

Sinus node and metabolic cardiac agents

A small group of cardiac drugs that work outside the big families: ivabradine slows the sinus node's own pacemaker current, while ranolazine and trimetazidine make ischaemic heart muscle work more efficiently without lowering blood pressure.

Online guide: <https://www.medguideglobal.com/pharmacology/cardiovascular/sinus-node-and-metabolic-agents>

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Quick revision

One Liner: These are the cardiac drugs that do not fit the main families: ivabradine blocks the pacemaker or funny current in the sinoatrial node and slows the heart without touching contraction, ranolazine blocks the late sodium current so ischaemic muscle is less calcium-loaded, trimetazidine shifts the heart from burning fat to burning glucose, and nicorandil opens ATP-sensitive potassium channels.

1. Ivabradine selectively blocks the funny current, written I(f), by inhibiting hyperpolarisation-activated cyclic nucleotide-gated channels in the sinoatrial node. [1]
2. Blocking that current slows the phase 4 pacemaker depolarisation of the sinoatrial node, which is what lowers the heart rate. [5]
3. Ivabradine reduces heart rate but does not affect myocardial contraction, relaxation or ventricular repolarisation - the property that separates it from a beta blocker. [1]
4. Its licensed heart failure role requires symptomatic stable heart failure with an ejection fraction of 35% or less, sinus rhythm, a resting heart rate of at least 70 beats per minute and a maximally tolerated beta blocker already in place. [1]
5. Phosphenes - brief luminous visual disturbances - are the signature ivabradine adverse effect, occurring in 3% of patients in the SHIFT trial against under 1% on placebo. [1]
6. Ivabradine increases the risk of atrial fibrillation, and the drug is discontinued if atrial fibrillation occurs. [1]
7. Ranolazine inhibits the late inward sodium current in ischaemic heart muscle cells, lowering intracellular sodium and therefore the calcium that enters through sodium-calcium exchange. [2]
8. Less intracellular calcium means lower ventricular wall tension and lower myocardial oxygen consumption, achieved without significantly changing blood pressure or heart rate. [2]
9. Ranolazine also prolongs the QT interval by inhibiting the rapid delayed rectifier potassium current, yet its main late-sodium action is credited with the low risk of torsades de pointes despite that prolongation. [2]
10. Trimetazidine inhibits mitochondrial long-chain 3-ketoacyl coenzyme A thiolase, shifting cardiac energy production from fatty acid oxidation towards glucose oxidation. [6]
11. Burning glucose rather than fat is oxygen-sparing, producing about 15% more ATP per unit of oxygen used, and it happens without any detectable effect on heart rate or vascular tone. [6]
12. Trimetazidine can cause extrapyramidal complications, which makes it unsuitable for people with Parkinson disease. [6]
13. Nicorandil opens ATP-sensitive potassium channels, shortening action potential recovery, refractoriness and repolarisation reserve in cardiomyocytes other than sinoatrial node cells, with shortened QT intervals. [5]
14. Ivabradine is metabolised extensively by CYP3A4, and concurrent use of a potent CYP3A4 inhibitor is contraindicated. [1]
15. Ranolazine is also mainly a CYP3A4 substrate, so strong inhibitors and inducers of that enzyme are contraindicated with it as well. [2]
16. The evidence base for trimetazidine is more modest than its mechanism suggests; a meta-analysis of double-blind trials found it was not beneficial as monotherapy for any studied outcome. [7]

Overview

1. This group collects the cardiac drugs that do not belong to any of the large mechanism families. What they share is negative rather than positive: none of them works through the renin-angiotensin system, adrenergic receptors, calcium channels, the nephron or the clotting cascade. They are gathered here because each acts on a target that is worth studying on its own, and because in practice they are all used as additions to conventional therapy rather than instead of it. [2][1]
2. Ivabradine is the sinus node agent. Sinoatrial node cells drift slowly upward towards threshold between beats, and that drift is carried by a current named the funny current, I(f), flowing through hyperpolarisation-activated cyclic nucleotide-gated channels. Ivabradine blocks that current, so the drift takes longer and the heart beats less often. Crucially, it reduces heart rate without affecting myocardial contraction, relaxation or ventricular repolarisation, which is precisely what separates it from a beta blocker. [1][5]
3. Ranolazine and trimetazidine are the metabolic agents, and both improve ischaemia without altering the circulation. Ranolazine inhibits the late inward sodium current of ischaemic myocytes, so intracellular sodium falls, less calcium is drawn in by sodium-calcium exchange, wall tension eases and oxygen consumption drops - all with no significant change in blood pressure or heart rate. Trimetazidine works one level further back, shifting the fuel the heart burns from fatty acids to glucose, which produces more ATP for the same oxygen. [2][6]
4. Nicorandil sits slightly apart again, opening ATP-sensitive potassium channels and shortening action potential recovery in cardiomyocytes other than those of the sinoatrial node. Across the whole group the evidence is uneven and the positioning is deliberately second-line: ranolazine is recommended for people still symptomatic on standard antianginal therapy, trimetazidine holds only a class IIb recommendation in European guidance, and nicorandil is described as a second-line option in stable angina. [5][2][6]

Classification and drug examples

Intro: The useful division here is by target, because that is the only thing these agents do not share. One acts on the pacemaker current of the sinoatrial node, two act on how ischaemic muscle handles ions or fuel, and one opens potassium channels.

1. Name: Sinus node agents - funny current inhibition

1. Note: Drugs that lower heart rate by acting on the sinoatrial node's own pacemaker current rather than on adrenergic receptors or calcium channels. The revised Vaughan Williams scheme gives HCN channel blockers their own category, class 0.

Name: Ivabradine

Route: Oral

Note: Selectively blocks the I(f) funny current by inhibiting HCN4 channels, reducing the rate of phase 4 pacemaker depolarisation. It lowers heart rate without affecting contraction, relaxation or ventricular repolarisation. Extensively metabolised by CYP3A4, with an active major metabolite. [1][5] [5][1]

2. Name: Metabolic and late sodium current agents

2. Note: Agents that improve the balance between myocardial oxygen supply and demand from inside the cell, either by reducing calcium loading or by changing the fuel burnt. Neither meaningfully alters heart rate or blood pressure, which is what makes them add-on options when haemodynamic headroom has run out.

1. Name: Ranolazine

1. Route: Oral

1. Note: Inhibits the late inward sodium current in ischaemic myocytes, lowering intracellular sodium and the calcium that follows it in, so wall tension and oxygen consumption fall. It also inhibits the rapid delayed rectifier potassium current and therefore prolongs the QT interval. Mainly a CYP3A4 substrate. [2]

2. Name: Trimetazidine

2. Route: Oral

2. Note: Inhibits mitochondrial long-chain 3-ketoacyl coenzyme A thiolase, moving cardiac metabolism from fatty acid oxidation towards the more oxygen-efficient oxidation of glucose. It has no detectable chronotropic or vasomotor effect, and it is contraindicated in Parkinson disease. [6] [2][6]

3. Name: Potassium channel activators

3. Note: Agents that open ATP-sensitive potassium channels in cardiac muscle. In the revised Vaughan Williams classification they occupy a category of their own as metabolically dependent potassium channel openers.

Name: Nicorandil

Route: Oral

Note: Opens ATP-sensitive potassium channels, shortening action potential recovery, refractoriness and repolarisation reserve in all cardiomyocytes other than sinoatrial node cells, with shortening of the QT interval. Described as a second-line option in stable angina. [5] [5]

Mechanism of action

Summary: Four separate targets sit under one heading. Ivabradine blocks the HCN channels carrying the sinoatrial funny current, slowing the pacemaker without touching contraction. Ranolazine blocks the late sodium current so ischaemic cells accumulate less calcium. Trimetazidine blocks a mitochondrial thiolase and switches the heart's fuel to glucose. Nicorandil opens ATP-sensitive potassium channels.

Target: HCN (funny current) channels of the sinoatrial node; the late inward sodium current; mitochondrial long-chain 3-ketoacyl coenzyme A thiolase; ATP-sensitive potassium channels

1. Step: 1

1. Title: The sinoatrial node sets its own rate with the funny current

1. Detail: Between beats, pacemaker cells depolarise slowly towards threshold in what is called phase 4. That slow rise is carried by I(f), flowing through hyperpolarisation-activated cyclic nucleotide-gated channels. [5][1]

2. Step: 2

2. Title: Ivabradine blocks that current selectively

2. Detail: By inhibiting HCN4 channels it reduces the phase 4 depolarisation rate, so each cell takes longer to reach threshold and the heart rate falls. Contraction, relaxation and ventricular repolarisation are unaffected. [1]

3. Step: 3

3. Title: A slower rate helps the failing or ischaemic heart

3. Detail: Fewer beats mean less oxygen demand and a longer diastolic filling period. That is the rationale for its use in symptomatic heart failure with a reduced ejection fraction and in stable angina. [1][5]

4. Step: 4

4. Title: Ischaemic myocytes carry an abnormal late sodium current

4. Detail: During ischaemia a persistent inward sodium leak raises intracellular sodium, which drives calcium in through the sodium-calcium exchanger and leaves the cell calcium-overloaded and stiff. [2]

5. Step: 5

5. Title: Ranolazine interrupts that leak

5. Detail: Inhibiting the late inward sodium current lowers intracellular sodium and therefore calcium entry, which decreases ventricular wall tension and myocardial oxygen consumption without significantly affecting blood pressure or heart rate. [2]

6. Step: 6

6. Title: Ranolazine also touches repolarisation

6. Detail: At therapeutic concentrations it inhibits the rapid delayed rectifier potassium current, which prolongs the QT interval; its dominant late sodium action is credited with the low torsades risk that accompanies that prolongation. [2]

7. Step: 7

7. Title: Trimetazidine changes the fuel the heart burns

7. Detail: Inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase shifts metabolism from fatty acid oxidation

towards glucose oxidation. Glucose is oxygen-sparing, producing around 15% more ATP for the same oxygen, and there is no accompanying change in heart rate or vessel tone. [6]

8. Step: 8

8. Title: Nicorandil opens ATP-sensitive potassium channels

8. Detail: Opening these channels shortens action potential recovery, refractoriness and repolarisation reserve in cardiomyocytes other than sinoatrial node cells, and shortens the QT interval. [5]

Major clinical uses

1. Drug: Ivabradine

1. Indication: Symptomatic stable heart failure with an ejection fraction of 35% or less, in sinus rhythm, with a resting heart rate of at least 70 beats per minute, on a maximally tolerated beta blocker

1. Line: targeted

1. Note: The purpose is reduction of heart failure hospitalisation. All four eligibility conditions have to be met together, which is what makes this the most examinable indication in the group. [1]

2. Drug: Ivabradine

2. Indication: Stable angina, and symptomatic heart failure due to dilated cardiomyopathy in children older than six months

2. Line: alternative

2. Note: The paediatric approval is a distinct licensed indication; the angina role reflects the same rate-reducing mechanism applied to oxygen demand. [5][1]

3. Drug: Ranolazine

3. Indication: Chronic stable angina in ischaemic heart disease, as an adjunct to standard therapy

3. Line: alternative

3. Note: 2023 ACC/AHA guidance recommends it for chronic coronary disease that remains symptomatic despite beta blockers, calcium channel blockers or long-acting nitrates. It is added to antiplatelet, statin and renin-angiotensin therapy rather than replacing them. [2]

4. Drug: Ranolazine

4. Indication: Off-label use in selected ventricular arrhythmias, including haemodynamically stable ventricular tachycardia, and in long QT syndrome type 3

4. Line: alternative

4. Note: In long QT syndrome type 3 it has been used to shorten the corrected QT interval and reduce recurrent arrhythmia - the reverse of what its QT effect would suggest. Amiodarone and sotalol remain the primary antiarrhythmic treatments. [2]

5. Drug: Trimetazidine

5. Indication: Chronic stable angina, microvascular angina and refractory angina, added to conventional therapy

5. Line: alternative

5. Note: European guidance gives it only a class IIb level of recommendation, and a meta-analysis found no benefit from it as monotherapy on the outcomes studied, so it belongs firmly in the add-on category. [6][7]

6. Drug: Nicorandil

6. Indication: Stable angina as a second-line option, and use during percutaneous coronary intervention

6. Line: alternative

6. Note: Nicorandil use during percutaneous coronary intervention is described as capable of reducing the rate of ventricular arrhythmia in patients with ST-elevation myocardial infarction. [5]

Pharmacokinetics

1. Drug: Ivabradine

1. Route: Oral

1. Absorption: Peak plasma concentration about one hour after an oral dose; bioavailability around 40% because of first-pass metabolism, and it is taken with food to improve absorption
1. Metabolism: Extensive hepatic metabolism by CYP3A4-mediated oxidation, producing a major metabolite with similar pharmacological activity
1. Elimination: Only about 4% of an administered dose is excreted unchanged in the urine
1. Half Life: Distribution half-life about two hours, elimination half-life about six hours
1. Dose Adjust: Contraindicated with potent CYP3A4 inhibitors and in severe hepatic impairment (Child-Pugh C); approximately 70% bound to plasma proteins [1]
2. Drug: Ranolazine
2. Route: Oral
2. Absorption: Peak plasma concentrations within two to five hours, with steady state reached in about three days
2. Metabolism: Rapid hepatic metabolism, principally by CYP3A4 with a minor CYP2D6 contribution; more than 40 metabolites appear in plasma
2. Elimination: About 75% of a dose is excreted renally and the remainder in the faeces
2. Half Life: Approximately seven hours
2. Dose Adjust: Contraindicated with strong CYP3A inhibitors or inducers and in liver cirrhosis; reduction is required with moderate CYP3A4 inhibitors, and renal indices are monitored when creatinine clearance is below 60 mL/min [2]
3. Drug: Trimetazidine
3. Route: Oral
3. Absorption: See a current prescribing reference
3. Metabolism: See a current prescribing reference
3. Elimination: See a current prescribing reference
3. Half Life: See a current prescribing reference
3. Dose Adjust: A reduced amount is described for older patients and for those with moderate renal impairment [6]
1. CYP3A4 is the shared metabolic bottleneck of this group: both ivabradine and ranolazine are principally handled by that enzyme, so the same inhibitors and inducers matter for each of them. [1][2]
2. Ranolazine is roughly 65% bound to serum protein, mainly to alpha-1-acid glycoprotein, with a steady-state volume of distribution of 85 to 180 litres. [2]
3. Hepatic impairment exaggerates ranolazine's effect on the corrected QT interval, with roughly threefold increases described across mild to severe liver disease, and cirrhosis is a contraindication. [2]
4. Monitoring described for ivabradine covers cardiac rhythm, heart rate, blood pressure and symptoms of bradycardia; pregnant patients are additionally watched for preterm birth, and the drug is contraindicated in pregnancy. [1]
5. This page gives no dose regimens by design. Amounts, titration steps and maximum exposures depend on age, renal and hepatic function and interacting drugs, and belong in a prescribing reference used by the treating clinician.

Adverse effects

1. Effect: Phosphenes
1. Detail: Brief luminous visual disturbances, the distinctive ivabradine effect, reported in 3% of patients on the drug in the SHIFT trial against less than 1% on placebo. [1]
2. Effect: Bradycardia
2. Detail: Symptomatic bradycardia occurred in 5% of ivabradine-treated patients in SHIFT compared with 1% on placebo, which follows directly from the intended mechanism. [1]
3. Effect: Neurological and sensory effects with ranolazine
3. Detail: Dizziness, headache, nausea, confusion, tinnitus, vertigo and blurred vision are among the commonly reported events. [2]
4. Effect: Gastrointestinal upset and headache with trimetazidine
4. Detail: These are the routine tolerability issues described for the drug, separate from its neurological concern. [6]

1. Effect: Ulceration with nicorandil

1. Detail: Nicorandil causes serious ulceration of the gastrointestinal tract, skin, mucosa, genital area and eye, which may progress to perforation, haemorrhage, fistula or abscess. Ulceration can begin at any point during treatment, including years after starting, and the toxicity is dose-dependent.

1. Action: Nicorandil is stopped when ulceration occurs, since withdrawing the drug is what allows healing, and an alternative anti-anginal is considered. [3][4]

2. Effect: Atrial fibrillation with ivabradine

2. Detail: The drug increases the risk of atrial fibrillation, which matters doubly because its licensed heart failure indication requires the patient to be in sinus rhythm.

2. Action: Ivabradine is discontinued if atrial fibrillation occurs. [1]

3. Effect: Severe sinus bradycardia and asystole

3. Detail: Severe cases of ivabradine-related bradycardia may present with prolonged periods of asystole that can be refractory to atropine.

3. Action: Cardiac rhythm, heart rate and blood pressure are monitored, and a resting heart rate below 60 beats per minute is a contraindication to starting. [1]

4. Effect: QT prolongation with ranolazine

4. Detail: Inhibition of the rapid delayed rectifier potassium current lengthens the QT interval. Torsades de pointes was not reported as an adverse effect in the clinical trials, but risk may rise where other QT-prolonging medicines are taken, and hepatic impairment magnifies the effect.

4. Action: The corrected QT interval is monitored in patients taking ranolazine alongside other QT-prolonging drugs, and caution applies where there is a family history of long QT syndrome. [2]

5. Effect: Uncommon but serious ranolazine reactions

5. Detail: Syncope, haematuria, bradycardia, hypotension and orthostatic hypotension are described, alongside thrombocytopenia, leukopenia, pancytopenia, eosinophilia, angioedema, renal failure and pulmonary fibrosis. Rare cases of ranolazine-induced myopathy have been documented, generally with a favourable outcome after stopping.

5. Action: Recognition prompts reassessment of the drug by the treating clinician; renal indices are followed when creatinine clearance is below 60 mL/min. [2]

6. Effect: Extrapyramidal complications with trimetazidine

6. Detail: Some patients develop movement-disorder features, which is the reason the drug is regarded as unsuitable for people with Parkinson disease.

6. Action: New or worsening movement symptoms prompt review by the treating clinician. [6]

1. Drug: Ivabradine

1. Effect: Phosphenes, symptomatic bradycardia and an increased risk of atrial fibrillation - three effects that all trace back to where the drug acts. [1]

2. Drug: Ranolazine

2. Effect: QT prolongation without the expected torsades signal, together with a broad list of uncommon haematological, renal and pulmonary reactions. [2]

3. Drug: Trimetazidine

3. Effect: Extrapyramidal complications, which convert an otherwise well-tolerated metabolic agent into a drug that has to be avoided in movement disorders. [6]

Contraindications, precautions and interactions

1. Ivabradine in decompensated heart failure, and where blood pressure is below 90/50 mmHg. [1]

2. Ivabradine where there are conduction abnormalities such as sick sinus syndrome, sinoatrial block or third-degree atrioventricular block, or where the resting heart rate is below 60 beats per minute. [1]

3. Ivabradine in severe hepatic impairment classified as Child-Pugh C, and alongside a potent CYP3A4 inhibitor. [1]

4. Ivabradine in pregnancy; breastfeeding is also not recommended, since there are no human milk data and animal

studies show the drug in rat milk. [1]

5. Ranolazine with strong CYP3A inhibitors such as ketoconazole, clarithromycin or nelfinavir, and with CYP3A4 inducers such as rifampicin, phenobarbital or St John's wort. [2]

6. Ranolazine in liver cirrhosis. [2]

7. Trimetazidine in Parkinson disease and similar movement disorders. [6]

1. Concurrent negative chronotropic therapy with ivabradine, including digoxin, amiodarone or an additional beta blocker, because bradycardia risk adds up. [1]

2. Hepatic impairment with ranolazine short of cirrhosis, where corrected QT prolongation is exaggerated roughly threefold across mild to severe liver disease. [2]

3. A family history of long QT syndrome, or concurrent QT-prolonging medicines, in a patient taking ranolazine. [2]

4. Creatinine clearance below 60 mL/min with ranolazine, where serum creatinine, urea and urine output are followed. [2]

5. Older patients and those with moderate renal impairment taking trimetazidine, for whom a reduced amount is described. [6]

1. With: Potent CYP3A4 inhibitors - azole antifungals, macrolides, HIV protease inhibitors, verapamil, diltiazem

1. Effect: Raise ivabradine exposure, and their coadministration with ivabradine is contraindicated; the moderate inhibitors among them also require ranolazine to be reduced. [1][2]

2. With: CYP3A4 inducers - rifampicin, barbiturates, phenytoin, St John's wort

2. Effect: Lower exposure to ivabradine and are contraindicated with ranolazine. [1][2]

3. With: Digoxin

3. Effect: Adds to bradycardia risk with ivabradine; with ranolazine the interaction is transport-based, since digoxin is a P-glycoprotein substrate whose exposure increases and may need adjustment. [1][2]

4. With: Amiodarone and additional beta blockers

4. Effect: Combined with ivabradine they increase the risk of bradycardia, because all of them slow the heart by different routes. [1]

5. With: Metformin

5. Effect: Ranolazine has been shown to increase plasma concentrations of metformin, so the total daily metformin exposure is capped when the two are combined. [2]

6. With: Other QT-prolonging medicines

6. Effect: Increase the arrhythmic risk associated with ranolazine's QT prolongation, and the corrected QT interval is monitored when they are combined. [2]

7. With: P-glycoprotein inhibitors such as ciclosporin

7. Effect: Require ranolazine adjustment based on clinical response. [2]

Comparison tables

1. Title: Four agents, four different targets

1. Caption: Nothing in this group shares a mechanism, so the table is the fastest way to keep them apart. Therapy choice is governed by a current prescribing reference.

1. Key: drug

1. Label: Drug

1. Is Row Header: true

2. Key: target

2. Label: Molecular target

3. Key: haemodynamics

3. Label: Effect on rate and blood pressure

4. Key: use

4. Label: Principal use

1. Drug: Ivabradine
 1. Target: HCN channels carrying the sinoatrial funny current I(f)
 1. Haemodynamics: Lowers heart rate; no effect on contraction, relaxation or ventricular repolarisation
 1. Use: Symptomatic heart failure with ejection fraction 35% or less in sinus rhythm; stable angina [1][5]
 2. Drug: Ranolazine
 2. Target: Late inward sodium current in ischaemic myocytes
 2. Haemodynamics: No significant effect on blood pressure or heart rate; prolongs the QT interval
 2. Use: Chronic stable angina as an adjunct when symptoms persist on standard therapy [2]
 3. Drug: Trimetazidine
 3. Target: Mitochondrial long-chain 3-ketoacyl coenzyme A thiolase
 3. Haemodynamics: No detectable chronotropic or vasomotor effect
 3. Use: Add-on for chronic stable, microvascular and refractory angina; class IIb in European guidance [6]
 4. Drug: Nicorandil
 4. Target: ATP-sensitive potassium channels
 4. Haemodynamics: Shortens action potential recovery and the QT interval, sparing sinoatrial node cells
 4. Use: Second-line option in stable angina; used during percutaneous coronary intervention [5]
2. Title: The safety issue that identifies each drug
2. Caption: Examiners test the one reaction that belongs to a single agent. Recognition prompts review by the treating clinician, not self-directed change.
1. Key: drug
 1. Label: Drug
 1. Is Row Header: true
 2. Key: issue
 2. Label: Signature safety issue
 3. Key: consequence
 3. Label: What follows from it
1. Drug: Ivabradine
 1. Issue: Phosphenes, bradycardia and new atrial fibrillation
 1. Consequence: The drug is stopped if atrial fibrillation develops, and a resting heart rate under 60 beats per minute is a bar to starting [1]
 2. Drug: Ranolazine
 2. Issue: QT prolongation via inhibition of the rapid delayed rectifier current
 2. Consequence: Corrected QT monitoring where other QT-prolonging drugs are used; cirrhosis is an outright contraindication [2]
 3. Drug: Trimetazidine
 3. Issue: Extrapyrarnidal complications
 3. Consequence: Contraindicated in Parkinson disease and related movement disorders [6]
 4. Drug: Nicorandil
 4. Issue: Ulceration of the gastrointestinal tract, skin, mucosa and eye, which may progress to perforation, haemorrhage or fistula
 4. Consequence: Nicorandil is stopped when ulceration appears, because stopping the drug is what allows healing; this risk is why it sits as a second-line rather than first-line anti-anginal [3][4]

High-yield exam pearls

1. Pearl: Ivabradine slows the heart without weakening it.
 1. Why: It reduces heart rate by blocking the sinoatrial pacemaker current, but leaves myocardial contraction, relaxation and ventricular repolarisation untouched. That is exactly what a beta blocker cannot claim, and it is the reason

ivabradine has a role in patients who remain tachycardic on the maximum beta blocker they can tolerate. [1]

2. Pearl: The funny current is the pacemaker's own clock.

2. Why: I(f) drives the phase 4 slow depolarisation that takes a sinoatrial node cell up to threshold. Blocking it stretches out that climb, so beats come less often; the revised Vaughan Williams scheme gives HCN channel blockers their own category, class 0. [5][1]

3. Pearl: Phosphenes are the ivabradine question.

3. Why: They are brief luminous visual disturbances and they belong to this drug alone among the cardiac agents. In the SHIFT trial they occurred in 3% of treated patients against less than 1% on placebo, which makes them a favourite single-drug identification cue. [1]

4. Pearl: Ranolazine treats ischaemia without touching the haemodynamics.

4. Why: By inhibiting the late sodium current it reduces the calcium overload of ischaemic myocytes, lowering wall tension and oxygen consumption without a significant effect on blood pressure or heart rate. That makes it usable when hypotension or bradycardia already limits conventional antianginal therapy. [2]

5. Pearl: Ranolazine lengthens the QT interval but rarely causes torsades.

5. Why: It inhibits the rapid delayed rectifier potassium current at therapeutic concentrations, which prolongs the QT interval; the countervailing late sodium channel blockade is credited with the low torsades risk. The caution still applies when other QT-prolonging drugs are on board. [2]

6. Pearl: Trimetazidine changes the fuel, not the flow.

6. Why: Inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase moves the heart from fatty acid oxidation to glucose oxidation, which yields roughly 15% more ATP per unit of oxygen. Nothing about heart rate or vessel calibre changes. [6]

7. Pearl: Two of these drugs share a metabolic bottleneck.

7. Why: Ivabradine and ranolazine are both principally CYP3A4 substrates, so azole antifungals, macrolides, protease inhibitors, verapamil and diltiazem raise exposure to either, and rifampicin, barbiturates, phenytoin and St John's wort lower it. [1][2]

8. Pearl: Each agent has one movement or vision clue attached to it.

8. Why: Ivabradine gives phosphenes, trimetazidine gives extrapyramidal effects that rule it out in Parkinson disease, and ranolazine gives a spread of neurological effects including dizziness, tinnitus, vertigo and blurred vision. Matching the clue to the drug is the usual exam task. [1][6][2]

Common exam traps

1. Trap: "Ivabradine is basically a beta blocker without the asthma problem."

1. Correction: It works on a different target entirely. Ivabradine blocks the sinoatrial funny current and leaves contraction, relaxation and repolarisation unchanged, whereas a beta blocker reduces contractility as well as rate. Its licensed heart failure use assumes a maximally tolerated beta blocker is already being taken. [1]

2. Trap: "Ivabradine can be used for rate control in atrial fibrillation."

2. Correction: The opposite. It acts on the sinoatrial node and its licensed heart failure use requires normal sinus rhythm; it increases the risk of atrial fibrillation, and the drug is discontinued if atrial fibrillation develops. [1]

3. Trap: "Ranolazine lowers blood pressure like the other antianginal drugs."

3. Correction: It reduces wall tension and myocardial oxygen consumption without significantly affecting blood pressure or heart rate, which is why it is positioned as an add-on for patients still symptomatic on beta blockers, calcium channel blockers or long-acting nitrates. [2]

4. Trap: "A drug that prolongs the QT interval must carry a high torsades risk."

4. Correction: Ranolazine prolongs the QT interval through inhibition of the rapid delayed rectifier current, yet torsades de pointes was not reported as an adverse effect in its clinical trials, and the low risk is attributed to its late sodium channel action. Risk does rise alongside other QT-prolonging medicines. [2]

5. Trap: "Trimetazidine is a vasodilator."

5. Correction: It is a metabolic modifier. Its effects occur without any detectable chronotropic or vasomotor action, because it works by shifting myocardial substrate use from fatty acids to glucose rather than by changing vessel calibre. [6]
6. Trap: "A neat mechanism means strong outcome evidence."
6. Correction: Not here. Trimetazidine carries only a class IIb recommendation in European guidance, and a meta-analysis of randomised double-blind trials concluded that it was not beneficial as monotherapy for any of the outcomes studied. [6][7]
7. Trap: "Nicorandil is just another nitrate."
7. Correction: In the revised Vaughan Williams scheme it is classified among metabolically dependent potassium channel openers. It opens ATP-sensitive potassium channels, which shortens action potential recovery, refractoriness and repolarisation reserve in cardiomyocytes other than those of the sinoatrial node, and shortens rather than lengthens the QT interval. [5]

Self-test questions

1. Question: What does ivabradine block, and where?
 1. L-type calcium channels in the atrioventricular node
 2. The funny current I(f), carried by HCN channels in the sinoatrial node
 3. Beta-1 adrenergic receptors throughout the myocardium
 4. The late sodium current in ischaemic ventricular muscle

1. Explanation: Ivabradine selectively blocks the funny current, I(f), by inhibiting hyperpolarisation-activated cyclic nucleotide-gated channels in the sinoatrial node. Inhibiting that current reduces the rate of phase 4 pacemaker depolarisation and so lowers the heart rate. [1][5]
2. Question: Which property distinguishes ivabradine from a beta blocker?
 1. It reduces heart rate without affecting contraction, relaxation or ventricular repolarisation
 2. It has no effect on heart rate at all
 3. It prolongs the QT interval markedly
 4. It works only in atrial fibrillation

2. Explanation: Ivabradine reduces heart rate but does not affect myocardial contraction, relaxation or ventricular repolarisation. That is why it can be added when a patient with heart failure remains tachycardic on the maximum beta blocker dose they can tolerate. [1]
3. Question: Which visual adverse effect is characteristic of ivabradine?
 1. Corneal microdeposits
 2. Xanthopsia, a yellow-green tint to vision
 3. Phosphenes, brief luminous visual disturbances
 4. Bitemporal field loss

3. Explanation: Phosphenes are the distinctive ivabradine visual phenomenon. In the SHIFT trial they occurred in 3% of patients taking ivabradine compared with less than 1% of those on placebo. Corneal microdeposits point to amiodarone and xanthopsia to digoxin. [1]
4. Question: How does ranolazine reduce myocardial oxygen consumption?
 1. By dilating the coronary arteries
 2. By slowing the sinoatrial node
 3. By inhibiting the late inward sodium current, which lowers intracellular calcium and wall tension
 4. By blocking beta-1 receptors

4. Explanation: Ranolazine inhibits the late inward sodium current in ischaemic cardiac myocytes. Intracellular sodium falls, so less calcium enters through the sodium-calcium exchanger, ventricular wall tension decreases and oxygen consumption falls - without significantly affecting blood pressure or heart rate. [2]
5. Question: What is the mechanism of trimetazidine?

1. Inhibition of mitochondrial long-chain 3-ketoacyl coenzyme A thiolase, shifting metabolism towards glucose oxidation
2. Blockade of ATP-sensitive potassium channels
3. Stimulation of soluble guanylate cyclase
4. Inhibition of the sodium-potassium ATPase
5. Explanation: Trimetazidine inhibits mitochondrial long-chain 3-ketoacyl coenzyme A thiolase, moving cardiac energy production away from fatty acid oxidation towards glucose oxidation. Glucose metabolism is oxygen-sparing, yielding about 15% more ATP per unit of oxygen, and the effect occurs with no detectable chronotropic or vasomotor change.

[6]

6. Question: Which condition makes trimetazidine unsuitable?

1. Asthma
2. Parkinson disease and similar movement disorders
3. Type 2 diabetes
4. Chronic kidney disease stage 1

6. Explanation: Some patients experience extrapyramidal complications with trimetazidine, which makes it unsuitable in Parkinson disease. Caution is also advised in older patients and in those with moderate renal impairment, who need a reduced amount. [6]

7. Question: Why is a potent CYP3A4 inhibitor contraindicated with ivabradine?

1. Because it prevents ivabradine from being absorbed
2. Because ivabradine undergoes extensive CYP3A4-mediated metabolism, so inhibition raises its exposure
3. Because it converts ivabradine into a beta blocker
4. Because it causes the drug to be excreted unchanged

7. Explanation: Ivabradine undergoes extensive hepatic metabolism by CYP3A4-mediated oxidation, so a potent inhibitor of that enzyme raises drug exposure and the associated bradycardia risk. Strong inhibitors named include azole antifungals, macrolides, HIV protease inhibitors, verapamil and diltiazem. [1]

8. Question: How is nicorandil classified in the revised Vaughan Williams scheme?

1. As a sodium channel blocker
2. As an HCN channel blocker
3. As a metabolically dependent potassium channel opener
4. As a beta-adrenergic antagonist

8. Explanation: Nicorandil is listed among metabolically dependent potassium channel openers. It opens ATP-sensitive potassium channels, shortening action potential recovery, refractoriness and repolarisation reserve in cardiomyocytes other than sinoatrial node cells, and shortening the QT interval. [5]

Frequently asked questions

1. Question: What is the funny current, and why is it called that?

1. Answer: It is the slow inward current that drives sinoatrial pacemaker cells up towards threshold between beats, carried by hyperpolarisation-activated cyclic nucleotide-gated channels and written I(f). It earned the name because, unusually, it switches on when the membrane becomes more negative rather than less. Ivabradine blocks it. [1][5]

2. Question: How is ivabradine different from a beta blocker?

2. Answer: Both slow the heart, but by different routes and with different collateral effects. Ivabradine acts only on the sinoatrial pacemaker current and does not affect myocardial contraction, relaxation or ventricular repolarisation, whereas beta blockade reduces contractility as well as rate. Its heart failure licence in fact assumes a beta blocker is already being taken at the maximum tolerated dose. [1]

3. Question: What are phosphenes?

3. Answer: They are brief luminous visual sensations - a transient enhanced brightness in part of the visual field - and they are the characteristic ivabradine adverse effect. In the SHIFT trial they affected 3% of treated patients compared with under 1% of those given placebo. [1]

4. Question: Why is ivabradine stopped if atrial fibrillation develops?

4. Answer: Because the drug both increases the risk of atrial fibrillation and depends on sinus rhythm to work - it acts on the sinoatrial node, which no longer controls the rate once fibrillation takes over. The reference guidance is to discontinue it if atrial fibrillation occurs. [1]

5. Question: How can ranolazine treat angina without lowering blood pressure?

5. Answer: Because it works inside the cell rather than on the circulation. Inhibiting the late sodium current lowers intracellular sodium, so less calcium is drawn in; the resulting fall in ventricular wall tension reduces oxygen consumption with no significant change in blood pressure or heart rate. [2]

6. Question: If ranolazine prolongs the QT interval, why is it not considered a torsades risk?

6. Answer: It does inhibit the rapid delayed rectifier potassium current, which lengthens the QT interval, but torsades de pointes was not reported as an adverse effect in its clinical trials. The low risk is attributed to its dominant late sodium channel action. The risk may still rise alongside other QT-prolonging drugs or in hepatic impairment. [2]

7. Question: What does trimetazidine actually do?

7. Answer: It changes the heart's fuel. By inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase it shifts energy production from fatty acid oxidation to glucose oxidation, which produces roughly 15% more ATP per unit of oxygen consumed. There is no accompanying effect on heart rate or vessel tone. [6]

8. Question: Are these drugs first-line treatments?

8. Answer: No. Ranolazine is recommended for chronic coronary disease still symptomatic on beta blockers, calcium channel blockers or long-acting nitrates; trimetazidine holds only a class IIb recommendation in European guidance and showed no benefit as monotherapy in a meta-analysis; nicorandil is described as a second-line option; and ivabradine's heart failure use presumes a maximally tolerated beta blocker is already in place. [2][6][7][1]

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