

# Calcium Channel Blockers in Cardiac Surgery: Efficacy, Administration, and Clinical Outcomes in Arterial Graft Management

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## ABSTRACT

Calcium channel blockers (CCBs) have emerged as important therapeutic agents in cardiac surgery, particularly for preventing arterial graft spasm during coronary artery bypass grafting (CABG). This literature review synthesizes evidence on CCB efficacy, administration methods, and clinical outcomes in cardiac surgery patients. A comprehensive analysis of 25 studies spanning 1987-2025 reveals consistent short-term benefits of CCB therapy in preventing arterial graft spasm and improving immediate surgical outcomes. CCBs, including diltiazem, verapamil, nicardipine, and amlodipine, show robust short-term efficacy in improving graft flow rates and reducing perioperative complications, with emerging agents like efonidipine offering novel dual-channel blocking activity. While observational studies suggest sustained benefits, randomized controlled trials question prolonged treatment necessity. Therefore, the long-term effectiveness of these medications remains controversial. Critical gaps include insufficient large-scale randomized trials, unclear optimal treatment duration, and limited patient stratification research. Future investigations should focus on multi-center randomized controlled trials, novel dual-channel blocking agents, and personalized treatment approaches based on patient-specific risk factors.

**Keywords:** Calcium channel blockers; arterial graft management; coronary artery bypass grafting; CABG; cardiac surgery

## INTRODUCTION

Coronary artery bypass grafting (CABG) represents one of the most frequently performed cardiac procedures worldwide, with approximately 400,000 procedures conducted annually in the United States alone (1). A critical complication that can compromise surgical outcomes is arterial graft spasm, which can lead to

graft failure, myocardial infarction, and increased mortality (2, 3). While spasm occurs perioperatively in approximately 0.43% of all CABG procedures, He and Taggart suggest this is likely an underestimate (2). This phenomenon is particularly problematic with arterial grafts, especially radial artery grafts. Indeed, these have become increasingly popular due to their superior long-term patency compared to saphenous vein grafts (3).

The pathophysiology of arterial graft spasm involves excessive vasoconstriction mediated primarily through increased intracellular calcium concentrations in vascular smooth muscle cells. He and Taggart (2016) explain that complications often occur when these concentrations are not well regulated (2). When calcium

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channels are activated, calcium influx triggers muscle contraction, leading to arterial narrowing that can severely compromise blood flow to the myocardium. This understanding has led to the investigation of calcium channel blockers (CCBs) as a potential therapeutic intervention to prevent and treat graft spasm.

As was stated by Mussa *et al.* in 2003, several treatment approaches exist for managing arterial graft spasm, including topical vasodilators like papaverine, systemic nitrates, and alpha-adrenergic blockers such as phenoxybenzamine (4). However, according to Kalus & Lober (2001), the optimal approach remains controversial, with no universally accepted gold standard (5). Myers & Fremes (2003) found that while some centers routinely administer prophylactic antispasmodic therapy, others adopt a more selective approach based on individual patient risk factors (6).

The purpose of this review is to synthesize existing literature on the use of calcium channel blockers in cardiac surgery, specifically examining their efficacy in preventing arterial graft spasm, optimal administration methods, and long-term clinical outcomes. This analysis is particularly timely given recent conflicting evidence regarding the most effective duration of CCB therapy and the emergence of newer calcium channel blocking agents with potentially superior pharmacological profiles.

## MECHANISM OF ACTION AND PHARMACOLOGICAL BASIS

Calcium is the most abundant mineral in the human body, with 99% residing in bones and teeth. Although only the remaining 1% is found in blood and soft tissue,

calcium ions ( $\text{Ca}^{2+}$ ) play a central role in the electrical activation that triggers the mechanical contraction of heart cells to pump blood (7, 8). After entering cardiac muscle cells via ion channels,  $\text{Ca}^{2+}$  can bind to the troponin complex (i.e., the pumping machinery), which controls the interaction between actin-myosin filaments that exert contractile forces on the cytoskeleton (9).

The effectiveness of calcium channel blockers in preventing arterial graft spasm stems from their ability to block calcium influx through voltage-gated calcium channels in vascular smooth muscle cells, leading to vasodilation (10). He (2013) provides clinical classification of arterial grafts used in CABG, explaining differences in patency and emergence of spasm, and notes that calcium channel blockers such as verapamil, nicardipine, and diltiazem have been demonstrated as effective vasodilators, though verapamil has a bradycardic effect (slow heart rate below 60 bpm in adults) (11).

Different CCBs demonstrate varying selectivity for Long-lasting opening (L-type) versus Transient opening (T-type) calcium channels, which may respond differently to different CCBs, enabling different therapeutic effects (12). Traditional agents like diltiazem and verapamil primarily target L-type channels, while newer agents such as efonidipine block both L-type and T-type channels, potentially offering superior antispasmodic effects. Differences between major CCB agents are summarized in Table 1. Yin *et al.* (2025) tested efonidipine on human internal mammary artery (IMA) samples from 54 bypass surgery patients and found it effectively prevented and reversed arterial spasm through its dual L-type and T-type calcium channel blocking action, making it more effective than existing treatments (13).

**Table 1.** Short-Term Efficacy of Major CCB Agents

Agent	Mechanism	Key Short-Term Benefits	Advantages	Limitations
Verapamil	L-type CCB	<ul style="list-style-type: none"> <li>Increased radial artery flow</li> <li>Effective vasodilator</li> <li>Treats postoperative atrial dysrhythmias</li> </ul>	<ul style="list-style-type: none"> <li>Broad efficacy against multiple vasoconstrictors when combined with nitroglycerin</li> <li>Effectiveness dose-dependent</li> <li>Additional antiarrhythmic benefits</li> </ul>	<ul style="list-style-type: none"> <li>Bradycardic effect (slows heart rate below 60 bpm)</li> <li>Relatively short duration of action</li> <li>Systemic side effects (hypotension)</li> </ul>
Diltiazem	L-type CCB	<ul style="list-style-type: none"> <li>Reduces perioperative ischemia</li> <li>Decreases heart rate and inotropy</li> </ul>	<ul style="list-style-type: none"> <li>Effective when concentration exceeds 96 ng/mL</li> <li>Well-established clinical use</li> <li>Reduces systolic function appropriately</li> </ul>	<ul style="list-style-type: none"> <li>No significant outcome advantages found in on-pump CABG (Zhang <i>et al.</i> 2022)</li> <li>Potential side effects with chronic use</li> <li>Effectiveness questioned in specific contexts</li> </ul>

Continued Table 1. Short-Term Efficacy of Major CCB Agents

Agent	Mechanism	Key Short-Term Benefits	Advantages	Limitations
Nicardipine	L-type CCB	<ul style="list-style-type: none"> <li>Increased radial artery flow (20@47 mL/min)</li> <li>Comparable to verapamil in effectiveness</li> </ul>	<ul style="list-style-type: none"> <li>Safe and effective substitute to verapamil (No difference in flow improvement or perioperative complications)</li> </ul>	<ul style="list-style-type: none"> <li>Large standard deviations in flow measurements (~15 mL/min)</li> <li>Limited comparative studies</li> <li>Systemic side effects possible</li> </ul>
Amlodipine	L-type CCB	<ul style="list-style-type: none"> <li>Counteracts multiple vasoconstrictors (KCl, urotensin-II, U46619)</li> <li>Prevents IMA spasm</li> </ul>	<ul style="list-style-type: none"> <li>Both relaxing effect and depression of contraction demonstrated</li> <li>Effective in frequently used IMA grafts</li> <li>Second most common agent in Canadian practice</li> </ul>	<ul style="list-style-type: none"> <li>Relatively modest sample sizes in studies (n=78 artery rings)</li> <li>Side effects should be considered in chronic use decisions</li> <li>Limited head-to-head comparisons</li> </ul>
Enfonidipine	Dual L-type and T-type CCB	<ul style="list-style-type: none"> <li>Effectively prevents and reverses arterial spasm</li> <li>Superior antispasmodic effects</li> </ul>	<ul style="list-style-type: none"> <li>Novel dual-channel blocking mechanism</li> <li>More effective than existing single-channel treatments</li> <li>Tested on human IMA samples (n=54)</li> </ul>	<ul style="list-style-type: none"> <li>Newer agent with limited clinical trial data</li> <li>Requires further large-scale validation</li> <li>Cost-effectiveness not yet established</li> <li>Not yet widely available</li> </ul>

## SHORT-TERM EFFICACY AND IMMEDIATE PERIOPERATIVE BENEFITS

Multiple studies demonstrate consistent perioperative benefits of CCB therapy. Bai *et al.* (2010) showed that amlodipine effectively counteracted various vasoconstrictors including potassium chloride, urotensin-II, and U46619 (a thromboxane mimetic which may induce vasospasm) in human IMA samples, concluding this drug may be used to prevent spasm in the IMA frequently used in CABG (14, 15). This study's strength lies in examining both the relaxing effect of amlodipine prior to contraction induced by vasoconstrictors and the depression of contraction by amlodipine, though the sample size was relatively modest (n=78 IMA rings from 42 patients).

Similarly, Özdemir *et al.* (2019) found that both verapamil and nicardipine significantly increased radial artery conduit flow from 20 mL/min to 47 mL/min during surgery, demonstrating substantial immediate clinical benefits (16). This prospective randomized study of 131 patients concluded that nicardipine is a safe and effective alternative to verapamil, with no significant difference in flow improvement or postoperative complications between the two drugs, though large standard deviations were noted (around 15 mL/min).

Comparative studies reveal important differences between various CCBs. Mussa *et al.* (2003) compared topical antispasmodic agents using standardized testing on radial artery rings and found that verapamil/nitroglycerin solution demonstrated broad efficacy against multiple vasoconstrictors but had a relatively short duration of action, whereas phenoxybenzamine showed more prolonged effectiveness, specifically against catecholamine-mediated vasospasm (4). These findings suggest that CCB selection should be tailored based on the anticipated duration of effect and specific mechanisms of spasm.

Colson *et al.* (1992) demonstrated that diltiazem reduces perioperative ischemia for patients undergoing CABG by decreasing heart rate, inotropy (forcefulness of contractions), and systolic function when concentration exceeded 96 ng/mL (17). The study's consideration of physiological factors and generalizable conclusions to other cardiac procedures strengthen its clinical relevance.

Studies demonstrate that perioperative efficacy may depend on application method. Mohapatra *et al.* (2017) demonstrated that application via organ bath technique (submerging the graft in solution containing the CCB before grafting) achieved superior vasodilatory effects compared to spray application, with the organ bath method producing an 82.6% increase in left internal

thoracic artery blood flow versus 57.6% with topical spray application (18). Nitroglycerin and verapamil solution applied via organ bath technique achieved the highest proportional increase in blood flow.

## CLINICAL PRACTICE PATTERNS

The literature reveals significant variation in CCB administration approaches, with important implications for clinical effectiveness. Traditional systemic administration through oral or intravenous routes provides consistent drug levels but may be associated with systemic side effects including hypotension and bradycardia (Murphy & Wechsler, 1987) (19). Murphy and Wechsler noted that calcium channel blockers such as verapamil can treat post-operative disorders like atrial flutter and fibrillation, resolve coronary artery spasms during surgery, and protect ischemic myocardia from damage (19).

The perioperative application of CCBs extends beyond spasm prevention. By tracking serum levels of 109 patients, Ferraris *et al.* (1987) demonstrated in a randomized, double-blind study that oral administration of verapamil significantly reduced postoperative atrial dysrhythmias, with effectiveness dependent on dosage (20). Aimed at reducing bias, the double-blind nature of this experimental design adds rigor to the finding that CCBs provide multiple cardiovascular benefits in the perioperative period.

While some form of antispasmodic therapy is often used in clinics, the specific medication and prescribed duration can vary significantly. Myers and Fremes (2003) surveyed 27 Canadian cardiac surgery centers and found that 25 routinely used antispasmodic prophylaxis with calcium channel blockers, most frequently diltiazem, followed by nifedipine and amlodipine (6). However, this uniformity in practice was not necessarily supported by consistent evidence regarding optimal duration of therapy, with many papers revealing no noticeable difference in patency rates measured through angiography after a couple years if CCB therapy was stopped after 1 year.

## HYPERTENSION MANAGEMENT AND CARDIOVASCULAR STABILITY

A common complication associated with CABG, perioperative hypertension can also be managed effectively with CCBs. For instance, in Lin & Ma's 2018 systematic review and meta-analysis of 1,743 cases, CCBs exhibited significantly better treatment success

rates for perioperative hypertension compared to other antihypertensive medications, while also presenting a good safety profile (23).

Bottussi *et al.* (2025) performed a systematic review examining clevidipine for perioperative hypertension management, analyzing studies from 1997-2023 amounting to 2,066 patients (24). They found clevidipine effectively treats perioperative hypertension with useful properties such as a short half-life, though noted the need for a broader analysis spanning more diverse populations.

However, Biccard & Howell (2008) present important safety considerations, arguing that dihydropyridine calcium channel blockers (which includes clevidipine) may be dangerous during non-cardiac surgery because they cause reflex increases in heart rate that can lead to cardiac complications (25). They emphasize that proper evaluation of perioperative cardiac medications requires physiological context from variables like heart rate, blood pressure, body weight, serum potassium, and blood glucose, as these may explain much of the benefit or harm associated with these drugs during surgery.

## LONG-TERM EFFECTIVENESS AND CONTROVERSIAL DURATION

Perhaps the most controversial aspect of CCB therapy in cardiac surgery relates to optimal treatment duration. The evidence presents striking contradictions between observational studies and randomized controlled trials. Gaudino *et al.* (2019) conducted a large observational study of nearly 1,000 patients and found that CCB therapy significantly reduced major adverse cardiac events by approximately 48% and graft occlusion by 80% over a nine-year follow-up period (26). The study's strengths include its large sample size, rigorous statistical analysis with adjustments, and longitudinal nature tracking outcomes at 3, 6, and 9 years. However, as an observational study, its ability to establish causality and reject possible confounders is limited.

These findings contrast with randomized controlled trial evidence, which can minimize bias implicit in observational studies. Gaudino *et al.* (2005) also performed a smaller randomized controlled trial of 100 consecutive patients and found no significant differences in clinical outcomes, myocardial scintigraphy results, or graft patency rates between patients receiving oral diltiazem (120 mg daily) versus no CCB therapy at one-year follow-up (27). Endovascular serotonin testing showed that calcium channel blockers did not prevent radial artery spasm, leading to the conclusion that

prophylactic CCB therapy in radial artery graft patients appears unsubstantiated.

Several methodological factors may explain this contradiction. Ruel and Sun (2019) provide editorial commentary on this contradiction, expressing caution about the observational findings due to significant baseline differences between CCB and non-CCB groups that could have influenced results despite statistical adjustments (28). They emphasize the importance of distinguishing between observational evidence and randomized controlled trial data.

Gaudino *et al.* (2005) proposed a biological explanation for the apparent decline in CCB effectiveness over time, suggesting that radial arteries undergo remodeling and lose their muscular components, becoming more similar to internal mammary arteries (29). This “arterial remodeling hypothesis” provides a theoretical framework for understanding why CCBs may be most beneficial in the early postoperative period but less effective for long-term graft maintenance beyond approximately 5 years. They note that side effects of drugs such as amlodipine and diltiazem should be considered in chronic use decisions.

### SUBGROUP INSIGHTS AND PREDICTIVE FACTORS

Several studies have explored which patient populations derive the greatest benefit from CCB therapy. Miyahara *et al.* (2025), Wijeyesundera *et al.* (2004) and Ueshima *et al.* (2023) found that CCB use was beneficial in various contexts, particularly for patients with coronary artery disease or chronic limb-threatening ischemia, while it presented no significant impact otherwise (30, 31, 32).

Miyahara *et al.* (2025) examined CCB use in 993 patients undergoing transcatheter aortic valve intervention for severe aortic stenosis between 2017-2023 (30). They found that CCB use was associated with better outcomes specifically in patients with coronary artery disease, demonstrating that effect depends on the subgroup.

Similarly, Wijeyesundera *et al.* (2004) analyzed outcomes in 6,619 patients undergoing various cardiac surgeries and found that calcium channel blockers appeared to significantly reduce patient mortality for procedures such as CABG, though not for heart transplants (31). The study’s large sample size and rigorous statistical analysis using propensity analysis provide strong evidence, though the study is over 20

years old.

Ueshima *et al.* (2023) investigated CCB use as adjunctive therapy with endovascular treatment for lower-extremity artery disease, analyzing outcomes using propensity score matching (32). They found that CCB use was associated with significantly fewer major adverse limb events in the overall cohort and both fewer major adverse cardiac/cerebrovascular events and major adverse limb events specifically in patients with chronic limb-threatening ischemia, while showing no significant benefit in patients with intermittent claudication. This suggests CCB therapy may be particularly beneficial for more severe forms of vascular disease.

### COMPARATIVE EFFECTIVENESS AND DRUG SELECTION

Studies comparing different CCBs reveal important selection considerations. Zhang *et al.* (2022) specifically examined perioperative diltiazem therapy in patients undergoing coronary artery bypass grafting while on cardiopulmonary bypass and found no significant outcome advantages (neither short-term nor long-term) due to diltiazem use (33). This challenges the effectiveness of this particular CCB in this specific context.

The organ bath technique, used by both Bai *et al.* (2010) and Mohapatra *et al.* (2017), appears to be an emerging standard practice for evaluating CCB effectiveness in vitro (15, 18). This technique allows for standardized testing conditions and more precise measurement of vasodilatory effects compared to other application methods.

Kalus and Lober (2001) provided historical perspective, noting that evidence supporting use of CCBs or nitrates to prevent radial artery spasm was inconclusive at that time (5). They analyzed various observational studies reporting high patency rates (87-100%) but concluded that no definitive conclusions could be drawn due to frequent lack of control groups, emphasizing the need for randomized controlled trials. This historical context demonstrates the evolution of understanding in this field over the past 25 years.

### CURRENT EVIDENCE GAPS AND FUTURE RESEARCH DIRECTIONS

This comprehensive review reveals several critical gaps in the current literature. Most notably, there’s a lack of large-scale randomized controlled trials with

adequate statistical power to definitively establish optimal CCB selection, dosing regimens, and treatment duration. Many studies rely on observational designs or small sample sizes, limiting the strength of evidence for clinical decision-making.

The optimal duration of CCB therapy remains unclear, with conflicting evidence about whether treatment should continue beyond one year. The contradiction between the Gaudino *et al.* studies (2005 vs. 2019) highlights this controversy and the challenge of reconciling observational versus controlled trial evidence (26, 27).

Additionally, there is insufficient research on patient stratification to identify which populations derive the greatest benefit from CCB therapy. While subgroup analyses show benefits for patients with coronary artery disease, other groups such as patients with chronic angina have yet to be adequately studied (30). The mechanisms underlying the apparent temporal decline in CCB effectiveness, particularly the arterial remodeling hypothesis, require further investigation to inform evidence-based treatment guidelines (29).

The literature also lacks comprehensive cost-effectiveness analyses. As noted in previous surveys, some patients discontinue CCB treatment due to intolerance or disease aggravation, making it important to study which patients benefit from CCB treatment and what costs are associated with treatment failure (6).

Missing from current research are adequate investigations of CCB interactions with other perioperative medications and cardioplegic solutions, as highlighted by Murphy and Wechsler (1987) (19). While this gap was identified decades ago, current literature suggests these interactions remain incompletely understood. Most studies focus on short-term outcomes, with insufficient long-term follow-up data to establish definitive guidelines for chronic CCB use in cardiac surgery patients. The few long-term studies available present contradictory findings, emphasizing the need for extended follow-up in future research (26, 27).

Future research priorities should focus on conducting multi-center randomized controlled trials with standardized outcome measures and extended follow-up periods. Investigation of novel CCB agents with dual L- and T-type channel blocking activity, such as efonidipine, may offer improved therapeutic options and warrants clinical trials (13).

Development of personalized treatment approaches based on patient-specific risk factors represents an important frontier. Research measuring the thickness of

the media of radial artery grafts could provide insight into the arterial remodeling hypothesis and help predict which patients would benefit most from extended CCB therapy (29). Finally, pharmacoeconomic analyses are necessary to assess the cost-effectiveness of short-term versus prolonged CCB therapy in the context of varying clinical outcomes and patient intolerance.

## CONCLUSION

This comprehensive review provides historical context over four decades until present day and reveals that calcium channel blockers demonstrate consistent short-term efficacy in preventing arterial graft spasm and improving immediate surgical outcomes during cardiac surgery. Multiple studies across different CCB agents and administration methods show significant improvements in graft flow rates and reduction in perioperative complications (4, 15, 16, 19). The evidence supporting immediate perioperative benefits is robust, with various CCBs (diltiazem, verapamil, nicardipine, and amlodipine) showing clear effectiveness.

However, the evidence regarding long-term therapy remains highly conflicted, with large observational studies suggesting sustained benefits while randomized controlled trials question the necessity of prolonged treatment (26, 27). The proposed arterial remodeling hypothesis provides a plausible biological explanation for the temporal decline in CCB effectiveness, suggesting that radial arteries lose their muscular components over time, becoming more similar to internal mammary arteries (29).

The evolution of CCB therapy in cardiac surgery demonstrates both progress and persistent challenges. While newer agents like efonidipine offer promising dual-channel blocking capabilities (13), and sophisticated administration techniques like the organ bath method improve drug delivery (19), fundamental questions about optimal treatment duration and patient selection remain unanswered.

Critical gaps in the current literature include insufficient large-scale randomized controlled trials, unclear optimal treatment duration, limited understanding of CCB interactions with other perioperative medications (19), and inadequate patient stratification research. Other limitations include potential publication bias, as positive short-term findings may reflect selective publication of favorable results, with negative or null findings less likely to appear in the literature. The striking contradictions between observational studies and randomized trials

highlight the need for more rigorous study designs and longer follow-up periods (26, 27).

The field would benefit significantly from multi-center randomized controlled trials with extended follow-up periods, investigation of cost-effectiveness, and development of evidence-based guidelines for different patient populations. The evolution toward personalized medicine approaches and the development of novel CCB agents with enhanced pharmacological profiles represent promising directions for future research.

Until definitive evidence becomes available, clinicians must balance the clear short-term benefits of CCB therapy against the uncertain long-term advantages, considering individual patient factors, institutional practices, and the growing evidence base in their decision-making process. The consistent short-term benefits support continued use of CCBs in the immediate perioperative period, while the controversial long-term evidence suggests that extended therapy decisions should be individualized based on patient-specific risk factors and clinical judgment.

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#### CONFLICT OF INTEREST

The author declares that there are no conflicts of interest regarding the publication of this article.

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