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Drug-Induced Cardiovascular Disorders

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Abstract

As the variety and range of pharmaceutical agents available to the medical profession continues to expand, one unavoidable effect will be an increase in drug-induced disease, including cardiovascular disorders. However, given the high rates of cardiovascular disease and prevalence of recognised cardiovascular risk factors in the population, it is sometimes impossible to conclusively attribute any individual patients' ill health to one particular drug. As a result, the relationship between drugs and cardiovascular disease is often difficult to quantify. This review discusses specific forms of drug-induced cardiovascular disease such as heart failure, left ventricular systolic dysfunction, hypertension and arrhythmia. Suspected culprit drugs for all disorders are highlighted. Specific attention is given to certain drug groups with a strong association with one or more forms of cardiovascular disease: these include anthracyclines, antipsychotics, NSAIDs and cyclo-oxygenase 2 inhibitors. Additionally, advice is offered on how physicians might distinguish drug-induced cardiovascular disorders from other aetiologies.

Over recent decades, the development and prescribing of drugs has grown exponentially and pharmaceutical treatments are now available for almost every identified disease. One undesirable consequence of this is an increase in drug-related illness including cardiovascular disorders. Drugs may cause cardiovascular disease by various mechanisms including direct myocyte injury, the alteration of biochemical processes or stimulating allergic reactions. The outcome can vary in severity from benign to fatal.

Given the high rates of cardiovascular disease and prevalence of recognised cardiovascular risk factors in developed countries, it is sometimes difficult to conclusively attribute any individual patient's ill health to one particular drug. Who can say that a myocardial infarction (MI) in a 55-year-old smoker taking a cyclo-oxygenase (COX)-2 inhibitor would not have occurred anyway? Was the ventricular arrhythmia in a 70-year-old woman with previous bypass surgery due to ischaemia or the clarithromycin she was taking for a chest infection? Or both? We can assess whether an increased risk of cardiovascular disease exists with a drug but often only with retrospective analysis; this method is open to bias and counterargument. Confusingly, similar studies of drug-induced illness may have differing conclusions. As such, it is often impossible to accurately quantify the strength of relationship between a drug and cardiovascular disease.

This review intends to highlight drugs with a recognised association with cardiovascular disease and examine the evidence for these associations. In clinical practice, physicians and pharmacists must be aware of the adverse effects of all the medicines they prescribe and always consider drugs as a cause of ill health, particularly when no alternative cause is apparent. A full drug history is imperative for all patients. On the other hand, it is important to recognise that a drug with a strong association with a particular cardiovascular or other adverse effect could be entirely blameless and that alternative causes should not be discounted.

Data for this review were identified from MEDLINE searches. Two approaches were used: the cardiovascular disorder in question was used as a keyword, with the subheading of 'chemically-induced', and certain drugs were inserted as keywords, with the subheading of 'adverse effects'. Searches were refined to the period from January 1990 to September 2006, English language and/or review articles.

1. Drug-Induced Cardiovascular Disease

1.1 Left Ventricular Systolic Dysfunction (LVSD) and Heart Failure (HF)

It is important to understand the interaction between heart failure (HF) and left ventricular systolic dysfunction (LVSD). The two disorders are not synonymous, but clearly there is a large degree of overlap. However, it is worth recognising that 50% of individuals with LVSD are asymptomatic[1] (and

thus do not have HF), and up to 50% of patients with HF do not have LVSD.[2,3] Drugs may precipitate deteriorating symptoms of HF in individuals with established HF; alternatively, drugs can cause *de novo* LVSD in a previously well individual.

1.1.1 Drug-Induced LVSD

HF due to LVSD affects up to 3% of the population and is most often due to coronary artery disease or hypertension.[1,4] LVSD itself can occasionally be attributable to drug therapy (table I). This may occur soon after administration as an acute toxic reaction simulating a myocarditis or, alternatively, it may present years later as chronic HF due to cardiomyopathy.

A large number of cytotoxic agents are associated with the development of LVSD. Anthracyclines and trastuzumab are the most widely recognised culprits and will be discussed in greater detail. However, other cytotoxic agents may cause LVSD. Mitoxantrone is structurally related to anthracyclines and is used in multiple sclerosis as well as for malignancy. However, dose-dependant cardiotoxicity is a problem regardless of the indication.[5] Cyclophosphamide can be cardiotoxic via an unknown mechanism; acute reversible LVSD and fatal cardiomyopathy have been described.[6] Paclitaxel may cause LVSD; one study using it in combination with doxorubicin found higher rates of HF than could be attributed to doxorubicin alone.[7] Although rare, HF has been associated with fluorouracil and cytarabine.

Table I. Drugs associated with left ventricular systolic dysfunction (LVSD) or worsening heart failure (HF)

Drugs causing LVSD
Cytotoxic agents
anthracyclines
trastuzumab
Antipsychotics
clozapine
atypical antipsychotics
Carbamazepine
Tricyclic antidepressants
Chloroquine
Hydroxychloroquine
Interferon-α
Interleukin-2
TNFα antagonists
Drugs exacerbating HF
NSAIDs
COX-2 inhibitors
Corticosteroids
Thiazolidinediones
Calcium channel antagonists
non-dihydropyridines
β-Adrenoceptor antagonists
Unproven associations
Doxazosin
β_2-Adrenoceptor agonists

COX = cyclo-oxygenase; **TNF** = tumour necrosis factor.

Several antipsychotic drugs have been associated with the development of myocarditis or cardiomyopathy, particularly newer atypical agents such as amisulpride, quetiapine and risperidone.[8-10] However, clozapine has the strongest association. This was first brought to widespread attention in 1999 when Killian et al.[11] identified 15 cases of myocarditis and eight cases of cardiomyopathy among 8000 patients treated with clozapine. Subsequent studies have confirmed the association.[12,13]

The potential cardiovascular effects of tricyclic antidepressants (TCAs) have probably played a role in their dwindling use. They become highly concentrated in myocardial tissue and this may affect myocardial contractility; animal studies indicate they have a negative inotropic effect.[14] Carbamazepine is similar to TCAs in structure and mode of action, and reversible LVSD with acute HF following deliberate overdose has been reported.[15] Chronic HF associated with TCAs and carbamazepine has also been reported.[16,17] The association between these drugs and LVSD is not strong; nevertheless, physicians should be aware of this potential adverse effect.

Chloroquine and hydroxychloroquine have established roles in the treatment of autoimmune disorders. Acute decreased myocardial contractility following administration of chloroquine and hydroxychloroquine is seen in animals and has also been reported in humans following overdose.[18,19]

A rare but recognised complication of the chronic use of hydroxychloroquine and chloroquine is the development of cardiomyopathy, probably secondary to interference with intracellular lysosomal function. There are 20 case reports of chloroquine-induced cardiomyopathy compared with four cases for

hydroxychloroquine.[20,21] Complications develop following many years of treatment and echocardiography typically reveals bi-ventricular hypertrophy in addition to LVSD. Drug cessation usually results in improved LV function.

1.1.2 Drug-Induced Decompensated HF

Drugs can lead to decompensated HF (table I). NSAIDs are the most readily recognised drug group that do this. Renal perfusion is reduced in HF and prostaglandins become increasingly important in controlling renal plasma flow and fluid homeostasis. NSAIDs interrupt prostaglandin synthesis resulting in salt and water retention. Prostaglandin production requires both COX-1 and COX-2; thus, COX-2 inhibitors may also cause decompensated HF.[22] Corticosteroids, particularly those with a strong mineralocorticoid action, will also lead to fluid retention and should be used with caution in patients with LVSD.

Thiazolidinediones (TDZs) such as pioglitazone and rosiglitazone are recent additions to the treatment options for patients with type 2 diabetes mellitus, 12% of whom have HF.[23] There is much to suggest that TDZs may be beneficial in HF due to possible favourable effect on coronary vasodilation, vascular endothelium, cardiovascular risk factors and ventricular remodelling. Indeed, pioglitazone has been shown to reduce the incidence of adverse cardiovascular effects in patients with type 2 diabetes.[24]

However, fluid retention is a dose-dependant effect of all TDZs and can increase the intravascular volume by as much as 7% – this is even more marked in patients taking concomitant insulin.[25] Fluid accumulation may be due to vascular leakage from endothelial vasodilation or TDZs may potentiate the effect of insulin on fluid retention. Predictably therefore, deterioration in HF symptoms and accounts of pulmonary oedema has been reported.[26] Brain natriuretic peptide could be a useful tool in identifying HF patients at risk of clinically important fluid retention.[27] However, current best practice is that TDZs be avoided in patients with New York Heart Association (NYHA) class III–IV HF.

Tumour necrosis factor (TNF)-α antagonists such as adalimumab, etanercept and infliximab are recombinant antibodies licensed for use in rheumatoid arthritis, psoriasis and inflammatory bowel disease. Elevated TNFα levels are seen in patients with chronic HF and it was thought that TNFα blockers may be beneficial in this condition. Etanercept showed no benefit over placebo,[28] whereas with infliximab there was a trend to increased mortality and hospitalisation rates.[29] This and other evidence[30] indicates that TNFα blockers may worsen or initiate HF and this should be appreciated by anyone intending to use these treatments.

Interferon-α is used for treatment of some malignancies and chronic viral hepatitis B and C. There are reports of reversible acute and chronic HF associated with its use.[31,32] HF has been reported following administration of interleukin-2,[33,34] used subcutaneously in metastatic renal carcinoma.

1.1.3 Cardiovascular Drugs and HF

β-Adrenoceptor antagonists (β-blockers) are first-line therapy for LVSD of any cause. However, they do have negative inotropic and chronotropic effects and can precipitate decompensated HF if administered too aggressively. This provides the rationale for the 'start low and go slow' approach recommended for β-blocker titration in HF.

Calcium channel antagonists have an established role in the management of angina and hypertension, both of which are common in HF. Non-dihydropyridines exert a negative chronotropic effect and possibly reduce myocardial contractility. Verapamil exerts unfavourable haemodynamic changes when administered to patients with LVSD,[35] and diltiazem has been shown to have increased association with HF following MI.[36] The vasodilatory effects of dihydropyridines should theoretically be beneficial in HF; however, no studies have provided evidence for this.

The ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) study[37] raised concerns about the possibility of increased incidence of HF in hypertensive patients receiving doxazosin therapy, and indeed the doxazosin arm of this study was aborted because of this. These findings proved controversial[38,39] and the risk is not clarified. The best practice for management of hypertension in patients with HF is to avoid verapamil and diltiazem, whereas dihydropyridines

and doxazosin should only be used with caution in cases of hypertension resistant to other agents.[40]

1.1.4 β_2-Adrenoceptor Agonists and Cardiotoxicity

The possibility of an association between β_2-adrenoceptor agonist (β_2-agonist) use and cardiotoxicity has received some recent attention. Coughlin et al.[41] first raised the possibility of a link between idiopathic dilated cardiomyopathy and β_2-agonist use. This retrospective study demonstrated a 3-fold increased risk of cardiomyopathy with the use of oral or inhaled β_2-agonists.[41] Further studies have not confirmed this association between β_2-agonist use and idiopathic cardiomyopathy, but one study did identify increased hospital admissions rates with deteriorating HF in patients with LVSD using inhaled β_2-agonists.[42]

A physiological explanation for this has not been elucidated. β_2-Agonists exert a small positive inotropic and chronotropic effects on the heart and this could conceivably lead to myocyte necrosis in situations of myocardial hypoxia.[43] Regular exposure to β_2-agonists leads to decreased β_2-receptor responsiveness and this could theoretically lead to deteriorating LVSD[44] in patients with HF, where β_1-receptor numbers are already reduced. However, this is merely speculative.

These associations could have alternative explanations. Patients developing dyspnoea due to the onset of cardiomyopathy or deteriorating HF may be prescribed inhaler therapy, or increase inhaler self-medication, in the belief that their symptoms are respiratory in origin.

At present, the association between β_2-agonists and cardiovascular disease is unclear and this is a target for future research. However, their symptomatic benefit in obstructive lung disease ensures their continued use in these disorders.

1.2 Hypertension

Medications are an uncommon cause of hypertension but some drugs are recognised culprits (table II). Unfortunately, many of these drugs have unquestionable benefits and drug cessation is not always the best option.

Human recombinant erythropoietin is used for the treatment of anaemia in patients with chronic renal failure (CRF); in recent years, it has also been trialled for the treatment of anaemia associated with chronic HF. A well recognised complication of its use is a propensity to cause hypertension. When used in CRF, 30% of patients develop new or worsening hypertension,[45] and this is more likely in patients on dialysis or in patients with a history of hypertension. Regular monitoring of blood pressure is essential in patients with CRF on erythropoietin and doses should be reduced if hypertension is noted. These patients already have elevated cardiovascular risk and iatrogenic hypertension should be avoided. Initial HF studies using erythropoietin have not found hypertension to be a significant problem.[46]

Table II. Drugs associated with hypertension

Erythropoietin
Combined oral contraceptives
Ciclosporin
Tacrolimus
Venlafaxine
Corticosteroids
HAART
NSAIDs
COX-2 inhibitors

COX = cyclo-oxygenase; **HAART** = highly active antiretroviral therapy.

A possible mechanism of erythropoietin-induced hypertension is vasoconstriction due to a direct action on vascular smooth muscle or by increasing endothelin-1 production.[47] Increased blood viscosity may also have a role.

Ciclosporin and tacrolimus are immunosupressants used following organ transplantation but their benefit in this role is diminished by their ability to cause adverse cardiovascular effects including hypertension and dyslipidaemia. Ciclosporin causes hypertension in the majority of patients irrespective of its indication and concomitant corticosteroids will exacerbate this further. When used following cardiac transplantation, hypertension is almost universal and is seen in up to 85% of liver transplantees and renal transplantees taking ciclosporin.[48] Hypertension is induced by widespread systemic vasoconstriction, possibly due to endothelin and prostaglandin effects.

For obvious reasons, ciclosporin-induced hypertension in transplantees cannot be treated by simply

withdrawing the drug and the choice of antihypertensive agent is important. The renin-angiotensin system is not involved in producing hypertension;[49] therefore, drugs affecting this system are ineffective. Diuretics may exacerbate renal impairment and verapamil and diltiazem interfere with ciclosporin metabolism. Dihydropyridine calcium channel antagonists appear to be the preferred choice with β-blockers as second-line.[48]

Increased blood pressure has long been associated with corticosteroids, and has even been described with topical creams and nasal sprays.[50,51] Twenty percent of patients with iatrogenic Cushing's syndrome exhibit hypertension.[52] Corticosteroid preparations differ in their glucocorticoid and mineralocorticoid effect; however, because hypertension is driven by both effects,[53] any corticosteroid can increase blood pressure.

The observation that a number of women develop hypertension whilst taking combined oral contraceptives (COC) is inarguable but the reported incidence varies from 4% to 18%.[54,55] Women with a history of hypertension during pregnancy or a family history of hypertension are more likely to develop COC-related hypertension, suggesting a genetic predisposition.[56,57]

It was originally thought that the oestrogen component of the COC was responsible for increasing blood pressure as oestrogen increases renin production and angiotensinogen levels.[58] This led to the development of COC with reduced oestrogen content and although a reduction in the incidence of COC-induced hypertension was seen, this may have simply reflected more judicious prescribing. Indeed, some studies have found that the progesterone component, rather than oestrogen, correlates better with the development of hypertension.[56,59]

The antidepressant venlafaxine is thought to cause hypertension in 10–20% of all patients when taken at higher dosage (>150mg).[60] However, this may be even more prevalent in elderly patients. A small study assessing venlafaxine in patients aged >60 years old found that its use was associated with an increase in blood pressure in one-quarter of previously normotensive individuals, and over one half of individuals with previously documented hypertension.[61] This becomes increasingly pertinent when we consider that, in the elderly, the efficacy of venlafaxine as an antidepressant is not clear cut.[62]

NSAIDs and COX-2 inhibitors cause small increases in blood pressure via their effect on salt and water retention; however, this is rarely clinically significant. NSAIDs increase mean blood pressure by only 1–2mm Hg,[63,64] with a slightly larger increase in those with established hypertension. This affect on hypertensive patients may be due to interference with metabolism of antihypertensive medications.[65,66]

1.3 Acute Cardiovascular Events Including Myocardial Infarction (MI) and Stroke

Acute cardiovascular events such as MI and stroke are leading causes of mortality in developed countries. Some drugs are known to exacerbate cardiovascular risk factors (table III), such as those already discussed that cause hypertension, but some drugs appear to independently increase the risk of acute events. However, attributing a MI or stroke to drug therapy in individual patients is difficult, if not impossible.

The introduction of COX-2 inhibitors in the late 20th century promised effective analgesia without the gastrointestinal complications of NSAIDs. However, it is now apparent that some COX-2 inhibitors increase the risk of cardiovascular events.[67-69] This led to scrutiny of the cardiovascular safety of

Table III. Drugs and cardiovascular events

Drugs associated with increased risk of acute cardiovascular events
COX-2 inhibitors
NSAIDs
Atypical antipsychotics
Combined oral contraceptives
HAART
Erythropoietin
Hormone replacement therapy
Drugs associated with cardiovascular risk factors
Corticosteroids (hypertension, dyslipidaemia, diabetes mellitus)
Ciclosporin/tacrolimus (hypertension, dyslipidaemia)
NSAIDs/COX-2 inhibitors (hypertension [minimal])
Erythropoietin (hypertension)
HAART (dyslipidaemia)

COX = cyclo-oxygenase; **HAART** = highly active anti-retroviral therapy.

NSAIDs and the discovery that these drugs, used for many years, also carry adverse cardiovascular risk.[70]

Both COC and hormone replacement therapy (HRT) have been in widespread use since the middle part of the 20th century. In addition to causing hypertension, COC have been identified as carrying a risk of MI, stroke and venous thromboembolic disease.[71,72] HRT was originally heralded as a strong weapon against postmenopausal cardiovascular disease in women; however, recent evidence has cast doubt on its protective role, and even identified HRT as potentially pro-atherothrombotic.[73-75] Male hormone treatment has also raised concerns regarding a cardiovascular risk.[76]

Highly active antiretroviral therapy (HAART), including protease inhibitors (PI), has significantly improved quality of life and survival in HIV-infected individuals. However, there appears to be an increased risk of MI in this patient group.[77,78] The HIV virus itself may damage coronary arteries via cytokine activation and disturbance of cell signalling[79] but this increased risk may be drug-related. PI are known to cause a metabolic disorder including lipodystrophy, hyperlipidaemia and insulin-resistance,[80] and 74% of patients with HAART-associated metabolic syndromes also exhibit hypertension,[81] all of which are pro-atherosclerotic. Increased risk of thrombosis is also seen in patients with HIV and again may be secondary to the virus or HAART.[82]

Studies have shown an increased risk of thrombotic events, including MI in patients receiving erythropoietin.[83] In addition to its ability to increase blood pressure, erythropoietin increases blood viscosity and platelet activation.[84]

Evidence of increased risk of stroke[85,86] and pulmonary embolism[87,88] has been found against antipsychotic agents with newer agents carrying the highest risk. Sudden cardiac death is unfortunately common in patients with a psychiatric history, and there are justifiable concerns that a number of these deaths are secondary to medication. Additionally, there has been recent controversy regarding the association of stroke and antipsychotic use in elderly patients with dementia.

Table IV. Proarrhythmic drugs

All antiarrhythmic agents
Macrolide antibacterials (clarithromycin, erythromycin)
Fluoroquinolone antibacterials (ciprofloxacin, ofloxacin)
Cotrimoxazole (trimethoprim/sulfamethoxazole)
Antifungals (ketoconazole, amphotericin B)
Antimalarials (quinines, mefloquine, halofantrine)
Tricyclic antidepressants
Carbamazepine
Antipsychotics (phenothiazines, haloperidol)
β-Adrenoceptor agonists
Cisapride
Terfenadine

1.4 Arrhythmias

Cardiac arrhythmias are potentially the most devastating drug-induced adverse effect, particularly with non-cardiac medications. Torsade de Pointes (TdP) and ventricular arrhythmias due to prolongation of the QT interval are perhaps the more concerning arrhythmias but brady arrhythmias secondary to conduction delays are also important.

1.4.1 Proarrhythmia with Antiarrhythmic Agents

All antiarrhythmic drugs influence cardiac conduction and should be viewed, paradoxically, as potentially proarrhythmic. Some argue that any benefit in arrhythmia control with many of these agents is outweighed by their propensity to cause arrhythmic deaths. Recent meta-analysis evidence suggests that in atrial fibrillation, all antiarrhythmic agents (excluding amiodarone and propafenone) increased proarrhythmia.[89] At the other extreme, the use of β-blockers can reduce the possibility of ischaemic driven arrhythmias but may precipitate atrioventricular block, particularly in the elderly.

The arguments regarding proarrhythmia with antiarrhythmic agents are extensive and controversial, and outside the remit of this review article.

1.4.2 Proarrhythmia With Non-Cardiac Drugs

There is a wide range of non-cardiac drugs associated with proarrhythmia (table IV). Cisapride, a pro-kinetic agent, was withdrawn from the market after >300 cases of ventricular arrhythmias secondary to QT interval prolongation were reported to the US FDA.[90,91] The non-sedating antihistamines terfenadine and astemizole were both withdrawn in the late 1990s for the same reason, with QT interval

prolongation having been first reported a decade earlier.[92,93] Fexofenadine, the active moiety of terfenadine remains available. It is worth noting that approximately only 1 in 120 000 patients administered cisapride developed TdP, but this is clearly too large a risk for a drug prescribed for benign conditions.[94]

Antibacterials associated with QT interval prolongation and arrhythmia include macrolides[95] (clarithromycin, erythromycin), fluoroquinolones[96] (ciprofloxacin, ofloxacin) and antifungal agents[97,98] (azoles, amphotericin B). Most antimalarial therapy has been derived from quinine, a drug similar to quinidine; thus, many antimalarial treatments are proarrhythmic, particularly when administered intravenously. Mefloquine, used for malaria prophylaxis, is thought to be relatively safe from a cardiac point of view but sinus bradycardia and aberrant atrioventricular conduction have been described.[99,100] Halofantrine is a recently introduced amino-alcohol used for cure of malaria in cases of chloroquine resistance; QT interval prolongation is associated with its use.[101]

TCAs and carbamazepine affect sodium channels and also have a quinidine-like action but are usually only proarrhythmic in overdose. At high serum levels, TCAs can cause conduction delays, supraventricular arrhythmias or ventricular arrhythmias.[102] Carbamazepine causes an equally wide variety of arrhythmias but does so less commonly and is indicative of severe poisoning.[103]

Older antipsychotics have a recognised association with ventricular arrhythmias. Phenothiazines such as chlorpromazine and thioridazine both cause QT interval prolongation with thioridazine appearing to have the stronger association with arrhythmia.[104,105] Atypical antipsychotics cause QT interval prolongation to a lesser degree and arrhythmia is rare. Haloperidol has been associated with TdP but no reports exist for clozapine or risperidone.[106,107]

β_2-Agonists cause sinus tachycardia by virtue of their effect on cardiac and peripheral β adrenergic receptors but TdP has been reported.[108] This ability of β_2-agonists to prolong the QT interval is enhanced by their hypokalaemic effect. In addition, patients with chronic obstructive pulmonary disease (COPD) and chronic hypoxia may have a subclinical autonomic neuropathy,[109] which will also tend to prolong the QT interval.

1.4.3 Factors Influencing Drug-Related Arrhythmia

Drugs can lead to arrhythmias in any individual but LVSD, myocardial ischaemia, pre-existing atrial arrhythmias or a long baseline QT interval render a patient more susceptible.[110] Electrolyte imbalance is also a factor with hypokalaemia, hypocalcaemia and hypomagnesaemia all associated with QT prolongation.

The identification of human ether-a-go-go related gene (hERG) potassium channels in 1994 as vital components of cardiac electrical conduction has also shed light on the phenomenon of proarrhythmic drugs.[111] Inherited mutations affecting hERG channels results in proarrhythmic long QT interval conditions, such as Romano-Ward syndrome, but it is recognised that drugs affecting hERG channels can have a similar affect. Antiarrhythmics that prolong the QT interval such as amiodarone, flecainide or quinidine do so in part by blocking hERG channels.

A large number of non-cardiac drugs can affect hERG channels, including many of those discussed previously, thus explaining their proarrhythmic potential.[111] It is now routine practice that all new pharmaceutical agents are assessed for hERG channel activity early in the development phase, and this should prevent circumstances such as those involving cisapride and terfenadine from occurring again in the future. It is possible that genetic polymorphisms result in hERG channels that are more susceptible to pharmacological blockage. Further research may identify patients at higher risk of drug-induced arrhythmia.

Drug metabolism or interaction may also play a role in inducing arrhythmia. Drugs that inhibit liver enzymes may lead to increased plasma levels of proarrhythmic drugs. This is best demonstrated with the acknowledgement that most documented arrhythmias with ketoconazole occurred when it was co-administered with terfenadine.[112] Ketoconazole inhibits the cytochrome P450 isoenzyme responsible for metabolising terfenadine. Liver disease or renal impairment may also lead to higher plasma levels of proarrhythmic drugs.

1.5 Pericardial Disease

Drugs are rarely associated with pericardial disease. Drug-induced lupus (DIL) affects the pericardium infrequently;[113] this disorder being most strongly associated with procainamide and hydralazine (table V). Pericarditis with or without an effusion will almost always be accompanied by systemic symptoms, arthralgia and myalgia. Antinuclear antibodies aid with diagnosis and any suspected drug should be discontinued. Pericardial involvement is more common in systemic lupus erythematosus (SLE) than with DIL, and SLE can be exacerbated by drugs (table V).

Table V. Drugs and pericardial disease

Commonly used drugs associated with drug-induced lupus
Strong association
Procainamide
Hydralazine
Quinidine
Moderate association
Methyldopa
Captopril
Chlorpromazine
Isoniazid
Carbamazepine
Penicillamine
Sulfasalazine
Weak association
Enalapril
Disopyramide
Atenolol
Labetalol
Lithium
Phenytoin
HMG-CoA reductase inhibitors
Levodopa
Interferon-α
Drugs that exacerbate SLE
NSAIDS
Antibacterials
penicillins
cephalosporins
erythromycin
tetracyclines
sulfonamide
Antiepileptic drugs
Hydralazine
Cimetidine
Para-aminosalicylic acid

SLE = systemic lupus erythematosus.

There are many cases in the literature of drug-related pericarditis or pericardial effusion that have not been attributed to a lupus-like syndrome. Clozapine[114,115] and 5-aminosalicylic acids[116,117] have a number of reports. Constrictive pericarditis has been associated with bromocriptine[118,119] and cabergoline[120,121] treatments for Parkinson's disease.

1.6 Valvular Disease

Valvular disease has become much less common since the introduction of penicillin significantly reduced the prevalence of rheumatic fever. Drug-induced cardiac valvular disease is extremely rare but some drugs can cause this. Fenfluramine and dexfenfluramine were commonly prescribed appetite suppressants until an association with a carcinoid syndrome-like valvular regurgitation was described in 1997.[122] Recent evidence has identified ergot-derived dopamine agonists pergolide and cabergoline, used in parkinsonism, carry an increased risk for the development of regurgitant valvular disease affecting both sides of the heart.[123]

2. Specific Drug Groups

It is apparent that as we examine the drugs related to particular cardiovascular disorders, some names appear repeatedly. Additionally, some drugs have very strong associations with a particular disorder. These specific drug groups are discussed further.

2.1 Cytotoxics

2.1.1 Anthracyclines

The introduction of doxorubicin in the mid-20th century improved cancer therapy immeasurably. However, it soon became apparent that it was associated with significant cardiotoxicity and this has proven a consistent problem with all subsequent anthracycline preparations. Although there are some reports of rapid-onset LVSD following anthracycline administration,[124] it is usually associated with the development of chronic cardiomyopathy many years after its use.

Cardiotoxicity is dose-dependant. The risk is minimised by restricting the cumulative doxorubicin dose to <400 mg/m^2 with significantly increased rates of cardiomyopathy with doses >550 mg/m^2. The incidence of HF has been reported as 18% at doses between 551 and 600 mg/m^2, increasing further to 36% at doses greater than this.[125,126]

Although some reports of cardiomyopathy regression exist,[127] anthracycline-induced cardiomyopathy should be considered as an irreversible process. There is specific evidence of symptomatic benefit with β-blockers,[128,129] but management is similar to that for any cause of LVSD with cardiac transplantation the only definitive treatment.[130,131]

2.1.2 Anthracycline Cardiotoxicity-Mechanism and Methods of Reducing Risk

The mechanism of anthracycline-induced cardiomyopathy is probably oxidative myocyte injury. Doxorubicin generates free radicals formation whilst simultaneously reducing the production of endogenous antioxidants;[132] myocytes are particularly vulnerable to oxidative stress due to the relatively low levels of antioxidants in the heart.[133]

Cardiotoxicity has not lead to withdrawal of anthracyclines from general use largely because of their antineoplastic efficacy. Instead, attempts have been made to identify methods of reducing the cardiac risk. Minimising anthracycline dosage is practiced, as is its co-administration with other cytotoxic drugs tailored to specific tumours. A slower rate of drug infusion seems to result in reduced cardiotoxicity,[134] but the anti-tumour effect may be compromised. Concomitant administration of antioxidant agents such as dexrazoxane, coenzyme Q (ubidecarenone),[135] probucol and HMG-CoA reductase inhibitors ('statins') may be cardioprotective. Dexrazoxane has shown some promising results but it may cause myelosupression and potentially interferes with the anti-tumour effect.[136,137] A promising new strategy is the development of liposomal anthracycline formulations, which are not readily taken up into myocytes.[138]

All patients exposed to anthracyclines should be considered at risk of cardiomyopathy but older age, prior irradiation, concomitant administration of other chemotherapeutic agents and underlying heart disease make this more likely.[139] Cardiac biomarkers, such as troponins and natriuretic peptides, may help risk stratification but their role is not yet defined.[126]

2.1.3 Trastuzumab

Up to 25% of women diagnosed with breast cancer have tumours that are human epidermal growth factor receptor 2 (HER-2) positive. This form of breast cancer is particularly aggressive, being associated with high rates of relapse and death. Trastuzumab is a humanised monoclonal antibody that targets the HER-2 receptor and has proven to be very effective in treating these tumours. Unfortunately, there are recognised cardiac adverse effects and retrospective analysis has found an association with cardiomyopathy.[140,141] This has led to controversy as to whether the benefit of trastuzumab seen in breast cancer mortality is outweighed by the risk of serious cardiac disease.

There is undoubtedly an independent risk of cardiomyopathy associated with trastuzumab. However, as patients with breast cancer have rarely been treated with trastuzumab alone, the absolute risk has yet to be fully quantified. Six percent of patients treated with trastuzumab monotherapy developed HF, although many of these cases had also been treated with anthracyclines in the past.[141] When used in combination with an anthracycline, 28% of patients developed symptomatic cardiomyopathy.[142] It may be that trastuzumab potentiates the cardiotoxic effect of anthracyclines by an unknown mechanism, but it is likely that it causes cardiotoxicity by another independent mechanism.

Encouragingly, there is evidence that trastuzumab-induced cardiomyopathy, unlike anthracyclines, may be reversible on drug cessation,[143,144] although this remains unverified.

2.2 Cyclo-Oxygenase (COX)-2 and NSAIDs

Despite improvements in drug design and efficacy for a wide variety of illnesses, the choice available to physicians to provide analgesia remains modest and dogged by adverse effects. Opiates cause drowsiness, constipation and dependence, whereas traditional NSAIDs can impair renal function, exacerbate HF and cause gastrointestinal bleeding.

NSAIDs act by reducing prostaglandin production by inhibiting both COX-1 and COX-2. It has long been thought that the analgesic aspect was

generated by COX-2 inhibition and that the adverse gastrointestinal effects were COX-1 mediated. This lead to the development of selective COX-2 inhibitors, such as celecoxib, valdecoxib and others.

COX-2 inhibitors still have some of the adverse effects seen with NSAIDs, namely the ability to increase blood pressure and to exacerbate HF via salt and water retention. Gastrointestinal complications are less common with COX-2 inhibitors,[145,146] and these drugs were initially thought to be a success. However, soon after their release on the market, it became evident that some COX-2 inhibitors increase the risk of MI and stroke.[67-69,146]

2.2.1 COX-2 Inhibitors, NSAIDs and MI

An increased MI rate with rofecoxib was an unexpected finding from the VIGOR (Vioxx Gastrointestinal Outcomes Research) study,[146] which was designed to assess the effect of rofecoxib on the rate of gastrointestinal bleeding compared with naproxen. It was argued that this represented the cardioprotective effect of naproxen, which has aspirin (acetylsalicylic acid)-like qualities. In 2005, the APPROVe (Adenomatous Polyp Prevention with Vioxx) study,[67] which compared rofecoxib and placebo on the rate of adenomatous polyp recurrence, found a 2-fold increase in thrombotic events in the rofecoxib arm and the drug was withdrawn from the market following this.

Valdecoxib was withdrawn 6 months later. Studies assessing its effectiveness following surgery found significantly higher rates of MI, stroke and cardiac arrest associated with its use.[68,69]

Only a few COX-2 inhibitors remain on the market but there are concerns that increased cardiovascular risk is a class effect of these drugs. A study comparing celecoxib and placebo in adenoma prevention did see higher rates of a composite endpoint of MI, stroke and HF in patients treated with celecoxib.[147]

There are a number of mechanisms by which COX-2 inhibition may increase the risk of cardiovascular events. COX-2 inhibitors can increase systemic blood pressure slightly but may accelerate atherosclerosis via effects on mitochondrial oxidative phosphorylation or monocyte chemotaxis.[148] There is probably also a prothrombotic effect of COX-2 inhibition.[149] Thromboxane is a prothrombotic prostanoid that depends on COX-1 for its production whilst prostacyclin (epoprostenol), an antithrombotic agent, is produced using COX-2. Preferential COX-2 inhibition will lead to reduced levels of prostacyclin with a lesser effect on thromboxane, potentially leading to a prothrombotic state.

As the association between COX-2 inhibition and adverse cardiovascular events became apparent, NSAIDs have come under further scrutiny. Different NSAIDs have differing relative effects on COX-1 and COX-2; aspirin as an example, acts almost exclusively on COX-1 and thus has an antithrombotic effect. However, some NSAIDs act predominantly on COX-2 and may therefore carry the same risk as COX-2 inhibitors.

The CLASS (Celecoxib Long-term Arthritis Safety Study) trial,[150] comparing celecoxib with ibuprofen/diclofenac, was similar in size and design to VIGOR; however, although MI was slightly more common in the celecoxib arm, the overall event rate between the groups did not differ. The MEDAL (Multinational Etoricoxib and Diclofenac Arthritis Long-term) study[151] found that the rate of cardiovascular events with diclofenac was the same as with etoricoxib, not surprising given they have similar COX profiles. Meta-analysis has concluded that high-dose ibuprofen and diclofenac, such as COX-2 inhibitors, are associated with an increased risk of vascular events; naproxen does not appear to carry increased risk, reflecting its strong COX-1 propensity.[70,146]

Thus, it appears that both NSAIDS and COX-2 inhibitors are associated with a higher risk of cardiovascular events including MI or stroke. Although some COX-2 inhibitors have been withdrawn from the market, NSAIDs have been available for very many years and are even sold over the counter. A large number of patients depend on these analgesics to control pain and, with a lack of alternative effective treatments, removing these drugs from circulation is not a feasible option.

2.3 Neuro-Psychiatric Agents

2.3.1 Antipsychotics

Schizophrenia carries a poor prognosis, decreasing life expectancy by a mean of 15 years.[152] Although a proportion of this is secondary to suicide,

patients with schizophrenia are twice as likely to experience adverse cardiovascular events as the general population.[153] This can largely be explained by increased rates of smoking, uncontrolled hypertension, diabetes and obesity. However, antipsychotic agents have long been associated with adverse cardiac effects and this may also contribute to overall mortality.

As already discussed, older antipsychotics are associated with QT interval prolongation and ventricular arrhythmias. These agents are also associated with an increased risk of venous thromboembolism[87,88,154] by platelet activation or anticardiolipin antibody production. This may be expounded by their sedative effect, resulting in reduced mobility and dehydration with subsequent haemoconcentration.

Atypical antipsychotics such as risperidone, clozapine and amisulpride have much weaker associations with both venous thromboembolism and arrhythmia; however, they have a stronger association with the development of myocarditis or cardiomyopathy.[8-10] Clozapine has the strongest association, with a number of studies demonstrating this.[11-13]

The first case of clozapine-associated myocarditis to be reported was in 1980[155] following an accidental overdose but most cases have occurred with therapeutic doses. Symptoms of fever and dyspnoea usually appear after approximately 4 weeks of treatment with mortality as high as 50%.[156] In survivors, improvement is seen following clozapine withdrawal.

The pathophysiology is not known. A drug-induced type 1 hypersensitivity reaction is possible as seen with other drugs. This is supported by the finding of peripheral eosinophilia in one-third of cases and half of autopsied hearts, revealing eosinophilic infiltrates in the myocardium.[156] A clozapine-associated hypereosinophilic syndrome has been suggested[13] and other unproven hypotheses include a direct toxic effect on the myocardium or a genetic defect in clozapine metabolism.

The development of chronic cardiomyopathy with long-term clozapine use is less frequently reported than the myocarditis syndrome. The median time to the development of cardiomyopathy is 9 months, although it can present following as many as 7 years of treatment.[11,157] There may be free-radical mediated injury similar to anthracycline-induced cardiomyopathy, or it may represent natural progression from a sub-clinical myocarditis.

2.3.2 Antipsychotics and Dementia

Adverse cardiovascular events associated with atypical antipsychotics also extend to those patients without psychosis. These medications are used in patients with dementia to control aggression, anxiety and other behavioural and psychological problems. Cognitive impairment of any aetiology is a strong independent risk factor for ischaemic stroke;[158] however, the possibility that atypical antipsychotics increase this risk further was first reported in 2002.[85] Analysis of 11 randomised controlled trials concluded that the relative risk of cerebrovascular adverse events (CVAE) with risperidone and olanzapine compared with placebo was 3.2 and 1.8, respectively.[86]

There are a few mechanisms by which antipsychotics could increase the stroke risk, in addition to their potential to precipitate venous thromboembolism. Hyperprolactinaemia, an adverse effect of all antipsychotic agents, may accelerate atherosclerosis by affecting endothelial function and insulin sensitivity.[159]

This apparent increased risk of CVAE is a concern, although further scrutiny of these studies has cast doubt on their conclusion. The definition of CVAE was open to misclassification and overlap, encompassing a wide range of events including ischaemic stroke, transient ischaemic attack, cerebrovascular accident and cerebrovascular disturbance. When divided into serious (defined as death, life threatening, requiring hospitalisation, persistent disability, etc.) and non-serious events, examination of the risperidone studies showed no difference between risperidone and placebo in terms of serious CVAE frequency.[160] Non-serious CVAE were more frequent with risperidone but included episodes such as 'brief unresponsiveness', which may not have represented primary cerebrovascular pathology. The olanzapine studies do not allow CVAE to be divided into serious and non-serious events; however, olanzapine appears to have no increased risk of stroke compared with risperidone or typical antipsychotics.[161]

The evidence of increased risk of stroke with antipsychotic use in dementia is not as robust as initial studies suggested. However, they are probably best avoided in this patient group.

2.3.3 Antidepressants

Antidepressants are another class of drugs that have a poor reputation regarding cardiac adverse effects. As with antipsychotics, the older agents in general carry an increased risk. TCAs have been used for many years but, as already discussed, are associated with LVSD and arrhythmia. Postural hypotension, tachycardia and syncope are also associated with their use, particularly in older patients, in addition to many non-cardiac adverse effects.

Selective serotonin reuptake inhibitors (SSRIs) have largely replaced TCAs for treating mild-to-moderate depression and are also used to treat anxiety and panic disorders. They have a much better adverse-effect profile and there are no associations with arrhythmia or LVSD. Even in overdose, arrhythmia is uncommon, with only citalopram having any significant effect on the QT interval.[162] The main concern about SSRIs has been a potential increased risk for suicidal idealation, although there are suspicions regarding cardiovascular toxicity.[163] An association between SSRIs and vasoconstrictive or haemorrhagic stroke has been investigated. However, large scale reviews have concluded that SSRIs have a very low rate of cerebrovascular adverse reactions.[163]

Venlafaxine, a serotonin and noradrenaline (norepinephrine) reuptake inhibitor, has already been discussed as causing hypertension. Other recognised adverse effects include palpitation, vasodilation and QT interval prolongation (rarely). Because of concerns regarding cardiotoxicity, it is contraindicated in patients with heart disease or hypertension, and an ECG should be performed before treatment is commenced.

2.4 Hormone Therapy

2.4.1 Female Hormone Therapy

Both COC and HRT have been in widespread use since the middle part of the 20th century. COC were first introduced in the 1950s but case reports of pulmonary embolism,[164] MI[165] and stroke[166] associated with their use appeared within a decade.

Oestrogen and progesterone increase pro-coagulant factors (factors VII, X, XII) and reduce anticoagulant factors (factor S, antithrombin) by unknown mechanisms, possibly at a cellular level.[167] Studies have shown that COC increase the risk of venous thrombosis, at least 3-fold,[71] including deep venous thrombosis, pulmonary embolism and cavernous sinus thrombosis. The risk is higher in people with inherited clotting factor deficiencies such as factor 5 Leiden;[168,169] however, there is no association with age or smoking. Lowering the oestrogen content of COC does not appear to have reduced the risk of venous thrombosis,[72] and newer 'third generation' COC containing alternative progesterones may carry an even higher risk.[71]

As already discussed, COC can cause hypertension but may also accelerate atherosclerosis via interfering with aspects of lipoprotein, glucose and insulin metabolism.[170,171] As such, COC increases the risk of stroke and MI. The risk of MI is increased as much as 5-fold,[172] although it appears to only occur in women already at risk of cardiovascular disease, such as smokers and those with hypertension. Studies have shown that COC add negligible or no increased risk of MI in people without other major cardiovascular risk factors.[72,173,174] The risk of ischaemic stroke with COC is increased 4-fold and is again higher in smokers and those with hypertension. A history of migraine also confers an increased risk of COC associated stroke,[175] although this may represent patent foramen ovales and paradoxical embolism.

It is important not to overstate the dangers of cardiovascular events associated with COC. At a population level, the overall risk is low and 87% of MIs in young women occur in those not taking COC.[176]

2.4.2 Hormone Replacement Therapy and Cardiovascular Disease

The observation that women experience major cardiovascular events at a higher rate following menopause suggests that HRT could confer some protection from theses events, and early studies appeared to confirm this.[177,178] However, the Framingham Heart study in 1985[73] was the first to counter this theory, demonstrating a 50% increase in cardiovascular mortality and a 100% increased risk of stroke associated with HRT.

Recent large studies assessing the cardiovascular effect of HRT have yielded conflicting results. Reduced risk of coronary events,[179] increased risk of coronary heart disease,[74] increased risk of stroke[75] and no significant cardiovascular effect[176] have all been reported. Some authors suggest that HRT may have a dual effect, being prothrombotic in the short-term but becoming antiatherogenic with prolonged use.[180] The picture is unclear, and meta-analysis of the major studies has concluded that there is insufficient evidence to support or refute any association between HRT and cardiovascular risk to women.[181] At the present time, there is no longer any justification for prescribing HRT simply as a method of reducing cardiovascular risk.

2.4.3 Male Hormone Therapy

Male hormones have also been linked to cardiovascular disease.[76] Hypoandrogenaemia in men and hyperandrogenaemia in women are associated with insulin resistance, central obesity and adverse lipid profiles. However, there is no strong evidence to support an independent association between androgen levels and cardiovascular events in either men or women. Exogenous androgen therapy, traditionally used for hypogonadism in men, is finding new roles as male contraception and treatment of a number of chronic medical conditions. This has been shown to have both adverse and beneficial effects on cardiovascular risk profiles and there is no evidence that exogenous androgens increase cardiovascular risk.

2.5 Non-Prescription Drugs

Patients presenting with cardiovascular disorders may deny taking any regular prescribed medications but the possibility of their illness being drug-related may still exist. The use of herbal medicines, recreational drugs or illicitly obtained drugs may be overlooked. It is important that physicians are aware of all potential toxins being ingested by patients, prescribed or otherwise.

2.5.1 Recreational Drugs

Cocaine is one of the most common illicit drugs used in the UK and US, and it has many cardiovascular complications.[182] Absorbed quickly through mucous membranes, it is a potent sympathomimetic agent acting via both α and β receptors and with muscarinic receptors.

The highest risk of cardiovascular complications with cocaine use is within the first hour after ingestion.[183] Myocardial ischaemia is induced by increased heart rate and blood pressure combined with coronary vasospasm with users often reporting chest pain. Cocaine also induces platelet activation and has been associated with coronary artery dissection. These effects explain why cocaine increases the risk of MI 24-fold.[184] Reversible cardiomyopathy, acute myocarditis and arrhythmias have all been reported with cocaine.[185-187] It also increases the risk of left-sided endocarditis,[188] via valvular injury secondary to sudden haemodynamic changes.

Narcotic analgesics (heroin or morphine) may cause a variety of arrhythmias, and the inhalation of volatile substances ('glue sniffing') can precipitate lethal arrhythmias.[189] Both amphetamines and 3, 4-methylenedioxymethamphetamine (ecstasy) induce hyperadrenergic states and MI has also been reported with these drugs.[190]

2.5.2 Herbal Medicines

The alternative medicine industry is becoming increasingly popular. As many as 3% of English speaking adults in the US report having taken herbal remedies[191] and this figure may well be higher in non-English speakers. The scientific knowledge of many herbal medicines is sparse, although some cardiovascular effects are recognised.

Veratrum (hellebore) was used for the treatment of hypertension but has fallen out of favour as a result of complications such as heart block and hypotension.[192] Topical application of aconite (monkshood) as an anti-inflammatory can cause fatal arrhythmias, and herbal diuretics such as broom, corn silk and dandelion may lead to QT interval prolongation and ventricular arrhythmias.[193]

Herbal glycosides are found in a wide variety of natural sources and accidental poisoning or suicide attempts with herbal glycosides are not rare, with oleander the most commonly associated herb in the US.[194]

Ephedra (Ma huang) is the herb from which ephedrine was derived. It is used worldwide in many herbal forms including herbal ecstasy and khat for weight loss and energy improvement. Reported

complications include MI, cardiomyopathy, arrhythmias and sudden death.[195-197]

St Johns wort, or hypericum, has been used for centuries for a variety of illnesses. More recently, it has become increasing used as a herbal antidepressant. It is not associated with any particular cardiovascular adverse effect. However, it is important that physicians recognise that it influences the metabolism of many commonly used cardiovascular drugs, such as warfarin, statins and digoxin.[198]

The list of available herbal remedies is extensive and their full pathophysiology is not known. Physicians should recommend patients stop taking any herbal medicines that they suspect is causing cardiovascular disease.

2.5.3 Other Non-Prescribed Drugs

As already discussed, fenfluramine and dexfenfluramine can cause cardiac valvular disease.[122] These drugs have now been removed from the market but may still be used illegally or secreted in herbal diet pills.[199]

Anabolic steroids are used illegally by some athletes to increase performance. Their use is associated with hypertension, left ventricular hypertrophy, myocardial ischaemia and sudden death.[200] This effect is not entirely reversible following cessation,[201] and athletes presenting with cardiovascular disease should be questioned about current or past use.

3. Differentiating Drug-Induced Cardiovascular Disease from Other Aetiologies

The challenge for physicians assessing patients with cardiovascular disease is to distinguish drug-induced disease from other aetiologies. Drug-induced disease will be responsible for only a small fraction of the overall burden of disease and may be easily overlooked. The clinical presentation of a drug-induced cardiovascular disorder will be identical to that secondary to other causes.

Even if one strongly suspects that a drug has been responsible for ill health, it is often impossible to prove. A thorough drug history and awareness of common drug culprits are a physician's best weapons in distinguishing drug-related cardiovascular disease.

3.1 LVSD

LVSD secondary to drugs will appear on echo as global ventricular hypokinesia. This will often distinguish it from ischaemic LVSD, where regional wall motion abnormalities are apparent. Bi-ventricular hypertrophy is characteristic of chloroquine- and hydroxychloroquine-induced cardiomyopathy, but this may also be present in hypertensive heart disease. A peripheral eosinophilia is present in approximately one-third of clozapine-induced myocarditis;[156] however, this test would be neither specific nor sensitive for diagnosing this condition.

The timing to onset of symptoms will rarely help in identifying drug-induced LVSD. For example, anthracycline- or clozapine-induced cardiomyopathy typically present many years after their use, but can occur within weeks to months afterwards.

Myocardial biopsy may help distinguish clozapine-induced myocarditis (eosinophilic infiltrate)[156] or chloroquine-induced cardiomyopathy (myocyte hypertrophy, vacuolated cytoplasm),[21] but this is rarely performed in clinical practice.

3.2 Decompensated HF

A proportion of hospital admissions with decompensated HF will be secondary to drugs. However, it is worth remembering that the absence of drugs, or non-compliance, will be responsible for 15% of cases.[202] Onset of symptoms typically occurs within days or weeks of starting the culprit drug. NSAIDs, verapamil and TDZs are frequently to blame. It is important to ask specifically about NSAIDs, as they may be non-prescribed.

3.3 Hypertension

Drugs associated with hypertension are usually identifiable from a careful drug history. If such drugs are to be introduced (venlafaxine, COC), it would be prudent for physicians to check blood pressure before drug commencement and at regular intervals following this. If hypertension is seen, the drug should be stopped and blood pressure monitored to ensure it returns to baseline levels. It can take up to 1 year for COC-induced hypertension to recover.[59]

Table VI. Drugs associated with cardiovascular disease

Drugs	Acute myocarditis	LVSD/exacerbation of heart failure	Myocardial infarction or stroke	Hypertension	Arrhythmia	Pericardial disease[a]	Other
Antineoplastic agents							
Anthracyclines	+	+++	−	−	+ (during administration)	−	
Trastuzumab	−	++	−	−	−	−	
Paclitaxel	−	+	−	−	−	−	
Cyclophosphamide	+	+	−	−	−	−	
Neuro-psychiatric drugs							
Clozapine	+++	++	−	−	− (prolonged QT interval)	−	
Risperidone	+	−	+	−	− (prolonged QT interval)	−	
Olanzapine	−	−	+	−	++	−	
Phenothiazines	−	−	−	−	++	+	
Haloperidol	−	−	−	−	+	−	
Venlafaxine	−	−	−	++	−	−	
TCAs/carbamazepine	+ (in overdose)	+	−	−	++ (in severe overdose)	+	
Female hormones							
Oral contraceptive	−	−	++	++	−	−	Venous thrombosis
Hormone replacement	−	−	+/− ?	−	−	−	
Analgesia							
NSAIDs	−	++	++	+ (mild)	−	++	
COX-2 inhibitors	−	++	++	+ (mild)	−	−	
Cardiovascular drugs							
β-Adrenoceptor antagonists	−	+	−	−	−	−	
Verapamil/diltiazem	−	++	−	−	−	−	
Doxazosin	−	?	−	−	−	−	
Antimicrobials							
Penicillins	−		−	−	−	++	
Macrolides	−	−	−	−	++	+	
Fluoroquinolones	−	−	−	−	++	−	
Amphotericin	−	−	−	−	+++	−	
Sulfonamides	−	−	−	−	+	+	
Antimalarial	−	−	−	−	+	−	
Immunomodulators							
Chloroquine/ hydroxychloroquine	+	++	−	−	+ (prolonged QT interval)	−	

Continued next page

Table VI. Contd

Drugs	Acute myocarditis	LVSD/exacerbation of heart failure	Myocardial infarction or stroke	Hypertension	Arrhythmia	Pericardial disease[a]	Other
TNFα antagonists	–	+	–	–	–	–	
Others							
Corticosteroids							Dyslipidaemia, glucose intolerance
Erythropoietin	–	++	–	‡	–	–	Venous thrombosis
Calcineurin inhibitors	–	–	+	‡	–	–	Dyslipidaemia
β_2-Adrenoceptor agonists	–	–	–	‡	–	–	
HAART	–	+?	–	–	‡	–	Dyslipidaemia
Recreational drugs							
Cocaine	++	++	++	‡	‡	–	Endocarditis
Opiates	–	–	–	–	+	–	Venous thrombosis, endocarditis

a Drug-induced lupus or systemic lupus erythematosis exacerbation.

COX = cyclo-oxygenase; **HAART** = highly active anti-retroviral therapy; **LVSD** = left ventricular systolic dysfunction; **TCAs** = tricyclic antidepressants; **TNF** = tumour necrosis factor; **–** indicates no association; **+** indicates weak association; **++** indicates recognised association; **+++** indicates strong association; **?** indicates association not clarified.

3.4 MI and Stroke

A MI or stroke secondary to drugs will be clinically identical to those caused by other aetiologies. If drugs known to exacerbate risk factors (corticosteroids, HAART, ciclosporin) cannot be discontinued for clinical reasons, stringent control of blood pressure, diabetes and lipid levels is essential to minimise the risk of cardiovascular events.

3.5 Arrhythmia

Ventricular arrhythmias are of primary concern when discussing drug proarrhythmia. TdP and ventricular tachycardiain the absence of myocardial ischaemia or electrolyte imbalance should always prompt a look at drug history. A resting 12-lead ECG is useful, to look specifically at the QT interval. Suspected culprit drugs should be stopped if possible. Ambulatory ECG may be required and specialist input should be sought.

4. Conclusion

Drug-induced cardiovascular disorders are often difficult to distinguish from cardiovascular disease from other causes. If drugs are to blame, they may be only partly responsible. Many of the drugs discussed in this review are extremely effective at their intended role and the risk of serious cardiovascular complications is low (table VI). It is important to weigh up the benefits and risks of any drug. A high clinical awareness of drug-induced cardiovascular disease is essential and continued pharmacovigilence is imperative if the medical profession is to maintain their patients' trust.

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