Dataset for amiodarone adverse events compared to placebo using data from randomized controlled trials

Morgan K. Moroia, Mohammed Ruziehb, *, Nader M. Aboujamousc, Mehrdad Ghahramanib, Gerald V. Naccarellib, John Mandrolad, Andrew J. Foyb

a Penn State College of Medicine, Hershey, PA, USA
b Penn State Heart and Vascular Institute, Hershey, PA, USA
c Penn State Department of Internal Medicine, Hershey, PA, USA
d Baptist Health Louisville, Louisville, KY, USA

Abstract

The dataset presented here provides a detailed description of the adverse events of amiodarone versus placebo using data from 43 randomized controlled trials. Two authors (M.M., M.R.) independently extracted the data. The dataset also includes baseline patient characteristics, amiodarone loading and maintenance doses, as well as forest plots describing the relative risk (RR) of developing an adverse event related to the pulmonary, thyroid, hepatic, cardiac, skin, gastrointestinal, neurological, and ocular systems. The Mantel-Haenszel random effects model was used to determine the relative risk of adverse events of amiodarone compared to placebo. This dataset is complementary to our article “Meta-analysis Comparing the Relative Risk of Adverse Events for Amiodarone Versus Placebo”, which was published in the American Journal of Cardiology [1]. The data can be used to assess certain adverse events and their relation to amiodarone loading and/or maintenance dose.

© 2019 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
1. Data

The raw dataset contains the number of events and number of patient-year for the amiodarone and placebo arm of each study (reads in xlsx format, each organ system in a separate sheet). Patients’ characteristics are summarized in Tables 1 and 2. The number and incident rate of events are listed in Table 4. The rate of adverse events in the amiodarone arm for each organ system, and the rate of drug discontinuation compared to placebo are illustrated in Figs. 1–9.

2. Experimental design, materials, and methods

The protocol was developed by three authors (M.M., M.R., A.F.) and revised by all authors. PubMed, Google Scholar, the Cochrane Central Register for randomized controlled trials, and ClinicalTrials.gov were searched for studies that analyzed the use of amiodarone regardless of indication or efficacy of therapy (latest search was conducted on October 10, 2018). Articles were identified using key search terms: amiodarone, adverse events, side effects, placebo, atrial fibrillation, atrial flutter, ventricular tachycardia, arrhythmias, liver, skin, thyroid, eye, and lung.
Baseline patient characteristics. Forty-three randomized control trials \([2–20]\) were studied, and 11,395 patients were included (5792 patients in the amiodarone group, 5603 patients in the placebo group). Average age was 62.0 years for patients receiving amiodarone and 62.3 years for patients receiving placebo. Follow up time ranged from 1 week–6 months for studies with follow up \(<\)12 months. Indications for amiodarone therapy were suppression of atrial and ventricular arrhythmias, and maintenance dose for amiodarone ranged from 200 to 600 mg daily. Raw data for the adverse events is provided in the supplement material.

| First author | Year | Medical condition | Percent with IHD | Reason for intervention | Mean follow-up (days) | Mean Age (yrs) | Male Gender (%) |
|--------------|------|-------------------|-----------------|------------------------|----------------------|----------------|-----------------|
| Greco 1989   |      | Patients with anterior MI | 100% | Reduce mortality and morbidity | Until discharge | 160 | 54 85 |
| Hamer 1989   |      | Congestive heart failure | 18% 60% | Arrhythmia control, exercise tolerance and ventricular function | Until discharge | 180 | 10 20 mg/kg |
| Hohnloser 1991 | Post CABG | NA 100% | Suppression of SVT and ventricular arrhythmias | 4 | 1125 | 4 |
| Meyer 1993   |      | Stable angina | 59% 100% | Limiting angina pectoris | 60 400 | 30 200 50 |
| Mahmarian 1994 | Systolic heart failure and NSVT | 24% 49% | Suppression of ventricular arrhythmias | 90 422 | 30 50 or 100 54 |
| Donovan 1995 |      | Patients with recent-onset AF | NA 48% | Restoration of sinus rhythm | Until discharge | 15 7 mg/kg |
| Galve 1996   |      | Newly diagnosed AF | NA NA | Rhythm control | 1200 5 mg/kg | 1 1 N/A |
| Gentile 1996 |      | Elderly patients with systolic heart failure | <40% 61% | Reduce sudden cardiac death | 180 400 | 30 100 150 |
| Daoud 1997   |      | Patients undergoing open heart surgery | 48% 60% | Prevention of post-op AF | 30 200–1000 | 13 ± 7 |
| Kochiadakis 1998 | Patients with recent onset AF | 50% NA | Restoration of sinus rhythm | 1 2100 3000 | 1 1 N/A N/A |
| Cotter 1999  |      | Patients with paroxysmal AF | Majority 43% | Restoration of sinus rhythm | 30 2100 | 3000 |
| Kochiadakis 1999 | Patients with persistent AF | <45% 50% NA | Restoration of sinus rhythm | 30 460 20 mg/kg | 28 28 |
| Redle 1999   |      | Patients undergoing CABG | 49% 100% | Prevention of post-op AF | 10 430 | 11 11 |
| Bianconi 2000 | Patients with AF or AFL | NA 15% | Acute termination of AF or flutter | 3–7 5 mg/kg | 1 1 N/A N/A |
| Elizari 2000 |      | Patients with acute MI | NA 100% | Reduce morbidity/mortality | 180 900 | 3 N/A N/A |

(continued on next page)
| First author | Year | Medical condition | Average Ejection fraction | Percent with IHD | Reason for intervention | Mean follow-up (days) | Average Load Dose (mg/day) | Load (# of days) | Average Maintenance Dose (mg/day) | Maintenance (# of days) | No. of Pts | Mean age (yrs) | Male Gender (%) | Placebo arm No. of Pts | Mean age (yrs) | Male Gender (%) |
|--------------|------|-------------------|---------------------------|-----------------|------------------------|---------------------|---------------------------|-----------------|-----------------------------------|--------------------|------------|----------------|----------------|------------------------|----------------|----------------|
| Lee          | 2000 | Patients undergoing CABG | 59%                       | 100%            | Prevention of post-op AF | 18                  | 150 + 0.4/kg              | 8               | N/A                               | N/A                | 74         | 66             | 54             | 76 65 55               |
| Peuhkurinen  | 2000 | Patients with recent-onset AF | 63%                       | 21%             | Restoration of sinus rhythm | 1                  | 30 mg/kg                  | 1               | N/A                               | N/A                | 31         | 56             | 81             | 31 62 65               |
| Vardas       | 2000 | Patients with AF | 51%                       | NA              | Restoration of sinus rhythm | 30                 | 600                      | 28              | N/A                               | N/A                | 108        | 64             | 49.1           | 100 65 49              |
| Giri         | 2001 | Patients undergoing CABG, valve or combined | 43%                       | 98%             | Prevention of post-op AF | 9                  | 1000                     | 6; 10           | N/A                               | N/A                | 120        | 72.7          | 78             | 100 72.5 74            |
| Maras        | 2001 | Patients undergoing CABG | 44%                       | 100%            | Prevention of post-op AF | 7                  | 325                      | 8               | N/A                               | N/A                | 159        | 58.3           | 80             | 156 57.3 76            |
| White        | 2002 | Patients undergoing open heart surgery | 43%                       | 35%             | Prevention of post-op AF | 21–42              | 1200–1400               | >10; >6        | N/A                               | N/A                | 120        | 72.6          | 78.3           | 100 72.5 74            |
| Yagdi        | 2003 | Patients undergoing CABG | 48%                       | 100%            | Prevention of post-op AF | 30                 | 400–600 + 10/kg          | 2; 5; 5        | N/A                               | N/A                | 77         | 59.3           | 80.5           | 80 61.1 73.7           |
| Auer         | 2004 | Patients undergoing open heart surgery | 69%                       | 64%             | Prevention of post-op AF | 12                 | 667                      | 9               | N/A                               | N/A                | 63         | 64             | 58.7           | 65 63 58.5             |
| Mitchell     | 2005 | Patients undergoing CABG, valve replacement, repair | 58%                       | 75%             | Prevention of post-op atrial tachyarrhythmia | 13                 | 10 mg/kg                 | 13              | N/A                               | N/A                | 299        | 61.3           | 82.6           | 302 61.9 81.8           |
| Alcalde      | 2006 | Patients undergoing CABG | 53%                       | 100%            | Prevention of post-op AF & AFL | 10                 | 1800                     | 1–3            | N/A                               | N/A                | 46         | 61             | 63             | 47 61.1 70.2           |
| Budeus       | 2006 | Patients undergoing CABG | 63%                       | 100%            | Prevention of post-op AF | 0.5                | 640                      | N/A            | 7                                | N/A                | 55         | 64.9           | 87.3           | 55 66.7 76.4           |
| Zebis        | 2007 | Patients undergoing CABG | 55%                       | 100%            | Prevention of post-op AF | 30                 | 1200                     | N/A            | 5                                | N/A                | 125        | 67             | 86             | 125 67 80              |
| Gu           | 2009 | Patients undergoing off-pump CABG | 61%                       | 100%            | Prevention of post-op AF | 21                 | 200 + 70 mg/kg           | 17             | N/A                               | N/A                | 100        | 73.6           | 75             | 110 74.2 72            |
| Balla        | 2011 | Newly diagnosed AF | NA                        | NA              | Rhythm control for AF | 1                  | 30 mg/kg                 | 1               | N/A                               | N/A                | 40         | 58.9           | 72.5           | 40 58.6 60             |
| Khitri       | 2012 | AF, AFL | 59%                       | 15%             | Rhythm control | 90                | 330                      | 30             | 200                              | 60                 | 108        | 64.9           | 73.1           | 162 62.4 64.9           |
| Riber        | 2013 | Lung cancer surgery | NA                        | 2%              | Prevention of post-op AF | 30                 | 1200                     | 5              | N/A                               | N/A                | 122        | 66             | 49             | 120 67 47              |
| Darkner      | 2014 | AF patients undergoing RFA | 50%                       | 7%              | Rhythm control after ablation | 180               | 400                      | 30             | 200                              | 26                 | 104        | 62             | 81             | 108 61 86              |

AF: Atrial fibrillation, AFL: Atrial flutter, CABG: Coronary artery bypass graft, IHD: Ischemic heart disease, MI: myocardial infarction, NA: Not available, NSVT: Non-sustained ventricular tachycardia, RFA: Radiofrequency ablation.
Baseline patient characteristics. Forty-three randomized control trials [2–20] were studied, and 11,395 patients were included (5792 patients in the amiodarone group, 5603 patients in the placebo group). Average age was 62.0 years for patients receiving amiodarone and 62.3 years for patients receiving placebo. Follow up time ranged from 12–54 months in studies with follow up ≥ 12 months. Indications for amiodarone therapy were suppression of atrial and ventricular arrhythmias, and maintenance dose for amiodarone ranged from 200 to 600 mg daily. Raw data for the adverse events is provided in the supplement material.

| First author | Year | Medical condition | Average ejection fraction | Percent with IHD | Reason for intervention | Mean follow-up (months) | Average Load dose (mg/day) | Average Load (day) | Average maintenance dose (mg) | Average maintenance (days) | Amiodarone arm | Placebo arm |
|--------------|------|-------------------|--------------------------|------------------|-------------------------|-------------------------|--------------------------|------------------|-----------------------------|--------------------------|----------------|-------------|
| Nicklas      | 1991 | Heart failure and frequent ventricular ectopy | 20% | 52% | Reduce sudden cardiac death | 12 | 400 | 28 | 200 | 215 | 49 | 56 | 83.7 | 52 | 59 | 86.5 |
| Ceremuzynski | 1992 | Post MI | Majority > 40% | 100% | Reduce mortality and ventricular arrhythmias | Improve mortality | 12 | 800 | 7 | 200–400 | 306 | 305 | 59.4 | 71.1 | 308 | 58.6 | 68.2 |
| Singh[36]    | 1995 | Patients with CHF and vent arrhythmia | <40% | 71% | Resuscitated ventricular fibrillation or arrhythmic death | All-cause mortality | 45 | 800 | 14 | 328 | 1246 | 336 | 65 | 99.1 | 338 | 66.1 | 98.8 |
| Cairns       | 1997 | Survivors of MI with frequent or repetitive PVCs | NA | 100% | Evaluate pulmonary toxicity | 21.5 | 20/kg | 14 | 200–400 | 365–730 | 606 | 64 | 82.5 | 596 | 64 | 82 |
| Julian       | 1997 | Survivors of MI and EF ≤ 40% | 30% | 35% | Evaluate pulmonary toxicity | 21 | 450 | 112 | 200 | 253–618 | 743 | 59.6 | 83.8 | 743 | 60.2 | 84.9 |
| Singh        | 1997 | Patients with CHF, COPD and patients undergoing surgery | 25–30% | NA | Evaluate pulmonary toxicity | 45 | 800 | 14 | 300–400 | 365–1620 | 269 | 65 | N/A | 250 | 65.8 | N/A |
| Kochiadakis  | 2000 | Paroxysmal AF | 55% | NA | Rhythm control | 22 | 12.5/kg | 14 | 200 | 720 | 65 | 63.2 | 52.3 | 60 | 62.8 | 51.7 |
| Channer      | 2004 | Persistent AF undergoing DCCV | 59% | 30% | Rhythm control | 54 | 800 | 14 | 200 | 364 | 61 | 66 | 77 | 38 | 68 | 79 |
| Vora         | 2004 | Patients with chronic rheumatic AF | 56% | NA | Rhythm or rate control | 12 | 600 | 10 | 200 | 355 | 48 | 39.5 | 47.9 | 48 | 38 | 45.8 |
| Singh        | 2005 | Persistent AF | 25% | 1% | Rhythm control | 12 | 700 | 28 | 200–300 | >365 | 267 | 67.1 | 99.3 | 137 | 67.7 | 99.3 |
| Vilvanathan  | 2016 | AF in patients post BMV | 58% | 1% | Rhythm control for AF | 12 | 500 | 28 | 200 | 365 | 44 | 38.8 | 20.5 | 45 | 37.6 | 34.1 |

AF: Atrial fibrillation, BMV: balloon mitral valvuloplasty, CHF: congestive heart failure, COPD: chronic obstructive pulmonary disease, DCCV: direct current cardioversion, EF: Ejection fraction, IHD: Ischemic heart disease, MI: myocardial infarction, NA: Not available, PVC: premature ventricular contraction.
Table 3
Risk of bias. Majority of trials included in this analysis were double blinded, decreasing both performance and detection biases.

| Bias                                | Study          | Judgement | Support for Judgement                      |
|-------------------------------------|----------------|-----------|--------------------------------------------|
| Random sequence generation          | Greco 1989     | Low risk  | Randomized on a consecutive basis          |
| (selection bias)                    | Hamer 1989     | Unknown   | Unclear method of randomization            |
|                                     | Hohnloser 1991 | Unknown   | Unclear method of randomization            |
|                                     | Nicklas 1991   | Unknown   | Unclear method of randomization            |
|                                     | Ceremuzynski 1992 | Unknown | Unclear method of randomization          |
|                                     | Meyer 1993     | Unknown   | Unclear method of randomization            |
|                                     | Mahmaran 1994  | Unknown   | Unclear method of randomization            |
|                                     | Donovan 1995   | Unknown   | Unclear method of randomization            |
|                                     | Singh 1995     | Unknown   | Unclear method of randomization            |
|                                     | Galve 1996     | Low risk  | Randomized on a consecutive basis          |
|                                     | Gentile 1996   | Unknown   | Unclear method of randomization            |
|                                     | Cairns 1997    | Low risk  | Computer generated randomization           |
|                                     | Daoud 1997     | Unknown   | Unclear method of randomization            |
|                                     | Julian 1997    | Low risk  | Computer generated randomization           |
|                                     | Singh 1997     | Unknown   | Unclear method of randomization            |
|                                     | Kochiadakis 1998 | Low risk | Randomized on a consecutive basis                 |
|                                     | Cotter 1999    | Unknown   | Unclear method of randomization            |
|                                     | Kochiadakis 1999 | Low risk | Randomized on a consecutive basis                 |
|                                     | Redle 1999     | Unknown   | Unclear method of randomization            |
|                                     | Bianconi 2000  | Unknown   | Unclear method of randomization            |
|                                     | Elizari 2000   | Low risk  | Random numeric sequence                     |
|                                     | Kochiadakis 2000 | Unknown | Unclear method of randomization            |
|                                     | Lee 2000       | Unknown   | Unclear method of randomization            |
|                                     | Peuhkurinen 2000 | Unknown | Unclear method of randomization            |
|                                     | Vardas 2000    | Unknown   | Unclear method of randomization            |
|                                     | Giri 2001      | Unknown   | Unclear method of randomization            |
|                                     | Maras 2001     | Unknown   | Unclear method of randomization            |
|                                     | White 2002     | Low risk  | Computer generated randomization           |
|                                     | Yagdi 2003     | Unknown   | Unclear method of randomization            |
|                                     | Auer 2004      | Low risk  | Randomization table                         |
|                                     | Channer 2004   | Low risk  | Random numeric sequence                     |
|                                     | Vora 2004      | Unknown   | Unclear method of randomization            |
|                                     | Mitchell 2005  | Low risk  | Computer generated randomization           |
|                                     | Singh 2005     | Low risk  | Permuted-block randomization               |
| Study Year   | Allocation Concealment | Risk Level | Method of Randomization                      |
|-------------|------------------------|------------|---------------------------------------------|
| Alcalde 2006| Unknown                | Unclear    | Method                                     |
| Budeus 2006 | Low risk               | Computer   | Generated Randomization                    |
| Zebis 2007  | Low risk               | Computer   | Generated Randomization                    |
| Gu 2009     | Low risk               | Computer   | Generated Randomization                    |
| Balla 2011  | Low risk               | Number     | Assignment by Envelope                     |
| Darkner 2012| Low risk               | Randomization Code |
| Khitri 2012 | Unknown                | Unclear    | Method                                     |
| Riber 2013  | Low risk               | Computer   | Generated Randomization                    |
| Vilvanathan 2016 | Unknown          | Unclear    | Method                                     |
| Greco 1989  | High risk              | Randomized on a consecutive basis |
| Hamer 1989  | Unknown                | Unclear    | Method                                     |
| Hohnloser 1991 | Unknown                | Unclear    | Method                                     |
| Nicklas 1991 | Unknown                | Unclear    | Method                                     |
| Ceremuzynski 1992 | Unknown            | Unclear    | Method                                     |
| Meyer 1993  | Unknown                | Unclear    | Method                                     |
| Mahmarian 1994 | Unknown               | Unclear    | Method                                     |
| Donovan 1995 | Unknown                | Unclear    | Method                                     |
| Singh 1995  | Unknown                | Unclear    | Method                                     |
| Galve 1996  | High risk              | Randomized on a consecutive basis |
| Gentile 1996 | Unknown                | Unclear    | Method                                     |
| Cairns 1997 | Low risk               | Computer   | Generated Randomization                    |
| Daoud 1997  | Unknown                | Unclear    | Method                                     |
| Julian 1997 | Low risk               | Computer   | Generated Randomization                    |
| Singh 1997  | Unknown                | Unclear    | Method                                     |
| Kochiadakis 1998 | High risk            | Randomized on a consecutive basis |
| Cotter 1999 | Unknown                | Unclear    | Method                                     |
| Kochiadakis 1999 | High risk           | Randomized on a consecutive basis |
| Redle 1999  | Unknown                | Unclear    | Method                                     |
| Bianconi 2000 | Unknown               | Unclear    | Method                                     |
| Elizari 2000 | Low risk               | Random     | Numeric Sequence                           |
| Kochiadakis 2000 | Unknown            | Unclear    | Method                                     |
| Lee 2000    | Unknown                | Unclear    | Method                                     |
| Peuhkurinen 2000 | Unknown           | Unclear    | Method                                     |
| Vardas 2000 | Unknown                | Unclear    | Method                                     |
| Study          | Risk Level | Randomization Method                  |
|---------------|------------|---------------------------------------|
| Giri 2001     | Low Risk   | Unclear method of randomization       |
| Maras 2001    | Low Risk   | Computer generated randomization      |
| White 2002    | Low Risk   | Computer generated randomization      |
| Yagdi 2003    | Low Risk   | Computer generated randomization      |
| Auer 2004     | Low Risk   | Randomization table                   |
| Channer 2004  | Low Risk   | Random numeric sequence               |
| Vora 2004     | Low Risk   | Computer generated randomization      |
| Mitchell 2005 | Low Risk   | Computer generated randomization      |
| Singh 2005    | Low Risk   | Permuted-block randomization          |
| Alcalde 2006  | Low Risk   | Computer generated randomization      |
| Budeus 2006   | Low Risk   | Computer generated randomization      |
| Zebis 2007    | Low Risk   | Computer generated randomization      |
| Gu 2009       | Low Risk   | Computer generated randomization      |
| Balla 2011    | Low Risk   | Number assignment by envelope         |
| Darkner 2012  | Low Risk   | Randomization code                    |
| Khitri 2012   | Low Risk   | Computer generated randomization      |
| Riber 2013    | Low Risk   | Computer generated randomization      |
| Vilvanathan 2016 | Low Risk   | Computer generated randomization      |

Blinding of participants and personnel (performance bias):

| Study          | Risk Level | Blinding Details                     |
|---------------|------------|-------------------------------------|
| Greco 1989    | High Risk  | Participants were not blinded        |
| Hamer 1989    | Low Risk   | Double blinded design                |
| Hohnloser 1991| High Risk  | Participants were not blinded        |
| Nicklas 1991  | Low Risk   | Double blinded design                |
| Ceremuzynski 1992 | Low Risk | Double blinded design               |
| Meyer 1993    | Low Risk   | Double blinded design                |
| Mahmarijan 1994| Low Risk | Double blinded design                |
| Donovan 1995  | Low Risk   | Double blinded design                |
| Singh 1995    | Low Risk   | Double blinded design                |
| Galve 1996    | Unknown    | Blinding not specified               |
| Gentile 1996  | Low Risk   | Double blinded design                |
| Cairns 1997   | Low Risk   | Double blinded design                |
| Daoud 1997    | Low Risk   | Double blinded design                |
| Julian 1997   | Low Risk   | Double blinded design                |
| Singh 1997    | Low Risk   | Double blinded design                |
| Study            | Risk   | Design                  |
|------------------|--------|-------------------------|
| Kochiadakis 1998 | Low    | Double blind design     |
| Cotter 1999      | Unknown| Blinding not specified  |
| Kochiadakis 1999 | Low    | Participants were blinded|
| Redle 1999       | Low    | Double blinded design   |
| Bianconi 2000    | Low    | Double blinded design   |
| Elizari 2000     | Low    | Double blinded design   |
| Kochiadakis 2000 | Low    | Participants were blinded|
| Lee 2000         | Low    | Double blinded design   |
| Peukhurinen 2000 | Unknown| Blinding not specified  |
| Vardas 2000      | Unknown| Blinding not specified  |
| Giri 2001        | Low    | Double blinded design   |
| Maras 2001       | Low    | Double blinded design   |
| White 2002       | Low    | Double blinded design   |
| Yagdi 2003       | Low    | Double blinded design   |
| Auer 2004        | Low    | Double blinded design   |
| Channer 2004     | Low    | Double blinded design   |
| Vora 2004        | Low    | Double blinded design   |
| Mitchell 2005    | Low    | Double blinded design   |
| Singh 2005       | Low    | Double blinded design   |
| Alcalde 2006     | Low    | Double blinded design   |
| Budeus 2006      | Low    | Double blinded design   |
| Zebis 2007       | Low    | Double blinded design   |
| Gu 2009          | Low    | Double blinded design   |
| Balla 2011       | Low    | Participants were blinded|
| Darkner 2012     | Low    | Double blinded design   |
| Khitri 2012      | Unknown| Blinding not specified  |
| Riber 2013       | Low    | Double blinded design   |
| Vilvanathan 2016 | Unknown| Blinding not specified  |

**Blinding of outcome assessment (detection bias)**

| Study            | Risk   | Design                  |
|------------------|--------|-------------------------|
| Greco 1989       | High   | Outcome assessors were not blinded|
| Hamer 1989       | Low    | Double blinded design   |
| Hohnloser 1991   | High   | Outcome assessors were not blinded|
| Nicklas 1991     | Low    | Double blinded design   |
| Ceremuzynski 1992 | Low   | Double blinded design   |
| Study             | Risk Level | Design             |
|------------------|------------|--------------------|
| Meyer 1993       | Low        | Double blinded     |
| Mahmarian 1994   | Low        | Double blinded     |
| Donovan 1995     | Low        | Double blinded     |
| Singh 1995       | Low        | Double blinded     |
| Galve 1996       | Unknown    | Blinding not specified |
| Gentile 1996     | Low        | Double blinded     |
| Cairns 1997      | Low        | Double blinded     |
| Daoud 1997       | Low        | Double blinded     |
| Julian 1997      | Low        | Double blinded     |
| Singh 1997       | Low        | Double blinded     |
| Kochiadakis 1998 | Low        | Double blinded     |
| Cotter 1999      | Unknown    | Blinding not specified |
| Kochiadakis 1999 | High       | Outcome assessors were not blinded |
| Redle 1999       | Low        | Double blinded     |
| Bianconi 2000    | Low        | Double blinded     |
| Elizari 2000     | Low        | Double blinded     |
| Kochiadakis 2000 | High       | Outcome assessors were not blinded |
| Lee 2000         | Low        | Double blinded     |
| Peuhkurinen 2000 | Unknown    | Blinding not specified |
| Vardas 2000      | Unknown    | Blinding not specified |
| Giri 2001        | Low        | Double blinded     |
| Maras 2001       | Low        | Double blinded     |
| White 2002       | Low        | Double blinded     |
| Yagdi 2003       | Low        | Double blinded     |
| Auer 2004        | Low        | Double blinded     |
| Channer 2004     | Low        | Double blinded     |
| Vora 2004        | Low        | Double blinded     |
| Mitchell 2005    | Low        | Double blinded     |
| Singh 2005       | Low        | Double blinded     |
| Alcalde 2006     | Low        | Double blinded     |
| Budeus 2006      | Low        | Double blinded     |
| Zebis 2007       | Low        | Double blinded     |
| Gu 2009          | Low        | Double blinded     |
| Balla 2011       | High       | Outcome assessors were not blinded |
| Darkner 2012     | Low        | Double blinded     |
| Khitri 2012      | Unknown    | Blinding not specified |
| Riber 2013       | Low        | Double blinded     |
| Incomplete outcome data addressed (attrition bias) | Vilvanathan 2016 | Unknown | Blinding not specified |
|--------------------------------------------------|------------------|---------|------------------------|
| Greco 1989                                        | Low risk         | No significant attrition |
| Hamer 1989                                        | Low risk         | No significant attrition |
| Hohnloser 1991                                    | Low risk         | No significant attrition |
| Nicklas 1991                                      | Low risk         | No significant attrition |
| Ceremuzynski 1992                                | Low risk         | No significant attrition |
| Meyer 1993                                        | Low risk         | No significant attrition |
| Mahmarian 1994                                   | Low risk         | No significant attrition |
| Donovan 1995                                     | Low risk         | No significant attrition |
| Singh 1995                                        | Low risk         | No significant attrition |
| Galve 1996                                        | Low risk         | No significant attrition |
| Gentile 1996                                     | Low risk         | No significant attrition |
| Cairns 1997                                       | Low risk         | No significant attrition |
| Daoud 1997                                        | Low risk         | No significant attrition |
| Julian 1997                                       | Low risk         | No significant attrition |
| Singh 1997                                        | Low risk         | No significant attrition |
| Kocsiadakis 1998                                 | Low risk         | No significant attrition |
| Cotter 1999                                       | Low risk         | No significant attrition |
| Kocsiadakis 1999                                 | Low risk         | No significant attrition |
| Redle 1999                                        | Low risk         | No significant attrition |
| Bianconi 2000                                     | Low risk         | No significant attrition |
| Elizari 2000                                      | High risk        | Early study termination |
| Kocsiadakis 2000                                 | Low risk         | No significant attrition |
| Lee 2000                                          | Low risk         | No significant attrition |
| Peukurinen 2000                                  | Low risk         | No significant attrition |
| Vardas 2000                                       | Low risk         | No significant attrition |
| Giri 2001                                         | Low risk         | No significant attrition |
| Maras 2001                                        | Low risk         | No significant attrition |
| White 2002                                        | Low risk         | No significant attrition |
| Yagdi 2003                                        | Low risk         | No significant attrition |
| Auer 2004                                         | Low risk         | No significant attrition |
| Channer 2004                                      | Low risk         | No significant attrition |
| Vora 2004                                         | Low risk         | No significant attrition |
| Year      | Risk  | Attrition          |
|-----------|-------|--------------------|
| Mitchell 2005 | Low risk |                     |
| Singh 2005    | Low risk | No significant attrition |
| Alcalde 2006 | Low risk | No significant attrition |
| Budeus 2006  | Low risk | No significant attrition |
| Zebis 2007   | Low risk | No significant attrition |
| Gu 2009      | Low risk | No significant attrition |
| Balla 2011   | Low risk | No significant attrition |
| Darkner 2012 | Low risk | No significant attrition |
| Khatri 2012  | Low risk | No significant attrition |
| Riber 2013   | Low risk | No significant attrition |
| Vilvanathan 2016 | Low risk | No significant attrition |

**Selective reporting (reporting bias)**

| Year      | Risk  |
|-----------|-------|
| Greco 1989 | Low risk |
| Hamer 1989 | Low risk |
| Hohnloser 1991 | Low risk |
| Nicklas 1991 | Low risk |
| Ceremuzynski 1992 | Low risk |
| Meyer 1993  | Low risk |
| Mahmarian 1994 | Low risk |
| Donovan 1995 | Low risk |
| Singh 1995  | Low risk |
| Galve 1996  | Low risk |
| Gentile 1996 | Low risk |
| Cairns 1997 | Low risk |
| Daoud 1997  | Low risk |
| Julian 1997 | Low risk |
| Singh 1997  | Low risk |
| Kochiadakis 1998 | Low risk |
| Cotter 1999 | Low risk |
| Kochiadakis 1999 | Low risk |
| Redle 1999  | Low risk |
| Bianconi 2000 | Low risk |
| Elizari 2000 | Low risk |
| Kochiadakis 2000 | Low risk |
| Lee 2000    | Low risk |
References of all identified studies were also hand-searched for inclusion to identify additional relevant studies [1].

All articles were then independently reviewed for inclusion in this analysis by two authors (M.M., M.R.). Inclusion criteria were: 1) randomized control trial, 2) documentation of adverse events and drug discontinuation due to adverse events, 3) presence of placebo arm. Data on sample size, follow up, and outcomes were then extracted. Discrepancies were discussed and resolved by consensus.

Primary outcomes of this analysis were pulmonary, hepatic, thyroid, ocular, cardiac, skin, and neurological adverse events, as well as drug discontinuation related to adverse side effects. Specific adverse events within each organ system were also reported. All adverse events were presented as incident rate per 10,000 person-years.

The Cochrane Risk of Bias table and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) System were utilized to determine risk of bias and quality of the outcomes in all trials incorporated into this analysis (Table 3).

RevMan version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration; Copenhagen, Denmark) was used to conduct the primary analysis. Relative risk (RR) was determined for all studies using the Mantel-Haenszel random effects model with 95% confidence interval (CI) to establish the likelihood of adverse events. A secondary analysis was also performed to determine the RR for studies with follow up < 12 months and ≥12 months. Sensitivity analyses were used to show the robustness of the results. Heterogeneity was calculated using I², a value which represents the percentage of variability in the effect risk estimate among studies due to heterogeneity rather than chance (I² <25% considered as low, I² between 25% and 75% as intermediate, I² >75% considered as high). Begg’s funnel plots method was utilized to investigate potential publication bias. A p-value of <0.05 was used to determine statistical significance.

| Reference               | Risk  |
|-------------------------|-------|
| Peuhkurinen 2000        | Low risk |
| Vardas 2000             | Low risk |
| Giri 2001               | Low risk |
| Maras 2001              | Low risk |
| White 2002              | Low risk |
| Yagdi 2003              | Low risk |
| Auer 2004               | Low risk |
| Channer 2004            | Low risk |
| Vora 2004               | Low risk |
| Mitchell 2005           | Low risk |
| Singh 2005              | Low risk |
| Alcalde 2006            | Low risk |
| Budeus 2006             | Low risk |
| Zebis 2007              | Low risk |
| Gu 2009                 | Low risk |
| Balla 2011              | Low risk |
| Darkner 2012            | Low risk |
| Khitri 2012             | Low risk |
| Riber 2013              | Low risk |
| Vilvanathan 2016        | Low risk |

Highlighted are studies with follow up ≥ 12 months.
| Organ System | Follow Up ≥ 12 Months, No. of Events (Events/10,000 Patient Year) | All, No. of Events (Events/10,000 Patient Year) |
|--------------|-------------|---------------|
|              | Amiodarone Arm | Placebo | RR (95% CI), P value | Amiodarone Arm | Placebo | RR (95% CI), P value |
| Pulmonary Adverse Events | | | | | | |
| Pulmonary Fibrosis | 8 (13) | 6 (11) | 8 (12) | 6 (11) | | |
| Cough | 0 (0) | 0 (0) | 1 (1) | 0 (0) | | |
| Lung Infiltrates | 0 (0) | 0 (0) | 1 (1) | 0 (0) | | |
| Unspecified | 77 (124) | 40 (70) | 77 (115) | 40 (65) | | |
| Total | 85 (136) | 46 (81) | 1.74 (1.21–2.50), 0.003 | 87 (129) | 46 (74) | 1.77 (1.24–2.52), 0.002 |
| Thyroid Adverse Events | | | | | | |
| Clinical Hyperthyroidism | 19 (36) | 4 (8) | 19 (33) | 5 (9) | | |
| Clinical Hypothyroidism | 27 (52) | 0 (0) | 27 (47) | 0 (0) | | |
| Subclinical Change in TFT | 13 (25) | 3 (6) | 40 (70) | 8 (15) | | |
| Unspecified | 24 (46) | 5 (11) | 29 (51) | 9 (17) | | |
| Total | 83 (159) | 12 (25) | 5.32 (2.99–9.44), < 0.001 | 115 (201) | 22 (42) | 4.44 (2.87–6.89), < 0.001 |
| Liver Adverse Events | | | | | | |
| Liver Failure | 0 (0) | 0 (0) | 0 (0) | 0 (0) | | |
| Elevated Liver Enzymes | 8 (15) | 3 (6) | 10 (18) | 5 (10) | | |
| Unspecified | 21 (40) | 8 (17) | 21 (37) | 8 (15) | | |
| Total | 29 (56) | 11 (23) | 2.42 (1.23–4.74), 0.01 | 31 (54) | 13 (25) | 2.27 (1.20–4.29), 0.01 |
| Cardiac Adverse Events | | | | | | |
| Bradycardia/Rhythmias | 100 (192) | 34 (72) | 267 (468) | 128 (244) | | |
| Hypotension | 0 (0) | 0 (0) | 98 (172) | 65 (124) | | |
| Long QT | 5 (10) | 0 (0) | 18 (32) | 0 (0) | | |
| Torsade de Pointes | 0 (0) | 0 (0) | 0 (0) | 0 (0) | | |
| Worsening Heart Failure | 1 (2) | 1 (2) | 5 (9) | 5 (10) | | |
| Unspecified Conduction Disease | 0 (0) | 0 (0) | 46 (81) | 32 (61) | | |
| Unspecified | 0 (0) | 0 (0) | 6 (11) | 6 (11) | | |
| Total | 106 (203) | 35 (74) | 2.76 (1.91–3.98), < 0.001 | 440 (771) | 236 (450) | 1.94 (1.39–2.71), < 0.001 |
| Skin Adverse Events | | | | | | |
| Blue/Gray Discoloration of Skin | 2 (4) | 3 (6) | 2 (4) | 3 (6) | | |
| Photosensitivity | 1 (2) | 0 (0) | 11 (19) | 0 (0) | | |
| Unspecified Rash/Flushing | 21 (40) | 9 (19) | 33 (58) | 9 (17) | | |
| Total | 24 (46) | 12 (25) | 1.51 (0.73–3.11), 0.26 | 46 (81) | 12 (23) | 1.99 (1.04–3.78), 0.04 |
| GI Adverse Events | | | | | | |
| Dyspepsia/Nausea/Vomiting | 20 (38) | 16 (34) | 122 (214) | 74 (141) | | |
| Diarrhea | 0 (0) | 0 (0) | 8 (14) | 4 (8) | | |
| Unspecified | 35 (67) | 25 (53) | 62 (109) | 33 (63) | | |
| Total | 55 (105) | 41 (86) | 1.36 (0.91–2.04), 0.14 | 192 (336) | 111 (212) | 1.63 (1.18–2.24), 0.003 |
| Neuro adverse events | Ataxia or gait disturbances | Headache | Dizziness | Tremor | Peripheral neuropathy | Unspecified |
|----------------------|----------------------------|----------|-----------|--------|-----------------------|-------------|
|                      | 17 (33)                    | 6 (13)   | 17 (30)   | 6 (11) |                       |             |
| Ocular adverse events| Corneal microdeposits      | 9 (17)   | 0 (0)     | 9 (16) | 0 (0)                 |             |
|                      | 19 (40)                    | 0 (0)    | 0 (0)     | 1 (2)  | 0 (0)                 |             |
|                      | Blue vision spots          | 0 (0)    | 0 (0)     | 1 (2)  | 0 (0)                 |             |
|                      | Unspecified                | 10 (19)  | 5 (11)    | 10 (18)| 5 (10)                |             |
| Total                | 19 (36)                    | 5 (11)   | 4.41 (0.48–0.86), 0.19 | 21 (37) | 5 (10)                | 3.01 (0.87–10.36), 0.08 |
| Drug discontinuation | 552 (1230)                 | 284 (650)| 2.01 (1.46–2.78), < 0.001 | 795 (1614)| 431 (896)          | 1.79 (1.45–2.19), < 0.001 |
### Table 1: Pulmonary adverse events

| Study or Subgroup | Amiodarone Events | Placebo Events | Risk Ratio M-H, Random, 95% CI Year |
|-------------------|-------------------|----------------|-------------------------------------|
| Hamer 1989        | 0 8 0 7           |                | Not estimable 1989                  |
| Greco 1989        | 0 7 0 7           |                | Not estimable 1989                  |
| Nicklas 1991      | 0 49 0 52         |                | Not estimable 1991                  |
| Ceremuzynski 1992 | 1 305 0 308 1.2% 3.03 [0.12, 74.07] 1992 |                |                                    |
| Meyer 1993        | 0 5 0 5           |                | Not estimable 1993                  |
| Mahmoran 1994     | 0 8 0 4           |                | Not estimable 1994                  |
| Singh 1995        | 10 1260 4 1268 9.4% 2.52 [0.79, 8.00] 1995 |                |                                    |
| Donovan 1995      | 0 1 0 1           |                | Not estimable 1995                  |
| Galve 1996        | 0 2 0 2           |                | Not estimable 1996                  |
| Gentle 1996       | 0 12 0 11         |                | Not estimable 1996                  |
| Cairns 1997       | 23 1086 7 1068 17.8% 3.23 [1.39, 7.50] 1997 |                |                                    |
| Julian 1997       | 39 1300 30 1300 57.3% 1.30 [0.81, 2.08] 1997 |                |                                    |
| Singh 1997        | 10 1009 4 938 9.5% 2.32 [0.73, 7.38] 1997 |                |                                    |
| Daoud 1997        | 0 5 0 5           |                | Not estimable 1997                  |
| Kochiadakis 1998  | 0 0 0 0           |                | Not estimable 1998                  |
| Kochiadakis 1999  | 0 3 0 3           |                | Not estimable 1999                  |
| Redu 1999         | 0 2 0 2           |                | Not estimable 1999                  |
| Cotter 1999       | 0 4 0 4           |                | Not estimable 1999                  |
| Lee 2000          | 0 4 0 4           |                | Not estimable 2000                  |
| Kochiadakis 2000  | 0 119 0 110       |                | Not estimable 2000                  |
| Peuhkurinien 2000 | 0 0 0 0           |                | Not estimable 2000                  |
| Vardas 2000       | 0 9 0 8           |                | Not estimable 2000                  |
| Bianconi 2000     | 0 1 0 1           |                | Not estimable 2000                  |
| Elizari 2000      | 1 271 0 266 1.2% 2.94 [0.12, 71.97] 2000 |                |                                    |
| Maras 2001        | 0 3 0 3           |                | Not estimable 2001                  |
| Giri 2001         | 0 3 0 3           |                | Not estimable 2001                  |
| White 2002        | 0 15 0 13         |                | Not estimable 2002                  |
| Yagdi 2003        | 0 6 0 7           |                | Not estimable 2003                  |
| Channer 2004      | 0 275 0 171       |                | Not estimable 2004                  |
| Auer 2004         | 0 2 0 2           |                | Not estimable 2004                  |
| Vora 2004         | 0 48 0 48         |                | Not estimable 2004                  |
| Singh 2005        | 2 734 1 377 2.2% 1.03 [0.09, 11.29] 2005 |                |                                    |
| Mitchell 2005     | 1 12 0 12 1.3% 3.00 [0.13, 67.06] 2005 |                |                                    |
| Alcaldé 2006      | 0 1 0 1           |                | Not estimable 2006                  |
| Budeus 2006       | 0 2 0 2           |                | Not estimable 2006                  |
| Zebis 2007        | 0 10 0 10         |                | Not estimable 2007                  |
| Gu 2009           | 0 5 0 6           |                | Not estimable 2009                  |
| Balla 2011        | 0 0 0 0           |                | Not estimable 2011                  |
| Khitri 2012       | 0 27 0 41         |                | Not estimable 2012                  |
| Darkner 2012      | 0 52 0 54         |                | Not estimable 2012                  |
| Riber 2013        | 0 10 0 10         |                | Not estimable 2013                  |
| Vilvanathan 2016  | 0 44 0 45         |                | Not estimable 2016                  |

**Total (95% CI)**: 6719 6179 100.0% 1.77 [1.24, 2.52]

**Total events**: 87 46

**Heterogeneity**: Tau² = 0.00; Chi² = 4.73, df = 7 (P = 0.69); I² = 0%

**Test for overall effect**: Z = 3.13 (P = 0.002)

---

**Fig. 1.** Pulmonary adverse events. “Total” represents total events per 10,000 person-years. The incident rate of pulmonary adverse events per 10,000 person-years was higher in the amiodarone group versus placebo (129 vs 74; RR: 1.77; 95% CI [1.24–2.52], P = 0.002, I²: 0%).
Fig. 2. Thyroid adverse events. "Total" represents total events per 10,000 person-years. The incident rate of thyroid adverse events per 10,000 person-years was higher in the amiodarone group versus placebo (201 vs 42; RR: 4.44; 95% CI [2.87–6.89], P < 0.001, I²: 0%).
Fig. 3. Liver adverse events. "Total represents total events per 10,000 person-years. Liver adverse events were rare, but the rate of liver adverse events per 10,000 person-years was still higher in the amiodarone group versus placebo (54 vs 25; RR: 2.27; 95% CI [1.20–4.29]; P = 0.01, I^2: 0%)."
Fig. 4. Cardiac adverse events. “Total” represents total events per 10,000 person-years. Cardiac adverse events were the most commonly reported adverse events for both groups. The incident rate of cardiac adverse events per 10,000 person-years was higher in patients receiving amiodarone versus placebo (771 vs 450; RR: 1.94; 95% CI [1.39–2.71], P = 0.0001, I²: 23%).
The incident rate of skin adverse events was higher in the amiodarone group versus placebo (81 vs 23; RR: 1.99; 95% CI [1.04–3.78], P = 0.04, I²: 0%).

**Fig. 5.** Skin adverse events. “Total” represents total events per 10,000 person-years.
**Fig. 6.** Gastrointestinal adverse events. “Total” represents total events per 10,000 person-years. The incident rate of gastrointestinal adverse events was higher in patients receiving amiodarone compared to those receiving placebo (336 vs 212; RR: 1.63; 95% CI [1.18–2.24], P = 0.003, I²: 14%).

| Study or Subgroup | Amiodarone Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Year |
|-------------------|-------------------|-------|----------------|-------|--------|-------------------------------|------|
| Greco 1989        | 0                 | 7     | 0              | 7     | Not estimable                   | 1989 |
| Harner 1989       | 4                 | 8     | 0              | 7     | 1.3% 8.00 [0.51, 126.67]         | 1989 |
| Nicklas 1991      | 0                 | 49    | 0              | 52    | Not estimable                   | 1991 |
| Cermenyński 1992  | 0                 | 305   | 2              | 308   | 1.1% 0.20 [0.01, 4.19]           | 1992 |
| Meyer 1993        | 0                 | 5     | 0              | 5     | Not estimable                   | 1993 |
| Mahmariyan 1994   | 0                 | 8     | 0              | 4     | Not estimable                   | 1994 |
| Donovan 1995      | 0                 | 1     | 0              | 1     | Not estimable                   | 1995 |
| Singh 1995        | 20                | 1260  | 16             | 1268  | 17.2% 1.26 [0.65, 2.42]          | 1995 |
| Galve 1996        | 0                 | 2     | 2              | 2     | 1.5% 0.20 [0.02, 2.64]           | 1996 |
| Gentile 1996      | 0                 | 12    | 0              | 11    | Not estimable                   | 1996 |
| Dassou 1997       | 1                 | 5     | 1              | 5     | 1.6% 1.00 [0.08, 11.99]          | 1997 |
| Julian 1997       | 22                | 1300  | 15             | 1300  | 17.2% 1.47 [0.76, 2.81]          | 1997 |
| Cairns 1997       | 13                | 1086  | 8              | 1068  | 10.9% 1.60 [0.67, 3.84]          | 1997 |
| Kochiadakis 1998  | 0                 | 0     | 0              | 0     | Not estimable                   | 1998 |
| Cotter 1999       | 0                 | 4     | 0              | 4     | Not estimable                   | 1999 |
| Kochiadakis 1999  | 0                 | 3     | 0              | 3     | Not estimable                   | 1999 |
| Redle 1999        | 2                 | 2     | 0              | 2     | 1.5% 5.00 [0.38, 66.01]          | 1999 |
| Bianconi 2000     | 0                 | 1     | 0              | 1     | Not estimable                   | 2000 |
| Elizas 2000       | 0                 | 271   | 0              | 266   | Not estimable                   | 2000 |
| Lee 2000          | 0                 | 4     | 0              | 4     | Not estimable                   | 2000 |
| Peuhkurinen 2000  | 4                 | 0     | 2              | 0     | Not estimable                   | 2000 |
| Yardas 2000       | 0                 | 9     | 0              | 8     | Not estimable                   | 2000 |
| Kochiadakis 2000  | 0                 | 119   | 0              | 110   | Not estimable                   | 2000 |
| Giri 2001         | 32                | 3     | 16             | 3     | Not estimable                   | 2001 |
| Maras 2001        | 0                 | 3     | 0              | 3     | Not estimable                   | 2001 |
| White 2002        | 32                | 15    | 16             | 13    | Not estimable                   | 2002 |
| Yapli 2003        | 0                 | 6     | 0              | 7     | Not estimable                   | 2003 |
| Auer 2004         | 13                | 2     | 13             | 2     | Not estimable                   | 2004 |
| Yora 2004         | 0                 | 48    | 0              | 48    | Not estimable                   | 2004 |
| Channer 2004      | 0                 | 275   | 0              | 171   | Not estimable                   | 2004 |
| Mitchell 2005     | 8                 | 12    | 6              | 12    | 15.8% 1.33 [0.67, 2.67]          | 2005 |
| Singh 2005        | 0                 | 734   | 0              | 377   | Not estimable                   | 2005 |
| Budeus 2006       | 3                 | 2     | 0              | 2     | Not estimable                   | 2006 |
| Acalde 2006       | 1                 | 1     | 1              | 1     | 7.1% 1.00 [0.32, 3.10]           | 2006 |
| Zebis 2007        | 0                 | 10    | 0              | 10    | Not estimable                   | 2007 |
| Gu 2009           | 2                 | 5     | 1              | 6     | 2.3% 2.40 [0.30, 19.34]          | 2009 |
| Balle 2011        | 2                 | 0     | 0              | 0     | Not estimable                   | 2011 |
| Khtri 2012        | 7                 | 27    | 5              | 41    | 8.2% 2.13 [0.75, 6.01]           | 2012 |
| Darkeni 2012      | 26                | 52    | 7              | 54    | 14.2% 3.86 [1.84, 8.11]          | 2012 |
| Riber 2013        | 0                 | 10    | 0              | 10    | Not estimable                   | 2013 |
| Vilvanathan 2016  | 0                 | 44    | 0              | 45    | Not estimable                   | 2016 |

**Total** (95% CI) 5710 5241 100.0% 1.63 [1.18, 2.24]

**Total events** 192 111

Heterogeneity: Tau² = 0.05; Chi² = 13.88, df = 12 (P = 0.31); I² = 14%

Test for overall effect: Z = 2.96 (P = 0.003)
Fig. 7. Neurological adverse events. "Total" represents total events per 10,000 person-years. The incident rate of neurological adverse events per 10,000 person-years was higher in the amiodarone group versus placebo (140 vs 76; RR: 1.93; 95% CI [1.41–2.65], P < 0.001, I²: 0%).
Fig. 8. Ocular adverse events. "Total" represents total events per 10,000 person-years. The incident rate of ocular adverse events per 10,000 person-years was higher in patients receiving amiodarone versus placebo; however, this never reached statistical significance (37 vs 10; RR: 3.01; 95% CI [0.87–10.36], P = 0.08, I²: 30%).

| Study or Subgroup | Amiodarone Events | Amiodarone Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI Year | Risk Ratio M-H, Random, 95% CI |
|-------------------|-------------------|------------------|----------------|--------------|--------|------------------------------------|--------------------------------|
| Greco 1989        | 0                 | 7                | 0              | 7            | Not estimable | 1989 |                                   |
| Hamer 1989        | 1                 | 8                | 0              | 7            | 13.2%   | 2.67 [0.13, 56.63] 1989            |
| Nicklas 1991      | 0                 | 49               | 0              | 52           | Not estimable | 1991 |
| Cerezuynski 1992  | 9                 | 305              | 0              | 308          | 14.8%   | 19.19 [1.12, 328.20] 1992         |
| Meyer 1993        | 0                 | 5                | 0              | 5            | Not estimable | 1993 |
| Mahmalian 1994    | 0                 | 8                | 0              | 4            | Not estimable | 1994 |
| Donovan 1995      | 1                 | 1                | 0              | 1            | 17.6%   | 3.00 [0.24, 37.67] 1995           |
| Singh 1995        | 0                 | 1260             | 0              | 1268         | Not estimable | 1995 |
| Gentile 1996      | 0                 | 12               | 0              | 11           | Not estimable | 1996 |
| Galve 1996        | 0                 | 2                | 0              | 2            | Not estimable | 1996 |
| Daoud 1997        | 0                 | 5                | 0              | 5            | Not estimable | 1997 |
| Julian 1997       | 5                 | 1300             | 5              | 1300         | 40.1%   | 1.09 [0.29, 4.45] 1997           |
| Cairns 1997       | 5                 | 1086             | 0              | 1068         | 14.4%   | 10.82 [0.60, 195.40] 1997        |
| Kochiakdis 1998   | 0                 | 0                | 0              | 0            | Not estimable | 1998 |
| Cotter 1999       | 0                 | 4                | 0              | 4            | Not estimable | 1999 |
| Kochiakdis 1999   | 0                 | 3                | 0              | 3            | Not estimable | 1999 |
| Redle 1999        | 0                 | 2                | 0              | 2            | Not estimable | 1999 |
| Eliari 2000       | 0                 | 271              | 0              | 266          | Not estimable | 2000 |
| Lee 2000          | 0                 | 4                | 0              | 4            | Not estimable | 2000 |
| Peuhkurinen 2000  | 0                 | 0                | 0              | 0            | Not estimable | 2000 |
| Vardas 2000       | 0                 | 9                | 0              | 8            | Not estimable | 2000 |
| Kochiakdis 2000   | 0                 | 119              | 0              | 110          | Not estimable | 2000 |
| Bianconi 2000     | 0                 | 1                | 0              | 1            | Not estimable | 2000 |
| Giri 2001         | 0                 | 3                | 0              | 3            | Not estimable | 2001 |
| Maras 2001        | 0                 | 3                | 0              | 3            | Not estimable | 2001 |
| White 2002        | 0                 | 15               | 0              | 13           | Not estimable | 2002 |
| Yaghi 2003        | 0                 | 6                | 0              | 7            | Not estimable | 2003 |
| Auer 2004         | 0                 | 2                | 0              | 2            | Not estimable | 2004 |
| Vora 2004         | 0                 | 48               | 0              | 48           | Not estimable | 2004 |
| Chaner 2004       | 0                 | 275              | 0              | 171          | Not estimable | 2004 |
| Singh 2005        | 0                 | 734              | 0              | 377          | Not estimable | 2005 |
| Mitchell 2005     | 0                 | 12               | 0              | 12           | Not estimable | 2005 |
| Budeus 2006       | 0                 | 2                | 0              | 2            | Not estimable | 2006 |
| Alcalde 2006      | 0                 | 1                | 0              | 1            | Not estimable | 2006 |
| Zebris 2007       | 0                 | 10               | 0              | 10           | Not estimable | 2007 |
| Gu 2009           | 0                 | 5                | 0              | 6            | Not estimable | 2009 |
| Ball 2011         | 0                 | 0                | 0              | 0            | Not estimable | 2011 |
| Khtri 2012        | 0                 | 27               | 0              | 41           | Not estimable | 2012 |
| Darkner 2012      | 0                 | 52               | 0              | 54           | Not estimable | 2012 |
| Riber 2013        | 0                 | 10               | 0              | 10           | Not estimable | 2013 |
| Vilvanathan 2016  | 0                 | 44               | 0              | 45           | Not estimable | 2016 |

Total (95% CI): 5710 5241 100.0% 3.01 [0.87, 10.36]

Total events: 21

Heterogeneity: Tau² = 0.59; Chi² = 5.69, df = 4 (P = 0.22); I² = 30%

Test for overall effect: Z = 1.74 (P = 0.08)
Fig. 9. Rates of drug discontinuation. "Total" represents total events per 10,000 person-years. The incident rate of drug discontinuation secondary to side effects per 10,000 person-years was higher in the amiodarone group versus placebo (1614 vs 896; RR: 1.79; 95% CI [1.45–2.19], P < 0.001, I²: 43%).
Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dib.2019.104835.

References

[1] M. Ruzieh, M.K. Moroi, N.M. Aboujamous, M. Ghahramani, G.V. Naccarelli, J. Mandrola, A.J. Foy, Meta-analysis comparing the relative risk of adverse events for amiodarone versus placebo, 50002–9149(19)31046-X, Am. J. Cardiol. (2019), https:// doi.org/10.1016/j.amjcard.2019.09.008 [Epub ahead of print].

[2] R. Greco, D.’Alterio, M. Schiattarella, B. Musto, S. Wolff, A.S. Boccia, N. Mininni. Intravenous amiodarone in acute anterior myocardial infarction: a controlled study, Cardiovasc. Drugs Ther. 2 (6) (1989) 791–794.

[3] A.W. Hamer, L.B. Alkes, J.A. Johns, Beneficial effects of low dose amiodarone in patients with congestive cardiac failure: a placebo-controlled trial, J. Am. Coll. Cardiol. 14 (7) (1989) 1768–1774.

[4] S.H. Hohnloser, T. Meinertz, T. Dammacher, K. Steiert, E. Jahnchen, M. Zehender, G. Freidrich, H. Just, Electrocardiographic and antiarrhythmic effects of intravenous amiodarone: results of a prospective, placebo-controlled study, Am. Heart J. 121 (1 Pt 1) (1991) 89–95.

[5] B.J. Meyer, F.W. Amann, Additional antiangiogenic efficacy of amiodarone in patients with limiting angina pectoris, Am. Heart J. 125 (4) (1993) 996–1001.

[6] J.J. Mahmarian, F.W. Smart, J.A. Moyé, J.B. Young, M.J. Francis, C.L. Kingsry, M.S. Verani, C.M. Pratt, Exploring the minimal dose of amiodarone with antiarrhythmic and hemodynamic activity, Am. J. Cardiol. 74 (7) (1994) 681–686.

[7] K.D. Donovan, B.M. Power, B.E. Hockings, G.J. Dobb, K.Y. Lee, Intravenous flecainide versus amiodarone for recent-onset atrial fibrillation, Am. J. Cardiol. 75 (10) (1995) 693–697.

[8] E. Galve, T. Rius, R. Ballester, M.A. Artaza, J.M. Arnau, D. Garcia-Dorado, J. Soler-Soler, Intravenous amiodarone in treatment of recent-onset atrial fibrillation: results of a randomized, controlled study, J. Am. Coll. Cardiol. 27 (5) (1996) 1079–1082.

[9] S. Gentile, A. Vignoli, G. Tommasielli, P. Guadalerio, G. Mirra, D. Manzella, A. Varricchio, D. Simeone, M. Varricchio, Effect of low dose Amiodarone on the incidence of sudden death in elderly patients with congestive heart failure: a double-blind, placebo-controlled study, Arch. Gerontol. Geriat. 22 (Suppl. 1) (1996) 191–195.

[10] E.G. Daoud, S.A. Strickberger, K.C. Man, R. Goyal, G.M. Deeb, S.F. Bolling, F.D. Pagani, C. Bitar, M.D. Meissner, F. Morady, Preoperative amiodarone as prophylaxis against atrial fibrillation after heart surgery, N. Engl. J. Med. 337 (25) (1997) 1785–1791.

[11] G.E. Kochiadakis, N.E. Igoumenidis, E.N. Simantirakis, M.E. Marketou, F.I. Parthenakis, N.E. Mezilis, P.E. Vardas, Intravenous propafenone versus intravenous amiodarone in the management of atrial fibrillation of recent onset: a placebo-controlled study, Pacing Clin. Electrophysiol. 21 (11 Pt 2) (1998) 2475–2479.

[12] G. Cotter, C. Matt, E. Kaluski, E. Metzker-Cotter, M. Koren, I. Litinsky, R. Simantov, Y. Moskovich, R. Zaidenstein, E. Peleg, Z. Vered, A. Golik, Conversion of recent onset paroxysmal atrial fibrillation to normal sinus rhythm: the effect of no treatment and high-dose amiodarone. A randomized, placebo-controlled study, Eur. Heart J. 20 (24) (1999) 1833–1842.

[13] G.E. Kochiadakis, N.E. Igoumenidis, M.C. Solomou, M.D. Kaleboubas, G.I. Chlouverakis, P.E. Vardas, Efficacy of amiodarone for the termination of persistent atrial fibrillation, Am. J. Cardiol. 83 (1) (1999) 58–61.

[14] J.D. Redlie, S. Khurana, R. Marzan, P.A. McCullough, J.R. Stewart, D.C. Westveer, W.W. O’Neill, J.S. Bassett, N.A. Tepe, H.I. Frumin, Prophylactic oral amiodarone compared with placebo for prevention of atrial fibrillation after coronary artery bypass surgery, Am. Heart J. 138 (1 Pt. 1) (1999) 144–150.

[15] L. Bianconi, A. Castro, M. Dinelli, P. Albani, A. Pappalardo, E. Richardi, M. Santini, Comparison of intravenously administered dofetilide versus amiodarone in the acute termination of atrial fibrillation and flutter. A multicentre, randomized, double-blind, placebo-controlled study, Eur. Heart J. 21 (15) (2000) 1265–1273.

[16] M.V. Elizari, J.M. Martinez, C. Belziti, M. Ciruzzi, R. Perez de la Hoz, A. Sinisi, J. Carbajales, O. Scapin, J. Garguechivich, L. Girotti, A. Cagide, Morbidity and mortality following early administration of amiodarone in acute myocardial infarction. GEMICA study investigators, GEMA Group, Buenos Aires, Argentina. Grupo de Estudios Multicentricos en Argentina, Eur. Heart J. 21 (3) (2000) 198–205.

[17] S.H. Hohnloser, T. Meinertz, T. Dammacher, K. Steiert, E. Jahnchen, M. Zehender, G. Freidrich, H. Just, Electrocardiographic and antiarrhythmic effects of intravenous amiodarone: results of a prospective, placebo-controlled study, Cardiovasc. Drugs Ther. 2 (6) (1989) 791–794.

[18] K. Peuhkurinen, M. Niemelä, A. Ylitalo, M. Linnaluoto, M. Lilja, J. Juvonen, Effectiveness of amiodarone as a single oral dose for recent-onset atrial fibrillation, Am. J. Cardiol. 85 (4) (2000) 462–465.

[19] P.E. Vardas, G.E. Kochiadakis, N.E. Igoumenidis, A.M. Tsatsakis, E.N. Simantirakis, G.I. Chlouverakis, Amiodarone as a first-choice drug for restoring sinus rhythm in patients with atrial fibrillation: a randomized, controlled study, Chest 117 (6) (2000) 1538–1545.

[20] S. Fass, C.M. White, A.B. Dunn, K. Felton, L. Freeman-Bosco, P. Reddy, J.P. Tsikouris, H.A. Wilcox, J. Kluger, Oral amiodarone for prevention of atrial fibrillation after open heart surgery, the Atrial Fibrillation Suppression Trial (AFIST): a randomised placebo-controlled trial, Lancet 357 (9259) (2001) 830–836.