Author’s response to reviews

Title: Assessing Cardiovascular Risk in Chronic Kidney Disease Patients Prior to Kidney Transplantation: Clinical Usefulness of a Standardised Cardiovascular Assessment Protocol

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Response to reviewers

BNEP-D-17-00247: Assessing Cardiovascular Risk in Chronic Kidney Disease Patients Prior to Kidney Transplantation: Clinical Usefulness of a Standardised Cardiovascular Assessment Protocol

Dear Professor Ciro Esposito

We highly appreciate the reviewers’ comments, which have greatly improved the quality of the manuscript. The improvements include the “discussion of DSE” as suggested by Dr Gregorini and clarifying the “aim of the study” with changes in introduction, results and conclusion sections as suggested by Dr Messa.

We have done a point-by-point response to the comments as below (in red) and all changes are tracked in the revised Manuscript (Main body - BNEP-D-17-00247 R1)
Reviewer 1: Dr Gregorini; comments and response

Ramphul et al screened a cohort of patients on waiting list for kidney transplantation for coronary artery disease. The cardiovascular screening method applied consists in the clinical evaluation protocol in use in author's transplant center and based on the European Renal Best Practice, UK Renal Association and British Transplant Society published recommendations. The outcomes were described in terms of cardiac, cardiovascular events and death. The work-up cardiovascular screening suggested in this article is currently used in many others transplantation centers. Despite the relatively small sample size and the follow-up period of medium length, this study is equally informative in the light of the rapid evolution of the ischemic heart disease in End Stage Renal Disease patients. The authors themselves declare these points as the main limits of the study. The results are clear and well reported thanks to easily consultable figures and tables.

A suggestion for the authors is to expand the "discussion section" with a brief reflection on the role of dobutamine stress echocardiography in diabetic and nephropathic patients, since in these patients the basal coronary flow could be elevated already in condition of rest, so with a poor increase in response to dobutamine.

We appreciate the comments and have added the following to the discussion:

‘Similarly, the safety, feasibility and accuracy of DSE in diabetic patients has been verified [31] despite the potential for impaired inducible ischaemia due to autonomic phenomena and reduced coronary flow reserve as a result of increased basal coronary flow [32]’

The statistical methods applied are consistent and correct.

Reviewer 2: Dr Messa; Comments and response

This is a retrospective study directed to evaluate the efficacy of the protocol utilized in the transplant centre of the authors for the assessment of the risk for cardiac events in patients to be submitted to a renal transplant (RTx). The main reported result was that dobutamine stress echocardiography (DSE), performed in all the high-risk patients, was effective in identifying the presence of a coronary artery disease (CAD).

Though the study could be of a certain interest, it has a number of limitations which should be carefully addressed.

- Overall, the aim(s) of the study was(are) not completely clear:
We appreciate the comment. To clarify the aim we have altered the last paragraph of the introduction as follows:

‘The aim of this study was to evaluate the results of a standardised protocol, using DSE and CA, to screen prospective renal transplant recipients for coronary artery disease; and specifically whether, in this population, (i) the risk stratification model was suitable at identifying high-risk patients, (ii) DSE in the high-risk patients was able to identify those at high risk of cardiovascular events and require coronary angiography, and (iii) DSE followed by CA could identify those patients likely to benefit from coronary revascularisation.’

- The results are described in an unclear way

We have rearranged the ‘Results’ section to make the results clearer and make for easier reading. We have used the following subheadings in the order below:

Characteristic and events during follow-up
Low risk patients
High risk patients
Dobutamine Stress Echocardiography
Coronary Angiography

- The criteria for the definition of ischemic heart disease (IHD), peripheral vascular disease (PVD), and congestive cardiac failure (CHF) should be detailed

We have added the definitions to the ‘Methods’ section

- Given that the assessment protocol was not directed to explore the risk of stroke, transient ischaemic cerebral attack (TIA), and/or progression of PVD, but was specifically directed to predicting the cardiac risk, in my opinion it is not appropriate to include these non cardiologic events to calculating the annual event rate (AER)

The primary outcome was to explore the risk of all cardiovascular events which includes stroke/TIA and PVD and therefore we feel it is important to include these events in calculating annual event rates.
Furthermore, the authors included in the AERs also the cases of death for sepsis, metastatic cancer and unknown causes: the inclusion of these events is inappropriate for the evaluation of the appropriateness of the assessment protocol for the cardiac risk.

All causes of death were included to reflect all-cause mortality which is an important outcome in our patients.

The evaluation of the outcomes in the high-risk group is biased by the fact that almost all the patients submitted to coronary angiography (CA) did not receive a renal transplant, leaving unanswered the main question about the outcome of RTx patients with an asymptomatic coronary disease with or without a previous CAD correction.

We appreciate Dr Messa’s comments but this was not the aim of our study.

Results, lines 281-282: it is not clear if the 7 patients referred for Coronary artery bypass graft (CABG) are included in the 18 patients described above (lines 277-279)

The 7 patients referred for CABG are included in the 18 patients – we have made changes to make this clearer.

Figure 2: the reported number do not appear completely consistent: (lower right panel: 70+40 = 11)

In 1 patient a DSE could not be performed – this is documented in the legend below the figure.

The only real conclusion that can be drawn from these results is that clinical stratification of cardiac risk in patients with end stage renal disease to be listed for RTx can predict major clinical outcome occurrence.

We have changed the conclusion as follows:

‘The study suggests that in a cohort of patients referred for kidney transplantation, the standardised risk stratification protocol is effective at identifying the patients at high risk of cardiovascular events and death. Although this study does not statistically demonstrate DSE to be effective at identifying those at risk of CAD and events, there were proportionally more patients with events amongst the patients with a positive DSE. The coronary angiogram triggered
by positive DSE or clinical symptoms, correctly identifies the patients at greatest risk of cardiovascular events and death during follow-up but event-rates remained high despite coronary revascularisation.