Review

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Fenoldopam for Renal Protection in Cardiac Surgery: Pharmacology, Clinical Applications, and Evolving Perspectives

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Abstract: This comprehensive review examines the role of fenoldopam, a selective dopamine-1 receptor agonist, in preventing and treating acute kidney injury (AKI) during cardiac surgery. AKI remains a significant complication in cardiac surgery, associated with increased morbidity, mortality, and healthcare costs. The review explores fenoldopam's pharmacological properties, mechanism of action, and clinical applications, synthesizing evidence from randomized controlled trials, meta-analyses, and observational studies. While some studies have shown promising results in improving renal function and reducing AKI incidence, others have failed to demonstrate significant benefits. The review discusses these conflicting findings, explores potential reasons for discrepancies, and identifies areas requiring further research. It also compares fenoldopam to other renoprotective strategies, including dopamine, diuretics, and N-acetylcysteine. The safety profile of fenoldopam, including common side effects and contraindications, is addressed. Current guidelines and recommendations for fenoldopam use in cardiac surgery are presented, along with a cost-effectiveness analysis. The review concludes by outlining future research directions and potential new applications of fenoldopam in cardiac surgery. By providing a thorough overview of the current state of knowledge, this review aims to facilitate informed decision-making for clinicians and researchers while highlighting areas for future investigation.

Keywords: acute kidney injury; aki; renoprotection; dopamine-1 receptor agonist; ischemia-reperfusion injury; cardiopulmonary bypass; renal blood flow; pharmacological intervention; perioperative care

1. Introduction

Cardiac surgery, while often life-saving, is associated with significant risks, including acute kidney injury (AKI). The incidence of AKI following cardiac surgery ranges from 8.9% to 39%, depending on the definition used and the specific patient population [1,2]. This complication is associated with increased morbidity, mortality, length of hospital stay, and healthcare costs [3,4]. Fenoldopam is a selective dopamine-1 receptor agonist that has gained attention in recent years as a potential renoprotective agent in cardiac surgery [5]. Originally approved for the treatment of severe hypertension, Fenoldopam has been investigated for its ability to increase renal blood flow and urine output, potentially mitigating the risk of AKI in high-risk patients [6,7]. The kidneys are particularly vulnerable during cardiac surgery due to several factors, including hemodynamic changes, ischemia-reperfusion injury, inflammation, and oxidative stress [8,9]. These insults can lead to AKI, which not only affects short-term outcomes but can also have long-term consequences, including the

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development of chronic kidney disease [10]. Therefore, strategies to protect renal function during and after cardiac surgery are of paramount importance. Traditional approaches to renal protection have included maintaining adequate perfusion pressure, optimizing fluid management, and avoiding nephrotoxic agents [11]. However, these measures alone have not been sufficient to significantly reduce the incidence of AKI, leading to a search for pharmacological interventions that could provide additional protection [12]. This comprehensive review aims to examine the pharmacological properties of Fenoldopam and its mechanism of action in the context of renal protection, evaluating the clinical evidence for the use of Fenoldopam in cardiac surgery, including its efficacy in preventing and treating AKI. We also compare Fenoldopam to other renoprotective strategies used in cardiac surgery and analyze the safety profile and cost-effectiveness of Fenoldopam in this setting. It ultimately discusses current guidelines and recommendations for the use of Fenoldopam in cardiac surgery and identifies areas for future research and potential new applications, providing to clinicians and researchers with a comprehensive understanding of its potential benefits and limitations, facilitating informed decision-making and highlighting areas for further investigation.

2. Pharmacology of Fenoldopam

Fenoldopam is a selective dopamine-1 (D1) receptor agonist, with no significant activity at dopamine-2 (D2) or α-adrenergic receptors (Figure 1) [13]. Its primary mechanism of action involves the stimulation of D1 receptors in the renal, mesenteric, and coronary vascular beds. In the kidneys, fenoldopam activates D1 receptors on the renal tubules and vasculature, leading to vasodilation of the afferent and efferent arterioles, as well as the arcuate and interlobular arteries [14].

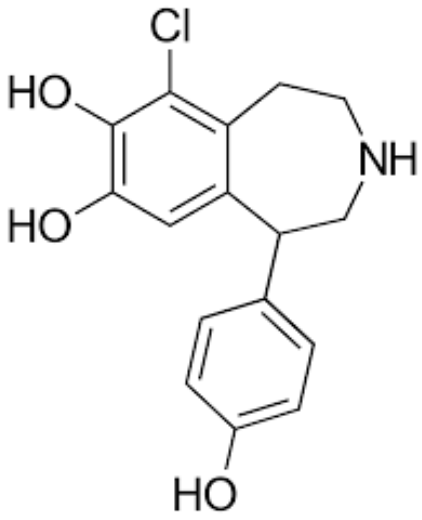

Figure 1. Chemical structure of Fenoldopam.

This vasodilation results in increased renal blood flow, glomerular filtration rate (GFR), and sodium excretion [15]. Fenoldopam is administered intravenously [16]. It has a rapid onset of action, with hemodynamic effects observed within 5 minutes [17]. The drug has a short half-life of approximately 5-10 minutes, allowing for precise titration and quick offset of effects upon discontinuation [18]. Fenoldopam is primarily metabolized in the liver through conjugation, with no active metabolites identified. Approximately 90% of the drug is excreted in the urine within 24 hours, with the remainer eliminated in feces [19]. The primary pharmacodynamic effects of fenoldopam are related to its renal actions. At therapeutic doses, fenoldopam increases renal blood flow by 30-40%, enhances GFR by 15-20%, and promotes natriuresis and diuresis [20]. These effects are dose-dependent and occur without significant changes in heart rate or cardiac output. In addition to its renal effects, Fenoldopam has been shown to have systemic vasodilatory properties, leading to a reduction in blood pressure [21]. This effect is particularly pronounced in hypertensive patients but is also observed to a lesser extent in normotensive individuals [22]. Fenoldopam also exhibits potential anti-

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inflammatory and anti-oxidative properties, which may contribute to its renoprotective effects in the setting of ischemia-reperfusion injury [23]. These properties include the suppression of pro-inflammatory cytokines and the reduction of oxidative stress markers [24]. The drug's pharmacodynamic profile makes it particularly attractive for use in cardiac surgery, where maintaining renal perfusion and function is crucial. However, the systemic vasodilatory effects necessitate careful monitoring and potential adjustments in concurrent vasopressor therapy [6].

3. Renal Protection in Cardiac Surgery

The incidence of AKI in this setting ranges from 8.9% to 39%, depending on the definition used and the specific patient population [1]. Understanding the pathophysiology of AKI in cardiac surgery and implementing effective renoprotective strategies are crucial for improving patients' outcomes. The development of AKI in cardiac surgery is multifactorial and involves complex interactions between patient-related risk factors and perioperative events [8]. Key mechanisms include ischemia-reperfusion injury, hemodynamic instability, systemic inflammatory response, exposure to nephrotoxins, embolic events, and hemodilution. Cardiopulmonary bypass (CPB) can lead to periods of renal hypoperfusion followed by reperfusion, triggering oxidative stress and inflammation [25]. Fluctuations in blood pressure and cardiac output during surgery can compromise renal perfusion [26], while CPB initiates a systemic inflammatory cascade that contributes to renal injury [27]. Exposure to contrast agents, antibiotics, and other medications can exacerbate renal damage [28], and atherosclerotic debris or air emboli can cause renal microinfarcts [29]. Additionally, CPB-induced hemodilution can reduce oxygen delivery to the kidneys [30]. Several strategies have been employed to mitigate the risk of AKI in cardiac surgery. These include optimizing hemodynamics by maintaining adequate mean arterial pressure and cardiac output to ensure renal perfusion [31], and implementing balanced fluid management to avoid both hypovolemia and fluid overload [32]. Minimizing exposure to potentially harmful agents and adjusting drug dosages appropriately is crucial [33]. In some cases, performing coronary artery bypass grafting without CPB (off-pump surgery) may reduce the risk of AKI [34]. Some studies suggest that pulsatile flow during CPB may better preserve renal function compared to non-pulsatile flow [35]. Remote ischemic preconditioning, involving brief periods of limb ischemia before surgery, may confer renoprotection, although results have been mixed [36]. Various pharmacological agents have been investigated for their potential renoprotective effects, including N-acetylcysteine, statins, and erythropoietin, with varying degrees of success [12]. Despite these measures, AKI remains a significant challenge in cardiac surgery, highlighting the need for novel and more effective renoprotective strategies. The investigation of Fenoldopam as a potential renoprotective agent represents one such approach [5].

4. Clinical Applications of Fenoldopam in Cardiac Surgery

The use of Fenoldopam in cardiac surgery has been explored in various clinical contexts, with the primary goal of preserving renal function and preventing AKI. Its applications span the preoperative, intraoperative, and postoperative phases of cardiac surgery, each with distinct considerations and potential benefits. Preoperative administration of Fenoldopam has been investigated as a strategy to optimize renal function before cardiac surgery, particularly in high-risk patients. Cogliati et al. (2007) conducted a randomized clinical study involving 193 patients undergoing cardiac surgery with CPB [15]. They administered Fenoldopam (0.1 μg/kg/min) or placebo for 24 hours before surgery. The Fenoldopam group showed significantly lower incidence of AKI (12.6% vs. 27.6%, $p = 0.02$) and shorter intensive care unit stay. This study suggested that preoperative Fenoldopam infusion might have a protective effect on renal function in high-risk cardiac surgery patients. The intraoperative use of Fenoldopam has been the focus of several studies, aiming to mitigate the renal stress associated with CPB. Ranucci et al. (2010) evaluated the effects of intraoperative Fenoldopam in a randomized trial of 80 patients undergoing cardiac surgery with CPB [37]. Fenoldopam was administered at a dose of 0.1 μg/kg/min from the onset of CPB until 12 hours postoperatively. The Fenoldopam group demonstrated better urine output, lower serum creatinine levels, and a reduced incidence of AKI

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compared to the control group. The application of Fenoldopam in the postoperative period has also been explored, particularly in patients showing early signs of renal dysfunction. Tumlin et al. (2009) conducted a multicenter, randomized, double-blind, placebo-controlled trial involving 155 cardiac surgery patients with early acute renal dysfunction [22]. Fenoldopam (0.1 μg/kg/min) or placebo was administered for up to 96 hours postoperatively. While the primary endpoint of dialysis-free survival at 21 days did not reach statistical significance, the Fenoldopam group showed trends towards improved renal function and reduced mortality.Despite these promising results, it's important to note that not all studies have shown consistent benefits. For instance, Bove et al. (2014) conducted a large multicenter randomized trial involving 667 cardiac surgery patients and found no significant difference in the incidence of AKI between the Fenoldopam and placebo groups [38].

5. Evidence from Clinical Trials

The efficacy of Fenoldopam in preventing and treating AKI in cardiac surgery has been the subject of numerous clinical trials, yielding a mix of promising results and conflicting evidence. This section provides a comprehensive overview of the key RCTs, meta-analyses, and observational studies that have shaped our understanding of Fenoldopam's role in this clinical context (Table 1).

Table 1. Summary

Study	N. Patients	Dosing of Fenoldopam	Comparison	Results	Outcomes
Cogliati et al.	193 (95 Fenoldopam; 98 Placebo)	0.1 mcg/kg/min	Placebo	Serum creatinine baseline: 1.8 ± 0.4 mg/dL Fenoldopam; 1.9 ± 0.3 mg/dL Placebol; After 24 hours: 1.6 ± 0.2 mg/dL Fenoldopam; 2.5 ± 0.6 mg/dL Placebo; After 48 hours: 1.5 ± 0.3 mg/dL Fenoldopam; 2.8 ± 0.4 mg/dL Placebo	Fenoldopam prevented acute kidney injury in a high-risk population undergoing cardiac surgery
Ranucci et al.	80 (40 Fenoldopam; 40 Placebo)	0.1 mcg/kg/min	Placebo	Serum creatinine baseline: 1.39±1.65 mg/dL Fenoldopam; 1.08±0.43 mg/dL Placebo; After 12h: 1.1±0.2 mg/dL Fenoldopam; 1.3±0.9 mg/dL Placebo	Fenoldopam significantly improves renal function and prevents AKI and major morbidity.
Barr et al.	79 (19 Fenoldopam; 20 N-acetylcysteine; 21 Fenoldopam+N-acetylcysteine; 19 Placebo)	0.1 mcg/kg/min	N-acetylcysteine 600 mg os twice a day	Creatinine clearance from preoperative to postoperative day 3: -1.47±2 mL/min Fenoldopam; -0.67±2 mL/min N-acetylcysteine; -3.08±1.95 mL/min Fenoldopam+N-acetylcysteine; -8.15±2.18 mL/min Placebo	Perioperative fenoldopam and N-acetylcysteine abrogate the early postoperative decline in renal function of patients who have chronic renal insufficiency
Tumlin et al.	155 (80 Fenoldopam; 75 Placebo)	0.1 mcg/kg/min	Placebo	Incidence of dialysis therapy or all-cause mortality at 21 days: 27.5% Fenoldopam; 38.7% Placebo. Serum creatinine baseline: 1.17 mg/dL Fenoldopam; 1.25 mg/dL Placebo 2.25 mg/dL; After 72h: 2.0 mg/dL Fenoldopam; 2.25mg/dL Placebo	Fenoldopam does not reduce the incidence of death or dialysis therapy in intensive care unit patients with early ATN
Bove et al.	667 (338 Fenoldopam; 329 Placebo)	0.1 mcg/kg/min	Placebo	RRT: 20% Fenoldopam; 18% Placebo; Mortality at 30 days: 23% Fenoldopam; 22% Placebo	Fenoldopam did not reduce the need for renal replacement therapy or risk of 30-day mortality, but was associated with increased of hypotension

AKI: Acute Kidney Injury; ATN: Acute Tubular Necrosis; RRT: Renal Replacement Therapy.

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Several landmark RCTs have evaluated Fenoldopam in cardiac surgery. Cogliati et al. (2007) conducted a single-center RCT involving 193 high-risk cardiac surgery patients [15]. They found that preoperative Fenoldopam infusion (0.1 μg/kg/min for 24 hours before surgery) significantly reduced the incidence of AKI compared to placebo (12.6% vs. 27.6%, p = 0.02). This study suggested a potential protective effect of Fenoldopam when administered preoperatively. Conversely, a large multicenter RCT by Landoni et al. (2014) in over 20 Italian hospitals found no significant difference in the incidence of AKI between Fenoldopam and placebo groups [39]. Fenoldopam was administered at 0.1 μg/kg/min from the onset of cardiopulmonary bypass for 96 hours or until ICU discharge. The primary endpoint of AKI incidence was similar in both groups (Fenoldopam 20% vs. placebo 18%; p = 0.47). Bove et al. (2014) conducted a double-blind RCT of patients undergoing cardiac surgery with cardiopulmonary bypass [38]. They found that 20% of patients in Fenoldopam group and 18% in placebo group received renal replacement therapy (p = 0.47). Several meta-analyses have attempted to synthesize the available evidence. Landoni et al. (2007) performed a meta-analysis of 16 RCTs involving 1,290 patients and found that Fenoldopam significantly reduced the risk of acute renal failure (OR 0.43, 95% CI 0.32-0.59, p < 0.001) and the need for renal replacement therapy (OR 0.54, 95% CI 0.34-0.84, p = 0.007) [6]. A more recent meta-analysis by Gillies et al. (2015) included 6 RCTs specific to cardiac surgery [5]. They found that Fenoldopam was associated with a reduced incidence of AKI (RR 0.46, 95% CI 0.27-0.79) and a lower requirement for renal replacement therapy (RR 0.27, 95% CI 0.06-1.19). However, they noted significant heterogeneity among studies and emphasized the need for larger, high-quality trials. The evidence from clinical trials presents a mixed picture of Fenoldopam's efficacy in preventing and treating AKI in cardiac surgery. While some studies have shown promising results, others have failed to demonstrate significant benefits. The heterogeneity in study designs, patient populations, dosing regimens, and definitions of AKI contribute to the difficulty in drawing definitive conclusions. Future large-scale, multicenter RCTs with standardized protocols are needed to clarify the role of Fenoldopam in this clinical setting. Additionally, identifying specific patient subgroups that may benefit most from Fenoldopam therapy remains an important area for further investigation.

6. Comparison with Other Renoprotective Strategies

The search for effective renoprotective strategies in cardiac surgery has led to the investigation of various pharmacological and non-pharmacological interventions. Fenoldopam's efficacy and safety profile must be considered in the context of these alternative approaches. This section compares Fenoldopam with other commonly used or studied renoprotective strategies in cardiac surgery.

6.1. Dopamine

Dopamine, a precursor to Fenoldopam, was once widely used for renal protection due to its presumed ability to increase renal blood flow at low doses. However, several studies and meta-analyses have failed to demonstrate consistent benefits. Friedrich et al. (2005) conducted a meta-analysis of 61 trials involving 3,359 patients and found no significant benefit of low-dose Dopamine in preventing acute renal failure, need for dialysis, or mortality [40]. Unlike Fenoldopam, Dopamine acts on both D1 and D2 receptors, as well as α and β adrenergic receptors, leading to potentially undesirable systemic effects. Fenoldopam's selective D1 receptor agonism may provide a more targeted renal protective effect with fewer systemic side effects compared to Dopamine [6,41].

6.2. Diuretics

Loop diuretics, particularly furosemide, have been widely used in an attempt to prevent or treat AKI in cardiac surgery. However, their efficacy in this context remains controversial. A meta-analysis by Ho and Power (2010) found no significant benefit of Furosemide in preventing or treating AKI in adults [42]. In contrast, Fenoldopam's mechanism of action focuses on improving renal blood flow rather than simply increasing urine output. Some studies have suggested that the combination of

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Fenoldopam and Furosemide may be more effective than either agent alone in managing fluid balance and preserving renal function in critically ill patients [43].

6.3. N-Acetylcysteine

N-acetylcysteine (NAC) has been studied for its potential antioxidant and renoprotective effects. A meta-analysis by Adabag et al. (2008) of 10 randomized controlled trials in cardiac surgery found that NAC did not significantly reduce the incidence of postoperative AKI or mortality [44]. Some studies have explored the combination of Fenoldopam and NAC, suggesting potential synergistic effects, but further research is needed to confirm these findings [32,45].

6.4. Statins

Preoperative Statin therapy has shown some promise in reducing the risk of AKI after cardiac surgery. A meta-analysis by Kuhn et al. (2014) found that preoperative Statin therapy was associated with a reduced incidence of AKI (RR 0.76, 95% CI 0.67-0.87) [46]. While the mechanism differs from Fenoldopam, the potential complementary effects of combining statins with fenoldopam warrant further investigation.

While each of these strategies has shown varying degrees of promise, Fenoldopam's unique mechanism of action and targeted effect on renal vasculature distinguish it from other approaches. The ideal renoprotective strategy may involve a combination of interventions, tailored to individual patient risk factors and surgical characteristics. Future research should focus on head-to-head comparisons between Fenoldopam and other renoprotective strategies, as well as investigating potential synergistic effects of combination therapies.

7. Safety Profile and Side Effects

The use of Fenoldopam in cardiac surgery necessitates a thorough understanding of its safety profile and potential side effects. The most frequently reported side effect of Fenoldopam is hypotension, which is directly related to its vasodilatory properties [13]. In a meta-analysis by Landoni et al. (2007), the incidence of hypotension was significantly higher in patients receiving Fenoldopam compared to control groups [6]. This effect is dose-dependent and generally manageable with dose adjustment or concurrent vasopressor use. However, it underscores the importance of careful hemodynamic monitoring during Fenoldopam administration, particularly in the perioperative setting where blood pressure fluctuations can be critical. Other commonly reported side effects include: tachycardia, in response to Fenoldopam-induced vasodilation [47]; headache, likely related to cerebral vasodilation [14]; flushing, for skin vasodilation [5]; nausea and vomiting [15]. These side effects are transient and resolve upon discontinuation of the drug or dose adjustment.

7.1. Contraindications and Precautions

Fenoldopam is contraindicated in patients with known hypersensitivity to the drug or any of its components. Caution is advised in patients with: glaucoma, as Fenoldopam can increase intraocular pressure; intracranial hypertension, due to cerebral vasodilation; severe aortic stenosis [20]; Fenoldopam can increase urinary potassium excretion [48]. Drug interactions are another important consideration: concomitant use of Fenoldopam with beta-blockers or other vasodilators or antihypertensive agents may result in additive hypotensive effects [38,49]. In the context of cardiac surgery, the potential for Fenoldopam to cause hypotension is of particular concern. Perioperative hypotension can compromise organ perfusion and potentially negate any renoprotective benefits. Therefore, careful titration of Fenoldopam and close hemodynamic monitoring are crucial [39] and this suggests that lower doses may offer a more favorable balance between renoprotective effects and hemodynamic stability. Long-term safety data on Fenoldopam use in cardiac surgery patients are limited, as most studies have focused on short-term perioperative use. Further research is needed to evaluate potential long-term effects or delayed complications.

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8. Cost-Effectiveness Analysis

The adoption of Fenoldopam as a renoprotective strategy in cardiac surgery necessitates a thorough evaluation of its cost-effectiveness. While the potential benefits of reducing AKI incidence and severity are clear, the associated costs of fenoldopam administration must be weighed against these benefits and compared to alternative strategies. A recent study by Bove et al. (2014) incorporated economic data into their randomized controlled trial of Fenoldopam in cardiac surgery patients [38]. While they did not find a significant difference in AKI incidence between Fenoldopam and placebo groups, they noted that Fenoldopam use was associated with reduced need for RRT, which has significant cost implications. The authors estimated that the use of Fenoldopam could result in cost savings of approximately €1,800 per patient, primarily due to avoided RRT costs. However, these findings must be interpreted cautiously. The cost-effectiveness of Fenoldopam may vary based on the patient's risk profile, more convenient in high-risk patients who are more likely to develop AKI [39], on the local healthcare costs [4], on dosing regimen, and on incidence of side effects. A comprehensive cost-effectiveness analysis should also consider the long-term economic impact of preventing AKI. Coca et al. (2012) demonstrated that even mild AKI is associated with increased long-term risks of chronic kidney disease and mortality [50]. Preventing these long-term sequelae could result in substantial cost savings over time, although quantifying these benefits in the context of fenoldopam use remains challenging. It's also important to compare the cost-effectiveness of Fenoldopam to other renoprotective strategies. For instance, remote ischemic preconditioning has shown promise in reducing AKI in cardiac surgery and may be more cost-effective due to its non-pharmacological nature [36]. Similarly, the cost-effectiveness of Fenoldopam should be compared to that of other pharmacological interventions such as statins or N-acetylcysteine [51]. Future cost-effectiveness analyses should aim to incorporate data from larger, multicenter trials and consider a broader range of outcomes, including long-term renal function and quality of life measures. Additionally, as personalized medicine advances, identifying specific patient subgroups in which fenoldopam is most cost-effective will be crucial for optimizing its use in clinical practice.

9. Current Guidelines and Recommendations

The use of fenoldopam in cardiac surgery has been the subject of ongoing debate and research, leading to varying recommendations across different guidelines and expert consensus statements. This section summarizes the current stance of major cardiovascular and nephrology societies regarding the use of fenoldopam for renoprotection in cardiac surgery. The 2021 European Association for Cardio-Thoracic Surgery (EACTS)/European Association of Cardiothoracic Anaesthesiology (EACTA) Guidelines do not specifically recommend Fenoldopam for renoprotection [52]. These guidelines focus more on overall strategies to prevent acute AKI, such as maintaining adequate perfusion pressure and avoiding nephrotoxic agents. The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury, updated in 2012, does not provide a specific recommendation for Fenoldopam use in cardiac surgery [53]. However, they do suggest that fenoldopam may be considered in high-risk patients undergoing cardiac surgery, based on low-quality evidence. The American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines for Coronary Artery Bypass Graft Surgery, last updated in 2011, do not mention Fenoldopam as a renoprotective strategy [54]. This omission likely reflects the mixed evidence available at the time of guideline development. The Society of Thoracic Surgeons (STS) Practice Guideline Series: Blood Glucose Management During Adult Cardiac Surgery, published in 2009, briefly mentions Fenoldopam as a potential renoprotective agent but does not provide a specific recommendation for its use [55]. The European Society of Intensive Care Medicine (ESICM) consensus statement on prevention of acute kidney injury, published in 2017, mentions Fenoldopam but does not recommend its routine use for prevention of cardiac surgery-associated AKI due to conflicting evidence [56]. It's important to note that the lack of strong recommendations for Fenoldopam use in major guidelines does not necessarily preclude its potential benefits in specific clinical scenarios. Many guidelines acknowledge the need for individualized

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patient care and the consideration of emerging therapies in high-risk populations. Several expert consensus statements and review articles have provided more nuanced recommendations:

A 2016 expert consensus statement on renal protection in cardiac surgery suggests that Fenoldopam may be considered in high-risk patients, particularly those with pre-existing renal dysfunction [57]. A 2018 review by Bellomo et al. on perioperative kidney protection strategies mentions Fenoldopam as a potential option but emphasizes the need for further large-scale trials before widespread adoption [58]. The 2019 Canadian Society of Nephrology commentary on the KDIGO clinical practice guideline on AKI suggests that Fenoldopam may be considered in select high-risk patients undergoing cardiac surgery, but emphasizes the need for careful hemodynamic monitoring [59]. In conclusion, current guidelines and recommendations regarding Fenoldopam use in cardiac surgery are cautious and generally do not provide strong endorsements for its routine use. This reflects the mixed evidence from clinical trials and the need for further high-quality studies. Clinicians considering Fenoldopam as a renoprotective strategy should carefully weigh the potential benefits against risks, considering individual patient factors and institutional experiences. As new evidence emerges, it is likely that future guideline updates will provide more definitive recommendations on the role of Fenoldopam in cardiac surgery-associated AKI prevention and management.

10. Future Directions

Several ongoing clinical trials are investigating various aspects of Fenoldopam use in cardiac surgery. The FINNAKI-FENO trial (NCT04612985) is a large, multicenter, randomized controlled trial evaluating the efficacy of Fenoldopam in preventing AKI in high-risk cardiac surgery patients. Another trial (NCT04434482) is investigating the combination of remote ischemic preconditioning and Fenoldopam for renoprotection in cardiac surgery. This approach may offer synergistic benefits and could potentially overcome some of the limitations of Fenoldopam monotherapy. The KIDNEY-CARE trial (NCT04612998) is exploring the use of a biomarker-guided approach to initiate Fenoldopam therapy in cardiac surgery patients at high risk for AKI. This personalized medicine approach could help identify patients most likely to benefit from Fenoldopam. Future research should also explore optimization of Fenoldopam dosing [5]; combination therapies, investigating the potential synergistic effects of Fenoldopam with other renoprotective agents; extended follow-up, to assess the impact of fenoldopam-mediated renoprotection on chronic kidney disease progression and long-term mortality [50]; genetic factors, [60]; novel delivery methods [61]; biomarker-guided therapy [57]; cost-effectiveness studies [4]; integration with artificial intelligence; non-cardiac surgery applications [62]; and mechanistic studies [23]. As these research directions are pursued, it will be crucial to conduct well-designed, adequately powered studies that address the limitations of previous trials. The future of Fenoldopam in cardiac surgery will likely depend on our ability to identify the right patients, optimize dosing strategies, and potentially combine it with other renoprotective approaches.

11. Conclusions

Fenoldopam, a selective dopamine-1 receptor agonist, has shown potential for renoprotection in cardiac surgery, particularly in high-risk patients, but evidence remains mixed. Safety considerations, primarily related to its vasodilatory effects, necessitate careful patient selection and close hemodynamic monitoring during administration. The role of Fenoldopam in cardiac surgery remains an area of active research and debate. While current evidence suggests potential benefits in certain patient populations, there are still significant gaps in our understanding that need to be addressed. Current guidelines do not strongly endorse routine use of Fenoldopam in cardiac surgery, reflecting the need for more definitive evidence from large-scale clinical trials. Future research directions, including biomarker-guided therapy and combination approaches, may help refine Fenoldopam's role in preventing acute kidney injury. The decision to use Fenoldopam should be made on a case-by-case basis, considering individual patient risk factors, institutional experience, and the latest available evidence, while awaiting results from ongoing clinical trials and further research to fully

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elucidate its optimal use in cardiac surgery. Future research directions should focus on refining the use of Fenoldopam and exploring new avenues for renoprotection in cardiac surgery.

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