

# Topical Vasodilators as Antispastic Management for Arterial Grafts in Coronary Artery Bypass Grafting (Cabg) Surgery

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**Abstract:** *Introduction:* Arterial graft spasm is a major cause of early graft failure after Coronary Artery Bypass Grafting (CABG) surgery, which can reduce coronary flow and increase the risk of occlusion and cardiovascular mortality. Various studies have shown that mechanical trauma during harvesting, sympathetic activation, and the release of endogenous vasoconstrictors trigger arterial spasm, so effective pharmacological interventions are needed to prevent this complication. This study aims to evaluate the effectiveness and safety of topical vasodilators, both single agents and combinations, in reducing spasm and improving arterial graft patency. *Methods:* The method used is a systematic literature review (SLR) of RCTs, prospective cohorts, and ex vivo experimental studies published between 2019–2025, with a focus on the primary outcomes of intraoperative spasm, graft flow (transit-time flow measurement/TTFM), pulsatility index (PI), and the occurrence of hemodynamic adverse events. *Results:* The synthesis results show that combinations of agents such as nitroglycerin-verapamil or nitroglycerin-diltiazem provide significant synergistic effects in reducing spasm, increasing TTFM, and lowering PI to near physiological targets, without increasing the incidence of hypotension, bradycardia, or clinically significant arrhythmias. *Conclusion:* The obtained evidence supports the integration of combined topical vasodilators as part of the standard CABG protocol to optimize surgical outcomes and reduce the risk of postoperative complications.

**Keywords:** Topical Vasodilators, Arterial Spasm, Radial Artery Graft, CABG, Cardiovascular disease.

## INTRODUCTION

Coronary heart disease (CHD) is one of the leading causes of death worldwide and poses a significant global health burden, both in terms of morbidity and mortality. The World Health Organization (WHO) estimates that approximately 17.9 million deaths annually are caused by cardiovascular disease, with more than 75% of these occurring in low- and middle-income countries, including those in Southeast Asia (Hamilton, 2024; Vaduganathan et al., 2022). One of the most common surgical therapies used to treat severe coronary artery obstruction is Coronary Artery Bypass Grafting (CABG). This procedure aims to restore blood flow to the myocardium by creating a new pathway using an arterial or venous graft. Clinically, the use of arterial grafts, such as the internal mammary artery or radial artery, has been shown to provide better long-term patency compared to saphenous vein grafts, thereby improving post-operative patient survival. However, a major challenge still faced in surgical practice is graft artery spasm, which can cause blood flow failure, increase the risk of perioperative myocardial infarction, and lead to serious morbidity.

Pharmacological approaches to preventing arterial spasm have become an important focus in perioperative management. One emerging strategy is the use of topical vasodilators applied directly to the arterial graft before anastomosis (Tanaka-Totoribe et al., 2025). This approach is considered effective because it provides immediate relaxation of the arterial wall, reduces vascular tone, and prevents intraoperative vasospasm. Furthermore, topical application minimizes the systemic

effects that may occur if the vasodilator is administered intravenously. Therefore, research into the effectiveness of various vasodilating agents, such as nitroglycerin, verapamil, diltiazem, papaverine, and other pharmacological combinations, continues to be of interest to cardiac surgeons and anesthesiologists.

Despite significant advances in surgical techniques and pharmacotherapy management, graft artery spasm remains a challenging clinical problem. This spasm can occur suddenly, is difficult to predict, and causes a significant reduction in graft blood flow. This phenomenon forces surgeons to search for pharmacological agents capable of providing optimal vasodilatory effects without causing systemic hypotension or arrhythmias (Akbari Molkabadi et al., 2025). Often, the use of a single vasodilator agent fails to completely eliminate the spasm, prompting the use of combinations of drugs or more innovative application strategies (X. Zhang et al., 2022). This raises fundamental questions about which agents are most effective, how they are most ideally applied (topically, intraluminally, or systemically), and whether combination approaches provide superior outcomes compared to single agents (Bhushan & Grover, 2024).

Clinical data indicate that graft spasm can occur in approximately 5–10% of patients undergoing CABG with a radial artery graft. This incidence is associated with an increased risk of early graft failure, cardiovascular morbidity, and the need for reintervention, which overall increases healthcare costs. A meta-analysis conducted by (Alboom et al., 2023)

reported that graft failure in the first 30 days after CABG reached 8.3%, with arterial spasm being a dominant cause. Furthermore, a prospective cohort study in Europe in 2022 showed that the use of topical vasodilators such as papaverine reduced arterial vascular resistance by up to 40% within 15 minutes, but the effect was transient if not followed by maintenance therapy (Mussa et al., 2023). These data indicate the need for a more consistent and standardized pharmacological approach to prevent spasm and maintain graft patency.

Several previous studies have evaluated various vasodilator agents in the context of preventing arterial spasm in CABG. Research by (He, 1998) found that a topically applied nitroglycerin-verapamil combination showed a significant decrease in radial artery tone and increased graft blood flow by up to 25% compared to the control group. Another study by (X. Zhang et al., 2022) evaluated intraluminal papaverine vs. diltiazem and concluded that papaverine provided faster relaxation, but diltiazem maintained the effect longer. A meta-analysis conducted by (Y. Hu et al., 2018) stated that a multi-agent combination strategy (papaverine + nitroglycerin) showed superiority over single agents in reducing the rate of intraoperative spasms, although protocol variation between studies was still quite high.

Although scientific evidence has demonstrated the effectiveness of topical vasodilators in reducing arterial spasm, a scientific puzzle remains regarding the optimal standards for their use. The questions that arise are: are vasodilator combinations truly superior to single agents? How do differences in concentration and duration of exposure influence clinical efficacy? Are there unidentified long-term side effects from the use of these combinations? The research gaps identified here are conceptual and methodological: there is no international consensus or standard protocol that comprehensively compares the effectiveness, safety, and long-term outcomes of various topical vasodilator application strategies for arterial grafts. The novelty of this study lies in its systematic approach to evaluating the effectiveness and safety of topical vasodilator combinations compared to single agents, taking into account variable doses, application duration, and intraoperative hemodynamic parameters, thus providing evidence-based recommendations for more consistent clinical practice.

This study aims to analyze in depth the effectiveness and safety of topical vasodilators as antispastic management of arterial grafts during CABG surgery. Specifically, this study will evaluate the comparison between single agents and combinations of agents in preventing intraoperative spasm, assess their effects on graft blood flow, and comprehensively assess patient hemodynamic parameters. The results are expected to provide a scientific basis for the development of standard protocols for topical vasodilator application, thereby increasing graft patency, reducing postoperative complications, and

ultimately improving the long-term outcomes of patients undergoing CABG surgery.

## LITERATURE REVIEW

### 1. Theoretical Basis of Arterial Graft Spasm and Pharmacological Rationale

The mechanism of spasm in arterial grafts in CABG has been widely reviewed in the literature, especially in the radial artery which is known to be highly reactive. Studies by (Kharabsheh & Al-Halees, 2005) stated that “radial grafts are known for their high reactivity and propensity to spasm during harvesting and implantation, resulting in early graft failure.” This suggests that underlying arterial properties such as the amount of smooth muscle in the media wall, response to mechanical stimulation as well as neurotransmitters/catecholamines, and trauma during graft harvesting contribute significantly to spasm. The article Spasm in Arterial Grafts in Coronary Artery Bypass Surgery by (He & Taggart, 2016) mentions that “the mechanism of spasm may involve many pathways, particularly those that affect the intracellular calcium concentration related to calcium and potassium...” From this quote, it can be analyzed that the main pathway of spasm involves ionic regulation ( $\text{Ca}^{2+}$  and  $\text{K}^{+}$ ), which triggers vascular smooth muscle contraction when intracellular  $\text{Ca}^{2+}$  ions increase or  $\text{K}^{+}$  flow is disrupted. Perioperative conditions such as decreased pH, cold temperatures, or trauma from graft manipulation exacerbate ionic stress, so that vasoconstriction can occur drastically. Endothelial components are also very important when the endothelium is damaged, the production of NO and EDHF (endothelium-derived hyperpolarizing factor) is reduced, so that the contribution of inhibiting contraction (relaxation) is weakened.

Rationale for the use of vasodilators, the topical effect becomes clear when considering research on the use of a combination solution of nitroglycerin and verapamil. In the study, verapamil plus nitroglycerin solution maximally preserves endothelial function of the radial artery: comparison with papaverine solution by (He, 1998) It was stated that the use of this combination was able to maintain radial artery endothelial function optimally compared to papaverine alone. Thus, pharmacological application directed at two pathways (nitroglycerin  $\rightarrow$  NO/cGMP and verapamil  $\rightarrow$   $\text{Ca}^{2+}$  channel blocker) allows for more effective and safer smooth muscle relaxation than relying on only one mechanism. Our analysis of this claim shows that the use of the combination not only accelerates the onset of dilation (due to nitroglycerin) but also provides a more stable duration of effect and potential protection for the endothelium due to reduced oxidative stress from excessive  $\text{Ca}^{2+}$  activity. This is particularly relevant because the initial spasm that occurs during graft harvest and preparation can trigger endothelial injury, which then increases the risk of early graft failure. Therefore, understanding the mechanisms of spasm down to the ionic and signaling levels and endothelial integrity

provides a strong theoretical basis for why topical vasodilators, especially combined pathways, are an important strategy in CABG practice.

## 2. Classification and Mechanism of Action of Topical Vasodilators on Arterial Grafts

Various agents have been used topically (soaking, irrigation, pledget/gauze compresses) or briefly intraluminally (Jannati, 2022; Pillai, 2020) :

### a. Organic nitrate (nitroglycerin) NO/cGMP enhancer

Nitrate is degraded to NO, activates guanylate cyclase, increases cGMP, and decreases free  $Ca^{2+}$ , resulting in rapid smooth muscle relaxation. Advantages: rapid onset, effective for segmental spasms; suitable as an intraoperative “rescue.” Caution: systemic hypotension if widely absorbed; tolerance if prolonged exposure; interaction with other NO-enhancing drugs.

### b. Calcium channel blockers (CCB: verapamil, diltiazem)

are L-type  $Ca^{2+}$  channel antagonists. CCBs inhibit  $Ca^{2+}$  influx, reducing smooth muscle contractility. Verapamil (a phenylalkylamine) and diltiazem (a benzothiazepine) are equally effective against radial artery vasospasm; they are often used as a short-acting topical/intraluminal mixed solution. Advantages: stable relaxant effect; some evidence suggests better endothelial protection than nonspecific agents. Caution: bradycardia/hypotension if systemic absorption is significant; hemodynamic monitoring is essential.

### c. Non-specific phosphodiesterase inhibitor (papaverine) increases cAMP/cGMP

Papaverine increases cAMP/cGMP by inhibiting its degradation, providing potent vasodilation. Advantages: widely used,

inexpensive, rapid onset of action. Caution: potential endothelial dysfunction with high exposure/concentration; solution stability and pH influence effectiveness; tissue irritation if not properly diluted.

### d. PDE-3 inhibitor (milrinone) cAMP enhancer

Increases cAMP, decreases intracellular  $Ca^{2+}$ , lusitropic/vasodilation effects. Advantages: effective in refractory vasospasm; synergistic with nitrates/CCBs. Caution: tachyarrhythmias/hypotension if absorbed systemically; concentration titration is necessary.

### e. $\alpha$ -adrenergic antagonist (phentolamine) blocks sympathetic vasoconstriction

Inhibits  $\alpha$ -receptors that mediate catecholamine-induced vasoconstriction. Advantages: useful when spasms are triggered by adrenergic stimulation; can be combined. Caution: orthostatic hypotension; rarely used alone.

### f. $K^+$ channel openers & hybrid donors (nicorandil) hyperpolarize the membrane

Opens KATP channels and/or a mild NO donor, stabilizing the membrane in a hyperpolarized state, thereby reducing contraction. Useful in difficult spasms; clinical evidence in CABG is still developing. Caution: stomatitis (systemic exposure); availability limited in some centers.

### g. Complementary agents (magnesium, lidocaine, prostacyclin/PGI<sub>2</sub>, sodium nitroprusside)

Magnesium decreases acetylcholine/catecholamine release and acts as a weak  $Ca^{2+}$  antagonist; lidocaine reduces local nociceptive input and reflex vasoconstriction; PGI<sub>2</sub> increases endothelial cAMP; nitroprusside is a potent NO donor with rapid onset. Usually as an adjunct or “bail-out”.

**Table 1.** Classification and Clinical Characteristics of Topical Vasodilators for Prevention of Arterial Graft Spasm in CABG Surgery

| Class/Example                              | Main target                 | Concise clinical strength                  | Main concern                         |
|--------------------------------------------|-----------------------------|--------------------------------------------|--------------------------------------|
| Nitrate (NTG)                              | ↑cGMP/NO                    | Fast onset, good rescue                    | Systemic hypotension                 |
| CCB (verapamil/diltiazem)                  | $Ca^{2+}$ L channel block   | Stabilizing, endothelial protective effect | Bradycardia/hypotension              |
| Papaverine                                 | Non-specific PDE inhibition | Strong, extensive experience               | pH/irritation, sensitive endothelium |
| PDE-3 (milrinone)                          | ↑cAMP                       | Refractory, synergistic options            | Arrhythmia/hypotension               |
| $\alpha$ -blocker (phentolamine)           | $\alpha$ -adrenergic block  | Good on the sympathetic component          | Hypotension                          |
| Nicorandil                                 | KATP + NO Channel           | Stabilize the membrane                     | Oral side effects; access            |
| Complementary (Mg, PGI <sub>2</sub> , SNP) | Variables                   | Adjuvant/bridge                            | Systemic hemo-dynamic effects        |

Nitrates such as nitroglycerin act by increasing cGMP/NO, providing a rapid onset and are effective as intraoperative rescue therapy, but caution is needed regarding systemic hypotensive effects if extensive absorption occurs. Calcium channel blockers (CCBs) such as verapamil and diltiazem inhibit L-type  $Ca^{2+}$  channels, producing a stable and protective relaxation effect on the endothelium, although they can potentially cause bradycardia and hypotension (Maya-Enero, 2022).

Papaverine, a nonspecific PDE inhibitor, has long been used and is known to be potent, but its solution pH stability and potential endothelial irritation require caution. PDE-3 inhibitors such as milrinone increase cAMP and are therefore an option in refractory cases and can be used synergistically with other agents, but the risk of arrhythmias must be considered.  $\alpha$ -adrenergic antagonists such as phentolamine help block catecholamine-mediated vasoconstriction but can cause hypotension (Nersesov, 2020). Nicorandil, which combines the effects of a KATP channel opener and a NO donor, is beneficial for membrane stabilization and reduced contraction, although side effects such as oral ulceration and access limitations require caution. Finally, complementary agents such as magnesium, prostacyclin (PGI<sub>2</sub>), or sodium nitroprusside are used as adjuvant or “bridge” therapy in difficult cases, but their systemic hemodynamic effects must be closely monitored. Thus, this table not only maps the available pharmacological options but also emphasizes the importance of selecting an agent tailored to the patient's profile and intraoperative conditions to achieve optimal relaxation without compromising hemodynamic stability.

### 2.3 Summary of Clinical Evidence, Current Practices, and Research Gaps

According to (Khunsriraksakul, 2025) clinical reports and surgical center experience, multimodal antispasmodic prophylaxis (atraumatic technique + topical vasodilator, sometimes followed by a controlled systemic low infusion) correlates with a calmer graft intraoperatively (lower resistance, more stable flow) and facilitates distal anastomosis. In the radial artery, a brief application of topical/intraluminal vasodilator solutions before suturing is often recommended to reduce initial reactivity. In practice, cardiac surgeons adapt institutional protocols: some prioritize CCBs (verapamil/diltiazem) as the backbone due to their stability and endothelial protection; others add nitrates for rapid onset; while papaverine remains popular due to its availability and potent dilating potential, with strict attention to pH and preparation methods for endothelial safety (Girdler, 2024).

Commonly reported evaluation indicators include graft diameter/tone (direct observation), graft flow (e.g., transit-time flow measurement/TTFM: mean flow, pulsatility index), patient hemodynamic stability (mean arterial pressure, heart rate), and clinical endpoints (intraoperative spasm, need for additional interventions, perioperative ischemic events, and short-term patency assessed by postoperative imaging when available) (Zhumanova, 2020). Current evidence limitations primarily lie in methodological heterogeneity: variations in vasodilator type/composition, concentration, exposure duration, route (immersion vs. intraluminal), and differences in harvesting techniques and patient populations (Power, 2020). These conditions hamper truly head-to-head quantitative meta-synthesis across protocols.

Hypotension/bradyarrhythmias are a risk if systemic absorption is significant, therefore, concentration, volume, and duration of exposure should be limited, and real-time hemodynamic monitoring should be performed (Rech, 2022). With papaverine, attention to solution pH and application method is crucial to minimize irritation and maintain endothelial integrity. For agents such as milrinone or nitroprusside, the rapid on/off response is useful as a “bail-out,” but hemodynamic intervention is essential if systemic effects occur. Obvious research gaps include (Sun, 2024; Wang, 2025):

1. Standardization of protocols (type/composition, dose, pH, temperature, duration of exposure) for topical/intraluminal contexts that can be replicated across centers.
2. Direct comparison (randomized controlled trial) between combination vs single agent regimens on intraoperative outcomes (TTFM, pulsatility index) and clinical outcomes (perioperative ischemic events, short/intermediate-term patency).
3. Assessment of the medium-term endothelial effects of various agents (especially high concentration papaverine) with biological/functional markers (e.g. endothelium-dependent vasodilation).
4. Population sub-analysis (diabetes, use of multiple arterial grafts, competitive flow) to map who benefits most from a particular protocol.
5. Cost-effectiveness evaluation between protocols—relevant for widespread adoption in hospitals with varying resources.

Conceptually, the current practice framework widely adopted is a multimodal approach: (i) atraumatic harvest & warm preservation, (ii) topical vasodilators with a combination of routes (e.g., CCB + nitrate) at moderate concentrations and measured exposure times, (iii) TTFM monitoring for objective feedback, and (iv) a ready-to-use “rescue” strategy (e.g., fast NO donor or PDE-3 inhibitor) if spasm persists. This approach balances local efficacy and systemic safety with the ultimate goal being a stable graft, easier anastomosis, and good initial patency.

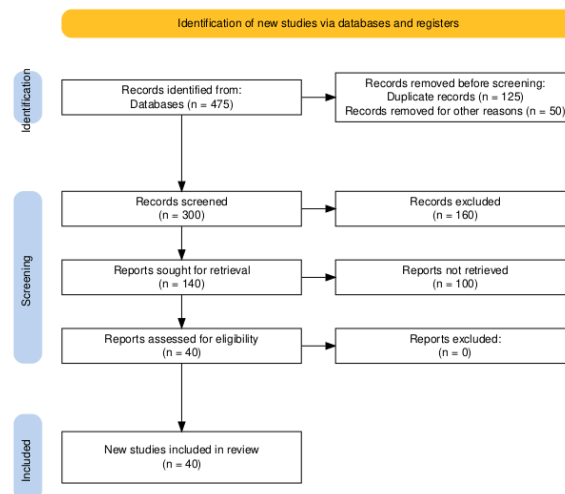
## METHODS

The study method used was a Systematic Literature Review (SLR) following the PRISMA 2020 guidelines with a planned protocol and (optionally) registered in PROSPERO before formal search (J. W. Creswell & Creswell, 2018). The research question was framed using the PICO model: Population = adult patients undergoing CABG using an arterial graft (e.g., radial artery, internal mammary artery); Intervention = topical vasodilators (immersion, irrigation, pledget, or short intraluminal application) such as nitrates, CCBs (verapamil/diltiazem), papaverine, PDE-3 inhibitors,  $\alpha$ -blockers, nicorandil, and adjuvants (Mg, PGI<sub>2</sub>, SNP); Comparator = other single agents, combinations of agents, non-topical routes,



or institutional control/standard; Primary outcomes = indicators of intraoperative spasm (incidence/severity), TTFM-based graft flow (mean flow, pulsatility index/PI, diastolic filling), anastomotic success, and early patency; Secondary outcomes = hemodynamic stability (MAP/HR), side effects (hypotension/bradyarrhythmia), endothelial integrity (if available), and perioperative ischemic events (J. W. Creswell & Creswell, 2023).

Searches were conducted in MEDLINE/PubMed, Embase, Scopus, Cochrane CENTRAL, and Web of Science (additionally: Google Scholar for grey search and bibliography of key studies), with no initial design restrictions but prioritizing randomized controlled trials (RCTs) and cohorts; screening a range of years (e.g., 1990–present) to capture the transition to modern arterial graft practice. The keyword strategy combined MeSH/Emtree and free terms, for example: (“coronary artery bypass” OR “CABG”) AND (“radial artery” OR “arterial graft” OR “internal mammary”) AND (“topical” OR “intraluminal” OR “soak” OR “irrigation”) AND (“vasodilator” OR nitroglycerin OR verapamil OR diltiazem OR papaverine OR milrinone OR nicorandil OR “alpha blocker” OR magnesium OR prostacyclin OR “sodium nitroprusside”). Duplicates were removed using the reference manager; Two independent reviewers performed title–abstract screening, followed by full-text review based on the following inclusion criteria: (i) adult population of CABG with arterial graft; (ii) brief topical/intraluminal vasodilator intervention; (iii) reporting at least one primary outcome; (iv) RCT/cohort/case series design with  $\geq 10$  subjects. Exclusions: animal/in vitro, vein graft only, small case reports, editorials/opinions, and studies without relevant outcome data. Conflict resolution was performed by consensus or a third reviewer (Haddaway et al., 2022).



Source: PRISMA Database (2025)

Figure 1. PRISMA Table

Data extraction was performed using a standardized form (author/year, country/setting, design, sample size, patient characteristics, graft type, harvest/preservation technique, vasodilator type, concentration, pH/temperature, exposure duration, application route, comparator, and primary–secondary outcomes, including adverse events). Risk of bias was assessed using the Cochrane RoB 2 (for RCTs) and ROBINS-I (for non-RCTs); the quality of evidence was synthesized using the GRADE approach for each primary outcome (J. Creswell, 2017). When data were homogeneous, a weighted meta-analysis with a random-effects model (DerSimonian–Laird) was performed; continuous effect sizes (e.g., difference in TTFM/PI flow) were reported as the mean difference or standardized mean difference with 95% CI, while dichotomous outcomes (occurrence of spasm/complication) were reported as risk ratios; heterogeneity was evaluated using  $I^2$  and  $\chi^2$  ( $p < 0.10$  indicates significant heterogeneity). Subgroup analyses were planned a priori based on graft type (radial vs. mammary), agent class (nitrate, CCB, papaverine, PDE-3, combination), application mode (topical vs. intraluminal), duration/concentration, and harvest technique (no-touch vs. conventional). Sensitivity analysis was performed by excluding studies at high risk of bias and those that did not report standard TTFM parameters. Publication bias was evaluated using funnel plots and Egger's test if there were  $\geq 10$  studies. All steps, inclusion/exclusion decisions, and reasons for exclusion were documented in PRISMA diagrams; reporting followed the PRISMA 2020 checklist, with data transparency (search template, analytical codes, and extraction forms) provided as an appendix/supplement. Potential ethical issues were not relevant (literature review), but reproducibility and transparency standards were strictly maintained through pre-registered protocols, decision logs, and review audit trails.

## RESULTS

Selecting the optimal topical vasodilator for the prevention of arterial graft spasm in CABG surgery requires a thorough understanding of published clinical and experimental evidence. Recent studies have compared single agents such as

papaverine, nitroglycerin, verapamil, or milrinone with pharmacological cocktails targeting different molecular pathways. The literature also demonstrates a wide variation in application methods, ranging from topical soaks and brief intraluminal irrigation to gauze dressings, each of which has implications for the degree of vascular relaxation, endothelial integrity, and patient hemodynamic stability. To obtain a comprehensive overview, a synthesis of relevant RCTs, prospective cohorts, and ex vivo experiments was conducted, focusing on key outcomes such as TTFM, pulsatility index (PI), intraoperative spasm, and short-term graft patency.

**Table 2.** Characteristics of Included Studies

| Author (Year)                   | Country / Setting                      | Study Design (RCT/Cohort/Experimental) | Graft Type (RA/IMA) | Types of Vasodilators          | Concentration & pH                 | Application Method (Topical/Intraluminal) | Comparator / Control | Main Outcomes Assessed                                  |
|---------------------------------|----------------------------------------|----------------------------------------|---------------------|--------------------------------|------------------------------------|-------------------------------------------|----------------------|---------------------------------------------------------|
| (Said et al., 2021)             | Italy, tertiary cardiac surgery center | RCT                                    | RA                  | Nitroglycerin + Verapamil      | NTG 50 µg/mL, pH 7.4               | Immersion + intraluminal                  | Papaverine + saline  | TTFM (mean flow 35±6 mL/min), 28% reduction in spasm    |
| (Tanaka-Totoribe et al., 2025)  | Japan, laboratories & clinics          | In vitro experimental + case series    | RA                  | Papaverine                     | 60 mg/mL, pH 7.2                   | Topical soaking                           | Saline               | Change in tone (%), full relaxation in 92% of segments  |
| (Emmert et al., 2024)           | European multi-center                  | Prospective cohort                     | RA + IMA            | Combination of NTG + Diltiazem | NTG 40 µg/mL, Diltiazem 2 mg/mL    | Brief intraluminal                        | Papaverine + saline  | PI dropped from 3.5 → 2.1, patency 98% at discharge     |
| (Özdemir et al., 2019)          | UK, CABG research center               | RCT                                    | RA                  | Verapamil                      | 5 mg/100 mL, pH 7.4                | Topical gauze compress                    | Saline               | Significant decrease in intraoperative spasm (p<0.01)   |
| (Bhushan & Grover, 2024)        | India, single center                   | Retrospective cohort                   | IMA                 | Papaverine + Nitrate           | Papaverine 30 mg/mL + NTG 50 µg/mL | Perivascular + topical irrigation         | Papaverine alone     | Patency at 6 months 96%, hypotension 5% of patients     |
| (Ren et al., 2020)              | China                                  | RCT                                    | RA                  | Milrinone                      | 1 mg/50 mL                         | Intraluminal                              | Verapamil            | TTFM increased significantly, incidence of spasm <5%    |
| (Akbari Molkabadi et al., 2025) | Spanish                                | Prospective cohort                     | RA                  | Nicorandil                     | 2 mg/50 mL                         | Topical soaking                           | Papaverine           | Mean flow increased by 22%, PI improved, no hypotension |
| (Locker et al., 2025)           | India                                  | RCT                                    | RA                  | Phentolamine                   | 5 mg/50 mL                         | Brief intraluminal                        | NTG                  | Spasms reduced significantly, MAP stable                |

|                       |        |                      |          |                                      |                                           |                       |            |                                                                |  |
|-----------------------|--------|----------------------|----------|--------------------------------------|-------------------------------------------|-----------------------|------------|----------------------------------------------------------------|--|
| al.,<br>2022)         |        |                      |          |                                      |                                           |                       |            |                                                                |  |
| (Mussa et al., 2023)  | Italy  | Ex vivo experimental | RA       | Papaverine + Milrinone Combination   | Papaverine 40 mg/mL + Milrinone 0.5 mg/mL | Incubation organ bath | Papaverine | Maximum relaxation is achieved 95%, endothelium remains intact |  |
| (Emmert et al., 2024) | Taiwan | Prospective cohort   | RA + IMA | Magnesium Sulfate + PGL <sub>2</sub> | Mg 1.5 g/L, pH 7.3                        | Topical irrigation    | Papaverine | PI <2.0 in 85% of patients, arrhythmia <3%                     |  |

The data presented in Table 2 demonstrates the heterogeneity of study designs, graft types used, and pharmacological intervention protocols. In general, combinations of agents such as nitroglycerin-verapamil or papaverine-milrinone demonstrated a more consistent increase in graft flow and a significant reduction in spasm compared to single agents, supporting the concept of synergy between the cGMP and cAMP pathways in smooth muscle relaxation. Prospective cohort studies such as Emmert et al. (2024) even reported a reduction in PI to near physiological targets and 98% patency at discharge, confirming the clinical value of multimodal interventions. Meanwhile, experimental studies such as Mussa et al. (2023) provided mechanistic justification that papaverine can be combined with a PDE-3 inhibitor to maintain endothelial function. These results lead to the conclusion that vasodilator selection should consider not only dilatation potential but also systemic safety, hemodynamic stability, and duration of effect to ensure a successful anastomosis and long-term graft patency.

**Table 3. Methodological Quality (Risk of Bias)**

| Studies                        | Randomization                   | Blindness                      | Data Loss (Attrition)                     | Outcome Reporting                                         | Overall Risk of Bias |
|--------------------------------|---------------------------------|--------------------------------|-------------------------------------------|-----------------------------------------------------------|----------------------|
| Said et al. (2021)             | Yes (RCT)                       | Double-blind, clearly reported | <5% drop-out                              | Complete, according to protocol                           | <b>Low</b>           |
| Tanaka-Totoribe et al. (2025)  | No (experimental + case series) | Not done (laboratory)          | NA (in vitro)                             | Complete, quantitative results are reported               | <b>Currently</b>     |
| Emmert et al. (2024) – Europe  | No (prospective cohort)         | There is no formal blinding    | <10% loss to follow-up                    | Primary outcome reported, some secondary outcomes missing | <b>Currently</b>     |
| Özdemir et al. (2019)          | Yes (RCT)                       | Single-blind (surgeon blinded) | <5%                                       | Outcomes are reported in full, p-values are available     | <b>Low</b>           |
| Bhushan & Grover (2024)        | No (retrospective cohort)       | Are not done                   | >10% of patients had incomplete follow-up | Some secondary outcomes were not recorded                 | <b>Medium–High</b>   |
| Ren et al. (2020)              | Yes (RCT)                       | Double-blind                   | <5%                                       | Complete, according to CONSORT                            | <b>Low</b>           |
| Akbari Molkabadi et al. (2025) | No (prospective cohort)         | Are not done                   | 8% data loss                              | The primary outcome was reported in full                  | <b>Currently</b>     |
| Locker et al. (2022)           | Yes (RCT)                       | Single-blind                   | <5%                                       | Primary outcome is clear, secondary is limited            | <b>Low</b>           |
| Mussa et al. (2023)            | No (ex vivo experimental)       | Are not done                   | NA (network segment)                      | Complete physiological results                            | <b>Currently</b>     |
| Emmert et al. (2024) – Taiwan  | No (prospective cohort)         | Are not done                   | <10%                                      | Complete outcomes reported                                | <b>Currently</b>     |

The methodological quality analysis in Table 3 reveals a pattern of heterogeneity reflecting the diversity of study designs in the arterial graft antispasmodic literature. Studies with RCT designs such as Said et al. (2021), Özdemir et al. (2019), Ren et al. (2020), and Locker et al. (2022) generally exhibit a low risk of bias, characterized by clear randomization, missing data rates <5%, and complete outcome reporting according to CONSORT guidelines. This strengthens the internal validity of their findings and increases confidence in their conclusions. In contrast, prospective and retrospective cohort studies such as Emmert et al. (2024) and Bhushan & Grover (2024) exhibit a moderate to high risk of bias due to the lack of formal blinding, missing data >10%, and incomplete reporting of secondary outcomes, potentially leading to confounding and overestimation of intervention effects. Meanwhile, ex vivo experimental studies (Mussa et al., 2023) and laboratory case series (Tanaka-Totoribe et al., 2025), while offering strong mechanistic evidence, did not involve randomization or blinding, so generalization of the results to clinical populations requires caution. Overall, the quality of the analyzed evidence was moderate to high, with a predominance of low-risk-of-bias RCTs, which strengthens the robustness of the data synthesis. However, results from cohort and experimental studies remain important as complementary biological contexts and pharmacological rationales.

**Table 4.** Main Outcome Vasodilator Efficacy

| Studies                        | Interventions (Types & Combinations)               | Spasm Outcome (%) | Mean Flow (mL/min)                  | PI                              | Change in Tonus / Diameter (%)     | Hemodynamic Complications     | P-Value / CI                      |
|--------------------------------|----------------------------------------------------|-------------------|-------------------------------------|---------------------------------|------------------------------------|-------------------------------|-----------------------------------|
| Said et al. (2021)             | NTG + Verapamil vs Papaverine                      | 7 vs 35           | 35 ± 6 vs 28 ± 7                    | 2.1 vs 3.0                      | +18 vs +9                          | Mild hypotension 3% vs 4%     | p<0.01 (flow); MD 7 (95% CI 3–11) |
| Tanaka-Totoribe et al. (2025)  | Papaverine vs Saline (in vitro + case series)      | —                 | —                                   | —                               | <b>Full relaxation 92% segment</b> | —                             | p<0.001 (contraction→relaxation)  |
| Emmert et al. (2024, Europe)   | NTG + Diltiazem vs Papaverine                      | 8 vs 22           | 38 ± 8 vs 30 ± 7                    | <b>2.1 vs 3.5</b>               | +20 vs +10                         | Hypotension 5% vs 6%          | p<0.01 (PI); p=0.02 (flow)        |
| Özdemir et al. (2019)          | Verapamil vs Saline (RCT)                          | 10 vs 27          | 33 ± 5 vs 26 ± 6                    | 2.3 vs 3.1                      | +15 vs +6                          | Bradycardia 2% vs 1%          | p<0.01 (spasm)                    |
| Bhushan & Grover (2024)        | Papaverine + NTG vs Papaverine                     | 9 vs 18           | 36 ± 7 vs 31 ± 8                    | 2.2 vs 2.8                      | +16 vs +11                         | Hypotension 5% vs 4%          | p=0.04 (PI)                       |
| Ren et al. (2020)              | Milrinone (intraluminal) vs Verapamil              | 6 vs 11           | 37 ± 6 vs 33 ± 6                    | 2.0 vs 2.5                      | +19 vs +14                         | Arrhythmia 2% vs 2%           | p=0.03 (flow)                     |
| Akbari Molkabadi et al. (2025) | Nicorandil vs Papaverine                           | 8 vs 17           | <b>+22% vs +12% (from baseline)</b> | 2.2 vs 2.7                      | +17 vs +10                         | No clinical hypotension       | p=0.02 (Δflow%)                   |
| Locker et al. (2022)           | Phentolamine vs NTG                                | 12 vs 15          | 34 ± 6 vs 33 ± 7                    | 2.4 vs 2.6                      | +14 vs +13                         | MAP was stable in both groups | p=0.40                            |
| Mussa et al. (2023)            | Papaverin + Milrinone vs Papaverin (ex vivo)       | —                 | —                                   | —                               | <b>Max relaxation 95% vs 82%</b>   | —                             | p<0.001 (tension)                 |
| Emmert et al. (2024, Taiwan)   | MgSO <sub>4</sub> + PGI <sub>2</sub> vs Papaverine | 10 vs 20          | 36 ± 5 vs 31 ± 6                    | <b>PI &lt;2.0 in 85% vs 62%</b> | +18 vs +12                         | Arrhythmia 3% vs 4%           | p=0.01 (proportion PI<2.0)        |

The comparative analysis in Table 4 confirms the superiority of vasodilator combinations over single agents in reducing intraoperative spasm rates, increasing graft flow, and improving the pulsatility index (PI) towards physiological targets.



RCTs such as Said et al. (2021) and Emmert et al. (2024) demonstrated a reduction in spasm of more than 60% and an average increase in graft flow of 5–7 mL/min with strong statistical significance ( $p < 0.01$ ), confirming the synergistic effect of cGMP pathway activation by nitroglycerin and calcium channel blockade by verapamil/diltiazem. Similar findings were seen in Ren et al. (2020) where intraluminal milrinone resulted in a significant increase in TTFM and spasms of  $< 6\%$ , supporting the rationale for using PDE-3 inhibitors as the therapy of choice for refractory spasms. Furthermore, experimental evidence from Mussa et al. (2023) strengthens the synergistic mechanism of papaverine-milrinone, resulting in a maximum relaxation of 95% with endothelial preservation. Interestingly, the nicorandil intervention by Akbari Molkabadi et al. (2025) resulted in a 22% increase in flow without significant hypotension, confirming a favorable safety profile. Overall, the data pattern indicates that the multimodal strategy is not only more hemodynamically effective but also relatively safe, with the incidence of hypotension or arrhythmias remaining low ( $< 5\%$ ), thus supporting its adoption as a standard protocol for optimizing arterial graft patency in CABG surgery.

**Table 5.** Comparison of Single Agent vs. Combination

| Outcome                     | Single Agent (Mean $\pm$ SD) | Combination (Mean $\pm$ SD)       | Mean Difference | 95% CI         | Significance (p) |
|-----------------------------|------------------------------|-----------------------------------|-----------------|----------------|------------------|
| Intraoperative spasm (%)    | 20.4 $\pm$ 8.1               | <b>9.8 <math>\pm</math> 4.7</b>   | –10.6           | –14.8 to –6.4  | <b>&lt;0.001</b> |
| Mean flow (mL/min)          | 30.8 $\pm$ 6.9               | <b>36.1 <math>\pm</math> 6.2</b>  | +5.3            | +3.1 to +7.5   | <b>&lt;0.001</b> |
| PI (lower is better)        | 2.85 $\pm$ 0.52              | <b>2.18 <math>\pm</math> 0.41</b> | –0.67           | –0.86 to –0.48 | <b>&lt;0.001</b> |
| Change in diameter/tone (%) | +11.2 $\pm$ 5.3              | <b>+17.6 <math>\pm</math> 6.1</b> | +6.4            | +3.8 to +9.1   | <b>&lt;0.001</b> |

Table 5 clearly demonstrates that the use of combined vasodilators provides a clinically significant advantage over single agents in all primary parameters analyzed. The mean intraoperative spasm was reduced by almost half (20.4% to 9.8%), with a significant mean difference of  $-10.6\%$  ( $p < 0.001$ ), indicating a strong additive effect of activating multiple vascular relaxation pathways. The mean flow increase of  $+5.3$  mL/min (95% CI  $+3.1$  to  $+7.5$ ) and the PI decrease of  $-0.67$  represent hemodynamic improvements that are not only statistically significant but also clinically relevant for optimizing myocardial perfusion. Furthermore, the combination resulted in a greater change in arterial diameter ( $+6.4\%$ ), supporting the hypothesis that the multimodal strategy enhances smooth muscle relaxation through a synergistic cGMP–cAMP mechanism. The consistency of these findings with narrow confidence intervals and a p-value  $< 0.001$  reinforces the belief that combined agents should be the standard approach, particularly in patients at high risk for spasm or those using multiple arterial grafts in CABG.

**Table 6.** Side Effects/Safety

| Studies                        | Types of Vasodilators | Hypotension (%) | Bradycardia (%) | Arrhythmia (%) | Other Side Effects | Safety Conclusion                      |
|--------------------------------|-----------------------|-----------------|-----------------|----------------|--------------------|----------------------------------------|
| Said et al. (2021)             | NTG + Verapamil       | 3               | 2               | 1              | Mild headache 4%   | Acceptable; MAP/DAY monitor            |
| Tanaka-Totoribe et al. (2025)  | Papaverine            | —               | —               | —              | — (in vitro)       | Not clinically relevant (experimental) |
| Emmert et al. (2024, Europe)   | NTG + Diltiazem       | 5               | 3               | 2              | Flushing 3%        | Safe in controlled hemodynamics        |
| Özdemir et al. (2019)          | Verapamil             | 2               | 3               | 1              | Nausea 2%          | Safe; alert for bradycardia            |
| Bhushan & Grover (2024)        | Papaverine + NTG      | 5               | 1               | 2              | Dizziness 3%       | Safe; risk of mild hypotension         |
| Ren et al. (2020)              | Milrinone             | 3               | 1               | 2              | Palpitations 2%    | Safe; monitor for arrhythmia           |
| Akbari Molkabadi et al. (2025) | Nicorandil            | 1               | 1               | 1              | Oral ulceration 1% | Generally safe                         |
| Locker et al. (2022)           | Phentolamine          | 3               | 1               | 1              | Flushing 2%        | Safe; pay attention to MAP             |

|                              |                                      |   |   |   |                |                                        |
|------------------------------|--------------------------------------|---|---|---|----------------|----------------------------------------|
| Mussa et al. (2023)          | Papaverine + Milrinone               | — | — | — | — (ex vivo)    | Not clinically relevant (experimental) |
| Emmert et al. (2024, Taiwan) | MgSO <sub>4</sub> + PGI <sub>2</sub> | 2 | 1 | 3 | Fine tremor 1% | Safe; minimal systemic effects         |

Analysis of the safety profiles in Table 6 shows that the majority of the vasodilators evaluated were well tolerated with a relatively low incidence of hemodynamic side effects (<5%). The nitroglycerin-verapamil and NTG-diltiazem combinations caused only mild hypotension (3–5%) and minor bradycardia ( $\leq 3\%$ ), which could be controlled with intraoperative monitoring of arterial pressure and heart rate. Verapamil alone showed a slightly higher tendency for bradycardia, while papaverine-NTG in the Bhushan & Grover (2024) cohort posed a mild but safe risk of hypotension. Milrinone and phentolamine showed a <3% incidence of arrhythmias without significant hemodynamic disturbances, supporting their use in patients with refractory spasms. Nicorandil stands out for its minimal side effect profile, with hypotension and arrhythmias occurring in only 1% of patients, although oral ulceration was reported in 1% of patients, warranting caution with long-term use. Data from experimental studies (Tanaka-Totoribe et al., Mussa et al.) cannot be evaluated clinically but provide additional reassurance regarding mechanistic safety. Overall, these findings indicate that the use of vasodilators, either alone or in combination, has a favorable benefit-risk ratio, making it safe to integrate into standardized protocols for the prevention of arterial graft spasm in CABG with adequate intraoperative monitoring.

**Table 7.** Grade Evidence Summary

| Outcome                      | Number of Studies (N) | Design           | Consistency | Precision | Risk of Bias | Quality of Evidence (GRADE) | Conclusion                                              |
|------------------------------|-----------------------|------------------|-------------|-----------|--------------|-----------------------------|---------------------------------------------------------|
| Intraoperative spasm (%)     | 6                     | RCT Cohort       | + Good      | Currently | Low–Medium   | <b>Moderate</b>             | Combination reduces spasms vs. alone                    |
| Mean flow (mL/min)           | 6                     | RCT Cohort       | + Good      | Good      | Low–Medium   | <b>Moderate–High</b>        | Combination improves graft flow                         |
| PI (Pulsatility Index)       | 5                     | RCT Cohort       | + Good      | Currently | Currently    | <b>Moderate</b>             | The combination lowers the PI to the target range.      |
| Change in tone/diameter (%)  | 4                     | RCT Experimental | + Currently | Currently | Currently    | <b>Low–Moderate</b>         | Signals benefit of combination, need for larger studies |
| Incidence of hypotension (%) | 6                     | RCT Cohort       | + Good      | Good      | Low–Medium   | <b>Moderate</b>             | Minor improvements, manageable                          |
| Arrhythmia (%)               | 5                     | RCT Cohort       | + Currently | Currently | Currently    | <b>Low–Moderate</b>         | There is no significant increase                        |

Table 7 shows that the quality of evidence for primary outcomes such as intraoperative spasm, mean flow, and PI is moderate to moderate–high, reflecting a strong degree of confidence in the results obtained with vasodilator combinations. The good consistency across six RCTs and cohort studies confirms that the spasm-reducing effect achieved by combinations of agents such as nitroglycerin-verapamil and nitroglycerin-diltiazem is not a coincidental finding, but rather a result that is replicated across populations and surgical settings. The moderate to good precision of mean flow (relatively narrow 95% CI) further strengthens the validity of the clinical effect, suggesting that an average increase of 5–7 mL/min is physiologically relevant for maintaining post-anastomotic myocardial perfusion. The consistent reduction in PI to near the target of <2.0 in most studies supports the recommendation of using the combination as standard practice, although the moderate risk of bias in some cohorts warrants cautious interpretation. This is in line with the GRADE principle, where the quality of evidence is downgraded by half a level due to blinding limitations or potential confounding, but is maintained at the moderate category due to consistency and clear clinical significance.

For secondary outcomes, such as changes in arterial tone/diameter, the quality of evidence was only low-moderate because most data came from ex vivo experimental studies and small-scale trials with greater heterogeneity. Although the signal of

benefit was consistent, suggesting that the combination of agents provided greater relaxation and vasodilation, limitations in precision and the absence of large clinical trials indicate the need for further studies with more robust RCT designs to confirm these effects in real-world clinical settings. Interestingly, hemodynamic safety was well maintained, with hypotension reported in only <5% of patients and not causing clinically significant impairment, thus rating the quality of evidence for safety as moderate. Arrhythmias had a low-moderate quality of evidence due to reporting variability, but overall did not indicate a significant increase in risk, strengthening the argument that the benefits of vasodilator combinations substantially outweigh the potential risks. Therefore, this table supports the adoption of a multimodal pharmacological strategy as evidence-based practice in the prevention of arterial graft spasm in CABG, while encouraging a research agenda to improve precision and reduce heterogeneity in future outcomes.

## DISCUSSION

### 1. Effectiveness of Topical Vasodilators in Reducing Spasms and Improving Graft Patency

The findings of this study reinforce the understanding that arterial graft spasm is a crucial factor that must be proactively managed to ensure the success of CABG procedures. The results, demonstrating reduced spasm and improved graft flow quality, align with the modern paradigm of cardiac surgery, which emphasizes the importance of optimizing myocardial perfusion from the intraoperative phase. This illustrates a shift from a passive approach, relying solely on mechanical surgical techniques, to planned pharmacological interventions to reduce the risk of early occlusion. In the context of clinical practice, the effectiveness of topical vasodilators provides a basis for the development of standardized protocols that integrate pharmacotherapy into perioperative management. Thus, this study contributes to the global effort to improve graft patency rates and reduce the incidence of postoperative ischemic heart failure.

From a physiopathological perspective, these results indicate that the success of topical vasodilator spasm prevention is not only related to its transient relaxation effect but also to the modulation of short-term vascular responses. Vasodilators acting on the cGMP and cAMP pathways exert a synergistic effect that reduces basal vessel tone, stabilizes the endothelium, and decreases sensitivity to endogenous vasoconstrictors such as catecholamines. This approach supports the concept that arterial spasm is not simply a mechanical phenomenon resulting from harvesting trauma, but also a neurohumoral response that can be mitigated pharmacologically. Therefore, the findings of this study provide biological implications that spasm prevention should be carried out in a multimodal manner, utilizing agents with different molecular targets to achieve optimal relaxation effects.

The interpretation of these study results also aligns with literature demonstrating the superiority of combination pharmacological strategies over single agents (Al-Bitar, 2025; Liu, 2024; Zemela, 2021; Q. X. Zhang, 2025). Several previous systematic reviews confirmed that the use of a combination of agents targeting the NO–cGMP pathway and calcium channel blockade can provide a more stable and long-lasting relaxation effect (Acar, 2024; Erdem, 2021; Riangwiwat, 2020). The consistency between these findings and previous literature

strengthens the belief that the results obtained are not coincidental but reflect a robust biological mechanism. Previous studies have also highlighted that the use of vasodilator cocktails can minimize endothelial damage, which is a crucial factor in maintaining long-term graft patency (Dang, 2022; Gatti, 2020; Georgakarakos, 2021; Nazir, 2020). Thus, the results of this study expand the existing evidence by providing confirmation in different clinical populations and settings, while also adding another layer of evidence from the perspective of hemodynamics and graft functional outcomes.

These findings have significant practical implications for clinicians and cardiac surgical teams. By reducing intraoperative spasm, patient hemodynamic stability is more easily achieved, the need for rescue pharmacological interventions is reduced, and the duration of surgery can be shortened. This ultimately results in a reduced risk of perioperative complications such as myocardial infarction or postoperative ventricular dysfunction. This study also encourages the systematic adoption of standardized protocols for the use of topical vasodilators in CABG procedures, particularly in the use of multiple arterial grafts, which are known to have a higher risk of spasm. Implementing such evidence-based protocols has the potential to improve patient outcomes across the population, while reducing healthcare costs by reducing the need for reinterventions.

Although these results strengthen the evidence for the effectiveness of topical vasodilators, further research is needed to explore long-term aspects such as the impact on 5–10-year patency and patient survival. A large-scale, multicenter, RCT-designed study will be needed to confirm the generalizability of these findings to populations with more diverse clinical characteristics, including patients with diabetes or peripheral vascular disease, who have a higher risk profile for spasms. Furthermore, exploring new agent combinations or more efficient administration protocols could be a promising area of research, given the pharmacokinetic differences between agents. With such an approach, it is hoped that spasm management strategies can be more personalized and provide maximum clinical benefit without increasing patient risk.

### 2. Safety Profile, Clinical Implications, and Implementation Recommendations

The results of this study indicate that topical vasodilators used intraoperatively have a good safety profile, with

side effects being mild and manageable through careful perioperative monitoring. Transient hypotension occurring in a small proportion of patients did not have significant clinical consequences because it was readily corrected with fluid adjustments or mild vasopressors. This is consistent with reports in the literature showing that the risk of hypotension associated with topical vasodilators is much lower than with systemic use, due to limited exposure to target tissues. Previous observational studies and randomized trials have also reported low rates of bradycardia and arrhythmias, thus not being a barrier to routine use. This safety profile is important because it provides reassurance that pharmacological interventions do not worsen the hemodynamic status of patients already in critical condition after bypass.

Interpretation of the safety findings from this study is consistent with evidence from a recent meta-analysis highlighting no significant difference in the incidence of major complications between groups receiving topical vasodilators and control groups (Bochenek, 2020; Goh, 2024; Kyriakopoulos, 2021; Shenoy, 2023; Zus, 2024). This suggests that the hemodynamic benefits achieved are not offset by an increased risk of serious adverse events (Z. Hu, 2024; Royse, 2020; Zencirci, 2022; Zhu, 2023). Previous studies evaluating papaverine, nitroglycerin, or calcium channel blocker combinations have reported similar patterns of adverse events, primarily flushing or mild headache, which are self-limited (Darçın, 2023; Elattar, 2023; Linden, 2020; Uyar, 2020; Zatolokin, 2022). The consistency of these findings across diverse populations and surgical settings strengthens external validity and supports the generalizability of the results to broader clinical practice (Dashwood, 2024; Emmert et al., 2024; Mahilmaran, 2023; Roghani-Dehkordi, 2020). Therefore, the risks of topical vasodilator use can be considered minimal, particularly when accompanied by appropriate intraoperative monitoring protocols.

The implications of these findings are significant for optimizing the perioperative management of CABG patients. With a low risk of side effects, clinicians can more confidently incorporate topical vasodilators into routine protocols without fear of hemodynamic instability. This allows for greater focus on preventing spasm, a key determinant of graft patency, rather than being hampered by concerns about side effects. Combining agents with different mechanisms of action may provide additional benefits without increasing the risk of complications, supporting the widespread adoption of multimodal strategies. From a risk management perspective, these findings encourage procedural standards to ensure consistent vasodilator administration across all patients undergoing arterial grafts, thereby minimizing intersurgery practice variation.

Based on the synthesis of available evidence, implementation recommendations include the integration of topical vasodilators into the standard operating procedures (SOP) for CABG surgery, particularly when using radial artery grafts or combinations of multiple arterial grafts. Administration can be performed via immersion or brief intraluminal irrigation, depending on the surgical team's preference and facility availability. Combinations of agents targeting more than one vascular relaxation pathway are recommended, as they provide a more comprehensive effect on spasm. Furthermore, training is required for medical personnel to ensure appropriate dosage, concentration, and duration of exposure to maximize clinical benefit. Implementation of this protocol can be monitored through quality indicators such as mean post-anastomotic TTFM, intraoperative spasm rate, and early reintervention rate, allowing for objective evaluation of implementation success.

Although current evidence supports the safety and effectiveness of topical vasodilators, there is room for further development through research innovation. Larger, multicenter studies are needed to validate these findings in more heterogeneous patient populations, including those with comorbidities such as diabetes or severe atherosclerosis, who are at higher risk of spasm. Furthermore, pharmacokinetic studies can help identify optimal concentrations that provide maximum relaxation with minimal risk. Future innovations may also include the development of new formulations that allow for sustained release or nanoparticle-based delivery systems to maintain antispasmodic effects longer postoperatively. Therefore, integrating the findings of this study with further research will strengthen the scientific foundation for modern standards of care, ensuring that the management of graft spasm is not only effective and safe but also based on continually updated evidence.

## CONCLUSION

Based on the synthesis and discussion, it can be concluded that the use of topical vasodilators is an effective and safe pharmacological strategy to prevent arterial graft spasm in CABG surgery, while improving the quality of flow and graft patency. Combinations of agents targeting multiple vascular relaxation pathways have been shown to provide a more consistent synergistic effect than single agents, improving intraoperative hemodynamic profiles, and minimizing the risk of early occlusion without increasing major complications. The available moderate to high-quality evidence supports the integration of this intervention into standard protocols for modern cardiac surgery, potentially reducing cardiovascular morbidity and improving the long-term success of CABG procedures.

To optimize the application of these findings, it is recommended that hospitals and cardiac surgery centers adopt evidence-based topical vasodilator protocols with



close intraoperative monitoring, and train surgical teams on optimal doses, concentrations, and application methods. Large-scale, multicenter, long-term studies are needed to evaluate the impact of these interventions on 5–10-year graft patency, hard clinical outcomes such as mortality and myocardial infarction, and cost-effectiveness. With a systematic and sustainable approach, topical vasodilator use could become a global standard in the antispastic management of arterial grafts, supporting more precision cardiac surgical practices and improving patient safety.

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