

Glucose Targets From UKPDS, ADVANCE,
to ACCORD:
How Low Should We Go?

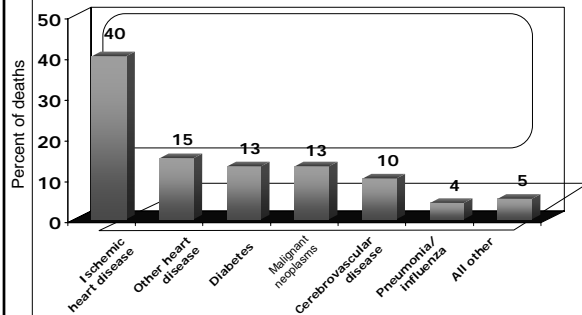
ENDO Update 2009
Kathleen Dungan, MD



ARS1

- 63 YOM with a 10-year H/o T2DM treated with metformin and sulfonylurea. He had a CABG 2 years ago. His BP is 132/80, HbA1C 7.1%, LDLc 99 mg/dl, HDLc 50mg/dl, TG 130 mg/dl.
 - Which of the following is most likely to reduce his *cardiovascular risk*?
- A) Byetta
B) Statin
C) ACE Inhibitor
D) B + C

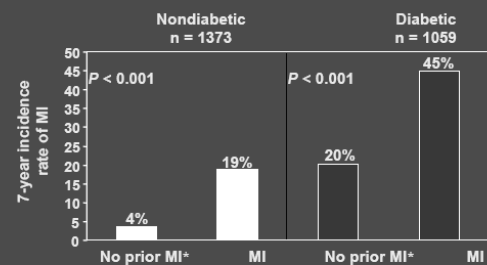
Causes of Death in People With Diabetes



Geiss LS, et al. In: Diabetes in America. National Institutes of Health;1995.

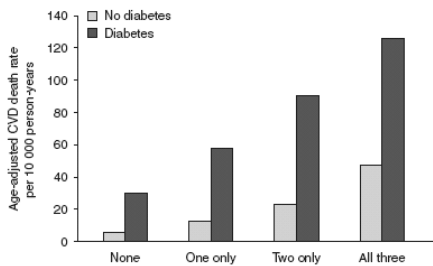
www.hypertensiononline.org

Type 2 diabetes and CHD: 7-year incidence of fatal/nonfatal MI (East West Study)



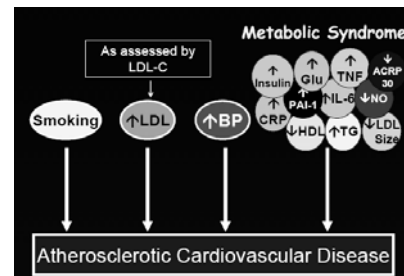
MI = myocardial infarction. * These patients had no prior MI at baseline. Haffner SM, et al. *N Engl J Med.* 1998;339:229-234.

Risk Factors for CVD Mortality in DM



Age-adjusted CVD death rates by number of CVD risk factors in men: HTN, ↑ Cholesterol & smoking
MRFIT trial; *Diabetes Care* 1993 Feb; 16 (2): 434-44

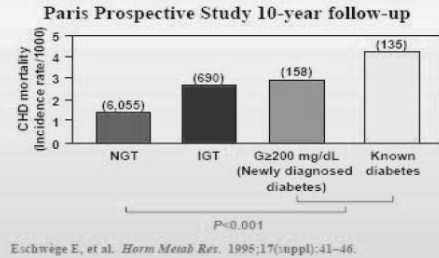
Classical and Nonclassical Risk Factors



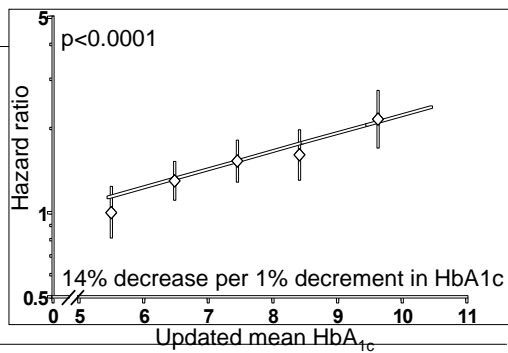
Where Does Glucose Fit into the Equation?



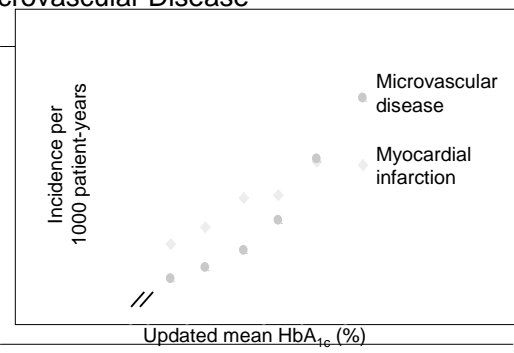
IGT Progressively increases risk of CHD Mortality



UKPDS: All Cause Mortality



UKPDS: Myocardial Infarction and Microvascular Disease



UKPDS: Order of Importance of Risk Factors for CAD (Baseline Epidemiologic Data)

Variable	Pvalue
LDLc	<0.0001
HDLc	0.0001
HbA1c	0.0022
SBP	0.0065
Smoking	0.056

N=2693 patients

Adapted from Turner et al. *BMJ* 1998;316:B23-B28

ACCORD STUDY —*nejm* 2008; 358: 2545-2559

- 10251 patients randomized to intensive or standard therapy
- Primary outcome: composite of nonfatal MI, nonfatal stroke or CVD death.

	Intensive	Standard	HR (95% CI)	P-value
Primary Outcome	352	371	0.90 (0.78-1.04)	0.16
Deaths	257	203	1.22 (1.01-1.46)	0.04
A1c	6.4	7.5		

ACCORD: Unexpected Adverse Events

nejm 2008; 358:2545-2559

□ Non-explanatory variables

- Drugs
- Drug combinations
- Weight Gain
- Hypoglycemia

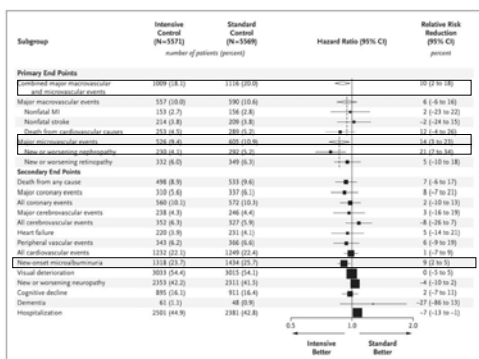


ADVANCE

NEJM 2008; 358:2560-2572

- 11,140 patients with T2DM
 - Randomized to intensive (use of gliclazide plus other drugs) vs. standard (without gliclazide) therapy
- Median FU of 5 yrs
- A1c 6.5 vs. 7.3%
- Primary outcome: major macrovascular and microvascular events, assessed jointly or separately

ADVANCE: Outcomes



NEJM 2008; 358:2560-2572

VETERAN AFFAIRS DIABETES TRIAL

- 1791 patients randomized to intensive or standard therapy
- A1c 6.9 vs. 8.5
- CV deaths
 - Underpowered
- No difference in macrovascular or microvascular outcomes

NEJM 2009; 360(2): 129

Comparison of Participant Characteristics

	ACCORD	ADVANCE	VADT
n	10,251	11,140	1,791
Mean age (years)	62	66	60
Duration of diabetes (yrs)	10	8	11.5
Sex (% male/female)	39/61	42/58	97/3
History of CVD (%)	35	32	40
BMI (kg/m ²)	32	28	31
☆Median baseline A1C (%)	8.1	7.2	9.4
☆On insulin at baseline (%)	35	1.5	52

Diabetes Care 32:187-192, 2009

Comparison of Protocol Characteristics

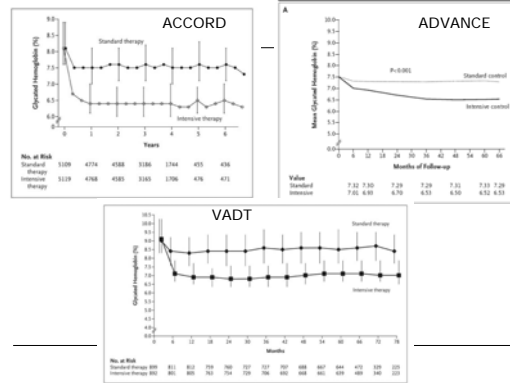
	ACCORD	ADVANCE	VADT
A1C goals (%)	<6.0 vs. 7.0-7.9	6.5 vs. "based on local guidelines"	<6.0 vs. separation of 1.5
Protocol for glycemic control	Multiple drugs in both arms	Multiple drugs added to gliclazide vs. multiple drugs with no gliclazide	Multiple drugs in both arms
Management of other risk factors	Embedded BP and lipid trials	Embedded BP trial	Protocol for intensive treatment in both arms

Diabetes Care 32:187-192, 2009

On-Study Characteristics

	ACCORD	ADVANCE	VADT
Median follow-up (yrs)	3.5	5	5.6
Achieved median A1C (%)	6.4 vs. 7.5	6.3 vs. 7.0	6.9 vs. 8.5
On insulin at study end (%)	77 vs. 55*	40 vs. 24	89 vs. 74
On TZD at study end (%)	91 vs. 58*	17 vs. 11	53 vs. 42
On statin at study end (%)	88 vs. 88*	46 vs. 48	85 vs. 83
On aspirin at study end (%)	76 vs. 76*	57 vs. 55	88 vs. 86
Mean BP study end (mmHg)			
Intensive arm	126/67	136/74	127/68
Standard arm	127/68	138/74	125/69
Weight changes (kg)			
Intensive arm	+3.5	-0.1	+7.8
Standard arm	+0.4	-1.0	+3.4
Severe hypoglycemia (%)			
Intensive arm	16.2	2.7	21.2
Standard arm	5.1	1.5	9.9

Comparison of A1C Reduction



Comparison of Outcomes

	ACCORD	ADVANCE	VADT
Definition of primary outcome	Nonfatal MI, nonfatal stroke, CVD death	Microvascular plus macrovascular (nonfatal MI, nonfatal stroke, CVD death) outcomes	Nonfatal MI, nonfatal stroke, CVD death, hospitalization for heart failure, revascularization
Primary outcome HR (95% CI)	0.90 (0.78-1.04)	0.9 (0.82-0.98); macrovascular 0.94 (0.84-1.06)	0.88 (0.74-1.05)
Mortality HR (95% CI)	1.22 (1.01-1.46)	0.93 (0.83-1.06)	1.07 (0.81-1.42)

Diabetes Care 32:187-192, 2009

Why no CVD Benefit?

- Patients likely had CVD at baseline
 - glycemic control may play a greater role before CVD is well developed
- All 3 studies had lower rates of CVD than originally predicted
 - Benefit may require longer/larger studies
- Compared intensive to modest (not poor) control (A1c >9% may still be harmful)

Diabetes Care 32:187-192, 2009

Reconciliation of Differences

- Effect of glycemic control is probably modest compared to other RFs
- Differences are due to treatment strategy and patient population, not the A1C per se
- Patients who can easily control with diet or pharmacotherapy do not need to raise their A1C

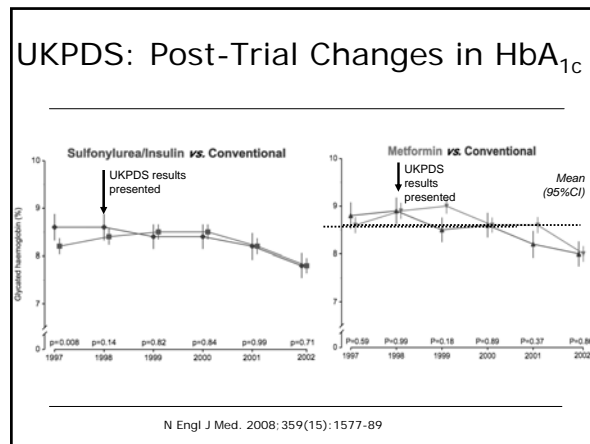
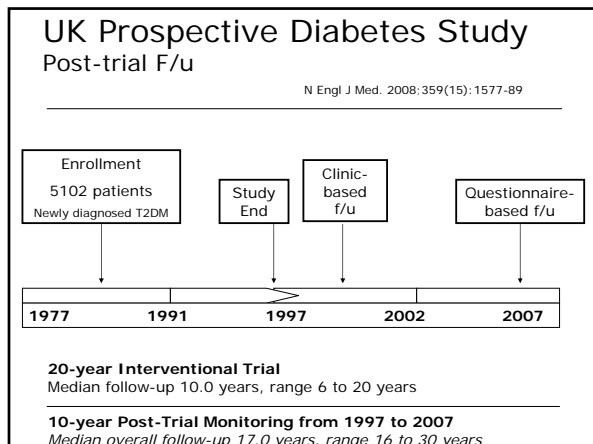


Diabetes Care 32:187-192, 2009

Does anyone attain CV risk reduction*? Subgroup analysis

	ACCORD	ADVANCE	VADT
Duration of DM			Benefit < 12 yr
Age	No	Benefit < 65 yr	
Baseline A1c	Benefit < 8.0%	Benefit < 7.2%	
BMI		Benefit < 28	
Microvascular disease at baseline		Benefit if no	
CVD at baseline	Benefit if no prior CV event	Benefit if no known CVD	Benefit low baseline coronary calcium score

*Primary outcome



Legacy Effect of Earlier Glucose Control

After median 8.5 years post-trial follow-up

Aggregate Endpoint	1997	2007
Any diabetes related endpoint	RRR: 12% P: 0.029	9% 0.040
Microvascular disease	RRR: 25% P: 0.0099	24% 0.001
Myocardial infarction	RRR: 16% P: 0.052	15% 0.014
All-cause mortality	RRR: 6% P: 0.44	13% 0.007

RRR = Relative Risk Reduction, P = Log Rank

N Engl J Med. 2008;359(15):1577-89

Post-Trial F/u of UKPDS and DCCT: Metabolic Memory

Despite early loss of glycemic differences, a continued reduction in microvascular risk and emergent risk reductions for myocardial infarction and all-cause mortality were observed during 10 years post-trial follow-up.

Steno-2 Supports Aggressive Multifactorial Intervention in Type 2 Diabetes

- Target-driven, long-term, intensified intervention aimed at multiple risk factors in patients with type 2 diabetes and microalbuminuria
 - Blood pressure < 130/80 mm Hg
 - A1C < 6.5%
 - Total cholesterol < 175 mg/dL
 - Triglycerides < 150 mg/dL
- Produced risk reductions in CV and microvascular outcomes
 - Primary outcome (combined CV disease) 53% decrease
 - Nephropathy 61% decrease
 - Retinopathy 58% decrease
 - Autonomic neuropathy 63% decrease

N Engl J Med. 2008;358(6):580-91.

ARS2

In which of the following might you expect a reduction in CVD following implementation of tight glycemic control?

- 58 YOM with 1 year h/o T2DM and h/o AMI. He has no known microvascular complications. He is currently taking metformin 1000 mg BID. His A1c is 7.4% on no therapy
- 45 YOF with 14 year h/o T2DM c/b retinopathy, microalbuminuria. On glimeperide, metformin, byetta. No known CVD. A1c 7.4%
- 65 YOM with 7 year h/o T2DM without known complications (micro or macro), A1c >9% on Lantus QDAY, humalog QAC
- 55 YOF with 3 year h/o T2DM without known complications (micro or macro), A1c 7% on Metformin monotherapy
- None of the above.

Take Home Message

Diabetes Care 32:187-192, 2009

- HbA1c <7% in **most patients with diabetes** (reduce microvascular disease)
- HbA1c closer to 6% in **select individuals**-the young, shorter duration of DM, no CVD, longer life expectancy
- Optimal prevention of CVD requires multiple risk factor management

HH-60G Pave
Hawk Helicopter -
Photo by Lance
Chisung
U.S. Air Force Photo



Great White
Breaching - Photo
by Charles Maxwell