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[Intervention Review]

Antiplatelet agents for chronic kidney disease

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ABSTRACT

There is no abstract. The objectives are as follows:

To evaluate the benefits and harms of antiplatelet therapy in patients with any form of kidney disease, including patients with CKD not receiving renal replacement therapy (RRT), patients receiving any form of dialysis, and kidney transplant recipients.

PLAIN LANGUAGE SUMMARY

[Plain language title]

[Summary text]

BACKGROUND

Description of the condition

Cardiovascular disease is the leading cause of morbidity and mortality in all stages of chronic kidney disease (CKD) (Casas 2005; Keith 2004; Mann 2001; Norris 2006; Sarnak 2003; Weiner 2004a; Weiner 2004b) including the CKD of renal transplant recipients (US Renal Data system. 2008, Australia and New Zealand Dialysis and Transplant registry (ANZDATA), (Aakhus 1999; Kasiske 2000; Ojo 2000). Compared with the general population, the risk of cardiovascular disease is increased two-fold in early CKD (Go 2004) and 10 to 20-fold in dialysis patients (Fort 2005) in whom it accounts for 50% of all deaths (Collins 2003). Population representative surveys in Australia (AusDiab Survey 2003) and United States (NHANES 2010) have shown a CKD prevalence of approximately 16% in the adult population. With the increasing prevalence of some of the known risk factors for CKD including hypertension, obesity and diabetes (Fields 2004; Koren-Morag 2006; Mokdad 2003), the burden of CKD and its complications are projected to increase and to significantly contribute to global health care expenditure.

How the intervention might work

Platelets play a pivotal role in thrombosis and various available antiplatelet agents block platelet activation and aggregation at various points in the thrombotic cascade. Currently available data suggests that antiplatelet agents might be beneficial in patients with CKD for primary (ATT 2002; Ruilope 2001) and secondary (Berger 2003; McCullough 2002) prevention of cardiovascular events. Antiplatelet agents might have beneficial effects on the kidney, possibly reducing proteinuria and protecting renal function in patients with glomerulonephritis (Taji 2006; Zauner 1994), and improving graft function in people with kidney transplants (Bonomini 1986; Frasca 1986). However some have reported that the efficacy of antiplatelet therapy in CKD might be lower than for other high cardiovascular risk populations (Best 2008). Despite this, the Kidney Disease Outcomes Quality Initiative guideline program (KDOQI) has supported the use of aspirin for primary prevention of cardiovascular disease in CKD. Antiplatelet agents appear to have a modest effect on the preservation of arteriovenous fistula patency (Dember 2008). Their use for fistula preservation and as part of a multi-factorial intervention strategy for patients with CKD is advocated by guideline groups (British Renal Association, Caring for Australians with Renal Impairment (CARI) group and Canadian Society of Nephrology).

Why it is important to do this review

To date, there has been no formal meta-analysis of the benefits and harms of antiplatelet agents in patients with CKD. In contrast to the general population, patients with CKD have a combination of traditional and non traditional cardiovascular risk factors (Foley 1998; Foley 2003; Roberts 2006; Shah 2008). In addition, people with CKD might have different mechanisms for cardiovascular disease, including arrhythmia and congestive heart failure (Amann 2003; Curtis 2005; Dikow 2005; Foley 1995; Remppis 2008), altered pharmacokinetics (Mosenkis 2004; Scheen 2008) and impaired haemostasis (Kaw 2006; Remuzzi 1988; Wattanakit 2008; Zwaginga 1991). Compared to patients without CKD, these factors might expose them to a different spectrum of risk and benefit from antiplatelet therapy.

This systematic review aims to assess the relative benefits and harms of any antiplatelet agents for the prevention of cardiovascular disease and kidney disease progression in patients with CKD.

OBJECTIVES

To evaluate the benefits and harms of antiplatelet therapy in patients with any form of kidney disease, including patients with CKD not receiving renal replacement therapy (RRT), patients receiving any form of dialysis, and kidney transplant recipients.

METHODS

Criteria for considering studies for this review

Types of studies

We will consider for inclusion all RCTs of any antiplatelet agent in patients with CKD where the duration of follow-up was two months or longer. We define patients with CKD as those who are receiving any form of RRT, have a functioning kidney transplant, or have impaired kidney function defined as a reduced glomerular filtration rate (GFR < 60 mL/min/1.73 m^2), the presence of other markers of kidney damage such as proteinuria (KDOQI stages 1-5), an elevated serum creatinine (SCr > 120 mmol/L) or as defined by study authors. Data from CKD subgroups within studies with broader inclusion criteria (e.g. people from the general population, people with diabetes, people with cardiovascular disease), which report outcomes for participants with CKD, will also be considered for inclusion.

Types of participants

All adults (>18 years of age) with CKD as defined above. Separate analyses will be undertaken for:

- Kidney transplant recipients
- Individuals undergoing any form of maintenance dialysis therapy
- People with CKD stage 1-4 and CKD stage 5 who are not receiving RRT, as defined by KDOQI guidelines or as defined by author

Types of interventions

We will include studies of any antiplatelet agent. Agents can be administered at any dose or route of administration, and be compared with placebo, no treatment, different dose of the same or different antiplatelet agents, different administration regimens of the same or different agent, or different combinations of antiplatelet agents. Antiplatelet agents will include (but not limited to): acetylsalicylic acid (aspirin), adenosine reuptake inhibitors (dipyridamole), adenosine diphosphate receptor inhibitors (ticlopidine and clopidogrel), phosphodiesterase 3 inhibitors (cilostazol), $P2Y_{12}$ antagonists (prasugrel, ticagrelor, cangrelor, elinogrel), glycoprotein IIB/IIIA inhibitors (abciximab, eptifibatide, tirofiban, defibrotide), sulfinpyrazone, or preparations in which one or more antiplatelet agents are combined with other drugs.

Studies in which participants receive co-interventions other than antiplatelet agents will also be included.

We will exclude studies in which duration of follow-up was fewer than two months.

Types of outcome measures

- Cardiovascular events
  - Composite endpoints of major adverse cardiovascular events (myocardial infarction, stroke)
  - Myocardial infarction (fatal or non-fatal)
  - Ischaemic stroke (fatal or non-fatal)
- Death
  - All-cause mortality
  - Cardiovascular including sudden death
  - Bleeding related
- Kidney outcomes
  - Incidence of end-stage kidney disease requiring RRT
  - Doubling of SCr or other threshold of renal dysfunction as defined by authors
  - End of treatment SCr (mg/dL or mmol/L)
  - Change in SCr from beginning to end of treatment
  - End of treatment GFR (mL/min or mL/min/1.73 m^2) assessed by any measure or change from beginning to end of treatment
  - New onset albuminuria (urinary albumin to creatinine ratio (ACR): > 3.5 mg/mmol (women) or > 2.5 mg/mmol (men))
  - Regression of microalbuminuria to normoalbuminuria (< 3.5 mg/mmol (women) or < 2.5 mg/mmol (men)); or macroalbuminuria (urinary ACR > 35 mg/mmol (women), > 25 mg/mmol (men)) to microalbuminuria or normoalbuminuria or as defined by authors
  - Change in albuminuria from beginning to end of treatment
  - End of treatment albuminuria (mg/mmol or µg/min)
  - Change in albuminuria from beginning to end of treatment
  - End of treatment 24 hour urine protein excretion (g/24 h) or change from beginning to end of treatment
- Antiplatelet agents' specific toxicity
  - Fatal bleeding events
  - Major bleeding events (defined as haemorrhage or any bleeding episode that necessitates hospitalisation, transfusion, or as defined by study authors)
  - Minor bleeding events
  - Any bleeding event (major or minor)
  - Gastro-intestinal disturbances (abdominal pain or peptic ulcer disease, or as defined by the authors)
- All-cause hospitalisation
- Treatment crossover or withdrawal
- Any other adverse event as reported by triallists
- Interruption of treatment (treatment withdrawals) for any reason

Search methods for identification of studies

Electronic searches

We will conduct electronic searches of the following databases:

1. The Cochrane Renal Group's specialised register and the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane library (most recent) will be searched. These registers contain the hand searched results of conference proceedings from general and speciality meetings. This is an ongoing activity across the Cochrane Collaboration and is both retrospective and prospective. Therefore we will not specifically search conference proceedings. Please refer to The Cochrane Renal Group's Module in *The Cochrane Library* for the most up-to-date list of conference proceedings (Renal Group 2010).
2. MEDLINE (from 1966) using the optimally sensitive strategy developed by the Cochrane Collaboration for the identification of RCTs (Lefebvre 2008) with a search strategy developed with input from the Cochrane Renal Group's Trial Search Co-ordinator.
3. EMBASE (from 1980) using the optimally sensitive strategy developed by the Cochrane Collaboration for the identification of RCTs (Lefebvre 2008) with a search strategy developed with input from the Cochrane Renal Group's Trial Search Co-ordinator.

See Appendix 1 for search terms used.

Additionally, we will search the US registry of federally and privately supported clinical studies at http://www.clinicaltrials.gov/ for ongoing or unpublished RCTs that meet our inclusion criteria.

Searching other resources

Also handsearching will be performed, i.e. checking the reference lists of retrieved studies and systematic reviews to identify other relevant studies. Resulting references will be double-checked and matched with the results of the systematic literature search. Corresponding authors of all large studies with broader inclusion will also be contacted to obtain data for the CKD population if available.

Data collection and analysis

Selection of studies

All RCTs enrolling patients with CKD as defines above, including patients on RRT and recipients of a kidney transplant will be considered. RCT including participants without CKD will be excluded unless specific subpopulation data for those with CKD are available.

Based on the search strategy described, we will identify titles and abstracts that may be relevant to this systematic review. Two independent authors will then screen the titles and abstracts and select the ones that meet the inclusion criteria. Discrepancies in selection will be resolved by discussion or by the review of an experienced arbitrator.

Studies reported in non-English language journals will be translated before assessment and the process will be defined in the review.

Data extraction and management

Two authors will independently read the full text of extracted articles, assess their methodological quality and include studies that meet the inclusion criteria. Where more than one publication of one study exists, reports will be grouped together and only the publication with the most complete data will be used in the analyses. Where relevant outcomes are only published in earlier versions this data will be used. Any discrepancy between published versions will be highlighted.

Two independent authors will use standardised data forms to extract data on:

- Study design
- Participants: patients baseline characteristics including age, gender, race, diabetic status (% with diabetes and type of diabetes), hypertension status (% with hypertension), smoking status (% smokers), visceral obesity (% with visceral obesity as defined by authors), previous cardiovascular events (% with) and history of cardiovascular diseases (% with), stage of CKD
- Interventions and comparisons: different antiplatelet agents and different doses and route of administration used
- Outcomes: all-cause mortality, cardiovascular events and mortality, renal outcomes and toxicity

Assessment of risk of bias in included studies

The quality of included studies will be formally assessed by looking at standard quality domains using the risk of bias assessment tool (Higgins 2008).

- Was there adequate sequence generation?
- Was allocation adequately concealed?
- Was knowledge of the allocated interventions adequately prevented during the study?
- Were incomplete outcome data adequately addressed?
- Are reports of the study free of suggestion of selective outcome reporting?
- Was the study apparently free of other problems that could put it at a risk of bias?

We will make explicit judgements (Appendix 2) regarding whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). With reference to the six points as described above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias by undertaking sensitivity analyses.

Measures of treatment effect

For dichotomous outcomes, e.g. death, cardiovascular events etc. results will be expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement are used to assess the effects of treatment (e.g. creatinine clearance (CrCl), GFR, SCr, proteinuria), the mean difference (MD) and its 95% CI will be used, or the standardised mean difference (SMD) and its 95% CI if different scales have been used.

Unit of analysis issues

Data in different metrics will be analysed by converting reported values to SI units. The final results will be presented in International System (SI) units with conventional units in parentheses.

Dealing with missing data

If possible, data for each outcome of interest will be evaluated, regardless of whether the analysis is based on intention-to-treat (ITT) or how complete the data are. In particular, drop-out rates will be investigated and reported in detail such as drop-out due to discontinuation of study drug, treatment failure, death, withdrawal of consent or loss to follow-up. Missing data will be imputed when possible and details will be reported.

Assessment of heterogeneity

We will test for heterogeneity with Cochran's Q, which follows a Chi^2 distribution with n-1 degrees of freedom, and an alpha of < 0.10 used for statistical significance. The extent of heterogeneity will be assessed with I^2, which ranges between 0% and 100% and expresses the proportion of between group variability that is attributable to heterogeneity rather than chance (Higgins 2003). I^2 values above 75% are typically held to signify extreme heterogeneity, whereas 25% and 50% correspond to low and medium levels of heterogeneity, respectively. However, considerable clinical heterogeneity is expected, therefore random effects models will be used for analysing the data.

Assessment of reporting biases

We will test for asymmetries in the inverted funnel plots (i.e. for systematic differences in the effect sizes between more precise and less precise studies) using the original (Egger 1997) and modified Egger tests (Harbord 2006) and the Begg and Mazumdar correlation test (Begg 1994). There are many potential explanations for why an inverted funnel plot may be asymmetric, including chance, heterogeneity, publication and reporting bias (Terrin 2005). We will refrain from judging funnel plot asymmetries based on visual inspection as this has been shown to be misleading in empirical research (Lau 2006). Publication bias will also be evaluated by testing the robustness of the results according to publication, namely, publication as full manuscript in a peer reviewed journal versus studies published as abstracts/text/letters/editorials and publication.

Data synthesis

Data will be pooled using the random effects model. The fixed effects model will also be analysed to ensure robustness of the model chosen and susceptibility to outliers. Methodological quality of the selected studies will be reviewed by two independent authors using the Cochrane Renal Group checklist.

The GRADE approach developed by Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE Working Group) will be used for evaluating the quality of evidence for outcomes to be reported. Based on the GRADE approach, the quality of a body of evidence, in terms of the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest, will be defined. Quality of a body of evidence involves consideration of within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Table 1). Four levels of quality (Table 2) will be assigned to the evidence.

Subgroup analysis and investigation of heterogeneity

Heterogeneity will be investigated by analysing the data using subgroups according to the following parameters:

- Population characteristics
  - Stage of CKD (pre-dialysis/conservative treatment, dialysis, transplant, and KDOQI stages 1-5)
  - Presence or absence of co-morbidities (diabetes, hypertension, dyslipidaemia, smoking, obesity, family history of cardiovascular disease, baseline cardiovascular

disease); percentage of patients with these co-morbidities in each study
    * Age
    * Gender
    * Mean systolic blood pressure (below 140 mm Hg versus 140 mm Hg or above)
    * Ethnicity (White, Afro-American, Asian, other)
    * Presence or absence of previous cardiovascular events (e.g. primary versus secondary prevention)
    * Time on dialysis (fewer than three years versus three years or more) and modalities of dialysis (haemodialysis versus peritoneal dialysis)
    * Time with a functioning transplant (fewer than three years versus three years or more)
- Intervention characteristics
    * Types, doses and route of administration of the antiplatelet agents
    * Duration of intervention (less than 6 months, 6 to 12 months, greater than 12 months)

If sufficient studies are available, we will conduct sensitivity analysis based on allocation concealment, blinding of participants, investigators and outcome assessors, attrition (above or below 10%), ITT analysis, and premature discontinuation of the study.

We will perform univariate meta-regression according to previously described methods if sufficient studies are identified (Palmer 2007).

Sensitivity analysis

Sensitivity analyses will be undertaken to explore the robustness of findings to key decisions in the review process. These will be determined as the review process takes place (Higgins 2008). Where direct comparisons studies between anti-platelet agents are not available, we will attempt to perform indirect comparisons of anti-platelet agent versus anti-platelet agent if sufficient data are available (Song 2003). Sensitivity analysis will be undertaken to explore the influence of the study methods quality on the results.

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ADDITIONAL TABLES

Table 1. Levels of quality of the body of evidence using the GRADE approach

Underlying methodology	Quality rating
RCTs; or double-upgraded observational studies.	High
Downgraded RCTs; or upgraded observational studies.	Moderate
Double-downgraded RCTs; or observational studies.	Low
Triple-downgraded RCTs; or downgraded observational studies; or case series/case	Very low

Table 2. Factors that may decrease the quality level of a body of evidence

1. Limitations in the design and implementation of available studies suggesting high likelihood of bias.
2. Indirectness of evidence (indirect population, intervention, control, outcomes).
3. Unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses).
4. Imprecision of results (wide confidence intervals).
5. High probability of publication bias.

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor Phosphodiesterase Inhibitors explode all trees 2. MeSH descriptor Adenosine Diphosphate, this term only with qualifier: AI 3. MeSH descriptor Platelet Glycoprotein GPIIb-IIIa Complex, this term only with qualifier: AI 4. ((antiplatelet next agent*) or (anti-platelet next agent*)):ti,ab,kw 5. ((antiplatelet therap*) or (anti-platelet therap*)):ti,ab,kw 6. (platelet next aggregation next inhibit*):ti,ab,kw 7. (phosphodiesterase next inhibit*):ti,ab,kw 8. (thrombocyte next aggregation next inhibit*):ti,ab,kw 9. ((antithrombocytic next agent*) or (anti-thrombocytic next agent*)):ti,ab,kw 10.((antithrombocytic next therap*) or (anti-thrombocytic next therap*)):ti,ab,kw 11.alprostadil:ti,ab,kw 12.aspirin:ti,ab,kw 13.acetylsalicylic acid:ti,ab,kw 14.((adenosine next reuptake inhibit*) or (adenosine re-uptake inhibit*)):ti,ab,kw 15.(adenosine next diphosphate next receptor next inhibit*):ti,ab,kw 16.dipyridamole:ti,ab,kw 17.disintegrins:ti,ab,kw 18.epoprostenol:ti,ab,kw 19.iloprost:ti,ab,kw 20.ketanserin:ti,ab,kw 21.milrinone:ti,ab,kw 22.pentoxifylline:ti,ab,kw 23.(S-nitrosoglutathione):ti,ab,kw 24.S-nitrosothiols:ti,ab,kw 25.trapidil:ti,ab,kw 26.ticlopidine:ti,ab,kw 27.clopidogrel:ti,ab,kw 28.(sulfinpyrazone or sulphinpyrazone):ti,ab,kw 29.cilostazol:ti,ab,kw 30.(P2Y12 NEAR/2 antagonis*):ti,ab,kw

(Continued)

	31.prasugrel:ti,ab,kw 32.ticagrelor:ti,ab,kw 33.cangrelor:ti,ab,kw 34.elinogrel:ti,ab,kw 35."glycoprotein IIB/IIIA inhibitors":ti,ab,kw 36.abciximab:ti,ab,kw 37.eptifibatide:ti,ab,kw 38.tirofiban:ti,ab,kw 39.defibrotide:ti,ab,kw 40.picotamide:ti,ab,kw 41.beraprost:ti,ab,kw 42.ticlid:ti,ab,kw 43.aggrenox:ti,ab,kw 44.ditazole:ti,ab,kw 45.(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44) 46.dialysis:ti,ab,kw 47.(hemodialysis or haemodialysis):ti,ab,kw 48.(hemofiltration or haemofiltration):ti,ab,kw 49.(hemodiafiltration or haemodiafiltration):ti,ab,kw 50.(PD or CAPD or CCPD or APD):ti,ab,kw 51.(renal next insufficiency):ti,ab,kw 52.(kidney next failure):ti,ab,kw 53.(kidney next disease*):ti,ab,kw 54.ur*emi*:ti,ab,kw 55.((chronic next kidney) or (chronic next renal)):ti,ab,kw 56.(CKF or CKD or CRF or CRD):ti,ab,kw 57.predialysis:ti,ab,kw 58.((end-stage next renal) or (end-stage next kidney) or (endstage next renal) or (endstage next kidney)):ti,ab,kw 59.(ESKD or ESRD or ESKF or ESRF):ti,ab,kw 60.((kidney next transplant*) or (renal next transplant*) or (kidney next *graft*) or (renal next *graft*)):ti,ab,tw 61.(#46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60) 62.(#45 AND #61)
MEDLINE	1. exp Platelet Aggregation Inhibitors/ 2. exp Phosphodiesterase Inhibitors/ 3. Adenosine Diphosphate/ai [Antagonists & Inhibitors] 4. Platelet Glycoprotein GPIIb-IIIa Complex/ai [Antagonists & Inhibitors] 5. Sulfinpyrazone/ 6. (antiplatelet agents$ or anti-platelet agent$).tw. 7. (antiplatelet therap$ or anti-platelet therap$).tw. 8. platelet aggregation inhibit$.tw. 9. phosphodiesterase inhibit$.tw. 10.thrombocyte aggregation inhibit$.tw. 11.(antithrombocytic agent$ or anti-thrombocytic agent$).tw. 12.(antithrombocytic therap$ or anti-thrombocytic therap$).tw. 13.alprostadil.tw.

(Continued)

14.aspirin.tw.
15.acetylsalicylic acid.tw.
16.(adenosine reuptake inhibit$ or adenosine re-uptake inhibit$).tw.
17.adenosine diphosphate receptor inhibit$.tw.
18.dipyridamole.tw.
19.disintegrins.tw.
20.epoprostenol.tw.
21.iloprost.tw.
22.ketanserin.tw.
23.milrinone.tw.
24.pentoxifylline.tw.
25.S-nitrosoglutathione.tw.
26.S-nitrosothioles.tw.
27.trapidil.tw.
28.ticlopidine.tw.
29.clopidogrel.tw.
30.(sulfinpyrazone or sulphinpyrazone).tw.
31.cilostazol.tw.
32.(P2Y12 adj2 antagonis$).tw.
33.prasugrel.tw.
34.ticagrelor.tw.
35.cangrelor.tw.
36.elinogrel.tw.
37."glycoprotein IIB/IIIA inhibitors".tw.
38.abciximab.tw.
39.eptifibatide.tw.
40.tirofiban.tw.
41.defibrotide.tw.
42.picotamide.tw.
43.beraprost.tw.
44.ticlid.tw.
45.aggrenox.tw.
46.ditazole.tw.
47.or/1-46
48.exp Renal Dialysis/
49.(hemodialysis or haemodialysis).tw.
50.(hemofiltration or haemofiltration).tw.
51.(hemodiafiltration or haemodiafiltration).tw.
52.dialysis.tw.
53.(PD or CAPD or CCPD or APD).tw.
54.Renal Insufficiency/
55.Kidney Failure/
56.exp Renal Insufficiency, Chronic/
57.Kidney Diseases/
58.Uremia/
59.(end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
60.(ESRF or ESKF or ESRD or ESKD).tw.
61.(chronic kidney or chronic renal).tw.
62.(CKF or CKD or CRF or CRD).tw.
63.(predialysis or pre-dialysis).tw.
64.ur?emi$.tw.

(Continued)

	65.or/48-64 66.and/47,65
EMBASE	1. exp Antithrombocytic Agent/ 2. exp Phosphodiesterase Inhibitor/ 3. Defibrotide/ 4. platelet aggregation inhibit$.tw. 5. (antiplatelet agents$ or anti-platelet agent$).tw. 6. (antiplatelet therap$ or anti-platelet therap$).tw. 7. thrombocyte aggregation inhibit$.tw. 8. (antithrombocytic agent$ or anti-thrombocytic agent$).tw. 9. (antithrombocytic therap$ or anti-thrombocytic therap$).tw. 10.adenosine diphosphate receptor inhibit$.tw. 11.phophodiesterase inhibit$.tw. 12.(adenosine reuptake inhibit$ or adenosine re-uptake inhibit$).tw. 13.aspirin.tw. 14.acetylsalicylic acid.tw. 15.dipyridamole.tw. 16.ticlopidine.tw. 17.clopidogrel.tw. 18.(sulfinpyrazone or sulphinpyrazone).tw. 19.cilostazol.tw. 20.(P2Y12 adj2 antagonis$).tw. 21.prasugrel.tw. 22.ticagrelor.tw. 23.cangrelor.tw. 24.elinogrel.tw. 25."glycoprotein IIB/IIIA inhibit$".tw. 26.abciximab.tw. 27.eptifibatide.tw. 28.tirofiban.tw. 29.defibrotide.tw. 30.picotamide.tw. 31.beraprost.tw. 32.ticlid.tw. 33.aggrenox.tw. 34.ditazole.tw. 35.or/1-34 36.exp Renal Replacement Therapy/ 37.(hemodialysis or haemodialysis).tw 38.(hemofiltration or haemofiltration).tw. 39.(hemodiafiltration or haemodiafiltration).tw. 40.dialysis.tw. 41.(PD or CAPD or CCPD or APD).tw. 42.Kidney Disease/ 43.Chronic Kidney Disease/ 44.Kidney Failure/ 45.Chronic Kidney Failure/ 46.Uremia/ 47.(chronic kidney or chronic renal).tw. 48.(CKF or CKD or CRF or CRD).tw. 49.(end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.

(Continued)

50.(ESRF or ESKF or ESRD or ESKD).tw.
51.ur?emi$.tw.
52.exp Kidney Transplantation/
53.or/36-52
54.and/35,53

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Was there adequate sequence generation?	*Yes (low risk of bias):* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	No (high risk of bias): Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Was allocation adequately concealed?	*Yes (low risk of bias):* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	No (high risk of bias): Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Was knowledge of the allocated interventions adequately prevented during the study?	*Yes (low risk of bias):* No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken; either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.
	No (high risk of bias): No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken; either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.
	Unclear: Insufficient information to permit judgement of ‘Yes’ or ‘No'
Were incomplete outcome data adequately addressed?	*Yes (low risk of bias):* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized dif-

(Continued)

	ference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	No (high risk of bias): Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement of 'Yes' or 'No'.
Are reports of the study free of suggestion of selective outcome reporting?	*Yes (low risk of bias):* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	No (high risk of bias): Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement of 'Yes' or 'No'.
Was the study apparently free of other problems that could put it at a risk of bias?	*Yes (low risk of bias):* The study appears to be free of other sources of bias.
	No (high risk of bias): Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to permit judgement of 'Yes' or 'No'.

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol:MR, SP
2. Study selection:MR, LDM, SP
3. Extract data from studies:MR, LDM, SP
4. Enter data into RevMan:MR, LDM, SP
5. Carry out the analysis:MR, LDM, SP
6. Interpret the analysis:MR, LDM, SP, JC, VP, SZ, AW, MJ, GFMS
7. Draft the final review:MR, LDM, SP, JC, VP, SZ, AW, MJ, GFMS
8. Disagreement resolution:GFMS
9. Update the review:SP, GFMS

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

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INDEX TERMS

Medical Subject Headings (MeSH)

Cause of Death; Hemorrhage [chemically induced]; Myocardial Infarction [*prevention & control]; Platelet Aggregation Inhibitors [adverse effects] [*therapeutic use]; Primary Prevention; Randomized Controlled Trials as Topic; Renal Insufficiency, Chronic [*complications] [mortality]; Stroke [*prevention & control]

MeSH check words

Humans