DEP Lazio
Dipartimento di Epidemiologia del Servizio Sanitario Regionale Regione Lazio

SISTEMA SANITARIO REGIONALE
ASL ROMA E
REGIONE LAZIO

Sintesi delle conoscenze scientifiche sull'efficacia comparativa di EPO in pazienti con anemia da malattia renale cronica

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Obiettivo

Valutare l'efficacia comparativa e la sicurezza delle epoietine in pazienti affetti da anemia dovuta a malattia renale cronica

1. PICO

P	Adulti (>18 anni) affetti da anemia dovuta a malattia renale cronica
I	EPO (epoietina alfa, epoietina beta, epoietina zeta, epoietina theta, darbepoetin beta, methoxy polyethylene glycol-epoetin beta, biosimilari)
C	EPO originator vs EPO biosimilare; EPO originator vs EPO originator; biosimilare vs biosimilare;
O	Livello di Hb; Prevenzione delle trasfusioni; Affaticamento; Dispnea Mortalità per tutte le cause; Mortalità per cause cardiovascolari; Infarto del miocardio fatale o non fatale; Ictus fatale o non fatale; Trombosi vascolare; Ipertensione; Eventi cardiovascori maggiori :Malattia renale in stadio terminale

2. Ricerca degli studi

- Revisioni sistematiche della letteratura: PubMed and the Cochrane Library up to July 2015
- Studi primari (RCT e CCT): CENTRAL (issue 11, 2015), PubMed (from 18/02/2014 to 18/11/2015) EMBASE (from 11/02/2014 to 18/11/2015)

RS: N= 7 → **Palmer 2014 con 24/56 da includere**
Buona qualità metodologica
(AMSTAR checklist =7/8)

RCT N=268 → 20 in full text → 6 inclusi

In totale 30 studi inclusi

3. Risultati: Caratteristiche degli studi

- I 30 studi sono stati pubblicati tra il 2011 e il 2015,
- Avevano una durata media di 9 mesi
- Sono stati condotti in quasi tutti i Paesi del mondo a parte l'Africa Centrale e del Nord
- 7843 pazienti inclusi
- 21/30 studi includevano pazienti in emodialisi o in dialisi peritoneale (3/21)

Confronti

I confronti considerati nei 30 studi inclusi sono:

- ✓ **Epoietina α verso EPO biosimilare: 10 studi, 3160 pazienti**
- ✓ Epoietina α verso darbepoietina α: 10 studi, 2338 pazienti
- ✓ Epoietina β verso methoxy polyethylene glycol-epoietina β : 3 studi, 332 pazienti
- ✓ Darbepoietina α verso methoxy polyethylene glycol-epoietina beta: 6 studi, 1833 pazienti

Inoltre

Epoietina β verso EPO biosimilare: 1 studio, 288 pazienti

Epoietina β verso darbepoietina α : 1 studio, 219 pazienti

Esiti considerati

Efficacia:

1.Trasfusioni: 12 studi

2. Affaticamento: 4 studi

3. Dispnea: 3 studi

Sicurezza:

4. Mortalità per tutte le cause: 23 studi

5. Mortalità per cause cardiovascolari: 8 studi

6. Ipertensione: 19 studi

7. Ictus: 10 studi

8. Infarto: 8 studi

9. Trombosi vascolare: 8 studi

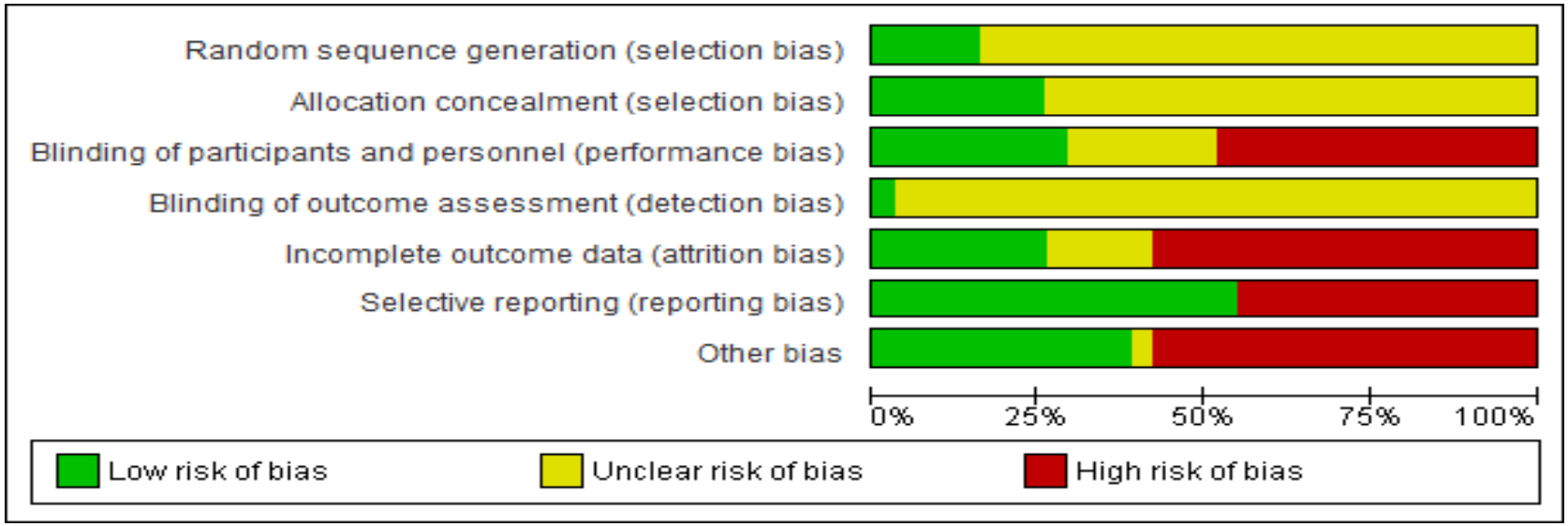
10. Eventi cardiovascolari maggiori: 3 studi

11. Malattia renale in stadio terminale: 4 studi

GRADE determinants of quality

- detailed design and execution (risk of bias)
- Consistency (variation in size effect, overlap in confidence intervals, statistical significance of heterogeneity)
- Directness (differences in patients, interventions, comparisons, surrogates outcomes)
- Precision (small sample size, wide confidence intervals)
- Other bias (one or more of: sponsor involved in study design, analysis, or authorship; imbalance between treatment comparisons and/or premature termination of trial)

Risk of bias degli studi inclusi



Other bias: **22/30 sponsorizzati dall'Industria**, di questi in **15/22 lo sponsor era coinvolto come autore e nell'analisi dei dati**

Results of the comparison Epoetin α versus Biosimilar

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Epoetin α versus Biosimilar (95% CI)
Mean Hb level at the end of the study Objective	1178 (3 studies) 11 months	⊕⊕⊖⊖ **LOW**[1] due to risk of bias			The mean Hb level at the end of the study in the intervention groups was **0.08 higher** (-0.05 lower to 0.2 higher)
Blood Transfusion Objective	1823 (3 studies) 12 months	⊕⊕⊖⊖ **LOW**[2] due to risk of bias	**RR 0.73** (0.44 to 1.21)	**Study population**	
				54 per 1000	**15 fewer per 1000** (from 30 fewer to 11 more)
Fatigue Subjective	286 (2 studies) 3 months	⊕⊕⊖⊖ **LOW**[3] due to risk of bias	**RR 0.49** (0.18 to 1.32)	**Study population**	
				73 per 1000	**37 fewer per 1000** (from 60 fewer to 23 more)
Breathlessness Subjective	794 (2 studies)	⊕⊕⊖⊖ **LOW**[4] due to risk of bias	**RR 0.71** (0.41 to 1.23)	**Study population**	
				100 per 1000	**29 fewer per 1000** (from 59 fewer to 23 more)
All-cause mortality Objective	2294 (8 studies) 8 months	⊕⊖⊖⊖ **VERY LOW**[5,6] due to risk of bias, inconsistency	**RR 0.94** (0.52 to 1.7)	**Study population**	
				49 per 1000	**3 fewer per 1000** (from 23 fewer to 34 more)
Cardiovascular mortality Objective	657 (2 studies) 8.5 months	⊕⊕⊖⊖ **LOW**[4] due to risk of bias	**RR 0.54** (0.22 to 1.34)	**Study population**	
				50 per 1000	**23 fewer per 1000** (from 39 fewer to 17 more)
Myocardial infarction Objective	748 (3 studies) 4 months	⊕⊕⊖⊖ **LOW**[7] due to risk of bias	**RR 1.22** (0.5 to 2.99)	**Study population**	
				22 per 1000	**5 more per 1000** (from 11 fewer to 43 more)
Stroke Objective	825 (4 studies) 3.7 months	⊕⊖⊖⊖ **VERY LOW**[8,9] due to risk of bias, inconsistency	**RR 0.92** (0.4 to 2.09)	**Study population**	
				27 per 1000	**2 fewer per 1000** (from 16 fewer to 29 more)
Hypertension Objective	1571 (5 studies) 4.2 months	⊕⊕⊖⊖ **LOW**[10] due to risk of bias	**RR 1.62** (0.98 to 2.66)	**Study population**	
				28 per 1000	**17 more per 1000** (from 1 fewer to 47 more)
Vascular access thrombosis Objective	930 (3 studies) 4 months	⊕⊕⊖⊖ **LOW**[11] due to risk of bias	**RR 1.67** (0.32 to 8.85)	**Study population**	
				22 per 1000	**15 more per 1000** (from 15 fewer to 171 more)

[5] High risk: six studies for attrition bias, four studies for other risk of bias, three for reporting bias and two for performance bias. Unclear risk for the other bias for the majority of the studies

[6] Variability in results and statistical significance of heterogeneity

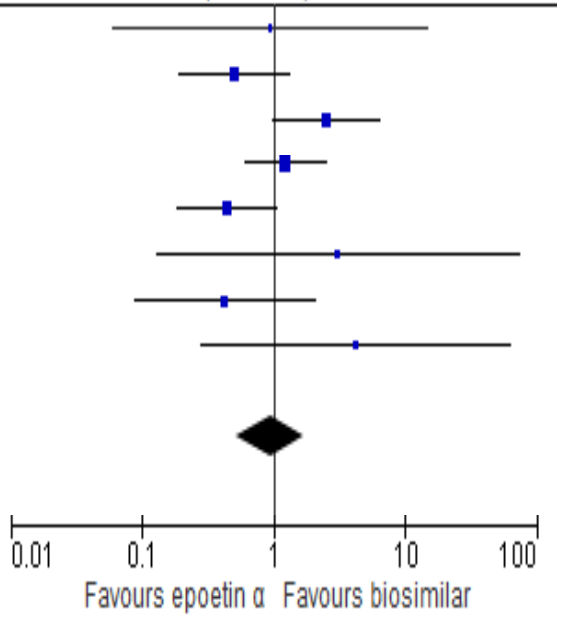
Results of the comparison Epoetin α versus Biosimilar

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Epoetin α versus Biosimilar (95% CI)
Mean Hb level at the end of the study Objective	1178 (3 studies) 11 months	⊕⊕⊖⊖ **LOW**[1] due to risk of bias			The mean Hb level at the end of the study in the intervention groups was **0.08 higher** (-0.05 lower to 0.2 higher)
Blood Transfusion Objective	1823 (3 studies) 12 months	⊕⊕⊖⊖ **LOW**[2] due to risk of bias	**RR 0.73** (0.44 to 1.21)	**Study population**	
				54 per 1000	**15 fewer per 1000** (from 30 fewer to 11 more)
Fatigue Subjective	286 (2 studies) 3 months	⊕⊕⊖⊖ **LOW**[3] due to risk of bias	**RR 0.49** (0.18 to 1.32)	**Study population**	
				73 per 1000	**37 fewer per 1000** (from 60 fewer to 23 more)
Breathlessness Subjective	794 (2 studies)	⊕⊕⊖⊖ **LOW**[4] due to risk of bias	**RR 0.71** (0.41 to 1.23)	**Study population**	
				100 per 1000	**29 fewer per 1000** (from 59 fewer to 23 more)
All-cause mortality Objective	2294 (8 studies) 8 months	⊕⊖⊖⊖ **VERY LOW**[5,6] due to risk of bias, inconsistency	**RR 0.94** (0.52 to 1.7)	**Study population**	
				49 per 1000	**3 fewer per 1000** (from 23 fewer to 34 more)
Cardiovascular mortality Objective	657 (2 studies) 8.5 months	⊕⊕⊖⊖ **LOW**[4] due to risk of bias	**RR 0.54** (0.22 to 1.34)	**Study population**	
				50 per 1000	**23 fewer per 1000** (from 39 fewer to 17 more)
Myocardial infarction Objective	748 (3 studies) 4 months	⊕⊕⊖⊖ **LOW**[7] due to risk of bias	**RR 1.22** (0.5 to 2.99)	**Study population**	
				22 per 1000	**5 more per 1000** (from 11 fewer to 43 more)
Stroke Objective	825 (4 studies) 3.7 months	⊕⊖⊖⊖ **VERY LOW**[8,9] due to risk of bias, inconsistency	**RR 0.92** (0.4 to 2.09)	**Study population**	
				27 per 1000	**2 fewer per 1000** (from 16 fewer to 29 more)
Hypertension Objective	1571 (5 studies) 4.2 months	⊕⊕⊖⊖ **LOW**[10] due to risk of bias	**RR 1.62** (0.98 to 2.66)	**Study population**	
				28 per 1000	**17 more per 1000** (from 1 fewer to 47 more)
Vascular access thrombosis Objective	930 (3 studies) 4 months	⊕⊕⊖⊖ **LOW**[11] due to risk of bias	**RR 1.67** (0.32 to 8.85)	**Study population**	
				22 per 1000	**15 more per 1000** (from 15 fewer to 171 more)

Study or Subgroup	Epoetin α Events	Total	Biosimilar Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Goh 2007	1	92	1	87	4.0%	0.95 [0.06, 14.89]
Haag-Weber 2009	5	164	19	314	17.8%	0.50 [0.19, 1.32]
Haag-Weber 2012	14	163	6	174	18.5%	2.49 [0.98, 6.33]
Krivoshiev 2008	16	304	13	305	22.8%	1.23 [0.60, 2.52]
Krivoshiev 2010	7	230	16	232	19.7%	0.44 [0.19, 1.05]
Milutinovic 2006	1	38	0	39	3.1%	3.08 [0.13, 73.26]
Picon 2014	2	36	5	38	9.9%	0.42 [0.09, 2.04]
Spinowitz 2006	1	15	1	63	4.1%	4.20 [0.28, 63.38]
Total (95% CI)		**1042**		**1252**	**100.0%**	**0.94 [0.52, 1.70]**
Total events	47		61			

Heterogeneity: $Tau^2 = 0.26$; $Chi^2 = 11.97$, df = 7 (P = 0.10); $I^2 = 42\%$

Test for overall effect: Z = 0.20 (P = 0.84)



Notes

[1] Two studies at high risk for attrition bias and two for other bias. Unclear risk for the other bias for the majority of the studies

[2] Three studies with high risk of attrition bias; one at high risk of other bias. Unclear risk for the other bias for the majority of the studies

[3] One study at high risk of performance and attrition bias and one for other risk of bias. Unclear risk for the other bias for both studies

[4] Two studies at high risk for attrition bias; one study at high risk for performance and other risk bias. Unclear risk for the other bias for both studies

[5] High risk: six studies for attrition bias, four studies for other risk of bias, three for reporting bias and two for performance bias. Unclear risk for the other bias for the majority of the studies

[6] Variability in results and statistical significance of heterogeneity

[7] Two studies at high risk for attrition bias and other bias and one study at high risk for performance bias. Unclear risk for the other bias for the other studies

[8] Three studies at high risk of attrition bias, two high risk of performance and other bias. Unclear risk for the other bias for the majority of the studies

[9] Variability in results and variation in size of effect

[10] High risk: four studies for attrition bias, two for performing and other risk of bias. Unclear risk for the other bias for the majority of the studies

[11] High risk: two studies for attrition, one for performance and other risk of bias. Unclear risk for the other bias for the majority of the studies

Results of the comparison Epoetin α versus Darbepoetin α

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Epoetin α versus Darbepoetin α (95% CI)
Mean Hb level at the end of the study Objective	347 (3 studies) 10.6 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, inconsistency			The mean Hb level at the end of the study in the intervention groups was **-0.54 lower** (-1.54 lower to 0.46 higher)
Blood transfusion Objective	1191 (3 studies) 9.6 months	⊕⊖⊖⊖ **VERY LOW**[3,4] due to risk of bias, inconsistency	**RR 2.18** (1.31 to 3.62)	**Study population**	
				36 per 1000	**43 more per 1000** (from 11 more to 95 more)
Fatigue Subjective	551 (2 studies) 9.5 months	⊕⊕⊖⊖ **LOW**[5] due to risk of bias	**RR 0.94** (0.63 to 1.42)	**Study population**	
				179 per 1000	**11 fewer per 1000** (from 66 fewer to 75 more)
All-cause mortality Objective	1265 (7 studies) 8.7 months	⊕⊕⊖⊖ **LOW**[6] due to risk of bias	**RR 1.11** (0.6 to 2.06)	**Study population**	
				33 per 1000	**4 more per 1000** (from 13 fewer to 35 more)
Cardiovascular mortality Objective	487 (2 studies) 11.5 months	⊕⊕⊖⊖ **LOW**[7] due to risk of bias	**RR 2.12** (0.32 to 14.23)	**Study population**	
				7 per 1000	**8 more per 1000** (from 5 fewer to 91 more)
Myocardial infarction Objective	941 (3 studies) 11 months	⊕⊖⊖⊖ **VERY LOW**[8,9] due to risk of bias, inconsistency	**RR 0.88** (0.32 to 2.42)	**Study population**	
				18 per 1000	**2 fewer per 1000** (from 12 fewer to 26 more)
Major cardiovascular events Objecve	437 (2 studies) 13.5 months	⊕⊕⊖⊖ **LOW**[10] due to risk of bias	**RR 0.2** (0.01 to 4.16)	**Study population**	
				9 per 1000	**8 fewer per 1000** (from 9 fewer to 30 more)

Results of the comparison Epoetin α versus Darbepoetin α

Stroke Objective	1112 (4 studies) 12.5 months	⨁⊖⊖⊖ **VERY LOW**[9,11] due to risk of bias, inconsistency	**RR 1.11** (0.33 to 3.81)	**9 per 1000**	**1 more per 1000** (from 6 fewer to 26 more)
Hypertension Objective	1628 (6 studies) 10 weeks	⨁⨁⊖⊖ **LOW**[12] due to risk of bias	**RR 0.95** (0.7 to 1.29)	**Study population**	
				177 per 1000	**9 fewer per 1000** (from 53 fewer to 51 more)
Vascular access thtombosis Objective	1084 (3 studies) 10 months	⨁⨁⊖⊖ **LOW**[13] due to risk of bias	**RR 1.12** (0.76 to 1.66)	**Study population**	
				75 per 1000	**9 more per 1000** (from 18 fewer to 50 more)
End-stage kidney disease Objective	552 (3 studies) 13 weeks	⨁⨁⊖⊖ **LOW**[14] due to risk of bias	**RR 1.35** (0.82 to 2.23)	**Study population**	
				98 per 1000	**34 more per 1000** (from 18 fewer to 120 more)

Notes

[1] Two study at high risk for attrition bias and one for performance bias. Unclear risk for the other bias for the majority of the studies
[2] High heterogeneity
[3] Three studies at high risk for attrition bias and other bias, two studies at high risk for performance bias and one for reporting bias. Unclear risk for the other bias for the majority of the studies
[4] Overlap in confidence interval
[5] Two studies at high risk of reporting and other risk of bias, one of performance and of attrition bias. Unclear risk for the other bias for both studies
[6] High risk: five studies for other bias, four for reporting, attrition and performance bias. Unclear risk for the other bias for the majority of the studies
[7] Both studies at high risk for performance, attrition and other bias. Unclear risk for the other bias for both studies
[8] High risk: three studies for attrition bias, two for other bias and one each for reporting and performance bias. Unclear risk for the other bias in the majority of the studies
[9] Variabilty in results and variation in size effect
[10] Both studies at high risk of attrition bias and 1 each of performance and other bias. Unclear risk for the other bias for both studies
[11] All studies at high risk of performance bias, two of performance and other bias and one of reporting bias. Unclear risk for the other bias in the majority of the studies
[12] Four studies at high risk for attrition, performance and other bias; two studies at high risk for reporting bias. Unclear risk for the other bias in the majority of the studies
[13] Two studies at high risk for reporting, attrition, performance and other bias. Unclear risk for the other bias in the majority of the studies
[14] Two studies at high risk for attrition and performance bias, one for other bias. Unclear risk for the other bias in the majority of the studies

Results of the comparison Epoetin β versus Methoxy polyethylene glycol-epoetin β

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Epoetin β versus Methoxy polyethylene glycol-epoetin β (95% CI)
Mean Hb level at the end of study Objective	275 (2 studies) 12.5 months	⨁⨁⨁⨀ **MODERATE**[1] due to risk of bias			The mean Hb level at the end of study in the intervention groups was **0.21 higher** (-0.41 lower to 0.82 higher)
Blood transfusion Objective	261 (2 studies) 16.5 months	⨁⨁⨀⨀ **LOW**[2] due to risk of bias	**RR 0.44** (0.13 to 1.52)	**Study population**	
				86 per 1000	**48 fewer per 1000** (from 75 fewer to 45 more)
All-cause mortality Objective	275 (2 studies) 12.5 months	⨁⨁⨁⨀ **MODERATE**[1] due to risk of bias	**RR 0.45** (0.05 to 3.97)	**Study population**	
				16 per 1000	**9 fewer per 1000** (from 16 fewer to 49 more)
Hypertension Objective	261 (2 studies) 16.5 months	⨁⨀⨀⨀ **VERY LOW**[2,3] due to risk of bias, inconsistency	**RR 0.76** (0.2 to 2.95)	**Study population**	
				178 per 1000	**43 fewer per 1000** (from 143 fewer to 347 more)

Notes

[1] One study at high risk for performance, reporting and other bias. Unclear risk for the other bias in both studies
[2] Two studies at high risk for reporting and other bias, one for performance bias. Unclear risk for the other bias in both studies
[3] Variability in results and variation in size effect

Results of the comparison Darbepoetin α versus Methoxy polyethylene glycol-epoetin β

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Darbepoetin α versus Methoxy polyethylene glycol-epoetin β (95% CI)
Blood transfusion Objective	1191 (4 studies) 11 months	⊕⊕⊖⊖ **LOW**[1] due to risk of bias	**RR 0.94** (0.48 to 1.86)	**Study population**	
				89 per 1000	**5 fewer per 1000** (from 46 fewer to 77 more)
All-cause mortality Objective	1429 (4 studies) 12.7 months	⊕⊕⊖⊖ **LOW**[2] due to risk of bias	**RR 0.91** (0.61 to 1.37)	**Study population**	
				65 per 1000	**6 fewer per 1000** (from 25 fewer to 24 more)
Cardiovascular mortality Objective	938 (3 studies) 13 months	⊕⊕⊖⊖ **LOW**[3] due to risk of bias	**RR 0.7** (0.33 to 1.46)	**Study population**	
				37 per 1000	**11 fewer per 1000** (from 24 fewer to 17 more)
Myocardial infarction Objective	739 (3 studies) 12 months	⊕⊖⊖⊖ **VERY LOW**[4,5] due to risk of bias, inconsistency	**RR 0.84** (0.15 to 4.67)	**Study population**	
				8 per 1000	**1 fewer per 1000** (from 7 fewer to 30 more)
Stroke Objective	739 (3 studies) 12 months	⊕⊖⊖⊖ **VERY LOW**[4,5] due to risk of bias, inconsistency	**RR 1.76** (0.36 to 8.65)	**Study population**	
				5 per 1000	**4 more per 1000** (from 3 fewer to 41 more)
Hypertension Objective	1497 (5 studies) 11.4 months	⊕⊕⊖⊖ **LOW**[6] due to risk of bias	**RR 0.95** (0.66 to 1.36)	**Study population**	
				130 per 1000	**6 fewer per 1000** (from 44 fewer to 47 more)

Notes

[1] All studies at high risk for other bias, 3 at high risk for performance bias and 1 for attrition bias. Unclear risk for the other bias in the majority of the studies
[2] All studies at high risk for performance and other bias, 2 at high risk for attrition bias and 1 for reporting bias. Unclear risk for the other bias in the majority of the studies
[3] 3 studies at high risk of performance bias and other bias, 1 at high risk for attrition bias. Unclear risk for the other bias in the majority of the studies
[4] 2 studies at high risk of performance bias and other bias, 1 for attrition bias. Unclear risk for the other bias in the majority of the studies
[5] Variability in results and variation in size effect
[6] All studies at high risk of other bias, 4 at high risk of performance bias, 2 high risk for reporting and attrition bias. Unclear risk for the other bias in the majority of the studies

- **epoetin β versus darbepoetin α,** 1 studio, 217 pazienti

2 outcomes: all-cause mortality and hypertension, results did not shown any statistical difference between the two treatments;

- **epoetin β versus biosimilar epoetin θ**, 1 studio, 290 pazienti

2 outcomes all-cause mortality and cardiovascular mortality, results did not shown any statistical difference between the two treatments;

L’unico risultato statisticamente significativo riguardava il confronto tra epoietina alfa verso darbopoietina alfa per l’esito trasfusioni e dava un risultato in favore della darbopoietina alfa.

Per tutti gli altri esiti e confronti, non si sono riscontrate differenze in termini di efficacia e sicurezza.

Sulla base di questi risultati non si evidenziano differenze tra i farmaci in studio

La qualità delle prove era abbastanza bassa
moderata in 2/31
bassa in 21/31
molto bassa 8/31
per cui ulteriori ricerche potrebbero modificare questi risultati

Ci sarebbe bisogno di studi di migliore qualità