

Prevention of MACROvascular Complications of Diabetes

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Conflicts of Interest

None

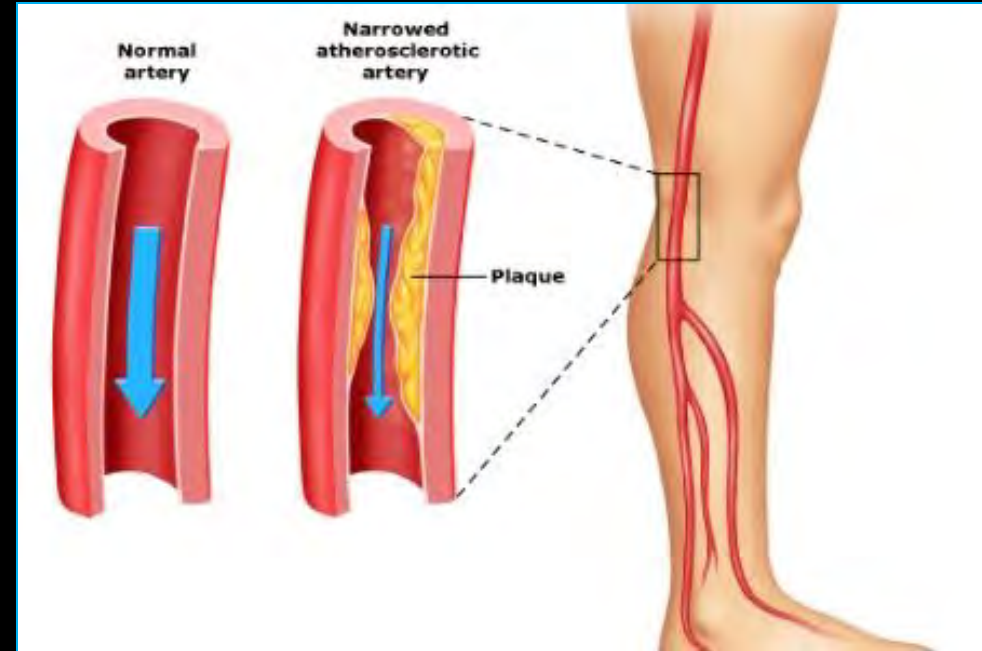
Objectives

1. To recognize macrovascular complications as the leading cause of death in people with diabetes
2. To be familiar with risk factors for macrovascular complications of diabetes
3. To understand the impact of multifactorial risk reduction on outcomes in patients with diabetes

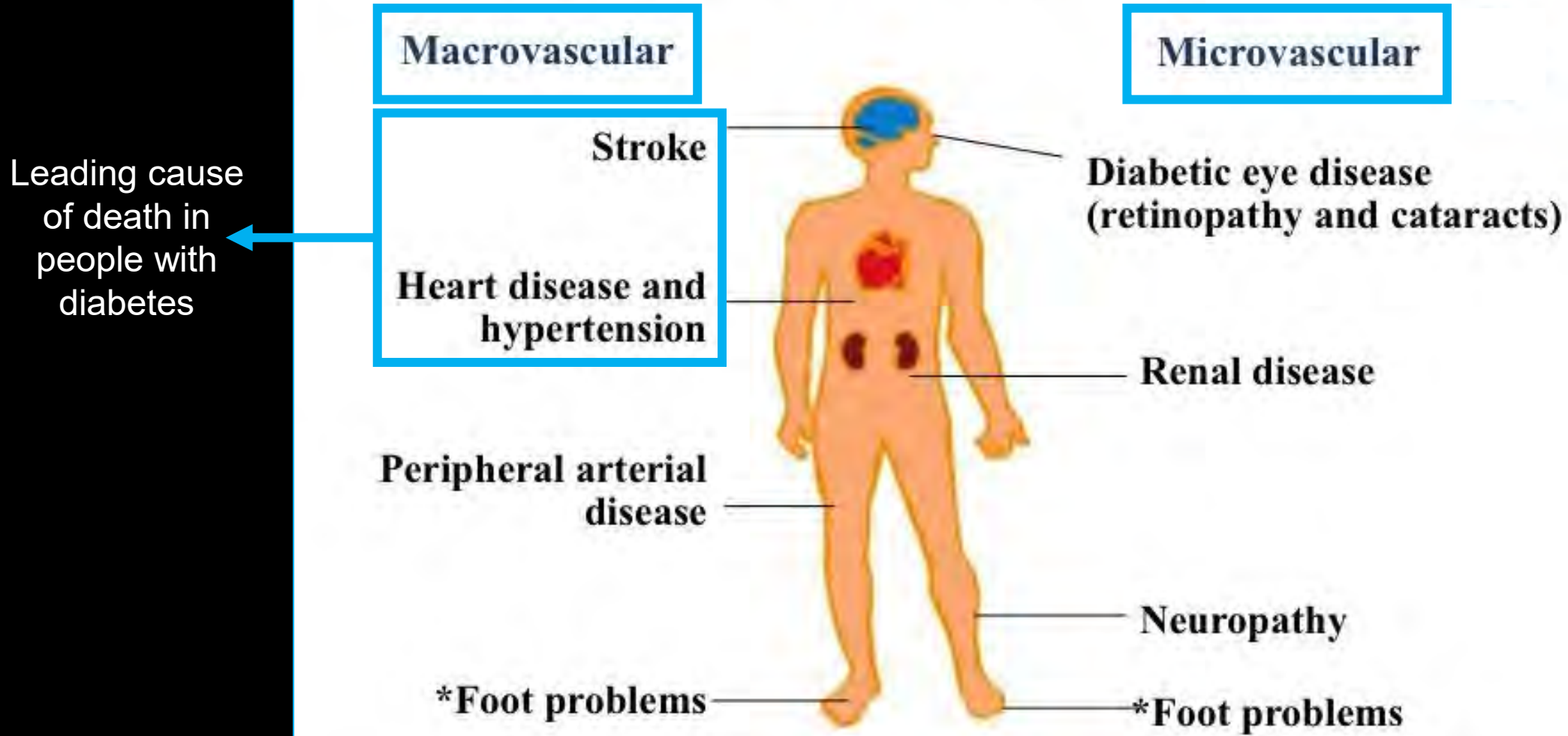
Microvascular =
small vessel disease



Macrovascular =
large vessel disease



Overview of Diabetic Complications



SUPPLEMENT
1

AMERICAN DIABETES ASSOCIATION

STANDARDS OF MEDICAL CARE IN DIABETES—2018

Diabetes Care 2018;41(S1).

Screening for Coronary Artery Disease (CAD)

Screening

- In asymptomatic patients, routine screening for coronary artery disease is not recommended as it does not improve outcomes as long as atherosclerotic cardiovascular disease risk factors are treated. **A**



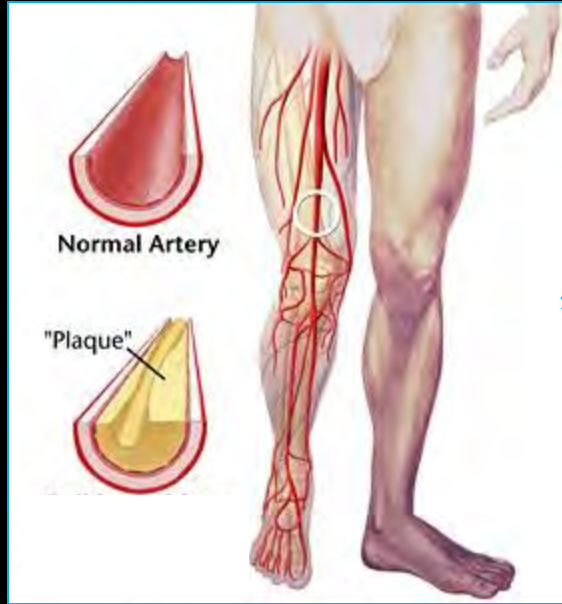
Diabetes Care 2018;41(S1).

Stroke

No ADA guidelines for
screening for
cerebrovascular disease in
asymptomatic patients



Peripheral Arterial Disease (PAD)



Cholesterol
(plaque)
embolization



Severe
ischemia in
setting of
infection



Screening for Peripheral Arterial Disease (PAD)

- **PAD**
 - Routine foot examination (including pulses)
 - Ankle brachial index (ABI)
 - Symptomatic patients (claudication)
 - Asymptomatic
 - Not specifically addressed in 2018 ADA guidelines

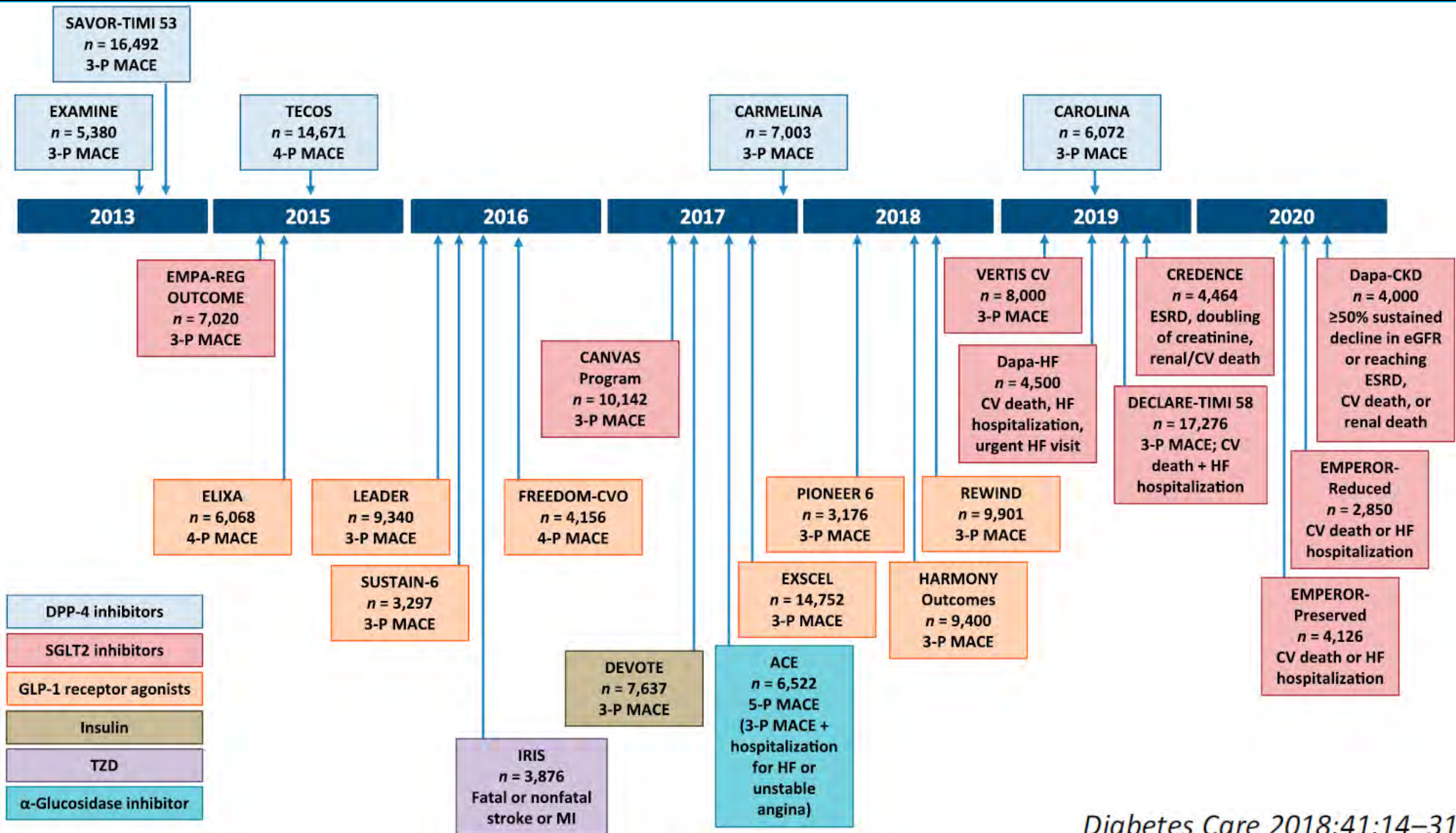
Why isn't there greater emphasis on screening for these macrovascular complications?



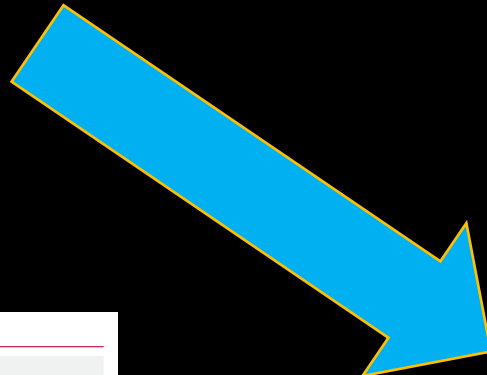
A1c target: $< 7-8\%$

Blood pressure target: $< 140/90$

Cholesterol treatment: Statins



Therapies added to metformin should be based on presence or absence of CVD



2018

- A1C is less than 9%, **consider Monotherapy.**
- A1C is greater than or equal to 9%, **consider Dual Therapy.**
- A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy Lifestyle Management + Metformin

Initiate metformin therapy if no contraindications* (See Table 8.1)

A1C at target after 3 months of monotherapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Dual Therapy

Dual Therapy Lifestyle Management + Metformin + Additional Agent

ASCVD? **Yes:** - Add agent proven to reduce major adverse

Dual Therapy Lifestyle Management + Metformin + Additional Agent

ASCVD?

Yes: - Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and **Table 8.1**)

No: - Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy.**

Monotherapy Metformin

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, move to Dual Therapy.

Dual Therapy Metformin + Sulfonyleurea

EFFICACY*	high
HYPO RISK	moderate risk
WEIGHT	gain
SIDE EFFECTS	hypoglycemia
COSTS*	low

If A1C target not achieved after approximately 3 months of dual therapy, move to Triple Therapy.

Triple Therapy Metformin + Sulfonyleurea + TZD or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin*

TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin*	or GLP-1-RA	or Insulin*	or GLP-1-RA
or Insulin*	or Insulin*	or Insulin*	or Insulin*	or Insulin*	or Insulin*

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

Combination Injectable Therapy (See Figure 8.2)

A1C at target after 3 months of triple therapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Combination Injectable Therapy (See Figure 8.2)

Combination Injectable Therapy (See Figure 8.2)

See Table 8.1 for a helpful comparison of CV/renal effects of available hyperglycemic agents

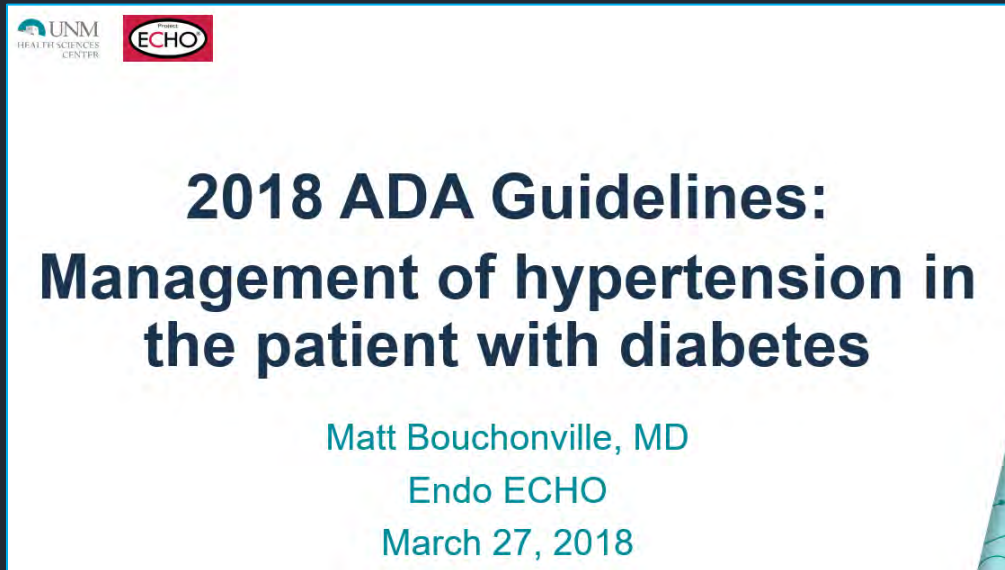
Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ	Renal Effects	
			ASCVD	CHF			Progression of DKD	Dosing/Use considerations

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

A1c target: < 7-8%

Blood pressure target: < 140/90



(Happy to share
these slides with
you!)

Cholesterol treatment: Statins

Diabetes Care 2018;41(S1).

A1c target: < 7-8%

Blood pressure target: < 140/90



Cholesterol treatment: Statins

Revised statin guidelines for 2018

Table 9.2—Recommendations for statin and combination treatment in adults with diabetes

Age	ASCVD	Recommended statin intensity [^] and combination treatment*
<40 years	No	None [†]
	Yes	High <ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> • If LDL cholesterol ≥ 70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)

*In addition to lifestyle therapy. [^]For patients who do not tolerate the intended intensity of statin, the maximally tolerated statin dose should be used. [†]Moderate-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. ASCVD risk factors include LDL cholesterol ≥ 100 mg/dL (2.6 mmol/L), high blood pressure, smoking, chronic kidney disease, albuminuria, and family history of premature ASCVD. [‡]High-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. [#]Adults aged <40 years with prevalent ASCVD were not well represented in clinical trials of non-statin–based LDL reduction. Before initiating combination lipid-lowering therapy, consider the potential for further ASCVD risk reduction, drug-specific adverse effects, and patient preferences.

- Consolidated middle and older ages
- Less aggressive recommendations for younger patients
- Increased emphasis on LDL targets

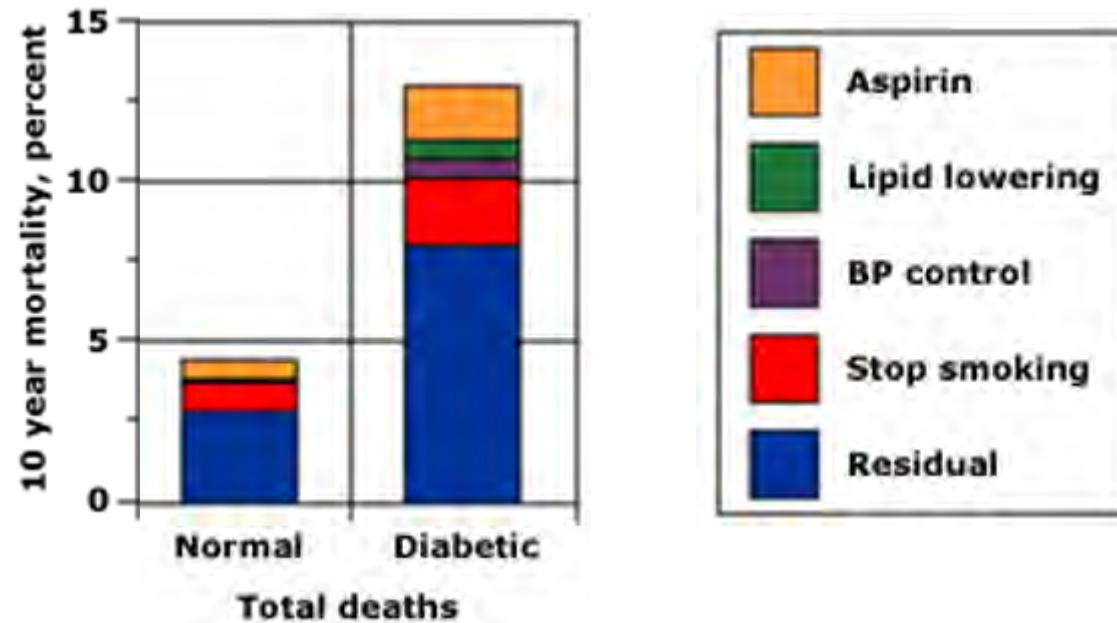
How about other interventions besides
blood glucose, blood pressure, and
cholesterol lowering?

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

Increased cardiovascular risk in type 2 diabetes



UpToDate®

Data from Yudkin, JS, BMJ 1993; 306:1313.

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

Aspirin



Secondary prevention

Primary 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**
- Aspirin therapy (75–162 mg/day) may be considered as a primary prevention strategy in those with type 1 or type 2 diabetes who are at increased cardiovascular risk. This includes most men and women with diabetes aged ≥ 50 years who have at least one additional major risk factor (family history of premature atherosclerotic cardiovascular disease, hypertension, dyslipidemia, smoking, or albuminuria) and are not at increased risk of bleeding. **C**

Diabetes Care 2018;41(S1).

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VOL. 368 NO. 14

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

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for the PREDIMED Study Investigators*

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

(PREDIMED Study)

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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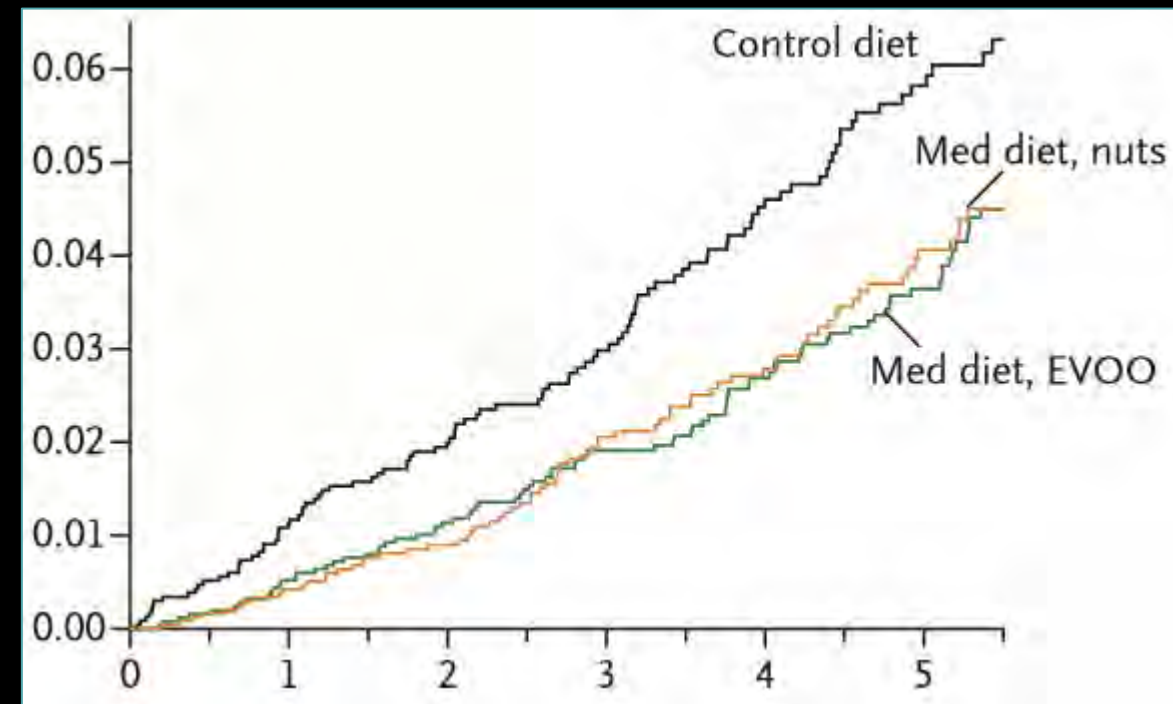
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for the PREDIMED Study Investigators*

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

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



What happens when we combine all of
these interventions?



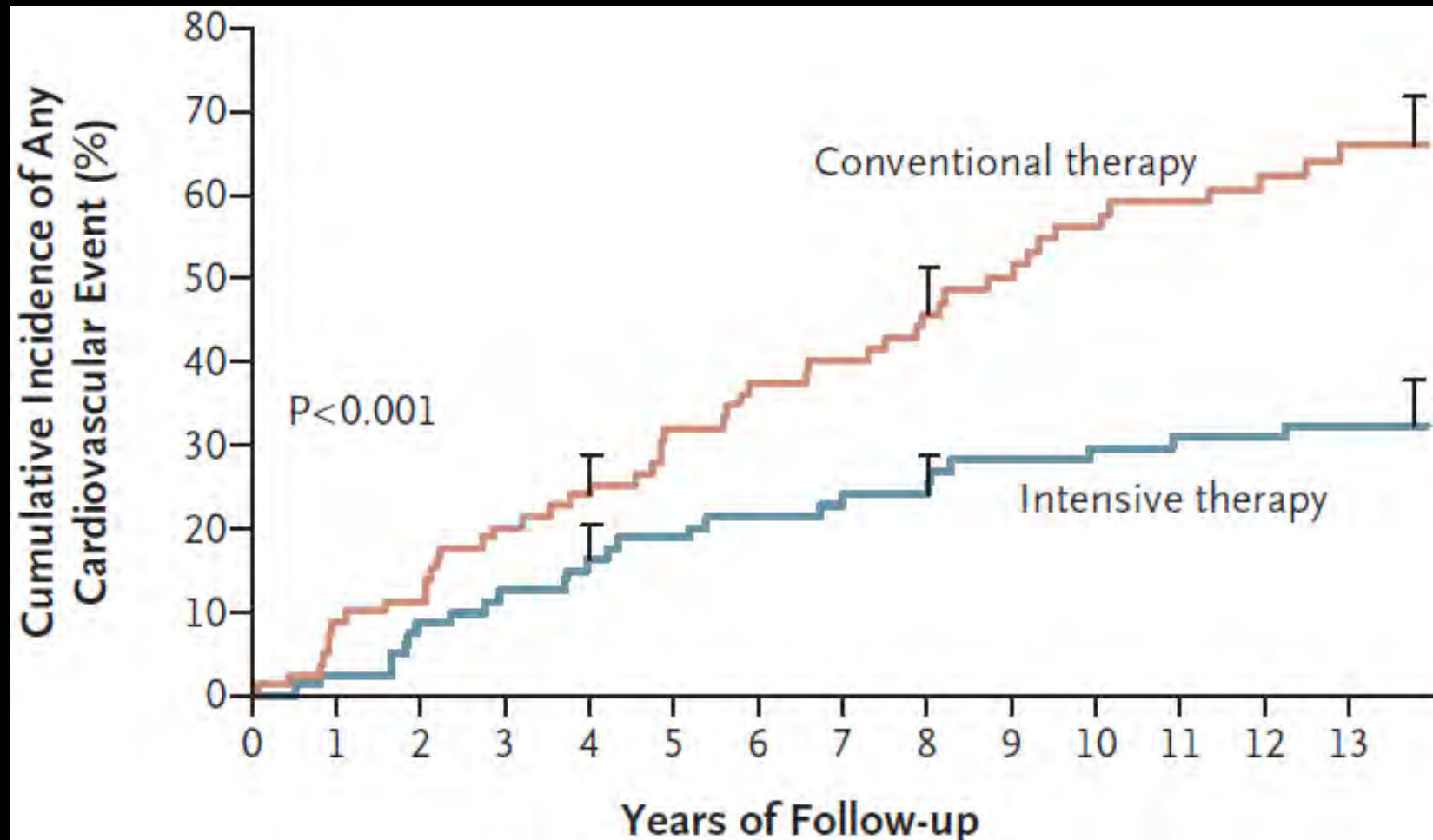
Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes

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.

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

Cardiovascular death reduced by 57%

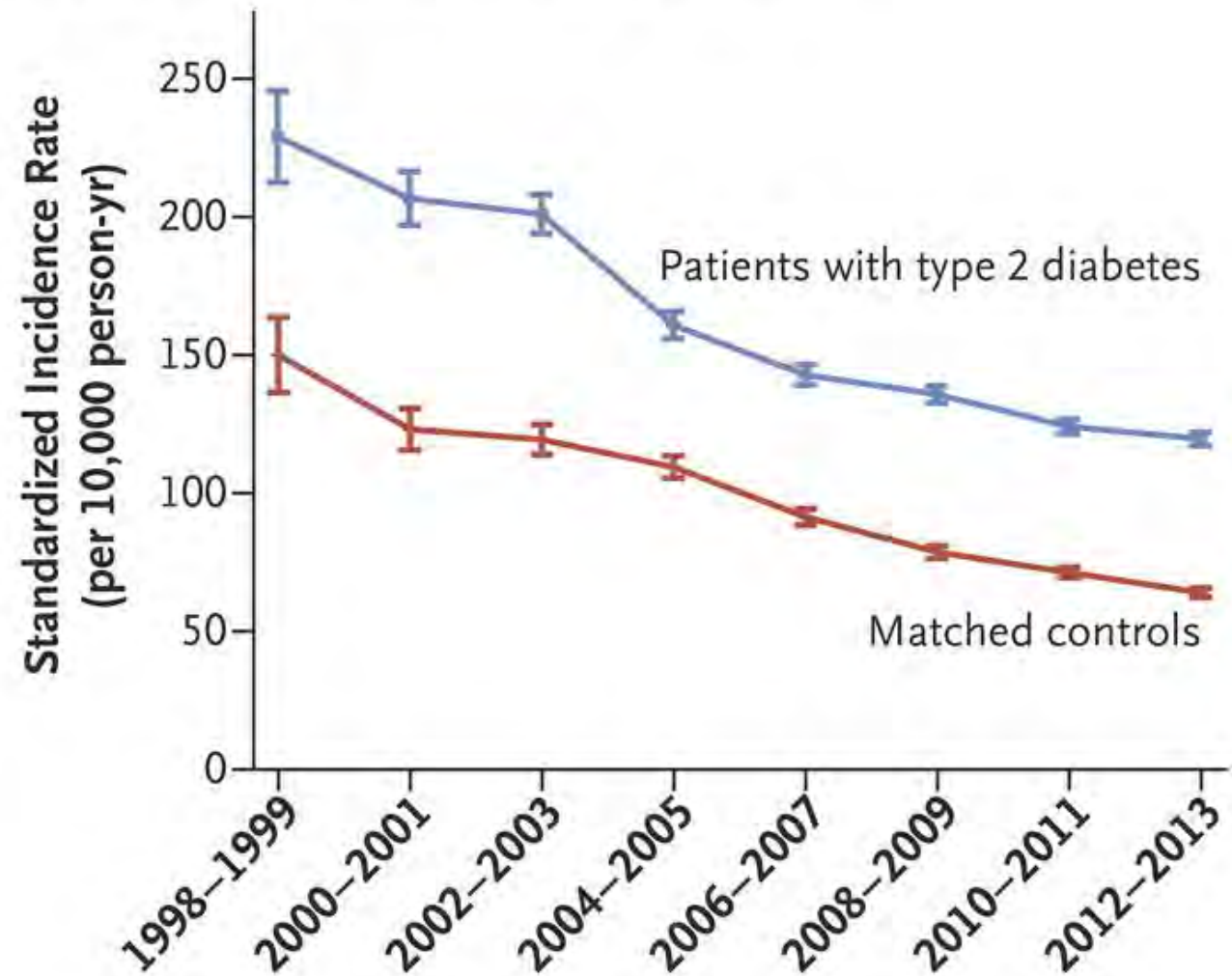


Real world experience:

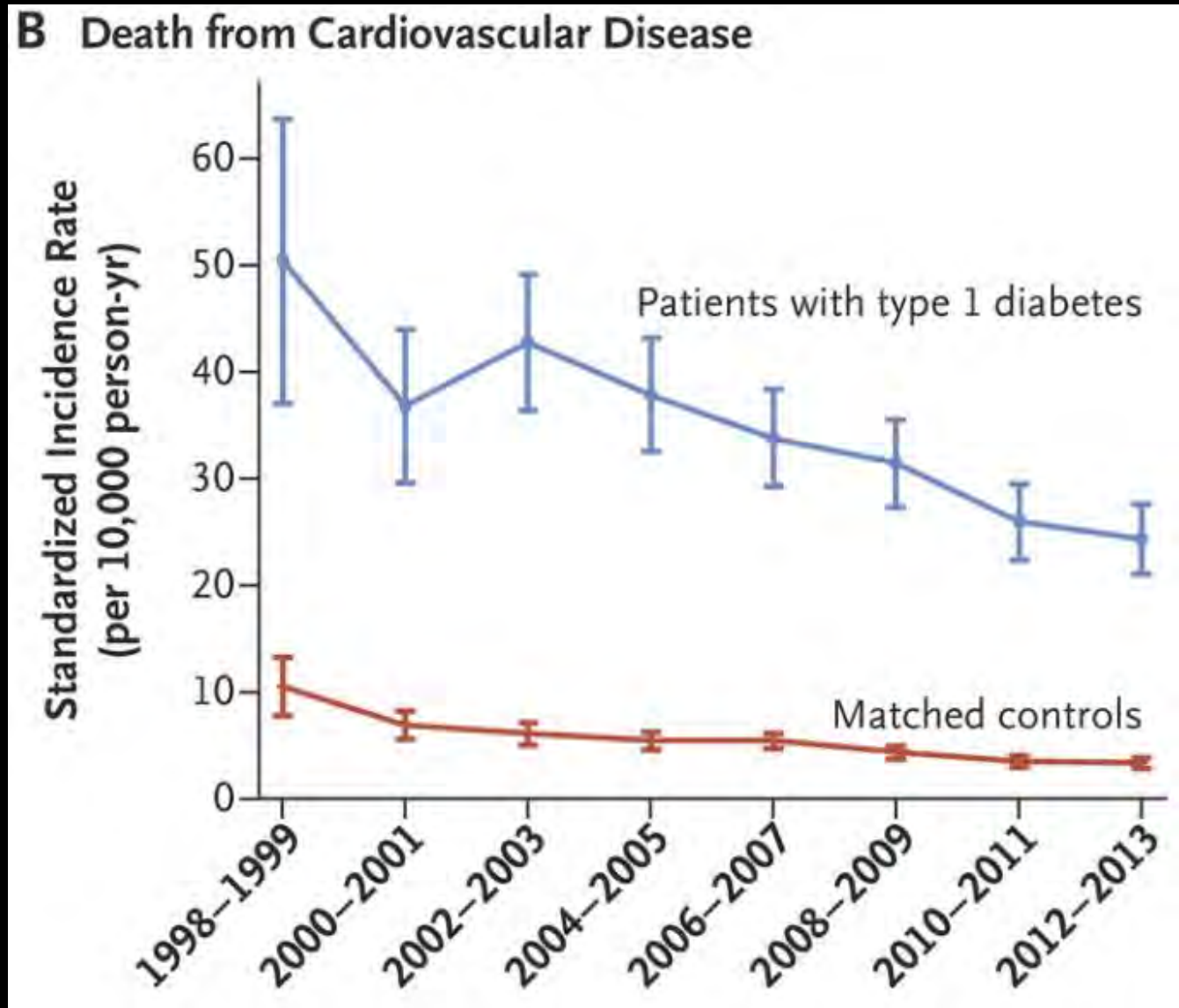
How is greater recognition of the impact of
multifactorial intervention affecting
cardiovascular outcomes in patients with
diabetes?

Fewer
patients with
type 2
diabetes
dying of
CVD

B Death from Cardiovascular Disease



Fewer
patients with
type 1
diabetes
dying of
CVD



Questions?