

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

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## GUIDELINES

1. **Antiplatelet and anticoagulant therapy**
  - a. **Efficacy:** no recommendations possible based on Level I or II evidence.
  - b. **Safety:** the use of low-dose aspirin (100mg) in patients with a serum creatinine  $\geq 150 \mu\text{mol/L}$ , or in patients on haemodialysis or peritoneal dialysis, or in patients with a functioning renal transplant is associated with a 3-fold increased risk of minor bleeds but no increased risk of major bleeds. (Level II)
2. **Beta-blockers**
  - a. **Efficacy and safety:** no recommendations possible based on Level I or II evidence.
3. **Angiotensin converting enzyme inhibitor**
  - a. **Efficacy:** in diabetic and non-diabetic patients with chronic kidney disease stages 2-4 and stable coronary artery disease with preserved left ventricular function ( $\text{EF} > 40\%$ ), the use of Angiotensin converting enzyme inhibitor (specifically ramipril, perindopril and trandalopril) is associated with a reduction in the incidence of myocardial infarction, cardiovascular death and all cause death. (Level II).
  - b. **Efficacy:** in diabetic and non-diabetic patients with chronic kidney disease stages 2-4 presenting with acute coronary syndrome and impaired left ventricular function ( $\text{EF} \leq 40\%$ ), the use of Angiotensin converting enzyme inhibitor (specifically captopril) is associated with a reduction in the incidence of myocardial infarction, cardiovascular death, development of heart failure and all cause death. (Level II).
  - c. **Safety:** no recommendations possible based on Level I or II evidence.
4. **Angiotensin receptor blockers**
  - a. **Efficacy and safety:** no recommendations possible based on Level I or II evidence.

## SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

1. **Antiplatelet and anticoagulant therapy**
  - b. **Aspirin:** in patients with chronic kidney disease (CKD) stages 2-5 (serum creatinine  $\geq 115 \mu\text{mol/L}$  to dialysis) and stable coronary artery disease (CAD), the use of low dose aspirin is associated with a reduced risk of myocardial infarction (MI), cardiac mortality and total mortality.
  - c. **Glycoprotein (GP) IIb/IIIa inhibitors:** in patients with CKD stage 2-5 presenting with an acute coronary syndrome, the use of GP IIb/IIIa inhibitors may be associated with a reduced risk of MI and mortality. In patients with CKD stage 2-5 undergoing non-urgent percutaneous coronary intervention (PCI), the use of GP IIb/IIIa inhibitors may be associated with a reduced risk of MI and mortality. In patients with CKD stage 2-5, the use of GP IIb/IIIa inhibitors may be associated with an increased risk of major bleeding.
  - d. **Low molecular weight heparin (LMWH):** in patients with CKD stage 4 presenting an acute coronary syndrome, the use of LMWH (specifically enoxaparin) is associated with similar risk for MI, death, need for urgent revascularisation or major bleeding

when compared with unfractionated heparin. The use of LMWH in patients with CKD stage  $\geq 2$  is not associated with an increased risk of major bleeding, if dose adjusted to creatinine clearance.

- e. Thrombin inhibitor bivalirudin: in patients with CKD stage 2 undergoing PCI, the use of bivalirudin was associated with a reduced risk of MI, mortality or urgent revascularisation. In patients with CKD stage 2 undergoing PCI, the use of bivalirudin was associated with a reduced risk of major or minor haemorrhage or the need for transfusion of  $\geq 2$  U packed red cells.
2. Beta-blockers: in patients with CKD stage 2-5, the use of beta-blocker therapy post acute MI is associated with a reduced risk for in-hospital and 30-day mortality. In patients with CKD stage 2-5, the use of beta-blocker therapy for chronic stable CAD with heart failure is associated with a reduced risk for 1-year mortality. In patients with CKD stage 5, the use of beta-blocker therapy for chronic stable CAD without heart failure is associated with a reduced risk for heart failure, cardiac and all-cause death.
  3. Angiotensin converting enzyme inhibitor (ACEi): in patients with CKD stage 5, the use of ACEi therapy post acute MI is associated with a reduced risk for 30-day mortality. In patients  $\geq 65$  years with advanced CKD (serum creatinine  $\geq 265$   $\mu\text{mol/L}$ ), the use of ACEi therapy for post MI complicated by impaired LV function ( $\text{EF} \leq 40\%$ ) is associated with a improved 1 year survival rates. The use of ACEi therapy in CKD patients is associated with an increased risk for cough and angioedema.
  4. Angiotensin receptor blockers (ARB): in patients with diabetic nephropathy and serum creatinine 115 – 265  $\mu\text{mol/L}$ , and in hypertensive patients with non-diabetic CKD (creatinine  $> 106$   $\mu\text{mol/L}$  and  $< 177\mu\text{mol/L}$ ), the use of ARB therapy is associated with a reduced risk of significant heart failure episodes.

## Implementation and audit

No recommendation.

## Background

There is a 2-50-fold increased risk of cardiovascular disease (CVD) in patients with 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-MI 1- and 2-year mortality rates are 61% and 75%, respectively. [2] There is an independent, graded risk of death and cardiovascular events associated with reduced estimated glomerular filtration rate [3], and this relationship is also seen in survivors of acute MI. [4,5]

Medical management of chronic stable CAD and acute coronary syndromes (ACS) have been extensively studied in the general population leading to evidence-based clinical practice guidelines. There are landmark trials that have firmly established roles for antiplatelet and anticoagulant therapies, beta-blocker therapy, and ACEi/ARB therapy 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 under use of these therapeutic options in CKD patients. [4,6,7]

The aim of this guideline is to review the literature and assess the benefits and harms of medical management (excluding lipid-lowering therapy) of chronic stable CAD and ACS in patients with CKD, including the dialysis and transplant populations.

## 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 search was carried out in Medline (1950 - September Week 2, 2007). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

**Date of search/es:** 19 September 2007.

## What is the evidence?

**Randomised controlled trials (RCT):** The limited RCT data examining the therapeutic options for the medical management of chronic stable CAD or ACS 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.

### *Antiplatelet and anticoagulation therapy*

#### **Aspirin**

There is 1 post-hoc subgroup analysis of the hypertension optimal treatment study (HOT), a RCT examining whether the addition of low dose aspirin (75mg/day) to antihypertensive treatment reduces major cardiovascular events. [8,9] This study recruited 18,790 patients with a diastolic blood pressure between 100 and 115 mmHg and randomly allocated them to receive aspirin or placebo. 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, 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, 681 on aspirin). [9] In this subgroup of CKD patients, there was a 45% RRR in the combined primary endpoint and an 86% RRR in risk for MI. There was also a 45% RRR in cardiovascular mortality and a 39% RRR in total mortality. Risk of bleeding was not significantly different between the CKD and non-CKD group.

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. [10] CKD was defined as a cockcroft gault (CG) 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). In contrast, a recent prospective observational study examined aspirin prescription and outcomes in haemodialysis patients within the dialysis outcomes and practice patterns study (DOPPS) and showed an increased risk of MI (1.21) and cardiac events (RR 1.08) in a total sample of 16,471 haemodialysis patients and in a subgroup of haemodialysis patients with known cardiac disease (RR 1.21). [11] While this conflicting result may be a result of a number of confounding biases related to prospective observation studies, the findings highlight a need for well designed RCTs.

Two studies have examined the efficacy of aspirin in ACS. The first study performed a retrospective analysis of prospectively collected registry data to examine the effect of aspirin and beta-blocker therapy after MI in CKD patients. [12] Chronic kidney disease was defined using an abbreviated version of the CG formula as weight was not available in the database. Of 1724 patients, 731 had a creatinine clearance < 63mL/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% 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 also examined prospectively collected registry data, but specifically examined the effect of aspirin, beta-blocker and ACEi therapy post acute myocardial infarction (AMI) in dialysis patients only (stage 5 CKD). [13] The cohort study 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 0.64, 95% CI: 0.50 - 0.80) for this outcome.

There is 1 RCT examining the safety of simvastatin and aspirin in CKD patients (serum creatinine  $\geq$  150  $\mu$ mol/L or on dialysis) and patients with functioning renal transplants using a 2x2 factorial design. [14] Overall, 448 patients with CKD were randomly assigned to simvastatin, aspirin, placebo or simvastatin and aspirin (242 predialysis patients with a creatinine level  $\geq$  150  $\mu$ mol/L), 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%]; P = NS, not significant), although there was a 3-fold excess of minor bleeds (34 of 225 [15%] versus 12 of 223 patients [5%]; P = 0.001). Among those with predialysis CKD or a functioning transplant at baseline, aspirin did not increase the number of patients who progressed to dialysis therapy (7 of 187 [4%] versus 6 of 188 patients [3%]; P = NS) or experienced a greater than 20% increase in creatinine level (63 of 187 patients [34%] versus 56 of 188 patients [30%]; P = NS).

### **Clopidogrel**

Efficacy and safety of clopidogrel has not been examined in CKD subgroups.

### **Glycoprotein IIb/IIIa inhibitors**

There are limited studies examining the safety and efficacy of these agents in CKD patients and the results are conflicting.

There are 2 studies that have examined the efficacy of GP IIb/IIIa inhibitors in CKD using post-hoc analyses of CKD subgroups in larger RCTs in the general population. The first study examined the effect of adding tirofiban to heparin compared with heparin alone for patients presenting with an ACS in the PRISM-PLUS trial. [15] Creatinine clearance was estimated using the CG 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, these results included patients with an estimated creatinine clearance of > 75 mL/min and were performed using creatinine clearance as a continuous variable in regression models; subgroup analysis of the different CKD stages were difficult to interpret due to small numbers. This study also found that there was no worsening of the bleeding risk associated with tirofiban use in patients with renal insufficiency.

The second study examined the associations of creatinine clearance with outcomes in a trial of eptifibatid therapy in patients who underwent PCI in the enhanced suppression of the platelet IIb/IIIa receptor with integrilin therapy (ESPRIT) trial. [16] The primary outcome was death, MI, urgent revascularisation or thrombotic bailout therapy at 48-hours. Patients were randomly

assigned to placebo or eptifibatide as an adjunct to stent implantation. Creatinine clearance was calculated using the CG formula and CKD was defined as a creatinine clearance < 60 mL/min (n = 1,755 with CrCl ≥60 mL/min and 289 with CrCl <60 mL/min). The unadjusted odds ratio for the primary outcome at 48 hours was 0.94 with eptifibatide therapy, but lost significance after adjusting for baseline values, as did treatment interaction with creatinine clearance. Eptifibatide use was not associated with an increase in bleeding risk.

Another retrospective observational study examined the in-hospital outcome and influence of GP IIb/IIIa inhibitors on patients with ACS across a range of renal function. [17] 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. Although the use of GP IIb/IIIa antagonists was associated with a 2-fold increase in major bleeding, there was an associated 66% reduction (95% CI: 0.12 - 0.98) in in-hospital mortality after controlling for renal dysfunction.

A small retrospective analysis of the GP IIb/IIIa inhibitor abciximab in 182 consecutive CKD patients (creatinine ≥ 177µmol/L to dialysis) undergoing non-urgent PCI showed a 30% reduction in death or MI during the first 30 days in the abciximab group compared with those that did not receive abciximab, but this was not statistically significant [18]. There were no significant differences in major bleeding complications between the 2 groups. 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. [19] Another small case cohort study described a 5-fold increased risk of bleeding with abciximab when used during PCI in CKD patients (creatinine ≥ 115 µmol/L to dialysis; 44 predialysis and 5 on dialysis) compared with non-CKD patients receiving abciximab. [20] However, this could be attributed to the presence of renal insufficiency as the appropriate comparator group of CKD patients undergoing PCI without abciximab was not included.

### **Low molecular weight heparin**

There is only 1 study examining the efficacy and safety of LMWH (specifically enoxaparin) in CKD. This is a retrospective analysis of treatment effects in patients who were obese and patients with severe renal impairment from the efficacy safety subcutaneous enoxaparin in non-q-wave coronary events (ESSENCE) and thrombolysis in myocardial infarction (TIMI) 11B trials, in which patients were treated with enoxaparin or unfractionated heparin (UFH). [21] Patients with severe renal impairment were defined as those with a creatinine clearance of ≤ 30 mL/min estimated with the CG formula. The primary composite endpoint was death, MI, and urgent revascularization and was not significantly different in enoxaparin treated patients compared with UFH treated patients with CKD. There were no significant differences in major or any haemorrhages between enoxaparin and UFH in patients with CKD. Another study examined the safety of enoxaparin in patients unsuitable for the ESSENCE and TIMI 11B trial. 174 patients who received enoxaparin for ACS were followed for 30 days. Use of enoxaparin dose adjusted to creatinine clearance was not associated with excess bleeding. [22]

### **Thrombin inhibitor bivalirudin**

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 CG formula in patients with an available baseline serum creatinine (>90 [normal n = 1,578], 90 to 60 [mild n = 2,163], 59 to 30 [moderate n = 1,255], and <30 mL/min [severe n = 39]). [23] 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 renal impairment (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 renal impairment (OR 0.45, 95% CI: 0.21 - to 0.96) and moderate renal impairment (OR 0.46, 95% CI: 0.30 - 0.70). The

OR for the reduction in the quadruple ischaemic and bleeding endpoint was only significant in the groups with mild renal impairment (absolute reduction 5.8%, OR value and 95% CI not given) and moderate renal impairment (absolute reduction 7.7%, OR value and 95% CI not given).

### ***Beta-blocker therapy***

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

There is a prospective cohort study that 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. [10] Chronic kidney disease was defined as a CG 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. Users of beta-blockers in patients with CKD was associated with a lower 12-month mortality (OR 0.75, 95% CI: 0.62 - 0.90).

Two studies 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 MI in CKD patients. [12] Chronic kidney disease was defined using an abbreviated version of the CG formula as weight was not available in the database. Of 1724 patients, 731 had a creatinine clearance < 63mL/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% 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 also examined prospectively collected registry data, but specifically examined the effect of aspirin, beta-blocker and ACEi therapy post-AMI in dialysis patients only (stage 5 CKD). [13] The cohort studied consisted of 145,740 patients without ESKD and 1025 patients on dialysis. The primary outcome examined was post-AMI 30-day mortality, and use of beta-blockers was associated with a lower (RR 0.78, 95% CI: 0.60 - 0.90) for this outcome. 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). [24]

### ***Angiotensin converting enzyme inhibitor therapy***

The efficacy of ACEi therapy for CAD and ACS management has been assessed using post-hoc analyses of a large trial within the general population. The first study used a post-hoc analysis of the heart outcomes and prevention evaluation (HOPE) study, which was a randomized, double-blind, multinational trial examining the effect of ramipril on cardiovascular events in 980 patients with mild renal insufficiency (serum creatinine  $\geq 124$   $\mu\text{mol/L}$  and < 200  $\mu\text{mol/L}$ ) and 8307 patients with normal renal function (serum creatinine < 124  $\mu\text{mol/L}$ ). Both diabetic and non-diabetic patients were included and patients were required to have an ejection fraction > 40%. The patients were followed for between 3.5 - 5.5 years. The primary outcome measure was the incidence of cardiovascular death, MI, or stroke. Ramipril reduced the incidence of the primary outcome in patients with and those without renal insufficiency (hazard ratio, 0.80 vs. 0.79;  $P > 0.2$  for the difference). [25] In this study use of ramipril was associated with increased risk for angioedema and cough compared with placebo.

The next two studies examined the efficacy of perindopril and trandalopril in CKD patients. The first of these was a double-blinded RCT and it sought to examine whether the cardioprotective effects of perindopril are modified by renal function in patients with stable CAD. A total of 12,056 patients with stable CAD without heart failure, were randomized to perindopril or placebo. Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated modification of diet in renal disease (MDRD) equation and 52% had an eGFR < 75mL/min/1.73m<sup>2</sup>. During follow-up, the primary endpoint (cardiovascular death, non-fatal MI, or resuscitated cardiac arrest) occurred in 454 of 5,761 patients (7.9%) with eGFR  $\geq 75$  mL/min and in 631 of 6,295 patients (10.0%) with

eGFR mL/min <75 mL/min. Treatment benefits of perindopril were apparent in both patient groups either with eGFR ≥75 mL/min (HR 0.77, 95% CI: 0.64 - 0.93) or eGFR <75mL/min (HR 0.84, 95% CI: 0.72 - 0.98). The next study, examined whether renal function modifies the effectiveness of ACE inhibition in patients with stable CAD and preserved systolic function enrolled in the prevention of events with ACE inhibition trial (PEACE). [26] A total of 8,290 patients were randomly assigned to receive trandolapril (target, 4 mg/d) or placebo. The eGFR was calculated with the 4-point MDRD equation in 8280 patients in whom creatinine measures were available before randomization. Trandolapril was associated with a reduction in total mortality in patients with reduced renal function (adjusted HR 0.73, 95% CI: 0.54 - 1.00) but not in patients with preserved renal function (adjusted HR 0.94, 95% CI: 0.78 - 1.13).

The fourth study is a post-hoc analysis of a larger double-blind RCT that examined the effect of ACEi therapy with captopril on cardiovascular events post MI in patients with impaired left ventricular function (EF ≤ 40%) in the survival and ventricular enlargement (SAVE) trial. Of the 2231 patients enrolled in SAVE, baseline creatinine was available in 2183 and used to calculate GFR 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).

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. [13] 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. [27]

### **Angiotensin receptor blocker therapy**

There are 2 double-blinded RCTs examining the efficacy of ARB therapy as renoprotective agents +in patients with Type 2 diabetic nephropathy. In both these studies, the secondary endpoint examined was cardiovascular events. In the first study, 1715 hypertensive patients with nephropathy due to Type 2 diabetes (creatinine 88-265 µmol/L in women and 100-265 µmol/L in men), were randomised to treatment with irbesartan (300 mg daily), amlodipine (10 mg daily), or placebo. The target blood pressure was 135/85 mmHg or less in all groups. There were no significant differences in the secondary, cardiovascular composite endpoint which consisted of cardiovascular death, non-fatal MI and heart failure resulting in hospitalisation. [28] This study was underpowered to adequately assess this endpoint. The second study compared losartan (50 to 100 mg once daily) with placebo in 1513 patients with type 2 diabetic nephropathy (creatinine 115 – 265 µmol/L). The secondary endpoints which was a composite of morbidity and mortality from cardiovascular causes was similar in the two groups, although the rate of first hospitalization for heart failure was significantly lower with losartan (RRR 32 %, P = 0.005). A third study compared the efficacy of candesartan added with conventional therapy with conventional therapy in 141 hypertensive, non-diabetic CKD patients (creatinine > 106 µmol/L and < 177µmol/L). This was an open-label randomised study with a mean follow-up time of 3.1 years with the primary outcome of hospitalisation due to MI, stroke or heart failure. There was no difference in this outcome between the candesartan and conventional therapy groups in both patients with and without a past history of cardiovascular events. In the subgroup without a past history of CVD, the reduction in heart failure events was significant (candesartan 4/33 and conventional 13/38). The interpretation of these findings is limited by the small sample size in the subgroup analysis and the use of an endpoint that was not pre-defined.

## **What do the other guidelines say?**

**Kidney Disease Outcomes Quality Initiative:** No recommendation.

**UK Renal Association:** No recommendation.

**Canadian Society of Nephrology:** No recommendation.

**European Best Practice Guidelines:** No recommendation.

**International Guidelines:** No recommendation.

## **Suggestions for future research**

No recommendation.

## **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

1. Baigent C, Burbury K, Wheeler D. Premature cardiovascular disease in chronic renal failure. *Lancet* 2000; **356**:147-52.
2. Herzog CA, Ma JZ, Collins AJ. Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. *N Engl J Med* 1998; **339**:799-805.
3. Go AS, Chertow GM, Fan D *et al*. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; **351**:1296-305.
4. Wright RS, Reeder GS, Herzog CA *et al*. Acute myocardial infarction and renal dysfunction: a high-risk combination. *Ann Intern Med* 2002; **137**: 563-70.
5. Anavekar NS, McMurray JJ, Velazquez EJ *et al*. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 2004; **351**:1285-95.
6. Reddan DN, Szczech L, Bhapkar MV *et al*. Renal function, concomitant medication use and outcomes following acute coronary syndromes. *Nephrol Dial Transplant* 2005; **20**:2105-12.
7. Shlipak MG, Heidenreich PA, Noguchi H *et al*. Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. *Ann Intern Med* 2002; **137**:555-62.
8. Hansson L, Zanchetti A, Carruthers SG *et al*. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998; **351**:1755-62.
9. Zanchetti A, Hansson L, Dahlof B *et al*. Benefit and harm of low-dose aspirin in well-treated hypertensives at different baseline cardiovascular risk. *J Hypertens* 2002; **20**:2301-07.
10. Ezekowitz J, McAlister FA, Humphries KH *et al*. The association among renal insufficiency, pharmacotherapy, and outcomes in 6,427 patients with heart failure and coronary artery disease. *J Am Coll Cardiol* 2004; **44**:1587-92.
11. Ethier J, Bragg-Gresham JL, Piera L *et al*. Aspirin prescription and outcomes in hemodialysis patients: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 2007; **50**:602-11.
12. McCullough PA, Sandberg KR, Borzak S *et al*. Benefits of aspirin and beta-blockade after myocardial infarction in patients with chronic kidney disease. *Am Heart J* 2002; **144**:226-32.
13. Berger AK, Duval S, Krumholz HM. Aspirin, beta-blocker, and angiotensin-converting enzyme inhibitor therapy in patients with end-stage renal disease and an acute myocardial infarction. *J Am Coll Cardiol* 2003; **42**:201-08.
14. Baigent C, Landray M, Leaper C *et al*. First United Kingdom Heart and Renal Protection (UK-HARP-I) study: biochemical efficacy and safety of simvastatin and safety of low-dose aspirin in chronic kidney disease. *Am J Kidney Dis* 2005; **45**:473-84.
15. Januzzi JL Jr, Snapinn SM, DiBattiste PM *et al*. Benefits and safety of tirofiban among acute coronary syndrome patients with mild to moderate renal insufficiency: results from the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial. *Circulation* 2002; **105**:2361-66.
16. Reddan DN, O'Shea JC, Sarembock IJ *et al*. Treatment effects of eptifibatide in planned coronary stent implantation in patients with chronic kidney disease (ESPRIT Trial). *Am J Cardiol* 2003; **91**:17-21.
17. Freeman RV, Mehta RH, Al Badr W *et al*. Influence of concurrent renal dysfunction on outcomes of patients with acute coronary syndromes and implications of the use of glycoprotein IIb/IIIa inhibitors. *J Am Coll Cardiol* 2003; **41**:718-24.
18. Jeremias A, Bhatt DL, Chew DP *et al*. Safety of abciximab during percutaneous coronary intervention in patients with chronic renal insufficiency. *Am J Cardiol* 2002; **89**:1209-11.
19. Best PJ, Lennon R, Gersh BJ *et al*. Safety of abciximab in patients with chronic renal insufficiency who are undergoing percutaneous coronary interventions. *Am Heart J* 2003; **146**:345-50.
20. Frilling B, Zahn R, Fraiture B *et al*. Comparison of efficacy and complication rates after percutaneous coronary interventions in patients with and without renal insufficiency treated with abciximab. *Am J Cardiol* 2002; **89**:450-52.

21. Spinler SA, Inverso SM, Cohen M *et al.* Safety and efficacy of unfractionated heparin versus enoxaparin in patients who are obese and patients with severe renal impairment: analysis from the ESSENCE and TIMI 11B studies. *Am Heart J* 2003; **146**:33-41.
22. Collet JP, Montalescot G, Fine E *et al.* Enoxaparin in unstable angina patients who would have been excluded from randomized pivotal trials. *J Am Coll Cardiol* 2003; **41**:8-14.
23. Chew DP, Bhatt DL, Kimball W *et al.* Bivalirudin provides increasing benefit with decreasing renal function: a meta-analysis of randomized trials. *Am J Cardiol* 2003; **92**:919-23.
24. Abbott KC, Trespalacios FC, Agodoa LY *et al.* Beta-Blocker use in long-term dialysis patients: association with hospitalized heart failure and mortality. *Arch Intern Med* 2004; **164**:2465-71.
25. Mann JF, Gerstein HC, Pogue J *et al.* Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. *Ann Intern Med* 2001; **134**:629-36.
26. Solomon SD, Rice MM, Jablonski A *et al.* Renal function and effectiveness of angiotensin-converting enzyme inhibitor therapy in patients with chronic stable coronary disease in the Prevention of Events with ACE inhibition (PEACE) trial. *Circulation* 2006; **114**:26-31.
27. Frances CD, Noguchi H, Massie BM *et al.* Are we inhibited? Renal insufficiency should not preclude the use of ACE inhibitors for patients with myocardial infarction and depressed left ventricular function. *Arch Intern Med* 2000; **160**:2645-50.
28. Lewis EJ, Hunsicker LG, Clarke WR *et al.* Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; **345**:851-60.