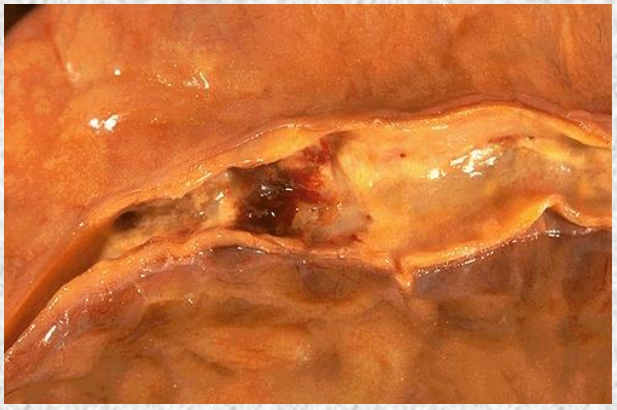
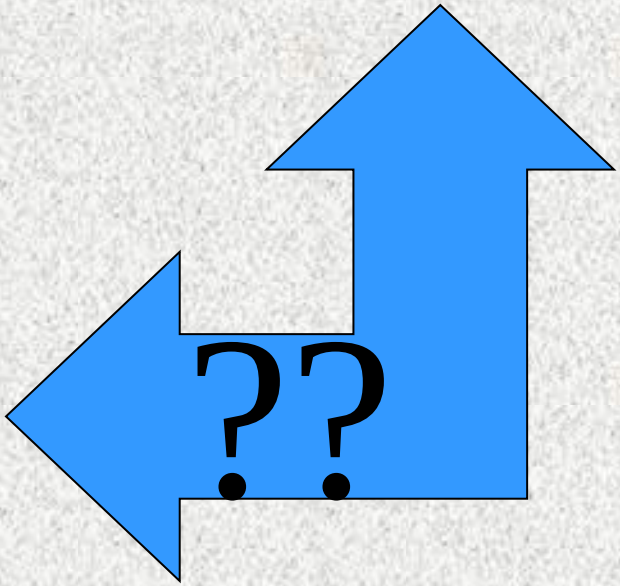


Hyperglycemia



Pathophysiology of Cardiovascular *Mortality*-II

Might Increased Membrane Depolarization and Enhanced Arrhythmogenicity Be Missing Links?

-A Meta-Analysis Across Several Trials and Disciplines

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Medical Director,
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pharmanet

1) Are glycemic control and cardiovascular *mortality* strongly associated?

Cardiovascular ***Mortality*** in Diabetes[1]

TABLE 1
Hazard Ratios of Cause-Specific Mortality
And Glycemia in Older-Onset Diabetes Patients
(*WESDR*)

Cause of Death	Hazard Ratio for Each 1% Increase in *Baseline* Glycohemoglobin*
Diabetes Mortality	1.32 (1.21-1.43)
Ischemic Heart Disease	1.10 (1.04-1.17)
Stroke	1.17 (1.05-1.30)
Cancer	0.99 (0.88-1.10)

*Adjusted for other risk factors such as smoking, hypertension, etc.

Moss SE et al.
Arch Intern Med 1994 Nov 14;154(21):2473-9

Each 1% increase in Hb A_{Ic} is associated with an 8% increased risk of heart failure (95% CI 5% to 12%) - Iribarren et all, *Circulation.* 2001;103:2668.

UMDS

Dr. Harry Keen (1968)[2]

"It is, of course, possible to formulate three standard hypotheses to explain the relationship - that A causes B, that B causes A, or that both A and B are caused by C. We have chosen to examine what is perhaps the most likely and potentially the most useful of these explanations - that hyperglycemia contributes causally to the development of the arterial lesions. It is a useful explanation because there is long experience and knowledge of methods aimed at lowering the blood sugar: the possibility of intervening in the progress of a disease process is one which stimulates both the interest of the doctor and the co-operation of the patient." (Keen H, Jarrett, RJ, Chlouverakis C, Boyns DR, The effect of treatment of moderate hyperglycemia on the incidence of arterial disease. *Postgrad. Med.J*. [1968] **44**:960)

2) Is there any evidence that control of glycemia impacts on atherogenesis, *per se*?

The NEW ENGLAND JOURNAL of MEDICINE

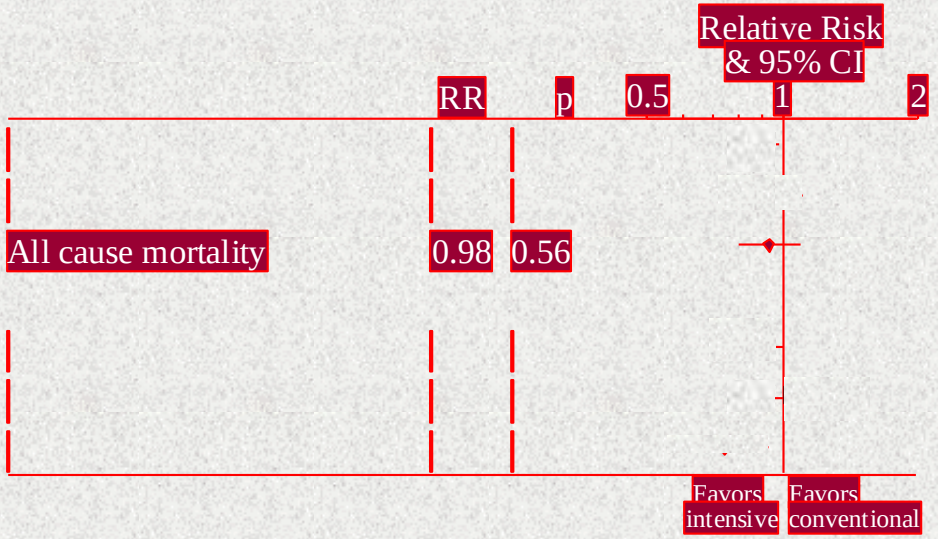
Yes: DCCT Data Shows Delayed Carotid Intimal Hyperplasia in Tightly Controlled Group

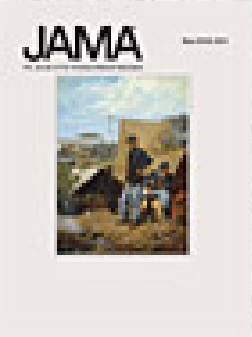
The mean progression of the intima–media thickness was significantly less in the group that had received intensive therapy during the DCCT than in the group that had received conventional therapy (progression of the intima–media thickness of the common carotid artery, 0.032 vs. 0.046 mm; P=0.01; and progression of the combined intima–media thickness of the common and internal carotid arteries, –0.155 vs. 0.007; P=0.02) after adjustment for other risk factors. (*NEJM* [2003] **348:**2294-2303)

Q:-Does Altering *Glycemic Control* Over the Long-Term Have Any Impact Upon Cardiovascular ***Mortality,*** however? [2]

- A:- No
  - (UGDP-1971)

Aggregate Clinical Endpoints in the UGDP



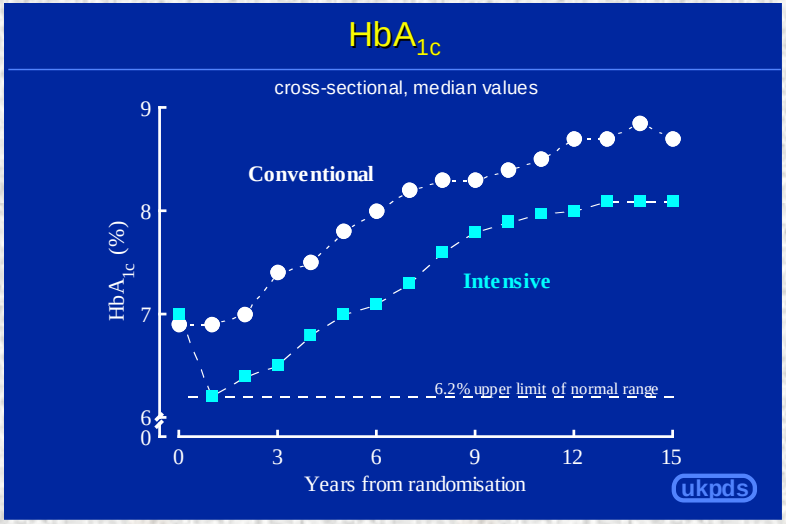


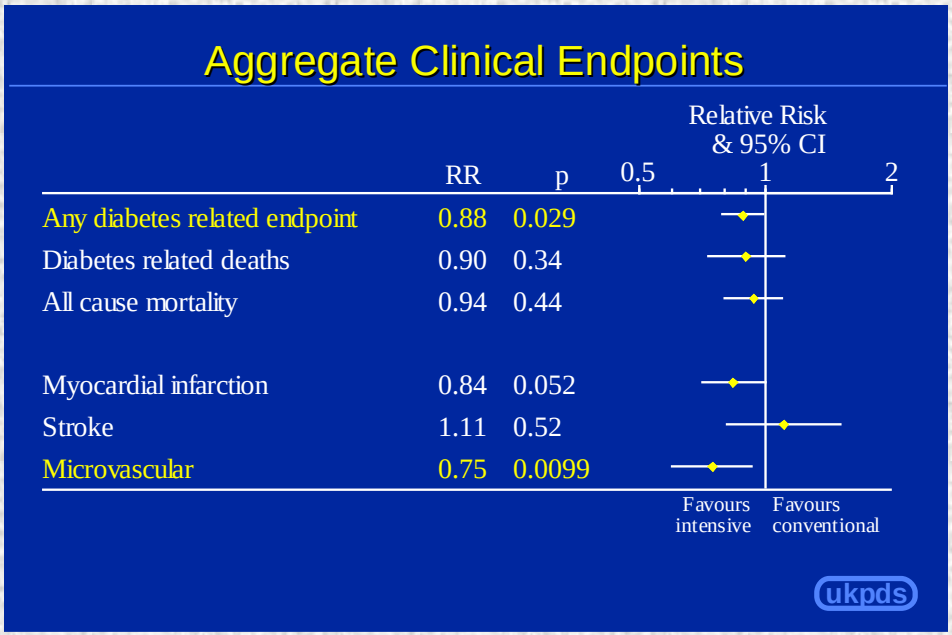
JAMA 1971 Nov;218(9):1400-10

Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. 3. Clinical implications of UGDP results. Goldner MG, Knatterud GL, Prout TE.

Q:-Does Altering *Glycemic Control* Over the Long-Term Have Any Impact Upon Cardiovascular *Mortality*?[2]

- A:- No
  - (UKPDS-1999)





3) What are the effects of insulin upon target-cellular membrane potentials?

Insulin Hyperpolarizes the Membranes of Target Cells

Insulin depolarization of skeletal muscle in absence of external Na+.

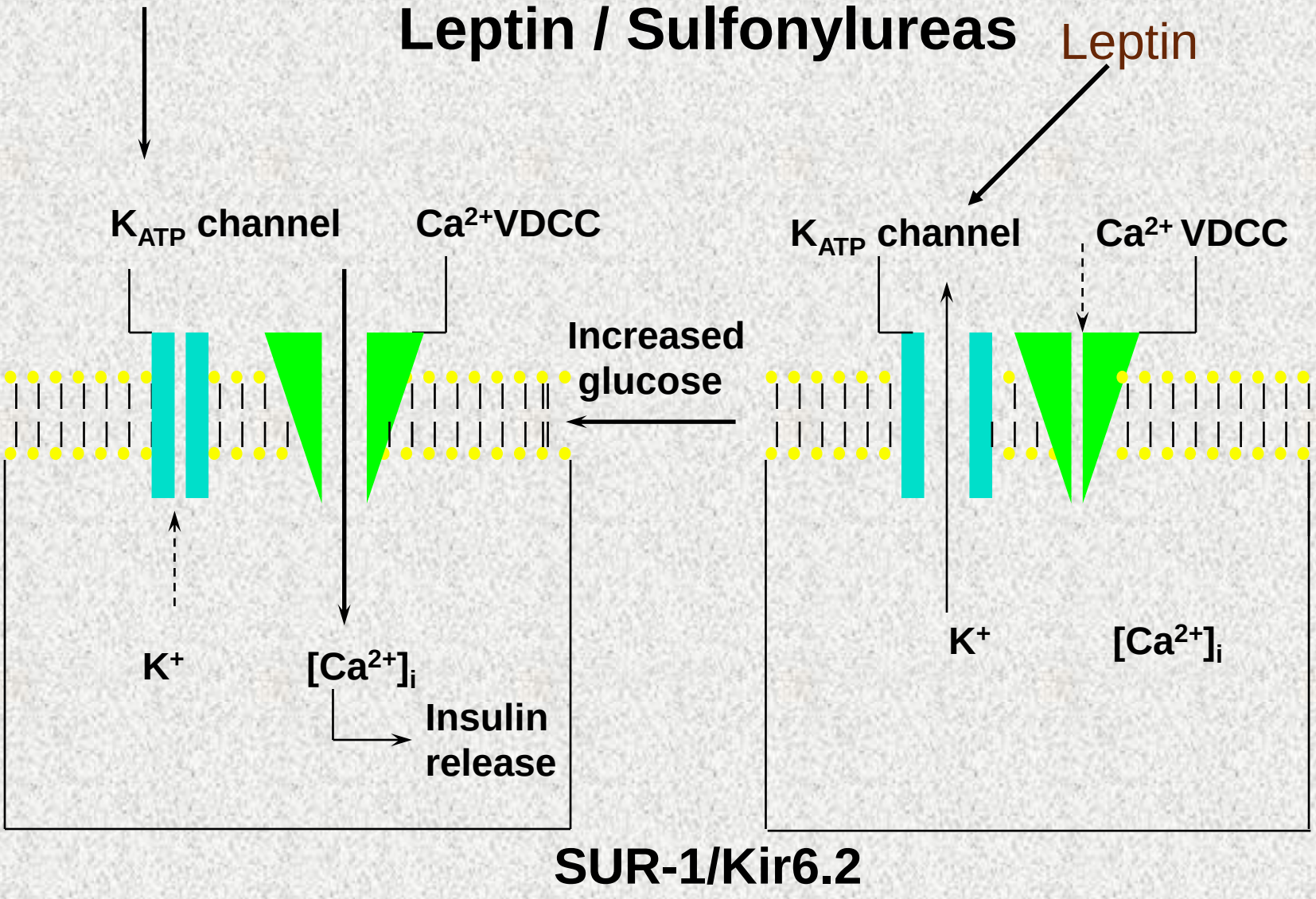
Wu FS, Rogus E, Zierler K.

Department of Physiology, Johns Hopkins University School of Medicine, Baltimore, Maryland.

Three mechanisms have been proposed by which insulin might increase the electrical potential difference across the cell membrane of some of its main target cells: stimulation of an electrogenic pump; increased permeability to K+ (PK); and decreased ratio of permeability to Na+ (PNa) compared to PK, with an absolute decrease in permeability to both ions. Our laboratory has reported that ***insulin-induced hyperpolarization*** (IIH) of rat skeletal muscle is not due to stimulation of a ouabain-inhibitable pump and that insulin decreases 42K efflux, apparently eliminating the first two candidate mechanisms. If the remaining hypothesis is correct, when Na+ is removed from the bathing solution, insulin should depolarize, not hyperpolarize. It did. With Tris or N-methyl-D-glucamine substituted for Na+, insulin depolarized by approximately 3 mV. Ouabain had no effect. PNa decreased by greater than 90%; PK was reduced by less than 40%. The main component of the immediate mechanism of IIH is the near elimination of PNa. Furthermore, when a poorly permeable cation was substituted for Na+, muscles hyperpolarized in the absence of insulin. This gave us an opportunity to test the hypothesis that hyperpolarization is a link in the insulin-transduction chain. Consistent with this hypothesis, rat muscles hyperpolarized in this manner in the absence of insulin took up more glucose than paired controls in normal Na+ solution. (*Diabetes* [1989] Mar;**38**(3):333-7)

4) What are the effects of sulfonylurea agents upon target-cellular membrane potentials?

Mechanism of Action
Leptin / Sulfonylureas

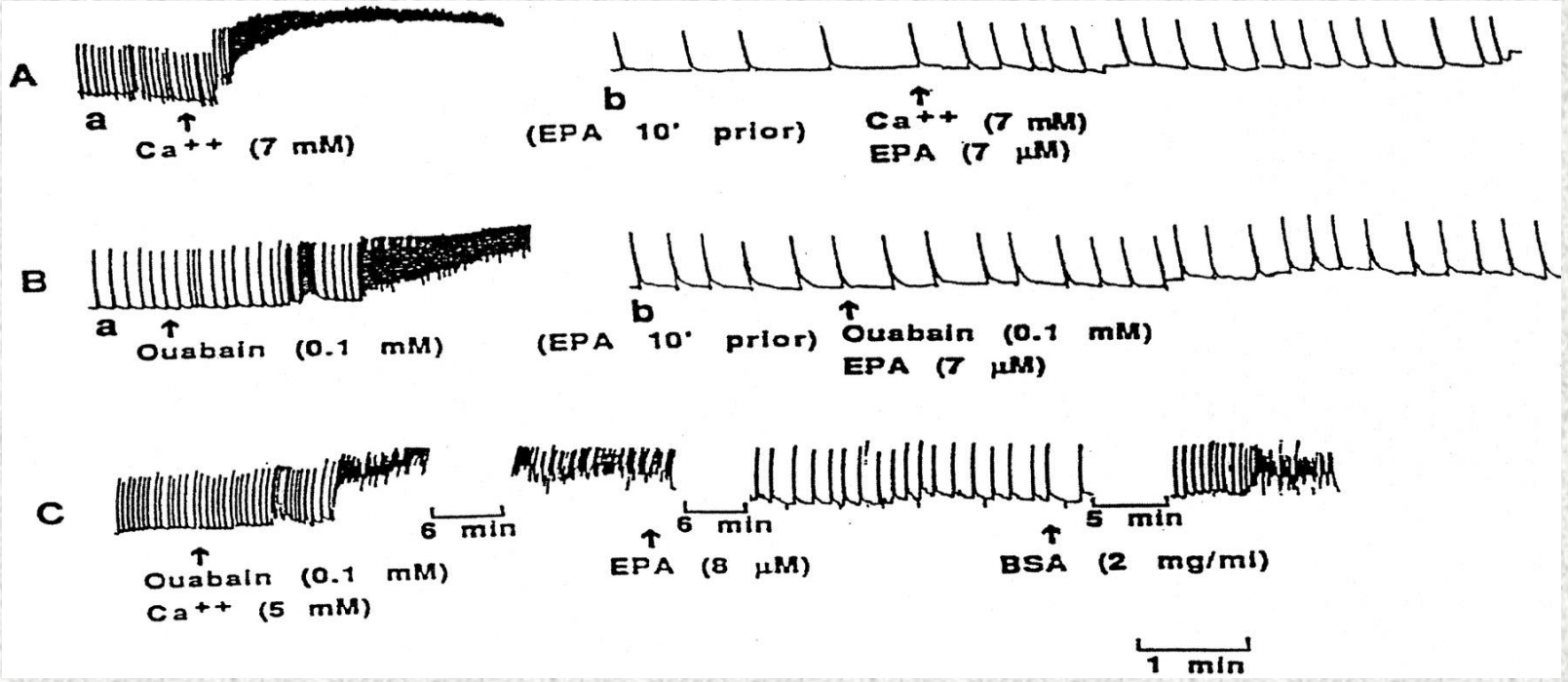


5) Could relative *depolarization* of insulin target-cells (which associate with insulin-resistance and hyperglycemia) enhance cardiovascular *mortality*?

Arrhythmogenic Potential of Depolarized Cells-1

Our current hypothesis regarding the mechanism of action of the n-3 PUFAs [or insulin-rji] to prevent fatal arrhythmias is based on their actions to inhibit the fast, voltage-dependent sodium current[30–32] and the L-type calcium currents.[33] With an MI, a gradient of depolarization of cardiomyocytes occurs. In the central core of the ischemic zone, cells rapidly depolarize and die. The depolarization results from deficiency of ATP in the ischemic cells, which causes a dysfunctional Na,K-ATPase and the rise of interstitial K^+ concentrations in the ischemic zone. However, at the periphery of the ischemic zone, myocytes may be only partially depolarized. They become hyperexcitable because their resting membrane has become more positive, approaching the threshold for generating action potentials (activating fast Na^+ channels). Thus, any additional small depolarizing stimulus (eg, current of injury) may elicit an action potential, which, if it occurs at a vulnerable moment during the cardiac electrical cycle, may initiate an arrhythmia. With nonhomogeneous rates of conduction pathways in the ischemic tissue, reentry arrhythmias are likely. In the presence of the n-3 PUFAs, however, a voltage-dependent shift of the steady state inactivation curve to more hyperpolarized potentials occurs. The consequence of this hyperpolarizing shift is that sodium channel availability is decreased, and the potential necessary to return these Na^+ channels in partially depolarized myocytes to a closed but activatable state is physiologically unobtainable. Also, these partially depolarized cells have Na^+ channels, which in milliseconds can slip into "resting inactivation" in response to subthreshold depolarizations without eliciting an action potential,[34,35] and they do this even faster in the presence of the fish oil fatty acids.[31,32] The results of these effects of the n-3 PUFAs [or insulin-rji] is that these partially depolarized myocytes are quickly made inexcitable, and their potential arrhythmic mischief is aborted. Myocytes with normal membrane potentials in the nonischemic myocardium will not be so drastically affected by the PUFAs and will continue to function normally. In our opinion, this effect of the n-3 PUFAs [or insulin-rji] on Na^+ channels and their effect to inhibit L-type Ca^{2+} channels[33] and prevent triggered arrhythmic afterpotential discharges caused by excessive cytosolic Ca^{2+} fluctuations are the major mechanisms for the antiarrhythmic effects of these PUFAs [or insulin-rji].

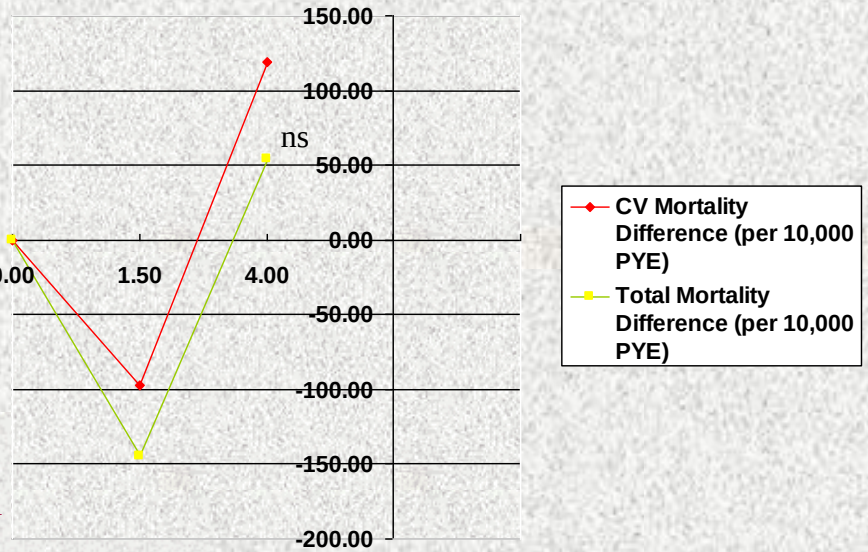
Arrhythmogenic Potential of Depolarized Cells-2



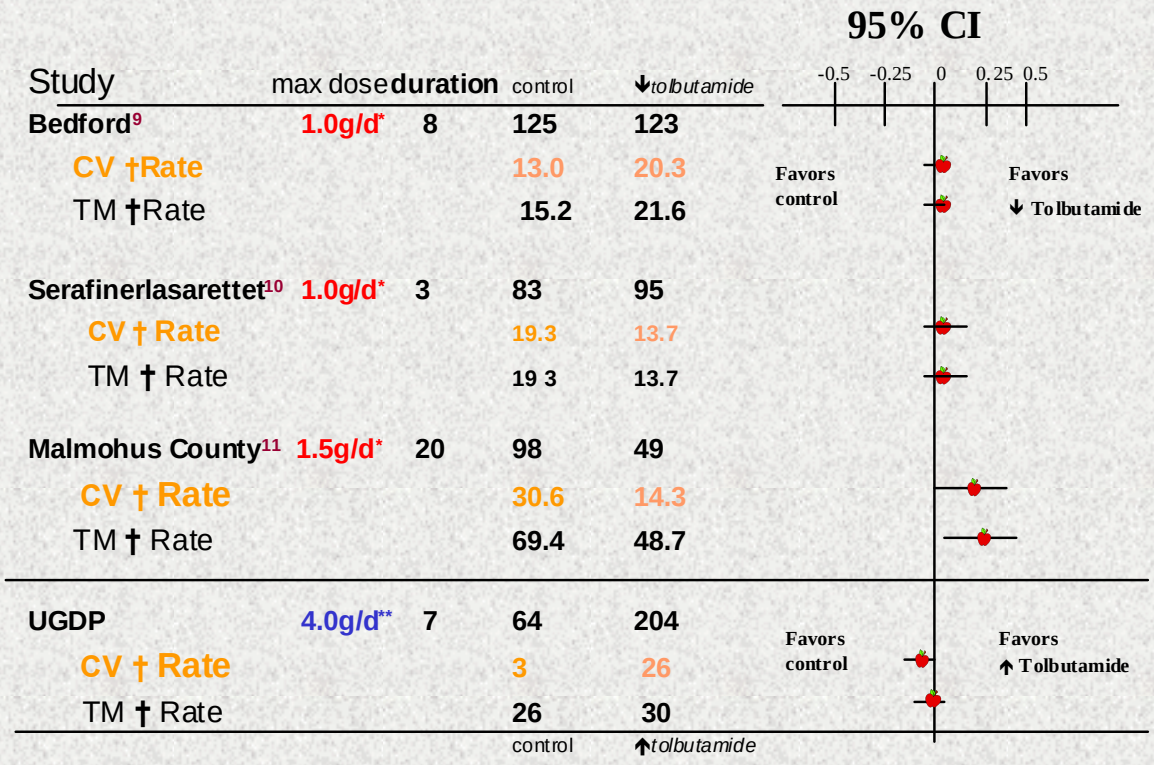
Prevention and termination of arrhythmias by EPA.[25] Perfusion of myocytes with medium containing 7 mmol/L Ca^{2+} (A, a) or 0.1 mmol/L ouabain (B, a) induced contracture and fibrillation of myocytes. Washing cells with medium containing Ca^{2+} 1.2 mmol/L returned fibrillations to original beating rate (not shown). Myocytes were then perfused with medium containing 7 µmol/L EPA. When beating rate had slowed (5 to 8 bpm), addition of 7 mmol/L Ca^{2+} (A, b) or 0.1 mmol/L ouabain (B, b) failed to induce contractures or fibrillations. Slow beating rates were returned to original rates by perfusion with albumin (not shown). C, Fibrillation was induced by ouabain (0.1 mmol/L) plus Ca^{2+} (5 mmol/L) in perfusing medium. Addition of EPA (8 µmol/L) terminated fibrillation. Subsequent addition of delipidated BSA 2 mg/mL, still in presence of ouabain and high Ca^{2+} concentrations, extracted free EPA, and fibrillation resumed. (Leaf A et al, Circulation [*2003*] **107**:2646)

6) Are agents which enhance endothelial membrane depolarization (e.g., *extracellular Ca^{++},ouabain, isoproterenol, lysophosphatidyl choline and acylcarnitine, thromboxane, A23187, tolbutamide) associated with enhanced cardiovascular *mortality*?

Tolbutamide *Mortality* Dose-Responsiveness



Total and Cardiovascular Excess Mortality for Low and High Doses of Tolbutamide[1,9,10,11]



*titrated to max dose without hypoglycemia

**fixed dose

7) Are agents which enhance endothelial membrane *hyper*polarization (e.g., insulin, n-3 pufas) associated with reduced cardiovascular *mortality*?

Mortality in diabetic patients with AMI is predicted by age, previous heart failure, and severity of the glycometabolic state at admission but not by conventional risk factors or sex. Intensive insulin treatment reduced long-term mortality despite high admission blood glucose and Hb A_{Ic}.“

Glycometabolic State at Admission: Important Risk Marker of Mortality in Conventionally Treated Patients With Diabetes Mellitus and Acute Myocardial Infarction (*Circulation.* 1999;99:2626-2632.)

Long-Term Results From the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) Study

Klas Malmberg, MD, PhD; Anna Norhammar, MD; Hans Wedel, PhD; Lars Rydén, MD, PhD

“***The early effect of low-dose (1 g/d) n-3 PUFAs on total mortality and sudden death supports the hypothesis of an antiarrhythmic effect of this drug. Such a result is consistent with the wealth of evidence coming from laboratory experiments on isolated myocytes, animal models, and epidemiological and clinical studies***”.

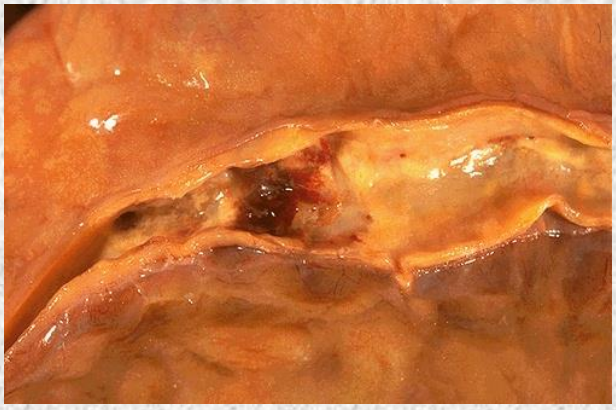
Early Protection Against Sudden Death by n-3 Polyunsaturated Fatty Acids After Myocardial Infarction .Time-Course Analysis of the Results of the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico (GISSI)-Prevenzione ((*Circulation.* 2002;105:1897.)}

8) Are there any data suggesting enhanced low-level adrenergic activity in the metabolic syndrome?

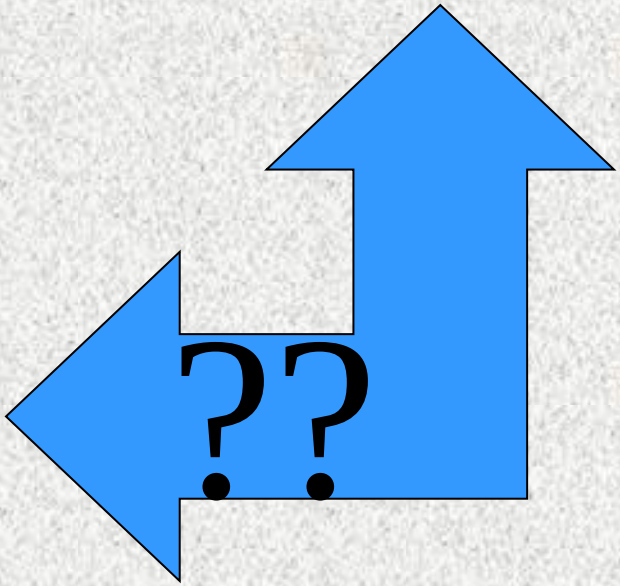
Adrenocortical, Autonomic, and Inflammatory Causes of the Metabolic Syndrome
Nested Case-Control Study

		Metabolic Syndrome Cases				
	No. of Controls:Cases	Controls Quintile Definitio*	Quintile Definition*	Difference	*P*	ATPIII Definition	Difference	*P*
Catecholamine output								
Urinary normetanephrine, µg/d	152:28	177 (151, 207)	233 (185, 293)	0.02		231 (182, 293)	0.04	
Urinary metanephrine, µg/d	152:28	116 (96, 139)	123 (94, 161)	0.66		109 (83, 143)	0.44	
Cardiac autonomic activity								
Heart rate (from RR intervals), bpm	127:25	64.5 (60, 69)	72.3 (67, 78)	0.002		73.1 (68, 79)	0.002	
Heart rate variability (SDRR)	127:25	42.5 (36, 49)	32.3 (24, 40)	0.006		28.5 (21, 37)	0.001	
Total power, ms^2	127:25	1427 (1048, 1944)	749 (500, 1123)	<0.001		639.6 (426, 960)	<0.001	
Low-frequency power, ms^2	127:25	429 (308, 597)	217 (141, 334)	<0.001		182.3 (118, 282)	<0.001	
High-frequency power, ms^2	127:25	148 (99, 220)	70.1 (42, 118)	0.002		50.4 (30, 85)	<0.001	

Brunner EJ et al *(Circulation* [2002]**106**:2659.)



Hyperglycemia



Pathophysiology of Cardiovascular *Mortality*

How Might Increased Membrane Depolarization and Enhanced Arrhythmogenicity Be Missing Links?

Cardiovascular *Mortality*

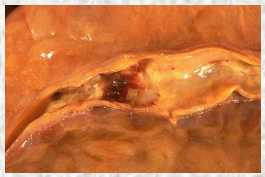
“Hyperadrenergic State”

Endothelial Depolarization

Atherogenesis

Dysmetabolic Syndrome (Insulin Resistance)

Membrane-Depolarizing Rx? (secretagogues)



(Insulin)

Hyperglycemia