

scale in predicting symptomatic vasospasm, especially identifying patients at highest risk, with higher inter- and intra-observer agreement.<sup>[2]</sup> In the present study, larger aneurysms were no more likely to have a higher maximum SAH clot burden using the BNI scale. Using the BNI scale, the higher the grade, the more likely the risk for vasospasm. Comparing patients with a BNI scale grade of 5 patients with a grade of 1 produced an odds ratio greater than 11.

The authors concluded that the location of a ruptured aneurysm minimally affects the maximum thickness of the SAH clot but is predictive of symptomatic vasospasm or clinical deterioration from delayed cerebral ischemia in pericallosal aneurysms. The worst 1-year mRS outcomes in this cohort of patients were noted in those with posterior circulation aneurysms or pericallosal artery aneurysms. Patients experiencing stroke had higher mean clot burden.<sup>[1]</sup>

Sheth *et al.*, found no significant influence of intraoperative rerupture during open surgical clip placement on the rate of angiographic or symptomatic vasospasm. These results did not justify early aggressive treatment with blood pressure augmentation and intravascular volume expansion to prevent delayed cerebral ischemia. Also, vasospasm rates were similar in patients treated with coil embolization vis-a-vis clipping, suggesting that drainage of the subarachnoid blood during open surgical treatment offsets vessel irritation by direct handling.<sup>[3]</sup> Aneurysm coiling and increased clot clearance were independently associated with decreased severity of angiographic vasospasm in multivariate analysis, although there were no differences in clot clearance between coiled and clipped patients.<sup>[4]</sup>

The randomized, double-blind, placebo-controlled, phase 3, CONSCIOUS-2 trial in patients with aneurysmal subarachnoid haemorrhage undergoing surgical clipping showed that clazosentan, an endothelin receptor antagonist, at 5 mg/h had no significant effect on mortality and vasospasm-related morbidity or functional outcome.<sup>[5]</sup> Oral administration of cilostazol was found effective in preventing cerebral vasospasm with a low risk of severe adverse events in a multicenter, randomized open label blinded endpoint trial. Further studies are required to assess the impact of these interventions on a larger scale.<sup>[6]</sup>

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**Brar SS, Aharonian V, Mansukhani P, *et al.* Haemodynamic-guided fluid administration for the prevention of contrast-induced acute kidney injury: The POSEIDON randomised controlled trial. *Lancet* 2014;383:1814-23.**

The administration of intravenous fluid remains the cornerstone treatment for the prevention of contrast-induced acute kidney injury (CI-AKI). Data from the Prevention of Radiocontrast-Induced Nephropathy Clinical Evaluation (PRINCE) study indicate that increasing the urine flow rate (>150 mL/h) reduces the toxic effect of contrast media (CM). Volume expansion with normal saline might reduce contrast-mediated injury by expanding plasma volume, reducing renin activation and loss of nitric oxide, reducing production of reactive oxygen species, and through dilution of contrast within the tubular lumen.<sup>[1]</sup> However, no well-defined protocols exist to guide fluid administration in this treatment.

In a randomised, parallel-group, comparator-controlled, single-blind phase 3 trial published in the *Lancet* 2014, Brar *et al.*, studied the efficacy of a new fluid protocol based on the left ventricular end-diastolic pressure (LVEDP) for the prevention of CI-AKI in patients undergoing cardiac catheterization (the POSEIDON trial). LVEDP is a haemodynamic parameter and can be used to establish intravascular volume status. The primary outcome was the occurrence of CI-AKI, which was defined as a greater than 25% or greater than 0.5 mg/dL increase in serum creatinine concentration. Between Oct 10, 2010 and July 17, 2012,

396 patients aged 18 years or older undergoing cardiac catheterisation with an estimated glomerular filtration rate of 60 mL/min per 1.73 m<sup>2</sup> or less and one or more of several risk factors (diabetes mellitus, history of congestive heart failure, hypertension or age older than 75 years) were randomly allocated in a 1:1 ratio to LVEDP-guided volume expansion ( $n = 196$ ) or the control group ( $n = 200$ ) who received a standard fluid administration protocol. Exclusion criteria included inability to obtain consent from participants, emergency cardiac catheterisation (e.g., primary percutaneous coronary intervention for ST-segment elevation myocardial infarction), renal replacement therapy, exposure to radiographic contrast media within the previous 2 days, allergy to radiographic contrast media, acute decompensated heart failure, severe valvular heart disease, mechanical aortic prosthesis, left ventricular thrombus, history of kidney or heart transplantation and change in estimated GFR of 7.5% or more per day or a cumulative change of 15% or more during the preceding 2 or more days. Patients and laboratory personnel were masked to treatment assignment, but the physicians who did the procedures were not masked. N-acetylcysteine (NAC) use was defined as 600 mg twice daily for 2 days, starting the day before the index procedure, and use was at the discretion of the referring physician. If started, the 2-day course was completed.

Both groups received intravenous 0.9% sodium chloride at 3 mL/kg for 1 h before cardiac catheterization. LVEDP was measured by an angled 5 French or 6 French pigtail catheter placed in the mid cavity of the left ventricle and attached to standard haemodynamic monitoring software. (Xper; Phillips, Melbourne, FL, USA). The fluid rate was adjusted according to the LVEDP as follows: 5 mL/kg/h for LVEDP lower than 13 mmHg; 3 mL/kg/h for LVEDP of 13-18 mmHg and 1.5 mL/kg/h for LVEDP higher than 18 mmHg. The control group was hydrated at 1.5 mL/kg/h. The fluid rate was set at the start of the procedure (before contrast exposure), continued for the duration of the procedure and for 4 h post-procedure in both groups. Analyses were by intention to treat. Adverse events were assessed at 30 days and 6 months, and all such events were classified by staff who was masked to treatment assignment. Serum creatinine was measured at 1-4 days post procedure noting the highest value and 2-8 weeks after the index procedure.

The main findings of the POSEIDON trial were that CI-AKI occurred less frequently in patients in the LVEDP group (6.7% [12/178]) than in the control group (16.3% [28/172]; relative risk 0.41, 95% CI 0.22-0.79;  $P = 0.005$ ). In patients with stable renal insufficiency undergoing cardiac catheterisation and followed up for 6 months post-procedure,

LVEDP-guided fluid administration as compared with standard treatment resulted in a significant 68% relative reduction (9.5% absolute reduction) in the primary endpoint of CI-AKI and a significant 59% relative reduction (6.4% absolute reduction) in major adverse clinical events. Hydration treatment was terminated prematurely because of shortness of breath (safety endpoint) in three patients in each group. They concluded that LVEDP-guided fluid administration was safe and effective in preventing CI-AKI in patients undergoing cardiac catheterisation.<sup>[2]</sup>

The POSEIDON trial has been criticized for its emphasis on patients with medium risk category for AKI. Also, more than 50% of patients had normal LVEDP and only 15% had high values.<sup>[3]</sup> Further studies are warranted to examine the effect of LVEDP-guided fluid administration in patients with high LVEDP, therefore, targeting the dysfunctional heart, where the normal Frank Starling mechanisms would not apply.

Some studies have shown the advantages of CI-AKI prophylaxis with NAC and sodium bicarbonate solution. The Renal Insufficiency After Contrast Media Administration Trial I (REMEDIAL I) trial showed that the combined strategy of volume supplementation with sodium bicarbonate and NAC was better than normal saline and NAC alone or a combination of normal saline, ascorbic acid, and NAC in preventing CI-AKI inpatients at low to medium risk. However, in high-risk patients, the rate of CI-AKI remained high.<sup>[4]</sup>

The randomised, multicenter, investigator-driven REMEDIAL II trial by Briguori *et al.*, showed that RenalGuard therapy was found superior to sodium bicarbonate and NAC in preventing CI-AKI in high-risk patients. The RenalGuard System, which creates high urine output and fluid balancing, may be beneficial in preventing CI-AKI. Patients with an estimated glomerular filtration rate  $\leq 30$  mL/min/1.73 m<sup>2</sup> and/or a risk score  $\geq 11$  were randomly assigned to sodium bicarbonate solution and NAC (control group) or hydration with saline and NAC controlled by the RenalGuard System and furosemide (RenalGuard group). The primary end point was an increase of  $\geq 0.3$  mg/dL in the serum creatinine concentration at 48 hours after the procedure. CI-AKI occurred in 16 of 146 patients in the RenalGuard group (11%) and in 30 of 146 patients in the control group (20.5%; odds ratio, 0.47; 95% confidence interval, 0.24-0.92). There were 142 patients (48.5%) with an estimated glomerular filtration rate  $\leq 30$  mL/min/1.73 m<sup>2</sup> and 149 patients (51.5%) with only a risk score  $\geq 11$ . Subgroup analysis according to inclusion criteria showed a similarly lower risk of adverse events (estimated glomerular filtration rate  $\leq 30$  mL/min/1.73 m<sup>2</sup> odds ratio, 0.44; risk score  $\geq 11$ : odds ratio, 0.45;

$P$  for interaction = 0.97. The rate of in-hospital dialysis (4.1% versus 0.7%;  $P = 0.056$ ) were higher in the control group.<sup>[5]</sup> Further studies are needed to compare LVEDP-guided versus RenalGuard system-guided hydration regimens.

A recent study examined the role of vitamin E (tocopherol) in preventing CI-AKI and concluded that prophylactic oral  $\alpha$ - or  $\gamma$ -tocopherol with 0.9% saline protected against CI-AKI in patients with chronic kidney disease (CKD) undergoing coronary procedures. In this study, 305 patients were randomly assigned to prophylaxis administration with 0.9% saline infusions plus daily oral medication comprised of either (i) placebo ( $n = 101$ ), (ii)  $\alpha$ -tocopherol ( $n = 102$ ) or (iii)  $\gamma$ -tocopherol ( $n = 102$ ) starting 5 days before and ending 2 days after coronary procedures. CI-AKI developed in 14.9% in the placebo group, 4.9% in the  $\alpha$ -tocopherol group ( $P = 0.02$  versus the placebo group) and 5.9% in the  $\gamma$ -tocopherol group ( $P = 0.04$  versus the placebo group). In patients with diabetes, hypertension, anaemia, aged over 55 years, males or with contrast agent dosages  $>120$  mL,  $\alpha$ -tocopherol showed a greater effect than  $\gamma$ -tocopherol when compared with the placebo group ( $P < 0.05$ ).<sup>[6]</sup> This strategy should be compared to the abovementioned strategies to ascertain its effect vis-a-vis fluid protocols and NAC use for preventing CI-AKI in elective radiographic procedures.

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**Rapsomaniki E, Timmis A, George J, *et al.* Blood pressure and incidence of twelve cardiovascular diseases: Lifetime risks, healthy life-years lost and age-specific associations in 1.25 million people. *Lancet* 2014;383:1899-911.**

The associations of blood pressure with the different clinical presentations of incident cardiovascular diseases in a contemporary population have not been studied thoroughly. Twelve different presentations of cardiovascular disease were analysed for associations with blood pressure in this study published in the *Lancet* 2014.

Electronic health records from 1997 to 2010 in the CALIBER (CARDiovascular research using LInked Bespoke studies and Electronic health Records) programme, from 225 primary care practices registered with it, were used to set up a cohort of 1.25 million patients, 30 years of age or older and initially free from cardiovascular disease, 20% of whom received blood pressure-lowering treatments. The heterogeneity in the age-specific associations of clinically measured blood pressure with 12 acute and chronic cardiovascular diseases were studied, and estimated lifetime risks (up to 95 years of age) and cardiovascular disease-free life years lost adjusted for other risk factors at index ages 30, 60 and 80 years were calculated. Patients' blood pressure was measured at initial presentation at primary care clinic closest to index date, and they were classified as hypertensive at a blood pressure higher than 140/90 mmHg. Isolated systolic hypertension ( $>140$  mmHg) and isolated diastolic hypertension ( $>90$  mmHg) were also noted. The cardiovascular diseases recorded were stable and unstable angina, myocardial infarction, unheralded coronary artery disease death, heart failure, sudden cardiac death, transient ischaemic attack, ischaemic stroke, subarachnoid haemorrhage, intracerebral haemorrhage, peripheral arterial disease and abdominal aortic aneurysm.<sup>[1]</sup> Unclassified stroke was considered an ischaemic stroke, as 87% of all unclassified strokes have been shown as ischaemic origin in previous studies.<sup>[2]</sup>

During 5.2 years median follow-up, 83098 initial cardiovascular disease presentations were recorded. In each age group, the lowest risk for cardiovascular disease was in people with systolic blood pressure of 90-114 mmHg and diastolic blood pressure of 60-74 mmHg, with no evidence of a J-shaped increased risk at lower blood pressures. Associations with high systolic blood pressure were highest for intracerebral haemorrhage (hazard ratio 1.44 [95% CI 1.32-1.58]), subarachnoid haemorrhage (1.43 [1.25-1.63]), and stable angina (1.41 [1.36-1.46]) and weakest for abdominal