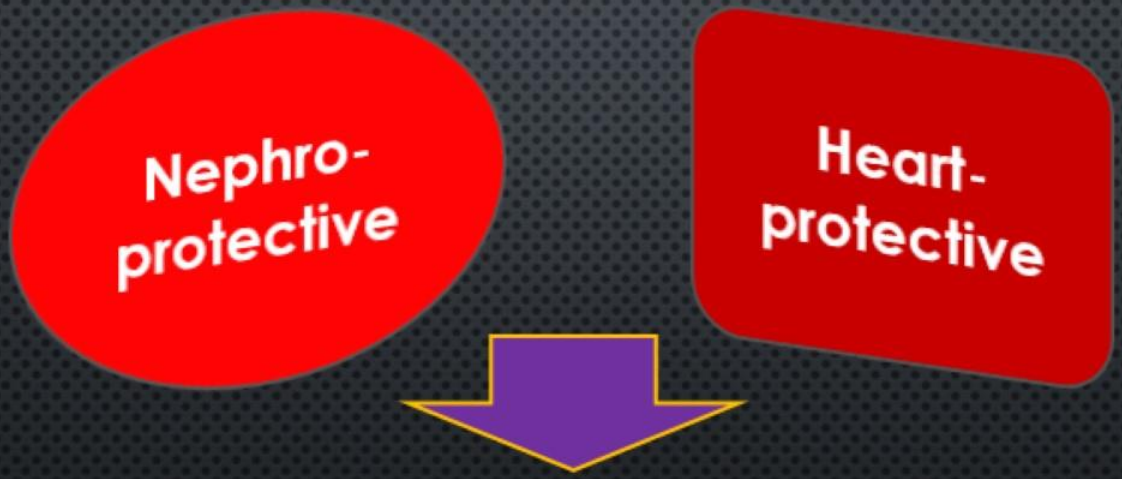
INFLUENCING CV RISK WITH ANTIHYPERGLYCEMIC AGENTS: SGLT2 INHIBITORS AND INCRETIN BASED THERAPIES

"Novel new cardiorenal agents for diabetes"



Vascular protective
Type 2 diabetes patients

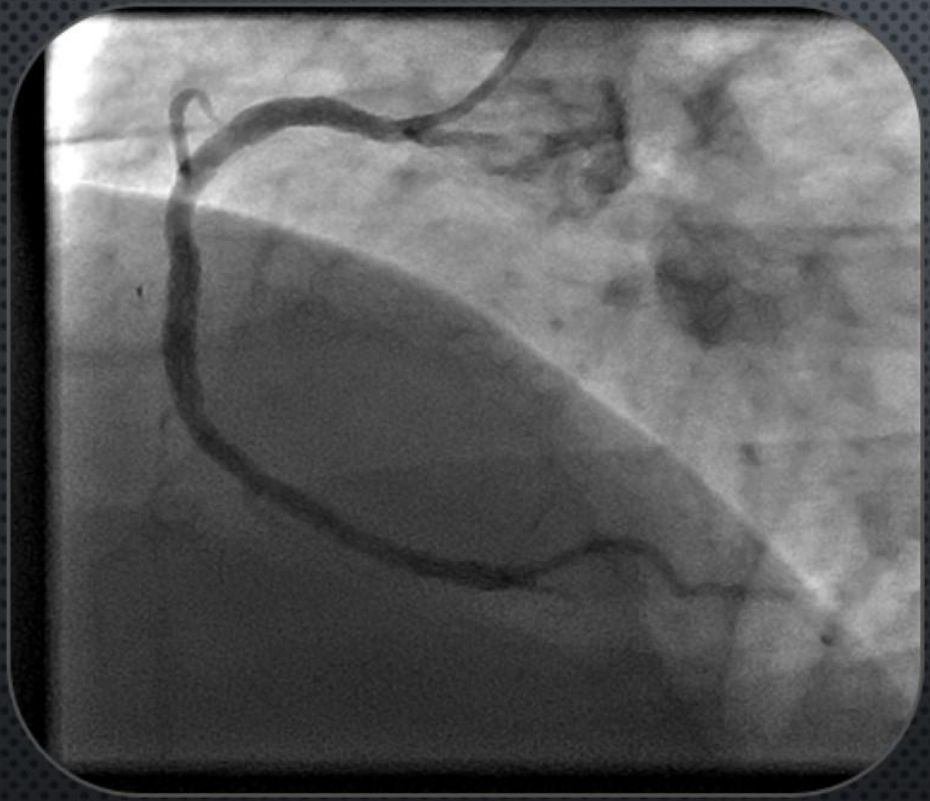
CONFLICTS OF INTEREST

Medical research with multiple companies, governmental and private industry

Lecture today involves more than companies with FDA approval of these compounds

Clinical translational pathobiology

HT diabetes patient and the interventional cardiologist

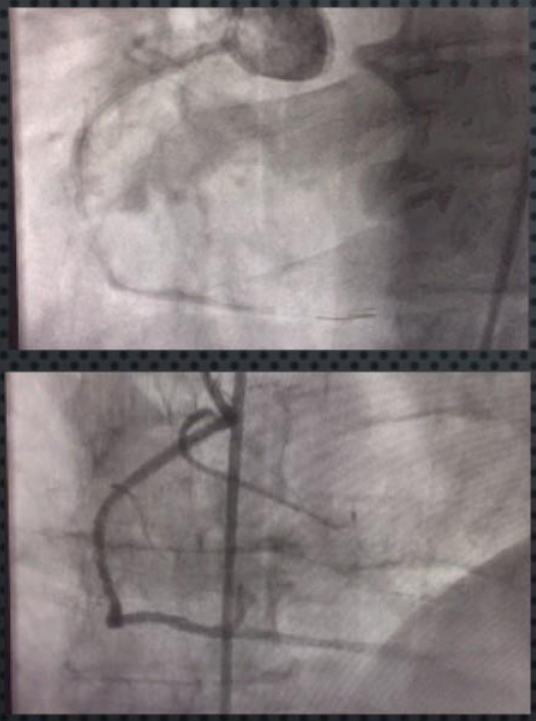


Cath due to atypical chest pain
HbA1c 8.2 metformin
HT - HCTZ

Hispanic T2DM with BP 142/87
Normal Texas Weight (BMI 33)
Welder with 5 children 3x wives

1 year later

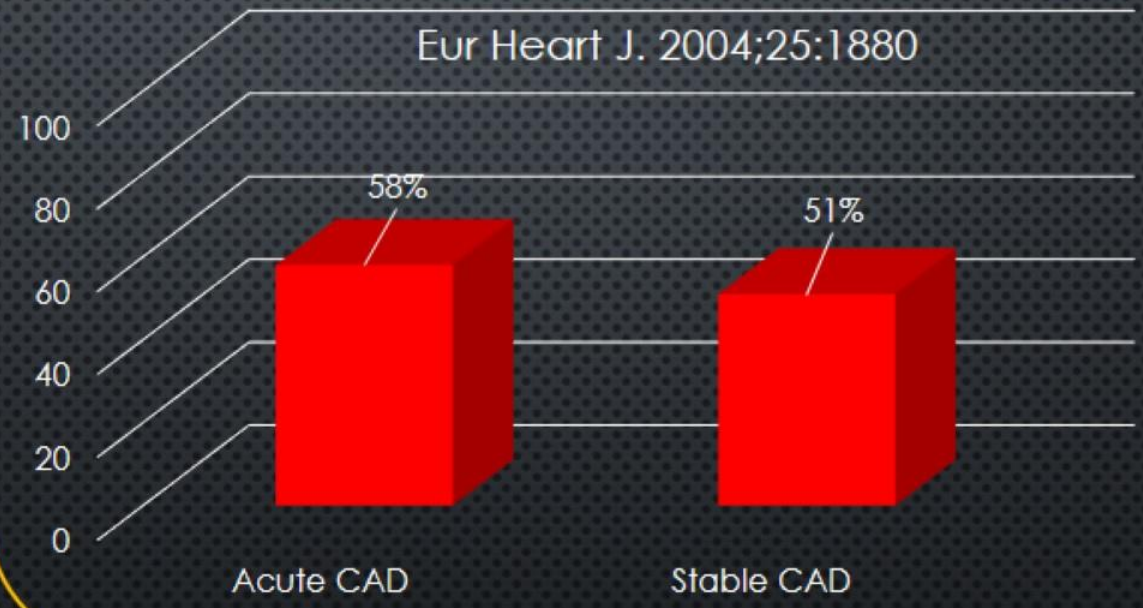
Routine day
Acute MI: 3 am



Young Hispanic male
BP 145/70
CC 45 cc/min
Low HDL
High triglycerides
Blood sugar at MI 304
HbA1c 8.8

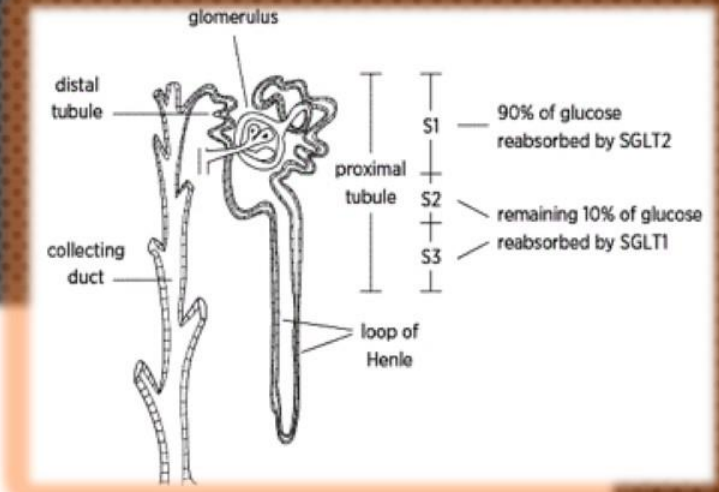
- **High incidence of undiagnosed diabetes in acute myocardial infarction patients**

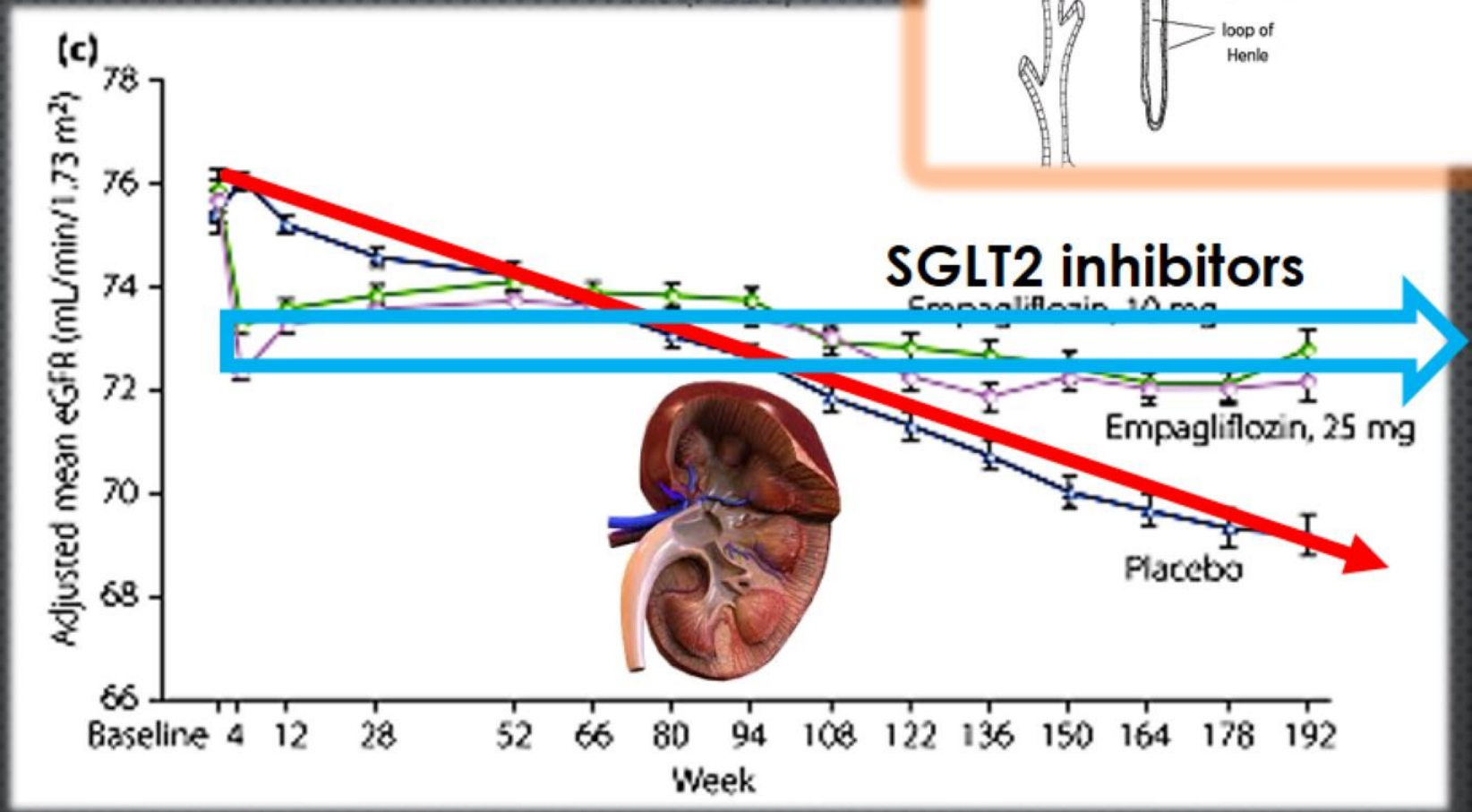
Percentage of patients seen by cardiologist without known diabetes



Significant CV risk factors exist 10 yrs before diagnosis of diabetes..Rancho Bernardo study Am J Epid 1990:131:443

BENEFICIAL DIABETES KIDNEY PROTECTION WITH SGLT2 INHIBITORS





….you or your family have diabetes….LOOK…on top of ACEI/ARB

No Rx drug is free of side effects

BEST: Great lifestyle with hand picked parents

Incretins: GLP 1 agonist

LEADER
SUSTAIN-6

….High quality clinical trials with cost of > 3 billion dollars

SGLT2 inhibitors

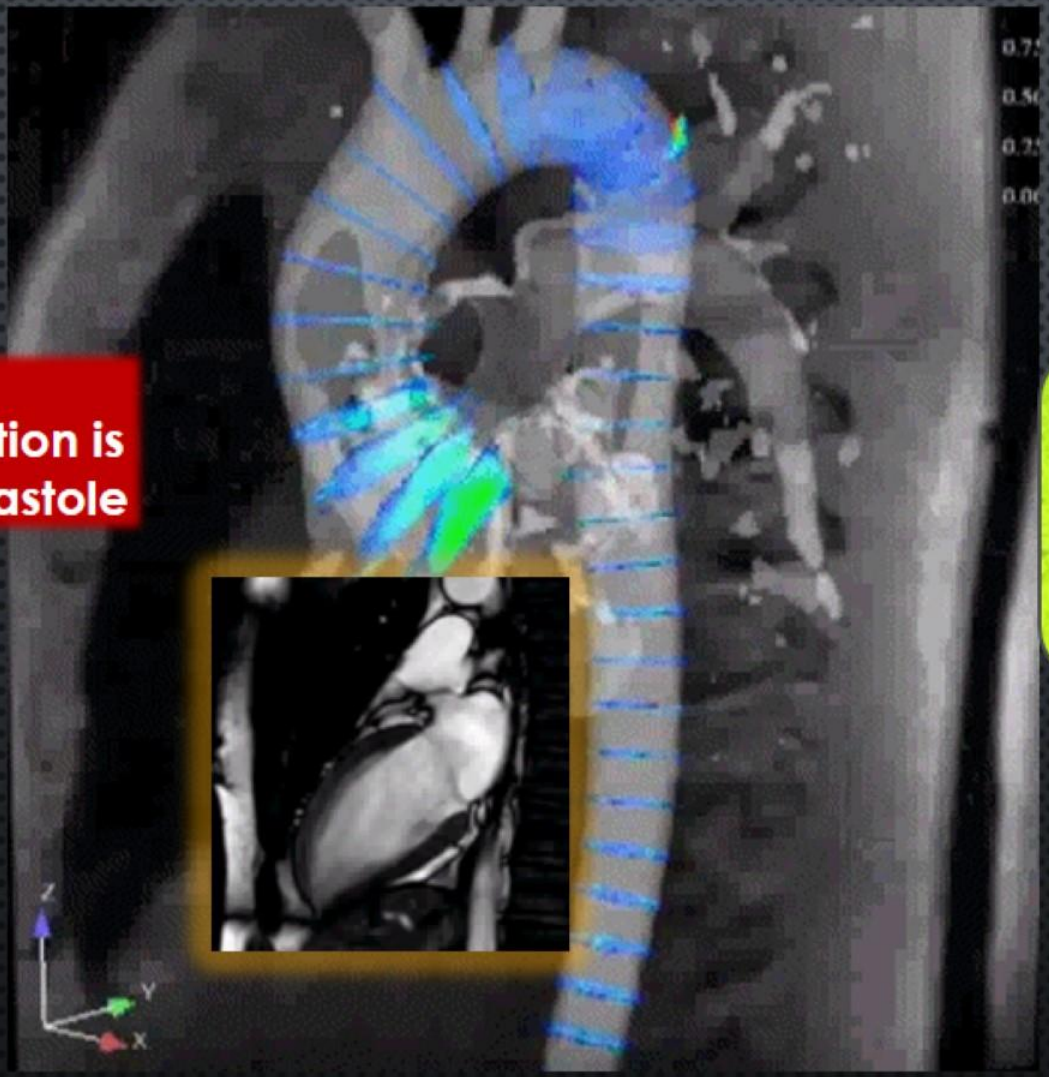
EMPA REG
CANVAS

Major factor effecting oxygen consumption

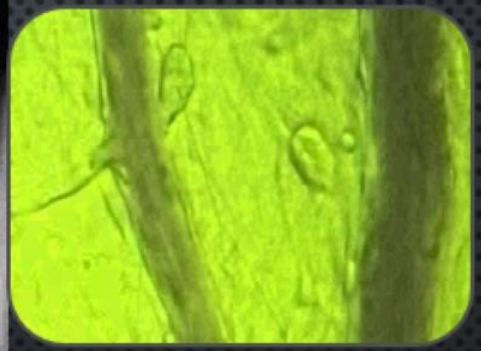
Heart rate
Blood pressure
Heart size
Afterload

↓ MVO2-reduces ischemia

ARTERIAL COMPLIANCE REDUCES AFTERLOAD ON HEART

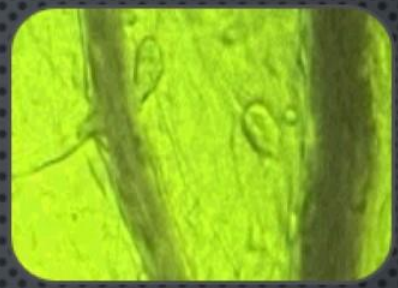


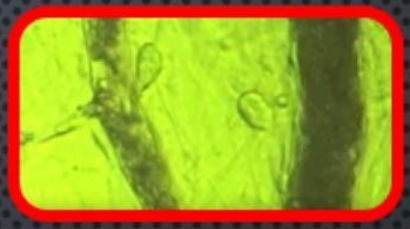
60% of microcirculation is fed during diastole



Virchow's triad
Atherothrombosis

Diabetes
Small vessel disease





Slow flow

Endothelial injury

Infection
LDL 5-
endothelial cell apoptosis

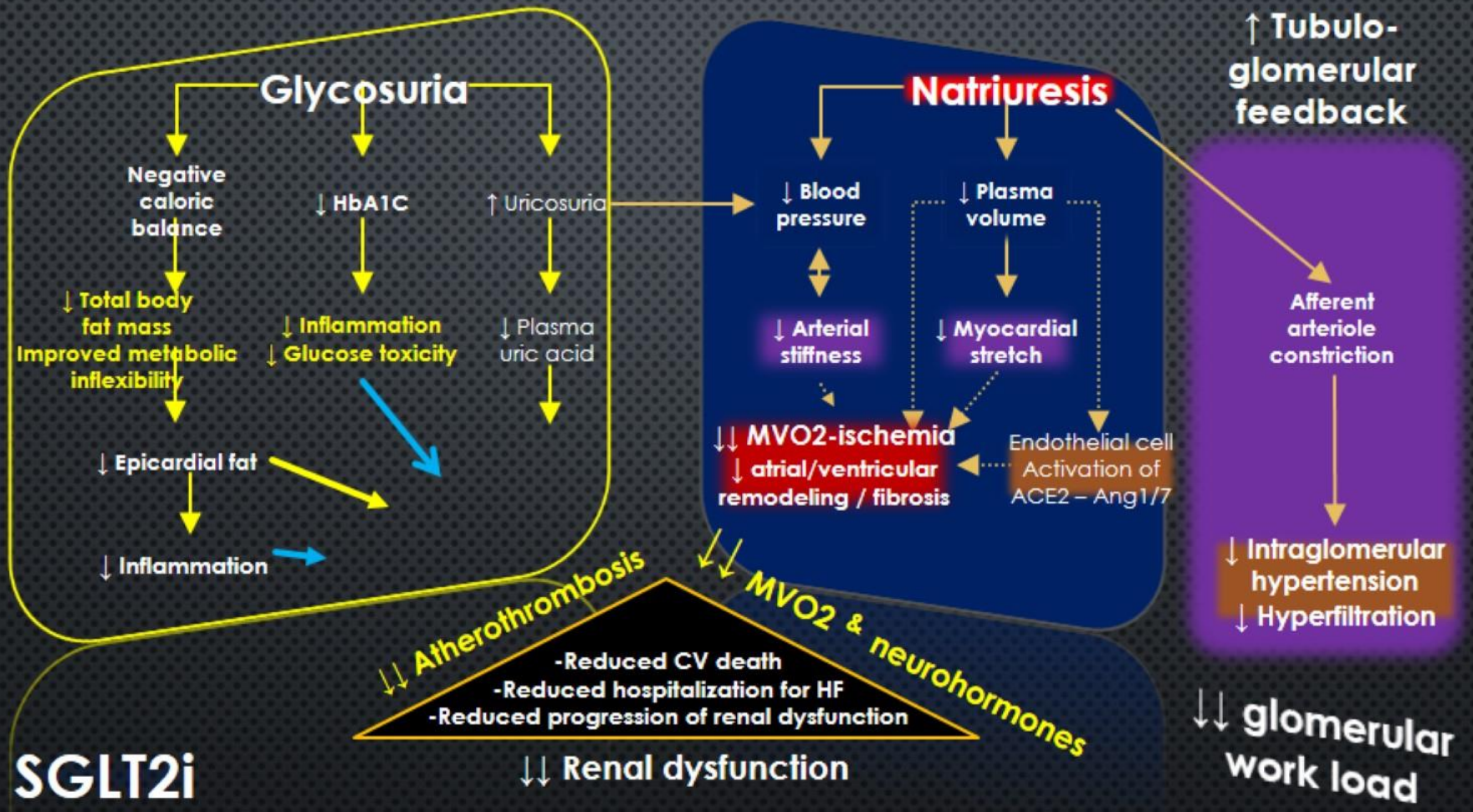
↑↑ coagulation

↑ PAI-1

Whats new

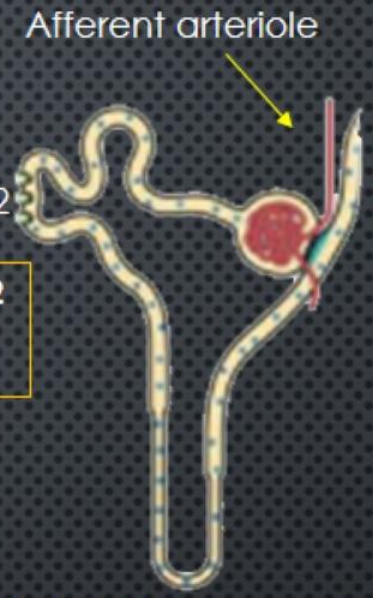
SGLT2 inhibitor pathophysiology

CV AND RENAL EFFECTS OF SGLT2 INHIBITORS



800 cc fluid 24-48 hours
300 cc / day
2 cans coke

TRANSLATIONAL BIOLOGY OF NEW CV AGENT SGLT2 INHIBITORS



Patient perspective

Weight loss
Lower BP
Less shortness of breath

eGFR ↓↓ 5 cc/min/1.73m²
↓ 30-40% albuminuria

Osmotic diuresis / natriuresis (plasma volume contraction) → **↓↓ SBP 4-6 mm**

(Activation of renal tubuloglomerular feedback)

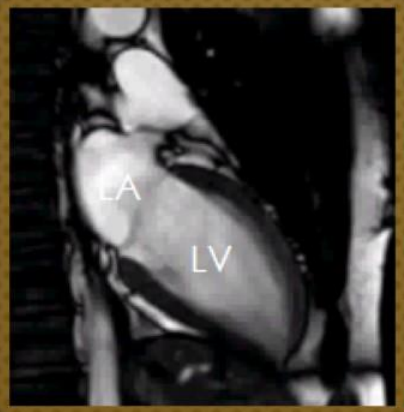
↑↑ macula densa sodium / chloride delivery

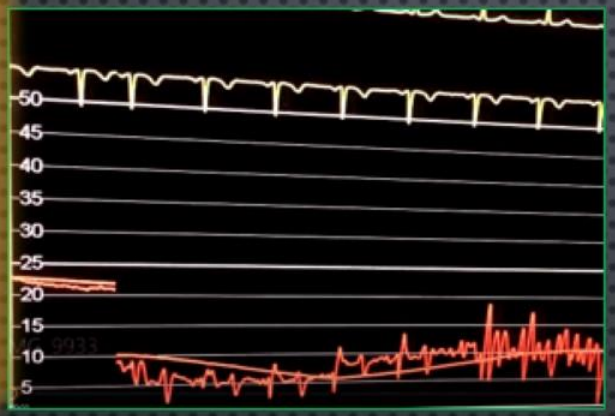
Afferent vasoconstriction

800 cc fluid acutely
150-300 cc daily
2 cans of coke in calories per day

Adapted from Heerspink

48 y/o Hispanic women
Type 2 diabetes





300 cc of NS
Very SOB

Patient very short of breath

Diuretic IV

LVEDP
Left ventricular end diastolic pressure

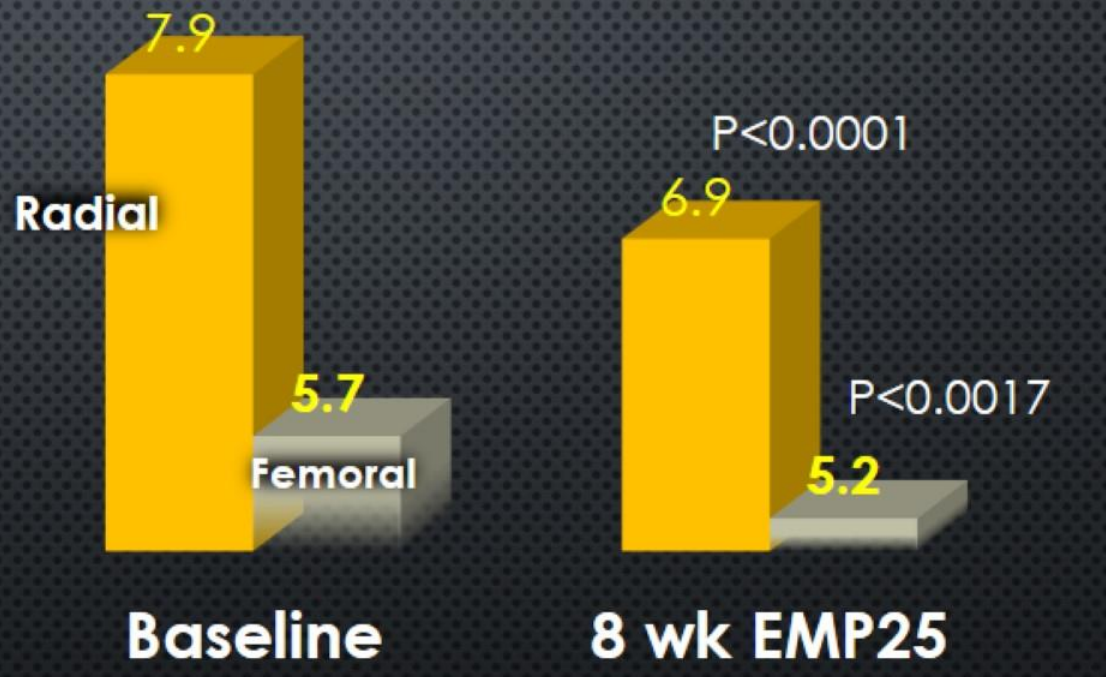
Chilton

SIGNIFICANT REDUCTION IN PULSE WAVE VELOCITY WITH SGLT2 INHIBITOR

N=40
Hyperglycemic clamp

Baseline
8 wks EMP25

Baseline
SBP 112
HR 72
Noradr level .77
8 weeks EMP25
SBP 110
HR 70
Noradr level .70



Cardiovascular Diabetology 2014, 13:28

HIGH QUALITY PROSPECTIVE RANDOMIZED CV ENDPOINT TRIALS

CV Benefits

		↓ CV events	↓ CV death	↓ hospitalization for HF	% events/yr
SGLT2 inhibitors	EMPA	+	+	+	4.5%
	CANVAS	+	-	+	4.95%
GLP1 agonist	LEADER	+	-/+	-	3.7%
	SUSTAIN-6	+	-	-	4.5%
DPPIV inhibitors	SAVOR	-	-	-	2.5%
	EXAMINE	-	-	-	7-8%
	TECOS	-	-	-	3.25%
NEPI/AT1	PARADIGM HF	+	+	+	10.25%
Lipid lowering	STATINS-4S	+	-	+	1.7%
	PCSK9 I	+	-	-	4.86%
	FOURIER	+	-	-	3.8%

ONLY if significant

Chilton pending publication

TRANSLATIONAL RELATIONSHIPS

Hypertrophy/fibrosis

AJC Pham 2017

New CV drugs for diabetes that reduce CV death

>80% have hypertension

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.

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ORIGINAL ARTICLE

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*

N Engl J Med 2016; 375:311-322 | July 28, 2016 | DOI: 10.1056/NEJMoa1603827

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Abstract | Article | References | Citing Articles (519) | Letters | Metrics

Type 2 diabetes is a complex metabolic disorder that is characterized by hyperglycemia and associated with a high risk of cardiovascular, microvascular, and other complications.[1,2] Although glycemic control is associated with reductions in the risk of microvascular complications, the macrovascular benefits of glycemic control are less certain. Furthermore, concern has been raised about the cardiovascular safety of antihyperglycemic therapies.[3] Consequently, regulatory authorities have mandated cardiovascular safety assessments of new diabetes treatments.[4,5]

QUICK TAKE VIDEO SUMMARY

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

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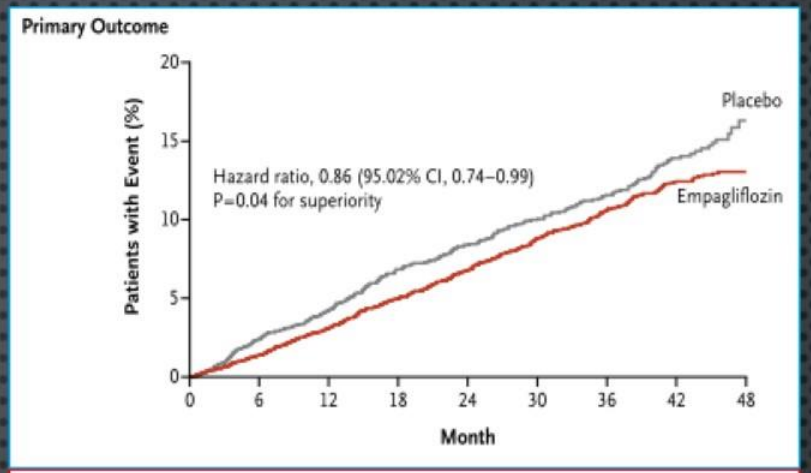
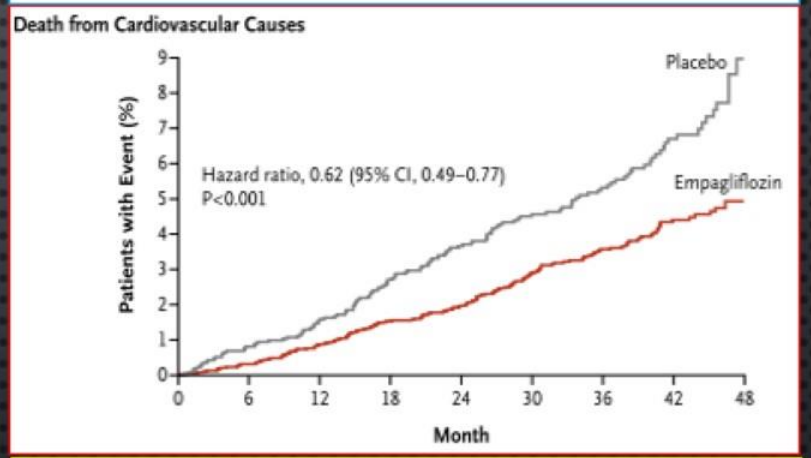
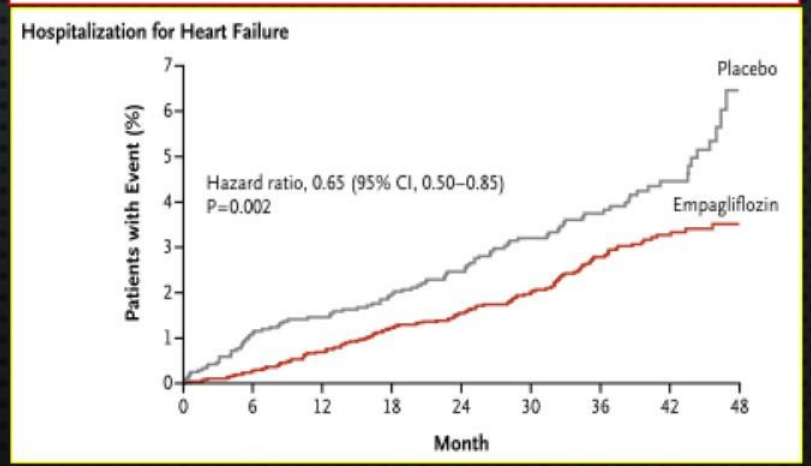
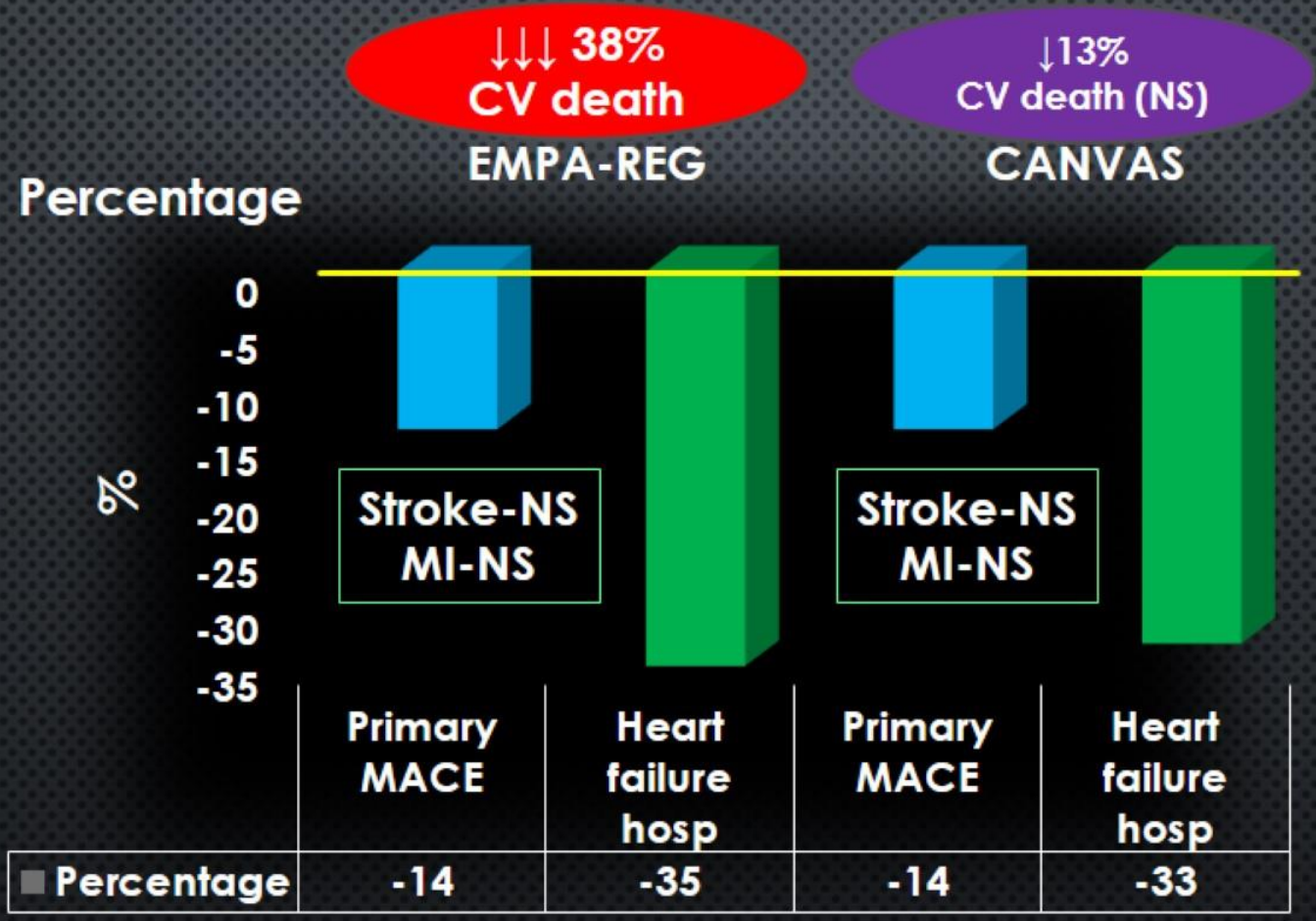
NEJM 2015;373:2117





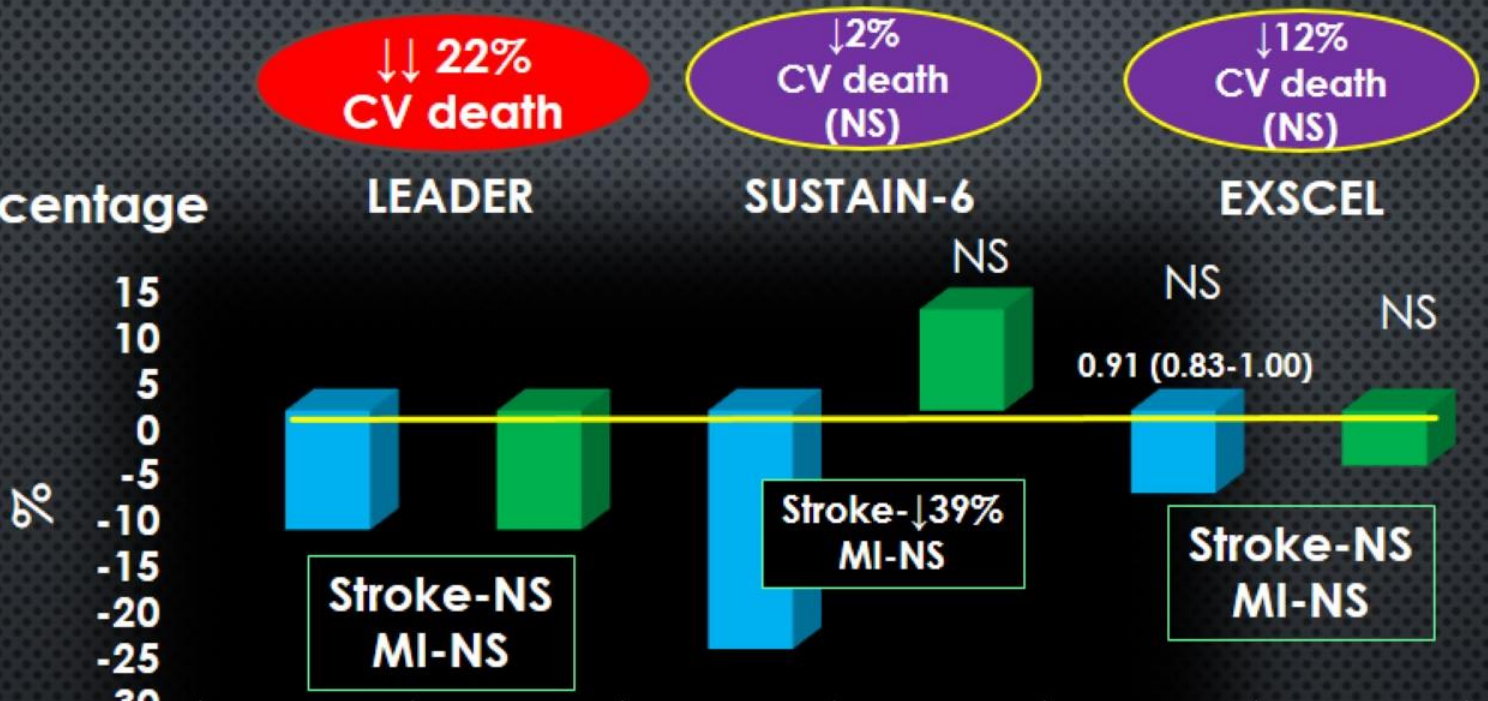


SGLT 2 INHIBITORS AND CV EVENTS



Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

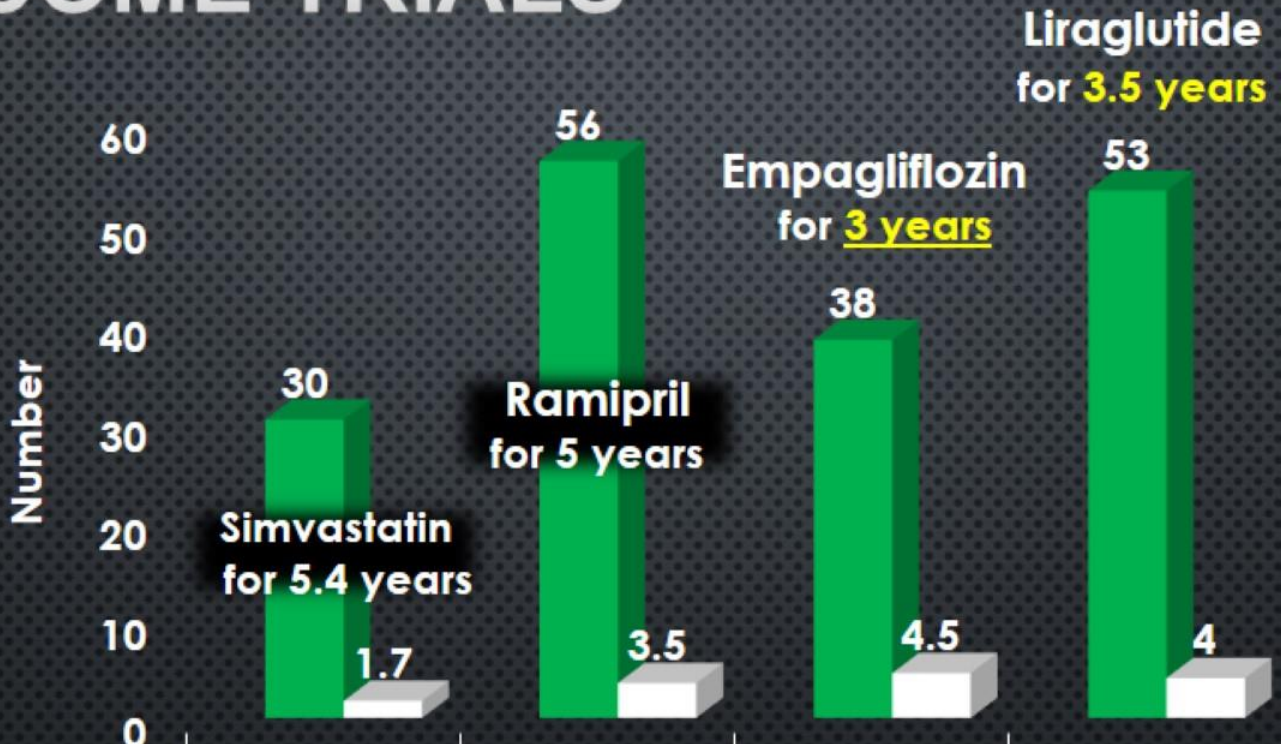
GLP 1 AGONIST AND CV EVENTS



	Primary MACE	Heart failure hosp	Primary MACE	Heart failure hosp	Primary MACE	Heart failure hosp
Percentage	-13	-13	-26	11	-9	-6

Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

HIGH RISK CV OUTCOME TRIALS



	4S trial	HOPE	EMPA-REG	LEADER
NNT	30	56	38	53
Event rate per year	1.7 %	3.5	4.5	4

DOI:10.1056/NEJMoa1504720