A focused review on optimal coronary revascularisation in patients with chronic kidney disease

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Abstract

Concomitant chronic kidney disease (CKD) and coronary artery disease (CAD) is known to have poor outcomes. With a thorough literature review, we discuss the pathophysiological basis behind accelerated atherosclerosis in CKD, and the role of percutaneous coronary intervention (PCI) in these patients, focusing on drug-eluting stents, coronary artery bypass grafting, and adverse outcomes. We discuss factors contributing to poor outcomes in these patients, and the need for more work in this subgroup.

KEYWORDS

- atherectomy
- bare metal stent
- drug-eluting stent
- renal insufficiency
- stent thrombosis

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Abbreviations

BMS  bare metal stent(s)
CABG  coronary artery bypass grafting
CAC  coronary artery calcification
CAD  coronary artery disease
CHF  congestive heart failure
CKD  chronic kidney disease
DAPT  dual antiplatelet therapy
DES  drug-eluting stent(s)
EES  everolimus-eluting stent(s)
eGFR  estimated glomerular filtration rate
ESRD  end-stage renal disease
LVD  left ventricular dysfunction
MI  myocardial infarction
OAS  orbital atherectomy system
PCI  percutaneous coronary intervention
RA  rotational atherectomy
SES  sirolimus-eluting stent(s)
ST  stent thrombosis
TLR  target lesion revascularisation
TVF  target vessel failure
TVR  target vessel revascularisation

Introduction

Chronic kidney disease (CKD) is defined as the presence of kidney damage or reduced kidney function (eGFR <60 mL/min/1.73 m²) for ≥3 months¹. Most studies concluded that an eGFR <60 mL/min/1.73 m² is associated with increased risk of restenosis, recurrent myocardial infarction (MI), congestive heart failure (CHF) and mortality².

The current recommendation for DES use in end-stage renal disease (ESRD) patients is deduced from extrapolation of information from patients with normal renal function³. Furthermore, CKD is sub-classified into stages 1-5, each associated with different mortality and revascularisation events with best pharmacological therapy, PCI, and coronary artery bypass grafting (CABG).

Unique vascular pathobiology in CKD

Inflammation drives atherosclerosis⁴. CKD patients have co-existing traditional cardiovascular risk factors propagating inflammation. Among non-traditional risk factors, contributors to inflammation include advanced glycated end products (AGEs), uraemia, peritoneal dialysis and haemodialysis⁵.

Retention of AGEs secondary to decreased renal function causes oxidative damage, recruitment of mononuclear cells and an inflammation, which is intensified by fluid retention via bacterial or endotoxin translocation from bowel oedema, producing pro-inflammatory cytokines (interleukin-6 [IL-6], high-sensitivity CRP [hsCRP]) (Figure 1). These are not adequately cleared secondary to uraemia. This is of clinical importance as IL-6 and hsCRP are independent predictors of mortality in CKD⁶.

Reduced renal function is associated with disruption of the balance between endothelin and nitric oxide, functional platelet abnormalities and coagulopathy⁷, predisposing to atherosclerosis.

Efficacy and safety of DES compared to BMS/CABG

The bare metal stent (BMS) superseded balloon angioplasty as the treatment of choice following improved angiographic and clinical outcomes. However, BMS-related adverse events such as in-stent restenosis with rates of 20-30%⁸ led to the development of the drug-eluting stent (DES) which shares the same complications but at a delayed interval.

Figure 1. Pathophysiology of accelerated atherosclerosis in CKD. AGEs: advanced glycated end products; CKD: chronic kidney disease; DM: diabetes mellitus; HLD: hyperlipidaemia; hsCRP: high-sensitivity C-reactive protein; HTN: hypertension; IL-6: interleukin-6
New-generation DES with a reduced load of antiproliferative drugs, thinner metallic struts and improved biocompatibility of stent polymer are the new standard of care. The NORSTENT trial failed to demonstrate benefits in mortality and non-fatal MI with the use of DES over BMS but revealed benefits in stent thrombosis and repeat revascularisation. Furthermore, NORSTENT did not target patients with CKD where the improved designs of new-generation DES might be less thrombogenic. Also, a recent meta-analysis comparing DES and BMS use in CKD patients concluded with observed benefits seen across mortality, MI, stent thrombosis (ST) and target vessel revascularisation (TVR). No difference was observed between first- and second-generation DES.

A meta-analysis comparing second-generation DES (everolimus-eluting stent [EES]) with CABG reported increased rates of MI and repeat revascularisation in patients receiving EES, despite comparable mortality rates. Hence, there might be a role for consideration of CABG in patients who are surgically fit to improve their quality of life.

**Comparative outcomes of DES versus BMS in CKD**

Mortality rates are inversely related to the degree of renal dysfunction, with tripling of mortality rates in patients with both CAD and severe CKD compared to patients with normal renal function.

**Mortality**

Tsai et al (Table 1) reported benefits in all-cause mortality with DES compared to BMS in patients with normal renal function and in those with CKD. This was echoed by similar findings in a post hoc analysis of the PRODIGY trial and in a study by Jeong et al. However, Lemos et al reported insignificant differences in mortality despite improvements in clinical restenosis.

The benefits of second-over first-generation DES in the CKD population are unclear, with a retrospective analysis failing to demonstrate mortality benefits with the use of second-generation DES, probably due to systemic factors which are recognised to worsen oxidative stress and systemic inflammation independently. Other contributing factors include left ventricular dysfunction (LVD) which is associated with adverse outcomes post PCI.

**STENT THROMBOSIS**

An increased risk of stent thrombosis secondary to abnormal vascular pathobiology in CKD was demonstrated by a study which found that rates of ST were significantly raised in CKD compared to normal renal function at one-year follow-up post DES implantation.

In PRODIGY, the number needed to treat to prevent one definite or probable ST at two-year follow-up was 20 in CKD patients versus 50 in patients with normal renal function, reinforcing the significant benefits of DES.

The higher incidence of ST in CKD is related to increased severity of systemic atherosclerosis, and diffuse and calcified coronary artery disease which increases the risk of stent malapposition and underexpansion. Restenosis rates following PCI range from 60-81% when assessed via repeat coronary angiography. In contrast to patients with normal kidneys, clinical restenosis is not raised in patients with CKD, suggesting silent progression of cardiac ischaemia, hence a high risk of adverse cardiac events.

**TARGET VESSEL/LESION REVASCULARISATION**

The benefits of DES over BMS in relation to TVR/target lesion revascularisation (TLR) are unclear. While several studies have demonstrated a reduced incidence of repeat revascularisation with DES compared to BMS, Tsai et al work on DES implantation demonstrated a significant reduction in repeat revascularisation only in patients with normal renal function. Besides inflammation, alternative explanations include antiplatelet resistance observed in chronic renal failure. Nevertheless, a lack of guideline-directed antiplatelet therapy in the CKD population might be contributory, which needs to be explored further.

**NON-FATAL MI**

The incidence of higher MI rates post PCI is universally increased in CKD patients compared to those with normal renal function. Despite an overall raised incidence of post-PCI MI in CKD patients, the use of DES over BMS is associated with reduced MI rates. Increased MI rates in CKD patients despite DES use indicate that systemic inflammation and/or metabolic derangement have a greater impact on endpoints. This is insufficiently addressed by the local effects of antiproliferatives in current DES.

In summary, the current evidence suggests that CKD is an independent predictor of mortality, MI and stent thrombosis. Also, DES are superior to BMS in the CKD population, with the caveat that the requirement for dual antiplatelet therapy (DAPT) is unlikely to disrupt subsequent non-cardiac treatment.

**Revascularisation in ESRD/haemodialysis DES VS. BMS**

In line with contemporary guidelines advocating the use of DES in ESRD patients on dialysis, a meta-analysis has demonstrated mortality and adverse cardiac event benefits in ESRD patients who are treated with DES.

Despite a lack of benefit at one-year follow-up, Ishii et al reported reduced revascularisation rates in haemodialysis patients treated with DES over BMS on longer follow-up. This suggests the need for adequate endothelialisation of the deployed stent in the uraemic state, hence the need for extended follow-up.

**FIRST- VS. SECOND-GENERATION DES**

Despite a paucity of data on outcomes of second-generation DES in patients on maintenance haemodialysis, ESRD and haemodialysis are recognised as major predictors of adverse outcome following first-generation DES implantation, with approximately double the incidence of target vessel failure (TVF) in patients who received sirolimus-eluting stents (SES) compared to non-haemodialysis patients.

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<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Study Size</th>
<th>CKD (eGFR &lt; 60 ml/min/1.73 m²)</th>
<th>Comparison/Intervention</th>
<th>DES Stent Use</th>
<th>Primary Outcome</th>
<th>Secondary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crimi et al</td>
<td>Multicentre RCT</td>
<td>1,981</td>
<td>373 (18.8%)</td>
<td>BMS vs. DES (PES/EES/ZES)</td>
<td>1,484 (75%)</td>
<td>Definite/probable ST</td>
<td>Composite of MI, stroke, death, and all-cause mortality</td>
</tr>
<tr>
<td>Miao et al</td>
<td>Single-centre prospective</td>
<td>2,862</td>
<td>445 (15.5%)</td>
<td>DES-related ST in CKD vs. normal renal function</td>
<td>2,862 (100%)</td>
<td>Definite/probable ST</td>
<td>Composite of all-cause mortality, non-fatal MI, TVR</td>
</tr>
<tr>
<td>Tsai et al</td>
<td>Multicentre prospective</td>
<td>283,593</td>
<td>121,446 (42.8%)</td>
<td>DES vs. BMS</td>
<td>218,540 (77.1%)</td>
<td>All-cause mortality, MI, repeat revascularisation, bleeding</td>
<td>NALower in DES-treated patients regardless of renal function.</td>
</tr>
<tr>
<td>Roberts et al</td>
<td>Single-centre prospective</td>
<td>4,687</td>
<td>1,543 (33%)</td>
<td>CABG vs. MM CABG vs. BMS CABG vs. DES</td>
<td>1,278 (27%)</td>
<td>All-cause mortality</td>
<td>Composite of death, MI, repeat revascularisation, bleeding</td>
</tr>
<tr>
<td>Lemos et al</td>
<td>Retrospective</td>
<td>1,080</td>
<td>186 (17.2%)</td>
<td>DES vs. BMS</td>
<td>537 (49.7%)</td>
<td>All-cause mortality</td>
<td>Repeat revascularisation</td>
</tr>
<tr>
<td>Wanha et al</td>
<td>Retrospective</td>
<td>1,908</td>
<td>331 (17.3%)</td>
<td>DES-I (PES, SES) vs. DES-II (EES, ZES, BES)</td>
<td>1,908 (100%)</td>
<td>DES efficacy: MACCE (MI, TVR, death, stroke) DES safety: ST</td>
<td>NAReduced with SES in both CKD and normal renal function.</td>
</tr>
<tr>
<td>Cooper et al</td>
<td>Retrospective</td>
<td>483,914</td>
<td>379,034 (78.3%)</td>
<td>CABG</td>
<td></td>
<td>All-cause mortality (within 30 days of CABG)</td>
<td>Stroke, repeat CABG</td>
</tr>
</tbody>
</table>

BES: biolimus-eluting stent; BMS: bare metal stent; CABG: coronary artery bypass grafting; CKD: chronic kidney disease; ESRD: end-stage renal disease; HR: hazard ratio; MACCE: major adverse cardiac and cerebral events; MI: myocardial infarction; PCI: percutaneous coronary intervention; MM: medical management; NA: not available; TVR: target vessel revascularisation; ZES: zotarolimus-eluting stent.
Table 2. Summary of studies comparing coronary revascularisation approaches in ESRD (dialysis-dependent).

<table>
<thead>
<tr>
<th>Study design</th>
<th>Study size</th>
<th>ESRD</th>
<th>Comparison/intervention</th>
<th>DES stent use</th>
<th>Primary outcome</th>
<th>Secondary outcomes</th>
<th>All-cause mortality</th>
<th>Stent thrombosis</th>
<th>Repeat revascularisation</th>
<th>Non-fatal MI</th>
<th>Additional comments</th>
<th>Follow-up period</th>
<th>Inclusion period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al1</td>
<td>Meta-analysis</td>
<td>62,250</td>
<td>62,250 (100%)</td>
<td>DES vs. BMS</td>
<td>NR</td>
<td>All-cause mortality MI</td>
<td>For early mortality MACE, TVR/TLR</td>
<td>NA</td>
<td>Favour DES</td>
<td>NR</td>
<td>Favour DES</td>
<td>Non-significant difference</td>
<td>NA</td>
</tr>
<tr>
<td>Ishii et al36</td>
<td>Retrospective</td>
<td>505</td>
<td>505</td>
<td>DES vs. BMS</td>
<td>SES, PES</td>
<td>TLR</td>
<td>Composite of cardiovascular death, non-fatal MI, ST, TLR</td>
<td>Non-significant difference</td>
<td>Non-significant difference</td>
<td>Favour DES (beyond 1 year)</td>
<td>Non-significant difference</td>
<td>NA</td>
<td>42 months</td>
</tr>
<tr>
<td>Saka-kibara et al37</td>
<td>Single-centre prospective</td>
<td>100</td>
<td>100</td>
<td>DES-I vs. DES-II</td>
<td>SES (50%), EES (50%)</td>
<td>Restenosis at 8-month follow-up</td>
<td>MACE (all-cause death, non-fatal MI, TLR)</td>
<td>Non-significant difference</td>
<td>Non-significant difference</td>
<td>Non-significant difference</td>
<td>Non-significant difference</td>
<td>EES reduced restenosis rates compared to SES</td>
<td>8 months</td>
</tr>
<tr>
<td>Nevis et al38</td>
<td>Systematic review</td>
<td>32,388</td>
<td>32,388 (100%)</td>
<td>CABG vs. PCI</td>
<td>NR</td>
<td>Short-term (30 days) or long-term (≥1 year) mortality</td>
<td>NA</td>
<td>Short-term: favours PCI, Long-term: favours CABG</td>
<td>NA</td>
<td>Favour CABG</td>
<td>NA</td>
<td>Favour CABG</td>
<td>PCI: 28 months, CABG: 31 months</td>
</tr>
</tbody>
</table>

BMS: bare metal stent; CABG: coronary artery bypass grafting; CKD: chronic kidney disease; DES: drug-eluting stent; DES-I: first-generation DES; DES-II: second-generation DES; EES: everolimus-eluting stent; ESRD: end-stage renal disease; MACE: major adverse cardiac events; MI: myocardial infarction; NA: not applicable; NR: not recorded; PCI: percutaneous coronary intervention; SES: sirolimus-eluting stent; ST: stent thrombosis; TLR: target lesion revascularisation; TVF: target vessel failure; TLR: target vessel revascularisation

When implemented on maintenance haemodialysis patients, EES significantly reduced the incidence of restenosis compared to SES with an equal safety profile32, with consistent results in improvements in diameter stenosis on follow-up compared with the OUCH-PRO registry31. Mechanisms for reduction in restenosis rates include reduced arterial injury and inflammation secondary to thinner struts and polymer of second-generation DES, respectively32,33.

**PCI vs. CABG**

Despite increased early post-CABG mortality in ESRD34,35, Zheng et al36 demonstrated significant long-term benefits in mortality, MI, and repeat revascularisation compared to PCI. Supporting this is a systematic review reporting benefits in repeat revascularisation and major adverse cardiac events (MACE) with CABG, despite a higher early mortality risk36. The proposed pathophysiology includes significant medial calcification in haemodialysis patients, predisposing to stent underexpansion, reduced efficacy of eluted drugs and suboptimal endothelialisation of stent struts, culminating in restenosis and stent thrombosis37.

Nevertheless, there is an elevated baseline risk of long-term mortality in haemodialysis patients regardless of the choice of revascularisation technique39.

**Rotational atherectomy (RA) for the treatment of coronary artery calcification (CAC)**

Severely calcified coronary lesions have lower PCI success rates, higher complication rates, and suboptimal long-term results. Contemporary PCI guidelines recommend RA as an option for heavily calcified lesions that might not be adequately traversed or dilated prior to stent implantation39.

The ROTAXUS trial, comparing RA followed by stenting or stenting alone in complex native CAD, demonstrated higher success with use of RA and higher acute lumen gain post PCI. However, in-stent late lumen loss was significantly higher in the RA group compared to DES alone40, indicating that rotablation alone failed to increase the efficacy of DES.

The Diamondback 360° coronary orbital atherectomy system (OAS; Cardiovascular Systems, Inc., St. Paul, MN, USA) presents an alternative in revascularisation of CACs. ORBIT I demonstrated 98% device success (≤50% residual stenosis post-OAS treatment) while ORBIT II exceeded primary safety (freedom from MACE at 30 days) and efficacy (residual stenosis <50% post stent without in-hospital major cardiac events) endpoints, highlighting its suitability for implementation in CACs. Furthermore, subgroup analysis of DES use revealed a lower rate of TLR compared to BMS41,42.

Besides technique, the approach to complex CACs should include accurate lesion assessment and characterisation which is poorly delineated by angiography alone41,43. Optical coherence tomography might be the supplemental imaging modality of choice for the assessment of intraluminal calcium thickness41. Accurate assessment will facilitate optimal stent placement, reduce stent underexpansion, malapposition, damage to the DES polymer coating and subsequent drug delivery44. Compared to bail-out atherectomy, planned atherectomy is associated with a reduced procedural time, less use of contrast and reduced rates of complications44.
Overall, our review suggests that, while results regarding mortality benefit are mixed when DES are compared with BMS in both CKD and ESRD, DES are shown to improve rates of MI and repeat revascularisation. There is no significant benefit of second-generation DES. The benefits of rotational atherectomy warrant consideration for planned instead of bail-out use in appropriate lesions.

**Choice and duration of DAPT in CKD**

DAPT use post PCI is critical to minimise the rate of adverse cardiovascular events. Contemporary European and US guidelines recommend a DAPT duration of six to 12 months post DES deployment, followed by lifelong aspirin. However, no consensus for DAPT drugs and duration in patients with CKD/ESRD exists, owing to the lack of clinical trials. Though not targeted at CKD patients, the DAPT trial demonstrated that prolonged DAPT (30 months) significantly decreased rates of ST and the composite outcome of death, MI, and stroke, at the expense of bleeding. However, the extrapolation of findings from a non-CKD/ESRD population into this high-risk population is probably inappropriate, due to an increased incidence of cardiovascular events or bleeding complications after PCI in haemodialysis patients.

Both CKD and prolonged DAPT independently predict elevated bleeding complications. However, it is uncertain whether prolonged DAPT worsens bleeding risk in CKD patients.

A pooled analysis comparing the safety and efficacy of short-term (three to six months) versus long-term (≥12 months) DAPT post DES implantation in CKD patients found that the presence and degree of CKD have no effect on the rates of coronary thrombotic events, regardless of the duration of DAPT, which is in sync with a study by Baber et al., where severity of CKD has no effect on cardiovascular risk post DAPT cessation. Further, Chen et al’s analysis in the haemodialysis subgroup reported a six-month DAPT duration cut-off that reduces post-PCI death or MI, but shows no difference in long-term outcomes when compared to longer duration of DAPT (>6 months). However, these studies used clopidogrel instead of more potent P2Y12 inhibitors such as prasugrel or ticagrelor, which may have had an impact on overall study outcome.

In summary, CKD and DAPT independently predict bleeding risk, while CKD contributes to an increased risk of ST. A lack of consensus regarding antiplatelet therapy in CKD/ESRD leads to a reduced use due to a perceived lack of benefit, coupled with fear of coagulopathy and antiplatelet resistance. Also, our review suggests that thrombotic complications post cessation of DAPT are independent of the severity of CKD. Future studies concerning DAPT and bleeding complications ought to have a uniform use of antiplatelets and duration to minimise possible confounding effects on stent choice and CKD severity.

**Role of CABG in CKD**

The 2014 European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) Guidelines on myocardial revascularisation recommend CABG over PCI in patients with moderate to severe CKD and multivessel CAD, considering acceptable surgical risks and life expectancy beyond one year.

Given complex coronary lesions in CKD, findings from ASCERT reporting long-term mortality benefits with CABG over PCI in multivessel CAD could be applied. Though patients with CKD often have more complex coronary lesions with multivessel disease, increased coronary calcification, and the presence of thrombus in culprit coronary lesions, their SYNTAX score is comparable to patients with normal kidneys. CABG should be considered since extensive coronary calcifications reduce PCI success rates and is also associated with significant improvements in symptoms and mortality.

The FREEDOM trial comparing coronary revascularisation techniques in CKD concluded that CKD is an independent risk factor for adverse events regardless of revascularisation strategy, where there is no evidence of additional benefit in outcomes according to CKD severity. Being an independent risk factor for stent thrombosis, coronary revascularisation in CKD has shifted in favour of CABG especially on long-term follow-up. Nevertheless, CABG is superior to PCI with regard to reductions in rates of MI and repeat revascularisation regardless of renal function provided patients do not present with acute coronary syndrome. Comparing rates of adverse events in CABG against BMS in CKD/ESRD, CABG is associated with reduced mortality rates though there was statistical significance only in severe CKD (eGFR <30 mL/min/1.73 m²). A subsequent analysis comparing CABG against DES observed a trend towards mortality reduction for CABG without statistical significance. No mortality difference was observed in patients on dialysis, regardless of revascularisation strategy.

However, a five-year follow-up on the SYNTAX trial demonstrated that a statistically significant long-term benefit in mortality, MI and stroke is associated with revascularisation with CABG over DES. Differences in event rates were attributed to the higher rates of all-cause death and repeat revascularisation in the CKD population who received DES, secondary to diffuse atherosclerosis and reduced prevalence of guideline-directed antiplatelet therapy.

In conclusion, CKD and ESRD are independent risk factors for adverse events regardless of revascularisation strategy. CABG is associated with long-term benefits in both mortality and adverse cardiac events both in patients with CKD and in those with ESRD. However, physicians and patients ought to consider and accept higher risks of early complications such as mortality and stroke, stressing the importance of patient selection.

**Conclusions**

Despite an increasing prevalence of patients with CKD and CAD, there remain limited studies evaluating the optimum method of coronary revascularisation, and DAPT duration in this subgroup.

Our review highlights the following. 1) CKD is an independent predictor of mortality, MI and stent thrombosis. 2) DES is superior to BMS in a CKD population. 3) CKD and DAPT are independent predictors of bleeding complications post PCI, though the severity of symptoms and mortality.
of CKD seems not to affect the rates of coronary thrombotic events. 4) CABG is the revascularisation modality of choice (Table 3) in CKD patients who are surgically fit due to mortality and symptomatic benefits, and the reduced need for repeat revascularisation compared to PCI. 5) It is also imperative for a consensus on DAPT choice and duration to be validated to maximise the benefits of high-risk, invasive procedures in this fragile subset of patients.

Table 3. Summary of findings and clinical implications.

<table>
<thead>
<tr>
<th>What is already known</th>
<th>Patients with CKD have an increased risk of post-PCI adverse events compared to the general population. DES is generally associated with improved outcomes compared to BMS in both the general population and CKD patients. DES implantation in the ESRD population on regular dialysis shows a reduced rate of revascularisation over longer follow-up (&gt;1 year).</th>
</tr>
</thead>
<tbody>
<tr>
<td>What this review adds</td>
<td>No study focusing on DAPT duration post PCI in CKD/ESRD patients has yet been done. Results from available trials highlight that adverse events are higher in the CKD population. Among the CKD population, there is no observable benefit in extending DAPT duration beyond 12 months. In non-dialysis-dependent CKD patients, CABG improves mortality, repeat revascularisation and MI compared to PCI. There is no mortality difference when comparing first- and second-generation DES, while comparison of DES with BMS yields mixed results. In ESRD on regular haemodialysis, CABG provides long-term benefit despite short-term increased risk of adverse events. There is no significant mortality difference when first- and second-generation DES are compared, though there is a reduced repeat revascularisation rate with second-generation DES. Finally, DES provides mortality benefit over BMS.</td>
</tr>
<tr>
<td>Clinical implications &amp; future directions</td>
<td>CABG is still the intervention of choice for CKD/ESRD patients requiring coronary revascularisation, provided fitness for surgery. CKD/ESRD patients will greatly benefit from RCTs/prospective studies focusing on DAPT choice and duration, especially in the advent of novel P2Y12 inhibitors and second-generation DES.</td>
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Conflict of interest statement
The authors have no conflicts of interest to declare.

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