FEATURE

CVD in chronic kidney disease
What do we know?

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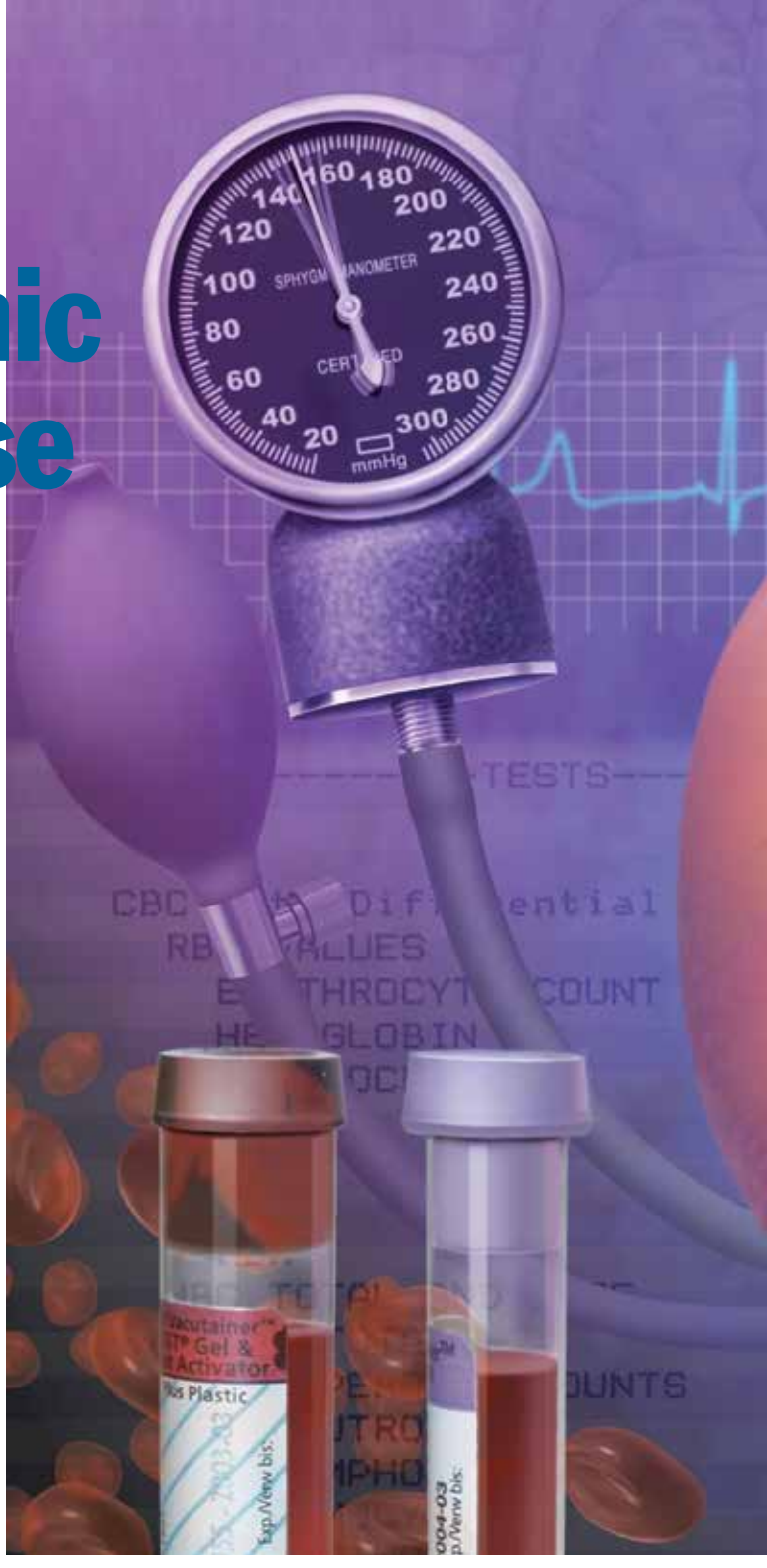
In patients with chronic kidney disease (CKD), cardiovascular disease (CVD) is more frequent and severe, and is often under-recognised and undertreated when compared with the general population. Evidence is now emerging on the efficacy of various management strategies in preventing CVD in people with CKD.



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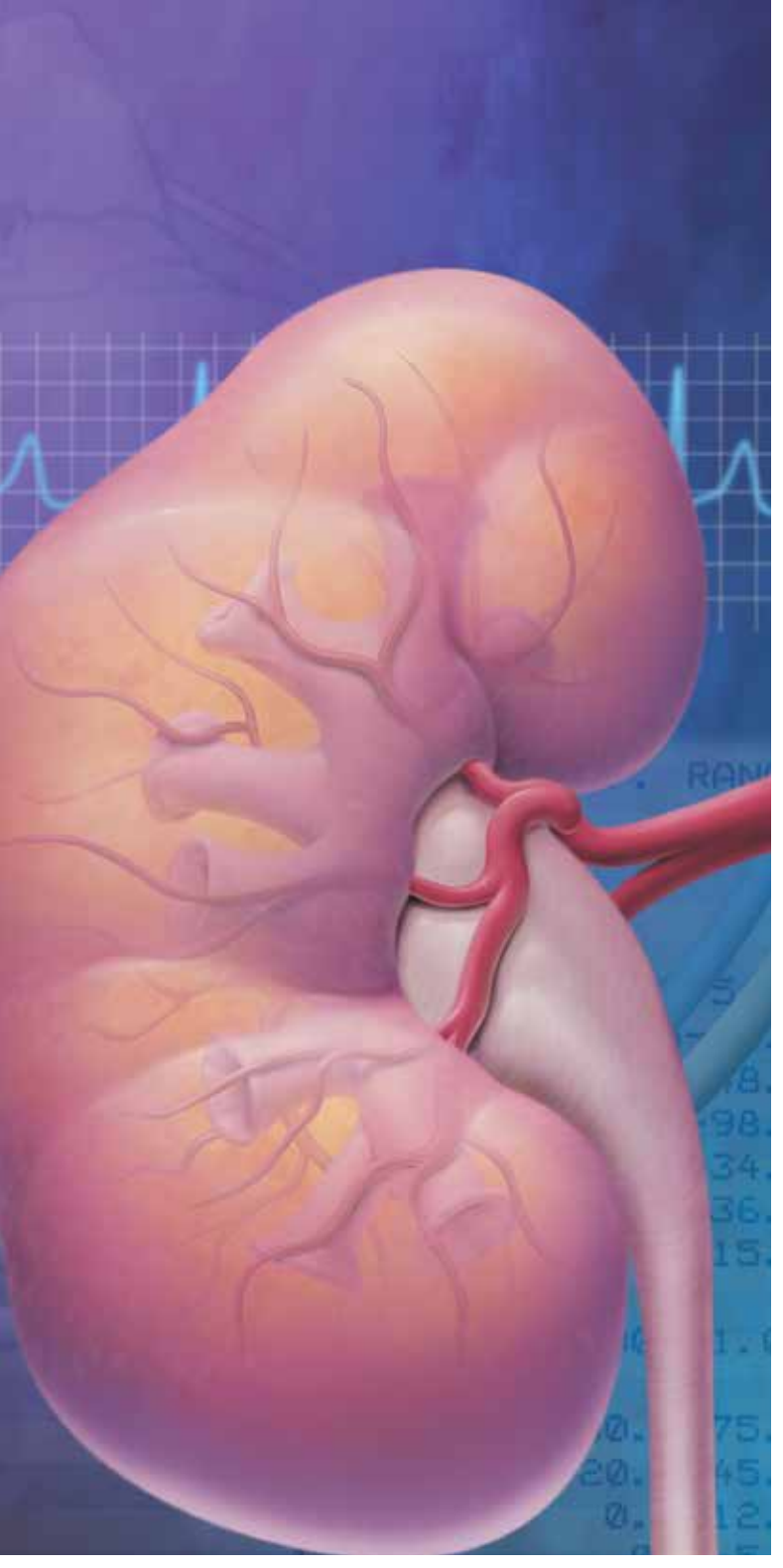
Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for more than three months.[1] Kidney function is often measured as estimated glomerular filtration rate (eGFR), calculated from the serum creatinine level. It is estimated that around 10 to 15% of the adult general population has CKD, and it is increasingly recognised as a major clinical and public health concern.[2,3]

CKD causes significant morbidity, premature death and decreased quality of life,[4,5] and a proportion of people with CKD eventually develop end-stage kidney disease (ESKD) requiring dialysis or kidney



transplantation. CKD is now also well recognised as a potent risk factor for cardiovascular disease (CVD). As renal function declines below an eGFR of 60 mL/min/1.73 m^2, the relative risk for cardiovascular (CV) mortality progressively increases, compared with people without CKD, and is increased almost 10-fold in the setting of CKD with diabetes.[6] The presence of albuminuria further increases the risk of CV events, and is additive to the risk conferred by reduced eGFR. The excess CVD risk associated with CKD has been shown to exceed that conveyed by diabetes alone.[7]

CVD risk prediction tools do not currently incorporate this additional risk in their algorithms, leading to underestimation of risk and, therefore, to suboptimal primary prevention measures in patients with CKD.[8] Additionally, there has been uncertainty about whether preventive strategies proven to be effective in the general population can be similarly applied to the CKD population, given potential differences in pathophysiology as well as drug metabolism.

The routine exclusion of patients with advanced CKD from most clinical trials of CVD therapies created significant gaps in evidence on the relevance of existing standards of care to these patients. More recent trials conducted specifically in this population, along with analyses of CKD subgroups involved in broader populations and systematic reviews of all of these, have shed some light on the appropriate management of CKD and are discussed below.

Key points

- **Chronic kidney disease (CKD) is well recognised as a potent risk factor for cardiovascular disease (CVD), but few trials have specifically addressed the prevention of CVD in the CKD population.**
- **Although specific evidence in the CKD population is limited, smoking cessation, exercise, dietary salt reduction and weight loss are generally recommended in patients at all CKD stages.**
- **Lipid-lowering therapy with a statin or a statin plus ezetimibe is recommended in patients with CKD (not requiring dialysis); the role of statins in those with end-stage kidney disease (ESKD) is less certain.**
- **Evidence supports the lowering of blood pressure (BP) in patients with CKD, aiming for a systolic BP target below 140 mmHg, and below 130 mmHg for those with CKD and proteinuria.**
- **Agents acting via the renin-angiotensin system are recommended in patients with CKD primarily for their renal benefit; their efficacy in those with ESKD is less clear.**
- **Antiplatelet agents should be used in a similar manner in CKD as they are in the general population, but with even greater caution in patients with CKD at increased risk of bleeding.**

Lifestyle modification

Lifestyle modifications have not been widely studied specifically in patients with CKD. Although epidemiological studies have consistently shown smoking is associated with a high risk of developing CKD,[9,10] a small trial that tested a multifactorial intervention including smoking cessation did not show significant CV benefits.[11] Nonetheless, the large benefit of smoking cessation in the general population,[12] the lack of a plausible reason as to why this should not be observed in people with CKD and the likely effect of smoking on increasing loss of kidney function mean that smoking cessation should be recommended.

A high dietary sodium intake is a strong determinant of high blood pressure and fluid retention in patients with CKD, both of which are particularly common in these patients. A review of seven intervention studies (n = 6250) among individuals without CKD showed that dietary sodium restriction was associated with a 20% reduction in CV events during follow up.[13] Sodium restriction in CKD populations has been shown to potentiate the effects of renin-angiotensin system (RAS) blockade on albuminuria, which is expected to translate to renal and CV protective effects.[14]

Even fewer data are available regarding the effects of exercise or weight loss in CKD populations, with no clear benefit demonstrated in several small and underpowered studies.[11,15]

Although specific evidence of the efficacy of lifestyle modification in this population remains limited, smoking cessation, exercise, dietary salt reduction and weight loss are simple, reasonable interventions and are generally recommended in patients at all CKD stages.[16]

Lipid lowering

Statins and ezetimibe

The *KDIGO [Kidney Disease Improving Global Outcomes] Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease* recommends commencement of treatment with a statin or a statin plus ezetimibe in adults aged 50 years or above with CKD (not requiring dialysis) or in patients who have had a kidney transplant with eGFR less than 60 mL/min/1.73 m^2.[17] This recommendation is principally based on the Study of Heart And Renal Protection (SHARP), a trial involving about 9500 participants with CKD that showed that those randomised to simvastatin plus ezetimibe had a 17% reduction in risk of major atherosclerotic events (coronary death, myocardial infarction, nonhaemorrhagic stroke or any revascularisation) compared with those randomised to placebo.[18] It is also supported by post-hoc analyses of randomised trials of statin versus placebo that focused on the subset of participants with CKD and which suggest statins reduce the relative risk of CV events to a similar degree in patients with and without CKD.[19]

The role of statins in ESKD is less certain, with meta-analyses of results of randomised trials clearly showing that the relative risk is reduced compared with people with preserved kidney function, although the absolute risk reduction is likely to be similar.[20,21] This may well be due to a similar effect on atherosclerotic events being drowned out by a larger number of nonatherosclerotic CV events.

Reflecting this uncertainty, the KDIGO guidelines recommend that statins or a statin/ezetimibe combination not be initiated in adults with dialysis-dependent CKD. However, if these patients are already taking these medications at the time of dialysis initiation, the treatment ought to be continued.[17]

Although there were concerns over the well-documented side effects (rhabdomyolysis, myalgia and deranged liver function test) with statin use in patients with CKD, especially with high dosages, recent evidence has confirmed there is no difference in side effect profiles between statins and placebo even in patients with reduced kidney function.[18,21]

LDL-cholesterol levels

Although low-density lipoprotein (LDL)-cholesterol levels are widely used in estimating future CVD risk in the general population, they are less reliable for assessing coronary risk in patients with CKD. Among patients with pre-dialysis CKD, the magnitude of risk associated with LDL-cholesterol levels decreases with progression of the stage of CKD.[22] For patients undergoing dialysis who have the lowest level of LDL- and total cholesterol, the all-cause and CVD mortality remains extremely high.[23,24] Hence, the evidence argues against the use of LDL-cholesterol levels to identify patients requiring treatment. Instead it suggests consideration of absolute risk for coronary events, such as history of known coronary disease, diabetes, prior ischaemic stroke or estimated 10-year incidence of coronary death or nonfatal MI greater than 10%,[17] although Australian PBS criteria do not yet take this approach. As CKD itself is a risk factor for CV events, a reduced treatment threshold may be appropriate.

Fibrates

Fewer data exist for other lipid-lowering agents. Fibrates have been shown to prevent CV events in the general population, with particular benefit for coronary events.[25] Secondary analyses of trial subsets with CKD suggest similar benefits in this population.[26] Fibrates transiently and reversibly increase serum creatinine levels, and this has limited their use in CKD, but the trial data suggest that this does not translate into renal harm, and that there may in fact be protection of kidney function.[26,27]

Reducing blood pressure

Blood pressure (BP) is a strong and clear driver of CV events in the general population, and also in people with CKD. It is often elevated as kidney function reduces, and is also a strong risk factor for progression to kidney failure.[28] Recent analyses from the Blood Pressure Lowering Treatment Trialists' Collaboration assessed 26 randomised trials involving more than 150,000 participants, approximately 30,000 of whom had early stage CKD (mostly stage 3a).[29] They showed that treatment with ACE inhibitors and calcium channel blockers produced almost identical 17% reductions for each 5 mmHg reduction in systolic BP in the risk of CV events in participants with and without CKD.

Blood pressure targets

The optimal target for BP in both the general population and in people with CKD has been a matter of controversy. Several randomised trials have assessed the impact of different BP targets in both these groups. In the general population, a systematic review of a number of trials found that intensive BP lowering reduced the risk of CV events as well as ESKD.[30] A similar review in people with CKD had far less power and was unable to show benefits of reducing BP on CV events, but it found a reduced risk of ESKD in participants with CKD and proteinuria whereas the data in CKD patients without proteinuria were conflicting.[31]

The *KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease* therefore recommend BP lowering in people with CKD, aiming for a systolic BP target below 140 mmHg, and a lower target of below 130 mmHg for people with CKD and proteinuria.[16]

The best approach for people who have ESKD is even less certain. Several small trials were pooled in a systematic review, which found BP lowering reduced CV events in people receiving dialysis,[32] but optimal targets are not known. More studies in people on dialysis are needed to define the best treatment approach for this population.

Renin-angiotensin system (RAS) blockade

RAS blockade reduces the risk of ESKD in people with diabetes-associated nephropathy independent of blood pressure.[33,34] The Blood Pressure Lowering Treatment Trialists' Collaboration has shown that ACE inhibitors also prevent CV events in patients with CKD, although the effects were not superior to other classes of antihypertensive agents in head-to-head comparisons.[29] Nonetheless, agents acting via the RAS can reduce the risk of CVD and CKD progression in both diabetic and nondiabetic nephropathy. Therefore, they are recommended in patients with CKD primarily for their renal benefit, particularly for those individuals with proteinuria. Use of these agents requires careful monitoring of patients' serum potassium and kidney function.

The renal benefits of agents acting on RAS led to great enthusiasm for dual blockade. However, a number of trials in the general population and in people with CKD have shown that dual RAS blockade does not reduce the risk of CV events, and is associated with an increased risk of adverse outcomes including acute kidney injury and hyperkalaemia.[35-37] This consistently increased risk suggests that the use of combination therapy in CKD cohorts should be avoided, and this is reflected in current guidelines.

Aldosterone antagonists

Spironolactone is a commonly used agent in congestive heart failure and is also used as a second-line agent in proteinuric CKD. A Cochrane meta-analysis involving 11 trials (n = 991) showed that use of an aldosterone antagonist with an ACE inhibitor and/or an angiotensin receptor blocker, significantly reduced 24-hour proteinuria and BP, but was not associated with an improvement in eGFR.[38] It was associated with a significantly higher risk of hyperkalaemia, more so if dual RAS blockade was used concurrently, and even when a more selective aldosterone antagonist (eplerenone) was used. However, these studies were small and of short duration (two to 20 months), and used proteinuria as a surrogate marker, so that mortality and hard renal endpoint data are lacking. Hence care should be taken when considering the use of aldosterone antagonists in patients with CKD.

Beta blockers

In a recent systematic review of six placebo-controlled trials involving 5972 participants with CKD and heart failure, Badve, et al. showed that use of beta blockers reduced the risk of all-cause and CV mortality.[39] The randomised controlled trial Hypertension in Hemodialysis Treated with Atenolol or Lisinopril (HDPAL) compared treatment with atenolol or lisinopril in patients with hypertension undergoing haemodialysis.[40] It showed there was a greater systolic BP lowering, of 5.6 mmHg, with atenolol despite ultrafiltration, and a greater number of antihypertensive medications were used in the lisinopril group. The CV event rate was more than double with lisinopril compared with atenolol (relative risk [RR], 2.36, p = 0.001). The lisinopril group also had a significantly higher rate of serious adverse events such as congestive heart failure requiring hospitalisation, hypertensive crisis and hyperkalaemia. This effect was seen as early as three months and was sustained until the end of the trial, which was terminated early as recommended by the trial Data and Safety Monitoring Board, based on clear evidence of benefit in the atenolol treated group. The findings of HDPAL also support the use of beta blockers in ESKD but raise questions about the role of RAS blockade in patients with this stage of kidney disease. Currently, there are insufficient data to recommend one agent over the other, especially in patients with more advanced CKD.

Use of antiplatelet agents

Data are sparse regarding the efficacy of aspirin in advanced CKD. The authors of a recent Cochrane systemic review analysed 44 studies comparing an antiplatelet agent with placebo or no treatment (21,460 participants) and six studies directly comparing one antiplatelet agent with another (5679 participants). They found that antiplatelet agents reduced the risk of myocardial infarction (RR, 0.87; 95% confidence interval [CI] 0.76 to 0.99) but not all-cause mortality, CV mortality or stroke compared with placebo.[41] Post-hoc subgroup analyses of randomised trials suggested that the protective effect of daily aspirin may be increased in individuals with eGFR below 45 mL/min/1.73 m^2,[42] but both studies also showed a higher incidence of bleeding (major and minor) in patients with CKD. These data suggest that antiplatelet agents should be used in a similar manner in CKD as they are in the general population, but that they should be used with even greater caution in patients with CKD who are at an increased risk of bleeding. Additional studies in this area are urgently needed.

The Figure summarises the evidence from meta-analyses and systematic reviews for various interventions, including aspirin, on the risk of CV events in CKD populations.

Glycaemic control

There are few specific data helping to define optimal glycaemic control in CKD populations with diabetes, particularly as measures of glycaemic control such as glycated haemoglobin may have reduced accuracy due to increased red cell turnover in these populations.

Some data suggest tight glycaemic control improves kidney outcomes. Long-term follow up of people with type 1 diabetes and nephropathy in the Diabetes Control and Complication Trial showed a significantly preserved GFR in the intensive glycaemic arms.[43] The

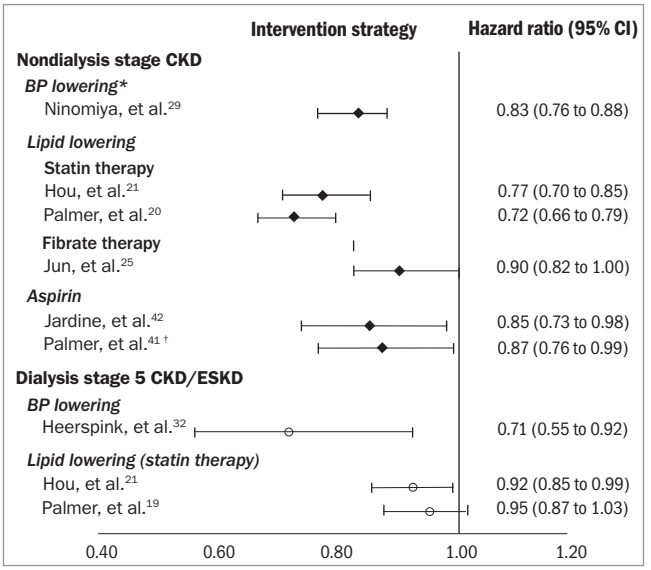


Figure. Summary of the evidence from meta-analyses and systematic reviews for intervention strategies on the risk of cardiovascular events in CKD populations.

* Per 5 mmHg reduction in systolic BP; † Nonfatal myocardial infarction.

Abbreviations: BP = blood pressure; CI = confidence interval; CKD = chronic kidney disease; ESKD = end-stage kidney disease.

Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study also showed a significant reduction in ESKD in the intensive glycaemic control arm, although tighter blood glucose control did not have any effect on macrovascular outcomes.[44] On the contrary, overall mortality was increased in the intensive glycaemic control arm in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial;[45] however, this may have been the result of the specific regimen used, as it has not been observed in other studies. We await the results of large randomised controlled trials on newer antidiabetic agents such as sodium glucose cotransporter-2 (SGLT-2) inhibitors (e.g. canagliflozin in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation [CREDENCE] trial) and dipeptidyl peptidase-4 (DDP-4) inhibitors (e.g. linagliptin in the Cardiovascular Safety & Renal Microvascular Outcome Study with Linagliptin [CARMELINA trial]), specifically addressing the renal and cardioprotective effects in addition to glycaemic control.

Conclusion

With the better understanding of the pathomechanistic link between CKD and CVD, increasing evidence demonstrates that the pathology, diagnosis and complications of CVD have greater similarities than differences in the presence of CKD. Thus, although the risk to benefit relationship of management strategies evaluated in the general population may differ significantly in the CKD population, the evidence to date generally supports similar approaches can be taken with regard to lipid lowering, blood pressure reduction, use of antiplatelet agents and glycaemic control. Although few trials specifically address CVD in patients with CKD, increased awareness of this may stimulate future trials in the area. In the meantime, currently available international guidelines provide high-quality evidence-based resources for clinical practice. **CT**

References

A list of references is included in the website version (www.medicinetoday.com.au) of this article.

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