The ARCHITECT and Alinity urine NGAL assays, urine NephroCheck test, and urine and plasma BioPorto NGAL tests to help assess the risk of acute kidney injury for people who are being considered for admission to critical care

ADDENDUM to the EAG assessment report

Produced by Aberdeen Health Technology Assessment Group

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Does not contain CIC/AIC

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REASON FOR ADDENDUM SUBMISSION

After submission of the EAG assessment report, the NICE Technical Team requested the risk of bias assessment of the Meersch et al. study (*Meersch M, Schmidt C, Hoffmeier A, et al. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. Intensive Care Med 2017; 43(11), 1551-61*), which was used to inform the economic model.

This Addendum presents the results of such risk of bias assessment.

Risk of bias assessment of the Meersch et al.'s 2017 study.

The Meersch et al., study was a single centre RCT conducted in Germany. The study assessed the effects of a "KDIGO bundle" compared with standard care in a total of 276 high risk patients undergoing cardiac surgery. The patients were identified using a biomarker-based approach (urine NephroCheck test ≥0.3) test) and the KDIGO bundle consisted in the optimization of volume status and hemodynamics, avoidance of nephrotoxic drugs, and prevention of hyperglycemia. The primary outcome was the rate of AKI defined by KDIGO criteria within the first 72 hours after surgery. Secondary endpoints included severity of AKI and 90-day mortality. It is worth noting that while the study was powered to assess the rate of AKI, it was not powered to assess mortality.

The study's exclusion criteria were pre-existing AKI, pregnancy; glomerulo-nephritis, interstitial nephritis or vasculitis; CKD with eGFR < 30 ml/min; dialysis dependent CKD, prior kidney transplant; patients on mechanical assist devices.

Two members of the EAG independently assessed the risk of bias of the Meersch et al.'s study using the Cochrane risk of bias tool *(Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions. John Wiley & Son Publication, 2008).* The results of the risk of bias assessment are shown in Table 1 below.

The study was assessed as having low risk of bias on most domains. The main limitation of the study was that investigators were not blinded to the intervention groups; however, blinded of investigators was impracticable due to the nature of the intervention and the fact that high risk patients were selected on the basis of the NephroCheck test results. In the study protocol provided as supplementary material, blinding was reported for i) individual patients, ii) investigators obtaining data and iii) endpoint committee, but no further details were provided. However, the following sentence in the discussion section '*the study was not blinded, which could contribute to measurement bias*' casts some doubts on whether the outcomes assessors were indeed blinded. Similarly, due to the nature of the intervention, it is difficult to fathom how blinding of patients could have been achieved successfully. The authors state that physicians who applied the intervention were independent of the anesthesia and perioperative care, which was performed by an experienced anesthesia team, and of the endpoint

assessment. However, it is unclear whether the physicians who treated patients in the standard care group were aware of the elevated NephroCheck results.

The authors also pointed out that the hemodynamic optimization, glycemic control and deferring ACE/ARBs (angiotensin converting enzyme inhibitors or angiotensin II receptor blockers) for the first 48 hours after cardiac surgery may be already part of the post-operative management in other clinical centres.

The EAG is of the opinion that the results of the Meersch et al.'s study are likely to be generalisable to the UK and other countries with regard to patients undergoing cardiac surgery. However, it is worth pointing out that the nature of the AKI insult (ischaemia/reperfusion, post-operative haemodynamic, oxidative stress, haemolysis, in people with cardiac comorbidity) is specific to this context (cardiac surgery) and it is unlikely it can be generalisable to other clinical contexts.

Table 1 Risk of bias assessment according to the Cochrane Risk of Bias tool

Domains	**Judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	Quote: 'Randomization codes were computer generated and concealed from investigators.'
Allocation concealment (selection bias)	Low	Quote: 'Randomization codes were computer generated and concealed from investigators. […] The allocation of the patients was performed by an independent investigator neither involved in the standard care of patients nor in the application of the intervention.'
Blinding of participants and personnel (performance bias) All outcomes	High	The authors acknowledge in the Discussion section that 'the study was not blinded …' Though not stated by the study's authors, it seems that the nature of the intervention did not allow masking of the study.
Blinding of outcome assessment (detection bias): AKI defined by KDIGO criteria	Unclear	Insufficient/unclear information about blinding of outcome assessors. Quote: 'Data collectors, outcome adjudicators and analysts were completely independent of the standard care of the patients as well as the physician who applied the intervention.' In the trial protocol the authors report blinding for 'i) individual patients, ii) investigators obtaining data and iii) endpoint committee' but no further

		details are given. In the Discussion section the authors state that 'the study was not blinded, which could contribute to measurement bias.'
Incomplete outcome data (Attrition bias): Occurrence of AKI	Low	All randomised participants were considered (138 in each group).
Incomplete outcome data (Attrition bias): Severity of AKI	Low	All randomised participants were considered (138 in each group.)
Incomplete outcome data (Attrition bias): 90-day mortality	Low	Analysis included 134/138 (97%) in the control group and 137/138 (99%) in the intervention group.
Selective reporting (reporting bias)	Low	The study reported all key outcomes specified in the protocol.
Other bias	Unclear	The study was funded, partly, by the manufacturer of the NephroCheck test.

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