PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Acute Care QUAliTy in chronic Kidney disease (ACQUATIK)- a prospective cohort study exploring outcomes of patients with chronic kidney disease
AUTHORS	Arnold, Julia; Hayer, Manvir; Sharif, Adnan; Begaj, Irena; Tabriez, Mohammed; Bagnall, David; Ray, Daniel; Hoye, Ciaron; Nazir, Masood; Dutton, Mary; Fifer, Lesley; Kirkham, Katie; Sims, Don; Townend, Jonathan; Gill, Paramjit; Dasgupta, Indranil; Cockwell, Paul; Ferro, Charles

VERSION 1 - REVIEW

REVIEWER	D Goldsmith Guy's Hospital London
REVIEW RETURNED	26-Nov-2014

GENERAL COMMENTS	This is a trial protocol and as such, the trial cannot now be influenced by review. It is a worthwhile trial and one that should receive support.

REVIEWER	Yusuke Okuda Shiga University of Medical Science, JAPAN
REVIEW RETURNED	24-Mar-2015

GENERAL COMMENTS	Comment to the authors In the manuscript entitled “Acute Care QUAliTy in Chronic Kidney disease (ACQUATIK) – a prospective cohort study exploring outcomes of patients with chronic kidney disease,” the authors present the protocol of the ACQUATIK study, its aim being the elucidation of the benefits and potential risks of treatment for cardiovascular disease (CVD) in patients with CKD treated by general practice (not renal specialist) physicians. The participants were selected from inpatients of Birmingham University Hospitals Birmingham, England, NHS Foundation Trust, or Heart of England NHS Foundation Trust and were asked to give their informed consent to participate in the study. Readmission rate (the primary outcome) and seven secondary outcomes were compared between patients with CKD and those without CKD. In addition, tertiary outcomes are set. Despite the fact that some previous studies have already reported the benefits of treatment in patients with and

	without CKD, as stated in this manuscript, a systematic approach to demonstrate these benefits appears to be missing. Elucidation of the differences in treatment and CVD treatment outcomes between patients with CKD and patients with no CKD has clinical significance. However, I found some of the authors' explanations, mainly about outcomes of this study, difficult to follow. General comments 1. I have some difficulty understanding why the authors selected overall readmission rate rather than readmission rate for CVD only as the primary endpoint of this study. Because relationship between CKD and CVD is emphasized in the Introduction section, readmission rate for CVD (secondary outcome #1), mortality due to CVD (secondary outcome #2) or the risk-to-benefit ratio of treatment (secondary outcome #4) should be the primary endpoint. If the authors want to select overall readmission rate, explanation for how the primary endpoint was selected should be provided, and the clinical relevance of overall readmission rate is described in the Introduction section in stead of relationship between CKD and CVD. 2. I am afraid that medications for patients with CKD vary depending on the primary cause of the CKD. For example, patients with CKD due to diabetic nephropathy (compared to other patients with CKD) may need more frequent hospitalization for CKD-unrelated purposes (such as diabetes education or diabetic retinopathy surgery). When it is the primary disease, CKD may have a greater effect on the primary outcome. The authors should provide their opinion about the impact of CKD as the primary disease in the manuscript. 3. Although I guess that the authors intend to emphasize the usefulness of the system of the ACQUATIK study and potential to export the system to most hospitals and primary care practices in England through the results, how to demonstrate those is unclear. The secondary outcomes #3 and #7 might be concerned with this objective, but more detailed methods is required. I agree that QOF, HES, and ONS can allow the study of a patient journey through primary and secondary care, and can improve the quality of ACQUATIK study. 4. Analysis by age, sex, ethnicity and so on, should be performed for adjusting confounders influencing the primary and secondary outcomes. The results of the analysis should not be regarded as tertiary outcomes. 5. Primary endpoint should be specified in the Abstract.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Goldsmith
Institution and Country Guy's Hospital London
Please state any competing interests or state ‘None declared’: None

This is a trial protocol and as such, the trial cannot now be influenced by review. It is a worthwhile

trial and one that should receive support.

We are encouraged that Reviewer 1 recognises our study is worthwhile and should be supported. We are publishing the study protocol as part of best practice and we agree it would be very difficult to make substantial changes at this stage.

Reviewer 2's comments:
Reviewer Name Yusuke Okuda
Institution and Country Shiga University of Medical Science, JAPAN
Please state any competing interests or state 'None declared': None declared

In the manuscript entitled "Acute Care QUAliTy in Chronic Kidney disease (ACQUATIK) – a prospective cohort study exploring outcomes of patients with chronic kidney disease," the authors present the protocol of the ACQUATIK study, its aim being the elucidation of the benefits and potential risks of treatment for cardiovascular disease (CVD) in patients with CKD treated by general practice (not renal specialist) physicians. The participants were selected from inpatients of Birmingham University Hospitals Birmingham, England, NHS Foundation Trust, or Heart of England NHS Foundation Trust and were asked to give their informed consent to participate in the study. Readmission rate (the primary outcome) and seven secondary outcomes were compared between patients with CKD and those without CKD. In addition, tertiary outcomes are set. Despite the fact that some previous studies have already reported the benefits of treatment in patients with and without CKD, as stated in this manuscript, a systematic approach to demonstrate these benefits appears to be missing. Elucidation of the differences in treatment and CVD treatment outcomes between patients with CKD and patients with no CKD has clinical significance. However, I found some of the authors' explanations, mainly about outcomes of this study, difficult to follow.

We acknowledge these comments and agree that there is a need to further demonstrate differences in treatments received by patients with and without CKD. We apologise that some of the explanations have not been easy to follow and we have attempted to clarify them below.

General comments

1. I have some difficulty understanding why the authors selected overall readmission rate rather than readmission rate for CVD only as the primary endpoint of this study. Because relationship between CKD and CVD is emphasized in the Introduction section, readmission rate for CVD (secondary outcome #1), mortality due to CVD (secondary outcome #2) or the risk-to-benefit ratio of treatment (secondary outcome #4) should be the primary endpoint. If the authors want to select overall readmission rate, explanation for how the primary endpoint was selected should be provided, and the clinical relevance of overall readmission rate is described in the Introduction section instead of relationship between CKD and CVD.

It is clear after rereading the manuscript that the reasons for our chosen primary endpoint require explanation and we apologise for this omission.

We opted for total readmission rate, rather than readmission rate for cardiovascular disease alone, as the primary endpoint for a number of reasons. Firstly the study was powered on total readmission rate for patients with CKD versus patients without CKD as this is the available data. Secondly, a hospital readmission is a more robust measure than an admission for cardiovascular disease as this second classification is based on a single primary admission code and may not reflect the true nature of the admission, especially if a patient presents with more than one medical condition simultaneously. For example, an admission with a hip-fracture would be coded as such and may not necessarily reflect an underlying cardiovascular cause such as a cardiac arrhythmia or iatrogenic hypotensive episode. Thirdly, we are interested in readmissions potentially caused by treatments for cardiovascular disease, for example a gastrointestinal haemorrhage after initiating aspirin following a myocardial infarction. These two admissions (hip-fracture after a hypotensive episode and gastrointestinal bleed with aspirin), although highly relevant to our study, would not have formed part of our primary endpoint. Finally, hospital readmission for any cause is seen as a marker of quality of care. This is the main aim of the ACQUATIK study.

We have now added statements to this effect as highlighted in the revised manuscript.

2. I am afraid that medications for patients with CKD vary depending on the primary cause of the CKD. For example, patients with CKD due to diabetic nephropathy (compared to other patients with CKD) may need more frequent hospitalization for CKD-unrelated purposes (such as diabetes education or diabetic retinopathy surgery). When it is the primary disease, CKD may have a greater effect on the primary outcome. The authors should provide their opinion about the impact of CKD as the primary disease in the manuscript.

This is a sound observation. We have expanded the 'Analyses' section of the manuscript and believe this is now much clearer and addresses Reviewer 2's point.

"In the ACQUATIK study patients with renal disease under secondary care nephrology follow-up have been excluded. Therefore the majority of diagnoses coded within HES and primary care databases will include common systemic conditions such as hypertension and diabetes mellitus as the aetiology of CKD, rather than primary renal glomerulonephritides which would invariably be under secondary care follow-up in the UK. Conditions such as diabetes mellitus will also be present in the non-CKD group and will form part of the pre-specified analysis of comorbidities during data analysis."

3. Although I guess that the authors intend to emphasize the usefulness of the system of the ACQUATIK study and potential to export the system to most hospitals and primary care practices in England through the results, how to demonstrate those is unclear. The secondary outcomes #3 and #7 might be concerned with this objective, but more detailed methods is required. I agree that QOF, HES, and ONS can allow the study of a patient journey through primary and secondary care, and can improve the quality of ACQUATIK study.

We are pleased that Reviewer 2 acknowledges the usefulness of the electronic systems QOF, HES and ONS to follow a patient on their journey through primary and secondary care. All primary care practices are required to record QOF data. Submission of data by hospitals to HES is also compulsory in England. Furthermore there is a legal requirement in England to register all deaths and these must

be recorded by the ONS. The systems to collate all this data have been developed in one hospital and Clinical Commissioning Group (clinically led groups that include all GPs in that area) and are being tested in a second CCG and hospital. Whether these systems are truly exportable to most hospitals and primary care practices can only be formally tested by either extending the ACQUATIK study or, as is our intention, by conducting a future multi-centre trial in a wider geographical area. We have now added a statement to this effect in the 'Methods and analysis' section of the manuscript.

4. Analysis by age, sex, ethnicity and so on, should be performed for adjusting confounders influencing the primary and secondary outcomes. The results of the analysis should not be regarded as tertiary outcomes.

We have now removed the tertiary outcomes of the study. We have changed the manuscript to reflect that analysis of patient demographics will be included as part of the primary and secondary outcomes as suggested.

5. Primary endpoint should be specified in the Abstract.

We apologise for this omission and have now amended the abstract to include the primary endpoint.