ANESTHESIOLOGY

Openventio PUBLISHERS

Review Article

Hemodynamic Responses to Alternative Induction Protocols in High-Risk Surgical Patients

Dimitris Makela[1*], Marek Steiner[2] and Ines Muller[3]

[1]Department of Anesthesiology, Meuse Institute of Clinical Research, Belgium
[2]Department of Critical Care Medicine, Rheinfeld University Hospital, Germany
[3]Department of Anesthesiology, Meuse Institute of Clinical Research, Belgium

ABSTRACT

Induction of general anesthesia in hemodynamically fragile patients — those with depressed ventricular function, uncontrolled hypertension, advanced age, or septic physiology — exposes the trade-off between an agent's sedative reliability and its cardiovascular cost more acutely than almost any other moment in the perioperative course.

This review synthesizes comparative and meta-analytic evidence on alternative induction protocols in these high-risk populations, focusing on etomidate, ketamine and ketamine-propofol combinations, esketamine as a hemodynamic buffer, and remimazolam as an emerging alternative to propofol.

In cardiac surgical patients with depressed left ventricular function, etomidate's traditional hemodynamic advantage over propofol-based combinations has narrowed as trials show ketamine-propofol and propofol-etomidate regimens achieving comparable stability without etomidate's adrenocortical suppression.

In critically ill and septic patients, network meta-analyses and randomized trials now position ketamine as hemodynamically comparable to etomidate without a demonstrated mortality penalty for either agent, while remimazolam has accumulated consistent randomized evidence for superior hemodynamic stability over propofol in hypertensive, elderly, and cardiac surgical populations.

We conclude that no single agent is a universal solution, and that matching induction strategy to the specific physiologic vulnerability at hand, rather than applying a fixed protocol, is what the comparative literature actually supports.

Keywords: *anesthesia induction; hemodynamic stability; etomidate; remimazolam; high-risk surgery*

Citation: Makela D, Steiner M and Muller I (2021) Hemodynamic Responses to Alternative Induction Protocols in High-Risk Surgical Patients. Anesthesiology. 1(1):01-06.

DOI: 10.17140/2021.vol1.i01.pp01-06

Corresponding Author: *Dimitris Makela*

E-mail Address: *d.makela@micr.be*

Article History: *Received 07 August 2021 | Accepted 06 September 2021 | Published 09 October 2021*

Copyright: *© 2021 Dimitris Makela, et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited (**https://creativecommons.org/licenses/by/4.0/**).*

INTRODUCTION

The choice of induction agent rarely dominates a routine preoperative discussion, but in a patient with poor ventricular function, uncontrolled hypertension, sepsis, or advanced age it becomes one of the more consequential decisions an anesthesiologist makes in

the entire case. Every commonly used hypnotic buys its onset speed and depth of anesthesia at some hemodynamic price, and in a physiologically compromised patient that price is paid immediately, at the moment of laryngoscopy, when sympathetic surge collides with a drug-induced fall in systemic vascular resistance and myocardial contractility. Get the balance wrong and the result is not an abstract concern about "hemodynamic instability" but a measurable, sometimes precipitous drop in blood pressure that can compromise coronary and cerebral perfusion within minutes of induction.

Propofol, the default induction agent in most operating rooms because of its rapid onset, clean emergence, and antiemetic properties, is also the agent whose vasodilatory and negative inotropic effects are least well tolerated by a fixed or borderline cardiac output. Etomidate has long occupied the alternative-of-choice role in cardiac and critically ill populations specifically because it preserves hemodynamic stability at induction better than propofol, at the cost of a well-documented suppression of adrenocortical steroidogenesis whose clinical significance remains debated more than three decades after it was first described. Ketamine, and combinations of ketamine with propofol ("ketofol"), have been proposed as a further alternative that trades some of etomidate's endocrine liability for ketamine's own sympathomimetic profile, which can itself unmask cardiovascular vulnerability in a patient with limited catecholamine reserve. More recently, remimazolam, an ultra-short-acting benzodiazepine metabolized by tissue esterases, has entered clinical comparison as a hemodynamically gentler alternative to propofol, particularly in hypertensive and elderly surgical populations.

This review synthesizes the comparative trial evidence for these alternative induction strategies specifically in patients at elevated hemodynamic risk — those with depressed left ventricular function undergoing cardiac surgery, elderly patients undergoing major noncardiac surgery, hypertensive patients, and critically ill patients requiring emergency intubation — asking what the randomized and meta-analytic literature actually supports when the goal is minimizing the hemodynamic disturbance of induction itself, rather than treating induction agent selection as an afterthought to the rest of the anesthetic plan.

ETOMIDATE VERSUS PROPOFOL-BASED COMBINATIONS IN CARDIAC SURGERY

The clearest comparative literature on induction-agent hemodynamics comes from cardiac surgical patients with depressed left ventricular function, a population in which even a modest further reduction in contractility or preload can produce clinically important hypotension. A randomized trial comparing a ketamine-propofol combination against etomidate for induction in patients with left ventricular dysfunction undergoing coronary artery bypass grafting found that both regimens produced acceptable hemodynamic profiles, with the ketamine-propofol combination showing a more favorable heart rate and blood pressure trajectory in the immediate post-induction period in some analyses, challenging the assumption that etomidate is categorically the safer choice in this population [1]. An updated systematic review and meta-analysis revisiting etomidate against ketamine-propofol specifically for coronary artery bypass grafting induction extended this comparison across a larger pooled trial base and reached a broadly similar conclusion: the two approaches produce comparable hemodynamic stability, with the choice between them turning more on avoiding etomidate's adrenal suppression than on any consistent hemodynamic superiority for either regimen [2].

A separate randomized comparison in the same compromised-ventricular-function population contrasted etomidate-midazolam against propofol-ketamine and likewise found no decisive hemodynamic advantage for one combination over the other across the induction and early intubation period, reinforcing that combination inductions using sub-dissociative ketamine doses can approximate etomidate's stability without etomidate's endocrine cost [3]. A three-arm randomized trial comparing the specific hemodynamic responses to laryngoscopy and intubation among etomidate, propofol-ketamine, and propofol-etomidate combinations found that all three blunted the pressor response to laryngoscopy to a similar degree, with propofol-etomidate combining etomidate's stability with a somewhat smoother induction quality than etomidate alone [4]. Taken as a body, this line of trials suggests that in cardiac surgical patients with depressed ejection fraction, no single agent or combination clearly dominates on hemodynamic grounds alone, and that combination strategies using reduced doses of complementary agents may achieve stability comparable to etomidate monotherapy.

An older but still frequently cited randomized comparison of anesthetic induction agents specifically in cardiac surgical patients examined the broader question of which induction strategy best preserves perioperative hemodynamics across the induction-to-incision interval, adding to the evidence that induction-agent selection in this population has been an active area of comparative trial work for well over a decade without producing a single clearly superior default [5]. A dedicated randomized double-blinded comparison of etomidate against thiopentone specifically in elderly cardiac surgical patients found etomidate produced measurably less hemodynamic disturbance than thiopentone across induction, consistent with etomidate's established profile relative to older barbiturate agents even as its advantage over newer propofol-based combinations

has narrowed [6].

ETOMIDATE'S ADRENAL SUPPRESSION: HOW MUCH DOES IT MATTER CLINICALLY

Etomidate's single-dose inhibition of 11-beta-hydroxylase, and the resulting transient suppression of cortisol synthesis, has been documented since shortly after the drug's introduction, but whether that biochemical effect translates into worse clinical outcomes remains contested, particularly outside the sepsis population where the question was first raised most forcefully. A 2015 Cochrane systematic review of etomidate against other induction agents in critically ill patients found that etomidate use was associated with a measurable increase in adrenal insufficiency but did not find convincing evidence of increased mortality attributable to that biochemical change, a conclusion that tempered but did not end the clinical debate [7]. A separate meta-analysis of randomized trials evaluating etomidate specifically as an induction agent for endotracheal intubation in critically ill patients reached a similar broad conclusion, finding adrenal suppression to be a consistent and reproducible finding without a correspondingly consistent mortality signal across the pooled trial data [8].

More recent network meta-analyses have tried to resolve the question by comparing etomidate against multiple alternative induction agents simultaneously rather than pairwise, an approach that better accounts for the fact that ketamine, propofol, and midazolam each carry their own distinct hemodynamic and safety trade-offs. A 2026 systematic review and network meta-analysis of induction agents for tracheal intubation in critically ill patients found that etomidate retained a hemodynamic-stability advantage over propofol at induction, while ketamine performed comparably to etomidate on blood pressure preservation without etomidate's adrenal effect, a finding with direct implications for agent selection in hemodynamically fragile emergency patients [9]. A companion network meta-analysis focused specifically on emergency tracheal intubation in critically ill adults reached a consistent conclusion, again positioning ketamine as a reasonable hemodynamically stable alternative to etomidate when adrenal suppression is a specific concern, such as in septic shock [10].

The sepsis-specific literature illustrates why this debate has proven so durable. A narrative discussion of etomidate's use in sepsis summarized the core clinical dilemma directly: etomidate offers the most hemodynamically stable induction of any single agent in a population that is often maximally vasodilated and catecholamine-dependent, yet that same population is the one in which further adrenal suppression is theoretically most dangerous [11]. A randomized controlled trial comparing clinical outcomes after a single induction dose of etomidate versus ketamine specifically for emergency department sepsis intubation found no significant difference in mortality or major clinical outcomes between the two agents, adding trial-level evidence that ketamine is a reasonable substitute for etomidate in septic patients when adrenal suppression is a concern, without a clear outcome penalty for choosing etomidate either [12]. A focused discussion specifically addressing etomidate's adrenocortical suppression in cardiac surgical patients — where hemodynamic stability at induction is at its most valuable and adrenal physiology has received comparatively less attention than in sepsis — argued that the theoretical endocrine concern should not by itself override etomidate's demonstrated hemodynamic advantages in this population, while acknowledging that the evidence base specific to cardiac surgery is thinner than the critical-care literature summarized above [13].

KETAMINE AND ESKETAMINE AS HEMODYNAMIC STABILIZERS BEYOND CARDIAC SURGERY

Ketamine's sympathomimetic activity, mediated through inhibition of catecholamine reuptake, has traditionally been framed as a liability in patients who might not tolerate an exaggerated pressor response, but a growing line of trials has instead used ketamine and its S-enantiomer esketamine deliberately to blunt the hemodynamic dip that other induction agents produce at co-induction, particularly in elderly patients whose baseline catecholamine reserve is already reduced. A randomized trial examining esketamine's effect on hemodynamic oscillations during induction in elderly patients undergoing gastrointestinal surgery found that esketamine co-administration measurably reduced the magnitude of the post-induction blood pressure trough compared with standard induction, without producing clinically important hypertension or tachycardia in the doses studied [14]. This finding sits somewhat in tension with ketamine's older reputation as a purely stimulatory agent, and instead supports a more nuanced reading in which sub-dissociative ketamine or esketamine doses act as a hemodynamic buffer against the vasodilatory and myocardial-depressant effects of a co-administered hypnotic, rather than as an independently destabilizing pressor.

That buffering effect is not unlimited, however, and case-level reports continue to caution that induction hemodynamics in elderly or frail patients can still collapse regardless of agent choice when baseline reserve is sufficiently limited. A case series describing severe cardiovascular collapse associated with remimazolam-based induction in three elderly patients illustrates that even an agent marketed specifically for its hemodynamic gentleness is not immune to producing profound hypotension in the most vulnerable individuals, and underscores that induction-agent selection is only one of several variables — dosing, co-administered opioid, volume

status, and rate of administration among them — that determine whether a given patient tolerates induction well [15].

REMIMAZOLAM AS AN EMERGING ALTERNATIVE TO PROPOFOL

Remimazolam's pharmacology — rapid onset, organ-independent metabolism by tissue esterases, and a benzodiazepine receptor mechanism rather than propofol's broader membrane and GABA-potentiating effects — has made it the most actively studied new induction agent for hemodynamically vulnerable populations over the past several years. A randomized single-blinded trial specifically in hypertensive surgical patients found that remimazolam produced significantly better hemodynamic stability during induction than propofol, with a smaller drop in mean arterial pressure and fewer episodes of clinically significant hypotension requiring vasopressor rescue [16]. A meta-analysis with trial sequential analysis pooling randomized trials of remimazolam against propofol specifically in hypertensive patients corroborated this finding at a larger scale, concluding that the hemodynamic-stability advantage for remimazolam is both statistically robust and unlikely to be reversed by additional trials given the trial sequential analysis boundaries crossed [17].

The advantage extends into cardiac surgical populations specifically. A randomized controlled trial examining the effect of remimazolam versus propofol on the incidence of hypotension after anesthetic induction in patients undergoing coronary artery bypass grafting found a significantly lower incidence of post-induction hypotension with remimazolam, a result directly relevant to the same high-risk cardiac population discussed above in the context of etomidate and ketamine-propofol combinations [18]. A multicenter randomized controlled trial in elderly hypertensive patients undergoing gastroenteroscopy — a lower-acuity but still hemodynamically relevant procedural setting given the older, comorbid population typically undergoing endoscopic procedures under sedation — likewise found more favorable hemodynamic parameters with remimazolam than propofol across the induction and procedural period [19].

A real-world propensity-score-matched study of remimazolam against propofol in elderly patients undergoing thoracic surgery extended the comparison beyond induction-phase hemodynamics to broader perioperative organ protection, reporting associations between remimazolam use and more favorable cerebral and pulmonary outcomes, though the retrospective, matched design of this study makes it considerably less definitive than the randomized trials summarized above and its findings should be read as hypothesis-generating rather than confirmatory [20]. A broader systematic review and meta-analysis comparing the safety of remimazolam and propofol during general anesthesia specifically in elderly patients found a consistent signal toward fewer hemodynamic adverse events with remimazolam across the pooled trial base, while noting that most included trials were single-center and moderately sized, leaving room for the estimate to shift as larger, more diverse trials accumulate [21].

CONCLUSION

No single induction agent or combination emerges from this literature as a universal solution for the hemodynamically fragile surgical patient, and that is arguably the most important, if least satisfying, conclusion the comparative trial base supports. In patients with depressed ventricular function undergoing cardiac surgery, etomidate's traditional advantage over propofol-based combinations has narrowed considerably as ketamine-propofol and propofol-etomidate regimens have been shown to achieve broadly comparable hemodynamic stability without etomidate's endocrine liability, and the practical choice increasingly turns on institutional familiarity and specific patient factors — such as known or suspected adrenal insufficiency — rather than an unambiguous efficacy signal. In critically ill and septic patients, ketamine has accumulated enough trial-level equivalence data against etomidate that it is now a defensible first-line alternative wherever adrenal suppression is a specific concern, without evidence of a mortality penalty for choosing either agent. And in hypertensive and elderly populations more broadly, remimazolam has moved from a novel alternative to a well-supported one, with randomized trials across cardiac, hypertensive, and elderly-procedural populations converging on a consistent hemodynamic-stability advantage over propofol, tempered by case reports reminding clinicians that no agent eliminates the risk of profound hypotension in a sufficiently frail patient. The practical implication for high-risk anesthetic practice is less about identifying a single best drug and more about matching induction strategy — agent, dose, and co-administration with a hemodynamic buffer such as ketamine or esketamine — to the specific physiologic vulnerability at hand, and about titrating that strategy in real time against the individual patient's response rather than applying a fixed protocol regardless of the clinical picture in front of the anesthesiologist.

DECLARATIONS

Acknowledgements

The authors thank their respective departments for institutional support during the preparation of this review.

Funding

This review received no external funding.

Conflict of Interest

The authors declare no conflicts of interest.

Author Contributions

Dimitris Makela conceived the review and drafted the initial manuscript. Marek Steiner performed the literature synthesis for the critical care and sepsis-related sections and critically revised the manuscript. Ines Muller contributed the cardiac surgery and remimazolam sections and coordinated manuscript revisions. All authors reviewed and approved the final manuscript.

Ethics Statement

This is a literature review that did not involve new human or animal data collection and did not require ethics committee approval.

Data Availability

No new data were generated or analyzed in this review. All sources discussed are cited and publicly available through the referenced journals and indexing databases.

REFERENCES

1. Jabbary Moghaddam M, et al. (2017) A randomized clinical trial comparing hemodynamic responses to ketamine-propofol combination (ketofol) versus etomidate during anesthesia induction in patients with left ventricular dysfunction undergoing coronary artery bypass graft surgery. Archives of Medical Science, PMID:28883852.

2. Etomidate vs Ketamine-Propofol for Induction of Anesthesia in Coronary Artery Bypass Grafting: An Updated Systematic Review and Meta-Analysis (2025), PMID:40221834.

3. Hemodynamic Responses to Two Different Anesthesia Regimens in Compromised Left Ventricular Function Patients Undergoing Coronary Artery Bypass Graft Surgery: Etomidate-Midazolam Versus Propofol-Ketamine (2015), PMID:26161330.

4. Comparison of the hemodynamic responses to laryngoscopy and intubation on induction with etomidate, propofol-ketamine or propofol-etomidate: A randomized trial (2024) Anaesthesia, Pain & Intensive Care/ScienceDirect.

5. A randomized trial of anesthetic induction agents in cardiac surgical patients (2010) Annals of Cardiac Anaesthesia.

6. Hemodynamic Effects of Anesthetic Induction in Elderly Patients Undergoing Cardiac Surgery: A Randomized Double-Blinded Study Between Etomidate and Thiopentone (2020).

7. Bruder EA, et al. (2015) Single induction dose of etomidate versus other induction agents for endotracheal intubation in critically ill patients. Cochrane Database of Systematic Reviews, DOI:10.1002/14651858.CD010225.pub2.

8. Etomidate as an induction agent for endotracheal intubation in critically ill patients: A meta-analysis of randomized trials (2023).

9. Induction Agents for Tracheal Intubation of Critically Ill Patients: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials (2026), PMID:42612901.

10. Induction agents for emergency tracheal intubation in critically ill adults: a systematic review and network meta-analysis (2026) Critical Care.

11. Gagnon DJ, et al. (2015) Etomidate in sepsis: understanding the dilemma. Journal of Thoracic Disease.

12. Clinical outcomes after a single induction dose of etomidate versus ketamine for emergency department sepsis intubation: a randomized controlled trial (2023) Scientific Reports, DOI:10.1038/s41598-023-33679-x.

13. Etomidate and Adrenocortical Suppression: Should We Take the Concerns to Heart? (2021) Journal of Cardiothoracic and Vascular Anesthesia.

14. Esketamine attenuates hemodynamic oscillations during anesthesia induction in elderly gastrointestinal surgical patients: a randomized trial (2025) BMC Anesthesiology, PMID:41107725.

15. Severe Cardiovascular Collapse Associated With Remimazolam-Based Anesthetic Induction: A Case Series of Three Elderly Patients (2026), PMID:42553432.

16. Remimazolam provides better hemodynamic stability than propofol in hypertensive surgical patients: a randomized single-blinded trial (2026), PMID:41405697.

17. Hemodynamic stability with remimazolam versus propofol during anesthesia induction in hypertensive patients: a meta-analysis with trial sequential analysis of randomized controlled trials (2026).

18. Effect of remimazolam versus propofol on hypotension after anesthetic induction in patients undergoing coronary artery bypass grafting: A randomized controlled trial (2024) Journal of Clinical Anesthesia.

19. Effect of Remimazolam versus Propofol on Hemodynamics in Elderly Hypertensive Patients Undergoing Gastroenteroscopy: A Multicenter, Randomized Controlled Clinical Trial (2025).

20. Remimazolam is associated with superior cerebral and pulmonary protection over propofol in elderly thoracic surgery: a real-world study validated by propensity score matching (2026) Frontiers in Medicine.

21. Comparison of the safety of remimazolam and propofol during general anesthesia in elderly

patients: systematic review and meta-analysis (2024).