Medical management of coronary artery disease (excluding lipid-lowering therapy)

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GUIDELINES

**Acute coronary syndrome**

a. We recommend that all chronic kidney disease patients, including haemodialysis, peritoneal dialysis and transplant patients, should be treated as per the general population when presenting with an acute coronary syndrome (ST-elevation myocardial infarction [STEMI] or non-ST-elevation acute coronary syndrome [NSTEMI]) with regards to reperfusion therapy, antiplatelet therapy (aspirin and clopidogrel), anticoagulant therapies (heparin, thrombin and glycoprotein IIb/IIIa inhibitors), beta-blockers and angiotensin-converting enzyme inhibitors (1C).

b. We recommend that reperfusion therapy give preference to primary percutaneous coronary intervention over fibrinolysis (1D).

**Chronic stable coronary artery disease**

c. We recommend that all chronic kidney disease patients, including haemodialysis, peritoneal dialysis and transplant patients, should be treated for chronic stable coronary artery disease as the general population with regards to antiplatelet therapies, beta-blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers* (1D).

**Safety of therapy**

d. We recommend that all patients with chronic kidney disease with an estimated glomerular filtration rate <60 mL/minute, and specifically those with an estimated glomerular filtration rate <30 mL/minute undergoing antiplatelet or anticoagulant therapy, are considered as being at increased risk of bleeding. Dose adjustment of specific antiplatelet and anticoagulant drugs, specifically enoxaparin, bivalirudin, and glycoprotein IIb/IIIa inhibitors eptifibatide and tirofiban, is recommended. (1A).

e. In chronic kidney disease patients with an estimated glomerular filtration rate <30 mL/minute we recommend that caution be exercised when using enoxaparin for acute coronary syndromes, with a preference for (empirical or based on anti-Xa levels) dose adjustment in an effort to lower bleeding risk (1B). Caution should also be exercised using glycoprotein IIb/IIIa inhibitors in chronic kidney disease (CKD) patients with acute coronary syndromes due to increased bleeding risk (1C).

f. We recommend that in CKD patients at risk for, or with stable cardiovascular disease single antiplatelet agents (low-dose aspirin, dipyridamole, clopidogrel or ticlopidine) can be used without an increased risk in major bleeding events (1B).

g. We recommend that combination antiplatelet therapy with high-dose aspirin (325 mg) and clopidogrel or warfarin not be used in haemodialysis patients due to an increased risk of significant bleeding requiring hospitalisation or transfusion (1B).

* For angiotensin-converting enzyme inhibitors and angiotensin receptor blockers refer to The KHA-CARI Guidelines on ‘Cardiovascular effects of blood pressure lowering in patients with chronic kidney disease’.
UNGRADED SUGGESTIONS FOR CLINICAL CARE

- Due to the ease of reversibility, unfractionated heparin (UFH) may be used in place of LMWH particularly in patients with an eGFR ≤30mL/min, with standardised monitoring of clotting times (APPT) (Ungraded).

[Note: Data support an increased risk for bleeding with the use of LMWH or UFH in patients with increasing degrees of renal dysfunction, and in particular those with a CrCl ≤30mL/min, however, they do not support an increased risk of bleeding with the use of LMWH compared with UFH within subgroups of CKD. The increased risk of bleeding in patients with eGFR ≤30 mL/min on LMWH is possibly abrogated by the use of anti-Xa adjusted dosing schedules, but these strategies have not been well tested in patients with renal insufficiency].

IMPLEMENTATION AND AUDIT

Implementation of these guidelines should be undertaken in conjunction and collaboration with cardiology services at respective hospitals. In the absence of randomised controlled trials, it is critical that management and practice patterns, as well as outcomes, be audited regularly. Specifically in acute coronary syndromes, registries may facilitate collection of these data with greater accuracy.

BACKGROUND

There is a two- to 50-fold increased risk of cardiovascular disease (CVD) in patients with chronic kidney disease (CKD), with approximately 40–50% of the mortality of patients with stage 5 CKD on renal replacement treatment being attributed to CVD [1]. For dialysis patients, the post-myocardial infarction (MI) one- and two-year mortality rates are 61% and 75%, respectively [2]. Furthermore, there is an independent, graded increased risk of death and cardiovascular (CV) events associated with reduced estimated glomerular filtration rate (eGFR) [3], and this relationship is also seen in survivors of acute MI (AMI) and non-ST-elevation acute coronary syndromes (NSTE-ACS) [4-6].

Medical management of acute coronary syndromes (ACS), which include ST-elevation MI (STEMI) and NSTE-ACS, and chronic stable coronary artery disease (CAD), has been extensively studied in the general population leading to evidence-based national clinical practice guidelines [7-9](ESC 2011, ESC 2012, ACCF 2012, ACCF 2013). There are landmark trials that have firmly established roles for reperfusion and primary percutaneous coronary intervention (PCI), antiplatelet and anticoagulant therapies, beta-blocker therapy, and angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy for ACS in the general population. In the majority of these trials patients with moderate-to-severe renal impairment have been excluded, leading to unanswered concerns about efficacy and safety, and consequently significant underuse of these therapeutic options in CKD patients [4, 6, 10, 11].

The aim of this guideline is to review the literature and assess the benefits and harms of medical management, specifically reperfusion therapy, antiplatelet and anticoagulant therapies, beta-blocker therapy, and ACE inhibitor/ARB therapy (but excluding lipid-lowering therapy), of ACS and chronic stable CAD in patients with CKD, including the dialysis and transplant populations. The benefits examined are:

1. The risk of MI and CV death in patients presenting with ACS, including the risk of coronary restenosis in patients with an ACS undergoing a PCI and receiving associated antiplatelet and/or anticoagulant therapy.
2. The risk of MI and CV death in patients with chronic stable CAD.

The harms examined relate to serious adverse events reported in the literature in relation to the aforementioned medical therapies.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for chronic kidney disease, end-stage kidney disease and renal replacement therapy were combined with MeSH terms and text words for coronary
disease and then combined with MeSH terms and text words for platelet aggregation inhibitors, anticoagulants, aspirin, clopidogrel, adrenergic beta-antagonists, beta blockers, heparin, ACE inhibitors, nitrates, calcium channel blockers, thrombolytic therapy, angioplasty, coronary artery bypass and then combined with the Cochrane highly sensitive search strategy for randomised controlled trials. The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

**Date of search/es:** 19 September 2007 and updated search 23 February 2011 and April 2013.

**WHAT IS THE EVIDENCE?**

There is limited evidence regarding the management of acute coronary syndromes (ACS) or chronic stable coronary artery disease (CAD) in CKD.

**Randomised controlled trials (RCT):** The limited RCT data examining the therapeutic options for the medical management of ACS or chronic stable CAD is all taken from post-hoc analyses of RCT from the general population where patients with CKD were identified based on serum creatinine and/or estimated GFR, and outcomes analysed. These limitations also apply to assessing harms of ACS therapies. Specifically with regards to harm of anticoagulant therapies, data regarding harm has been extrapolated from trials using anticoagulants for non-cardiac indications.

**Prospective and retrospective registry data or observational cohorts:** A significant proportion of the evidence for ACS therapies is derived from observational data providing a lower grade of evidence.

**General Population Guidelines:** The management of ACS in the general population was examined through the extensive guidelines available [7-9]. It is notable that the latest addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the Management of ACS highlights the significance of reduced bleeding risk being associated with improved outcome for patients with ACS in the general population, and recommends including an eGFR <60mL/min when calculating bleeding risk scores to tailor anticoagulant therapy [9]. These Guidelines favour an approach of improving net clinical outcome by reducing bleeding risk in patients assessed to be at high risk of bleeding, a marker for which is renal dysfunction (eGFR < 60 mL/min).

**ACUTE CORONARY SYNDROME**

**a. Reperfusion therapy for ST-Elevation Myocardial Infarction (STEMI)**

Meta-analyses in the general population favour primary PCI over fibrinolysis with a RRR 46% (CI 30%, 58%) for the combined criteria of death or re-infarction [12, 13]. General population Guidelines support this recommendation without specifically including or excluding CKD patients [8, 9]. No RCT data are available in CKD patients and both therapies are underutilised in CKD. There is one retrospective cohort study showing that use of any reperfusion therapy is associated with a decreased OR of death in CKD patients (OR 0.7 95% CI 0.6, 0.9) [4]. There is a perceived possible risk of increase bleeding with fibrinolysis in CKD patients leading other Renal Guideline Bodies to recommend PCI over thrombolysis but with ungraded evidence.

In the general population, adjuvant therapy that is advocated with reperfusion therapy includes aspirin and clopidogrel, as well as LMWH [7]. Glycoprotein (GP) IIb/IIIa inhibitors are occasionally used with primary PCI but should be avoided with fibrinolytic therapy [7]. There are no data regarding the use of adjuvant therapies during reperfusion for STEMI in CKD patients.

**b. Antiplatelet therapy: Clopidogrel added to aspirin for ACS**

**Efficacy**

The efficacy of adding clopidogrel to aspirin for ACS in CKD has been examined in post-hoc analyses of 2 major studies (CURE and CREDO) [14, 15]. The CURE study (Clopidogrel in Unstable Angina to Prevent Recurrent Events) was a randomised controlled trial of clopidogrel or placebo added to aspirin (75-325mg) for 12,253 patients with unstable angina [14]. The primary outcome was cardiovascular death, non-fatal myocardial infarction or stroke at 1 year and in the post hoc analysis outcomes were examined by tertiles of eGFR (<64, 64-81.2, and >81.3 mL/min). Clopidogrel use was associated with an 11%, 32% and 26% RRR for the primary outcome from lowest to highest tertile of eGFR, but the confidence interval just crossed 1 in the lowest tertile. The CREDO study (Clopidogrel for Reduction of Events During Observation) was a randomised controlled trial of adding clopidogrel or placebo to aspirin (81-325mg) in 2002 patients undergoing percutaneous coronary intervention of which only half had unstable angina. The primary outcome was the same as in the CURE trial and for the post hoc
analysis patients were divided into tertiles of eGFR (<60, 60-89, >89 mL/min) [15]. In this study, a benefit of clopidogrel was only seen in the highest eGFR tertile (RRR 58%), with no significant benefit in the middle and the lowest tertiles. Of note, recent evidence suggests that clopidogrel responsiveness predicts outcome in ACS in CKD patients, with variable concentrations of active clopidogrel in advanced CKD [16]. This may in part explain lower clopidogrel efficacy in the lower tertiles of eGFR.

The newer thienopyridine, prasugrel is faster acting with less variability and proven efficacy in the non-CKD population with greater bleeding risk [17]. It remains to be tested in CKD patients.

Similar efficacy data is not available for dialysis or transplant patient groups. However, there are 2 retrospective analyses of prospectively collected registry data examining the effect of aspirin therapy after MI in CKD patients. In the first study, CKD was defined using an abbreviated version of the Cockcroft-Gault formula as weight was not available in the database [18]. Of 1724 patients, 731 had a creatinine clearance <63 mL/min and 47 were on dialysis. Combined aspirin and beta-blocker use was associated with a significantly lower in-hospital mortality rate (RRR 78% on dialysis, RRR 64.3% creatinine clearance <46 mL/min, RRR 69% creatinine clearance 46-63 mL/min and RRR 75% creatinine clearance 63-81.5 mL/min). The second study examined the effect of aspirin, beta-blocker and ACEi therapy post-acute myocardial infarction (AMI) in dialysis patients only (stage 5 CKD) [19]. The cohort consisted of 145,740 patients without end-stage kidney disease (ESKD) and 1025 patients on dialysis. The primary outcome examined was post-AMI 30-day mortality, and use of aspirin was associated with a lower RR (RR 0.64, 95% CI: 0.50 - 0.80) for this outcome.

**Safety**

Regarding major bleeding events as a measure of safety of anti-platelet therapy in ACS, in the CURE study addition of clopidogrel was associated with an increased risk of major bleeding in the highest eGFR tertile with a trend to increased major bleeding in the middle tertile but no increased risk in the lowest tertile (eGFR <64 mL/min RR 1.12 95% CI 0.83, 1.51; eGFR 64-81.2 mL/min RR 1.40 95% CI 0.97, 2.20; eGFR >81.3 mL/min RR 1.83 95% 1.23, 2.73). [14]

In the CREDO study major bleeding followed to 1 year was not significantly increased in any tertile of eGFR (eGFR <60 mL/min RR 1.124 95% CI 0.511, 2.476; eGFR 60-89 mL/min RR 1.595 95% CI 0.970, 2.621; eGFR ≥90 mL/min RR 1.168 95% 1.741, 1.841). [15]

Similar safety data is not available for dialysis or transplant patient groups. The safety data from the use of antiplatelet agents for access patency or in chronic stable coronary artery disease are discussed below under the section on Chronic Stable Coronary Artery Disease.

Thus, in summary there are very limited efficacy data supporting adding clopidogrel to low-dose aspirin for ACS in patients with impaired eGFR < 60 mL/min with safety data suggesting no significant increase in bleeding in this group. This lack of efficacy and perceived safety may relate to recent evidence suggesting impaired clopidogrel activity in advanced CKD.

c. **Low molecular weight heparins and fondaparinux for ACS**

**Efficacy**

The efficacy of Low Molecular Weight Heparin (LMWH) over Unfractionated Heparin (UFH) has been examined in post-hoc analyses of the EXTRACT-TIMI 25 and ESSENCE and TIMI 11B trials, and in one prospective observational registry.

The EXTRACT-TIMI 25 trial (Enoxaparin and Thrombolysis Reperfusion in Myocardial Infarction Treatment – Treatment in Myocardial Infarction 25) was a RCT of enoxaparin versus UFH as an adjunct to fibrinolysis for STEMI. The post-hoc analysis of the impact of renal dysfunction on the primary end-point of 30-day all-cause mortality or non-fatal recurrent MI, divided 20,479 patients into 4 strata of creatinine clearance (CrCl) [20]. The primary end-point was significantly reduced in patients with a CrCl >60 m/min only: (CrCl< 90mL/min OR 0.69 95% CI 0.56, 0.84; CrCl >60-90 OR 0.78, 95% CI 0.66, 0.92; CrCl 30-60 mL./min OR 0.94 95% CI 0.78, 1.12; CrCl <30 OR 0.74 95% CI 0.38, 1.44).

The ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events) and TIMI (Thrombolysis in Myocardial Infarction) 11B trials examined the primary composite endpoint of death, MI, and urgent revascularization in patients presenting with ACS randomised to enoxaparin or UFH. In the post-hoc analysis, patients with severe renal impairment were defined as those with a CrCl of ≤30 mL/min (n = 143) estimated with the Cockcroft-Gault formula, and compared with patients with a CrCl >30 mL/min (n = 6826) [21]. The primary end-point was not significantly different in enoxaparin treated patients compared with UFH treated patients with a CrCl ≤30 mL/min (OR 0.52, 95% CI 0.23, 1.19) compared with a significant reduction in the end-point in patients with CrCl >30 mL/min (OR 0.84, 95% CI 0.74, 0.95, p < 0.01).
A prospective observational study from the Global Registry of Acute Coronary Events (GRACE) compared absolute difference in 30-day mortality according to tertiles of CrCl between 3,709 patients receiving UFH and 4,966 receiving LMWH [22]. LMWH was associated with improved 30-day mortality in the normal renal function (CrCl >60 mL/min) and moderate renal dysfunction groups (CrCl >30 to ≤60 mL/min) but not in the severe renal dysfunction group (CrCI ≤ 30 mL/min).

Fondaparinux

There is insufficient data to recommend one LMWH over the other, and the data in CKD predominantly includes enoxaparin. Recently, a post-hoc analysis of the OASIS-5 study (Organisation to Assess Strategies in Ischaemic Syndromes – 5) comparing dose-adjusted enoxaparin with fondaparinux (a pentasaccharide inhibitor of factor Xa) in a RCT for the management of ACS (NSTE-ACS), examined the primary outcome of death, myocardial infarction or refractory ischaemia according to the GRACE risk score which is stratified for serum creatinine [23]. Of the 20,078 patients randomised, 6% had a serum creatinine > 140 µmol/L, 17% had a serum creatinine between 106-140 µmol/L and 77% had a serum creatinine < 106 µmol/L. As in the original study, fondaparinux was non-inferior to enoxaparin in all 3 levels of GRACE risk (Low risk HR 0.90, 95% CI 0.75, 1.08; Intermediate risk HR 0.89, 95% CI 0.77, 1.03; High risk HR 0.95, 95% CI 0.85, 1.06) and fondaparinux had a significantly reduced risk of major bleeding (Low risk HR 0.55, 95% CI 0.39, 0.77; Intermediate risk HR 0.53, 95% CI 0.40, 0.70; High risk HR 0.50, 95% CI 0.38, 0.64). This net clinical benefit of fondaparinux over enoxaparin has also been demonstrated in a previous post-hoc analysis of OASIS-5 examining outcomes based on quartiles of eGFR calculated using the MDRD formula [24]. In patients with a GFR < 58 mL/min/1.73 m², at 9 days, death, myocardial infarction, or refractory ischemia occurred in 6.7% of patients receiving fondaparinux and 7.4% of those receiving enoxaparin (HR 0.90, 95% CI 0.73, 1.11); major bleeding occurred in 2.8% and 6.4%, respectively (HR 0.42, CI 0.32, 0.56). The rates of the composite end point (cardiovascular events and bleeding) were lower with fondaparinux than with enoxaparin in all quartiles of GFR, but the differences were statistically significant only among patients with a GFR < 58 mL/min/1.73 m². However, fondaparinux use is currently contraindicated if eGFR < 30 mL/min as it is predominantly cleared by the kidneys, and it requires dose adjustment in patients with eGFR 30-60 mL/min.

Safety

In the ExTRACT – TIMI 25 study, risk of major bleeding with LMWH compared with UFH was not increased in the highest stratum of CrCl (CrCl> 90mL/min OR 0.1.49 95% CI 0.89, 2.48) with a significant increase in the next 2 strata (CrCl >60-90 OR 1.91, 95% CI 1.30, 2.82; CrCl 30-60 mL./min OR 1.73, 95% CI 1.11, 2.70) but not reaching significance in the lowest stratum of CrCl (CrCl <30 OR 3.60, 95% CI 0.67, 19.21) [20].

In the ESSENCE and TIMI 11B studies, the risk of major bleed (OR 1.53, 95% CI 0.37, 6.32) or any bleed (OR 1.04, 95% CI 0.42, 2.59) was not increased with the use of LMWH compared with UFH in the group with severe renal dysfunction (CrCl ≤ 30 mL/min). In the group with CrCl > 30 mL/min on LMWH compared with UFH, major bleeds were not increased (OR 1.2, 95% CI 0.77, 1.94) but any bleeds were significantly increased (OR 2.71, 95% CI 2.20, 3.34) [21].

In the ExTRACT – TIMI 25 study and in the ESSENCE and TIMI 11B studies, risk for major bleeding and any bleeding increased 2-5-fold from highest to lowest stratum of CrCl irrespective of type of heparin used [20, 21].

There is one meta-analysis of 12 RCTs using therapeutic, prophylactic and adjusted doses of LMWH for indications that include ACS predominantly, examining bleeding risk in 4,971 patients with severe renal insufficiency (eGFR < 30 mL/min but not on dialysis) [25]. This showed a significantly increased risk of bleeding with all LMWH in patients CrCl ≤ 30 mL/min compared with > 30mL/min (OR 2.25, 95% 1.19, 4.27). In the subgroup of patients receiving therapeutic doses of enoxaparin this risk was increased further (OR 3.88, 95% CI 1.78, 8.45) whereas in the subgroup receiving adjusted dose enoxaparin the bleeding risk was not significantly increased (OR 0.58 95%CI 0.09, 3.78). This meta-analysis did not compare LMWH to UFH within CKD subgroups.

An earlier meta-analysis of RCTs comparing LMWH to UFH for the prevention of circuit thrombosis in haemodialysis patients showed no increase in all bleeding events (RR 0.96, 95%CI 0.27, 3.43), access compression time (RR -0.87, 95% CI -2.75, 1.02) and circuit thrombosis (RR 1.15, 95%CI 0.70, 1.91) between the 2 treatment arms [26].

Finally, while the post-hoc analyses of the OASIS-5 study suggest a net clinical benefit of fondaparinux over enoxaparin due to significantly lower bleeding risk in the high GRACE risk group with higher serum
creatinine or the lowest quartile of eGFR [20, 23, 24], fondaparinux is contraindicated for use in patients with eGFR < 30 mL/min.

In summary these data do not support an efficacy benefit of enoxaparin over UFH in treatment of ACS in patients with a CrCl ≤ 30mL/min, with limited and conflicting evidence for benefit of enoxaparin in patients with CrCl 30-60 mL/min. Furthermore, while these data support an increased risk for bleeding with the use of LMWH in patients with increasing degrees of renal dysfunction, and in particular those with a CrCl ≤ 30mL/min, they do not support an increased risk of bleeding with the use of LMWH compared with UFH within subgroups of CKD. The increased risk of bleeding in patients with CrCl ≤ 30mL/min on LMWH is possibly abrogated by the use of anti-Xa adjusted dosing schedules, but these strategies have not been well tested in patients with renal insufficiency. Further data on the benefits of fondaparinux in mild-to-moderate CKD are required before it can be recommended for use in ACS management.

d. Glycoprotein Iib/IIa inhibitors

The General Population Guidelines place the role of GP IIb/IIIa inhibitors as adjunctive therapy to heparin for STEMI, downstream during percutaneous coronary interventions (PCI), or upstream as adjunctive therapy for progressive high-risk NSTE-ACS only if there is recurrent ischaemia [7, 9]. There are limited studies examining the safety and efficacy of these agents in CKD patients and the results are conflicting.

Efficacy and Safety

There are 2 studies that have examined the efficacy and safety of GP Iib/IIa inhibitors in CKD using post-hoc analyses of CKD subgroups from larger RCTs in the general population.

The first post-hoc analysis examined the effect of adding tirofiban to heparin compared with heparin alone for patients with mild-to-moderate renal insufficiency presenting with an ACS in the PRISM-PLUS trial (Platelet Receptor Inhibition in Ischaemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms) [27]. Creatinine clearance was estimated using the Cockcroft-Gault formula for those patients who had a serum creatinine either pre- or post-randomisation (1,537 of a total 1,915 patients). The benefit of therapy on the composite endpoint of death, MI, and refractory ischaemia at 48 hours, 7 days, 30 days and 6 months was assessed. Tirofiban use was associated with a significant reduction of this composite endpoint at 48 hours (OR 0.68, 95% CI: 0.46, 1.0), 7 days (OR 0.68, 95% CI: 0.52, 0.88), 30 days (OR 0.78, 95% CI: 0.63, 0.98) and 6 months (OR 0.81, 95% CI: 0.68, 0.98). However, this analysis included patients with an estimated creatinine clearance of > 75 mL/min and was performed using creatinine clearance as a continuous variable in regression models; subgroup analyses of the different CKD stages were difficult to interpret due to small numbers. Safety: This study found that there was an incremental risk of bleeding when tirofiban was added to heparin but that it was not amplified in CKD patients.

The second study examined the associations of creatinine clearance with outcomes in a trial of eptifibatide therapy versus placebo in patients who underwent PCI with stent placement in the ESPRIT trial (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy) [28]. The primary outcome was death, MI, urgent revascularisation or thrombotic bailout therapy at 48 hours and 30 days. Patients were randomly assigned to placebo or eptifibatide as an adjunct to stent implantation. Creatinine clearance was calculated using the Cockcroft-Gault formula and CKD was defined as a CrCl < 60 mL/min (n = 1,755 with CrCl ≥60 mL/min and 289 with CrCl <60 mL/min). In the subgroup with CrCl < 60 mL/min the primary outcome was significantly lower in the eptifibatide group at 48 hrs (OR 0.52, (%CI 0.33, 0.81) and at 30 days (OR 0.53, 95% CI 0.34, 0.83). This treatment effect was also seen in the group with CrCl ≥ 60 mL/min; however the interaction of treatment with creatinine clearance was not significant at 48hrs or 30 days. Safety: Eptifibatide use was not associated with an increase in bleeding risk (Any bleed OR 0.99, 95% CI 0.87, 1.13; Interaction with CrCl p = 0.791).

There are a series of observational studies examining outcomes with the use of GP Iib/IIa inhibitors in CKD.

i) A prospective observational registry of abciximab use in PCI in 1040 patients, described outcomes in CKD patients (creatinine ≥ 115 µmol/L to dialysis; 44 predialysis and 5 on dialysis) compared with non-CKD patients receiving abciximab [29]. Procedural success and in-hospital mortality was not significantly different between CKD and non-CKD patients. Safety: This study described a 5-fold increased risk of bleeding with abciximab when used during PCI in patients with CKD compared with patients without CKD. However, this is attributed to the presence of renal insufficiency as the appropriate comparator group of CKD patients undergoing PCI without abciximab was not included.
ii) A retrospective observational study examined the in-hospital outcome and influence of any GP Iib/IIIa inhibitor on patients with ACS across a range of renal function [30]. Patients presenting with an ACS were stratified according to renal function assessed by calculated creatinine clearance using the CG formula at presentation (Normal ≥ 90mL/min, n = 338; 60-89 mL/min n = 241; 30-59 mL/min n = 222; <30 mL/min n = 63; on dialysis n = 25).

Primary outcome measures included in-hospital mortality and major bleeding events. The use of GP Iib/IIIa inhibitors was associated with a 30% reduction in death or MI during the first 30 days in the abciximab group (16%) compared with those that did not receive abciximab (23%), but this was not statistically significant [31].

**Safety:** There were no significant differences in major bleeding complications between the 2 groups (21% Abciximab versus 15% No abciximab). This is consistent with another retrospective analysis of registry data of 4,158 patients who received abciximab while undergoing PCI in whom the risk of bleeding was not associated with the degree of renal impairment (OR 1.18, 95% CI 0.99, 1.39) [32].

In summary, there are limited data and the data are of suboptimal quality regarding the efficacy of GP Iib/IIIa inhibitors in CKD patients. There is significant concern of increased bleeding risk with the use of these agents in CKD. The General Population Guidelines advise caution with the use of these agents if possible in patients at increased bleeding risk, with consideration for alternative agents such as the thrombin inhibitor, bivalirudin [9]. Currently the available GP Iib/IIIa inhibitors are abciximab which is not reliant on renal clearance and does not need dose adjustment, tirofiban which has 65% renal clearance with a recommended 50% dose reduction if CrCl < 30mL/min, and eptifibatide which has 50% renal clearance requiring a 50% dose reduction in patients with a serum creatinine between 176 – 354 µmol/L but with no data to support use in more severe degrees of renal dysfunction.

b. Thrombin inhibitor bivalirudin

**Efficacy and Safety**

There is 1 meta-analysis of 3 randomized trials (n = 5,035) comparing bivalirudin with heparin during PCI, with outcomes stratified by estimated creatinine clearance using the Cockcroft-Gault formula in patients with an available baseline serum creatinine (>90 [No CKD] n = 1,578, 90 to 60 [mild CKD] n = 2,163, 59 to 30 [moderate CKD] n = 1,255, and <30 mL/min [severe CKD] n = 39) [33].

Dialysis patients were excluded. The composite endpoints of (1) death, MI or revascularization, (2) haemorrhage, or (3) all 4 endpoints combined were assessed. The odds ratio (OR) for the reduction in the triple ischaemic endpoint was only significant in the group with mild CKD (OR 0.73, 95% CI: 0.53, 0.99). The OR for the reduction in major haemorrhage was only significant in the groups with no CKD (OR 0.45, 95% CI: 0.21, 0.96) and moderate CKD (OR 0.46, 95% CI: 0.30, 0.70). The OR for the reduction in the quadruple ischaemic and bleeding endpoint was significant in the groups with mild renal impairment (absolute reduction 5.8%, OR value and 95% CI not given) and moderate real impairment (absolute reduction 7.7%, OR value and 95% CI not given). There were no bleeding events in the severe CKD group.

More recently, there has been a post-hoc analysis of outcomes in patients with CKD in the ACUITY study (Acute Catheterisation and Urgent Intervention Triage Strategy) which was an open-label RCT of moderate to high risk ACS patients assigned to either heparin and GP Iib/IIIa inhibitor, bivalirudin and GP Iib/IIIa inhibitor or bivalirudin monotherapy [34]. There were 3 primary 30-day end-points i) composite ischaemia defined as all cause death, myocardial infarction or unplanned revascularisation for ischaemia ii) major bleeding iii) net clinical outcome which is a composite of i) and ii). CKD was defined as a Cockcroft-Gault CrCl < 60 mL/min, present in 2468 of the 12939 patients; CrCL < 30 mL/min was an exclusion criteria. The composite ischaemia outcome was similar in bivalirudin monotherapy compared with heparin/GP Iib/IIIa inhibitor (RR 1.18, 95% CI 0.88, 1.57) as was the net clinical outcome (RR 0.95, 95% CI 0.77, 1.18), but bivalirudin monotherapy was associated with significantly less bleeding (RR 0.64, 95% CI 0.45, 0.89). The bivalirudin/GP Iib/IIIa combination group composite ischaemia and net clinical outcomes were similar to heparin/GP Iib/IIIa inhibitor; however, the advantage of a lower bleeding risk was no longer seen with bivalirudin/GP Iib/IIIa inhibitor combination.
In summary there is limited evidence of moderate quality supporting the efficacy and safety of bivalirudin monotherapy during PCI for ACS in patients with mild to moderate CKD (CrCl > 30 mL/min) with very limited to no data for dialysis patients.

f. Beta-blockers in ACS

There are no RCTs examining the efficacy of beta-blocker therapy for ACS in CKD patients.

There are 2 observational studies that have examined the efficacy of beta-blockers in ACS. The first study performed a retrospective analysis of prospectively collected registry data to examine the effect of combined aspirin and beta-blocker therapy after acute myocardial infarction (AMI) in CKD patients, including haemodialysis patients [18]. Chronic kidney disease was defined as a CrCl < 63 mL/min using an abbreviated version of the Cockcroft-Gault formula as weight was not available in the database. Of 1724 patients, 731 had a CrCl < 63 mL/min and 47 were on dialysis. Aspirin and beta-blocker use was associated with a significantly lower in-hospital mortality rate (RRR 78% on dialysis, RRR 64.3% CrCl < 46 mL/min, RRR 69% CrCl 46-63 mL/min and RRR 75% CrCl 63 - 81.5 mL/min). The second study also examined prospectively collected registry data, but specifically examined the effect of aspirin, beta-blocker and Angiotensin converting enzyme inhibitor (ACEi) therapy post-AMI in dialysis patients only (stage 5 CKD) [19]. The cohort studied consisted of 145,740 patients without end-stage kidney disease and 1025 patients on dialysis. The primary outcome examined was post-AMI 30-day mortality, and use of beta-blockers was associated with a 22% risk reduction (RR 0.78, 95% CI: 0.60, 0.90).

In summary there is only low grade evidence for the use of beta blockers in the setting of ACS in patients with CKD. However, this therapy is highly unlikely to be subjected to RCTs in the future.

The role of beta-blockers in the therapy of heart failure in CKD patients is discussed in the ‘Heart Failure Section of the Cardiovascular Disease in CKD’ KHA-CARI Guidelines.

g. Angiotensin Converting Enzyme Inhibitors (ACEi)

There are no RCTs examining the efficacy of ACEi in ACS in CKD patients.

There is a post-hoc analysis of outcomes in CKD patients enrolled in the SAVE (Survival and Ventricular Enlargement) trial, which was a double-blind RCT that examined the effect of ACEi therapy with captopril on cardiovascular events (all-cause mortality, CV mortality, development of heart failure or recurrent MI) post MI in patients with impaired left ventricular function (ejection fraction ≤ 40%) [35]. Of the 2231 patients enrolled in SAVE, baseline creatinine was available in 2183 and used to calculate eGFR using the MDRD formula. Captopril prevented 12.4 CVD events/ 100 in the CKD group (n = 719, eGFR < 60 mL/min) compared with 5.5/100 in the control group (n = 1464, eGFR > 60 mL/min). Thus the RRR due to captopril was 31% in CKD patients versus 20% in non-CKD patients but the interaction between study drug and CKD was not statistically significant (p = 0.29).

The effect of ACEi therapy post-AMI in dialysis patients (stage 5 CKD) has been examined in a retrospective analysis of prospectively collected registry data [19]. The cohort studied consisted of 145,740 patients without end-stage renal disease and 1025 patients on dialysis. The primary outcome examined was post-AMI 30-day mortality, and use of ACEi was associated with a lower (RR 0.58, 95% CI: 0.42, 0.77) for this outcome. In another retrospective cohort study of 20,902 Medicare beneficiaries, the use of ACEi therapy in elderly (> 65 years) patients with impaired left ventricular function (ejection fraction ≤ 40%) post-AMI and serum creatinine > 265 µmol/L was associated with a 37% increase in 1-year survival compared with a 16% increase in those with a serum creatinine < 265 µmol/L [36].

In summary there is only low grade evidence for the use of ACEi in the setting of ACS (post-AMI) in patients with CKD.

CHRONIC STABLE CORONARY ARTERY DISEASE

a. Aspirin and Clopidogrel

Efficacy

There are no RCT specifically examining the efficacy of aspirin alone or clopidogrel alone for the management of chronic stable CAD in CKD, dialysis or renal transplant patients.

In haemodialysis patients data examining the efficacy of aspirin has been extrapolated from studies of access patency or from prospective and retrospective observational studies:

The ATC (Antithrombotic Trialists’ Collaboration) conducted a meta-analysis of randomised trials of anti-platelet therapy for the prevention of death, myocardial infarction and stroke in high risk patients [37]. This included a subgroup of haemodialysis patients (n = 2,632) in 14 trials of anti-platelet agents
used for maintenance of access patency with up to a 12-18 month follow up in some trials. Anti-platelet therapy was associated with a 41% proportional reduction (standard error 16%) in serious vascular events. DOPPS (Dialysis Outcomes and Practice Patterns Study) was a prospective observational study of 16,471 haemodialysis patients examining the association between aspirin prescription and outcomes [38]. While all-cause mortality was not increased (RR 0.99, 95% CI 0.93, 1.05), aspirin prescription was associated with an increased risk for any cardiac event (RR 1.08, 95% 1.02, 1.14) and myocardial infarction (RR 1.21 95% CI 1.06, 1.38) but a reduced risk for stroke (RR 0.82, 95% CI 0.69, 0.98). More recently, a retrospective observational study of 41,425 haemodialysis patients showed that aspirin prescription was associated with an increased risk of all-cause mortality (RR 1.06, 95% CI 1.01, 1.11) as was clopidogrel prescription (RR 1.24, 95% CI 1.13, 1.35) [39]. These 2 observational studies provide conflicting evidence compared with the ATC meta-analysis which may be a consequence of confounding by indication and should be interpreted cautiously. Another prospective cohort study examined the effect of aspirin, beta-blocker, ACEi and statin use on 12-month mortality in CKD patients with heart failure and angiographically proven CAD [40]. CKD was defined as a Cockcroft-Gault estimated creatinine clearance of < 60mL/min and out of a total of 6,427 registry patients with heart failure and CAD, 2,047 had a creatinine clearance 30-59 mL/min and 466 had a creatinine clearance < 30mL/min, of which 192 were on dialysis. It was noted that CKD patients had significantly lower use of aspirin, beta-blockers, ACEi and statins, and mortality rates worsened with lower creatinine clearance. However, users of aspirin had a lower 12-month mortality (OR 0.69, 95% CI: 0.57 - 0.85).

While the secondary prevention data for aspirin in CKD is limited, there are 2 post-hoc analyses of the HOT (Hypertension Optimal Treatment) study, a primary prevention study of aspirin in patients with diastolic hypertension. HOT is a RCT examining whether the addition of low dose aspirin (75mg/day) to antihypertensive treatment reduces major cardiovascular events in 18,790 patients 50-80 years of age with a diastolic blood pressure between 100 and 115 mmHg, randomly allocated to receive aspirin or placebo [41-43]. The study was double-blinded and had an average follow-up time of 3.8 years. The principal result showed 15% reduction in the combined primary endpoint (fatal and non-fatal MI, fatal and non-fatal stroke and other cardiovascular death (P = 0.03) and 36% reduction in MI (P = 0.002). Subsequently, in the first published post-hoc analysis, subgroup outcome analyses were performed based on the presence or absence of 7 different risk factors including serum creatinine (impaired renal function/CKD group serum creatinine range 115 - 177 µmol/L, n = 1367 with 681 on aspirin) [42]. In this subgroup of CKD patients, the RR for the combined primary endpoint was significantly reduced at 0.595 (95% CI 0.387, 0.913), with no significant increase in major bleeds (RR 1.50, 95% CI 0.67, 3.34). This effectively translates to preventing 12.9 events at the cost of 2 bleeds per 1000 patient years of aspirin treatment. A more recent post-hoc analysis of the HOT study examined the same combined primary outcome per tertile of eGFR calculated using the Modification of Diet in Renal Disease equation [43]. This analysis showed that aspirin therapy produced greater reduction in major cardiovascular events in hypertensive CKD patients than patients with normal eGFR. The RR for the combined primary outcome was 0.91 (95% CI 0.76, 1.09), 0.85 (95% CI 0.61, 1.17) and 0.34 (95% CI 0.17, 0.67) for patients with a baseline eGFR of ≥ 60mL/min, 45-59 mL/min and < 45mL/min (p trend 0.03). The RR for major bleeding was 1.52 (95% CI 1.11, 2.08), 1.7 (95% CI 0.74, 3.88) and 2.81 (95% CI 0.92, 8.84) for patients with a baseline eGFR of ≥ 60mL/min, 45-59 mL/min and < 45mL/min (p trend 0.03). Thus, major bleeding was not significantly different in the lower eGFR group, and treating 1000 patients for 3.8 years would prevent 76 events at the cost of 27 major bleeds.

b. Clopidogrel

While clopidogrel monotherapy may be indicated for aspirin allergy, there are no randomised controlled trials examining the efficacy and safety of clopidogrel in CKD, dialysis or transplant subgroups. The CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) study showed a significant RR reduction of 8.7% (95% CI 0.3%, 16.5%) in favour of clopidogrel in reducing the composite outcome of ischaemic stroke, myocardial infarction or vascular death in patients with cerebrovascular, coronary and peripheral vascular disease but without significant renal impairment [44]. This study has not been subjected to post hoc analyses for CKD subgroups. Of note in a randomised controlled trial of clopidogrel for prevention arteriovenous fistula failure in haemodialysis patients, there was no reduction in the secondary endpoint of atherosclerotic events over a 6 month follow up [45]. The CHARISMA trial (Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilisation, Management and Avoidance) examined the effect of aspirin combined with clopidogrel or placebo on occurrence of MI, stroke or CV death in patients with symptomatic and asymptomatic atherosclerotic disease (but not acute coronary syndrome) [46]. In a post-hoc analysis of patients with diabetic nephropathy defined as presence of microalbuminuria (urine albumin ≥ 30 µg/mL) but with no recorded creatinine results, patients assigned to clopidogrel had a significant increase in overall (HR 1.8, 95% CI 1.2, 2.7, p =0.006) and CV mortality (HR 1.7 95% CI 1.1, 2.9, p=0.028) over a median follow up of 28 months [46].
Safety of Aspirin and/or Clopidogrel

The safety of combination aspirin and clopidogrel therapy was examined in a randomised controlled trial of clopidogrel 75mg and high dose aspirin 325mg for the prevention of arteriovenous graft thrombosis in haemodialysis patients [47]. This study was stopped early due to an increased risk of major bleeding in the treatment arm (HR 1.98 95% CI 1.19, 3.28). In a systematic review of 16 studies examining the safety of anti-platelet agents in haemodialysis patients when used for access patency, the authors concluded that combination anti-platelet therapy increases the risk for major bleeding in haemodialysis patients [48]. These findings were predominantly derived from the study of combination clopidogrel and high dose aspirin for AVG thrombosis described previously, but included other studies using aspirin alone or in combination with ticlopidine, sulfipyrazone, dipymidole or warfarin. Methodological weaknesses in the 16 studies, including inconsistent definition of bleeding events and study heterogeneity limited the conclusions that could be made from this review.

Regarding safety data for the use of aspirin alone in CKD patients, the UK-HARP-1 study (Heart and Renal Protection Study) examined the safety of simvastatin and aspirin in CKD patients (serum creatinine ≥ 150 µmol/L or on dialysis) and patients with functioning renal transplants using a 2x2 factorial design [49]. Overall, 448 patients with CKD were randomly assigned to simvastatin, aspirin, simvastatin and aspirin, or placebo (242 pre-dialysis patients, 73 patients on dialysis therapy, and 133 patients with a functioning transplant). Compliance with study treatments was 80% at 12 months. Allocation to treatment with 100 mg of aspirin daily was not associated with an excess of major bleeds (aspirin, 4 of 225 patients [2%] versus placebo, 6 of 223 patients [3%]; RR 0.66 (95% CI 0.19, 2.31), although there was a 3-fold excess of minor bleeds (34 of 225 [15%] versus 12 of 223 patients [5%]; RR 2.81 (95% CI 1.49, 5.28), P = 0.001). Among those with pre-dialysis CKD or a functioning transplant, aspirin did not increase the number of patients who progressed to dialysis therapy (7 of 187 [4%] versus 6 of 188 patients [3%]) or the number of patients who experienced a greater than 20% increase in creatinine level (63 of 187 patients [34%] versus 56 of 188 patients [30%]; RR 1.13 (95% CI 0.84, 1.52)). Similarly, in the ATC (Antithrombotic Trialists’ Collaboration) meta-analysis of randomised trials of anti-platelet therapy for the prevention of death, myocardial infarction and stroke in high risk patients, the use of anti-platelet therapy in dialysis patients was not associated with an increased risk of major bleeding (2% Anti-platelet group, 2.3% Controls) [37]. Of the 2 observational studies examining aspirin prescription and outcomes in haemodialysis patients, the DOPPS study showed no significant increased risk of major bleeds with aspirin use [38]. In the other study, Chan et al showed no increase in bleeding associated with mortality or hospitalisation with aspirin prescription, but significantly increased bleeding associated with mortality (HR 2.74 95% CI 1.26, 6.00) and hospitalisation (RR 1.39 95%CI 1.08, 1.80) in those receiving clopidogrel prescription [39].

c. Beta-blocker therapy

There are no RCTs examining the efficacy of beta-blocker therapy for chronic stable coronary artery disease in CKD patients.

In CKD patients without heart failure there are limited observational data supporting the use of beta-blockers for chronic stable coronary artery disease management. The DOPPS (Dialysis Outcomes and Practice Patterns) study recently published data from a Japanese cohort showing that among 2,286 randomly selected haemodialysis patients, 11.9% were on beta-blockers and despite a higher prevalence of coronary artery disease and hypertension among beta-blocker users, beta blocker use was independently associated with reduced all-cause mortality (HR 0.48, 95% CI 0.25, 0.88) [50]. Another retrospective cohort study of 2,550 dialysis patients showed that beta-blocker use in dialysis patients without heart failure (n = 1578) reduced the risk of heart failure and cardiac death (RR 0.77, 95% CI: 0.61 - 0.97) [51].

There are higher grades of evidence for the cardio-protective efficacy of beta-blockers in CKD patients with heart failure and these are discussed in the ‘Heart Failure Section of the Cardiovascular Disease in CKD’ KHA-CARI Guidelines.

d. Angiotensin converting enzyme inhibitor and Angiotensin receptor blocker therapy

Refer to Section on ‘Cardiovascular Effects of Blood Pressure Lowering in Patients with CKD’ under the ‘Cardiovascular Disease in CKD’ KHA-CARI Guidelines.
SUMMARY OF EVIDENCE

There is little high quality evidence regarding the management of ACS or chronic stable CAD in patients with CKD. The randomised controlled (RCT) data examining the therapeutic options for the medical management of ACS or chronic stable CAD are all taken from post-hoc analyses of RCTs from the general population where patients with CKD were identified based on serum creatinine and/or estimated GFR, and outcomes analysed. These limitations also apply to assessing harms of ACS therapies. Specifically with regards to harm of anticoagulant therapies, data have been extrapolated from trials using anticoagulants for non-cardiac indications. Prospective and retrospective registry data or observational cohorts provide a significant proportion of the evidence for ACS therapies.

The management of ACS in the general population has been published in the extensive guidelines available [7-9]. These guidelines support the use of PCI in favour of thrombolysis without specifically including or excluding CKD patients. It is notable that the latest addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the Management of ACS highlights the significance of reduced bleeding risk being associated with improved outcome for patients with ACS in the general population, and recommends including an eGFR <60mL/min when calculating bleeding risk scores to tailor anticoagulant therapy [9]. These Guidelines favour an approach of improving net clinical outcome by reducing bleeding risk in patients assessed to be at high risk of bleeding, a marker for which is renal dysfunction (eGFR < 60 mL/min). There is a perceived risk of increase bleeding in CKD patients that has led to other renal guideline groups recommending PCI over thrombolysis but with ungraded evidence, however KHA-CARI have assigned a 1D grading reflecting the general population guidelines.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative:
Refer to the “Cardiovascular effects of blood pressure lowering in patients with chronic kidney disease” topic for KDOQI recommendations related to use of antihypertensive agents in CKD. There are no specific recommendations in relation to CAD in CKD.

The “K/DOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients” [52] include the following recommendations relevant to CAD.

2.6 Patients undergoing planned invasive procedures for evaluation or treatment of CAD should be assessed for hemorrhagic risk and presence of anemia, as anticoagulants and/or antiplatelet agents may be administered adjunctively for percutaneous coronary intervention. (C)

3.1 All dialysis patients presenting with ACS should be treated as in the nondialysis population, with the exception of specific attention to drugs that have altered clearances in kidney failure (e.g., low molecular weight heparin). These therapies include percutaneous coronary intervention (PCI), CABG, anti-platelet agents, beta-blockers, thrombolytic therapy, and lipid-lowering agents. (C)
3.1.a Dialysis patients with ST-segment elevation MI should receive acute reperfusion therapy (as do patients in the nondialysis population). With the potential for increased hemorrhagic risk associated with thrombolytic therapy, emergent PCI is the preferred treatment if it is available. (C)

3.2 The timing of dialysis in the first 48 hours after ACS should take into account individual risk factors. (C)

4.1 The medical management of chronic CAD in dialysis patients should follow that of the general population. In particular, patients should receive acetylsalicylic acid (ASA), beta-blockers, nitroglycerin, ACE inhibitors or angiotensin receptor blockers (ARB), statins, and/or calcium-channel blockers (CCB) as indicated. Dose adjustments are required for medications that are renally excreted or dialyzed. (C)

4.2 Unique aspects of management in the dialysis population include:
4.2.a Maintenance of hemodynamic dry weight. (C)
4.2.b Maintenance of hemoglobin levels in accordance with K/DOQI Guidelines.52 (B)
4.2.c Modification of dosing regimens so that cardiovascular medications do not adversely impact the delivery of dialysis and ultrafiltration. Nocturnal dosing of medications should be considered. (C)
4.2.d Loop diuretics to increase urine output may be helpful for those patients with substantial residual renal function. (C)

4.3 In patients with obstructive CAD lesions, PCI and CABG are appropriate revascularization techniques. (C)
4.3.a Drug-eluting or conventional stents should be implemented according to local practice. The incidence of restenosis after PCI with drug-eluting stents is reduced in the nondialysis population. As the risk of restenosis is higher in dialysis patients, the use of drug-eluting stents is favored.
4.3.b Patients with three-vessel and/or Left main disease should undergo CABG as preferred therapy. (C)

UK Renal Association:

“The Cardiovascular Disease in CKD” [53] guidelines include the following recommendations.

3. Cardiovascular disease in CKD (CVD) (Guideline CVD 3.1-3.6)

Guideline 3.1 - CVD: Secondary prevention of cardiovascular risk
We recommend that CKD stage 1-3 patients with a history of chronic stable angina, acute coronary syndrome, myocardial infarction, stroke, peripheral vascular disease, or who undergo surgical or angiographic coronary revascularisation, should be prescribed aspirin, an ACE inhibitor, a beta-blocker, and an HMG–CoA reductase inhibitor unless contraindicated as per NICE Guidance. (1B)

Guideline 3.2 - CVD: Secondary prevention of cardiovascular risk
We suggest that CKD stage 4/5 patients (including those on dialysis and after transplantation) with a history of chronic stable angina, acute coronary syndrome, myocardial infarction, stroke, peripheral vascular disease, or who undergo surgical or angiographic coronary revascularisation, should be prescribed aspirin, an ACE inhibitor, a beta-blocker, and an HMG–CoA reductase inhibitor unless contraindicated as per NICE Guidance. (2C)

Guideline 3.3 - CVD: Secondary prevention of cardiovascular risk
We suggest that aspirin and clopidogrel may be indicated for up to 12 months post angioplasty and stenting and in non-ST elevation MI but may have an excess of bleeding complications. (2C)

Guideline 3.4 - CVD: Secondary prevention of cardiovascular risk
We suggest that aspirin is indicated for secondary prevention but not primary prevention of vascular disease in renal failure. (2C)

Guideline 3.5 - CVD: Secondary prevention of cardiovascular risk
We suggest that the doses of ACE inhibitors and beta-blockers should be titrated upwards to the maximal effective or tolerated dose. (2C)

Guideline 3.6 - CVD: Secondary prevention of cardiovascular risk
We suggest that patients on lipid-lowering drug treatment should have total cholesterol reduced by 25% or to below 4 mmol/l, or LDL-cholesterol to below 2 mmol/l, or reduced by 30%, whichever reductions are the greatest. (2B)

Canadian Society of Nephrology:
No recommendations in relation to CAD.

European Best Practice Guidelines: No recommendations
International Guidelines: No recommendations

SUGGESTIONS FOR FUTURE RESEARCH

1. Enoxaparin dose finding study for stages of CKD using anti-Xa levels with monitoring of bleeding risk.
2. Clopidogrel dose finding study for stages of CKD using ADP-induced platelet activation with monitoring of bleeding risk.
3. RCT of clopidogrel versus aspirin in CKD patients at high risk for ischaemic events.
4. RCT of prasugrel versus clopidogrel in CKD patients with clopidogrel resistance.
5. RCT of fondaparinux versus enoxaparin in NSTE-ACS in patients with mild to moderate CKD (eGFR > 30 mL/min)
6. RCT of bivalirudin versus heparin/GP IIb/IIIa inhibitor during PCI in CKD patients, including dialysis patients.

CONFLICT OF INTEREST

Gursharan Dogra has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.
REFERENCES


53. UK Renal Association, CLINICAL PRACTICE GUIDELINES: Cardiovascular Disease in CKD. 2010.


### APPENDICES

#### Table 1. Characteristics of included studies

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<tr>
<th>Study ID</th>
<th>N</th>
<th>Study design</th>
<th>Description - Participants and Interventions</th>
<th>Follow up (months)</th>
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</table>
- ESRD – 5.1 (2.2-12.1)  
- <35 ml/min – 5.4 (2.9-10.3)  
- 35-50 ml/min – 4.1 (2.3-7.2)  
- 50- 5 ml/min – 1.9 (1.1-3.1)  
Logistic regression HR (95% CI) – post discharge death  
- ESRD – 5.4 (3.0-9.7)  
- <35 ml/min – 1.9 (1.2-3.0)  
- 35-50 ml/min – 2.2 (1.5-3.3)  
- 50-75 ml/min – 2.4 (1.7-3.3)  
- Use of reperfusion – 0.7 (0.6-0.9)  
Limitations: bias associated with retrospective analysis and generalizability associated with single centre. |
| Keltai et al (2007) [14] CURE | 12,253 | Sub group analysis of a randomised double blind placebo-controlled trial. Multi centre – Nth America, Europe, Israel | Patients hospitalised within 24 hours of onset of acute coronary syndrome symptoms. Patients with high risk of bleeding excluded. Sub group analysis on basis of renal function at baseline. Clopidogrel (300 mg loading dose, 75 mg/day) vs placebo. Primary outcome: composite of cardiovascular death, non-fatal MI or stroke. | Mean 9 months Range 3-12 | RR for primary outcome - clopidogrel vs placebo (95% CI)  
- <64 ml/min - 0.89 (0.76-1.05)  
- 64-81 ml/min – 0.68 (0.56-0.84)  
- >81 ml/min – 0.74 (0.60-0.93)  
Life threatening bleeding risk – clopidogrel vs placebo (95% CI)  
- <64 ml/min - 0.89 (0.60-1.31)  
- 64-81 ml/min – 1.23 (0.78-1.93)  
- >81 ml/min – 1.65 (1.01-2.70)  
Minor bleeding risk – clopidogrel vs placebo (95% CI)  
- <64 ml/min - 1.50 (1.21-1.86)  
- 64-81 ml/min – 1.61 (1.27-2.06)  
- >81 ml/min – 1.65 (1.56-2.61)  
Limitations: Potential for residual confounding associated with sub group analysis. eGFR estimated only at baseline. Potential selection bias associated with patients having very low renal function. |
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<th>Study ID</th>
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| Best et al (2008) [15] CREDO | 2,002 | Sub group analysis of a randomised double blind placebo-controlled trial. Multi centre – Nth America | Patients referred for PCI or coronary angiogram with symptomatic CAD and ischemia. Excluded individuals with serum creatinine >3 mg/dL. Clopidogrel (300 mg loading dose, 75 mg/day) vs placebo. (Both received standard therapy including aspirin). Primary outcome: composite of cardiovascular death, non-fatal MI or stroke. | 12 | HR for primary composite outcome at 1 year – clopidogrel vs placebo (95% CI)  
- >90 ml/min – 0.42 (0.26-0.69)  
- 89-60 ml/min – 0.80 (0.51-1.25)  
- <60 ml/min - 1.41 (0.81-2.45)  
RR for major bleeding – clopidogrel vs placebo (95%)  
- >90 ml/min – 1.17 (0.74-1.84)  
- 89-60 ml/min – 1.60 (0.97-2.83)  
- <60 ml/min – 1.12 (0.51-1.19)  
RR for minor bleeding – clopidogrel vs placebo (95%)  
- >90 ml/min – 0.93 (0.50-1.73)  
- 89-60 ml/min – 1.58 (0.88-2.83)  
- <60 ml/min – 1.08 (0.82-1.42)  
Limitations: Potential for residual confounding associated with sub group analysis. eGFR estimated only at baseline. Potential selection bias associated with patients having very low renal function. |
Age adjusted risk reduction for in hospital mortality with aspirin and beta-blocker relative to patients who received neither drug (P,0.0001 for all):  
- >82 ml/min – 80%  
- 82-63 ml/min – 75%  
- 63-46 ml/min – 69%  
- <46 ml/min – 64%  
- Dialysis – 78%  
No significant trends in rate of bleeding observed.  
Limitations: bias associated with medical registry analysis and generalizability associated with single centre. |
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| Berger et al(2003) [19] | 146,765          | Retrospective registry review. US Cooperative Cardiovascular Project matched with USRDS | Patients >65 years presenting with clinical evidence of AMI. Primary outcome post AMI 30 day mortality.                             | NA                 | Use of aspirin or beta-blockers less likely in dialysis patients. 30 day mortality in all patients:  
  - Dialysis 29.0%, non ESKD 18.3% (P<0.001)  
  RRR in 30 day mortality with aspirin use:  
  - Dialysis 50% (P<0.001), non ESKD 63% (P<0.001)  
  RRR in 30 day mortality with beta-blocker use:  
  - Dialysis 40% (P<0.001), non ESKD 56% (P<0.001)  
  RRR in 30 day mortality with ACEi use:  
  - Dialysis 48% (P<0.001), non ESKD 27% (P<0.001)  
  No adverse events including bleeding reported. Limitations: bias associated with retrospective review of medical registry. Short term outcomes assessment. |
  Primary outcome: composite of death from any cause or nonfatal MI within 30 days of randomisation.  
  Enoxaparin vs. unfractionated heparin | 30 days             | In multivariable regression model:  
  - CrCl was an independent predictor of death  
    - OR 1.27 (95%CI 1.24-1.31)  
    - 10ml/min decrement in CrCl  
    - Death of MI: OR 1.14 (95%CI 1.13-1.17)  
    - Stroke: OR 1.26 (95%CI 1.19-1.35)  
    - Intracranial haemorrhage: OR 1.24 (95%CI 1.15-1.35)  
    - Major bleed OR 1.16 (95%CI 1.10-1.22)  
    - Minor bleed OR 1.16 (95%CI 1.11-1.21)  
  Rates of death similar between enoxaparin and heparin irrespective of CrCl with the exception of the >90 ml/min group where the composite outcome was significantly lower in the enoxaparin group (OR 0.69 [0.56-0.84]).  
  Major and minor bleeding significantly greater in the 30-60 ml/min and 60-90 ml/min groups.  
  Limitation: No indication has been provided as to the 10% of patients not categorised according to CrCl. Potential for residual confounding associated with sub group analysis. eGFR estimated only at baseline. ESRD excluded. |
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<tr>
<td>Spinler et al (2003) [21] ESSENCE and TIMI IIB</td>
<td>ESSENCE – 3,171</td>
<td>Sub group analysis of 2 randomised double blind placebo controlled trials. Multi-centre international (ESSENCE and TIMI IIB)</td>
<td><strong>ESSENCE and TIMI IIB - Patients with recent onset of angina and confirmed evidence of ischaemic heart disease randomised within 24 hours of onset.</strong>&lt;br&gt;<strong>Primary outcome:</strong>&lt;br&gt; ESSENCE composite of death from any cause or nonfatal MI or recurrence of angina within 14 days.&lt;br&gt; TIMI IIB composite of death from any cause or nonfatal MI or urgent revascularisation.&lt;br&gt; Enoxaparin vs. unfractionated heparin (ESSENCE and TIMI IIB)</td>
<td>30 days ESSENCE 35 days TIMI IIB</td>
<td>Logistic regress analysis for effect of enoxaparin treatment in patients with and without renal impairment (&lt;30 ml/min CrCl):&lt;br&gt; - Death at 43 days – OR 0.43 (0.17,1.12)&lt;br&gt; - MI at 43 days – OR 1.45 (0.39,5.40)&lt;br&gt; - Any bleeding – OR 1.04 (0.42,2.59)&lt;br&gt; There was a significantly lower rate of MI in patients without renal impairment who received enoxaparin (4.8 vs 6.0% P&lt;0.05).&lt;br&gt; There was no difference in death between patients with or without renal impairment.&lt;br&gt; There was a significantly higher rate of bleeding in patients without renal impairment who received enoxaparin (9.8 vs 3.9% P&lt;0.001).&lt;br&gt; Limitations: Potential for residual confounding associated with sub group analysis. eGFR estimated only at baseline. ESRD excluded. Low numbers of ≤30 ml/min.</td>
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<td>Collet et al (2005) [22]</td>
<td>24,309 (GRACE) 16,049 (meeting inclusion criteria)</td>
<td>Review of multinational, prospective, ACS registry.</td>
<td><strong>GRACE patients with non-ST-segment elevation acute coronary syndrome or unstable angina.</strong></td>
<td>NA</td>
<td>Adjusted ORs (95% CI) for 30 day mortality:&lt;br&gt; - CrCl &lt;30 ml/min – OR 3.64 (2.64-5.01)&lt;br&gt; - CrCl 30-60 ml/min – OR 1.58 (1.21-2.10)&lt;br&gt; Adjusted ORs (95% CI) for in-hospital major bleeding:&lt;br&gt; - CrCl &lt;30 ml/min – OR 2.51 (1.82-3.54)&lt;br&gt; - CrCl 30-60 ml/min – OR 1.58 (1.02-1.71)&lt;br&gt; Limitations: Incomplete CrCl data (25% of eligible patients). Bias associated with medical registry analysis.</td>
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</table>
| Joyner et al (2009) [23] OASIS-5 | 20,078 | Serum creatinine (mg/dL) | Sub group analysis of a randomised double blind double-dummy placebo-controlled trial. | 3-6 | Primary composite outcome at 9 days similar across GRACE risk score groups.  
GRACE risk score associated with increased mortality at 180 days in the treatment groups (fondaparinux vs enoxaparin):  
  - Low risk – 180 day mortality – 7.1 and 6.2%  
  - Intermediate risk - 180 day mortality – 10.2 and 8.7%  
  - High risk - 180 day mortality – 20.7 and 19.1%  
The impact of fondaparinux vs enoxaparin on composite primary outcome at 180 days similar across the 3 GRACE risk score groups (low, intermediate, high):  
  - Low risk - HR 0.90 (0.75-1.08)  
  - Intermediate risk – HR 0.89 (0.77-1.03)  
  - High risk – HR 0.95 (0.85-1.06)  
Trend to increase in major bleeding at 9 days with increasing GRACE score.  
Limitations: Potential for residual confounding associated with sub group analysis. Serum creatinine estimated only at baseline. ESRD excluded. The GRACE score is an aggregate of risk factors one of which is serum creatinine and thus provides an indirect measure of the association between renal function at trial outcomes. |
| Fox et al (2007) [24] OASIS 5 | 20,078 | eGFR (mL/min/1.73m²) | Sub group analysis of a randomised double blind double-dummy placebo-controlled trial. | 3-6 | No significant difference in 9 day composite outcome with treatment or between eGFR groups.  
- <58 mL/min/1.73m² – HR 0.90 (0.73-1.11)  
- 58-71 mL/min/1.73m² – HR 1.10 (0.88-1.38)  
- 71-86 mL/min/1.73m² – HR 1.03 (0.80-1.33)  
- ≥86 mL/min/1.73m² – HR 1.05 (0.82-1.34)  
Major bleeding events at 9 days reduced in fondaparinux vs enoxaparin and lowest in lowest eGFR group:  
- <58 mL/min/1.73m² – HR 0.42 (0.32-0.56)  
- 58-71 mL/min/1.73m² – HR 0.53 (0.39-0.72)  
- 71-86 mL/min/1.73m² – HR 0.66 (0.46-0.95)  
- ≥86 mL/min/1.73m² – HR 0.61 (0.41-0.90)  
The absolute benefits were only significant in the <58 mL/min/1.73m² group.  
Limitations: Potential for residual confounding associated with sub group analysis. Serum creatinine estimated only at baseline. ESRD excluded. |

For Joyner et al (2009) [23] OASIS-5:  
- Sub group analysis of a randomised double blind double-dummy placebo-controlled trial.  
- Patients with non-ST-segment elevation ACS randomised within 24 hours of symptoms.  
- Daily fondaparinux vs. twice daily enoxaparin.  
- Primary outcome composite of death, myocardial infarction, or refractory ischemia at nine days.  
- Sub group analysis on basis of GRACE score which incorporates serum creatinine.  
- GRACE risk score associated with increased mortality at 180 days in the treatment groups (fondaparinux vs enoxaparin):  
  - Low risk – 180 day mortality – 7.1 and 6.2%  
  - Intermediate risk - 180 day mortality – 10.2 and 8.7%  
  - High risk - 180 day mortality – 20.7 and 19.1%  
- The impact of fondaparinux vs enoxaparin on composite primary outcome at 180 days similar across the 3 GRACE risk score groups (low, intermediate, high):  
  - Low risk - HR 0.90 (0.75-1.08)  
  - Intermediate risk – HR 0.89 (0.77-1.03)  
  - High risk – HR 0.95 (0.85-1.06)  
- Trend to increase in major bleeding at 9 days with increasing GRACE score.  
- Limitations: Potential for residual confounding associated with sub group analysis. Serum creatinine estimated only at baseline. ESRD excluded. The GRACE score is an aggregate of risk factors one of which is serum creatinine and thus provides an indirect measure of the association between renal function at trial outcomes.  

For Fox et al (2007) [24] OASIS 5:  
- Sub group analysis of a randomised double blind double-dummy placebo-controlled trial.  
- Patients with non-ST-segment elevation ACS randomised within 24 hours of symptoms.  
- Daily fondaparinux vs. twice daily enoxaparin.  
- Primary outcome composite of death, myocardial infarction, or refractory ischemia at nine days.  
- Sub group analysis on basis of GRACE score which incorporates serum creatinine.  
- No significant difference in 9 day composite outcome with treatment or between eGFR groups.  
- eGFR groups:  
  - <58 mL/min/1.73m² – HR 0.90 (0.73-1.11)  
  - 58-71 mL/min/1.73m² – HR 1.10 (0.88-1.38)  
  - 71-86 mL/min/1.73m² – HR 1.03 (0.80-1.33)  
  - ≥86 mL/min/1.73m² – HR 1.05 (0.82-1.34)  
- Major bleeding events at 9 days reduced in fondaparinux vs enoxaparin and lowest in lowest eGFR group:  
  - <58 mL/min/1.73m² – HR 0.42 (0.32-0.56)  
  - 58-71 mL/min/1.73m² – HR 0.53 (0.39-0.72)  
  - 71-86 mL/min/1.73m² – HR 0.66 (0.46-0.95)  
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- The absolute benefits were only significant in the <58 mL/min/1.73m² group.  
- Limitations: Potential for residual confounding associated with sub group analysis. Serum creatinine estimated only at baseline. ESRD excluded.
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<tr>
<th>Study ID</th>
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</tr>
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</table>
| Lim et al  | 17 studies (645 patients)              | Systematic review and meta-analysis of RCTs                                  | RCTs comparing commercially available (in Canada) low molecular weight heparins (LMWH) with another anticoagulant for the prevention of circuit thrombosis in patients receiving chronic haemodialysis or haemofiltration. Outcomes: Bleeding or thrombosis of the extracorporeal circuit. | 1 day to 36 months | All bleeding risk (6 studies; 202 patients) LMWH vs UFH  
  ● Risk ratio 0.96 (95%CI 0.27,3.43)  
  Vascular compression time (4 studies; 182 patients) LMWH vs UFH  
  ● Weighted mean difference -0.87 (-2.75-1.02)  
  Circuit thrombosis (7 studies; 6567 patients) LMWH vs UFH  
  ● Risk ratio 1.15 (0.70,1.91)  
 Limitation: Not an ACS population.                                                                                                                                             |
| (2004) [26] |                                        |                                                                               |                                                                                                             |                    |                                                                                                                                                                                                                                                                          |
| Lim et al  | 2 RCTs (3,934 patients) 16 observational | Systematic review of RCTs and observational studies                          | RCTs and observational studies of LMWH in non-dialysis-dependant patients with renal insufficiency (CrCl ≤30ml/min). Outcomes: anti-Xa or bleeding.                           |                    | Major bleeding events in patients with CrCl ≤30 ml/min compared to patients with CrCl >30 ml/min.  
  ● All treatment comparison (12 studies, 4971 patients) – OR 2.25 (1.19-4.27)  
  ● Therapeutic dose of enoxaparin (7 studies, 4287 patients) – OR 3.88 (1.78-8.45)  
 Limitations: 10 of the 12 studies included in meta-analysis are observational and the 2 RCTs are sub group analysis. Therefore results are subject to the range of biases associated with observational studies and sub group analyses. |
<p>| (2006) [25] | (2,147 patients)                       |                                                                               |                                                                                                             |                    |                                                                                                                                                                                                                                                                          |</p>
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<tbody>
<tr>
<td>Januzzi et al (2002) [27]</td>
<td>1915</td>
<td>Sub group analysis of a randomised double blind placebo-controlled trial. Multi-centre international.</td>
<td>Patients with unstable angina or non-Q-wave myocardial infarction</td>
<td>6 months</td>
<td>Decreasing renal function is a risk factor for adverse outcomes with risk significantly reduced across all renal function levels in the tirofiban plus heparin group compared to heparin alone.</td>
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<td></td>
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<td>Tirofiban plus heparin vs. heparin plus tirofiban placebo vs. placebo</td>
<td></td>
<td>Incidence of composite endpoint at 30 days for CrCl (ml/min) groups for the tirofiban plus heparin and heparin treatment groups</td>
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<td>Primary outcome: composite of death from any cause, new myocardial infarction, or refractory ischemia within seven days after randomisation.</td>
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<td>- ≤30 – 50% vs 50%</td>
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<td>- 30-60 – 25% vs 30%</td>
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<td>- 60-75 – 19% vs 19%</td>
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<td>- &gt;75 – 11% vs 16%</td>
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<td>Incidence of Death/MI at 30 days for CrCl (ml/min) groups for the tirofiban plus heparin and heparin treatment groups</td>
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<td>- ≤30 – 15% vs 25%</td>
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<td>- 30-60 – 13% vs 15%</td>
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<td>- 60-75 – 9% vs 10%</td>
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<td>- &gt;75 – 4% vs 10%</td>
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<td>The OR for any bleeding for CrCl ≤30 compared to &gt;75 ml/min: 1.57 (P&lt;0.001)</td>
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<td>Limitation: It is not possible with the data provided to evaluate the association between CrCl and the primary outcomes or adverse events. Potential for residual confounding associated with sub group analysis. Serum creatinine estimated only at baseline. Excluded ESRD.</td>
</tr>
<tr>
<td>Reddan et al (2003) [28]</td>
<td>2044</td>
<td>Sub group analysis of a double blind randomised controlled trial. Multi-centre North America</td>
<td>Patients scheduled for PCI without planned use of a Gp IIb/IIIa inhibitor.</td>
<td>30 days</td>
<td>Adjusted ORs (95% CI) for eptifibatide vs placebo with CrCl (ml/min):</td>
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<td></td>
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<td>Eptifibatide vs placebo as an adjunct to PCI.</td>
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<td>Primary outcome at 48 hrs</td>
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<td>Primary outcome – composite of death, MI, urgent target vessel revascularisation and thrombotic bailout within 30 days.</td>
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<td>- 60 – 0.52 (0.33-0.81)</td>
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<td>- 90 – 0.64 (0.46-0.89)</td>
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<td>Primary outcome at 30 days</td>
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<td>- 60 – 0.53 (0.34-0.83)</td>
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<td>- 90 – 0.68 (0.49-0.94)</td>
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<td>The OR (95% CI) for any bleeding for eptifibatide vs placebo was 0.99 (0.97-1.13) with no significant (P=0.79) interaction with CrCl.</td>
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<td>Limitations: Potential for residual confounding associated with sub group analysis. Serum creatinine estimated only at baseline. Low incidence of bleeding may limit ability to detect treatment and subgroup effect.</td>
</tr>
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</table>
| Frilling et al (2002) [29] | 1,040      | Registry review. Single centre Germany | Ludwigshafen IIb/III-Antagonist Registry of PCI patients treated with abciximab. Impaired renal function defined as serum creatinine $\geq$1.3 mg/dL. | NA                | OR (95% CI) for renal insufficient compared to normal patients:  
  - Procedural success – 0.66 (0.15-2.88)  
  - In-hospital mortality – 2.45 (0.55-10.86)  
  - Any bleeding – 3.24 (0.93-11.26)  
  - Major bleeding – 7.86 (1.54-40.09)  
  - Minor bleeding – 1.42 (0.18-10.99)  
  Multivariate analysis OR (95% CI):  
  - Any bleeding - 5.1 (1.9-13.8).  
Limitations: Biases associated with registry review. Small number of patients with renal insufficiency. Single centre. Serum creatinine only at baseline. |
| Freeman et al (2003) [30] | 889        | ACS patient database. Single-centre US | Adults (>18 years) presenting with unstable angina or acute MI not precipitated or accompanied by a significant comorbidity. | NA                | Multivariate ORs (95% CI) for in-hospital mortality with worsening CrCl stratum:  
  - Including Ilb/IIa antagonist as a covariate: 1.67 (1.18-2.37)  
  - Excluding Ilb/IIa antagonist as a covariate: 1.74 (1.23-2.46)  
  Multivariate OR (95% CI) for overall protective effect of Ilb/IIa antagonist:  
  - 0.34 (0.12-0.98)  
Bleeding events significantly increase with worsening CrCl stratum not requiring dialysis (P=0.03). Adjusted OR (95% CI) for increased bleeding events with Ilb/IIa antagonist treatment after controlling for CrCl:  
  - 2.13 (1.39-3.27)  
Limitations: Biases associated with registry review. Single centre. Serum creatinine determined only at baseline. Limited recording of Ilb/IIa antagonist treatment. Impact of renal function on treatment decisions is unknown. |
| Jerimias et al (2002) [31] | 190        | Review of hospital records. Single-centre US | Consecutive patients who underwent PCI excluding those with cardiogenic shock. | NA                | ORs (95% CI) for patients treated with abciximab:  
  - Death within 30 days – 0.27 (0.07-1.01)  
  - Major bleeding - 1.51 (0.70-3.26)  
Limitations: Biases associated with registry review. Small number of patients with renal insufficiency. Single centre. Serum creatinine only at baseline. Differences in treatments associated with patients on dialysis. |
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</table>
| Best et al (2003) [32] | 4158           | Review of clinic register.                        | All patients who underwent a PCI procedure.                                                                   | NA                | Renal insufficiency was associated with increased minor bleeding (P<0.001) but not with major bleeding (P=0.61).  
Conditional OR (95% CI) for a 10 ml/min decrease in CrCl from 90 ml/min:  
- Major bleeding – 0.9 (0.79-1.02)  
- Minor bleeding – 1.04 (0.89-1.23)  
Conditional OR (95% CI) associated with abciximab treatment:  
- Major bleeding (all patients) – 2.14 (1.12-4.10)  
- Minor bleeding (all patients) – 2.49 (1.12-5.55)  
- Major bleeding (abciximab treated) – 1.18 (0.99-1.39)  
- Minor bleeding (abciximab treated) – 1.01 (0.83-1.23)  
Limitations: Limitations: Biases associated with registry review. Unknown number of patients with renal insufficiency. Single centre. Serum creatinine only at baseline. Differences in treatments associated with patients with renal insufficiency are unknown. |
| Chew et al (2003) [33] | 3 trials (5,035 patients) | CrCl ≤30 (39), 30-59 (1255), 60-90 (2163), >90 (1578) | Meta-analysis of randomised controlled trials comparing bivalirudin with heparin in patients who underwent PCI where baseline serum creatinine was reported. Excluded patients with serum creatinine >3.0 mg/dL. | NA                | ORs (95% CI) associated with bivalirudin:  
- Death/MI or urgent revascularisation (all patients): 0.75 (0.59-0.96)  
- Major bleeding (all patients): 0.40 (0.26-0.61)  
- Triple endpoint (normal renal function): 0.79 (0.52-1.18)  
- Triple endpoint (mild renal insufficiency): 0.73 (0.53-0.99)  
- Triple endpoint (moderate renal insufficiency): 0.77 (0.55-1.07)  
- Triple endpoint (severe renal insufficiency): 0.81 (0.12-5.23)  
- Major bleeding (normal renal function): 0.45 (0.21-0.96)  
- Major bleeding (mild renal insufficiency): 0.46 (0.09-1.86)  
- Major bleeding (moderate renal insufficiency): 0.46 (0.30-0.70)  
Limitations: The meta-analysis is of subgroups from randomised controlled trials and thus subject to the associated biases. Low numbers of patients with CrCl <30 ml/min. Trials excluded dialysis patients. Search strategy not provided. |
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<tr>
<td>Mehran et al</td>
<td>13,819</td>
<td>Sub group analysis of an open-label randomised controlled trial.</td>
<td>Adults (&gt;18 years) with symptoms of unstable angina lasting at least 10 minutes in the preceding 24 hours with: (1) new ST-segment depression or transient elevation of at least 1 mm, (2) troponin I or T or creatine kinase–MB elevation, (3) known coronary artery disease, or (4) all 4 other Thrombolysis Myocardial Infarction (TIM I) unstable angina risk criteria positive. Heparin plus a GPI vs. Bivalirudin plus a GPI vs. Bivalirudin alone. Primary outcome – composite death, MI, unplanned revascularisation at 30 days. Major bleeding at 30 days. Composite plus major bleeding at 30 days.</td>
<td>12 months</td>
<td>ORs (95% CI) for clinical outcomes at 30 days and 1 year for patients with CrCl &lt;60 ml/min compared to ≥60 ml/min:</td>
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<tr>
<td>(2009) [34]</td>
<td></td>
<td>Multi-centre international.</td>
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<td>• Composite primary outcome at 30 days – 1.55 (1.36-1.77)</td>
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<td>• Death (any cause) at 30 days – 2.70 (2.02-3.59)</td>
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<td></td>
<td>• Major bleeding at 30 days – 2.52 (2.15-2.95)</td>
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<td>• Composite primary outcome at 1 year – 1.50 (1.38-1.64)</td>
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<td>• Mortality – 2.84 (2.38-3.39)</td>
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<td>ORs (95% CI) for bivalirudin alone vs heparin plus GPI in patients with CrCl &lt;60 ml/min:</td>
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<td>• Composite primary outcome at 30 days – 1.18 (0.88-1.57)</td>
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<td>• Death (any cause) at 30 days – 1.36 (0.77-2.41)</td>
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<td>• Major bleeding at 30 days – 0.64 (0.45-0.89)</td>
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<td>• Composite primary outcome at 1 year – 1.20 (0.96-1.48)</td>
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<td>• Mortality – 0.99 (0.69-1.42)</td>
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<td>Limitations: Potential for residual confounding associated with sub group analysis. Serum creatinine estimated only at baseline. ESRD excluded.</td>
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Tokmakova et al (2004) [35] | 2,231. | 2,231. | Sub group analysis of a double blind randomised controlled trial. Multi-centre North America. | | Adult ≥21 years with AMI and left ventricular dysfunction occurring within 16 days of randomisation. Captopril vs. placebo. Outcomes - all cause mortality, fatal, non-fatal major cardiovascular events, development of severe heart failure and development of congestive heart failure. Multivariable HRs (95% CI) for eGFR (ml/min/1.73m$^2$) groups compared to those with eGFR ≥75 ml/min/1.73m$^2$: All-cause mortality | | Average 42 (range 24 to 60) | | Limitations: Potential for residual confounding associated with sub group analysis. | |
Frances et al (2000) [36] | 78,522 | 20,902 with LVEF <40%, SrCr>3mg/dL (1,582) SrC≤3mg/dL (19,350) | Retrospective review of medical records database. US Medicare | NA | HR (95% CI) for 1 year mortality associated with ACEi use at hospital discharge: | | | Limitations: Biases associated with registry review. Renal function based on highest serum creatinine value during hospitalisation and not at time of discharge. Unable to determine whether ACEi treatment occurred after discharge (i.e. cross over bias). |
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<td>ATC (2002) [37]</td>
<td>287 trials. 135,000 patients (antiplatelet vs. control) 77,000 patients (comparison of antiplatelets). 14 trials including 2,632 haemodialysis patients.</td>
<td>Systematic review and meta-analysis of randomised controlled trials. Published and unpublished trials to September 1997 comparing antiplatelet with control or comparing different antiplatelets. Patients considered to be at high annual risk of vascular events due to preexisting disease. Primary outcome “serious vascular event”</td>
<td>12-18 months (haemodialysis)</td>
<td>In haemodialysis patients, antiplatelet treatment after placement of a dialysis shunt or fistula was associated with a 41% (SE 16%) proportional reduction in serious vascular events. Major extra cranial bleeds were not significantly different: 27/133 (2.0%) antiplatelet vs 31/1371 (2.3%) adjusted control. Limitations: The number of serious vascular events in the haemodialysis trials was small (99) as was the number of major extra cranial bleeds (46).</td>
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</tbody>
</table>
| Ethier et al (2007) [38] (DOPPS I,II) | 28,320 | Prospective cohort. Multi-centre – international. | Adult haemodialysis patients randomly selected from 307 dialysis centres. | NA | Relative risks (95% CI) in patients administered aspirin compared to those not administered aspirin:  
- All-cause mortality – 0.99 (0.93-1.05)  
- Any cardiac event – 1.08 (1.02-1.14)  
- MI – 1.21 (1.06-1.38)  
- Stroke - 0.82 (0.69-0.98)  
- Gastrointestinal bleeding – 1.01 (0.88-1.17)  
Limitations: Potential biases associated with an observational study. Associations with aspirin potentially affected by indication bias, however sensitivity analyses were performed. Similarly for potential survivor bias. Potential for underreporting of aspirin use. |
| Chan et al (2009) [39] | 41,425 | Warfarin – 8.3% Clopidogrel – 10.0% Aspirin – 30.4%. At least 2 drugs – 8.1% None - 59.7% | Incident initiating long-term haemodialysis with minimum of 3 months follow-up. Primary outcome – mortality. Secondary outcomes – death and hospitalisation from bleeding. | Minimum 3 months of records after initiation of dialysis. | Mortality hazard ratios (95% CI) for patients taking aspirin: Unadjusted – 1.17 (1.12-1.22) Adjusted – 0.95 (0.92-1.00) Mortality hazard ratios (95% CI) for patients taking clopidogrel: Unadjusted – 1.50 (1.39-1.52) Adjusted – 1.15 (1.07-1.25)  
Limitations: Potential biases associated with a retrospective observational study. Associations with aspirin and clopidogrel potentially affected by indication bias, however sensitivity analyses were performed. Potential selection bias due to exclusion of 16% of incident dialysis patients due to inadequate follow-up time. |
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<th>Follow up (months)</th>
<th>Comments and results</th>
</tr>
</thead>
</table>
| Ezekowtz et al (2004) [40] | 6,427   | **Prospective cohort**. Two province based medical registers - Canada         | All patients undergoing coronary angiography in British Columbia and Alberta. Analysis restricted to patients with heart failure with CAD (>50% stenosis) proven after angiography. | 12 months         | CKD patients less likely to be prescribed beta-blockers, ACEi, aspirin or statins.  
Adjusted all-cause mortality OR (95% CI) with prescribed medications:  
Beta-blockers amongst eGFR groups (ml/min/1.73 m^2):  
- All – 0.75 (0.62-0.90)  
- ≥60 – 0.54 (0.39-0.75)  
- 59-30 – 0.75 (0.57-0.98)  
- <30 – 1.21 (0.76-1.93)  
ACEi:  
- All – 0.97 (0.81-1.16)  
- ≥60 – 0.72 (0.48-0.99)  
- 59-30 – 1.15 (0.88-1.49)  
- <30 – 1.10 (0.69-1.73)  
Aspirin:  
- All – 0.69 (0.57-0.85)  
- ≥60 – 0.63 (0.45-0.89)  
- 59-30 – 0.75 (0.56-0.99)  
- <30 – 0.76 (0.46-1.25)  
Statins  
- All – 0.79 (0.64-0.97)  
- ≥60 – 0.73 (0.52-1.01)  
- 59-30 – 0.0.81 (0.60-1.10)  
- <30 – 0.96 (0.57-1.63)  
Limitations: Potential biases associated with observational study of medical registers.  
Medication prescription only available at baseline as is serum creatinine used for eGFR. No data on biomarkers of a number of potential confounders. Relatively low mortality rate. No Hb data to allow assessment of association between anaemia and poorer outcome with HF. |
<table>
<thead>
<tr>
<th>Study ID</th>
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<tbody>
<tr>
<td>Zanchetti et al (2002) [42] and Jardine et al (2010) [43]</td>
<td>18,790</td>
<td>Sub group analysis of a double blind randomised controlled trial. Multi-centre international.</td>
<td>Patients aged 50-80 years with hypertension and a diastolic BP between 100 and 115 mmHg. Randomised to 3 BP pressure target groups (≤90, ≤85, ≤80). Step wise antihypertensive therapy 1. Felodipine, 2. ACEi or beta-blockers. 3. Dosing titrations (felodipine). 4. Dosing titrations (ACEi and beta-blockers). 5. Diuretic. Randomised to low dose aspirin vs. placebo. Primary outcome: major CVD events (MI, stroke, CVD death). Major bleeding.</td>
<td>3.8 years (average)</td>
<td>RR (95% CI) for sub group with serum creatinine &gt;1.3 mg/dL treated with aspirin compared to those with:  - Major cardiovascular event – 0.55 (0.37-0.81)  - MI – 0.14 (0.074-0.48)  - Major bleeds – 1.50 (0.67-3.34) Serum creatinine was the only significant sub-group treatment interaction. HR (95%CI) associated with halving of eGFR  - Major cardiovascular events – 1.84 (1.37-2.46)  - MI – 1.84 (1.09-3.11)  - CVD mortality – 1.99 (1.32-2.99)  - Any bleeding – 1.77 (1.09-2.86) HR (95%CI) associated in the aspirin treatment with eGFR ml/min/1.73 m². Major CVD events  - All – 0.85 (0.73-0.98)  - ≥60 – 0.91 (0.76-1.09)  - 45-59 – 0.85 (0.61-1.17)  - &lt;45 – 0.34 (0.17-0.67) MI  - All – 0.71 (0.58-0.88)  - ≥60 – 0.78 (0.61-1.00)  - 45-59 – 0.64 (0.39-1.03)  - &lt;45 – 0.31 (0.11-0.85) Major bleeding  - All – 1.61 (1.21-2.14)  - ≥60 – 1.52 (1.11-2.08)  - 45-59 – 1.70 (0.74-3.88)  - &lt;45 – 2.81 (0.90-8.84) Limitations: Only a small proportion of the study population had an eGFR &lt;45. Low numbers with Stage 4 or above CKD. Unlike CVD outcomes bleeding episodes were not validated. Participants were selected with elevated BP and thus of high CVD risk. Potential for residual confounding associated with sub group analysis. Serum creatinine determined at baseline.</td>
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<tr>
<td>Dember et al (2008) [45]</td>
<td>876</td>
<td>Randomised controlled trial. Multi-centre US</td>
<td>Haemodialysis (current or intended) patients undergoing creation of a new upper extremity fistula. Clopidogrel vs. placebo. Primary outcome – thrombosis. Adverse events – bleeding, hospitalisation and death.</td>
<td>6 months</td>
<td>No significant difference in serious adverse events between treatment groups. RR (95%CI) for selected serious adverse events for clopidogrel compared to placebo: ● Any serious adverse event – 0.82 (0.61-1.10) ● Any bleeding – 1.07 (0.49-2.32) ● Hospitalisation – 0.82 (0.61-1.11) ● Death – 0.99 (0.25-3.93) Limitations: Study limited to haemodialysis patients. Serious adverse events are secondary outcomes.</td>
</tr>
<tr>
<td>Dasgupta et al (2009) [46]</td>
<td>15,603</td>
<td>Sub-group analysis of a randomised double blind placebo controlled trial. Multi-centre international</td>
<td>Patients ≥45 years with multiple atherothrombotic risk factors, documented coronary disease, documented cerebrovascular disease, or documented symptomatic peripheral arterial disease. Clopidogrel plus low dose aspirin vs. placebo plus low dose aspirin. Primary outcome: MI, stroke or CV death.</td>
<td>28 months (median)</td>
<td>HR (95% CI) for patients with diabetic nephropathy treated with clopidogrel vs. Placebo: ● Overall death – 1.6 (1.1-2.4) ● CV death – 1.7 (1.1-2.6) ● Overall CV death/MI/stroke - 1.1 (0.8-1.6) ● Nonfatal MI – 0.8 (0.4-1.3) ● Nonfatal stroke – 0.9 (0.5-1.7) ● Severe bleeding – 1.8 (0.9-3.3) ● Moderate bleeding – 1.2 (0.7-2.0) Limitations: No estimate of GFR, nephropathy based only on presence of microalbuminuria. No assessment of kidney function in non-diabetic group. Potential for residual confounding associated with sub group analysis.</td>
</tr>
<tr>
<td>Kaufman et al (2003) [47]</td>
<td>200</td>
<td>Randomised double blind controlled trial. Multi-centre US Dept of Veterans Affairs</td>
<td>Adults ≥21 years undergoing haemodialysis at least 3 time a week with a PTFE graft in the arm. Exclusion criteria included life expectancy &lt;2 years and uncontrolled hypertension. Clopidogrel plus aspirin vs. matching double placebos. Primary outcome time to first episode of thrombosis. Adverse events: bleeding events.</td>
<td>24 months (intended – however terminated earlier actual follow up not clear))</td>
<td>Bleeding events for patients treated with clopidogrel and aspirin compared to placebo: ● Cumulative incidence of bleeding - HR 1.98 (95% CI 1.19-3.28) ● Absolute risk increase – 0.18 (95% CI 0.06-0.31) ● The number of major bleeding events did not differ significantly between treatment and placebo groups. Limitations: Study limited to haemodialysis veterans affairs patients from with low risk of bleeding. High rate of treatment discontinuation and early termination of trial. Adverse events are secondary outcomes.</td>
</tr>
<tr>
<td>Study ID</td>
<td>N</td>
<td>Study design</td>
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<td>Follow up (months)</td>
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<tr>
<td>Hiremath et al (2009) [48]</td>
<td>16 studies (40,676 patients)</td>
<td>Systematic review of observational and randomised controlled trials.</td>
<td>Clinical trials and observational studies of antiplatelet agents in the dialysis population including 10 or more ESRD patients. Primary outcome: risk of bleeding with antiplatelet agent.</td>
<td>Minimum of 3 months.</td>
<td>Conclude that there is inadequate evidence from RCTs to adequately address the risk-benefit of use of antiplatelets in dialysis patients. Limitations: Narrative review limited to dialysis patients. Includes retrospective and prospective observational studies.</td>
</tr>
</tbody>
</table>
| Baigent et al (2005) [49] | 448       | Randomised controlled trial.                      | Pre-dialysis adults (>18 years) with most recent SrCr ≥1.7 mg/dL, dialysis patient, renal transplant patient with no contraindication for aspirin. Simvastatin plus aspirin vs. simvastatin only vs. aspirin only vs. double placebo. Primary outcome: risk of major bleeding.                                                                                                                                                                                                                                                                   | 12 months         | RR (95% CI) of bleeding in all patients treated with aspirin compared to placebo:  
  - Any bleed – 2.22 (1.29-3.81)  
  - Minor bleed – 2.81 (1.49-5.28)  
  - Major bleed – 0.66 (0.19-3.81)  
 Limitations: Pilot study. Small number of major bleeds. Low variation in ethnicity (predominantly white). Insufficient numbers to assess CKD sub groups.                                                                                                                                                                                                                                                                                                                                                                                      |
| Nakao et al (2008) [50] | 2,286     | Prospective cohort.                               | Japanese haemodialysis patients enrolled in DOPPS II.                                                                                                                                                                                                                                                                                                                                                                                                                         | NA                | Adjusted HR (95% CI) for long term risk of death for patients (12% of cohort) treated with beta-blockers compared to those not treated with beta-blockers:  
  - 0.48 (0.25-0.88)  
 Patients treated with beta-blockers had higher prevalence of hypertension and coronary heart disease and received ACEi, ARB and CCB therapies more frequently. Limitations: Potential biases associated with observational study. Residual confounding associated with patients treated with beta-blockers – e.g. contraindications for beta-blocker use not known. Length of use, dose and prior medication use unknown. Restricted to Japanese haemodialysis cohort.                                                                                                                                                                                                                                                                                                                                                                     |
| Abbott et al (2004) [51] | 2,550     | Retrospective review of medical registry (USRDS). | All eligible patients who initiated peritoneal dialysis and a 20% random sample of patients who initiated haemodialysis. Limited to patients for which Medicare claims, which were used as primary source of outcome data, were available.                                                                                                                                                                                                                                                                                                                        | NA                | Adjusted HR (95%CI) for beta-blocker use:  
  - De novo heart failure – 0.69 (0.52-0.91)  
  - De novo heart failure or cardiac death – 0.77 (0.61-0.97)  
  - Recurrent heart failure – 1.11 (0.83-1.49)  
 Limitations: Potential biases associated with retrospective registry studies e.g. indication bias for the use of beta-blockers. Cannot account for changes in medication use.                                                                                                                                                                                                                                                                                                                                                                                  |
Table 2. Quality of randomised trials

<table>
<thead>
<tr>
<th>Study ID (author, year)</th>
<th>Method of allocation concealment *</th>
<th>Blinding (participants)</th>
<th>Blinding (investigators)</th>
<th>Blinding (outcome assessors)</th>
<th>Intention-to-treat analysis †</th>
<th>Loss to follow up (%)</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keltai et al (2007) (see [54, 55])</td>
<td>Central computerised allocation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Discontinued study medication: 21.1% clopidogrel 18.8% placebo</td>
<td>No limitations (0)</td>
</tr>
<tr>
<td>Best et al (2008) [15] (see [56])</td>
<td>Allocated drug package with unique 4 digit number.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>3.6 % intervention 4.5 % placebo Discontinued study medication: 39.0% clopidogrel 40.0% placebo</td>
<td>No limitations (0)</td>
</tr>
<tr>
<td>Fox et al (2007) [20] (see [57, 58])</td>
<td>Central computerised allocation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>&lt;0.1% across treatment groups</td>
<td>No limitations (0)</td>
</tr>
<tr>
<td>Spinler et al (2003) [21] (see [59, 60])</td>
<td>ESSENCE and TIMI IIB – not specified</td>
<td>ESSENCE and TIMI IIB - Yes</td>
<td>ESSENCE TIMI IIB - Yes</td>
<td>ESSENCE TIMI IIB - Yes</td>
<td>ESSENCE TIMI IIB - Yes</td>
<td>ESSENCE – 18% discontinued either treatment or control (no difference between) TIMI IIB – 8% withdrew consent.</td>
<td>No limitations (0)</td>
</tr>
<tr>
<td>Joyner et al (2007) and Fox et al (2007) [23, 24] (see [61, 62])</td>
<td>Central computerised allocation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>&lt;1%</td>
<td>No limitations (0)</td>
</tr>
<tr>
<td>Januzzi et al (2002) (see [63])</td>
<td>Sealed opaque envelopes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Not stated</td>
<td>No limitations (0)</td>
</tr>
<tr>
<td>Reddan et al (2003) [28] (see [64])</td>
<td>Unique site randomisation schedule</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>29 (1.5%)</td>
<td>No limitations (0)</td>
</tr>
<tr>
<td>Mehran et al (2009) [34] (see [65])</td>
<td>Interactive voice response phone randomisation.</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>213 (1.5%)</td>
<td>Serious limitations (~1)</td>
</tr>
<tr>
<td>Tokmakova et al (2004) [35] (see [66])</td>
<td>Computer generated assignment</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>6 (0.3%)</td>
<td>No limitations (0)</td>
</tr>
<tr>
<td>Study ID (author, year)</td>
<td>Method of allocation concealment *</td>
<td>Blinding (participants)</td>
<td>Blinding (investigators)</td>
<td>Blinding (outcome assessors)</td>
<td>Intention-to-treat analysis †</td>
<td>Loss to follow up (%)</td>
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<tr>
<td>Zanchetti et al (2002) and Jardine et al (2010) (see HOT study [41])</td>
<td>Central committee.</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>490 (2.6%)</td>
<td>No limitations (0)</td>
</tr>
<tr>
<td>Dember et al (2008) [45]</td>
<td>Computer generated block randomisation.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (however censored for individuals who could not have patency determined)</td>
<td>33 (3.8%)</td>
<td>No limitations (0)</td>
</tr>
<tr>
<td>Dasgupta et al (2009) [46] (see [67])</td>
<td>Central interactive voice activated randomisation.</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>&lt;1%</td>
<td>No limitations (0)</td>
</tr>
<tr>
<td>Kaufman et al (2003) [47]</td>
<td>Central by coordinating centre using randomisation number to assign medication.</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>No loss to follow-up. Treatment discontinuation rate: Treatment – 38%; Placebo – 35%</td>
<td>Serious limitations (-1)</td>
</tr>
<tr>
<td>Baigent et al (2005) [49]</td>
<td>Central randomisation centre.</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>16 (3.6%) Treatment discontinuation rate 18 to 20%.</td>
<td>Serious limitations (-1)</td>
</tr>
</tbody>
</table>

* Choose between: central; third party (e.g. pharmacy); sequentially labelled opaque sealed envelopes; alternation; not specified.
† Choose between: yes; no; unclear.
Limitations - choose between: 0 - no limitations; (-1) serious limitations; (-2) very serious limitations.