Original Article

A double-blind randomised feasibility trial of angiotensin-2 in cardiac surgery*

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Summary

Acute kidney injury is common after cardiac surgery. Vasoplegic hypotension may contribute to kidney injury, and different vasopressors may have variable effects on kidney function. We conducted a double-blind, randomised feasibility trial comparing peri-operative angiotensin-2 with noradrenaline. We randomly allocated 60 patients at two centres to a blinded equipotent angiotensin-2 or noradrenaline infusion intra-operatively and for up to 48 h postoperatively, titrated to mean arterial pressure of 70–80 mmHg. Primary feasibility outcomes included consent rate, protocol adherence, infusion duration, mean arterial pressure maintenance in the target range and major adverse outcomes. Secondary outcomes included kidney injury rate. The consent rate was 47%. Protocol adherence was 100% in the angiotensin-2 group and 94% in the noradrenaline group. Study drug duration was median (IQR [range]) 217 (160–270 [30–315]) vs. 185 (135–301 [0–480]) min (p = 0.78) min intra-operatively, and 5 (0–16 [0–48]) vs. 14.5 (4.8–29 [0–48]) hours (p = 0.075) postoperatively for angiotensin-2 and noradrenaline, respectively. The mean arterial pressure target was achieved postoperatively in 25 of 28 (89%) of the angiotensin-2 group and 27 of 32 (84%) of the noradrenaline group. One participant had a stroke, one required extracorporeal support and three required renal replacement therapy, all in the noradrenaline group (p = 0.99, p = 0.99 and p = 0.1). Acute kidney injury occurred in 7 of 28 in the angiotensin-2 group vs. 12 of 32 patients in the noradrenaline group (p = 0.31). This pilot study suggests that a trial comparing angiotensin-2 with noradrenaline is feasible. Its findings justify further investigations of angiotensin-2 in cardiac surgery.

Introduction

Acute kidney injury (AKI) is common after cardiac surgery [1]. It is associated with worse long-term outcomes, including chronic kidney disease and mortality [2]. Its causes are thought to be multifactorial and include reduced renal perfusion pressure and reduced renal blood flow [1]. Vasoplegia appears to be partially responsible for reduced renal perfusion and reversing its effects may improve renal perfusion [3]. Accordingly, vasopressor therapy may prove useful.

Vasopressors, of which noradrenaline and vasopressin are the most well studied, are commonly used intra-operatively and postoperatively in cardiac surgery, to maintain systemic vascular resistance. [4]. Despite this, there are few large clinical trials investigating these drugs [5]. Other drugs such as adrenaline, phenylephrine or methylene blue are less commonly used. More recently, angiotensin-2 has been proposed as useful in the setting of vasoplegia after cardiac surgery [6–8].

Angiotensin-2 is a potent vasoconstrictor. In a recent large trial, it was shown to be effective in restoring blood pressure in patients with catecholamine-resistant shock [9]. In a post-hoc analysis of the same study, patients who experienced AKI requiring renal replacement therapy and who were randomly allocated to receive angiotensin-2 had higher rates of renal recovery compared with those who received placebo [10]. In sheep sepsis models, angiotensin-2 (relative to noradrenaline) improved blood pressure and creatinine clearance, without compromising renal medullary oxygenation [11]. Elevated renin levels have been found to be predictive of cardiovascular instability and AKI after cardiac surgery [12]. The association between renin–angiotensin system inhibiting drugs and AKI has been widely studied in cardiac surgery, and while results are variable, many studies have favoured an association [13–15]. Overall, this evidence suggests that angiotensin-2 could be an effective vasopressor to prevent kidney injury in patients undergoing cardiac surgery. However, to date, angiotensin-2 infusion in the context of cardiac surgery has only been assessed in small studies or case reports [6, 8, 16–19]. There have been no double-blind randomised controlled trials comparing angiotensin-2 with noradrenaline in cardiac surgery.

We hypothesised that a feasibility trial comparing angiotensin-2 with noradrenaline in a cardiac surgery population at elevated risk of AKI could be successfully conducted and that the results of such a trial would inform the design of appropriately powered future studies of the effect of angiotensin-2 on renal function in cardiac surgery.

Methods

We performed a double-blind, randomised, feasibility trial of angiotensin-2 to reduce acute kidney injury (A-TRAK study) at two metropolitan hospitals in Melbourne, Australia. Approval was granted by the Austin Human Research Ethics Committee and the trial was registered with the Australian and New Zealand Clinical Trials Registry. Written informed consent was obtained from trial participants. Reporting was carried out according to the CONSORT extension for pilot and feasibility studies [20].

Participants were screened at outpatient clinics and using inpatient pre-operative lists. Patients aged > 18 y, scheduled to undergo cardiac surgery, at an elevated risk of AKI having coronary artery bypass grafting (CABG), valve repair/replacements or combined CABG/valve replacement procedures were included in the study. Elevated AKI risk was defined by a score of ≥ 3.5 points using the following risk score: pre-operative haemoglobin < 130 g.l^{-1} (2 points); pre-operative creatinine > 100 μmol.l^{-1} (2 points); age > 70 y (1.5 points), BMI > 30 kg.m^{-2} (1.5 points) and New York Heart Association (NYHA) status 4 (1.5 points). [21] Due to initial slow recruitment, this threshold was amended to a score of ≥ 1.5 points after the recruitment of seven patients. Exclusion criteria included the following: major aortic, transplant and pulmonary thrombo-endarterectomy surgery; patients requiring pre-operative vasoactive support; pre-operative dialysis; pre-existing uncontrolled hypertension; asthma with lung function tests demonstrating reversible airway obstruction; severe left ventricular systolic dysfunction (ejection fraction < 30%); inadequate English comprehension or a cognitive impediment to consent; and pregnant or breastfeeding people. Patients already taking renin–angiotensin system inhibiting drugs (either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) were not excluded. The local practice at both hospitals was to advise patients to omit renin–angiotensin system inhibiting drugs for at least 24 h before the procedure; renin–angiotensin system inhibiting drug status and timing were recorded.

Patients were randomly allocated to the angiotensin-2 or noradrenaline group. The randomisation sequence was computer generated, random and stratified by site and emergency surgery status in blocks of two, four and six. The sequence was generated and uploaded to a REDCap database by a research affiliate not otherwise involved in the study. Patients were allocated to a study group just before surgery. Participants, the clinicians caring for them and researchers assessing outcomes were blinded to group allocation. To ensure adequate blinding, the drug was

constituted and provided to clinicians in equipotent vasopressor concentrations in bags of 250 ml or 500 ml sodium chloride solution by a member of research staff not involved in outcome assessment. A relative potency of angiotensin-2: noradrenaline of 10:1 was assumed based on current literature [22]. As such, the drug was constituted as 40 mcg.ml^{-1} noradrenaline or 4 mcg.ml^{-1} angiotensin-2.

Study drug infusion was connected after induction of anaesthesia and before the start of cardiopulmonary bypass. Conduct of other aspects of anaesthesia and ICU care was not formally standardised and left to the discretion of the treating clinicians. The study drug was started if the mean arterial pressure (MAP) was < 70 mmHg and other causes of hypotension such as hypovolaemia or inadequate inotropy were excluded (Fig. 1). The study drug was administered centrally and started at a weight-based infusion rate in millilitres per hour using an infusion table and a flow chart was given to clinicians (online Supporting Information, Appendix S1). Starting rates were equivalent to 0.02 mcg.kg^{-1}.min^{-1} noradrenaline or 2 ng.kg^{-1}.min^{-1} angiotensin-2. A range of rates from 0.01–0.4 mcg.kg^{-1}.min^{-1} and 1–40 ng.kg^{-1}.min^{-1}, respectively, were allowed. Study drug could be titrated up or down to maintain the target pressure range every 5 min or paused at any time at clinician discretion (e.g. in response to a need to reduce blood pressure before or during aortic cannulation). Other open label vasoactive and inotropic drugs were allowed at clinician discretion. The study drug was continued during cardiopulmonary bypass aiming at a target oxygen delivery (DO^2) of 280 ml.min.m^2 or cardiac index of > 2.2 l.min.m^2. The protocol was continued postoperatively for up to 48 h or until discharge from ICU, whichever occurred sooner.

This pilot study aimed to evaluate key feasibility outcomes. Primary feasibility outcomes and thresholds for feasibility included: consent rate of > 40% of patients approached; protocol adherence of > 80% (where non-adherence was defined by stopping study drug early and/or exchange for open label vasopressor); duration of study drug infusion > 4 h in 50% of patients and > 12 h in 25% of patients; blood pressure target (MAP > 70 mmHg) maintained for > 50% of the time intra-operatively and for 48 h in ICU using study drug as defined by medical record (recorded as negative if open label vasopressor infusion used); and minimal or absent major adverse events including: in-hospital mortality within 30 days of procedure; unplanned requirement for extracorporeal circulatory support; permanent stroke (as defined by Australian and New Zealand Society of Cardiothoracic Surgeons) and requirement for renal replacement therapy. Thresholds, where given, were chosen pragmatically a priori.

Secondary outcomes were used to aid in safety assessment, estimates of possible efficacy and sample size planning for a possible subsequent larger trial. They included the following outcomes: maximum change in creatinine from pre-operative up to 7 days postoperatively; AKI presence and stage by Kidney Disease Improving Global Outcomes criteria [23]; 6-h creatinine clearance immediately postoperatively; study drug infusion maximum rate, duration and total volume used at each peri-operative stage; fluid use; adrenaline, milrinone, noradrenaline, vasopressin and other vasoactive infusion use and maximum infusion rate; adverse events in hospital including severe hypertension while infusion running (MAP > 120 mmHg) with adverse effect (e.g. left ventricular failure or aortic dissection); deep vein thrombosis; new onset atrial fibrillation; arterial thrombosis; peripheral ischaemia and thrombocytopenia (platelet count < 50 $\times$ 10^9 l^{-1}); ICU and hospital length of stay; haemodynamic indices (cardiac output, systemic and pulmonary pressures) intra-operatively and in ICU; urine output intra-operatively and over the first 48 h; glucose, pH and lactate levels postoperatively and for up to 3 days.

A sample size of 60 patients was chosen pragmatically to ensure sufficient preliminary data to inform a future larger phase-2 study. A statistical analysis plan was developed and published online before analysis of the data [24]. The statistician conducting analysis was blinded to treatment group and all analyses were finalised before unblinding. Analysis was carried out on an intention-to-treat basis for all randomised participants who underwent cardiac surgery. Differences between study outcomes were analysed. For binary outcomes, a generalised linear model with binomial distribution and identity link was used. For continuous outcomes, we used a generalised linear model with Gaussian distribution or quantile model for skewed data. For ordinal outcomes, we used a cumulative logistic model. A two-sided p-value of 0.05 was considered significant. Where data were missing, groups were analysed by available data. Analysis was conducted using R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 463 patients were screened for suitability between 30 March 2021 and 19 September 2021 (Fig. 2). Overall, 202 of 463 (43%) screened patients were eligible to participate. Of those, 131 were approached for formal consent, of whom 61 agreed to participate (47%). Seven patients were randomly allocated from the original criteria,
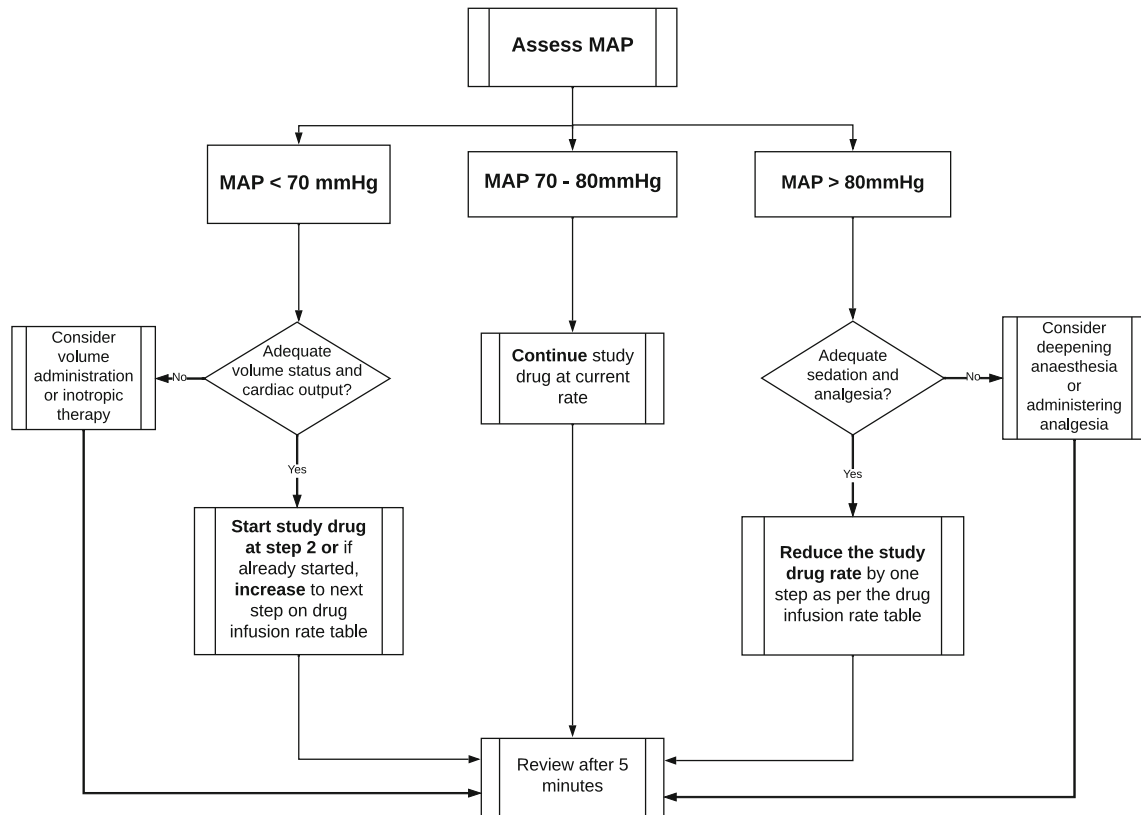
Figure 1 Flowchart describing management protocol for mean arterial pressure (MAP) and drug infusion during the peri-operative period.

of whom four were allocated to angiotensin-2 and three to noradrenaline. One patient was excluded from analysis after randomisation because surgery did not proceed. Of the remainder, 28 participants were allocated to the angiotensin-2 group and 32 were allocated to the noradrenaline group. Overall, open label noradrenaline was administered to three participants in the angiotensin-2 group and four participants in the noradrenaline group. Two participants in the noradrenaline group had their interventions discontinued due to unexpected surgical complexity, with the attending clinician deciding to administer only unblinded drugs.

Baseline characteristics were similar between the two groups (Table 1). Primary feasibility outcomes are shown in Table 2. Protocol adherence was 100% in the angiotensin-2 group and 94% in the noradrenaline group. Mean arterial pressure was maintained without additional vasopressor infusions at > 70 mmHg for >50% of the duration intra-operatively in 25 of 28 (89%) of the angiotensin-2 group and 30 of 32 (94%) of the noradrenaline group (p = 0.54), and postoperatively for 48 h in 25 of 28 (89%) of the angiotensin-2 group and 27 of 32 (84%) of the noradrenaline group (p = 0.58).

Intra-operative characteristics are shown in Table 3. The intra-operative duration, rate and volume of study drug infused were similar between the two groups. Adrenaline was used in 2 of 28 (7%) patients in the angiotensin-2 group vs. 6 of 32 (19%) in the noradrenaline group in (p = 0.26).

Postoperative characteristics in ICU are shown in Table 4. Angiotensin-2 was infused postoperatively for a median (IQR [range]) of 5 (0–16 [0–48]) h compared with 14.5 (5–29 [0–48]) h for noradrenaline (p = 0.075). Other findings were similar between the groups.

Secondary outcomes are shown in Table 2. The overall AKI rate for the study was 32%. There was no difference in the peak change in creatinine for 7 days between the two groups (median (IQR [range])) 8 ((−2.5–24.8) [−38–104]) $\mu mol.l^{-1}$ in the angiotensin-2 group vs. 11 (2.2–36.5 [−11–109]) $\mu mol.l^{-1}$ for the noradrenaline group (p = 0.63)). The AKI rate in the angiotensin-2 group was 7 of 28 (25%) vs. 12 of 32 (38%) for the noradrenaline group (p = 0.31). There were no differences in other complications. Hospital length of stay was a median (IQR [range]) of 6.3 (6.1–7.6 [5–14.1]) days in the angiotensin-2 group vs. 8.1 (5.9–9.5 [5–39.9]) days in the noradrenaline group (p = 0.04).
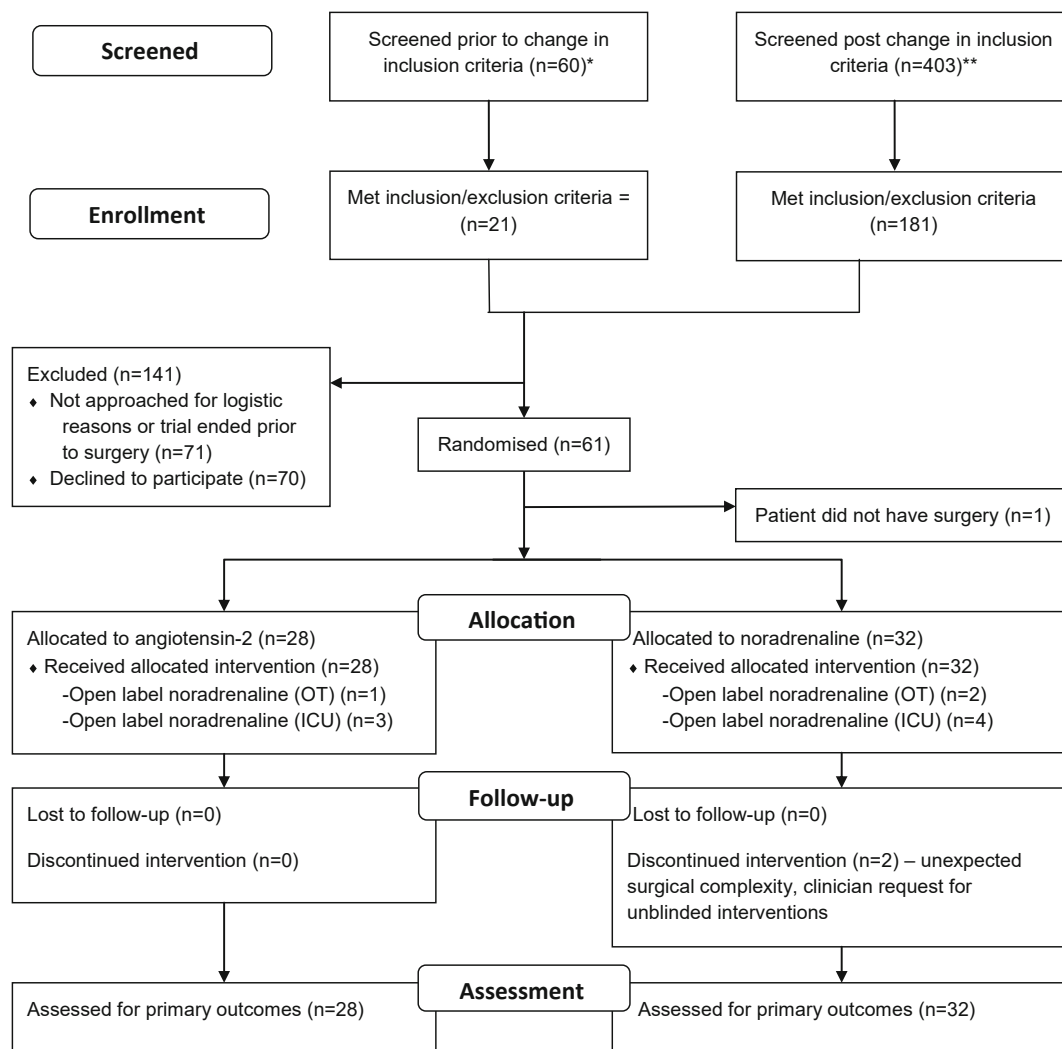
Figure 2 CONSORT diagram. *Inclusion criteria of AKI score >> 3.5; **inclusion criteria of AKI score >> 1.5; ICU, intensive care unit; OT, operating theatre.

Discussion

This pilot randomised controlled trial supports the feasibility of a larger study comparing angiotensin-2 with noradrenaline infusion to maintain peri-operative MAP in cardiac surgery. The study suggests that the protocol was safe, with similar overall outcomes to those expected in a cardiac surgery population. It was acceptable to clinicians and patients, with good consent and adherence rates. Angiotensin-2 appeared to be similar in efficacy compared with noradrenaline in terms of ability to maintain MAP for the defined period.

Our study shows that an appreciable duration and volume of vasopressor infusion was required to maintain a MAP > 70 mmHg in the peri-operative period in most cardiac surgical patients using the treatment algorithm. At least three-quarters of patients required > 4 h of vasopressor support and more than half needed > 12 h of

support. Given that the protocol reinforced the need to correct inotropic and volume status before using vasopressor, this implies that the vasopressor requirement was a result of a degree of persistent vasoplegia. In addition, there were no significant between-group differences in the ability to maintain the MAP target. At this level of exposure, it is plausible that vasopressors with alternative mechanisms of action could affect renal outcomes in a larger trial.

The outcome rate for any stage AKI was 32%, with 37.5% in the noradrenaline control group. This finding suggests that any future trial with a relative risk reduction of 25% (absolute risk reduction 8%) would require a total sample size of at least 824 for 80% power to detect a difference with an α statistic of 0.05. Alternatively, a sample size of 360 would be required to detect a difference in mean δ creatinine of 10 μmol l^{-1} (as found in this pilot). This could

Table 1 Baseline characteristics of the included patients. Values are median (IQR [range]) or number (proportion).

	Angiotensin-2 n = 28	Noradrenaline n = 32
Age; y	70.8 (61.2–73.7 [47.2–81.4])	69.3 (63.9–74.7[46.1–78.7])
>70 y	17 (61%)	14 (44%)
Sex; male	24 (86%)	29 (91%)
BMI; kg.m^{-2}	31.6 (27.8–35.1 [22.4–47.2])	29.4 (27.5–33.2 [24.1–44.5])
>25 kg.m^{-2}	27 (96%)	28 (88%)
Urgency of surgery		
Elective	15 (54%)	15 (47%)
Urgent	13 (46%)	15 (47%)
Emergency	0	2 (6%)
Type of surgery		
CABG only	23 (82%)	23 (72%)
Valve	2 (7%)	4 (13%)
Valve + CABG	3 (11%)	5 (16%)
Co-existing pathology		
Diabetes	15 (54%)	13 (41%)
Hypertension	26 (93%)	26 (81%)
Use of ACEi or ARB		
No	7 (25%)	11 (34%)
ACEi	10 (36%)	9 (28%)
ARB	11 (39%)	12 (38%)
Time from ACEi/ARB to surgery; h	29.2 (24.5–48.9 [0.75–216.5])	25 (24.0–39.6 [0.75–192.6])
NYHA classification		
1	8 (29%)	6 (19%)
2	15 (54%)	19 (59%)
3	5 (18%)	6 (19%)
4	0	1 (3%)
Estimated ejection fraction		
Normal (EF > 60%)	16 (57%)	14 (44%)
Mild impairment (EF 45–60%)	11 (39%)	11 (34%)
Moderate (EF 30–45%)	1 (4%)	7 (22%)
Peripheral vascular disease	3 (11%)	5 (16%
Hypercholesterolemia	25 (89%)	23 (72%)
Pre-operative pathology		
Haemoglobin; g.l^{-1}	139.0 (129.0–149.2 [96.0–170.0])	142.5 (129.0–150.0 [109.0–166.0])
<130 g.l^{-1}	7 (25%)	8 (25%)
Creatinine; µmol.l^{-1}	89.5 (72.8–106.0 [62.0–148.0])	91.5 (76.5–104.5 [62.0–192.0])
>100 µmol.l^{-1}	10 (35%)	14 (44%)
Acute kidney injury predictive score	3.5 (1.5–3.5 [1.5–7.0])*	2.5 (1.5–3.5 [1.5–5.5])

CABG, coronary artery bypass graft; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-2 receptor blocker; NYHA, New York Heart Association; EF, ejection fraction.
*One patient had a score of 0 due to an error reading pre-operative creatinine.

provide a proof of concept for a larger trial investigating a binary outcome such as AKI or requirement for renal replacement therapy. Just under half of the patients screened and those approached were eligible for, and consented to, participate, respectively. These findings suggest that recruitment for a larger trial would also be practically feasible.

Given that the intra-operative drug utilisation volume was very similar, it appears likely that on a population basis the relative potency is accurate. Drug utilisation volume

Table 2 Study outcomes. Values are number (proportion) or median (IQR [range]).

	Angiotensin-2 n = 28	Noradrenaline n = 32	Effect estimate (95%CI)	p value
Primary feasibility outcomes				
Study drug infusion > 4 h	21 (75%)	29 (91%)	RD, −15.62 (−34.83–3.58)	0.11
Study drug infusion > 12 h	12 (43%)	20 (63%)	RD, −19.64 (−45.41–6.13)	0.13
Mean arterial pressure > 70 mmHg*				
Intra-operatively	25 (89%)	30 (94%)	RD, −4.46 (−18.98–10.05)	0.54
During first 48 h in ICU	25 (89%)	27 (84%)	RD, 4.91 (−12.95–22.77)	0.58
Protocol adherence	28 (100%)	30 (94%)	RD, 6.25 (−3.06–15.56)	0.18
Major adverse outcome				
Hospital mortality	0	0	–	–
Renal replacement therapy	0	3 (9%)	RD, −9.38 (−20.59–1.84)	0.10
Extracorporeal circulatory support	0	1 (3%)	–	0.99
New permanent stroke	0	1 (3%)	RD, −3.12 (−9.82–3.57)	0.99
Secondary outcomes				
Acute kidney injury within 7 days:	7 (25%)	12 (38%)	RD, −12.50 (−36.79–11.79)	0.31
1	6/7 (86%)	7/12 (58%)	–	–
2	1/7 (14%)	2/12 (17%)	–	–
3	0	3/12 (25%)	–	–
Peak creatinine in 7 days; $\mu mol.l^{-1}$	89.5 (74.8–121.8 [64.0–209.0])	107.5 (91.8–151.2 [69.0–224.0])	MD, −16.87 (−43.58–9.84)	0.22
Creatinine clearance in 6 h; $\mu mol.l^{-1}$	77.0 (60.0–105.0 [35.0–167.0])	89.5 (69.2–115.0 [39.0–137.0])	MD, −12.10 (−37.60–13.40)	0.36
Delta creatinine; $\mu mol.l^{-1}$	8.0 (−2.5–24.8 [−38.0–104.0])	11.0 (2.2–36.5 [−11.0–109.0])	MD, −3.49 (−17.76–10.77)	0.63
Complications				
Left ventricular failure	0	0	–	–
Aortic dissection	0	0	–	–
Major haemorrhage	0	0	–	–
Deep vein thrombosis	0	2 (6%)	RD, −6.25 (−15.56–3.06)	0.18
New onset atrial fibrillation	6 (21%)	7 (22%)	RD, −0.45 (−22.15–21.26)	0.97
Delirium	3 (11%)	3 (9%)	RD, 1.34 (−14.46–17.14)	0.87
Platelet count < 50 × $10^9.l^{-1}$	0	1 (3%)	RD, −3.12 (−9.82–3.57)	0.35
Fungal infection	0	0	–	–
Arterial thrombosis	0	0	–	–
Peripheral ischaemia	0	1 (3%)	RD, −3.12 (−9.82–3.57)	0.35
ICU length of stay; h	39.4 (25.3–64.6 [16.8–214.6])	49.9 (42.5–92.2 [19.7–340.6])	MD, −10.63 (−26.99–5.74)	0.21
Hospital length of stay; days	6.3 (6.1–7.6 [5.0–14.1])	8.1 (5.9–9.5 [5.0–39.9])	MD, −1.78 (−3.47 to −0.09)	0.04

ICU, intensive care unit; RD, risk difference; MD, median difference.
Delta creatinine is the difference between pre-operative creatinine and highest creatinine within 7 days.
*Using study drug without additional vasopressor infusion, for > 50% of duration.

postoperatively was higher in the noradrenaline group (although this difference was not statistically significant). This result could reflect a chance finding or the result of small imbalances in study group baseline characteristics, or could be the result of an actual difference in potency in more severe and prolonged vasodilation compared with the 10:1 ratio expected from previous studies.

Overall rates of major adverse and other outcomes were similar to those expected in this population. Length of stay was longer in the noradrenaline group. This may have

Table 3 Intra-operative characteristics. Values are median (IQR [range]) or number (proportion).

	Angiotensin-2 (n = 28)	Noradrenaline (n = 32)	p value
Study drug infusion details			
Study drug total duration; min	217.5 (160.0–270.0 [30.0–315.0])	185.0 (135.0–301.2 [0.0–480.0])	0.78
Percentage of intra-operative time	76.1 (50.7–84.0 [10.0–96.0])	74.3 (46.6–82.6 [0.0–96.0])	0.45
Percentage of bypass time	100.0 (60.0–100.0 [0.0–100.0])	100.0 (75.0–100.0 [0.0–100.0])	0.87
Highest rate; ml.min^{-1}	6.8 (4.2–14.7 [2.3–57.0])	7.1 (3.7–11.7 [0.0–57.0])	0.53
Total volume; ml	10.8 (5.5–26.8 [3.3–79.0])	13.4 (5.9–28.5 [0.0–70.3])	0.88
Other vasopressors and inotropes			
Use of adrenaline	2 (7%)	6 (19%)	0.26
Highest rate; µg.min^{-1}	3.5 (3.2–3.8 [3.0–4.0])	2.0 (2.0–2.0 [1.0–8]0.0)	0.16
Use of milrinone*	2 (7%)	4 (13%)	0.68
Use of open label noradrenaline	1 (4%)	2 (6%)	0.999
Highest rate; µg.min^{-1}	4.0 (4.0–4.0 [4.0–4.0])	5.5 (3.8–7.2 [2.0–9.0])	0.999
Use of vasopressin	0	0	-
Fluid administration and output			
Volume of colloid and crystalloid; ml	1000 (500–1000 [250–1600])	1000 (500–1000 [0–3000])	0.36
Blood product transfusion (any)	4 (14%)	9 (28%)	0.22
Red blood cell transfusion	2 (7%)	3 (9%)	0.57
Urine output; ml	475 (207–855 [0–1400])	460 (295–820 [10–1840])	0.87
Cardiac output; l.min^{-1}			
Pre-bypass	4.0 (3.2–4.4 [2.7–4.9])	3.6 (2.6–4.3 [1.7–4.2])	0.23
Post-bypass	5.0 (4.1–5.6 [2.1–8.2])	5.5 (4.0–5.9 [2.0–8.6])	0.75
Duration of surgery; h	4.2 (3.6–4.9 [2.8–5.9])	4.5 (3.5–5.3 [1.7–8.4])	0.47
Duration of bypass; min	97 (82–120 [63–221])	109 (95–123 [31–295])	0.44
Duration of aortic cross clamping; min	84 (69–99 [46–146])	90 (77–99 [22–212])	0.26

*Milrinone rate not included as angiotensin group only given loading doses.

been a chance finding given multiplicity of testing. While rates of AKI were higher in the noradrenaline group, this finding was not statistically significant, and these outcomes should be assessed as part of an appropriately powered larger study.

To our knowledge, this is the first blinded randomised trial comparing angiotensin-2 with noradrenaline in patients undergoing cardiac surgery. One previous randomised study compared angiotensin-2 infusion with phenylephrine in 20 patients who had been taking ACE inhibitors and found no difference in renal outcomes [19]. We are only aware of one large-scale vasopressor study in cardiac surgery to use a double-blinded study drug [25]. In this study, there was a beneficial effect on a composite outcome using vasopressin vs. noradrenaline, mainly driven by a reduction in AKI rates. One other non-randomised, retrospective study administered angiotensin-2 to 20 patients who were found to have a renin increase postoperatively in addition to a vasopressor requirement at 4 h post-surgery. These patients were compared with those who only received noradrenaline. It found a reduction in noradrenaline use but was insufficiently powered for other outcomes [26]. A post-hoc analysis of 16 cardiac surgery patients in the study by Klijian et al. noted effective restoration of blood pressure in the angiotensin-2 group vs. placebo [6]. Other studies include a post-marketing study, including 28 patients with postoperative vasoplegia, of whom approximately two-thirds were classed as angiotensin-2 responders [27], and case reports of angiotensin-2 use in the context of profound vasoplegia [8, 16]. No study of sufficient size or design has investigated patient-centred outcomes in the cardiac surgical population.

The strengths of our study include a randomised, double-blinded design, allowing bias and confounding to be minimised. The study occurred at two independent centres, and across multiple disciplines (anaesthesia, cardiac surgery and intensive care) improving the generalisability of our findings. Adherence to the protocol was high across clinical areas, which we believe was due to

Table 4 Characteristics during ICU admission. Values are median (IQR [range]) or number (proportion).

	Angiotensin-2 n = 28	Noradrenaline n = 32	p value
Study drug infusion details			
Study drug duration; h	5.0 (0.0–16.0 [0.0–48.0])	14.5 (4.8–29.0 [0.0–48.0])	0.08
Proportion of ICU time	12.2 (0.0–37.6 [0.0–100.0])	30.2 (12.3–38.5 [0.0–100.0])	0.18
Highest rate; ml.min^{-1}	4.1 (0.0–8.7 [0.0–57.0])	7.1 (3.1–16.3 [0.0–57.0])	0.11
Total volume; ml	16.0 (0.0–50.4 [0.0–971.0])	40.0 (19.8–164.3 [0.0–2336.0])	0.08
Other vasopressors and inotropes			
Adrenaline	3 (11%)	6 (19%)	0.48
Highest rate; μg.min^{-1}	3.0 (2.5–3.5 [2.0–4.0])	2.0 (2.0–4.2 [2.0–10.0])	0.78
Milrinone	4 (14%)	7 (22%)	0.52
Highest rate; μg.min^{-1}	0.1 (0.1–0.2 [0.1–0.3])	0.1 (0.1–0.2 [0.1–0.3])	0.99
Noradrenaline	3 (11%)	4 (13%)	0.99
Highest rate; μg.min^{-1}	5.0 (4.4–13.5 [3.8–22.0])	42.0 (24.2–53.5 [4.0–55.0])	0.16
Vasopressin	0 (0%)	4 (13%)	0.12
Highest rate; u.h^{-1}	-	0.04 (0.04–0.04 [0.03–0.04])	-
Methylene blue	0 (0%)	1 (3%)	0.99
Blood product transfusion	5 (18%)	4 (13%)	0.72
Volume of colloid and crystalloid; ml	1909 (1191–3336 [405–7736])	2369 (1722–3425 [300–8279])	0.35
Biochemistry			
Highest glucose in the first 72 h; mmol.l^{-1}	11.0 (9.5–14.8 [8.1–21.9])	11.1 (10.1–15.8 [7.5–23.2])	0.77
Highest lactate; mmol.l^{-1}	2.6 (1.9–3.4 [1.3–7.0])	2.4 (1.9–3.4 [1.4–9.4])	0.90
Lowest lactate; mmol.l^{-1}	1.0 (0.9–1.2 [0.5–1.7])	1.1 (0.9–1.2 [0.5–1.9])	0.85
Lowest pH	7.32 (7.30–7.34 [7.22–7.38])	7.32 (7.29–7.37 [7.15–7.41])	0.51
In the first 48 h of ICU admission			
Highest cardiac index; l.min.m^{-2}	3.0 (2.5–3.5 [2.2–4.9])	2.7 (2.5–3.4 [1.9–5.0])	0.40
Lowest cardiac index; l.min.m^{-2}	2.2 (1.8–2.5 [1.3–3.9])	2.0 (1.7–2.3 [0.5–2.6])	0.31
Urine output; ml			
First 24 h	1424 (1163–1837 [595–2530])	1415 (1195–1975 [169–4058])	0.88
Second 24 h	1204 (932–1898 [725–2520])	1270 (919–1560 [85–2400])	0.53

ICU, intensive care unit. Unless stated otherwise, data relate to first 48 h.

the good integration and communication among medical specialities.

We acknowledge several limitations. The small, feasibility study design resulted in some imbalance in baseline characteristics, which may have resulted in similar small differences in outcomes. However, these would be addressed in a larger study, and adjustment for these in this study did not significantly change the outcomes.

The inclusion criteria were broadened during the study to improve recruitment. However, this reflects the objectives of a pilot or feasibility study. We aimed to recruit a population at elevated risk of AKI using a previously published risk score. The baseline risk of AKI in the Australian cardiac surgical population is approximately 25% [21]. Our initial attempt to recruit patients with a score ≥ 3.5 points corresponded to a predicted AKI risk of 37% in this

population but resulted in too few eligible patients. To broaden our pool of potential participants, we reduced the required score to ≥ 1.5 points (population predicted risk of AKI 29%). Early intervention to change the inclusion criteria is likely to have resulted in a more reliable outcome rate for future study planning. The thresholds chosen to signify appropriate consent rate, treatment duration and effect were relatively arbitrary. Nonetheless, we feel they represent a pragmatic approach to the conditions required to make a future study worthwhile, both clinically and practically. Renin–angiotensin system inhibiting drugs were not discontinued for inclusion in the study. This may have introduced heterogeneity of drug effect by timing and type of renin–angiotensin system inhibiting drug.

We have demonstrated that our approach to comparing angiotensin-2 infusion with noradrenaline is

feasible, appears safe and was acceptable to clinicians. Data from this study will help in the design of a future, larger, randomised trial.

Acknowledgements

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Supporting Information

Additional supporting information may be found online via the journal website.

Appendix S1. Quick reference guide flow chart.