IMPACT OF DIABETES DRUGS ON CARDIOVASCULAR AND RENAL DISEASE IN TYPE 2 DIABETES Roma, 2-3 febbraio 2018

# Effetto dei nuovi farmaci sul cuore: GLP1-RA

#### Stefano Genovese

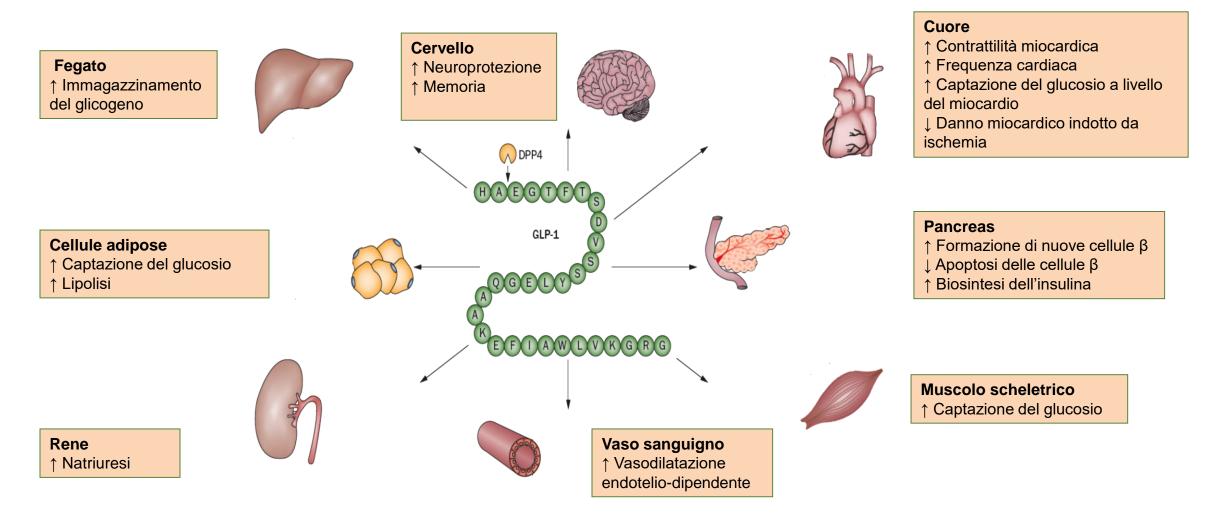
UO di Diabetologia, Endocrinologia e Malattie Metaboliche



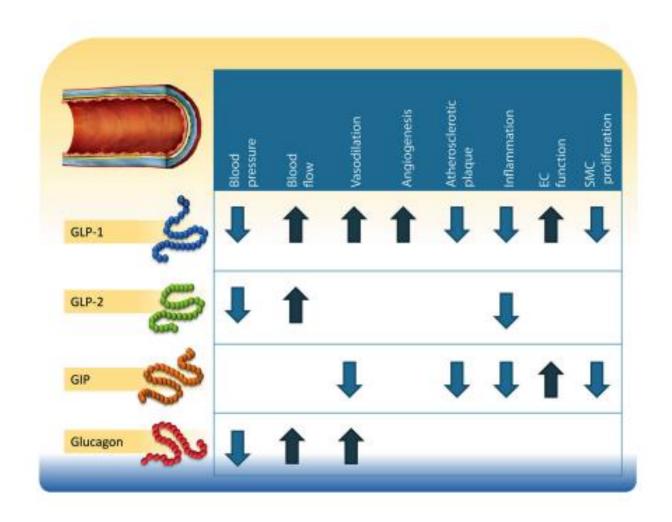
### Disclosure Statement

- Stefano Genovese, in the last three years, has received speaking and/or consulting fees from:
  - Abbott Diabetes Care
  - AstraZeneca
  - Boehringer Ingelheim
  - Bristol-Myers Squibb
  - Bruno Farmaceutici
  - Eli Lilly
  - Janssen
  - Lifescan
  - Merck Sharp & Dohme
  - Novartis
  - Novo Nordisk
  - Sanofi
  - Takeda
- and research grants from:
  - Novartis

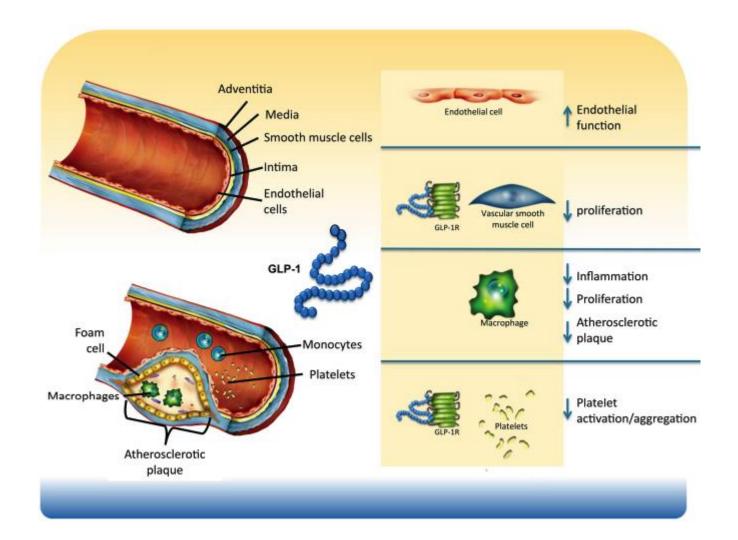
### GLP-1: un ampio spettro di azioni biologiche



### CV effects of incretins

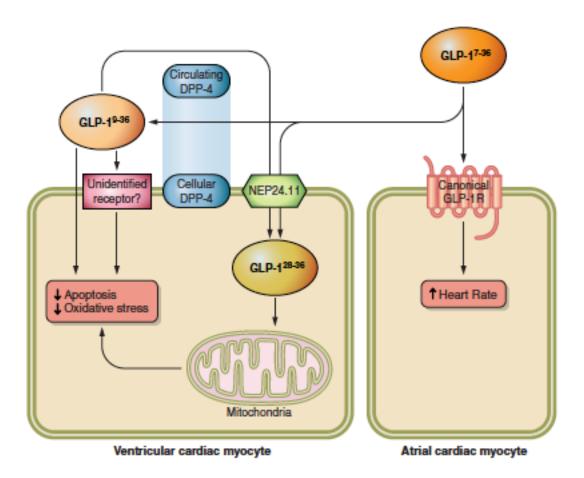


### Effects of GLP-1 on atherosclerosis

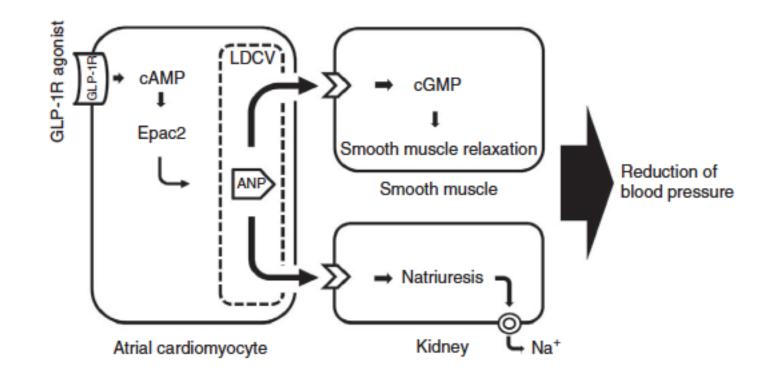


#### Myocardial effect of GLP 1

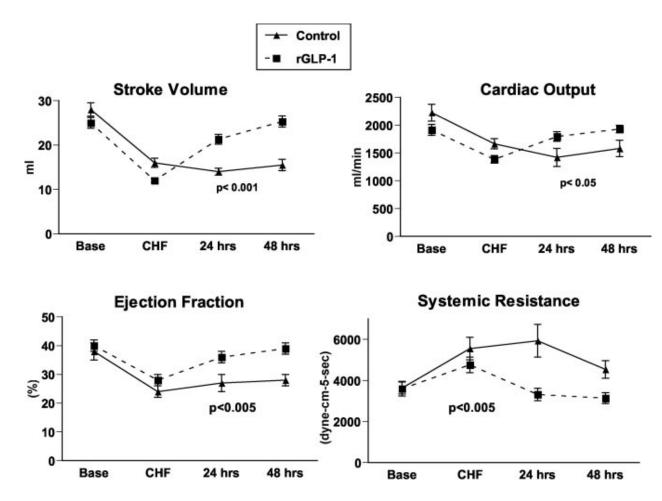
Potential GLP-1-mediated actions in atrial and ventricular cardiac myocytes



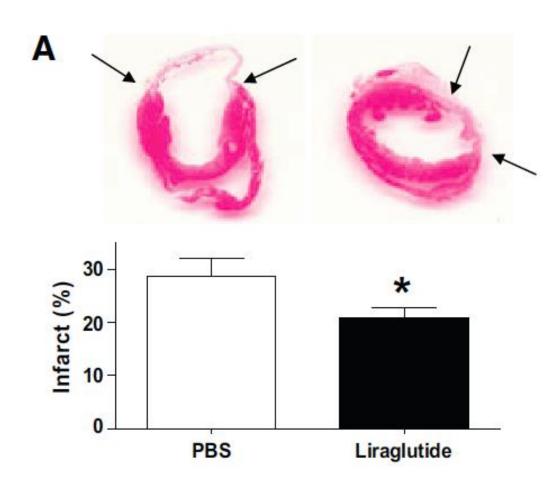
GLP-1 receptor activation and Epac2 link atrial natriuretic peptide secretion to control of blood pressure



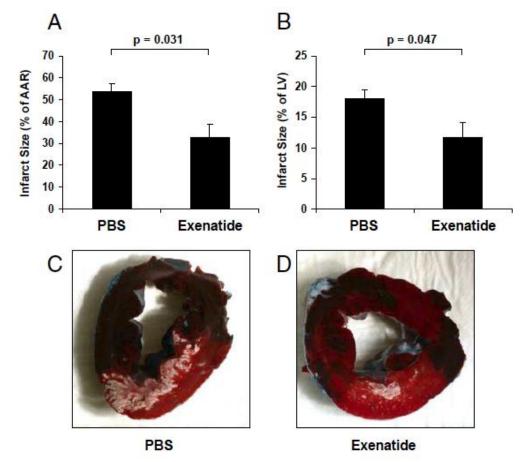
Effects of rGLP-1 on cardiac function in dogs with pacing-induced dilated cardiomyopathy



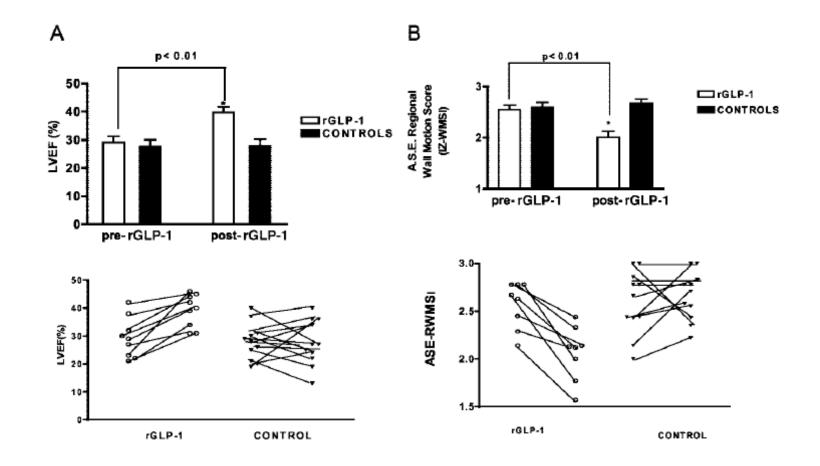
# Effects of liraglutide pretreatment on infarct size in mice with experimental MI



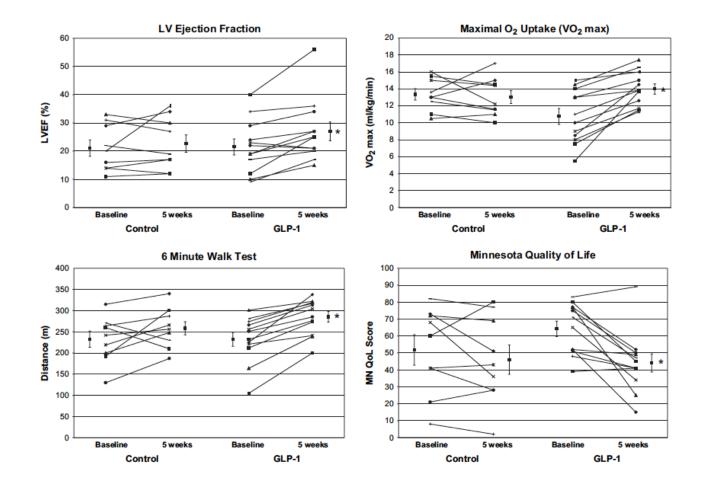
Exenatide reduces infarct size and improves cardiac function in a porcine model of ischemia and reperfusion injury



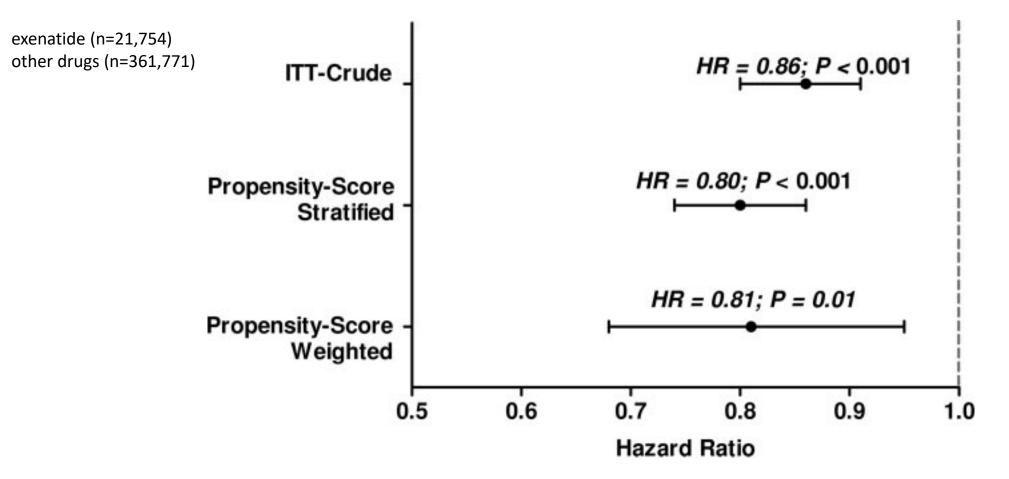
# Effects of GLP-1 in patients with AMI and LV dysfunction after successful reperfusion



# GLP-1 infusion improves LV ejection fraction and functional status in non diabetic patients with CHF



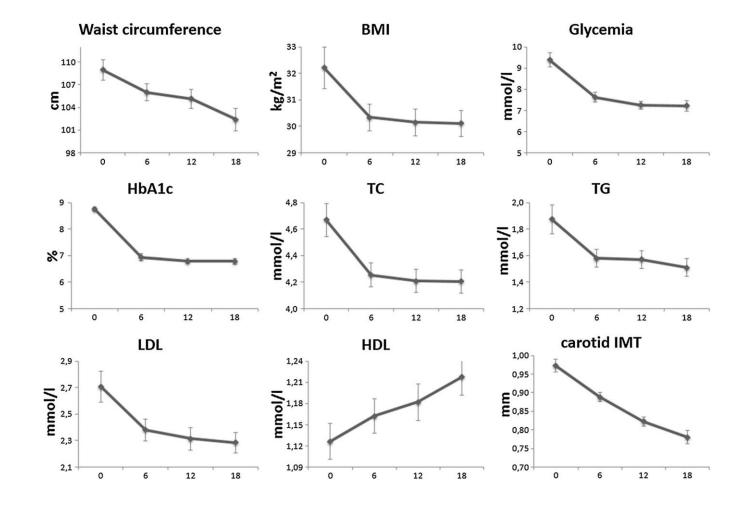
Risk of CVD events in T2DM patients treated with exenatide: a retrospective analysis of the LifeLink database



# The effects of GLP-1 based therapies on: BNP, hsCRP and PAI-1

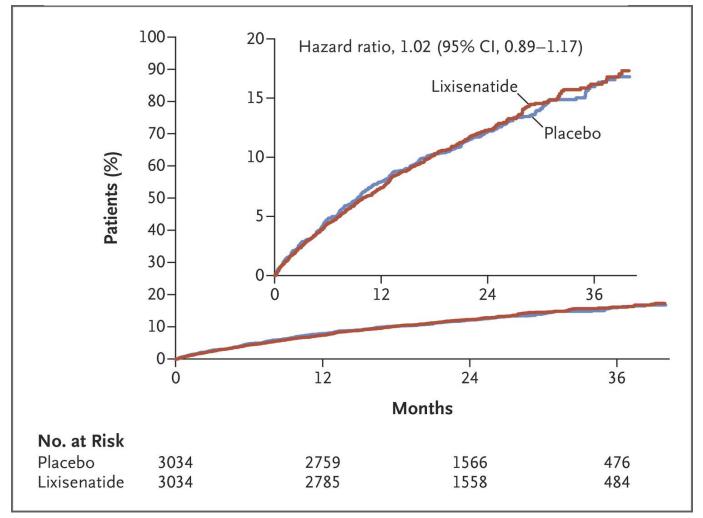
		GLP-1			Control			Mean Difference	Mean Difference
Study or Subgroup	Mea	n SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Bergenstal et al 2010 E	xt -2	3 98	160	33	118	165	13.5%	-56.00 [-79.55, -32.45]	
Seino et al 2010	-26.8	5 75	264	28.7	79	129	19.3%	-55.55 [-71.91, -39.19]	
Courreges et al 2008	-3	8 47	41	0	43	42	16.6%	-38.00 [-57.39, -18.61]	
Kaku et al 2010		4 87		14.58	85	74	11.5%	-35.10 [-62.03, -8.17]	
Bergenstal et al 2010 S	- TI	2 77	166	33	118	165	15.0%	-35.00 [-56.48, -13.52]	
Nauck et al 2013	1	2 40	118	38	50	113	24.1%	-26.00 [-37.71, -14.29]	
Total (95% CI)			832			688	100.0%	-40.16 [-51.50, -28.81]	•
Heterogeneity: Tau <sup>2</sup> = 1	03.59; Chi <sup>a</sup>	= 10.	82, df =	5 (P =	0.06); P	= 54%	,		-50 -25 0 25 50
Test for overall effect: Z	= 6.94 (P <	0.000	001)						-50 -25 0 25 50 Effective Ineffective
	GLF	1		6	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean		Total			Total	Woight	IV, Random, 95% Cl	IV, Random, 95% Cl
Nauck et al 2013	-0.2	8.6	118	2.2	8.5	31	0.4%	-2.40 [-5.77, 0.97] -	
Nakamura et al 2014	-0.2	3.6	34	1.27	5.59	31	0.4%	-2.26 [-4.57, 0.05]	
Forst et al 2012		4.21	21	0.2	2.78	19	0.8%	0.40 [-1.79, 2.59]	
Kelly et al 2012	-0.4	2.2	25	-0.4	2.70	25	2.7%	0.00 [-1.22, 1.22]	
Kaku et al 2012		1.65		-0.4	2.2	74	9.8%		
		1.49	83	-0.25	1.62	70	9.8%	0.26 [-0.32, 0.84]	
Derosa et al 2014		0.34		-0.04	0.44	29		-0.30 [-0.80, 0.20]	
Bunck et al 2010							30.5%	-0.47 [-0.67, -0.27]	
Seino et al 2010	-0.166 0.	126	264	0.06	0.117	129	42.7%	-0.23 [-0.25, -0.20]	
Total (95% CI)			658				100.0%	-0.27 [-0.48, -0.07]	•
Heterogeneity: Tau <sup>2</sup> = 0.				P = 0.0	6); l² = -	48%			-4 -2 0 2 4
Test for overall effect: Z	= 2.61 (P =	0.009	)						Effective Ineffective
		GLP-1			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mear	n SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Forst et al 2012	-22.7	51	21	18.18	3 29	19	10.7%	-40.88 [-66.29, -15.47]	
Nauck et al 2013	-27.7	45	118	5.2	2 39	113	15.9%	-32.90 [-43.75, -22.05]	
Courreges et al 2008	-29	40	41	0	) 49	42	12.9%	-29.00 [-48.22, -9.78]	
Seino et al 2010	2.47	32.3	264	11.9	3 24.4	129	17.3%	-9.43 [-15.17, -3.69]	-
Kaku et al 2010	0.18	67	83	5.48	3 56	74	12.9%	-5.30 [-24.55, 13.95]	
Bergenstal et al 2010 E	xt -8	58	160	-15	5 59	165	15.3%	7.00 [-5.72, 19.72]	
Bergenstal et al 2010 S	IT -4	62	166	-15	5 59	165	15.2%	11.00 [-2.04, 24.04]	-
Total (95% CI)			853			707	100.0%	-12.90 [-25.98, 0.18]	•
Heterogeneity: Tau <sup>2</sup> = 2			56, df =	6 (P < (	0.00001	l); l² = 8	86%		-50 -25 0 25 50
Test for overall effect: Z	= 1.93 (P =	0.05)							Effective Ineffective

### Changes in cardio-metabolic parameters with liraglutide: 18-month prospective, real-world study



ORIGINAL ARTICLE

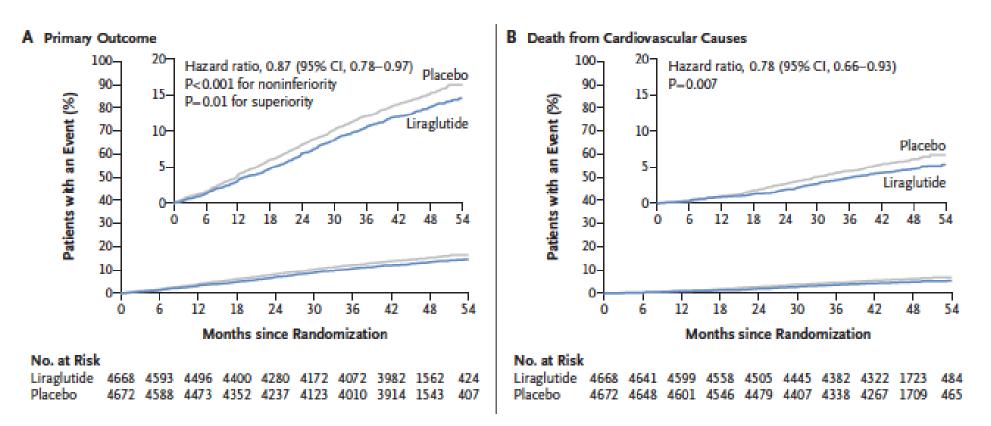
#### Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome



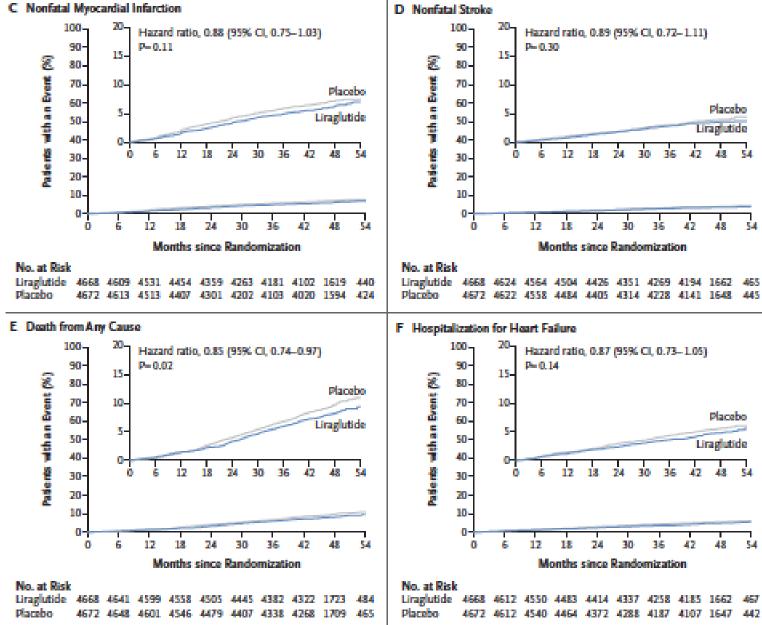
Pfeffer MA et al. N Engl J Med 2015;373:2247-2257.

ORIGINAL ARTICLE

#### Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

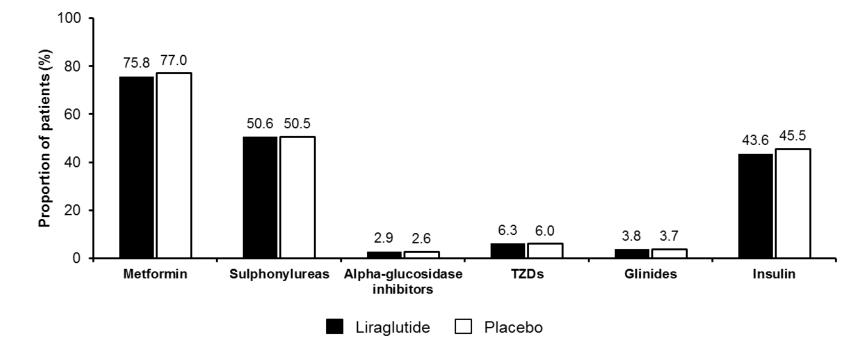


Marso SP et al N Engl J Med. 2016 Sep 15. [Epub ahead of print]



no. of events/no. of patients (%)         Primary analysis       9340       608/4658 (13.0)       694/4672 (14.9)       Image: Constraint of the second s	P Value fo Placebo Hazard Ratio (95% CI) Interaction
Sex Female 3337 183/1657 (11.0) 209/1680 (12.4) Male 603 427/3011 (1.1) 428/2920 (12.5) Age c 60 yr 2221 140/1197 (11.7) 166/1124 (1.4) Case 0.072-0.59 260 yr 7019 468/3471 (13.5) 528/3548 (14.9) Europe 2296 207/1639 (12.6) 252/1657 (15.2) Europe 3296 207/1639 (12.6) 252/1657 (15.2) Asia 711 24/360 (5.7) 37/351 (0.5) Rest of the world 2486 165/1268 (13.0) 189/1218 (15.5) Rest of the world 2486 165/1268 (13.0) 189/1218 (15.5) Rest of the world 2486 165/1268 (13.0) 189/1218 (15.5) Faisa 711 24/370 (12.7) 59/407 (14.5) Black 777 47/370 (12.8) 261/1831 (14.3) H 4 0.39 (0.79-1.00) Blody mass index s10 y 0.36 10.07 100 Edwinasy index s11 yr 4429 265/216 (12.4) 33/2428 (13.7) Black 777 77/36 (12.2) 21/27 (12.8) 16/223 (13.7) Black 777 77/36 (12.2) 21/27 (12.8) 16/223 (13.7) Black 777 77/37 (12.8) 16/23 (12.3) Black 777 77/37 (12.8) 46/203 (12.4) 33/2428 (13.7) Black 777 77/37 (12.8) 46/203 (12.7) Black 777 77/36 (12.8) 21/253 (12.7) Black 777 77/36 (12.8) 21/253 (12.7) Black 777 77/37 7182 436/3552 (12.3) Black 777 77/36 (12.2) 28/170 (15.5) Black 777 77/36 (12.2) 28/170 (15.5) Black 777 77/37 7182 436/3552 (12.3) Black 777 77/36 (12.2) 28/170 (	/no. of patients (%)
female       337       183/1657 (11.0)       209/1680 (12.4)       Image       0.88 (0.72-0.08)         Male       6003       425/2011 (14.1)       485/2922 (16.2)       Image       0.86 (0.75-0.98)         s60 yr       221       140/1197 (11.7)       166/1124 (14.8)       Image       0.90 (0.79-1.02)         Geographic region       Europe       329       207/1639 (12.6)       252/1657 (15.2)       Image       0.82 (0.68-0.98)         North America       2147 (21/30 (67)       37/351 (0.5)       Image       0.82 (0.88-0.98)       0.83 (0.82-1.02)         Rest of the world       2466       165/1266 (13.0)       189/1218 (15.5)       Image       0.83 (0.82-1.02)         Black       717       47/1370 (12.7)       59/187 (02.2)       Image       0.57 (0.62-0.37)         Other       339       27/112 (12.8)       56/178 (02.0)       Image       0.83 (0.82-1.02)         Black       777 47/1370 (12.7)       59/187 (02.2)       Image       0.57 (0.54-0.42)       0.57 (0.54-0.42)         Other       339       27/21 (12.8)       56/178 (52.0)       Image       0.74 (0.54-0.22)       0.54 (0.37-0.02)         Black       777       47/1370 (12.7)       56/178 (52.5)       Image       0.66 (0.81-0.12)       0.66 (0.81-0.12) <td>0) 694/4672 (14.9) - 0.87 (0.78-0.97)</td>	0) 694/4672 (14.9) - 0.87 (0.78-0.97)
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	0.84
c60 yr       2321       140/1197 (11.7)       166/1124 (14.8)       0.78 (0.62-0.57)         s60 yr       2321       140/1197 (11.7)       166/1124 (14.8)       0.78 (0.62-0.57)         zeographic region       2107       458/3471 (13.5)       528/3548 (14.9)       0.78 (0.62-0.57)         Europe       3296       207/1639 (12.6)       252/1657 (15.2)       0.68 (0.68-0.38)         North America       2147       212/1401 (15.1)       216/1446 (14.9)       1.01 (0.44-1.22)         Asia       711       24/360 (6.7)       37/351 (0.5)       0.52 (0.58-0.38)         Rest of the world       2486       165/1268 (13.0)       189/1218 (15.5)       0.54 (0.68-1.03)         Back       777       47/370 (12.7)       59/407 (14.5)       0.90 (0.80-1.02)       0.54 (0.30-1.22)         Asian       936       40/471 (8.5)       56/455 (12.0)       0.70 (0.46-1.04)       0.58 (0.37-1.00)         Uther       389       27/211 (12.8)       36/178 (20.2)       0.70 (0.46-1.04)       0.59 (0.37-1.00)         Uther       389       27/211 (12.8)       36/178 (20.2)       0.51 (0.37-1.00)       0.59 (0.37-1.02)         Non-Hispanic       134       68/580 (11.7)       86/585 (15.5)       0.74 (0.54-1.02)       0.58 (0.67-1.05) <td< td=""><td>0) 209/1680 (12.4) 0.88 (0.72-1.08)</td></td<>	0) 209/1680 (12.4) 0.88 (0.72-1.08)
<60 yr	1) 485/2992 (16.2) • 0.86 (0.75–0.98)
a60 yr       7019       468/3471 (13.5)       528/3548 (14.9)       ●●●       0.90 (0.79-1.02)         leographic region       3296       207/1639 (12.6)       252/1657 (15.2)       ●●●       0.82 (0.68-0.98)         North America       2447       212/1401 (15.1)       216/1446 (14.9)       ●●●       1.01 (0.34-1.22)         Asia       711       24/360 (6.7)       37/351 (0.5)       ●●●       0.82 (0.68-0.98)         Rest of the world       2486       165/1268 (11.0)       189/1218 (15.5)       ●●●       0.90 (0.30-1.02)         Black       777       47/370 (12.7)       59/407 (4.5)       ●●●       0.87 (0.59-1.27)         Asian       936       40/471 (5.5)       56/456 (12.0)       0.87 (0.59-1.27)       0.81 (0.37-1.00)         thing group       Hispanic       1334       68/580 (11.7)       86/554 (15.5)       ●●●       0.74 (0.54-1.02)         Non-Hispanic       8206       540/4088 (13.2)       668/4118 (1.8)       ●       0.89 (0.79-1.00)         lobdy-mass index       =       0.39 (0.76-1.04)       0.38 (0.76-0.05)       0.38 (0.76-0.05)         s3.36       4768       289/2340 (12.4)       333/2428 (13.7)       ●●●       0.82 (0.70-0.97)         sycate themoglobin       =       =	0.27
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	7) 166/1124 (14.8) • 0.78 (0.62–0.97)
	5) 528/3548 (14.9) + 0.90 (0.79–1.02)
North America       2847       212/1401 (15.1)       216/1446 (14.9)       101 (0.84-1.22)         Asia       711       24/360 (6.7)       37/351 (0.5)       0.62 (0.37-1.64)         Rest of the world       2466       165/1268 (13.0)       189/1218 (15.5)       0.83 (0.68-1.03)         tace       777       47/370 (12.7)       59/407 (4.5)       0.83 (0.68-1.03)         Black       777       47/370 (12.7)       59/407 (4.5)       0.87 (0.59-1.27)         Asian       936       40/471 (8.5)       56/455 (12.0)       0.70 (0.46-1.04)         Other       389       27/211 (12.8)       36/178 (02.2)       0.81 (0.37-1.00)         Hispanic       1134       68/350 (11.7)       86/554 (15.5)       0.74 (0.54-1.02)         Non-Hispanic       2104       44/174 (13.8)       26/1831 (14.3)       0.89 (0.79-1.00)         Sold chromolobin       33       5574       52/122 (12.6)       31/2837 (15.2)       0.82 (0.70-0.93)         Sold thromolobin       33       289/2340 (12.4)       33/2428 (13.7)       0.40 (0.72-0.98)         Sold to disbets       211 yr       4429       26/2121 (1.3)       1.40       0.82 (0.70-0.97)         Sold of disbets       211 yr       4892       340/2441 (13.9)       376/2451 (15.3) <td>0.20</td>	0.20
Asia 711 24/360 (6.7) 37/351 (0.5) $0.52 (0.37-1.04)$ Rest of the world 2486 165/1268 (13.0) 189/1218 (15.5) $0.52 (0.37-1.04)$ Rest of the world 2486 165/1268 (13.0) 189/1218 (15.5) $0.83 (0.58-1.03)$ lace $0.52 (0.37-1.04)$ Black 777 47/370 (12.7) 59/407 (14.5) $0.90 (0.80-1.02)$ Black 777 47/370 (12.7) 59/407 (14.5) $0.90 (0.80-1.02)$ Asian 936 40/471 (8.5) 56/465 (1.0) $0.90 (0.80-1.02)$ Chere 389 27/211 (12.8) 36/178 (0.2) $0.61 (0.37-1.00)$ this group Hispanic 1134 68/580 (11.7) 86/554 (15.5) $0.74 (0.54-1.02)$ Non-Hispanic 8206 540/4088 (13.2) 668/4118 (14.8) $0.89 (0.79-1.00)$ thody-mass index < 30 3574 241/1743 (13.8) 261/1831 (14.3) $0.96 (0.81-1.15)>30 5757 367/2920 (12.6) 431/2837 (15.2)$ $0.82 (0.71-0.94)= 8.3%$ 4768 289/2340 (12.4) 333/2428 (13.7) = 8.3% 4768 289/2340 (12.4) 337/2428 (13.7) = 0.82 (0.70-0.97) = 0.82 (0.70-0.97) = 0.82 (0.70-0.97) = 0.82 (0.70-0.97) = 0.82 (0.70-0.97) = 0.83 (0.74-0.03) = 0.83 (0.74-0.03) = 0.83 (0.74-0.33) = 0.99 (0.78-1.04) = 0.83 (0.74-0.93) = 0.99 (0.78-1.04) = 0.83 (0.74-0.93) = 0.99 (0.78-1.04) = 0.83 (0.74-0.93) = 0.99 (0.78-1.04) = 0.83 (0.74-0.93) = 0.99 (0.78-1.04) = 0.99 (0.78-1.04) = 0.83 (0.74-0.93) = 0.99 (0.78-1.04) = 0.83 (0.74-0.93) = 0.99 (0.78-1.04) = 0.99 (0.78-1	5) 252/1657 (15.2) • 0.82 (0.68–0.98)
Rest of the world       2486       165/1268 (13.0)       189/1218 (15.5)       0.83 (0.68-1.03)         tace       White       7238       49/3616 (13.7)       543/3622 (15.0)       0.90 (0.80-1.02)         Black       777       47/370 (12.7)       59/407 (14.5)       0.87 (0.59-1.27)         Asian       936       40/471 (8.5)       56/455 (12.0)       0.70 (0.46-1.04)         Other       389       27/211 (12.8)       36/178 (20.2)       0.61 (0.37-1.00)         Hispanic       1134       68/580 (11.7)       86/554 (15.5)       0.74 (0.54-1.02)         Non-Hispanic       8206       540/408 (13.2)       608/4118 (14.8)       1.60       0.89 (0.79-1.00)         Iody-mass index       230       3577       367/2920 (12.6)       431/2837 (15.2)       0.82 (0.71-0.04)       0.89 (0.79-1.00)         Joycated hemoglobin       ≤335       4572       319/2328 (13.7)       361/2244 (16.1)       0.89 (0.76-1.05)       >8.3%       0.82 (0.71-0.05)       >8.3%       0.82 (0.70-0.97)       >11 yr       4892       340/2441 (13.9)       376/2451 (15.3)       0.82 (0.70-0.97)       >1.81 (14.6)       0.99 (0.78-1.04)       0.84 (0.72-0.8)       0.82 (0.70-0.97)       >1.91 yr       4892       340/2441 (13.9)       376/2451 (15.3)       0.84 (0.72-0.8)       0.83 (0.74	i) 216/1446 (14.9) 1.01 (0.84–1.22)
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	37/351 (10.5) 0.62 (0.37-1.04)
White       723       494/3616 (13.7)       543/3622 (15.0)       Image: Constraint of the second seco	0.83 (0.68-1.03)
Black 777 4/370 (12.7) 59/407 (14.5) Asian 936 40/471 (8.5) 56/465 (12.0) Other 389 27/211 (12.8) 36/178 (20.2) Hispanic 1134 68/580 (11.7) 86/554 (15.5) Hispanic 1134 68/580 (11.7) 86/554 (15.5) Non-Hispanic 8206 540/4088 (13.2) 608/4118 (14.8) < 30 0.74 (0.54-1.02) Non-Hispanic 8206 540/4088 (13.2) 608/4118 (14.8) < 30 0.74 (0.54-1.02) Non-Hispanic 8206 540/4088 (13.2) 608/4118 (14.8) < 30 0.74 (0.54-1.02) < 30 0.74 (0.54-1.02) < 30 0.757 367/2920 (12.6) 431/2837 (15.2) < 30 0.87 (0.79-1.00) < 333/2428 (13.7) 0.89 (0.76-1.05) > 8.3% 4768 289/2340 (12.4) 333/2428 (13.7) < 30 0.87 (0.70-0.97) > 8.3% 4768 289/2340 (12.4) 336/2243 (13.7) < 30 0.82 (0.70-0.97) > 11 yr 4892 340/244 (13.9) 376/2451 (15.3) < 0.82 (0.70-0.97) > 11 yr 4892 340/2441 (13.9) 376/2451 (15.3) < 0.83 (0.74-0.93) = 560 yr of age and risk factors for CVD 1742 72/837 (8.6) 65/905 (7.2) $< 0.83 (0.74-0.93)> 560 yr of age and risk factors for CVD 1742 72/837 (8.6) 65/905 (7.2) < 0.94 (0.72-1.21)No 8035 496/015 (12.4) 575/4020 (14.3)< 0.94 (0.72-1.21)No 8035 496/015 (12.4) 575/4020 (14.3)< 0.94 (0.72-1.21)No 8035 496/015 (12.4) 575/4020 (14.3)< 0.94 (0.72-1.21)No 8036 496/015 (12.4) 575/4020 (14.3)< 0.95 (0.78-0.96)< 0.76 (0.58-0.98)> 1 Oral antidiabetic agent 1818 99/922 (10.7) 125/896 (4.0)< 0.75 (0.58-0.98)> 1 Oral antidiabetic agent 199/191/1515 (1.6) 196/1482 (13.2)< 0.76 (0.58-0.98)> 1 Oral antidiabetic agent 199/192 (10.7) 125/896 (1.0)< 0.75 (0.58-0.98)> 1 Oral antidiabetic agent 1737 71/361 (19.7) 86/376 (2.29)< 0.76 (0.58-0.98)> 1 Oral antidiabetic agent 1737 71/361 (19.7) 86/376 (2.29)< 0.78 (0.58-0.98)> 0.73 (0.42-1.25)< 0.78 (0.58-0.58)> 0.73 (0.42-1.25)< 0.78 (0.58-0.58)> 0.73 (0.42-1.25)< 0.78 (0.57-0.85)> 0.73 (0.42-1.25)< 0.78 (0.58-0.58)> 0.73 (0.42-1.25)< 0.78 (0.58-0.58)> 0.73 (0.42-1.25)< 0.78 (0.58-0.58)> 0.73 (0.42-1.25)< 0.78 (0.58-0.58)$	0.32
Black 777 4/370 (12.7) \$9/407 (14.5) Asian 936 40/471 (8.5) 56/455 (12.0) Other 389 27/211 (12.8) 36/178 (20.2) Hispanic 1134 68/580 (11.7) 86/554 (15.5) Hispanic 28206 540/4088 (13.2) 608/4118 (14.8) Hispanic 28206 540/4088 (13.2) 608/4118 (14.8) Sology-mass index sology-mass index sology of age and established CVD 7598 sology of age and risk factors for CVD 1742 72/837 (8.5) sology of age and risk factors for CVD 1742 72/837 (8.5) sology of age and risk factors for CVD 1742 72/837 (8.5) sology of age and risk factors for CVD 1742 72/837 (8.5) sology of age and risk factors for CVD 1742 72/837 (8.5) sology of age and risk factors for CVD 1742 72/837 (8.5) sology of age and risk factors for CVD 1742 72/837 (8.5) sology of age and risk factors for CVD 1742 72/837 (8.5) sology of age and risk factors for CVD 1742 72/837 (8.5) sology of age and risk factors for CVD 1742 72/837 (8.5) sology of age and risk factors for CVD 1742 72/837 (8.5) sology of age and risk factors for CVD 1742 72/837 (8.5) sology of age and risk factors for CVD 1742 72/837 (8.5) sology of age and risk factors for CVD 1742 72/837 (8.5) sology of age and risk factors for CVD 1742 72/837 (8.5) sology of age and risk factors for CVD 1742 72/837 (8.5) sology of age and risk factors for CVD 1742 72/837 (8.5) sology of age and risk factors for CVD 1742 72/837 (13.3) sology and risk factors for CVD 1742 72/8	7) 543/3622 (15.0) ++ 0.90 (0.80-1.02)
Other       389       27/211 (12.8)       36/178 (20.2)       0.61 (0.37-1.00)         Hispanic       1134       68/580 (11.7)       86/554 (15.5)       0.74 (0.54-1.02)         Hispanic       8206       540/4088 (13.2)       608/4118 (14.8)       0.89 (0.79-1.00)         hon-Hispanic       8206       540/4088 (13.2)       608/4118 (14.8)       0.96 (0.81-1.15)         ≤30       3574       241/1743 (13.8)       261/1831 (14.3)       0.96 (0.81-1.15)         >30       5757       367/2920 (12.6)       431/2837 (15.2)       0.94 (0.72-0.98)         Vipcated hemoglobin       =	
Hispanic       1134       68/580 (11.7)       86/554 (15.5)       →       0.74 (0.54-1.02)         Non-Hispanic       8206       540/4088 (13.2)       608/4118 (14.8)       →       0.89 (0.79-1.00)         bdy-mass index       =30       3574       241/1743 (13.8)       261/1831 (14.3)       →       0.96 (0.81-1.15)         >30       5757       367/2920 (12.6)       431/2837 (15.2)       →       0.82 (0.71-0.94)         Silycated hemoglobin       =8.3%       4768       289/2340 (12.4)       333/2428 (13.7)       →       0.89 (0.76-1.05)         >8.396       4572       319/2328 (13.7)       361/2244 (16.1)       →       0.84 (0.72-0.98)         Duration of diabetes       =       =       1       910 (0.78-1.04)       116/2213 (14.3)       →       0.82 (0.70-0.97)         >11 yr       4829       265/2216 (12.0)       316/2213 (14.3)       →       0.82 (0.70-0.97)       119/518 (15.6)       0.90 (0.78-1.04)         isk of CVD       >>       >>       55/936 (72.1)       1.20 (0.86-1.67)       →       0.83 (0.74-0.93)       >       0.94 (0.72-1.21)       No       8035       496/4015 (12.4)       575/4020 (14.3)       →       0.94 (0.72-1.21)       No       0.85 (0.76-0.96)       0.75 (0.58-0.98)       > <td< td=""><td>56/465 (12.0) 0.70 (0.46-1.04)</td></td<>	56/465 (12.0) 0.70 (0.46-1.04)
thnic group Hispanic 1134 68/S80 (11.7) 86/S54 (15.5) → 0.74 (0.54-1.02) Non-Hispanic 8206 540/4088 (13.2) 608/4118 (14.8) → 0.89 (0.79-1.00) Idody-mass index ≤30 3574 241/1743 (13.8) 261/1831 (14.3) → 0.96 (0.81-1.15) >30 5757 367/2920 (12.6) 431/2837 (15.2) → 0.82 (0.71-0.94) Silvcated hemoglobin ≤8.3% 4768 289/2340 (12.4) 333/2428 (13.7) → 0.89 (0.76-1.05) >8.3% 4768 289/2340 (12.4) 333/2428 (13.7) → 0.89 (0.76-1.05) >8.3% 4768 289/2340 (12.4) 333/2428 (13.7) → 0.89 (0.76-1.05) >8.3% 4768 289/2340 (12.4) 336/2214 (16.1) → 0.82 (0.70-0.97) >11 yr 4892 340/2441 (13.9) 376/2451 (15.3) → 0.82 (0.70-0.97) >11 yr 4892 340/2441 (13.9) 376/2451 (15.3) → 0.82 (0.70-0.97) >50 yr of age and established CVD 7598 536/3831 (14.0) 629/3767 (16.7) → 0.83 (0.74-0.93) ≈60 yr of age and established CVD 7598 536/3831 (14.0) 629/3767 (16.7) → 0.83 (0.74-0.93) ≈60 yr of age and established CVD 7598 546/3831 (12.4) 575/4020 (14.3) → 0.85 (0.76-0.96) ntidiabetic therapy 1 Oral antidiabetic agent 1818 99/922 (10.7) 125/896 (14.0) → 0.75 (0.58-0.98) >1 Oral antidiabetic agent 1818 99/922 (10.7) 125/896 (14.0) → 0.75 (0.58-0.98) >1 Oral antidiabetic agent 377 71/361 (19.7) 86/376 (22.9) → 0.85 (0.75-0.56) Insulin witho oral antidiabetic agent 377 71/361 (19.7) 86/376 (22.9) → 0.86 (0.63-1.17) None 366 24/196 (12.2) 28/170 (16.5) → 0.86 (0.63-1.17) None 366 24/196 (12.2) 28/170 (16.5) → 0.86 (0.63-1.17) None 366 24/196 (12.2) 28/170 (16.5) → 0.73 (0.42-1.25) tenal function Severe or moderate disease <0 ml/min/1.73 m <sup>2</sup> 2158 172/1116 (15.4) 223/1042 (21.4) → 0.89 (0.57-0.83) ≈60 ml/min/1.73 m <sup>2</sup> 224 25/117 (21.4) 26/107 (24.3) → 0.89 (0.57-0.85) 30 ml/min/1.73 m <sup>2</sup> 224 25/117 (21.4) 26/107 (24.3) → 0.89 (0.57-0.45) 30 ml/min/1.73 m <sup>2</sup> 224 25/117 (21.4) 26/107 (24.3) → 0.89 (0.57-0.45)	36/178 (20.2) 0.61 (0.37-1.00)
Non-Hispanic       8206       540/4088 (13.2)       608/4118 (14.8)       Image: Constraint of the second sec	0.30
body-mass index         ≤30       3574       241/1743 (13.8)       261/1831 (14.3)         >30       5757       367/2920 (12.6)       431/2837 (15.2)         bilycated hemoglobin       ≤8.3%       4572       319/2328 (13.7)         ≤8.3%       4572       319/2328 (13.7)       561/2244 (16.1)         Duration of diabetes       ≤11 yr       4429       265/216 (12.0)       316/2213 (14.3)         ≤11 yr       4429       265/2216 (12.0)       316/2213 (14.3)       Image: transmitted in the image in the imag	86/554 (15.5) 0.74 (0.54-1.02)
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	2) 608/4118 (14.8) + 0.89 (0.79-1.00)
>30       5757       367/2920 (12.6)       431/2837 (15.2)       →       0.82 (0.71-0.94)         idycated hemoglobin       =       83%       4768       289/2340 (12.4)       333/2428 (13.7)       →       0.89 (0.76-1.05)         >8.3%       4572       319/2328 (13.7)       361/2244 (16.1)       →       0.84 (0.72-0.98)         Duration of diabetes       =       0.81 (0.74-0.93)       0.82 (0.70-0.97)         >11 yr       4892       265/2216 (12.0)       316/2213 (14.3)       →       0.82 (0.70-0.97)         >11 yr       4892       340/2441 (13.9)       376/2451 (15.3)       →       0.90 (0.78-1.04)         isk of CVD       >       536/3831 (14.0)       629/3767 (16.7)       →       0.83 (0.74-0.93)         >60 yr of age and established CVD       7598       536/3831 (14.0)       629/3767 (16.7)       →       0.83 (0.74-0.93)         Yes       1305       112/653 (17.2)       119/652 (18.3)       →       0.94 (0.72-1.21)         No       8035       496/4015 (12.4)       575/4020 (14.3)       →       0.85 (0.76-0.96)         Intidiabetic agent       1818       99/922 (10.7)       125/896 (14.0)       →       0.95 (0.78-1.16)         Insulin without anal antidiabetic agent       1818       99/922 (10	0.15
Silycated hemoglobin       ≤8.3%       4768       289/2340 (12.4)       333/2428 (13.7)       Image: Constraint of the set of the se	8) 261/1831 (14.3) 0.96 (0.81–1.15)
Shycated hemoglobin ≤8.3% 4768 289/2340 (12.4) 333/2428 (13.7) >8.3% 4572 319/2328 (13.7) 361/2244 (16.1) ↓ 0.89 (0.76-1.05) >8.3% 4572 319/2328 (13.7) 361/2244 (16.1) ↓ 0.84 (0.72-0.98) Duration of diabetes ≤11 yr 4429 265/2216 (12.0) 316/2213 (14.3) >11 yr 4892 340/2441 (13.9) 376/2451 (15.3) ↓ 0.90 (0.78-1.04) tisk of CVD ≥50 yr of age and established CVD 7598 536/3831 (14.0) 629/3767 (16.7) ≥50 yr of age and established CVD 7598 536/3831 (14.0) 629/3767 (16.7) ≥50 yr of age and risk factors for CVD 1742 72/837 (8.6) 65/905 (7.2) → 0.83 (0.74-0.93) ≥60 yr of age and risk factors for CVD 1742 72/837 (8.6) 65/905 (7.2) → 0.84 (0.72-1.21) No 8035 496/4015 (12.4) 575/4020 (14.3) → 0.85 (0.76-0.96) witidiabetic therapy 1 Oral antidiabetic agent 1818 99/922 (10.7) 125/896 (14.0) → 0.75 (0.58-0.98) >1 Oral antidiabetic agent 2997 191/1515 (12.6) 196/1482 (13.2) → 0.75 (0.58-0.98) >1 Oral antidiabetic agent 3422 223/1674 (13.3) 259/1748 (14.8) → 0.95 (0.78-1.16) Insulin without oral antidiabetic agent 737 71/361 (19.7) 86/376 (22.9) → 0.86 (0.61-1.17) None 366 24/196 (12.2) 28/170 (16.5) ↓ 0.94 (0.87-1.05) Insulin without oral antidiabetic agent 737 71/361 (15.4) 223/1042 (21.4) ≥60 m//min/1.73 m <sup>2</sup> 2158 172/1116 (15.4) 223/1042 (21.4) ≤60 m//min/1.73 m <sup>2</sup> 2158 172/1116 (15.4) 223/1042 (21.4) ≤60 m//min/1.73 m <sup>2</sup> 2158 172/1116 (15.4) 223/1042 (21.4) ≤60 m//min/1.73 m <sup>2</sup> 214 236/3552 (12.3) 471/3630 (13.0) ↓ 0.94 (0.83-1.07) Severe disease <30 mi/min/1.73 m <sup>2</sup> 224 25/117 (21.4) 26/107 [24.3]	5) 431/2837 (15.2) - 0.82 (0.71-0.94)
≤8.3%       4768       289/2340 (12.4)       333/2428 (13.7)       Image: Constraint of the set o	0.58
Suration of diabetes       ≤11 yr       4429       265/2216 (12.0)       316/2213 (14.3)       Image: the start of the star	4) 333/2428 (13.7) 0.89 (0.76-1.05)
Duration of diabetes       ≤11 yr       4429       265/2216 (12.0)       316/2213 (14.3)       →       0.82 (0.70–0.97)         >11 yr       4892       340/2441 (13.9)       376/2451 (15.3)       →       0.90 (0.78–1.04)         ±tisk of CVD       >       536/3831 (14.0)       629/3767 (16.7)       →       0.83 (0.74–0.93)         ≥50 yr of age and established CVD       7598       536/3831 (14.0)       629/3767 (16.7)       →       0.83 (0.74–0.93)         ≥60 yr of age and risk factors for CVD       1742       72/837 (8.6)       65/905 (7.2)       →       1.20 (0.86–1.67)         Chronic heart failure         9       925 (17.2)       119/652 (18.3)       →       0.94 (0.72–1.21)         No       8035       496/4015 (12.4)       575/4020 (14.3)       →       0.85 (0.76–0.96)         I Oral antidiabetic agent       1818       99/922 (10.7)       125/896 (14.0)       →       0.75 (0.58–0.98)         > 1 Oral antidiabetic agent       1818       99/922 (10.7)       125/896 (14.0)       →       0.95 (0.78–1.16)         Insulin with oral antidiabetic agent       3422       223/1674 (13.3)       259/1748 (14.8)       →       0.89 (0.74–1.06)         Insulin without oral antidiabetic agent       3422       223/1674 (13.3) <t< td=""><td>7) 361/2244 (16.1) • • • • 0.84 (0.72–0.98)</td></t<>	7) 361/2244 (16.1) • • • • 0.84 (0.72–0.98)
>11 yr       4892       340/2441 (13.9)       376/2451 (15.3)       ●●●       0.90 (0.78–1.04)         tisk of CVD       ≥50 yr of age and established CVD       7598       536/3831 (14.0)       629/3767 (16.7)       ●●●       0.83 (0.74–0.93)         ≥50 yr of age and risk factors for CVD       1742       72/837 (8.6)       65/905 (7.2)       ●●●       1.20 (0.86–1.67)         Chronic heart failure          0.94 (0.72–1.21)       0.94 (0.72–1.21)         No       8035       496/4015 (12.4)       575/4020 (14.3)       ●●●       0.85 (0.76–0.96)         Intidiabetic agent       1818       99/922 (10.7)       125/896 (14.0)       ●●●       0.75 (0.58–0.98)         > 1 Oral antidiabetic agent       1818       99/922 (10.7)       125/896 (14.0)       ●●●       0.95 (0.78–1.16)         Insulin with oral antidiabetic agent       1818       99/922 (10.7)       125/896 (14.0)       ●●●       0.95 (0.78–1.16)         Insulin with oral antidiabetic agent       297       191/1515 (12.6)       196/1482 (13.2)       ●●●       0.98 (0.74–1.06)         Insulin without oral antidiabetic agent       737       71/361 (19.7)       86/376 (22.9)       ●●●       0.86 (0.63–1.17)         None       366       24/196 (12.2)       28/170 (16.5)	0.42
>11 yr       4892       340/2441 (13.9)       376/2451 (15.3)       ●●●       0.90 (0.78–1.04)         tisk of CVD       ≥50 yr of age and established CVD       7598       536/3831 (14.0)       629/3767 (16.7)       ●●●       0.83 (0.74–0.93)         ≥50 yr of age and risk factors for CVD       1742       72/837 (8.6)       65/905 (7.2)       ●●●       1.20 (0.86–1.67)         Chronic heart failure          0.94 (0.72–1.21)       0.94 (0.72–1.21)         No       8035       496/4015 (12.4)       575/4020 (14.3)       ●●●       0.85 (0.76–0.96)         Intidiabetic agent       1818       99/922 (10.7)       125/896 (14.0)       ●●●       0.75 (0.58–0.98)         > 1 Oral antidiabetic agent       1818       99/922 (10.7)       125/896 (14.0)       ●●●       0.95 (0.78–1.16)         Insulin with oral antidiabetic agent       1818       99/922 (10.7)       125/896 (14.0)       ●●●       0.95 (0.78–1.16)         Insulin with oral antidiabetic agent       297       191/1515 (12.6)       196/1482 (13.2)       ●●●       0.98 (0.74–1.06)         Insulin without oral antidiabetic agent       737       71/361 (19.7)       86/376 (22.9)       ●●●       0.86 (0.63–1.17)         None       366       24/196 (12.2)       28/170 (16.5)	0) 316/2213 (14.3) 0.82 (0.70-0.97)
tisk of CVD       ≥50 yr of age and established CVD       7598       536/3831 (14.0)       629/3767 (16.7)       Image: constraint of the stablished CVD       0.83 (0.74-0.93)         ≥60 yr of age and risk factors for CVD       1742       72/837 (8.6)       65/905 (7.2)       Image: constraint of the stablished CVD       1.20 (0.86-1.67)         Chronic heart failure       Yes       1305       112/653 (17.2)       119/652 (18.3)       Image: constraint of the stablished CVD       0.94 (0.72-1.21)         No       8035       496/4015 (12.4)       575/4020 (14.3)       Image: constraint of the stablished const	
≥60 yr of age and risk factors for CVD       1742       72/837 (8.6)       65/905 (7.2)       1.20 (0.86-1.67)         Chronic heart failure       Yes       1305       112/653 (17.2)       119/652 (18.3)       0.94 (0.72-1.21)         No       8035       496/4015 (12.4)       575/4020 (14.3)       0.85 (0.76-0.96)         Intidiabetic agent       1818       99/922 (10.7)       125/896 (14.0)       0.75 (0.58-0.98)         >1 Oral antidiabetic agent       2997       191/1515 (12.6)       196/1482 (13.2)       0.95 (0.78-1.16)         Insulin with oral antidiabetic agent       3422       223/1674 (13.3)       259/1748 (14.8)       0.89 (0.74-1.06)         Insulin without al antidiabetic agent       3422       223/1674 (13.3)       259/1748 (14.8)       0.89 (0.74-1.06)         Insulin without al antidiabetic agent       737       71/361 (19.7)       86/376 (22.9)       0.86 (0.63-1.17)         None       366       24/196 (12.2)       28/170 (16.5)       0.73 (0.42-1.25)         tenal function       Severe or moderate disease       0.69 (0.57-0.85)       0.69 (0.57-0.85)         ≤60 ml/min/1.73 m²       2158       172/1116 (15.4)       223/1042 (21.4)       0.69 (0.57-0.85)         ≥60 ml/min/1.73 m²       2182       436/3552 (12.3)       471/3630 (13.0)       0.94 (0.83-1.07) </td <td>0.04</td>	0.04
≥60 yr of age and risk factors for CVD       1742       72/837 (8.6)       65/905 (7.2)       1.20 (0.86-1.67)         Chronic heart failure       Yes       1305       112/653 (17.2)       119/652 (18.3)       0.94 (0.72-1.21)         No       8035       496/4015 (12.4)       575/4020 (14.3)       0.85 (0.76-0.96)         Intidiabetic agent       1818       99/922 (10.7)       125/896 (14.0)       0.75 (0.58-0.98)         >1 Oral antidiabetic agent       2997       191/1515 (12.6)       196/1482 (13.2)       0.95 (0.78-1.16)         Insulin with oral antidiabetic agent       3422       223/1674 (13.3)       259/1748 (14.8)       0.89 (0.74-1.06)         Insulin without al antidiabetic agent       3422       223/1674 (13.3)       259/1748 (14.8)       0.89 (0.74-1.06)         Insulin without al antidiabetic agent       737       71/361 (19.7)       86/376 (22.9)       0.86 (0.63-1.17)         None       366       24/196 (12.2)       28/170 (16.5)       0.73 (0.42-1.25)         tenal function       Severe or moderate disease       0.69 (0.57-0.85)       0.69 (0.57-0.85)         ≤60 ml/min/1.73 m²       2158       172/1116 (15.4)       223/1042 (21.4)       0.69 (0.57-0.85)         ≥60 ml/min/1.73 m²       2182       436/3552 (12.3)       471/3630 (13.0)       0.94 (0.83-1.07) </td <td>0.83 (0.74-0.93)</td>	0.83 (0.74-0.93)
Chronic heart failure       Yes       1305       112/653       (17.2)       119/652       (18.3)       0.94       0.72–1.21)         No       8035       496/4015       (12.4)       575/4020       (14.3)       0.85       (0.76–0.96)         Indiabetic agent       1818       99/922       (10.7)       125/896       (14.0)       0.75       (0.58–0.98)         > 1 Oral antidiabetic agent       2997       191/1515       (12.6)       196/1482       (13.2)       0.95       (0.78–1.16)         Insulin with oral antidiabetic agent       3422       223/1674       (13.3)       259/1748       (14.8)       0.89       (0.74–1.06)         Insulin without oral antidiabetic agent       3422       223/1674       (13.3)       259/1748       (14.8)       0.89       (0.74–1.06)         Insulin without oral antidiabetic agent       366       24/196       (12.2)       28/170       (16.5)       0.73       (0.42–1.25)         tenal function       Severe or moderate disease        0.73       (0.42–1.25)       0.69       (0.57–0.85)       260 ml/min/1.73 m²       7182       436/3552       (12.3)       471/3630       13.0)       471/3630       0.94       (0.83–1.07)       Severe disease        0.89       (0.51	
No         8035         496/4015 (12.4)         575/4020 (14.3)         Image: Constraint of the second	0.53
No         8035         496/4015 (12.4)         575/4020 (14.3)         Image: Constraint of the system of the	119/652 (18.3) 0.94 (0.72-1.21)
1 Oral antidiabetic agent       1818       99/922 (10.7)       125/896 (14.0)       ●●●●●●●●●●●●●●●●●●●●●●●●●●●●●●●●●●●●	
1 Oral antidiabetic agent       1818       99/922 (10.7)       125/896 (14.0)       ●●●●●       0.75 (0.58–0.98)         >1 Oral antidiabetic agent       2997       191/1515 (12.6)       196/1482 (13.2)       ●●●●●       0.95 (0.78–1.16)         Insulin with oral antidiabetic agent       3422       223/1674 (13.3)       259/1748 (14.8)       ●●●●●       0.89 (0.74–1.06)         Insulin without oral antidiabetic agent       737       71/361 (19.7)       86/376 (22.9)       ●●●●●●       0.86 (0.63–1.17)         None       366       24/196 (12.2)       28/170 (16.5)       ●●●●●       0.73 (0.42–1.25)         tenal function	0.73
>1 Oral antidiabetic agent       2997       19/1515 (12.6)       196/1482 (13.2)       ●●●       0.95 (0.78–1.16)         Insulin with oral antidiabetic agent       3422       223/1674 (13.3)       259/1748 (14.8)       ●●●       0.89 (0.74–1.06)         Insulin without oral antidiabetic agent       737       71/361 (19.7)       86/376 (22.9)       ●●●●       0.86 (0.63–1.17)         None       366       24/196 (12.2)       28/170 (16.5)       ●●●●       0.73 (0.42–1.25)         Iteral function       Severe or moderate disease        0.69 (0.57–0.85)       ≥60 ml/min/1.73 m²       7182       436/3552 (12.3)       471/3630 (13.0)       ●●●●       0.94 (0.83–1.07)         Severe disease          0.94 (0.83–1.07)       Severe disease          <30 ml/min/1.73 m²	125/896 (14.0) 0.75 (0.58-0.98)
Insulin with oral antidiabetic agent       3422       223/1674 (13.3)       259/1748 (14.8)       ●●●●●●●●●●●●●●●●●●●●●●●●●●●●●●●●●●●●	
Insulin without oral antidiabetic agent       737       71/361 (19.7)       86/376 (22.9)       ●       0.86 (0.63-1.17)         None       366       24/196 (12.2)       28/170 (16.5)       0.73 (0.42-1.25)         Itenal function       0.69 (0.57-0.85)       0.69 (0.57-0.85)         ≥60 ml/min/1.73 m²       7182       436/3552 (12.3)       471/3630 (13.0)       ●       0.94 (0.83-1.07)         Severe disease         0.69 (0.57-0.85)       0.94 (0.83-1.07)         Severe disease         0.94 (0.83-1.07)	
None         366         24/196 (12.2)         28/170 (16.5)         ●         0.73 (0.42–1.25)           tenal function	
tenal function           Severe or moderate disease           <60 ml/min/1.73 m²	
Severe or moderate disease         <60 ml/min/1.73 m²	
<60 ml/min/1.73 m²	0.01
≥60 ml/min/1.73 m <sup>2</sup> 7182 436/3552 (12.3) 471/3630 (13.0) Severe disease <30 ml/min/1.73 m <sup>2</sup> 224 25/117 (21.4) 26/107 [24.3) 0.89 (0.51–1.54)	
Severe disease         <224         25/117 (21.4)         26/107 (24.3)           0.89 (0.51–1.54)	·// (/
<30 ml/min/1.73 m <sup>2</sup> 224 25/117 (21.4) 26/107 (24.3) 0.89 (0.51–1.54)	0.93
	5) 000/4303 (14.0) (4.0)
0.2 1.0 2.0	

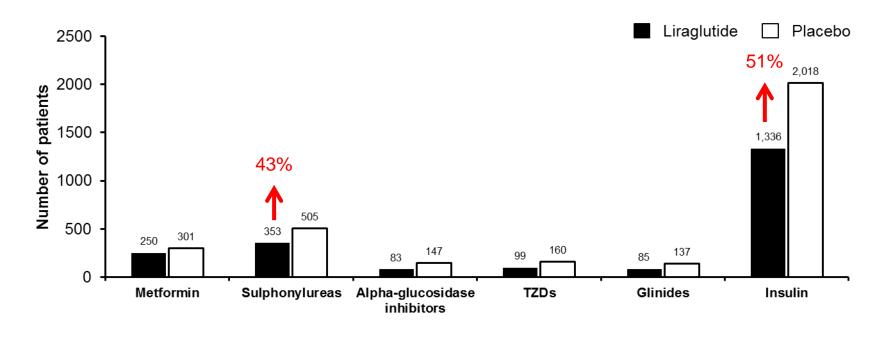
#### LEADER Study Anti-hyperglycemic medication at baseline



TZD: thiazolidinediones.

#### LEADER Study

Anti-hyperglycemic medications introduced during trial

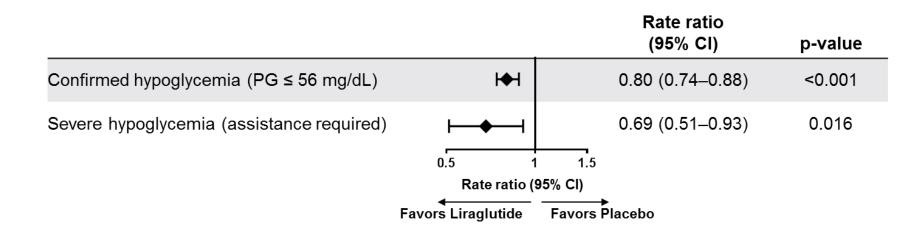


Additional classes added	Liraglutide	Placebo
DPP-4 inhibitors	149	170
GLP-1RAs	87	139
SGLT-2 inhibitors	100	130

DPP-4: dipeptidyl peptidase-4; GLP-1RA: glucagon-like peptide-1 receptor agonist; SGLT-2: sodium-glucose co-transporter-2; TZD: thiazolidinedione.

Marso SP et al N Engl J Med. 2016 Sep 15. [Epub ahead of print]

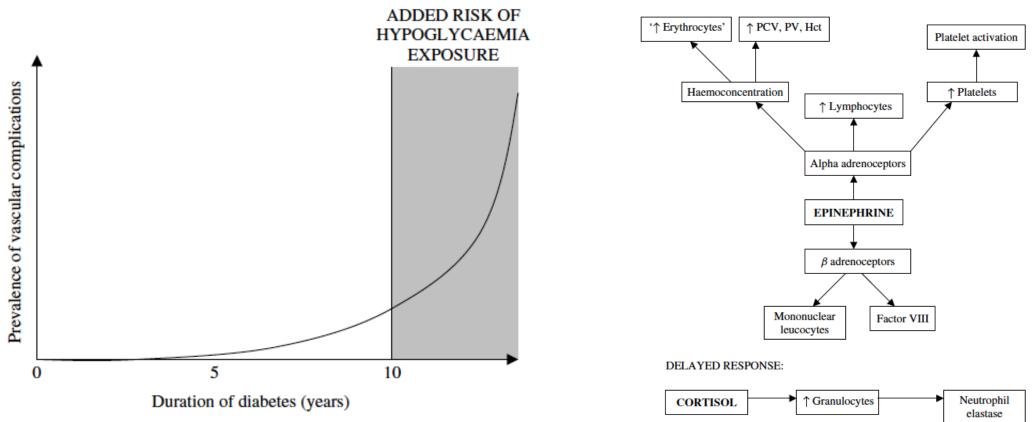
#### LEADER Study Hypoglycemia

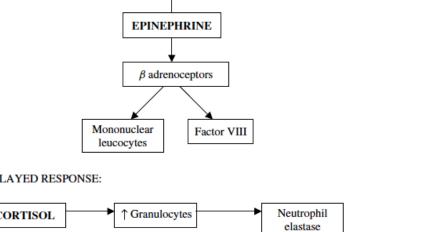


Confirmed hypoglycemia was defined as plasma glucose level of less than 56 mg per deciliter (3.1 mmol per liter) or a severe event. Severe hypoglycemia was defined as hypoglycemia for which the patient required assistance from a third party. Analyzed using a negative binomial regression model.

CI: confidence interval; PG: plasma glucose.

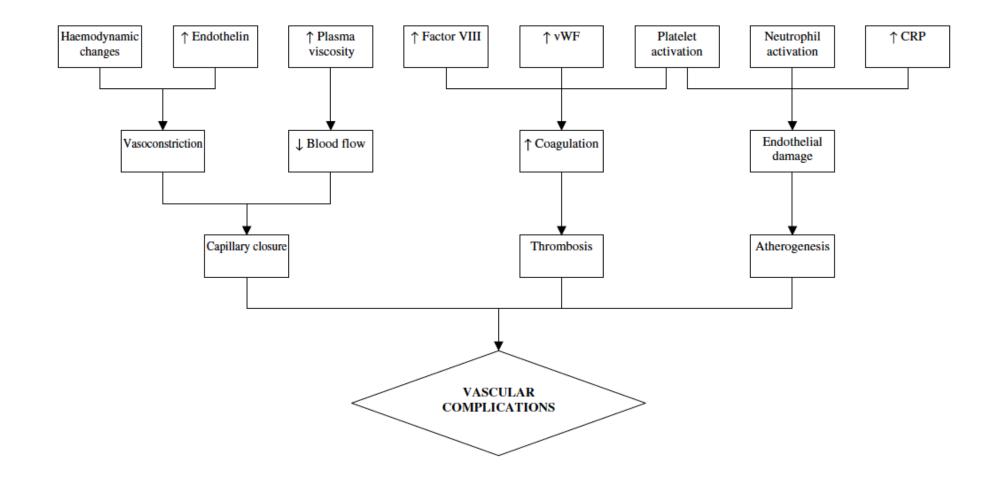
#### Hypoglycaemia and CV morbidity



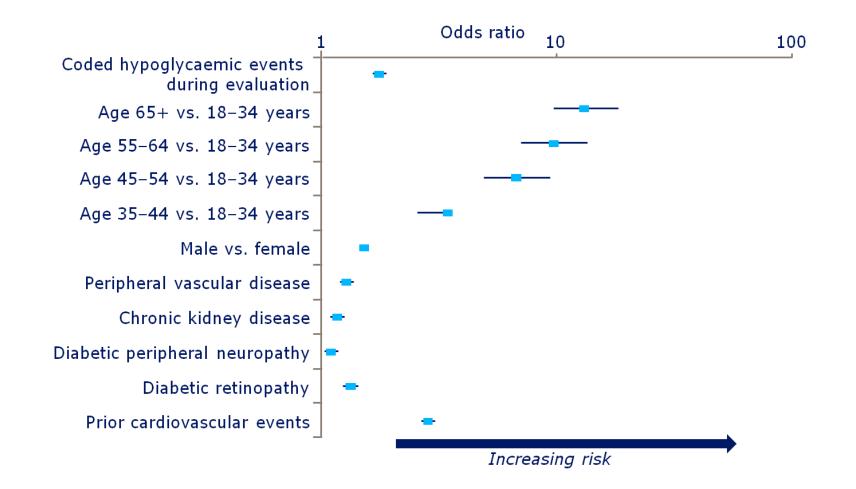


IMMEDIATE RESPONSE:

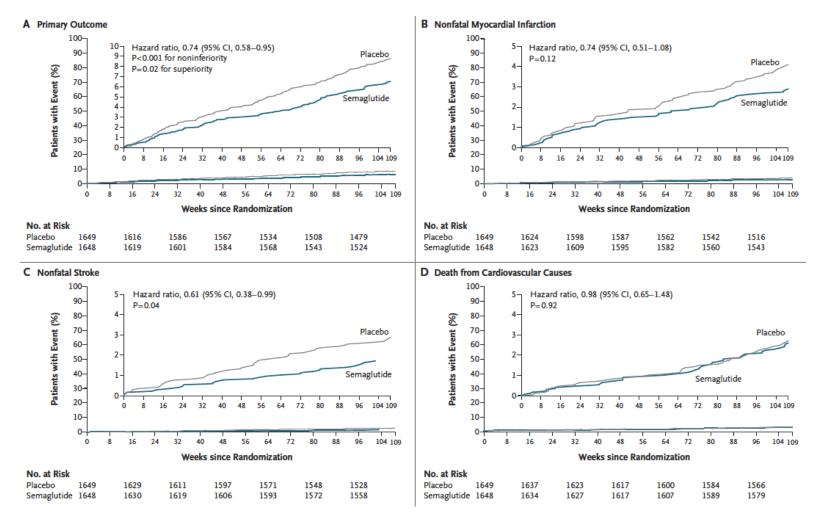
#### Hypoglycaemia and CV morbidity



Hypoglycemic events and increased risk of acute cardiovascular events in T2DM patients

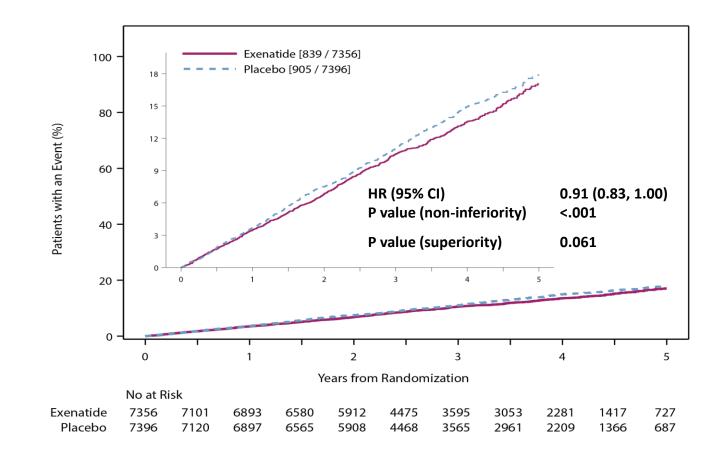


### Semaglutide and CV risk SUSTAIN-6 trial



Marso SP et al N Engl J Med. 2016 Sep 15. [Epub ahead of print]

EXSCEL Study: Primary Composite Cardiovascular Outcome Intention-to-Treat Analysis for Non-inferiority and Superiority

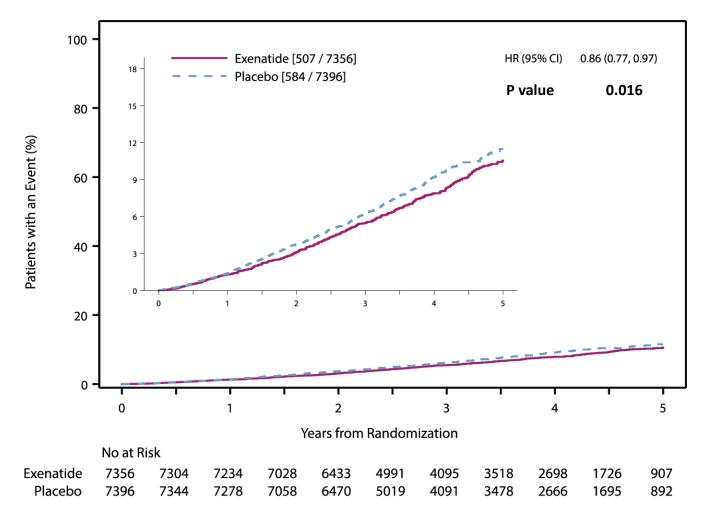


### Primary Composite Cardiovascular Outcome Intention-to-Treat Analysis

	Exenatide N=7356	Placebo N=7396		Hazard Ratio	95% CI	P value
MACE	839 (11.4%)	905 (12.2%)		0.91	0.83, 1.00	<.001 (non-inferiority)
	3.7 per 100 pt-yrs	4.0 per 100 pt-yr	'S	0.51	0.00, 1.00	0.061 (superiority)
CV-death	229	258 —		0.88	0.73, 1.05	
er death	(3.1%)	(3.5%)				0.620
Non-fatal MI	455	470		0.95	0.84, 1.09	0.628 (homogeneity
	(6.2%)	(6.4%)	-	0.55	0.01, 1.00	among components)
Non-fatal stroke	155	177		- 0.86	0.70, 1.07	components)
	(2.1%)	(2.4%)	-	0.80	0.70, 1.07	
	0	0,5	 1 	1,5	2	
				acebo		
		Tavc	oured far	voured		7 ( 20, 277/42), 4220 42

Holman RR et al. N Engl J Med. 2017 Sep 28;377(13):1228-1239

### All-Cause Mortality Intention-to-Treat Analysis



Holman RR et al. N Engl J Med. 2017 Sep 28;377(13):1228-1239

### Two Broad Categories of Clinical Trial Designs

In 1967, Schwartz and Lellouch differentiated clinical trials into pragmatic versus explanatory approaches.<sup>1</sup>
 There is a continuum rather than a dichotomy between the two approaches.<sup>2</sup>

#### Key Differences Between Trials With Explanatory and Pragmatic Designs<sup>2-4</sup>

	Explanatory	Pragmatic	
Objective	Evaluates if a treatment will work under optimal conditions	Evaluates if a treatment will work under routine practice conditions	
Validity	High internal validity <sup>a</sup>	High external validity <sup>b</sup>	
Sample size	Smaller	Larger	
Patient population	Homogenous, highly selected	Heterogeneous, little or no selection	
Design/setting	Sophisticated design with well-defined controlled environment	Simple design with broad diverse setting	
Intervention	Comparison to placebo	Comparison to usual care/standard of care	
Phase of trial	Mostly Phase II to III	Mostly Phase IV	
Relevance to practice	Indirect—little effort to match trial design to the usual setting in which intervention will be used	Direct—trial designed to match the setting in which intervention will be used	

<sup>a</sup>Ability to determine cause-effect relationships; <sup>b</sup>Ability to generalize the results in extended populations and clinical settings.

Schwartz D et al. J Chronic Dis 1967;20:637-648;
 Zwarenstein M et al. BMJ. 2008;337: a2390;

3. Patsopoulos NA. Dialogues Clin Neurosci. 2011;13:217-224;

4. Alford L. NZ J Physiother. 2007;35:12-16.

### EXSCEL (Pragmatic Trial) Versus LEADER (Exploratory Trial)

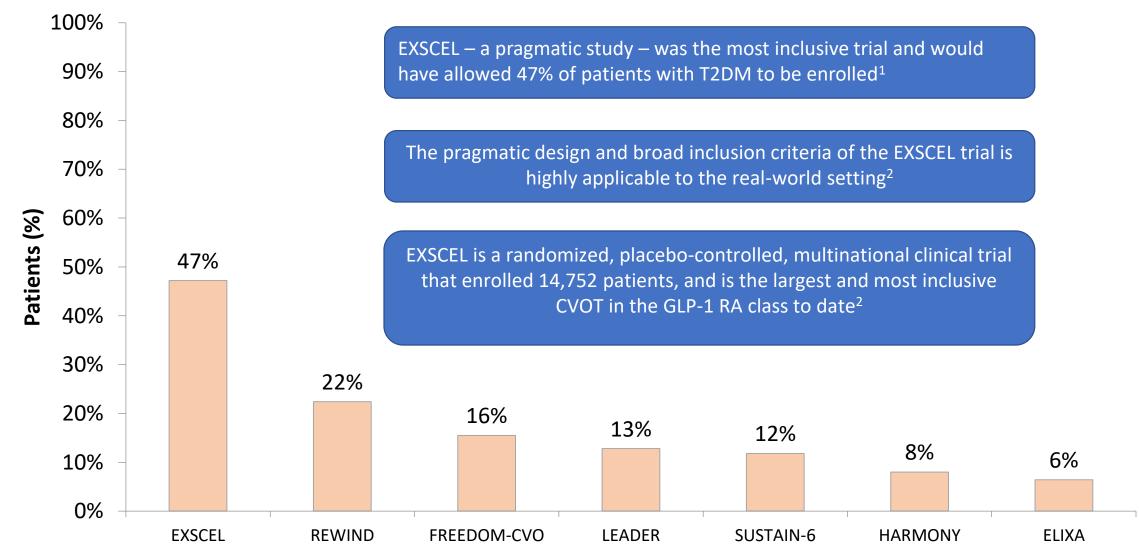
	EXSCEL <sup>1,2</sup> (exenatide once weekly)	LEADER <sup>3,4</sup> (liraglutide)		
Study design	Pragmatic, landomized, parallel-group, placebo-controlled, international trial	Randomized, double-blind, placebo-controlled, multicenter, international trial		
Population	<ul> <li>T2DM patients ≥18 years, Ht A1c 6.5% to 10%,</li> <li>with or without CV risk factors or prior CV events</li> <li>Key exclusion: T1DM; history of ketoacidosis, gastroparesis, pancreatitis; prior/current GLP-1 RA use; planned/anticipated revascularization procedure; pregnancy; ESRD or eGFR &lt;30 mL/min/1.73m<sup>2</sup>; familial/personal history of medullary thyroid cancer or MEN2 or baseline calcitonin level &gt;40 ng/L</li> </ul>	<ul> <li>T2DM patients, HbA1c ≥7.0%, ≥50 years with CVD or ≥60 years with 1 or more CV risk factors</li> <li>Key exclusion: T1DM; use of GLP-1 RA DPP-4i, pramlintide, rapid-acting insulin; familial/personal history of MEN2 or medullary thyroid cancer, acute coronary or cerebrovascular event (≤14 days); calcitonin ≥50 ng/L; end-stage liver disease; current continuous renal replacement therapy</li> </ul>		
Study treatments	EQW 2 mg + usual careª OR Placebo QW + usual careª	2-week run-in period with daily placebo injections followed by: Liraglutide 0.6 to 1.8 mg QD + standard of care <sup>b</sup> OR Placebo QD + standard of care <sup>b</sup>		
Add-on glycemic therapy	Any glucose-lowering agent such as insulin, TZD, SU, α-GI, DPP-4i, or SGLT-2i	Insulin, TZD, SU, or α-GI		
Patients, N	14,752	9340		
Study duration	1360 confirmed primary composite CV endpoint events	60 months (max) + ≥611 primary composite CV endpoint events		
Primary CV endpoint	Composite of • CV death • Nonfatal MI • Nonfatal stroke	Composite of <ul> <li>CV death</li> <li>Nonfatal MI</li> <li>Nonfatal stroke</li> </ul>		

<sup>a</sup>Patients were managed by their usual care provider and treated according to local standards of care for diabetes and cardiovascular risk factor management; <sup>b</sup>Standard of care guidelines were developed by the LEADER global expert panel and national study leaders in participating countries and included a protocol for the treatment of risk factors and concomitant use of medications.

GLP-1 RA = glucagon-like peptide-1 receptor agonist; HbA1c = glycated hemoglobin; MEN2 = multiple endocrine neoplasia type 2; MI = myocardial infarction; QW = once weekly; SGLT-2i = sodium-glucose co-transporter-2 inhibitor; SU = sulfonylurea; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione.

1. Holman RR et al. Article and supplementary appendix. Am Heart J. 2016;174:103-110; 2. Mentz RJ et al. Am Heart J. 2017;187:1-9; 3. Marso SP et al. Article, online protocol, and supplementary appendix. N Engl J Med. 2016; 375:311-322; 4. Marso SP et al. Am Heart J. 2013;166:823-830.e5.

## US Patients With T2DM Who Meet the Eligibility Criteria for GLP-1 RA CVOTs $^{\rm 1}$



CVOT = cardiovascular outcomes trial; GLP-1 RA = glucagon-like peptide-1 receptor agonist; T2DM = type 2 diabetes mellitus.

1. Wittbrodt ET et al. Poster presented at: 77th American Diabetes Association Scientific Sessions; June 9-13, 2017; San Diego, CA. Poster 1515-P; 2. Mentz RJ et al. Am Heart J. 2017;187:1-9.

#### Conclusioni

- La malattia cardiovascolare è la causa più frequente di morbilità e mortalità nel paziente affetto da diabete mellito di tipo 2
- Il GLP-1 svolge importanti effetti cardiovascolari dimostrati sia in modelli sperimentali sia nell'uomo
- Nei CVOT i GLP-1 RA si sono dimostrati superiori al placebo nella protezione cardiovascolare e nella riduzione della mortalità



#### Thank you for your attention

