RCGP LEARNING

# DRUG INDUCED HEART DISEASE


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One Day Essentials | Cardiology

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# Drug-Induced Heart Disease

## What we prescribe every day — and what it does to the heart

A talk for primary care · 8 September 2026

# What this session will enable

A practical framework for the consultation — not a memorisation exercise

1. **Recognise the cardiovascular phenotypes of medicine-related harm — rhythm, muscle, valves, arteries, fluid retention**
2. **Identify the high-yield QT-prolonging medicines, and the patients in whom they matter**
3. **Apply a structured response to a prolonged QT interval — at 480 ms and at 500 ms**
4. **Recognise the cardiovascular toxicities of modern cancer therapy, and the one that is an emergency**
5. **Know when to stop, when to monitor, when to refer — and who to telephone before the patient leaves**

Everything in this talk is a decision you can make in a ten-minute appointment with a computer, a phlebotomy form and a telephone.

01

# How common is this?

# Adverse drug reactions put people in hospital

## And the drugs responsible are overwhelmingly the ones initiated and continued in primary care

**6.5%**

**of hospital admissions**

Prospective study of 18,820 adults, Merseyside. 80% of these ADRs directly caused the admission. Median 8 bed-days; about 4% of bed capacity.

**16.5%**

**of medical admissions (2019)**

Repeat study, same city, 1,187 medical admissions. Around 40% judged avoidable. Mean 10.5 medicines against 7.8 in those without an ADR.

**Top 4**

**culprit drug classes**

Low-dose aspirin, diuretics, warfarin and NSAIDs in 2004. Diuretics were top of the list again in 2019.

### Be careful with the trend

These two figures are not like-for-like: the 2004 study counted ADR-related admissions across all adult admissions; the 2019 study counted medical admissions only, and included ADRs that merely contributed. The direction of travel is real — polypharmacy and multimorbidity — but do not quote it as a straight doubling.

### 14% of drug withdrawals are cardiac

Of 462 worldwide post-marketing withdrawals 1953–2013, cardiotoxicity was the fourth commonest reason — after liver, immune and neurological harm. Median time from first reported reaction to withdrawal: six years.

### 7 of 10 US withdrawals, 1997–2000

Went for cardiovascular reasons — five of them for torsades de pointes. Eight of the ten posed a greater risk to women than to men. Terfenadine, cisapride, rofecoxib, sibutramine, rosiglitazone: all were once ordinary prescriptions.

*Three of the four leading culprit classes in 2004 were cardiovascular medicines.*

Pirmohamed M et al. BMJ 2004;329:15–19 · Osanlou R et al. BMJ Open 2022;12:e055551 · Onakpoya IJ et al. BMC Medicine 2016;14:10 · US GAO-01-286R (2001)

# Five ways a drug damages the heart

The categories overlap, and the mechanisms compound one another

1

### Rhythm & conduction

QT prolongation and torsades · bradycardia and AV block · new atrial fibrillation · proarrhythmia in the scarred heart

WHERE MOST PRIMARY CARE RISK SITS

2

### Myocardium

LV dysfunction, heart failure, myocarditis and cardiomyopathy: anthracyclines, clozapine, alcohol, anabolic steroids, checkpoint inhibitors

OFTEN REVERSIBLE IF FOUND EARLY

3

### Valves & pulmonary circulation

5-HT2B agonism produces fibrotic, non-calcific regurgitation: fenfluramines, ergot dopamine agonists, benfluorex

RARE NOW — BUT A BEAUTIFUL MECHANISM

4

### Coronary & vascular

Thrombosis, vasospasm and hypertension: NSAIDs and coxibs, fluoropyrimidines, VEGF inhibitors, triptans, cocaine

THE BIGGEST POPULATION-LEVEL HARM

5

### Fluid & metabolic

Sodium and water retention, renal impairment, potassium and magnesium depletion: diuretics, NSAIDs, steroids, PPIs

THE ENABLER BEHIND THE OTHER FOUR

The weighting today is deliberate: most of the talk sits in the first box, because most of what you prescribe sits there too. And at every consultation, one question — could this be the drug chart rather than the disease?

02

# Drug-induced arrhythmia

The QT interval — mechanism, the drug list, and what to do when it is long

# Margaret, 82

Case one — telephone consultation, Tuesday morning

THE CALL

Productive cough, feels rotten, temperature 38.1 °C. Three days of loose stool last week. She sounds tired but not unwell enough for admission.

*You are minded to give her an antibiotic.*

The prescription you are about to write

## Clarithromycin 500 mg bd

*Hold that thought. We come back to Margaret at the end of this section.*

### Her repeat prescriptions

- Bendroflumethiazide 2.5 mg — for hypertension
- Citalopram 20 mg — started after her husband died
- Omeprazole 20 mg — on it for years, nobody has reviewed it
- Donepezil 10 mg — early Alzheimer's disease
- Furosemide 20 mg — added by the heart failure nurse in March

# One channel explains almost the whole drug list

Mechanism — and the idea that makes the rest of this section make sense

## iKr channel blockade

The drug blocks the IKr potassium channel — a large, greasy binding pocket that is promiscuous for lipophilic basic molecules

→

## Delay

Repolarisation is delayed. The action potential lengthens. The QT interval on the surface ECG grows

→

## Early After Depolarisation (EAD)

Calcium channels recover and reopen — early afterdepolarisations, seen as an ectopic falling on the T wave

→

## TdP

Trigger meets dispersed repolarisation: torsades de pointes. Usually syncope; sometimes ventricular fibrillation

**Repolarisation reserve — why most people come to no harm, and some do**

Repolarisation is delivered by several redundant outward currents, not one. Block IKr and the others normally take up the slack — which is why most people given a QT-prolonging drug lengthen their QT by a few milliseconds and come to no harm. Reserve is spent by low potassium and magnesium, bradycardia, structural heart disease, female sex, older age.

*"The drug does not cause torsades. The drug landing on an empty reserve causes torsades."*

Roden DM. J Intern Med 2006;259:59–69 · Roden DM. JACC 2016;67:1639–50 · CredibleMeds clinical overview

# Who has no reserve left?

The medicine is rarely the sole cause — risk stacks

### Ask these at the point of prescribing

- Female sex, and age over 65
- Potassium at or below 3.5 — or magnesium never checked
- Pulse below 50, or anything else slowing the heart
- Heart failure, LVH, prior MI, cardiomyopathy
- Renal or hepatic impairment — sotalol, amisulpride and levofloxacin accumulate
- Already on one QT-prolonging drug, or on a CYP3A4 or CYP2C19 inhibitor
- Vomiting, diarrhoea, an eating disorder, a recent cardioversion
- Family history of sudden death, unexplained drowning or unexplained seizures

**Patient substrate** Female sex · older age · congenital LQTS · structural heart disease

**Physiology** Bradycardia · pauses · AV block

**Electrolytes & illness** Low $K^+$, $Mg^{2+}$, $Ca^{2+}$ · vomiting · diarrhoea · starvation

**Clearance & interaction** Renal or hepatic impairment · CYP inhibition · acute illness

**Drug burden** High dose · rapid escalation · two or more QT drugs together

Torsades de pointes

The Tisdale risk score gets one thing exactly right: two QT-prolonging drugs together is the heaviest single weight on the sheet — heavier than sepsis, heart failure or an acute MI.

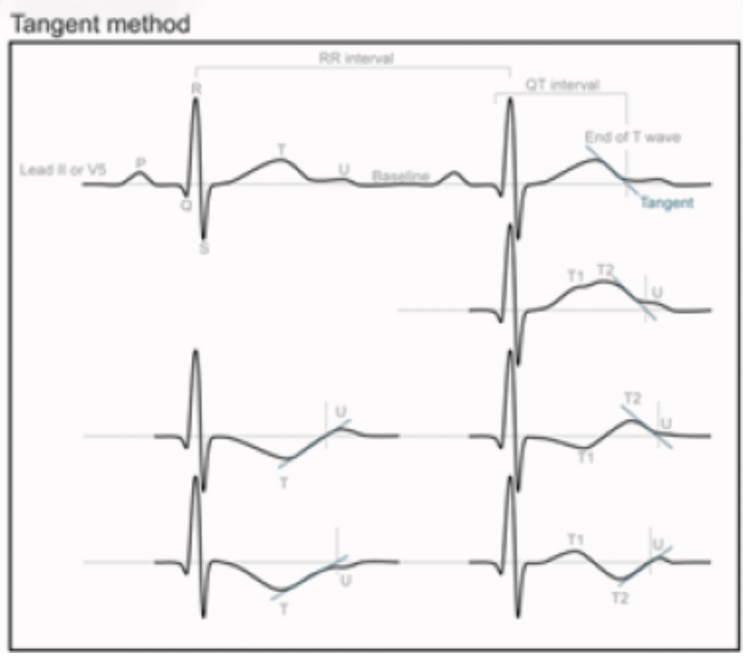
Tisdale JE et al. Circ Cardiovasc Qual Outcomes 2013;6:479–87 · Drew BJ et al. Circulation 2010;121:1047–60

# How to measure QTc manually

Before you act on a QTc, make sure you can measure it properly

The tangent method and is defined as the intersection of a tangent to the steepest slope of the last limb of the T wave and the isoelectric baseline, defined as the voltage at QRS onset.

*A QTc is a decision aid, not a diagnosis. Repeat it, measure it manually between 440 and 540 ms, and look at the QRS.*




*https://www.escardio.org/communities/councils/genomics/scientific-documents-and-publications/cardiogenomics-insights/volume-9/how-to-measure-the-qt-interval/*

# The numbers that change what you do

## Thresholds

### 450 / 460 ms
**UPPER LIMIT OF NORMAL**

- Men / women.
- UK psychiatric guidance often acts at 440 / 470 instead — different purposes, and worth saying out loud rather than pretending one number is the answer.

### > 500 ms
**ACT**

- Marked prolongation and substantially increased torsades risk.
- This is the action threshold in essentially every guideline, whatever the starting point.

### + 60 ms
**ACT**

- A rise of 60 ms or more from the patient's own baseline is high risk even if the absolute value is still under 500.
- This is why a baseline ECG earns its keep.

### Keep the risk in proportion

In a recent primary care study of patients started on QT-prolonging psychotropics, 5 of 85 developed QTc prolongation, none were high risk, and there were no cases of torsades.

The aim of this talk is vigilance, not paralysis. Nobody should leave here frightened of prescribing citalopram.

### But when it happens, it is serious

In population surveillance of symptomatic long QT, 60% of cases were drug-related, 72% had a QTc over 500 ms and 53% were hypokalaemic — and 43% required cardiac resuscitation.

Spontaneous reporting captured about a twelfth of the true incidence.

Drew BJ et al. Circulation 2010;121:1047–60 · Sarganas G et al. Europace 2014;16:101–8 · Garg D et al. Fam Pract 2026;43:cmag048

# Known Risk of torsades — the ones you actually prescribe

## The list, part one

**CredibleMeds "Known Risk" means: prolongs the QT and is clearly associated with torsades even when taken as recommended.**

| Class | Known Risk agents | The point for primary care |
|---|---|---|
| **Antibiotics** | Clarithromycin · erythromycin · azithromycin · ciprofloxacin · levofloxacin · moxifloxacin | Macrolides are a double hit: QT risk plus potent CYP3A4 inhibition. Azithromycin spares the interaction but not the QT. |
| **Antifungals** | Fluconazole | The single 150 mg capsule for thrush is probably the commonest QT-prolonging prescription in general practice. |
| **Antidepressants** | Citalopram · escitalopram | Dose-dependent and MHRA-restricted. Sertraline is only Conditional Risk — hence its first-line status in cardiac disease. |
| **Antiemetics** | Ondansetron · domperidone | Both Known Risk. Cyclizine is on no list at all, and is the easy swap. |
| **Antimalarials** | Hydroxychloroquine · chloroquine | Moved to Known Risk in October 2019 — before COVID, not because of it. High rheumatology and dermatology volumes. |
| **Antipsychotics** | Haloperidol · pimozide · chlorpromazine · levomepromazine · sulpiride | Aripiprazole is the usual switch target; lurasidone and cariprazine have essentially no QT effect. |
| **Cardiac** | Amiodarone · sotalol · flecainide · dronedarone · ivabradine (upgraded 2024) | Sotalol's effect is greatest at slow rates and rises with renal impairment — the classic accumulation trap. |
| **Others** | Methadone · donepezil · anagrelide · cilostazol | Donepezil is the sleeper: huge volumes, in exactly the demographic with least reserve, and it slows the heart as well. |

CredibleMeds QTdrugs lists (crediblemeds.org — free registration; revised three to four times a year, so check the live list)

# “Conditional Risk” does not mean safer

## The list, part two — the enablers

**Associated with torsades only under certain circumstances — excessive dose, low potassium, an interacting drug — or by creating the conditions that induce it.**

| Agent | Why it is on the list | Where it bites |
|---|---|---|
| **Loop and thiazide diuretics**<br>**furosemide, bendroflumethiazide, indapamide** | They do not block IKr at all. They qualify by causing hypokalaemia and hypomagnesaemia — emptying the reserve for something else. | Loop diuretic use is an independent risk factor even after accounting for the potassium level. |
| **Proton pump inhibitors**<br>**omeprazole, lansoprazole, esomeprazole** | Chronic use causes hypomagnesaemia. Also CYP2C19 inhibition, which raises citalopram and escitalopram levels. | Check magnesium in long-term users on any QT drug. It is not on a routine U&E. |
| **Amitriptyline, clomipramine, trazodone, quetiapine, olanzapine** | Risk emerges in overdose, in hypokalaemia, or stacked with another QT drug, rather than at ordinary therapeutic doses. | Enormous low-dose amitriptyline prescribing for neuropathic pain and migraine sits here. |
| **Quinine, hydroxyzine, itraconazole, ketoconazole, metronidazole** | Direct or interaction-mediated. The azoles are dangerous mostly as potent CYP3A4 inhibitors, raising someone else’s levels. | Quinine for nocturnal cramps is discouraged anyway — this is one more reason. |

Bendroflumethiazide plus citalopram plus omeprazole plus clarithromycin is not an exotic combination. It is a dangerous cocktail.

CredibleMeds category definitions and QTdrugs lists

# The UK rules you are expected to know

## MHRA Drug Safety Updates

| Drug (date) | Maximum dose | And also |
|---|---|---|
| **Citalopram / escitalopram (Dec 2011)** | Citalopram 40 mg; over 65 or hepatic impairment 20 mg. Escitalopram 20 mg; over 65 or hepatic impairment 10 mg | Contraindicated in congenital long QT, in known QT prolongation and in combination with other QT-prolonging medicines. Correct electrolytes before starting. If the QTc exceeds 500 ms, withdraw gradually. |
| **Domperidone (May 2014)** | 10 mg up to three times daily, adults and adolescents 35 kg and over. Not usually beyond one week | Now licensed for nausea and vomiting only. Contraindicated in cardiac disease, in heart failure, with other QT drugs, and with potent CYP3A4 inhibitors regardless of their own QT effect. |
| **Hydroxyzine (Apr 2015)** | Adults 100 mg/day; elderly 50 mg/day, and only if use cannot be avoided | Do not prescribe to anyone with a prolonged QT or with risk factors for one — including cardiovascular disease, electrolyte imbalance, bradycardia or a family history of sudden death. |
| **Ondansetron IV (Jul 2013)** | Single IV dose no more than 16 mg under 75 years; no more than 8 mg at 75 and over | Dilute and infuse over at least 15 minutes in anyone 65 or over. Oral dosing is unrestricted — but the drug is Known Risk by any route. |

### Two things that are widely believed and are not actually MHRA rules

There is no numerical citalopram dose cap for patients taking omeprazole — the wording is only that a reduction may be necessary. And the fluoroquinolone restrictions of 2019 and 2024 are about tendons, neurology and aneurysm, not the QT interval.

gov.uk Drug Safety Update: citalopram/escitalopram Dec 2011 · domperidone May 2014 · hydroxyzine Apr 2015 · IV ondansetron Jul 2013

# You have an ECG in front of you. Now what?

## Management

**First, before anything else: repeat it, measure it manually if it is between 440 and 540 ms, and check the QRS width.**

### 450–480 ms

**MODIFY THE CONTEXT**

- Check and correct potassium, magnesium and calcium — and check magnesium explicitly
- Review the whole list for other QT drugs and for CYP inhibitors; stop what is not essential
- Consider dose reduction, or a lower-risk agent in the same class
- Repeat the ECG in one to two weeks after any change. No urgent referral needed

### 480–500 ms

**ACT**

- Everything opposite, and now actively switch unless there is a compelling reason not to
- For citalopram and escitalopram the MHRA wording is: weigh benefit against risk, consider dose reduction or gradual withdrawal
- Correct electrolytes before any rechallenge
- Low threshold for cardiology advice

### > 500 ms or + 60 ms

**STOP AND REFER**

- Stop the suspected drug — but withdraw citalopram and escitalopram gradually, per the MHRA
- Do not stop antpyschotics abruptly. Manage the QT by other means and speak to the responsible psychiatrist first
- Correct electrolytes urgently. Urgent cardiology review
- With syncope or presyncope this is a 999 call — that patient may have had an aborted torsades

And do not reflexively stop essential specialist therapy in a stable patient — telephone the team that started it.

Synthesised from NHS Specialist Pharmacy Service, BHRS 2019 guidance, MHRA Drug Safety Updates and the AHA/ACCF 2010 statement

# Safer swaps

## The slide to photograph

| Instead of… | Consider | Why |
|---|---|---|
| **Clarithromycin or erythromycin** | Doxycycline, amoxicillin or co-amoxiclav | Neither is on the QT lists, and neither inhibits CYP3A4. If a macrolide is unavoidable, azithromycin at least avoids the interaction. |
| **Fluconazole for vaginal candidiasis** | Topical clotrimazole | No systemic exposure, no QT risk, no CYP inhibition. Probably the single easiest win in this whole talk. |
| **Citalopram or escitalopram** | Sertraline | Conditional Risk only, minimal cardiac interactions, and the SPS first-line choice in coronary disease. Mirtazapine is also reasonable. |
| **Amitriptyline for neuropathic pain** | Duloxetine, gabapentin or pregabalin | None appear on the CredibleMeds lists. Tricyclics also raise heart rate and prolong the PR interval. |
| **Ondansetron or domperidone** | Cyclizine | Cyclizine is on no list. Prochlorperazine is low-effect. Metoclopramide is Conditional Risk and capped at five days for other reasons. |
| **Haloperidol or quetiapine in agitation** | Aripiprazole — after non-drug measures | Essentially no QT effect at therapeutic doses, and the named switch target in UK algorithms. Lurasidone and cariprazine likewise. |
| **Hydroxyzine for itch** | Cetirizine or loratadine | Not on the lists — and hydroxyzine is contraindicated outright in anyone with QT risk factors. |
| **Quinine for night cramps** | Stretching, hydration, diuretic review | Conditional Risk plus other toxicity, and already discouraged for this indication. |
| **A long-term PPI, unreviewed** | Deprescribe or step down | Chronic use causes hypomagnesaemia — which is how a drug with no cardiac action ends up on a torsades list. |

CredibleMeds Therapeutic Options · NHS Specialist Pharmacy Service · medsafetyscan.org screens a whole medication list at once

# Back to Margaret

Case one, resolved

## Five hits on one reserve

- Bendroflumethiazide and furosemide — potassium and magnesium
- Citalopram 20 mg — Known Risk, and already at her age-appropriate maximum
- Omeprazole — magnesium loss, and CYP2C19 inhibition raising her citalopram level
- Donepezil — Known Risk, and it slows her heart
- Diarrhoea last week — more potassium out
- She is 82 and female: two more risk factors she cannot do anything about

## What you actually do

- Doxycycline instead of clarithromycin — no QT risk, no CYP3A4 inhibition
- U&E and magnesium today; aim for potassium ≥ 4.0 and magnesium in the upper half of the range
- ECG, given the number of hits and the donepezil — and check her pulse
- Flag the omeprazole and the citalopram for a structured medication review
- Remember: hypokalaemia will not correct until the magnesium is replete

## And tell her — this is the part we usually skip

"If you faint, feel like you are about to faint, or notice your heart racing or thumping out of the blue, contact us — and if you faint, that is urgent." Add a sick-day rule: get in touch if vomiting or diarrhoea lasts more than a day or two, because that is what turns a safe drug into a dangerous one. And tell any other prescriber, dentist or pharmacist what she is taking.

03

# Beyond the QT interval

Conduction and atrial fibrillation · heart muscle · valves · coronary arteries

# Slow rhythms, new atrial fibrillation — and digoxin

## Rhythm, continued

### Bradycardia and AV block

- Beta-blockers — including timolol eye drops, absorbed enough to slow the heart
- Beta-blocker plus verapamil or diltiazem — additive on conduction and contractility; watch the split-prescriber trap
- Donepezil and other AChE inhibitors — syncope aHR 1.76, bradycardia 1.69, pacemaker 1.49. A falls referral is not the answer
- Lithium — a normal level does not exclude it; 40% of reported cases were at or below therapeutic range
- Ivabradine — symptomatic bradycardia 5% against 1%; stop it if AF develops

### New atrial fibrillation — ask about these

- Alcohol — abstinence cut recurrence from 73% to 53% in a randomised trial. This is treatment, not lifestyle advice
- Levothyroxine over-replacement — the risk sits specifically at TSH below 0.1. Check it in every new AF on thyroxine
- Corticosteroids — at 7.5 mg prednisolone equivalent or more, OR 6.07. Below that, no significant excess
- Ibrutinib and other BTK inhibitors — AF in about 10% on ibrutinib; 2–4% on acalabrutinib or zanubrutinib

The drug is usually the unmasker, not the cause. In one series 42% of patients presenting with AV block were on a beta-blocker — and about 85% still needed a pacemaker. Stop the drug, but refer anyway if the block is high grade.

And the CAST lesson: flecainide and encainide suppressed post-MI ectopy beautifully and doubled mortality. Class Ic belongs only in a structurally normal heart — check before a pill-in-the-pocket script, and re-check if the patient later has an MI.

### Digoxin — still the classic

Toxicity happens inside the therapeutic range, and the precipitants are all yours: renal impairment, hypokalaemia from a diuretic, hypomagnesaemia, and interactions with amiodarone, verapamil, macrolides and itraconazole. Nausea and confusion in an elderly patient after a chest infection is the presentation; yellow-tinged vision is the giveaway; bidirectional VT is pathognomonic. The potassium predicts mortality better than the digoxin level does.

Gill SS et al. Arch Intern Med 2009 · Voskoboinik A et al. NEJM 2020 · van der Hooft CS et al. Arch Intern Med 2006 · CAST, NEJM 1991

# Five routes to drug-induced heart failure

## Mechanism predicts reversibility, monitoring and urgency

| Mechanism | High-yield drugs | What it means in practice |
|---|---|---|
| **Direct myocyte injury** | Anthracyclines · clozapine · high-dose cyclophosphamide | Dose-related and often persistent. Clozapine myocarditis (~0.7%, case fatality 8–13%) presents on days 14–28 as fever, tachycardia and malaise — the patient in week three with "flu" is the missed case. Ring the clozapine clinic the same day. |
| **Lost survival signalling** | HER2-targeted therapy — trastuzumab | Dysfunction, not death. Largely reversible with early detection and conventional heart failure therapy. |
| **Negative inotropy** | Verapamil and diltiazem in HFrEF · flecainide · disopyramide · dronedarone | Avoid in LV dysfunction, or use only under specialist direction. |
| **Fluid retention and renal effects** | NSAIDs and coxibs · corticosteroids · pioglitazone | The commonest cause of a decompensation you can actually reverse — and the one most often missed on the repeat screen. |
| **Toxic and inflammatory** | Alcohol · anabolic steroids · hydroxychloroquine · checkpoint inhibitors | Alcohol accounts for 23–47% of "idiopathic" dilated cardiomyopathy in heavy drinkers, and abstinence is treatment. Anabolic steroid users: mean LVEF 52% against 63%. |

Hydroxychloroquine is the quiet one: conduction disease dominates at 85%, median onset seven years. A new bundle branch block or AV block in someone on long-term hydroxychloroquine for RA or SLE is not incidental.

Page RL et al. Circulation 2016;134:e32–e69 · Siskind D et al. ANZJP 2020 · Domínguez F et al. Eur Heart J 2024;45:2294 · Baggish AL et al. Circulation 2017

# In decompensated heart failure, ask: what changed?

New oedema, 2–3 kg of weight, breathlessness or a creatinine rise after a medication change is a clinical trigger

### NSAIDs and coxibs

Sodium retention and renal haemodynamic effects — and they blunt the diuretic and the ACE inhibitor or ARB you have already prescribed

### Pioglitazone

Fluid retention. Avoid in symptomatic heart failure; it is a contraindication, not a caution

### Verapamil and diltiazem

Negative inotropy. Avoid in HFrEF unless specialist-directed — and remember they are CYP3A4 inhibitors too

### Systemic corticosteroids

Fluid retention, hypertension and metabolic deterioration — and a six-fold odds of new AF at 7.5 mg or more

### Class I and selected antiarrhythmics

Negative inotropy and proarrhythmia in the structurally abnormal heart

### Interactions and electrolytes

Renal deterioration, potassium disturbance and a changed drug concentration destabilise a compensated patient

**The single highest-yield habit on this slide**

When a heart failure patient decompensates, open the repeat screen before you open the referral form — and look specifically for an NSAID bought over the counter, a steroid course for a chest or a joint, and a rate-limiting calcium blocker started by someone else.

Page RL et al. Circulation 2016;134:e32–e69 · van der Hooft CS et al. Arch Intern Med 2006

# One receptor explains every drug that damages a valve

Valves

5-HT2B agonism on valvular interstitial cells → proliferation and matrix deposition → thickened, restricted, plaque-encased leaflets. Regurgitation, never stenosis, and characteristically without calcification. It is the same mechanism as carcinoid heart disease — which is the diagnostic clue.

### Fenfluramine and dexfenfluramine

Withdrawn in 1997 after 24 women developed valve disease within a year of starting fen-phen. Phentermine was exonerated — the culprit was fenfluramine's metabolite, norfenfluramine.

### Pergolide and cabergoline at Parkinson's doses

Two NEJM papers in January 2007 killed pergolide within months: moderate or severe regurgitation in 23% and 29% against 6% of controls. Non-ergot agonists carried no excess risk.

### Benfluorex — Mediator, France

The same molecule and the same receptor as fen-phen, sold in France for a different indication under a different name — and withdrawn twelve years later. A regulatory failure, not a scientific one.

### The question you will actually be asked: my patient is on long-term cabergoline for a prolactinoma

Hyperprolactinaemia doses are 10 to 50 times lower — 0.25 to 1 mg per week, not per day. Echo studies show a tricuspid regurgitation signal (OR 3.74), but the only hard-endpoint study, of 646 patients against 2,660 controls, found no excess valve replacement or heart failure at any cumulative dose. UK joint guidance: baseline echo before starting; at 2 mg per week or less, first surveillance scan at five years and five-yearly thereafter — not annually. Above 2 mg per week, annual. Do not attribute an incidental mild regurgitation to the drug without the fibrotic features.

Connolly HM et al. NEJM 1997;337:581 · Schade R and Zanettini R, NEJM 2007;356:29 and 39 · Steeds RP et al. BSE/BHVS/SfE position statement, Echo Res Pract 2019

# NSAIDs: the biggest population-level cardiac harm we cause

## Coronary and vascular

| Rate ratio against placebo | Coxibs | Diclofenac | Ibuprofen | Naproxen |
|---|---|---|---|---|
| **Major vascular events** | 1.37 | 1.41 | 1.44 | 0.93 |
| **Major coronary events** | 1.76 | 1.70 | 2.22 | 0.84 |
| **Heart failure hospitalisation** | 2.28 | 1.85 | 2.49 | 1.87 |

639 trials, over 300,000 patients. Absolute excess: about 3 additional major vascular events per 1,000 patients per year for coxibs and for diclofenac — the number worth quoting to a patient.

### Read the table three ways

- Diclofenac behaves like a coxib — 1.41 against 1.37
- Naproxen is the coronary outlier, because its long half-life sustains platelet COX-1 blockade
- Every one of them roughly doubles heart failure admissions, naproxen included
- Add the atrial fibrillation signal (RR 1.12; 1.53 in new users) and the blood pressure effect to the ledger

### What this means on Monday morning

- Systemic diclofenac is contraindicated in ischaemic heart disease, peripheral arterial disease, cerebrovascular disease and NYHA II–IV heart failure
- The contraindication does not apply to topical formulations — a genuinely useful and underused option
- Naproxen with a PPI is the pragmatic oral choice when the worry is coronary
- But there is no safe oral NSAID in heart failure or significant CKD

Bhala N et al, Coxib and traditional NSAID Trialists' Collaboration. Lancet 2013;382:769–79 · MHRA/EMA diclofenac review, June 2013 · PRECISION, NEJM 2016

# In resistant hypertension, the drug chart is a diagnostic test

Cheaper and faster than a renal artery duplex — and it is the mechanism by which several drugs in this talk cause harm

### NSAIDs

Prostaglandin-mediated sodium and water retention — and they blunt the ACE inhibitor, ARB and diuretic you have already prescribed

### Venlafaxine

Dose-dependent: sustained hypertension in 1.7% below 100 mg, rising to 9.1% above 300 mg. Check the dose before adding an antihypertensive

### VEGF inhibitors and TKIs

Number needed to harm of 6 for any hypertension. Expected, early, and a marker of on-target effect — treat it, do not stop the drug

### Ciclosporin and tacrolimus

Calcineurin-inhibitor vasoconstriction and sodium retention. Very common after transplantation

### ADHD stimulants

Beyond five years of use, adjusted OR 1.80 for hypertension. The signal is blood pressure, not arrhythmia — so measure it at every titration

### Decongestants, ESAs, combined oral contraceptives

Modest at population level but real in the susceptible individual. Erythropoiesis-stimulating agents: RR 1.49

### Liquorice

Glycyrrhizin blocks 11β-HSD2, so cortisol activates the mineralocorticoid receptor. Hypertension with hypokalaemia and both renin and aldosterone suppressed is nearly pathognomonic — and nobody asks

**Read the drug chart before you order the scan.**

Salerno SM et al. 2005 · Zhang L et al. 2024 · npj Precision Oncology 2018;2:13 · PLOS ONE ESA meta-analysis

04

# Cardio-oncology

You will not prescribe any of these drugs. You will see every one of these patients.

## 3.5m

**people living with cancer in the UK**

Up from about 3 million in 2020, with over 420,000 new diagnoses a year. Around one in four is living with long-term consequences of treatment.

## 10 of 20

**adult cancers carry excess heart failure risk**

In 126,120 UK survivors against 523,541 matched controls, drawn from primary care records — this is your own population.

## 1.9 yrs

**before CV death overtakes cancer death**

In over-80s with melanoma; 4.8 years in 60–79-year-olds with bladder cancer. Strongly age- and cancer-dependent — but real.

*QRISK3 does not ask about anthracyclines or mediastinal radiotherapy. Until it does, you are the risk calculator.*

# David, 64

Case two — a routine appointment, and you are twenty minutes behind

THE APPOINTMENT

Metastatic melanoma, five weeks into pembrolizumab. He books a routine appointment: “a bit breathless on the stairs, and my arms feel heavy — I thought it was the chemo catching up with me.”

**On examination**

- Pulse 96 and regular, blood pressure 118/74
- Chest clear, no oedema, oxygen saturation 97%
- Mild proximal weakness in both arms; he blames deconditioning
- He looks reasonably well.

The question

Routine bloods and review in a fortnight?

| ~1% | 50% | 34 d |
|---|---|---|
| incidence of ICI myocarditis | mortality, up to | median onset |

## This is a same-day emergency.

Troponin and ECG today, and speak to his oncology team before he leaves the building. The proximal weakness is not deconditioning — myositis overlaps with checkpoint-inhibitor myocarditis in about a quarter of cases, and it is the clue that turns a vague consultation into a diagnosis.

*The whole of this section is really one sentence: in a patient on a checkpoint inhibitor, a cardiac symptom is a medical emergency.*

# Checkpoint-inhibitor myocarditis

## The one not to miss

**Rare enough that you may see it once or twice in a career. Lethal enough that missing it once is the whole story.**

### ~1%
**INCIDENCE**

0.3–1.4%. Combination ipilimumab and nivolumab carries several times the monotherapy risk

### 27–50%
**MORTALITY**

Among the most lethal drug reactions in medicine, and the outcome turns on how fast steroids are started

### 34 days
**MEDIAN ONSET**

IQR 18–75 days; about 80% within the first ten weeks — but it has occurred two years in

### > 50%
**HAVE A NORMAL EF**

38% of major adverse events occurred with a normal ejection fraction. A reassuring echo does not exclude it

### How it actually presents

- Chest pain, breathlessness, palpitations, fatigue — often mild, and often blamed on the cancer
- Troponin raised in 94%; the ECG abnormal in over 89% — but a normal ECG does not exclude it
- The clue is the overlap: new myalgia, proximal weakness, ptosis or diplopia alongside it

### What you do, today

- Any cardiac symptom in a patient on a checkpoint inhibitor is a same-day assessment
- Troponin and ECG immediately; assume myocarditis until it is excluded
- Contact oncology before the patient leaves. Treatment is high-dose steroids, and delay is what kills

Mahmood SS et al. JACC 2018;71:1755–64 · Salem J-E et al. Lancet Oncol 2018;19:1579–89 · 2022 ESC Guidelines on cardio-oncology

# Same-day, not next-week

## Red flags in a patient on active cancer therapy

| If they are on… | And they report… | Then |
|---|---|---|
| **Any immune checkpoint inhibitor** | Any cardiac symptom at all — or new muscle weakness, ptosis or diplopia | Same day. Troponin, ECG, contact oncology. Assume myocarditis |
| **5-FU or capecitabine** | Chest pain during, or within 72 hours of, treatment | Stop the drug, ECG, same-day oncology. A normal troponin does not reassure |
| **Anthracycline or trastuzumab** | New breathlessness, orthopnoea, ankle swelling, falling exercise tolerance | NT-proBNP and ECG now, echo within the week, contact oncology |
| **VEGF inhibitor or TKI** | BP 180/110 or above, severe headache, visual disturbance, focal neurology | Urgent — this is the threshold at which cancer treatment is interrupted |
| **BTK inhibitor (ibrutinib)** | Palpitations or an irregular pulse; any bleeding | ECG for AF. Do not start warfarin. Discuss with haematology before anticoagulating |
| **Nilotinib or ponatinib** | Claudication, a cold or painful limb, TIA, angina | Urgent vascular or cardiology assessment — arterial occlusion is the class effect |
| **Trastuzumab deruxtecan** | A new dry cough or breathlessness | Think interstitial lung disease, not heart failure. Same-day oncology |

2022 ESC Guidelines on cardio-oncology, Eur Heart J 2022;43:4229–4361

# The survivor sitting in front of you

## Long-term care — the review that has no other owner

### The annual review the guideline mandates

- Blood pressure · lipids · HbA1c · ECG · natriuretic peptide
- Clinical review of symptoms and exercise tolerance
- Active management of smoking, weight, alcohol and exercise
- A Class I recommendation for anyone treated with a potentially cardiotoxic drug, or with radiotherapy exposing the heart

### The exposures worth coding in the record

- Cumulative anthracycline dose, especially 250 mg/m² doxorubicin-equivalent or more
- Left-sided breast radiotherapy; mediastinal radiotherapy for Hodgkin lymphoma
- Trastuzumab, particularly sequentially after an anthracycline
- Any cancer treated in childhood; any cardiac dysfunction documented during treatment

**NT-proBNP > 2,000 ng/L**

Specialist assessment and echocardiography within 2 weeks

**NT-proBNP 400 – 2,000**

Specialist assessment and echocardiography within 6 weeks

**NT-proBNP < 400 ng/L**

Heart failure less likely — but keep the differential wide: anaemia, effusion, PE, radiation lung fibrosis, drug-induced ILD, recurrence

### The blind spot

A normal NT-proBNP does not exclude cancer-therapy-related cardiac dysfunction. The ESC now grades it, and mild disease is defined by a fall in global longitudinal strain of more than 15% with a completely normal ejection fraction — invisible to a natriuretic peptide and to a standard echo report. If the pre-test probability is high, ask for an echo with strain, or refer, whatever the blood test says.

NICE NG106 · 2022 ESC Guidelines on cardio-oncology · BSE/BCOS echocardiography guideline, JACC CardioOncol 2021;3:1–16

# What do we miss?

## And what would help us recognise it?

# Seven things to take back to the surgery

1. Before a Known Risk drug, ask one question: has this patient any repolarisation reserve left? Age, sex, potassium, magnesium, pulse — and what they are already taking.
2. Correct the potassium and the magnesium before you blame the drug — and remember potassium will not correct until magnesium is replete.
3. Over 500 ms, or 60 ms up from baseline: stop and refer. Gradually for citalopram and escitalopram. Never for clozapine without speaking to psychiatry.
4. Topical clotrimazole instead of fluconazole. Doxycycline instead of clarithromycin. Sertraline instead of citalopram. Cyclizine instead of ondansetron.
5. When a heart failure patient decompensates, read the repeat screen first: an NSAID, a steroid course, pioglitazone or a rate-limiting calcium blocker.
6. Diclofenac carries coxib-level risk and is contraindicated in arterial disease and heart failure. No oral NSAID is safe in heart failure .
7. Any cardiac symptom in a patient on a checkpoint inhibitor is a same-day emergency. And every cancer survivor needs an annual cardiovascular review that nobody else is going to do.

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# Where to look things up

## Resources and key references

### Tools worth a bookmark

- crediblemeds.org — the QTdrugs lists, and Therapeutic Options for QT-sparing alternatives. Free, registration required, revised three to four times a year
- medsafetyscan.org — enter a whole medication list plus risk factors, and get a combined assessment
- sps.nhs.uk — NHS Specialist Pharmacy Service: managing medicines associated with QT prolongation
- brugadadrugs.org — for the patient with Brugada syndrome or a family history of sudden death

### Guidelines

- 2022 ESC Guidelines on cardio-oncology. Eur Heart J 2022;43:4229–4361
- MHRA Drug Safety Update archive at gov.uk — citalopram 2011, domperidone 2014, hydroxyzine 2015
- Page RL et al. Drugs that may cause or exacerbate heart failure. Circulation 2016;134:e32–e69
- NICE NG106 — chronic heart failure diagnosis and management

### Selected evidence cited in this talk

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