

Update in Diabetes, Lipids and Obesity

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Question: Will weight loss due to bariatric surgery decrease CV mortality in patients with obesity?

Methods

Design: Prospective, controlled

Patients: 4077

2010-bariatric

2037-conventional therapy

Follow-up period: mean 10.9 y

Outcomes: All-cause and CV mortality

- Results:

– Weight loss	<u>1-2 yrs</u>	<u>10 yrs</u>
• Lap band:	20%	14%
• Vertical band:	25%	16%
• Gastric bypass:	32%	25%

	<u>Surgery</u>	<u>Conventional</u>	<u>HR</u>
– All-cause mortality:	101	129	0.76
– CV deaths	43	53	
– Cardiac deaths	35	44	
– Fatal MI	13	25	
– Fatal cancer	29	47	

Take home message:

- Weight loss associated with bariatric surgery reduces all-cause, CV and cancer mortality
- Weight loss due to bariatric surgery is associated with beneficial changes in diabetes, CV risk factors, CV symptoms, CIMT, SDB
- Modest weight loss (5-10%) due to lifestyle change is associated with improved Cv and metabolic risk factors

New Engl J Med 2007;357:741-52

Question: Is the weight loss that occurs with gastric bypass surgery associated with reduced mortality?

- **Methods**

- Design: Retrospective cohort study
- Patients:
 - 7925 GBP
 - 7925 severe obesity: match age, gender, BMI
- Follow-up period: 7.1 y mean
- Outcomes: All-cause and specific mortality

- Results:

	<u>Surgery</u>	<u>Control</u>	<u>HR</u>
Mortality (per 10000 pt yrs)			
– All-cause	38	57	0.67
– CAD	2.6	5.9	0.44
– Diabetes	0.4	3.4	0.08
– Cancer	5.5	13.3	0.40
– Suicide/acc	11	6.4	1.58

Take home message

- GBP surgery is associated with reduced all-cause, CV and cancer mortality

- Suicide and accident mortality is increased despite improved QOL with GBP

Question: Will intensified multifactorial risk factor intervention reduce all-cause and cardiovascular mortality in type 2 diabetes?

Methods

Design: Observational (follow-on) 5.5 y after a RCT of intensive vs conventional Rx lasting 7.8y

Patients: 160 pts with T2D/microalbuminemia

Targets: HbA1c<6.5%, Chol<175 mg/dl, TG<150 mg/dl, BP<130/80 mm

Drugs: OHA/insulin, RAS blockers, LLD

Results:

1. Lab parameters @ 5.5 y
 - a. Similar
HbA1c, TC, LDLC, HDLC, BP, BMI
 - b. TG, 99 vs 148 mg/dl
2. ACM: 24(Int) vs 40(Conv): HR:0.54
3. CV mortality: 0.43
4. CV events: 0.41
5. Retinal photocoagulation: 0.45

Take home message:

- a. Intensive treatment of hyperglycemia and CV risk factors (RAS blockers, aspirin and LLA) reduces all-cause and CV mortality in type 2 diabetes.
- b. Enduring benefit (metabolic memory?) of excellent antecedent treatment.

N Engl J Med 2008;358:580-91

Question: Will intensive therapy of hyperglycemia reduce CV events in patients with type 2 diabetes

- **Methods**

- Design: RCT

- Patients: 10251 type 2 D; age 62.2 y

- CHD(35%) or CHD risk factors (65%)

- Baseline HBA1c, 8.1%

- Intervention: Individualized, to reduce HbA1c to <6.0%(Int) vs 7.0-7.9%(Conv)

- Outcomes:

- Composite: non-fatal MI/stroke, CVdeath

- Results:
 - HbA1c: 6.4% vs 7.5%--1y; within 4-6 mos
 - Primary outcome: 352(I) vs 371(C) HR 0.9
 - All-cause mortality, HR 1.22
 - Non CV death, HR 1.12
 - CV death, HR 1.35
 - Non-fatal MI HR 0.76
 - Severe hypoglycemia, 10.5 vs 3.5%
 - Weight gain, 28 vs 14%

- Hypoglycemic agents used:
 - Metformin, 95/87%
 - Secretagogues, 87/74%
 - TZDs, 92/58% (90% rosiglitazone)
 - Insulin, 77/55%
- Other drugs: statins, β -blockers, ASA

Take home message:

- Intensive treatment of hyperglycemia increases CV mortality in patients with type 2 diabetes who are at high CHD risk

N Engl J Med 2008;358:2545-59
ACCORD Study Group

Question: Will intensive glycemic control reduce vascular events in patients with type 2 diabetes?

- Methods:
 - Design: RCT
 - Patients: 11,140 type 2 diabetes
 - Intervention: Intensive vs conventional Rx
 - Modified release glicazide plus other drugs
 - Target HbA1c, 6.5%
 - Outcomes:
 - Major macrovascular events: non-fatal MI/stroke, CV death
 - Microvascular events

Results:

- HbA1c: 6.5 vs 7.3%
- Macrovasc events: 18.1 vs 20.0% HR, 0.9
- Microvasc events: 9.4 vs 10.9%
- No effect on all-cause or CV mortality
- Severe hypoglycemia: 2.7 vs 1.5%
- Hypoglycemic Rx:

	Intensive	Conventional
• Glicazide %	91	2
• Metformin %	74	67
• TZDs %	17	11
• Insulin %	41	24

- BP meds, statins, other LLD....ns

Take home messages:

- Intensive glycemic control neither decreases nor increases risk for macrovascular disease.
- Less intensive glycemic control, HbA1c 7%
- Address CV risk factors:
 - Smoking cessation
 - Diet/exercise
 - BP control
 - ASA
 - Statins
- Findings diminish potential role of postprandial glucose levels if HbA1c acceptable
- Intensive glycemic control may benefit younger type 2 patients with less advanced CV ds

Veterans Administration Diabetes Trial

Question: Will better glycemic control reduce CV ds risk in patients with type 2 diabetes?

Methods

Design: RCT

- optimize control of BP, lipids, TLC, ASA
- intensive vs std control of hyperglycemia
- 2-3 OHA plus insulin

Patients: 1791 US Veterans, 97% men

- Baseline HbA1c, 9.5%

Outcomes: CV ds events: MI, stroke, CHF,CABG, amputations, death

- Mean follow-up 6.25y

Results

-Treatment	<u>Int</u>	<u>Std</u>	
OHA %	90	74	
TZD-R %	72	62	
Met %.....obese			
Glimepiride %.....nonobese			
Insulin %	90	71	
-HbA1c %:	6.9	8.4	
-CV events (n)	231	263	HR, 0.88
-Severe hypoG %	21	10	

Take home message

- Intensive glycemic control will not reduce major CV events in patients with type 2 diabetes
- Reduce all CHD risk factors
- A1c marker for microvascular disease

reported at 2008 ADA

Question:

Will the further reduction in LDL-cholesterol produced by the addition of ezetimibe to statin therapy reduce progression of atherosclerosis?

Methods

Design: Double-blind RCT

- 80 mg simvastatin plus
- placebo (363) or 10 mg ezetimibe (357)

Patients: 720 pts with FH

Follow-up period: 24 months

Outcome: Change in CIMT and FIMT

Patient characteristics:

- age 46 y

- men=women

- previous statin use, 80%

- Baseline

 - LDL-C, 320 mg/dl

 - HDL-C, 47 mg/dl

 - hs-CRP, 1.7 mg/L

• Results	<u>SMV</u>	<u>SMV+EZ</u>
		%
– LDL-C	-39	-56
– HDL-C	+8	+10
– Hs-CRP	-23	-49
– Apo-B	-33	-47

No differences at 24 months in CIMT or FIMT

Take home message

- Ezetimibe does not have vascular benefit when added to maximum dose simvastatin despite substantial further reduction in LDL-cholesterol and hs-CRP
- Use maximum dose monotherapy with statins. Use other agents to achieve LDL-C goals. Ezetimibe should be reserved for those not able to tolerate other cholesterol-lowering drugs.

Issues:

- Use of surrogate/not clinical endpoints
 - Studies show changes in CIMT predict CV events
 - CIMT progresses on 40 mg SV but clinical events reduced in 4S
- Study groups at low risk b/c prior statin
- On-treatment LDL-C still too high
- FH is not representative of usual patients
- Non-statin LDL-C reduction decreases CV events
 - Does EZ have adverse off-target effects?

N Engl J Med 2008;358:1431-43

Question: Will aggressive reduction of LDL-C with simvastatin plus ezetimibe improve outcomes in patients with asymptomatic aortic stenosis?

- Methods

- Design: RCT

- Patients: n=1873

- mild/moderate asymptomatic AoSt

- SV/EZ (10/40 mg) vs placebo

- Outcomes:

- Primary: AoV replacement, morbidity, mortality

- Secondary: CHD events

- Follow-up period: ≥ 4 y

Results

- LDL-C reduced by 61% (76 mg/dl)
- No difference in aortic valve outcomes
- Atherosclerotic events decrease by 22%
- Cancer increased by 64% (4.1 vs 2.5%)

Take home message

- SV+EZ does not reduce progression of mild-moderate aortic stenosis
- SV+EZ reduces CV events but less than expected based upon reduction in LDL-C (based upon concept that 39 mg/dl=20%; CTT)
- Cancer risk increased by 64%-significance???