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ORIGINAL ARTICLE

Which beta-blocker should be used for the prevention of postoperative atrial fibrillation in cardiac surgery? A multi-treatment benefit-risk meta-analysis

Mohamed Zeinah [a,b,*], **Mohamed Elghanam** [a], **Umbertto Benedetto** [b]

[a] *Ain Shams University, Cairo, Egypt*
[b] *Oxford Heart Centre, UK*

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KEYWORDS

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Abstract *Background:* Post-operative atrial fibrillation (POAF) is amongst the most common complications following cardiac surgery. Current guidelines recommend oral beta-blockers as a first-line medication to prevent POAF. However, the ideal choice of beta-blocker is unclear, making a comprehensive review crucial. We aimed to provide a clinically useful summary of the results of a multiple-treatment meta-analysis of randomized controlled trials (RCT). Methods and Results: A MEDLINE/PubMed search was conducted to identify eligible RCTs. Efficacy (POAF prevention rate) and acceptability (dropout for side effect rate) outcomes were investigated. A frequentist approach to network meta-analysis using the graph-theoretical method was implemented to obtain network estimates. A total of 16 trials were included in the final analysis and 4727 subjects were investigated. Network estimates showed that betaxolol (OR 0.36; 95%CI 0.25–0.52), carvedilol (OR 0.36; 95%CI 0.23–0.58) and sotalol (OR 0.38; 95%CI 0.30–0.50) were more effective than propranolol (OR 0.51; 95%CI 0.27–0.95), metoprolol (OR 0.72; 95%CI 0.58–0.90) and atenolol (OR 0.81; 95%CI 0.42–1.56) in reducing the incidence of POAF when compared to placebo. Amongst beta-blockers investigated, carvedilol showed the best safety profile being associated with the lowest risk of patient dropped out for side effect (OR 1.14; 955CI 0.36–3.61). No evidence of heterogeneity/inconsistency was found in the whole network for both efficacy ($P = 0.8$) and acceptability ($P = 0.4$) outcomes. Conclusion: Overall, carvedilol was found to be effective in preventing POAF while maintaining a good safety profile.

* Corresponding author at: Ain Shams University, Cairo, Egypt.

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1. Introduction

Post-operative atrial fibrillation (POAF) is amongst the most common complications of cardiac surgery with reported incidence of 30% after coronary artery bypass graft, 40% after valve surgery, and 50% after combined procedures.[1] POAF has been shown to increase operative morbidity, including stroke[1,2] and has been associated with an increased length and costs of hospitalization. Furthermore, POAF may negatively affect late outcomes.[3]

The impact of POAF on patient outcomes has prompted much investigation into the optimal methods for the prevention and treatment of this complication.[4] There has been considerable interest in pharmacological prophylaxis against atrial fibrillation occurring after cardiac surgery.[4]

Although many approaches have been attempted,[4] current American Heart Association/American College of Cardiology and European Society of Cardiology guidelines recommend oral beta-blockers as a first-line medication to prevent POAF after cardiac surgery.[5,6] However, pharmacological characteristics differ considerably between oral beta-blockers and despite previous meta-analyses,[7–9] there remains confusion about the potential superiority as well as the safety profile of individual agents making a comprehensive, updated review important.

We report an overview of all randomized controlled trials (RCTs) that compared oral beta-blockers in terms of efficacy and acceptability in the prevention of POAF. We used mixed-treatment comparisons[10] (so-called network meta-analysis) to obtain a comprehensive benefit-risk comparison[11] of beta-blockers used in the prevention of POAF. We aimed to provide a clinically useful summary of the results of the multiple-treatment meta-analysis that can be used to guide treatment decisions.

2. Methods

2.1. Design

The present review was performed according to the Cochrane Collaboration and PRISMA statements.[12,13]

2.2. Search

A MEDLINE/PubMed search was conducted in June 2014 using the keywords "beta-blocker," "post-operative atrial

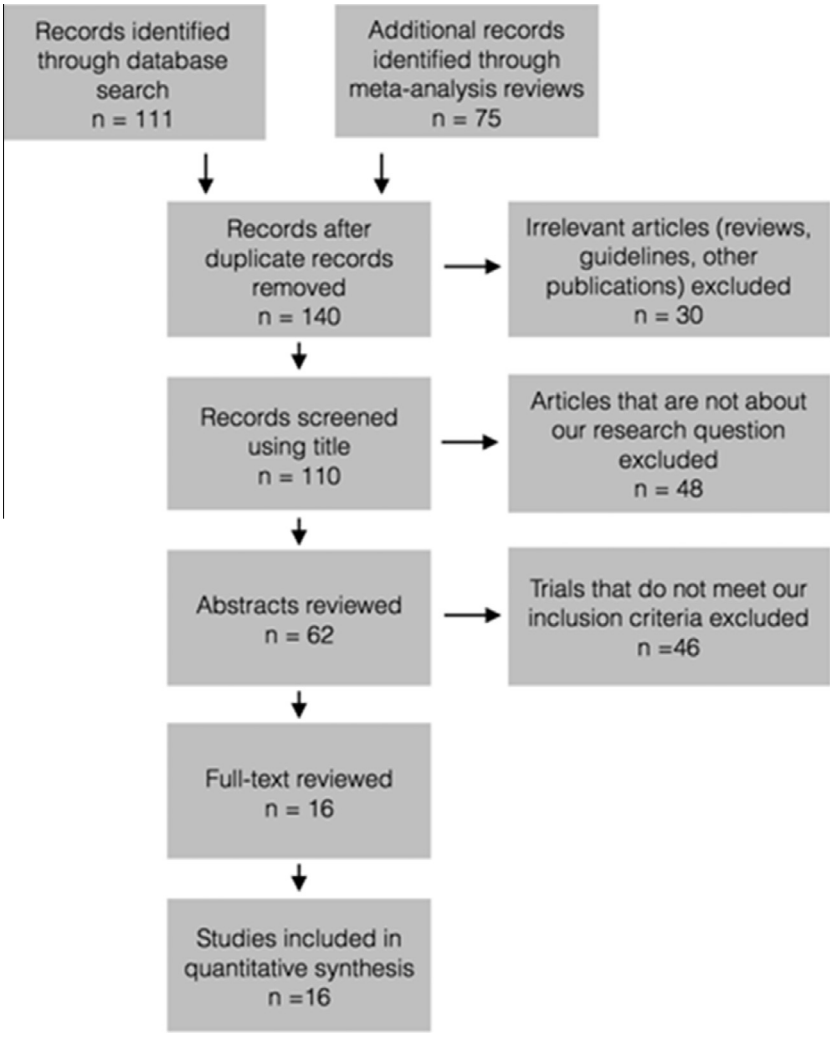

Figure 1 A flowchart showing data-collection and review process.

fibrillation," "cardiac surgery," and "randomized" or "randomised." In addition, Google Scholar, The Cochrane Library, and Scopus were also searched for pertinent citations.

2.3. Selection

Study selection was performed by two independent reviewers (UB, CN), with divergences resolved by consensus. Citations were first scanned at the title/abstract level. Short-listed studies were then retrieved in full-text.

2.4. Inclusion and exclusion criteria

Articles were included if they reported an RCT that compares the efficacy of oral beta-blockers to a placebo or another oral beta-blocker. Trials were the control arm received another drug (such as amiodarone), or no treatment was excluded from this study. For trials including more than two arms, only groups receiving oral beta-blockers or placebo were considered. When several publications reported on the same trial, the largest sample size comparison was selected.

2.5. Abstraction and appraisal

Data abstraction and study appraisal were performed by two independent reviewers (UB, CN). Key study and patient characteristics were extracted, including efficacy (POAF incidence) and safety outcomes (study drug withdrawal for side effects).

2.6. Analysis

Number of events in each arm was used to compute individual study log Odds Ratio (OR) and standard error for the efficacy and safety end-points. A frequentist approach to network meta-analysis using the graph-theoretical method was implemented to obtain network estimates.[14] As in pairwise meta-analysis, the Q statistic was estimated to measure the deviation from consistency.[15,16] A design-based decomposition of Cochran's Q was used for assessing the homogeneity in the whole network, the homogeneity within designs, and the homogeneity/consistency between designs.

All the analyses were conducted using R, version 3.1.0 and netmeta package (Gerta Rücker, Guido Schwarzer, Ulrike Krahn and Jochem König 2014. netmeta: Network meta-analysis with R.R package version 0.5–0. http://CRAN.Rproject.org/package = netmeta).

3. Results

The electronic searches yielded 140 potentially relevant studies, of which 110 potentially eligible articles were reviewed after duplicates were removed (Fig. 1). After screening the remaining articles and selecting those that met our criteria, we included 16 trials[17–32] published between 1990 and 2013 for the multiple-treatment meta-analysis investigating the following 6 oral beta-blocker regimes in the prevention of POAF: atenolol,[27,32] betaxolol,[22] carvedilol,[17,21,23,28] metoprolol,[17–19,21–25,28] propranolol[30] and sotalol.[18,20,24,26,27,29–31] Fig. 2 shows the network of eligible comparisons for the multiple-treatments meta-analysis. An overview of the characteristics of the trials included is reported in Table 1. A total of 11 trials enrolled only patients undergoing isolated CABG while the remaining 5 included patients undergoing concomitant valvular surgery. Twelve trials used continuous telemetry to monitor the incidence of POAF. Overall, 5199 individuals were randomly assigned to one of the 7 beta-blocker regimes and were included in the multiple-treatments meta-analysis. 4727 were included in the acceptability network meta-analysis. Median daily doses administered were as follows: atenolol 50 mg, betaxolol 20 mg, carvedilol 25 mg, metoprolol 125 mg, propranolol 60 mg, and sotalol 170 mg.

Network estimates showed that betaxolol (OR 0.36; 95%CI 0.25–0.52), carvedilol (OR 0.36; 95%CI 0.23–0.58) and sotalol (OR 0.38; 95%CI 0.30–0.50) were more effective than propranolol (OR 0.51; 95%CI 0.27–0.95), metoprolol (OR 0.72; 95% CI 0.58–0.90) and atenolol (OR 0.81; 95%CI 0.42–1.56) in reducing the incidence of POAF when compared to placebo (Fig. 3, left).

No evidence of heterogeneity/inconsistency was found in the whole network ($Q = 6.95$; $P = 0.8$), within designs ($Q = 4.91$; $P = 0.6$) and between designs ($Q = 2.04$; $P = 0.7$).

With regard to the safety profile, all beta-blockers investigated showed a trend towards an higher risk for drug discontinuation due to side-effects but metoprolol only significantly increased the risk of drug withdrawal when compared to placebo. Amongst beta-blockers investigated, carvedilol showed the best safety profile being associated with the lowest risk of patient dropped out for side effect (Fig. 3, right). No evidence of heterogeneity/inconsistency was found in the whole network ($Q = 6.2$; $P = 0.4$), within designs ($Q = 2.5$; $P = 0.4$) and between designs ($Q = 3.68$; $P = 0.2$).

Head to head comparison for the effectiveness and safety outcomes amongst the 6 beta-blockers investigated is reported in Fig. 4.

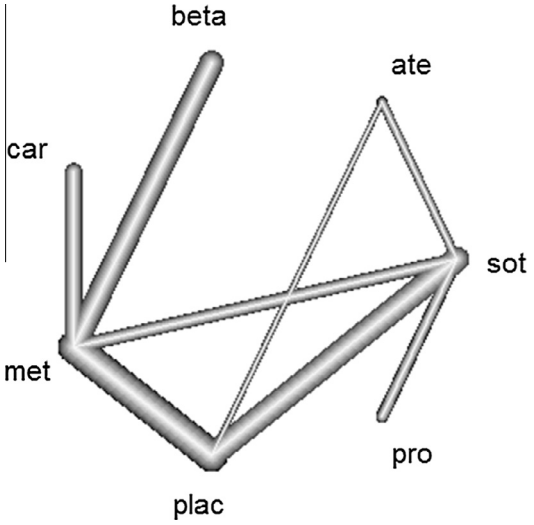

Figure 2 Network of eligible comparisons for the multiple-treatment meta-analysis for efficacy (postoperative atrial fibrillation prevention rate). The width of the lines is proportional to the number of trials comparing each pair of treatments (inverse standard error). The network of eligible comparisons for acceptability (dropout rate for side effect) analysis is similar. (ate = atenolol, beta = betaxolol, car = carvedilol, met = metoprolol, plac = placebo, pro = propranolol, sot = sotalol.)

Table 1 Summary of characteristics of studies included in this meta-analysis. (AF: atrial fibrillation, CABG: coronary artery bypass grafting; ECG: electrocardiogram; NK not known).

Study	Size	Mean age	% Female	Active treatment	Control Group	Maximum daily dose	Time of treatment	Definition of AF	ECG monitoring	Surgery type
Acikel 2008	110	60	28	Carvedilol	Metoprolol	Metoprolol 100 mg Carvedilol 25 mg	3 d pre-operatively, discontinued on the morning of surgery	AF $\geqslant$ 30 s	Continuous ECG	CABG
Auer 2004	253	65	40	Metoprolol, Sotalol	Placebo	Metoprolol 100 mg Sotalol 240 mg	24–48 h pre-operatively	AF > 5 min	Continuous ECG	CABG, valves
Connolly 2003	1000	NK	NK	Metoprolol	Placebo	Metoprolol 150 mg	Post-operatively for 14 days	NK	NK	CABG, valves
Gomes 1999	85	65	36	Sotalol	Placebo	Sotalol 240 mg	24–48 h pre-operatively up to post-operative day 4	AF $\geqslant$ 30 min	Continuous ECG	CABG, valves
Haghjoo 2007	120	61	47	Carvedilol	Metoprolol	Carvedilol 50 mg Metoprolol 100 mg	10 d pre-operatively	AF > 5 min	Continuous ECG	CABG
Iliuta 2009	1352	NK	NK	Betaxolol	Metoprolol	Betaxolol 20 mg Metoprolol 200 mg	2 d pre-operatively and at least 10d post-operatively	NK	Continuous ECG	CABG
Ozaydin 2013	311	NK	NK	Carvedilol	Metoprolol	Metoprolol 200 mg Carvedilol 25 mg	7 d pre-operatively	AF > 5 min	Continuous ECG	CABG, valves
Parikka 1998	191	NK	NK	Sotalol	Metoprolol	Metoprolol 150 mg Sotalol 240 mg	1 d post-operatively	Sustained AF $\geqslant$ 15 min	Continuous ECG	CABG
Paull 1997	100	63.4	11	Metoprolol	Placebo	Metoprolol 200 mg	24 h post-operatively	AF > 15 min	Continuous ECG	CABG
Pfisterer 1997	255	NK	NK	Sotalol	Placebo	Sotalol 160 mg	2 h pre-operatively	Any detectable AF	Continuous ECG	CABG, valves
Sanjuan 2004	253	66	NK	Sotalol	Atenolol	Atenolol 50 mg Sotalol 160 mg	1d pre-operatively	AF $\geqslant$ 10 min	Continuous ECG	CABG
Shahzamani 2011	60	NK	37	Carvedilol	Metoprolol	Carvedilol 25 mg Metoprolol 200 mg	14 d pre-operatively	NK	NK	CABG
Suttorp 1991	300	NK	NK	Sotalol	Placebo	Sotalol 240 mg	4–6 h post-operatively	AF	Continuous ECG	CABG

Suttorp 1990	429	NK	NK	Sotalol	Propranolol	Sotalol 240 mg Propranolol 80 mg	4–6 h post-operatively	AF > 30 s	Continuous ECG	CABG
Weber 1998	220	60	10	Sotalol	Placebo	Sotalol 160 mg	Day of operation for 3 months	Symptomatic AF episodes or asymptomatic episodes at a rate ⩾ 120/min	Continuous ECG	CABG
Yazicioglu 2002	160	56.8	22	Atenolol	Placebo	Atenolol 50 mg	3 d pre-operatively	NK	Continuous ECG	CABG

4. Discussion

Current American College of Cardiology (ACC)/American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines,[5,6] strongly recommend oral beta-blockers to prevent POAF in patients undergoing cardiac surgery.

One problem associated with the prophylactic use of beta-blockers to prevent POAF is that the majority of patients who do not develop POAF would still be vulnerable to the possible side effects.[33] Therefore there is an urgent need to identify which beta-blocker amongst the current alternatives has the best benefit-risk profile.

Our analysis was based on 16 studies including 5199 individuals randomly assigned to 7 different oral beta-blockers or matching placebos. Our findings will help to guide clinicians when it comes to choosing a beta-blocker to use for the prevention of POAF.

The beta-blockers investigated differ clinically and statistically. For the prevention of POAF, betaxolol, carvedilol and sotalol were more effective than propranolol, metoprolol and atenolol. On the other hand, carvedilol was found to be more acceptable than other beta-blockers because of its relative safety. Therefore carvedilol was a compromise strategy being an effective and safe alternatives.

The mechanisms underlying the better benefit-risk profile of carvedilol in the prevention of POAF are still unknown. There is now an increasing body of evidence that oxidative stress,[34] inflammation,[35,36] and increased sympathetic activation[37] are involved in the pathogenesis of POAF. Carvedilol is a beta-blocker with antioxidant and anti-inflammatory properties.[38,39] Moreover, carvedilol may have direct antiarrhythmic effect through electrophysiological traits, since it blocks multiple cationic channels (Na^+, K^+, and Ca^{2+}).[39] In addition, numerous trials indicate that carvedilol is better than conventional beta 1-selective beta-blockers in reducing sympathetic activation, a risk factor for atrial fibrillation.[39] From a pathophysiological point of view, it is plausible that the abovementioned properties of carvedilol might result in the favourable effect on the prevention of POAF with a lower beta-blockage. This could be the reason for better tolerability, hence reducing the risk of side-effects. Several potential study limitations should be considered. Most trials included in our analysis did not report adequate information about randomization and allocation concealment, and this might undermine the validity of overall findings. Most trials included a relatively small number of patients, and not all studies included the same covariates (type of operation, on-pump vs. off pump bypass surgery, concomitant medications). Additionally, the present network meta-analysis included a moderate number of trials ($n = 16$), which makes it difficult to conduct subgroup analyses. Unfortunately, in some of these trials, patients assigned to placebo who have previously been on beta-blockade probably suffered from beta-blocker withdrawal, thus causing a bias against the placebo groups. In fact, patients who have used preoperative beta-blockers that are withdrawn after surgery seem to be at a particularly high risk of POAF. Finally, various dosages of the individual agents were used with different times of administration.

In conclusion, our analysis suggests that carvedilol is candidate to be the preferred beta-blockers in terms of efficacy and

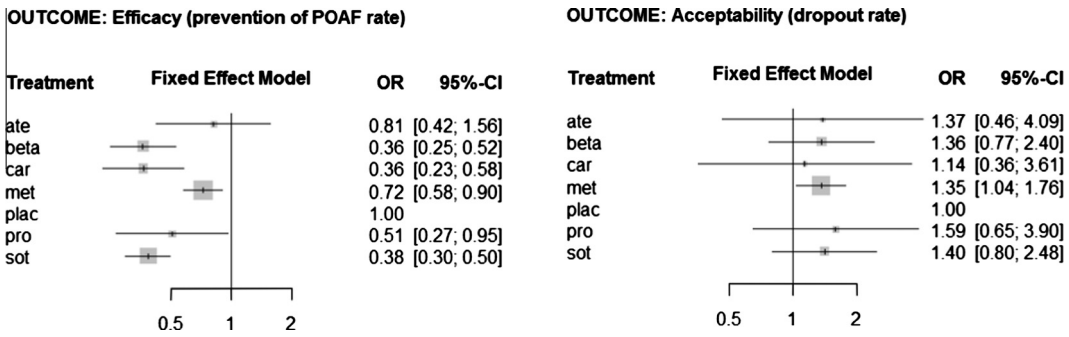

Figure 3 Forest plot for efficacy (left) and acceptability (right) of the 6 beta-blockers compared to placebo. (ate = atenolol, beta = betaxolol, car = carvedilol, met = metoprolol, plac = placebo, pro = propranolol, sot = sotalol.)

Efficacy (prevention of POAF rate) 95%CI | Comparison | Acceptability (dropout rate) 95% CI

ATENOLOL	**2.25** [1.07-4.72]	**2.24** [1.01-4.94]	1.13 [0.57-2.23]	1.61 [0.68-3.79]	**2.12** [1.12-3.99]
0.99 [0.29-3.32]	BETAXOLOL	0.99 [0.60-1.65]	**0.50** [0.37-0.67]	0.71 [0.35-1.47]	0.94 [0.61-1.44]
0.82 [0.17-3.99]	0.83 [0.24-2.86]	CARVEDILOL	**0.51** [0.34-0.76]	0.72 [0.33-1.56]	0.95 [0.57-1.58]
0.98 [0.32-2.96]	0.99 [0.60-1.64]	1.19 [0.38-3.67]	METOPROLOL	1.42 [0.74-2.74]	**1.87** [1.38-2.55]
1.15 [0.36-3.69]	1.16 [0.41-3.30]	1.39 [0.32-5.94]	1.17 [0.47-2.92]	PROPRANOLOL	1.32 [0.74-2.35]
1.02 [0.40-2.59]	1.03 [0.47-2.23]	1.23 [0.34-4.40]	1.03 [0.57-1.87]	0.88 [0.44-1.77]	SOTALOL

Figure 4 Efficacy and acceptability of the 6 beta-blockers. Drugs are reported in alphabetical order. Results are the ORs in the column defining treatment compared with the ORs in the row defining treatment. For efficacy, ORs higher than 1 favour the column-defining treatment. For acceptability, ORs higher than 1 favour the column-defining treatment. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold and underscored.

acceptability in the prevention of POAF and should be used as standard therapy. Current evidence suggests that beta-blocker prophylaxis is more effective when initiated preoperatively rather than postoperatively[5,6] and reinstitution of beta-blockers after surgery has been associated with a reduction of POAF.[5,6]

In addition, carvedilol should be considered as the standard comparator in phase III trials to increase the real-world applicability of the results. Furthermore, the need for new treatment to show either greater efficacy or acceptability than an existing standard therapy would serve as a disincentive to the development of alternative agents that offer little clinical benefit with increased costs.

Conflict of interest

No conflict to disclose.

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