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NITROGLYCERINE IN CONTEMPORARY CARDIOVASCULAR THERAPEUTICS: MOLECULAR MECHANISMS, CLINICAL APPLICATIONS, AND FUTURE PERSPECTIVES

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ABSTRACT
Nitroglycerine (glyceryl trinitrate) remains one of the most extensively utilized vasodilators in cardiovascular medicine, with a therapeutic legacy spanning over 150 years. Despite the emergence of novel anti-anginal and heart failure therapies, nitroglycerine continues to serve as a cornerstone agent for rapid symptomatic relief in angina pectoris and acute coronary syndromes. This review provides a comprehensive and mechanistically integrated analysis of nitroglycerine, encompassing its chemical characteristics, pharmacokinetic profile, nitric oxide–mediated signaling pathways, hemodynamic effects, clinical indications, adverse effects, drug interactions, and the phenomenon of nitrate tolerance. Particular emphasis is placed on mitochondrial aldehyde dehydrogenase (ALDH2)-dependent bioactivation, cyclic guanosine monophosphate (cGMP) signaling, and emerging insights into pharmacogenomic variability influencing therapeutic response. Contemporary clinical applications in acute coronary syndromes, hypertensive emergencies, pulmonary edema, perioperative blood pressure control, and special populations are critically examined alongside limitations related to tachyphylaxis and long-term efficacy. Furthermore, evolving research directions, including nanoformulations, sustained-release delivery systems, and comparative effectiveness against newer anti-anginal agents, are discussed to contextualize the modern relevance of this classical therapy. While nitroglycerine does not confer demonstrated mortality benefit in chronic coronary disease, its rapid onset of action and predictable hemodynamic profile sustain its indispensable role in acute cardiovascular care. Ongoing translational research aimed at optimizing delivery strategies and overcoming tolerance mechanisms may further refine its clinical utility in contemporary cardiovascular therapeutics.

KEYWORDS , Nitroglycerine, Organic nitrates, Vasodilator, Nitric oxide (NO), cGMP pathway, Angina pectoris, Myocardial infarction, Acute heart failure, Hypertensive emergency, Coronary vasodilation, Pharmacokinetics, Drug interactions, Nitrate tolerance, Transdermal patch, Sublingual nitroglycerine

INTRODUCTION

History of nitroglycerine

The history of nitroglycerine (glyceryl trinitrate) reflects a remarkable transition from chemical curiosity to cornerstone therapy in cardiovascular medicine. Nitroglycerine was first synthesized in 1847 by the Italian chemist Ascanio Sobrero in Turin while working in the laboratory of Theophile-Jules Pelouze. Sobrero observed that even minimal exposure produced intense, throbbing headaches, a physiological response that would later prove central to understanding its vascular effects. [1]Shortly thereafter, in 1849, the physician Constantin Hering conducted early human experiments, documenting the reproducible induction of headache and exploring its therapeutic implications within the framework of homeopathic principles under the name “glonoine.” The industrial and practical development of nitroglycerine was significantly advanced by Alfred Nobel, who recognized its explosive potential and engineered safer handling methods, including the invention of a detonator system that allowed controlled application. Ironically, despite suffering from angina pectoris later in life, Nobel reportedly declined treatment with the very compound that would become a mainstay of anti-anginal therapy.[2]During the same era, British investigators were exploring vasodilatory compounds such as amyl nitrite; in 1867, Lauder Brunton demonstrated its effectiveness in relieving angina, thereby laying the foundation for nitrate-based therapy. Building upon these observations, William Murrell first administered nitroglycerine for angina in 1876, establishing its clinical utility. Pharmaceutical refinement followed, including stabilization efforts by William Martindale, who developed portable formulations that improved therapeutic practicality. Industrial exposure to organic nitrates in the early twentieth century revealed phenomena such as tolerance and withdrawal effects, colloquially described as "Monday disease" and "Sunday heart attacks," thereby foreshadowing modern insights into nitrate tolerance and dependence. A transformative scientific breakthrough occurred in 1977 when Ferid Murad demonstrated that nitroglycerine exerts its biological action through the release of nitric oxide (NO), which activates cyclic guanosine monophosphate signaling in vascular smooth muscle. This discovery was further expanded by the seminal work of Robert F. Furchgott and John Zawadzki, who elucidated the role of the endothelium in vasorelaxation, and by Louis Ignarro and Salvador Moncada, who identified endothelial-derived relaxing factor as nitric oxide, thereby integrating nitrate pharmacology into the broader framework of endothelial biology. Today, glyceryl trinitrate remains the treatment of choice for rapid relief of angina pectoris due to its immediate onset of action, predictable hemodynamic effects, and extensive clinical validation. Although alternative organic and inorganic nitrates are available, the speed, reliability, and long-standing evidence supporting nitroglycerine continue to position it as a central therapeutic agent in ischemic heart disease, reflecting more than a century of translational progress from bench chemistry to lifesaving cardiovascular intervention.[1]

Importance of Nitroglycerine as a Vasodilator and First-Line Anti-Anginal Drug

Nitroglycerine is one of the most important and widely used vasodilators in cardiovascular medicine and remains a first-line drug for the management of angina pectoris. Its clinical importance is mainly due to its rapid onset of action, predictable efficacy, and ability to relieve myocardial ischemia effectively.[3]As a vasodilator, nitroglycerine primarily acts on venous blood vessels, causing venodilation and a significant reduction in venous return to the heart (preload). This decreases myocardial wall tension and oxygen demand, which is a key factor in relieving anginal pain.[4] At higher doses, nitroglycerine also causes arterial and coronary vasodilation, leading to reduced afterload and improved coronary blood flow, especially in ischemic areas of the myocardium. Nitroglycerine is considered a first-line anti-anginal drug because it provides rapid relief of acute anginal attacks, particularly when administered via the sublingual route. The onset of action occurs within minutes, making it highly effective in emergency situations. In chronic stable angina, long-acting formulations such as transdermal patches and sustained-release tablets help prevent recurrent episodes. Additionally, nitroglycerine is easy to administer, cost-effective, and well understood by clinicians, further supporting its first-line status. Despite the availability of newer anti-anginal agents, nitroglycerine continues to play a central role in both acute and chronic management of ischemic heart disease due to its proven efficacy, safety profile, and extensive clinical experience.[5]

Why This Review Is Needed: Relevance in Cardiology, Emergency Medicine, and Intensive Care Units

Despite being one of the oldest cardiovascular drugs in clinical practice, nitroglycerine continues to play a critical and irreplaceable role in modern cardiology, emergency medicine, and intensive care units (ICUs). The need for this review arises from the fact that nitroglycerine is frequently used across multiple acute care settings, yet variations in its administration, dosing strategies, and clinical interpretation persist among healthcare professionals. In cardiology, nitroglycerine remains a cornerstone in the management of ischemic heart disease, including stable angina, unstable angina, and acute myocardial infarction.[5] Although newer anti-anginal and vasodilator therapies have been introduced, nitroglycerine's rapid onset of action and proven efficacy in reducing myocardial oxygen demand continue to make it a first-line agent. However, evolving evidence regarding nitrate tolerance, genetic variability in nitric oxide metabolism, and long-term outcomes necessitates an updated and critical review of its role in contemporary practice. In emergency medicine, nitroglycerine is often administered as an immediate intervention for chest pain, acute pulmonary edema, and hypertensive emergencies. [4]Timely and appropriate use can be life-saving, while improper dosing or contraindicated use—such as in patients taking phosphodiesterase-5 inhibitors or those with right ventricular infarction—can lead to serious complications. A comprehensive review helps clarify best practices and reinforces safe clinical decision-making in high-pressure emergency settings. Within ICUs, intravenous nitroglycerine is commonly employed for precise hemodynamic control in patients with acute heart failure, postoperative cardiac conditions, and severe hypertension. Advances in critical care monitoring and individualized therapy highlight the need to reassess dosing protocols, safety considerations, and emerging alternatives.[5] This review aims to bridge existing knowledge gaps, integrate current evidence, and provide a unified understanding of nitroglycerine's continued relevance in acute and critical cardiovascular care.[4]

Methods

This narrative review was conducted through a structured and comprehensive literature search designed to synthesize historical foundations, mechanistic insights, and contemporary clinical evidence related to nitroglycerine therapy. Electronic databases including PubMed, Scopus, Web of Science, and Google Scholar were searched for relevant publications from January 1970 through December 2025. Search terms included "nitroglycerine," "glyceryl trinitrate," "organic nitrates," "nitric oxide signaling," "cGMP pathway," "ALDH2 polymorphism," "nitrate tolerance," "acute coronary syndrome," "heart failure," and "anti-anginal therapy."

Priority was given to randomized controlled trials, meta-analyses, major guideline documents, mechanistic translational studies, and landmark experimental investigations. Additional emphasis was placed on contemporary evidence evaluating comparative effectiveness with newer anti-anginal agents and emerging delivery technologies. Reference lists of selected articles were manually screened to ensure completeness. Non-English language articles and studies lacking methodological clarity were excluded. The final synthesis integrates pharmacological, molecular, and clinical perspectives to provide a comprehensive and updated evaluation of nitroglycerine in modern cardiovascular practice.

Chemistry and Pharmacological Classification of Nitroglycerine

Nitroglycerine is chemically classified as an organic nitrate and is structurally derived from glycerol in which three hydroxyl groups are esterified with nitric acid. Its chemical name, glyceryl trinitrate, reflects the presence of three nitrate groups attached to a glycerol

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backbone. This unique structure is responsible for its potent vasodilatory activity, as it serves as a source of nitric oxide within the body. Unlike inorganic nitrates, organic nitrates such as nitroglycerine require enzymatic activation to exert their pharmacological effects.[6]From a physicochemical perspective, nitroglycerine is a colourless to pale yellow, oily liquid with a slightly sweet odor. It is highly lipid-soluble, a property that allows rapid absorption across biological membranes, particularly when administered via sublingual, transdermal, or intravenous routes. However, it is poorly soluble in water and chemically unstable when exposed to heat, light, or shock, necessitating careful formulation and storage.[4]These physicochemical characteristics influence both its clinical handling and its rapid onset of action in acute settings. The metabolism of nitroglycerine is central to its therapeutic action. After administration, nitroglycerine undergoes enzymatic biotransformation primarily in vascular smooth muscle cells, where mitochondrial aldehyde dehydrogenase (ALDH2) plays a key role. This process leads to the release of nitric oxide or nitric oxide–related species. The generated nitric oxide activates soluble guanylate cyclase, increasing intracellular cyclic guanosine monophosphate (cGMP) levels. Elevated cGMP causes relaxation of vascular smooth muscle, resulting in vasodilation. This nitric oxide–mediated pathway explains both the rapid clinical effectiveness of nitroglycerine and its central role in cardiovascular therapeutics.[4]

Mechanism of Action of Nitroglycerine

Nitroglycerine produces its therapeutic effects through a well-defined biochemical pathway that ultimately results in vascular smooth muscle relaxation. Although nitroglycerine itself is not an active vasodilator, it acts as a prodrug that must undergo enzymatic conversion within the body to exert its effects.[6]

Enzymatic Biotransformation to Nitric Oxide (NO)

After administration, nitroglycerine enters vascular smooth muscle cells, where it is enzymatically metabolized. The key enzyme involved in this process is mitochondrial aldehyde dehydrogenase (ALDH2). This enzyme converts nitroglycerine into nitric oxide (NO) or NO-related intermediates. The mitochondria play a crucial role in this conversion, making intracellular energy-producing sites central to nitroglycerine's activity. Reduced ALDH2 activity, whether due to genetic variation or prolonged nitrate exposure, can diminish drug effectiveness and contribute to nitrate tolerance.[7]

NO–cGMP Signaling Pathway

Once released, nitric oxide rapidly diffuses into adjacent smooth muscle cells and activates the enzyme soluble guanylate cyclase. This activation leads to an increase in intracellular levels of cyclic guanosine monophosphate (cGMP). Elevated cGMP reduces intracellular calcium concentration and inhibits myosin light-chain phosphorylation, resulting in relaxation of vascular smooth muscle. This pathway forms the core mechanism responsible for the vasodilatory effects of nitroglycerine.[8]

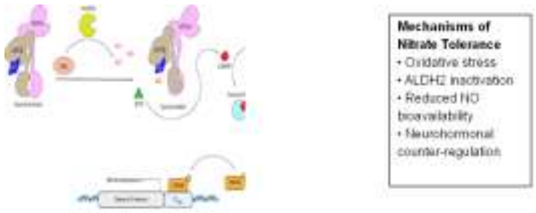

Figure 1 illustrates the NO–cGMP signaling cascade underlying nitroglycerine-mediated vasodilation.

Hemodynamic Effects

The hemodynamic effects of nitroglycerine are dose-dependent and involve differential actions across various vascular beds, ultimately contributing to its therapeutic efficacy in ischemic cardiovascular conditions.[9] At lower therapeutic concentrations, nitroglycerine predominantly induces venodilation, resulting in increased venous capacitance and reduced venous return to the heart, which in turn decreases preload and left ventricular end-diastolic pressure, thereby lowering myocardial wall tension and significantly reducing myocardial oxygen demand. As the dose increases, the vasodilatory effect extends to systemic arterial circulation, leading to a reduction in systemic vascular resistance and afterload, which further diminishes cardiac workload and enhances forward stroke volume in patients with compromised ventricular function. In addition to its systemic effects, nitroglycerine exerts direct action on the coronary vasculature by dilating large epicardial coronary arteries and improving collateral blood flow, thereby redistributing perfusion toward ischemic myocardial regions and enhancing oxygen delivery. Collectively, these integrated hemodynamic modifications underpin the clinical utility of nitroglycerine in the management of angina pectoris, acute myocardial ischemia, and heart failure–associated congestion.[4]

Pharmacokinetics of Nitroglycerine (ADME)

A comprehensive understanding of the pharmacokinetic profile of nitroglycerine is fundamental to optimizing its therapeutic application, as its absorption, distribution, metabolism, and elimination are highly dependent on the route of administration and formulation employed. Owing to its pronounced lipid solubility, nitroglycerine is rapidly absorbed across biological membranes, although the rate and extent of systemic availability vary considerably between delivery systems. Sublingual administration permits direct absorption through the oral mucosa into the systemic circulation, effectively bypassing first-pass hepatic metabolism and producing a rapid onset of action, typically within minutes, which makes this route particularly suitable for the prompt relief of acute anginal episodes. In contrast, intravenous administration ensures immediate and complete bioavailability, allowing precise dose titration and controlled hemodynamic management in emergency and intensive care settings. Transdermal formulations, including patches and ointments, enable gradual absorption through the skin and provide sustained plasma concentrations over extended periods, thereby supporting prophylactic therapy in chronic stable angina, albeit with a slower onset compared to sublingual preparations. Oral formulations are absorbed through the gastrointestinal tract but undergo extensive first-pass metabolism in the liver, resulting in reduced and variable systemic bioavailability, which limits their effectiveness in acute symptom control and confines their use primarily to maintenance therapy.[[10]]

Following systemic absorption, nitroglycerine distributes widely throughout the body, facilitated by its lipophilic character, which allows rapid penetration of cellular membranes and efficient delivery to vascular smooth muscle cells, the principal site of action. The drug exhibits moderate plasma protein binding and a relatively large apparent volume of distribution, ensuring prompt access to cardiovascular tissues, including the myocardium and systemic vasculature.[10]

Metabolic inactivation of nitroglycerine occurs extensively via both hepatic and extrahepatic pathways. Hepatic metabolism involves enzymatic denitration processes that generate dinitrate and mononitrate metabolites, some of which retain partial pharmacological activity. Extrahepatic metabolism, occurring within vascular smooth muscle cells, erythrocytes, and renal tissues, plays a critical role in bioactivation as well as clearance. Notably, mitochondrial aldehyde dehydrogenase (ALDH2) is a key enzyme responsible for converting nitroglycerine into nitric oxide or related intermediates, thereby linking pharmacokinetics to pharmacodynamic effect. Nitroglycerine is characterized by a very short plasma half-life, generally ranging from one to four minutes, reflecting rapid metabolic degradation and systemic clearance. Elimination occurs predominantly through hepatic pathways, with subsequent renal excretion of metabolites. This brief half-life necessitates continuous intravenous infusion in acute settings or the use of sustained-release

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and transdermal formulations for prolonged therapeutic effect.[6](fig.2)

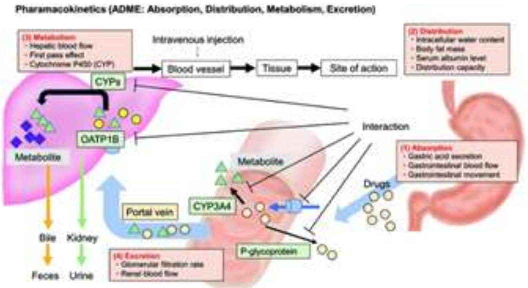

Fig.2 Overview of ADME pharmacokinetics illustrating oral drug absorption in the GI tract, distribution to tissues via bloodstream, hepatic metabolism (including first-pass effect via CYP enzymes and portal vein), and excretion through renal (urine) and biliary (feces) routes, with key influencing factors and transporters (e.g., P-glycoprotein, OATP1B).

Bioavailability remains a critical determinant of clinical efficacy, as sublingual and intravenous routes achieve high systemic exposure by circumventing hepatic first-pass metabolism, whereas oral preparations exhibit lower and less predictable bioavailability due to extensive hepatic degradation. Transdermal systems provide more stable plasma concentrations but may predispose patients to tolerance during prolonged exposure, underscoring the importance of individualized formulation selection based on clinical indication and therapeutic objectives.[10]

Table: Formulations and Routes of Administration of Nitroglycerine

Route / Formulation	Clinical Indication	Onset of Action	Duration of Action	Advantages	Disadvantages / Limitations
Sublingual tablets / spray	Acute anginal attack, emergency chest pain relief	1–3 minutes	20–30 minutes	Rapid onset, easy to use, bypasses first-pass metabolism, ideal for emergencies	Short duration, frequent dosing needed, headache and hypotension common
Intravenous (IV) infusion	Acute heart failure, myocardial infarction, hypertensive emergencies, ICU use	Immediate	Short; depends on infusion rate	Precise dose control, rapid titration, useful in critical care	Requires monitoring, hospital setting only, risk of severe hypotension
Transdermal patch / ointment	Chronic stable angina prophylaxis	30–60 minutes	12–24 hours	Sustained drug delivery, improves compliance, non-invasive	Delayed onset, nitrate tolerance, skin irritation possible
Oral extended-release tablets	Long-term prevention of angina	30–60 minutes	6–8 hours	Convenient for chronic therapy, reduced dosing frequency	Low bioavailability, first-pass metabolism, not useful for acute attacks
Buccal tablets	Prevention and treatment of angina	5–10 minutes	3–5 hours	Avoids first-pass metabolism, longer action than sublingual	Slower onset than sublingual, local irritation, patient discomfort

Clinical Applications of Nitroglycerine

Nitroglycerine is widely used across multiple clinical settings due to its potent vasodilatory effects, rapid onset of action, and flexible routes of administration. Its ability to reduce cardiac workload and improve myocardial perfusion makes it particularly valuable in acute and chronic cardiovascular conditions. [5]

Angina Pectoris (Acute and Chronic)

Nitroglycerine is a first-line therapy for both acute relief and long-term prevention of angina pectoris. In acute anginal attacks, sublingual nitroglycerine rapidly reduces chest pain by decreasing venous return, thereby lowering myocardial oxygen demand. For chronic stable angina, long-acting oral and transdermal formulations help prevent recurrent ischemic episodes. Clinical studies consistently demonstrate its effectiveness in improving exercise tolerance and reducing anginal frequency.[11]

Myocardial Infarction

In acute myocardial infarction, nitroglycerine is used to relieve ischemic chest pain and reduce preload and afterload, which decreases myocardial oxygen consumption. Intravenous administration allows controlled hemodynamic management, particularly in patients with hypertension or heart failure. However, its use is carefully avoided in right ventricular infarction and hypotensive patients.[12]

Congestive Heart Failure (Acute Decompensated HF)

Nitroglycerine is highly effective in acute decompensated heart failure, especially when associated with elevated blood pressure. By reducing preload and pulmonary congestion, it improves symptoms such as dyspnea and orthopnea. High-dose IV nitroglycerine has been shown to rapidly stabilize patients and reduce the need for mechanical ventilation.[13]

Hypertensive Emergencies

In hypertensive emergencies, nitroglycerine is used to achieve rapid and controlled blood pressure reduction, particularly when cardiac ischemia or heart failure is present. Its short half-life allows precise titration and minimizes the risk of prolonged hypotension.[14]

Pulmonary Edema

Nitroglycerine is a cornerstone in the management of acute cardiogenic pulmonary edema. Venous dilation reduces pulmonary capillary pressure, leading to rapid improvement in respiratory distress and oxygenation.[13]

Peri-operative Blood Pressure Control

During and after cardiac and non-cardiac surgeries, IV nitroglycerine is used to manage peri-operative hypertension and myocardial ischemia. It provides predictable hemodynamic control and reduces peri-operative cardiac complications.[15]

Obstetrics (Uterine Relaxation)

In obstetric practice, nitroglycerine is occasionally used for short-term uterine relaxation during procedures such as retained placenta removal or uterine inversion correction due to its rapid smooth muscle–relaxing properties.[16]

Other Emerging Uses

Emerging applications include treatment of esophageal spasm, anal fissures (topical use), and investigational roles in pulmonary hypertension and heart failure with preserved ejection fraction. Ongoing research continues to explore novel delivery systems and combination therapies.[17]

Contraindications of Nitroglycerine

Nitroglycerine, although highly effective in cardiovascular management, must be used with caution in specific clinical situations where its vasodilatory effects may lead to serious complications. The following conditions are considered important contraindications:

Hypotension: Nitroglycerine significantly lowers blood pressure by reducing preload and afterload. In patients with pre-existing hypotension (systolic blood pressure <90 mmHg) or those in circulatory shock, its administration may further compromise systemic perfusion and precipitate cardiovascular collapse.[18]

Concomitant Use with Phosphodiesterase-5 (PDE-5) Inhibitors: The combined use of nitroglycerine with PDE-5 inhibitors such as sildenafil, tadalafil, or vardenafil is strictly contraindicated. Both agents enhance the nitric oxide–cGMP pathway, leading to profound vasodilation. Their interaction can result in severe, life-threatening hypotension and syncope.[[19]]

Severe Anaemia: In patients with marked anaemia, oxygen-carrying capacity is already reduced. Nitroglycerine-induced vasodilation may worsen tissue hypoxia by further lowering perfusion pressure, thereby aggravating ischemic symptoms.

Right Ventricular Myocardial Infarction: In right ventricular infarction, cardiac output is highly dependent on adequate preload. Since nitroglycerine reduces venous return, its use in this setting can lead to a sudden drop in cardiac output and severe hypotension.

Careful patient evaluation and hemodynamic monitoring are therefore essential before initiating nitroglycerine therapy, particularly in acute care settings.[4]

Adverse Effects of Nitroglycerine

Although nitroglycerine is widely used and generally safe when administered appropriately, its vasodilatory action can produce predictable adverse effects. Most reactions are dose-related and reversible, but careful monitoring is essential, particularly in acute care settings.[20]

Headache (Classic Nitrate Headache): Headache is the most common side effect of nitroglycerine therapy. It occurs due to dilation of cerebral blood vessels, which increases intracranial vascular pressure. Patients often describe it as a throbbing or pulsating pain that appears soon after administration. While usually mild and self-limiting, it can be severe enough to affect compliance in long-term therapy. Over time, some patients develop partial tolerance to this effect.[18]

Hypotension: Because nitroglycerine reduces both preload and, at higher doses, afterload, a drop in blood pressure is expected. Excessive hypotension may present as dizziness, light-headedness, blurred vision, or even syncope. The risk increases in volume-depleted individuals or when combined with other antihypertensive medications.[18]

Reflex Tachycardia: A sudden fall in blood pressure may trigger a compensatory increase in heart rate through sympathetic activation. This reflex tachycardia can paradoxically increase myocardial oxygen demand, potentially reducing the anti-anginal benefit if not carefully managed.[18]

Methemoglobinemia (Rare): In rare cases, especially with high intravenous doses or prolonged use, nitroglycerine may oxidize hemoglobin to methemoglobin, reducing its oxygen-carrying capacity. Clinically, this may present as cyanosis unresponsive to oxygen therapy. Prompt recognition and treatment are important, though the condition remains uncommon.

Tolerance and Tachyphylaxis: One of the most clinically significant limitations of nitroglycerine is the development of tolerance with continuous exposure. Over time, the vasodilatory response diminishes, possibly due to reduced nitric oxide availability, oxidative stress, or impaired activity of mitochondrial aldehyde dehydrogenase (ALDH2). Tachyphylaxis, a rapid decrease in response, may also occur during continuous intravenous infusion. To minimize tolerance, a nitrate-free interval (typically 8–12 hours daily) is recommended in chronic therapy. Understanding these adverse effects helps clinicians balance therapeutic benefits with safety considerations and optimize long-term treatment strategies.[4]

Drug Interactions of Nitroglycerine

Nitroglycerine demonstrates clinically significant drug interactions that must be carefully considered in order to prevent adverse hemodynamic consequences, particularly because of its potent vasodilatory effect mediated through the nitric oxide–cGMP pathway. Concomitant administration with phosphodiesterase-5 (PDE-5)

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inhibitors—including sildenafil, tadalafil, and vardenafil—is strictly contraindicated, as these agents inhibit the breakdown of cyclic guanosine monophosphate (cGMP), thereby amplifying nitroglycerine-induced vasodilation and potentially causing profound, life-threatening hypotension, syncope, or cardiovascular collapse.[21] [22]Similarly, when used alongside antihypertensive medications such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-adrenergic blockers, calcium-channel blockers, or diuretics, the blood pressure–lowering effect may become additive or synergistic, increasing the risk of symptomatic hypotension and dizziness. Alcohol consumption further potentiates vasodilation by impairing vascular tone and autonomic regulation, thereby enhancing orthostatic hypotension and increasing the likelihood of fainting episodes.[23]In contrast, ergot derivatives, which are potent vasoconstrictors, may exhibit opposing vascular effects; however, their concurrent use can unpredictably alter coronary blood flow dynamics and potentially worsen ischemia in susceptible individuals. Despite these concerns, nitroglycerine is frequently and intentionally combined with beta-blockers or calcium-channel blockers in the management of chronic stable angina, as these agents counteract reflex tachycardia, reduce myocardial oxygen demand, and enhance overall anti-ischemic efficacy when used under appropriate clinical supervision. Careful evaluation of drug history and hemodynamic status is therefore essential before initiating nitroglycerine therapy, particularly in emergency and cardiovascular care settings.[24]

Comparative Effectiveness with Contemporary Anti-Anginal Therapies

Although nitroglycerine remains the gold standard for immediate relief of ischemic chest pain, its role in long-term disease modification has been increasingly re-evaluated in the context of newer anti-anginal agents such as ranolazine, ivabradine, trimetazidine, and beta-adrenergic blockers. Unlike beta-blockers and certain calcium-channel blockers, which have demonstrated mortality reduction in specific cardiovascular populations, nitroglycerine primarily provides symptomatic improvement without clear evidence of survival benefit in chronic stable coronary artery disease. Randomized clinical trials have consistently shown that short-acting nitroglycerine effectively reduces anginal frequency and improves exercise tolerance; however, sustained nitrate therapy has not demonstrated superiority in preventing myocardial infarction or reducing cardiovascular mortality. [25]
Furthermore, studies evaluating long-acting nitrates in heart failure with preserved ejection fraction (HFpEF) have failed to demonstrate functional benefit and, in some cases, have shown reduced daily activity levels, raising important questions regarding routine chronic nitrate use in this population. In contrast, ranolazine exerts anti-anginal effects through inhibition of the late sodium current without significant hemodynamic compromise, while ivabradine reduces heart rate via selective sinus node inhibition, offering alternative strategies in patients intolerant to hemodynamic modulation. Despite these advancements, nitroglycerine retains unique clinical value in acute settings due to its rapid onset, titratability in intravenous form, and predictable preload reduction, which newer agents do not replicate with equal immediacy. Thus, contemporary evidence supports a paradigm in which nitroglycerine serves as an essential agent for acute symptom relief and hemodynamic stabilization, whereas long-term management of ischemic heart disease increasingly relies on multimodal strategies integrating disease-modifying therapies and newer pharmacologic agents.[26]

Nitroglycerine Tolerance and Dependence

Nitroglycerine tolerance refers to the gradual reduction in the drug's hemodynamic and anti-anginal effectiveness during continuous or prolonged exposure, a phenomenon that develops due to multiple interconnected mechanisms, including decreased bioactivation of nitroglycerine secondary to impaired activity of mitochondrial aldehyde dehydrogenase (ALDH2), increased oxidative stress leading to inactivation of nitric oxide, depletion of intracellular sulfhydryl groups necessary for nitrate metabolism, neurohormonal counter-regulatory responses such as activation of the renin–angiotensin–aldosterone system and sympathetic nervous system, and reduced responsiveness of soluble guanylate cyclase within vascular smooth muscle cells, all of which ultimately blunt the nitric oxide–cGMP signaling pathway responsible for vasodilation.[4] Clinically, tolerance manifests as diminished relief of anginal symptoms, reduced preload and afterload reduction, and the need for escalating doses to achieve the same therapeutic response, thereby increasing the risk of adverse effects such as headache and hypotension; in some patients, a form of "dependence" may also be observed, where abrupt discontinuation after sustained high-dose therapy can lead to rebound angina, vasoconstriction, or hemodynamic instability due to heightened vascular sensitivity and neurohormonal activation.[27] To minimize these consequences, the implementation of a daily nitrate-free interval—typically lasting 8 to 12 hours, often scheduled during nighttime when myocardial oxygen demand is lower—is strongly recommended to allow restoration of vascular responsiveness, while additional strategies to prevent or attenuate tolerance include using the lowest effective dose, avoiding continuous high-dose intravenous infusions unless clinically necessary, employing intermittent rather than round-the-clock transdermal therapy, combining nitroglycerine with beta-blockers or calcium-channel blockers to reduce compensatory sympathetic activation, and addressing oxidative stress through optimized cardiovascular risk management, thereby preserving long-term efficacy while maintaining patient safety in both acute and chronic cardiovascular care settings.[4]

Special Populations

The administration of nitroglycerine in special populations requires individualized clinical judgment and careful monitoring, as physiological alterations, comorbid conditions, and variations in drug metabolism may significantly influence both its therapeutic response and safety profile; in pregnancy, although routine use is not generally recommended, nitroglycerine may be administered in carefully selected situations such as acute hypertensive crises, pulmonary edema, or for short-term uterine relaxation during obstetric procedures, provided that maternal blood pressure is closely monitored to avoid excessive hypotension that could compromise uteroplacental perfusion, and while limited clinical observations have not demonstrated consistent teratogenic effects, the absence of large controlled trials necessitates cautious use, particularly during early gestation, whereas during lactation, minimal transfer of the drug or its metabolites into breast milk is expected, yet clinical vigilance remains advisable to ensure neonatal safety. [28]In elderly patients, age-related reductions in vascular elasticity, diminished baroreceptor sensitivity, and the frequent presence of multiple comorbidities and concurrent medications increase susceptibility to orthostatic hypotension, dizziness, and syncope, thereby justifying initiation at lower doses with gradual titration and regular hemodynamic assessment. In individuals with renal impairment, although nitroglycerine itself undergoes predominant hepatic metabolism, its metabolites are eliminated through the kidneys, and therefore impaired renal clearance may potentially alter systemic exposure, making close monitoring of blood pressure and clinical response particularly important during intravenous therapy. Similarly, in patients with hepatic dysfunction, reduced metabolic capacity may influence the extent of first-pass metabolism and systemic availability of nitroglycerine, potentially enhancing or prolonging its vasodilatory effects, which underscores the need for dose adjustment and careful clinical supervision to prevent excessive hypotension or hemodynamic instability.[26]

Recent Advances and Emerging Research

Recent advances in cardiovascular pharmacology have renewed scientific interest in nitroglycerine and related nitrate therapies, particularly through the development of novel nitric oxide (NO) donors designed to provide more controlled and sustained release of NO while minimizing oxidative stress and reducing the risk of tolerance, as researchers aim to overcome the limitations associated with conventional organic nitrates by improving molecular stability, enhancing targeted vascular delivery, and preserving endothelial function.[29][30] Increasing attention has also been directed toward genetic variability in drug response, especially polymorphisms in the mitochondrial aldehyde dehydrogenase 2 (ALDH2) enzyme, which plays a critical role in the bioactivation of nitroglycerine, since reduced ALDH2 activity—observed in certain populations—may lead to diminished therapeutic efficacy and greater susceptibility to nitrate tolerance, thereby highlighting the potential for personalized treatment strategies based on pharmacogenomic profiling. In parallel, advances in pharmaceutical technology have led to the exploration of nanoformulations, including nanoparticle-based delivery systems and lipid-encapsulated carriers, which are being investigated to enhance bioavailability, achieve more predictable plasma concentrations, and reduce systemic adverse effects by enabling targeted and sustained vascular release.[31]Furthermore, the refinement of sustained-release nitrate preparations seeks to maintain therapeutic plasma levels while incorporating programmed nitrate-free intervals to limit tolerance development, thereby improving long-term compliance and clinical outcomes. Comparative effectiveness research has also evaluated nitroglycerine against newer anti-anginal agents such as ranolazine and ivabradine, suggesting that while modern therapies offer alternative mechanisms of action and may improve symptom control in selected patients, nitroglycerine continues to hold a central role in acute ischemic management due to its rapid onset, well-established safety profile, and extensive clinical experience, thereby reinforcing its ongoing relevance in both traditional and evolving cardiovascular treatment paradigms.[32]

Discussion

The present review synthesizes current evidence regarding the pharmacological properties, clinical applications, safety considerations, and emerging developments associated with nitroglycerine, underscoring its enduring significance as a rapid-acting vasodilator that exerts therapeutic benefit primarily through nitric oxide–mediated activation of the cyclic guanosine monophosphate pathway, leading to reduced preload, decreased myocardial oxygen demand, and improved coronary perfusion, thereby establishing its continued central role in the management of acute angina, myocardial infarction, hypertensive emergencies, and acute decompensated heart failure across cardiology, emergency medicine, and critical care settings. While accumulated clinical data consistently support its efficacy in symptom relief and hemodynamic stabilization, important gaps remain in the contemporary literature, particularly with respect to long-term outcome benefits beyond symptomatic control, the precise molecular mechanisms underlying nitrate tolerance, the clinical impact of mitochondrial aldehyde dehydrogenase 2 (ALDH2) polymorphisms on therapeutic responsiveness, and the optimal integration of sustained-release and nanoformulated preparations into routine practice. Comparative analyses of randomized trials and observational studies indicate that although newer anti-anginal agents such as ranolazine and ivabradine offer alternative mechanisms targeting myocardial metabolism and heart rate modulation, nitroglycerine retains a distinct advantage in acute ischemic scenarios because of its immediate onset of action, ease of titration, and predictable hemodynamic profile; however, heterogeneity in study design, dosing regimens, and patient populations limits direct comparison and highlights the need for large-scale, methodologically robust trials evaluating head-to-head efficacy, safety, and cost-effectiveness. Collectively, these findings suggest that while nitroglycerine remains indispensable in acute cardiovascular care, future research should focus on personalized therapeutic strategies, improved delivery systems to minimize tolerance, and evidence-based protocols that optimize its use in combination therapy, thereby ensuring that this longstanding pharmacologic agent continues to evolve in alignment with modern precision medicine and high-quality clinical practice standards.

Conclusion

Nitroglycerine continues to occupy a foundational position in cardiovascular therapeutics owing to its well-characterized nitric oxide–mediated mechanism of action, rapid hemodynamic effects, versatile routes of administration, and proven efficacy in the management of acute and chronic ischemic conditions, including angina pectoris, myocardial infarction, hypertensive emergencies, acute decompensated heart failure, and cardiogenic pulmonary edema. The present review consolidates evidence demonstrating that through enzymatic bioactivation—principally via mitochondrial aldehyde dehydrogenase (ALDH2)—nitroglycerine enhances cyclic guanosine monophosphate signaling, resulting in venous and arterial vasodilation, reduced preload and afterload, and improved coronary perfusion, thereby delivering prompt symptomatic relief and hemodynamic stabilization in high-risk clinical settings. Despite the emergence of newer anti-anginal and heart failure therapies with alternative mechanisms of action, nitroglycerine retains a distinct clinical advantage in acute care due to its immediate onset, titratability, and extensive safety experience across cardiology, emergency medicine, and intensive care practice.

However, challenges such as nitrate tolerance, interindividual variability in response related to ALDH2 polymorphisms, potential drug interactions, and limitations in long-term outcome data underscore the necessity for continued investigation. Future research should prioritize pharmacogenomic-guided therapy, development of advanced delivery systems including nanoformulations and optimized sustained-release preparations, and rigorously designed comparative effectiveness trials evaluating integration with contemporary cardiovascular agents. By aligning traditional nitrate therapy with modern precision medicine principles and evidence-based protocols, nitroglycerine is poised not only to maintain its established therapeutic relevance but also to evolve within the framework of next-generation cardiovascular care.

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