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Interventions for BK virus infection in kidney transplant recipients (Protocol)

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[Intervention Protocol]

Interventions for BK virus infection in kidney transplant recipients

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

This review aims to evaluate treatment options for BKV infection in kidney transplant recipients.

BACKGROUND

Description of the condition

Kidney transplantation continues to be the treatment of choice for patients with end-stage kidney disease due to the survival benefit in comparison with patients remaining on dialysis (Wolfe 1999). The potent immunosuppression regimens that are currently used have been relatively successful in reducing acute rejection and preserving the allograft. However, over-suppression of the immune system has been associated with the emergence of BK virus (BKV) infection (Brennan 2005; Hirsch 2005; Schold 2009).

BKV previously belonged to Polyomavirus genus of the Papovaviridae family, which consisted of papillomavirus and polyomavirus. In 1999, the International Committee of Taxonomy of virus classified it into Polyomaviridae family (DeCaprio 2013). It is believed that primary BKV infection occurs in the early decade of life. The overall IgG seroprevalence of BKV is approximately 82% (Egli 2009). Direct person-to-person contact or by exposure to contaminated surfaces, foods and water has been considered as the likely method of transmission (Hirsch 2014). The virus persists within the kidney tissue (Heritage 1981) and mostly does not cause any symptoms until it is reactivated (Hirsch 2002; Hirsch 2014). Interestingly, the data supports donor origin of the infection in kidney allograft recipients (Bohl 2005).

In the modern immunosuppression era, BKV nephropathy (BKN) typically occurs in 1% to 10% of kidney transplant patients; 95% of cases are caused by BKV and 5% by human polyomavirus 2 (formerly JC virus or John Cunningham virus) (Gonzalez 2015; Sawinski 2015b; Schwarz 2012). Without intervention, more than 90% of kidney transplant patients with BKN show decline of allograft function, which is followed by graft loss in at least 50% of cases (Hirsch 2014).

Risk factors associated with BKV infection include Human Leucocyte Antigen (HLA) mismatch, cadaveric donation, degree of ischaemia-reperfusion, female donor and male recipients, older age of recipients, ureteral stent insertion, acute rejection episodes, and immune-suppressive therapy (rabbit anti-thymocyte globulin (ATG) as induction with tacrolimus (TAC) and/or mycophenolate mofetil (MMF) as maintenance immunosuppression) (Brennan

2005; Borni-Duval 2013; Bressollette-Bodin 2005; Dharnidharka 2009; Gonzalez 2015; Hirsch 2005; Hirsch 2013; Pham 2014; Prince 2009; Schold 2009; Siparsky 2011). Additionally, a cohort study found that donor BKV neutralising serostatus is a strong predictor of the risk of post-transplant BK viraemia regardless of recipient neutralising serostatus (Abend 2017). The absence of HLA C7 allele in donor or recipient has also been associated with increased risk of sustained BK viraemia (Bohl 2005). In contrast, African-American ethnicity has been associated with lower prevalence of BKV infection (Sood 2012).

Renal biopsy with characteristic viral cytopathic changes in tubular epithelial cells and Simian Virus 40 (SV-40) immunohistochemistry is considered the gold standard for BKN diagnosis. Moreover, it provides the degree of chronic damage which can predict graft prognosis (Drachenberg 2004).

BKV detection by real-time polymerase chain reaction (PCR) of plasma with a threshold of 4.1 log 10 copies/mL has 100% sensitivity, ~90% specificity, 50% positive-predictive value and negative predictive value of 100% in BKN diagnosis (Bechert 2010; Pollara 2011; Viscount 2007). The current standard of care recommends monthly BKV quantitative plasma nucleic acid testing for the first three to six months post-transplantation; the frequency of testing can be reduced to three monthly until the first post-transplant year (Kasiske 2010). However, various factors contribute to the inter-assay variability in measuring BK viral loads are the differences, including sample type (urine versus plasma versus whole blood), DNA extraction and purification methods, differences in primer and probe sequences, differences in viral strains and sequences, different DNA preparation and PCR amplification conditions (Bechert 2010; Hoffman 2008; Randhawa 2011). Therefore, it is recommended to monitor the trend from the same laboratory.

On the other hand, BKV detection by PCR of urine with a threshold of 2.5E+07 copies/mL has 100% sensitivity, 92% specificity, 31% positive predictive value, and 100% negative predictive value. Furthermore, the presence of decoy cells in urine sample has 25% sensitivity and 84% specificity (Bechert 2010; Viscount 2007). The caveat for urine examination is that there is no increased risk of BKN in a patient with elevated BK viral load in the urine without the presence of BK viraemia (Brennan 2005; Hirsch 2013).

Management of BKV infection has been complicated. Most of the literature reiterates the importance of immune-suppression reduction (Brennan 2005; Hardinger 2010; Schaub 2010). However, this will expose the kidney recipients to increased risk of acute rejection which subsequently will reduce the overall graft and patient survival. Additionally, persistent BKV viraemia has been strongly associated with de novo class 2 donor-specific antibody (DSA) production (Sawinski 2015a). Retransplantation following allograft loss due to BKN has been reviewed as a possible treatment option. The data from Organ Procurement and Transplantation Network described an excellent short-term graft and patient survival, 94% and 98% respectively (Dharnidharka 2010). Transplant nephrectomy has not been shown to offer any protection against recurrent BKV replication. However, the clearance of BK viraemia before retransplantation should be achieved before surgery. (Dharnidharka 2010; Trofe-Clark 2016).

A systematic review published in 2010 found a death-censored graft loss rate of 8/100 patient-years for immune-suppression alone and 8 and 13/100 patients-years for the addition of cidofovir or leflunomide, respectively (Johnston 2010).

Description of the intervention

The mainstay of therapy for BKV infection is to improve BKV-specific immunity by reducing the intensity of maintenance immunosuppression or to administer medication with antiviral effect. The usual strategies in treating BKN are reducing the dose of calcineurin inhibitors (CNI) or MMF), cessation of azathioprine (AZA) or MMF, concomitant reduction of both CNI and antimetabolite, switching of CNI to mammalian target of rapamycin (mTOR) inhibitor, and switching of TAC to cyclosporine. Drugs with anti-polyoma effects such as cidofovir, leflunomide, FK778, and fluoroquinolones have also been used to enhance viral clearance and/or suppression. Some studies have also incorporated intravenous immunoglobulin to the regimen.

How the intervention might work

As the BKV reactivation typically occurs within first two years post-transplantation in which the patient receives a significantly higher dose of immunosuppression to prevent rejection, reduction of immunosuppression can theoretically improve viral clearance. Reduction of immunosuppression can include reduction of dose, switching to less potent immunosuppressive agents.

Cidofovir, a nucleoside analogue, decreases cytomegalovirus (CMV) replication by inhibiting viral DNA polymerase. It also has in vitro activity against BKV, but its mechanism of action in the BKV infection appears to be inhibition of intracellular BKV genome replication (Bernhoff 2008).

Leflunomide, a pyrimidine synthesis inhibitor, has been developed as a treatment of rheumatoid arthritis. Its metabolite has been shown to have antiviral properties against DNA viruses, such as CMV (Waldman 1999).

FK778, a derivative of the active metabolite of leflunomide has been shown to have antiviral activity against polyomavirus. Additionally, it reversibly binding to dihydro-orotate-dehydrogenase resulting in pyrimidine biosynthesis inhibition which was shown to prevent acute allograft rejection in experimental transplantation models in non-human (Schorlemmer 2001).

Fluroquinolones have been proposed for potential therapy for BKV infection due to in vitro data. It has activity against large T-antigen BKV helicase (Sharma 2011).

Commercially available preparation of intravenous immunoglobulin contains high titers of neutralising antibodies against BKV. These antibodies have direct neutralising activity against BKV (Randhawa 2006).

Why it is important to do this review

The management of BKV infection has been complicated. Most of the literature reiterates the importance of immune-suppression reduction. However, this will expose the kidney recipients to increased risk of acute rejection, which subsequently will reduce the overall graft and patient survival.

OBJECTIVES

This review aims to evaluate treatment options for BKV infection in kidney transplant recipients.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs), quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) and cohort studies will be included.

Types of participants

Inclusion criteria

Studies conducted in patients who received primary or repeat kidney transplant from a deceased or living donor. The patients will be included if there is documented BK viruria based on positive BKV PCR from a urine sample, BK viraemia or biopsy-proven BKN and received a specific intervention (immunosuppression reduction, antiviral, antibiotic, leflunomide, IVIG or combination therapy).

Exclusion criteria

Recipients of non-kidney or dual organ transplants will be excluded. In addition, case reports and case series will not be included.

Types of interventions

The review will compare the therapeutic effect of any intervention for BK infection. We propose conducting comparisons of the following interventions.

1. Immunosuppression reduction alone, which includes reduction of CNI followed by reduction of MMF, or cessation of anti-metabolite (AZA or MMF) followed with reduction of CNI, or switching CNI to mTOR inhibitor, or switching TAC to cyclosporine, or concomitant reduction of both CNI and anti-metabolite
2. Immunosuppression reduction with antiviral, which includes administration of cidofovir
3. Immunosuppression reduction with antibiotic, which includes administration of fluoroquinolone
4. Immunosuppression reduction with leflunomide
5. Immunosuppression reduction with FK778
6. Immunosuppression reduction with IVIG
7. Combination of above treatment.

Types of outcome measures

The outcomes selected include the relevant SONG core outcome sets as specified by the Standardised Outcomes in Nephrology initiative (SONG 2017).

Primary outcomes

- Graft health or survival.

Secondary outcomes

- Elimination of BK viruria or viraemia
- Development of de novo DSA
- Re-transplantation
- Death
- Cancer
- Cardiovascular disease
- Infection
- Life participation
- Therapy-related adverse events.

Search methods for identification of studies

Electronic searches

We will search the Cochrane Kidney and Transplant Register of Studies through contact with the Information Specialist using search terms relevant to this review. The Register contains studies identified from the following sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)

2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these searches, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the "Specialised Register" section of information about Cochrane Kidney and Transplant. See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Contact experts/organisations in the field seeking information about unpublished or incomplete studies.
3. Grey literature sources (e.g. abstracts, dissertations and theses), additional to those already included in the Cochrane Kidney and Transplant Register of Studies, will not be searched.

Data collection and analysis

Selection of studies

The search strategy described will be used to obtain titles and abstracts of studies that may be relevant to the review (Appendix 1). The titles and abstracts will be screened independently by two authors, who will discard studies that are not applicable; however studies and reviews that might include relevant data or information on studies will be retained initially. Two authors will independently assess retrieved abstracts and, if necessary the full text, of these studies to determine which studies satisfy the inclusion criteria.

Data extraction and management

Data extraction will be carried out independently by two authors using standard data extraction forms. Studies reported in non-English language journals will be translated before assessment. Where more than one publication of one study exists, reports will be grouped together and the publication with the most complete data will be used in the analyses. Where relevant outcomes are only published in earlier versions these data will be used. Any discrepancy between published versions will be highlighted.

Assessment of risk of bias in included studies

For RCTs the following items will be independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
    - Participants and personnel (performance bias)
    - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

For non-RCTS the Newcastle-Ottawa Scale (NOS) (www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf) will be used to assess quality (Appendix 3; Appendix 4).

- Selection: representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration that outcome of interest was not present at the start of study
- Potential confounding factors are underlying kidney pathology, post-transplant diabetes mellitus, live versus cadaveric donation, number of HLA mismatches, and ABO-compatibility
- Comparability: comparability of cohorts on the basis of the design or analysis
- Outcome: assessment of outcome, adequacy of follow-up and duration of follow-up.

Measures of treatment effect

For dichotomous outcomes such as viral clearance, acute rejection, graft survival, patient survival, and therapy-related adverse events 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 such as kidney function (serum creatinine and/or estimated glomerular filtration (eGFR)), the mean difference (MD) will be used. The other outcomes will be compared on similar scales. Outcomes from RCTs and non-RCTs will be reported separately.

Unit of analysis issues

If multiple groups are investigated in one study, we will use each group only one in the review. Data will be compared on similar scales. For RCTs with repeated measurements, we will consider the longest follow-up for the analysis

Dealing with missing data

Any further information required from the original author will be requested by written correspondence (e.g. emailing corresponding author) and any relevant information obtained in this manner will be included in the review. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat, as-treated and per-protocol population will be carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals will be investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) will be critically appraised (Higgins 2011).

Assessment of heterogeneity

We will first assess the heterogeneity by visual inspection of the forest plot. We will quantify statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than sampling error (Higgins 2003). A guide to the interpretation of I^2 values will be as follows.

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity.

The importance of the observed value of I^2 depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P-value from the Chi^2 test, or a confidence interval for I^2) (Higgins 2011).
Studies will be assessed based on their patient populations, treatments, and outcomes to decide whether meta-analysis is appropriate. Non-randomised studies will be assessed separately but in a similar manner to give maximum insight into available data. By default, standard outcomes will be represented in forest plots with or without totals for overall effect.

Assessment of reporting biases

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

Data synthesis

Data will be pooled using the random-effects model but the fixed-effect model will also be used to ensure robustness of the model chosen and susceptibility to outliers.Adjusted effect estimates will be preferred over unadjusted if the choice is available. If appropriate meta-analyses of adjusted estimates will use an inverse-variance weighted average. The data from RCTs and non-RCTs will be analysed and reported separately.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis will be used to explore possible sources of heterogeneity. Heterogeneity among participants could be related to age and renal pathology. Heterogeneity in treatments could be related to prior agent(s) used and the agent, dose and duration of therapy. 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 in order to explore the influence of the following factors on effect size.

- Repeating the analysis excluding unpublished studies
- Repeating the analysis taking account of risk of bias, as specified
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country.

'Summary of findings' tables

We will present the main results of the review in 'Summary of findings' (SOF) tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schunemann 2011a). The SOF tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008; GRADE 2011). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schunemann 2011b). We plan to present the following outcomes in the SOF tables.

- Graft survival (which include acute rejection and graft outcome)
- Elimination of virus (either viruria or viraemia)
- Development of de-novo DSA
- Death
- Retransplantation
- Therapy-related adverse events for respective intervention method.

Only RCTs results will be included in SOF tables. The results of non-RCTs (cohort studies) will be included in the discussion section.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. kidney transplant*:ti,ab,kw (Word variations have been searched) 2. "bk virus":ti,ab,kw (Word variations have been searched) 3. "bk viruria":ti,ab,kw (Word variations have been searched) 4. "bk viraemia":ti,ab,kw (Word variations have been searched) 5. "bk polyomavirus":ti,ab,kw (Word variations have been searched) 6. "bk nephropath*":ti,ab,kw (Word variations have been searched) 7. {or 2-6} 8. {and 1, 7}
MEDLINE	1. Kidney Transplantation/ 2. exp BK Virus/ 3. bk virus.tw. 4. bk viruria$.tw. 5. bk viraemia$.tw. 6. bk nephropath$.tw. 7. bk polyomavirus.tw. 8. or/2-7 9. and/1,8
EMBASE	1. exp kidney transplantation/ 2. BK virus/ 3. bk virus infection/ 4. bk virus.tw. 5. bk polyomavirus.tw. 6. bk viraemia$.tw. 7. bk viruria$.tw. 8. bk nephropath$.tw. 9. or/2-8 10. and/1,9

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random)

(*Continued*)

	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 Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*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 Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*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
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors	*Low risk of bias:* 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
	High risk of bias: 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

(*Continued*)

	could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data	*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 standardised 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
	High risk of bias: 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
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*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. sub-scales) 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

(*Continued*)

	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

Appendix 3. Risk of bias assessment - Newcastle Ottawa Scale Form

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1. Representativeness of the exposed cohort
   i) truly representative of the average ..... (describe) in the community *
   ii) somewhat representative of the average ..... in the community *
   iii) selected group of users (e.g. nurses, volunteers)
   iv) no description of the derivation of the cohort
2. Selection of the non-exposed cohort
   i) drawn from the same community as the exposed cohort *
   ii) drawn from a different source
   iii) no description of the derivation of the non-exposed cohort
3. Ascertainment of exposure
   i) secure record (e.g. surgical records) *
   ii) structured interview *
   iii) written self-report
   iv) no description
4. Demonstration that outcome of interest was not present at start of study
   i) yes *
   ii) no

Comparability

1. Comparability of cohorts on the basis of the design or analysis
   i) study controls for ..... (select the most important factor) *
   ii) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1. Assessment of outcome
   i) independent blind assessment *
   ii) record linkage *
   iii) self-report
   iv) no description
2. Was follow-up long enough for outcomes to occur
   i) yes (select an adequate follow up period for outcome of interest) *
   ii) no
3. Adequacy of follow-up of cohorts
   i) complete follow-up - all subjects accounted for *
   ii) subjects lost to follow-up unlikely to introduce bias - small number lost - <15 % follow-up, or description provided of those lost) *
   iii) follow-up rate < 85% and no description of those lost
   iv) no statement

Appendix 4. Risk of bias assessment - Newcastle Ottawa Scale

Coding manual for cohort studies

Selection

1. Representativeness of the exposed cohort

Item is assessing the representativeness of exposed individuals in the community, not the representativeness of the sample of women from some general population. For example, subjects derived from groups likely to contain middle class, better educated, health oriented women are likely to be representative of postmenopausal oestrogen users while they are not representative of all women (e.g. members of a health maintenance organisation (HMO) will be a representative sample of oestrogen users. While the HMO may have an under-representation of ethnic groups, the poor, and poorly educated, these excluded groups are not the predominant users of oestrogen). Allocation of stars as per rating sheet

2. Selection of the non-exposed cohort

Allocation of stars as per rating sheet.

3. Ascertainment of exposure

Allocation of stars as per rating sheet.

4. Demonstration that outcome of interest was not present at start of study

In the case of mortality studies, outcome of interest is still the presence of a disease/incident, rather than death. That is to say that a statement of no history of disease or incident earns a star.

Comparability

1. Comparability of cohorts on the basis of the design or analysis

A maximum of 2 stars can be allotted in this category. Either exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note; If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment. There may be multiple ratings for this item for different categories of exposure (e.g. ever versus never, current versus previous or never) Age =, Other controlled factors =

Outcome

1. Assessment of outcome

For some outcomes (e.g. fractured hip), reference to the medical record is sufficient to satisfy the requirement for confirmation of the fracture. This would not be adequate for vertebral fracture outcomes where reference to X-rays would be required.

1. Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (X-rays, medical records, etc.)
2. Record linkage (e.g. identified through ICD codes on database records)
3. Self-report (i.e. no reference to original medical records or X-rays to confirm the outcome)
4. No description.

2. Was follow-up long enough for outcomes to occur

An acceptable length of time should be decided before quality assessment begins (e.g. 5 yrs. for exposure to breast implants)

3. Adequacy of follow-up of cohorts

This item assesses the follow-up of the exposed and non-exposed cohorts to ensure that losses are not related to either the exposure or the outcome.
Allocation of stars as per rating sheet

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: DC, KK, GW
2. Study selection: DC and KK
3. Extract data from studies: DC and KK
4. Enter data into RevMan: DC
5. Carry out the analysis: DC and KK
6. Interpret the analysis: DC, KK, GW
7. Draft the final review: DC, KK, GW
8. Disagreement resolution: GW
9. Update the review: DC

DECLARATIONS OF INTEREST

1. Daniel Christiadi: none known
2. Krishna Karpe: none known
3. Giles Walters: none known