Heart Disease in Diabetes

Robin Goland, MD

Case #1

- 35yo Chinese male w/ PMH only significant for one episode of pancreatitis 10+ yrs ago resulting in transient insulin-dependent hyperglycemia, admitted after one month of worsening dyspnea on exertion, paroxysmal nocturnal dypsnea and cough, found to have low severe CHF on outpatient TTE (EF 15%), but no chest pain.
- Until 1 month prior to admission, in usual state of good health, developed shortness of breath/cough, thought to have viral bronchitis, treated with azithromycin. Symptoms did not improve. Subsequently traveled to high-altitude location for work, where symptoms worsened and was sent back home. ROS also positive for 5kg unintentional weight loss.
- Outpatient TTE: global hypokinesis w/ low systolic function, no valvular abnormalities.

Other pertinent information

- Current medications: none
- Allergies: NKDA
- SH: no EtOH/illicits but smokes 1/2ppd x 15 years. Born and raised in the United States, parents from China. Works as a musician, travels with an orchestra.
- Exam: Tachycardic (HR 104bpm) and mildly hypotensive (90/64), slightly overweight (ht 170cm wt 70kg BMI 25). No acanthosis nigricans. Normal thyroid, heart/lung exams, abdomen benign, mild LE edema to ankles.

Case #1 (cont'd)

- Labs notable for:
  - Troponin negative x3
  - Normal brain natriuretic peptide (BNP)
  - Normal electrolytes, LFTs, coags
  - HbA1c 10.6%
- EKG showed NSR@99bpm, possible left atrial enlargement, possible anterior infarct
- Underwent left heart cardiac catheterization:
  - 95% mid-Left Anterior Descending
  - 100% prox-Right Coronary w/ collateralization from septal branches
  - 90% mid-Left Circumflex

Case #1 (FSGs)

Date	Pre-Breakfast	Post-Breakfast	Pre-Lunch	Post-Lunch	Pre-Dinner	Post-Dinner	Bedtime
8/1	144		165		158		122
8/2	164						

These blood sugars are unusually good (on no T2D therapy) as compared to A1c of 10.6%. Lab repeated, repeat similarly elevated (10.4%). Suggests that outpatient hyperglycemia is mostly high-carb diet.

Case #1 – What's the next step?

- What CAD treatment is best for patients with diabetes?
  - Medical therapy
  - Medical therapy plus PCI (percutaneous coronary intervention)
  - Medical therapy plus CABG (coronary artery bypass graft surgery)
- Does improved diabetes care reduce macrovascular complications?
  - ACCORD, ADVANCE, VADT and UKPDS legacy trials
- What about other risk factors?
  - BP targets?
  - LDL targets? A brief discussion of the 2013 ACC/AHA Guidelines
  - TG targets? FIELD, ACCORD-Lipid trials

Type 2 DM is a well-established risk factor for cardiovascular disease

- Epidemiology – incidence of many diabetes-related outcomes is directly associated with degree of hyperglycemia (HbA1c). In particular, the risk for CVD is 2-3x greater in men with DM2 and 3-4x greater in women than non-diabetics.
- Prospective studies:
  - Framingham Study: relative risk of >2 for cardiovascular disease in all patients with DM2
  - San Antonio Heart Study: relative risk of 2.8-4.9 for all-cause and cardiovascular mortality in patients with uncontrolled DM2 (fasting glucose > 144mg/dl)

- >50% of all diabetes-related expenditures go toward care of its macrovascular complications, including coronary disease

Kannel and McGee, Diabetes Care, 1979
Wei et al, Diabetes Care, 1998

Why is CAD increased in Type 2 DM?

- Endothelial dysfunction
  - Both hyperglycemia, as well as endothelial insulin resistance *per se*, reduce vasodilator (NO, prostacyclin) production, as well as reparative mechanisms for endothelial injury
- Increased platelet reactivity and thrombogenicity
  - Increased platelet activation, leading to higher Thromboxane A2 and fibrinogen synthesis, leading to greater platelet adhesiveness
- Increased macrophage stress
  - Increased unfolded protein response due to hyperglycemia, macrophage insulin resistance and interaction with dysfunctional endothelium, leading to plaque necrosis
- Increased growth factors (IGF-1, FGFs, TGF-beta), leading to increased smooth muscle cell migration

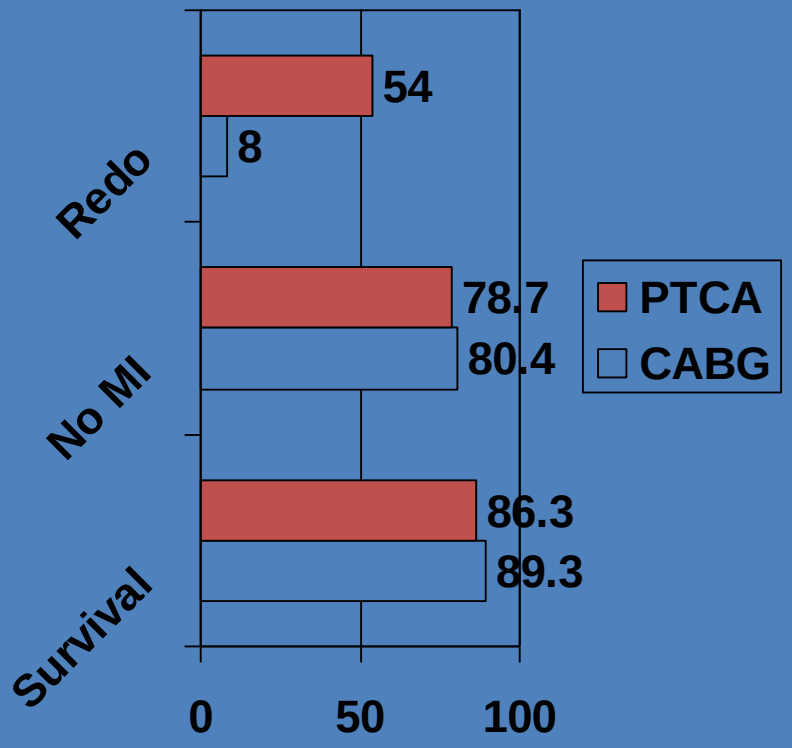
Tabas I, et al. Circ Res, 2010.

How best to treat CAD in DM2: The first clue came from the Bypass Angioplasty Revascularization Investigation (BARI) trial

- NHLBI funded prospective randomized trial of PTCA (balloon only, no stents) vs. CABG in multivessel CAD
- 1829 patients (CABG 914, PTCA 915), 90% white and 40% >65yo. 19% of patients with diabetes (type not specified, assume mostly T2D).
- Followed 5.4 years (3.8-6.8)
- Extent of disease: 41% three vessel, 3.5 clinical lesions → 98% with angina symptoms (65% unstable) in the preceding 6 weeks prior to intervention
- LVEF 57%

Alderman, et al. NEJM, 1996.

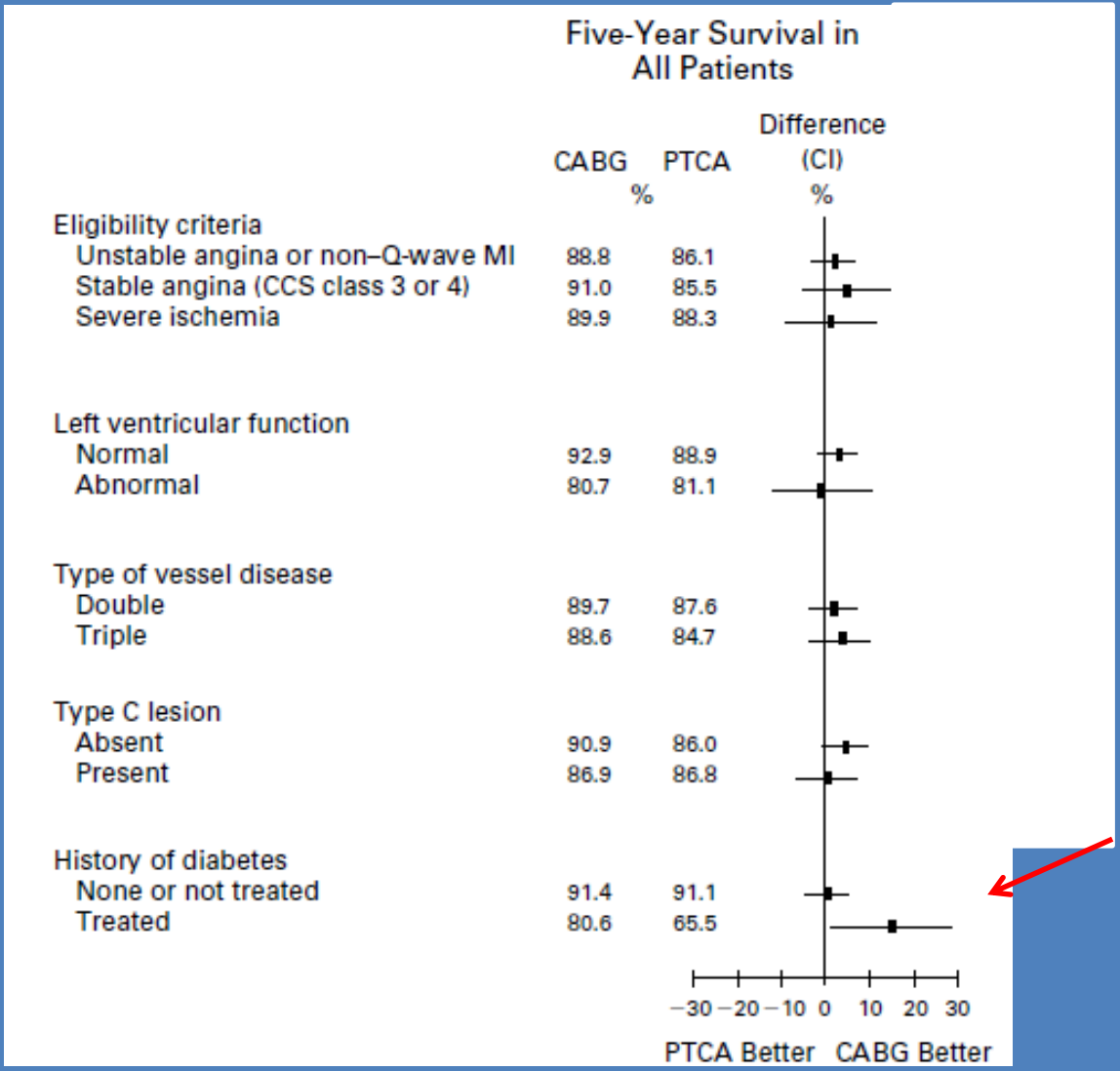
BARI – 5-year risk of mortality/MI unchanged between CABG and PTCA



- Mortality - same
- Q-wave MI - same
- Repeat procedures - increased with PTCA
- Rehospitalization - increased with PTCA

Alderman, et al. NEJM, 1996.

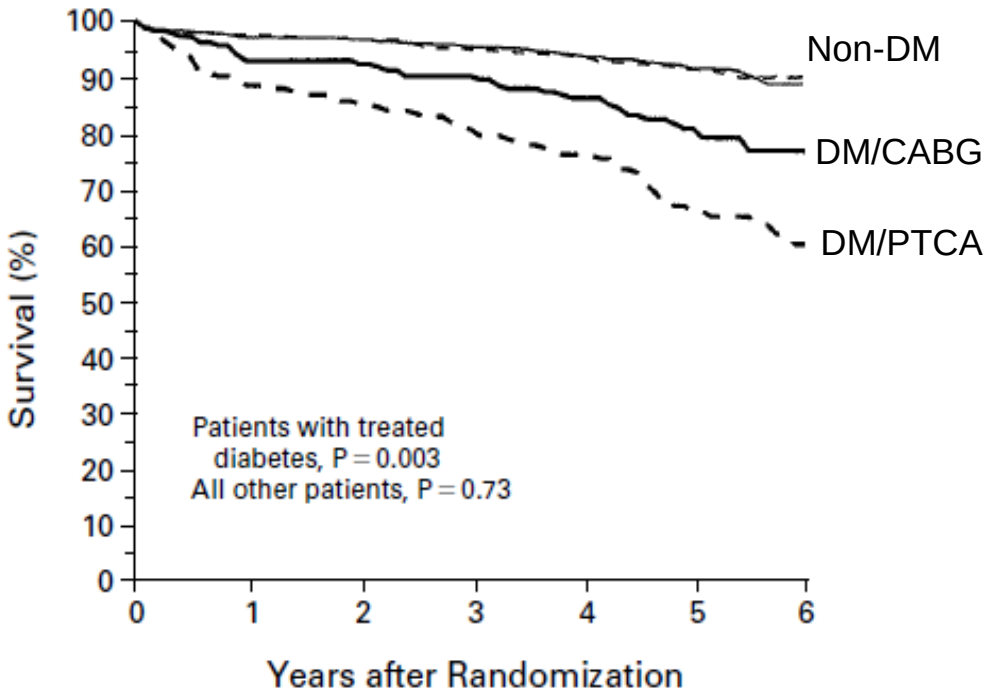
Signal for CABG superiority in patients with Diabetes?



Alderman, et al. NEJM, 1996.

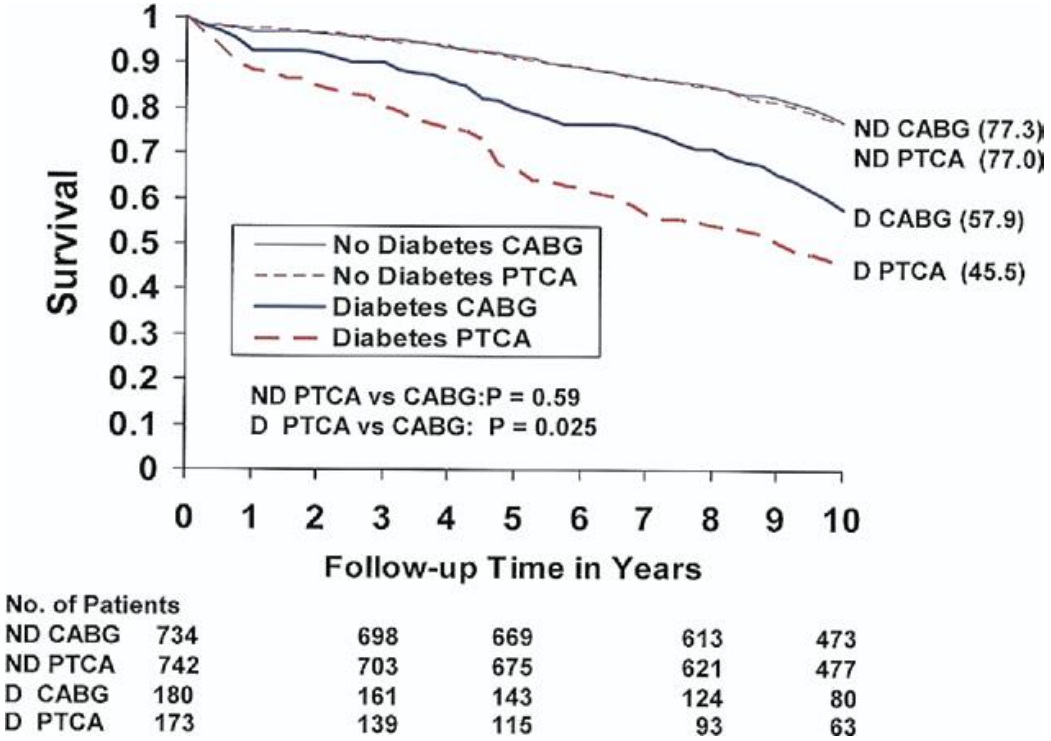
BARI - Diabetic Subgroup Survival

- Patients with DM fared worse than non-DM (expected)
- 5 year survival significantly worse in diabetics with PTCA (p=0.003)
- If diabetics excluded, survival same for both strategies.



Alderman, et al. NEJM, 1996.

BARI – 10-yr follow up: Survival benefit with CABG remained in diabetics

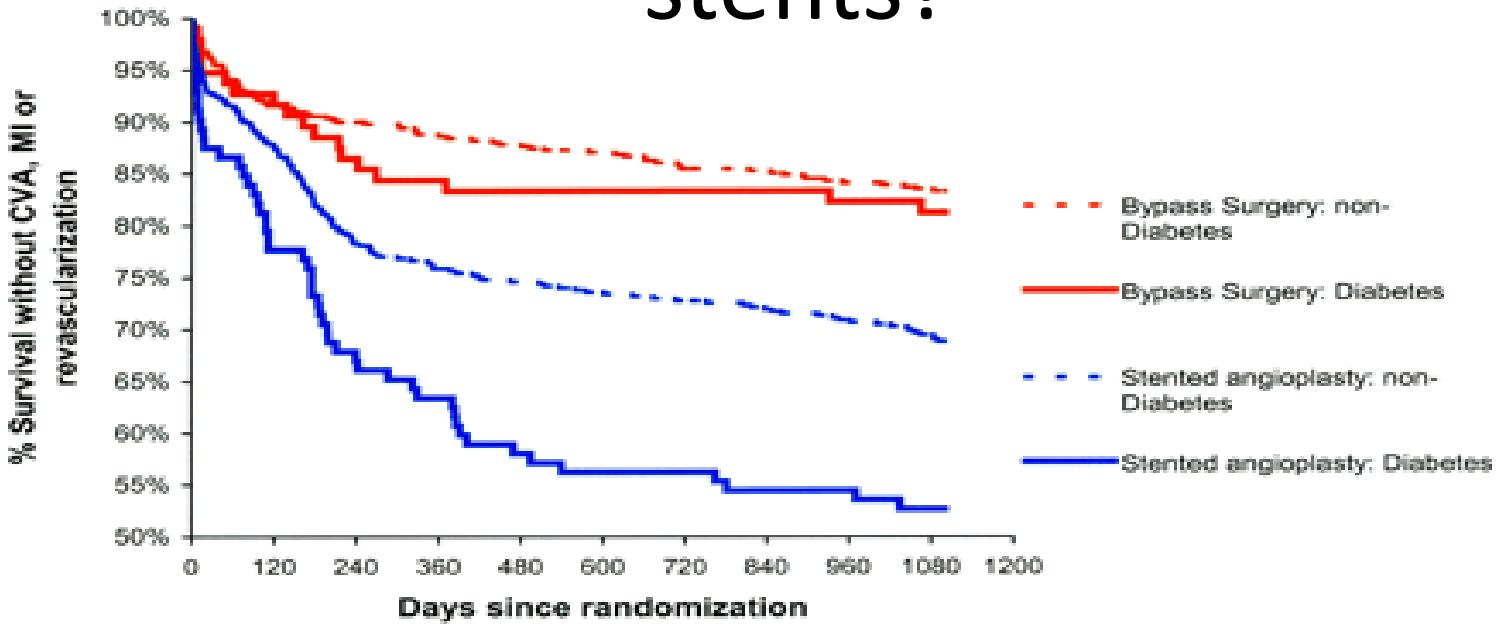


Brooks, et al. JACC, 2007.

Limits of BARI

- Diabetes subgroup had not been pre-specified, but was added *ad hoc* in 1992, after the trial was almost concluded
- Applicability to current populations?
  - PTCA became PCI, which further evolved from bare metal to drug-eluting stents
  - CABG techniques changed, in favor of arterial conduit, and off-pump procedures
  - Intraprocedural/postprocedural anti-platelet therapies became standard, as did use of high-dose statin

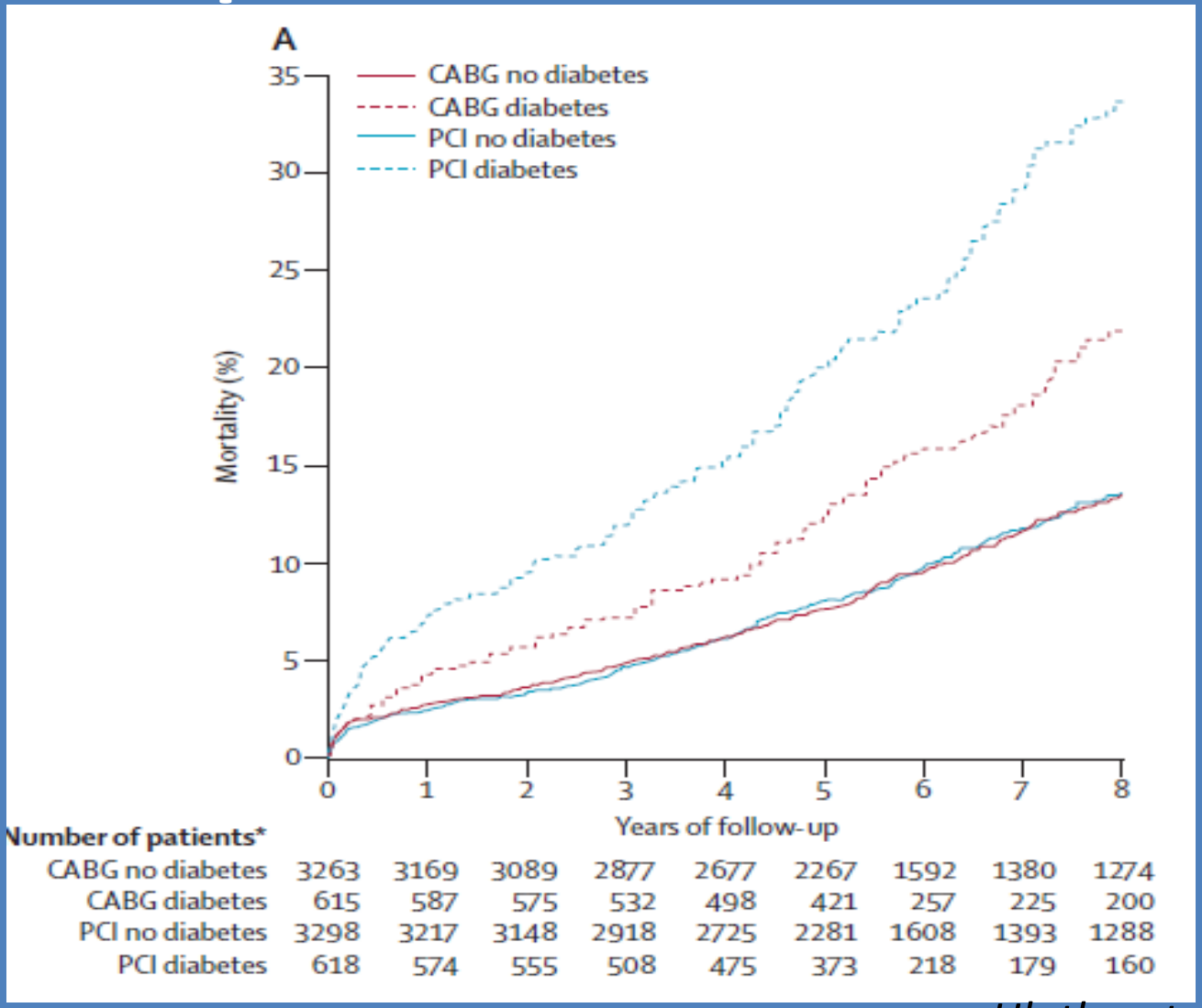
ARTS (Arterial Revascularization Therapies Study Group) – CABG > stents?



- Three year Kaplan-Meier event-free survival curves for death, CVA, MI or any repeat revascularization in diabetic (n=208) and nondiabetic (n=997) patients assigned to stenting or CABG. Not powered to assess survival benefit.

Serruys, et al. NEJM, 2001.

Meta-analysis - CABG superior for patients with diabetes



Number of patients*									
CABG no diabetes	3263	3169	3089	2877	2677	2267	1592	1380	1274
CABG diabetes	615	587	575	532	498	421	257	225	200
PCI no diabetes	3298	3217	3148	2918	2725	2281	1608	1393	1288
PCI diabetes	618	574	555	508	475	373	218	179	160

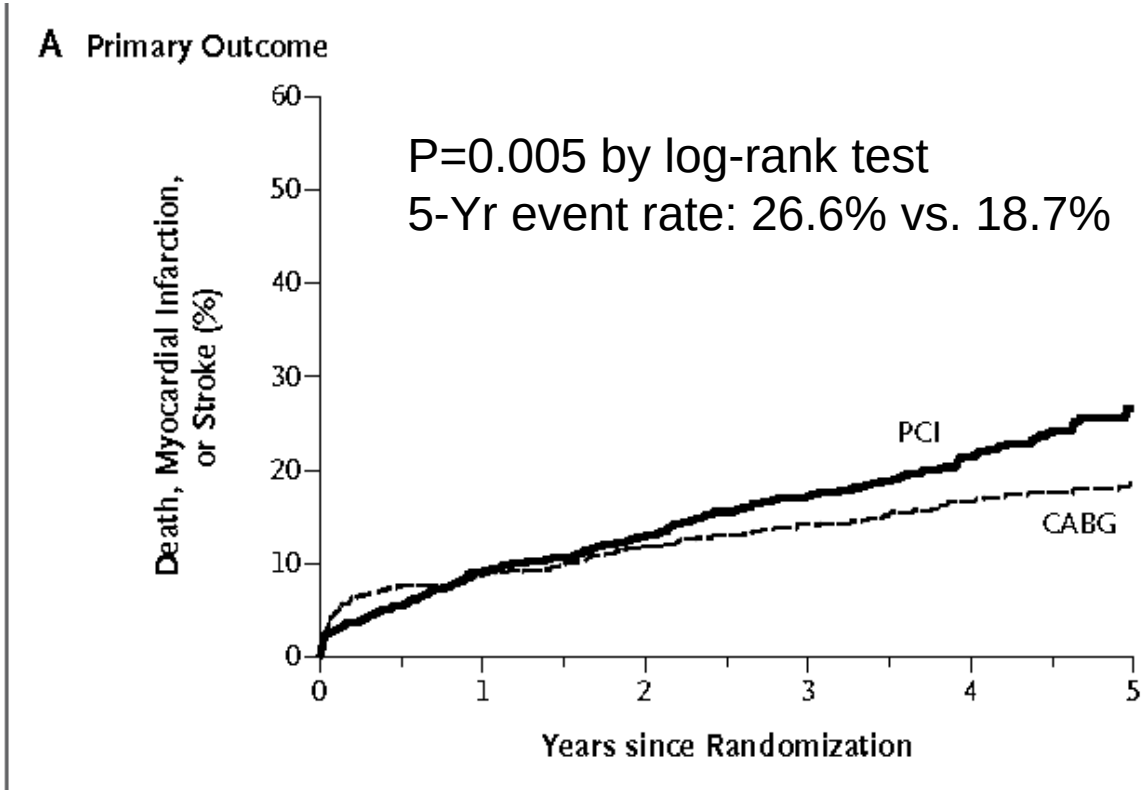
Hlatky, et al. Lancet, 2009.

To finally answer the PCI vs. CABG question in DM2 patients - the FREEDOM trial.

- International (140 centers) trial to determine risk/benefit of PCI (DES) v. CABG for multivessel (>/= 2 vessel) revascularization in patients with DM2. Large study - 1900 patients.
- Patients were similar demographically to BARI - avg 63yo, 71% male – but had higher rates of 3-vessel disease (83%).
- Baseline A1c: 7.8%
  - Insulin use 32%
- All on optimized medical therapy with goal:
  - LDL < 70
  - BP < 130/70
  - HbA1c 7.0%

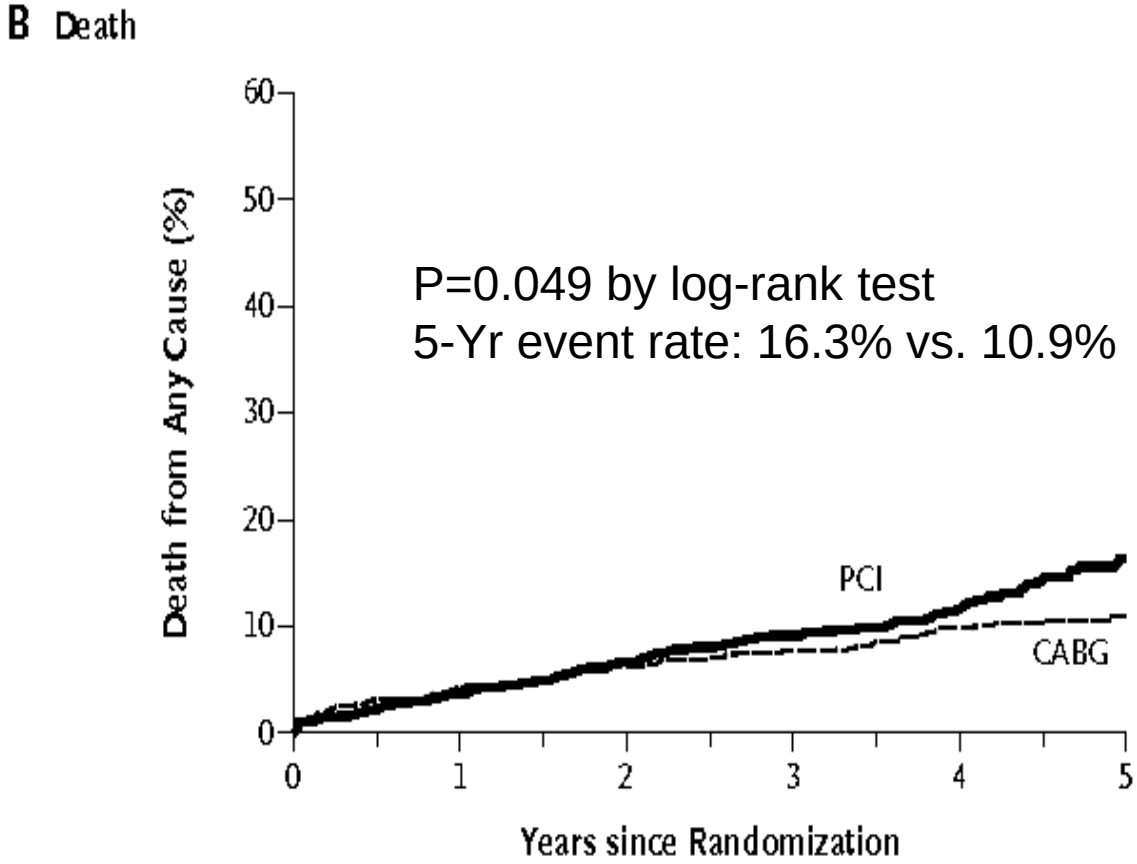
Farkouh, et al. NEJM, 2012.

FREEDOM Primary Endpoint: Reduced composite of death, MI or CVA in CABG arm



Farkouh, et al. NEJM, 2012.

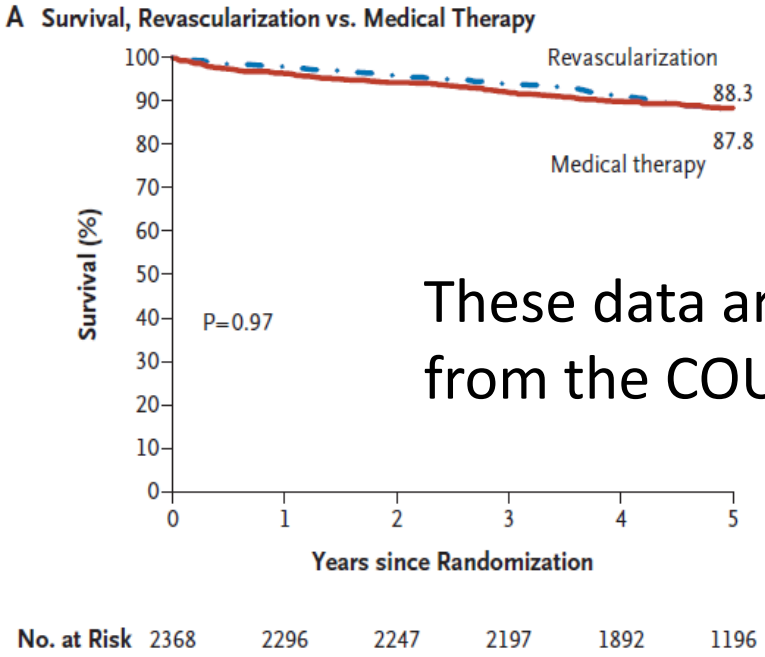
FREEDOM Secondary Endpoint: Reduced mortality with CABG



Farkouh, et al. NEJM, 2012.

So, the PCI vs. CABG question is seemingly answered… but is revascularization necessary?

In BARI-2D (Bypass-Angioplasty Revascularization Investigation 2 Diabetes), patients with DM2 and stable, primarily *single-vessel* ischemic cardiovascular disease were randomized to either prompt revascularization (by CABG or PCI) or medical therapy.



These data are similar to other data from the COURAGE trial.

Frye, et al. NEJM, 2009.

Conclusions (Revascularization options)

- Diabetic patients have increased risk of CVD than non-diabetics, and higher rates of restenosis following revascularization
- Coronary interventions with angioplasties and stents have expanded the management options for patients with diabetes, although optimal medical therapy (with excellent BP/lipid control) is still essential.
- For established CAD:
  - In multi-vessel disease, patients with DM2 are better managed with CABG (survival advantage over PCI)
  - In single vessel disease, medical therapy is equivalent to CABG/PCI

What About the Patient?

- What does the patient desire?
  - Expeditious diagnosis and therapy
  - Long term benefit
- What does the physician desire?

Back to Case #1

- CAD:
  - Underwent successful CABGx4 (LIMA-LAD, SVG-PL-PDA)
  - Post-operative CAD medication regimen included: B-blocker, ACEI and statin
  - 1yr post-op, EF has increased from 10-15% to 45% and patient is symptom free
- T2D:
  - Post-op, maintained on insulin drip as per CTICU post-CABG protocol, transitioned to low-dose subcutaneous glargine (5units daily) and aspart (0-3units/meal) regimen.
  - Discharged on glargine + repaglinide with high-CHO meals (CHF – caution with metformin/TZD; prior pancreatitis – caution with DPP4/GLP1)

What is optimal medical therapy? What should be the glycemic target?

- Is his risk of recurrent macrovascular complication reduced by tight glycemic control? What should be his A1c goal?
- Three trials, independently conceived, that evaluate whether intensive glycemic control (defined differently in each trial) as compared to standard therapy (again, different definitions) improve macrovascular and/or microvascular complication rates in diverse type 2 diabetic patient populations
  - ACCORD (Action to Control Cardiovascular Risk in Diabetes):
    - 77 centers in the United States and Canada
  - ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation):
    - 215 centers in 20 countries from Asia, Australia, Europe and North America
  - VADT (Veteran Affairs Diabetes Trial):
    - 20 centers in Veterans Affairs clinics in the United States

Why study this?

Epidemiology – incidence of many diabetes-related outcomes is directly associated with degree of hyperglycemia (HbA1c). In particular, the risk for CVD is 2-3x greater in men with DM2 and 3-4x greater in women than non-diabetics.

After adjustment for other risk factors, increase in 1% A1c above 7%:
18% increase in cardiovascular events (HOPE study, Lancet, 2000)
12-14% increase in death (Meta-analysis, Ann Intern Med, 2004)
37% increase in retinopathy or renal failure (UKPDS, Brit Med Journ, 2000)

UKPDS (UK Prospective Diabetes Study) #33

Clinical question:

Does intensive blood sugar control reduce the risk of macrovascular or microvascular complications of diabetes?

Treatment strategy:

1) Intensive arm = maintain fasting glucose <6 mmol/L (108 mg/dl) and in insulin-treated patients, pre-meal glucose of 4-7 mmol/L with sulfonylurea (glibenclamide or glipizide) or insulin (Ultratard or Humulin Zn +/- regular insulin to create basal/bolus therapy). If on >14 units/day, patients encouraged to do home glucose monitoring.
2) Standard arm = maintain fasting glucose <15 mmol/L (270 mg/dl) with dietary advice from dietician; if > 15 mmol/L, started on sulfonylurea or insulin +/- metformin

Primary outcome:

composite – any diabetes-related end point (death, MI, angina, CHF, CVA, renal failure, amputation, blindness or cataract/retinal surgery), as well as pre-specified outcomes re: microvascular and macrovascular complications

UKPDS Group, Lancet, 1998

UKPDS patient population = low risk

UKPDS recruited new-onset DM2 patients, specifically young to middle-aged (inclusion criteria of 25-65yo), with fasting glucose of >6 mmmol/L (108mg/dl), exclusion criteria including current angina/CHF or MI in the past year.

age: 53yr
sex: 55% male, 45% female
duration of DM2: <6 months, A1c 7%, glucose 8 mmol/L (144mg/dl)
previous cardiovascular event: 35%
weight: 78kg, BMI 27.8

UKPDS Group, Lancet, 1998

UKPDS - results

Reducing glucose exposure (HbA1c 7.0 % vs. 7.9 % over median 5 years), with sulfonylurea or insulin therapy, reduced the risk of “any diabetes-related endpoint” by 12% (P=0.029) and microvascular disease by 25% (P=0.0099), with a 16% trend to a reduced risk of myocardial infarction (P=0.052).

Fears that sulfonylurea or insulin therapies may be harmful were allayed, as no increase was observed with these agents in the incidence of cardiovascular deaths, myocardial infarction or sudden death. Although neither of these therapies impaired quality of life, both increased risk of hypoglycemia and weight gain.

What about more intensive glycemic control?

UKPDS Group, Lancet, 1998

ACCORD

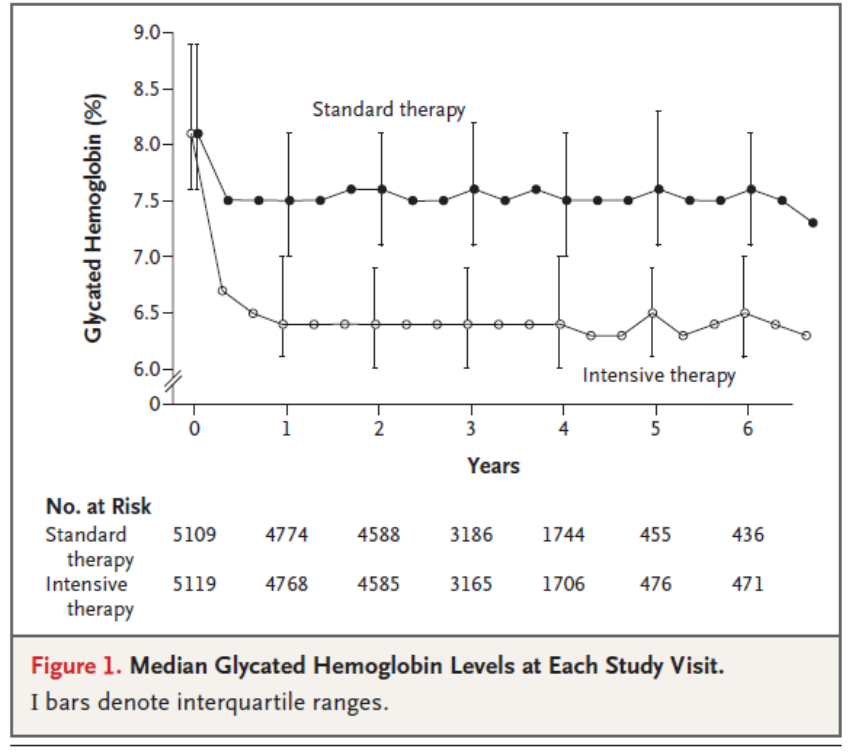


Figure 1. Median Glycated Hemoglobin Levels at Each Study Visit.
I bars denote interquartile ranges.

between-group difference: 1.1%

Clinical question:
Does targeting HbA1c to normal (<6%) reduce CV events as compared to standard therapy?

Treatment strategy:
1) Intensive arm = monthly visit x4mo → every other month after that w/ interim phone calls, target A1c <6%
2) Standard arm = every 4 month visits, target A1c <8%

Primary outcome:
composite - nonfatal MI, CVA, death from CV cause

ACCORD Study Group, New Eng J Med, 2008

ACCORD patient population = high risk

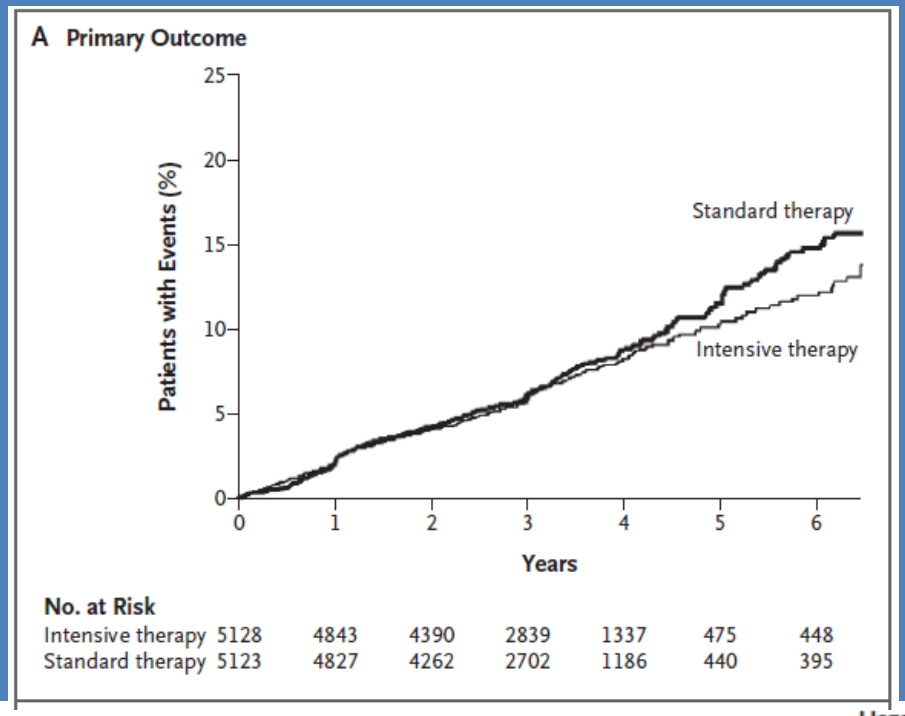
ACCORD was specifically designed to determine whether reducing HbA1c to normal would reduce CV events in middle-aged and older people (40-79yo) with DM2 and **established CVD** or **additional CV risk factors:**

1) *anatomic evidence of significant atherosclerosis*
2) *albuminura*
3) *LVH*
4) *2 additional risk factors for CVD (dyslipidemia, HTN, current smoking or obesity).*

age: 62.2yr
sex: 61% male, 39% female
duration of DM2: 10 years, A1c 8.3%, glucose 175mg/dl
previous cardiovascular event: 35%
weight: 93.5kg, BMI 32.2, waist circum 106.8cm

ACCORD Study Group, New Eng J Med, 2008

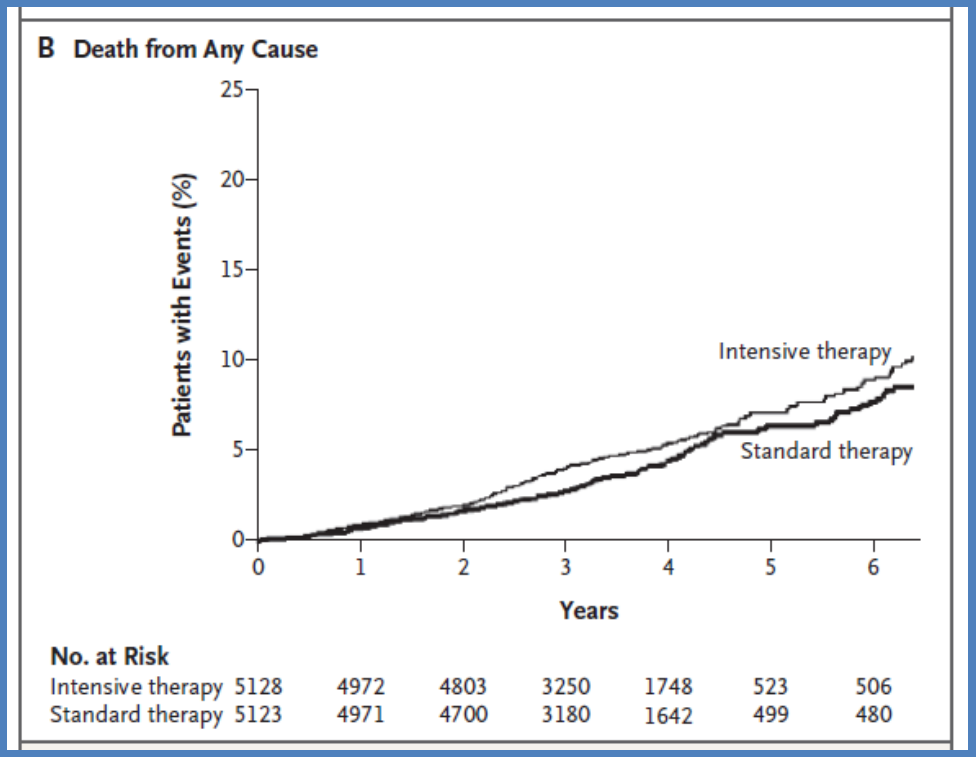
Decreased MI in intensive arm drives trend towards decreased primary outcome



Outcome	Intensive Therapy (N=5128)		Standard Therapy (N=5123)		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*% per yr*	*no. of patients (%)*	*% per yr*		
Primary outcome	352 (6.9)	2.11	371 (7.2)	2.29	0.90 (0.78–1.04)	0.16
Secondary outcome						
Death						
Any cause	257 (5.0)	1.41	203 (4.0)	1.14	1.22 (1.01–1.46)	0.04
Cardiovascular causes	135 (2.6)	0.79	94 (1.8)	0.56	1.35 (1.04–1.76)	0.02
Nonfatal myocardial infarction	186 (3.6)	1.11	235 (4.6)	1.45	0.76 (0.62–0.92)	0.004
Nonfatal stroke	67 (1.3)	0.39	61 (1.2)	0.37	1.06 (0.75–1.50)	0.74
Fatal or nonfatal congestive heart failure	152 (3.0)	0.90	124 (2.4)	0.75	1.18 (0.93–1.49)	0.17

ACCORD Study Group, New Eng J Med, 2008

Increased death from any cause with intensive glycemic control

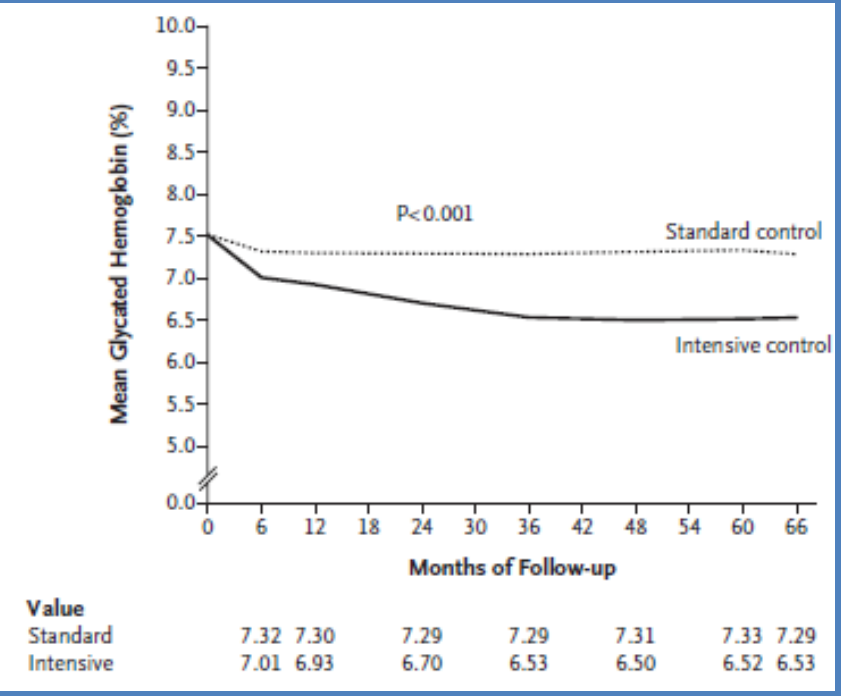


22% excess mortality w/ intensive therapy (p=0.04)

35% excess CV mortality w/ intensive therapy (p=0.02)

ACCORD Study Group, New Eng J Med, 2008

Is this reproducible? ADVANCE trial



between-group difference: 0.8%

ADVANCE Study Group, New Eng J Med, 2008

Clinical question:

Does targeting HbA1c to near-normal (<6.5%) *with gliclazide* plus other drugs reduce microvascular or macrovascular events as compared to standard therapy?

Treatment strategy:

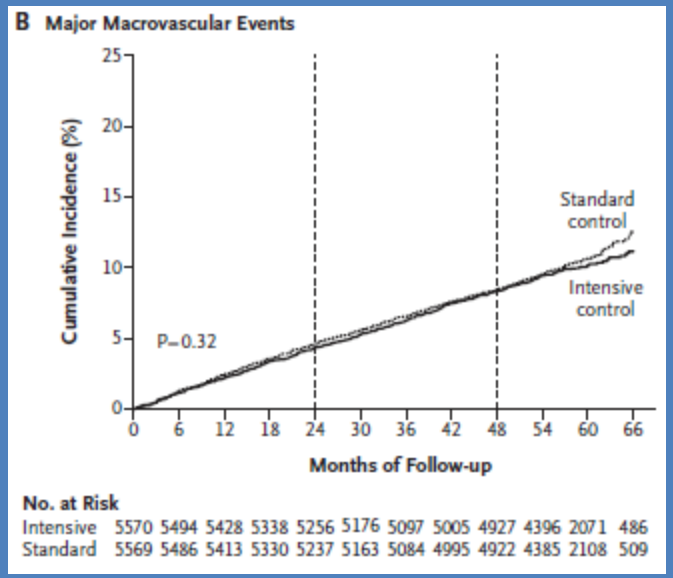
1) Intensive arm = addition of gliclazide, monthly visits x4mo → every 2-3 months after that
2) Standard arm = q3-6month visits

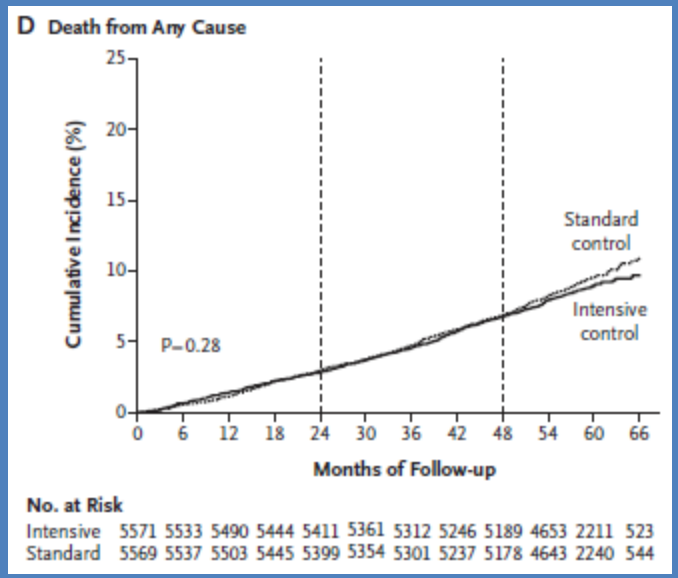
Primary outcome:

composite:

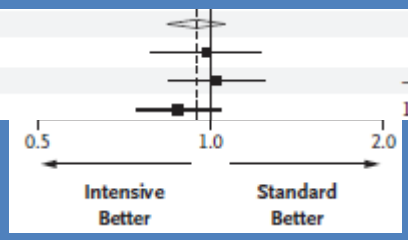
1) macrovascular = death from CV cause, nonfatal MI or nonfatal stroke
2) microvascular = new/worsening nephropathy or retinopathy
3) macrovascular + microvascular composite outcomes

ADVANCE: No difference in macrovascular events or death with intensive control



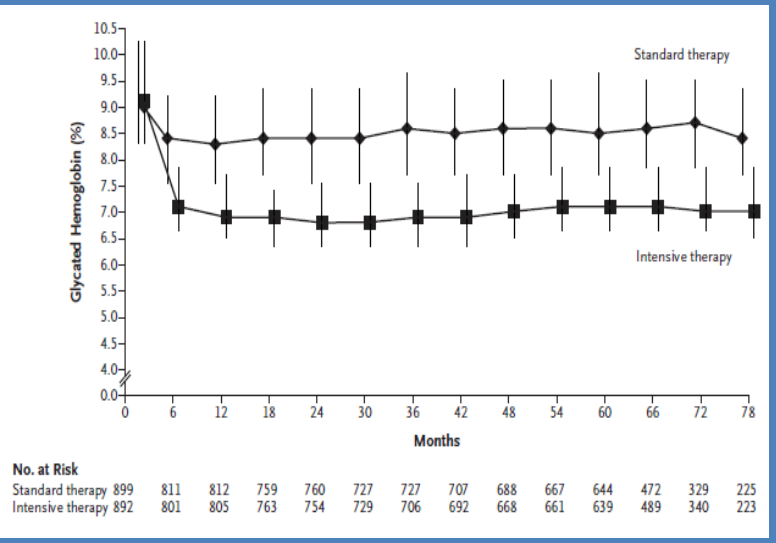


Major macrovascular events	557 (10.0)	590 (10.6)	6 (–6 to 16)
Nonfatal MI	153 (2.7)	156 (2.8)	2 (–23 to 22)
Nonfatal stroke	214 (3.8)	209 (3.8)	–2 (–24 to 15)
Death from cardiovascular causes	253 (4.5)	289 (5.2)	12 (–4 to 26)



ADVANCE Study Group, New Eng J Med, 2008

VADT – the tie-breaking trial?



between-group difference: 1.5%

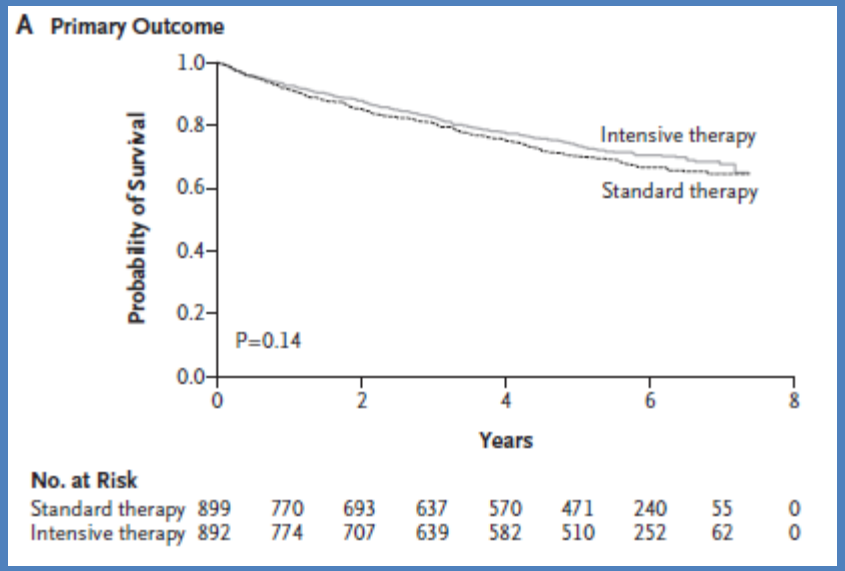
Clinical question:
Does reducing A1c in poorly controlled DM2 by 1.5% reduce macrovascular events as compared to standard therapy?

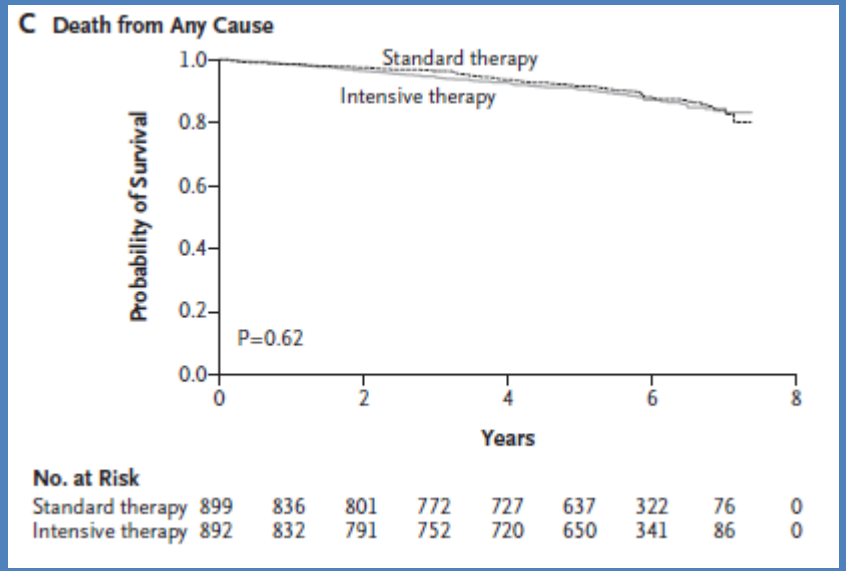
Treatment strategy:
1) Intensive arm = max dose metformin and rosiglitazone if BMI >27 (or glimepiride and rosiglitazone if BMI <27), then addition of insulin if A1c >6%
2) Standard arm = ½ dose of drug combinations as above, then insulin if A1c >9%.

Primary outcome:
composite of CV events (MI, CVA, death from CV cause, new or worsening CHF, surgical intervention for CV disease, inoperable CAD, amputation for ischemic gangrene)

Duckworth, et al, New Eng J Med, 2008

VADT: No difference in macrovascular events or death with intensive control





Duckworth, et al, New Eng J Med, 2008

Meta-analysis: No signal for increased death or for change in macrovascular outcomes

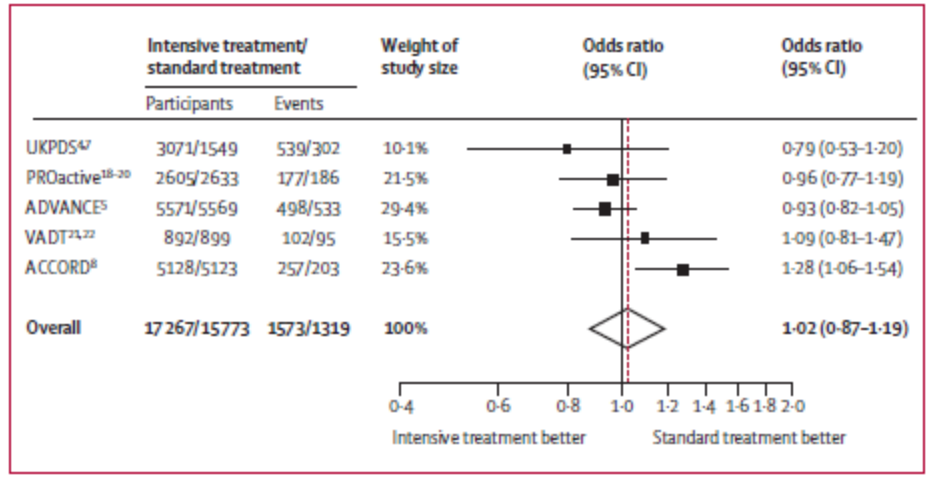


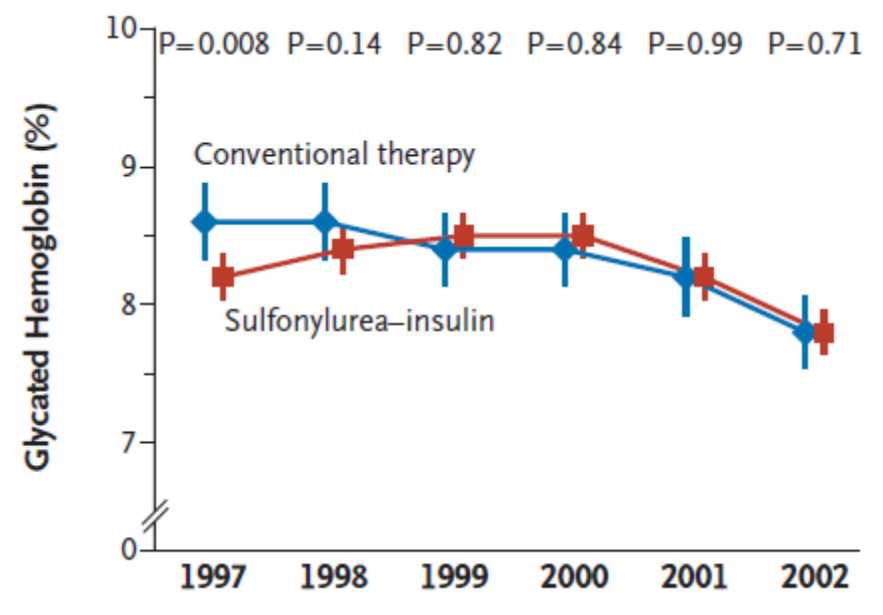
Figure 4: Probability of events of all-cause mortality with intensive glucose-lowering versus standard treatment

This conclusion persists even with exclusion of PROactive and/or UKPDS.

Ray, et al, Lancet, 2009

UPKDS Legacy

After UPKDS results were published in September 1998, patients and clinicians were advised to lower glucose levels as much as possible. Patients returned to community or hospital-based care according to clinical needs, with no attempt to maintain previously randomized therapy. Seen annually for 5 years in UKPDS clinics. >66,000 person-years of follow-up. 78% of patients entered post-trial monitoring. Difference in HbA1c disappeared within 1 year of follow-up.



Holman et al, New Eng J Med, 2008

Is there long-term cardiovascular benefit from intensive glycemic control?

Clinical question:
In a study of Type 1 diabetes (DCCT/EDIC), there was a delayed macrovascular benefit to better glycemic control – does a similar benefit exist in Type 2 diabetes?

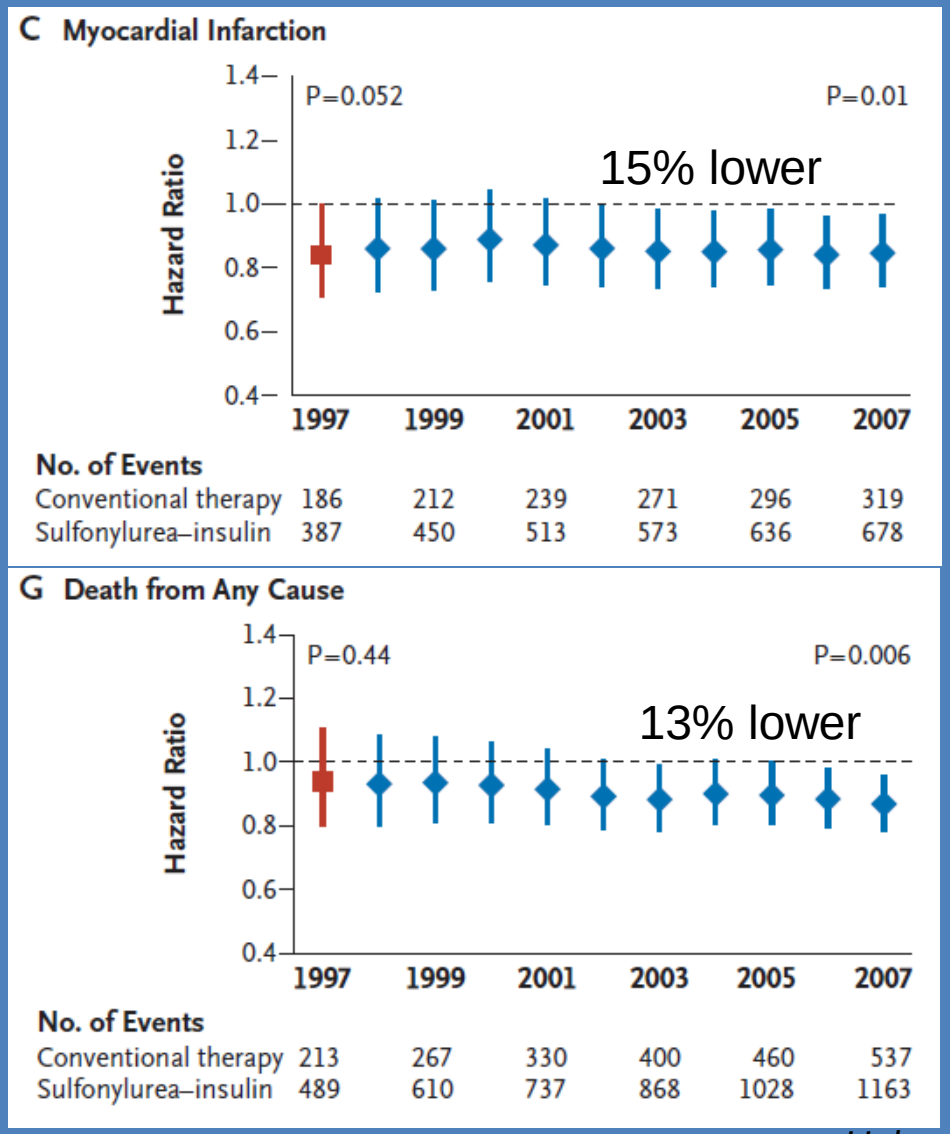
Treatment strategy:

1) Intensive arm = maintain fasting glucose <6 mM (108 mg/dl) and in insulin-treated patients, pre-meal glucose of 4-7 mM with sulfonylurea (glibenclamide or glipizide) or insulin (Ultratard or Humulin Zn +/- regular insulin to create basal/bolus therapy). If on >14 units/day, patients encouraged to do home glucose monitoring.
2) Standard arm = maintain fasting glucose <15 mM (270 mg/dl) with dietary advice from dietician; if >15 mM, started on sulfonylurea or insulin +/- metformin

Primary outcome:
composite – any diabetes-related end point (death, MI, angina, CHF, CVA, renal failure, amputation, blindness or cataract/retinal surgery), as well as pre-specified outcomes re: microvascular and macrovascular complications

Holman et al, New Eng J Med, 2008

Improved macrovascular endpoints (and less death) with earlier glycemic control



Holman et al, New Eng J Med, 2008

Conclusion – glycemic control is good

- UKPDS glycemic targets were modest (overall achieved A1c was 7% at 5 year follow-up, and 8% at 10 years and subsequent surveillance) and the standard therapy arm was fairly uncontrolled.
- Different medications used to prevent/treat cardiovascular disease than current.
- Patient population was much lower risk than ACCORD, etc (younger, with shorter duration of disease).

My view:

1) the lowest achievable A1c reduces risk of microvascular complications to the greatest extent - % reduction in risk persists during trial, and after
2) an A1c target of 7% reduces macrovascular complications, including hard endpoints (MI, death) as compared A1c >8%.
3) improved glycemic control likely has benefits that are not captured in routine trial lengths (3-5 years), and may produce greater long-term improvements in both micro- and macrovascular complications

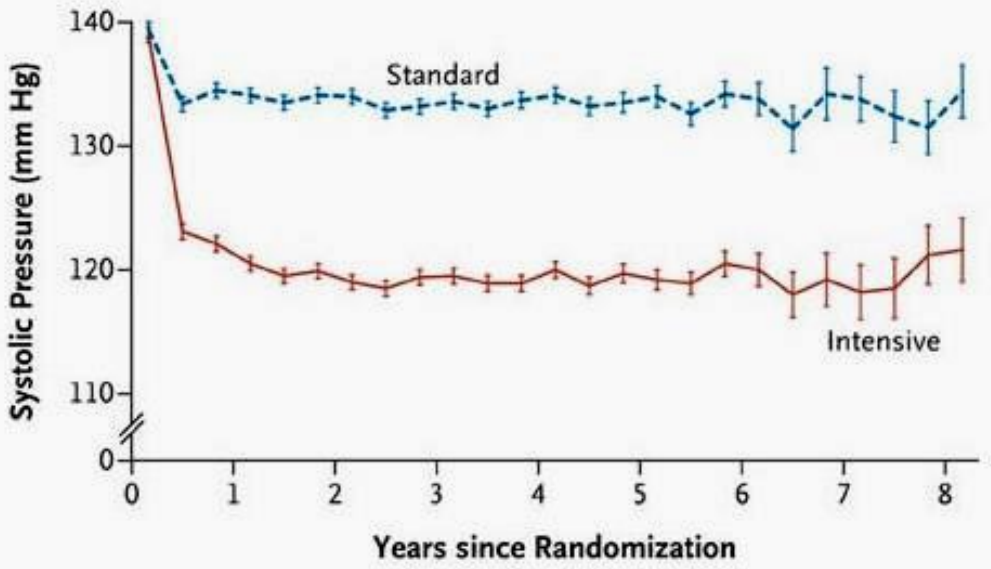
What is optimal medical therapy? Recommendations from ADA/AHA (2007)

- Lifestyle:
  - diet: medical nutrition therapy to induce 5-7% weight loss
  - exercise: to maintain weight loss as well as improve insulin sensitivity
  - tobacco cessation
- Blood pressure: target SBP <130, DBP <80; start therapy if BP > 140/90; 1st line therapy is ACEI or ARB, but multiple agents are often required for control
- Lipids: target LDL <100 mg/dl in patients with DM2 and 1+ CVD risk factors; treat triglycerides if >500 mg/dl
- Aspirin: (75-162mg/day) for patients >40 or with additional risk factors

Buse and Ginsberg, et al. Diabetes Care, 2007.

What about lower BP targets?

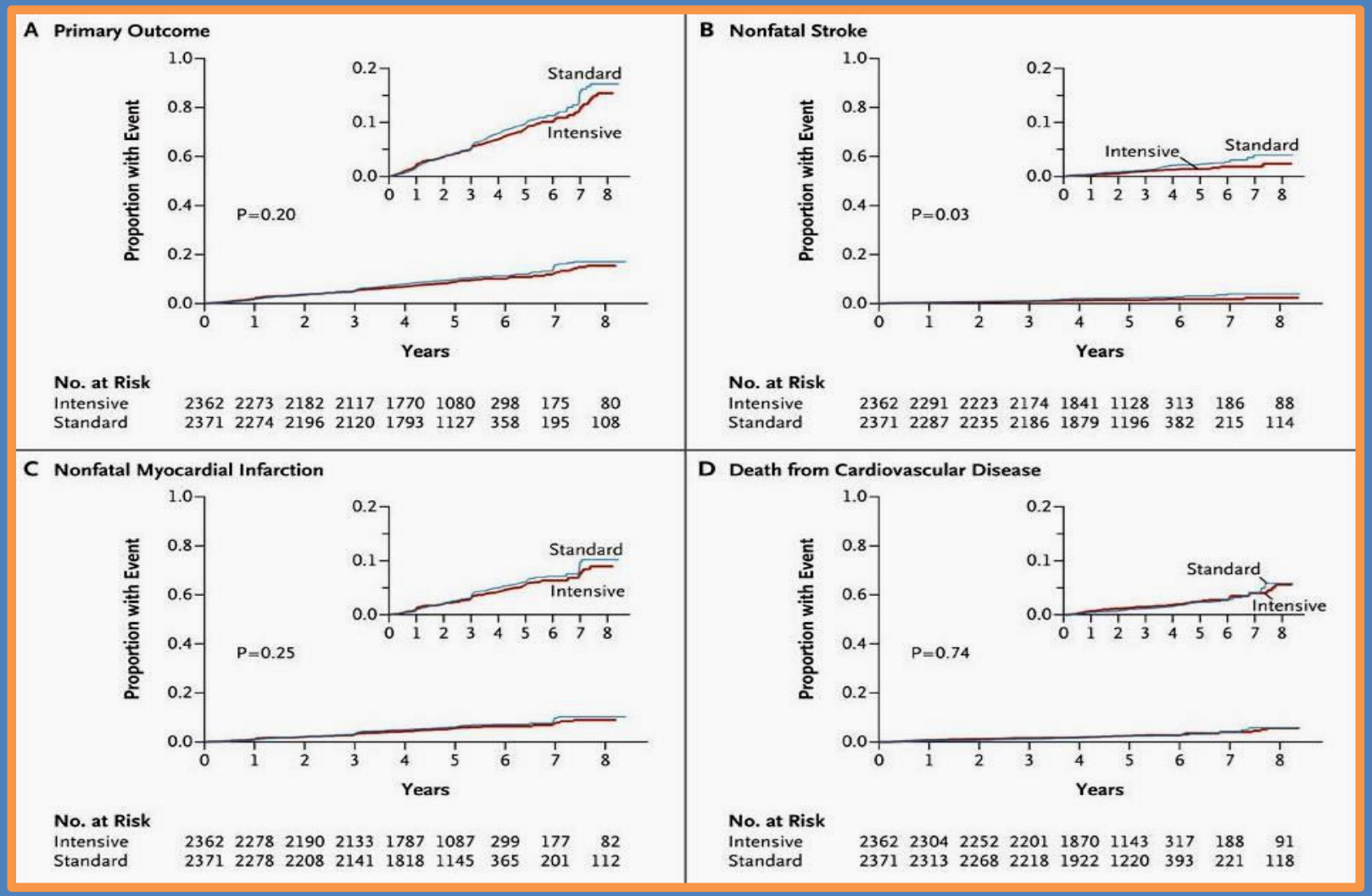
Action to Control Cardiovascular Risk in Diabetes (N=4733)



Mean No. of Medications Prescribed								
Intensive	3.2	3.4	3.4	3.5	3.5	3.5	3.4	3.4
Standard	1.9	2.1	2.1	2.2	2.2	2.3	2.3	2.3
No. of Patients								
Intensive	2174	2071	1973	1792	1150	445	156	156
Standard	2208	2136	2077	1860	1241	504	203	201

ACCORD Study Group. *N Engl J Med.* 2010;362:1575-1585.

No benefit of target SBP <120 vs <140 in CV outcomes or death



ACCORD Study Group. *N Engl J Med.* 2010;362:1575-1585.

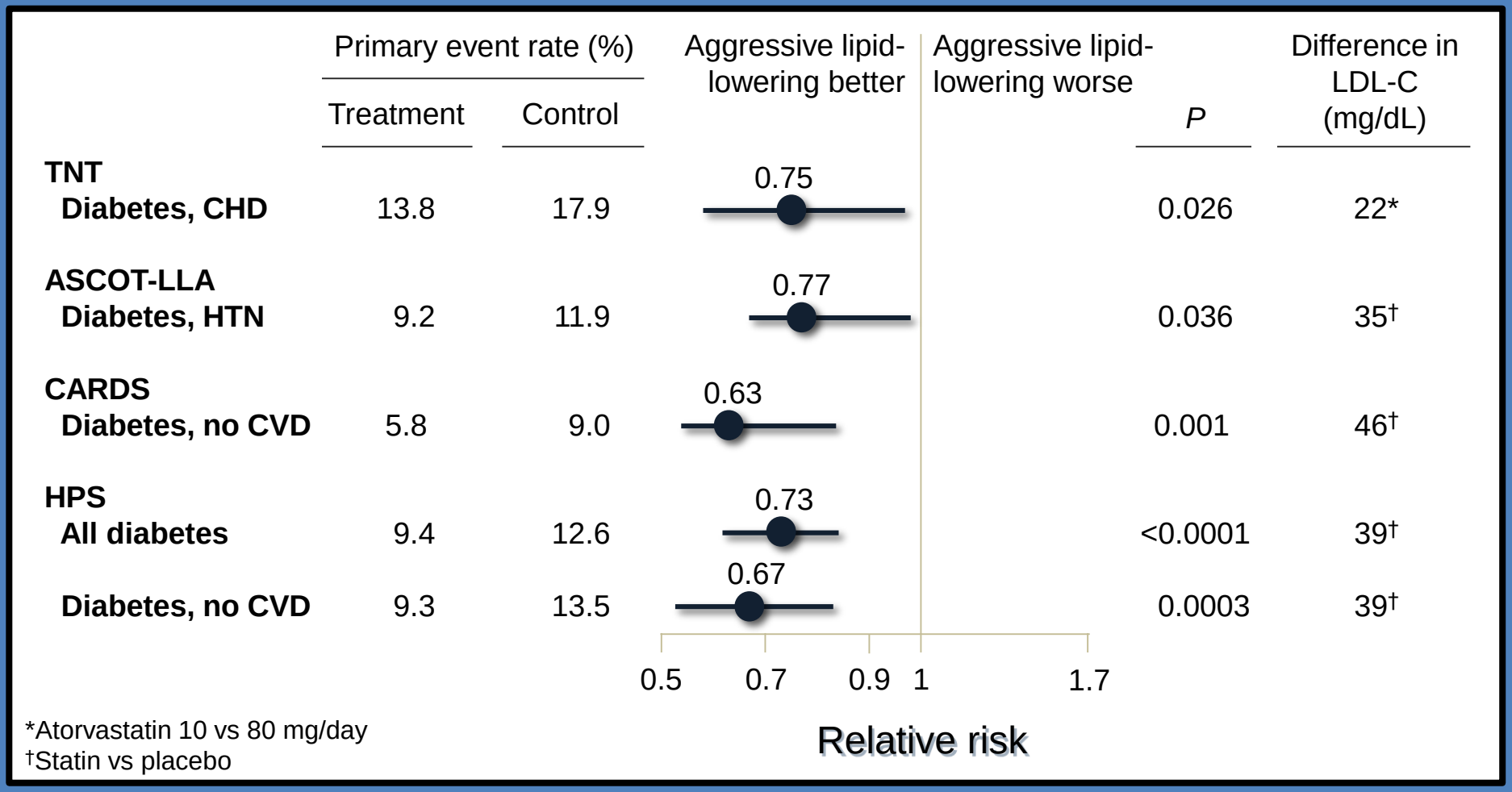
Hypertension management in T2D

Blood Pressure	Goal
Systolic	<140 mmHg
Diastolic	<90 mmHg

- Lower targets (<130/80 mm Hg) may be appropriate for certain individuals (younger patients) if it can be achieved without undue treatment burden.
- Multiple agents are usually required to achieve target BP, but an ACE inhibitor or ARB should be included in the BP-control regimens of patients with diabetes because of beneficial effects on the renin-angiotensin system. Use beta blockers cautiously; may decrease hypoglycemia awareness.
- BP treatment must be continued for benefits to be maintained

American Diabetes Association. *Diabetes Care.* 2015:38(Suppl. 1): S49-S57.

Lipids - benefits of aggressive LDL-C lowering in T2D patients



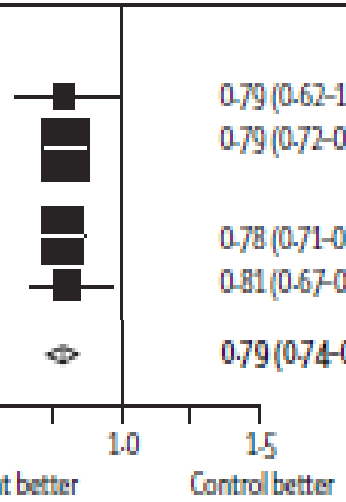
Shepherd J, et al. *Diabetes Care.* 2006;29:1220-1226. Sever PS, et al. *Diabetes Care.* 2005;28:1151-1157. Colhoun HM, et al. *Lancet.* 2004;364:685-696. HPS Collaborative Group. *Lancet.* 2003;361:2005-2016.

Meta-analysis of statins on CV events in patients with T1D or T2D

Patients with Diabetes
(N=18,686; 14 RCTs)

Risk Reduction in Major Vascular Events per mmol/L Decrease in LDL-C

Groups	Events (%) Treatment	Control	RR (CI)	Test for heterogenity or trend
Type of diabetes:				
Type 1 diabetes	147 (20·5%)	196 (26·2%)	0·79 (0·62–1·01)	χ^2_1=0·0; p=1·0
Type 2 diabetes	1318 (15·2%)	1586 (18·5%)	0·79 (0·72–0·87)	
Sex:				
Men	1082 (17·2%)	1332 (21·4%)	0·78 (0·71–0·86)	
Women	383 (12·4%)	450 (14·6%)	0·81 (0·67–0·97)	χ^2_1=0·1; p=0·7
All diabetes	**1465 (15·6%)**	**1782 (19·2%)**	**0·79 (0·74–0·84)**	



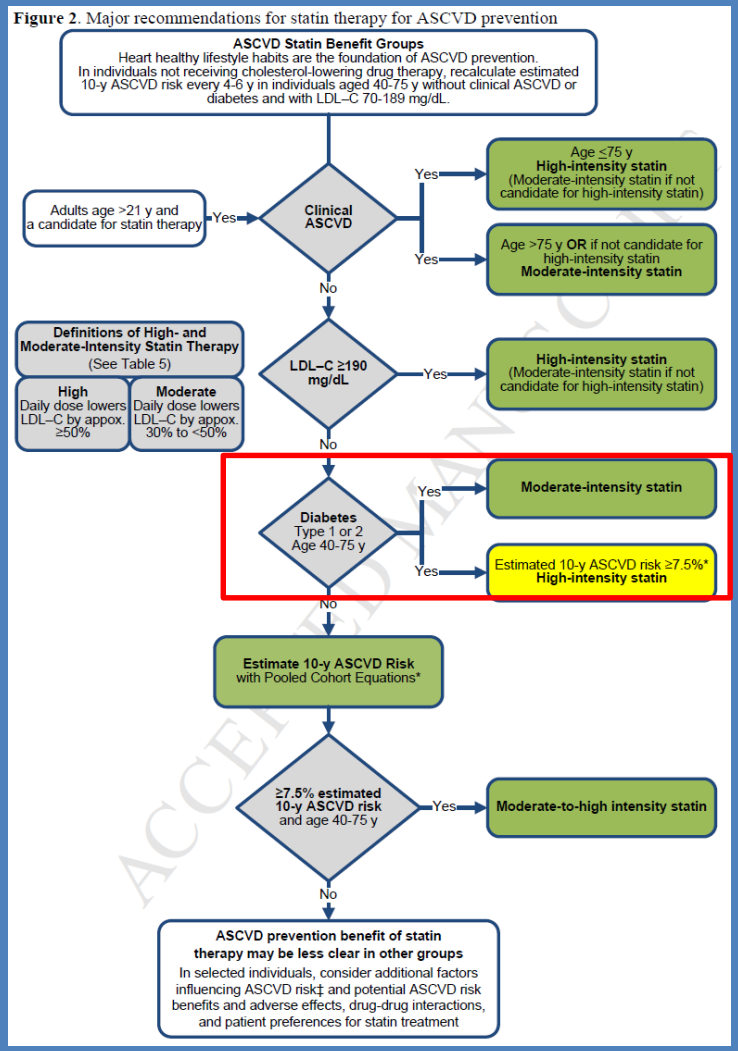
Global test for heterogeneity within subtotals: χ^2_{13}=13·9; p=0·4

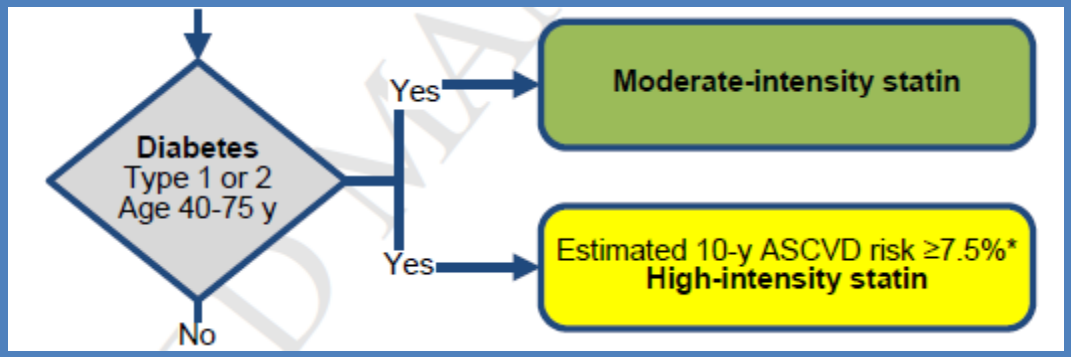
RR (99% CI)

RR (95% CI)

Cholesterol Treatment Trialists' Collaborators. *Lancet*. 2008;371:117-125.

Briefly, on the statin controversy…





The 2013 ACC/AHA guidelines advocate a departure from the current "Treat to Target" approach because:

1) It is not clear "what the target should be… or the magnitude of additional CV risk reduction" or lower targets
2) Does not take into account the "potential adverse effects from multidrug therapy to reach goal"

Stone et al, Circulation, 2013

What's a high-intensity statin?

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C on average, by <30%
Atorvastatin (40†)–80 mg **Rosuvastatin 20 *(40)* mg**	**Atorvastatin 10 *(20)* mg** **Rosuvastatin (*5*) 10 mg** **Simvastatin 20–40 mg‡** **Pravastatin 40 *(80)* mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg bid** *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

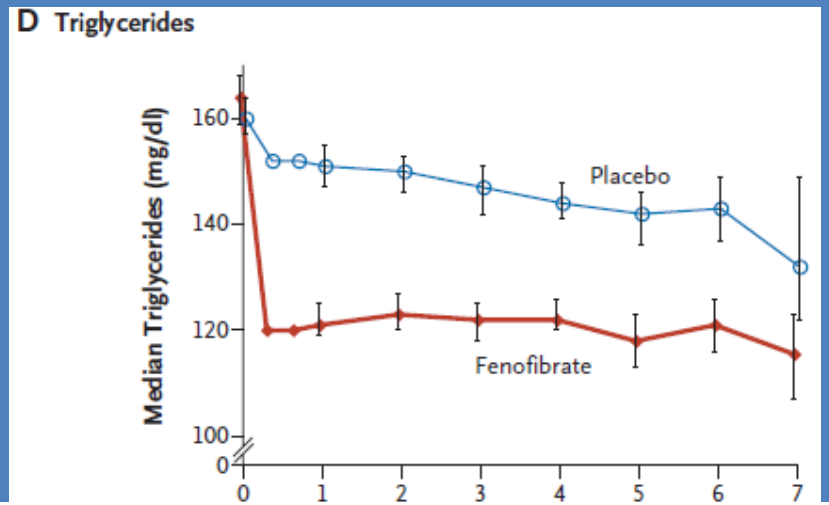
Stone et al, Circulation, 2013

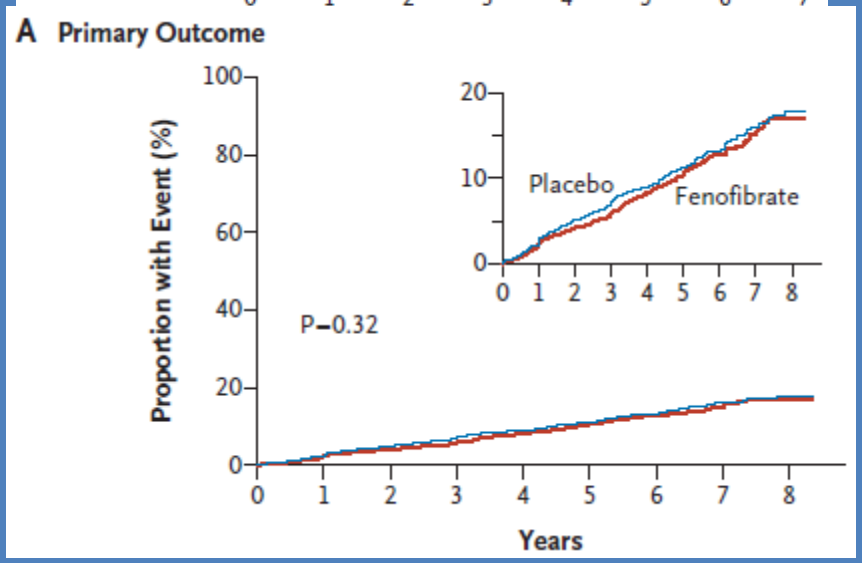
What about fibrates? ACCORD-Lipid

Clinical question:
Does addition of fibrate reduce CV events in patients with DM2 as compared to statin alone?

Treatment strategy:
1) Standard arm = simvastatin (dose adjusted as per Treat to Target algorithm)
2) Fibrate arm = simvastatin + fenofibrate 160mg daily (dose modified as per GFR)

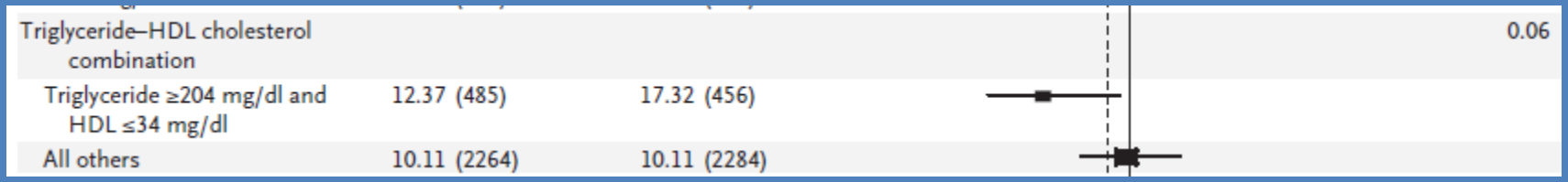
Primary outcome:
composite - nonfatal MI, CVA, death from CV cause





Ginsberg et al, NEJM, 2010

However, in patients with low HDL and very high TG, perhaps a benefit?



Ginsberg et al, NEJM, 2010

The dyslipidemic group with very low HDL and high TG made up 15% of the overall ACCORD Lipid cohort, and represented a pre-specified subgroup analysis. The overall conclusion that fibrates may be beneficial in this group was similar to post hoc analyses performed in prior fibrate studies, including:

1) Helsinki Heart Study
2) Bezafibrate Infarction Prevention Trial
3) FIELD (Fenofibrate Intervention and Event Lowering in Diabetes)

Ginsberg HN, Diabetes Care, 2011

Conclusion – lipid control is also good

My view:

1) Most patients with Type 2 Diabetes would benefit from a statin, due to high likelihood of meeting the “old” threshold of LDL >100mg/dL, making the new guidelines somewhat moot.
2) The rationale for Type 1 Diabetes is less clear, since these patients are less likely to have the same obesity-related, comorbid risk factors (ie, visceral adiposity, low HDL, hypertension, etc). In these patients, I do not routinely start a statin unless LDL >130 or age >40.
3) In picking a statin, I start with the drug and dose that is necessary to get to target.
4) Rarely do I use fibrates for primary CV protection – exclusively in patients who have already met LDL goal on statin, with high fasting triglycerides (usually >250 mg/dL) and low HDL (<34mg/dL) similar to the ACCORD-Lipid subgroup analysis

Case #2

66 yo M with well-controlled T2D (HbA1c 6.9% on metformin and sitagliptin) p/w chest pain. EKG does not reveal ST elevations, but has Q-waves across precordial leads, suggestive of old infarcts. Cardiac enzymes (troponin-T, CK-MB) elevated. Patient receives aspirin, clopidogrel (300mg) and supplemental oxygen, with nitrate for symptomatic relief as necessary. Diagnostic cardiac catheterization reveals 99% stenosis of the distal left anterior descending (LAD) and left circumflex (LCX) arteries.

What is the best next appropriate step?

A. Deploy bare-metal stents to LAD and LCX lesions
B. Deploy drug-eluting stents to LAD and LCX lesions
C. Start intensive medical management with high-intensity statin
D. Consult cardiac surgery for CABG planning

Case #2

66 yo M with well-controlled T2D (HbA1c 6.9% on metformin and sitagliptin) p/w chest pain. EKG does not reveal ST elevations, but has Q-waves across precordial leads, suggestive of old infarcts. Cardiac enzymes (troponin-T, CK-MB) elevated. Patient receives aspirin, clopidogrel (300mg) and supplemental oxygen, with nitrate for symptomatic relief as necessary. Diagnostic cardiac catheterization reveals 99% stenosis of the distal left anterior descending (LAD) and left circumflex (LCX) arteries.

What is the best next appropriate step?

A. Deploy bare-metal stents to LAD and LCX lesions
B. Deploy drug-eluting stents to LAD and LCX lesions
C. Start intensive medical management with high-intensity statin
D. Consult cardiac surgery for CABG planning

Case #3

25 yo F with 10yr of well-controlled T1D (HbA1c 6.5% using continuous subcutaneous insulin infusion), presents for annual visit. Her family history is unremarkable, and both parents are alive and well in their 60's. Fasting labs demonstrate HDL 74mg/dL, LDL 115mg/dL and triglycerides of 62mg/dL. Urine microalbumin and serum creatinine are normal.

What is the most evidence-based recommendation for primary prevention of CAD?

A. Advise her to maintain HbA1c <7%
B. Advise her to maintain HbA1c <7% and start ACEI
C. Advise her to maintain HbA1c <7% and start simvastatin 10mg
D. Advise her to maintain HbA1c <7% and start atorvastatin 20mg
E. Advise her to maintain HbA1c <7% and start aspirin 81mg

Case #3

25 yo F with 10yr of well-controlled T1D (HbA1c 6.5% using continuous subcutaneous insulin infusion), presents for annual visit. Her family history is unremarkable, and both parents are alive and well in their 60's. Fasting labs demonstrate HDL 74mg/dL, LDL 115mg/dL and triglycerides of 62mg/dL. Urine microalbumin and serum creatinine are normal.

What is the most evidence-based recommendation for primary prevention of CAD?

A. Advise her to maintain HbA1c <7%
B. Advise her to maintain HbA1c <7% and start ACEI
C. Advise her to maintain HbA1c <7% and start simvastatin 10mg
D. Advise her to maintain HbA1c <7% and start atorvastatin 20mg
E. Advise her to maintain HbA1c <7% and start aspirin 81mg