HOSPITAL MEDICINE SUMMIT

Individualizing Management of T2DM in the Hospital Setting to Reduce Macro and Microvascular Complications

INTEGRITY CONTINUING EDUCATION

PIM Postgraduate Institute for Medicine

This CME activity is provided by Integrity Continuing Education.
This CEU/CNE activity is co-provided by Postgraduate Institute for Medicine and Integrity Continuing Education.

This activity is supported by an educational grant from Boehringer Ingelheim Pharmaceuticals, Inc. and Lilly USA, LLC.

Faculty

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Professor of Medicine
Director
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San Antonio, Texas

Faculty Disclosures

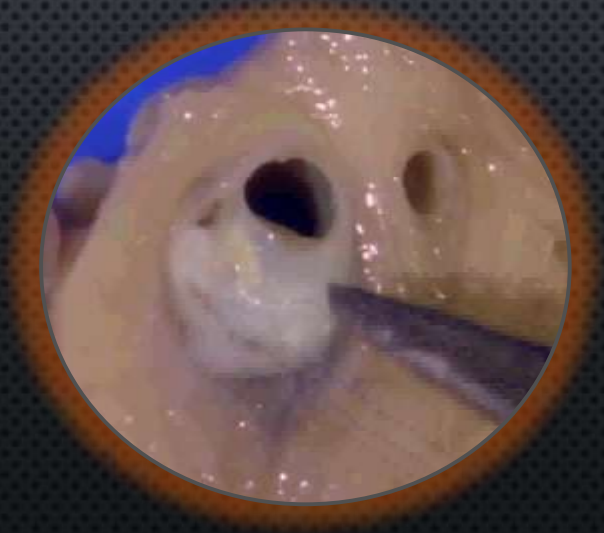
- Consultant: Boehringer Ingelheim, Merck Sharpe & Dohme, Novo Nordisk

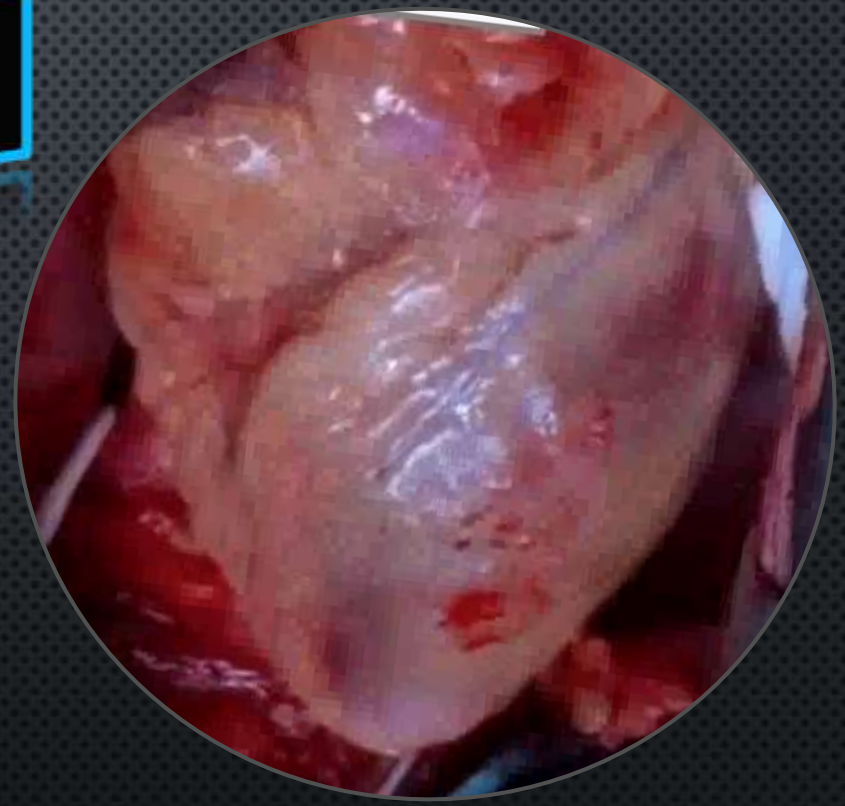
Learning Objectives

- Summarize correlations between macro and microvascular complications of uncontrolled T2DM and hospitalization
- Evaluate the risk/benefit profiles of novel T2DM therapies in achieving glycemic control and reducing vascular complications
- Employ evidence-based strategies to individualize treatment for diverse patients with T2DM to achieve glycemic control and reduce hospitalizations from vascular complications

INDIVIDUALIZING MANAGEMENT OF T2DM IN THE HOSPITAL SETTING TO REDUCE MACRO AND MICROVASCULAR COMPLICATIONS

"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

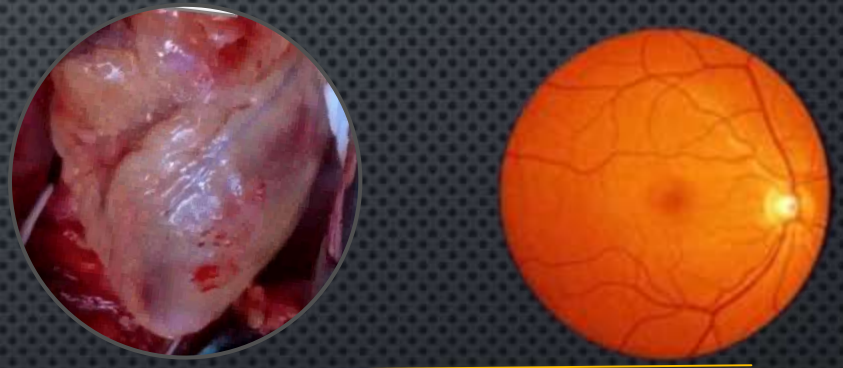
New treatments reduce cardiorenal events….but still need lower glucose

Risk / safety

- "Diabetes treatment in 21st century is event driven"

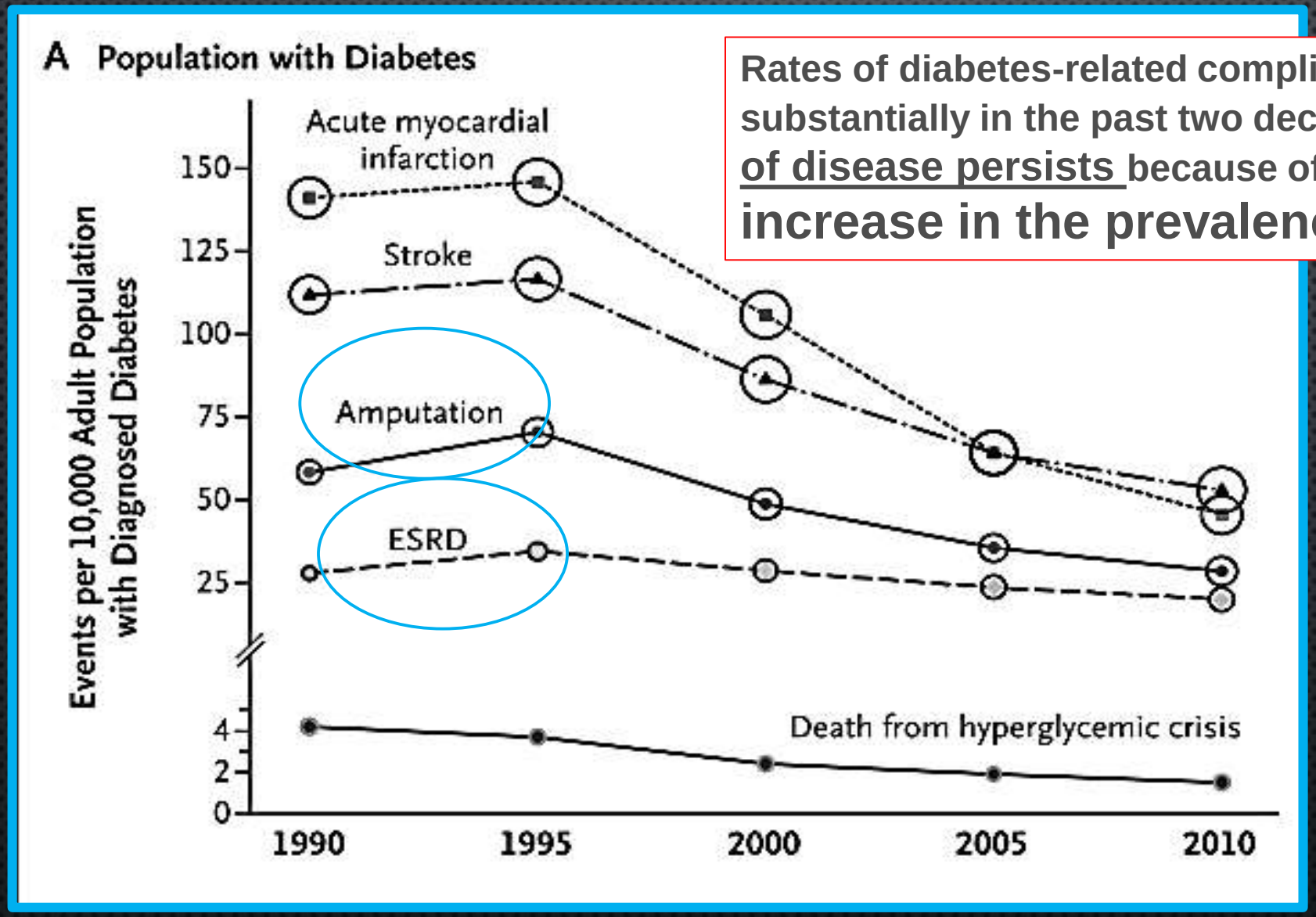
Benefit

Acute coronary syndrome and microvascular with type 2 diabetes



Both important to patients
Both insulin resistant

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

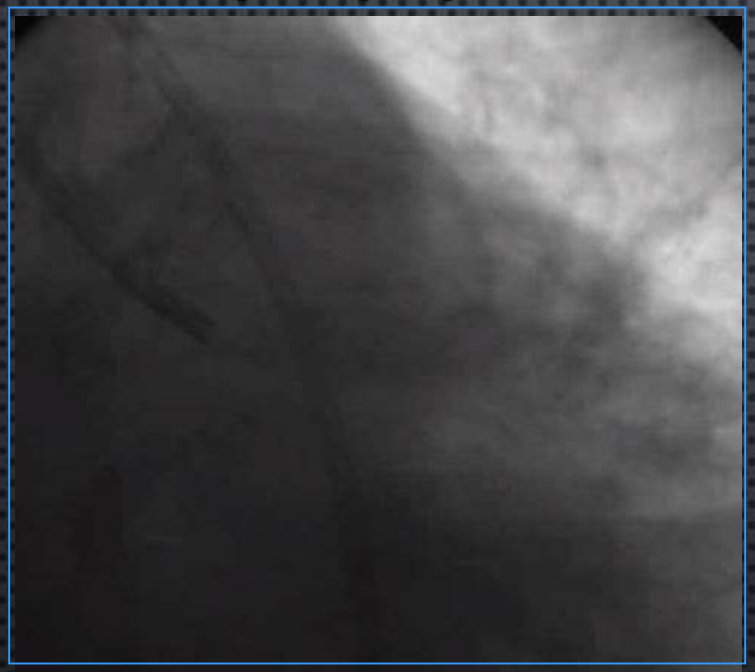
N=57000

N Engl J Med 2014; 370:1514-1523

Case 1

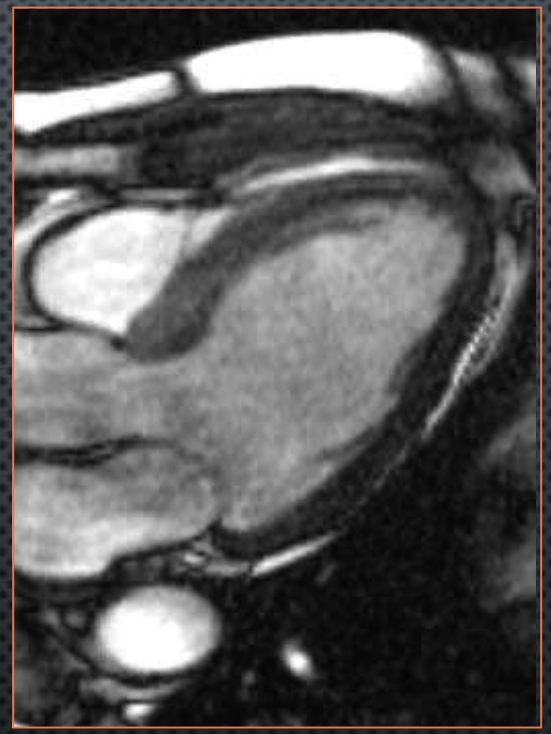
Clinical Practice

39 y/o physician

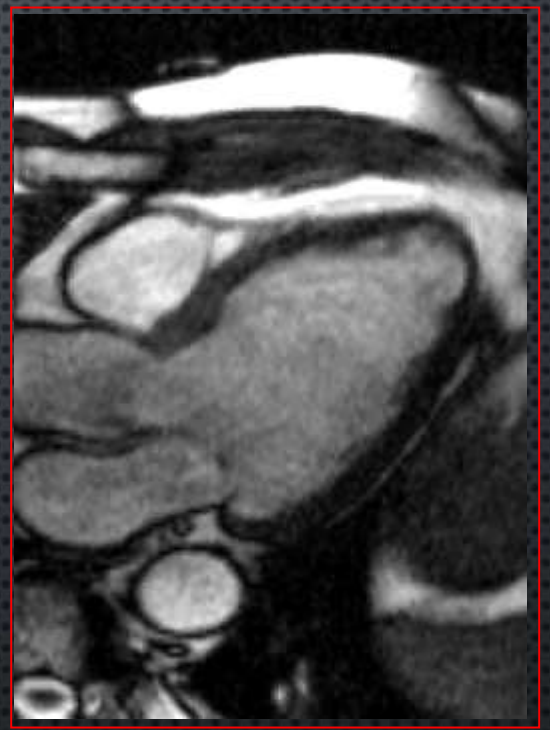


Negative history-except type 2 DM
BP @ cath lab 138/86

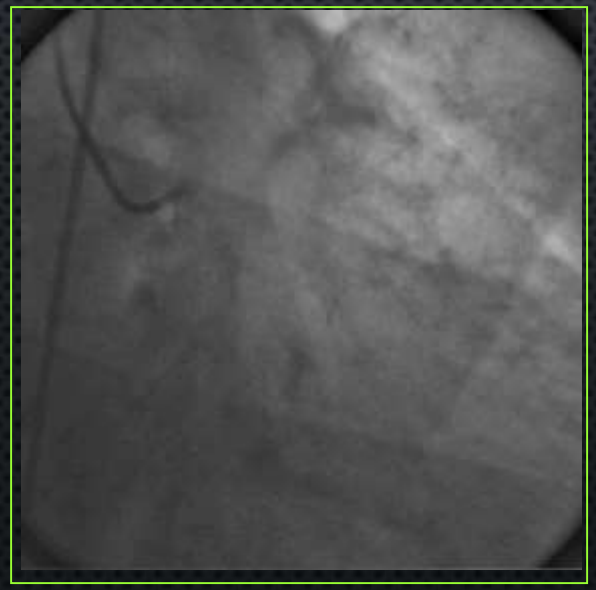
"Bad Day in Texas"



4 weeks



9 modifiable risk factors account for over 90% of the risk of an initial acute MI..INTERHEART



Smoking
No physical activity
Psychosocial stress

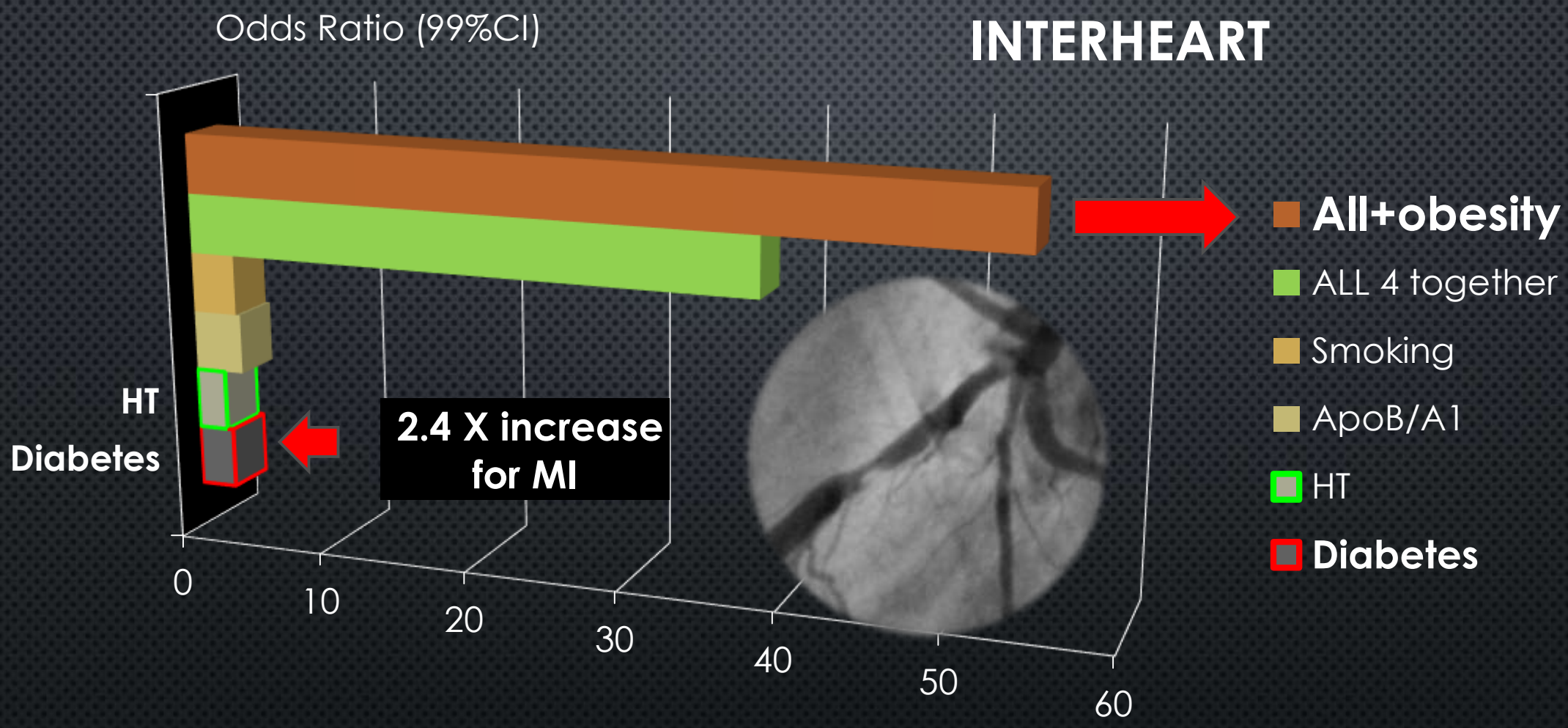
Too much alcohol
Abdominal obesity

Hyperlipidemia
Diabetes
Hypertension

Low fruits &
vegetables

Lancet September 11, 2004;364:937

RISK OF ACUTE MYOCARDIAL INFARCTION ASSOCIATED WITH SELECTED CV RISK FACTORS-80% FROM 4 MAJOR FACTORS



Adapted from Yusuf et al

Lancet 2004; 364: 937–52

WHICH DRUGS REDUCE CV DEATH

1. STATINS
2. SGLT 2 (EMPA-REG)
3. SGLT2 (CANVAS)
4. GLP-1 AGONIST (LEADER)
5. GLP-1 AGONIST (SUSTAIN-5)

Answer 2/4

Overview of new cardiovascular drugs for diabetes

ONLY POSITIVE CV TRIALS FOR DIABETES

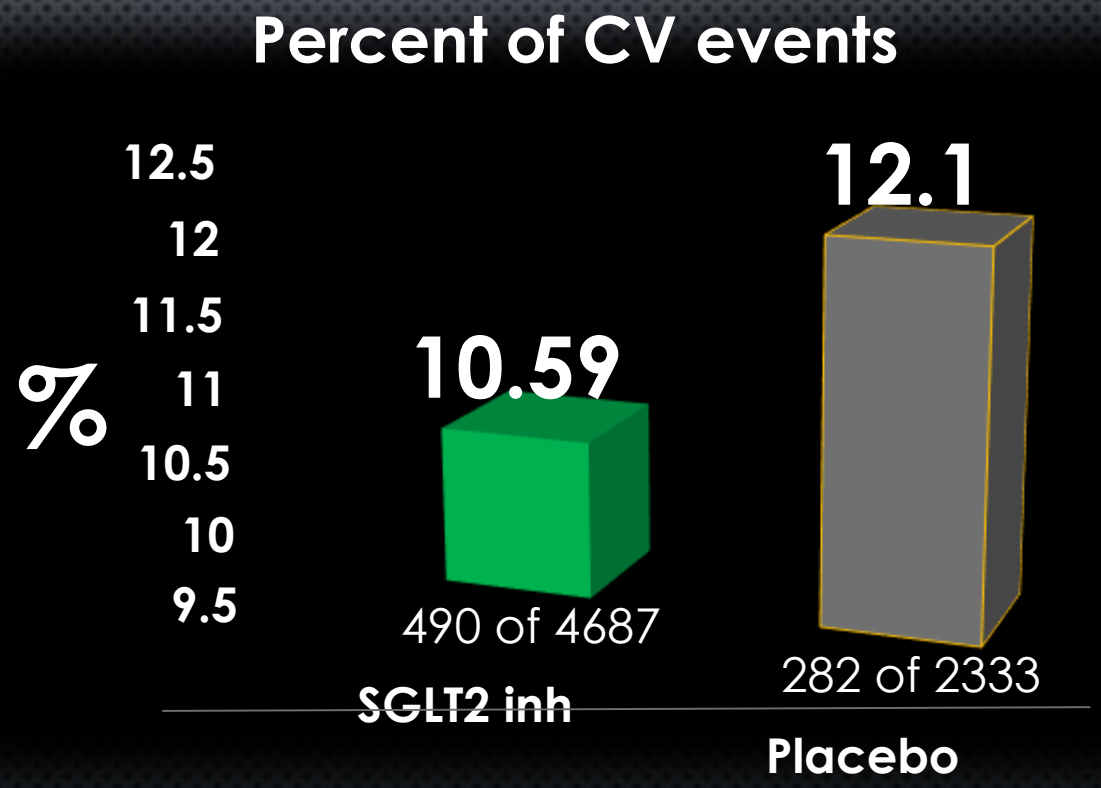
Drug	Trial	Inclusion	N	Mean	Baseline	HR-MACE	P-superiority
Pioglitazone	PROactive	Macrovascular disease	5,238	2.9 yrs	7.8%/7.9%	0.84 (0.72–0.98)	0.027
Empagliflozin	EMPA-REG	Established CV disease	7,028	2.6 yrs	8.07%/8.08%	0.86 (0.74–0.99)	0.04
Canagliflozin	CANVAS	ASCVD or >2 CV risk factors	10,142	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

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

- N=7020
- 3.1 YEARS



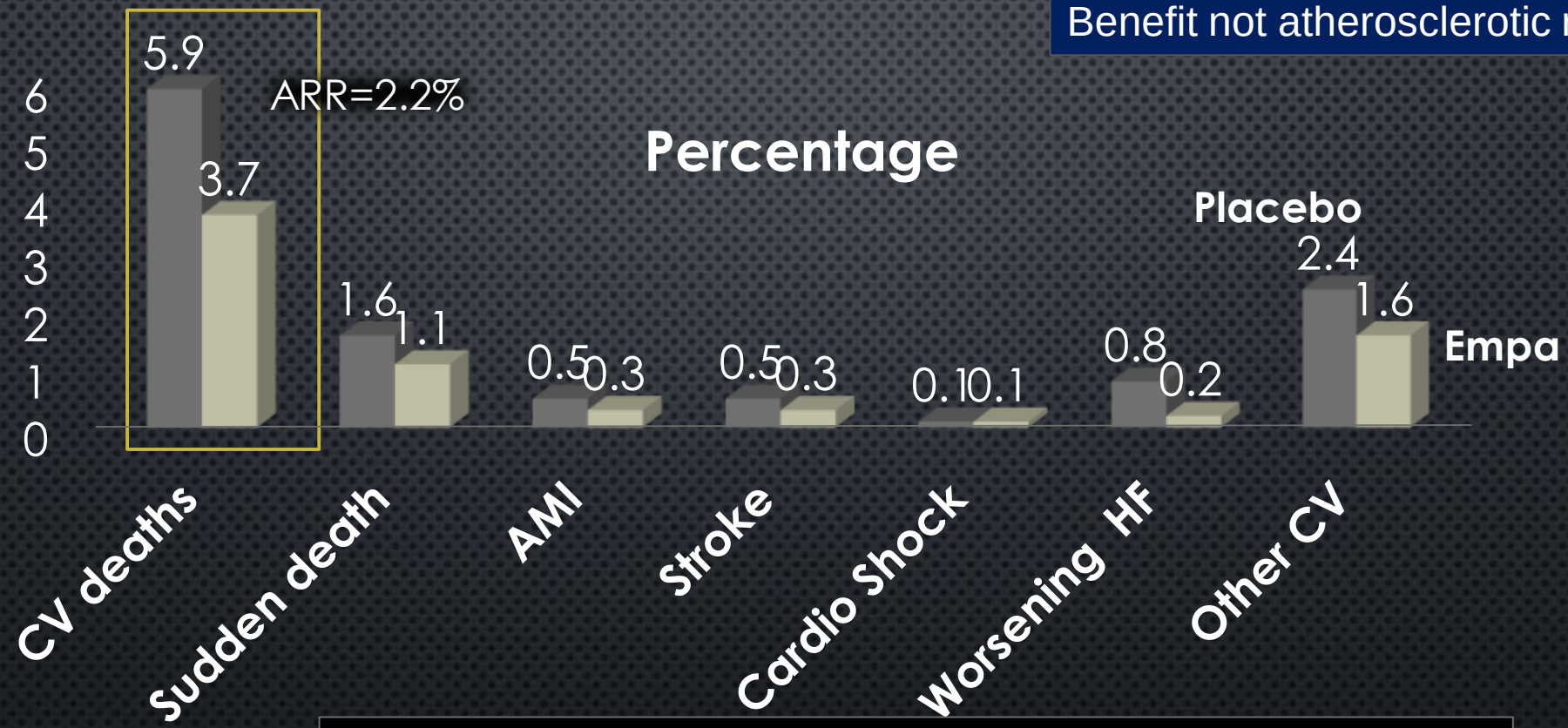
Primary composite outcome was death from nonfatal myocardial infarction, or nonfatal stroke

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

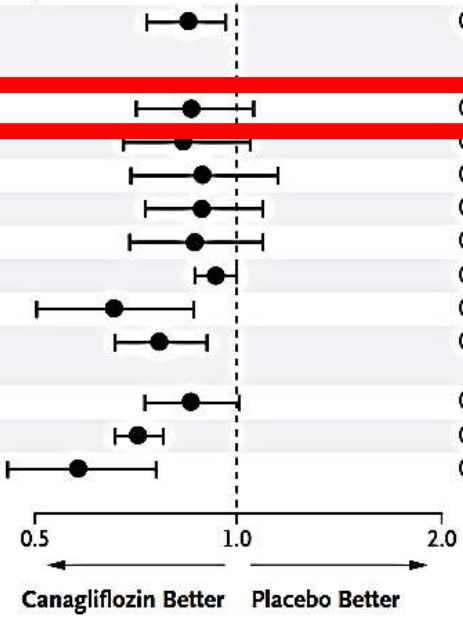
BACKGROUND

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.

Outcome	Canagliflozin (N=5795)	Placebo (N=4347)	Hazard Ratio (95% CI)
	no. of participants per 1000 patient-yr		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	26.9	31.5	0.86 (0.75–0.97)
Death from cardiovascular causes	11.6	12.8	0.87 (0.72–1.06)
Nonfatal myocardial infarction	9.7	11.6	0.85 (0.69–1.05)
Nonfatal stroke	7.1	8.4	0.90 (0.71–1.15)
Fatal or nonfatal myocardial infarction	11.2	12.6	0.89 (0.73–1.09)
Fatal or nonfatal stroke	7.9	9.6	0.87 (0.69–1.09)
Hospitalization for any cause	118.7	131.1	0.94 (0.88–1.00)
Hospitalization for heart failure	5.5	8.7	0.67 (0.52–0.87)
Death from cardiovascular causes or hospitalization for heart failure	16.3	20.8	0.78 (0.67–0.91)
Death from any cause	17.3	19.5	0.87 (0.74–1.01)
Progression of albuminuria	89.4	128.7	0.73 (0.67–0.79)
40% reduction in eGFR, renal-replacement therapy, or renal death	5.5	9.0	0.60 (0.47–0.77)



N Engl J Med 2017;377:644-57

CANVAS ORG.pdf

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., E.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

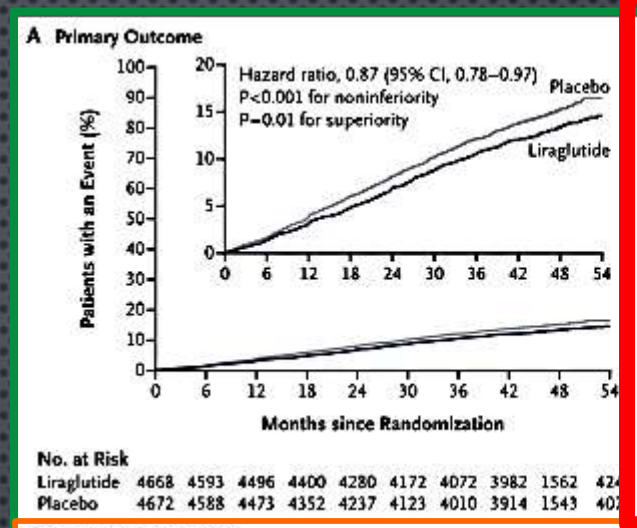
In this double-blind trial, we randomly assigned patients with type 2 diabetes and high cardiovascular risk to receive liraglutide or placebo. The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal 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.

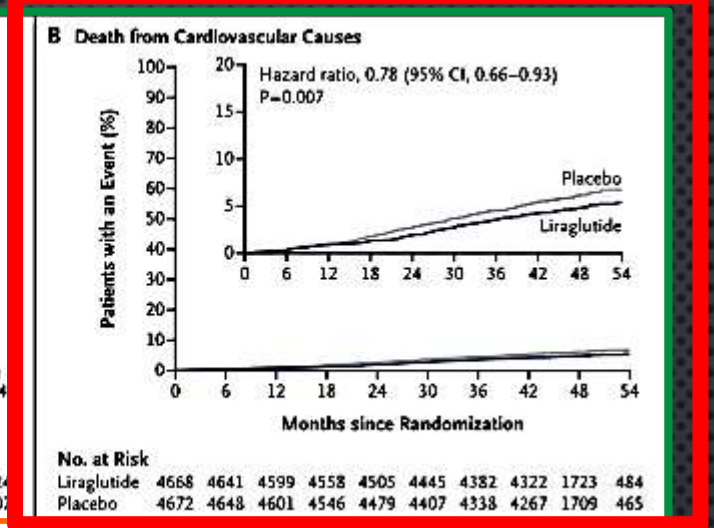
From the University of Texas Southwestern Medical Center, Dallas (S.P.M.); Massachusetts General Hospital, Boston (G.H.D.); Novo Nordisk, Bagsvaerd, Denmark (K.B.-F., P.K., L.S.R., M.S.); Friedrich Alexander University of Erlangen, Erlangen (J.F.E.M.), and St. Josef Hospital, Ruhr University, Bochum (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

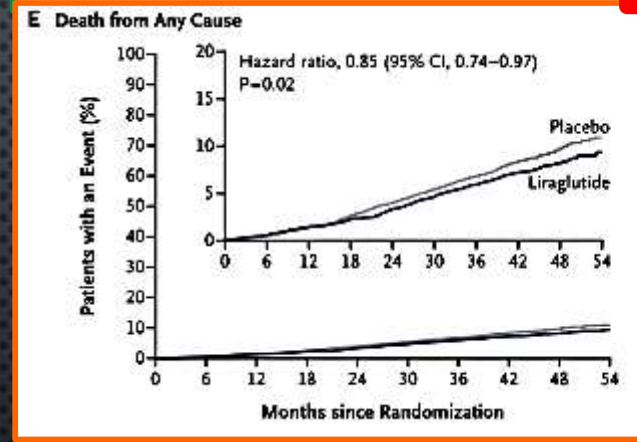
Primary composite outcome
in the time-to-event analysis was the
first occurrence of death from
cardiovascular
causes, nonfatal myocardial infarction,
or nonfatal stroke.

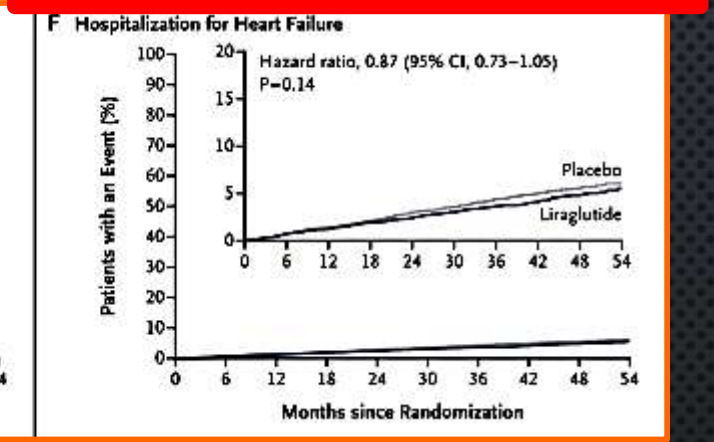
LEADER ORG.pdf

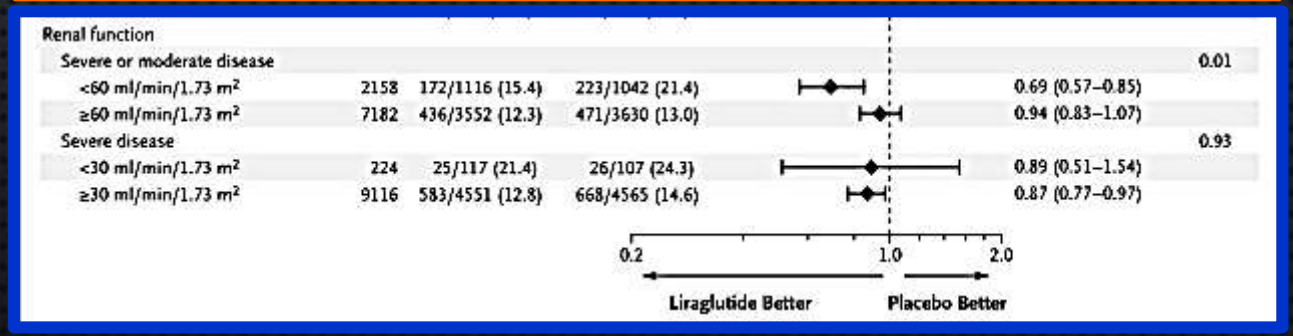
LEADER trial





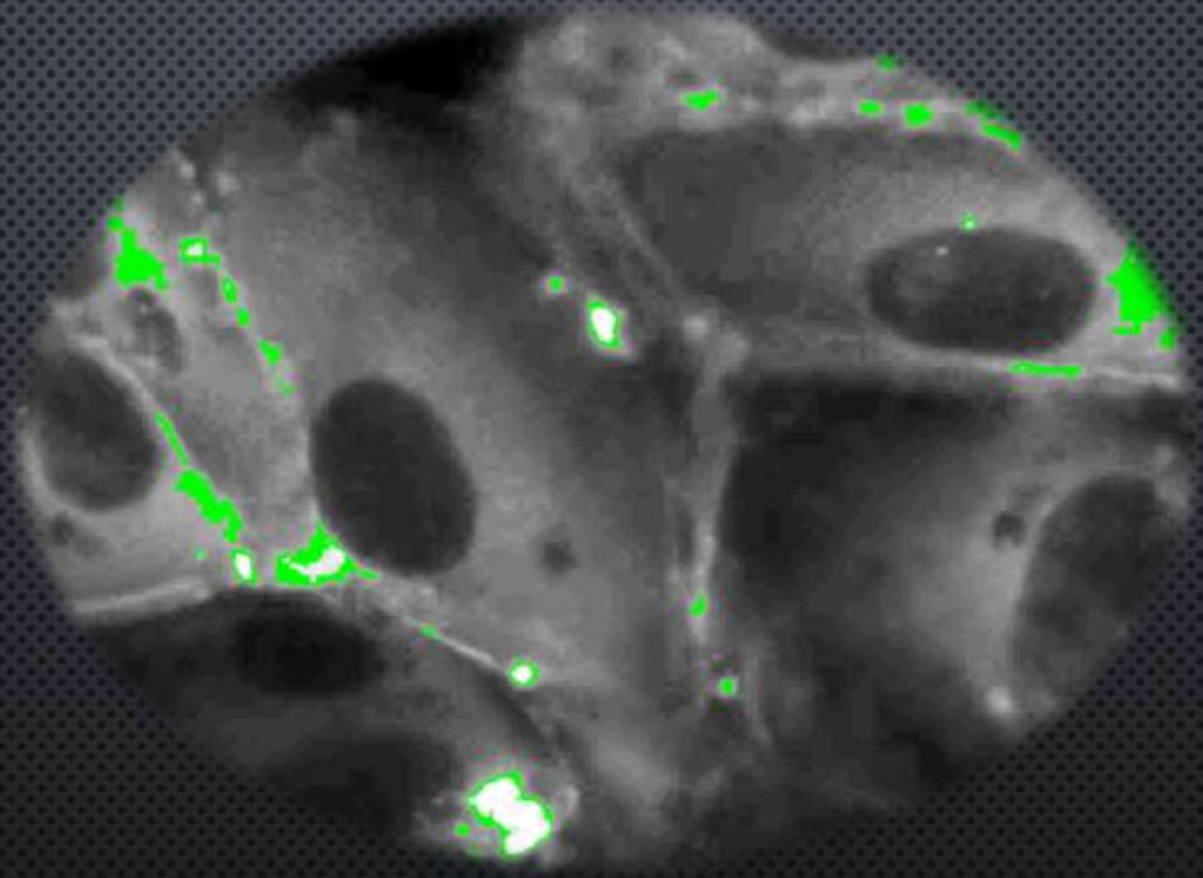






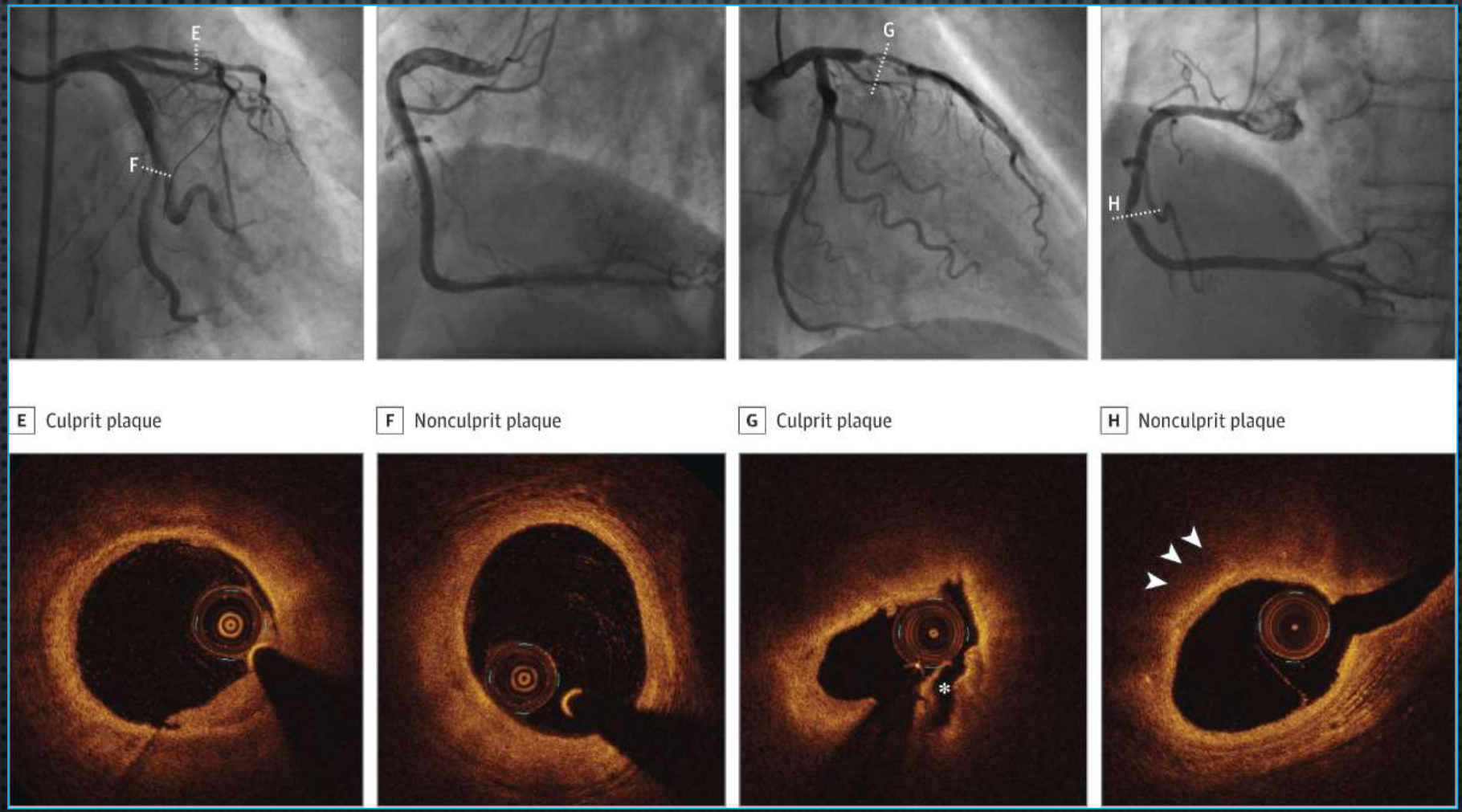
New translational biology of human coronaries

1 trillion CV/endocrine cells..(Hum Pathol. 1987;18(3):234)(0.2 pounds)



Endothelial cell health: "the target"

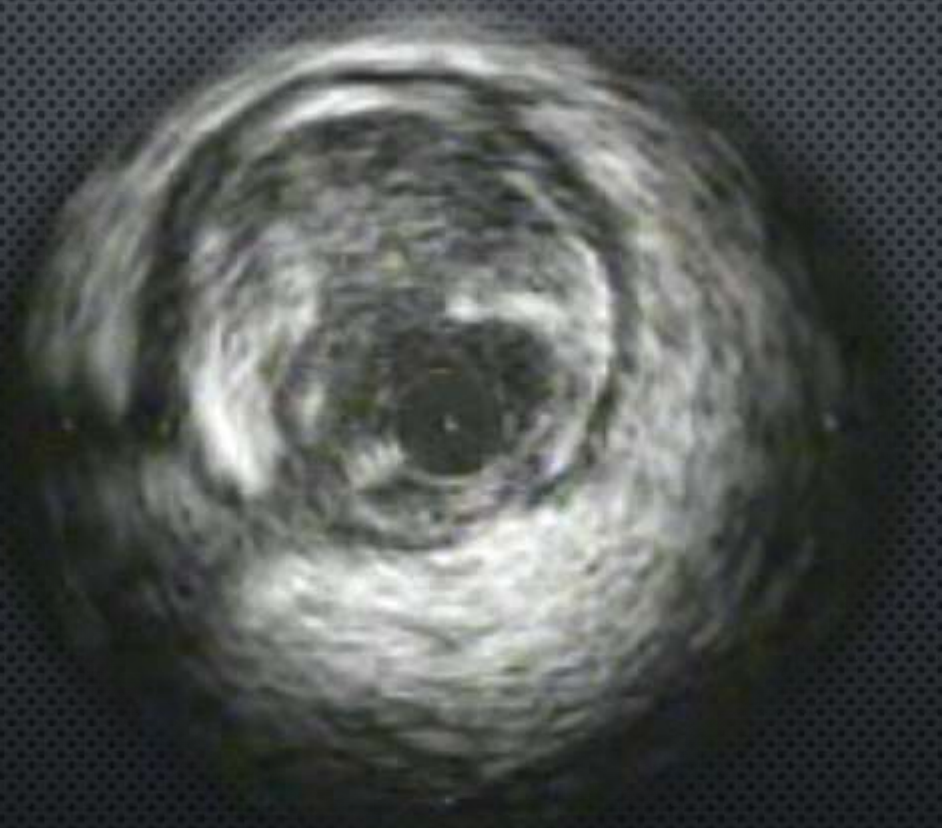
CHANGING DISEASES



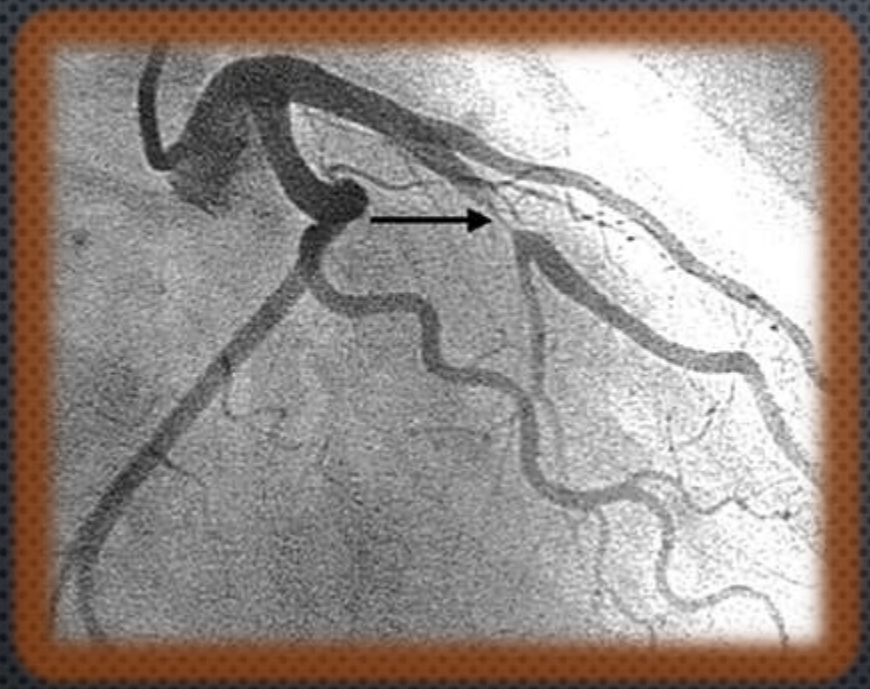
CIRCRESAHA.117.312494.full.pdf

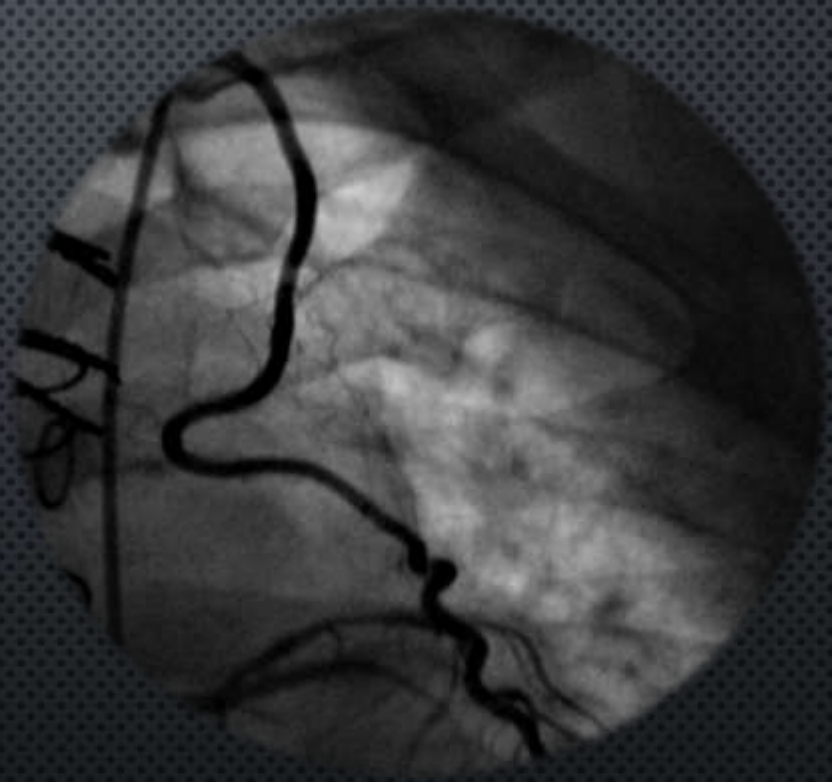
DOI : 10.1161/CIRCRESAHA.117.312494
JAMA Cardiol. 2018;3(3):207-214

Life changing event



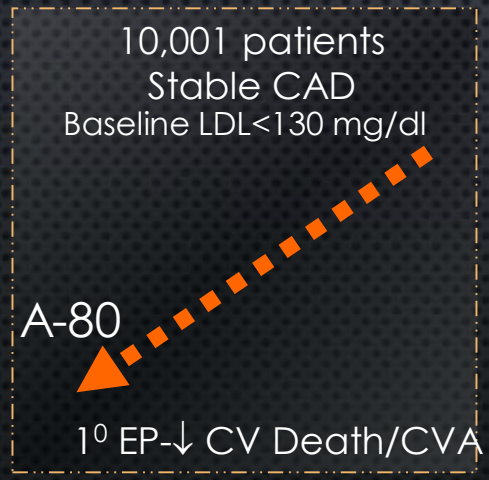
Macrovascular disease



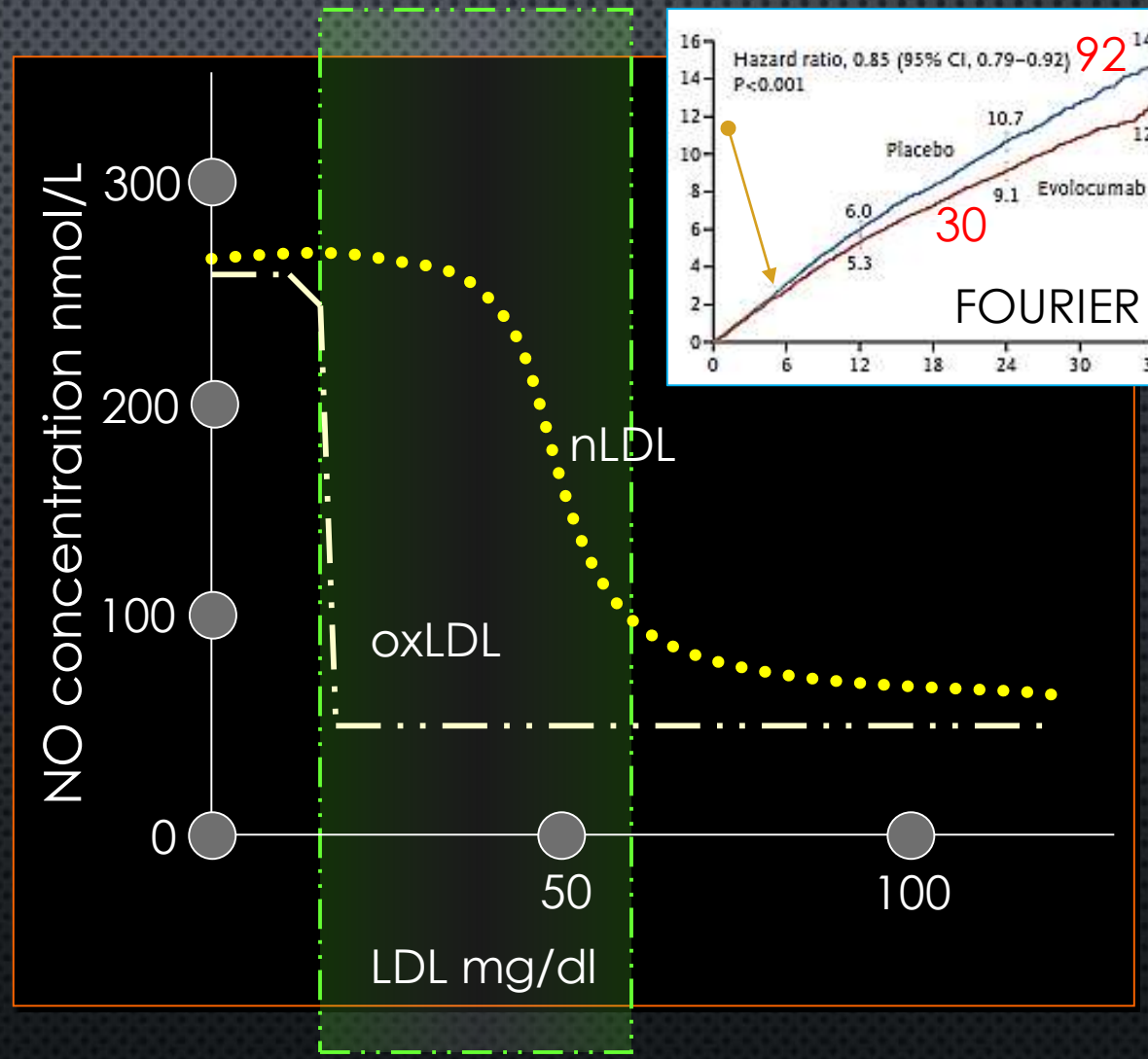


LOWERING LDL IS CRITICAL TO REDUCE CV EVENTS

- DIRECT ASSESSMENT BY MICROSENSOR
- BOVINE EC
- EXPOSED 1 HR TO ↑ LDL

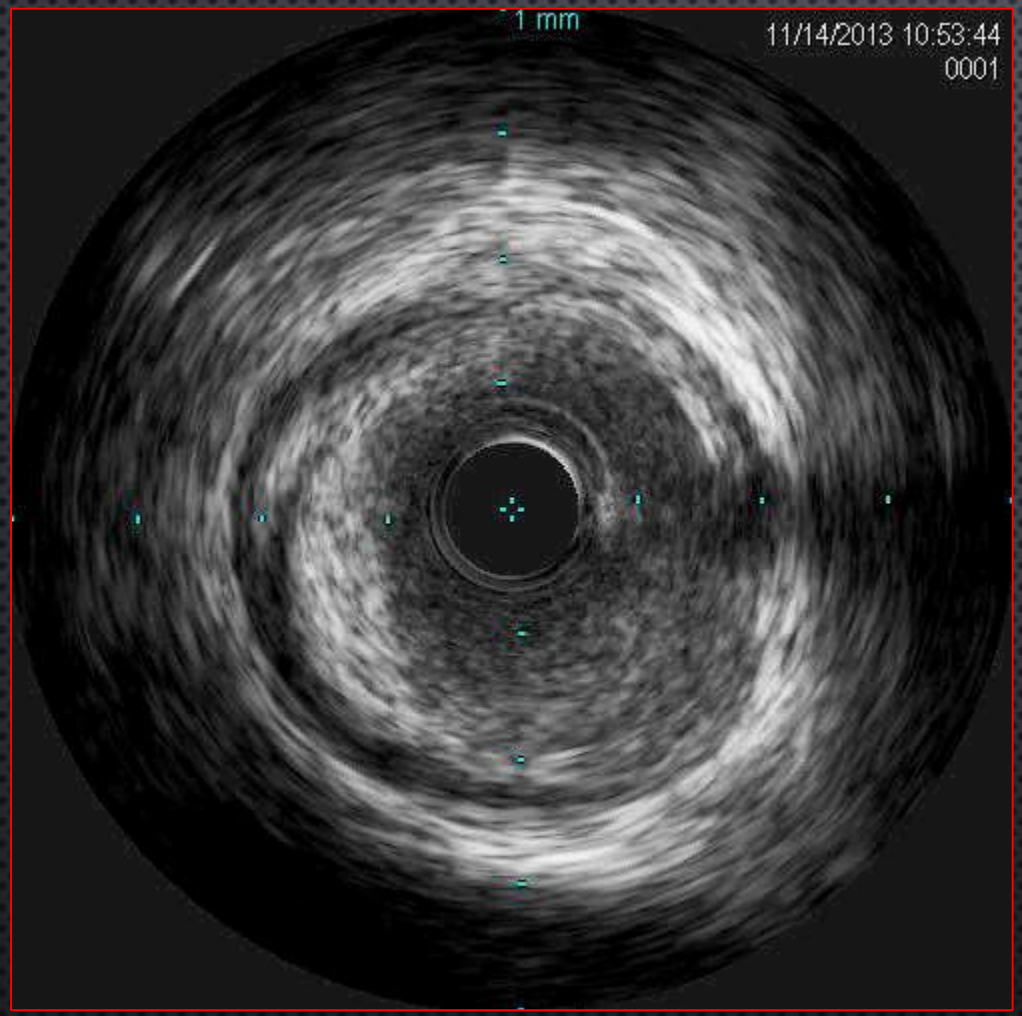


Humans-TNT…77 LDL
IMPROVE IT…53.2
FOURIER trial…30 mg/dl

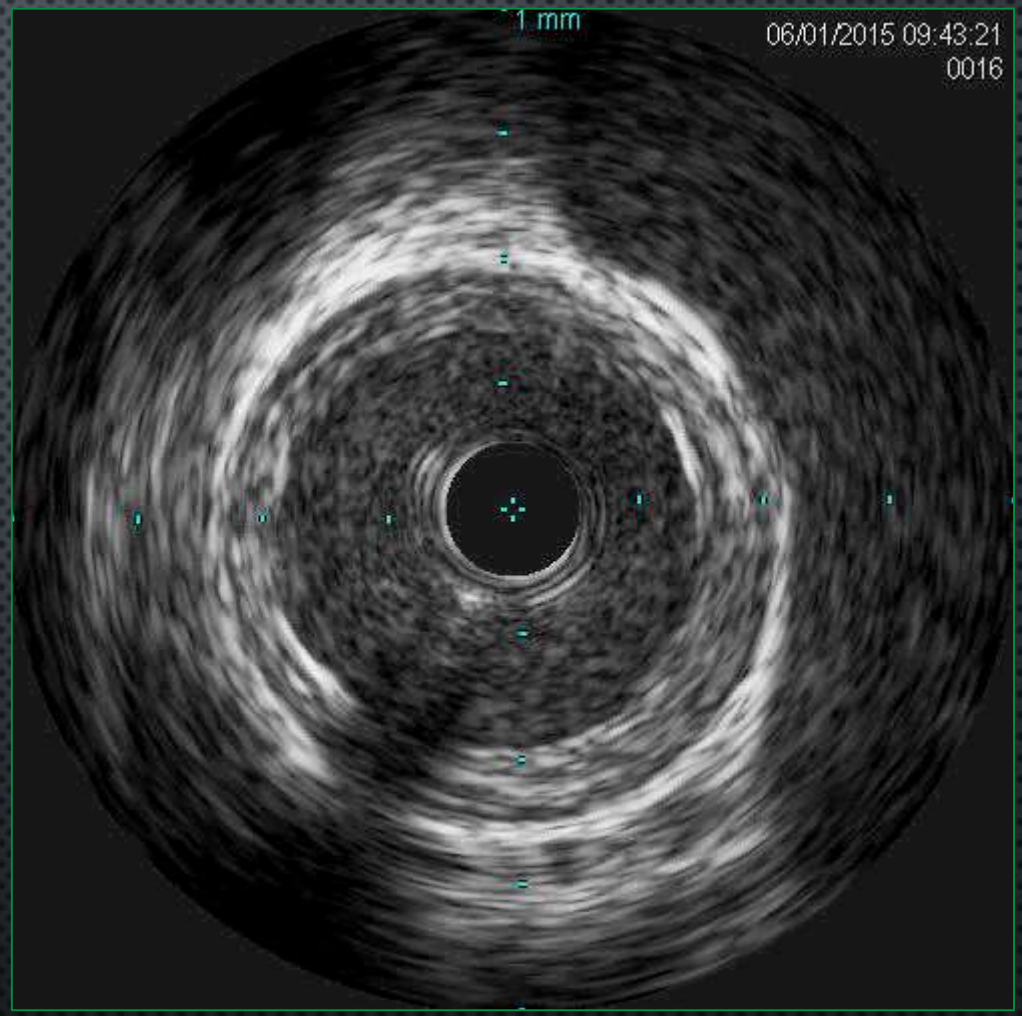


Circulation March 21, 2000;101:1261-1266

LDL-105



LDL-10



Glagov

Heart failure and diabetes

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

Insulin resistant cardiomyocyte

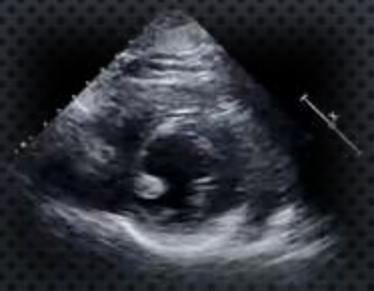
Preserved EF

Metabolic changes

Abnormal ventricular relaxation

Heart Fail. Rev. 17, 325–344
Herz 36, 102–115

Diastolic dysfunction



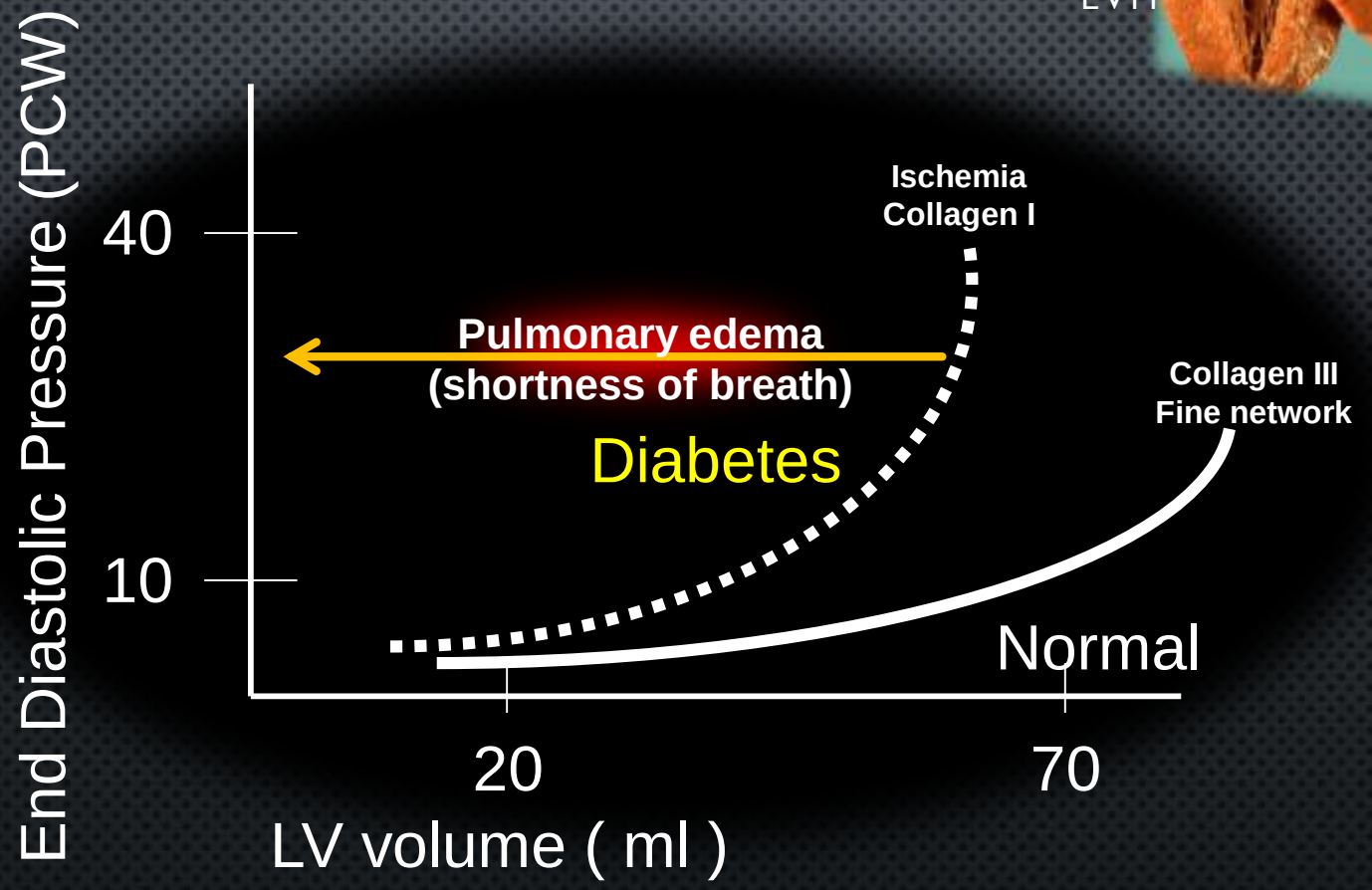
↑ reactive oxygen species
↑ fibrosis / stiffness

Structural changes

Abnormal ventricular arterial coupling (stiffness)

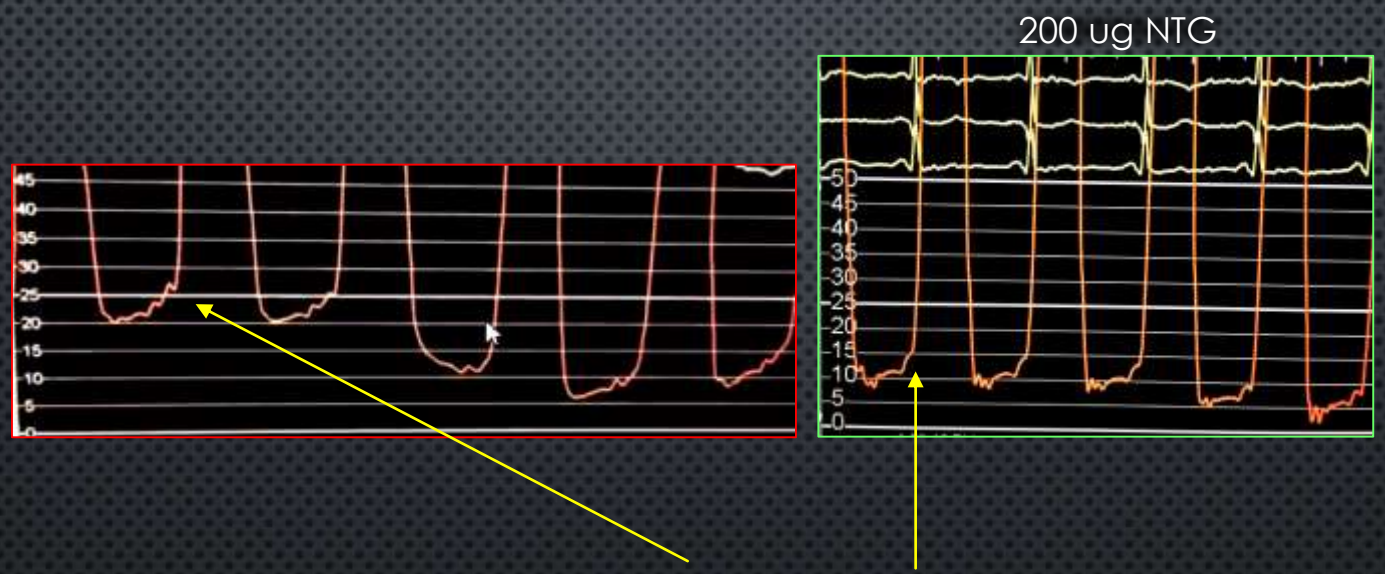
Chilton
Sowers..NATURE REVIEWS | ENDOCRINOLOGY 2016;12:144

DIASTOLIC HEART FAILURE IS COMMON IN DIABETES



Chilton-pending publication

Young obese T2DM female with SOB

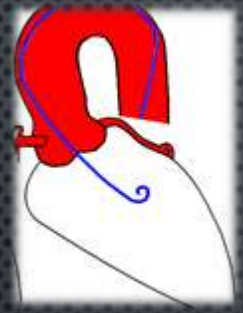


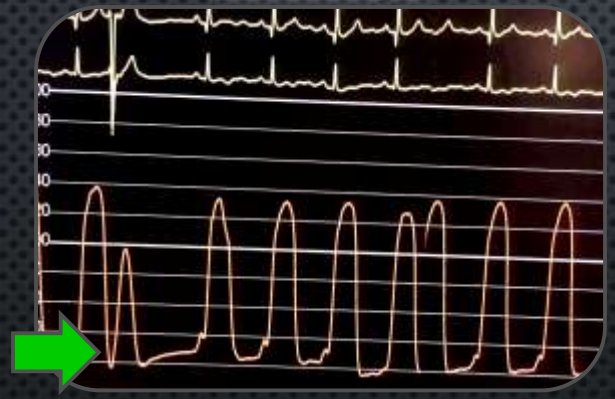
LVEDP
Left ventricular end diastolic pressure

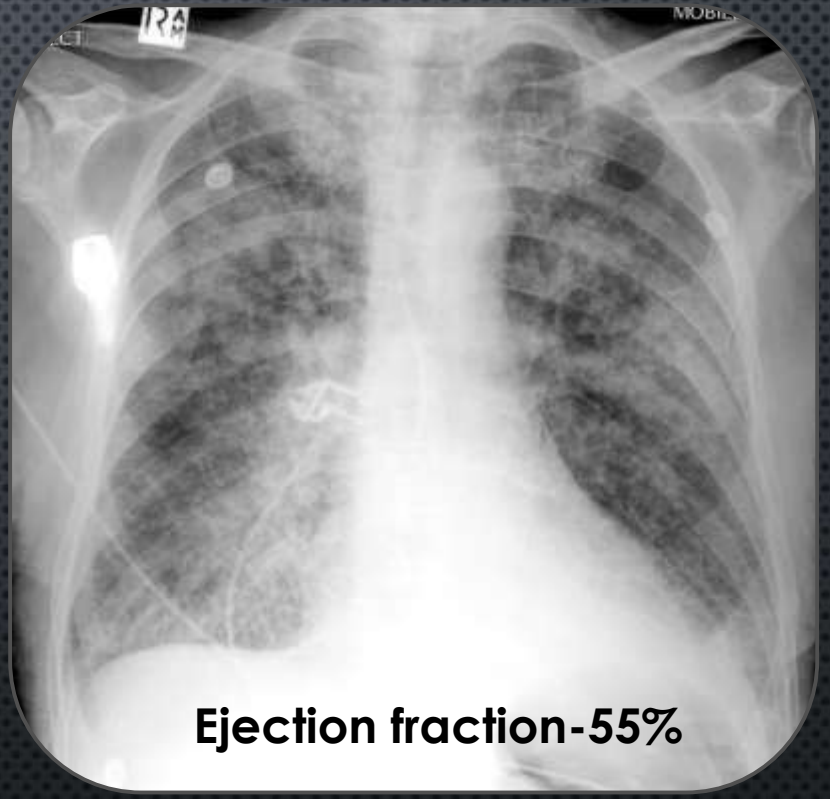
Nitric oxide

Chilton

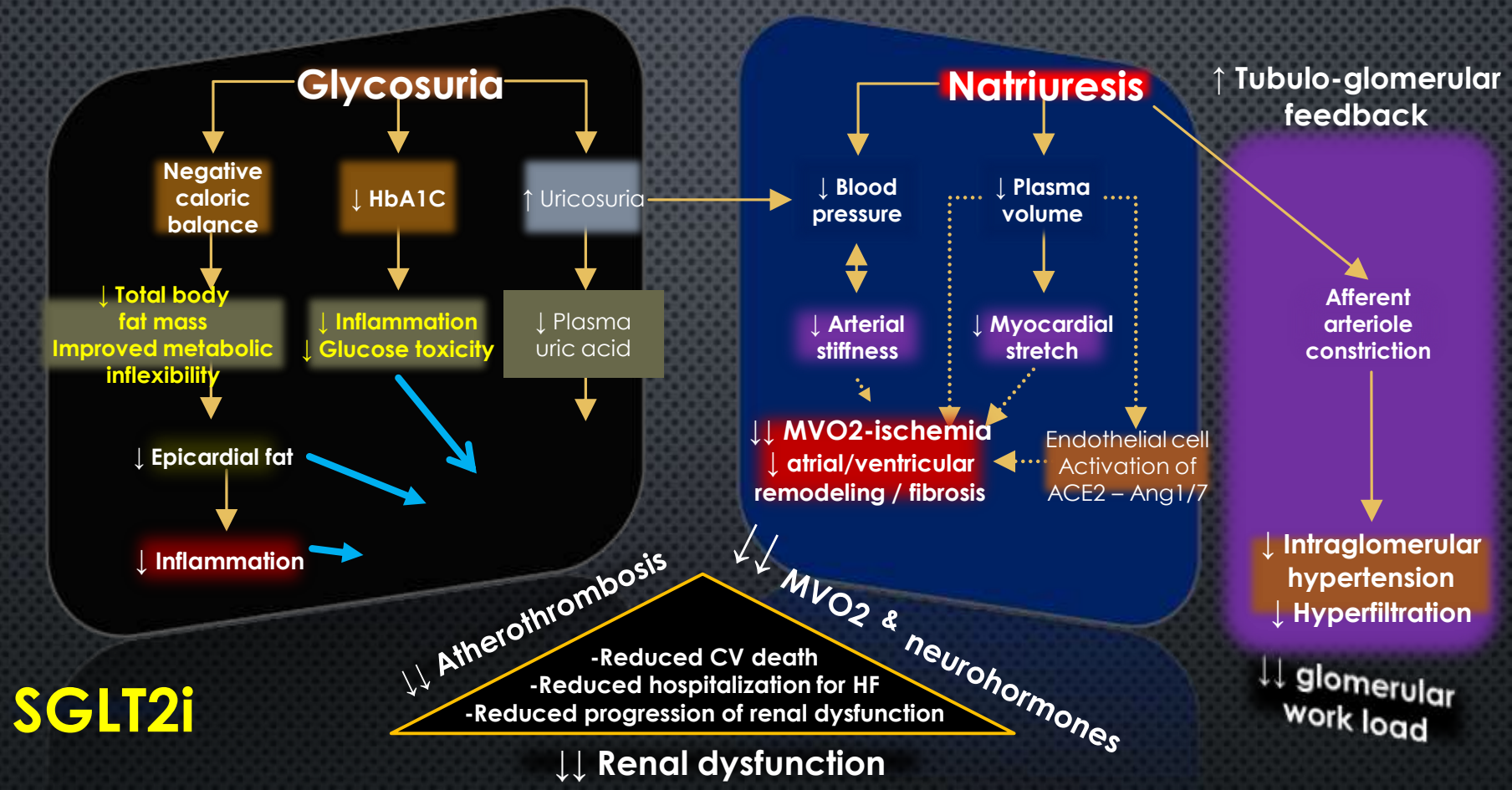
Diastolic heart failure-young diabetes patient







Ejection fraction-55%

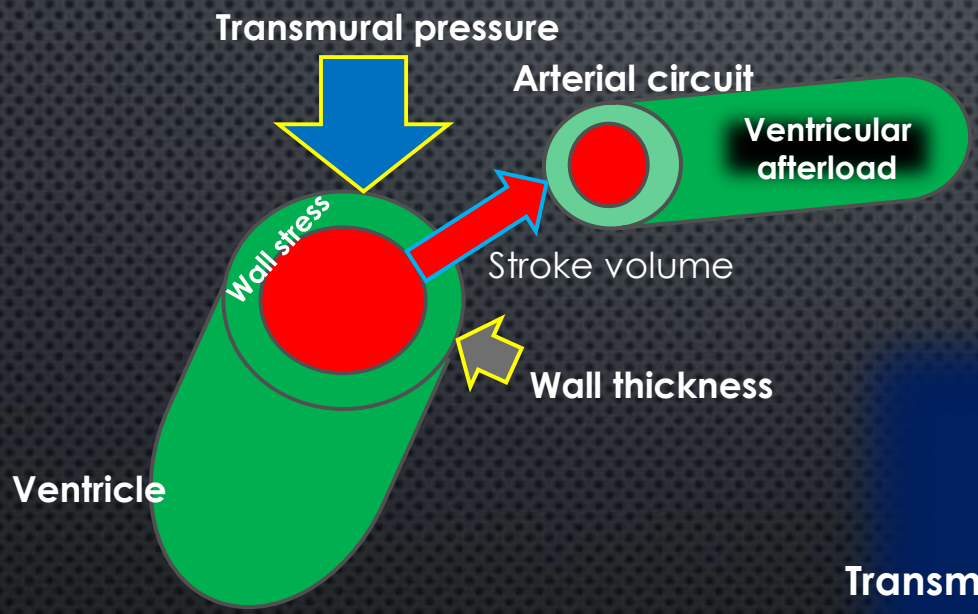


CV AND RENAL EFFECTS OF SGLT2 INHIBITORS

Ventricular arterial coupling

Metabolic changes
Sympathetic changes

Vascular compliance
Central aortic pressure
Pulse wave velocity



Law of Laplace

Wall tension- P x R/W

Transmural pressure

Wall thickness (W)

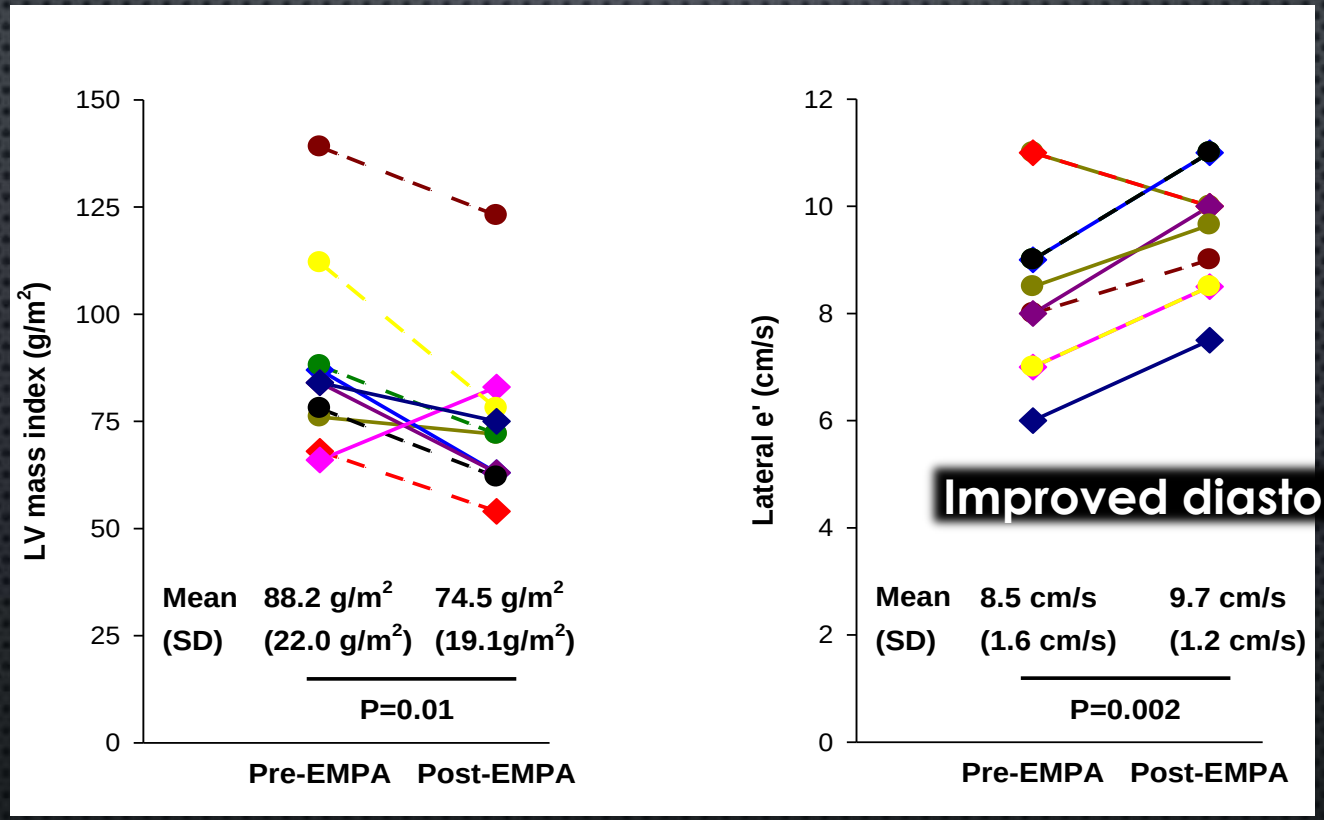
Radius (R)

Myocardial oxygen consumption

Chilton

LOWERS LV MASS AND IMPROVES DIASTOLIC FUNCTION

N = 10 with T2DM and established CVD
Baseline Age = 67.6 years Baseline A1C = 7.3%

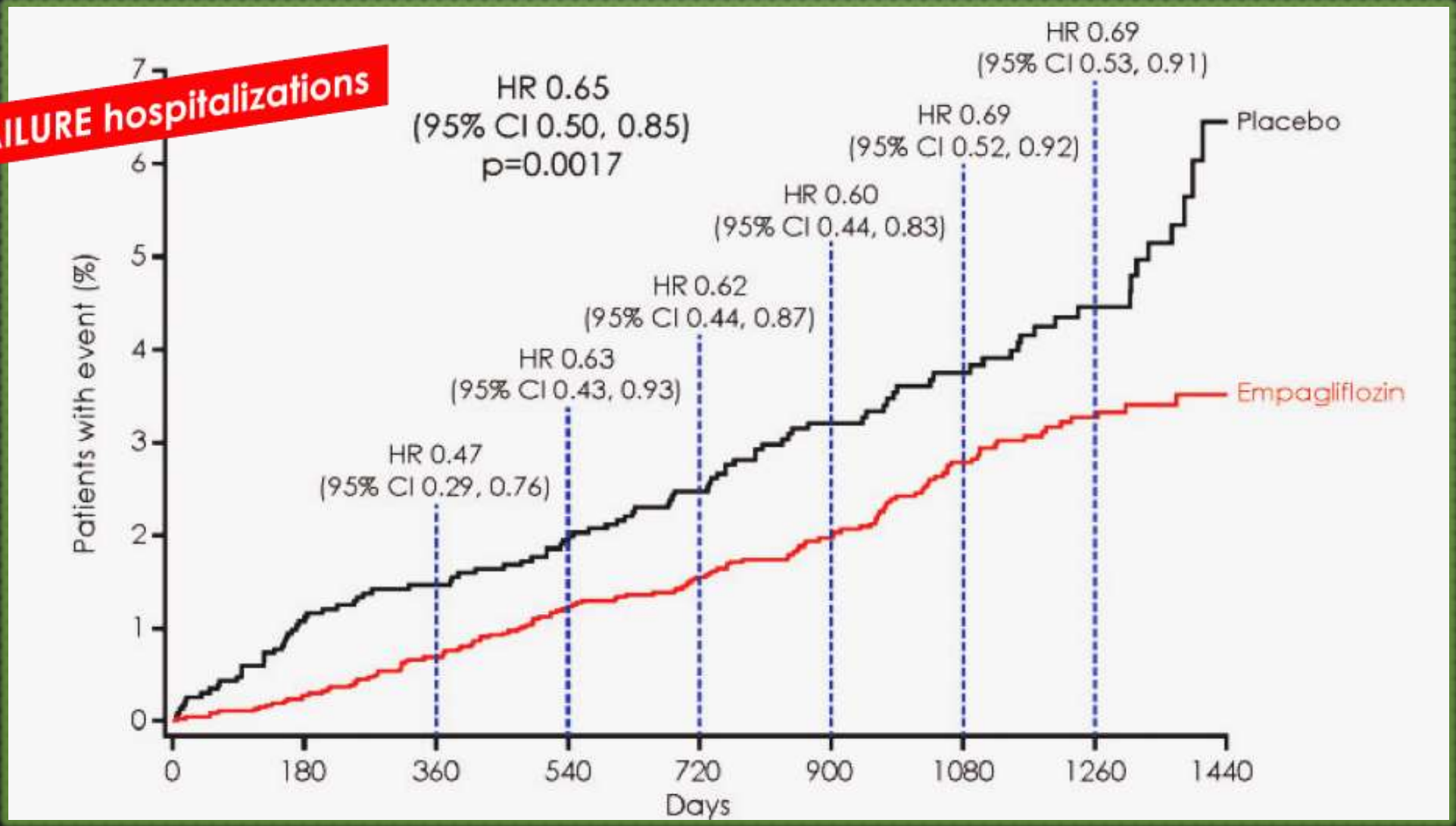


Improved diastolic function

3 months after SGLT2 inhibitor

Verma S et al. Diabetes Care. 2016. DOI: 10.2337/dc16-1312

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



empa HF results 2018.pdf

European Heart Journal (2018) 39, 363–370

ORIGINAL ARTICLE

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

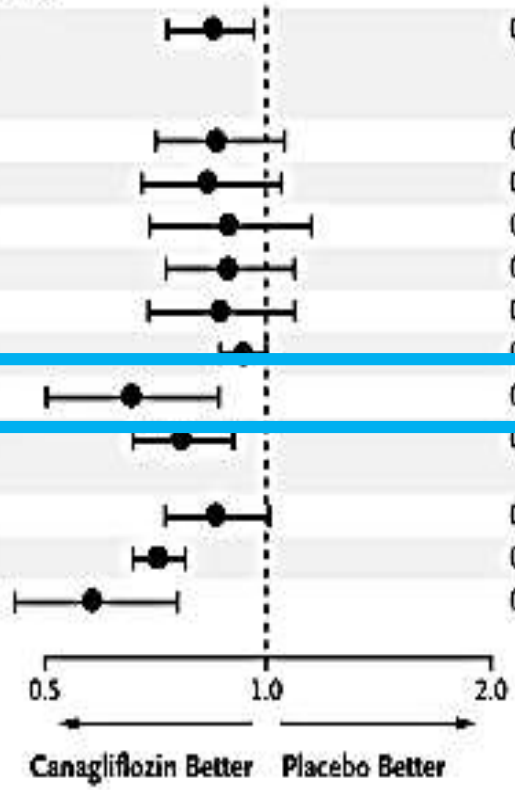
BACKGROUND

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.

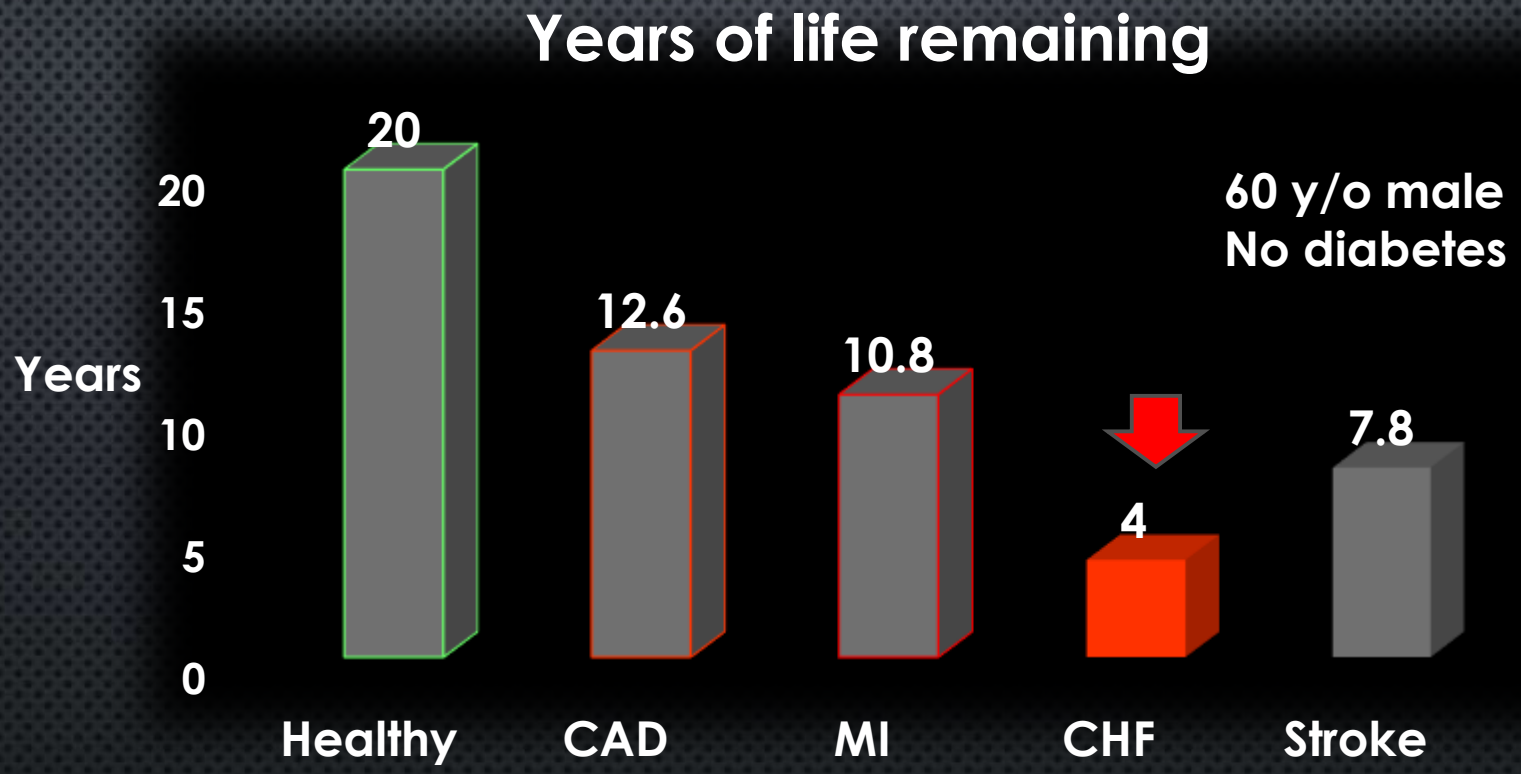
METHODS

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.

Outcome	Canagliflozin (N=5795)	Placebo (N=4347)	Hazard Ratio (95% CI)
	no. of participants per 1000 patient-yr		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	26.9	31.5	0.86 (0.75–0.97)
Death from cardiovascular causes	11.6	12.8	0.87 (0.72–1.06)
Nonfatal myocardial infarction	9.7	11.6	0.85 (0.69–1.05)
Nonfatal stroke	7.1	8.4	0.90 (0.71–1.15)
Fatal or nonfatal myocardial infarction	11.2	12.6	0.89 (0.73–1.09)
Fatal or nonfatal stroke	7.9	9.6	0.87 (0.69–1.09)
Hospitalization for heart failure	5.5	8.7	0.67 (0.52–0.87)
Death from cardiovascular causes or hospitalization for heart failure	16.3	20.8	0.78 (0.67–0.91)
Death from any cause	17.3	19.5	0.87 (0.74–1.01)
Progression of albuminuria	89.4	128.7	0.73 (0.67–0.79)
40% reduction in eGFR, renal-replacement therapy, or renal death	5.5	9.0	0.60 (0.47–0.77)



IMPORTANCE OF HEART FAILURE



Eur Heart J 2002; 23: 458–466

Framingham 40 year follow up
N=5070

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., E.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

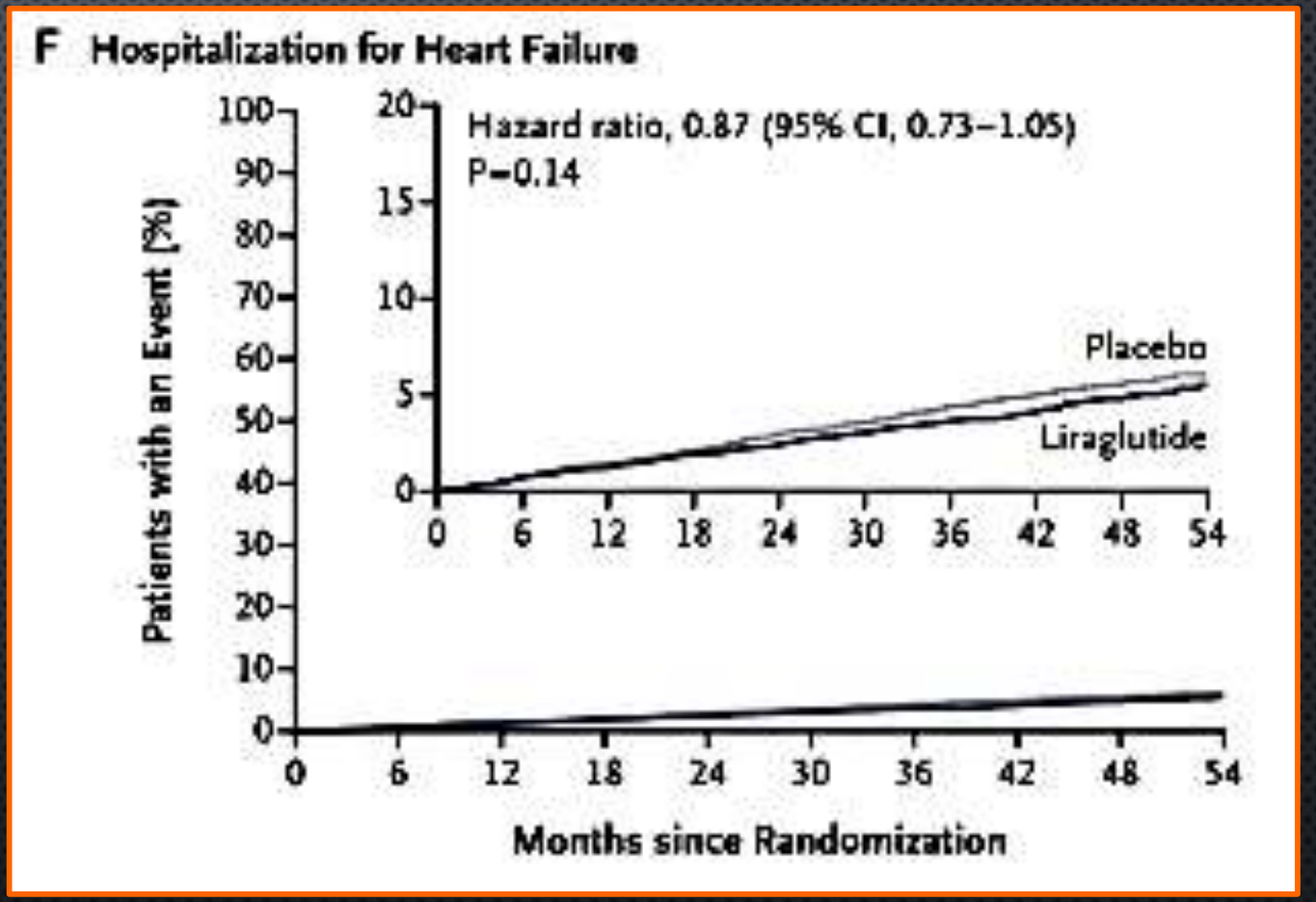
BACKGROUND

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



LEADER ORG.pdf

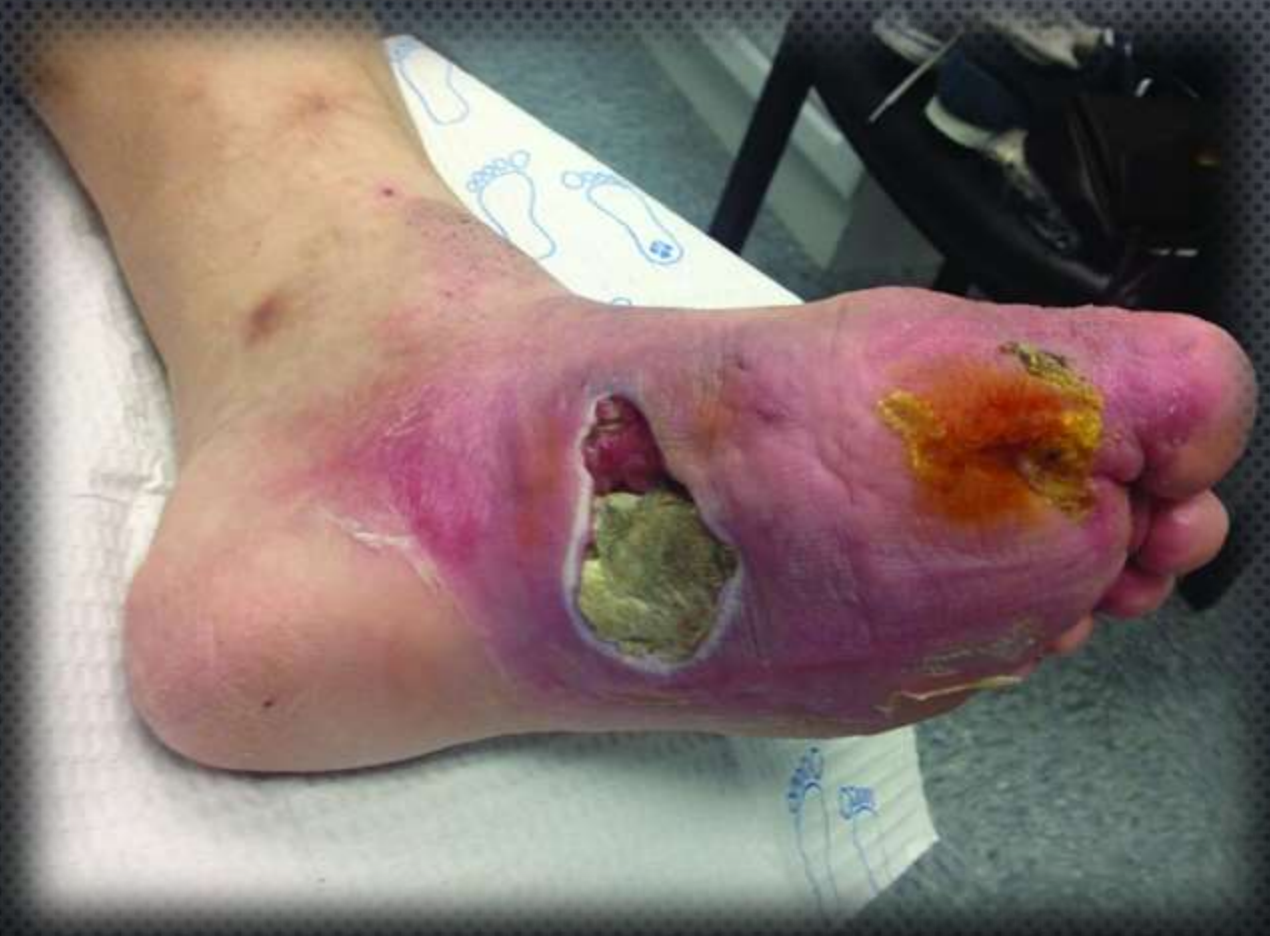
LEADER trial

New area of concern peripheral vascular disease

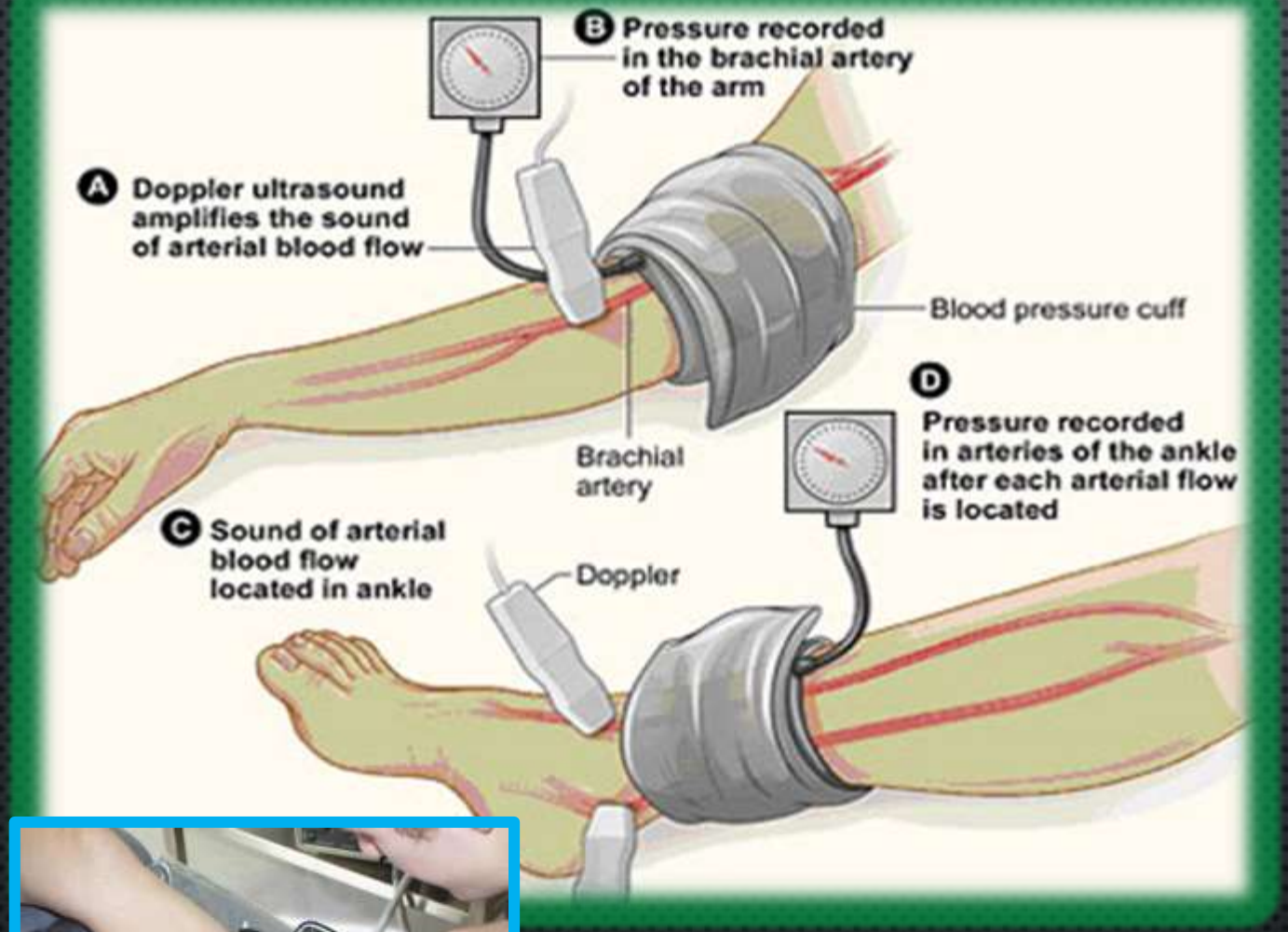
CANVUS ORG.pdf

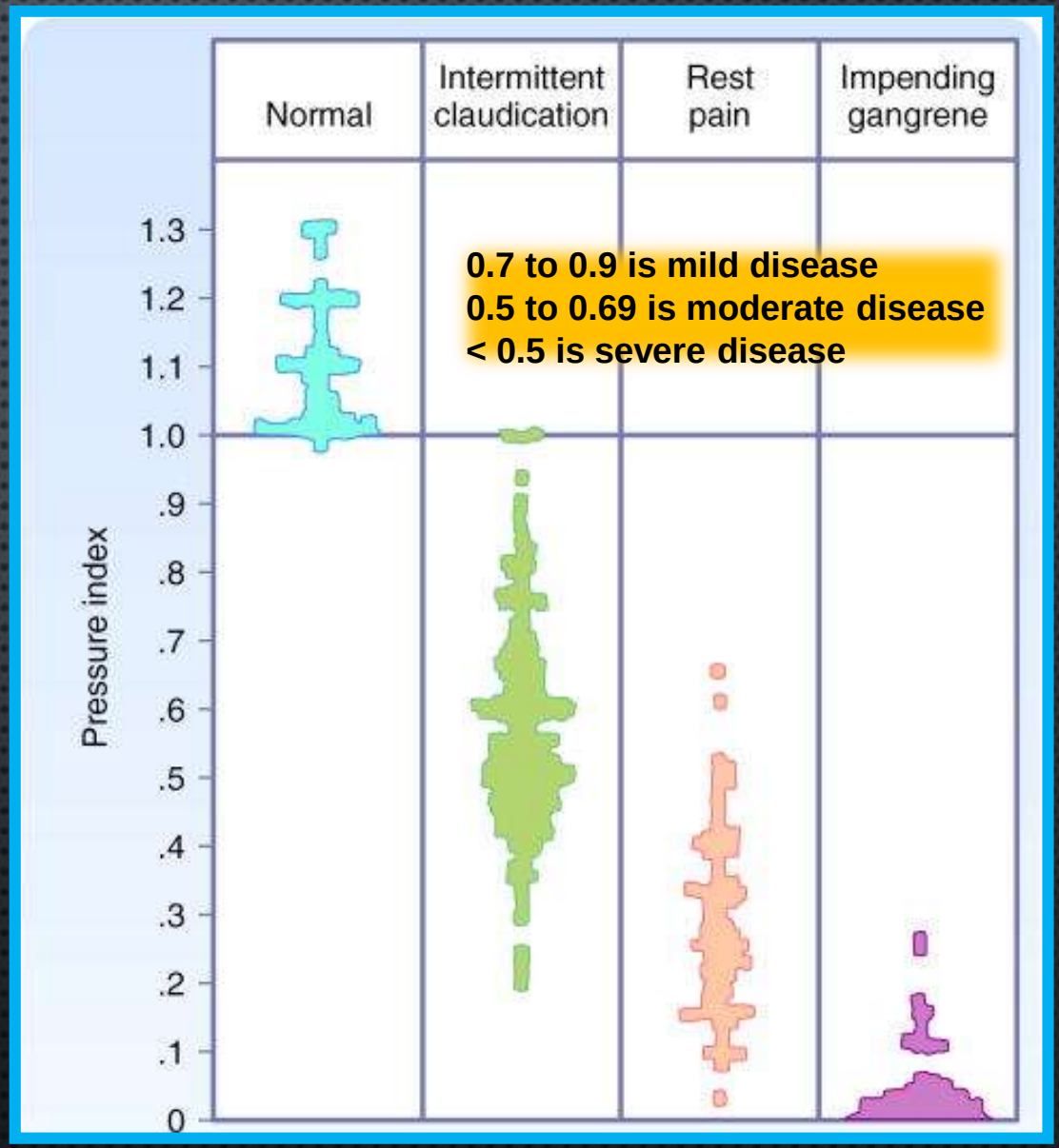
canvas nejmoa1611925_appendix.pdf

Microvascular



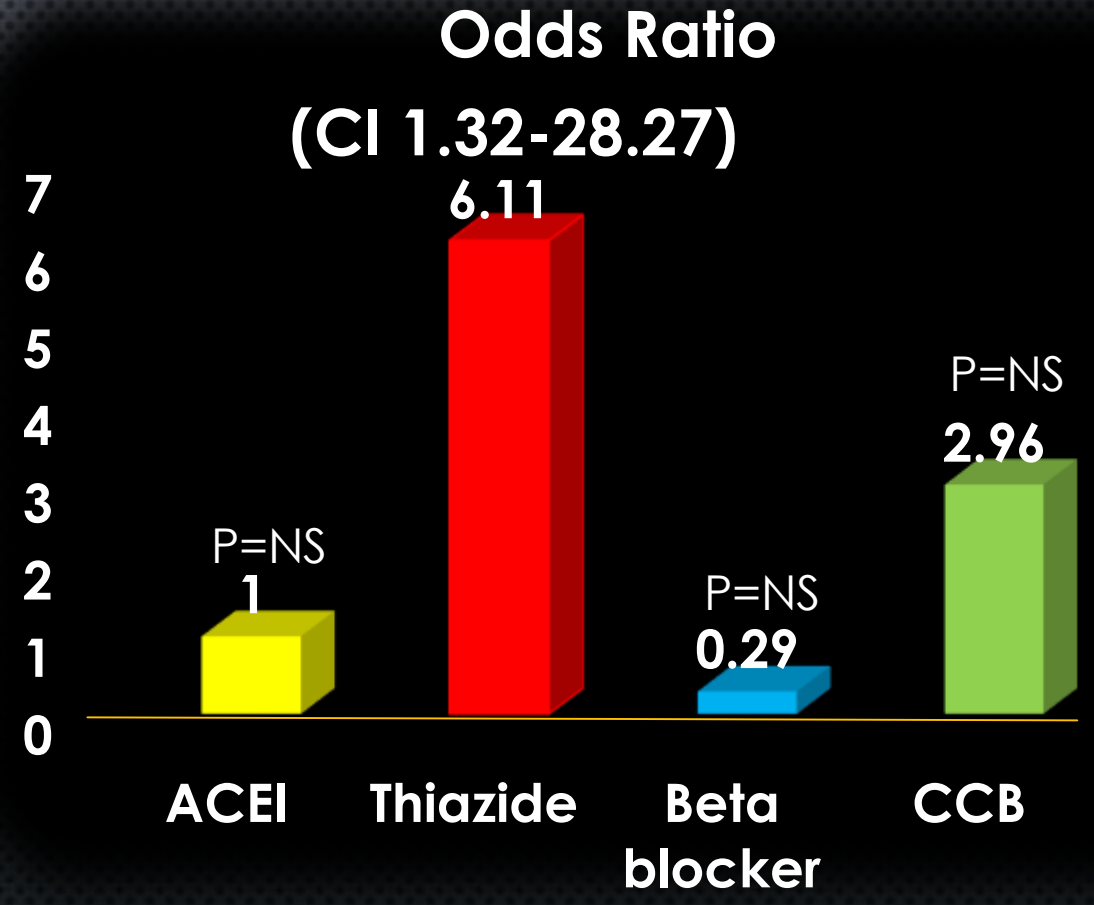
Increased in diabetes


B Pressure recorded in the brachial artery of the arm
A Doppler ultrasound amplifies the sound of arterial blood flow
Blood pressure cuff
Brachial artery
D Pressure recorded in arteries of the ankle after each arterial flow is located
C Sound of arterial blood flow located in ankle
Doppler


Normal
Intermittent claudication
Rest pain
Impending gangrene
Pressure index
1.3
1.2
1.1
1.0
.9
.8
.7
.6
.5
.4
.3
.2
.1
0
0.7 to 0.9 is mild disease
0.5 to 0.69 is moderate disease
< 0.5 is severe disease

THIAZIDE DIURETICS INCREASE LOWER EXTREMITY AMPUTATIONS IN T2DM

- PHARMO RECORD LINKAGE SYSTEM
- POST MARKETING SURVEILLANCE STUDY
- 8 DUTCH CITIES
  - STUDY N=120 PATIENTS
- ALL ON ANTI-HYPERTENSIVE AGENTS
- HISTORICAL PERSPECTIVE
  - AMPUTATIONS IN T2DM 3.9 PER 10,000 PATIENT YEARS



Pharmacoepidemiology and Drug Safety, 2004; 13: 139–146

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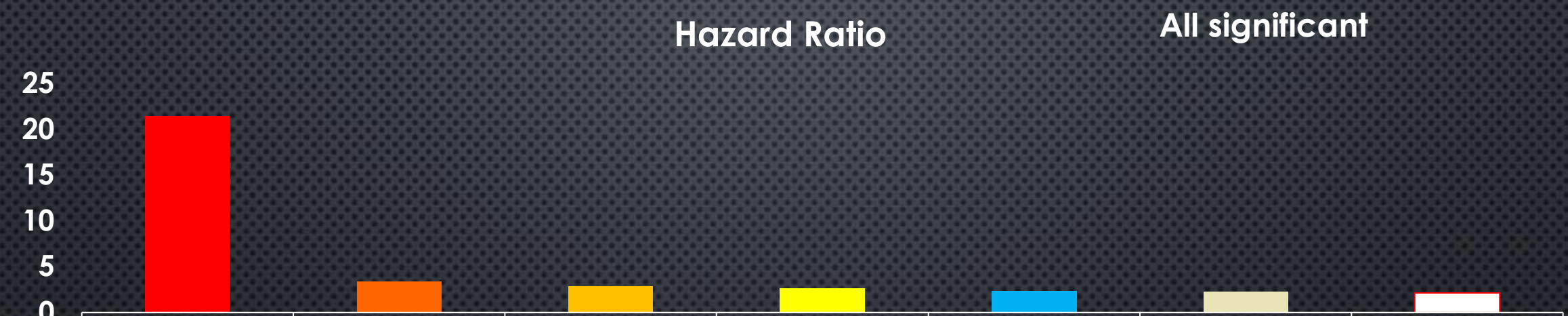
Table 2. Adverse Events.*

Event	Canagliflozin	Placebo	P Value†
	event rate per 1000 patient-yr		
All serious adverse events	104.3	120.0	0.04
Adverse events leading to discontinuation	35.5	32.8	0.07
Serious and nonserious adverse events of interest recorded in the CANVAS Program			
Amputation	6.3	3.4	<0.001

CANVUS ORG.pdf

canvas nejmoa1611925_appendix.pdf

CANVAS-EASD 15 SEPT 2017 AMPUTATION RISK FACTORS-UNIVARIATE ANALYSIS

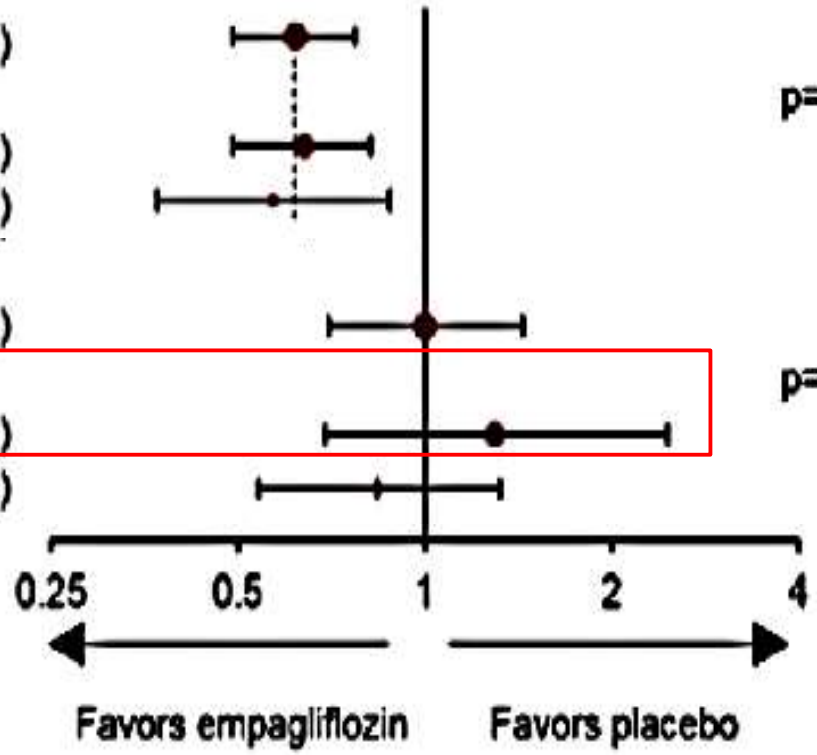


	Amputation history	Neuropathy	CV dx	Gender	Baseline use of insulin	Retinopathy	Loop diuretics
HR	21.42	3.38	2.87	2.62	2.37	2.28	2.12

EMPA- REG peripheral artery disease analysis

A

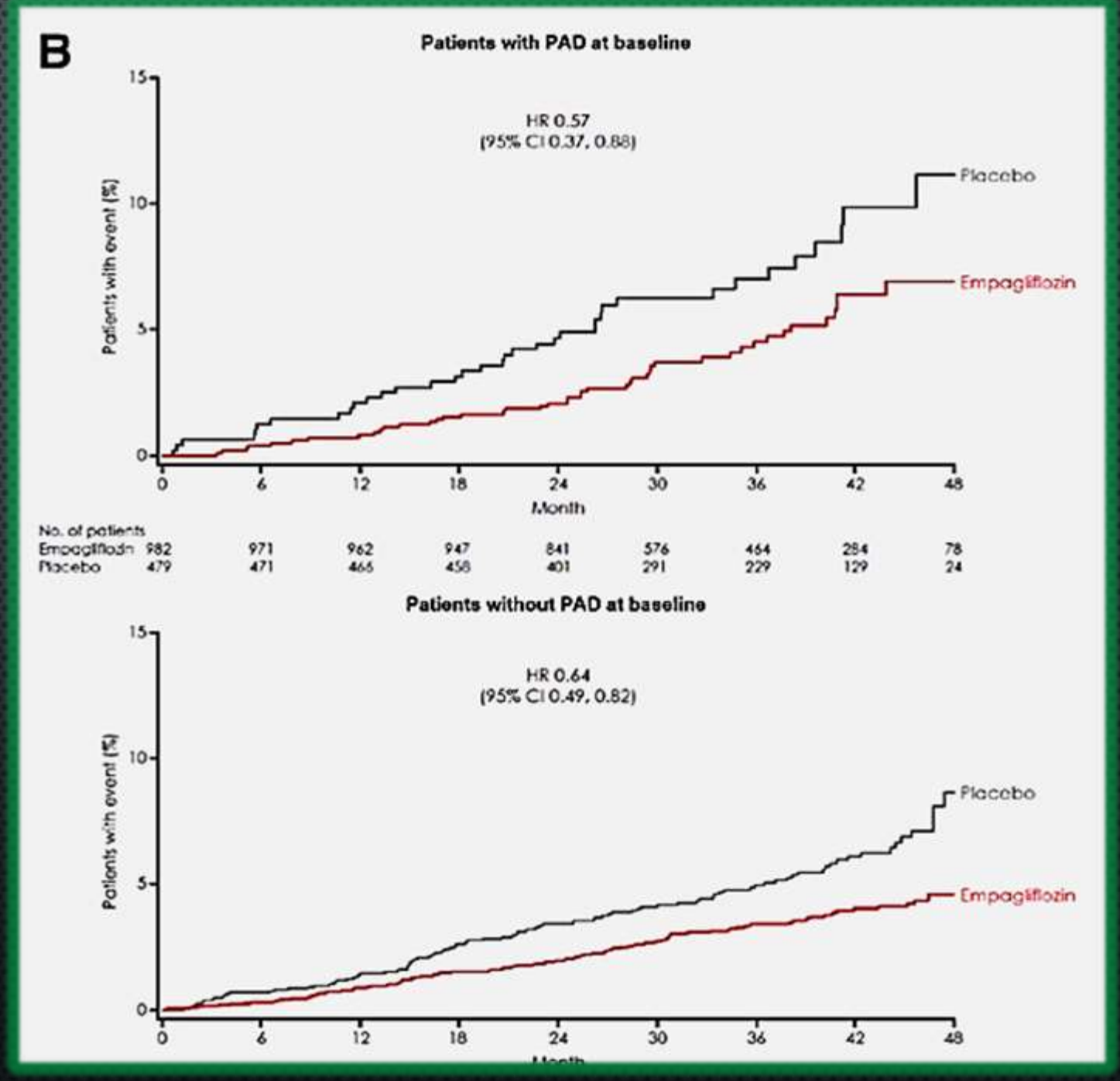
	Empagliflozin	Placebo	Hazard ratio (95% CI)	Treatment by subgroup interaction
	n with event/ N analyzed (%)			
CV death	2 groups			
All patients	172/4687 (3.7)	137/2333 (5.9)	0.62 (0.49, 0.77)	
PAD at baseline				p=0.6684
No	128/3704 (3.5)	101/1853 (5.5)	0.64 (0.49, 0.82)	
Yes	44/982 (4.5)	36/479 (7.5)	0.57 (0.37, 0.88)	
Lower limb amputation				
All patients	88/4687 (1.9)	43/2333 (1.8)	1.00 (0.70, 1.44)	
PAD at baseline				p=0.2752
No	34/3704 (0.9)	13/1853 (0.7)	1.30 (0.69, 2.46)	
Yes	54/982 (5.5)	30/479 (6.3)	0.84 (0.54, 1.32)	



PAD empa reg.pdf

Circulation. 2018;137:405–407

TIME TO CARDIOVASCULAR (CV) DEATH: BY PAD



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PAD empa reg.pdf

A

	Empagliflozin	Placebo	Hazard ratio (95% CI)
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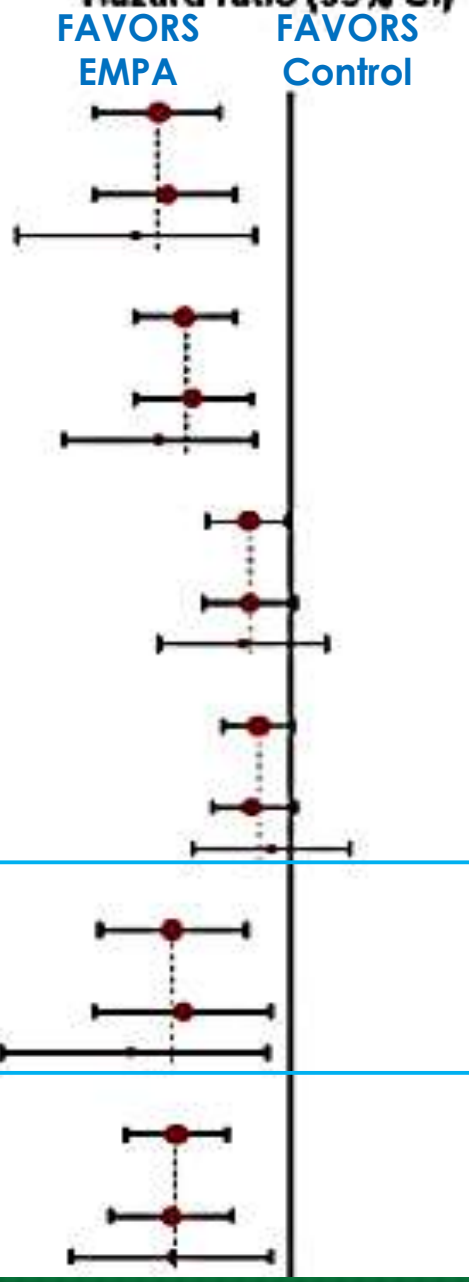
All patients	172/4687 (3.7)	137/2333 (5.9)	0.62 (0.49, 0.77)
PAD at baseline			
No	128/3704 (3.5)	101/1853 (5.5)	0.64 (0.49, 0.82)
Yes	44/982 (4.5)	36/479 (7.5)	0.57 (0.37, 0.88)
All-cause mortality			
All patients	269/4687 (5.7)	194/2333 (8.3)	0.68 (0.57, 0.82)
PAD at baseline			
No	195/3704 (5.3)	139/1853 (7.5)	0.70 (0.57, 0.87)
Yes	74/982 (7.5)	55/479 (11.5)	0.62 (0.44, 0.88)
3-point MACE			
All patients	490/4687 (10.5)	282/2333 (12.1)	0.86 (0.74, 0.99)
PAD at baseline			
No	370/3704 (10.0)	216/1853 (11.7)	0.86 (0.73, 1.02)
Yes	120/982 (12.2)	66/479 (13.8)	0.84 (0.62, 1.14)
4-point MACE			
All patients	599/4687 (12.8)	333/2333 (14.3)	0.89 (0.78, 1.01)
PAD at baseline			
No	460/3704 (12.4)	263/1853 (14.2)	0.87 (0.75, 1.02)
Yes	139/982 (14.2)	70/479 (14.6)	0.93 (0.70, 1.24)
Hospitalization for heart failure			
All patients	126/4687 (2.7)	95/2333 (4.1)	0.65 (0.50, 0.85)
PAD at baseline			
No	88/3704 (2.4)	66/1853 (3.6)	0.68 (0.49, 0.93)
Yes	38/982 (3.9)	29/479 (6.1)	0.56 (0.35, 0.92)
Heart failure hospitalization or CV death			
All patients	265/4687 (5.7)	198/2333 (8.5)	0.66 (0.55, 0.79)
PAD at baseline			
No	190/3704 (5.1)	147/1853 (7.9)	0.65 (0.52, 0.81)
Yes	75/982 (7.6)	51/479 (10.6)	0.65 (0.45, 0.93)

2 groups



PAD empa reg.pdf

Microvascular disease in diabetes with new cardiovascular drugs for diabetes

UKPDS 35

Reducing glucose is beneficial

Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study

Irene M Stratton, Amanda I Adler, H Andrew W Neil, David R Matthews, Susan E Manley, Carole A Cull, David Hadden, Robert C Turner, Rury R Holman on behalf of the UK Prospective Diabetes Study Group

Abstract

Objective To determine the relation between exposure to glycaemia over time and the risk of macrovascular or microvascular complications in patients with type 2 diabetes.

Design Prospective observational study.

Setting 23 hospital based clinics in England, Scotland, and Northern Ireland.

Participants 4585 white, Asian Indian, and Afro-Caribbean UKPDS patients, whether randomised or not to treatment, were included in analyses of incidence; of these, 3642 were included in analyses of relative risk.

after diagnosis of type 2 diabetes, which achieved a median haemoglobin A_1 (HbA_1) of 7.0% compared with 7.9% in those allocated to conventional treatment over a median 10.0 years of follow up, has shown a substantial reduction in the risk of microvascular complications, with a reduction in the risk of myocardial infarction of borderline significance.[1] Complementary information for estimates of the risk of complications at different levels of glycaemia can be obtained from observational analyses of data during the study.

In patients with type 2 diabetes previous prospective studies have shown an association between the degree of hyperglycaemia and increased risk of microvascular complications[2,3] sensory neuropathy[3,4] myo-

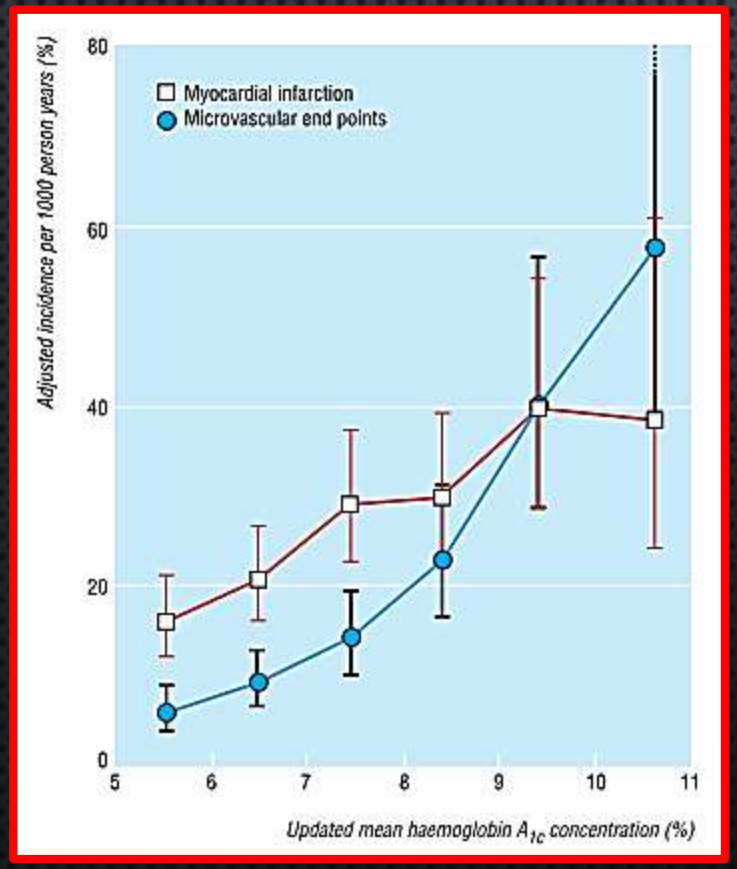
Editorial by Turner/Holman

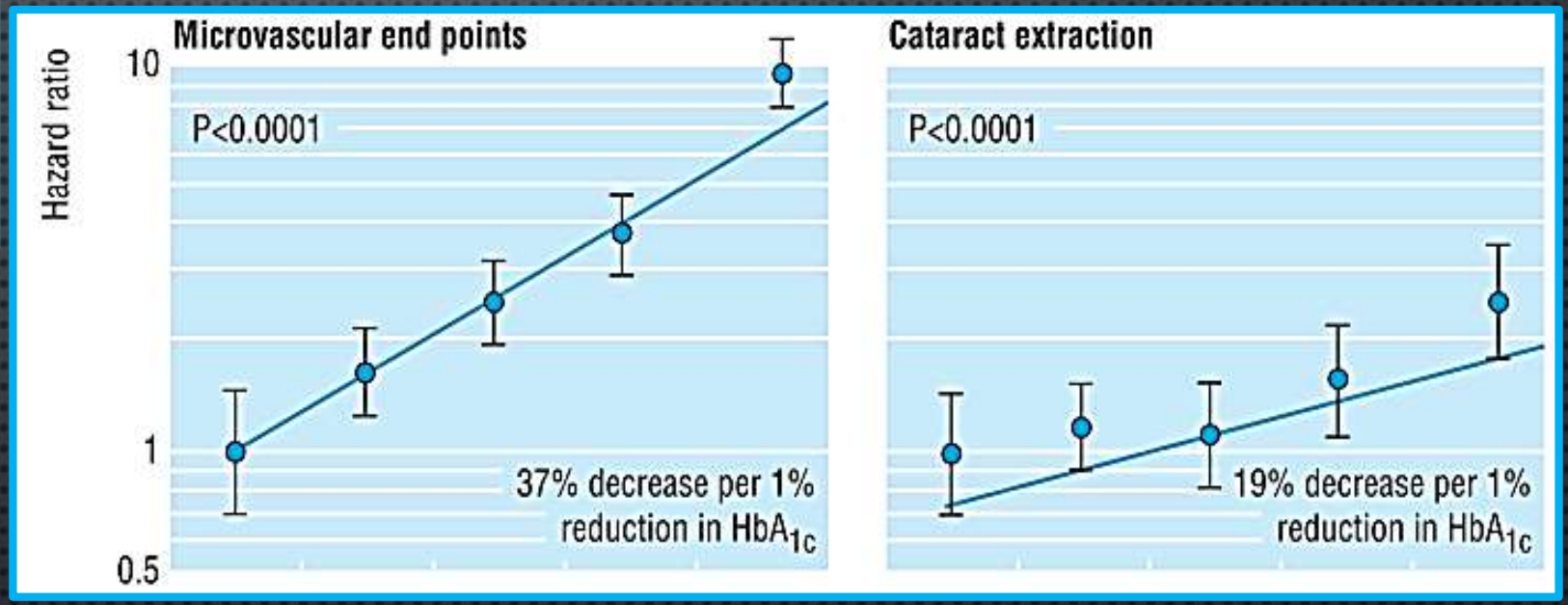
Diabetes Trials Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Radcliffe Infirmary, Oxford OX2 6HE

Irene M Stratton senior statistician

Amanda I Adler epidemiologist

Susan E Manley biochemist

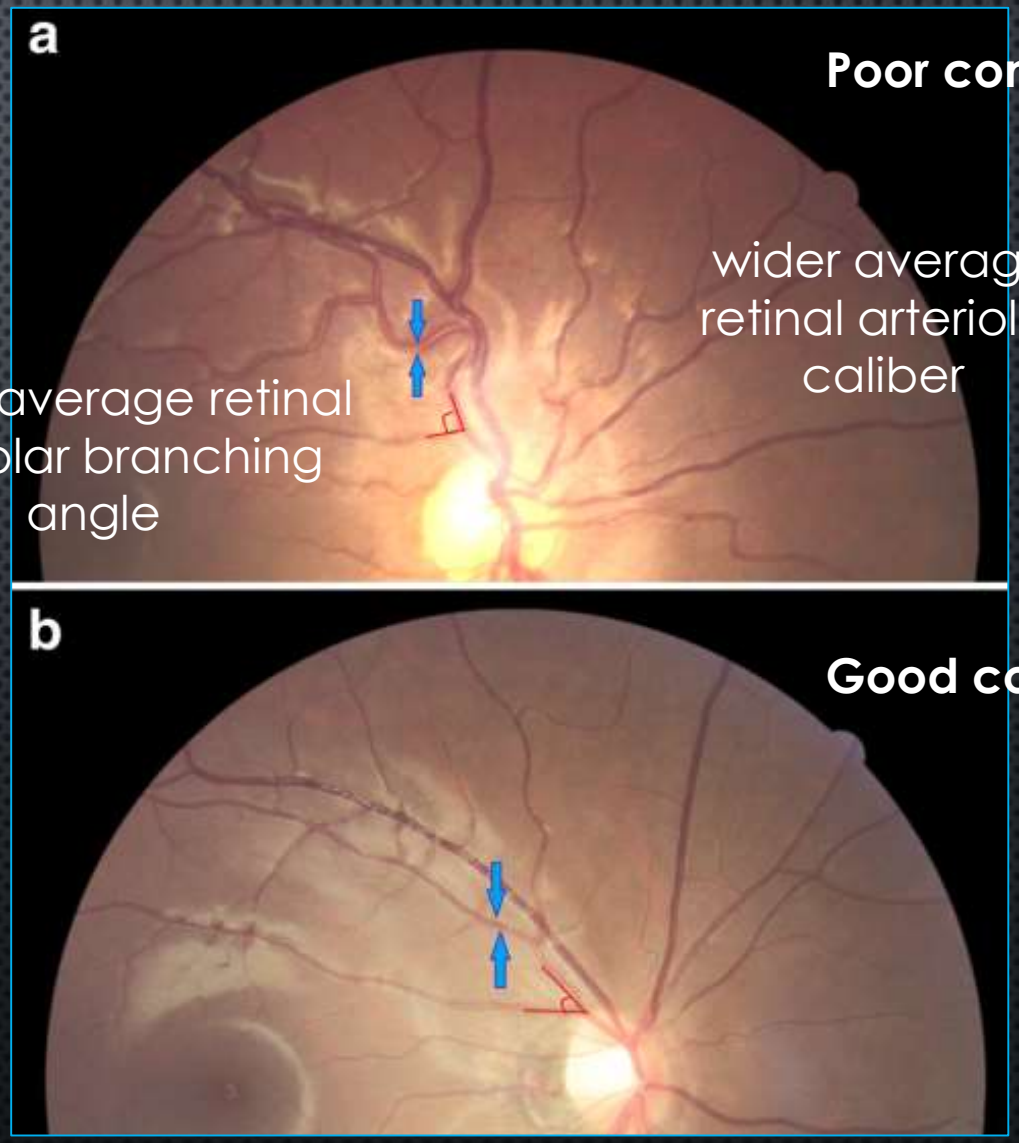




BMJ VOLUME 321 12 AUGUST 2000 bmj.com

POOR GLUCOSE CONTROL LEADS TO INCREASED MICROVASCULAR DISEASE

- TYPE 1 DIABETES CHILDREN
- SINGAPORE KK WOMEN'S AND CHILDREN HOSPITAL
- 55 PEDIATRIC T1D
- 1 YEAR FOLLOW UP
- RETINAL PHOTOGRAPHY-TRAINED GRADERS
- MULTIPLE LINEAR REGRESSION ADJUSTING FOR ETHNICITY, BMI, LDL AND DURATION OF



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

Poor blood sugar control in peds.pdf

Summary

Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials

Sophia Zoungas, Hisatomi Arima, Hertzel C Gerstein, Rury R Holman, Mark Woodward, Peter Reaven, Rodney A Hayward, Timothy Craven, Ruth L Coleman, John Chalmers, the Collaborators on Trials of Lowering Glucose (CONTROL) group

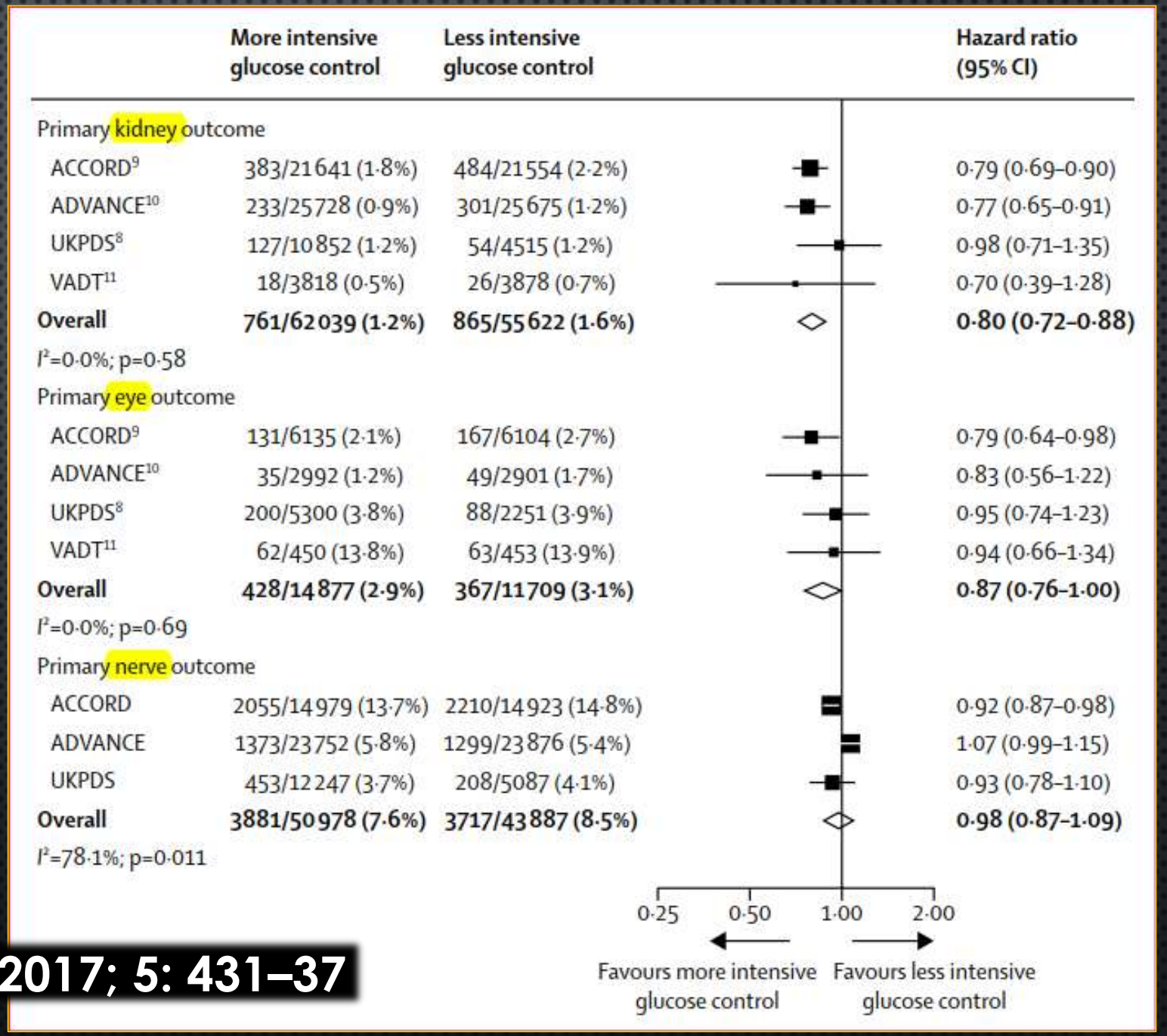
Summary

Background Intensive glucose control is understood to prevent complications in adults with type 2 diabetes. We aimed to more precisely estimate the effects of more intensive glucose control, compared with less intensive glucose control, on the risk of microvascular events.

Methods In this meta-analysis, we obtained de-identified individual participant data from large-scale randomised controlled trials assessing the effects of more intensive glucose control versus less intensive glucose control in adults with type 2 diabetes, with at least 1000 patient-years of follow-up in each treatment group and a minimum of 2 years average follow-up on randomised treatment. The prespecified and standardised primary outcomes were kidney events (a composite of end-stage kidney disease, renal death, development of an estimated glomerular filtration rate <30 mL/min per 1·73m², or development of overt diabetic nephropathy), eye events (a composite of requirement for retinal photocoagulation therapy or vitrectomy, development of proliferative retinopathy, or progression of diabetic retinopathy), and nerve events (a composite of new loss of vibratory sensation, ankle reflexes, or light touch). We used a random-effects model to calculate overall estimates of effect.

Findings We included four trials (ACCORD, ADVANCE, UKPDS, and VADT) with 27 049 participants. 1626 kidney events, 795 eye events, and 7598 nerve events were recorded during the follow-up period (median 5·0 years, IQR 4·5–5·0). Compared with less intensive glucose control, more intensive glucose control resulted in an absolute difference of –0·90% (95% CI –1·22 to –0·58) in mean HbA_{1c} at completion of follow-up. The relative risk was reduced by 20% for kidney events (hazard ratio 0·80, 95% CI 0·72 to 0·88; p<0·0001) and by 13% for eye events (0·87, 0·76 to 1·00; p=0·04), but was not reduced for nerve events (0·98, 0·87 to 1·09; p=0·68).

Interpretation More intensive glucose control over 5 years reduced both kidney and eye events. Glucose lowering remains important for the prevention of long-term microvascular complications in adults with type 2 diabetes.



Lancet Diabetes Endocrinol 2017; 5: 431–37

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

ABSTRACT

BACKGROUND

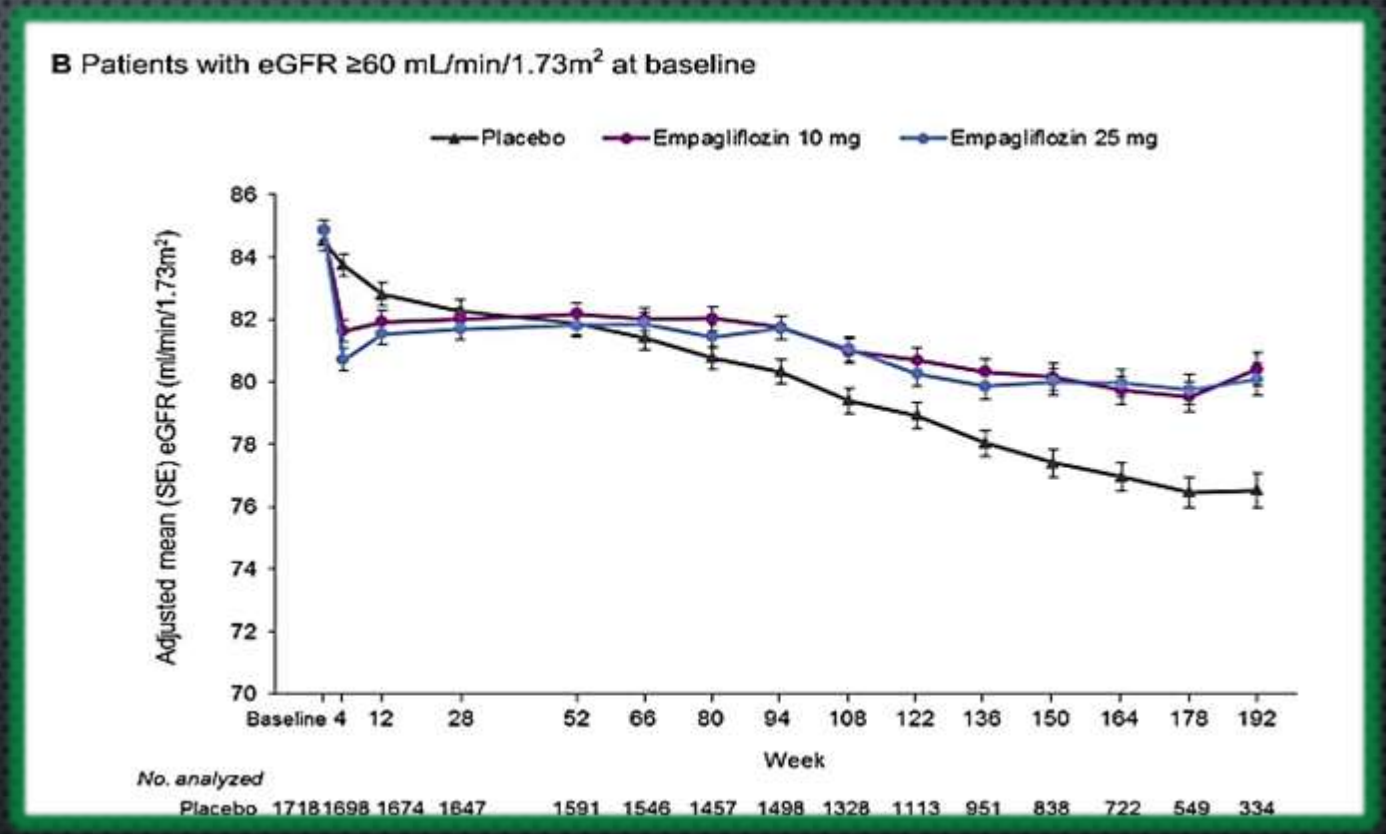
The effects of empagliflozin, an inhibitor of sodium–glucose cotransporter 2, in addition to standard care, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high cardiovascular risk are not known.

METHODS

We randomly assigned patients to receive 10 mg or 25 mg of empagliflozin or placebo once daily. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, as analyzed in the pooled empagliflozin group versus the placebo group. The key secondary composite outcome was the primary outcome plus hospitalization for unstable angina.

RESULTS

A total of 7020 patients were treated (median observation time, 3.1 years). The



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Fatal or nonfatal myocardial infarction	11.2	12.6	0.89 (0.73–1.09)
Fatal or nonfatal stroke	7.9	9.6	0.87 (0.69–1.09)
Hospitalization for any cause	118.7	131.1	0.94 (0.88–1.00)
Hospitalization for heart failure	5.5	8.7	0.67 (0.52–0.87)
Death from cardiovascular causes or hospitalization for heart failure	16.3	20.8	0.78 (0.67–0.91)
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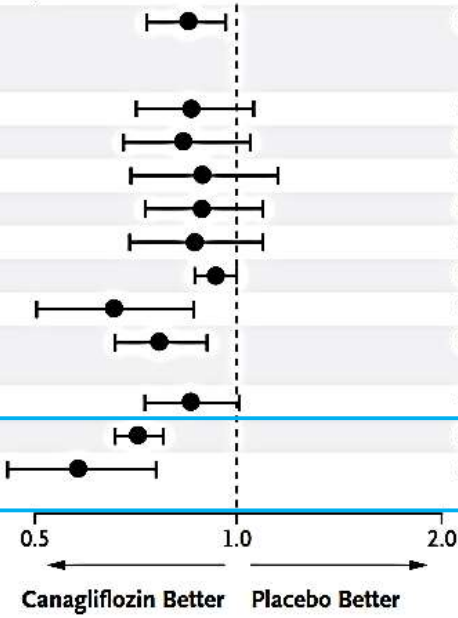

N Engl J Med 2017;377:644-57

CANVAS ORG.pdf

GLP-1 reduces kidney failure

The NEW ENGLAND JOURNAL of MEDICINE

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Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

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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.

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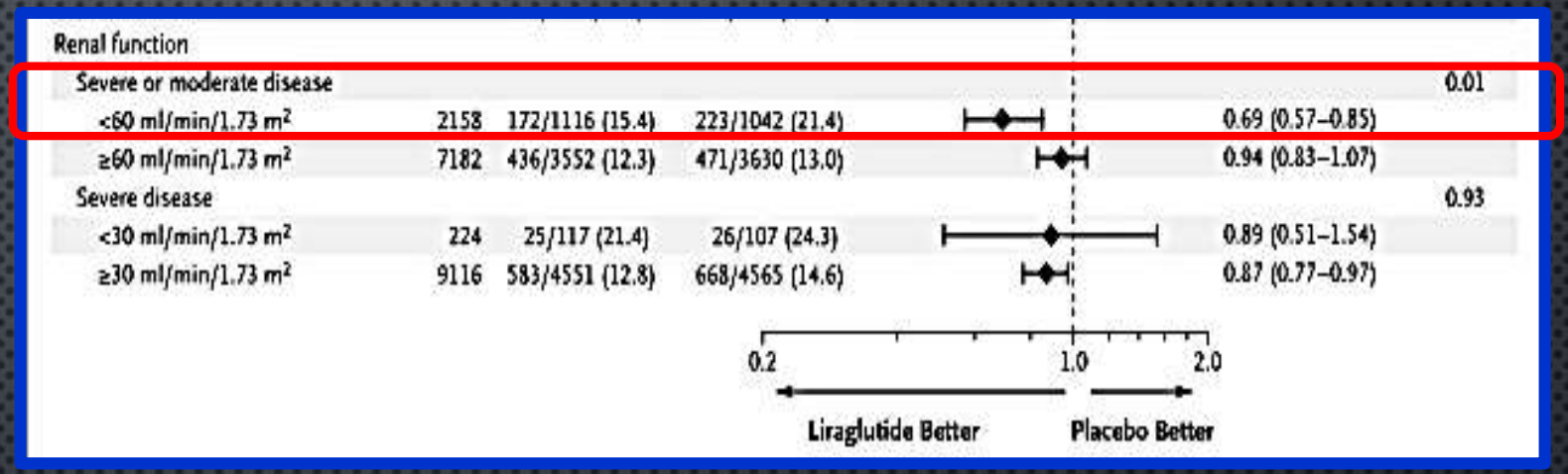


LEADER ORG.pdf

LEADER trial

ADA/AACE RECOMMENDED GLYCEMIC TARGETS FOR ICU AND NON-ICU SETTINGS

ICU	Non-ICU

• Initiate insulin therapy for persistent hyperglycemia (glucose>180 mg/dl)
• Treatment goal: For most patients, target a glucose level 140-180 mg/dl
• More stringent goals (110-140 mg/dl) may be appropriate for selected patients, if achievable without significant risk for hypoglycemia
	• No specific guidelines for insulin initiation
	• If treated with insulin:
	  • Pre-meal glucose <140 mg/dl
	  • Random glucose <180 mg/dl
	• More stringent targets may be appropriate for patients with previously tight glycemic control
	• Less stringent targets may be appropriate in patients with severe comorbidities

Available at: https://www.ncbi.nlm.nih.gov/books/NBK279093/?report=classic

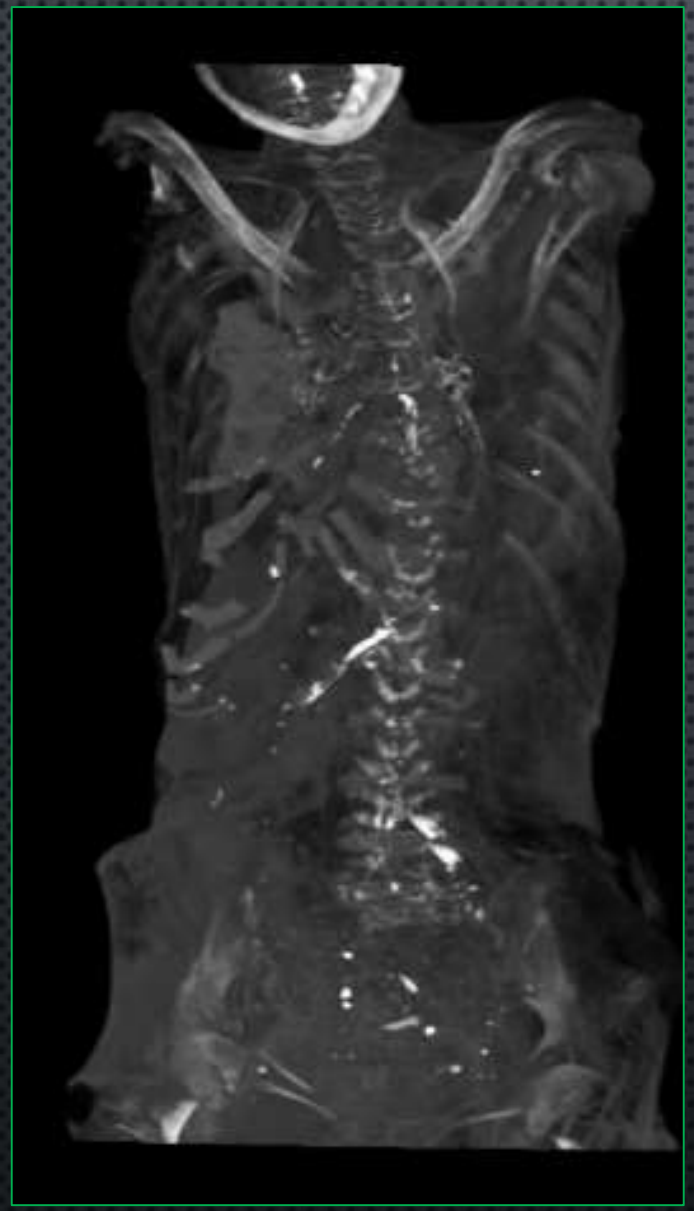
Closing comments

CV LOOK @ TYPE 2 DIABETES AGENTS

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



30 y/o Egyptian princess with atherosclerosis

Thank you

Clinical Pearls

- Patients with diabetes are at increased risk of vascular complications and hospitalizations for CV related events compared to patients without diabetes
- Diabetes and hypertension are among the 9 modifiable risk factors that account for >90% of the risk of initial acute MI
- For most hospitalized patients with diabetes, target a glucose level of 140-180 mg/dl
- Newer treatments for diabetes, including SGLT2 and GLP-1 indicators, have been shown to reduce micro and macrovascular events
- More intensive glucose control has been associated with a 20% reduction in kidney disease
- Prior to discharge of a patient with diabetes, ADA guidelines recommend measurement of hbA1c level

Thank You!