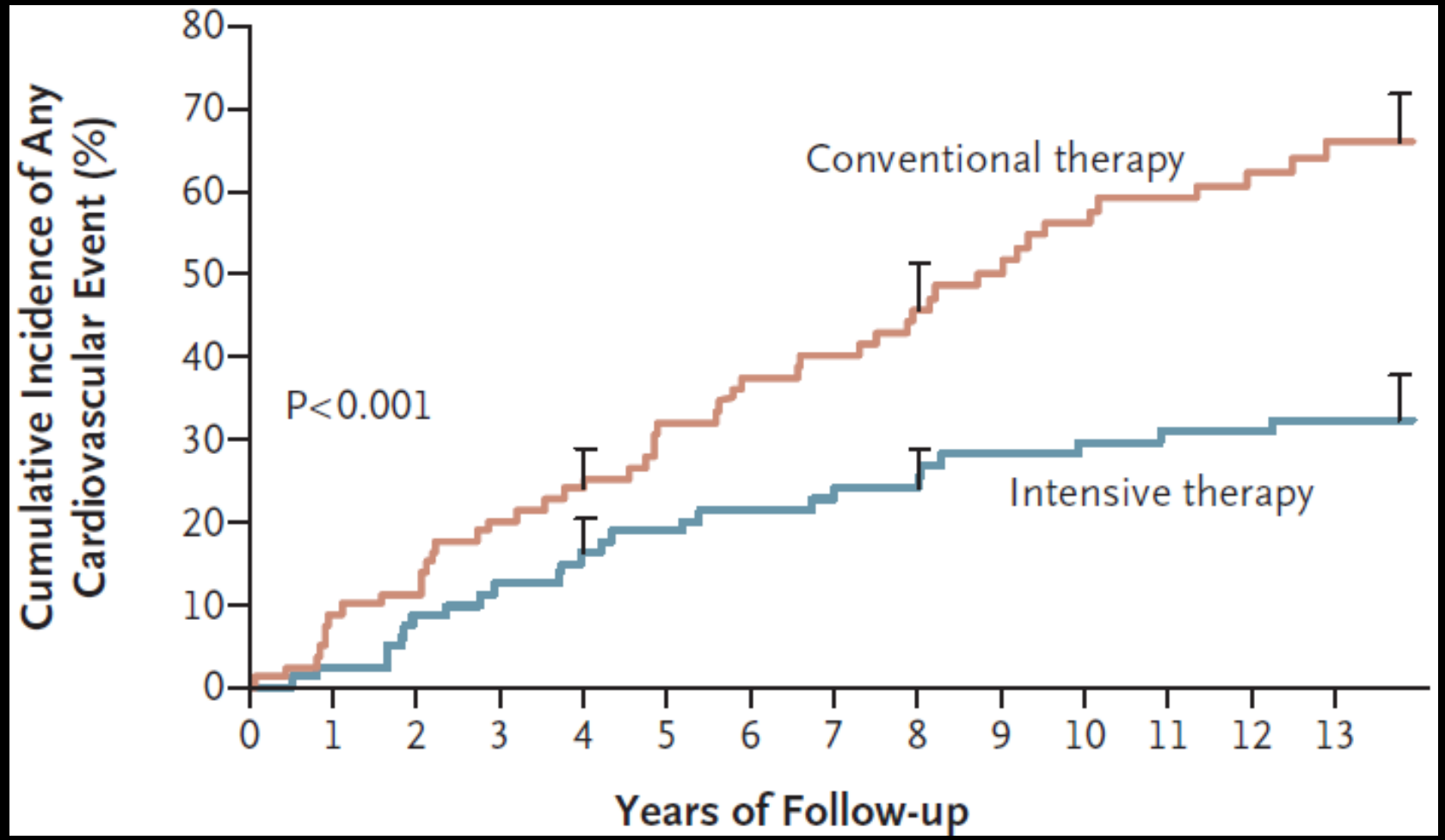
N ENGL J MED 358;6 WWW.NEJM.ORG FEBRUARY 7, 2008

Multifactorial Intervention

- **Subjects**
  - T2D (n=160)
  - Microalbuminuria
  - Mean age 55 yrs
  - Randomized to conventional vs intensive therapy
- **Goals of intervention**
  - A1c < 6.5%
  - Chol < 175 mg/dL
  - Trig < 150 mg/dL
  - SBP < 130 mmHg
  - DBP < 80 mmHg
  - ACE/ARB
  - ASA 81 mg/day

N ENGL J MED 358;6 WWW.NEJM.ORG FEBRUARY 7, 2008

Cardiovascular death reduced by 57%

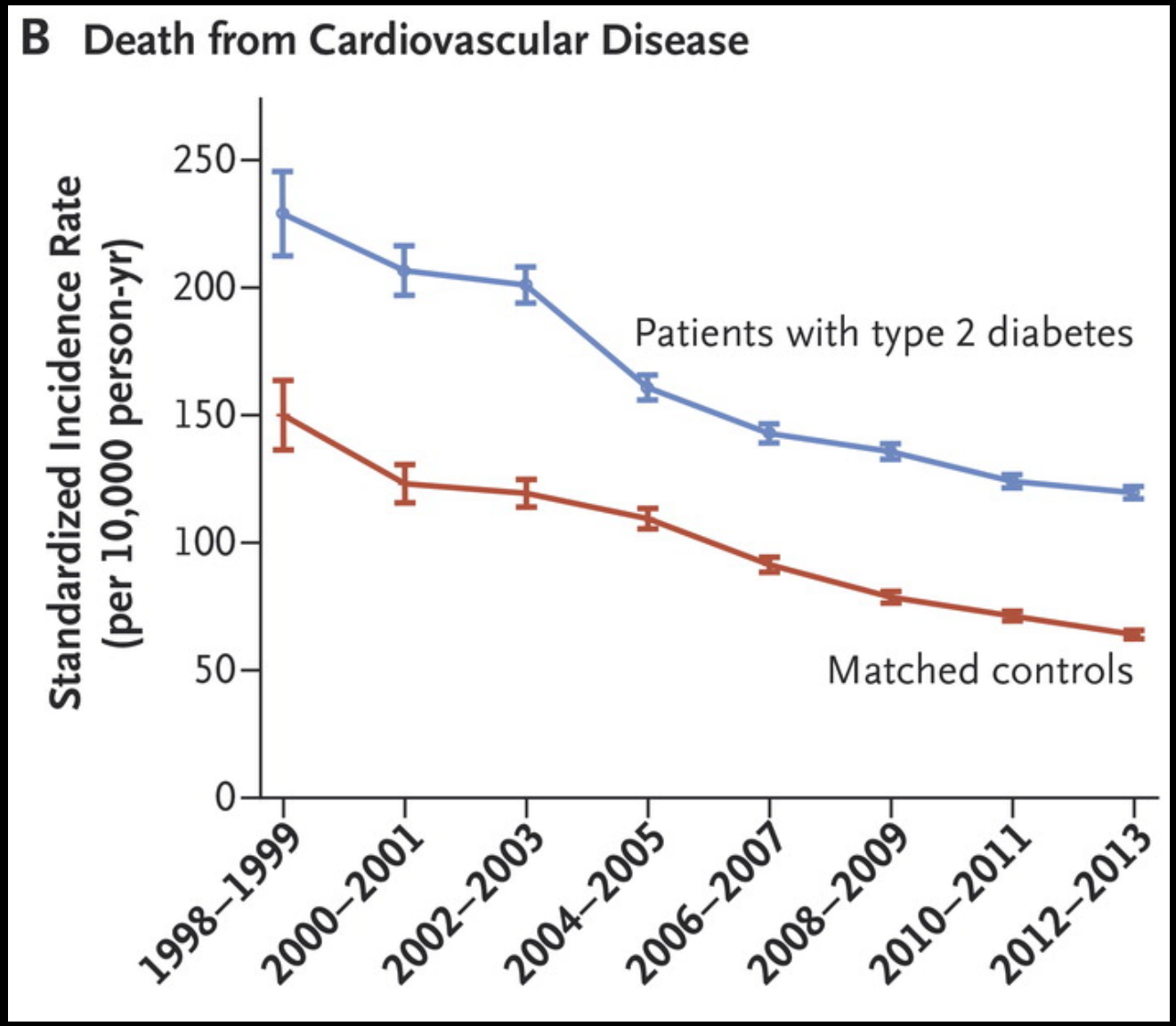


N ENGL J MED 358;6 WWW.NEJM.ORG FEBRUARY 7, 2008

Real world experience:

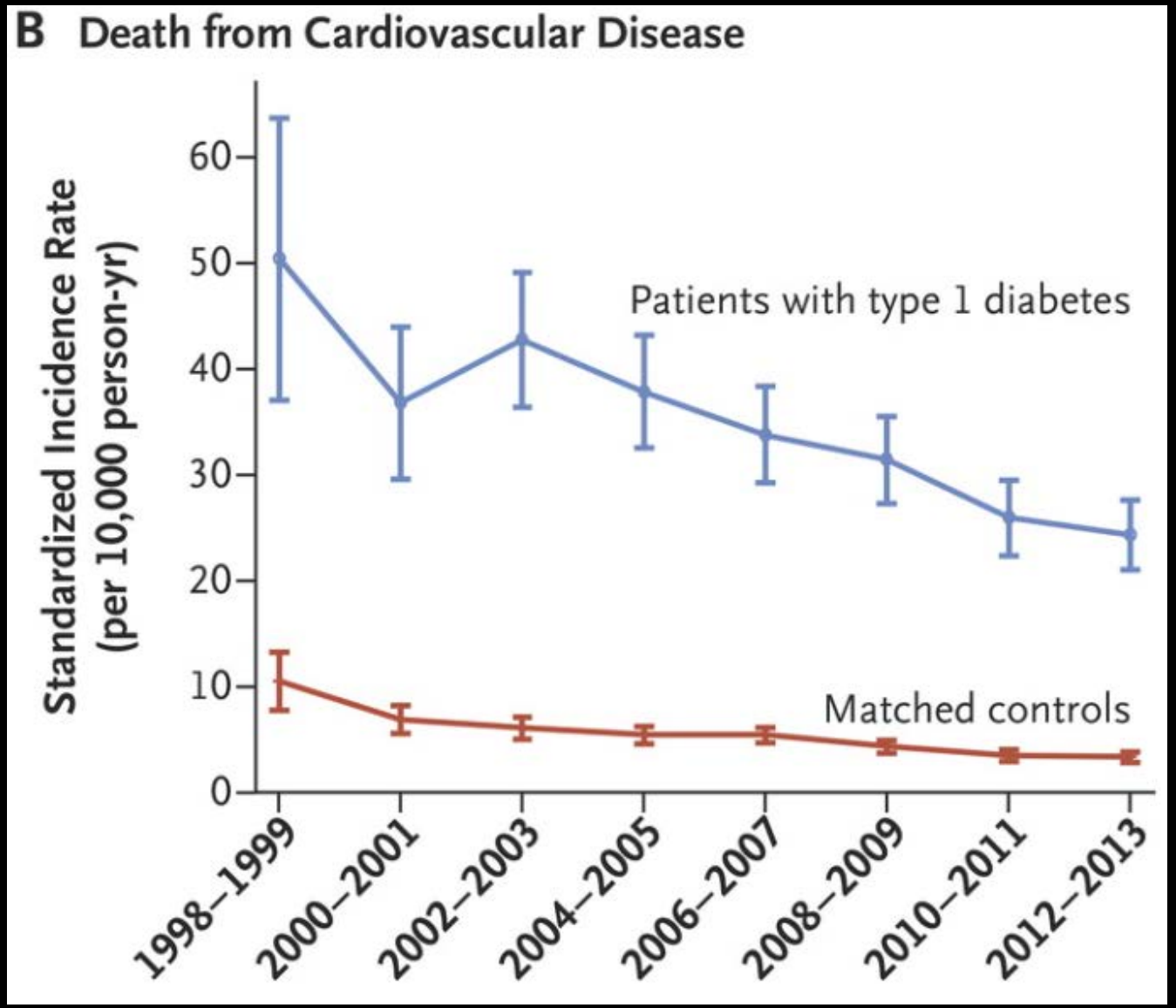
How is greater recognition of the impact of multifactorial intervention affecting cardiovascular outcomes in patients with diabetes?

Fewer patients with type 2 diabetes dying of CVD



N Engl J Med 2017;376:1407-18.

Fewer patients with type 1 diabetes dying of CVD



N Engl J Med 2017;376:1407-18.

Questions?