Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis

Sophie Ajandouz, Ben Vandermeer, Paolo Raggi, David C Mendelssohn, Trish Chatterley, Marlene Dorgan, Charmaine E Lok, David Eckett, Rose T Tsuyuki

Summary

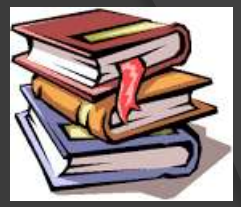
Background Phosphate binders (calcium-based and calcium-free) are recommended to lower serum phosphate and prevent hyperphosphatasemia in patients with chronic kidney disease, but their effects on mortality and cardiovascular outcomes are unknown. We aimed to update our meta-analysis on the effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease.

Methods We did a systematic review of articles published in any language after Aug 1, 2008, up until Oct 22, 2012, by searching Medline, Embase, International Pharmaceutical Abstracts, Cochrane Central Register of Controlled Trials, and Cumulative Index to Nursing and Allied Health Literature. We included all randomised and non-randomised trials that compared outcomes between patients with chronic kidney disease taking calcium-based phosphate binders with those taking non-calcium-based binders. Eligible studies, determined by consensus with predefined criteria, were reviewed, and data were extracted onto a standard form. We combined data from randomised trials to assess the primary outcome of all-cause mortality using the DerSimonian and Laird random effects model.

Findings Our search identified 847 reports, of which eight new studies (five randomised trials) met our inclusion criteria and were added to the ten (nine randomised trials) included in our previous meta-analysis. Analysis of the 11 randomised trials (4622 patients) that reported an outcome of mortality showed that patients assigned to non-calcium-based binders had a 22% reduction in all-cause mortality compared with those assigned to calcium-based phosphate binders (risk ratio 0·78, 95% CI 0·63–0·98).

Interpretation Non-calcium-based phosphate binders are associated with a decreased risk of all-cause mortality compared with calcium-based phosphate binders in patients with chronic kidney disease. Further studies are needed to identify causes of mortality and to assess whether mortality differs by type of non-calcium-based phosphate binder.

Funding None.



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<u>Interpretación</u>: Los quelantes No Cálcicos están asociados a una reducción del 22% en todas las causas de mortalidad entre de muerte en comparación a los quelantes cálcicos. Los quelantes no cálcicos usados fueron Carbonato de Lantano y Carbonato de Sevelamer.

Meta análisis sobre estudios publicados Sophie Jamal Lancet 2013

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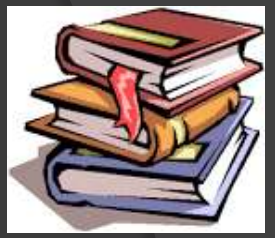


<u>Características :</u> Metanalisis con 847 reportes (4622 pacientes y se incluyeron estudios randomizados y no randomizados entre Agosto 2008 y octubre 2012.
Con selección de criterio a través del Sistema PRISMA guidlines .
Con palabras claves como Ca , Quelantes del Fosforo Diálisis, mortalidad

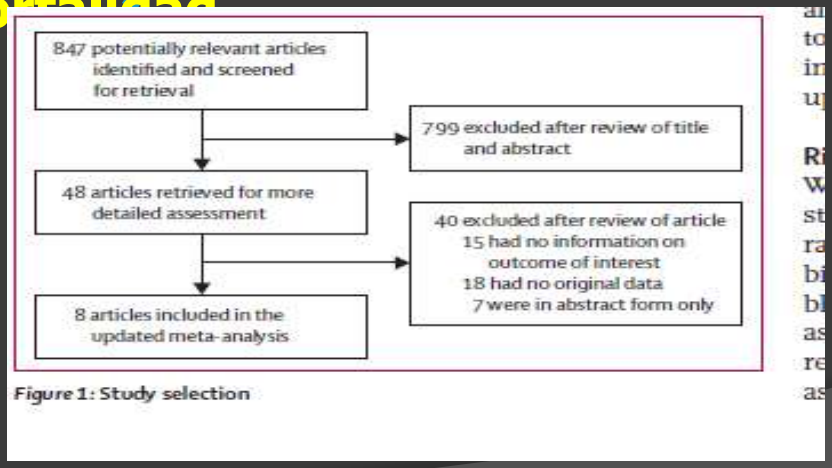
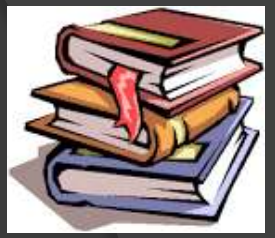


Figure 1: Study selection

Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis



En este estudio se evalúa que existe una clara relación entre Ca P producto y mortalidad cardiovascular.

La llave es un buen manejo de P a través de la quelación y la dieta .

Se determina también que en pacientes con IRC hay mayor incidencia de mortalidad..

La reducción de la mortalidad es menor con el uso de quelantes sin Ca y que hay evidencias de mayor calcificación en los grupos con quelación Cálcica.

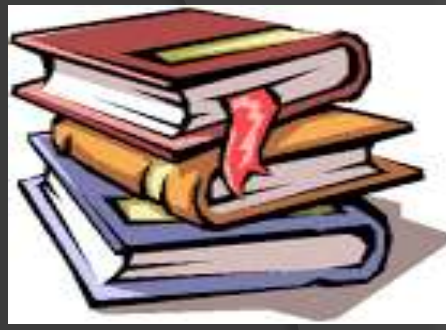
Características de estudios incluidos en el meta -análisis .

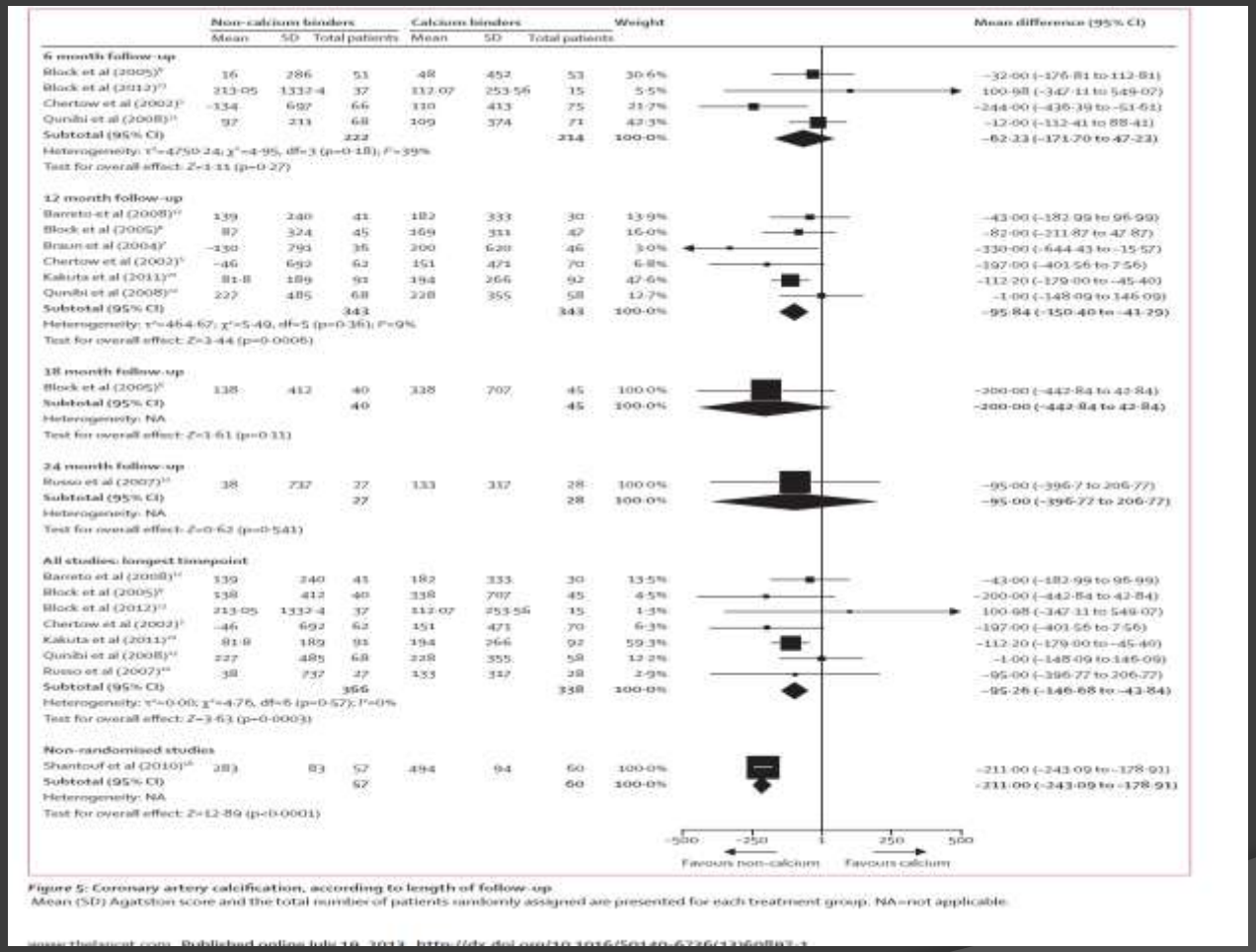
	Design	Dialysis status of patients	Mean age (years)	Sex (% female)	Diabetes (%)	Mean dialysis duration (months)	Non-calcium-based phosphate binder (n)	Calcium-based phosphate binder (n)	Follow-up (months)	Risk of bias score
Original studies										
Chertow et al (2002)[5]	RCT	Haemodialysis	57	35%	32·5%	39·0	Sevelamer (99)	Calcium acetate or calcium carbonate (101)	12	Unclear
Sadek et al (2003)[6]	RCT	Haemodialysis	..	..	..	..	Sevelamer (15)	Calcium carbonate (16)	5	Unclear
Braun et al (2004)[7]	RCT	Haemodialysis	56·5	37·5%	18·8%	63·4	Sevelamer (56)	Calcium carbonate (57)	12	High
Block et al (2005[8] and 2007[9])	RCT	Haemodialysis	58	37%	60·6%	2·9	Sevelamer (54)	Calcium acetate or calcium carbonate (55)	18, 44*	Low
Russo et al (2007)[10]	RCT	Non-dialysis	55	17%	..	..	Sevelamer (27)	Calcium carbonate (28)	24	High
Borzecki et al (2007)[11]	RCS	Haemodialysis	61·5	2·5%	48·6%	..	Sevelamer (608)	Calcium acetate or calcium carbonate (769)	24	NA
Barreto et al (2008)[12]	RCT	Haemodialysis	47	32%	14·1%	..	Sevelamer (52)	Calcium acetate (49)	12	Low
Qunibi et al (2008)[13]	RCT	Haemodialysis	59	49%	57·1%	22·2	Sevelamer (100)	Calcium acetate (103)	12	Low
Suki (2008)[14]	RCT	Haemodialysis	60	46%	50·2%	38·2	Sevelamer (1053)	Calcium acetate or calcium carbonate (1050)	20	High
Takei et al (2008)[15]	RCT	Haemodialysis	54	52%	35·7%	..	Sevelamer (22)	Calcium carbonate (20)	24	High
New studies										
Wilson et al (2009)[16]	RCT	Haemodialysis	54·3	0·7%	34·5%	40·2	Lanthanum (680)	Calcium acetate or calcium carbonate (674)	24	High
Panichi et al (2010)[17]	OS	Haemodialysis	66	36%	22·6%	..	Sevelamer (242)	Calcium acetate or calcium carbonate (310)	24	NA
Shantouf et al (2010)[18]	CS	Haemodialysis	54·6	33·3%	45·8%	..	Sevelamer (57)	Calcium carbonate or Calcium acetate (60)	NA	NA
Jean et al (2011)[19]	OS	Haemodialysis	68·0	43%	33·6%	62·6	Sevelamer (247)	Calcium carbonate (432)	42	NA
Kakuta et al (2011)[20]	RCT	Haemodialysis	58·0	46%	20·8%	118	Sevelamer (91)	Calcium carbonate (92)	12	Unclear
Toussaint et al (2011)[21]	RCT	Haemodialysis	57·4	35·6%	37·8%	..	Lanthanum (22)	Calcium carbonate (23)	18	High
Di Iorio et al (2012)[22]	RCT	Non-dialysis	57·9	39%	28%	..	Sevelamer (107)	Calcium carbonate (105)	36	Low
Block et al (2012)[23]	RCT	Non-dialysis	66·8	50·3%	57%	..	Lanthanum (28); sevelamer (30)	Calcium acetate (30)	9	Low

Our primary analyses included only RCTs. RCT=randomised controlled trial. RCS=retrospective cohort study. NA=not applicable. OS=observational study. CS=cross-sectional study. ..=data not reported.
*18 month follow-up in the original study; 44 months median follow-up in the long-term outcome study.

Table: Characteristics of studies included in the meta-analysis

Calcificación arterias coronarias Agatston score





	Non-calcium binders			Calcium binders			Weight	Mean difference (95% CI)
	Mean	SD	Total patients	Mean	SD	Total patients		
6 month follow-up								
Block et al (2005)[9]	16	286	51	48	452	53	30·6%	−32·00 (−176·81 to 112·81)
Block et al (2012)[23]	213·05	1332·4	37	112·07	253·56	15	5·5%	100·98 (−347·11 to 549·07)
Chertow et al (2002)[5]	−134	697	66	110	413	75	31·7%	−244·00 (−436·39 to −51·61)
Qunibi et al (2008)[11]	97	211	68	109	374	71	32·3%	−12·00 (−112·41 to 88·41)
Subtotal (95% CI)			222			214	100·0%	−62·23 (−171·70 to 47·23)
Heterogeneity: τ^2=4750·24; χ^2=4·95, df=3 (p=0·18); I^2=39%								
Test for overall effect: Z=1·11 (p=0·27)								
12 month follow-up								
Barreto et al (2008)[22]	139	240	41	182	333	30	13·9%	−43·00 (−182·99 to 96·99)
Block et al (2005)[9]	82	324	45	369	311	47	16·0%	−82·00 (−211·87 to 47·87)
Braun et al (2004)[7]	−130	793	36	200	620	46	10%	−330·00 (−644·43 to −15·57)
Chertow et al (2002)[5]	−46	692	62	151	471	70	6·8%	−197·00 (−401·56 to 7·56)
Kakuta et al (2011)[24]	81·8	189	91	194	266	92	47·6%	−112·20 (−179·00 to −45·40)
Qunibi et al (2008)[11]	227	485	68	228	355	58	12·7%	−1·00 (−148·09 to 146·09)
Subtotal (95% CI)			343			343	100·0%	−95·84 (−150·40 to −41·29)
Heterogeneity: τ^2=464·67; χ^2=5·49, df=5 (p=0·36); I^2=9%								
Test for overall effect: Z=3·44 (p=0·0006)								
18 month follow-up								
Block et al (2005)[9]	138	412	40	338	707	45	100·0%	−200·00 (−442·84 to 42·84)
Subtotal (95% CI)			40			45	100·0%	−200·00 (−442·84 to 42·84)
Heterogeneity: NA								
Test for overall effect: Z=1·61 (p=0·11)								
24 month follow-up								
Russo et al (2007)[10]	38	737	27	133	317	28	100·0%	−95·00 (−396·77 to 206·77)
Subtotal (95% CI)			27			28	100·0%	−95·00 (−396·77 to 206·77)
Heterogeneity: NA								
Test for overall effect: Z=0·62 (p=0·541)								
All studies: longest timepoint								
Barreto et al (2008)[22]	139	240	41	182	333	30	13·5%	−43·00 (−182·99 to 96·99)
Block et al (2005)[9]	138	412	40	338	707	45	4·5%	−200·00 (−442·84 to 42·84)
Block et al (2012)[23]	213·05	1332·4	37	112·07	253·56	15	1·3%	100·98 (−347·11 to 549·07)
Chertow et al (2002)[5]	−46	692	62	151	471	70	6·3%	−197·00 (−401·56 to 7·56)
Kakuta et al (2011)[24]	81·8	189	91	194	266	92	59·3%	−112·20 (−179·00 to −45·40)
Qunibi et al (2008)[11]	227	485	68	228	355	58	12·2%	−1·00 (−148·09 to 146·09)
Russo et al (2007)[10]	38	737	27	133	317	28	2·9%	−95·00 (−396·77 to 206·77)
Subtotal (95% CI)			366			338	100·0%	−95·26 (−146·68 to −43·84)
Heterogeneity: τ^2=0·00; χ^2=4·76, df=6 (p=0·57); I^2=0%								
Test for overall effect: Z=3·63 (p=0·0003)								
Non-randomised studies								
Shantouf et al (2010)[16]	283	83	57	494	94	60	100·0%	−211·00 (−243·09 to −178·91)
Subtotal (95% CI)			57			60	100·0%	−211·00 (−243·09 to −178·91)
Heterogeneity: NA								
Test for overall effect: Z=12·89 (p<0·0001)								

Figure 5: Coronary artery calcification, according to length of follow-up
Mean (SD) Agatston score and the total number of patients randomly assigned are presented for each treatment group. NA=not applicable.

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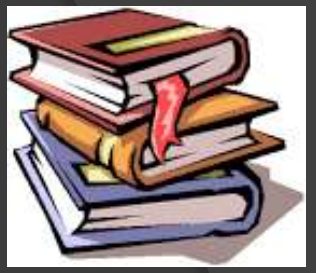
Estatus del paciente con ERC



	Non-calcium binders		Calcium binders		Weight	Risk ratio (95% CI)
	Events	Total patients	Events	Total patients		
Dialysis						
Barreto et al (2008)[12]	1	52	8	49	0·3%	0·12 (0·02–0·91)
Block et al (2007)[9]	11	60	23	67	3·2%	0·53 (0·28–1·00)
Borzecki et al (2007)[11]	148	608	228	769	20·6%	0·82 (0·69–0·98)
Chertow et al (2002)[5]	6	99	5	101	1·0%	1·22 (0·39–3·88)
Jean et al (2011)[19]	62	247	109	432	12·7%	0·99 (0·76–1·30)
Kakuta et al (2011)[20]	0	91	0	92		Not estimable
Panichi et al (2010)[17]	74	242	170	515	15·9%	0·93 (0·74–1·16)
Qunibi et al (2008)[13]	3	100	7	103	0·8%	0·44 (0·12–1·66)
Sadek et al (2003)[6]	1	21	3	21	0·3%	0·33 (0·04–2·95)
Suki (2008)[14]	267	1053	275	1050	24·5%	0·97 (0·84–1·12)
Takei et al (2008)[15]	0	22	0	20		Not estimable
Wilson et al (2009)[16]	135	680	157	674	17·9%	0·85 (0·70–1·05)
Subtotal (95% CI)	**708**	**3275**	**985**	**3893**	**97·0%**	**0·88 (0·79–0·99)**
Heterogeneity: τ^2=0·01; χ^2=11·52, df=9 (p=0·24); I^2=22%						
Test for overall effect: Z=2·23 (p=0·03)						
Predialysis						
Di Iorio et al (2012)[12]	12	107	22	105	3·0%	0·54 (0·28–1·03)
Russo et al (2007)[10]	0	27	0	28		Not estimable
Subtotal	**12**	**134**	**22**	**133**	**3·0%**	**0·54 (0·28–1·03)**
Heterogeneity: NA						
Test for overall effect: Z=1·89 (p=0·06)						
Total	**720**	**3409**	**1007**	**4026**	**100·0%**	**0·87 (0·77–0·97)**
Heterogeneity: τ^2=0·01; χ^2=13·88, df=10 (p=0·18); I^2=28%						
Test for overall effect: Z=2·40 (p=0·02)						
Test for subgroup differences χ^2=2·22, df=1 (p=0·14), I^2=55·0%						

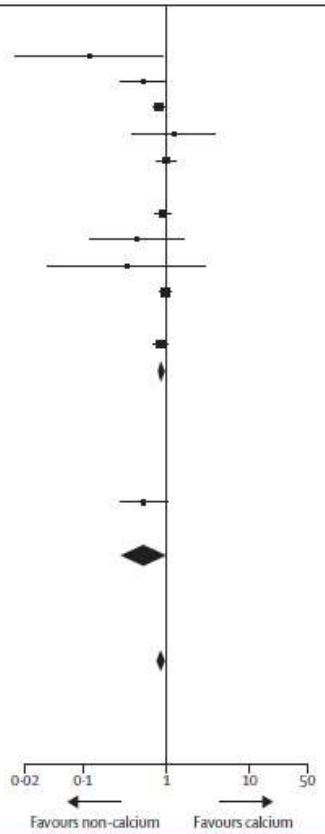
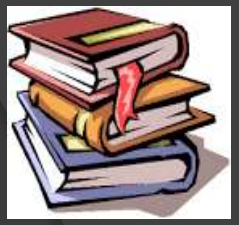


Figure 4: **All-cause mortality for each type of phosphate binder, according to dialysis status**
All-cause mortality by dialysis status, considering all trials that reported an outcome of mortality. Number of all mortality events and the total number of patients randomly assigned are presented for each treatment group.

Discusión:



El Meta –análisis incluyo 4622 pacientes y mostro una reducción del 22% en todas las causas de muerte en pacientes que recibieron Quelación con quelantes no cálcicos (Sevelamer- Lantano) en comparación a los que recibieron Quelación con calcio base.

13% en la reducción delos grupos randomizados y no randomizados

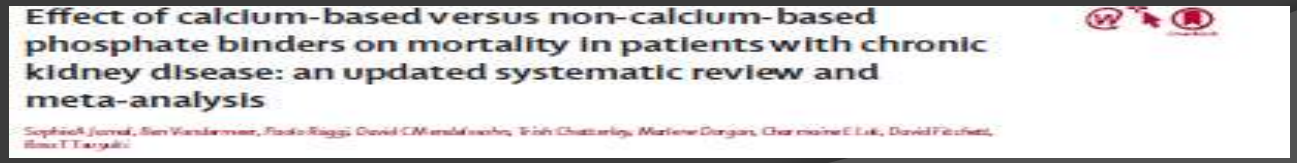
Se consideraron por separados pacientes en predialsis y en diálisis.

Parte del potencial descenso de mortalidad seria un enlentecimiento de la calcificación vascular secundaria a la quelación del P .

Se evaluó un incremento en calcificación coronaria en pacientes que recibían Quelación con Calcio.(En 7 estudios randomizados de los cuales 5 fueron incluidos en el meta- análisis)

No se encontró diferencias en descenso de mortalidad entre el mismo grupo de Quelación no cálcica.(Lantano vs Sevelamer)

Hay mayor calcificación en los grupos que recibía Quelación con Ca independientemente si era carbonato o acetato.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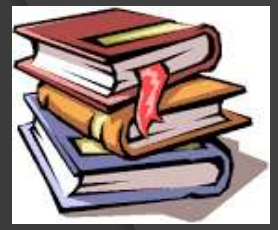
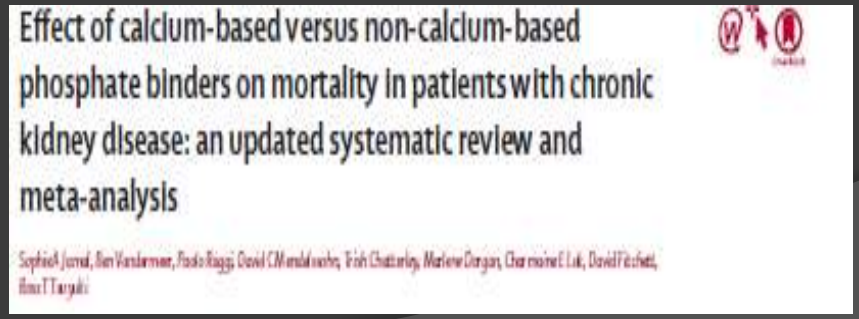
Limitaciones en el Meta -análisis



Primero la ausencia de nuevos estudios evaluando mortalidad cardiovascular y el tipo de quelante.

Asumen equivalencias entre la Quelación de Carbonato de Ca y Acetato de Ca en riesgo de Calcificación.

La heterogeneidad de grupo en control que incluye tiempos , etc.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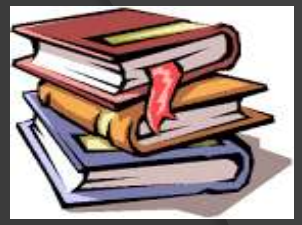
Se concluye

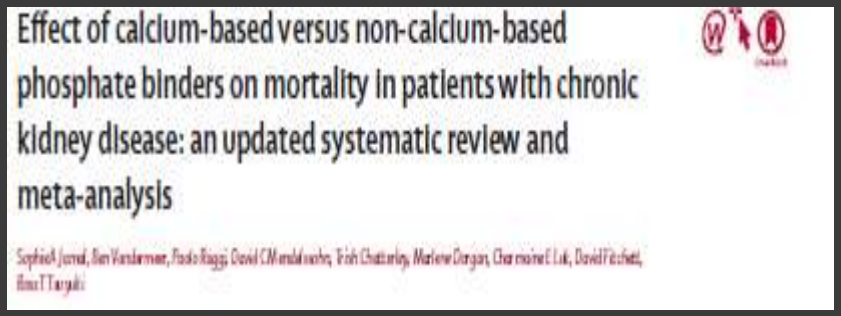


Pacientes con ERC tienen alto riesgo de mortalidad.

La hiperfosfatemia debe ser quelada por quelantes no cálcicos y cálcicos.

Estos últimos son mas económicos .

El beneficio de los no cálcicos es el enlentecimiento de la calcificación vascular.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