

Increased Mortality, Postoperative Morbidity, and Cost After Red Blood Cell Transfusion in Patients Having Cardiac Surgery

Red blood cell transfusion can both benefit and harm. To inform decisions about transfusion, investigators in the UK quantified associations of transfusion with clinical outcomes and cost in patients having cardiac surgery.

Clinical, hematology, and blood transfusion databases were linked with the UK population register. Additional hematocrit information was obtained from intensive care unit charts. Composite infection (respiratory or wound infection or septicemia) and ischemic outcomes (myocardial infarction, stroke, renal impairment, or failure) were pre-specified as co-primary end points. Secondary outcomes were resource use, cost, and survival. Associations were estimated by regression modeling with adjustment for potential confounding. All adult patients having cardiac surgery between April 1, 1996, and December 31, 2003, with key exposure and outcome data were included (98%). Adjusted odds ratios for composite infection (737 of 8516) and ischemic outcomes (832 of 8518) for transfused versus nontransfused patients were 3.38 (95% confidence interval [CI], 2.60 to 4.40) and 3.35 (95% CI, 2.68 to 4.35), respectively. Transfusion was associated with increased relative cost of admission (any transfusion, 1.42 times [95% CI, 1.37 to 1.46], varying from 1.11 for 1 U to 3.35 for > 9 U). At any time after their operations, transfused patients were less likely to have been discharged from hospital (hazard ratio [HR], 0.63; 95% CI, 0.60 to 0.67) and were more likely to have died (0 to 30 days: HR, 6.69; 95% CI, 3.66 to 15.1; 31 days to 1 year: HR, 2.59; 95% CI, 1.68 to 4.17; > 1 year: HR, 1.32; 95% CI, 1.08 to 1.64).

Conclusions: Red blood cell transfusion in patients having cardiac surgery is strongly associated with both infection and ischemic postoperative morbidity, hospital stay, increased early and late mortality, and hospital costs.

Circulation. 2007;116:2544-2552

Impact of the Metabolic Syndrome on Macrovascular and Microvascular Outcomes in Type 2 Diabetes Mellitus

The metabolic syndrome (MetS) and type 2 diabetes mellitus are both associated with increased cardiovascular disease risk.

Investigators examined retrospectively the degree to which the presence of MetS in individuals with type 2 diabetes mellitus increased their risk of diabetic complications using United Kingdom Prospective Diabetes Study data.

Of 5102 United Kingdom Prospective Diabetes Study patients recruited with newly diagnosed type 2 diabetes mellitus and followed up for a median of 10.3 years, 4542 had the requisite data for these analyses. After a 3-month dietary run-in, MetS, diagnosed with National Cholesterol Education Program Adult Treatment Panel III, World Health Organization, International Diabetes Federation, or European Group for the Study of Insulin Resistance criteria, was present in 61%, 38%, 54%, and 24%, respectively. Those with MetS by these criteria had increased cardiovascular disease risks relative to those without MetS of 1.33 (95% confidence interval 1.14 to 1.54), 1.45 (95% confidence interval 1.26 to 1.66), 1.23 (95% confidence interval 1.07 to 1.42), and 1.31 (95% confidence interval 1.10 to 1.57), respectively, but similar risks for microvascular complications. The positive predictive value of MetS for cardiovascular disease events, however, was only 18%, 13%, 18%, and 39%, respectively.

MetS, diagnosed by Adult Treatment Panel III, World Health Organization, or International Diabetes Federation criteria, identifies diabetic patients at greater risk of macrovascular but not microvascular complications. Poor discrimination by MetS with respect to cardiovascular disease outcomes means that it is of limited clinical value for cardiovascular disease risk stratification in type 2 diabetes mellitus.

Circulation. 2007;116:2119-2126

Rosuvastatin in Older Patients with Systolic Heart Failure

Patients with systolic heart failure have generally been excluded from statin trials. Acute coronary events are uncommon in this population, and statins have theoretical risks in these patients.

A total of 5011 patients at least 60 years of age with New York Heart Association class II, III, or IV ischemic, systolic heart failure were randomly assigned to receive 10 mg of rosuvastatin or placebo per day. The primary composite outcome was death from

cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Secondary outcomes included death from any cause, any coronary event, death from cardiovascular causes, and the number of hospitalizations.

As compared with the placebo group, patients in the rosuvastatin group had decreased levels of low-density lipoprotein cholesterol (difference between groups, 45.0%; $P < 0.001$) and of high-sensitivity C-reactive protein (difference between groups, 37.1%; $P < 0.001$). During a median follow-up of 32.8 months, the primary outcome occurred in 692 patients in the rosuvastatin group and 732 in the placebo group (hazard ratio, 0.92; 95% confidence interval [CI], 0.83 to 1.02; $P = 0.12$), and 728 patients and 759 patients, respectively, died (hazard ratio, 0.95; 95% CI, 0.86 to 1.05; $P = 0.31$). There were no significant differences between the two groups in the coronary outcome or death from cardiovascular causes. In a prespecified secondary analysis, there were fewer hospitalizations for cardiovascular causes in the rosuvastatin group (2193) than in the placebo group (2564) ($P < 0.001$). No excessive episodes of muscle-related or other adverse events occurred in the rosuvastatin group.

Rosuvastatin did not reduce the primary outcome or the number of deaths from any cause in older patients with systolic heart failure, although the drug did reduce the number of cardiovascular hospitalizations. The drug did not cause safety problems.

N Engl J Medicine. 2007; 357:2248-2261

CETP Inhibition Torcetrapib Increases Risk for Coronary Events

Inhibition of cholesteryl ester transfer protein (CETP) has been shown to have a substantial effect on plasma lipoprotein levels. We investigated whether torcetrapib, a potent CETP inhibitor, might reduce major cardiovascular events. The trial was terminated prematurely because of an increased risk of death and cardiac events in patients receiving torcetrapib.

Researches conducted a randomized, double-blind study involving 15,067 patients at high cardiovascular risk. The patients received either torcetrapib plus atorvastatin or atorvastatin alone. The primary outcome was the time to the first major cardiovascular event,

which was defined as death from coronary heart disease, nonfatal myocardial infarction, stroke, or hospitalization for unstable angina.

At 12 months in patients who received torcetrapib, there was an increase of 72.1% in high-density lipoprotein cholesterol and a decrease of 24.9% in low-density lipoprotein cholesterol, as compared with baseline ($P < 0.001$ for both comparisons), in addition to an increase of 5.4 mm Hg in systolic blood pressure, a decrease in serum potassium, and increases in serum sodium, bicarbonate, and aldosterone ($P < 0.001$ for all comparisons). There was also an increased risk of cardiovascular events (hazard ratio, 1.25; 95% confidence interval [CI], 1.09 to 1.44; $P = 0.001$) and death from any cause (hazard ratio, 1.58; 95% CI, 1.14 to 2.19; $P = 0.006$). Post hoc analyses showed an increased risk of death in patients treated with torcetrapib whose reduction in potassium or increase in bicarbonate was greater than the median change.

Torcetrapib therapy resulted in an increased risk of mortality and morbidity of unknown mechanism. Although there was evidence of an off-target effect of torcetrapib, we cannot rule out adverse effects related to CETP inhibition.

N Engl J Medicine. 2007; 357:2109-2122

Pioglitazone Improves Myocardial Blood Flow and Glucose Utilization in Nondiabetic Patients With Combined Hyperlipidemia

Investigators examined whether treatment with pioglitazone, added to conventional lipid-lowering therapy, would improve myocardial glucose utilization (MGU) and blood flow (MBF) in nondiabetic patients with familial combined hyperlipidemia (FCHL).

Thiazolidinediones were found to improve insulin sensitivity and MGU in type 2 diabetes and MBF in Mexican Americans with insulin resistance. Familial combined hyperlipidemia is a complex genetic disorder conferring a high risk of premature coronary artery disease, characterized by high serum cholesterol and/or triglyceride, low high-density lipoprotein (HDL) cholesterol, and insulin resistance.

The researchers undertook a randomized, double-blind, placebo-controlled study in 26 patients with FCHL, treated with pioglitazone or matching placebo 30 mg daily for 4 weeks, followed by 45 mg daily for 12 weeks. Positron

emission tomography was used to measure MBF at rest and during adenosine-induced hyperemia and MGU during euglycemic hyperinsulinemic clamp at baseline and after treatment.

Whereas no change was observed in the placebo group after treatment, patients receiving pioglitazone showed a significant increase in whole body glucose disposal (3.93 ± 1.59 mg/kg/min to 5.24 ± 1.65 mg/kg/min; $p = 0.004$) and MGU (0.62 ± 0.26 μ mol/g/min to 0.81 ± 0.14 μ mol/g/min; $p = 0.0007$), accompanied by a significant improvement in resting MBF (1.11 ± 0.20 ml/min/g to 1.25 ± 0.21 ml/min/g; $p = 0.008$). Furthermore, in the pioglitazone group HDL cholesterol (+28%; $p = 0.003$) and adiponectin (+156.2%; $p = 0.0001$) were increased and plasma insulin (-35%; $p = 0.017$) was reduced.

In patients with FCHL treated with conventional lipid-lowering therapy, the addition of pioglitazone led to significant improvements in MGU and MBF, with a favorable effect on blood lipid and metabolic parameters.

J. Am. Coll. Cardiol.2007;50: 2051-2058

Acute Effects of Initiation and Withdrawal of Cardiac Resynchronization Therapy on Papillary Muscle Dyssynchrony and Mitral Regurgitation

Researchers evaluated the relationship between dyssynchrony involving the mitral valve apparatus and the acute improvement in mitral regurgitation (MR) after cardiac resynchronization therapy (CRT). The effect of interruption of CRT at 6 months' follow-up on dyssynchrony and MR was also evaluated.

Mitral regurgitation may improve acutely after CRT, but the precise mechanism is not fully understood. Out of 63 consecutive patients with baseline MR, 25 patients showed an acute reduction in MR severity immediately after CRT. This selected group of 25 patients (age 68 ± 10 years, left ventricular ejection fraction $23 \pm 8\%$) was evaluated in the current study. Echocardiography including speckle tracking strain analysis was performed at baseline, after CRT initiation, and during interruption of CRT at 6 months' follow-up to study the relationship between dyssynchrony between the papillary muscles and severity of MR.

According to the inclusion criteria, all patients showed an immediate improvement in MR after

CRT (vena contracta width decreased from 0.54 ± 0.15 cm to 0.39 ± 0.13 cm; $p < 0.001$), accompanied by an improvement in mitral deformation indexes. Furthermore, dyssynchrony between the papillary muscles decreased from 169 ± 69 ms to 25 ± 26 ms ($p < 0.001$). Importantly, these beneficial effects were maintained at 6 months' follow-up, but acute loss of resynchronization (from 26 ± 28 ms to 134 ± 51 ms; $p < 0.001$) was observed after interruption of CRT, with an acute recurrence of MR and worsening in mitral deformation indexes.

Cardiac resynchronization therapy can acutely reduce MR in patients with dyssynchrony involving the papillary muscles; interruption of CRT at 6 months' follow-up, however, resulted in acute loss of resynchronization with recurrence of MR.

J. Am. Coll. Cardiol.2007; 50: 2071-2077

A Prospective Study of Cigarette Smoking and Risk of Incident Hypertension in Women

Investigators undertook this study to prospectively evaluate whether cigarette smoking was associated with an increased risk of developing hypertension. Smoking is a well-recognized risk factor for cardiovascular disease. Few prospective cohort studies have examined the relationship between smoking and hypertension.

Researchers conducted a prospective cohort study among 28,236 women in the Women's Health Study who were initially free of hypertension, cardiovascular disease, and cancer. Detailed risk factor information, including smoking status, was collected from self-reported questionnaires. We used Cox proportional hazards survival models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) of incident hypertension (defined as either new diagnosis, the initiation of antihypertensive medication, systolic blood pressure 140 mm Hg or diastolic blood pressure 90 mm Hg).

At baseline, 51% of women were never smokers, 36% were former smokers, 5% smoked 1 to 14 cigarettes, and 8% smoked 15 cigarettes per day. During a median of 9.8 years, there were 8,571 (30.4%) cases of incident hypertension. The age-adjusted HRs of developing hypertension among never, former, and current smokers of 1 to 14 and 15 cigarettes

per day were 1.00 (reference), 1.04 (95% CI 0.99 to 1.09), 1.00 (95% CI 0.90 to 1.10), and 1.10 (95% CI 1.01 to 1.19), respectively. In multivariable models further adjusting for lifestyle, clinical, and dietary variables, the corresponding HRs were 1.00 (reference), 1.03 (95% CI 0.98 to 1.08), 1.02 (95% CI 0.92 to 1.13), and 1.11 (95% CI 1.03 to 1.21), respectively. Among women who smoked 25 cigarettes per day, the multivariable HR was 1.21 (95% CI 1.06 to 1.39).

In this large cohort of women, cigarette smoking was modestly associated with an increased risk of developing hypertension, with an effect that was strongest among women smoking at least 15 cigarettes per day.

J. Am. Coll. Cardiol. 50: 2085-2092

Role of Right Ventricular Wall Motion Abnormalities in Risk Stratification and Prognosis of Patients Referred for Stress Echocardiography

The results of SE are usually interpreted based on wall motion abnormalities of the left ventricle (LV). There is increasing recognition of the prognostic importance of RV. However, RV is still a “forgotten” chamber during routine SE.

Investigators evaluated 2,703 patients referred for SE. The LV was evaluated on a 16-segment model 5-point scale and the RV was evaluated on a 3-segment model 5-point scale for wall motion abnormalities. An abnormal RV or LV was defined as one with new (ischemic) or fixed (infarction) wall motion abnormalities. Follow-up (2.7 ± 1.0 years) for confirmed myocardial infarction and cardiac death ($n = 122$) were obtained.

An abnormal RV was seen in 112 patients (4%). In the presence of an abnormal LV, patients with abnormal RV had a worse prognosis than those with normal RV. Abnormal RV was a significant predictor of events (adjusted hazard ratio 2.69, 95% confidence interval 1.22 to 5.92; $p = 0.014$) independent of LV ischemia and ejection fraction. A forward conditional Cox model showed that peak RV wall motion score index provided incremental prognostic value over rest and conventional SE variables (global chi-square increased from 141.4 to 161.8 to 197.0; $p < 0.0001$ and $p = 0.006$, respectively).

In patients referred for SE, RV wall motion

analysis provides prognostic value independent of LV ischemia and ejection fraction and provides incremental value over rest and conventional SE variables. Right ventricular wall motion analysis should be routinely performed in patients referred for SE for effective risk stratification.

J. Am. Coll. Cardiol. 2007;50: 1981-1989.

Clinical Factors, But Not C-Reactive Protein, Predict Progression of Calcific Aortic-Valve Disease: The Cardiovascular Health Study

Researchers examined the relationship between C-reactive protein (CRP) and calcific aortic valve disease in a large, randomly selected, population-based cohort. The pathobiology of calcific aortic stenosis involves an active inflammatory, atheromatous, osteogenic process. Elevations in CRP, a measure of systemic inflammation, have been associated with aortic stenosis.

Two-dimensional and Doppler echocardiography and CRP measurement were performed at baseline in 5,621 participants in the Cardiovascular Health Study. Multivariable analysis was used to identify CRP as a predictor of baseline and incident aortic stenosis. At a mean echocardiographic follow-up of 5 years, 9% of subjects with aortic sclerosis progressed to some degree of aortic stenosis. Increasing age (odds ratio [OR] 1.13, 95% confidence interval [CI] 1.09 to 1.16; $p < 0.001$) and male gender (OR 3.05, 95% CI 1.76 to 5.27; $p < 0.001$) were related to risk of incident aortic stenosis, whereas increasing height (OR 0.96, 95% CI 0.94 to 0.99; $p = 0.013$) and African-American ethnicity conveyed a lower risk (OR 0.49, 95% CI 0.25 to 0.95; $p = 0.035$). C-reactive protein, treated as a continuous variable, was not associated with baseline aortic stenosis, progression to aortic sclerosis (adjusted OR 0.93, 95% CI 0.85 to 1.02; $p = 0.107$), or progression to aortic stenosis (adjusted OR 0.85, 95% CI 0.70 to 1.03; $p = 0.092$).

In this large population-based cohort, approximately 9% of subjects with aortic sclerosis progressed to aortic stenosis over a 5-year follow-up period. There was no association between CRP levels and the presence of calcific aortic-valve disease or incident aortic stenosis. C-reactive protein appears to be a poor predictor of subclinical calcific aortic-valve disease.

J. Am. Coll. Cardiol. 2007;50: 1992-1998