Integrated care for people with chronic kidney disease – a systematic review of randomised controlled trials

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Abstract

This is the protocol for a systematic review of randomized trials which will evaluate the benefits and harms of integrated care for people with chronic kidney disease.

The review will be based on standard methods for systematic reviews of randomized trials.

Background

Chronic kidney disease is a worldwide public health problem with major social and economic implications (Zhang and Rothenbacher, 2008). The estimated global prevalence of the disease is about 10% to 13% (Couser et al, 2011; Szczech et al, 2009), and is increasing due to the rapid growth of other illness and life style related conditions such as diabetes, hypertension and obesity (Coresh et al, 2007; Grassmann et al, 2005). Given the rise of prevalence, chronic kidney disease has important patient as well as structural, logistics and financial implications (Zhang and Rothenbacher, 2008; Jha et al, 2013). Leading causes of chronic kidney disease vary per countries, but in high income countries like UK, Norway, USA and Australia, diabetes, hypertension and glomerulonephritis appear as the most common causes (Evans and Taal, 2015). Individuals with chronic kidney disease have higher risk for hospitalizations, cardiovascular events and mortality (Go et al, 2004). This population also faces more significant socioeconomic challenges, such as high poverty rate and low health literacy, all contributing to an increased likelihood of poor outcomes (Johns et al, 2015). Another factor which contributes to a more complex management and poor outcomes is that patients are
getting older. For example, an important portion of the dialysis population in most developed countries are over 70 years of age (Ronco et al, 2013).

**Description of the condition**

Chronic kidney disease is defined as the progressive loss of renal function and characterized by the gradual scarring of the kidney (Dipiro et al, 2011). Chronic kidney disease is categorized according to the level of kidney function into stages 1 to 5, according to the United States Kidney Disease Outcomes Quality Initiative (K/DOQI); Its stages are determined by the glomerular filtration rate (GFR) (Levey et al, 2003).

A more recent publication, the Kidney Disease Improving Guidelines Outcomes (KDIGO) clinical practice guidelines for the evaluation and management of chronic kidney disease present a slightly different categorization of chronic kidney disease stages. In this guideline, classification is based on three things: cause, GFR and albuminuria category (CGA). GFR categories are re-classified as G1, G2, G3a, G3b, G4 and G5 (Eknoyan et al, 2013).

Stages 1 and 2 are considered mild, while stages 3 and 4 are considered moderate and stage 5 is referred to as end stage kidney disease. Optimal management of chronic kidney disease is complex, as it is a multi-component disease. The aim of stages 1 to 4 chronic kidney disease management includes decreasing the progression to end stage kidney disease and the risk for cardiovascular complications through management of kidney functions and common factors of chronic kidney disease progression such as hypertension and diabetes (KDIGO, 2012; James, Hemmelgarn and Tonelli, 2010 ). The management of end stage kidney disease can include renal replacement therapy (RRT) in the form of dialysis or kidney transplant. End stage kidney disease is associated with extremely high mortality, morbidity and a substantially low quality of life (Foley, Parfrey and Sarnak, 1998). The high financial and social cost of end stage kidney disease to both individuals and society place it as a significant health priority in the field of non-communicable diseases (De Vecchi, Dratwa and Wiedemann, 1999).

In viewing chronic kidney disease as a disease process with a clinical, heterogeneous picture of progressive deterioration, an integrated system of care built on a disease management model is considered as an appropriate intervention strategy (CDC, 2010; Ronco et al, 2013; Braun et al, 2012). Ideally, it is based on active self-management to slow down progression of the disease, including daily, self-care, patient-physician collaboration, collaborative practice models and transfer of care (Ronco et al, 2013; Braun et al, 2012).
Description of the intervention

In the last decade, the concept of integrated care was introduced as a mean of improving quality and efficiency of care (WHO, 2011; Grone and Garcia-Barbero, 2001). Integrated care is found in the literature with a wide range of definitions (Kodner, 2009; Kodner, 2002; Ouwens et al, 2005; Burns and Pauly, 2012; Gonseth et al, 2004; Roccaforte et al, 2005; Badamgarav et al, 2003; Neumeyer-Gromen et al, 2004; Kodner and Spreeuwenberg; 2002; Nolte and Pitchforth, 2014). Integrated care can be described as “an organizational process of coordination that seeks to achieve seamless and continuous care, tailored to the patient’s needs, and based on a holistic view of the patient” (Mur-Veeman et al, 2003).

Integrated care interventions for chronic kidney disease people consist of an array of initiatives of coordination of services along the care continuum. Within the literature several terms have been used synonymously or in conjunction with integrated care, such as: disease management, managed care programs, case management, continuity of care, multidisciplinary care team, integrated care pathways and self-management support (Valentijn et al, 2015; Ouwens et al, 2005; Kodner 2009; Sun et al, 2013; McDonald et al, 2007). We define integrated care as a multifaceted organisational intervention, which include the following domains and underlying concepts (Valentijn et al, 2015):

Clinical domain

Interventions aimed at coordinating care at the individual patient level. Namely:

- **Case management**: Allocation of coordination tasks to an appointed individual (a case manager) or a small team who may or may not be responsible for the direct provision of care. The case manager (or team) takes responsibility for guiding individual patients through the complex care process in the most efficient, effective, and acceptable way, using phone, mailings or visits (Ouwens et al 2005).

- **Integrated care pathway** (also defined as clinical follow-up or clinical pathway): Structured multidisciplinary care plans which detail essential steps in the care of individual patients with a specific clinical problem and describe the patient’s expected clinical course (Ouwens et al, 2005; Campbell et al, 1998).
• **Self-management support**: A portfolio of techniques and tools to help patients to acquire the skills and knowledge to manage their own illness; and a fundamental transformation of the patient-caregiver relationship into a collaborative partnership (Da Silva 2011). It includes: 1) Health education and/or treatment; 2) Behavioural and motivation support; and 3) Active patient involvement and/or participation in the care process (Ouwens et al, 2005; RAND, 2012; Barlow et al, 2002).

**Professional domain**

Interventions aimed at coordinating care among different health care professionals. Namely:

• **Multidisciplinary care team** (also defined as interdisciplin ary teams, interdisciplinary clinics): A group of professionals who communicate with each other regularly about the care of a defined group of patients and participate in that care. It includes: 1) participation of professional caregivers from different disciplines, 2) revision of professional roles, and 3) regular team meetings (Ouwens et al, 2015; Kruis et al, 2013).

• **Continuity of care** (also defined as comprehensive health care, patient care planning or care coordination): The degree to which a series of discrete healthcare events is experienced as coherent and connected and consistent with the patient’s medical needs and personal context. It includes (1) Informational continuity: The use of information on past events and personal circumstances to make current care appropriate for each individual. (2) Management continuity: A consistent and coherent approach to the management of a health condition that is responsive to a patient’s changing needs. (3) Relational continuity: An ongoing therapeutic relationship between a patient and one or more providers. (Haggerty et al, 2003; McDonald et al, 2007)

**Organisational domain**

Interventions aimed at coordinating care among different organisational units. Namely:

• **Disease management**: A system of coordinated healthcare interventions and communications for populations with conditions in which patient self-care efforts are significant. Disease management supports the physician or practitioner/patient
relationship and plan of care, emphasizes prevention of exacerbations and complications utilizing evidence-based practice guidelines and patient empowerment strategies, and evaluates clinical, humanistic, and economic outcomes on an ongoing basis with the goal of improving overall health. It includes: 1) population identification process, 2) evidence-based practice guidelines, 3) collaborative practice model, 4) self-management education for patients, 5) process and outcomes measurement, 6) routine reporting, feedback loops and benchmarking (DMAA 2016; Steuten et al, 2006).

- **Managed care programs** (also defined as integrated delivery system): Health insurance plans intended to reduce unnecessary health care costs through a variety of mechanisms, including: economic incentives for physicians and patients to select less costly forms of care; programs for reviewing the medical necessity of specific services; increased beneficiary cost sharing; controls on inpatient admissions and lengths of stay; the establishment of cost-sharing incentives for outpatient surgery; selective contracting with health care providers; and the intensive management of high-cost health care cases. The programs may be provided in a variety of organisational settings, such as health maintenance organizations (HMO’s), preferred provider organizations (PPOs), integrated delivery system (IDS) or accountable care organizations (ACOs). (National Library of Medicine, 2016; Sekhri, 200; Sun et al. 2013)

**How the intervention might work**

Several reviews have linked integrated care intervention to a range of outcomes for people with other chronic diseases, including improvements in patient safety, health status and provision of health services (Gonseth et al, 2004; Roccaforte et al, 2005; Badamgarav et al, 2003; Neumeyer-Gromen et al, 2004). However, firm conclusions regarding the effectiveness of integrated care interventions cannot be made, due to the large heterogeneity in the interventions, study populations, outcome measurements and methodological quality (Pimouguet et al, 2010; Davies et al, 2008; Drewes et al, 2012; Elissen et al, 2012).

Chronic kidney disease management face the need for improvement on areas such as management of chronic kidney disease risk factors, complications, and timely preparation for end stage renal disease (Johns et al, 2015). There is a great variation in the symptoms, functional limitations and degree of psychological well-being of chronic kidney disease patients, as well as the progression of chronic kidney disease towards end stage kidney

Why is it important to do this review

Integrated care interventions have been identified as a central research priority by several scholars in response to the issues such as fragmentation and the need for improved management of the disease (Johns et al, 2015; Ronco et al; 2013; Steele, Hamilton and Aranaout, 2007; Wingard et al, 2007). The body of evidence concerning integrated care interventions among people with chronic kidney disease is insufficient (Maddux, McMurray and Nissenson, 2013; Ronco et al, 2013; Ramos and Molina, 2013). Hence, a systematic review is required to investigate the effectiveness of integrated care interventions in people with chronic kidney disease to better inform clinical and managerial decision making.

OBJECTIVES

This review aims to look for the benefits and harms of integrated care interventions on people with chronic kidney disease.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) or quasi randomized trials (trials in which allocation to the intervention was obtained by unconcealed ways such as alternation, etc.) looking at the benefits and harms of integrated care interventions on the outcomes defined further on in this
protocol, in people with chronic kidney disease. Cluster Randomized Controlled Trials (CRCTs) will also be included. The minimum duration of the trial should be 3 months.

Types of participants

Inclusion criteria

All people with chronic kidney disease in any stage will be included. No restrictions on gender or race will apply. Participants with any comorbidities will be included.

Exclusion criteria

Patients without chronic kidney disease will be excluded.

Types of interventions

We will include integrated care interventions reported as strategies to improve the care for patients with chronic kidney disease through the coordination of services along the care continuum, including organisational, financial, professional and patient-directed interventions. Namely, the following interventions will be included (as described in previous section):

1. Case management
2. Integrated care pathway
3. Self-management support
4. Multidisciplinary care team
5. Continuity of care
6. Disease management
7. Managed care programs

The criterion for inclusion is as follows: studies which specifically mention the above terms as their intervention or which matches the descriptions on the section “description of intervention” will be included.

The types of comparison foreseen are the following:

- Integrated care intervention versus usual care, as defined by authors
- Integrated care intervention versus any control
Types of outcomes measures

Primary outcomes

- All-cause mortality
- Major or fatal cardiovascular events as defined by the investigators (including but not limited to myocardial infarction, stroke, congestive heart failure, sudden death)
- Hospitalization
- Hospital-acquired infection rate
- Quality of life (any measure, as reported by study authors, for example the Short Form 36 Health Survey)

Secondary outcomes

- Adverse events, such as, but not limited to: fatigue, hypocalcaemia, hypercalcaemia, nausea, vomiting, upper respiratory tract infection, dyspnoea, muscle weakness, headache, paraesthesia, abdominal pain, diarrhoea, reflex tachycardia, constipation, bradycardia and heart block
- Cost and resource utilization (total cost per patient per year, GP visits per patient per year, specialists visits per patient per year, medication consumption in % of patients with medication, and of medication dosage per patient, % duplication of lab tests)
- Kidney function: SCr (mg/dL), GFR, estimated (e) GFR (mL/min or mL/min/1.73 m²); need for RRT; doubling of SCr; progression from micro- to macro albuminuria; regression from macro- to micro albuminuria and regression from micro- to norm albuminuria
- BP: systolic BP and diastolic BP (mm Hg) (3)
- PTH levels at end-of-treatment (any measure)
- Serum phosphorus at end-of-treatment (mg/dL)
- Serum calcium at end-of-treatment (mg/dL)
- Serum beta microglobulin at end of study
- Serum calcium by phosphorus product at end-of-treatment (mg²/dL²)
• Haemoglobin at end-of-treatment (g/dL; m/m²)
• Nutritional status: Albumin in g/L, at end of intervention, or change between beginning and end of intervention; Prealbumin in mg/L, at end of intervention, or change between beginning and end of intervention; Normalized protein catabolic rate in g/kg/d, at end of intervention, or change between beginning and end of intervention
• Wait list for kidney transplant
• Process related outcomes: Co-ordination of care, including accessibility of care, participation rate in the disease management program, satisfaction of health care providers and participants with regard to the program, or the extent to which disease management was implemented, from the perspective of the patient and the care giver

Search methods for identification of results

Electronic searches

We will search the CENTRAL, MEDLINE and EMBASE databases. See Appendix 1 for search terms used in strategies for this review. Application of the search strategies generated the following amount of hits, after removing duplications:

- CENTRAL (n=493)
- MEDLINE (n=794)
- EMBASE (n=1437)
- TOTAL (n=2,724)

Searching other resources

This review will also look into:

1. Reference lists of all reviewed articles, relevant studies and clinical practice guidelines.
2. Search for ClinicalTrials.gov for ongoing studies.

Data collection and analysis

Selection of studies
The application of the search strategies described in Appendix I will generate titles and abstracts that may be relevant to the review. Two authors (PV and FP) will screen those titles and abstracts independently, discarding studies which are not applicable. In order to determine which studies satisfy the inclusion criteria, two authors (PV and FP) will independently retrieve and evaluate full texts of studies. After comparing their individual lists, if any differences in opinions appear, they will be resolved by consensus through discussions. In case this fails, a third author will arbitrarily resolve the differences (BV or GS).

**Data extraction and management**

Two authors (PV and FP) will extract the data (see data extraction forms in Appendix II). Non-English reported studies will be translated before assessment is carried out. When two or more publications of a single study exist, they will be grouped, and only the publication with the most complete data set will be used for the analyses. In case relevant outcomes are only reported in earlier publications, these data will be used. Differences in opinions will follow the same criteria as per selection of studies: resolution by consensus through discussion between two authors (PV and FP) and, if this fails, arbitrary resolution by a third one (BV or GS).

**Assessment of risk of bias in included studies**

The following items will be independently assessed by two authors using the risk of bias assessment tool (Higgins and Green, 2011) (see Appendix III).

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Other bias

An assessment of ‘low risk’, ‘high risk’ or ‘unclear risk’ will be made for each of the items based on the risk of bias tool (Appendix III). This will be summarized as a figure. Two authors (PV and FP) will compare the results and discuss any differences in opinion. Any disagreements will be settled by a third author.
**Measures of treatment effects**

For dichotomous outcomes (e.g. deaths) results will be expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement are used to assess the effects of treatment (e.g. health related quality of life), the mean difference (MD) will be used, or the standardised mean difference (SMD) if different scales have been used.

**Unit of analysis issues**

In case a unit of analysis error occurrence in cluster-randomised controlled trials, we will do an adjustment by reducing the size of the trial to its “effective sample size” (Rao and Scott, 1992). To obtain the effective sample size of a single intervention group, we will divide the original sample size by the “design effect” \(1+[M-1]*ICC\), where \(M\) is the average cluster size and ICC is the intra-cluster correlation coefficient. For dichotomous data, both the number of participants and the number experiencing the event will be divided by the design effect. For continuous data, only the sample sizes will reduced; means and standard deviations will remain unchanged. (Higgins and Green, 2011).

In case of the appearance of multiple arms studies, all intervention groups that are relevant to the review will be included.

**Dealing with missing data**

Evaluation of important numerical data will be performed (e.g. number of screened and randomised patients, intention-to-treat [ITT] analysis). We will request further information required by emailing the corresponding author, and we will include relevant information obtained. Issues of missing data and imputation methods will be appraised (Higgins and Green, 2011). We will assume missing values that have a poor outcome. For continuous and dichotomous outcomes, we will calculate effect size (SMD, MD, RR) based on number of participants at a time point. If this is not available, we will use the number of randomised participants in each group at baseline.
Assessment of heterogeneity

Heterogeneity will be analysed using a Chi² test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I² test (Higgins and Green, 2011). I² values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

If possible, funnel plots will be used to assess for the potential existence of small study bias (Higgins and Green, 2011).

Data synthesis

If possible to pool data, which is unlikely due to the foreseen amount of subgroups and heterogeneity, we will use the random-effects model. The fixed effect model will also be used to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

We plan the following subgroup analysis to determine if outcomes differ among:

1. The setting of the integrated care intervention (e.g. primary, secondary, tertiary)
2. Design of the studies (e.g. individual randomisation, cluster randomisation)
3. Duration of the intervention

Heterogeneity among participants could be related to age, gender, ethnicity/race, renal pathology, type of dialysis and co-morbidities (CVD, hypertension, diabetes mellitus).

Heterogeneity in interventions could be related to the way the intervention is delivered (e.g. one-on-one, web based or in groups) or the duration of the intervention. If meta-analysis is not possible, adverse effects will be tabulated and assessed with descriptive techniques, as they are likely to be different for the various agents used. Where possible, the risk difference with 95% CI will be calculated for each adverse effect, either compared to no treatment or to another agent.
Sensitivity analysis

We will perform sensitivity analyses for the primary outcome measurements in order to explore the influence of the following factors on effect size:

- Repeat the analysis taking account of risk of bias, as specified
- Repeat the analysis excluding any very long or large studies to establish how much they dominate the results
- Repeat the analysis excluding studies using the following filters: diagnostic criteria, language of publications, stage of kidney disease (mild versus moderate end stage kidney disease)
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## APPENDICES

### Appendix I: Electronic search strategies

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Integrated care interventions on people with chronic kidney disease
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<td>20</td>
<td>community care/</td>
</tr>
<tr>
<td>21</td>
<td>health care planning/</td>
</tr>
<tr>
<td>22</td>
<td>((integrated or coordinated or co-ordinated or comprehensive or collaborative or transamural or continuity) adj5 (health* or care* or delivery or system*)).tw.</td>
</tr>
<tr>
<td>23</td>
<td>accountable care organization.tw.</td>
</tr>
<tr>
<td>24</td>
<td>health maintenance organization.tw.</td>
</tr>
<tr>
<td>25</td>
<td>(care management adj5 (program* or plan* or team* or clinic* or delivery or system*)).tw.</td>
</tr>
<tr>
<td>26</td>
<td>managed care.tw.</td>
</tr>
<tr>
<td>27</td>
<td>case management.tw.</td>
</tr>
<tr>
<td>28</td>
<td>(disease management adj5 (program* or plan* or team* or clinic* or delivery or system* or insurance)).tw.</td>
</tr>
<tr>
<td>29</td>
<td>((critical pathway* or clinical pathway* or clinical follow-up) adj5 (team* or clinic* or plan* or program* or care or health* or delivery or system*)).tw.</td>
</tr>
<tr>
<td>30</td>
<td>((integrated or coordinated or co-ordinated) adj5 (clinic* or team* or plan*)).tw.</td>
</tr>
<tr>
<td>31</td>
<td>((interdisciplin* or multidisciplin*) adj5 (team* or clinic* or plan* or program* or care or health* or delivery or system*)).tw.</td>
</tr>
<tr>
<td>32</td>
<td>continuity of care.tw.</td>
</tr>
<tr>
<td>33</td>
<td>((patient-centered or patient-centred) adj5 (team* or clinic* or plan* or program* or care or health* or delivery or system*)).tw.</td>
</tr>
<tr>
<td>34</td>
<td>((community care or community health) adj5 (program* or clinic* or plan* or team* or delivery or system*)).tw.</td>
</tr>
<tr>
<td>35</td>
<td>((self-management or self-care) adj5 (program* or clinic* or plan* or team* or delivery or system*)).tw.</td>
</tr>
<tr>
<td>36</td>
<td>12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35</td>
</tr>
<tr>
<td>37</td>
<td>11 and 36</td>
</tr>
</tbody>
</table>
Appendix II: Data extraction form

- General information on the paper
- Record number
- Author
- Year
- Journal
- Title
• Name of the reviewer

1. Study characteristics
   a. Country (USA, Canada, United Kingdom, Scandinavia, Australia, New Zealand, Netherlands, other – specify)
   b. Level of care provided (international, national, regional, single-center, not described)
   c. Location of care provided
   d. Type of participant patients (open ended)
   e. Type of participating providers (nephrologist, cardiologist, endocrinologist, other physicians, nurses, pharmacist, physiotherapist, psychologist, mixed – specify, other providers – specify, not clear)
   f. Type of participating stakeholders (patient groups, professional associations, governmental agencies, pharmaceutical companies, funders – e.g. social health insurance funds, other – specify, not clear)

2. General information on integrated care intervention(s)
   a. General description of integrated care intervention(s) – open ended
   b. Type of targeted behaviour (clinical prevention services, diagnosis, test ordering, referrals, procedures, prescribing, general management of a problem, patient education / advice, professional-patient communication, record keeping, financial – resource use, discharge planning, patient outcome, other – specify, not clear)

3. Type of integrated care intervention (Disease management, Managed care programme, Case management, Continuity of care, Multidisciplinary care team, Integrated care pathway, Self-management support and education, other – specify, not clear)

4. Reported effect
   a. Duration of study
   b. Unit of allocation (patient, provider, practice, institution, community, firm, clinic day, other – specify, not clear)
   c. Unit of analysis (patient, provider, practice, institution, community, firm, clinic day, other – specify, not clear)
   d. Groups compared: A – open ended; B – open ended
   e. Interventions compared: A – open ended; B – open ended
   f. Number of participants in each arm
   g. Outcomes (primary – mortality, hospitalization days per patient per year; secondary - Costs per patient per year, Cost effectiveness cost-utility, cost benefit, Resource utilisation (GP visits, specialists visits, medication consumption in % of patients with medication, and of medication dosage per patient, % duplication of lab tests), Number of hospital admissions, Number of Emergency Rooms admissions, Rate of decline in
GFR, Time to dialysis initiation, Vascular access (arterious venous fistula or central venous catheter) incidence and prevalence, Quality of life, Waiting times for nephrology consultation

### Appendix III: Risk of Bias assessment tool

<table>
<thead>
<tr>
<th>Potential source of bias</th>
<th>Assessment criteria</th>
</tr>
</thead>
</table>
| Random sequence generation | **Low risk of bias**: Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random)

**High risk of bias**: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention

**Unclear**: Insufficient information about the sequence generation process to permit judgement |
| --- | --- |
| Allocation concealment | **Low risk of bias**: Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes)

**High risk of bias**: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure

**Unclear**: Randomisation stated but no information on method used is available |
| Blinding of participants and personnel | **Low risk of bias**: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken

**High risk of bias**: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding |
<table>
<thead>
<tr>
<th><strong>Blinding of outcome assessment</strong></th>
<th>Unclear: Insufficient information to permit judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection bias due to knowledge of the allocated interventions by outcome assessors</td>
<td><strong>Low risk of bias:</strong> No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken</td>
</tr>
<tr>
<td></td>
<td><strong>High risk of bias:</strong> No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding</td>
</tr>
<tr>
<td><strong>Unclear:</strong> Insufficient information to permit judgement</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Incomplete outcome data</strong></th>
<th>Low risk of bias: No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attrition bias due to amount, nature or handling of incomplete outcome data</td>
<td><strong>High risk of bias:</strong> Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; ‘as-treated’ analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation</td>
</tr>
</tbody>
</table>
Selective reporting
Reporting bias due to selective outcome reporting

Unclear: Insufficient information to permit judgement

Low risk of bias: The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)

High risk of bias: Not all of the study’s pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study

Unclear: Insufficient information to permit judgement

Other bias
Bias due to problems not covered elsewhere in the table

Low risk of bias: The study appears to be free of other sources of bias.

High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem

Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: PV, FP, BV, GS
2. Study selection: PV, FP
3. Extract data from studies: PV
4. Review data extracted from studies: FP
5. Carry out the analysis: PV, BV
6. Interpret the analysis: PV, FP, BV, GS
7. Draft the final review: PV
8. Disagreement resolution: BV, GS

DECLARATIONS OF INTEREST

The authors FP and GS acknowledge that they have an affiliation with Diaverum Renal Service Group. FP and GS declare that Diaverum Renal Service Group does not have control over the resulting publication.

ACKNOWLEDGEMENTS

This research was funded by grant from Diaverum Renal Service Group, Munich, Germany. The views expressed are those of the authors and not necessarily those of Diaverum Renal Service Group.