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COCHRANE COMMENTARIES

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Antiplatelet agents for chronic kidney disease

What is in this review about?

This systematic review summarized the randomized trials evaluating the benefits and harms of antiplatelet agents (including aspirin, dipyridamole, thienopyridines (clopidogrel, ticlopidine), defibrotide, picotamide, sulfinpyrazone, and glycoprotein IIb/IIIa inhibitors (abciximab, tirofiban and eptifibatide)) in addition to standard treatment in people who have chronic kidney disease. We focus here on evidence of major cardiovascular events, mortality and bleeding.

What are the key findings?

In people with chronic kidney disease (estimated glomerular filtration rate below 60 mL/min per 1.73 m^2) who had an acute coronary syndrome or required percutaneous coronary revascularization, glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide or tirofiban) had little or no effect on myocardial infarction (six trials, 4850 participants; relative risk (RR) 0.93 (confidence interval (CI) 0.81–1.07)) or all-cause mortality (six trials, 4849 participants; RR 0.83 (CI 0.60–1.16)), but increased major bleeding (seven trials, 5365 participants; RR 1.45 (CI 1.04–2.04)). There were no data for cardiovascular death in the available trials. In people who had chronic kidney disease and had, or were at risk of, cardiovascular disease, antiplatelet therapy (aspirin, thienopyridines or dipyridamole, defibrotide, picotamide or sulfinpyrazone alone or in combination) prevented myocardial infarction (eight trials, 8194 participants; RR 0.68 (CI 0.51–0.90)) but had uncertain effects on mortality (22 trials, 10 895 participants; RR 0.95 (CI 0.80–1.12)) and cardiovascular mortality (17 trials; 8926 participants; RR 0.84 (CI 0.63–1.13)) (Fig. 1), major bleeding (18 trials, 10 216 participants; RR 1.31 (CI 0.94–1.83)) and stroke (10 trials, 9133 participants; RR 1.06 (CI 0.59–1.92)). There was no evidence that different antiplatelet agent classes had different effects on these outcomes. Prespecified analyses to test how treatment effects were affected by stage of chronic kidney disease and specifically in the setting of primary prevention were not possible in this review because of insufficient data.

What are the findings based on?

Forty-four studies (21 460 participants) compared antiplatelet therapy in addition to standard care against placebo and/or standard care alone. Of these, nine trials (9969 patients) were conducted in people who had an acute coronary syndrome or who were undergoing percutaneous intervention and examined glycoprotein IIb/IIIa inhibitors (abciximab, tirofiban or eptifibatide) with or without clopidogrel in addition to aspirin and heparin in the setting of chronic kidney disease stage 3–5. For these interventions, data were entirely based on post-hoc analysis for the subgroup with chronic kidney disease derived from larger trials. The remaining trials examined oral antiplatelet therapy in people who have chronic kidney disease (aspirin, thienopyridines or dipyridamole, defibrotide, picotamide, or sulfinpyrazone alone or in combination) and who were at risk of or who had stable cardiovascular disease. Overall, 19 studies (16 065 participants) included people who had chronic kidney disease stage 3–5, three studies (137 participants) enrolled recipients of a kidney transplant and 21 studies (4820 participants) were in people with chronic kidney disease stage 5D. Trial sample sizes (62–4087 participants; median 100 participants) were highly variable and follow up was continued on average for 9 months (range 1–61 months). Overall, there were limitations in study design that may have affected the reliability of results. These limitations were present in more than half of trials, and included concerns as to whether investigators were unaware of treatment allocation, adequate follow up occurred in all participants, and all relevant outcomes were measured and reported.

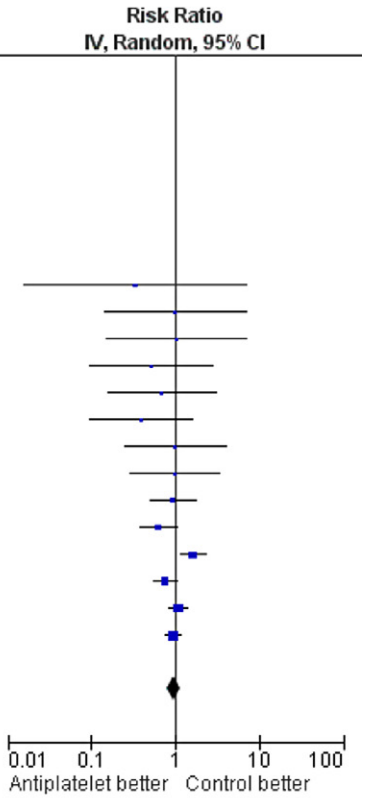
Implications for practice

- In people who had chronic kidney disease and acute coronary syndromes or were undergoing percutaneous coronary intervention, glycoprotein IIb/IIIa inhibitors had little or no effect on myocardial infarction, uncertain effects on total and cardiovascular mortality and stroke, but increased major bleeding.
- In people who had chronic kidney disease and were at risk of, or who had stable cardiovascular disease, antiplatelet therapy prevented myocardial infarction but had imprecise effects on total cardiovascular mortality, stroke and major bleeding.
- Whether the benefits and harms of antiplatelet therapy are different based on stage of kidney disease and whether antiplatelet agents are effective for primary prevention of cardiovascular events in the setting of chronic kidney disease remain uncertain.

All-cause mortality

Study or Subgroup	Antiplatelet agent Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Khajehdehi 2002	0	57	0	19		Not estimable
Kaegi 1974	0	30	0	32		Not estimable
Quarto Di Palo 1991	0	18	0	18		Not estimable
Zäuner 1994	0	10	0	8		Not estimable
Donadio 1984	0	25	0	25		Not estimable
Cheng 1998	0	19	0	12		Not estimable
Kobayashi 1980	0	50	0	57		Not estimable
Ell 1982	0	24	0	26		Not estimable
Michie 1977	0	8	1	8	0.3%	0.33 [0.02, 7.14]
UK-HARP-I Study 2005	2	225	2	223	0.8%	0.99 [0.14, 6.97]
Ghorbani 2009	2	46	2	47	0.8%	1.02 [0.15, 6.95]
Gröntoft 1998	2	129	4	131	1.0%	0.51 [0.09, 2.72]
Kaufman 2003	3	104	4	96	1.3%	0.69 [0.16, 3.01]
Sreedhara 1994	4	83	3	24	1.4%	0.39 [0.09, 1.61]
Dember 2008	4	441	4	436	1.5%	0.99 [0.25, 3.93]
Creek 1990	5	144	5	141	1.9%	0.98 [0.29, 3.31]
STOP Study 1995	17	398	19	413	6.1%	0.93 [0.49, 1.76]
Middleton 1992	23	451	37	452	8.9%	0.62 [0.38, 1.03]
CHARISMA Study 2009	73	1006	45	1003	14.3%	1.62 [1.13, 2.32]
HOT Study 2010	62	1791	84	1828	16.5%	0.75 [0.55, 1.04]
ETDRS 1992	46	79	57	106	20.9%	1.08 [0.84, 1.40]
Dixon 2009	105	321	115	328	24.3%	0.93 [0.75, 1.16]
Total (95% CI)		**5459**		**5433**	**100.0%**	**0.95 [0.80, 1.12]**
Total events	348		382			

Heterogeneity: Tau² = 0.02; Chi² = 16.73, df = 13 (P = 0.21); I² = 22%
Test for overall effect: Z = 0.61 (P = 0.54)



Cardiovascular mortality

Study or Subgroup	Antiplatelet agent Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Kaegi 1974	0	30	0	32		Not estimable
Donadio 1984	0	25	0	25		Not estimable
Zäuner 1994	0	10	0	8		Not estimable
Kobayashi 1980	0	50	0	57		Not estimable
Cheng 1998	0	18	0	12		Not estimable
Ell 1982	0	24	0	26		Not estimable
Quarto Di Palo 1991	0	18	0	18		Not estimable
Khajehdehi 2002	0	57	0	19		Not estimable
Michie 1977	0	8	1	8	0.9%	0.33 [0.02, 7.14]
UK-HARP-I Study 2005	1	225	1	223	1.1%	0.99 [0.06, 15.75]
Gröntoft 1998	2	129	4	131	2.8%	0.51 [0.09, 2.72]
Creek 1990	5	144	4	141	4.5%	1.22 [0.34, 4.46]
STOP Study 1995	7	398	11	413	7.8%	0.66 [0.26, 1.69]
Middleton 1992	21	451	30	452	16.5%	0.70 [0.41, 1.21]
HOT Study 2010	33	1791	47	1828	20.4%	0.72 [0.46, 1.11]
CHARISMA Study 2009	51	1006	31	1003	20.5%	1.64 [1.06, 2.54]
ETDRS 1992	32	79	39	67	25.3%	0.70 [0.50, 0.97]
Total (95% CI)		**4463**		**4463**	**100.0%**	**0.84 [0.63, 1.13]**
Total events	152		168			

Heterogeneity: Tau² = 0.06; Chi² = 12.40, df = 8 (P = 0.13); I² = 35%
Test for overall effect: Z = 1.13 (P = 0.26)

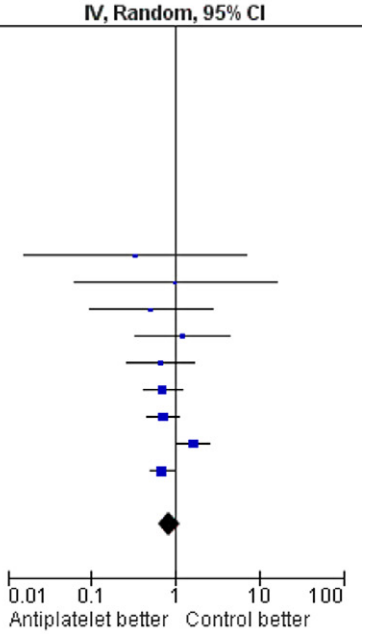


Fig. 1 Effect of antiplatelet therapy (all agents) plus standard care *versus* placebo and/or standard care alone on cardiovascular mortality in people who had chronic kidney disease. CI, confidence interval; IV, inverse variance.

Clinical perspective

Antiplatelet agents are widely used to prevent cardiovascular events in the general population. In people who have chronic kidney disease, occlusive atherosclerosis is a less common mechanism for major cardiovascular events and the bleeding risks may be higher than in the general population. Based on this review, major bleeding complications are an important factor to consider when making clinical decisions about prescribing glycoprotein IIb/IIIa inhibitors in people who have chronic kidney disease and acute coronary syndromes or who are undergoing percutaneous coronary interventions. This is particularly true given the lack of evidence for reduced mortality and cardiovascular events when using antiplatelet agents. Overall, benefits of antiplatelet therapy are limited to preventing myocardial infarction in people with chronic kidney disease with or without cardiovascular disease. Effects of antiplatelet therapy on total and cardiovascular mortality and major bleeding are incompletely understood.

Antiplatelet agents for chronic kidney disease. Palmer SC, Di Micco L, Razavian M, Craig JC, Perkovic V, Pellegrini F, Jardine MJ, Webster AC, Zoungas S, Strippoli GFM. *Cochrane Database of Systematic Reviews.* 2013:Issue 2. Art. No.: CD008834. DOI: 10.1002/14651858.CD008834.pub2

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