

# **The Strong Heart Study and SANDS: From Observation to Intervention**

Wm. James Howard, MD, MACP  
Washington Hospital Center  
Washington, DC

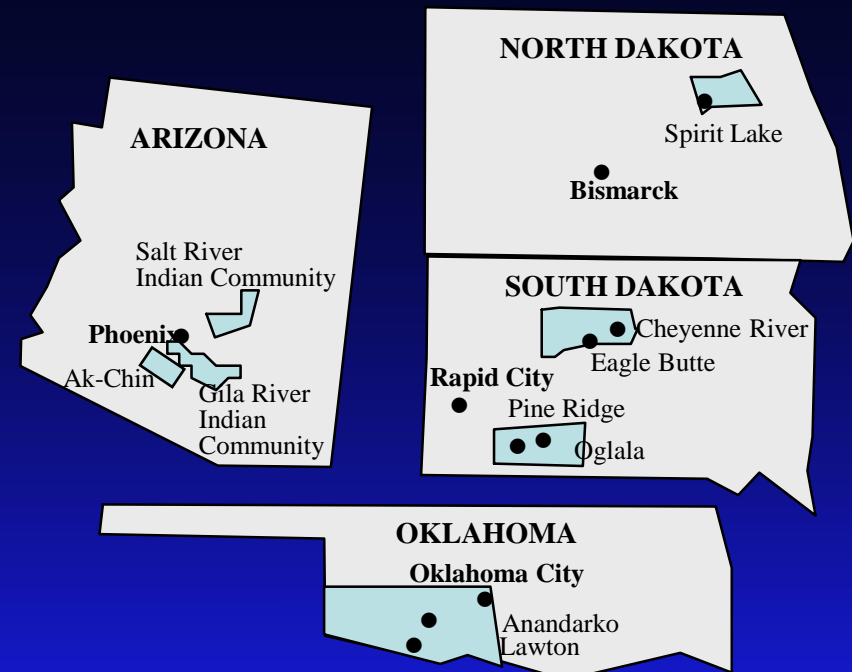
# Strong Heart Study Population 1988--2008

4549 American Indians ages 45-74  
years

**Arizona:** Pima/Maricopa/Papago in the Gila River, Salt River, and Ak-Chin Indian communities

**Oklahoma:** Apache, Caddo, Comanche, Delaware, Fort Sill Apache, Kiowa, and Wichita

**South/North Dakota:** Oglala Sioux and Cheyenne River Sioux (SD) and the Spirit Lake Tribe in the Fort Totten area (ND)



# Strong Heart Study Objectives

- Measure rates of CVD
- Measure levels of risk factors
- Determine the effect of diabetes on CVD
- Follow up to evaluate determinants of CVD
- Follow up to evaluate changes in risk factors



Rapid City

# What we learned from SHS 1988–2008

- There is an ‘epidemic’ of CVD in individuals with diabetes
- The prevalence of diabetes is significantly increased in this population
- LDL cholesterol is a strong predictor even though levels are generally low in this population. HR increases linearly from LDL-C of 70 mg/dl
- Blood pressure is a strong predictor, and it leads to nephropathy which also causes CVD



# What we learned from SHS 1988–2008

- CIMT and plaque predicts CVD events
- The rate of CIMT increase in individuals with diabetes is well characterized for the SHS cohort
- CVD event rates for those with diabetes in SHS have been determined



# SANDS

## Stop Atherosclerosis in Native Diabetics Study

JAMA 2008;299:1678-89



# SANDS HYPOTHESIS

Lowering LDL cholesterol and Blood Pressure to lower targets than are currently recommended will retard CVD and reduce residual risk

	<u>Control</u>	<u>Intervention</u>
LDL-C (mg/dl)	100	70
Non-HDL-C (mg/dl)	130	100
SBP(mm/Hg)	130/80	115/75

# Four Clinical Centers

- Phoenix area (Marie Russell, MD)
  - Primarily O'odham
- SW Oklahoma (Brice Poolaw, MD)
  - Apache, Caddo, Comanche, Delaware, Fort Sill Apache, Kiowa, and Wichita
- Rapid City, SD (Jeffrey Henderson, MD)
  - Primarily Oglala Sioux and Cheyenne River Sioux
- Chinle, AZ (James Galloway, MD)
  - Navajo





# Study Organization

- MD Principal Investigators
- **Mid-level practitioners**
- Community members as staff
- Lipid (WJ Howard) and BP (M Weir) Consultants











# Inclusion Criteria

- Diabetic Men and Women >40 yrs with no history of CVD event
- LDL > 100 mg/dl
- SBP > 130 mm Hg
- Able to measure carotid IMT



# Exclusion Criteria

- CHF Class III-IV
- H/O drug induced angioedema
- Creatinine  $>2.0$  women,  $>2.4$  men
- Malignancy within past 5 yrs
- SBP $>180$
- Transaminases 2X ULN
- TG $>400$
- Pregnancy or lactation
- Orthostatic hypotension
- Not likely to participate for 3 years of follow-up



# Algorithm for Lipid Management

## LDL Goal:

- Statin
- Ezetimibe, colesvelam

## Non-HDL Goal:

- Fenofibrate
- Omega-3 fatty acids
- Niacin



# Definition of Endpoints

- Primary Endpoint
  - Change in Common Carotid Artery IMT
- Secondary Endpoints
  - Changes in arterial cross-sectional area and plaque number
  - Changes in LV function and geometry
  - Clinical events





**499 men and women  
with diabetes**  
➤ 40 yrs old  
➤ SBP > 130, LDL > 100

**Usual  
Targets  
N=247**

**Lower  
Targets  
N=252**

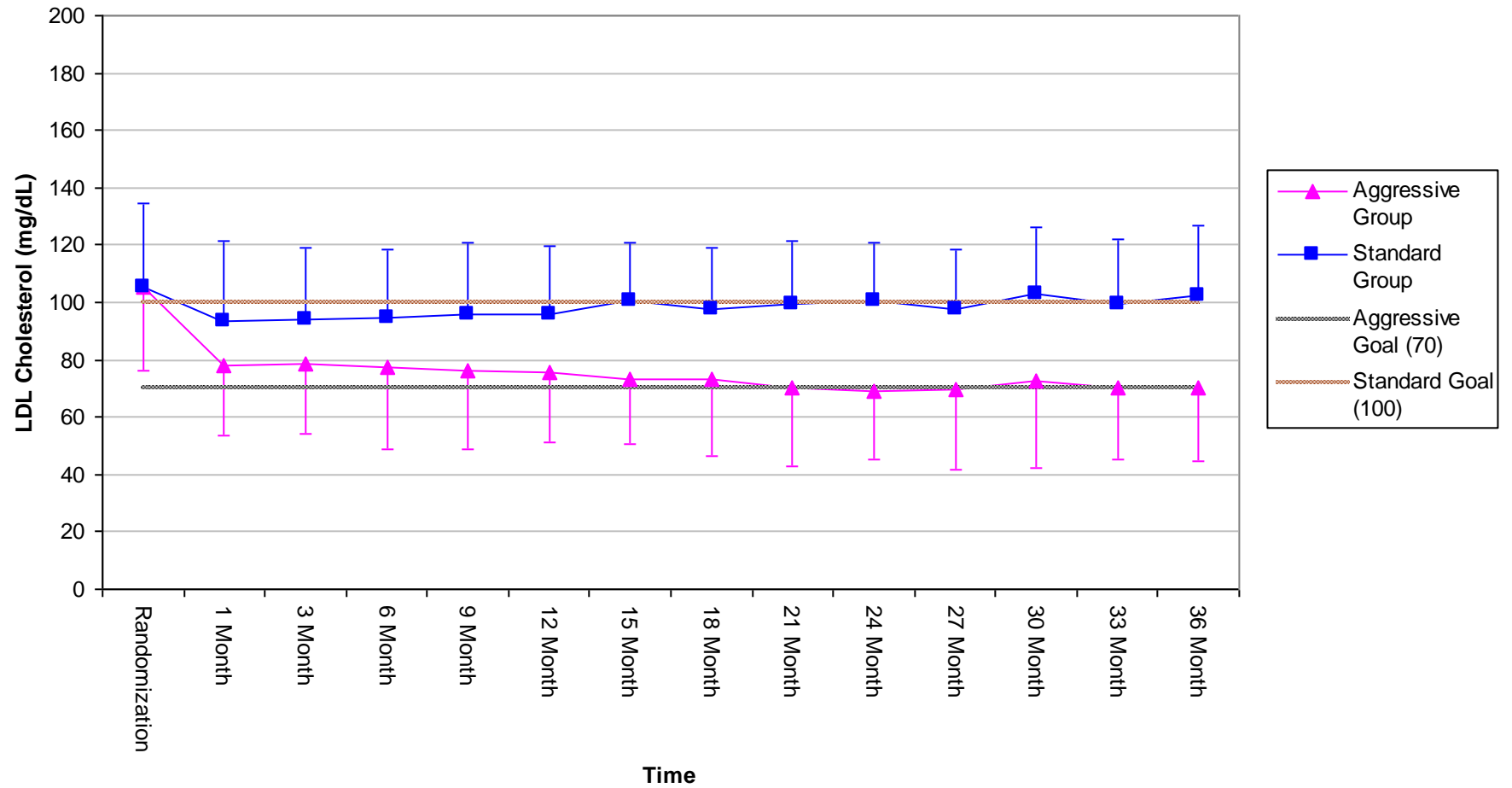
**Measure CVD using CIMT and cardiac  
ECHO at baseline, 18, and 36 mos. + CVD  
Surveillance—100%; > 92% SBP and LDL  
36 month CIMT 92% and 89%  
Missing CIMT imputed  
Deceased: 5 Std. and 3 Aggressive**

# Baseline Characteristics

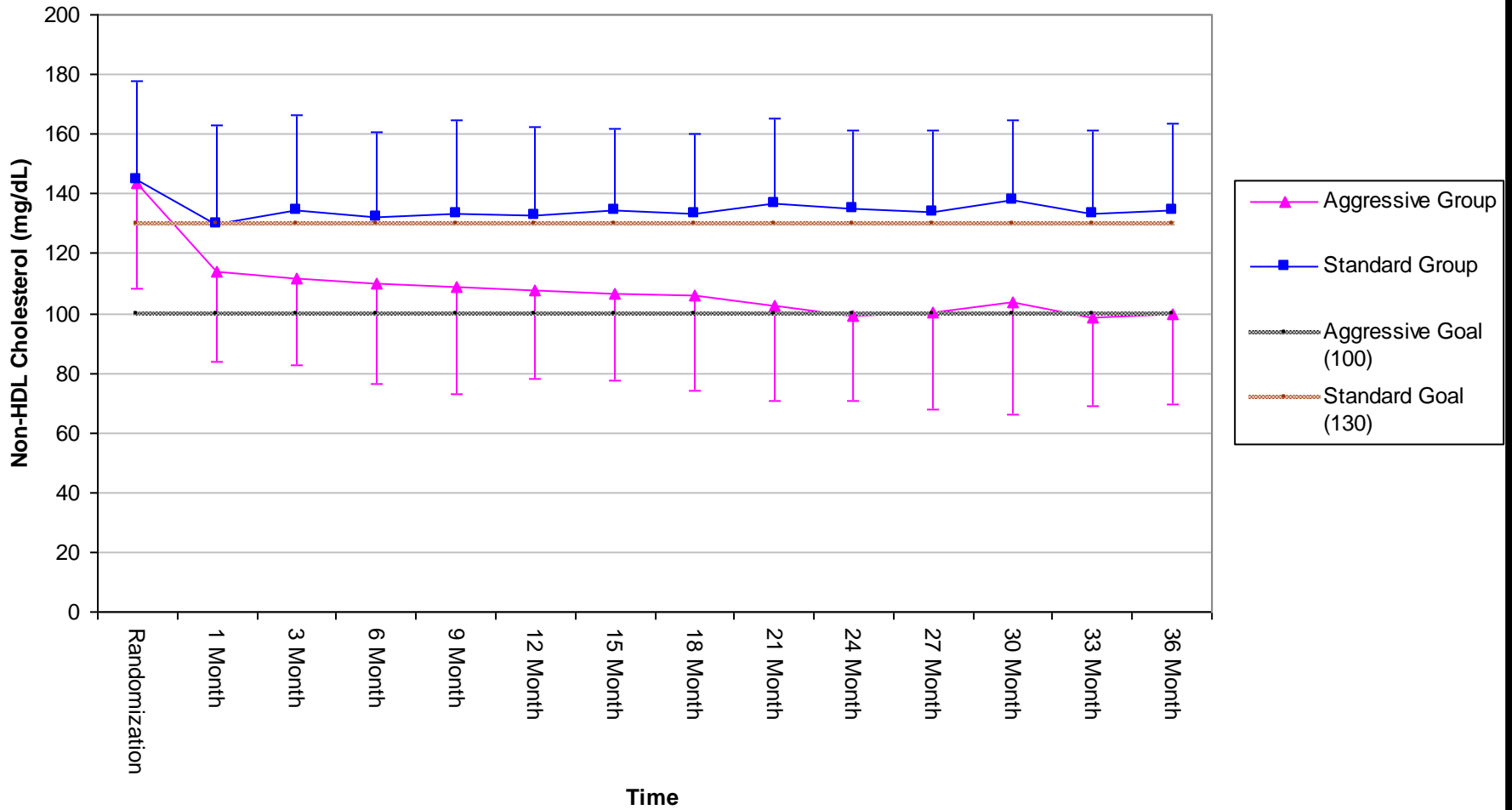
	Aggressive (252)	Standard (247)	P value
Women (%)	66	65	.73
Age (yrs)	55.3	56.9	.05
BMI (kg/m <sup>2</sup> )	34	33.7	.20
SBP	128	133	.20
LDL (mg/dl)	104	104	.99
HDL (mg//dl)	46	46	.99
TG (mg/dl)	158	168	.63
Non-HDL	138	140	.71
Smokers (%)	22	20	.58
HbA1c (%)	8.2	7.9	.13



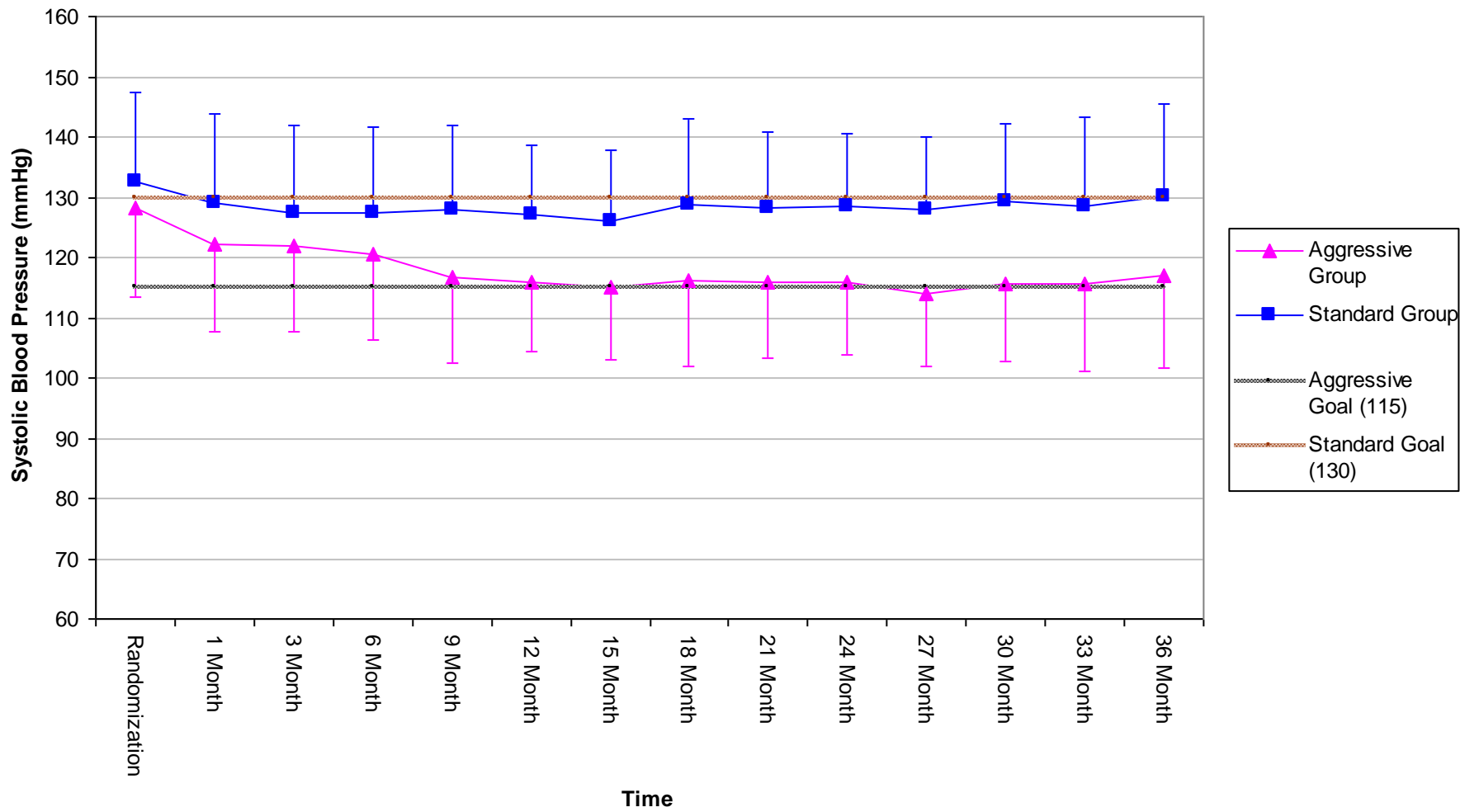
## LDL Cholesterol by Treatment Group



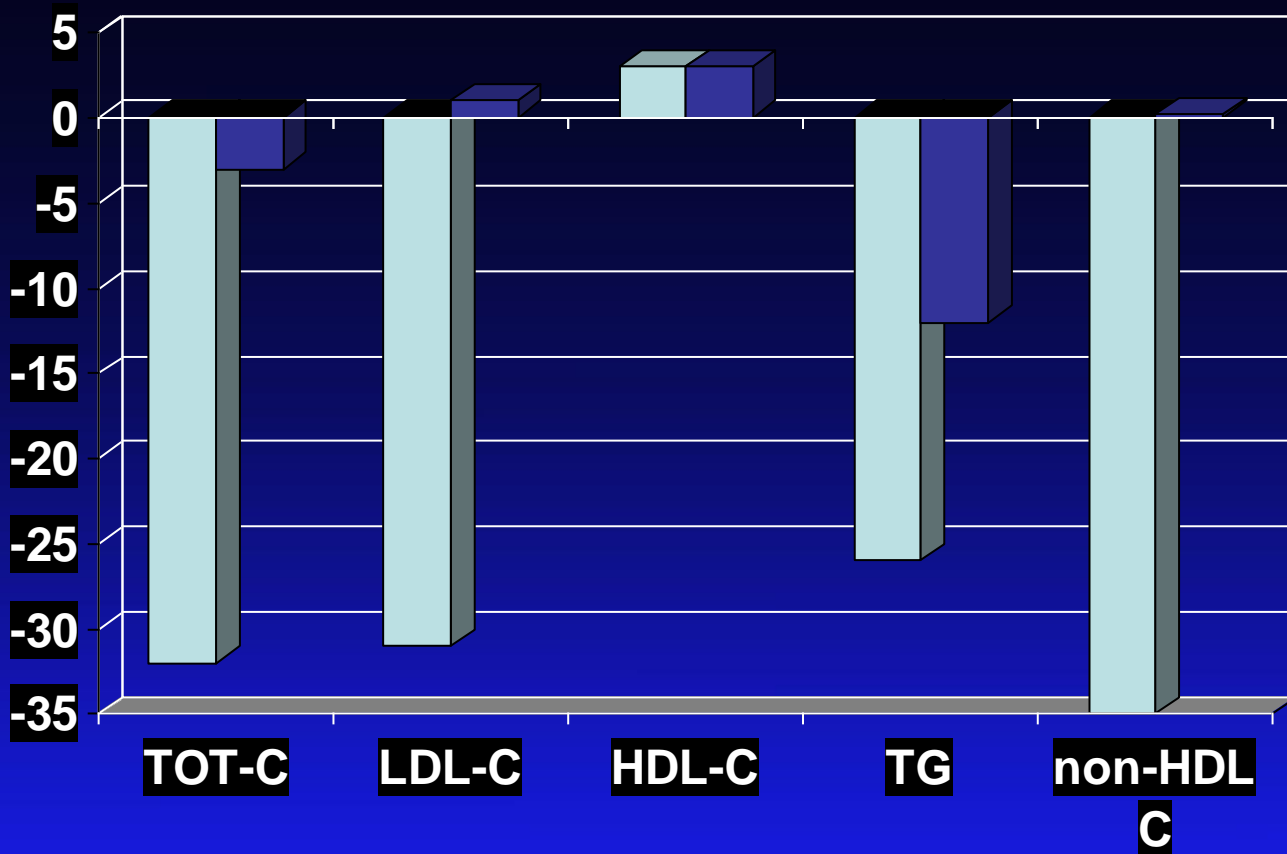
# Non-HDL Cholesterol by treatment Group



## Systolic Blood Pressure by Treatment Group



# Mean Changes in Lipids



mg/dL

Aggressive  
Standard

# Average Number of Drugs Required in Each Group

Lipid Lowering

Hypotensive



Standard

1.2

1.6



Aggressive

1.5

2.4



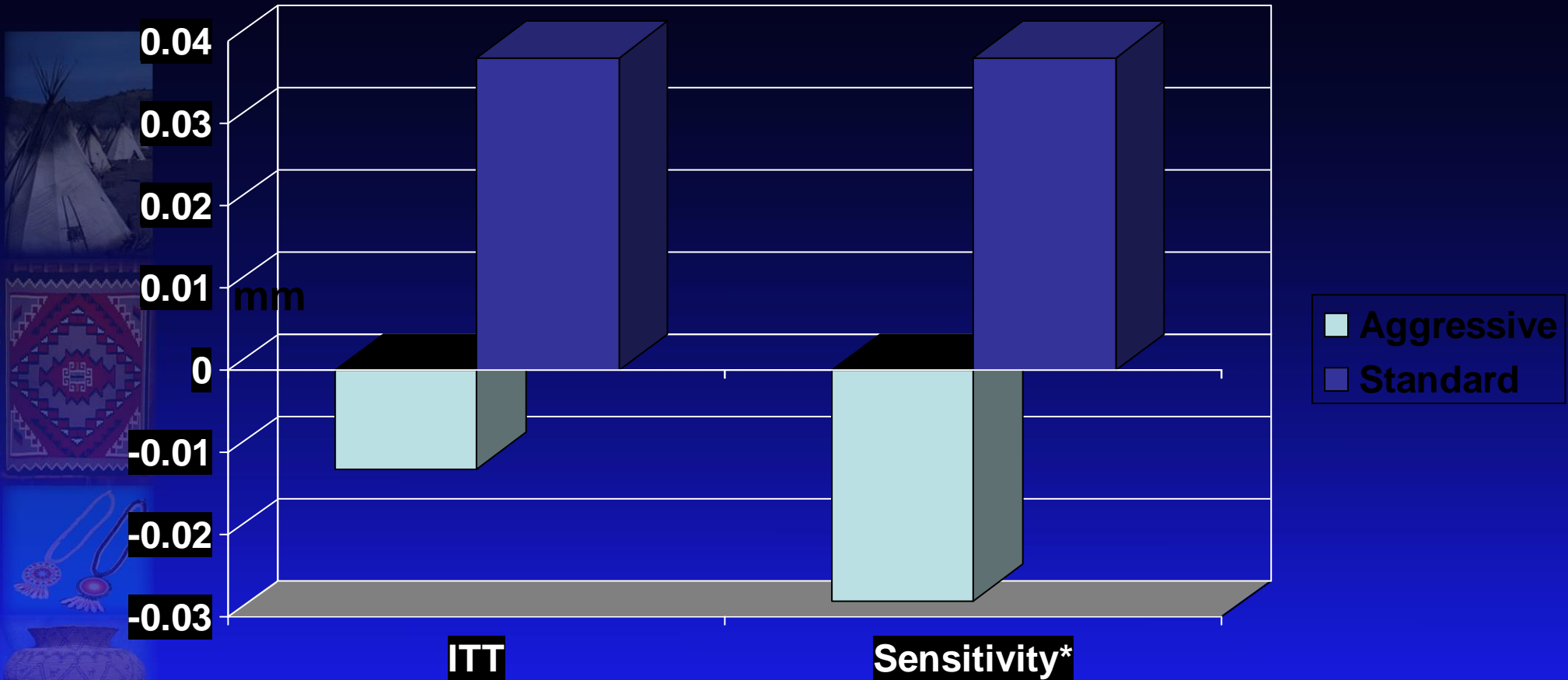
# Lipid Lowering Drugs by Class

	# of participants	p value
<b>Statins</b>		
Conventional Group	166 (68%)	<0.001
Aggressive Group	230 (91%)	
<b>Ezetimibe</b>		
Conventional Group	25 (10%)	<0.001
Aggressive Group	78 (31.%)	
<b>Fibric Acid Derivatives</b>		
Conventional Group	19 (8%)	<0.001
Aggressive Group	44 (18%)	
<b>Omega-3 Fatty Acid</b>		
Conventional Group	24 (10%)	0.097
Aggressive Group	35 (14%)	
<b>Niacin/Nicotinic Acid</b>		
Conventional Group	4 (2%)	NS
Aggressive Group	7 (3%)	



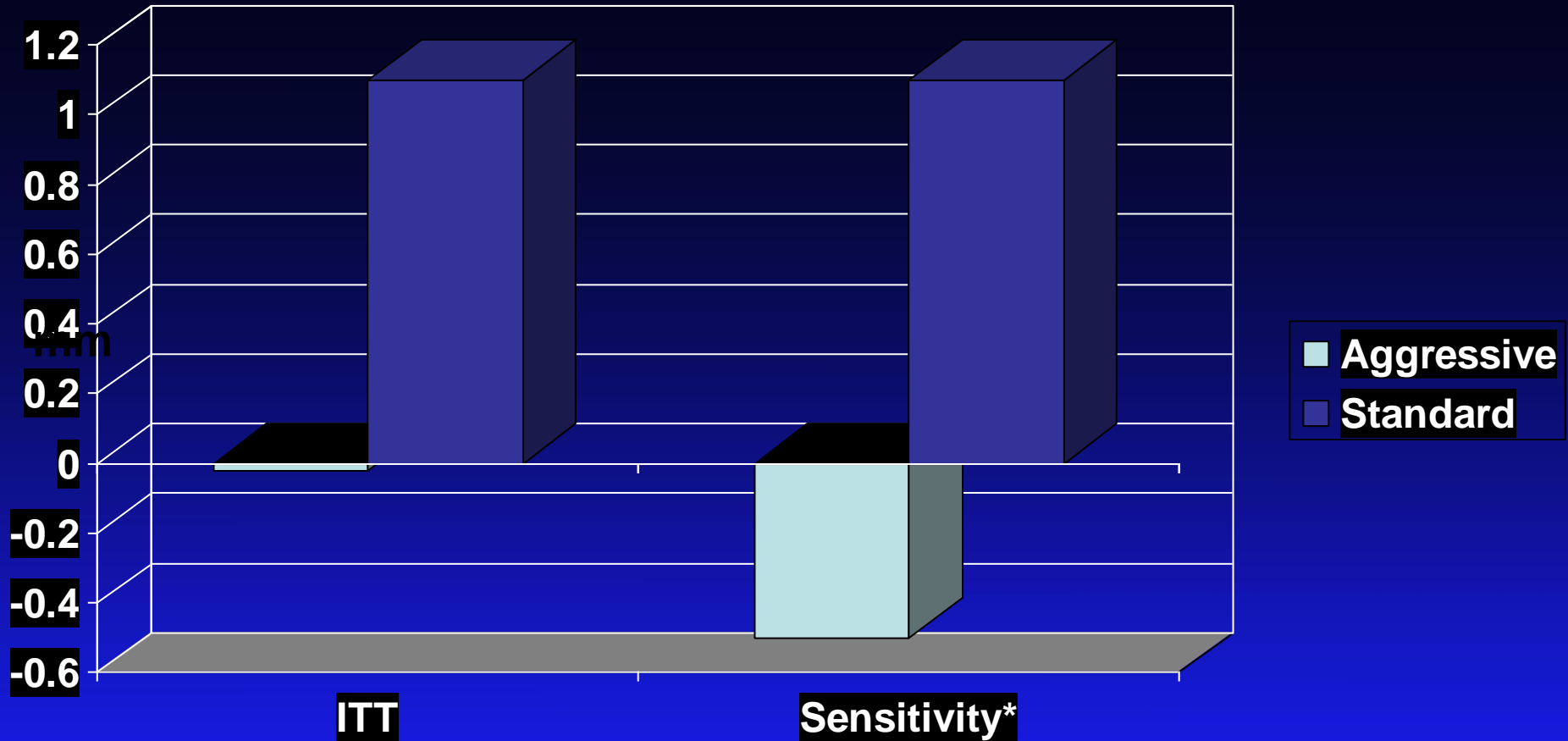


# Changes in IMT



\* Ppts (N=129) who maintained LDL-C<73 ; Group differences for each p<.001

# Changes Arterial Cross Sectional Area

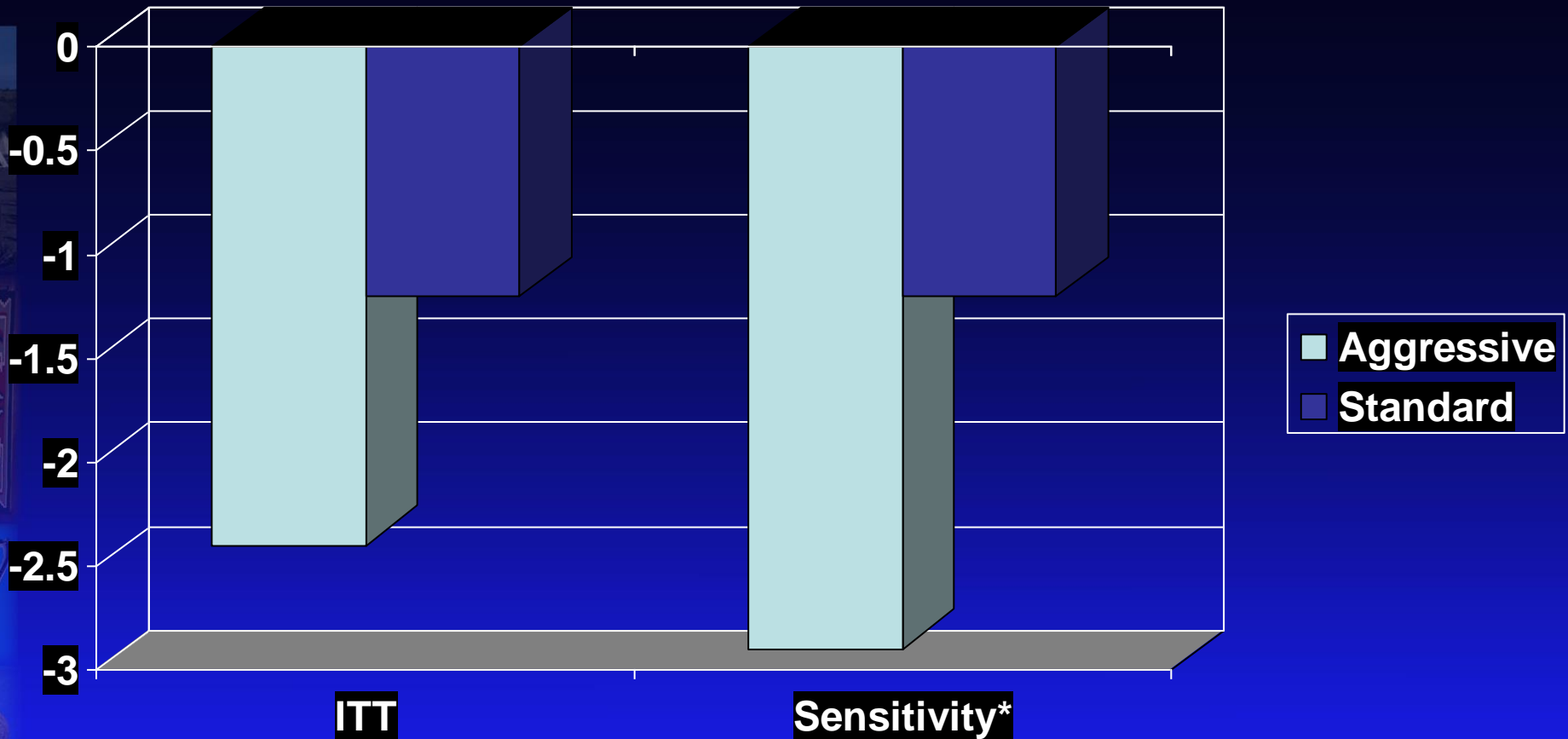


\* Ppts (N=129) who maintained LDL-C<73 ; Group differences for each measure p<.001

# Carotid IMT and Cross-Sectional Area

	Mean			
	Aggressive	Standard	Difference	P value
IMT Base (mm)	.808	.797		
18mo	.802	.804		
36mo	.796	.837		
Exp. 36 mo		+.08		
$\Delta$ 0-36mo	-.012	+.038	.050	<.001
Area Base (mm <sup>2</sup> )	17.4	17.3		
18mo	17.2	17.5		
36mo	17.5	18.4		
$\Delta$ 0-36mo	-.02	+.105	1.07	<.001

# Changes in LVmass index



Ppts (N=117) who maintained SBP<105 mm; Group differences both  $p < .02$

# Secondary Analyses

- No significant interactions were observed between treatment and age, BMI, sex, baseline LDL or BP, HbA1c, smoking, CRP, eGFR, or hypoglycemic meds.
- When these variables were included in the models that analyzed the end points, they did not significantly influence the results.
- In an ordered logit model, LDL-C change predicted probability of IMT decrease and SPB change predicted probability of LVM decrease

# Drug Related SAEs: Blood Pressure Drugs

	Conventional (N = 247)	Aggressive (N = 252)
# of SAEs Related to Medication	1	4

## Most Common SAEs

Syncope/Hypotension	1	2
Hyperkalemia*	0	2

## Most Common Drugs causing SAEs

    vasoactive plus diuretic meds  
    lisinopril

\* both participants had CRI

# CVD Events

CVD Events	Aggressive (n=252)	Standard (n=247)	P
Primary	11	8	.51
Secondary	1	3	.31
Total	12	11	.87
Rate/100 yrs (Expected 2.2 to 3.6)	1.6	1.5	.87
Non-CVD Deaths	2	4	.40

# Summary

- Aggressive and standard targets can be reached and maintained using stepped treatment algorithms and point of care LDL measures
- Rates of adverse events were similar to those seen in previous trials of the agents used, but there were significantly more AE's and SAE's attributable to blood pressure drugs in the aggressive treatment group
- Average number of drugs was 1.5 lipid and 2.3 blood pressure to achieve the aggressive targets and 1.2 and 1.6 to achieve standard targets





# Summary

- CIMT regressed in the aggressive group and progression was decreased in the standard group. There was no change in plaque score
- Carotid arterial cross sectional area also regressed in the aggressive group and progression decreased in the standard group
- There was a greater decrease in the LV Mass index in the aggressive group compared to the standard group
- The rate for CVD events was lower than expected in both groups and did not differ.



# Conclusions

- Reducing LDL-C and SBP to lower targets resulted in regression of carotid atherosclerosis and decrease in LV mass in individuals with type 2 diabetes
- Clinical event rate was low in both groups and did not differ
- Longer term follow-up will be necessary to determine whether the aggressive lipid and BP lowering results in favorable risks/benefits
- More emphasis should be placed on reaching conventional targets for both LDL-C and SBP in diabetic patients
- More trials are needed that evaluate treating to targets for lipids and BP rather than specific drug treatment regimens

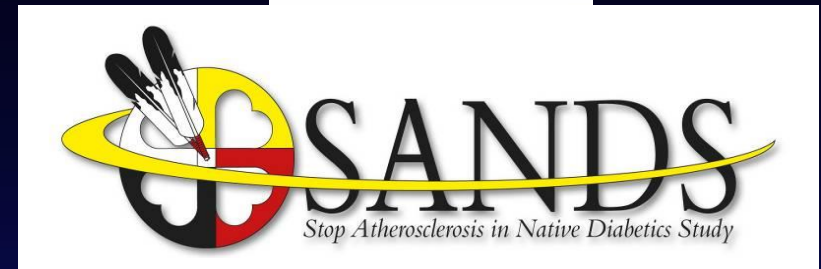


# Investigators

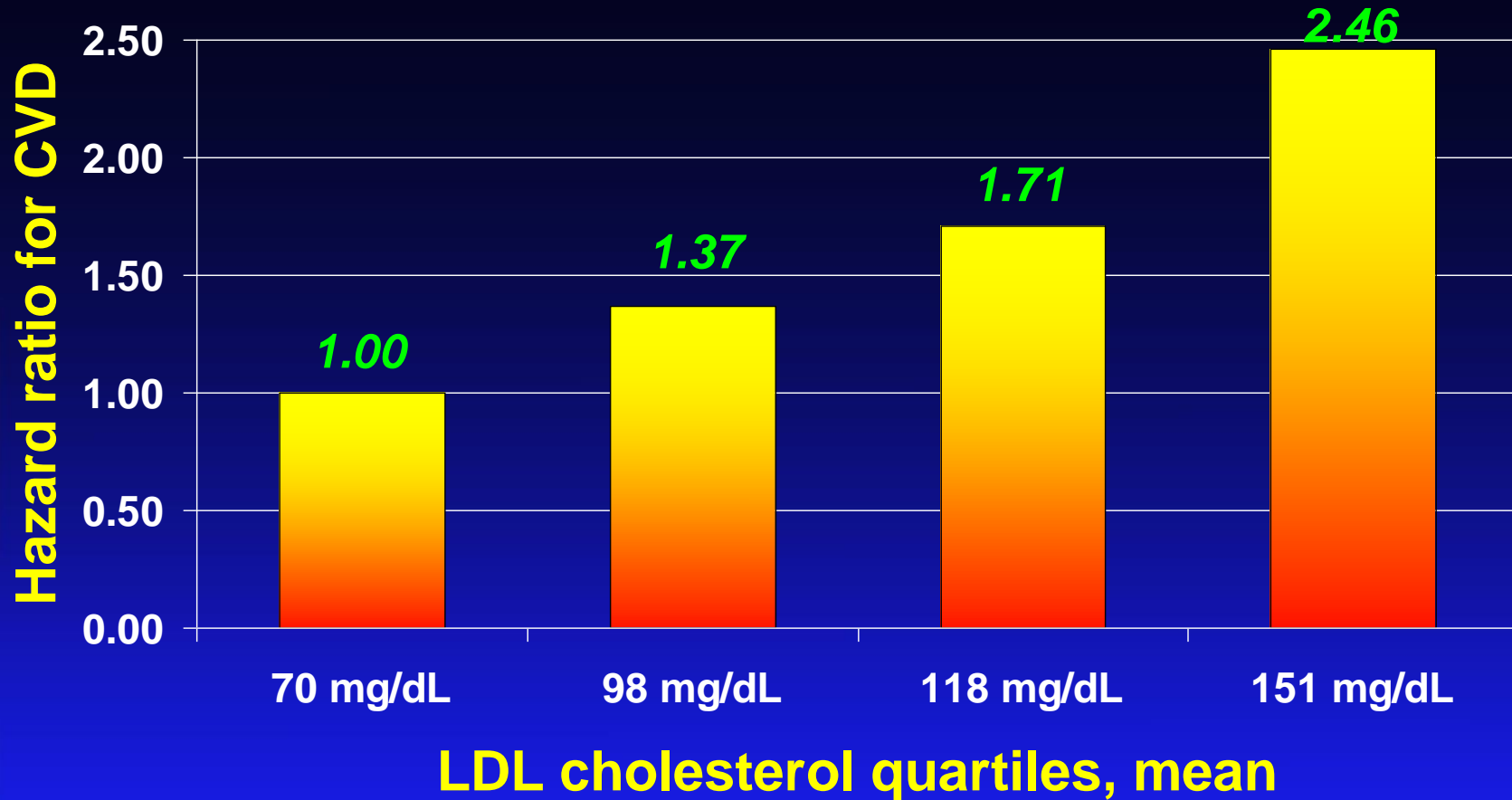
Barbara V. Howard, PhD  
Mary. J Roman, MD  
Richard B Devereux, MD  
Jerome L Fleg, MD  
James M. Galloway, MD  
Jeffrey A. Henderson MD, MPH  
Wm. James Howard, MD  
Elisa T Lee, PhD  
Mihriye Mete, PhD  
Bryce Poolaw, MD  
Robert E Ratner, MD  
Marie Russell, MD  
Angela Silverman MSN, CANP  
John Sorkin, MD  
Mario Stylianou, PhD  
Jason G. Umans MD, PhD  
Wenyu Wand, PhD  
Matthew R. Weir, MD  
Neil J Weissman, MD  
Charlton Wilson, MD  
Fawn Yeh, PhD  
Jianhui Zhu, MD

*Acknowledgements to the NHLBI—grant supp.*

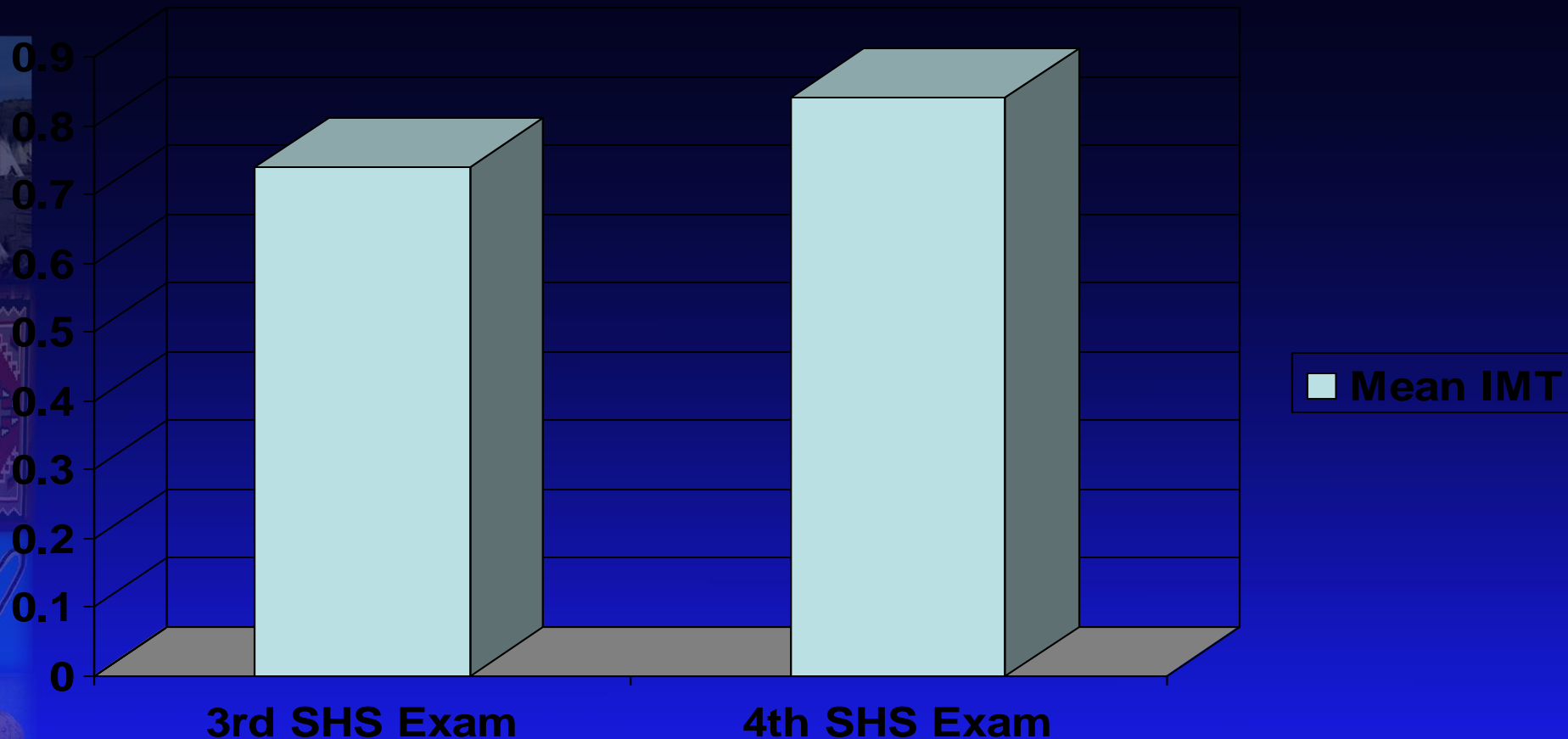
*Pfizer, Merck, and First Horizon Pharmacy--drug*



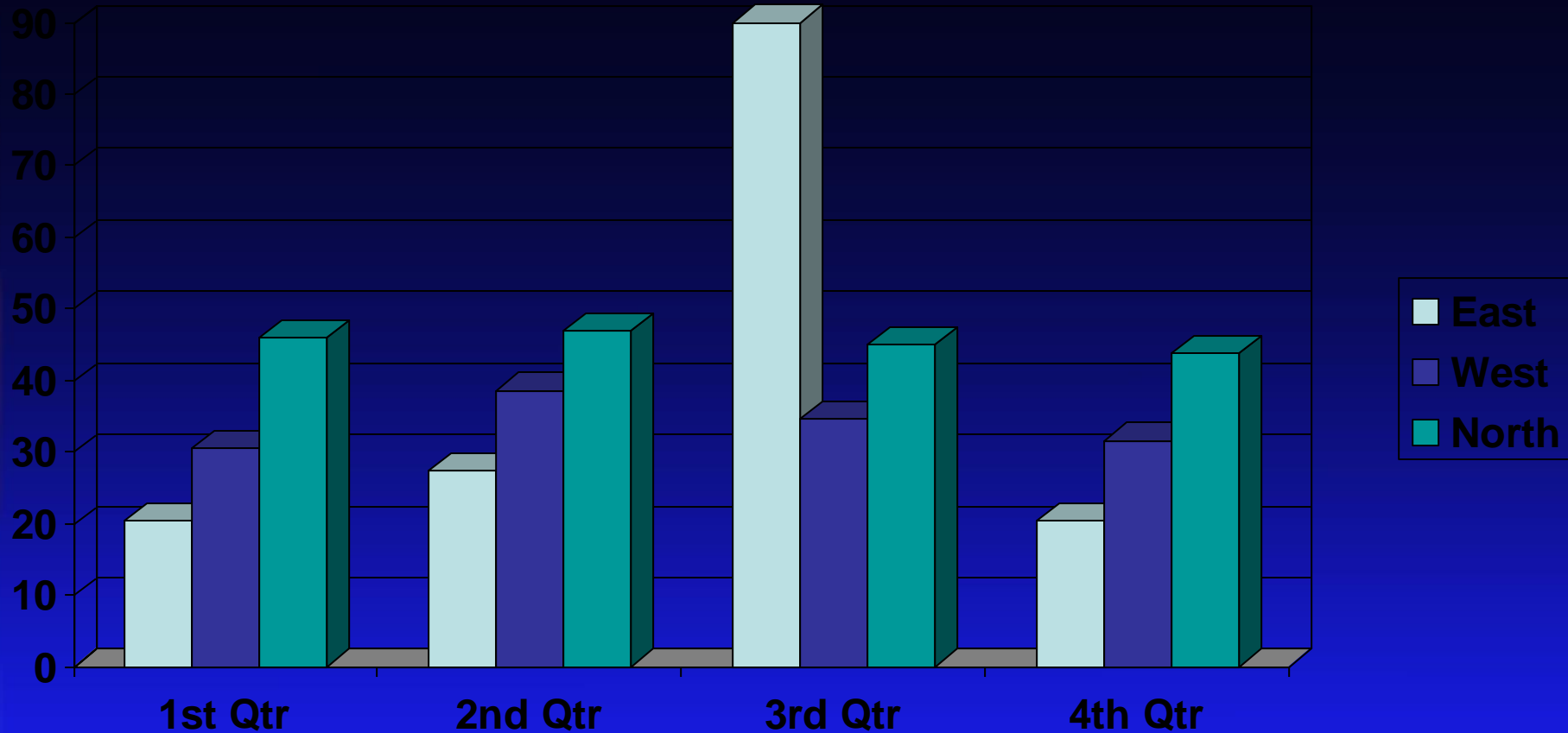
# CVD Hazard Ratios by Quartile of LDL Cholesterol in Diabetes



# Mean Carotid IMT (mm) at 3<sup>rd</sup> & 4<sup>th</sup> SHS Exams in 294 Diabetic Participants



# Mean Carotid IMT (mm) at 3<sup>rd</sup> & 4<sup>th</sup> SHS Exams in 294 Diabetic Participants



**499 men and women  
with diabetes**  
➤ **40 yrs old**  
➤ **SBP>130, LDL>100**

**Usual  
Targets  
N=247**

**Lower  
Targets  
N=252**

**Measure CVD using carotid  
and cardiac ECHO plus CVD events at baseline  
18 months and after 3 yrs f/u**





# Changes during trial (mean)

	Baseline		36 Months		Mean Change	
	AGG	STD	AGG	STD	AGG	STD
BMI	33.5	33.2	34	34	1	1
Waist	110	110	111	110	.3	.4
CRP	2.7	2.8	2.2	3.3	-.7	.9
Glucose	159	156	169	169	11	14
HbA1c	8..2	7.9	8.3	8.2	.1	.3

None of the changes differed between Aggressive and Standard Groups



# Use of Hypolipidemic Medications by Treatment Group

	Standard (n=247)	Aggressive (n=252)
No drug	38 (16%)	14 (6%)
1 drug	139 (57%)	128 (51%)
2 drugs	58 (24%)	92 (37%)
3 drugs	8 (3%)	16 (6%)
4 drugs	1 (.4%)	1 (.4%)
5 drugs	0	1 (.4%)
6 drugs	0	0
<b>Mean (S.D.)</b>	<b>1.2 (.73)</b>	<b>1.5 (.75)</b>



# Algorithm for Blood Pressure Control

- ACE or ARB
- HCTZ
- Atenolol or Nifedipine
- Add alternative step 3 agent
- Doxazocin
- Hydralizine or Minoxidil or Reserpine



# Use of Hypertensive Medications by Treatment Group

	Standard (n=272)	Aggressive (n=276)
No drug	46 (17%)	11 (4%)
1 drug	96 (35%)	65 (23%)
2 drugs	70 (26%)	71 (26%)
3 drugs	37 (14%)	70 (25%)
4 drugs	15 (5.5%)	42 (15%)
5 drugs	5 (2%)	12 (4%)
6 drugs	0	1 (.4%)
7 drugs	3(1%)	4(1%)
<b>Mean (S.D.)</b>	<b>1.6 (1.2)</b>	<b>2.4 (1.3)</b>



# Adverse Events



Aggressive

Standard

p

Adverse Events  
% (95%CI)

38.5(32-45)

26.7(21-32)

.005

Related to  
lipid drugs

18.3(14-23)

14.2(10-19)

.22

Related to BP  
drugs

26.6(21-32)

15.4(11-20)

.002

# Drug Related AEs: Blood Pressure Drugs

Standard

Aggressive

(N = 247)

(N = 252)

## Most Common AEs

Dizziness	17%	35%
Cough	11%	29 %
Fatigue	6%	11%

Orthostatic Hypotension (N)	3	2
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## Drugs with highest AEs(/100pyr)

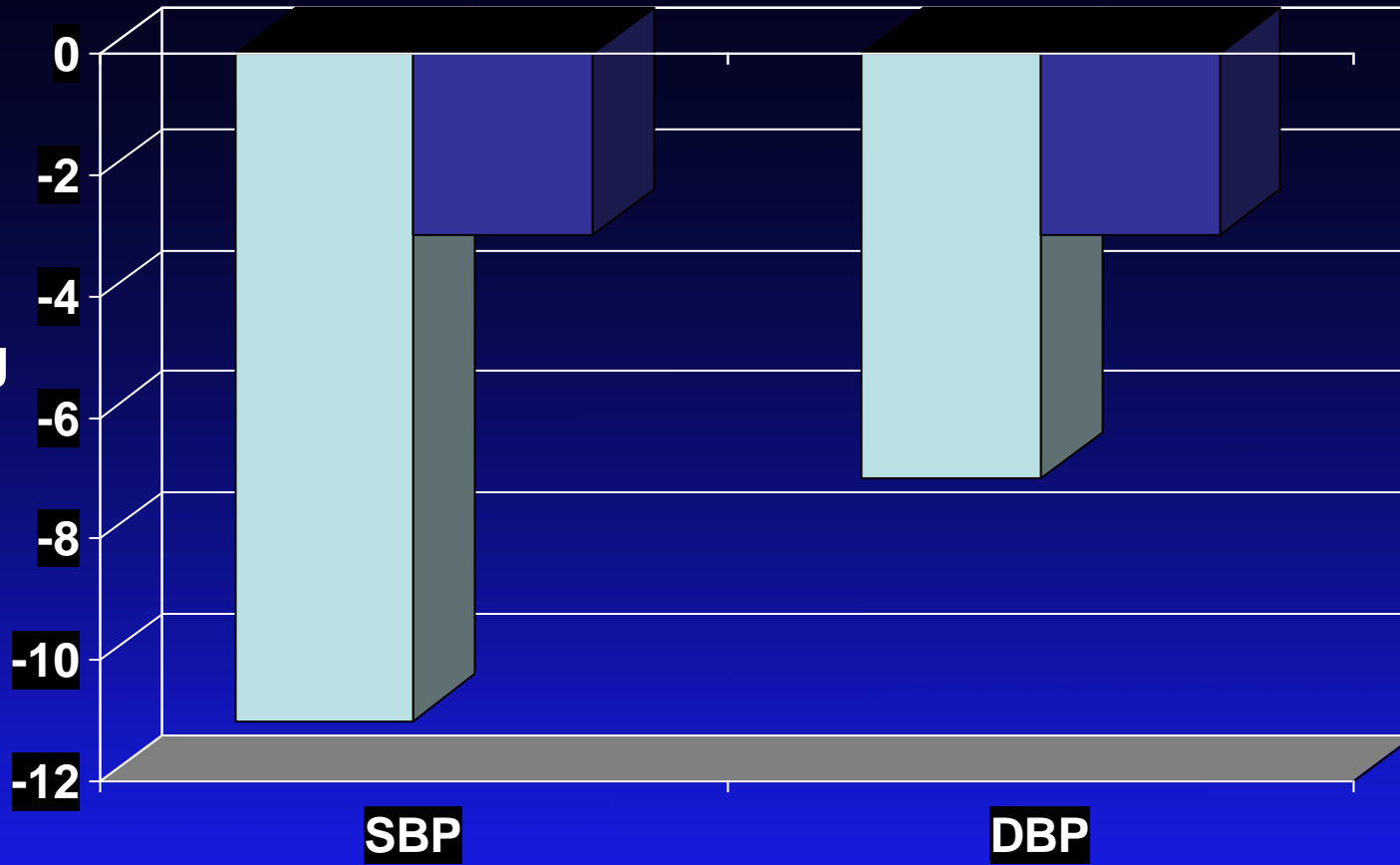
atenolol	4.52	8.86
lisinopril	4.44	6.15
amlodipine	4.57	5.13
HCTZ	4.30	4.12

# Change in IMT by Strata of Baseline Characteristics

CHARACTERISTIC	STRATA	P for INTERACTION
Age, years	<51, 51-60, >60	.99
BMI, kg/m <sup>2</sup>	<30, 30-35, >35	.12
Gender	Male, female	.25
LDL-C, mg/dl	<100, 100-130, >130	.73
Non-HDL C, mg/dl	<130, 130-160, >160	.95
SBP, mm Hg	<120, 120-130, 130	.54
HbA1c, %	<7, 7-8, >8	.22
CRP, mg/dl	<1.7, 1.7-4.5, >4.5	.62
eGFR, ml/min/1.78 m <sup>2</sup>	<78, 78-96, >96	.12
Smoker	Yes, no	.24



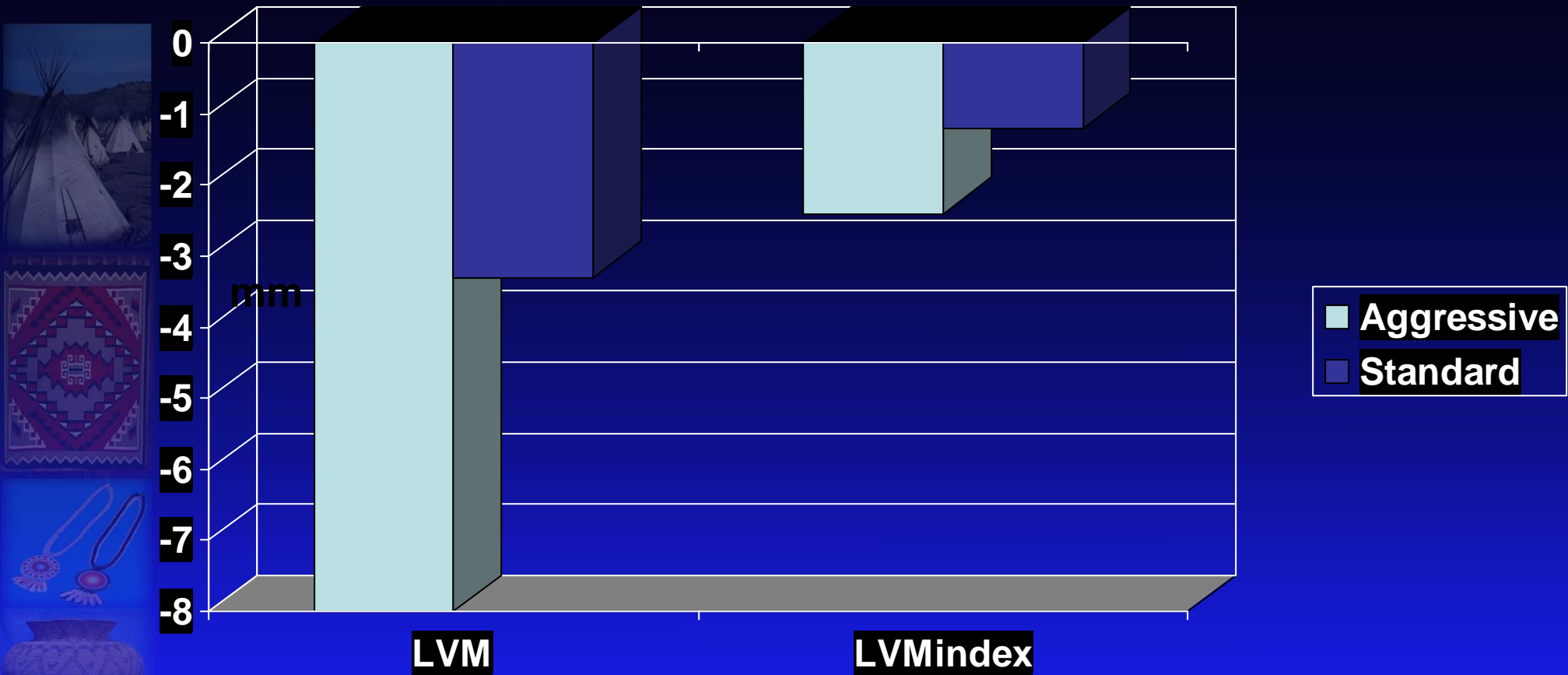
# Changes in Blood Pressure



■ Aggressive  
■ Standard



# Changes in LVmass and LVmass Index



Group differences:  $p < .02$  and  $p < .03$



# CVD Events

Events	No/100 person yrs (95%CI)		P value
	Aggressive	Standard	
Primary CVD	1.5(0.6-2.3)	1.1 (0.3-1.9)	.51
Other CVD	0.1(-0.1-0.4)	0.4(-0.1-0.9)	.31
Total CVD	1.6(0.7-2.5)	1.5(0.6-2.3)	.87
Non CVD deaths	0.3(-0.1-0.6)	0.5(0-10)	.40

# Carotid Plaque Score and Prevalence

	Mean			
	Aggressive	Standard	Diff	P value
Score Base	1.85	1.84		
18mo	2.02	2.02		
36mo	2.38	2.34		
$\Delta$ 0-36 mo	.54	.50	.03	.75
Plq% Base	74.6	76.5		
18mo	81.0	81.0		
36mo	86.5	84.2		
$\Delta$ 0-36 mo	11.9	7.7		



# Echocardiographic Measures

	Mean			
	Aggressive	Standard	Diff	P value
LVMi Base	41.2	40.5		
18 mo	37.6	38.8		
36 mo	38.9	39.4		
Δ 0-36 mo	-2.4	-1.2	1.3	<.03
EF Base	60.5	59.8		
18 mo	60	58.7		
36 mo	59.7	59.1		
Δ 0-36 mo	-.07	-.074	.03	.95



# Ordered Probability Analysis of Determinants of IMT and LVMi Changes

MODEL	Change in LDL-C		Change in SBP		Changes in Both LDL-C & SBP	
	Coeff(SE)	p	Coeff(SE)	p	Coeff(SE)	p
Dep. Var: IMT Change						
Baseline IMT mean	-2.10 (0.39)	.000	-2.12 (0.39)	.000	-2.08 (0.39)	.000
Change in LDL-C	0.004 (0.0015)	.007			0.0037 (0.0015)	.017
Change in SBP			0.0053 (0.0034)	.112	0.0035 (0.0035)	.317
Age	0.0179 (0.0073)	.013	0.0193 (0.0071)	.007	0.0185 (0.0073)	.011
BMI	0.0095 (0.0096)	.32	0.01230 (.00534)	.20	0.0112 (0.0097)	.25
LR chi-sq	45.3	.000	44.8	.000	47.3	.000
Dep. Var: LV Mass Index Change Category						
Baseline LV Mass	-0.057 (.009)	.000	-0.0633 (0.0093)	.000	-0.0612 (0.0092)	.000
Change in LDL-C	0.003 (0.0017)	.116			0.002 (0.002)	.374
Change in SBP			0.012 (0.004)	.001	0.012 (0.004)	.003
Age	0.008 (0.008)	.30	0.008 (0.0076)	.26	0.010 (0.008)	.18
BMI	0.049 (0.012)	.000	0.059 (0.012)	.000	0.058(0.013)	.000
LR chi-sq	52.1	.000	64.5	.000	64.9	.000