Long-Term Consequences of Acute Kidney Injury After Cardiac Surgery: A Systematic Review and Meta-Analysis

Carlos Corredor, MBBS, MRCP, FRCA, FFICM, Rebekah Thomson, Dip HE, BSc(Hons), and Nawaf Al-Subaie, MBChB, FRCA, EDIC, FFICM

Objectives: **To determine the effect of acute kidney injury (AKI) associated with cardiac surgery on long-term mortality.**

Design: **Systematic review and meta-analysis of 9 observational studies extracted from the MEDLINE and EMBASE electronic databases.**

Setting: **Hospitals undertaking cardiac surgery.**

Participants: **The study included 35,021 cardiac surgery patients from 9 observational studies.**

Interventions: **None.**

Measurements and Main Results: **Nine studies including 35,021 patients reported incidence of AKI data. The median incidence of AKI was 27.75% (IQR, 16.3%-38.86%). There was significant variation in the reported incidence (range, 11.97%-54%), which can be explained by the different AKI definitions used in the included studies. Eight studies provided adjusted effect size data with 95% confidence intervals on the impact of the occurrence of postoperative AKI and long-term mortality outcomes. Occurrence of postoperative AKI is associated with a significantly increased risk of long-term mortality (HR, 1.68; 95% CI, 1.45-1.95; $p < 0.00001$). Recovery of renal function before hospital discharge is associated with a lower long-term mortality risk (HR, 1.31; 95% CI, 1.16-1.47; $p < 0.00001$) compared with patients who experienced persistent abnormal renal function on hospital discharge (HR, 2.71; 95% CI, 1.26-5.82; $p = 0.01$).**

Conclusions: **There is wide variation in the reported incidence of AKI after cardiac surgery, reflecting the different AKI classification systems used. AKI after cardiac surgery is associated with an increased risk of long-term mortality. Patients with persistent renal dysfunction after hospital discharge carry a higher risk of AKI.**

KEY WORDS: acute kidney injury, cardiac surgery, meta-analysis, mortality, incidence

ACUTE KIDNEY INJURY (AKI) is a recognized complication after cardiac surgery. The association among cardiac surgery, cardiopulmonary bypass, and renal failure has been described since the 1970s, when AKI was thought to be an uncommon, but serious, complication.[1,2] The characterization of the full extent of the problem has been difficult because of the many different definitions and terminology used to define AKI over the past 30 years.

Introduction of consensus guidelines, including the RIFLE classification by the Acute Dialysis Quality Initiative (ADQI)[3] in 2004; subsequent modifications performed by the Acute Kidney Injury Network (AKIN)[4] in 2007; and more recently, guidelines issued by the Kidney Disease: Improving Global Outcomes working group (KDIGO),[5] have facilitated the study of AKI's effect in specific patient populations (Table S1 in the Supplementary material summarizes the characteristics of these classification systems).

AKI is associated with postoperative complications, increased duration of hospital stay, and greater healthcare costs.[6] AKI also is an independent predictor for in-hospital mortality, with an 8-fold increase in mortality.[6]

Studies of large databases of mixed critical care populations suggested that AKI is associated with decreased short- and long-term survival.[7,8] Previous systematic reviews also have highlighted the association between AKI and worse long-term outcomes in general hospitalized patient populations.[9,10] The strong relationship among AKI, subsequent development of chronic kidney disease (CKD), and increased risk of cardiovascular events has been postulated as the underlying mechanism.[11–14]

The etiology of AKI associated with cardiac surgery is multifactorial with unique variables, such as the use of cardiopulmonary bypass. Proposed causes include ischemia-reperfusion injury, microemboli, oxidative stress, and inflammation.[15]

Changes in the structure and function of the renal microvasculature, together with the triggering of inflammatory pathways after an episode of AKI, can lead to progressive structural renal damage.[16,17] In addition, AKI and CKD share risk factors that have been identified and validated in cardiac surgery patient populations.[18–20]

Clinical resolution in patients who develop AKI often is seen as the endpoint of interest during hospital admission after surgery. The long-term effects of an AKI episode often are under-recognized because they appear years after the initial surgery.

The authors conducted a systematic review and meta-analysis to characterize the lasting effects that AKI has on mortality in cardiac surgery populations. The authors also studied the reported incidence of AKI, taking into account the different classification systems used to define this complication.

METHODS

This systematic review and meta-analysis was conducted in accordance with the PRISMA[21] and MOOSE[22] guidelines.

Eligibility Criteria

Observational studies reporting the impact of AKI on long-term mortality outcomes in cardiac surgery patients were included. Studies were selected using the patient, problem, or population; intervention; comparison; outcomes; and study design (PICOS) framework as per published guidelines for structuring a research question (Table 1).[23,24]

From the Cardiothoracic Intensive Care Unit, St. George's Hospital NHS Foundation Trust, London, United Kingdom.

Address reprint requests to Carlos Corredor, MBBS, MRCP, FRCA, FFICM, Cardiothoracic Intensive Care Unit, St. George's Hospital NHS Foundation Trust, Blackshaw Road, London, SW17 0QT, United Kingdom. E-mail: carloscorredor@doctors.org.uk

1053-0770/2601-0001$36.00/0

http://dx.doi.org/10.1053/j.jvca.2015.07.013

Table 1. Population, Intervention, Comparator, Outcome, Study Design (PICOS) Framework for Study Selections

Population	Adult cardiothoracic surgery patients
Intervention	The occurrence of AKI after cardiothoracic surgery
Comparator	Cohort of patients who did not develop AKI after cardiothoracic surgery
Outcome	Primary: Mortality at longest follow-up; follow-up should be more than 1 year Secondary: Incidence of AKI in each study
Study design	Observational studies; review articles and case reports are excluded

Abbreviation: AKI, acute kidney injury.

The authors included studies using recognized definitions of AKI and/or serum creatinine measurements. The effect of AKI on long-term mortality had to be reported with an adjusted effect size and its 95% confidence interval for meta-analyses in order for the study to be included in the quantitative analysis. The authors planned sensitivity analysis for type of surgery, recovery of renal function before hospital discharge, and stages of AKI.

Information Sources and Search Strategy

The electronic databases MEDLINE and EMBASE (Ovid platform) were searched using search filters for observational studies developed by the Scottish Intercollegiate Guidelines Network.[25] The search was restricted to articles published in the English language, with publication dates fewer than 20 years old due to changing practices in cardiothoracic surgery and changing definitions of AKI. The database search was last updated in January 2015.

The following search terms were used: cardiac surgery, coronary artery bypass graft (CABG), heart surgery, acute kidney injury, renal failure, and kidney injury. A complete description of the search strategy can be found in the Supplementary material.

Study Selection

Two investigators (R.T. and C.C.) screened titles and abstracts initially obtained from the search strategy and excluded non-relevant or duplicate titles. Full text articles of studies fitting the eligibility criteria then were retrieved and assessed independently by 2 reviewers. Any discrepancies were resolved by discussion between the reviewers or by consulting a third author (N.A.).

Data Extraction

A predesigned data collection form was used to extract relevant data from each selected study. Two investigators (R.T. and C.C.) extracted data on the following items: study design, total number of patients, type of surgery, length of follow-up, and prevalence of AKI. The definition of AKI used for the study also was recorded.

Mortality data were recorded for longest follow-up when studies reported different follow-up intervals. The minimum mortality follow-up period considered was at least 1 year.

Quality Assessment

Study quality and risk of bias were assessed using the Newcastle-Ottawa Scale (NOS). The NOS uses a "start system" to judge studies in 3 broad domains: selection of the study groups, comparability of the groups, and the ascertaining of outcomes in the case of cohort studies.[26] Studies can score 1 point for each subset of assessment criteria, with the exception of the comparability domain, in which 2 points can be obtained. The authors then classified the studies as high risk (1-3 points), intermediate risk (4-5 points), and low risk (6-9 points).

Statistical Analysis

Prevalence data were analyzed using descriptive statistics, including proportions, median, and interquartile range.

The multivariate adjusted hazard ratios (HRs) and 95% confidence interval (CI) of each individual study were introduced to an inverse variance model to compute the summary HR. P values were 2-tailed and considered significant if $p < 0.05$.

The chi-square test (Cochran Q) statistic was used to suggest whether $Q > df$ (degrees of freedom) and confirm heterogeneity if $p < 0.10$.[27] The I^2 statistic was used to quantify heterogeneity across the studies, with values of 0%-24.9%, 25%-49.9%, 50%-74.9%, and 75%-100% regarded as none, low, moderate, and high values, respectively, of statistical heterogeneity.[28] Sensitivity analyses were performed using both a random and fixed-effects model. However, the random-effects model pooled data were reported preferably in the presence of significant heterogeneity. Possible sources of heterogeneity were identified using "remove-one" sensitivity analysis.

Statistical analysis was performed using Excel 2010 for Mac (Microsoft, Redmond, WA). The meta-analysis was carried out using review manager (RevMan 5.3) for Mac (Cochrane, London, United Kingdom).

Publication bias was assessed using visual analysis of the funnel plot and the Egger's test, which is a linear regression method that aims to quantify bias observed in the funnel plot, especially if the number of studies is small.[29] Comprehensive Meta-Analysis version 2.2.064 (Biostat, Englewood, NJ) was used to perform the Egger's regression.

RESULTS

Quality Assessment and Study Characteristics

Results from the literature search are summarized in Fig 1. Application of search strategy to electronic databases produced 186 potential titles. Titles then were screened, and 147 were identified as relevant for this study. Abstracts then were screened using the authors' inclusion criteria, and 14 studies were retrieved for further full text analysis. Nine papers were chosen for data extraction. Reasons for exclusion included short-term mortality outcomes reported,[30–32] examination of preoperative renal function as predictor of outcomes,[33] and lack