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Best evidence topic - Arrhythmia

Prophylactic Amiodarone effectively prevents post-operative atrial fibrillation

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Summary

A best evidence topic in cardiac surgery was written according to a structured protocol. The question addressed was whether prophylactic Amiodarone can safely reduce the incidence of atrial fibrillation (AF) post-cardiac surgery. Altogether 90 papers were found using the reported search, of which 12 presented the best evidence to answer the clinical question. The author, journal, date and country of publication, patient group studied, study type, relevant outcomes, results, and study weaknesses of these papers are tabulated. We conclude that there is strong evidence that both oral and intravenous Amiodarone given prophylactically reduces the incidence of post-operative AF, with a number needed to treat of only seven to prevent an episode of AF.

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Keywords: Evidence-based medicine; Thoracic surgery; Atrial fibrillation; Amiodarone; Review

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 in the bar with an American colleague while attending the European cardiothoracic conference in Monaco, and he is shocked that you do not give all your patients prophylactic Amiodarone to reduce the incidence of atrial fibrillation (AF). You find yourself unable to counter his arguments although you suspect that there must be a higher incidence of bradycardia and hypotension in his patients. Thus, as you are due to meet him on the conference golf course tomorrow; you therefore resolve to look up the evidence before teeing off!

3. Three part question

In [patients undergoing Cardiac Surgery] is [prophylactic Amiodarone] effective in [reducing the post-operative incidence of Atrial Fibrillation]

4. Search strategy

Medline 1966–July 2003 using the OVID interface.

[exp thoracic surgery/ OR cardiac surgery.mp. OR exp cardiac surgical procedures/ OR cardiac surgical procedures.mp. OR exp cardiopulmonary bypass/ OR exp coronary artery bypass/ OR CABG.mp] AND [exp amiodarone/ OR amiodarone.mp] AND [exp atrial fibrillation/ OR atrial fibrillation.mp]

5. Search outcome

90 abstracts were found, of which 78 were irrelevant. 11 RCTs and a meta-analysis were found [2–13] and these are shown in Table 1.

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Table 1
Best evidence papers

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Dorge et al., 2000 Annals of Thoracic Surgery, Germany [2]	150 patients undergoing CABG randomised to one of three groups: Group I, $N = 50$: 300 mg i.v. bolus of Amiodarone then 20 mg/kg per day for 3 days Group II, $N = 50$: 150 mg i.v. bolus of Amiodarone then 10 mg/kg per day for 3 days Group III, $N = 50$: placebo	PRCT (level 1b)	Atrial fibrillation measured using continuous ECG monitoring for 10 post-operative days Fast AF defined as ventricular response > 120 bpm Complications from amiodarone	New onset AF Group I 24% Group II 28% Group III 34% P -value N/S Fast AF Group I 14% Group II 24% Group III 32% P -value < 0.05 Group I vs Group III TFTs were mildly elevated in 11 patients Atrial pacing for bradycardia was required in 48% of Group 1 and 28% of group 3	Student's t to compare two groups is inappropriate when three categories exist. Kruskal–Wallis is the correct test. Young age group mean 61–63 years. Blinding methods not described. Not double blinded.
Daoud et al., 1997 NEJM, USA [3]	124 patients undergoing elective cardiac surgery (CABG 52, valve 41, CABG + valve 22, other 9) 64 patients received 600 mg/day orally for 7 days preoperatively, then 200 mg od until discharge 60 patients received placebo	Double-blind PRCT (level 1b)	Post-operative AF of > 5 min on ECG monitoring for 7 days No. of days in hospital	Amiodarone group 16 of 64 (25%) Control group 32 of 60 (53%) $P = 0.03$ Amiodarone group 6.5 ± 2.6 days Control group 7.9 ± 4.3 days $P = 0.04$	High rate of AF in control group. Perhaps due to high rate of valve surgery in this study (50%). Mean age is only 59 in this study. Cofounding factor is B-blocker use in Amiodarone group 40% vs control group 30%.
Giri et al. for the AFIST trialists, 2001 The Lancet, USA [4]	220 patients on B-blockers undergoing open heart surgery over the age of 60 (mean age 73) Slow loading $N = 120$: 200 mg tds for 5 days, 400 mg bd on day of surgery, 400 mg bd days 1–4 post-op, or placebo equivalent Rapid load $N = 100$: 400 mg qds for 1 day, 600 mg bd on day of surgery, 400 mg bd days 1–4 post-op, or placebo equivalent	Double-blind PRCT (level 1b)	Atrial fibrillation of over 5 min Symptomatic AF defined as hypotension, heart failure, palpitations, chest pain, SoB, syncope CVA, defined as neurological deficits for more than 24 h documented by a neurologist with confirmation on CT or MRI	Amiodarone group 22.5% Control group 38% $P = 0.01$ NNT = 6.5 Amiodarone group 4.2% Control group 18% $P = 0.001$ Amiodarone group 1.7% Control group 7.0% $P = 0.04$	89% of patients received B-blockers pre-op. No cases of pulmonary toxicity but routine CXRs not done. Nausea occurred occasionally in the Amiodarone group but no excess bradycardia was found.
Redle et al., 1999 American Heart Journal, USA [5]	143 patients undergoing CABG 73 patients given 2 g of Amiodarone in divided doses 1–4 days pre-op and 400 mg od for 7 days post-op. 70 patients given placebo	Double-blind PRCT (level 1b)	Post-operative AF Rate of fast AF at onset	Amiodarone group 24.7% Placebo group 32.8% $P = 0.30$ Amiodarone group 133 bpm Placebo group 153 bpm $P = 0.04$	Duration of AF, incidence of AF in those receiving B-blockers and Amiodarone, and hospital costs were also not different in the two groups.

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Table 1 (continued)

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Hohnloser et al., 1991 American Heart Journal, Germany [6]	77 patients after CABG Amiodarone group received 300 mg i.v. for 2 h, then 1200 mg every 24 h for 2 days and 900 mg every 24 h for 2 days	PRCT (level 1b)	Incidence of AF Nonsustained VT Complications	Amiodarone group 5% Control group 21% $P < 0.05$ Amiodarone group 3% Control group 16% $P < 0.05$ Amiodarone stopped in 18% of their patients due to QT prolongation	ECG monitoring only performed for 48 h post-operatively.
Butler et al., 1993 British Heart Journal, UK [7]	120 patients after CABG 60 patients received 15 mg/kg per day by continuous i.v. infusion after X-clamp removal, and 200 mg od for 5 days 60 patients had placebo	Double-blind PRCT (level 1b)	Incidence of arrhythmias Episodes of VT Complications	Amiodarone group 10% Control group 23% $P = 0.05$ Amiodarone group 15% Control group 33% $P = 0.02$ Bradycardia Amiodarone 78 vs 48% controls Pauses 7% Amiodarone vs 0% controls	Incidence of SVT and asymptomatic AF was not significantly different.
Guarnieri et al., for ARCH trial, 1999 American Journal Of Cardiology, USA [8]	300 patients undergoing open heart surgery Amiodarone group received 1 g/day i.v. for 2 days post-operatively	Double-blind PRCT (level 1b)	Incidence of AF Length of hospital stay	Amiodarone group 35% Control group 47% $P = 0.01$ Amiodarone group 7.6 Control group 8.2 $P = 0.34$	
Lee et al., 2000 Annals of Thoracic Surgery, Taiwan [9]	150 patients undergoing CABG 74 patients received Amiodarone, i.v., 150 mg loading dose then 0.4 mg/kg per h for 3 preoperative days and 5 post-operative days 76 controls had glucose infusion	Single blind PRCT (level 1b)	Incidence of AF Maximum rate during AF Complications	Amiodarone group 12% Control group 34% $P < 0.01$ Amiodarone group 107 Control group 138 $P < 0.01$ Two deaths from ventricular arrhythmia in both groups Two patients had Amiodarone stopped due to bradycardia	

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Table 1 (continued)

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Tokmakoglu et al., 2001 European Journal of Cardio-thoracic Surgery, Turkey [10]	241 consecutive patients undergoing CABG only Group I <i>N</i> = 77: Metoprolol 100 mg/24 h orally pre-op, 2 × 500 µg Digoxin i.v. on operating day, and 250 mg Digoxin orally and 100 mg metoprolol orally from day 1 to discharge Group II <i>N</i> = 72: 300 mg Amiodarone i.v. over 1 h and then 900 mg over 24 h immediately post-op, then 450 mg i.v. the next day then 200 mg tds orally until discharge Group III <i>N</i> = 92: control group and given no additional medication	PRCT (level 1b)	Post-operative AF measured by continuous ECG monitoring until discharge	Group I: 13/77 (16.8%) Group II: 6/72 (8.3%) Group III: 31/92 (33.6%) NNT = 4 <i>P</i> value of Group II to Group III is 0.001 Also significantly fewer clinical deteriorations due to AF and ventricular arrhythmias were found compared to controls	No blinding. No placebo used. Two patients had Amiodarone stopped due to AV block.
White et al., for AFIST, 2002 Annals of Thoracic Surgery, USA [11]	220 patients undergoing open heart surgery, over 60 years of age and all received preoperative Metoprolol Slow loading group: <i>N</i> = 56, 200 mg of oral Amiodarone tds for 5 days. 400 mg bd on day of surgery, 400 mg bd post-op days 1–4 Fast loading group (non-randomised): <i>N</i> = 64, 400 mg of Amiodarone qds for 1–4 days pre-op, 600 mg bd on day of surgery, 400 mg bd post-op days 1–4 Placebo <i>N</i> = 100	Double-blind PRCT (level 1b)	Rate of documented AF of more than 5 min duration Symptomatic AF Complications	Slow loading group 11/56 (19.6) Fast loading group 16/64 (25%) Placebo 38/100 (38%) <i>P</i> = 0.013 slow vs placebo <i>P</i> = 0.059 fast vs placebo NNT = 5.6 Slow loading group 1/56 (1.8) Fast loading group 4/64 (6.3%) Placebo 18/100 (18%) <i>P</i> < 0.001 slow vs placebo <i>P</i> = 0.023 fast vs placebo No differences between QT intervals (<i>P</i> = 0.073) No difference between groups of death ICU length of stay or CVA Increased rate of nausea in fast loading group compared to placebo	This is the same study group of patients as used by the AFIST group in the Lancet.

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Table 1 (continued)

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Yagdi et al., 2003 JTCVS, Turkey [12]	157 patients undergoing elective CABG, with B-blockers continued in all patients Amiodarone group 10 mg/kg per day for 48 h started 2 h after return to ICU. Then 600 mg/day for 5 days, 400 mg/day for 5 days and 200 mg/day for 20 days Placebo group 5% Glucose infusion followed by placebo	Double-blind PRCT (level 1b)	Post-operative AF of more than 5 min Maximum ventricular rate in pts with AF Complications	Amiodarone group 8/77 pts (10%) Placebo group 20/80 pts (25%) $P = 0.017$ Amiodarone group 105.9 ± 19.1 bpm Placebo group 126.0 ± 18.5 bpm $P = 0.03$ Amiodarone group 4 pts had treatment discontinued for bradycardia, and 10% of pts had hypotension control group 2 pts had treatment discontinued for bradycardia, and 5% of pts had hypotension	Randomization technique not stated.
Crystal et al., 2002 Circulation, New Zealand [13]	Systematic review of Medline, Embase, Cinhal, hand searching and scientific meetings up to April 2001 52 RCTs on prophylactic regimes for AF found of which 9 used Amiodarone	Meta-analysis (level 1a)	Post-operative AF Length of stay	Amiodarone groups 37% Control groups 22.5% (OR 0.48; CI 0.37–0.61) Amiodarone reduced LOS by 0.91 (0.24–1.59) days	Regimes of each study not examined. Does not include the study by Yagdi et al. [12].

6. Comment(s)

Nine of the 11 papers show a significant reduction in the incidence of atrial fibrillation with prophylactic Amiodarone. The remaining two showed a non-significant trend to lower AF. Included in these papers are two very well-conducted studies reported in the NEJM and the Lancet journals, respectively. Giri et al. reported a 'number needed to treat' of only 6.5 to prevent an occurrence of AF.

Complications were low in all studies except in that of Butler et al., who found a significantly higher rate of bradycardia and pauses in the Amiodarone group, and Hohnloser who had to stop Amiodarone in 18% of his patients due to QT prolongation. Significant bradycardia was investigated in all other studies, but found to be non-significant.

The results of most of these studies have been summarized by meta-analysis by Crystal et al. [13]. He combined the data from nine of these studies and found a rate of AF of 37% in all control groups but 22.5% in the amiodarone groups. This gives a number needed to treat of 6.9. He did not however summarise the data on the rates of complications.

Thus although it is clear that Amiodarone significantly reduces the incidence of AF, the optimal Amiodarone regime that should be employed remains unclear, as these

ranged from oral Amiodarone being started up to 7 days preoperatively to I.V. Amiodarone 2 h after return to ICU.

7. Clinical bottom line

There is strong evidence that both oral and intravenous Amiodarone given prophylactically reduces the incidence of post-operative AF, with a number needed to treat of only seven to prevent an episode of AF.

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