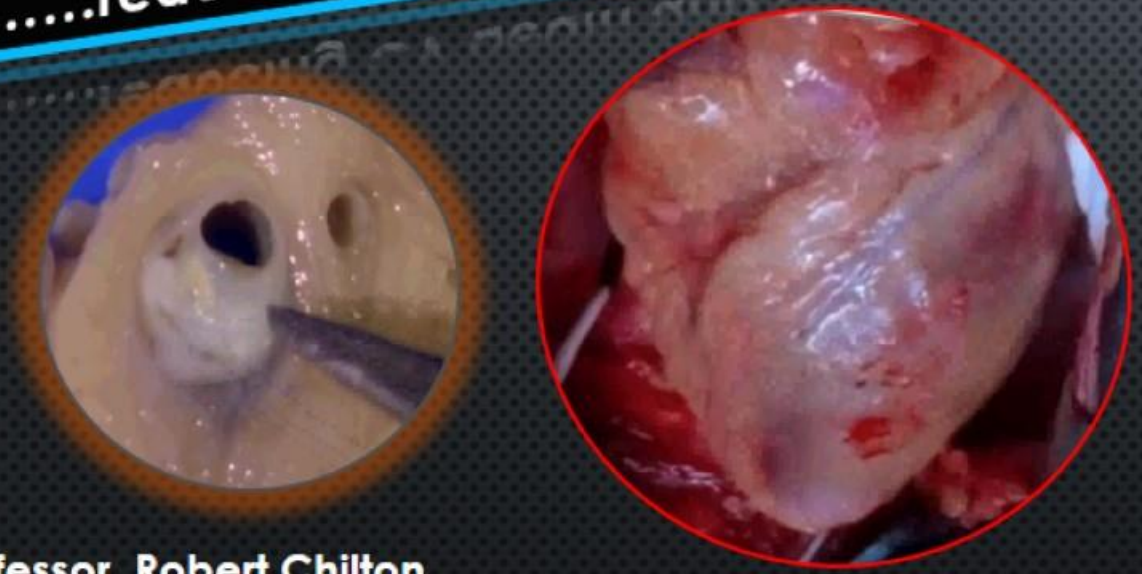
CONFLICTS OF INTEREST FOR THIS LECTURE

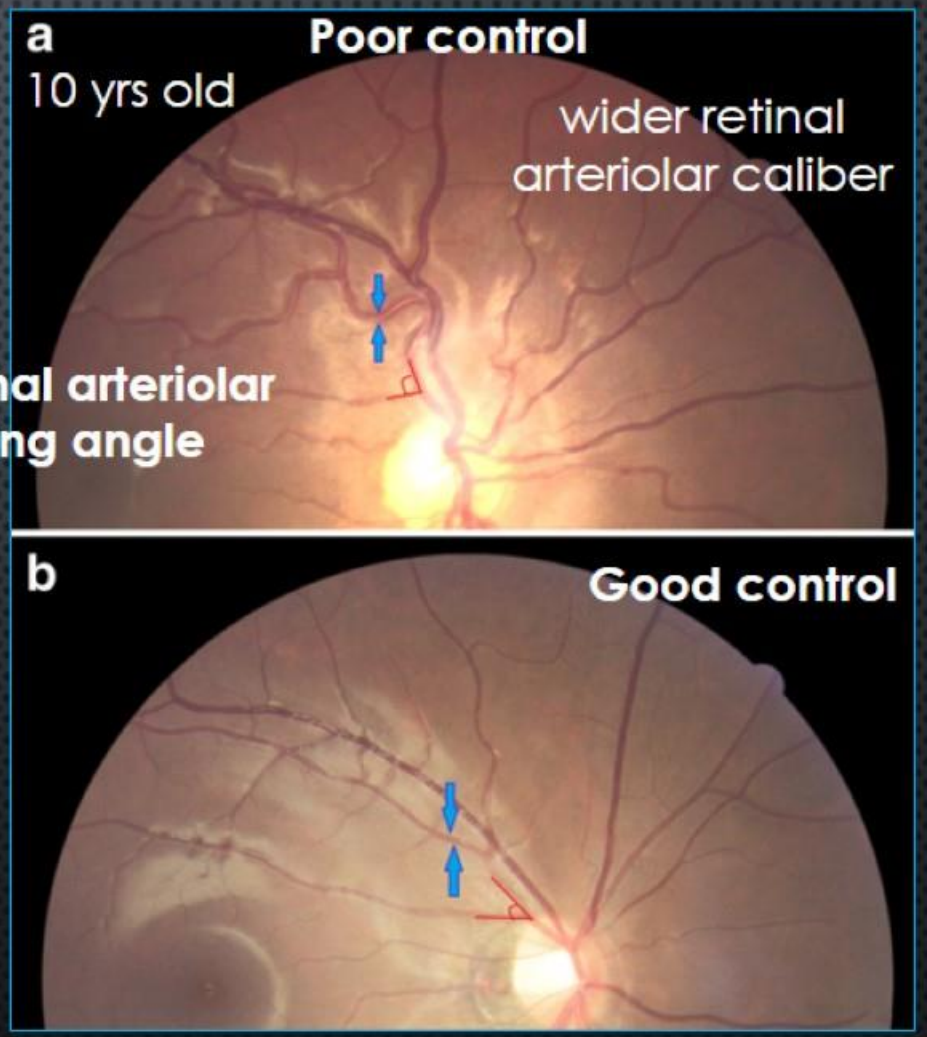
J & J
BI
Lilly
Sanofi
Novo
AZ
Pfizer

Cardiometabolic companies

DIABETIC HEART DISEASE: A TICKING TIME BOMB

"Birth of new CV drugs for diabetes patients"
.....reducing CV death and Cardiorenal events





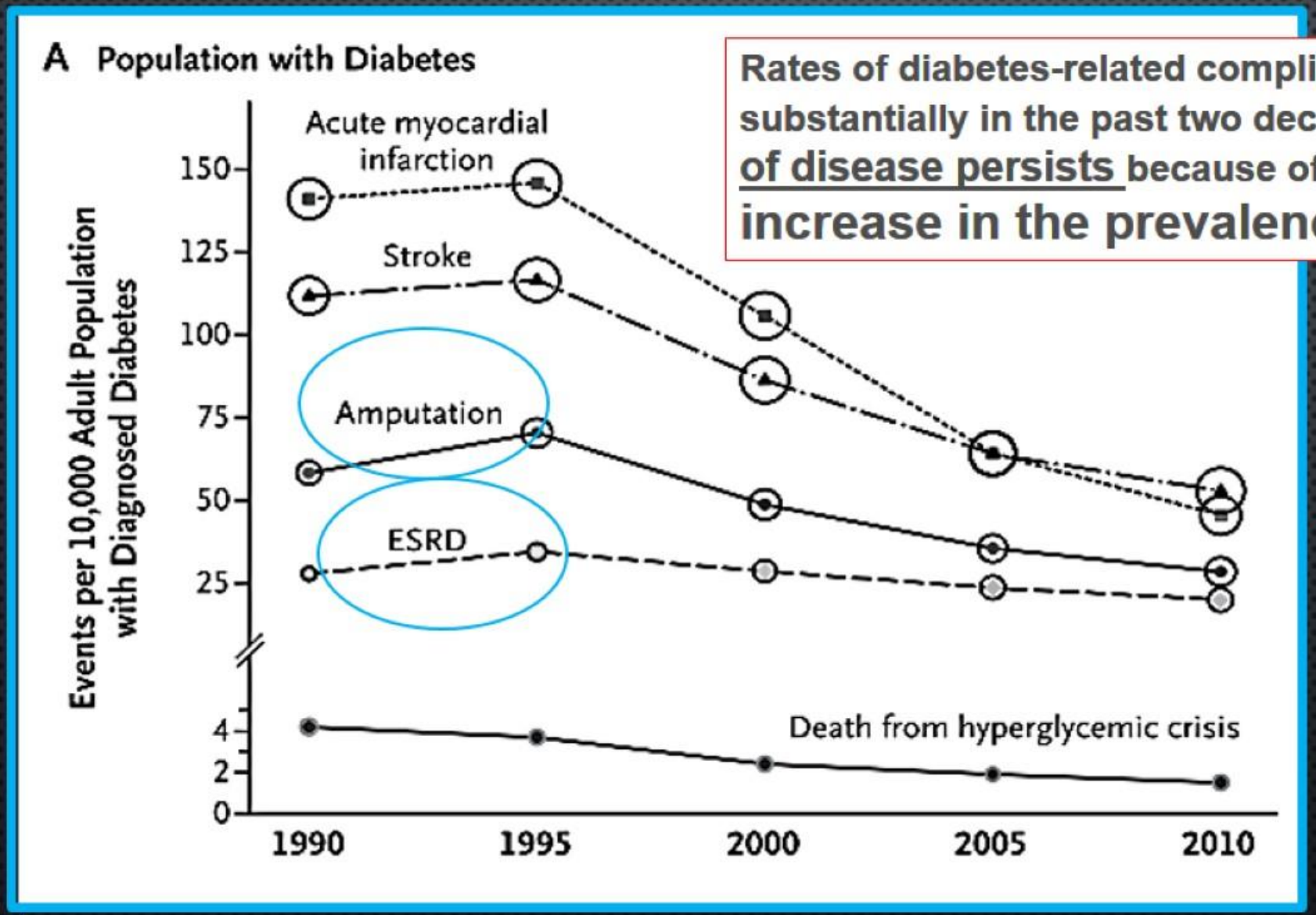
Professor Robert Chilton
University of Texas Health Science Center
San Antonio, Texas
Director of Cath Lab
Director clinical proteomics center

Li et al. BMC Ophthalmology (2017) 17:60

Objectives

- Translational science of diabetes
- Diabetes trials
- Current treatment considerations

U.S. National Vital Statistics



Rates of diabetes-related complications have declined substantially in the past two decades, but a large burden of disease persists because of the continued increase in the prevalence of diabetes

DM patients

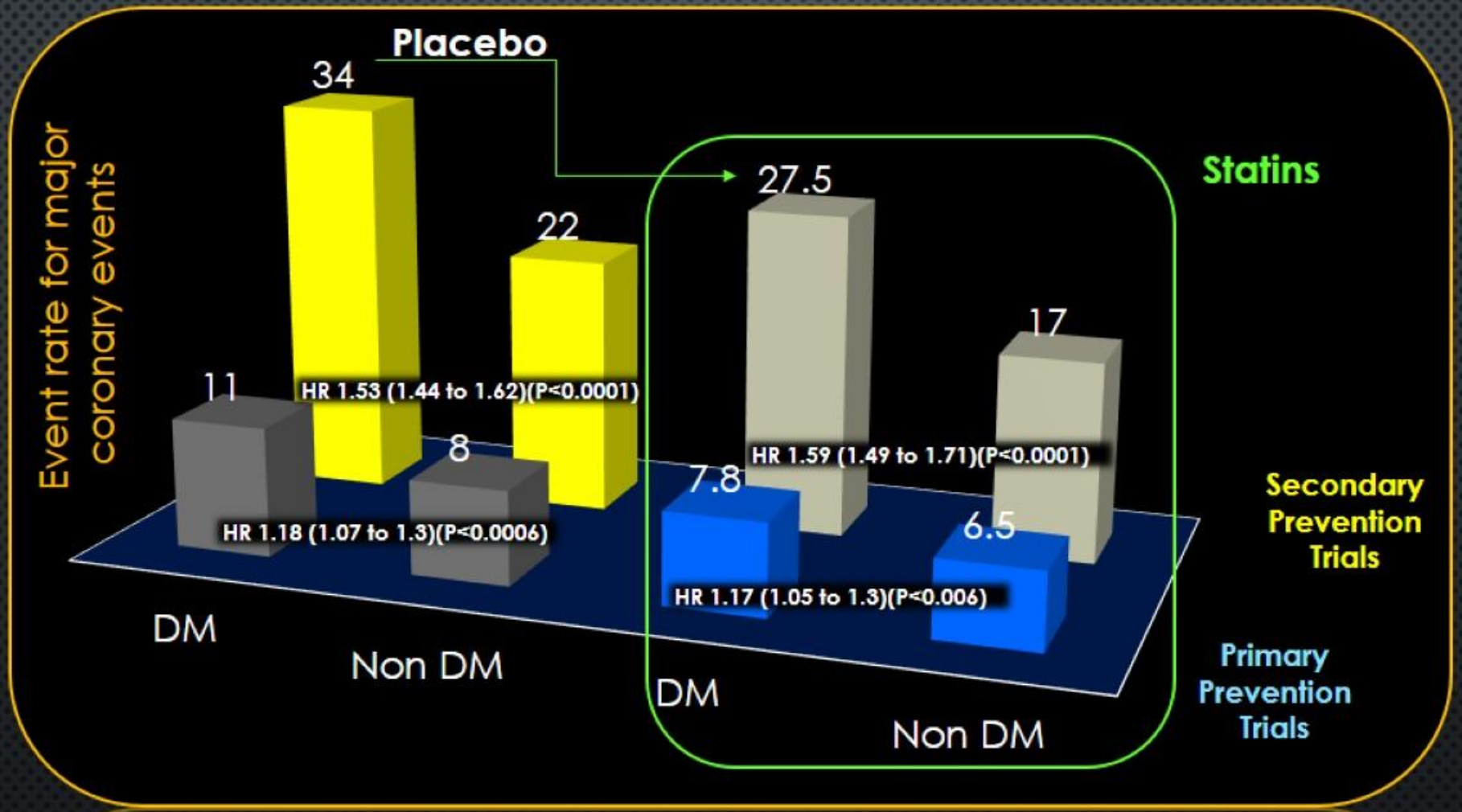
6-8 X higher

Overall population

N=57000

N Engl J Med 2014; 370:1514-1523

STATINS REDUCE MAJOR CORONARY EVENTS



4 to 5.1 years Cochrane
Meta-analysis of randomized controlled trials

BMJ, doi:10.1136/bmj.38793.468449.AE
published 3 April 2006

>2% per yr-Primary Prevention-Cochrine 2011

DIABETES IS COMPLEX

Environmental epigenetic effects

Birth/mom and dad
…genes count

Increasing insulin resistance

Endothelial dysfunction

Cellular dysfunction

Common risk factors recognized

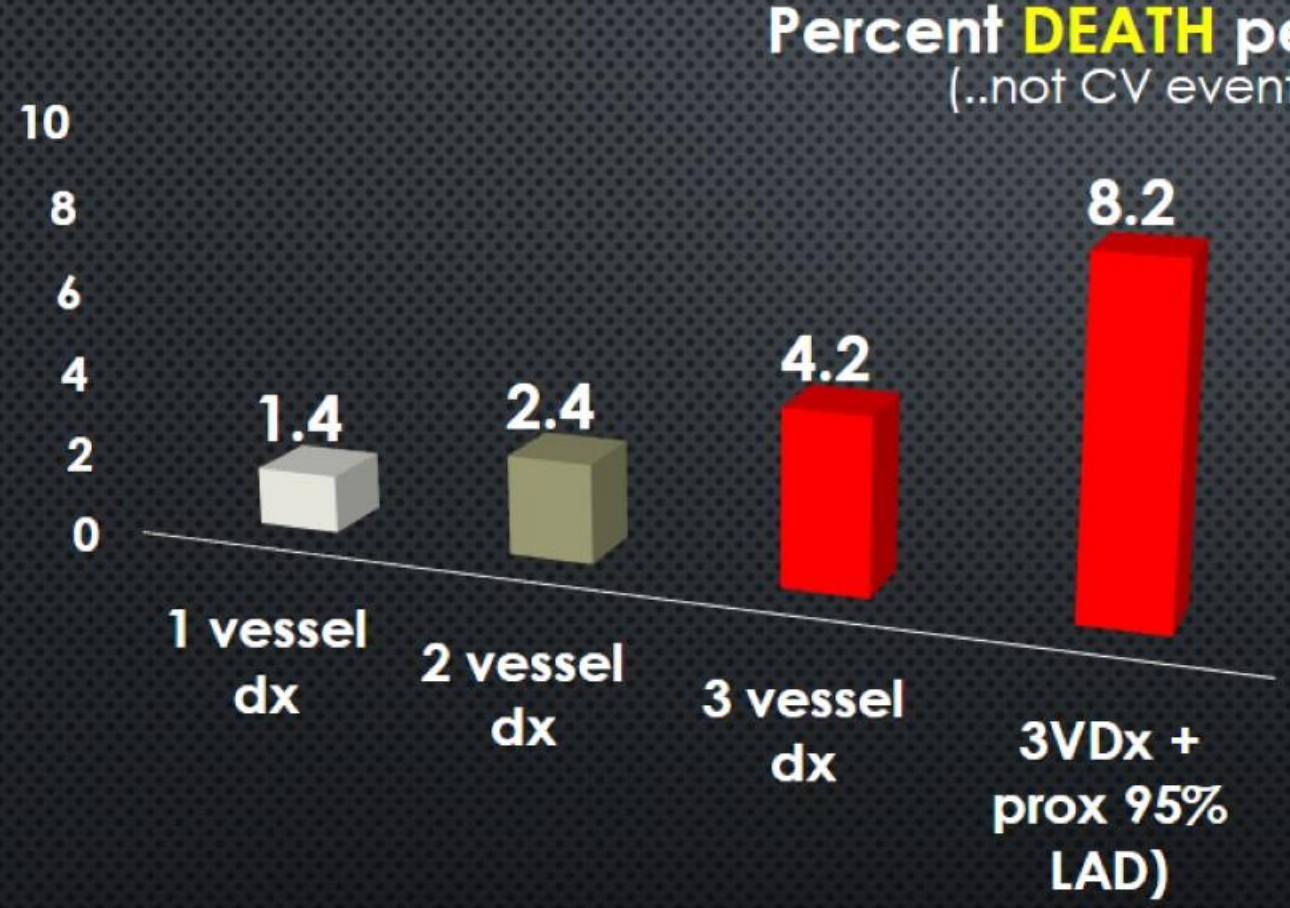
Treatment of numbers ≈ BP <120, LDL <50, hsCRP <0.1 etc

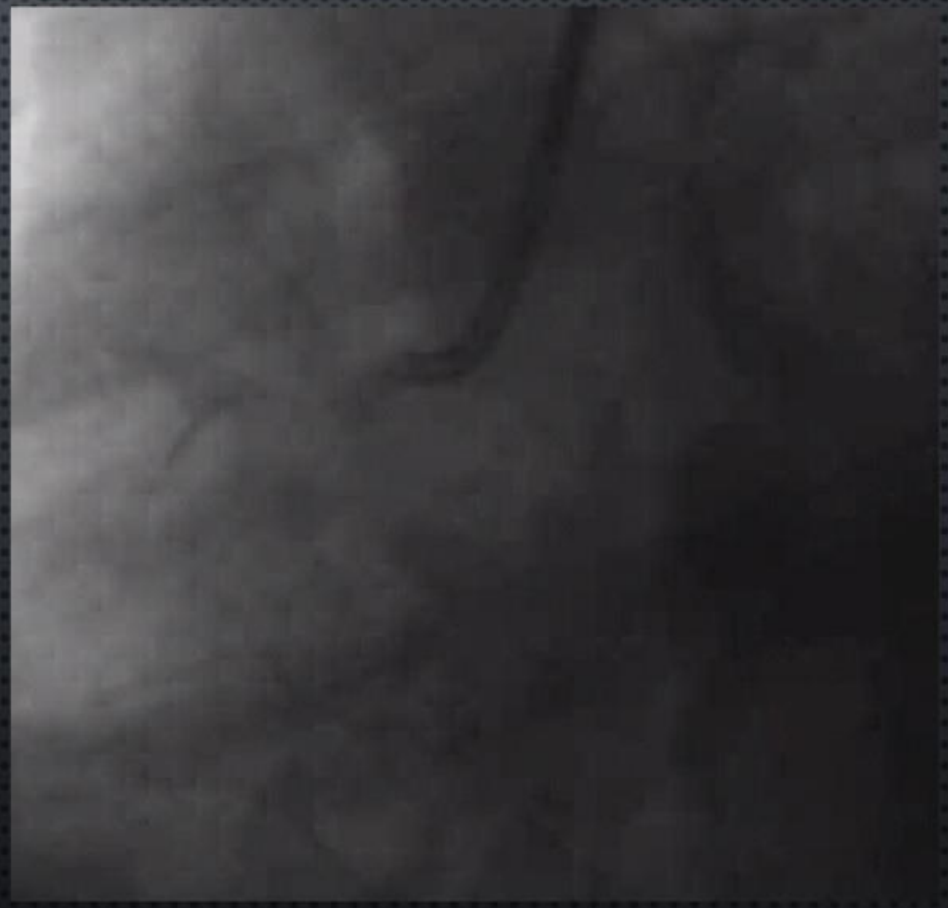
↑ CV risk For > 10yrs

Drugs primary treatment
Rarely lifestyle followed long term

Human awakening as vascular events occur
(Life span shortens 7-13 years)

YEARLY MORTALITY (DEATH) IN MEDICALLY TREATED PATIENTS BY CORONARY ANGIOGRAM





J Am Coll Cardiol. 1996;27:964–1047

WHAT PERCENTAGE ASYMPTOMATIC 30-40 YEAR OLD PEOPLE HAVE CORONARY ATHEROSCLEROSIS?

1. 10%
2. 40%
3. 50%
4. 60%
5. >70%

No diabetes

Atherosclerosis starts early

High Prevalence of Coronary Atherosclerosis in Asymptomatic Teenagers and Young Adults

Evidence From Intravascular Ultrasound

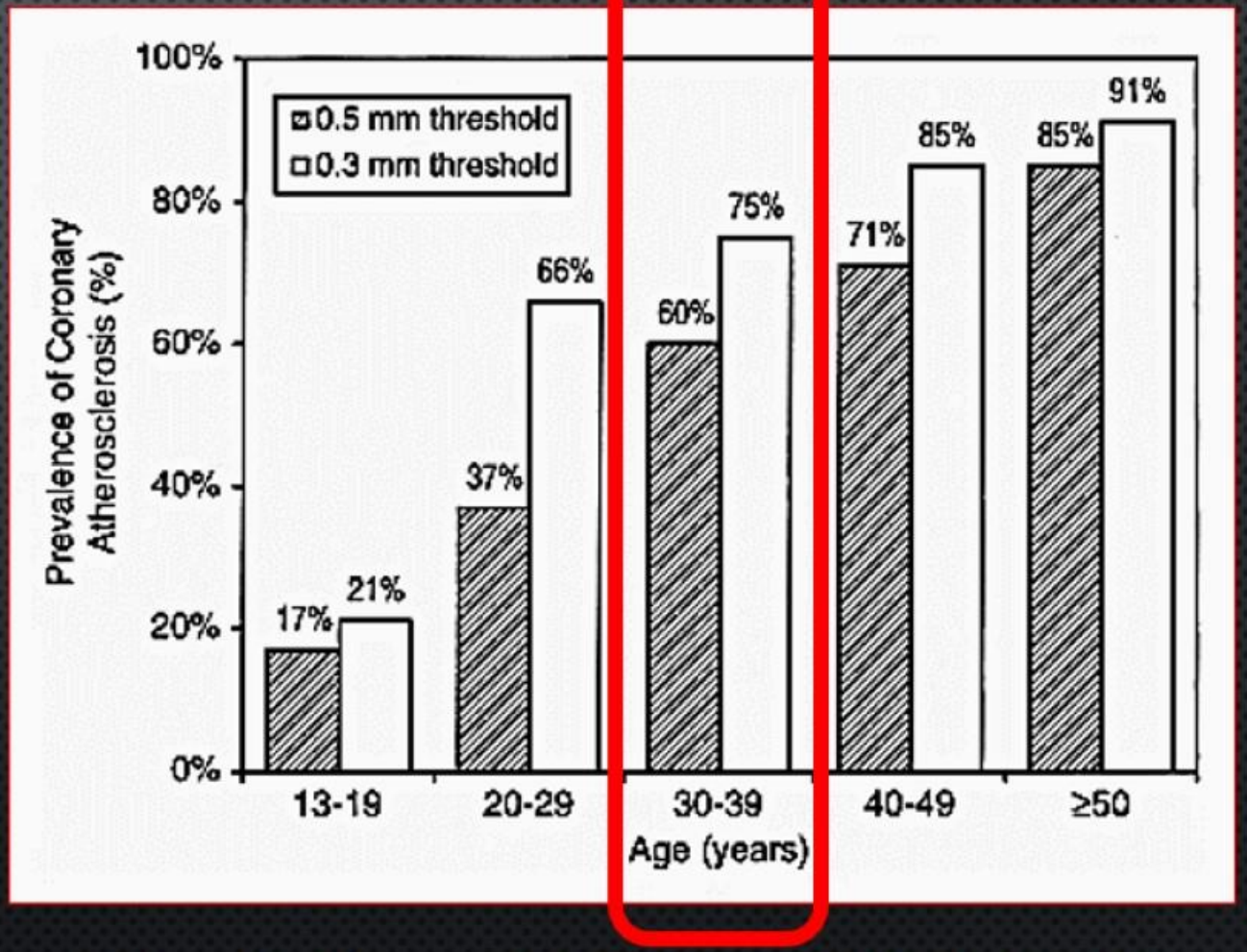
E. Murat Tuzcu, MD; Samir R. Kapadia, MD; Eralp Tutar, MD; Khaled M. Ziada, MD; Robert E. Hobbs, MD; Patrick M. McCarthy, MD; James B. Young, MD; Steven E. Nissen, MD

Background—Most of our knowledge about atherosclerosis at young ages is derived from necropsy studies, which have inherent limitations. Detailed, in vivo data on atherosclerosis in young individuals are limited. Intravascular ultrasonography provides a unique opportunity for in vivo characterization of early atherosclerosis in a clinically relevant context.

Methods and Results—Intravascular ultrasound was performed in 262 heart transplant recipients 30.9±13.2 days after transplantation to investigate coronary arteries in young asymptomatic subjects. The donor population consisted of 146 men and 116 women (mean age of 33.4±13.2 years). Extensive imaging of all possible (including distal) coronary segments was performed. Sites with the greatest and least intimal thickness in each CASS segment were measured in multiple coronary arteries. Sites with intimal thickness ≥0.5 mm were defined as atherosclerotic. A total of 2014 sites within 1477 segments in 574 coronary arteries (2.2 arteries per person) were analyzed. An atherosclerotic lesion was present in 136 patients, or 51.9%. The prevalence of atherosclerosis varied from 17% in individuals <20 years old to 85% in subjects ≥50 years old. In subjects with atherosclerosis, intimal thickness and area stenosis averaged 1.08±0.48 mm and 32.7±15.9%, respectively. For all age groups, the average intimal thickness was greater in men than women, although the prevalence of atherosclerosis was similar (52% in men and 51.7% in women).

Conclusions—This study demonstrates that coronary atherosclerosis begins at a young age and that lesions are present in 1 of 6 teenagers. These findings suggest the need for intensive efforts at coronary disease prevention in young adults.

(*Circulation*. 2001;103:2705-2710.)



Answer 5 > 70%

Circulation. 2001;103:2705-2710

WHAT IS THE % CV EVENT RATE @ 10 YEARS IN *TYPE 2 DIABETES PATIENTS THAT ARE OVERWEIGHT/OBESE*?

1. 2%
2. 4%
3. 6%
4. 18%
5. 30%

Look AHEAD trial

ORIGINAL ARTICLE

Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

The Look AHEAD Research Group*

ABSTRACT

BACKGROUND

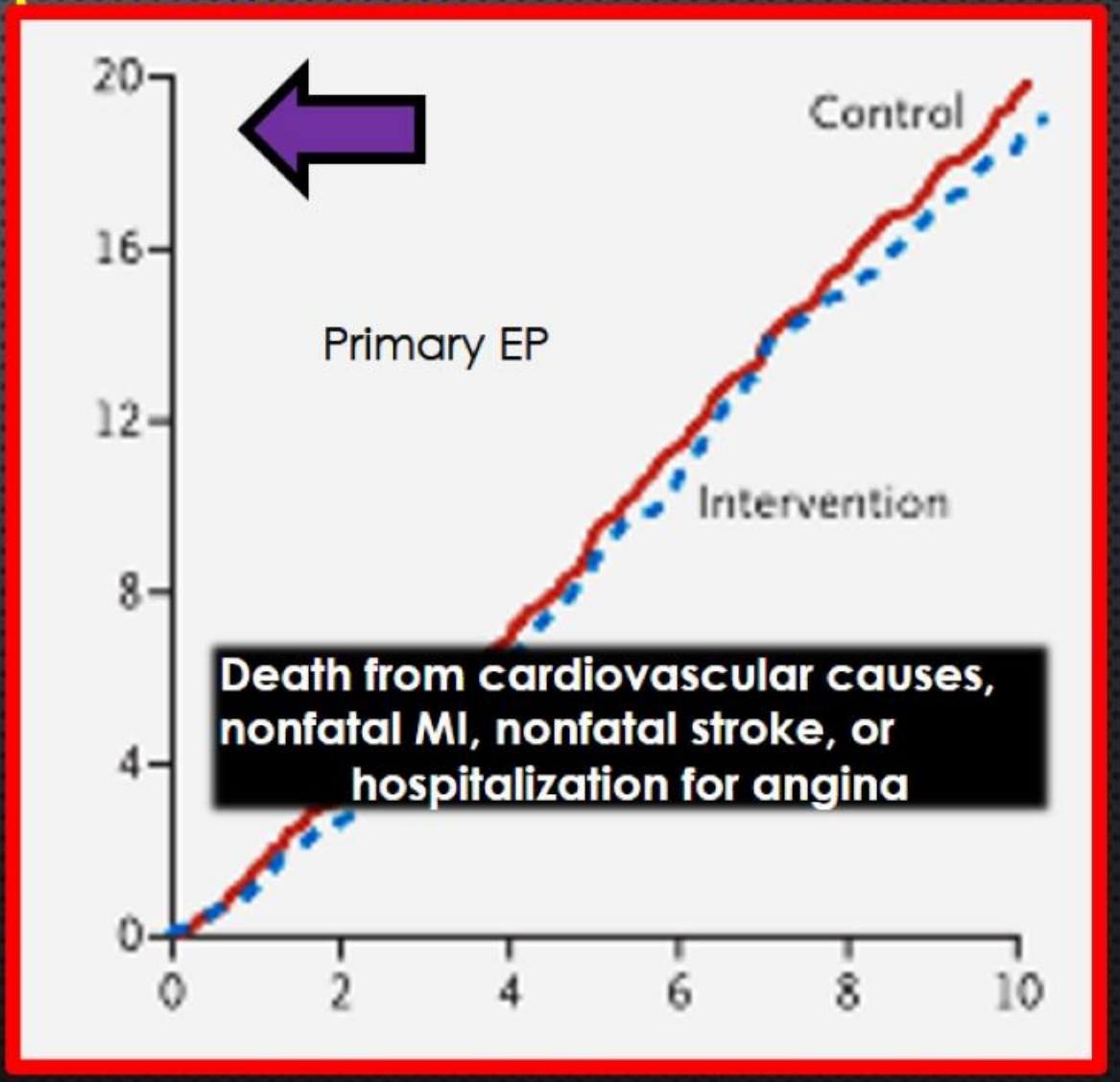
Weight loss is recommended for overweight or obese patients with type 2 diabetes on the basis of short-term studies, but long-term effects on cardiovascular disease remain unknown. We examined whether an intensive lifestyle intervention for weight loss would decrease cardiovascular morbidity and mortality among such patients.

Impact of Intensive Lifestyle Intervention on Depression and Health-Related Quality of Life in Type 2 Diabetes: The Look AHEAD Trial

N=5145 overweight/obese

N Engl J Med 2013;369:145-54

What is the CV event rate per year in type 2 diabetes?

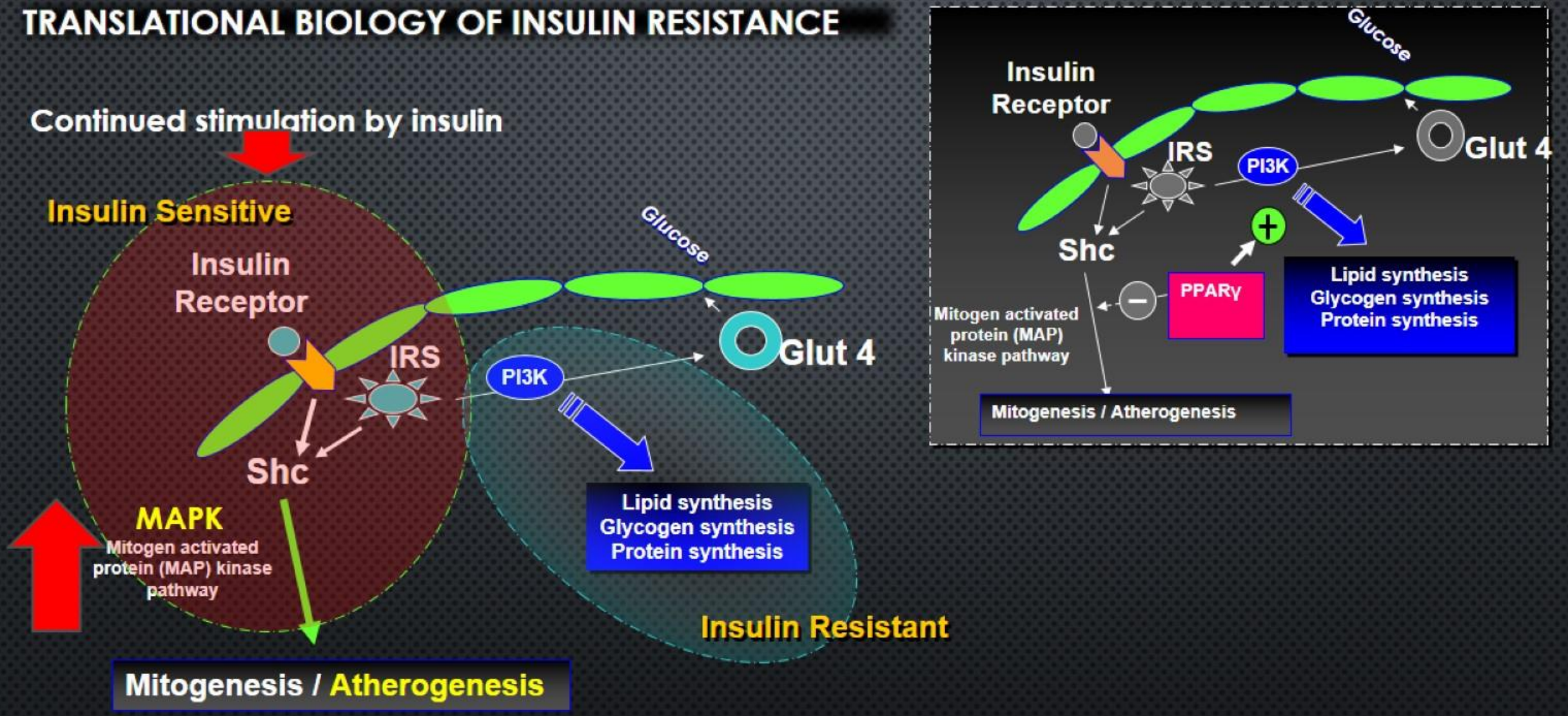


Look AHEAD

Outcome	Patients with Event	Control Group	Intervention Group	Hazard Ratio (95% CI)	P Value
Dead N=376	no.	no. of events (rate/100 person-yr)			
Myocardial infarction					
Fatal or nonfatal†	354	191 (0.84)	163 (0.71)	0.84 (0.68–1.04)	0.11
Fatal	16	11 (0.05)	5 (<0.02)	0.44 (0.15–1.26)	0.13
Nonfatal	342	183 (0.80)	159 (0.69)	0.86 (0.69–1.06)	0.16
Hospitalization for angina	390	196 (0.87)	194 (0.85)	0.97 (0.80–1.19)	0.79
Stroke	165	80 (0.34)	85 (0.36)	1.05 (0.77–1.42)	0.78
Heart failure	218	119 (0.51)	99 (0.42)	0.80 (0.61–1.04)	0.10
CABG	525	269 (1.21)	256 (1.14)	0.93 (0.78–1.10)	0.41

N Engl J Med 2013;369:145-54

TRANSLATIONAL BIOLOGY OF INSULIN RESISTANCE



Atherosclerosis Supplements 7 (2006) 11–15

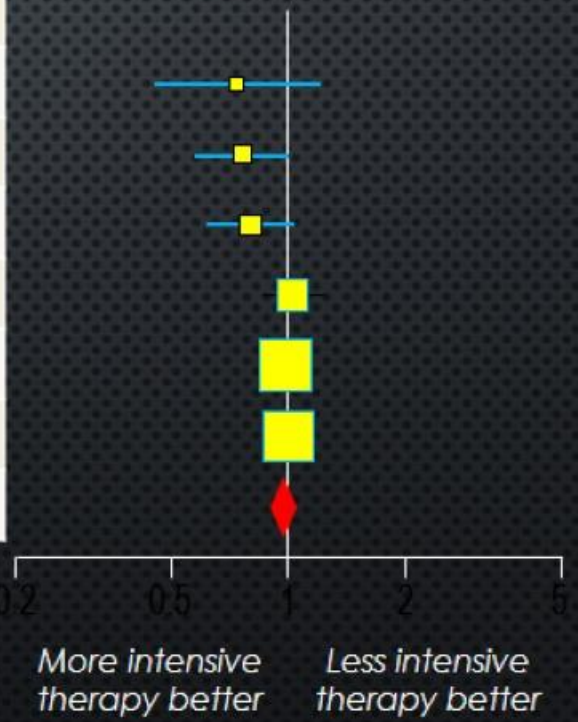
WHICH CARDIORENAL DRUGS REDUCE CV DEATH

1. STATINS
2. SGLT 2 (EMPA-REG) / GLP-1 AGONIST (LEADER)
3. PCSK9 INHIBITOR
4. DPP IV INHIBITOR
5. STATINS + PCSK9

MORE INTENSIVE LDL-C LOWERING & CV DEATH

No clear benefit on CV mortality

		# of CV Deaths		
Trial	**Year**	**More Intensive Rx Arm**	**Less Intensive Rx Arm**	**HR (95% CI)**
PROVE-IT TIMI 22	2004	27	36	0.74 (0.45-1.22)
A2Z	2004	86	111	0.76 (0.57-1.01)
TNT	2005	101	127	0.80 (0.61-1.03)
IDEAL	2005	223	218	1.03 (0.85-1.24)
SEARCH	2010	565	572	0.99 (0.88-1.11)
IMPROVE-IT	2015	538	537	1.00 (0.89-1.13)
Summary		**1540**	**1601**	**0.96 (0.90-1.03)**



NEJM 2004;350:1495-504
JAMA 2004;292:1307-16
NEJM 2005;352:1425-35
JAMA 2005;294:2437-45
Lancet 2010;376:1658-69
NEJM 2015;372:2387-97

ONLY POSITIVE CV TRIALS FOR DIABETES

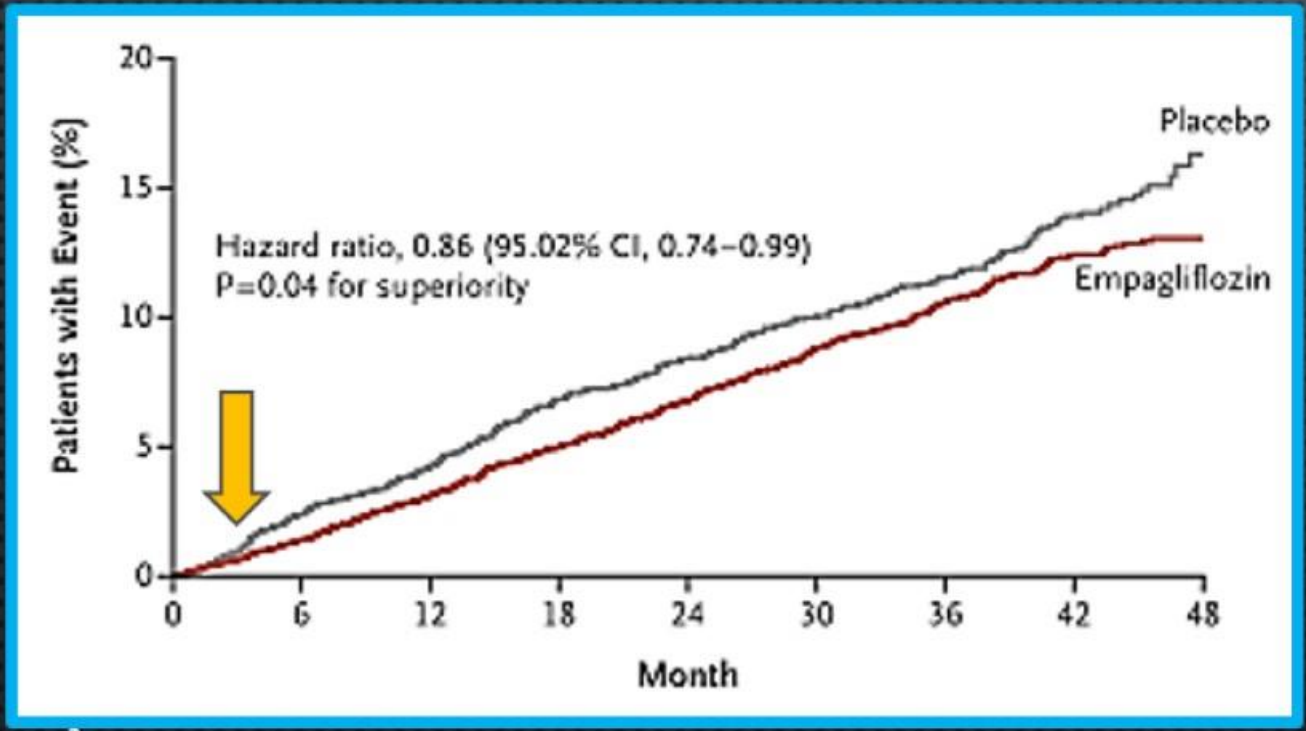
Drug	Trial	Inclusion	N	Mean	Baseline	HR-MACE	P-superiority
Pioglitazone	PROactive	Macrovascular disease	5,238	2.9 yrs	7.8%/7.9%	0.84 (0.72–0.98)	0.027
Empagliflozin	EMPA-REG	Established CV disease	7,028	2.6 yrs	8.07%/8.08%	0.86 (0.74–0.99)	0.04
Canagliflozin	CANVAS	ASCVD or >2 CV risk factors	10,142	3.6 yrs	8..2%/8.2%	0.86 (0.75–0.97)	0.02
Liraglutide	LEADER	High CV risk	9340	3.8 yrs	8.7/8.7	0.87 (0.78–0.97)	0.01
Semaglutide	SUSTAIN-6	Established CVD, CKD or HF	3297	2 yrs	8.7/8.7	0.74 (0.58-0.95)	0.02

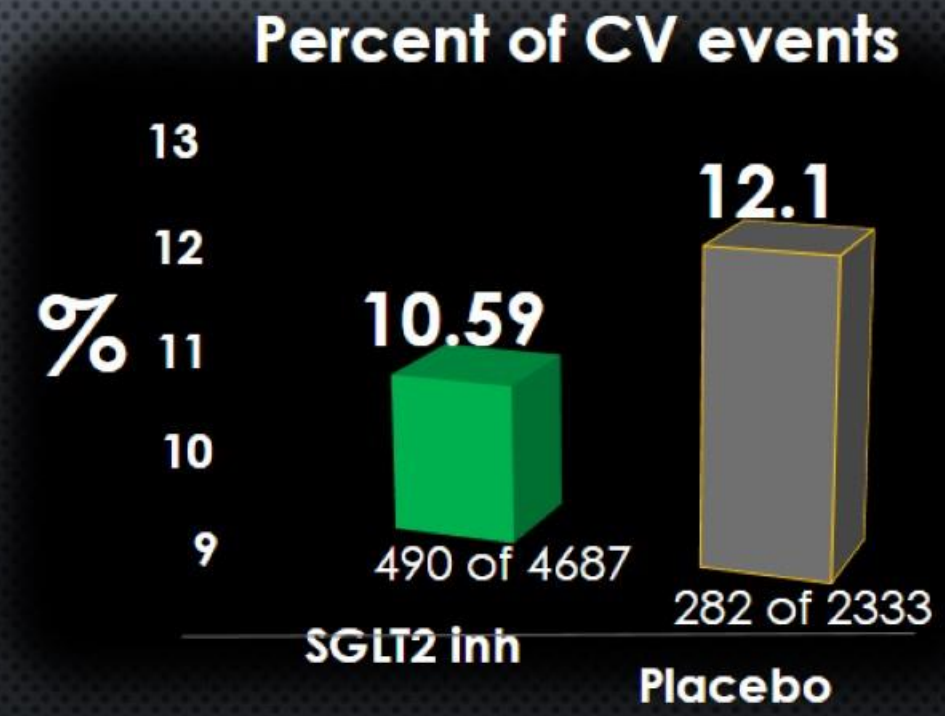
Chilton-2018 pending publication

EMPAGLIFLOZIN, AS COMPARED WITH PLACEBO, HAD A LOWER RATE OF THE PRIMARY COMPOSITE CV OUTCOMES

- N=7020
- 3.1 YEARS

0.86 (CI: 0.74 to 0.99)
P = 0.04 for superiority)





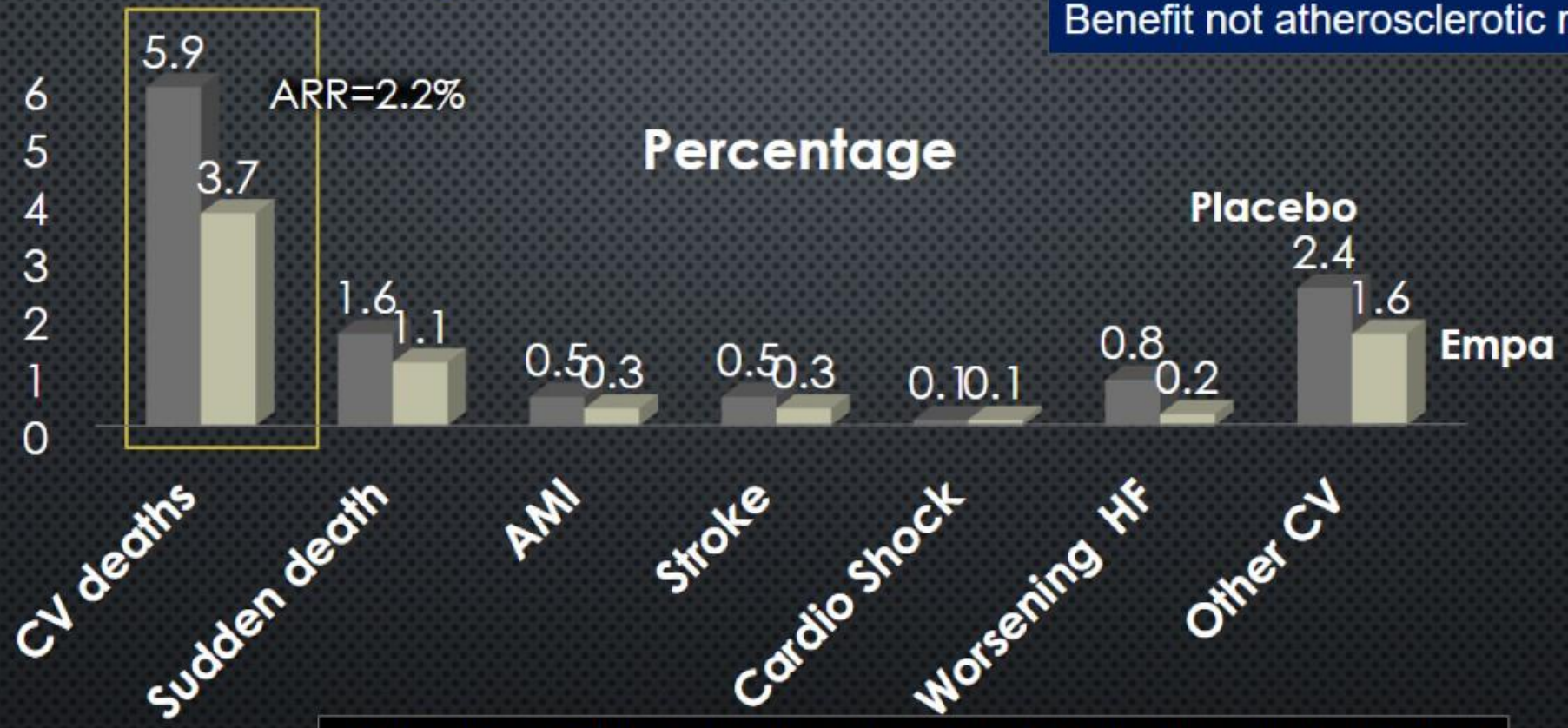
Primary composite outcome was death from nonfatal myocardial infarction, or nonfatal stroke

DOI: 10.1056/NEJMoa1504720
EASD 2015

CARDIOVASCULAR DEATH: NNT 39

0.62 (0.49–0.77) <0.001

No significant effect on MI or stroke..
Benefit not atherosclerotic related?



All deaths not attributed to the categories of CV death and not attributed to a non-CV cause were presumed CV deaths

DOI: 10.1056/NEJMoa1504720
EASD 2015

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*

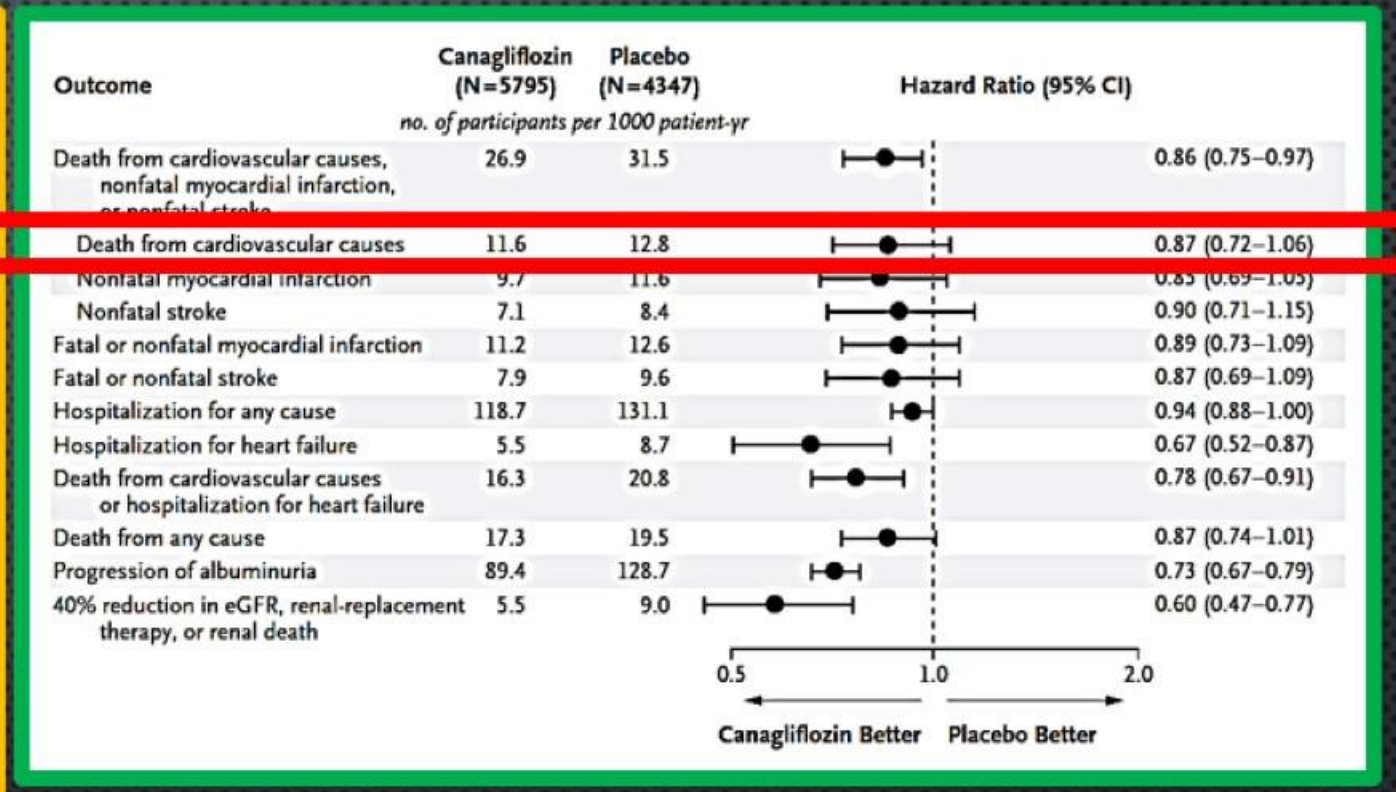
ABSTRACT

BACKGROUND

Canagliflozin is a sodium–glucose cotransporter 2 inhibitor that reduces glycemia as well as blood pressure, body weight, and albuminuria in people with diabetes. We report the effects of treatment with canagliflozin on cardiovascular, renal, and safety outcomes.

METHODS

The CANVAS Program integrated data from two trials involving a total of 10,142 participants with type 2 diabetes and high cardiovascular risk. Participants in each trial were randomly assigned to receive canagliflozin or placebo and were followed for a mean of 188.2 weeks. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.



N Engl J Med 2017;377:644-57

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 28, 2016 VOL. 375 NO. 4

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., F.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

ABSTRACT

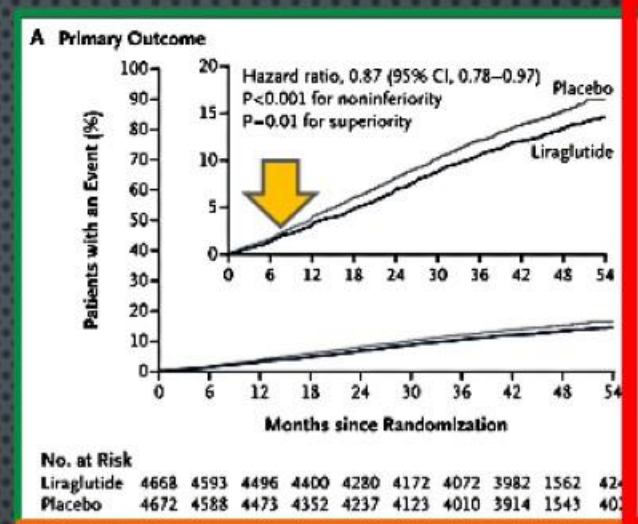
BACKGROUND
The cardiovascular effect of liraglutide, a glucagon-like peptide 1 analogue, when added to standard care in patients with type 2 diabetes, remains unknown.

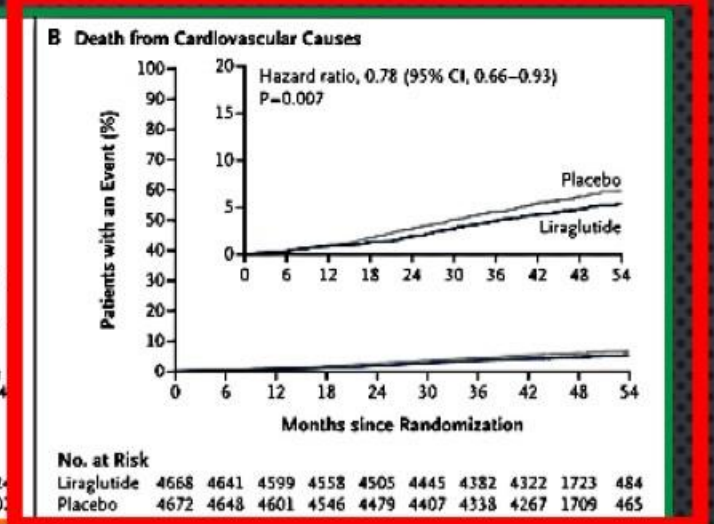
METHODS
In this double-blind trial, we randomly assigned patients with type 2 diabetes and high cardiovascular risk to receive liraglutide or placebo. The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The primary hypothesis was that liraglutide would be noninferior to placebo with regard to the primary outcome, with a margin of 1.30 for the upper boundary of the 95% confidence interval of the hazard ratio. No adjustments for multiplicity were performed for the prespecified exploratory outcomes.

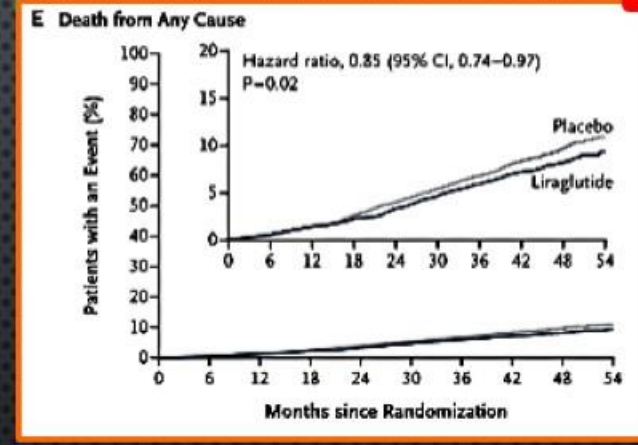
From the University of Texas Southwestern Medical Center, Dallas (S.P.M.); Massachusetts General Hospital, Boston (G.H.D.); Novo Nordisk, Bagsvaerd, Denmark (K.B.-F., P.K., L.S.R., M.S.); Friedrich Alexander University of Erlangen, Erlangen (J.F.E.M.), and St. Josef Hospital, Ruhr University, Bochum (M.A.N.) — both in Germany; Cleveland Clinic, Cleveland (S.E.N.); London School of Hygiene and Tropical Medicine Medical Statistics Unit (S.P.) and Imperial College London (N.R.P.), London; George Washington University Medical Center, Washington, DC (W.M.S.); Lunenfeld–Tanenbaum

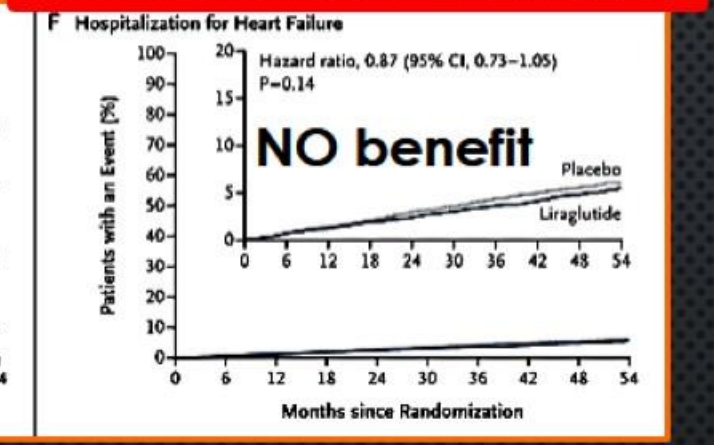
Primary composite outcome
in the time-to-event analysis was the
first occurrence of death from
cardiovascular
causes, nonfatal myocardial infarction,
or nonfatal stroke.

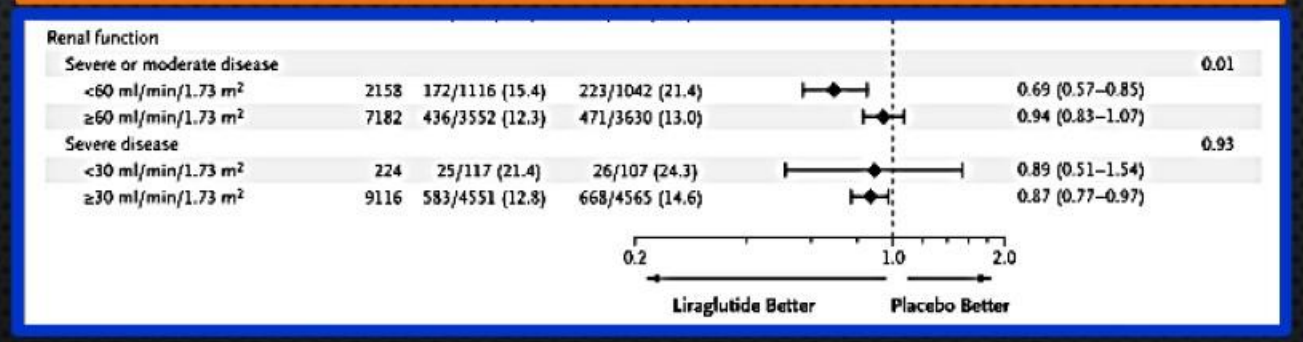
LEADER trial











Heart failure and diabetes

↓↓GLUT 4 uptake
Abnormal Ca handling
Mitochondrial dysfunction
Endoplasmic reticulum stress
Inflammation

Metabolic changes

Abnormal ventricular relaxation

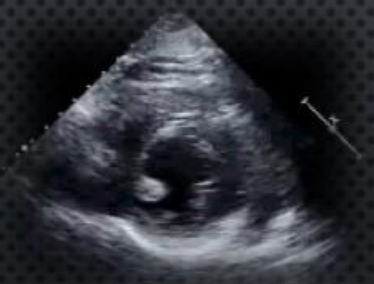
Heart Fail. Rev. 17, 325–344

Herz 36, 102–115

Insulin resistant cardiomyocyte

Diastolic dysfunction

Preserved EF



↑ reactive oxygen species
↑ fibrosis / stiffness

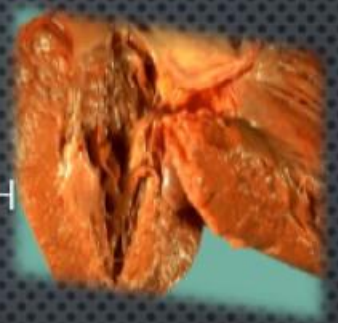
Structural changes

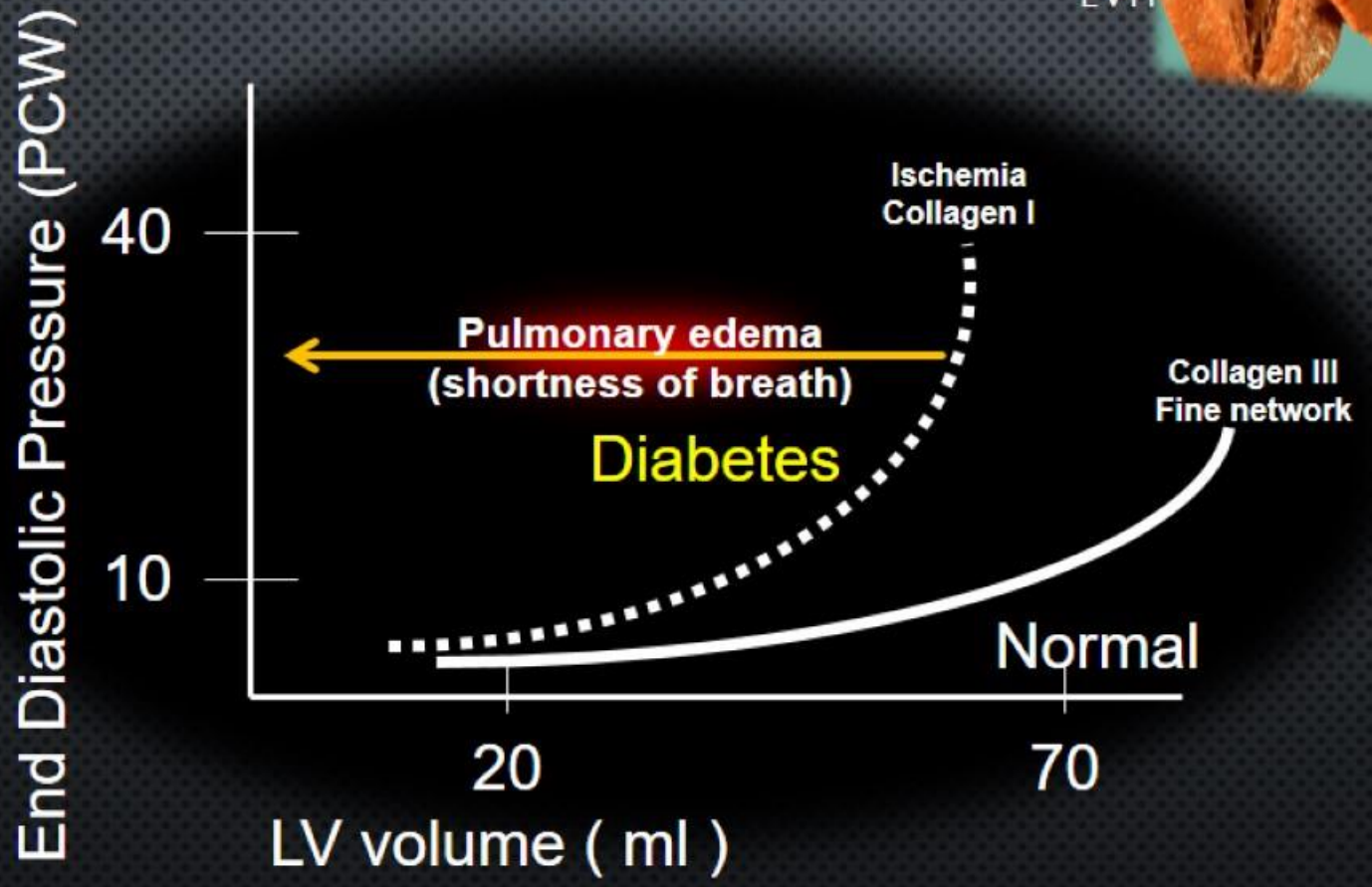
Abnormal ventricular arterial coupling (stiffness)

Chilton

Sowers..NATURE REVIEWS | ENDOCRINOLOGY 2016;12:144

DIASTOLIC HEART FAILURE IS COMMON IN DIABETES

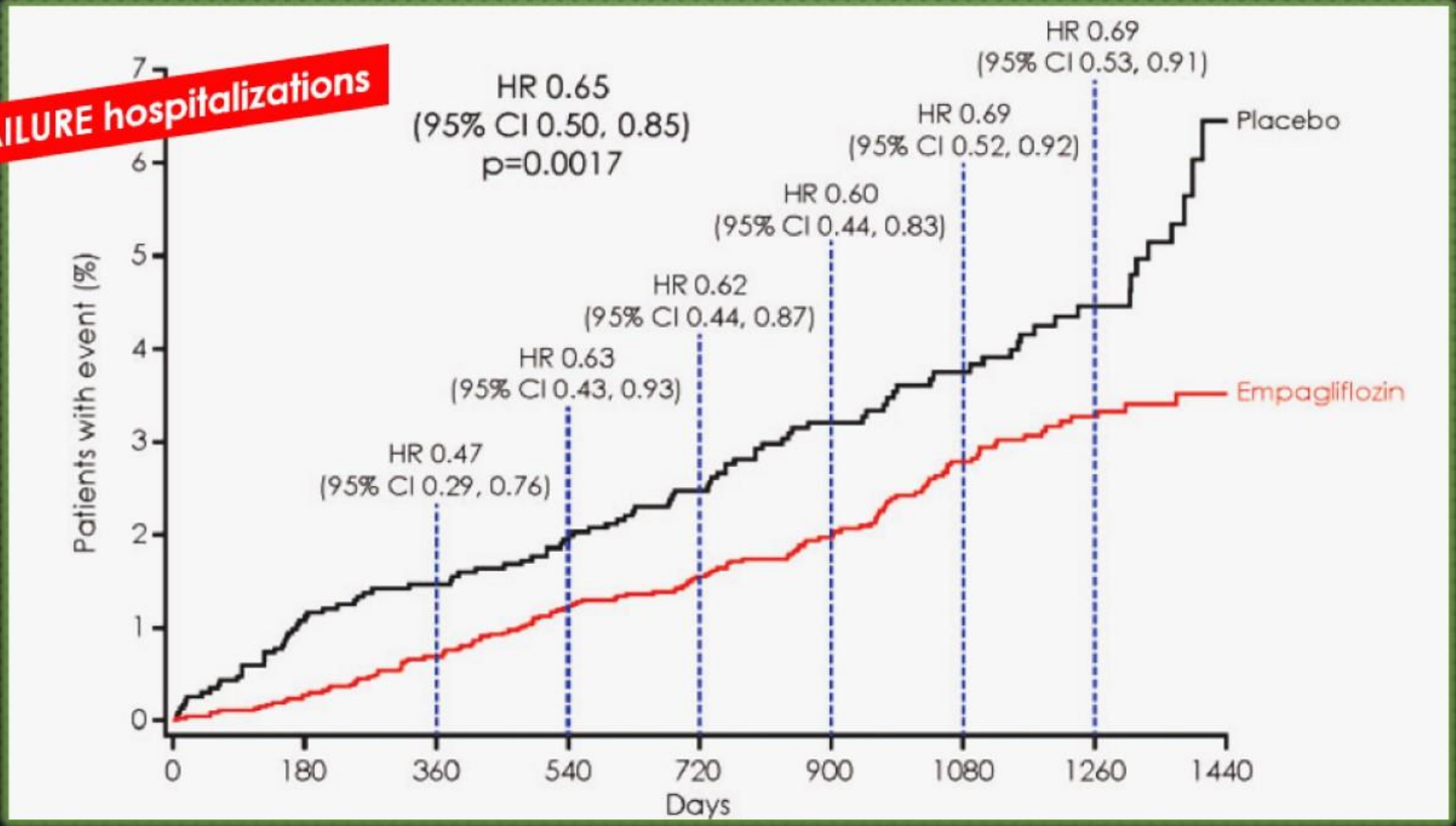




Chilton-pending publication

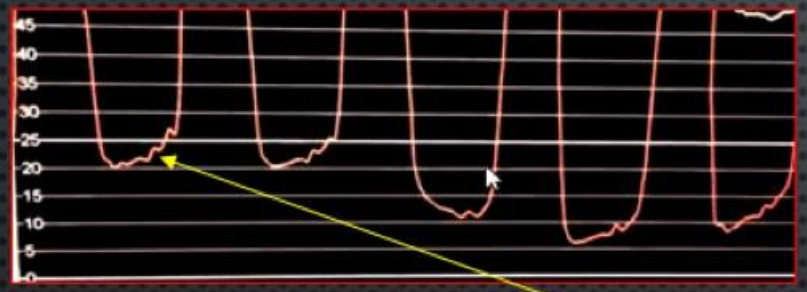
Risk reduction in HF hospitalization with empagliflozin vs. placebo over time

HEART FAILURE hospitalizations

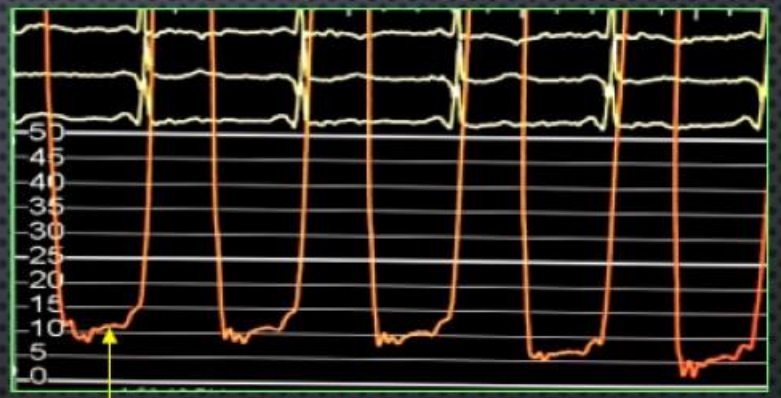


European Heart Journal (2018) 39, 363–370

Young obese T2DM female with SOB



200 ug NTG

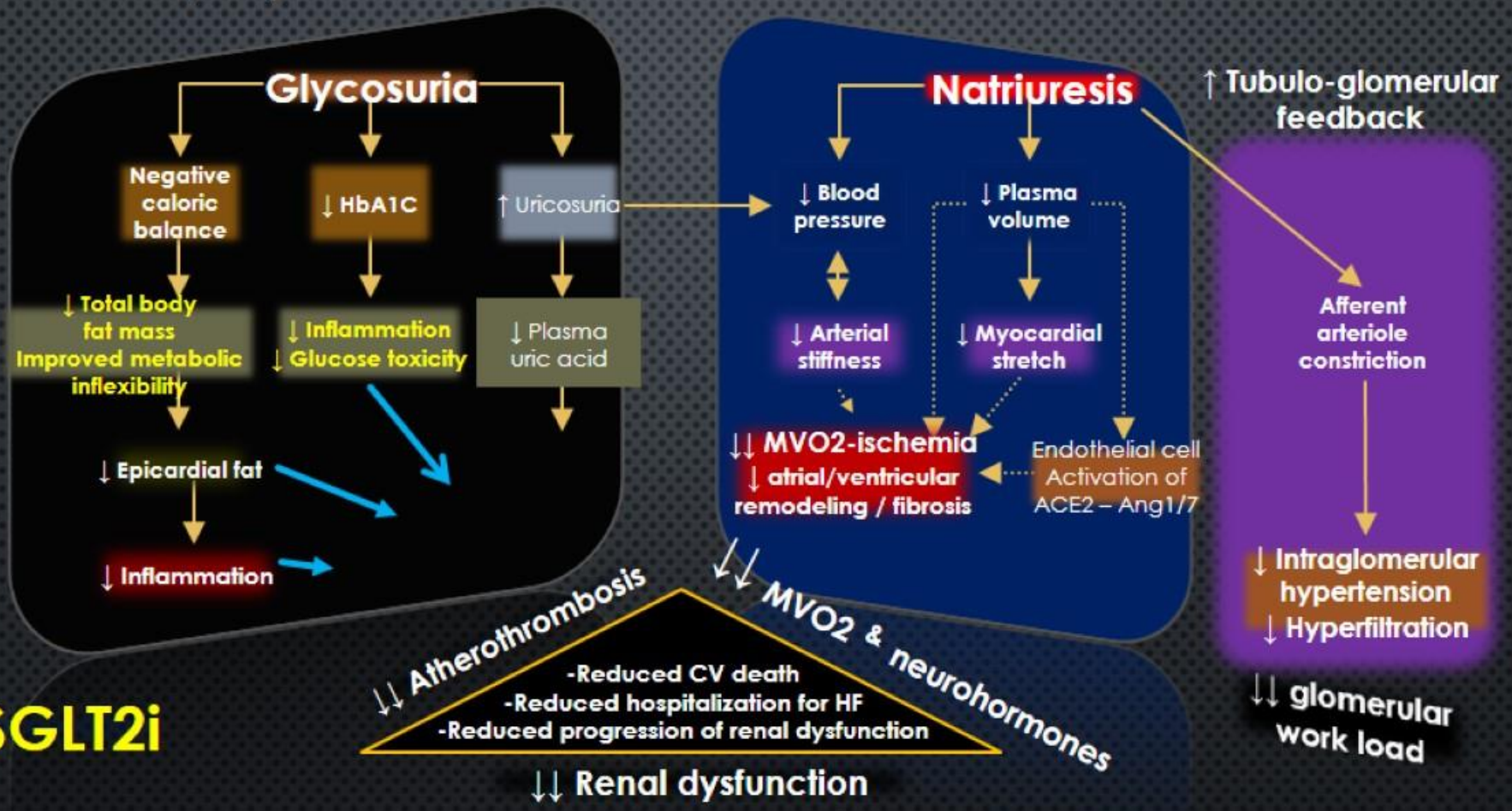


Nitric oxide

LVEDP
Left ventricular end diastolic pressure

Chilton

800 cc day 1 then 150-300/day
2 cans coke in calories/day



CV AND RENAL EFFECTS OF SGLT2 INHIBITORS....MEAN BP DROP 4 MMHG

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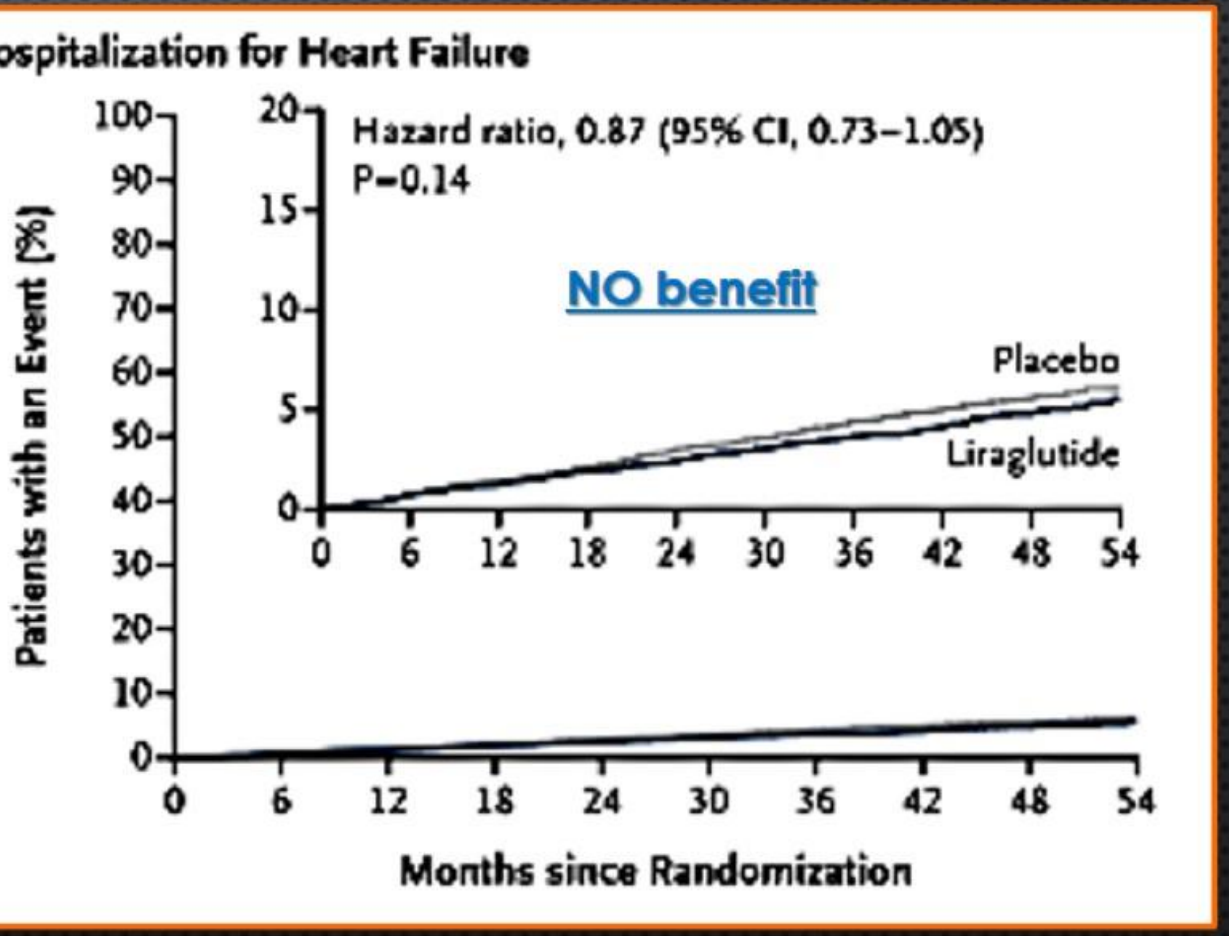
In this double-blind trial, we randomly assigned patients with type 2 diabetes and high cardiovascular risk to receive liraglutide or placebo. The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The primary hypothesis was that liraglutide would be noninferior to placebo with regard to the primary outcome, with a margin of 1.30 for the upper boundary of the 95% confidence interval of the hazard ratio. No adjustments for multiplicity were performed for the prespecified exploratory outcomes.

From the University of Texas Southwestern Medical Center, Dallas (S.P.M.); Massachusetts General Hospital, Boston (G.H.D.); Novo Nordisk, Bagsvaerd, Denmark (K.B.-F., P.K., L.S.R., M.S.); Friedrich Alexander University of Erlangen, Erlangen (J.F.E.M.), and St. Josef Hospital, Ruhr University, Bochum (M.A.N.) — both in Germany; Cleveland Clinic, Cleveland (S.E.N.); London School of Hygiene and Tropical Medicine Medical Statistics Unit (S.P.) and Imperial College London (N.R.P.), London; George Washington University Medical Center, Washington, DC (W.M.S.); Lunenfeld–Tanenbaum



LEADER trial

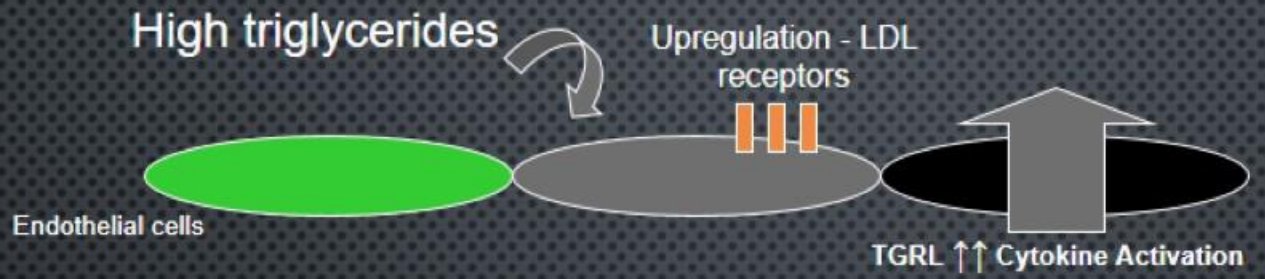
CV LOOK @ NEW CARDIOVASCULAR DRUGS FOR TYPE 2 DIABETES

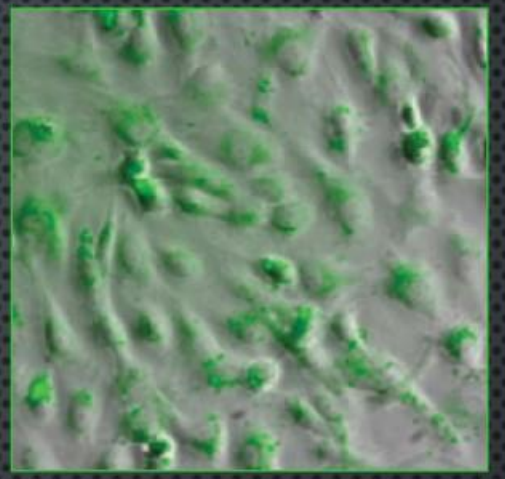
Trial	↓ CV events	↓ CV death	↓ heart failure hospitalizations	↓ Nephropathy
EMPA-SGLT2I	Yes	Yes	Yes	Yes
CANA	Yes	No	Yes	Yes
LIRA-GLP-1	Yes	Yes	No	Yes
SEMA	Yes	No	No	Yes

Already on standard of care

Chilton pending 2018

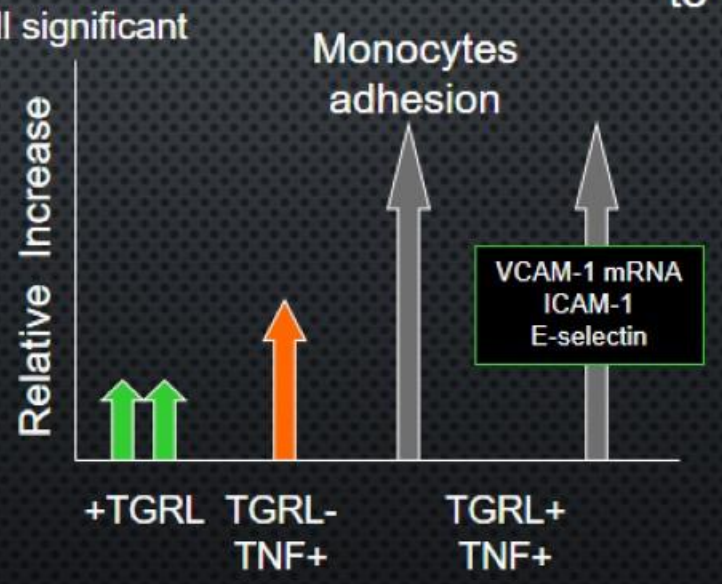
PRIMING VASCULAR ENDOTHELIAL CELLS FOR ENHANCED INFLAMMATORY RESPONSE





TGRL electron transfer-based fluorescence bound to HAECs treated for 2hrs

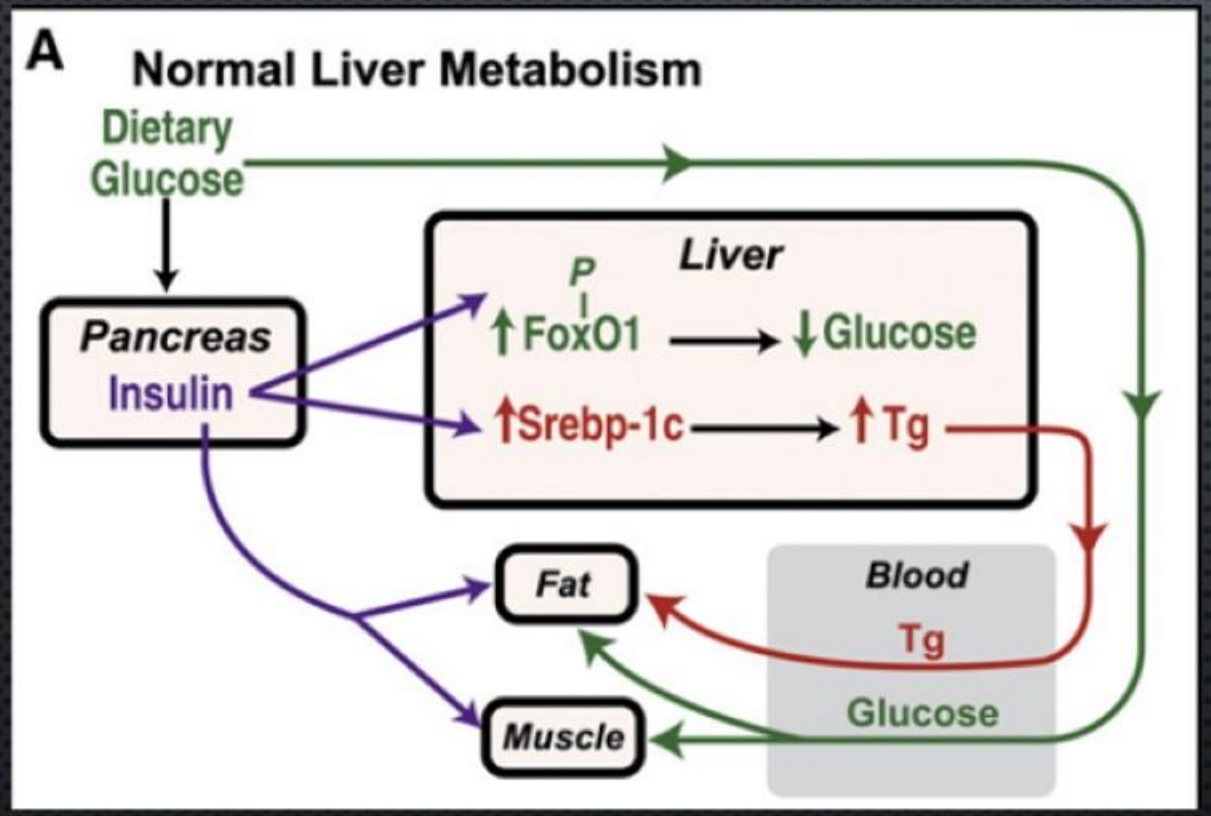
- TGRL ALONE NO INFLAMMATION IN HAEC
- TGRL ENHANCED INFLAMMATORY RESPONSE 10X TO CYTOKINE STIMULATION

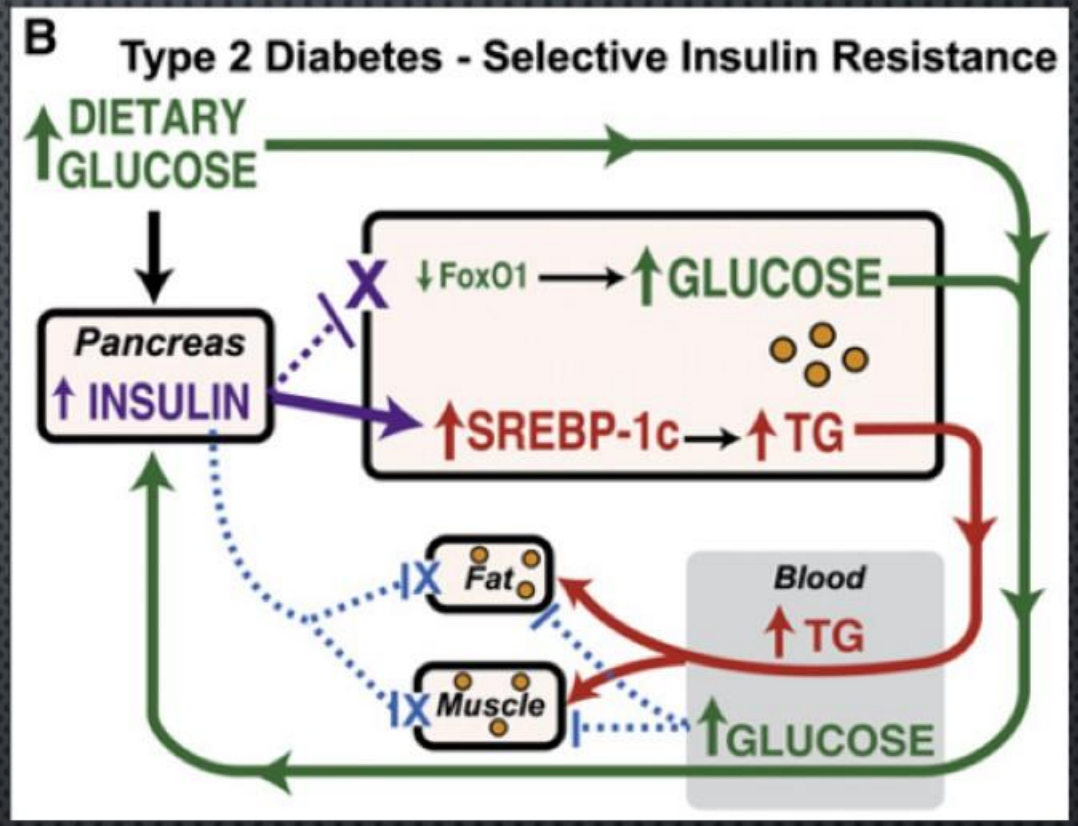


HAECs were repetitively incubated with dietary levels of freshly isolated TGRL for 2 hours per day for 1 to 3 days to mimic postprandial lipidemia.

Ting et al Circ Res Feb 2007;100:000

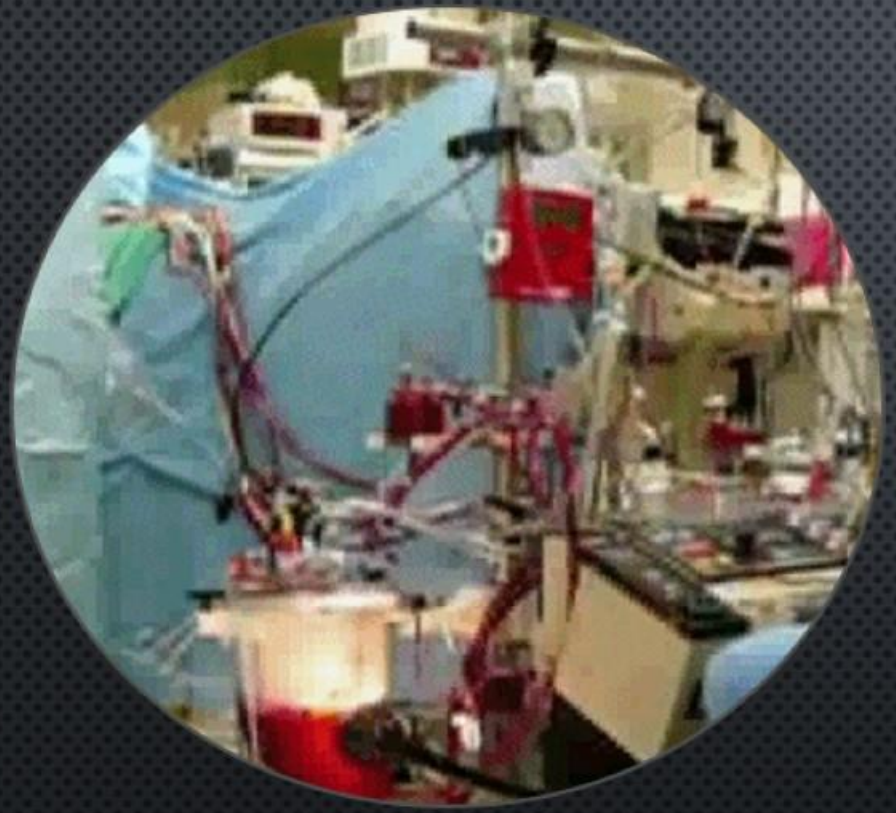
TARGETING METABOLICS

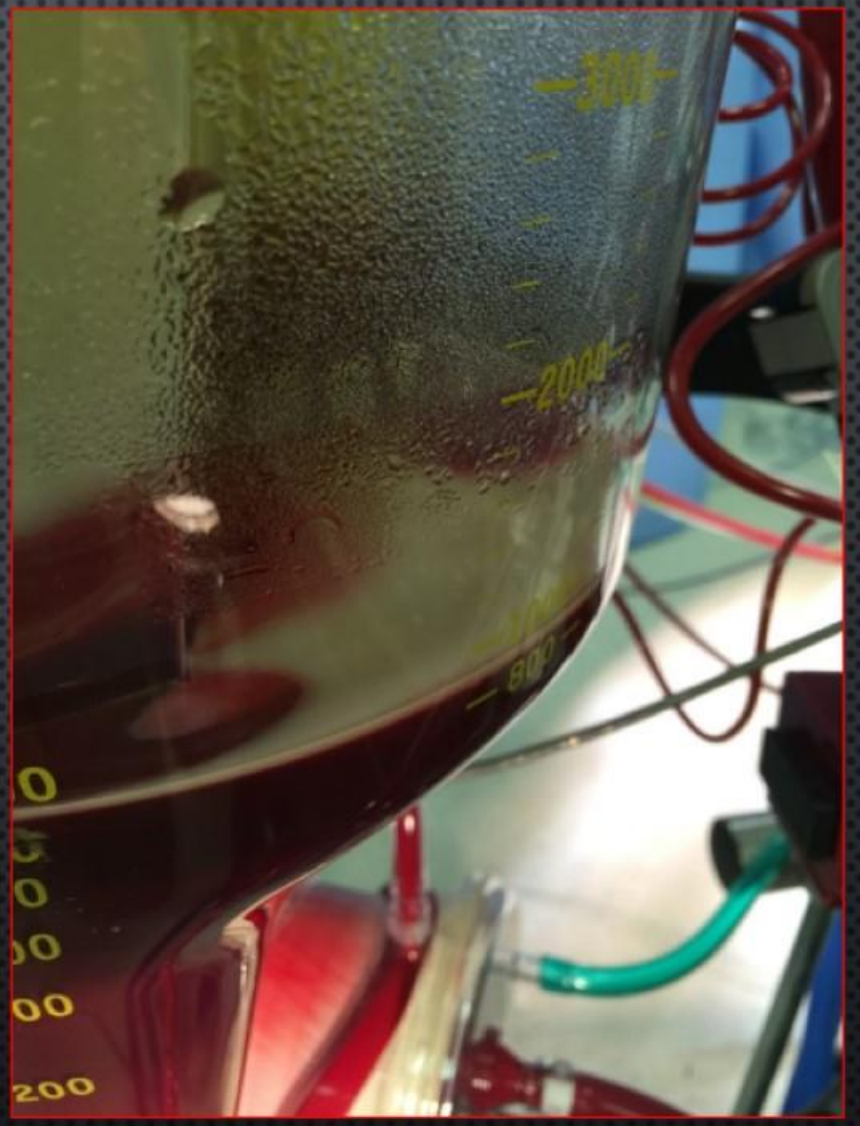




Selective insulin resistance in liver of mice with type 2 diabetes. Insulin fails to decrease gluconeogenesis, but it continues to stimulate synthesis of fatty acids and Tg. This produces the deadly combination of hyperglycemia and hypertriglyceridemia

LAST slide





Lifestyle is the best choice

Thank you

Post test

WHAT PERCENTAGE ASYMPTOMATIC 30-40 YEAR OLD PEOPLE HAVE CORONARY ATHEROSCLEROSIS?

1. 10%
2. 40%
3. 50%
4. 60%
5. >70%

No diabetes

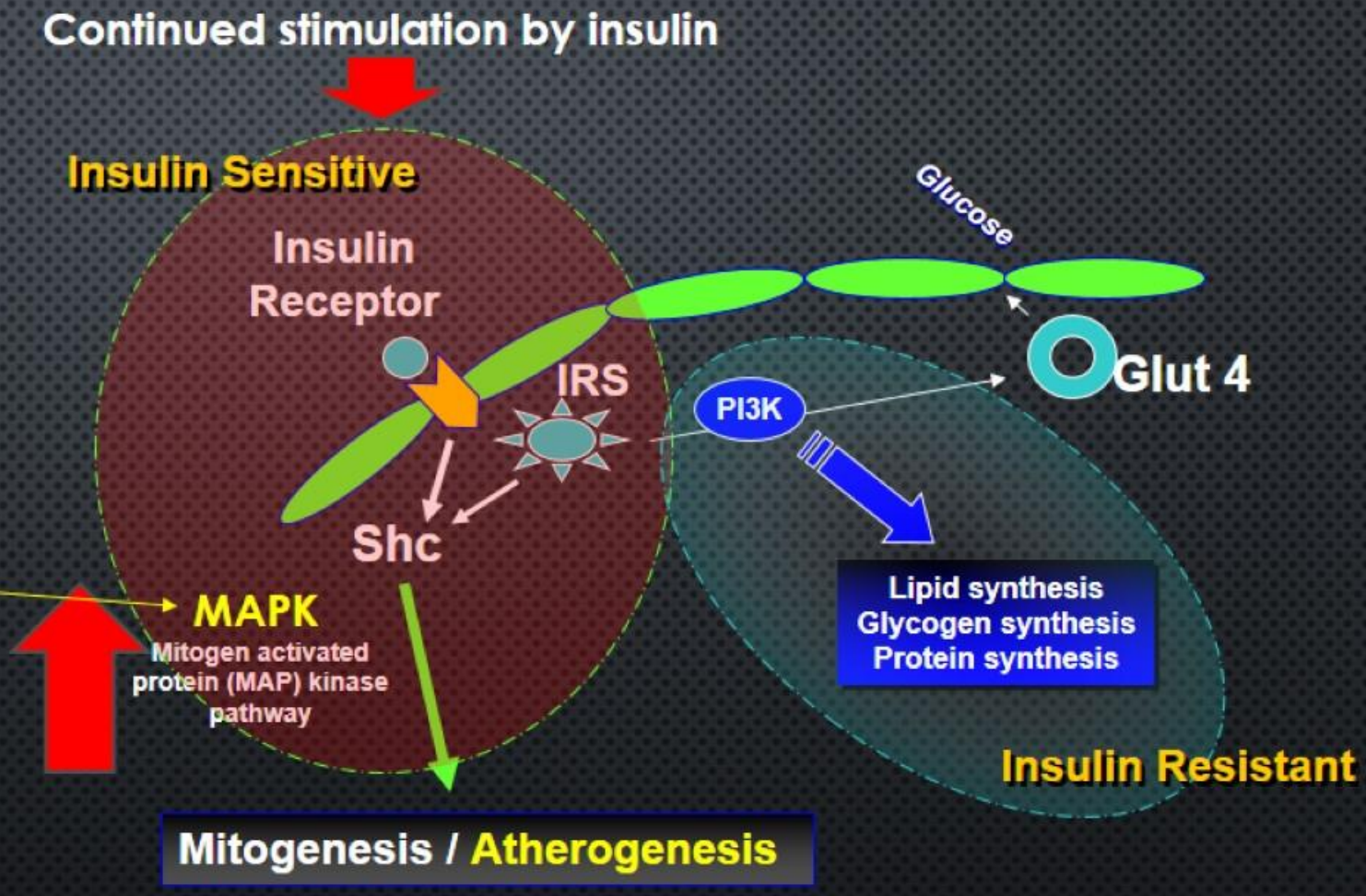
WHAT IS THE % CV EVENT RATE @ 10 YEARS IN TYPE 2 DIABETES PATIENTS THAT ARE OVERWEIGHT/OBESE?

1. 2%
2. 4%
3. 6%
4. 18%
5. 30%

Look AHEAD trial

WHAT CELLULAR PATHWAY CONTINUES TO BE INSULIN SENSITIVE IN DIABETES

1. HMG CoA PATHWAY
2. PPAR
3. SGLT2
4. MAP KINASE
5. PI3 KINASE



WHICH CARDIORENAL DRUGS REDUCE CV DEATH

1. STATINS
2. SGLT 2 (EMPA-REG) / GLP-1 AGONIST (LEADER)
3. PCSK9 INHIBITOR
4. DPP IV INHIBITOR
5. STATINS + PCSK9

Answer 2

....the end

Thanks