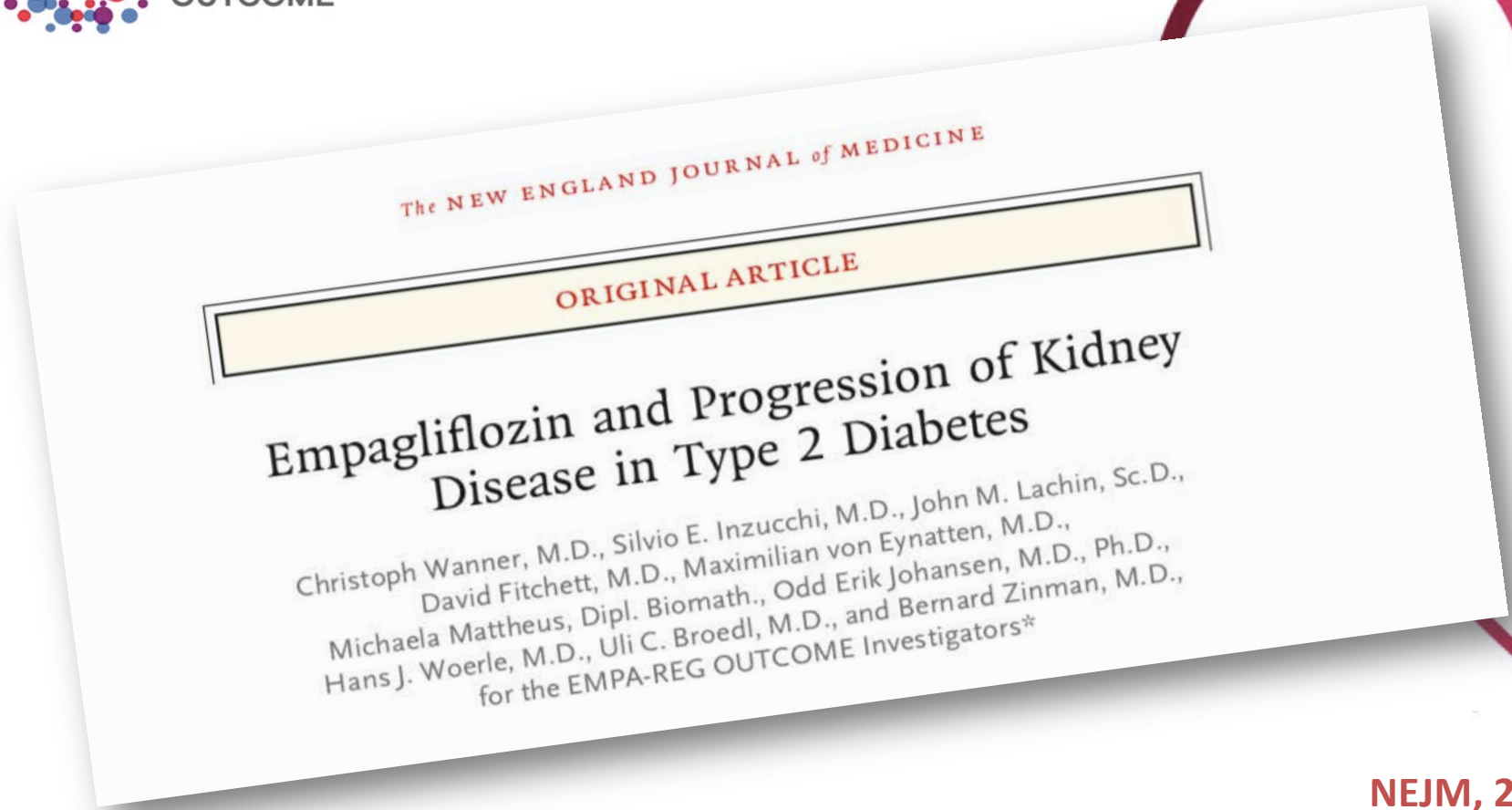
EMPA-REG OUTCOME®



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

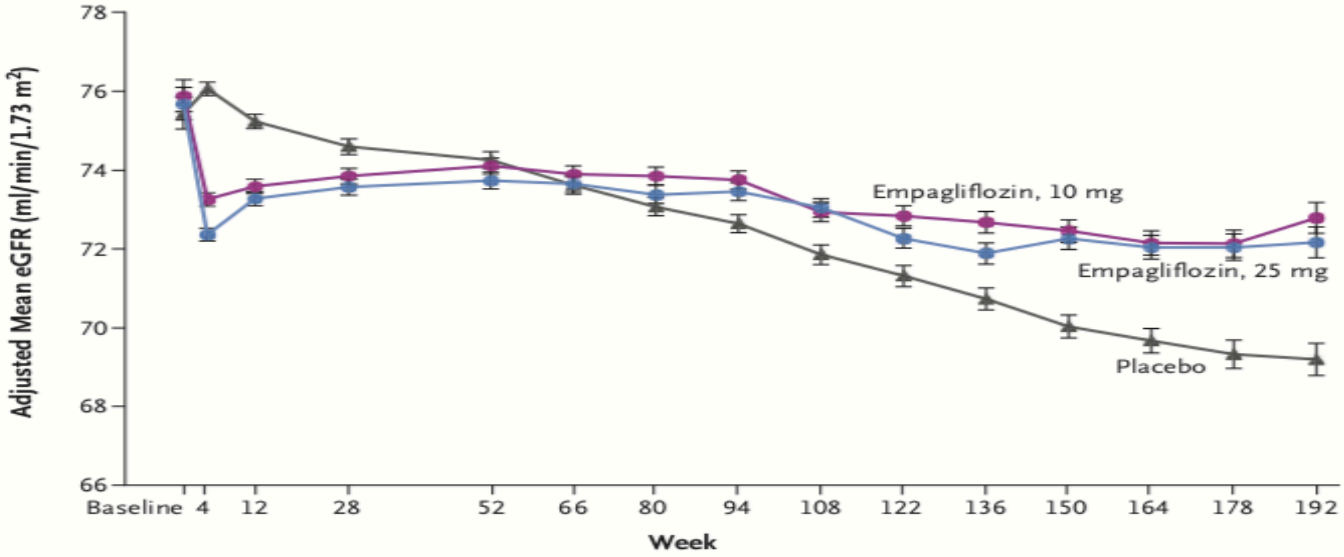
Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators*

NEJM, 28jul16

EMPA-REG OUTCOME®

A Change in eGFR over 192 Wk

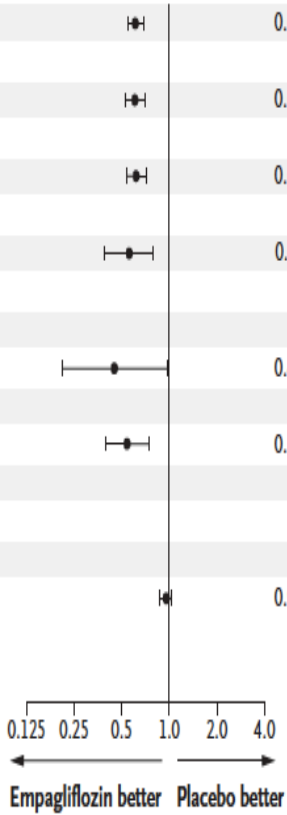


No. at Risk															
Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin, 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
Empagliflozin, 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524
No. in Follow-up Analysis															
Total	7020	7020	6996	6931	6864	6765	6696	6651	6068	5114	4443	3961	3488	2707	1703

NEJM, 28jul16

EMPA-REG OUTCOME®

Renal Outcome Measure	Empagliflozin no. with event/ no. analyzed (%)	Empagliflozin rate/1000 patient-yr	Placebo no. with event/ no. analyzed (%)	Placebo rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Incident or worsening nephropathy or cardiovascular death	675/4170 (16.2)	60.7	497/2102 (23.6)	95.9	0.61 (0.55–0.69)	<0.001
Incident or worsening nephropathy	525/4124 (12.7)	47.8	388/2061 (18.8)	76.0	0.61 (0.53–0.70)	<0.001
Progression to macroalbuminuria	459/4091 (11.2)	41.8	330/2033 (16.2)	64.9	0.62 (0.54–0.72)	<0.001
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2	70/4645 (1.5)	5.5	60/2323 (2.6)	9.7	0.56 (0.39–0.79)	<0.001
Initiation of renal-replacement therapy	13/4687 (0.3)	1.0	14/2333 (0.6)	2.1	0.45 (0.21–0.97)	0.04
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2, initiation of renal-replacement therapy, or death from renal disease	81/4645 (1.7)	6.3	71/2323 (3.1)	11.5	0.54 (0.40–0.75)	<0.001
Incident albuminuria in patients with a normal albumin level at baseline	1430/2779 (51.5)	252.5	703/1374 (51.2)	266.0	0.95 (0.87–1.04)	0.25



New or worsening nephropathy

Progresión to macro-albuminuria

Doubling of serum creatinine

Initiation of renal replacement therapy

ORIGINAL RESEARCH ARTICLE

Empagliflozin and Clinical Outcomes in Patients With Type 2 Diabetes Mellitus, Established Cardiovascular Disease, and Chronic Kidney Disease

What is the outcome in patients with pre-existing CKD?

American Heart Association®

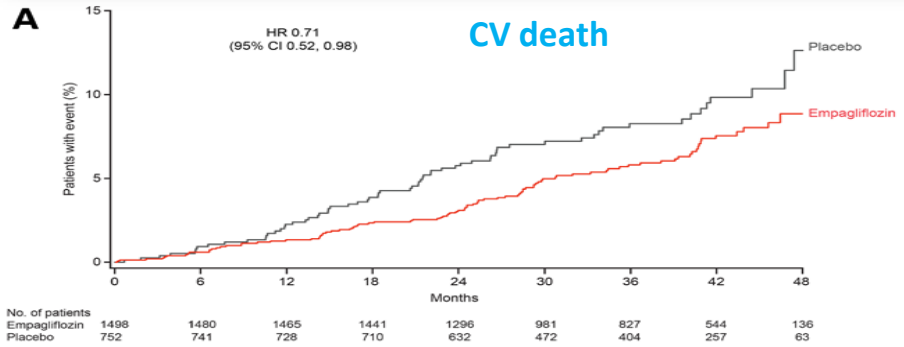
N= 2.250	Placebo (n=2333)	Empagliflozin 10 mg (n=2345)	Empagliflozin 25 mg (n=2342)
Prevalent kidney disease*	**752 (32.2%)**	**757 (32.3%)**	**741 (31.6%)**

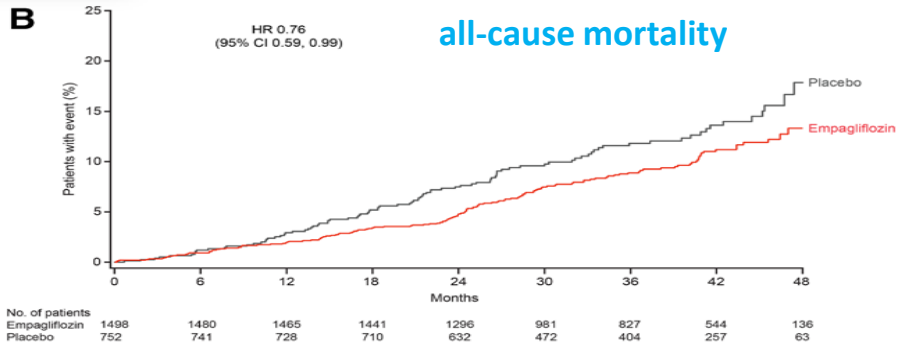
*eGFR (MDRD) 30–60 mL/min/1.73m2 **and/or** macroalbuminuria at baseline.

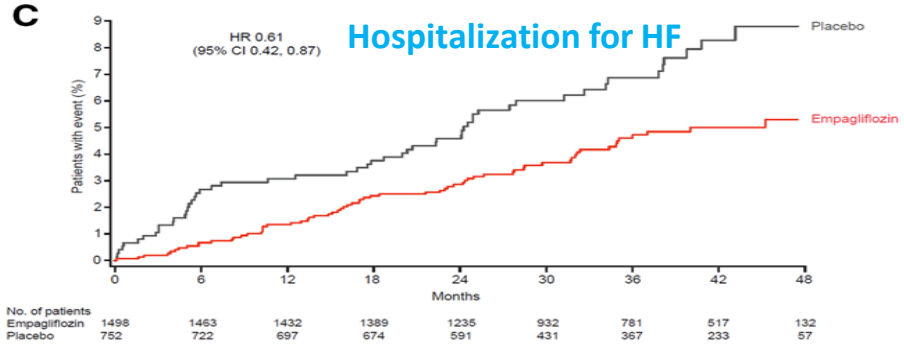
Circulation 2018;137:119-129

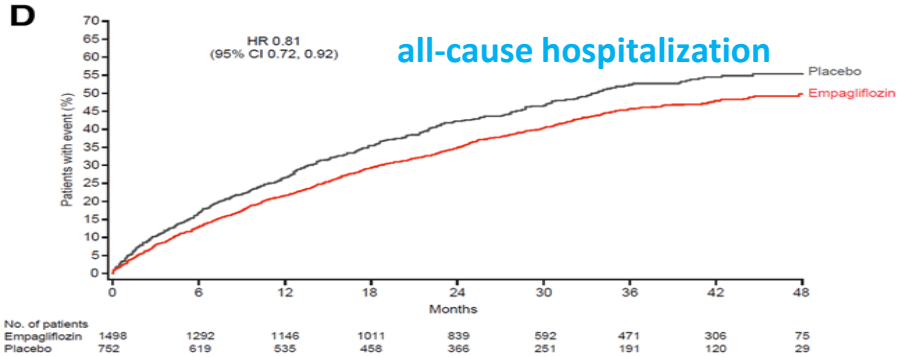
ORIGINAL RESEARCH ARTICLE

Empagliflozin and Clinical Outcomes in Patients With Type 2 Diabetes Mellitus, Established Cardiovascular Disease, and Chronic Kidney Disease







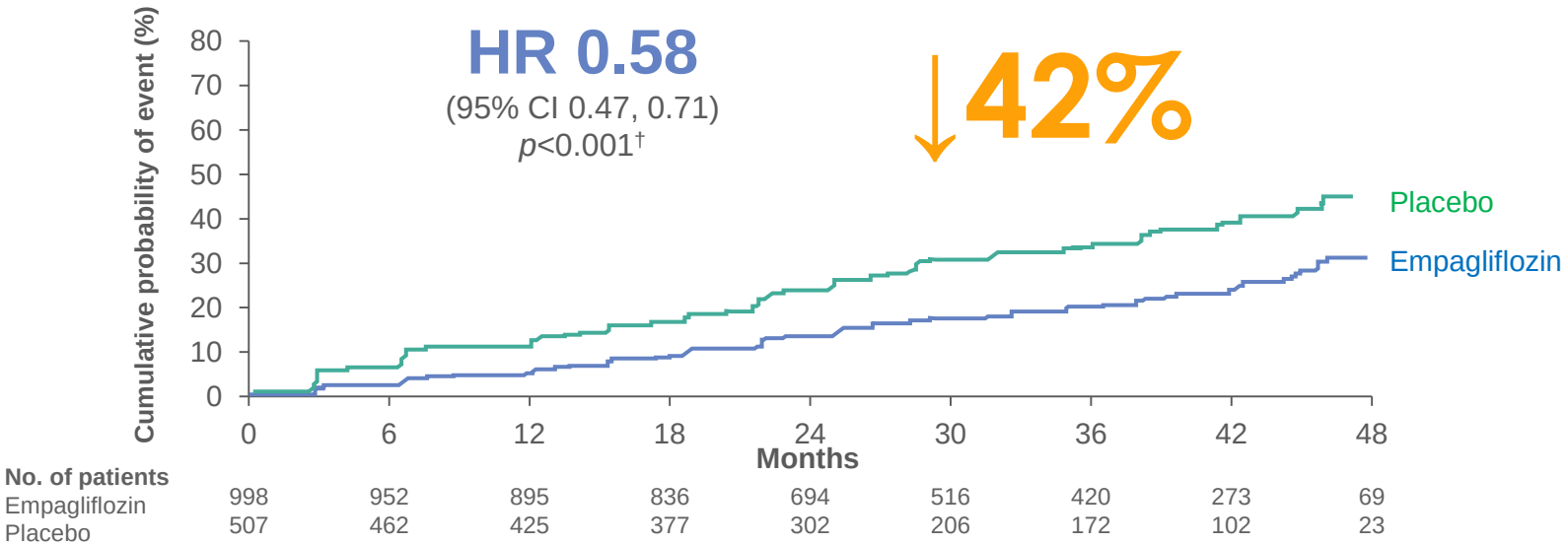


Circulation 2018;137:119-129

ORIGINAL RESEARCH ARTICLE

Empagliflozin and Clinical Outcomes in Patients With Type 2 Diabetes Mellitus, Established Cardiovascular Disease, and Chronic Kidney Disease

Incident or worsening nephropathy in patients with prevalent kidney disease*

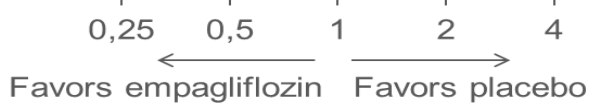


* Defined as eGFR (MDRD) <60 ml/min/1.73 m2 and/or macroalbuminuria (UACR >300 mg/g) at baseline; †Nominal p-value

Wanner C et al. N Engl J Med 2016;375:323

Empagliflozin reduces Mortality and HHF in patients with or without a history of MI or stroke at baseline

	Empagliflozin		Placebo		HR (95% CI)	Treatment by subgroup interaction
	n/N	%	n/N	%		
HHF						
All patients	126/4687	2.7	95/2333	4.1		
History of MI or stroke						p=0.5610
Yes	94/3048	3.1	67/1518	4.4		
No	32/1639	2.0	28/815	3.4		
HHF or CV death						
All patients	265/4687	5.7	198/2333	8.5		
History of MI or stroke						p=0.7696
Yes	196/3048	6.4	148/1518	9.7		
No	69/1639	4.2	50/815	6.1		



DOI: 10.1016/S0735-1097(18)32260-5
1719 JACC March 20, 2018. David H. Fitchett, Silvio E. Inzucchi et Al.

Diabetologia
https://doi.org/10.1007/s00125-018-4644-9

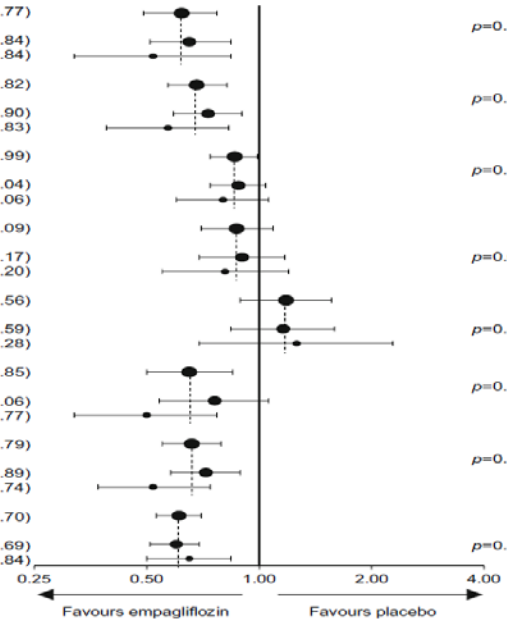
ARTICLE

Empagliflozin reduces cardiovascular events, mortality and renal events in participants with type 2 diabetes after coronary artery bypass graft surgery: subanalysis of the EMPA-REG OUTCOME® randomised trial

Subodh Verma[1] · C. David Mazer[2] · David Fitchett[3] · Silvio E. Inzucchi[4] · Egon Pfarr[5] · Jyothis T. George[6] · Bernard Zinman[7]

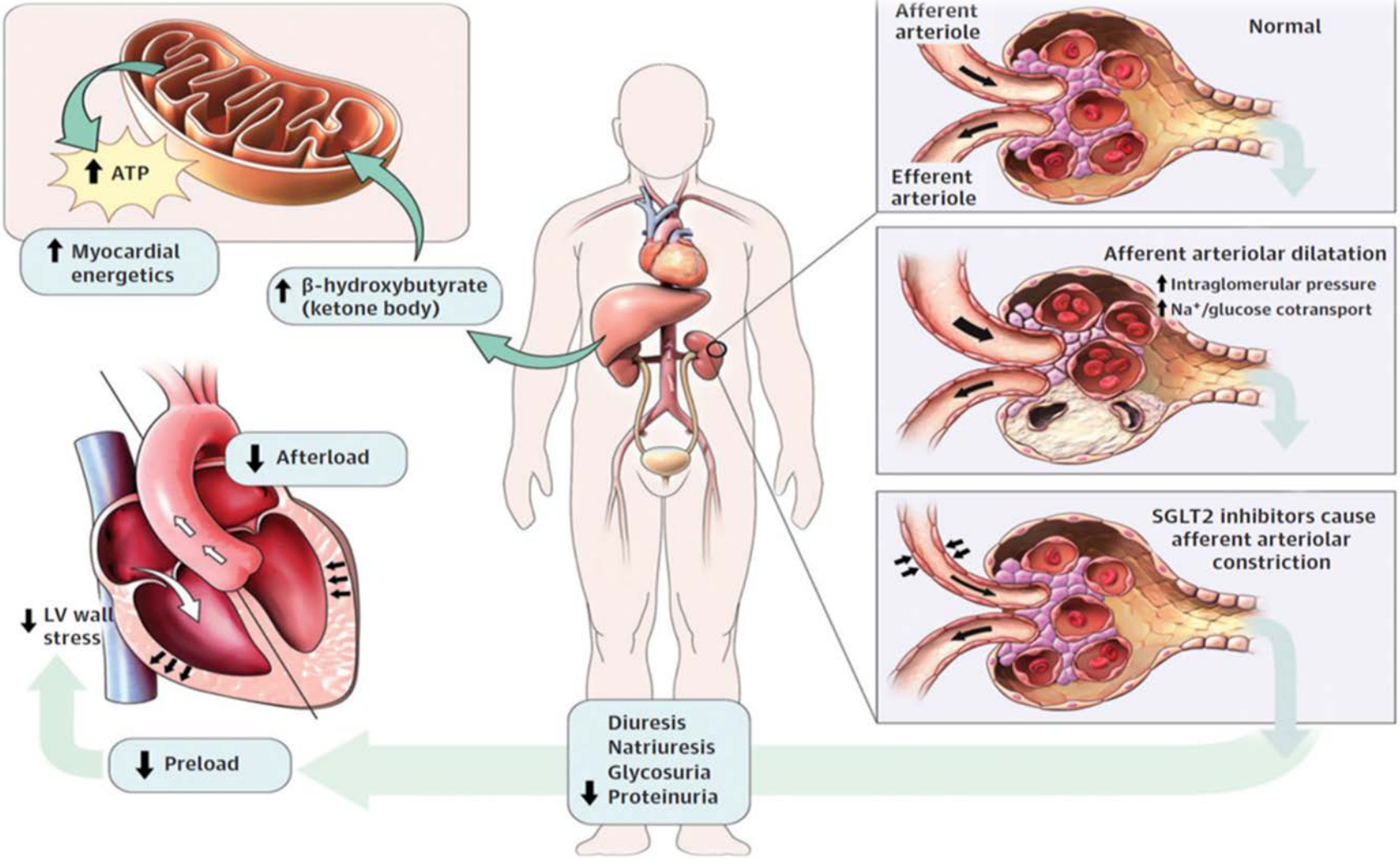
Received: 19 January 2018 / Accepted: 27 April 2018

	Empagliflozin	Placebo	HR (95% CI)	Treatment by subgroup interaction
	n with event/*n* analysed (%)			
CV death				
All participants	172/4687 (3.7)	137/2333 (5.9)	0.62 (0.49, 0.77)	
History of CABG				*p*=0.3976
No	137/3512 (3.9)	105/1770 (5.9)	0.65 (0.51, 0.84)	
Yes	35/1175 (3.0)	32/563 (5.7)	0.52 (0.32, 0.84)	
All-cause mortality				
All participants	269/4687 (5.7)	194/2333 (8.3)	0.68 (0.57, 0.82)	
History of CABG				*p*=0.2695
No	209/3512 (6.0)	144/1770 (8.1)	0.73 (0.59, 0.90)	
Yes	60/1175 (5.1)	50/563 (8.9)	0.57 (0.39, 0.83)	
Three-point MACE				
All participants	490/4687 (10.5)	282/2333 (12.1)	0.86 (0.74, 0.99)	
History of CABG				*p*=0.5586
No	365/3512 (10.4)	207/1770 (11.7)	0.88 (0.74, 1.04)	
Yes	125/1175 (10.6)	75/563 (13.3)	0.80 (0.60, 1.06)	
Fatal or non-fatal myocardial infarction				
All participants	223/4687 (4.8)	126/2333 (5.4)	0.87 (0.70, 1.09)	
History of CABG				*p*=0.6640
No	156/3512 (4.4)	86/1770 (4.9)	0.90 (0.69, 1.17)	
Yes	67/1175 (5.7)	40/563 (7.1)	0.81 (0.55, 1.20)	
Fatal or non-fatal stroke				
All participants	164/4687 (3.5)	69/2333 (3.0)	1.18 (0.89, 1.56)	
History of CABG				*p*=0.8116
No	125/3512 (3.6)	54/1770 (3.1)	1.16 (0.84, 1.59)	
Yes	39/1175 (3.3)	15/563 (2.7)	1.26 (0.69, 2.28)	
Hospitalisation for heart failure				
All participants	126/4687 (2.7)	95/2333 (4.1)	0.65 (0.50, 0.85)	
History of CABG				*p*=0.1359
No	87/3512 (2.5)	57/1770 (3.2)	0.76 (0.54, 1.06)	
Yes	39/1175 (3.3)	38/563 (6.7)	0.50 (0.32, 0.77)	
Heart failure hospitalisation or CV death				
All participants	265/4687 (5.7)	198/2333 (8.5)	0.66 (0.55, 0.79)	
History of CABG				*p*=0.1264
No	199/3512 (5.7)	138/1770 (7.8)	0.72 (0.58, 0.89)	
Yes	66/1175 (5.6)	60/563 (10.7)	0.52 (0.37, 0.74)	
Incident or worsening nephropathy				
All participants	525/4124 (12.7)	388/2061 (18.8)	0.61 (0.53, 0.70)	
History of CABG				*p*=0.5673
No	381/3096 (12.3)	294/1566 (18.8)	0.60 (0.51, 0.69)	
Yes	144/1028 (14.0)	94/495 (19.0)	0.65 (0.50, 0.84)	



Diabetologia 2018. Subodh Verma et Al. https://doi.org/10.1007/s00125-018-4644-9

JAMA Cardiology 2017; 21: doi:10.1001/jamacardio.2017.1891



Mecanismos Hemodinámicos

How Does Empagliflozin Reduce Cardiovascular Mortality? Insights From a Mediation Analysis of the EMPA-REG OUTCOME Trial

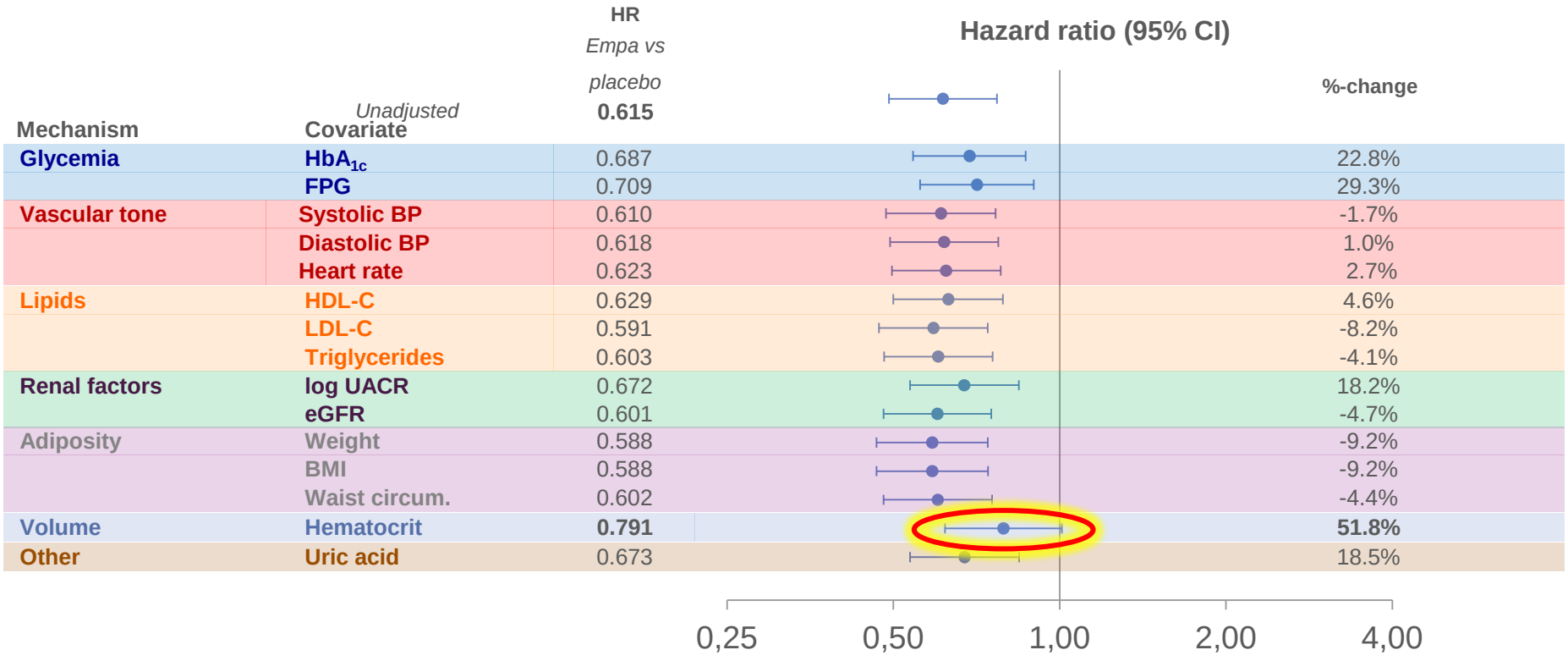
Silvio E. Inzucchi,[1] Bernard Zinman,[2] David Fitchett,[3] Christoph Wanner,[4] Ele Ferrannini,[5] Martin Schumacher,[6] Claudia Schmoor,[6] Kristin Ohneberg,[6] Odd Erik Johansen,[7] Jyothis T. George,[8] Stefan Hantel,[9] Erich Bluhmki,[9] and John M. Lachin[10]

Diabetes Care 2018;41:356–363 | https://doi.org/10.2337/dc17-1096

Modelo de regresión en el que se observa como el aumento del hematocrito asociado a la reducción de volumen plasmático media más del 50% en la reducción de mortalidad CV.

American Diabetes Association. Diabetes Care©

Univariate analysis of potential mediators of empa's CV mortality benefit: Updated mean

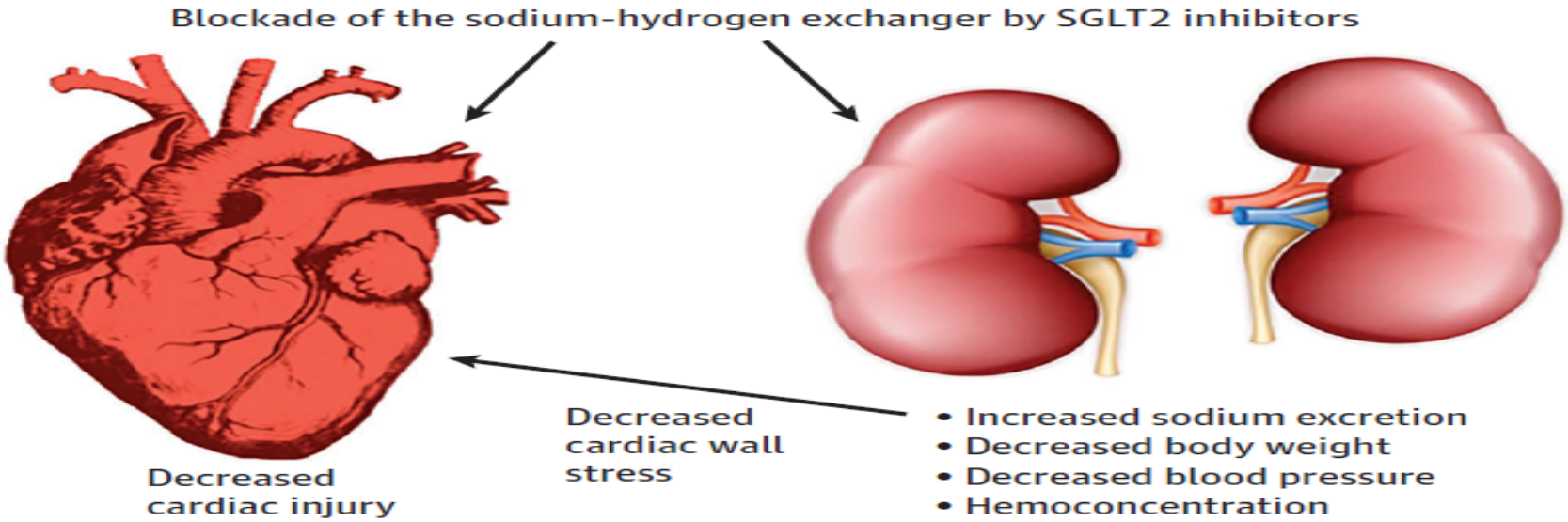


Diabetes Care 2018;41:356-363

American Diabetes Association. Diabetes Care

Mecanismos Cardíacos: Sodium-Hydrogen Exchanger

Figure. Cardioprotective Effect of Sodium-Glucose Cotransporter 2 (SGLT2) on Sodium-Hydrogen Exchange in the Heart and Kidneys



- It has been shown that the action of empagliflozin to inhibit the NHE leads to a reduction in intracellular calcium.
- Inhibition of NHE has been shown to minimize cardiomyocyte injury and to attenuate the development of cardiachypertrophy, fibrosis, remodeling, systolic dysfunction and heart failure.

JAMA Cardiol. 2017;2(9):1025-1029. doi:10.1001/jamacardio.2017.2275
Antonius Baartscheer et Al. DOI 10.1007/s00125-016-4134-x

Mecanismos Cardíacos: Beta-hidroxibutirato

Can a Shift in Fuel Energetics Explain the Beneficial Cardiorenal Outcomes in the EMPA-REG OUTCOME Study? A Unifying Hypothesis

Sunder Mudaliar, Sindura Alloju, and Robert R. Henry

Diabetes Care 2016;39:1115–1122 | DOI: 10.2337/dc16-0542

American Diabetes Association. Diabetes Care

CV Protection in the EMPA-REG OUTCOME Trial: A "Thrifty Substrate" Hypothesis

Ele Ferrannini,[1] Michael Mark,[2] and Eric Mayoux[2]

Diabetes Care 2016;39:1108–1114 | DOI: 10.2337/dc16-0330

ACC.18

674
JACC March 20, 2018
Volume 71, Issue 11

Heart Failure and Cardiomyopathies

EMPAGLIFLOZIN INDUCES A MYOCARDIAL METABOLIC SHIFT FROM GLUCOSE CONSUMPTION TO KETONE METABOLISM THAT MITIGATES ADVERSE CARDIAC REMODELING AND IMPROVES MYOCARDIAL CONTRACTILITY

Mecanismos Cardíacos: Beta-hidroxibutirato

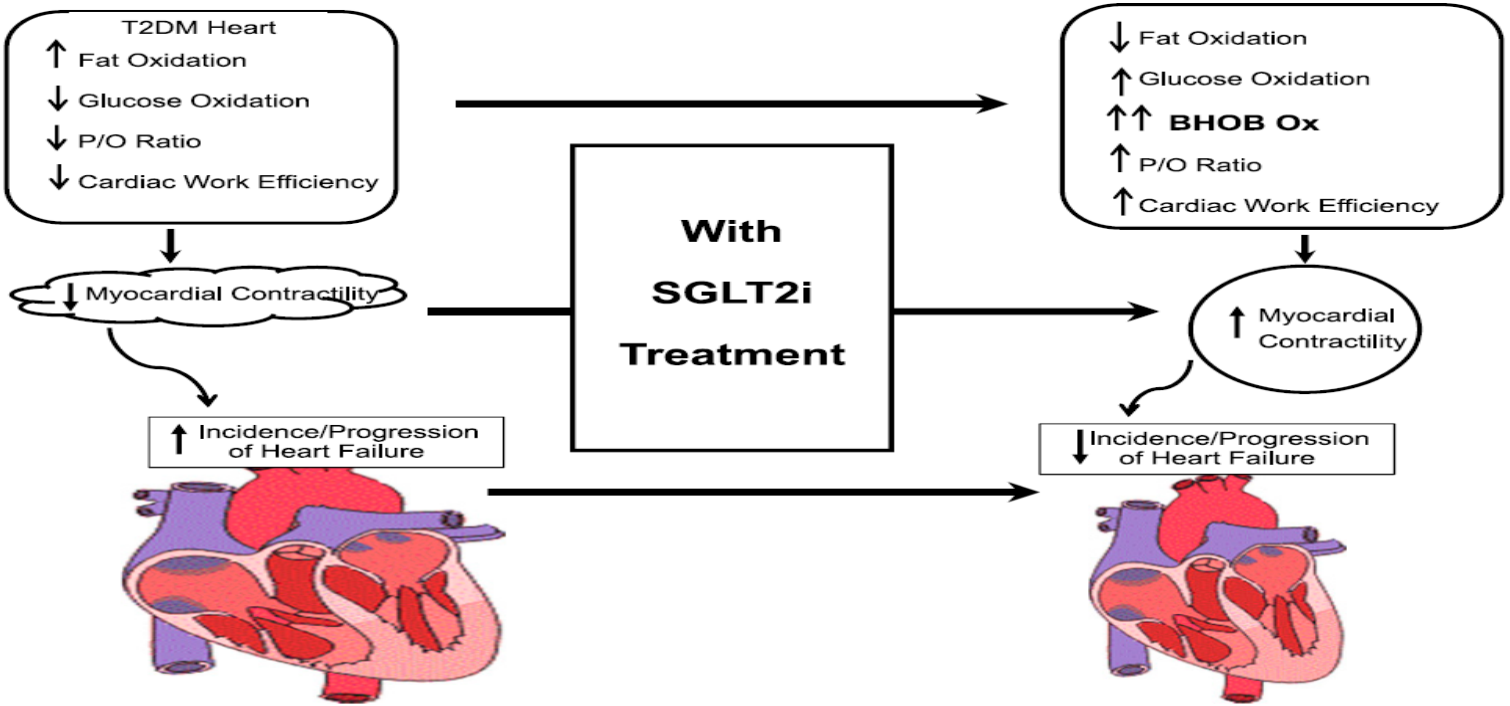
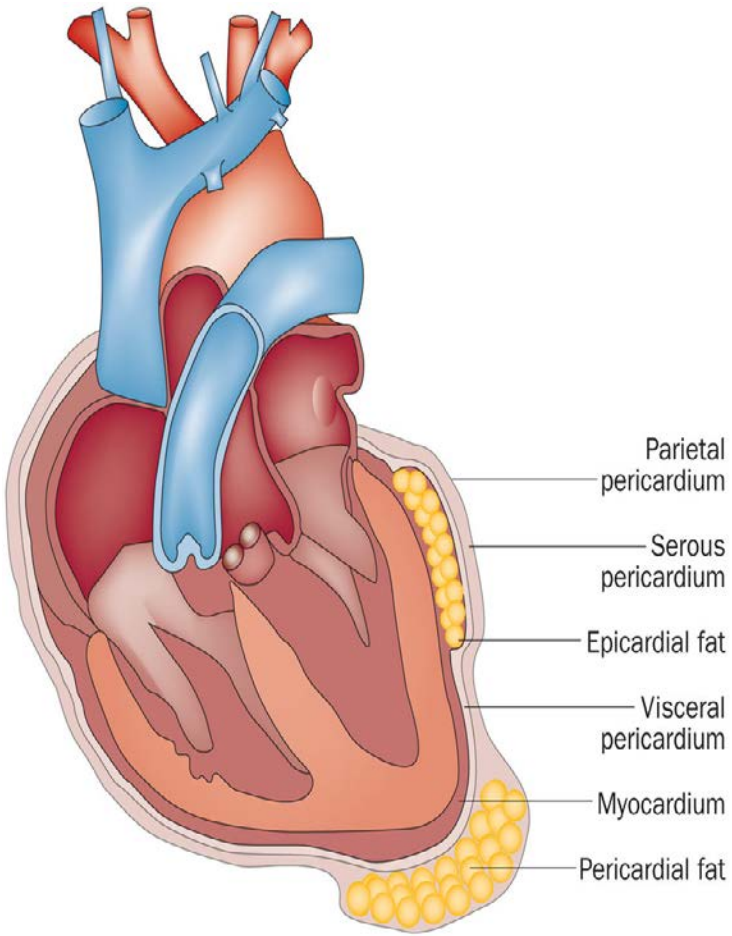


Figure 1—Postulated changes in myocardium fuel metabolism before and after SGLT2 inhibitor (SGLT2i) therapy. P/O ratio reflects the number of molecules of ATP produced per atom of oxygen reduced by the mitochondrial electron transport chain.

Diabetes Care 2016;39:1115–1122 | DOI: 10.2337/dc16-0542
Diabetes Care 2016;39:1108–1114 | DOI: 10.2337/dc16-0330



Diabetol Metab Syndr. 2017; 9: 78.
Published online 2017 Oct 4. doi: 10.1186/s13098-017-0275-4
PMCID: PMC562844
PMID: 2903400

Canagliflozin reduces epicardial fat in patients with type 2 diabetes mellitus

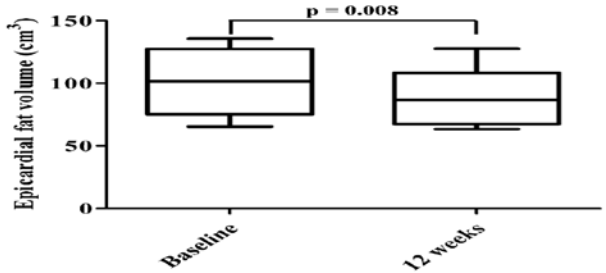
Shusuke Yagi,[1,2,3] Yukina Hirata,[4] Takayuki Ise,[1] Kenya Kusunose,[1] Hirotsugu Yamada,[1] Daiju Fukuda,[1,5]

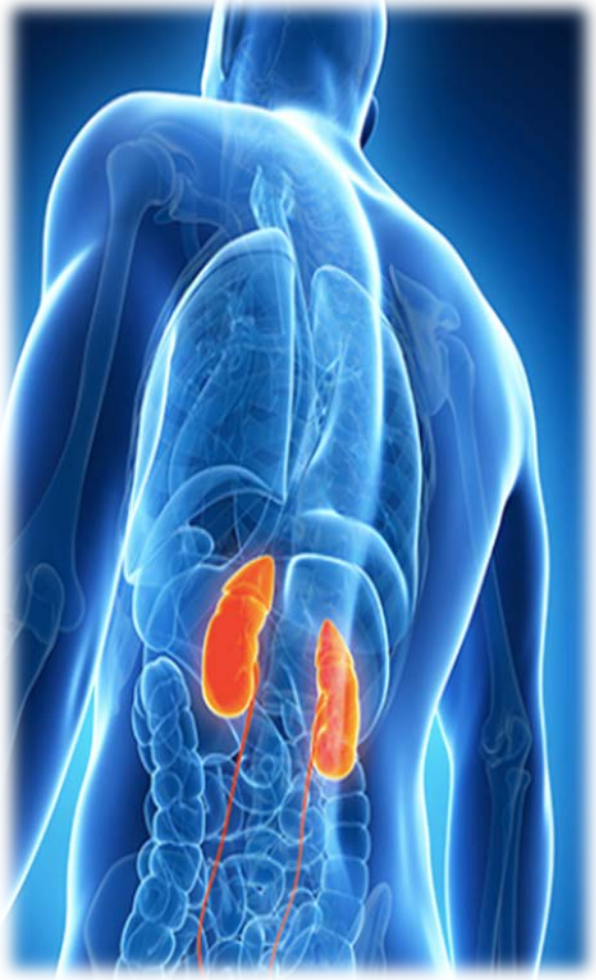
Canagliflozin treatment for 6 months reduced EAT thickness, as evaluated by echocardiography, in patients with T2D, independent of its effect on lowering blood glucose

Ipragliflozin Reduces Epicardial Fat Accumulation in Non-Obese Type 2 Diabetic Patients with Visceral Obesity: A Pilot Study

Diabetes Ther (2017) 8:851–861
DOI 10.1007/s13300-017-0279-y

Tatsuya Fukuda · Ryotaro Bouchi · Masahiro Terashima · Yuriko Sasahara





THE LANCET
Diabetes & Endocrinology

Articles

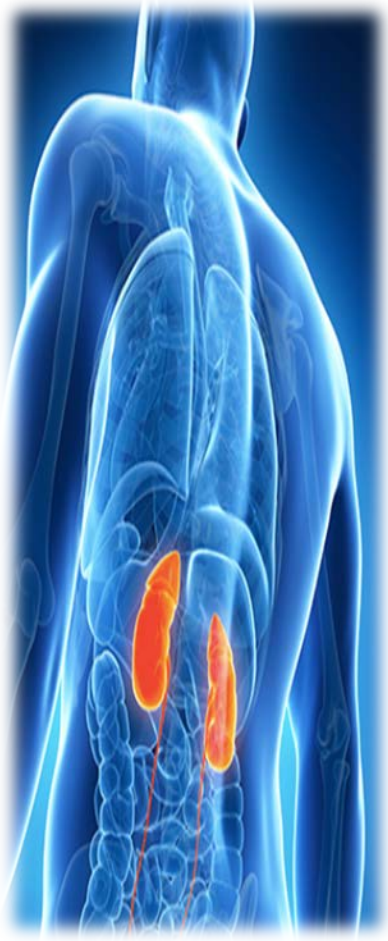
Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial

Dr David Z I Cherney, MD, Prof Bernard Zinman, MD, Silvio E Inzucchi, MD, Audrey Koitka-Weber, PhD, Michaela Mattheus, MSc, Maximilian von Eynatten, MD, Prof Christoph Wanner, MD

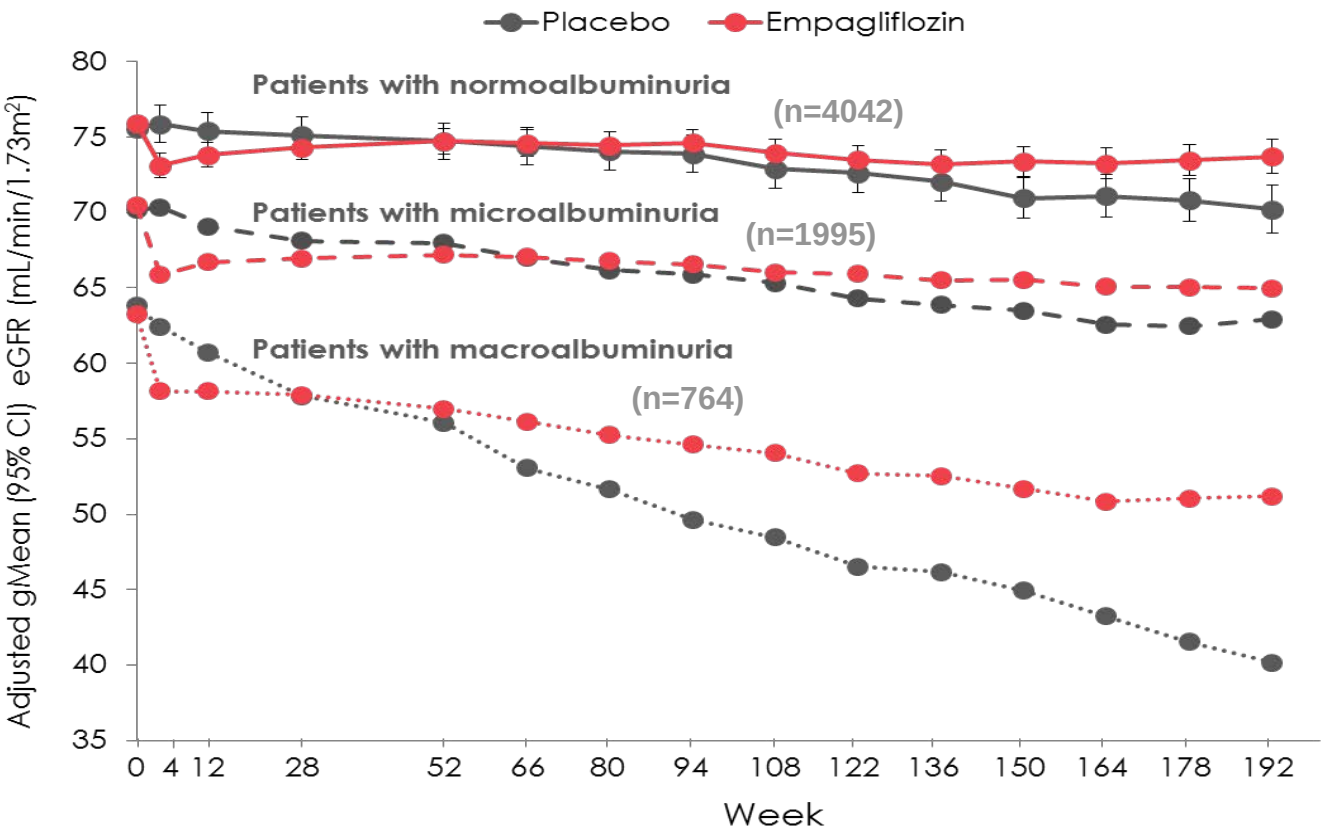
Published: 27 June 2017

PlumX Metrics

DOI: https://doi.org/10.1016/S2213-8587(17)30182-1 | CrossMark



eGFR (CKD-EPI) over 192 weeks



Lancet Diabetes Endocrinol 2017;5:610-621