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Drug-Induced Atrial Fibrillation

Yaman Kaakeh, PharmD[1,2], **Brian R. Overholser, PharmD**[1,2], **John C. Lopshire, MD, PhD**[2,3], and **James E. Tisdale, PharmD**[1,2]

[1]Department of Pharmacy Practice, College of Pharmacy, Purdue University, West Lafayette & Indianapolis, Indiana, USA

[2]Department of Medicine, School of Medicine, Indiana University, Indianapolis, Indiana, USA

[3]Krannert Institute of Cardiology, Indiana University, Indianapolis, Indiana, USA

Abstract

Atrial fibrillation (AF) is a common cardiac arrhythmia that is associated with severe consequences, including symptoms, hemodynamic instability, increased cardiovascular mortality, and stroke. While other arrhythmias such as torsades de pointes and sinus bradycardia are more typically thought of as drug-induced, AF may also be precipitated by drug therapy, although ascribing causality to drug-associated AF is more difficult than with other drug-induced arrhythmias. Drug-induced AF is more likely to occur in patients with risk factors and comorbidities that commonly coexist with AF, such as advanced age, alcohol consumption, family history of AF, hypertension, thyroid dysfunction, sleep apnea, and heart disease. New-onset AF has been associated with cardiovascular drugs such as adenosine, dobutamine, and milrinone. In addition, medications such as corticosteroids, ondansetron, and antineoplastic agents such as paclitaxel, mitoxantrone, and anthracyclines have been reported to induce AF. Whether bisphosphonate drugs are associated with new onset AF remains controversial and requires further study. The potential contribution of specific drug therapy should be considered when patients present with new onset AF.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice.[1] The prevalence of AF is 0.4–1%, and increases with age.[2, 3] AF is associated with symptoms, diminished quality of life, and leads to a doubling of the incidence of cardiovascular mortality and a 2–7-fold increase in the incidence of stroke.[1]

Etiologies and predisposing factors for AF are those that promote atrial and pulmonary vein dilatation and atrial fibrosis, and include hypertension, heart failure, valvular heart disease, coronary artery disease, inflammatory or infiltrative atrial disease, hyperthyroidism and a genetic predisposition (familial AF).[4] In addition, although drugs are more commonly recognized as causes of other arrhythmias such as torsades de pointes or sinus bradycardia, therapy with specific drugs has been associated with the development of AF.

Address for correspondence: James E. Tisdale, PharmD, College of Pharmacy, Purdue University, W7555 Myers Building, WHS, 1001 West 10th Street, Indianapolis, IN, USA 46202, 317-613-2315, ext 306, 317-613-2316 (fax), jtisdale@iupui.edu.

Drug-induced AF was comprehensively reviewed by van der Hooft et al in 2004.[5] Since that time, new information has become available regarding drug-induced AF, particularly in association with corticosteroids, as well as the controversial association of bisphosphonate drugs with AF. The purpose of this paper is to update and comprehensively review drug-induced AF, including specific drugs associated with this arrhythmia, incidences, and potential mechanisms. Illicit drugs and caffeine are beyond the scope of this review and are therefore not discussed.

Ascribing causality to drug-associated AF is difficult, due to the nature of reports of drug-induced AF, as well as due to the fact that, unlike drug-induced torsades de pointes, for which there is a biomarker of risk (QT interval), there is no clear biomarker for drug-induced AF. For some drugs, there are multiple studies assessing a potential association between a specific drug and new-onset AF, but many of the studies show conflicting results. Throughout this manuscript, we have used a literature-derived “Quality of Evidence” designation to indicate the quality of evidence associating specific drugs with the occurrence of AF (Table 1).[6]

1.1 Potential Mechanisms of Drug-Induced AF

The initiation of AF requires a trigger impulse, while the maintenance of AF requires an electrophysiological substrate.[4] There is evidence that triggering ectopic impulses can occur in pulmonary and other thoracic veins, near the atrial junction, or directly in the atrial muscle. Once an ectopic impulse is propagated to the atrium, a substrate is necessary to perpetuate the impulse through reentrant circuits. The susceptibility of the atria to reentry is related to cardiac wavelength; defined as the product of the atrial conduction velocity and the atrial effective refractory period (ERP). However, it has been suggested that rapid focal activity alone can prompt the generation of AF.[7, 8] Theoretically, drug-induced AF can occur through either pharmacologic stimulation that promotes ectopic impulses or by modulating the underlying substrate by shortening of cardiac wavelengths.

Some important risk factors for the generation of AF include advanced age, alcohol consumption, cardiac surgery, and a family history of AF. Additionally, comorbid conditions such as chronic obstructive pulmonary disease, hypertension, hyperthyroidism, sleep apnea, previous myocardial infarction and heart failure commonly coexist with the development of AF. Many of these risk factors influence underlying physiological and pathophysiological conditions that promote a substrate for AF. These risk factors occur frequently in patients where drug-induced AF is suspected and it is important to consider these when evaluating the potential for drug-induced AF.

Common underlying conditions that may induce AF include activation of the autonomic nervous system, local or systemic inflammation, atrial fibrosis, and atrial stretching. For example, paroxysmal AF is frequently preceded by brief changes in autonomic tone.[9] Both parasympathetic and sympathetic activation alter intracellular calcium dynamics and can shorten action potential duration and refractoriness.[10, 11] During sympathovagal stimulation there is decreased atrial repolarization in the presence of increased calcium transients, which may promote early afterdepolarizations and triggered activity.[10, 11] The result is an ectopic firing that has been proposed to be primarily localized to the sleeves of

atrial muscles that surround the pulmonary veins.[10, 11] In addition to these neurohormonal influences, structural and mechanical changes in the atria may be proarrhythmic. In experimental models, the mechano-electrical feedback associated with atrial stretching has been associated with alterations in atrial refractoriness. Additionally, atrial fibrosis can alter atrial conduction in a manner that can be proarrhythmic by facilitating reentry.

In summary, AF can result from a number of mechanisms that may be influenced by an underlying pathophysiological state and concurrent risk factors. Many of the drugs that have been linked to increasing the risk for AF modify these risk factors or underlying pathophysiological conditions.

2. Literature Search Methods

The PubMed, Medline, and Micromedex databases were selected to evaluate reports on drug-induced AF published in English between January 1978 and April 2011. Key words "atrial fibrillation" and "arrhythmia" combined with "drug-induced," "chemically-induced," "adverse effect," "adverse event," "associated with drug," "as cause of drug" and as side effect" were used. In some cases, reference citations from selected review articles were used as well. Additional screening was done by searching individual drug names. Medications for which AF is listed as a potential adverse effect, but without identified case reports, were excluded. Drugs associated with AF are listed in Table 2.

3. Cardiovascular Drugs

3.1 Cardiac Stimulants

3.1.1 Adenosine (Quality of evidence – High)—Although adenosine is effective at terminating supraventricular tachycardias with AV nodal involvement, it may induce AF with an incidence of 1–12%.[12–14] Episodes of adenosine-induced AF have been reported to be short-lived and transient during stress testing, as a result of adenosine's short half-life (10 seconds). A case-series of eight patients with adenosine-induced AF reported the duration ranged between 15 seconds to eight hours and converted to sinus rhythm without intervention or complication.[15] However, there can be significant clinical consequences in a subset of patients with an accessory pathway, such as those with Wolff-Parkinson-White syndrome. Case studies have reported hemodynamic instability due to a rapid ventricular response from adenosine-induced AF in patients with accessory pathways.[16, 17]

Adenosine is largely effective at terminating supraventricular tachycardias due to its slowing of AV nodal conduction. However, in atrial tissue, adenosine enhances activity of the acetylcholine-activated inward rectifier potassium current ($I_{K(ACh)}$).[18] The resulting shortening of atrial repolarization and effective refractory periods may promote reentry.[13, 19] In addition to its direct electrophysiological effects, adenosine may enhance adrenergic tone which may increase in the risk of AF.[20] In summary, adenosine may enhance the substrate for AF by direct electrophysiological effects or by enhancing autonomic tone. Although adenosine-induced AF is often clinically inconsequential, it can be of significant clinical importance when an accessory pathway is present. Although adenosine-induced AF is usually of short duration, patients undergoing therapy with

adenosine should be on continuous telemetry electrocardiogram (ECG) monitoring to identify AF should it occur.

3.1.2 Dobutamine (Quality of evidence – High)—Dobutamine is an inotropic agent that acts directly through β-adrenergic receptor activation to increase automaticity and conduction velocity while shortening effective refractory periods.[21] β-adrenergic receptor activation increases the risk of AF through enhancement of intracellular 3'-5'-cyclic adenosine monophosphate (cAMP). Increased cAMP activates protein kinase A, which enhances the activity of several target proteins such as the ryanodine receptor, phospholamban, and the L-type calcium channel, modulating intracellular calcium cycling. The resulting cytosolic calcium accumulation can trigger depolarizations in pulmonary veins and atrial tissue to trigger AF which can be perpetuated by reentry or rapid atrial depolarizations. Increased calcium loading triggers ectopic impulses and is one mechanism of adrenergically-mediated AF.[4, 22] Ventricular dysfunction after cardiac surgery can necessitate the administration of vasopressors and/or inotropic agents to maintain hemodynamic stability. Given the mechanism of neurally induced AF, it is not surprising that the use of an agent with a predominant adrenergic component is an independent predictor of postoperative AF.[23] In a sample of 127 patients undergoing cardiac surgery and treated with an inotropic agent, 49 (39%) developed postoperative AF [$p<0.01$ compared with 10 of 72 (14%) in the control group]. Dopamine and dobutamine were used in 44% and 41% of the patients that developed postoperative AF, respectively.[23] The outcomes of drug-induced AF in this population have not been assessed but the development of AF following cardiac surgery prolongs duration of hospital stay and increases morbidity.[24, 25]

The incidence of dobutamine induced AF is unclear in non-surgical patients with acute decompensated heart failure due to the lack of an appropriate comparator group. The best data available regarding dobutamine-induced AF in patients with acute decompensated heart failure was from clinical trials for levosimendan where dobutamine was used as the comparator drug. Levosimendan is a positive inotropic agent that is used for the management of acute decompensated heart failure in Europe but has not been approved for use in the United States. It is mechanistically distinct from dobutamine and the phosphodiesterase inhibitors (e.g. milrinone) because it does not exert its inotropic effects through β-adrenergic receptors nor does it increase intracellular cAMP. Levosimendan exerts its inotropic effects by directly binding to cardiac troponin C. It also possesses vasodilatory actions through modulation of the ATP-dependent potassium channel. Therefore, it was initially believed that levosimendan would not have arrhythmogenic effects since it does not enhance intracellular calcium dynamics through PKA activity. Patients with acute decompensated heart failure were randomized to levosimendan versus dobutamine in the Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) trial.[26] Patients administered levosimendan had a significantly greater incidence of AF than those who received dobutamine; 60/660 (9.1%) versus 40/660 (6.1%), respectively.[26] Since the SURVIVE trial, other evidence has been reported that levosimendan may not incur a greater risk over dobutamine in patients on optimal therapy for class III or IV heart failure including a β-blocker.[27] There is strong mechanistic theory to suggest that dobutamine would increase the risk for AF in patients with acute

decompensated heart failure. However, it is difficult to draw any solid conclusions regarding the incidence of dobutamine-induced AF in this high-risk population. Furthermore, the benefit of administering inotropic agents in these patients outweighs the risk of them developing AF. Therefore, the risk of dobutamine-induced AF should not preclude its use in decompensated heart failure.

Dobutamine stress echocardiography has been reported to induce AF in 1–4% of patients, with serious AF requiring treatment occurring in fewer than 0.18% of patients.[28–31] Dobutamine-induced AF during stress echocardiography is usually transient and spontaneously reverts to sinus rhythm within hours. Nonetheless, it can compromise the diagnostic value of the stress test and in some cases lead to hospitalization. Therefore, studies have been conducted to help identify patients at the highest risk for dobutamine-induced AF.[29, 32] Risk factors include hypertension and echocardiographic findings including left ventricular hypertrophy, increased left atrial diameter, and mitral regurgitation. The best predictor of dobutamine-induced AF is a history of AF. In summary, dobutamine-induced AF is relatively uncommon following stress echocardiography and to some extent can be predicted by a previous history of AF or current risk factors. Alternatives should be considered in patients at high risk or with previous AF undergoing stress echocardiography with dobutamine. However, given the transient nature of AF in most cases, the benefits of using dobutamine outweigh the risks in most cases. Patients receiving therapy with dobutamine should be on continuous telemetry ECG monitoring.

3.1.3 Milrinone (Quality of evidence – Moderate)—Milrinone is a phosphodiesterase inhibitor that increases intracellular cAMP while bypassing the β-adrenergic receptor pathway to exert a positive inotropic effect and vasodilation. Similar to dobutamine, milrinone administration likely results in cytosolic calcium accumulation which can trigger ectopic impulses in pulmonary veins or atrial tissue to promote AF. Therefore, it is not surprising that milrinone increased the risk of atrial arrhythmias when used for short-term for management of heart failure exacerbations that did not require the use of inotropic agents (4.6% versus 1.5%; $p<0.01$) in a randomized, placebo-controlled, clinical trial.[33] These numbers of AF induction are important to note in this population given the rare use of a placebo in the comparator group to assess the ability of a drug to induce AF. This is particularly important given the high incidence of AF during heart failure which is likely due to increased sympathetic tone and intracellular calcium accumulation.

The hemodynamic effects of dobutamine and milrinone, and subsequently the risk for the development of AF following cardiac surgery, were compared.[34] During the four hour infusion, 5% (n= 3) of the 60 patients that were administered milrinone developed AF versus 18% (n= 11) of the 60 patients that were administered dobutamine ($p=0.04$).[34] More recently, an interim analysis of an ongoing clinical trial identified milrinone as an independent risk factor for post-operative AF in patients undergoing elective cardiac surgery. Twenty nine percent (67/232) of the patients assessed developed post-operative AF. Milrinone administration was associated with a higher incidence of AF (58.2%) versus non-users (26.1%; $p<0.001$).[35] Post-operative AF increases the length of hospital stay and may been associated with increased mortality.[24, 25]

In summary, the use of milrinone for heart failure increases the risk of AF. Similar to dobutamine, the clinical use of milrinone should not be deterred during acute decompensated heart failure due to its ability to induce-AF. Due to the lack alternative inotropic agents that do not promote AF, the clinician should closely monitor and appropriately treat AF if it occurs during the course of therapy for acute decompensated heart failure. Additionally, the use of milrinone to preserve hemodynamic stability following cardiac surgery likely increases the risk for AF in a similar manner than that of dopamine and dobutamine. Alternatives to the use of inotropic agents to preserve hemodynamic stability following surgery should be considered given the wealth of data suggesting that post-operative AF increases morbidity and perhaps mortality. Patients undergoing therapy with milrinone should be on continuous telemetry ECG monitoring.

3.2 Antiarrhythmics

3.2.1 Flecainide and Propafenone (Quality of evidence – Moderate)—Several antiarrhythmic agents used for the conversion of AF can promote the transition to an atrial flutter-like arrhythmia. The mechanism for the conversion from AF to atrial flutter is likely due to stabilization of reentry by a prolongation of cardiac wavelength until one macro-reentrant circuit predominates. This phenomena has been reported for the Vaughn Williams Class IC agents, propafenone and flecainide, with a reported incidence up to 20 %.[36, 37] The treatment of antiarrhythmic drug induced atrial flutter with radiofrequency ablation may permit the continued administration of the antiarrhythmic agent. A detailed description of drug-induced atrial flutter is beyond the scope of this review.

3.2.2 Amiodarone (Quality of evidence – Low)—Amiodarone is an effective agent to convert AF and maintain sinus rhythm. Similar to other antiarrhythmic drugs, amiodarone administration can prompt arrhythmias similar to atrial flutter when administered to patients with AF.[38, 39] Additionally, in rare occurrences, amiodarone may indirectly promote AF through its non-cardiac adverse effects.

Amiodarone-induced thyrotoxicosis (AIT) has been reported in two case studies to indirectly promote AF.[40, 41] Both patients were receiving chronic oral amiodarone of approximately 1.5 and 2.5 years in duration. Both patients presented to the emergency department with palpitations and weakness that was identified as atrial fibrillation 5 and 6 months, respectively, after discontinuation of amiodarone treatment. In both cases AF was attributed to a newly diagnosed late-onset AIT. The delayed onset of AIT and subsequent amiodarone-induced AF may lead to an underestimation of the drug's ability to promote this arrhythmia. That is, if thyrotoxicosis occurs several months after amiodarone discontinuation, the potential for the drug to provoke AF may be overlooked. Nonetheless, once AF presents and is determined to be due to AIT, the precipitating factor of thyroid dysfunction should be treated. As mentioned, amiodarone-induced AF is uncommon, and the low potential for AF should not be a factor in prescribing decisions for most patients.

3.3 Calcium Channel Blockers (Quality of evidence – Low)

Calcium channel blockers (CCBs), both dihydropyridines and nondihydropyridines, have been reported to potentially increase the risk for AF for the past couple of decades despite

wide-spread use in the management of AF. It has recently been reported that in 682,993 hypertensive patients treated with angiotensin-converting enzyme (ACE) inhibitors, angiotensin II-receptor blockers, or β-blockers had a reduced risk of AF compared to those receiving CCBs.[42] This, of course, could be due to the reported beneficial effects of the former drugs or due to an increased risk from CCBs. Theoretically, CCBs could increase the risk for AF by a couple of mechanisms. First of all, the compensatory effect of decreased blood pressure may result in an increased sympathetic drive to promote neural-induced atrial fibrillation. Second of all, it has been demonstrated in dogs that verapamil promotes multiple circuit reentry by shortening atrial effective refractory periods and increases simultaneous wavefronts.[43] This resulted in an incidence of AF that was not seen in control or diltiazem treated dogs.[43] Finally, CCB induced AF was associated with left atrial overload in patients with hypertrophic cardiomyopathy.[44] This was suggested to be due to an increased left ventricular outflow gradient that was previously reported with sublingual nitroglycerin and other vasodillatory agents.[45]

4. Bisphosphonates (Quality of evidence – Low)

A large number of studies have been conducted regarding the possible association beteen bisphosphonate drugs and development of new-onset AF. However, much of the evidence is conflicting and equivocal. A summary of the evidence supporting or refuting an association between bisphosphonates and the development of AF is provided in Table 3.[46–63] The first evidence that bisphosphonates may be associated with AF was provided by the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial, which was a multicenter, randomized, double-blind, placebo-controlled study in 7,765 postmenopausal women with osteoporosis.[46] While once-yearly intravenous zoledronic acid 5 mg was effective for reducing the incidence of vertebral, hip and other fractures during the 3-year follow-up period, the incidence of “serious” AF was significantly higher in the zoledronic acid group (1.3%) than in the placebo group (0.5%; $p<0.001$).[46] A definition of “serious” AF was not provided in this study. There was no significant difference between the zoledronic acid and placebo groups in the overall incidence of AF. In the Fracture Intervention Trial (FIT), 6459 postmenopausal women with osteoporosis were randomized to receive oral alendronate 5 mg once daily or placebo.[64] There was a trend towards an increased incidence of serious AF (definition of “serious” was not provided) in patients treated with alendronate (1.5%) compared with placebo (1.0%, $p=0.07$); there was no significant difference between alendronate and placebo groups in the overall incidence of AF (2.5% vs 2.2%, $p=0.42$).[47]

In contrast to the findings of the HORIZON Pivotal Fracture Trial,[46] the HORIZON Recurrent Fracture Trial[48] reported no significant difference between the zoledronic acid and placebo groups in the incidence of serious AF. Similarly in a retrospective analysis of placebo-controlled phase 3 trials (approximately 15,000 patients, mean age 74 years, up to 3 years follow-up) in patients with osteoporosis, with there was no significant difference in the incidence of AF or serious AF associated with risedronate compared with placebo.[49]

In view of findings of increased risk of serious AF in studies described above, numerous investigators subsequently conducted cohort or case-control studies to determine possible

associations between bisphosphonate therapy and AF. Findings from some cohort studies supported a significant association between bisphosphonate use and development of AF[59, 62] while others did not.[50–52] One retrospective cohort study even reported that bisphosphonates may reduce, rather than increase, the risk of AF in older women with osteoporosis.[65] Findings from a case-control study reported an association between bisphosphonate use and AF,[61] while others did not.[53, 54] As a result of these disparate findings, several meta-analyses have been performed to determine if the weight of published evidence supports that bisphosphonate therapy induces AF.[55–58, 60, 63] These meta-analyses have also reported disparate findings (Table 3).

Overall, data regarding the association between bisphosphonate therapy and AF are equivocal, and it remains unclear whether bisphosphonate drugs contribute to the development of new AF. Reasons for the disparate findings from clinical trials and the various cohort studies and case-control studies are not entirely clear, although these studies differ in study design, patient inclusion, and data analysis, among other variations. Based on available data, bisphosphonate drugs should not be withheld from patients with osteoporosis or cancer based on concerns for the potential for AF. However, it seems prudent to monitor patients with pre-existing risk factors for signs and symptoms of AF who are receiving bisphosphonate drugs for the development of new-onset AF. Routine electrocardiograms are not warranted at this time.

5. Corticosteroids (Quality of evidence – Low)

Several published reports have associated corticosteroids, primarily methylprednisolone, with development of AF. AF has been attributed to the administration of high-dose methylprednisolone in pulse doses,[66–69] but also with lower dose intravenous or oral methylprednisolone therapy.[70–72] In a nested case-control study of individuals 55 years of age or older in Rotterdam, the Netherlands,[73] the adjusted odds ratio for new-onset AF associated with corticosteroid therapy was 3.75 (95% CI 2.38–5.87). The association was significant only among patients who received high doses (OR 6.07, 95% CI 3.90–9.42), defined as ≥ 7.5 mg prednisone equivalents daily. In another nested case-control study of primary care patients between the ages of 40–89 years enrolled in the United Kingdom General Practice Research Database, current corticosteroid use was associated with an increased risk of chronic AF (RR 2.49, 95% CI 1.56–3.97).[74] However, there was no significant association between corticosteroid use and development of paroxysmal AF.

In contrast, however, studies have found that corticosteroids are effective for prophylaxis of AF following CABG surgery.[75–78] Reasons that corticosteroids may be effective for prevention of post-CABG AF but associated with induction of AF in patients not undergoing surgery are unclear. Evidence indicates that AF may occur in part as a result of an inflammatory process; inflammation may be particularly important as a mechanism of postoperative AF, and corticosteroids may reduce the risk of post-CABG AF due to anti-inflammatory properties.[79] On the other hand, mechanisms by which corticosteroids may contribute to causing nonsurgical AF have been suggested,[73] and include sodium and fluid retention, leading to elevated atrial pressures; modulation of myocardial potassium efflux;[80] and promotion of the development of late potentials.[81] Additional research is

needed to clarify the effects of corticosteroids on inducing AF and/or preventing post-CABG AF.

6. Central Nervous System Agents

6.1 Ondansetron (Quality of evidence – Low)

Ondansetron is a 5-hydroxytryptamine 3 (5-HT_3) receptor antagonist used for prophylaxis and treatment of postoperative nausea and vomiting. Although ondansetron has been linked to acute myocardial ischemia and tachyarrhythmias, AF has not been widely reported. Two case reports discuss onset of AF shortly after the administration of a second intravenous dose of ondansetron 4 mg. The patients had unremarkable past medical histories and no evidence of cardiac disease upon further testing. Both cases reported the need for antiarrhythmics or direct current cardioversion to restore sinus rhythm. As discussed in the mechanisms section, sympathovagal stimulation during vomiting may play a role in AF development. Coronary vasoconstriction and the inhibition of the Bezold-Jarisch cardiac reflex have been suggested to play a role in ondansetron promoting AF.[82, 83]

7. Antineoplastic Agents

Antineoplastic agents are frequently used in combination with other antineoplastic agents, immunological agents, and steroids. Therefore, use of one or more agents that have the propensity to induce AF can theoretically put a patient at an increased risk of developing this arrhythmia. More research is needed to evaluate the potentially additive cardiac toxicities of multiple-agent chemotherapy regimens.

7.1 Paclitaxel (Quality of evidence – Low)

Paclitaxel, an antimicrotubule agent, induces atrial flutter and AF infrequently (up to 2%, and 1–1.7%, respectively).[84, 85] A retrospective study evaluated the cardiac toxicity of paclitaxel in 100 African-American patients with various cancers.[84] Doses ranged from 75 to 200 mg/m² and were administered every 1 to 3 weeks. Sinus tachycardia occurred in 26% of treated patients; AF occurred in 1%. The onset of cardiac disturbances ranged from day one to eight years after paclitaxel administration. These changes were described as mild, reversible, and likely dose-independent. Moreover, the authors indicated that 60% of the study population had underlying co-morbid conditions, and up to 80% had cardiac risk factors. The presence of paclitaxel likely potentiated AF development in this group of patients with many co-morbid conditions.

A single case of tachycardia and AF was reported in a phase II study during which 58 breast cancer patients received long-term weekly infusions of paclitaxel.[85] Paclitaxel was administered weekly at doses ranging between 60 and 90 mg/m², with patients receiving a median of 19 weekly infusions, corresponding to a median cumulative dose of 1280 mg/m². The authors suggested that some adverse effects, especially neurotoxicity and onychopathy, may be related to the cumulative dose of paclitaxel; but the relationship between cumulative dose and occurrence of AF is unknown. In an analysis of approximately 3400 patients in the National Cancer Institute’s adverse drug reaction database, atrial arrhythmias occurred in fewer than 0.2% of patients who received paclitaxel.[86]

7.2 Interleukin-2 (IL-2) (Quality of evidence – Moderate)

In a phase II trial of outpatient subcutaneous IL-2 combined with interferon alpha in 47 patients with metastatic renal cell cancer, 2 patients (4.3%) developed AF requiring treatment.[87] One of these patients developed treatment-related hyperthyroidism, which may have been the etiology of the AF. Similarly, AF developed in 4 of 93 patients with metastatic melanoma, metastatic renal cell cancer, and colorectal cancer (4.3%) in another analysis involving high-dose intravenous IL-2 plus lymphokine-activated killer cells.[88] In an analysis of 317 patients with various cancers treated with 423 courses of IL-2, 8% of the treatment courses resulted in AF.[89] Mechanisms of AF associated with IL-2 are unclear, although there is some evidence to suggest that elevation of plasma cytokine concentrations may be associated with AF.[90]

7.3 Anthracyclines (Doxorubicin and Mitoxantrone) (Quality of evidence – Low)

Anthracyclines are well-known for cardiotoxic effects, ranging from tachycardia to cardiomyopathy. Dilated cardiomyopathy is a dose-limiting factor for doxorubicin use.[91] A prospective study by Kilickap and colleagues investigated the arrhythmogenic effects of doxorubicin-containing regimens in 29 patients with various cancers in the acute/early (during and 23 hours after first infusion) and chronic/late (at least 6 weeks after last cycle) stages of treatment.[91] The median cumulative doxorubicin dosage was 50–480 mg/m². Abnormal cardiac rhythms were reported in 19 patients (65.5%) and 18 patients (64.2%) in the acute and chronic phases, respectively. Paroxysmal AF was recorded in 3 patients (10.3%) in the acute phase, but was not reported in the chronic phase. Concurrent use of antiemetic medications as well as various chemotherapy regimens (5-fluorouracil and cyclophosphamide) may have potentially contributed to a higher incidence of arrhythmias, including AF, in the acute phase. This study showed that rhythm disturbances can occur in both the acute and chronic phases after doxorubicin therapy. In the acute phase, it has been hypothesized that vasoactive substances, enhanced sympathetic discharge, and hypotension during and after doxorubicin infusion may play a role in the development of electrocardiographic changes and rhythm disturbances. Dilated cardiomyopathy leading to arrhythmias in the chronic stage is also a concern. This typically occurs several years after completion of therapy and the incidence is usually limited to less than 5% if the cumulative dose is less than 550 mg/m².[91]

Mitoxantrone has been associated with decreased left ventricular ejection fraction, irreversible cardiomyopathy, and heart failure. In a prospective study of 73 multiple sclerosis patients, AF developed in one patient with a history of ischemic heart disease after the second course of mitoxantrone. The patient, who had a previous history of ischemic heart disease and hypertension, was later excluded from the study, and no information regarding the duration of AF was provided.[92] There is some evidence to suggest that mitoxantrone's cardiac side effects may be related to higher cumulative doses.[92] Heart failure development can also lead to AF. In this specific case, it is plausible that AF may have been potentiated since mitoxantrone was administered in combination with methylprednisolone, another medication that has also been linked with development of AF.[73]

8. Summary

Several drug classes have been associated with AF. The strongest evidence of an association with new-onset AF exists for adenosine, dobutamine, aminophylline/theophylline, and alcohol bingingwith moderate –quality evidence available for milrinone, interleukin-2, cisplatin, melphalan, amifostine, and flecainide and propafenone (for atrial flutter). Bisphosphonate drugs and corticosteroids, predominantly high-dose methylprednisolone, have been reported in clinical trials to be associated with AF, but evidence is conflicting and equivocal. Therefore, the question as to whether bisphosphonate drugs and corticosteroids are associated with new onset AF remains controversial and requires further study. An association between AF and drugs such as dopamine, amiodarone, calcium channel blockers, ondansetron, paclitaxel, and anthracyclines is supported by relatively weak evidence, but cannot be ruled out. The potential contribution of specific drug therapy should be considered when patients present with new onset AF.

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Table 1

Quality of Evidence Associating Drugs with New-Onset Atrial Fibrillation (adapted from reference 6)

Quality of Evidence	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations (≥ 2 consistent, higher quality randomized controlled trials or multiple, consistent, observational studies with no major methodological flaws)
Moderate	Evidence is sufficient to determine effects on occurrence of AF, but the number, quality, size or consistency of included studies, generalizability to routine practice, or indirect nature of the evidence on induction of AF (≥ 1 higher quality trial with > 100 participants; ≥ 2 consistent, lower quality trials, or multiple, consistent observational studies with no major methodological flaws) limits the strength of the evidence
Low	Evidence is insufficient to assess the association of drugs with AF because the evidence is from case reports only, or because of limited number or power of studies, large and unexplained inconsistency between higher quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health care outcomes

Table 2

Medications Associated with the Development of Atrial Fibrillation

Drug Group	Quality of Evidence	Drugs
Cardiovascular	High	Acetylcholine, adenosine[a], dobutamine[a]
	Moderate	Flecainide,[b] milrinone, propafenone[b]
	Low	Amiodarone, atenolol, digoxin, diltiazem, dopamine, dopexamine, isosorbide mononitrate, levosimendan, losartan, nesiritide, thiazide diuretics, verapamil
Respiratory	High	Aminophylline/theophylline
	Moderate	--
	Low	Albuterol, arformoterol, corticosteroids, fluticasone, ipratropium, methylprednisolone[a], pseudoephedrine, salmeterol
Antineoplastic	High	--
	Moderate	Amifostine, cisplatin,[a] interleukin-2, melphalan[a]
	Low	Cyclophosphamide, docetaxel, doxorubicin, 5-fluorouracil, gemcitabine[a], interferon-α, lenalidomide, mitoxantrone, paclitaxel
CNS agents	High	--
	Moderate	--
	Low	Atropine, apomorphine[a], clozapine, fluoxetine, lacosamide, olanzapine, physostigmine[a], sumatriptan,[a] tranylcypromine, trazodone
Genitourinary	High	--
	Moderate	--
	Low	Sildenafil, vardenafil
Miscellaneous	High	Alcohol[c]
	Moderate	--
	Low	Azathioprine[b], anabolic steroids[a], bisphosphonates, caffeine, etanercept, nicotine, pentagastrin

[a]Medications reported in van der Hooft, 2004[5] with further evidence documented after 2004.

[b]Atrial flutter

[c]Predominantly alcohol binging

H = High; L = Low; M = Moderate

Table 3

Association of Bisphosphonate Drugs with the Development of Atrial Fibrillation

Drug	Study Design	Incidence[a]	Hazard Ratio[c]/Relative Risk/Odds Ratio (95% CI)	p
Studies Reporting an Association Between Bisphosphonate Drugs and Development of Atrial Fibrillation				
Zoledronic acid[46]	R, DB, PC	0.8%[b]		<0.001
Alendronate[47]	R, DB, PC	0.5%[b]	1.51 (0.97–2.40)	0.07
Oral bisphosphonates[59]	Cohort		1.18 (1.08–1.29)	
IV bisphosphonates[62]	Cohort		1.30 (1.18–1.43)	
Alendronate[61]	Case-control		1.86[d] (1.09–3.15)	
Bisphosphonates[55]	Meta-analysis		1.47[d] (1.01–2.14)[b]	
Bisphosphonates[60]	Meta-analysis		1.53[e] (1.17–2.00)	
Bisphosphonates[93]	Cohort		1.7 (1.2–2.4)	
Studies Reporting no Association Between Bisphosphonate Drugs and Development of Atrial Fibrillation				
Drug	**Study Design**	**Incidence[a]**	**Hazard Ratio[c]/Relative Risk/Odds Ratio (95% CI)**	
Zoledronic acid[46]	R, DB, PC	0.5%		
Alendronate[47]	R, DB, PC	0.3%	1.14 (0.83–1.57)	
Zoledronic acid[48]	R, DB, PC	0.2%		
Risedronate[49]	R, DB, PC	0.1%		
Bisphosphonates[50]	Cohort		0.90 (0.48–1.68)	
Bisphosphonates[50]	Cohort		0.82 (0.66–1.01)	
Alendronate[51]	Cohort		1.06 (0.85–1.32)	
Alendronate[52]	Cohort		1.05 (0.96–1.15)	
Etidronate[52]	Cohort		1.04 (0.98–1.10)	
Alendronate[53]	Case-control		1.09[d] (0.93–1.26)	
Risedronate[53]	Case-control		0.99[d] (0.78–1.26)	
Bisphosphonates[54]	Case-control		0.75[e] (0.49–1.16)[f]	
			0.96[e] (0.85–1.09)[g]	
Bisphosphonates[55]	Meta-analysis		1.14[d] (0.96–1.36)	
Bisphosphonates[56]	Meta-analysis		1.18[d] (0.84–1.66)	
			1.60[e] (0.61–3.75)	
Ibandronate[57]	Meta-analysis		1.15 (0.52–2.54)	
Bisphosphonates[58]	Meta-analysis		1.04[d] (0.92–1.16)	
Alendronate[63]			1.16[e] (0.87–1.55)	
			1.25[e] (0.82–1.93)[b]	
Bisphosphonates[94]	Cohort		0.92[e] (0.85–0.99)[h]	
			1.00[e] (0.87–1.16)[h]	

Studies Reporting an Association Between Bisphosphonate Drugs and Development of Atrial Fibrillation

Drug	Study Design	Incidence[a]	Hazard Ratio[c]/Relative Risk/Odds Ratio	p
			0.97[e] (0.79–1.20)[h]	
Zoledronic acid[95]	Retrospective, uncontrolled	0%		

DB =Double-blind; IV = Intravenous; PC = Placebo-controlled; R = Randomized

[a] Incidence in placebo group subtracted from incidence in bisphosphonate group

[b] Serious atrial fibrillation

[c] Hazard ratios unless otherwise indicated

[d] Odds ratio

[e] Relative risk

[f] New users

[g] Continuing users

[h] Three databases studied; relative risks provided for each database