Estudios de seguridad CV: cocientes de riesgo CV *(HR)*

	inh-SGLT- 2			ar-GLP-1							inh-DPP-4			
Estudio	**EMPA-REG[1]**	**CANVAS[2]**	**DECLARE[3]**	**ELIXA[4]**	**LEADER[5]**	**SUSTAIN[6]**	**EXSCEL[7]**	**HARMONY[8]**	**REWIND [13]**	**PIONEER 6 [14]**	**SAVOR-TIMI [9]**	**EXAMINE[10]**	**TECOS[11]**	**CARMELINA[12]**
	Empagliflozina	Canagliflozina	Dapagliflozina	Lixisenatida	Liraglutida	Semaglutida	Exenatida Lar	Albiglutida	Dulaglutida	Semaglutida oral	Saxagliptina	Alogliptina	Sitagliptina	Linagliptina
3pt MACE	**0,86** 0,74-0,99	**0,86** 0,75-0,97	**0,93** 0,84-1,03	**1,02** 0,89-1,17	**0,87** 0,78-0,97	**0,74** 0,58-0,95	**0,91** 0,83-1,00	**0,78** 0,68-0,90	**0,88** 0,79-0,99	**0,79** 0,57-1,11	**1,0** 0,89-1,08	**0,96** > 1,16	**0,98** 0,89-1,08	**1,02** 0,89-1,17
Muerte CV	**0,62** 0,49-0,77	**0,87** 0,72-1,06	**0,98** 0,82-1,17	**0,98** 0,78-1,22	**0,78** 0,66-0,93	**0,98** 0,65-1,48	**0,88** 0,76-1,02	**0,93** 0,73-1,19	**0,91** 0,78-1,06	**0,49** 0,27-0,92	**1,03** 0,87-1,22	**0,79** 0,60-1,04	**1,03** 0,89-1,19	**0,96** 0,81-1,14
IAM no fatal	**0,87** 0,70-1,09	**0,85** 0,69-1,05	**0,89** 0,77-1,01	**1,03** 0,87-1,22	**0,88** 0,75-1,03	**0,74** 0,51-1,08	**0,97** 0,85-1,10	**0,75** 0,61-0,90	**0,96** 0,79-1,16	**1,18** 0,73-1,90	**1,95** 0,80-1,22	**1,08** 0,88-1,33	**0,95** 0,81-1,11	**1,12** 0,90-1,40
Ictus no fatal	**1,24** 0,92-1,67	**0,90** 0,71-1,15	**1,01** 0,84-1,21	**1,12** 0,79-1,58	**0,89** 0,72-1,11	**0,61** 0,38-0,99	**0,85** 0,70-1,03	**0,86** 0,66-1,14	**0,76** 0,61-0,95	**0,74** 0,35-1,57	**1,11** 0,88-1,39	**0,91** 0,55-1.,0	**0,97** 0,89-1,08	**0,91** 0,67-1,23
Hospitalización por IC	**0,65** 0,50-0,85	**0,67** 0,52-0,87	**0,73** 0,61-0,88	**0,96** 0,75-1,23	**0,87** 0,73-1,05	**1,11** 0,77-1,61	**0,94** 0,78-1,13	**0,85** 0,70-1,04	**0,93** 0,77-1,12	**0,86** 0,48-1,55	**1,27** 1,07-1,51	**1,07** 0,78-1,15	**1,00** 0,83-1,20	**0,90** 0,74-1,08
Muerte por cualquier causa	**0.68** 0,57-0,82	**0,87** 0,74-1,01	**0,93** 0,82-1,04	**0,94** 0,78-1,13	**0,85** 0,74-0,97	**1,05** 0,74-1,50	**0,86** 0,77-0,97	**0,95** 0,79-1,16	**0,90** 0,80-1,01	**0,51** 0,31-0,84	**1,11** 0,96-1,27	**0,88** 0,71-1,09	**1,01** 0,90-1,14	**0,98** 0,84-1,13
objetivo primario* **Muerte CV o hospital. por IC			**0,83** 0,73-0,95											

EMPA-REG , CANVAS , DECLARE, LEADER, SUSTAIN, HARMONY, SAVOR-TIMI, EXAMINE, CARMELINA (**3-pt MACE:** Tiempo en primer evento de muerte CV, IAM no fatal o ictus no fatal)
TECOS , ELIXA (**4-pt MACE**: Tiempo en primer evento de muerte CV o IAM no fatal o ictus no fatal o hospitalización por angina inestable).

1.N Engl J Med 2015; 373:2117-2128, 2.N Engl J Med 2017; 377:644-657, 3.N Engl J Med 2018; 10 october 4. N Engl J Med 2015;373:2247-57 5.N Engl J Med 2016; 375:311-322 6.N Engl J Med 2016;375:1834-1844, 7. N Engl J Med 2017;377:1228-1239 8.The Lancet ; October 2,2018 9. N Engl J Med 2013;369:1317-26 10. N Engl J Med 2013;369:1327-35 11. N Engl J Med 2015;373:232-5 12. JAMA 2019;321(1):69-79 13. The Lancet ;june10,2019 14. N Engl J Med 2019; 381:841-851

J.Barrot (personal contribution)

Renal outcomes in T2DM

	SGLT- 2i				DPP-4i
Trial	**EMPA-REG** [1]	**CANVAS-R** [2]	**CREDENCE** [4]	**DECLARE-TIMI** [5]	**CARMELINA** [3]
	Empagliflozina	Canagliflozina	Canagliflozina	Dapagliflozina	Linagliptina
Study design	**eGFR > 30 ml/ min**	**eGFR > 30 ml/ min**	**eGFR 30 - 90 ml/ min** **UARC 300-5000 mg/g**	**eGFR ≥ 60 mL/min**	**eGFR 15−45 ml/min** **eGFR 45−75 ml/min and UACR >200**
mean eGFR (mL/min) **mean UARC** (mg/g)	**74.5** (25.9% < 60) **MDRD** **12.3** (59.4% < 30,11% >300)	**76.5** (20.1% < 60) **MDRD** **12.3** (69.8% < 30)	**56.2** (59.8% < 60) **CKD-EPI** **927** (76.6% 300-3000, 11.4% > 3000)	**85.2** (7.4% < 60) **CKD-EPI** **13.1** (67.9% < 30, 6.8% > 300)	**54.6** (62% < 60) **162** (80% > 30)
Follow-up period	**over 3.1 y**	**over 2.4 y**	**over 2.6 y**	**over 4.2 y**	**2.2 y**
composite **Kidney outcomes**	**doubling Creat. with eGF ≤ 45,** **RRT, or renal death**	**40% reduction eGF for at least 2 consecutive mesures** **ESKD, or renal death**	**doubling serum Creatinine,** **ESKD , or renal/CV death**	**≥ 40% reduction in eGF to < 60,** **ESKD, or renal/CV death**	**ESKD, death to renal failure** **or decline ≥ 40% in eGFR from baseline**
Kidney outcome	**0.54** 0.40-0.75, *p < 0.001*	**0.60** 0.47-0.77, p<0.001	**0.70 NNT 22** 0.59-0.82, *p= 0.00001*	**0.53** 0.43-0.66, *p <0.001*	**1.04** 0.89-1.22 , *p=0.62*
ESKD	**incident or worsening nephropathy or death from CV causes** **0.61** (0.40-0.75) *p < 0.001*		**0.68 NNT 43** 0.48-0.76	**0.31** 0.13-0.79, *p 0.013*	**ESKD, death to kidney failure, decline ≥ 40% in eGFR from baseline** **0.98** (0.82-1.18) *p 0.87*
ESKD, doubling creat., or renal death			**0.66 NNT 28** 0.53-0.81, *p< 0.001*	**0.41** 0.20-0.82, *p 0.012*	**Death due to renal failure or ESKD** **0.87** (0.69-1.10) *p 0.24*
composite microvascular end point					**0.86** 0.78-0.95, *p 0.0032*
albuminuria progression					**0.86** 0.78-0.95, *p=0.0034*

ESKD (end-stage kidney disease：eGFR < 15 mL/min , dialysis, kidney transplantation) , UARC (ratio of albumin to creatinine), RRT (renal-replacement therapy) , eGFR (estimation equation : CKD-EPI or MDRD)

1. *N Engl J Med 2016; 375:323-334 2.Engl J Med. 2017;377(7):644–57. https://doi.org/10.1056/nejmoa1611925. 3. JAMA. 2018 november .doi:10.1001/jama.2018.18269*
2. *4.N Engl J Med 2019, April. doi: 10.1056/NEJMoa1811744 5. Lancet Diab End* **2019** *June 9. http://dx.doi.org/10.1016/ S2213-8587(19)30180-9*

J.Barrot (personal contribution)

Cardiorenal outcomes in T2DM

	SGLT- 2i				DPP-4i
Trial	**EMPA-REG** [1]	**CANVAS-R** [2]	**CREDENCE** [4]	**DECLARE-TIMI** [5]	**CARMELINA** [3]
	Empagliflozina	Canagliflozina	Canagliflozina	Dapagliflozina	Linagliptina
Study design	**eGFR > 30 ml/ min**	**eGFR > 30 ml/ min**	**eGFR 30 - 90 ml/ min** **UARC 300-5000 mg/g**	**eGFR ≥ 60 mL/min**	**eGFR 15−45 ml/min** **eGFR 45−75 ml/min and UACR >200**
mean eGFR (mL/min) **mean UARC** (mg/g)	**74.5** (25.9% < 60) **MDRD** **12.3** (59.4% < 30,11% >300)	**76.5** (20.1% < 60) **MDRD** **12.3** (69.8% < 30)	**56.2** (59.8% < 60) **CKD-EPI** **927** (76.6% 300-3000, 11.4% > 3000)	**85.2** (7.4% < 60) **CKD-EPI** **13.1** (67.9% < 30, 6.8% > 300)	**54.6** (62% < 60) **162** (80% > 30)
Follow-up period	**over 3.1 y**	**over 2.4 y**	**over 2.6 y**	**over 4.2 y**	**2.2 y**
composite Kidney outcomes	**doubling Creat. with eGF ≤ 45, RRT, or renal death**	**40% reduction eGF for at least 2 consecutive mesures ESKD, or renal death**	**doubling serum Creatinine, ESKD , or renal/CV death**	**≥ 40% reduction in eGF to < 60, ESKD, or renal/CV death**	**ESKD, death to renal failure or decline ≥ 40% in eGFR from baseline**
Kidney outcome	**0.54** 0.40-0.75, *p < 0.001*	**0.60** 0.47-0.77, p<0.001	**0.70** 0.59-0.82, *p= 0.00001*	**0.53** 0.43-0.66, *p <0.001*	**1.04** 0.89-1.22 , *p=0.62*
HF hospitalization	**0.65** 0.50-0.85, *p 0.002*	**0.67** 0.52-0.87, *p 0.02*	**0.61** 0.47-0.80, *p<0.001*	**0.73** 0.61-0.88, *p 0.0008*	
HHF and CV death	**0.66** 0.55-0.79, *p< 0.001*	**0.78** 0.67-0.91, *p 0.0015*	**0.69** 0.57-0.83, *p<0.001*	**0.83** 0.73-0.95, *p 0.005*	
MACE ***Hazard Ratio***	**0.86** 0.74-0.99, *p 0.04*	**0.86** 0.75-0.97, *p 0.08*	**0.80** 0.67-0.95, *p 0.01*	**0.93** 0.84-1.03, *p 0.17*	

ESKD (end-stage kidney disease : eGFR < 15 mL/min , dialysis, kidney transplantation) , UARC (ratio of albumin to creatinine), RRT (renal-replacement therapy) , eGFR (estimation equation : CKD-EPI or MDRD)

1. *N Engl J Med 2016; 375:323-334* *2.Engl J Med. 2017;377(7):644–57. https://doi.org/10.1056/nejmoa1611925.* *3. JAMA. 2018 november .doi:10.1001/jama.2018.18269*
2. *4.N Engl J Med 2019, April. doi: 10.1056/NEJMoa1811744* *5. Lancet Diab End* **2019** *June 9. http://dx.doi.org/10.1016/ S2213-8587(19)30180-9*

J.Barrot (personal contribution)

Cardiovascular, Mortality and kidney outcomes with GLP-1ra in T2DM: a systematic review and meta-analysis of CV outcome trials

	ELIXA	LEADER	SUSTAIN-6	EXSCEL	HARMONY	REWIND	PIONEER-6	overall
	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Dulaglutide	Semaglutide o	
3-MACE	**1.02** 0.89-1.17	**0.87** 0.78-0.97	**0.74** 0.58-0.95	**0.91** 0.83-1.00	**0.78** 0.68-0.90	**0.88** 0.79-0.99	**0.79** 0.57-1.11	**0.88** 0.82-0.94
History of CVD		**0.83** 0.74-0.93	**0.72** 0.55-0.94	**0.90** 0.81-0.99		**0.87** 0.74-1.02	**0.83** 0.58-1.18	**0.86** 0.80-0.92
No history of CVD		**1.20** 0.86-1.67	**1.00** 0.41-2.44	**0.99** 0.77-1.28		**0.87** 0.74-1.02	**0.51** 0.15-1.71	**0.94** 0.83-1.07
CV death	**0.98** 0.78-1.22	**0.78** 0.66-0.93	**0.98** 0.65-1.48	**0.88** 0.76-1.02	**0.93** 0.73-1.19	**0.91** 0.78-1.06	**0.49** 0.27-0.92	**0.88** 0.81-0.96
fatal or no fatal MI	**1.03** 0.87-1.22	**0.86** 0.73-1.00	**0.81** 0.57-1.16	**0.97** 0.85-1.10	**0.75** 0.61-0.90	**0.96** 0.79-1.15	**1.18** 0.73-1.90	**0.91** 0.84-1.00
fatal or no fatal Stroke	**1.12** 0.79-1.58	**0.86** 0.71-1.06	**0.65** 0.41-1.03	**0.85** 0.70-1.03	**0.86** 0.66-1.14	**0.76** 0.62-0.94	**0.74** 0.35-1.57	**0.84** 0.76-0.93
All cause mortality	**0.94** 0.78-1.13	**0.85** 0.74-0.97	**1.05** 0.74-1.50	**0.86** 0.77-0.97	**0.95** 0.79-1.16	**0.90** 0.80-1.01	**0.51** 0.31-0.84	**0.88** 0.83-0.95



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J.Barrot (personal contribution)

Cardiovascular, Mortality and kidney outcomes with GLP-1ra in T2DM: a systematic review and meta-analysis of CV outcome trials

	ELIXA	LEADER	SUSTAIN-6	EXSCEL	HARMONY	REWIND	PIONEER-6	overall
	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Dulaglutide	Semaglutide o	
3-MACE	**1.02** 0.89-1.17	**0.87** 0.78-0.97	**0.74** 0.58-0.95	**0.91** 0.83-1.00	**0.78** 0.68-0.90	**0.88** 0.79-0.99	**0.79** 0.57-1.11	**0.88** 0.82-0.94
CV death	**0.98** 0.78-1.22	**0.78** 0.66-0.93	**0.98** 0.65-1.48	**0.88** 0.76-1.02	**0.93** 0.73-1.19	**0.91** 0.78-1.06	**0.49** 0.27-0.92	**0.88** 0.81-0.96
fatal or no fatal MI	**1.03** 0.87-1.22	**0.86** 0.73-1.00	**0.81** 0.57-1.16	**0.97** 0.85-1.10	**0.75** 0.61-0.90	**0.96** 0.79-1.15	**1.18** 0.73-1.90	**0.91** 0.84-1.00
fatal or no fatal Stroke	**1.12** 0.79-1.58	**0.86** 0.71-1.06	**0.65** 0.41-1.03	**0.85** 0.70-1.03	**0.86** 0.66-1.14	**0.76** 0.62-0.94	**0.74** 0.35-1.57	**0.84** 0.76-0.93
All cause mortality	**0.94** 0.78-1.13	**0.85** 0.74-0.97	**1.05** 0.74-1.50	**0.86** 0.77-0.97	**0.95** 0.79-1.16	**0.90** 0.80-1.01	**0.51** 0.31-0.84	**0.88** 0.83-0.95
Hospital for Heart failure	**0.96** 0.75-1.23	**0.87** 0.73-1.05	**1.11** 0.77-1.61	**0.94** 0.78-1.13	**0.71** 0.53-0.94	**0.93** 0.77-1.12	**0.86** 0.48-1.44	**0.91** 0.83-0.99
composite kidney outcome	**0.84** 0.68-1.02	**0.78** 0.67-0.92	**0.64** 0.46-0.88	**0.88** 0.76-1.01		**0.85** 0.77-0.93		**0.83** 0.78-0.89
worsening of Kidney function	**1.16** 0.74-1.83	**0.89** 0.67-1.19	**1.28** 0.64-2.58	**0.88** 0.74-1.05		**0.70** 0.57-0.85		**0.87** 0.73-1.03
incidence macro albuminuria	**0.81** 0.66-0.99	**0.74** 0.60-0.91	**0.54** 0.37-0.78	**0.79** 0.64-0.97		**0.77** 0.68-0.87		**0.76** 0.68-0.86

Kristensen. Lancet Diab Endoc 2019

J.Barrot (personal contribution)