Best evidence topic - Cardiac general

Should angiotensin converting enzyme inhibitors/angiotensin II receptor antagonists be omitted before cardiac surgery to avoid postoperative vasodilation?

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Summary

A best evidence topic in cardiac surgery was written according to a structured protocol. The question addressed was whether the omission of angiotensin converting inhibitors (ACEI)/angiotensin II receptor antagonists (AIIA) before cardiac surgery leads to avoidance of postoperative vasodilation. Using the reported search 421 papers were identified. Eleven papers including three randomised controlled trials (RCTs) represented the best evidence on the subject. The author, journal, date and country of publication, patient group studied, study type, relevant outcomes, results and study comments and weaknesses were tabulated for these. Whereas the three small RCTs on this topic provided conflicting evidence, the remaining seven large cohort and case-control studies confirmed that preoperative ACEI therapy resulted in postoperative low systemic vascular resistance (SVR)/vasoplegia. Only two small RCTs with conflicting conclusions specifically addressed the issue of omitting ACEI/AIIA before cardiac surgery. We conclude that preoperative administration of ACEI/AIIA in patients undergoing cardiac surgery contributes to lowering of SVR/vasoplegia postoperatively thereby making omission of ACEI/AIIA before cardiac surgery a rational strategy to avoid postoperative vasodilation. However, the current available evidence to support this strategy is weak.

Keywords: Angiotensin converting enzyme inhibitors; Angiotensin II receptor blockers; Systemic vascular resistance; Cardiac surgery; Evidence-based medicine

1. Introduction

A best evidence topic was constructed according to a structured protocol. This protocol is fully described in the ICVTS [1].

2. Clinical scenario

You are clerking a patient who has been admitted for elective coronary artery bypass grafting (CABG) the next day. The responsible consultant asks you to omit the morning dose of ACE inhibitor for this patient. When you ask him ‘why?’ he replies that patients who get a morning dose of ACE inhibitor before surgery need more vasoconstrictors and inotropes postoperatively. Although you omit the morning dose of ACE inhibitor for this patient, however, you are confused as none of the other consultants in the unit practice this strategy. To resolve this issue you decide to carry out a literature search.

3. Three-part question

In [patients prior to cardiac surgery] should [angiotensin converting enzyme inhibitors/angiotensin II receptor antagonists] be omitted to avoid [postoperative vasodilatation]?

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4. Search strategy

The English language scientific literature was reviewed primarily by searching Medline from 1950 through November 2007 using Ovid interface.

[Angiotensin converting enzyme inhibitors.mp OR exp ACE inhibitors OR Angiotensin II receptor blockers.mp OR exp Angiotensin II type 1 receptor blockers] AND [CABG.mp OR exp Thoracic surgery/OR Coronary art$ bypass.mp OR Cardiopulmonary bypass.mp OR exp Cardiovascular surgical procedures/OR exp Thoracic surgical procedures/OR exp Coronary artery bypass] AND [Vasodilation.mp OR exp vascular resistance.mp OR vasoplegi$.mp]

The ‘related articles’ function was used to broaden the search and all abstracts, studies, and citations scanned were reviewed. The reference lists of articles found through these searches were also reviewed for relevant articles.

5. Search outcome

A total of 421 papers were found using the search strategy. Eleven papers [2–12] including three RCTs [4, 7, 9] were deemed to represent the best evidence on the topic and are summarised in Table 1.
Table 1

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<thead>
<tr>
<th>Author, date, country and journal</th>
<th>Study type</th>
<th>Patient group</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses/Comments</th>
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<tr>
<td>Lee et al., 2005, J Int Med Res, Korea, [2]</td>
<td>Case control study (level 3b)</td>
<td>80 OPCAB patients divided into ACEI group (n=43) and control group (n=37)</td>
<td>Haemodynamic parameters measured at 5 time points: after pericardiotomy (T1), 10 min after the application of stabiliser to perform anastomoses of LAD (T2), OM (T3), and RCA (T4), and after pericardial suturing (T5)</td>
<td>No significant differences in the haemodynamic parameters measured were detected between the two groups, except for cardiac output, which was found to be significantly greater in the control group (P&lt;0.05)</td>
<td>Small sample size Non-randomised design Multiple confounding factors such as diabetes, hypertension which can affect haemodynamic parameters</td>
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<td>Devbhandari et al., 2004, Asian Cardiovasc Thorac Ann, UK, [3]</td>
<td>National survey (level 5)</td>
<td>Survey of 167 practicing UK cardiac surgeons. 105 responded</td>
<td>% age who felt benefit of stoppage of ACEI prior to cardiac surgery 39%</td>
<td>63% response rate Only UK surgeons surveyed</td>
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<td>Bertrand et al., 2001, Anesth Analg, France, [4]</td>
<td>RCT (level 1b)</td>
<td>37 patients chronically treated with AIIA for hypertension undergoing major vascular surgery were randomly assigned to two groups: Group I: AIIA discontinued on the day before surgery (n=18); Group II: AIIA given 1 h before anaesthesia (n=19)</td>
<td>Haemodynamic variables during induction of anaesthesia</td>
<td>Systolic arterial pressure was significantly decreased in Group II at 5, 15 and 23 min after induction of anaesthesia (P&lt;0.05)</td>
<td>Small sample size Haemodynamic study ended at incision</td>
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| Mekontso-Dessap et al., 2001, Ann Thorac Surg, France, [5] | 36 patients undergoing CABG who developed vasoplegic shock (VS) were compared with 72 control patients without post-CPB cardiogenic or VS | Multivariate logistic regression analysis to identify predisposing factors for the development of VS after CPB independent of ventricular function | Preoperative ACEI and IV heparin were independent predictors for post-CPB VS (relative risk of 2.26 and 2.78, respectively) | Small sample size
| Case control study (level 3b) |                                                                              |                                                                          |                                                                            | Non-randomised design                                                                 |
| Carrel et al., 2000, J Card Surg, Switzerland, [6] | 800 consecutive patients undergoing elective CABG and/or valve replacement | Incidence of postoperative low SVR | Temperature and duration of CPB, total cardioplegic volume infused, reduced left ventricular function, and preoperative treatment with ACEI were predictive factors for early postoperative vasoplegia | No control group
| Cohort study (level 2b) |                                                                              |                                                                          |                                                                            | Non-randomised design                                                                 |
| Pigott et al., 1999, Br J Anaesth, UK, [7] | 40 patients with good left ventricular function undergoing CABG, allocated randomly to continue ACE inhibitor medication before surgery (Group 1; n = 20) or omit (Group 2; n = 20) | Haemodynamic measurements of heart rate and arterial pressure were made at the following times: (1) on the ward before surgery; (2) before and (3) after induction of anaesthesia; (4) after intubation; (5) before and (6) after sternotomy; (7) before cannulation of the aorta; (8) after weaning from CPB; (9) at skin closure; (10) on admission to cardiac recovery; and (11), (12) hourly for first 2 h in the cardiac recovery unit | Arterial pressure measured in the ward before surgery (before omitting ACE inhibitors) was similar in both groups (P = ns), but patients in group 2 had a significantly greater mean arterial pressure over the whole study compared to patients in group 1 (P < 0.05) | Small sample size
| RCT (level 1b) |                                                                              |                                                                          |                                                                            | Only patients with good left ventricular function were recruited                           |
| Boeken et al., 1999, Thorac Cardiovasc Surg, Germany, [8] | 240 patients undergoing CABG or valve surgery were divided into three matched groups (group A: pre- and postoperative ACEI; group B: ACEI only pre-, not postoperatively; group C: no ACEI) | The need for catecholamines | Intraop. A: 35%; B: 35%; C: 15%; postop. A: 21.2%, B: 16.2%, C: 10% (P < 0.05) | Non-randomised design
| Case control study (level 3b) |                                                                              | The incidence of a ‘post-perfusion syndrome’ or systemic inflammatory response syndrome (SIRS) | In the ACEI groups (A and B) there were 9 patients with a postoperative SIRS, only 2 cases in group C | Patients with postoperative ACEI therapy also included

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<td>Webb et al., 1998, Eur J Cardiothorac Surg, UK, [9]</td>
<td>96 patients undergoing CABG were randomised to quinapril 20 mg (n=47) once daily or placebo (n=49) in a double-blind fashion, continued for up to 6 weeks prior to operation</td>
<td>Measurement of left ventricular function at the start of study</td>
<td>Quinapril group: 54.9 (13.8)% vs. Placebo group: 55.6 (13.2)% (P=ns)</td>
<td>Small sample size Other anti-anginal drugs with varying mechanisms of action not discontinued</td>
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<td>RCT (level 1b)</td>
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<td>Measurement of left ventricular function 3 months following surgery, after recommencement of pre-surgery anti-anginal therapy for 1 week</td>
<td>Quinapril group: 58.1 (13.6)%, vs. Placebo group: 56.9 (12.6)%) (P=ns)</td>
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<td>Effects on systemic vascular resistance (SVR) during bypass were calculated from perfusion records and vasoconstrictor use during operation was documented</td>
<td>The intra-operative BP and the SVR during bypass in the two treatment groups were not significantly different (P=0.94)</td>
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<td>The safety of the addition of quinapril to the anti-anginal regimen was assessed by measurement of systemic blood pressure (BP) after the first dose of study medication, measurement of intra-operative BP, administration of inotropes and any intra-operative complications</td>
<td>No first dose hypotension</td>
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<td>Deakin et al., 1998, Eur J Cardiothorac Surg, UK, [10]</td>
<td>62 patients undergoing CABG divided into two groups: ACEI group (n=21) and control group (n=41)</td>
<td>SVR was calculated at 1 min intervals during the rewarming phase of hypothermic CPB</td>
<td>Mean SVR in the ACE group was 978 dyne/s per cm² and in the control group was 1194 dyne/s per cm² (P=0.006)</td>
<td>Small sample size Non-randomised design The study did not distinguish whether the observed hypotension was a result of low SVR or low cardiac output</td>
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<td>Case control study (level 3b)</td>
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<td>Mean arterial pressure</td>
<td>Mean arterial pressure was 48.8 mmHg in the ACE group and 56.3 mmHg in the control group (P=0.004)</td>
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<td>The use of vasoactive drugs during and immediately after termination of CPB was recorded</td>
<td>There was a significant difference in vasoactive drug requirements between the groups (P&lt;0.01)</td>
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<td>Licker et al., 1996, Anesthesiology, Switzerland, [11]</td>
<td>Patients with preserved left ventricular function undergoing mitral valve replacement or CABG were divided into two groups according to preoperative drug therapy: patients receiving ACE inhibitors for at least 3 months ACEI group, (n=22) and those receiving other cardiovascular drug therapy control group, (n=19)</td>
<td>Systemic haemodynamic variables were recorded before surgery, after anaesthesia induction, during sternotomy, after aortic cross-clamping, after aortic unclamping, as well as after separation from CPB and during skin closure</td>
<td>Dose of fentanyl and midazolam needed for induction</td>
<td>Significantly less fentanyl and midazolam were given in the ACEI group (P&lt;0.05) Plasma renin activity was significantly greater in the ACEI group throughout the whole 24-h study period Plasma concentrations of angiotensin II did not differ between the two groups Similar changes in catecholamines angiotensin II, and plasma renin activity were found in the two groups in response to surgery and CPB The pressor and constrictor effects of norepinephrine infusion were attenuated markedly in the</td>
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<td>Case control study (level 3b)</td>
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<td>Blood was sampled repeatedly up to 24 h after surgery for hormone analysis</td>
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<td>Tuman et al., 1995, Anesth Analg, USA, [12]</td>
<td>4301 patients undergoing elective CABG and/or valve surgery divided into two groups: ACEI group (n=512) and control group (n=3782)</td>
<td>Influence of chronic preoperative ACE inhibitor use and other perioperative factors on the incidence of vasoconstrictor therapy required to maintain systolic blood pressure at more than 85 mmHg despite a normal cardiac output after CPB</td>
<td>ACEI group: the dose-response curves were shifted to the right and the slopes were decreased at the two study periods</td>
<td>Large sample size</td>
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6. Discussion

Lee et al. [2] in a case-control study showed that preoperative ACEI therapy significantly increased the amount of vasoconstrictor necessary to maintain the target blood pressure during obtuse marginal anastomosis during off-pump CABG.

Devbhandari et al. [3] published the results of a UK national survey to address the issue whether it is beneficial or not to stop ACEI before cardiac surgery. Questionnaires were sent to 167 currently practicing UK cardiac surgeons, out of which 105 (62%) replied back. Analysis of their responses revealed that majority (63%) were of the opinion that the use of ACEI leads to vasodilatation resulting in increased usage of fluids, inotropes and vasoconstrictors. However, there was no agreement on the issue of stopping it prior to surgery. Forty-one (39%) felt it was beneficial to stop the ACEI prior to surgery whereas 40 (38%) of them thought it was harmful to stop it. Twenty-one (20%) were of the opinion that it made no difference. Thirty-nine per cent of respondents practiced stopping the drug prior to planned operation.

Bertrand et al. [4] in a small RCT recruiting 37 patients, randomized to Group I: AIIA discontinued on the day before surgery (n=18); Group II: AIIA given 1 h before anaesthesia (n=19), showed that more severe hypotensive episodes (P<0.01), requiring vasoconstrictor treatment, occur after induction of general anaesthesia in patients chronically treated with AIIA and receiving this drug on the morning.
before operation, in comparison with those in whom AIIA were discontinued on the day before operation.

Mekontso-Dessap et al. [5] in a 2:1 case-control study, comparing 36 patients undergoing CABG who developed vasoplegia with 72 control patients without vasoplegia, and Carrel et al. [6] in a large prospective cohort study of 800 consecutive CABG patients, in which 115 patients developed a mild vasoplegia, and 60 patients suffered from severe vasoplegia, showed by logistic regression analysis that preoperative use of ACEI was an independent predictor for postoperative low SVR.

Pigott et al. [7] in their RCT, randomizing 40 patients with good left ventricular function to omit or continue ACEI before surgery, showed that there was no difference in hypotension on induction of anaesthesia or in the use of vasoconstrictors after CPB. Similar findings were reported by Webb et al. [9] in their double-blind RCT randomising 96 CABG patients to receive 20 mg minapril or placebo administered for six weeks preoperatively, with the final day of treatment being the morning of surgery.

On the other hand, Boeken et al. [8] in their study of 240 patients undergoing CABG or valve surgery, divided into three matched groups (group A: pre- and postoperative ACEI; group B: ACEI only pre-, not postoperatively; group C: no ACEI), reported that there were significant differences in the intra- and postoperative need for catecholamines in groups A and B compared to C (intraop. A: 35%, B: 35%, C: 15%; postop. A: 21.2%, B: 16.2%, C: 10%) \((P<0.05)\). In the ACEI groups (A and B) there were nine patients with a postoperative low SVR, only two cases in group C.

Deakin et al. [10] in their case-control study of 62 CABG patients also showed that preoperative ACEI therapy decreased SVR during the rewarming phase of CPB \((P=0.006)\) and increased post-bypass vasoactive drug requirements \((P<0.01)\).

Licker et al. [11] in their case-control study of 41 patients failed to show alteration in haemodynamic stability during cardiac surgery in patients on ACEI therapy. However, the pressor and constrictor effects of norepinephrine infusion were attenuated markedly in the ACEI group.

Tuman et al. [12] in their case-control study of 4301 patients showed that more patients on ACEI therapy exhibited low values of SVR \((P=0.0002)\) and required at least two vasoconstrictor infusions (phenylephrine, norepinephrine, or dopamine) \((P=0.0001)\) postoperatively.

7. Clinical bottom line

We conclude that preoperative administration of ACEI/ AIIA in patients undergoing cardiac surgery contributes to lowering of SVR/vasoplegia postoperatively thereby making omission of ACEI/AIIA before cardiac surgery a rational strategy to avoid postoperative vasodilation. However, the current available evidence to support this strategy is weak.

References


EComment: ACE inhibitors as antifibrotic agents in atrial fibrillation: potential relevance in cardiac surgery

Authors: Karsten Knobloch, Plastic, Hand and Reconstructive Surgery, Hannover Medical School, Hannover 30625, Germany; Andreas Gohritz, Marcus Spies, Peter M. Vogt
doi:10.1510/icvts.2007.174698A

Regarding the omission of ACE inhibitors or angiotensin II receptor antagonists before cardiac surgery [1] one should consider the potential beneficial effect of ACE inhibitors as an antifibrotic agent. Postoperative atrial fibrillation (POAF) complicates up to 8% of all non-cardiac surgeries, between 3% and 30% of non-cardiac thoracic surgeries, and between 16% and 46% of cardiac surgeries. POAF has been associated with increased morbidity, mortality, and longer, more costly hospital stays [2].

Given the fact that atrial fibrillation is the most frequent complication following cardiac surgery, recent studies have been reported that ACE inhibitors and angiotensin II receptor blockers are emerging drugs for the prevention of atrial fibrillation by modification of the renin-angiotensin-aldosterone system (RAAS) [3]. A meta-analysis of 11 randomized, controlled, parallel-design clinical trials evaluating effect of ACEIs or ARBs on the development of AF revealed that treatment with ACEIs or ARBs reduced the relative risk (RR) of AF in patients with hypertension by 23% and by 11% in patients after myocardial infarction. Reduction in AF was greatest in patients after electrical cardioversion and in patients with heart failure. Overall, inhibition of the RAAS reduced the RR of AF by 19% (RR 0.810, P < 0.001, 95% CI 0.759–0.865). However, the effect of ACE inhibitors/angiotensin II receptor blockers on the postoperative rate of atrial fibrillation is underdetermined as yet.

The combination of a renin angiotensin system inhibitors (RAAS-) and bepridil might be even superior for the maintenance of sinus rhythm after conversion from persistent atrial fibrillation [4].
Based on these reports the omission of ACE inhibitors or angiotensin II receptor antagonists before cardiac surgery might have an effect on the postoperative rate of atrial fibrillation, which has to be determined in further perspective trials.

References


eResponse: ACE inhibitors as antifibrotic agents in atrial fibrillation: potential relevance in cardiac surgery

Author: Shahzad G. Raja, Department of Cardiac Surgery, Harefield Hospital, Hill End Road, Harefield, UB9 6JH, Middlesex, UK
doi:10.1510/icvts.2007.174698A1

Knobloch et al. have raised an interesting issue related to our BET [1] regarding omission of angiotensin converting enzyme inhibitors (ACEIs)/angiotensin II receptor antagonists (ARBs) before cardiac surgery. They highlight the potential impact of omission of ACEIs or ARBs on increased incidence of postoperative atrial fibrillation (POAF) after cardiac surgery. There is no doubt that increasing evidence is emerging to suggest that ACEIs or ARBs have the potential to prevent POAF, possibly due to their ability to decrease left atrial stretching (secondary to afterload reduction and stroke volume increases), preserve serum potassium concentrations or reduce pathogenic atrial remodelling [2, 3]. However, it is important to understand that despite the publication of several meta-analyses [3, 4], none of which includes cardiac surgery patients, the evidence for this potential benefit of ACEIs or ARBs for cardiac surgical patients is extremely weak. To date the only significant study by White et al. [5] failed to show a statistically significant association between the preoperative ACEI or ARB use and reduction in the odds of developing POAF. The results of this study are relevant as it was a prospective cohort evaluation of the 338 patients undergoing coronary artery bypass grafting and/or valvular surgery from the AFIST II and III randomized controlled trials (RCTs).

Failure of White et al. [5] to replicate the results reported by the various other RCTs in non-cardiac surgical patients is perhaps due to the fact that population of cardiac surgery patients already has a high background utilization of both beta-blockers and prophylactic amiodarone, both of which are highly efficacious drugs in preventing POAF following cardiac surgery. Whether, an ACEI or ARB when administered alone would exert a larger or statistically significant effect is not known. Hence, the final part of the concluding statement of Knobloch et al. assumes more importance relative to the rest of their comment. There is no doubt that an RCT recruiting approximately 600 subjects, as suggested by White et al. [5] after conducting a post-hoc sample size calculation (α=0.05; ß=0.20), is urgently needed to discern if ACEIs or ARBs truly impact POAF.

References


