

RESEARCH MONOGRAPH . COMPOUND PROFILE

Trimetazidine

A cytoprotective anti-ischemic piperazine developed by Laboratoires Servier as the first metabolic modulator of cardiac energy substrate preference, distinguished from hemodynamic antianginal agents by its oxygen-sparing shift from long-chain fatty acid beta-oxidation to glucose oxidation through selective inhibition of mitochondrial long-chain 3-ketoacyl coenzyme A thiolase.

DOCUMENT	KDC-MN-1624
ISSUED	2026-05-21
REVISION	1.0
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COMPOUND CLASS	Piperazine-derived partial fatty acid oxidation inhibitor (p-FOX) and metabolic modulator of myocardial energy substrate utilization

ABSTRACT

Trimetazidine (1-(2,3,4-trimethoxybenzyl)piperazine) is a metabolic anti-ischemic agent developed by Laboratoires Servier in the late 1960s and first marketed in France in 1978 under the trade name Vastarel. It is registered in approximately 100 countries for the treatment of stable angina pectoris as add-on therapy to hemodynamic antianginal agents and, in certain jurisdictions, for symptomatic management of vertigo, tinnitus, and visual disturbance of vascular origin, although the European Medicines Agency restricted the latter indications following a 2012 Article 31 referral. The compound is not approved by the United States Food and Drug Administration and is not available in the United States, Canada, or the United Kingdom.

The molecular mechanism of trimetazidine is metabolic rather than hemodynamic. The compound selectively inhibits the mitochondrial long-chain 3-ketoacyl coenzyme A thiolase (3-KAT, also designated mitochondrial trifunctional protein thiolase), the terminal enzyme in the beta-oxidation spiral of long-chain fatty acids, with an IC₅₀ of approximately 75 nanomolar as originally reported by Kantor et al. (2000) in isolated working rat hearts, although subsequent work by MacInnes et al. (2003) using purified enzyme preparations challenged the direct enzymatic inhibition and proposed alternative upstream targets. The functional consequence of 3-KAT inhibition is a shift in myocardial energy substrate preference from fatty acid oxidation (which consumes more oxygen per mole of ATP generated) to glucose oxidation (which is approximately 12 percent more oxygen-efficient per unit of ATP), thereby preserving myocardial

high-energy phosphate pools under ischemic conditions without altering heart rate, blood pressure, coronary blood flow, or rate-pressure product. The compound additionally increases pyruvate dehydrogenase activity, reduces intracellular calcium overload, attenuates reactive oxygen species generation, decreases neutrophil infiltration in ischemic myocardium, and preserves intracellular pH homeostasis during ischemia and reperfusion.

The clinical evidence base for trimetazidine in stable angina pectoris is extensive. Multiple randomized controlled trials, including the TRIMPOL-I, TRIMPOL-II, and VASCO-angina studies, have demonstrated that trimetazidine as add-on therapy to beta-blockers, calcium channel blockers, or long-acting nitrates produces statistically significant improvements in total exercise duration, time to 1 mm ST-segment depression, and weekly angina attack frequency compared to placebo. The 2024 European Society of Cardiology guidelines for chronic coronary syndromes assign trimetazidine a Class IIb, Level of Evidence B recommendation as add-on antianginal therapy in patients with inadequate symptom control, a downgrade from the prior Class IIa designation that has been criticized by some experts as inconsistent with the available trial evidence. A separate and growing literature supports benefit in heart failure with reduced ejection fraction (HFrEF): multiple meta-analyses (Gao et al. 2011, Zhang et al. 2012, Weng et al. 2024) pooling data from over 1,500 patients have reported mean improvements in left ventricular ejection fraction of 6 to 7.5 percentage points, reductions in cardiac hospitalization (relative risk 0.43), and reductions in all-cause mortality (relative risk 0.47), leading to inclusion of trimetazidine in the 2021 ESC heart failure guidelines at a Class IIb level for relief of persistent angina in heart failure patients.

Pharmacokinetics are characterized by rapid and near-complete gastrointestinal absorption, approximately 90 percent oral bioavailability, a plasma elimination half-life of approximately 6 hours for the immediate-release formulation (approximately 12 hours for the modified-release 35 mg formulation), renal elimination of approximately 60 percent of the administered dose as unchanged drug, and minimal hepatic cytochrome P450-mediated metabolism with low drug-drug interaction potential. The compound is generally well tolerated; the principal adverse events are gastrointestinal disturbance (nausea, epigastric discomfort), asthenia, headache, and dizziness. The most clinically significant safety signal is the induction of reversible parkinsonian symptoms (rest tremor, bradykinesia, gait disturbance, rigidity) in a small fraction of patients, predominantly elderly, on prolonged therapy. This signal prompted the 2012 EMA Article 31 referral that resulted in new contraindications (Parkinson disease, parkinsonian symptoms, tremor, restless leg syndrome, severe renal impairment) and restriction of indications. Symptoms resolve in most patients within weeks to months of drug discontinuation. This monograph reviews the chemistry, synthesis, and structural pharmacology of trimetazidine; the metabolic mechanism of action in molecular detail; the comprehensive pharmacokinetic profile; the clinical evidence base across angina, heart failure, and investigational indications; sourcing and quality considerations; reconstitution and handling; stack-interaction implications; the adverse-event and safety signal record; and a structured comparative assessment of five alternative metabolic and antianginal agents against trimetazidine on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Trimetazidine.

Marketed names: Vastarel (Laboratoires Servier; France, many European Union member states), Preductal (Servier; Russian Federation, Central and Eastern European markets), Vastarel MR (modified-release formulation; multiple markets), Trimetazidin (generic markets, Turkey), Idaptan (generic markets), Modazidine (generic), Flavedon (generic, Russian Federation), Trimetazidine Servier (selected jurisdictions). The compound has been marketed under more than 60 trade names across approximately 100 countries [1].

Development codes: S 2746 (Servier internal designation). The compound does not carry a widely cited single development code in the pharmacological literature; it is referenced by its INN (trimetazidine) or by the marketed brand Vastarel.

Chemical Abstracts Service registry numbers: 5011-34-7 (free base), 13171-25-0 (dihydrochloride salt). The dihydrochloride is the formulated salt for all oral and parenteral preparations.

International Union of Pure and Applied Chemistry name: 1-(2,3,4-trimethoxybenzyl)piperazine. The compound is a 1-substituted piperazine bearing a 2,3,4-trimethoxybenzyl group at the 1-nitrogen position of the piperazine ring.

1.2 Structural class and chemistry

Trimetazidine is a substituted piperazine derivative. The piperazine ring is a saturated six-membered diamine heterocycle that appears as a pharmacophoric element in multiple drug classes (antipsychotics, antihistamines, antiretrovirals); in trimetazidine the piperazine is substituted at the 1-nitrogen by a 2,3,4-trimethoxybenzyl moiety that confers the metabolic activity at the mitochondrial fatty acid oxidation machinery. The compound does not belong to the hemodynamic antiangiinal classes (beta-adrenergic receptor antagonists, calcium channel blockers, organic nitrates, late sodium current inhibitors) and is instead classified as a metabolic modulator or cytoprotective anti-ischemic agent [2, 3].

Molecular formula: C₁₄H₂₂N₂O₃ (free base); C₁₄H₂₄Cl₂N₂O₃ (dihydrochloride salt).

Exact mass: 266.1630 g/mol (free base, monoisotopic).

Molecular weight: 266.34 g/mol (free base); 339.26 g/mol (dihydrochloride salt).

Physical properties: White to off-white crystalline powder. The dihydrochloride salt is freely soluble in water, soluble in methanol and ethanol, and sparingly soluble in apolar organic solvents. Melting point of the dihydrochloride salt is approximately 218 to 222 degrees Celsius. The compound has a calculated logP of approximately 0.85 (free base), consistent with moderate lipophilicity and good aqueous solubility.

Stereochemistry: Trimetazidine contains no stereocenters and is achiral. No enantiomeric considerations apply to sourcing, formulation, or pharmacological interpretation.

1.3 Synthesis

The synthesis of trimetazidine proceeds through condensation of 2,3,4-trimethoxybenzaldehyde with piperazine. The classical route involves reductive amination: the aldehyde condenses with piperazine in an appropriate solvent (methanol, ethanol, or toluene) to form the intermediate Schiff base (imine), which is reduced with sodium borohydride, sodium cyanoborohydride, or by catalytic hydrogenation (palladium on carbon, hydrogen atmosphere) to yield the secondary amine product [4]. The monoalkylated product (1-substituted piperazine) is separated from the dialkylated byproduct by column chromatography, recrystallization, or selective salt formation. The dihydrochloride salt is prepared by addition of two equivalents of hydrogen chloride (as concentrated hydrochloric acid or hydrogen chloride in ether) to the free base in ethanol or isopropanol, followed by recrystallization. Industrial synthesis optimizes the reductive amination for selectivity toward the monoalkylated product (using piperazine in stoichiometric excess) and for yield (typically 60 to 80 percent), purity (greater than 99 percent by HPLC), and removal of residual palladium catalyst and solvents. The compound is manufactured at multi-ton scale for global supply.

2. Abstract

Trimetazidine (1-(2,3,4-trimethoxybenzyl)piperazine dihydrochloride) is a metabolic anti-ischemic agent that modifies myocardial energy substrate utilization without altering hemodynamic parameters, representing a mechanistically distinct approach to the management of myocardial ischemia [1, 2]. Developed by Laboratoires Servier and first marketed in 1978, the compound has accumulated over four decades of clinical use in approximately 100 countries, principally for stable angina pectoris, and is the subject of an expanding evidence base in heart failure with reduced ejection fraction.

The principal molecular target, identified by Kantor et al. (2000), is the mitochondrial long-chain 3-ketoacyl coenzyme A thiolase (3-KAT), the terminal enzyme of the fatty acid beta-oxidation spiral, which trimetazidine inhibits at nanomolar concentrations in isolated working heart preparations [5]. Inhibition of long-chain fatty acid beta-oxidation produces a compensatory upregulation of glucose oxidation through the Randle cycle, and the resulting shift in substrate preference generates approximately 12 percent more ATP per molecule of oxygen consumed, an efficiency gain that preserves myocardial high-energy phosphate pools, reduces intracellular acidosis, and diminishes calcium overload during ischemia [6, 7]. The compound does not alter heart rate, blood pressure, coronary blood flow, or the rate-pressure product, and is therefore devoid of the hemodynamic liabilities (hypotension, reflex tachycardia, negative inotropy) that limit the dose titration of conventional antianginal agents.

The clinical evidence for stable angina encompasses multiple randomized controlled trials (TRIMPOL-I, TRIMPOL-II, VASCO-angina, TACT, and others) that demonstrate statistically and clinically significant improvements in exercise tolerance, time to ischemic threshold, and angina frequency when trimetazidine is added to background therapy with beta-blockers, calcium channel blockers, or nitrates [8, 9, 10, 11]. The heart failure evidence, pooled in meta-analyses by Gao et al. (2011) and Zhang et al. (2012), demonstrates mean improvements in left ventricular ejection fraction of 6 to 7.5 percentage points, reduced cardiac hospitalization, and reduced all-cause mortality across over 1,500 randomized patients [12, 13]. The 2024 European Society of Cardiology guidelines for chronic coronary syndromes assign trimetazidine a Class IIb recommendation as add-on therapy [14].

The compound is well tolerated at the registered dose of 35 mg modified-release twice daily. The principal safety concern is the induction of reversible parkinsonian symptoms (tremor, bradykinesia, gait disorder) in a small percentage of patients, predominantly elderly, on prolonged therapy, a signal that prompted a 2012 European Medicines Agency review resulting in restriction of indications, new contraindications, and enhanced pharmacovigilance [15, 16]. Trimetazidine is not approved by the United States Food and Drug Administration.

3. Discovery and Development History

3.1 Origin

Trimetazidine was synthesized in the laboratories of Laboratoires Servier (Suresnes, France) in the late 1960s as part of a medicinal chemistry program investigating piperazine derivatives for anti-ischemic activity. The rationale was to develop a compound that would protect the myocardium during ischemia through metabolic modulation rather than through hemodynamic modification, an approach that was novel at the time and that positioned the compound as the first in a new pharmacological class designated "cytoprotective anti-ischemic agents" or "metabolic modulators" [2, 3]. Early preclinical studies in the 1970s demonstrated that the compound preserved myocardial ATP levels, reduced lactate accumulation, and attenuated ultrastructural damage in isolated perfused rat hearts subjected to low-flow ischemia and reperfusion, without altering coronary flow or heart rate.

3.2 Antianginal registration and global expansion

Trimetazidine received its first marketing authorization in France in 1978 under the trade name Vastarel. The initial registered indications included prophylactic treatment of angina pectoris and symptomatic treatment of vertigo and tinnitus of vascular origin (the latter on the basis of the then-prevalent concept that inner ear ischemia contributed to these conditions). The compound was subsequently registered across Western and Eastern Europe, the Russian Federation, Latin America, the Middle East, East Asia, and Southeast Asia. By the early 2000s, it was available in approximately 100 countries. The compound was never submitted for registration in the United States, Canada, or the United Kingdom; the reasons were principally commercial (Servier did not maintain a regulatory or commercial presence in these markets during the compound's initial development period) rather than scientific.

3.3 Identification of the molecular target

For the first two decades after registration, the molecular mechanism of trimetazidine was described in general terms as "cytoprotective" and "anti-ischemic" without identification of a specific molecular target. The seminal mechanistic study was published by Kantor, Lucien, Kozak, and Lopaschuk in *Circulation Research* in 2000 [5]. Using isolated working rat hearts, Kantor et al. demonstrated that trimetazidine at therapeutically relevant concentrations selectively inhibited the long-chain isoform of 3-ketoacyl coenzyme A thiolase (IC₅₀ approximately 75 nanomolar) while requiring concentrations 100-fold to 1000-fold higher to inhibit the medium-chain and short-chain isoforms. The inhibition produced a measurable decrease in palmitate oxidation and a reciprocal increase in glucose oxidation in the working heart, with preservation of mechanical function.

3.4 Mechanistic debate

A subsequent study by MacInnes et al. (2003) in *Circulation Research* challenged the Kantor findings by reporting that trimetazidine at concentrations up to 100 micromolar failed to inhibit purified preparations of long-chain 3-KAT in broken-cell and reconstituted enzyme assays [17]. MacInnes et al. proposed that the antianginal benefit of trimetazidine might operate through an indirect metabolic mechanism or through targets upstream of 3-KAT. A reconciliation study by Lopaschuk et al. (2003) in the same journal demonstrated that the inhibition was reproducible in intact mitochondria and in the working heart preparation but not in broken-cell assays of the purified enzyme, suggesting that the inhibition depends on the intact mitochondrial membrane context or on a cofactor present in the intact organelle [18]. The current consensus, reflected in major reviews and guidelines, accepts 3-KAT inhibition in the intact mitochondrial context as the principal mechanism while acknowledging the possibility of additional or alternative targets [6, 7].

3.5 EMA review and indication restriction

In 2012, the European Medicines Agency (EMA) conducted an Article 31 referral review of trimetazidine-containing medicines in response to accumulating reports of parkinsonian symptoms and to questions about the adequacy of evidence for the vertigo, tinnitus, and visual disturbance indications [15]. The Committee for Medicinal Products for Human Use (CHMP) concluded that the benefit-risk balance remained favorable for stable angina pectoris as add-on therapy but that the bene-

fits no longer outweighed the risks for vertigo, tinnitus, and visual disturbance. The CHMP introduced new contraindications (Parkinson disease, parkinsonian symptoms, tremor, restless leg syndrome, severe renal impairment with creatinine clearance below 15 mL/min) and mandated enhanced product information regarding the risk of movement disorders.

3.6 Modified-release formulation

Servier developed a modified-release (MR) formulation containing 35 mg of trimetazidine dihydrochloride, providing sustained plasma concentrations and permitting twice-daily dosing in place of the original three-times-daily immediate-release 20 mg regimen. The MR formulation (Vastarel MR, Preductal MR) became the standard formulation in most markets and is the formulation studied in the majority of recent clinical trials.

4. Mechanism of Action

Trimetazidine is a metabolic modulator that acts at the level of mitochondrial substrate selection in the cardiomyocyte, shifting energy production from long-chain fatty acid beta-oxidation toward glucose oxidation. This mechanism is fundamentally distinct from the hemodynamic mechanisms of conventional antianginal agents and operates without altering myocardial oxygen supply or demand at the vascular or contractile level [2, 6].

4.1 Inhibition of mitochondrial long-chain 3-ketoacyl coenzyme A thiolase

The principal molecular target of trimetazidine is the long-chain isoform of 3-ketoacyl coenzyme A thiolase (3-KAT), the terminal enzyme in the mitochondrial fatty acid beta-oxidation spiral. In each cycle of beta-oxidation, a long-chain acyl-CoA substrate is processed by four sequential enzymes (acyl-CoA dehydrogenase, enoyl-CoA hydratase, 3-hydroxyacyl-CoA dehydrogenase, and 3-ketoacyl-CoA thiolase) to release one molecule of acetyl-CoA and a shortened acyl-CoA chain. The long-chain isoform of 3-KAT (which handles C12 to C16 substrates) is the specific isoform inhibited by trimetazidine, with an IC₅₀ of approximately 75 nanomolar in the intact working heart, whereas the medium-chain and short-chain isoforms require 10 to 100 micromolar and greater than 100 micromolar concentrations, respectively [5].

4.2 Metabolic shift: the Randle cycle mechanism

Inhibition of long-chain fatty acid beta-oxidation reduces acetyl-CoA flux from fatty acid sources into the tricarboxylic acid cycle. Through the operation of the Randle cycle (the reciprocal relationship between fatty acid and glucose oxidation described by Randle et al. in 1963), reduced fatty acid oxidation relieves the allosteric and covalent inhibition of pyruvate dehydrogenase and of the glucose oxidation pathway, resulting in increased glucose and lactate oxidation [6, 7]. The net effect is a shift in substrate preference: under normal aerobic conditions, the healthy human heart derives approximately 60 to 70 percent of its ATP from fatty acid oxidation and 20 to 30 percent from glucose oxidation; in the presence of trimetazidine, this ratio shifts toward approximately 50 percent from each source.

4.3 Oxygen efficiency and ATP preservation

The metabolic shift produces a quantifiable improvement in oxygen efficiency. The complete oxidation of one molecule of palmitate (C16) consumes 23 molecules of oxygen and yields 105 molecules of ATP (ATP/O₂ ratio of approximately 4.57); the complete oxidation of one molecule of glucose consumes 6 molecules of oxygen and yields 31 molecules of ATP (ATP/O₂ ratio of approximately 5.17). The glucose pathway is therefore approximately 12 percent more oxygen-efficient per unit of ATP generated [6]. Under ischemic conditions, where oxygen supply is limited, this efficiency gain translates to preserved high-energy phosphate (ATP, phosphocreatine) levels, reduced intracellular acidosis, and maintained ionic homeostasis (reduced intracellular sodium and calcium accumulation through preserved Na⁺/K⁺-ATPase and SERCA2a activity).

4.4 Additional cytoprotective mechanisms

Beyond the primary metabolic shift, trimetazidine produces several secondary cytoprotective effects that contribute to the overall anti-ischemic profile:

(a) Reduction of intracellular calcium overload through preservation of ATP-dependent calcium handling and through attenuation of the rise in cytosolic sodium that drives reverse-mode sodium-calcium exchange during ischemia [19].

(b) Attenuation of reactive oxygen species (ROS) generation during ischemia and reperfusion, through reduced delivery of reducing equivalents (FADH₂, NADH) from uncoupled fatty acid oxidation to the electron transport chain and through direct antioxidant properties attributed to the trimethoxybenzyl moiety [20].

(c) Preservation of mitochondrial membrane potential and reduction of mitochondrial permeability transition pore (mPTP) opening during reperfusion, thereby reducing apoptotic and necrotic cell death [21].

(d) Reduction of neutrophil infiltration into ischemic myocardium, documented in animal models of ischemia-reperfusion injury [22].

(e) Restoration of coupling between glycolysis and glucose oxidation, reducing proton production from uncoupled glycolysis and thereby preserving intracellular pH [6].

4.5 Hemodynamic neutrality

Trimetazidine does not alter heart rate, blood pressure, coronary blood flow, peripheral vascular resistance, or the rate-pressure product at therapeutic doses [2, 8]. This hemodynamic neutrality distinguishes the compound from all conventional antianginal classes and is both its principal advantage (no hemodynamic side effects, no dose-limiting hypotension, compatibility with all other antianginal agents) and its historical liability (difficulty in demonstrating mechanism to regulators and prescribers accustomed to hemodynamic targets as surrogate endpoints).

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Trimetazidine dihydrochloride is rapidly and almost completely absorbed from the gastrointestinal tract after oral administration. Oral bioavailability is approximately 90 percent, reflecting minimal first-pass hepatic metabolism [23]. For the immediate-release 20 mg tablet, time to peak plasma concentration (T_{max}) is approximately 1.5 to 2 hours after oral administration in the fasted state. For the modified-release 35 mg tablet, T_{max} is approximately 5 hours, with a broader and lower peak plasma concentration and a more sustained plasma profile permitting twice-daily dosing. Food modestly delays absorption of the MR formulation without significantly affecting total exposure (AUC). The steady-state peak plasma concentration after the MR 35 mg tablet twice daily is approximately 55 to 60 ng/mL [24].

5.2 Distribution

Volume of distribution is approximately 4.8 liters per kilogram, indicating moderate tissue distribution. Plasma protein binding is low, approximately 16 percent, predominantly to albumin. The compound distributes to cardiac tissue; cardiac-to-plasma concentration ratios in animal models have been reported at approximately 5 to 10, consistent with the lipophilic character of the free base and accumulation in mitochondria-rich tissue [23].

5.3 Metabolism

Trimetazidine undergoes limited hepatic metabolism. The primary metabolic pathways are oxidative demethylation of the methoxy groups on the trimethoxybenzyl moiety and oxidation of the piperazine ring, producing multiple polar metabolites. The compound does not undergo significant metabolism through cytochrome P450 isoforms; in vitro studies have demonstrated that trimetazidine is not a substrate, inhibitor, or inducer of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 at therapeutic concentrations [23, 24]. This profile confers a low drug-drug interaction poten-

tial, which is an important practical advantage given that the target patient population (elderly patients with coronary artery disease) typically receives multiple concurrent medications including statins, antiplatelet agents, antihypertensives, and antidiabetic agents.

5.4 Elimination

The compound is eliminated primarily by the kidneys. Approximately 60 percent of an administered dose is excreted unchanged in the urine, reflecting the predominant renal clearance pathway. The plasma elimination half-life is approximately 6 hours after the immediate-release formulation and approximately 12 hours after the modified-release formulation [24]. Total body clearance is approximately 40 to 50 liters per hour in subjects with normal renal function. In patients with moderate renal impairment (creatinine clearance 30 to 60 mL/min), exposure increases by approximately 1.5-fold and dose adjustment (35 mg once daily) is recommended. In severe renal impairment (creatinine clearance below 15 mL/min), the compound is contraindicated.

5.5 Routes of administration

The registered route of administration is oral. The modified-release 35 mg tablet taken twice daily (morning and evening, with food) is the standard dosing regimen in current clinical practice and the formulation studied in the majority of recent clinical trials. The immediate-release 20 mg tablet taken three times daily is an older formulation that remains available in some markets. No parenteral formulation is registered for clinical use; intravenous trimetazidine has been used in pre-clinical and early clinical research but is not a standard route.

5.6 Special populations

Elderly patients: Pharmacokinetic studies in elderly subjects (over 65 years) demonstrate modestly increased exposure due to age-related decline in renal function. Dose adjustment is not mandated by age alone but should be guided by estimated renal function. The elderly are the population at highest risk for parkinsonian adverse events.

Renal impairment: Dose reduction to 35 mg once daily is recommended for moderate renal impairment. The compound is contraindicated in severe renal impairment.

Hepatic impairment: No formal pharmacokinetic studies in hepatic impairment have been published. Given the predominantly renal elimination and low hepatic metabolism, substantial dose adjustment in hepatic impairment is not expected to be necessary.

Pediatric patients: The compound is not registered for pediatric use and no pediatric pharmacokinetic data are available.

6. Preclinical Pharmacology

6.1 Isolated heart models

The foundational preclinical pharmacology of trimetazidine was established in isolated perfused and working heart preparations. In the Langendorff and working heart models, trimetazidine at concentrations of 1 to 10 micromolar preserves left ventricular developed pressure, reduces end-diastolic pressure rise, maintains coronary flow, and reduces lactate accumulation during low-flow ischemia and reperfusion [5, 18]. The metabolic shift from fatty acid to glucose oxidation has been quantified by radiotracer methodology (14C-palmitate and 14C-glucose oxidation rates) and by nuclear magnetic resonance spectroscopy of high-energy phosphate metabolites.

6.2 In vivo ischemia-reperfusion models

In rat and dog models of regional myocardial ischemia (coronary artery ligation with reperfusion), trimetazidine at doses of 3 to 10 mg/kg intravenously reduces infarct size by 20 to 40 percent compared to vehicle control [22]. The reduction in infarct size is accompanied by reduced tissue malondialdehyde (a marker of lipid peroxidation), reduced tissue myeloperoxidase activity (a marker of neutrophil infiltration), and preserved myocardial phosphocreatine-to-ATP ratio measured by phosphorus-31 magnetic resonance spectroscopy.

6.3 Heart failure models

In rat models of chronic heart failure (post-myocardial infarction remodeling), chronic trimetazidine administration (10 mg/kg/day orally for 8 to 12 weeks) attenuates left ventricular dilatation, preserves ejection fraction, reduces interstitial fibrosis, and normalizes the shift in myosin heavy chain isoform expression from the alpha (fast) to the beta (slow) isoform that characterizes the failing heart [25]. These findings provided the preclinical rationale for the clinical investigation of trimetazidine in heart failure.

6.4 Neuroprotection models

Trimetazidine has been evaluated in cerebral ischemia models (middle cerebral artery occlusion in rats) and has shown modest reductions in infarct volume and neurological deficit score [26]. These findings have not been translated to clinical investigation in stroke but contributed to the historical registration for vertigo and tinnitus of vascular origin (subsequently withdrawn by the EMA in 2012).

7. Clinical Evidence Base

7.1 Stable angina pectoris: add-on therapy trials

The antianginal indication is the principal registered application of trimetazidine and is supported by multiple randomized controlled trials conducted across three decades.

TRIMPOL-I (1999): A multicenter, randomized, double-blind, placebo-controlled trial in 161 patients with stable exertional angina receiving background beta-blocker therapy. Trimetazidine MR 35 mg twice daily for 12 weeks produced significant improvements in total exercise duration (plus 52 seconds versus plus 16 seconds for placebo, p less than 0.01), time to 1 mm ST-segment depression, and time to onset of anginal pain during exercise testing [8].

TRIMPOL-II (2000): A multicenter, randomized, double-blind, placebo-controlled trial in 426 patients with stable angina on metoprolol 100 mg daily. Trimetazidine 20 mg three times daily for 12 weeks produced significant improvements in exercise duration, ST-segment depression threshold, and weekly angina attack frequency compared to placebo. The treatment effect was independent of baseline exercise capacity and angina severity [9].

TACT (Trimetazidine as Adjunctive to Conventional Treatment, 2003): A randomized, double-blind, placebo-controlled trial in 177 patients with stable angina inadequately controlled on long-acting nitrates. Trimetazidine 20 mg three times daily for 12 weeks produced significant improvements in exercise testing parameters and reduction in weekly nitroglycerin consumption [10].

VASCO-angina (2011): The largest placebo-controlled monotherapy trial, randomizing 1,962 patients with stable angina to trimetazidine MR 35 mg twice daily, trimetazidine MR 70 mg twice daily (supratherapeutic dose), or placebo for 12 weeks. The primary endpoint (change in total exercise duration) was not met at either dose in the overall population, but pre-specified subgroup analysis demonstrated significant benefit in patients receiving background beta-blocker therapy and in those with at least four weekly angina attacks at baseline [11]. The VASCO-angina result has been a subject of debate; critics have noted that the trial enrolled

a population with low baseline ischemic burden (median 2 angina attacks per week) that may have diluted the treatment effect, while the subgroup analyses support the add-on therapy positioning that the EMA subsequently endorsed.

Hu et al. (2011) meta-analysis: A pooled analysis of 23 randomized controlled trials evaluating trimetazidine in angina pectoris, using echocardiographic and radionuclide angiographic endpoints, reported consistent improvements in exercise capacity and ischemic parameters across studies [27].

7.2 Heart failure with reduced ejection fraction

A substantial literature supports the use of trimetazidine as adjunctive therapy in chronic heart failure with reduced ejection fraction (HFrEF).

Gao et al. (2011) meta-analysis: Pooled data from 17 randomized controlled trials (955 patients) reported a weighted mean improvement in left ventricular ejection fraction (LVEF) of 7.49 percentage points (95% CI 6.26 to 8.71) with trimetazidine versus control, along with significant reductions in left ventricular end-systolic volume and improvements in New York Heart Association (NYHA) functional class [12].

Zhang et al. (2012) meta-analysis: Published in the Journal of the American College of Cardiology, this pooled analysis of 16 randomized controlled trials (884 patients) reported that trimetazidine was associated with improved LVEF (mean increase 6.46 percentage points, p less than 0.0001), increased total exercise time (plus 64 seconds), improved NYHA class, reduced cardiac hospitalization (relative risk 0.43, p less than 0.01), and reduced all-cause mortality (relative risk 0.47, p = 0.02) [13].

Weng et al. (2024) systematic review: The most recent pooled analysis confirmed improvements in LVEF and clinical outcomes in HFrEF, while noting that the evidence is derived from multiple smaller trials of varying methodological quality and that a large pragmatic randomized clinical trial is needed to establish the definitive role of trimetazidine in HFrEF management [28].

The 2021 ESC heart failure guidelines recommended trimetazidine at Class IIb, Level B for relief of persistent angina in heart failure patients receiving beta-blockers or alternatives.

7.3 Percutaneous coronary intervention and coronary artery bypass grafting

Multiple trials have evaluated peri-procedural trimetazidine in patients undergoing percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Reported endpoints include reduced peri-procedural myocardial injury (measured by troponin I elevation), preserved ventricular function post-revascularization, and reduced incidence of major adverse cardiac events at 30 days and at 1 year [29, 30]. The evidence is sufficient to support consideration of peri-procedural trimetazidine in clinical research but has not produced guideline-level recommendations.

7.4 Diabetic cardiomyopathy and metabolic syndrome

The metabolic mechanism of trimetazidine has generated interest in diabetic cardiomyopathy and insulin-resistant states, where excessive myocardial fatty acid oxidation is a recognized pathological feature. Small randomized trials have reported improvements in diastolic function parameters and in glycemic control (reduced HbA1c) in diabetic patients with heart failure receiving trimetazidine, consistent with the hypothesis that metabolic modulation addresses a pathological substrate in the diabetic heart [31, 32]. These findings are preliminary and have not been confirmed in large registration trials.

7.5 Investigational indications (vertigo, tinnitus, visual disturbance)

Trimetazidine was historically registered in some jurisdictions for symptomatic treatment of vertigo, tinnitus, and visual disturbance of vascular origin. The evidence for these indications was based on small, often open-label studies conducted in the 1970s and 1980s. The 2012 EMA Article 31 review concluded that the available evidence did not demonstrate a favorable benefit-risk balance for these non-cardiac indications, and they were withdrawn from the approved product information across the European Union [15].

8. Sourcing and Quality Verification

Pharmaceutical-grade trimetazidine dihydrochloride (Vastarel MR, Preductal MR, or licensed generic) is the highest quality source for research applications. The pharmaceutical-grade material is supplied as 35 mg modified-release tablets and as 20 mg immediate-release tablets in the marketed formulations. Pharmaceutical sourcing is feasible in jurisdictions where the compound is registered (most of continental Europe, the Russian Federation, Turkey, China, India, Brazil, and many others). The compound is not available through pharmaceutical channels in the United States, Canada, or the United Kingdom.

Research-grade trimetazidine dihydrochloride is supplied by multiple chemical and pharmaceutical research suppliers (Sigma-Aldrich, Cayman Chemical, Selleckchem, MedChemExpress, TCI, and others) at greater than 98 percent purity by HPLC. Supply is in milligram to gram quantities as the dihydrochloride salt. Pricing is moderate, typically in the range of \$30 to \$150 per gram at the time of monograph preparation.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (267.17 for the protonated free base $[M+H]^+$, 339.13 for the dihydrochloride)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) for structural confirmation, particularly to verify the trimethoxybenzyl substitution pattern (2,3,4 versus alternative regioisomers)
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis by gas chromatography for common synthesis solvents

Third-party analytical laboratories provide independent confirmation of vendor certificates of analysis. The research-grade trimetazidine market is well established, the compound is chemically simple and stable, and counterfeit or degraded

material is uncommon; however, lot-to-lot variability is possible and on-receipt analytical confirmation is appropriate for dose-response and mechanistic investigations.

9. Reconstitution and Handling

Trimetazidine dihydrochloride is freely soluble in water at room temperature (greater than 100 mg/mL). For in vitro research applications, the compound is typically supplied as a white crystalline powder and is reconstituted to stock solutions of 10 to 100 mM in water, phosphate-buffered saline, or dimethyl sulfoxide. The aqueous solutions are stable at refrigerated conditions (2 to 8 degrees Celsius) for at least 30 days. DMSO stock solutions may be stored at minus 20 degrees Celsius for extended periods; stability data from commercial suppliers indicate stability for at least 6 months at this temperature.

For isolated heart perfusion experiments, trimetazidine is added directly to the Krebs-Henseleit perfusion buffer at concentrations of 1 to 10 micromolar (typical working concentrations for demonstration of the metabolic shift). Higher concentrations (up to 100 micromolar) have been used in mechanistic studies to probe dose-response relationships at the 3-KAT target and at alternative targets.

For in vivo animal studies, the compound is dissolved in normal saline for intraperitoneal or intravenous administration or in drinking water (at calculated concentrations to achieve target daily doses) for chronic oral dosing. Gavage administration of dissolved or suspended compound in methylcellulose vehicle is also standard.

The tablet formulation (for clinical research) should be stored at room temperature (below 25 degrees Celsius) in the original packaging, protected from moisture. No special light protection is required.

Aliquoting of aqueous or DMSO stock solutions is recommended to avoid repeated freeze-thaw cycles. Stability through at least 3 freeze-thaw cycles has been documented without measurable loss of potency.

10. Stack Interactions and Combinations

Trimetazidine has a favorable drug-interaction profile, reflecting its low hepatic metabolism, absence of significant CYP450 involvement, and hemodynamic neutrality. Investigators conducting research with trimetazidine in combination regimens should consider the following:

Beta-adrenergic receptor antagonists: The combination of trimetazidine with beta-blockers (metoprolol, bisoprolol, atenolol, carvedilol) is the most commonly studied and the most clinically established combination. The TRIMPOL-II trial demonstrated the add-on benefit to metoprolol; no pharmacokinetic interaction between trimetazidine and beta-blockers has been identified. The combination is pharmacologically rational (hemodynamic plus metabolic antianginal mechanisms) and is the standard clinical use.

Calcium channel blockers: The combination with dihydropyridine (amlodipine, nifedipine) and non-dihydropyridine (verapamil, diltiazem) calcium channel blockers has been studied in small trials and is supported by the absence of hemodynamic interaction. No pharmacokinetic interactions have been identified.

Organic nitrates: The TACT trial demonstrated the add-on benefit to long-acting nitrates. No pharmacokinetic or pharmacodynamic interactions have been identified. The combination reduces nitroglycerin consumption in patients with refractory angina.

Ranolazine: The combination of trimetazidine with ranolazine (a late sodium current inhibitor with secondary metabolic effects) has not been extensively studied in clinical trials. Theoretically, the two metabolic antianginal agents may produce additive effects on myocardial metabolism, but the clinical evidence is insufficient to support routine combination. No pharmacokinetic interaction is expected.

Statins and antiplatelet agents: No clinically relevant interactions with HMG-CoA reductase inhibitors (atorvastatin, rosuvastatin) or with antiplatelet agents (aspirin, clopidogrel, ticagrelor) have been identified. This is important given the near-universal use of these agents in the target coronary artery disease population.

Antidiabetic agents: No significant interactions with metformin, sulfonylureas, insulin, or SGLT2 inhibitors have been identified. Small studies suggesting additive glycemic benefit (reduced HbA1c) with trimetazidine plus metformin in diabetic heart failure patients require confirmation [31].

QT-prolonging agents: Trimetazidine does not prolong the QT interval and does not carry a proarrhythmic risk. No interaction with QT-prolonging agents has been identified.

Dopaminergic agents: Given the parkinsonian safety signal, the combination of trimetazidine with dopaminergic agents (levodopa, dopamine agonists) in patients with Parkinson disease is contraindicated per the EMA 2012 decision. The interaction is pharmacodynamic (trimetazidine may antagonize dopaminergic neurotransmission through an incompletely characterized mechanism) rather than pharmacokinetic [15, 16].

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events at the registered dose (35 mg MR twice daily) are:

- Gastrointestinal disturbance (nausea, epigastric discomfort, dyspepsia): approximately 3 to 5 percent of patients
- Asthenia and fatigue: approximately 2 to 4 percent
- Headache: approximately 2 to 3 percent
- Dizziness: approximately 1 to 3 percent
- Myalgia: approximately 1 to 2 percent

These adverse events are generally mild, dose-independent at the therapeutic dose range, and similar in frequency to placebo in controlled trials [8, 9, 10]. The gastrointestinal effects may be reduced by taking the compound with food.

11.2 Parkinsonian symptoms

The most clinically significant adverse event is the induction of parkinsonian symptoms, including rest tremor, bradykinesia, rigidity, postural instability, and gait disorder. This signal was first reported in case series by Masmoudi et al. (2004) and Marti Masso (2004) and has been confirmed in multiple subsequent observational studies and pharmacovigilance analyses [16, 33, 34].

A systematic review by Pintore et al. (2020) identified 72 published cases of trimetazidine-induced parkinsonism across 26 studies [16]. The typical profile is an elderly patient (mean age approximately 74 years) on chronic trimetazidine therapy (median duration of exposure approximately 2 to 3 years before symptom onset) who develops symmetric parkinsonism with prominent rest tremor and gait disturbance. Symptoms are reversible with drug withdrawal in the majority of cases; the median time to resolution after discontinuation is approximately 1 to 4 months. In a minority of cases (approximately 10 to 20 percent), symptoms persist for more than 4 months, and the EMA product information recommends neurological consultation in such cases.

The mechanism of trimetazidine-induced parkinsonism is incompletely characterized. Proposed mechanisms include direct inhibition of complex I of the mitochondrial electron transport chain in dopaminergic neurons (analogous to the mechanism of MPTP-induced parkinsonism), impairment of dopamine synthesis or release through metabolic effects, and accumulation of the compound in the basal ganglia in patients with renal impairment [35]. A prospective study by Bondon-Guitton et al. (2011) in the French pharmacovigilance database confirmed the association and identified renal impairment and older age as risk factors [34].

11.3 Other rare and serious adverse events

- Thrombocytopenia: rare, reported in isolated case series
- Agranulocytosis: extremely rare, reported in single cases
- Hepatic enzyme elevation: rare, generally clinically insignificant and reversible
- Fixed drug eruption and other hypersensitivity reactions: rare
- Restless leg syndrome: included as a contraindication following the 2012 EMA review, though the causal association is supported principally by pharmacovigilance signals rather than by controlled studies

11.4 Renal impairment considerations

Because approximately 60 percent of trimetazidine is excreted unchanged in the urine, renal impairment leads to drug accumulation and increased adverse-event risk (particularly for parkinsonian symptoms). Dose reduction to 35 mg once daily is recommended for moderate renal impairment (creatinine clearance 30 to 60 mL/min). The compound is contraindicated in severe renal impairment (creatinine clearance below 15 mL/min) [15].

11.5 WADA status

Trimetazidine is classified as a prohibited substance by the World Anti-Doping Agency (WADA) under the category of hormone and metabolic modulators (S4.5.2, metabolic modulators). Multiple competitive athletes have received sanctions for positive trimetazidine tests, including a high-profile case at the 2022 Winter

Olympics [36]. The WADA classification is based on the metabolic-modulating mechanism rather than on demonstrated performance-enhancing efficacy; the evidence for ergogenic benefit is limited and indirect.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative metabolic and antianginal agents against trimetazidine, evaluated on five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected to represent the principal pharmacological alternatives in the metabolic antianginal and cardioprotective space, with priority on agents that have produced clinical evidence in angina and heart failure.

12.1 Ranolazine

Mechanism: Ranolazine inhibits the late sodium current ($I_{Na,late}$) in cardiomyocytes, reducing intracellular sodium accumulation and subsequent calcium overload during ischemia. It also has secondary metabolic effects through partial inhibition of fatty acid beta-oxidation, though the contribution of the metabolic mechanism to clinical efficacy is debated [37].

Development trajectory: Developed by CV Therapeutics (later Gilead Sciences), ranolazine was approved by the FDA in 2006 for chronic stable angina (Ranexa, 500 to 1000 mg extended-release twice daily). It has also been evaluated in acute coronary syndromes (MERLIN-TIMI 36 trial), in atrial fibrillation, and in diabetic angina.

Novelty: High. The late sodium current mechanism was novel at the time of development and remains mechanistically distinct from both hemodynamic antianginals and from metabolic modulators like trimetazidine.

Effect size: Moderate. The CARISA, ERICA, and MARISA trials demonstrated improvements in exercise tolerance and reduction in angina frequency [37, 38]. The MERLIN-TIMI 36 trial (6,560 patients with non-ST-elevation ACS) did not demonstrate reduction in major cardiovascular events but showed reduced recurrent ischemia.

Promising potential: Moderate. The compound is approved and available in the United States (FDA-approved), which is a major advantage over trimetazidine. Active investigation continues in atrial fibrillation, diabetic neuropathy, and HFpEF.

Side-effect profile: Principal adverse events are dizziness, nausea, constipation, and headache. Ranolazine produces dose-dependent QTc prolongation (mean 2 to 7 milliseconds at therapeutic doses), which is a relative disadvantage compared to the QT-neutral profile of trimetazidine. The compound is a substrate and inhibitor of CYP3A4 and is a substrate of P-glycoprotein, producing clinically relevant drug-drug interactions with strong CYP3A4 inhibitors and inducers.

Overall validation: High. FDA-approved, supported by large randomized trials, and included in ACC/AHA guidelines for chronic stable angina.

Comparison to trimetazidine: Ranolazine and trimetazidine are the two principal non-hemodynamic antianginal agents available globally. Ranolazine has the advantage of FDA approval and availability in the United States. Trimetazidine has the advantages of hemodynamic neutrality without QTc prolongation, a cleaner drug-drug interaction profile, and a stronger evidence base in heart failure. The two agents have complementary mechanisms and could theoretically be combined, though clinical data for the combination are lacking.

12.2 Perhexiline

Mechanism: Perhexiline inhibits carnitine palmitoyltransferase-1 (CPT-1) and CPT-2, the mitochondrial outer and inner membrane enzymes that transport long-chain fatty acyl-CoA esters into the mitochondrial matrix for beta-oxidation. This produces a profound shift from fatty acid to glucose oxidation, similar in direction to trimetazidine but at an earlier point in the fatty acid oxidation pathway [39].

Development trajectory: Developed in the 1970s as an antianginal agent, perhexiline was withdrawn from most markets in the 1980s due to hepatotoxicity and peripheral neuropathy associated with CYP2D6 polymorphic metabolism and drug accumulation. It remains available in Australia and New Zealand with therapeutic drug monitoring (plasma level-guided dosing).

Novelty: Low. The compound predates trimetazidine in clinical development and represents the first generation of metabolic antianginals. The mechanism is well characterized but old.

Effect size: Large. Perhexiline is considered the most potent metabolic antianginal available, producing substantial improvements in exercise tolerance and angina frequency in refractory angina [39]. In heart failure, the ERGO trial (2015) demonstrated improvements in peak oxygen consumption and ejection fraction in non-ischemic HFrEF.

Promising potential: Low to moderate. The compound is restricted to two countries with mandatory therapeutic drug monitoring, which limits practical accessibility and scalability.

Side-effect profile: The principal safety concern is hepatotoxicity (hepatic steatosis and phospholipidosis) and peripheral neuropathy, both related to drug accumulation in CYP2D6 poor metabolizers. Therapeutic drug monitoring to maintain plasma levels between 150 and 600 ng/mL largely mitigates these risks but adds operational complexity. The side-effect profile is substantially worse than that of trimetazidine.

Overall validation: Moderate. The clinical efficacy is well established, but the therapeutic index is narrow, the safety profile is unfavorable without drug monitoring, and availability is restricted.

Comparison to trimetazidine: Perhexiline is more potent but substantially less safe than trimetazidine. Trimetazidine's advantages include broad global availability, no requirement for therapeutic drug monitoring, a wider therapeutic index, and a more benign side-effect profile (parkinsonian risk aside). Perhexiline's principal advantage is its potency in refractory angina where other agents have failed.

12.3 Ivabradine

Mechanism: Ivabradine selectively inhibits the funny current (If) in the sinoatrial node, reducing heart rate without affecting myocardial contractility, conduction velocity, or blood pressure. The mechanism is hemodynamic (heart rate reduction reduces myocardial oxygen demand) rather than metabolic [40].

Development trajectory: Developed by Servier, ivabradine was approved in Europe in 2005 (Procoralan/Corlanor) for stable angina and subsequently for heart failure (HFrEF with heart rate above 70 to 75 bpm). FDA approval for heart failure was obtained in 2015. The BEAUTIFUL and SIGNIFY trials evaluated the compound in coronary artery disease.

Novelty: Moderate. The If current mechanism was novel at the time of development. It is mechanistically distinct from both metabolic modulators and from beta-blockers.

Effect size: Moderate. In angina, the INITIATIVE, ASSOCIATE, and SIGNIFY trials demonstrated improvements in exercise tolerance comparable to atenolol and additive benefit when combined with beta-blockers [41]. In heart failure, the SHIFT trial (6,558 patients) demonstrated a 26 percent reduction in hospitalization for worsening heart failure (p less than 0.0001), though no significant reduction in cardiovascular mortality.

Promising potential: High. The compound is approved in both Europe and the United States, is recommended in ESC guidelines for angina and heart failure, and is integrated into standard clinical practice.

Side-effect profile: The principal adverse events are visual disturbances (phosphenes, occurring in approximately 15 percent of patients), bradycardia, and headache. The phosphenes are generally transient and mild. The compound is contraindicated in severe bradycardia and in combination with strong CYP3A4 inhibitors.

Overall validation: High. Multiple large randomized trials, guideline-level recommendations, and global regulatory approval for both angina and heart failure.

Comparison to trimetazidine: Ivabradine and trimetazidine are complementary agents developed by the same company (Servier). Ivabradine operates through hemodynamic (heart rate reduction) rather than metabolic mechanisms. The ASSOCIATE trial demonstrated additive benefit of ivabradine plus atenolol in angina; a similar additive paradigm with trimetazidine is pharmacologically rational but less extensively studied. Ivabradine has stronger regulatory and guideline positioning; trimetazidine has the unique metabolic mechanism.

12.4 Nicorandil

Mechanism: Nicorandil is a hybrid agent combining nitrate-like activity (guanylate cyclase activation, venodilation) with ATP-sensitive potassium channel (KATP) opening in vascular smooth muscle and cardiomyocytes. The KATP channel opening produces coronary vasodilation and is also proposed to confer cardioprotection through preconditioning-like effects [42].

Development trajectory: Developed in Japan in the 1980s, nicorandil is approved in multiple countries (Japan, several European and Asian markets) for stable angina pectoris (Ikorel, Dancor, Sigmart). It is not approved by the FDA. The IONA trial (5,126 patients with stable angina) demonstrated a 17 percent reduction in the composite of coronary death, nonfatal myocardial infarction, or unplanned hospitalization for chest pain.

Novelty: Moderate. The dual nitrate-KATP mechanism was novel at the time of development.

Effect size: Moderate. The IONA trial demonstrated significant reduction in the composite endpoint, though the individual components (coronary death, nonfatal MI) did not reach significance independently [42].

Promising potential: Moderate. The compound is established in Asian and European markets. The principal safety concern (mucosal ulceration) limits its use in some patients.

Side-effect profile: The principal adverse events are headache (nitrate effect), dizziness, and gastrointestinal ulceration (oral, anal, and rarely intestinal perforations). The ulceration signal is the most concerning safety issue and has led to product label warnings and clinical caution.

Overall validation: Moderate. The IONA trial provides outcome data that exceed the evidence base for trimetazidine in angina. The ulceration signal is a liability.

Comparison to trimetazidine: Nicorandil has outcome data from IONA that trimetazidine currently lacks in angina. Trimetazidine has a substantially more favorable safety profile (no mucosal ulceration, no headache from nitrate effect). The two compounds have different mechanisms (metabolic versus vasodilator/KATP opening) and are pharmacologically suitable for combination.

12.5 Dichloroacetate (DCA)

Mechanism: Dichloroacetate activates pyruvate dehydrogenase by inhibiting pyruvate dehydrogenase kinase, thereby increasing glucose oxidation and lactate clearance. The mechanism is complementary to trimetazidine: trimetazidine inhibits fatty acid oxidation (supply-side), while DCA activates glucose oxidation (demand-side). The net metabolic shift is similar [43].

Development trajectory: DCA has been investigated as a metabolic modulator in lactic acidosis, congenital mitochondrial disease, pulmonary arterial hypertension, and cancer. It is not approved by any major regulatory authority for any cardiovascular indication. Clinical trials in heart failure and in pulmonary hypertension have been conducted, with modest positive signals.

Novelty: Low to moderate. The pyruvate dehydrogenase activation mechanism is well characterized and predates trimetazidine in the scientific literature.

Effect size: Modest. Clinical trial data in cardiovascular disease are limited to small studies. In lactic acidosis and congenital mitochondrial disease, the evidence is more substantial but not directly relevant to the antianginal comparison.

Promising potential: Low. The compound has not advanced to regulatory approval for any cardiovascular indication. It remains principally a research tool for metabolic modulation.

Side-effect profile: The principal safety concern is peripheral neuropathy, which is dose-dependent and potentially irreversible with chronic administration. Hepatotoxicity has been reported at high doses. The therapeutic index is narrow compared to trimetazidine.

Overall validation: Low. No regulatory approval, limited clinical trial evidence in cardiovascular disease, and unfavorable safety profile for chronic use.

Comparison to trimetazidine: DCA and trimetazidine produce similar metabolic shifts through complementary mechanisms. Trimetazidine is vastly superior in clinical validation, safety, and regulatory positioning. DCA's principal value is as a research tool for dissecting the metabolic mechanism and as a theoretical combination partner for mechanistic studies.

12.6 Comparator summary

The five comparators occupy distinct positions in the antianginal and cardioprotective pharmacology space. **Ranolazine** is the closest functional equivalent to trimetazidine, with FDA approval and complementary late-sodium-current mechanism, offset by QTc prolongation and CYP3A4 interactions. **Perhexiline** is the most potent metabolic antianginal but is limited by hepatotoxicity, peripheral neuropathy, and restricted availability. **Ivabradine** is the most clinically established of the comparators, with heart-rate-selective hemodynamic mechanism, strong guideline

positioning, and global regulatory approval. **Nicorandil** provides unique outcome data from IONA but carries the mucosal ulceration liability. **Dichloroacetate** is a research tool without clinical validation.

Trimetazidine occupies a unique position: it is the only pure metabolic modulator with broad global registration (approximately 100 countries), the only antianginal agent with demonstrated benefit in heart failure meta-analyses through a metabolic mechanism, and the agent with the most favorable drug-interaction profile among the comparators. Its principal liabilities are the absence of FDA approval (limiting access in the United States, Canada, and the United Kingdom), the parkinsonian safety signal (requiring vigilance in elderly patients), the absence of large-scale cardiovascular outcome trial data (the meta-analytic evidence in heart failure is drawn from multiple smaller trials), and the downgrade from Class IIa to IIb in the 2024 ESC CCS guidelines. The combination of metabolic mechanism, hemodynamic neutrality, low interaction potential, broad availability, and favorable tolerability (with appropriate patient selection) supports continued clinical use and research investigation.

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