

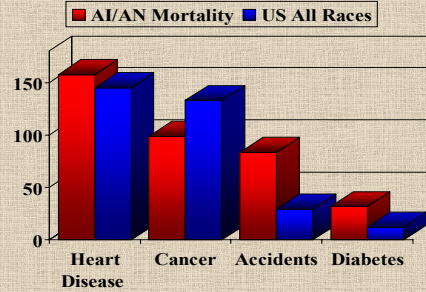
Reducing CVD Risk in Persons with Type 2 Diabetes

- CVD Risk Reduction in Patients with Diabetes
- Nuances in Native American Patients
- Special Considerations in Elderly

Stephen Rith-Najarian, MD

Diabetes Consultant, Indian Health Service

Mortality Rates American Indian and US All races



Trends in Indian Health: Age-adjusted data

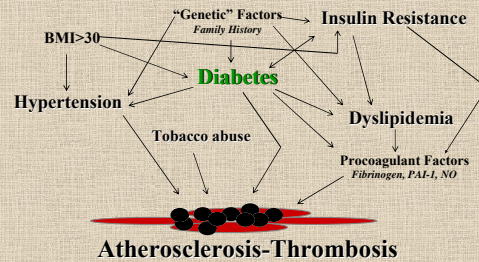
Contribution of Diabetes to CHD

Strong Heart Study

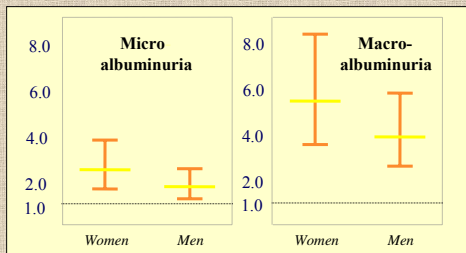
	Women	Men
Hazard Ratio	6.3	3.1
Prevalence	60%	50%
Attributable risk	76%	51%

Diabetes is the engine driving the increase in CVD

Vascular Disease and Diabetes A Web of Risk Factors



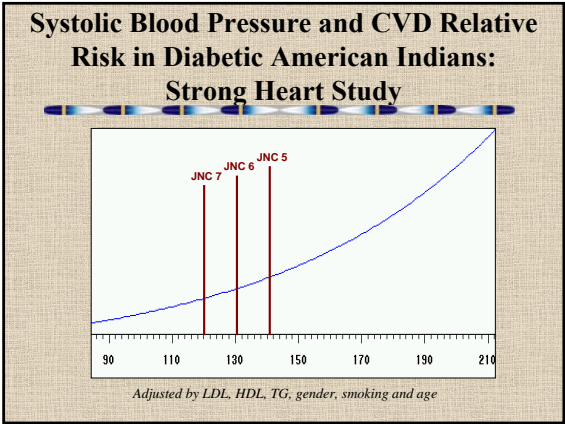
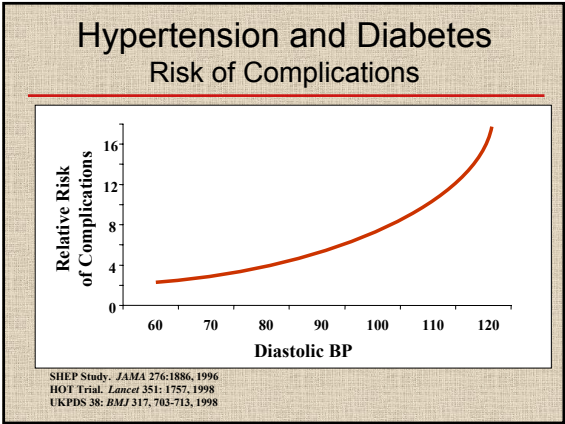
Hazard Ratios for Albuminuria as Predictor of CVD: Strong Heart Study



Lee Circulation 2006;113:2897-905

Reducing CVD Risk in Persons with Type 2 Diabetes ADA and IHS

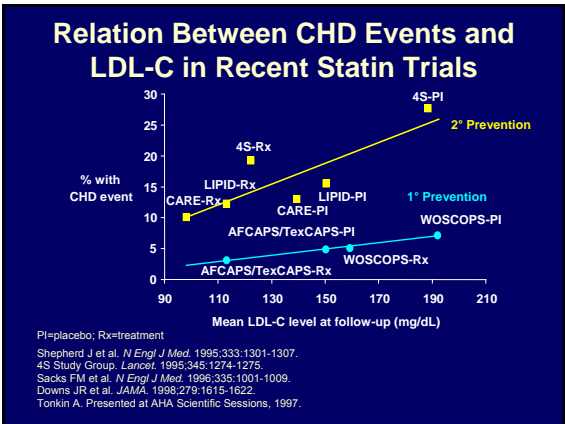
- BP Control
- Lipid Control
- Glycemic Control
- Smoking Cessation
- ASA

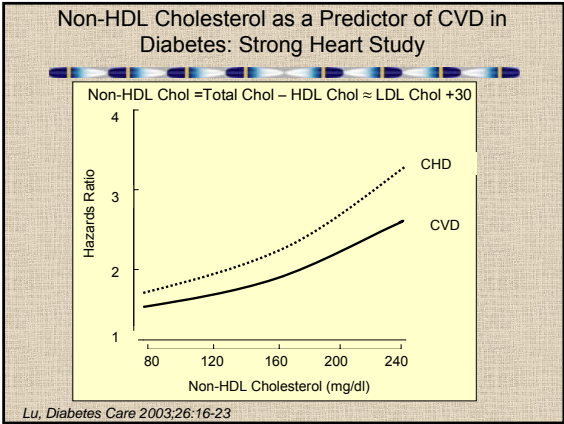


- ### ADA Recommendations for Hypertension Management in T2DM
- BP measured each visit w appropriate cuff
 - BP Targets < 130/80 (< 120/70 if CKD)
 - Titrate interventions Q 3 months
 - 130-140/80-90, start lifestyle
 - Then ACEI or ARBI
 - Most patients require ≥ 2 agents
 - Monitor K and Cr
 - Selected use of home monitoring
- Diabetes Care*, 2009; 32(SUPP 1):S13-61

- ### Advantage of ACEI and Diuretics in T2DM?
- ADVANCE trial had arm with fixed dose ACEI (perindopril) and diuretic (indapamide)
 - Associated with
 - Reduced combined microvascular and macrovascular outcomes
 - Reduced CVD and total mortality
 - may have been due to lower achieved BP in perindopril-indapamide arm
- MacMahon, Lancet* 370:829-840, 2007

- ### Accomplish Trial ACEI/CCB vs ACEI/Diuretic
- RTC benazepril-amlodipine vs benazepril-HCTZ
 - 60.4% with DM, 43% of which reached target (74% overall)
 - Target BP < 140/90, <130/80 if DM
 - Primary Outcome: CVD events and death
 - ACEI/CCB more favorable: ARR 2.2% and a RRR 19.6%
 - Findings remained significant when controlled for CHF events
 - Edema more common with Amlodipine, Dizziness with HCTZ
 - Findings in conflict with ALLHAT findings
- Jamerson, NEJM* 2008;359:2417-28





Reduction in 10-yr risk CVD in statin trials in patients with diabetes

Study (ref.)	CVD prevention	Statin dose and comparator	Risk reduction (%)
4S-DM (186)	2*	Simvastatin 20-40 mg vs. placebo	85.7 to 43.2
ASPEN 2* (191)	2*	Atorvastatin 10 mg vs. placebo	39.5 to 24.5
HPS-DM (187)	2*	Simvastatin 40 mg vs. placebo	43.8 to 36.3
CARE-DM (188)	2*	Pravastatin 40 mg vs. placebo	40.8 to 35.4
TNT-DM (189)	2*	Atorvastatin 80 mg vs. 10 mg	26.3 to 21.6
HPS-DM (187)	1*	Simvastatin 40 mg vs. placebo	17.5 to 11.5
CARDS (209)	1*	Atorvastatin 10 mg vs. placebo	11.5 to 7.5
ASPEN (191)	1*	Atorvastatin 10 mg vs. placebo	9.8 to 7.9
ASCOT-DM (190)	1*	Atorvastatin 10 mg vs. placebo	11.1 to 10.2

Diabetes Care, 2009; 32(SUPP 1):S13-61

- ### Reducing CVD Risk in T2DM Lipids
- Fasting lipid profile at least annually
 - Primary Target LDL <100 mg/dl (<70 high risk – CHD, CHD equivalent, or 10-yr CHD risk > 20%)
 - Secondary Targets HDL >50 mg/dl, TGs <150 mg/dl
 - Start Lifestyle: ↓ Chol, Trans fat, Sat fats; ↑ Exercise
 - Start Statin if CHD or CHD Risk factor
 - If unable to reach target on max Statin Rx,
 - 30-40% reduction in LDL from baseline is an alternative target
 - Consider combination therapy but outcomes and safety is limited
- DIABETES CARE, 2009; 32(SUPP 1):S13-61

ATP III/NCEP (Framingham) 10 Year CHD Risk calculator

<http://hp2010.nhlbi.nih.net/atpIII/calculator.asp?usertype=prof>

RR for Total Cholesterol in Framingham vs Strong Heart Study

	Men FHS	Men SHS	Women FHS	Women SHS
160-199	Ref	Ref	Ref	Ref
200-239	1.19	1.63	1.23	1.09
240-279	1.66	2.31	1.28	1.55
>= 280	1.93	2.87	1.71	2.57

SHS CVD Risk Calculator

<http://strongheart.uhsc.edu/chdcalculator/calculator.html>

Cardiovascular Disease and Diabetes, What is the role of glycemic control?

- Poor glycemic control associated with increased CVD risk (including AIs in SHS)
- No definitive studies showing that lowering BS *alone* decreases CVD morbidity and mortality
(*some evidence: metformin arm of UKPDS, EDIC study, and the Steno-2 trial*)
- Negative findings of ACCORD, ADVANCE, and VADT

International Expert Committee Report on role of A1C Assay in the Diagnosis of Diabetes

Pre-Diabetes

FBS 100-125 mg/dl
2-hr post 75gm CHO 140-199 mg/dl
HbA1c 6.0-6.4%

Diabetes

FBS >125 mg/dl*
2-hr post 75gm CHO ≥200 mg/dl*
RBS CHO ≥200 mg/dl plus symptoms
HbA1c ≥6.5%*

* Confirm with a repeat same test on separate day

International Expert Committee, Diabetes Care 2009;32:1-7

UKPDS Cardiovascular Risk Reduction

- 16% ↓ CV complications (fatal or nonfatal MI and sudden death) in intensive glycemic control arm ($P = 0.052$), no benefit on stroke
- 18% ↓ CVD events per % A1C drop, no glycemic threshold ($p < 0.05$)

UKPDS Group. *Lancet* 352:837-853, 1998

UKPDS Memory Effect of Glycemic Control: 10-yr follow up analysis intensive vs standard treatment group

Treatment	MI	All Cause Mortality	P value
metformin	↓33%	↓27%	<0.05
SU or Insulin	↓15%	↓13%	<.05

Holman, *N Engl J Med* 59:1577-1589, 2008

Summary of ACCORD, ADVANCE and VADT

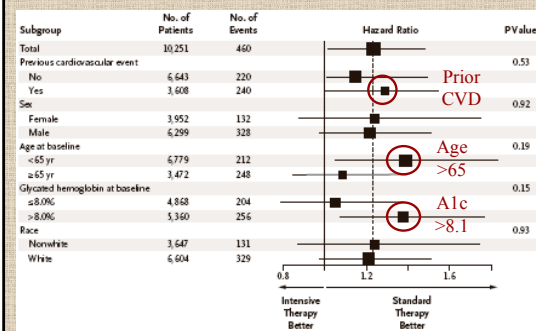
	ACCORD*	ADVANCE	VADT
Approach	Aggressive	Stepped	Stepped
A1C (%) (Intensive vs. Std)	6.4 vs. 7.5 †	6.4 vs. 7.0 †	6.9 vs. 8.4 †
CV Death (%) (Intensive vs. Std)	2.6 vs. 1.8 † (1.35 Hazard Ratio)	4.5 vs. 5.2	2.1 vs. 1.7
Hypoglycemia (% per year)	4.6 vs 1.5	1.8 vs 0.6	2.3 vs 1.1
Microvascular	-	nephropathy ↓ 21% retinopathy ↓ 5% NS	-
Take home	↑↑ hypoglycemia ↑ risk death in intensive arm	Glucose no impact on CV events, but ↓ Microvascular risk	Glucose control has no impact on CV events

*ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial halted intensive glucose group (2/6/08)

† significant difference between intensive and standard group

ACCORD Study Group. *NEJM* 2008, 359:2545-2556; ADVANCE Collaborative Group. *NEJM* 2008, 358:2560-2572; VADT Study Results ADA Scientific Session San Francisco, 2008. In Press. *Diabetes Obesity and Metabolism*, 2008

Hazard Ratios for the Primary Outcome and Death from Any Cause in Pre-specified Subgroups: ACCORD Study



N Engl J Med 358:24, 2008

ACCORD, ADVANCE, and VADT Lessons Learned for CVD

- Intensive glucose control does not reduce CVD mortality in T2DM, and **may** increase risk, especially in patients elderly with pre-existing CHD. *This may be related to the aggressive rate to reach targets*
- Aggressive A1c targets (<6.5%) were associated with a 3-fold increased risk hypoglycemia
- No excess CVD Mortality was seen with Rosiglitazone

ACCORD, ADVANCE, and VADT Lessons Learned- Continued

- Intensive control associated with reduced risk for nephropathy in ADVANCE.
- To reach and maintain A1c targets of <6.5 required frequent adjustments of multiple anti-diabetic medications
- Aggressive Targets (<6.5) are probably reasonable for healthy patients to reduce risk micro-vascular complications

ADA Consensus Statement A1C Goals

- 6-7%, if this can be achieved without significant hypoglycemia, especially in patients with short duration of DM, long life expectancy, and no significant CVD.
- less stringent A1C goals ~7% patients with a hx of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding DM in whom the general goal is difficult to attain despite DSME, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.

DIABETES CARE, 2009; 32(SUPP 1):S13-61

ADA Consensus Statement on Medical Management of Hyperglycemia in T2DM

- ✓ Achieve and Maintain near normoglycemia, A1c <7.0
- ✓ Initiate Therapy with Lifestyle and Metformin
- ✓ Rapid addition of medications, and transition to new regimens when targets are not achieved
- ✓ Early addition of insulin therapy in patients who do not met target goals

Nathan, Diabetes Care 2008;31:1-11

Depression and CVD Risk in Diabetes

- Depression 2x more common in DM and correlates with A1c. (among *American Indians, risk severe depression increases 22% per 1% A1c*)
- Depression and Diabetes associated with increased CVD Risk factors and CVD events
- Among elderly DM and Depression associated with increased CVD events and mortality
- Depression Rx (SSRI) in depressed patients with CVD associated with reduced re-infarction and mortality rate, although data in patients with diabetes is lacking

Nichols Diabetes Care 2003; 26:744-749
Calloun, J Diab Comp 2009; in press
Kinton, Gen Intern Med 2004; 19:1192-9
Diabetes Care 2003; 26:2822-28
Gallo, Am J Geriatric Psych, 2005; 13:748-755
Psychosom Med, 2004; 66:466-74

Reducing CVD Risk in Persons with Type 2 Diabetes

- CVD Risk Reduction in Patients with Diabetes
- Nuances in Native American Patients
- Special Considerations for CVD Risk Reduction in Elderly

Special Considerations for CVD Risk Reduction in Elderly

- Different Epidemiology
 - Increased risk CVD
 - Competing Mortality/Shorter Longevity
 - Greater proportion of women
- Limited Evidence, especially in > 80yrs
- Increased co-morbidity
- Differences in Drug handling: volume, hepatic and renal
- Poly-pharmacy and drug interactions
- Less tolerance for adverse effects
- Dementia
- Social

Aging and the prevalence of CVD factors in older American Indians: the Strong Heart Study

- Hypertension prevalence increased
- "low" HDL-C prevalence increase
- Diabetes prevalence increased
- Smoking prevalence decreased
- Overall, unfavorable changes in CVD risk factors

Rhoades, J Am Geriatr Soc, 2007;55:87-94

Evidence for Lifestyle changes for secondary prevention of CHD in Elderly

	Age (years)		
	<65	65–79	80+
Stop smoking	++	++	+
Lose weight			
BMI 25–29	++	+	–
BMI >30	++	++	++
Exercise	++	++	+
Dietary changes			
Less saturated fat	++	++	+
Less salt	++	++	+
More fish	++	+	?
ETOH 1–3 drinks/d	++	+	?

Bulpit, Heart 2005;91:396–400

Evidence for Medications for secondary prevention of CHD in Elderly

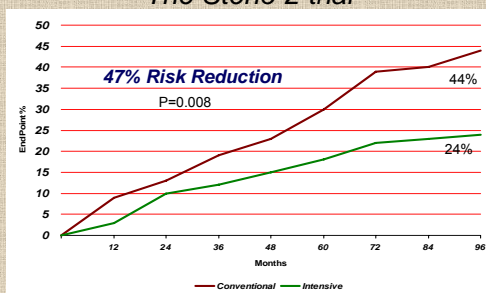
	Age (years)		
	<65	65–79	80+
Aspirin	++	++	+
β Blockers	++	+	?
ACE inhibitors	++	++	+
Other BP Rx	++	++	?
Statins	++	++	?
Glycemic control	+/-	+/-	?

Bulpit, Heart 2005;91:396–400
Affilio J ACC2008;51:37-45

Summary: CVD in Diabetes Therapies that Make a Difference

Treatment	CVD Benefit
Hyperlipidemia	↓ CV risk 25-55%
Hypertension	↓ CV events 15-40%
Aspirin therapy	↓ CV events by 20-61%
Metformin	↓ MI by 33%
Glucose lowering (legacy effect)	↓ 15-57%

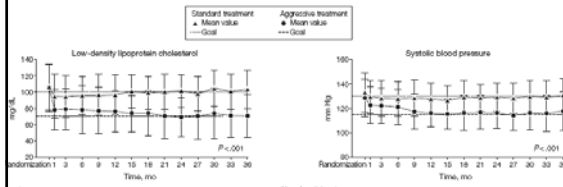
Multifactorial Intervention in DM *The Steno-2 trial*



Composite end-point: CV death, MI, CABG, PCI, stroke, LEA from ischemia, surgery for PVD
Gaede, NEJM 2003;348:383-393

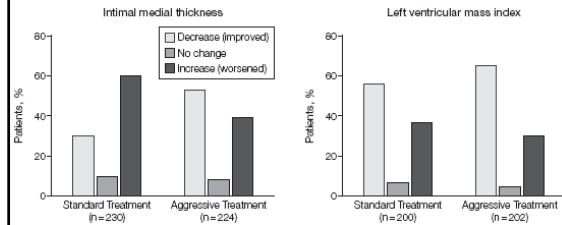
LDL Cholesterol and Systolic Blood Pressure Levels for SANDS Participants

Stop Atherosclerosis in Native Diabetics Study



Howard et al. JAMA. 2008;299:1678-1689

Categorical Changes in Left Ventricular Mass Index and Intimal Medial Thickness by Treatment Group: SANDS Trial



Howard et al. JAMA. 2008;299:1678-1689

Type 2 Diabetes - Standards of Care

