# Incidence of post-operative atrial fibrillation recurrence in patients discharged in sinus rhythm after cardiac surgery: A systematic review and meta-analysis

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## ABSTRACT

Post-operative atrial fibrillation (POAF) is associated with increased stroke risk and mortality post-discharge. POAF is often considered transient, however recurrence is likely under-recognized as symptoms are an unreliable guide. Surveillance post-discharge may identify asymptomatic POAF recurrences in patients discharged in sinus rhythm. Therefore, we performed a systematic review and meta-analysis of studies investigating POAF recurrence post-discharge, in patients with new-onset POAF following cardiac surgery who reverted to sinus rhythm prior to discharge. Two independent reviewers searched medical databases, clinical trial registries, reference lists, and the internet. From 6,525 studies screened, 8 studies were identified (n=1,157 participants; mean 66±10 years; 73% male). Monitoring methods included: telemetry during twice-daily exercise sessions (n=2); continuous telemetry for 3-weeks (n=1); daily 20-second ECG using wearable event recorder (n=1); 30-second single-lead ECG, 4x/day (n=1); and implanted continuous monitoring (n=2). Incidence rate of POAF recurrence identified through non-invasive monitoring in the first 4-weeks post-discharge was 28.3% (CI, 23.0-33.6%); recurring 12±5 days (mean ± SD) post-surgery. Incidence identified through implanted continuous monitoring was 61-100% within 2-years. Between 40-93% of episodes were asymptomatic. In one small study reporting stroke risk, 8/10 patients with recurrence were guideline-indicated (CHA2DS2-VASc score ≥2) for oral-anticoagulation for stroke prevention. Monitoring for POAF recurrence post-hospital discharge identifies significant numbers of early asymptomatic recurrences in patients at high risk of stroke, who may benefit from anticoagulation for stroke prevention. More intense monitoring is more likely to identify POAF recurrence. Future research is required to investigate the prognostic significance of POAF recurrence, especially stroke and mortality risk.



**Key words**

post-operative, atrial fibrillation, screening, recurrence, electrocardiogram

## INTRODUCTION

New-onset post-operative atrial fibrillation (POAF) occurs in 16-44% of patients following cardiac surgery prior to discharge,(1, 2) and is associated with an increased risk of postoperative complications such as stroke, respiratory failure, and pneumonia.(3) An episode of POAF after cardiac surgery is associated with a significantly increased long-term risk of embolic stroke (HR, 2.1; 95% CI, 1.4-3.1);(2) and increased all-cause mortality, with the overall ten-year survival for patients with POAF being 65.5% compared to 75.3% in those without POAF.(3) POAF is often thought to be transient as it often resolves spontaneously, and there is also uncertainty about the need for treatment.(4) Therefore, patients who convert to sinus rhythm prior to discharge are rarely monitored for recurrence. However, these patients with POAF have a 5-fold increased risk of developing long-term atrial fibrillation (AF).(5)

In current practice, routine surveillance for POAF recurrence largely falls to the patient and their GP, and generally relies on identification of AF symptoms. Symptoms occur in only 1/3 of all AF episodes,(6) and many symptoms experienced such as fatigue, dizziness, or shortness of breath are non-specific and easily confused with what might be expected during recovery from surgery. Notably, after discharge from cardiac surgery palpitations occur in only 30% of POAF recurrences.(7) Therefore, symptoms are unreliable as a guide to identify POAF recurrence.

The need for surveillance of POAF recurrence is advocated by many recent studies.(3, 5, 8-10) It is likely that surveillance post-discharge would identify patients with asymptomatic recurrences of AF who are at increased risk of stroke; however this is neither routinely implemented, nor recommended in guidelines.(11, 12) Therefore, the aim of this systematic review was to focus on patients with new-onset POAF deemed to be in stable sinus rhythm on discharge, and determine the recurrence of POAF identified through active screening after discharge. The secondary aim was to determine the stroke risk of the patients with recurrence of POAF after discharge.

## METHODS

### Search strategy

Relevant studies were identified by a search of the medical databases MEDLINE (to Feb 2017), EMBASE (to Feb 2017), and Cochrane Library (to Feb 2017); clinical trials registries; reference lists; and the Internet using Google search engine. The keyword search terms were atrial fibrillation AND (postoperative OR post-surgery OR post CABG OR post-surgical OR cardiac surgery OR heart surgery OR valve surgery) AND (detection OR screening OR identification OR incidence OR prevalence OR surveillance OR ECG OR Electrocardiogram OR monitoring OR recurrence OR case finding). Limits were applied for the years 1990 onwards, and for humans only. All languages were included.

For stage one of the review, two independent reviewers (GM, NL) reviewed all titles and abstracts from the search to identify potentially relevant articles. All relevant references were imported into Endnote X7 bibliographic software and duplicates removed. Where papers reported outcomes for the same study at different time points the longest follow-up point was used. In stage two, full text manuscripts were obtained for all potentially relevant studies and screened by the reviewers (GM, NL) against the inclusion and exclusion criteria.

Inclusion criteria:

- cardiac surgery population, with episode of new-onset POAF during hospitalization for cardiac surgery
- patients reverted to sinus rhythm prior to hospital discharge
- patients were actively screened for AF recurrence post-hospital discharge (no limits placed on timeframe)

Exclusion criteria:

- patients with known history of AF prior to surgery
- studies did not distinguish any known history of AF prior to surgery
- studies did not distinguish the patients who reverted to sinus rhythm prior to discharge
- studies only screened in the post-surgical in-patient period.

Outcome data were collected independently by two reviewers (GM, NL), on a pre-determined data-extraction form. In cases where data were unclear or not reported, the primary study authors were contacted. Quality of reporting and risk of bias in each study were assessed using the Newcastle-Ottawa scale.(13)

**Outcomes**

The primary outcome was recurrence of POAF following hospital discharge. Secondary outcomes were reported timeframe to first recurrence, symptomatic status of AF recurrences, stroke risk scores (i.e. $CHADS_2$ or $CHA_2DS_2$-VASc)(12), and eligibility and prescription of oral anticoagulation (OAC) therapy.

**Data analysis**

Meta analyses were performed on outcome data with the use of 'Comprehensive Meta-Analysis' software version 3.3 (Biostat, Inc). Incidence rates were calculated utilising random effects models, and heterogeneity tests were performed.

**RESULTS**

**Study selection and characteristics**

A total of 6,525 studies were screened against the inclusion and exclusion criteria and 56 full manuscripts were reviewed (Figure 1). Cohen's kappa coefficient for inter-rater agreement measured κ 0.47 (CI, 0.28 to 0.66) for stage one of the review process, and κ 0.78 (CI, 0.58

to 0.98) for stage two. Eight unique studies were ultimately included (Figure 1), with a combined total of 1,157 participants, a mean age of 66±10 years and 73% males.

The studies originated from Italy,(14-17) America,(18, 19) Russia,(20) and Australia(7) (Table 1). Study designs varied, including prospective randomised controlled trials,(15, 20) prospective cohorts,(7, 17-19) and retrospective cohorts.(14, 16) All studies recruited cardiac surgery patients with a transient episode of POAF, in sinus rhythm on discharge, with no history of AF and with stable sinus rhythm on admission. Participants were monitored for AF recurrence using a variation of 12 lead ECG, single lead ECG, 24-hour Holter monitor, telemetry, event recorders, and implanted devices (Table 1). Although AF guidelines define AF as any episode lasting ≥30 seconds,(12) AF definitions varied between each study (Table 1). The period of post-discharge monitoring ranged from two to four weeks, with three studies performing additional long-term follow-up up to 24 months (Table 1).

**Quality assessment**

Overall quality of reporting was moderate. All studies scored 8/9 stars on the Newcastle-Ottawa Scale, where 9 stars is the best score(13) however, against the STROBE reporting guidelines(21) five studies did not adequately report patient numbers at each stage, 6 studies did not report efforts to address potential study bias and 2 studies failed to address the limitations of the study (Supplement 1).

**Recurrence of post-operative AF**

When monitored with non-invasive monitoring in the first 2-4 weeks post discharge, the incidence rate (cases per 100 persons screened) of POAF recurrence was 28.3% (95% CI, 23.0 – 33.6%) (6 studies, n=1,125),(7, 14-18) according to random effects analysis (Figure 2). Heterogeneity between studies was low-moderate, $I^2$ = 30.0%: where a value of $I^2$ <25% is considered homogeneous and an $I^2$ value of 50% indicates moderate heterogeneity.(22) When monitored with an implanted device over a two-year period, a higher incidence of AF

recurrence was identified. The two implanted device studies reported an incidence of 60.9%(19) and 100%(20).

*Timeframe to first AF recurrence*

Of the 6 non-invasive monitoring studies, timeframe to first recurrence of POAF was reported in only 3 studies (n=332): all three studies noted that AF recurred a mean of 12 days post-surgery (Table 2).(7, 15, 16) One implanted device study reported that 39% (9/23) of participants had an AF recurrence within 3 months of surgery; but the mean time to first recurrence was 146 ± 250 days.(19)

*Symptomatic status of AF recurrences*

Five studies reported the symptomatic status of recurrent episodes of AF (Table 2). Recurrences were most commonly asymptomatic, ranging from 40-69% of episodes in the non-invasive monitoring studies.(7, 15, 16, 18) In the implanted device study reporting symptomatic status, 93% (13/14) of recurrences were asymptomatic.(19)

*Medications and AF post discharge*

Medications were not reported specifically for the patients with a POAF recurrence who were discharged home in sinus rhythm, results were reported for the whole study population. The effect of β-blocker medications were reported in five studies. Three studies indicated that β-blockers may reduce the recurrence of AF post discharge (23-25), and two studies reported no association between β-blockers and AF following discharge (26, 27) (Table 2). The effect of amiodarone medication was reported in only two small studies, both reporting no association with reducing AF post discharge (23, 26) (Table 2). Meta-analysis was not possible due to insufficient reporting of data in the majority of studies, especially in relation to listing the medications and dose.

*Stroke risk and oral anticoagulation prescription*

Stroke risk for patients with AF recurrence and eligibility for prescription of OAC was reported in only one study (n=42).(7) In this study, eight of the 10 patients with recurrent AF had a $CHA_2DS_2$-VASc score ≥2. However only 3/8 were on oral anticoagulation, with one of the three requiring warfarin because of a mechanical valve. Two studies reported that oral anticoagulation was routinely prescribed for recurrences of AF that lasted longer than 24 and 48 hours, however these studies did not report the numbers of patients in which this occurred, nor their calculated stroke risk scores.(15, 16)

**Late-onset POAF after discharge**

Incidence of late-onset POAF after hospital discharge was an additional finding reported in 3 studies (n=2,716).(14, 17, 18) For people with no in-hospital episode of AF, intermittent monitoring in the first 2-4 weeks post-discharge also identified individuals with late-onset POAF after hospital discharge: incidence rate (cases per 100 persons screened) 3.9% (95% CI, 2.7 – 5.4%) (Figure 3). Heterogeneity for these studies was moderate, $I^2$ = 50.3%: as defined by an $I^2$ value 50% indicating moderate heterogeneity.(22)

## DISCUSSION

### Statement of findings

Monitoring of patients discharged in stable sinus rhythm post-cardiac surgery, identifies POAF recurrence in 28.3 cases per 100 persons screened in the first 2-4 weeks post-discharge using non-invasive techniques; and implanted devices can identify recurrence in 60-100% of cases, suggesting that in-hospital episodes of new POAF are not necessarily isolated or transient. Importantly, most POAF recurrences are asymptomatic, therefore these episodes are unlikely to be recognised without the aid of additional monitoring post-discharge. Furthermore, in the one study that calculated stroke risk, 8/10 of patients with POAF recurrence had sufficient stroke risk (i.e. $CHA_2DS_2$-VASc score ≥2) to be considered eligible for OAC. This highlights the potential importance of early identification of POAF

recurrence through monitoring in the post-discharge period, and appropriate treatment and prescription of OAC to prevent stroke.

There are multiple hypotheses as to the mechanism for development of POAF following surgery patients. It has been reported that inflammation and the associated increase in plasma concentrations of C-reactive protein and interleukin-6 in conjunction with cardiac surgery may be associated with the development of AF.(28, 29) Other mechanisms include increased sympatho-adrenal activation post-surgery which prolongs the atrial refractive period and promotes ectopic activity, and oxidative stress following bypass surgery.(29, 30) However, it remains unknown why POAF develops in some patients and not others. Pre-existing risk factors that can lead to formation of an atrial AF substrate may also influence risk.(29) It is thought that POAF may occur after surgery when patients reach a 'pathophysiological threshold' of pro-arrhythmic factors due to a combination of pre-existing risk factors and post-surgical factors.(29, 31) There is a natural incidence of AF over and above that related to the surgery and the postoperative period, and this is likely to factor in the yield of AF detected from longer-term monitoring. But, it is possible that the patients who develop POAF after surgery may be those with some existing AF substrate changes, who are predisposed to develop AF both during the provocation of surgery, and spontaneously in the long term.

Risk scores have been developed to predict the development of new-onset POAF after cardiac surgery, such as the POAF score,(32) and the Brazilian risk score.(33) Although validated for predicting new-onset POAF, these scores have not been extended to predicting recurrence of POAF, but may be useful as recent evidence suggests new-onset AF is a predictor of long-term AF.(5) There is a 6-fold increase in the likelihood of clinical AF recurrence in patients with an episode of POAF compared to those without POAF, however late-onset POAF can also occur post-hospital discharge.(16) Incidence of late-onset POAF was a secondary finding of the studies included in our review, however other research has

identified similar incidences of 3.6 - 8% new AF after discharge.(10, 34) It is also probable that many in-hospital episodes of POAF go undetected. A study using Holter monitoring found 13% of all patients had ‘silent’ POAF during the post-cardiac surgery inpatient period, which was asymptomatic and remained undiagnosed at discharge.(9) ‘Silent’ POAF was associated with higher AF recurrence rate at 1-year follow-up.(9) It is therefore difficult to predict which patients are at higher risk of AF recurrence or AF development in the post-discharge period, suggesting perhaps that monitoring might also be indicated for patients without diagnosed POAF during the admission.

Identification of an appropriate means of monitoring is becoming increasingly important, given that the number of elderly patients undergoing cardiac surgery is projected to increase,(35) and age is a primary risk factor for development of both AF and stroke.(36, 37) Furthermore, obesity(38) and metabolic syndrome(39) are also associated with a higher incidence of POAF after cardiac surgery. We are therefore likely to see an increase in the incidence of POAF corresponding to the rise in obesity in the next 20 years, along with an associated increase in stroke, morbidity, mortality, and health system costs. The mode of surveillance will influence the number of cases of recurrent AF identified. Implanted devices with continual rhythm recording will pick up much more brief paroxysmal episodes than intermittent sampling, but the clinical significance of these episodes, like cardiac implanted device-detected atrial high rate episodes may be less than clinically detected AF or AF detected by intermittent brief recordings.(40, 41) While technology allowing centralised remote monitoring of multiple patients with implanted devices could make monitoring more feasible,(42) the likely lower risk in patients detected in this way needs to be taken into consideration. Patient tolerance, acceptance and compliance of an implanted device is an additional consideration, with 50% refusal rate reported from one study designed to have an implanted device for 2 years.(20)

Despite the clear evidence that POAF is a major cause of morbidity and mortality, and that asymptomatic POAF recurrences can be identified in the weeks following discharge, there is a lack of evidence in regard to the long-term effect of anticoagulation on stroke risk in POAF patients, and therefore no indication that treatment will be altered as a result of identifying POAF recurrence through monitoring.(12) POAF management guidelines recommend anticoagulation for at least 4-weeks post cardioversion of patients with POAF lasting >48 hours, and anticoagulation for 'high-risk patients' in which sinus rhythm was restored within 24 hours of onset.(11) The results of our study raise questions regarding which patients should be considered 'high-risk' and which patients are at risk of recurrence or late-onset AF, thus which patients should monitored.

Instigating monitoring comes at a cost, however could well be cost effective from the standpoint of stroke prevention. Although the studies in this review utilised devices for monitoring, there are also other low-cost methods to address detection of AF through improved patient education regarding symptom awareness and routine self-monitoring using pulse-palpation, and some handheld ECG devices have a fairly modest cost. To date, screening studies for primary AF detection using new devices, such as handheld single-lead ECGs, have all been demonstrated to be cost-effective.(43-47)

**Limitations**

The main limitation of this review is the small number of studies included and design of the studies. Participants were nonhomogeneous in regards age, cardiac procedure and comorbidities, and numbers in each trial were small with <100 participants in 5/8 studies. Study designs varied significantly between the studies, with only 2 randomized control trials, and method and timeframe for monitoring varied greatly between the trials. Furthermore, the majority of trials did not report data for our secondary objectives. Only 5 studies reported symptomatic status of AF episodes, the data regarding reduced recurrence with β-blockers was not conclusive, only two small studies investigated the effect of amiodarone, and only

one study with small numbers reported the stroke risk of patients identified with POAF recurrence. Therefore, there is insufficient strength in the available data to draw conclusions about stroke risk in this population, the need for anticoagulation treatment, and the effect of preventative treatments such as amiodarone and β-blockers.

This highlights a need for future studies to look at amiodarone and its role in preventing recurrence of POAF in this group of patients, and for more understanding of how antiarrhythmic medications such as amiodarone can influence prevention of recurrence. Furthermore, whilst 3/5 studies suggested a beneficial effect of β-blockers in the prevention of AF post discharge, it is worthy to note that most institutions prescribe β-blockers at the time of discharge as a process of continuing preoperative medications and not with the intention of offering antiarrhythmic protection. There is no evidence or uniformity in prescribing one particular β-blocker or any one specific dose to offer adequate antiarrhythmic protection. Further research is indicated to address these issues.

Whilst we know that stroke risk is increased in patients with an episode of POAF following cardiac surgery,(2) and asymptomatic AF episodes in the general population increase stroke risk,(41) and stroke risk from paroxysmal AF is sufficiently high to require anticoagulation;(48) this review highlights that there is insufficient evidence to determine the stroke risk of recurrences in patients with POAF who are discharged home and presumed to be in stable sinus rhythm. It is also uncertain whether the increased recurrence rate detected by continuous invasive recordings will have the same prognostic significance as recurrence detected by more brief or intermittent recordings. These data are required in order to inform recommendations for the length and intensity of monitoring required post discharge, and anticoagulation and preventative treatments for recurrences. Overall, the results of this review indicate a need for large-scale research to look at the prognostic significance of POAF recurrences and late-onset AF episodes after discharge, in relation to stroke, morbidity, and mortality, and therefore treatment implications and recommendations.

## CONCLUSION

Monitoring for POAF recurrence post-hospital discharge identifies significant numbers of asymptomatic recurrences in patients at high risk of stroke, who may benefit from early detection of POAF recurrence and anticoagulation for stroke prevention. More intense monitoring is more likely to identify POAF recurrence. Further large-scale studies are required to investigate the prognostic significance of POAF recurrence in relation to stroke and mortality risk.


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## CONFLICT OF INTEREST STATEMENT:

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**FIGURE LEGEND:**

Figure 1: Study selection

Figure 2: Forest-plot of incidence of recurrent POAF: using intermittent monitoring

Figure 3: Forest-plot of incidence of new onset POAF

**Table 1: Study characteristics**

| Author; Year | Country | Study design | Inclusion criteria | Exclusion criteria | Method of monitoring | Time period of monitoring | AF definition |
|---|---|---|---|---|---|---|---|
| **Intermittent monitoring** | | | | | | | |
| Ambrosetti et al; 2011 | Italy | Prospective registry study | Cardiac surgery; attending cardiac rehabilitation | Nil reported | Monitored during cardiac rehabilitation sessions<br>• Diagnostic method not standardized between centers; varied according to local protocol and access to continuous monitoring | 13±20 days post discharge | Clinically documented |
| Cioffi et al; 2000 | Italy | Randomised controlled trial | Cardiac surgery; referred to Rehabilitation Centre | Severe postop complications; Amiodarone treatment | Monitored during cardiac rehabilitation sessions<br>• One lead telemetry: during twice daily exercise sessions<br>• 12 lead ECG: weekly<br>• 24 hour Holter: 14 days & 10 months post-surgery | 21±2 days post discharge<br><br>Plus long term review at 10 months | Documented AF episodes lasting >2 mins |
| Cioffi et al; 2001 (retrospective arm only) | Italy | Retrospective analysis | CABG or valve surgery; referred to Rehabilitation Centre | >1/52 in Intensive Care; Amiodarone treatment | Monitored during cardiac rehabilitation sessions<br>• One lead telemetry: during twice daily exercise sessions<br>• 12 lead ECG: weekly<br>• 24 hour Holter: 14 days & 10 months post-surgery | 21±4 days post discharge<br><br>Plus long term review at 10 months | Documented AF episodes lasting >2 mins |
| Funk et al; 2003 | USA | Prospective longitudinal | CABG ± valve surgery | Post-operative stay >2/52; communication barrier | 20 second ECG once daily, plus extra if symptoms detected<br>• Wearable cardiac event recorder (King of Hearts Express recorder, Instromedix) | 2 weeks post discharge | Not defined |
| Giaccardi et al; 2011 | Italy | Prospective cohort | Isolated CABG; ≥65 yrs; attending cardiac rehabilitation | Cognitive or physical activity impairment; sleep apnoea; previous cardiothoracic surgery | Monitored 24 hours per day for the duration of cardiac rehabilitation<br>• Electrocardiogram telemetry | 3 weeks post discharge | Standard ECG criteria |
| Lowres et al; 2015 | Australia | Prospective cohort | Cardiac surgery | Communication barrier | 30 second ECG 3-4 x day, plus extra if symptoms detected<br>• Handheld single lead ECG (AliveCor Heart monitor) | 29±5 days post discharge | 30 second rhythm strip |
| **Implanted cardiac monitoring** | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Lomivorotov et al; 2014 | Russia | Randomised controlled study | CABG; >18 years | Unstable cardiac disease; pacemaker; antiarrhythmic or omega-3 treatment | Implanted continuous cardiac monitor (Reveal XT, Medtronic) | 24 months post operatively<br><br>Reviewed at 10 days; then 3, 6, 12 & 24 months | ≥30 seconds |
| El-Chami et al; 2016(19) | USA | Prospective cohort | CABG; $CHADS_2$ score ≥1 | Known AF history; valve surgery | Implanted continuous cardiac monitor (Reveal XT, Medtronic) | 25±10 months monitoring;<br><br>Reviewed monthly | Documented AF requiring treatment |

ECG: electrocardiogram; CABG: coronary artery bypass graft; $CHADS_2$: stroke risk score [C = congestive heart failure, H = hypertension, A = age ≥65, D = diabetes, $S_2$ = prior stroke or TIA]; AF: atrial fibrillation.

**Table 2: Study Outcomes**

| Author; Year | Age (mean± SD) | Male (%) | Number with POAF | POAF recurrence after discharge n (%) | Timeframe to recurrence | Symptom status of recurrences |
|---|---|---|---|---|---|---|
| **Intermittent monitoring** | | | | | | |
| Ambrosetti et al; 2011 | 67±10 | 75 | 623 | 141 (22.6%) | _ | _ |
| Cioffi et al; 2000 | 65±9 | 68 | 185 | 60 (32.4%) | 12±5 days post-surgery | 53% asymptomatic<br>47% symptomatic |
| Cioffi et al; 2001 (retrospective arm) | 62±10 | 72 | 93 | 35 (37.6%) | 12±4 days post-surgery | 48% asymptomatic<br>52% symptomatic and higher ventricular rate |
| Funk et al; 2003 | 64±11 | 73 | 117 | 31 (26.5%) | _ | 69% asymptomatic<br>17% palpitations<br>14% atypical symptoms |
| Giaccardi et al; 2011 | 74±6 | 57 | 65 | 22 (33.8%) | _ | _ |
| Lowres et al; 2015 | 69±9 | 80 | 42 | 10 (23.8%) | 12.5±6 days post-surgery | 40% asymptomatic<br>30% palpitations<br>22% atypical<br>11% mixture palpitations ± atypical |
| **Implanted cardiac monitoring** | | | | | | |
| Lomivorotov et al; 2014 | 62±5 | 95 | 9 | 9 (100%) | _ | _ |
| El-Chami et al; 2016 | 69±7 | 87 | 23 | 14 (60.8%)<br>(9 found in <3 months) | 146±250 days | 93% asymptomatic<br>7% symptomatic |

POAF: postoperative atrial fibrillation

**Table 3: Medications and POAF after discharge**

| Study | Medication/Dose | POAF after discharge % (number) | | P value |
|---|---|---|---|---|
| | | On medication | Not taking medication | |
| | **β-blocker** | | | |
| Ambrosetti; 2011 | - | 7% | 8.9% | 0.317 |
| Cioffi; 2000 | Atenolol 40±15mg/day, or Metoprolol 50mg/day, or Bisoprolol 5 mg/day | 10% (4/42) | 47% (25/50) # | <0.0001 |
| Cioffi; 2001 (retrospective arm) | Atenolol 25mg/day, or Metoprolol 100mg/day, or Bisoprolol 5 mg/day | 4.3% (5/116) | 21.5% (56/260) | <0.0001 |
| Funk; 2003 | "Preoperatively" | 10% (20/201) | 21% (21/101) | 0.01 |
| Giaccardi; 2011 | - | 26.2% (22/84) | 14.8% (11/74) | 0.081 |
| | **Amiodarone** | | | |
| Cioffi; 2000 | 250±50mg/day | 50% (29/62) | 47% (25/50) # | 0.85 |
| Giaccardi; 2011 | - | 28.3% (15/53) | 17.1% (18/105) | 0.103 |
| | **Amiodarone PLUS β-blocker** | | | |
| Cioffi; 2000 | Amiodarone 250±50mg/day; Atenolol 40±15mg/day, or Metoprolol 50mg/day, or Bisoprolol 5 mg/day | 9% (2/22) | 47% (25/50) # | 0.001 |
| | **ACE-I/ARB** | | | |
| Ambrosetti; 2011 | ACE-I/ARB | 6.1% | 9.3% | 0.08 |
| Cioffi; 2001 (retrospective arm) | ACE-I | 10.7% (3/28) | 16.6% (58/348) | 0.60 |
| Giaccardi; 2011 | ACE-I | 20.7% (23/111) | 21.3% (10/47) | 0.937 |

# = control group NOT taking either Amiodarone OR β-blocker; ACE-I = Angiotensin-converting-enzyme inhibitor; ARB = Angiotensin receptor blockers

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