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REVIEW

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Landiolol in perioperative and critical care: evidence, patient selection, and practical titration for targeted heart rate control: a narrative review

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Abstract

Landiolol enables rapid and titratable heart rate control in perioperative and critically ill patients. In supraventricular tachyarrhythmias and perioperative settings, available studies suggest effective rate control and acceptable hemodynamic tolerance. In sepsis and septic shock with persistent tachycardia, landiolol consistently lowers heart rate without increasing vasopressor requirements; however, randomized evidence does not demonstrate consistent benefits on major clinical outcomes, and current guidelines do not support its routine use. Emerging data on decatecholaminization strategies indicate that combining landiolol with non-adrenergic vasopressors may attenuate catecholamine-related toxicity and improve hemodynamic profiles. Experimental and perioperative studies also suggest potential anti-inflammatory effects through modulation of cytokine release. Overall, current evidence supports landiolol as a potentially useful option for acute heart rate control and selected cases of septic tachycardia. Nevertheless, given the heterogeneity of critically ill populations and the absence of clear outcome benefits in large randomized trials, its use should remain individualized and guided by careful hemodynamic monitoring, with particular attention to appropriate patient selection.

Keywords Landiolol, Supraventricular tachycardia, Atrial fibrillation, Septic shock, Decatecholaminization

Introduction

Landiolol is an ultra-short-acting, highly β_1-selective adrenergic antagonist characterized by rapid and titratable heart rate control. It can be administered via continuous intravenous infusion and its elimination half-life is approximately 3–4 min, allowing near-instantaneous titration and washout of effect [1]. By selectively blocking β_1-adrenergic receptors, landiolol reduces heart rate and prolongs diastolic filling time, thereby improving stroke volume and coronary perfusion with limited impact on vascular tone [2, 3].

In special populations, landiolol exhibits several pharmacokinetic and pharmacodynamic characteristics that guide its clinical use. Because it is primarily

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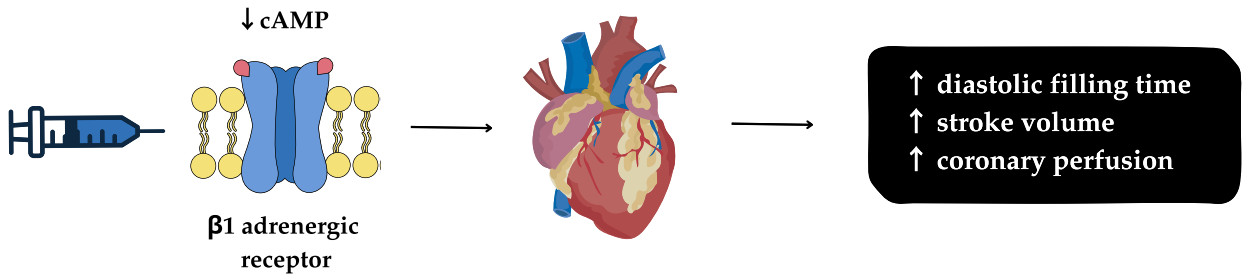

PHARMACOKINETICS PROFILE

- Onset: ~ 1 min
- Half-life: ~ 3-4 min
- Rapid wash-out
- Metabolism: plasma & hepatic esterases
- No relevant accumulation
- No renal adjustment (caution in liver disease)

PHARMACODYNAMICS PROFILE

- β1/β2 selectivity ratio (~255)
- ↓ cAMP → ↓ phase 4 depolarization slope
- Predominant negative chronotropic effect with limited negative inotropy
- Preserved SVR
- Minimal bronchial effect

Fig. 1 Pharmacological profile and mechanism of action of landiolol. Landiolol is a highly β_1-selective, ultra-short-acting adrenergic antagonist that reduces intracellular cyclic AMP (cAMP) following β_1-receptor blockade, leading to a predominant negative chronotropic effect. Its rapid onset, short half-life, and high β_1-selectivity allow precise and titratable heart rate control with limited systemic effects

metabolized by plasma and hepatic esterases, with renal clearance playing only a minor role, available data and clinical experience suggest that no dose adjustment is generally required in patients with renal dysfunction, including those with significant renal impairment or undergoing renal replacement therapy [4]. In contrast, hepatic impairment may influence landiolol exposure: in moderate to severe hepatic impairment (Child–Pugh B–C), higher plasma levels have been observed, which may lead to a more pronounced and prolonged effect. Although landiolol is titrated to clinical response, careful dose titration and close hemodynamic monitoring are warranted in this setting: in fact, the negative inotropic effect of landiolol is not negligible and may become clinically relevant in these patients. In elderly patients, no formal dose adjustment is mandated; however, greater comorbidity burden and an increased sensitivity to β-blockade call for careful, individualized titration [5]. Administration is performed via continuous infusion, preferably through a dedicated line. Loading boluses are generally avoided due to the risk of arterial hypotension or bradycardia (Fig. 1) [6]. Although its negative inotropic effect is relatively mild compared to less selective β-blockers, it may become clinically relevant in preload-dependent states or in patients with impaired ventricular function, requiring cautious use in these settings.

Landiolol use is contraindicated in patients with sinus bradycardia and in those with sick sinus syndrome. Similarly, it is contraindicated in patients with second- or third-degree atrioventricular block in the absence of a functioning pacemaker. Patients with decompensated heart failure not primarily driven by tachyarrhythmia, as well as those in cardiogenic shock, are at particular risk of further hemodynamic deterioration under β-blockade. Significant pulmonary hypertension with a risk of right ventricular failure is another setting in which landiolol is generally avoided, because negative inotropy or chronotropy may precipitate cardiovascular collapse, as the right ventricle has a limited overall reserve and relies predominantly on chronotropic adaptation to maintain cardiac output [6]. Since its initial approval, landiolol has been evaluated across a range of clinical scenarios. In perioperative care, it has been used to blunt adrenergic surges, particularly in cardiovascular and thoracic surgery, where supraventricular tachycardia and new-onset atrial fibrillation can precipitate myocardial ischemia [7]. In the intensive care setting, the principal role of landiolol has emerged in the management of sepsis-associated tachycardia and supraventricular tachyarrhythmias. Multiple studies have reported its efficacy in maintaining heart rate within target ranges (typically 60–90 bpm) without undue arterial hypotension, often outperforming esmolol in terms of hemodynamic stability and ease of titration,

Table 1 Intravenous β-blockers for acute rate control in critical care

Characteristic	Landiolol	Esmolol
Pharmacodynamics	β cardioselectivity β1/β2 ratio 255	β cardioselectivity decreases at higher doses
Onset	1 min	2 min
Half-life	3/4 min	9 min
Dose	Start low 1–5 mcg/kg/min, no routine bolus, titrate every 5–10 min to HR target, continuous infusion is the preferred approach Usual therapeutic range: 1–40 μg/kg/min (The maintenance dose can be increased up to 80 mcg/kg/min for a limited period of time)	25–300 mcg/kg/min (after optional 0.5 mg/kg bolus over 1 min)
Metabolism	Pseudocholinesterase	Pseudocholinesterase
Adverse effects	Rarely arterial hypotension, bradycardia	Arterial hypotension, bradycardia, bronchospasm

Pharmacological comparison of intravenous β-blockers commonly used for acute heart rate control, highlighting differences in pharmacodynamics and pharmacokinetics. Typical starting doses; ranges vary by indication and hemodynamic status

although direct comparative evidence remains limited and heterogeneous [3].

In this narrative review, conducted following the SANRA (Scale for the Assessment of Narrative Review Articles) recommendations to ensure methodological transparency and structured reporting, we performed a targeted search of major biomedical databases (PubMed, Embase, and Cochrane Library) to identify clinically relevant studies on landiolol use in perioperative and critical care settings. The search included combinations of the following keywords: "landiolol," "atrial fibrillation," "supraventricular tachycardia," "sepsis," "septic shock," and "cardiac surgery." Studies were selected based on their clinical relevance, with priority given to randomized controlled trials (RCTs), meta-analyses, systematic reviews, and high-quality observational studies. Given the narrative nature of this review, no formal systematic inclusion or exclusion criteria were applied. Our aim was to examine the recent literature and explore potential future areas of clinical interest, providing an updated, balanced, and clinically oriented overview of landiolol, its pharmacological properties, clinical applications, and emerging evidence across perioperative and critical care settings.

The use of landiolol in clinical practice

In contemporary clinical practice, landiolol is increasingly used as a flexible tool for short-term heart rate control across a range of clinical scenarios [8]. The most consolidated area of use is rapid rate control in atrial fibrillation (AF), particularly when associated with acute or decompensated heart failure and after cardiac surgery [9–11]. Instead, in the intensive care setting, sepsis and septic shock represent another important field of clinical application [12]. The use of landiolol in that context could offer pharmacological profiles that are not interchangeable with other short-acting intravenous β-blockers like esmolol. Landiolol, in fact, displays markedly higher β1-selectivity than esmolol, which translates into a more pronounced cardiac specificity with less engagement of β2-receptors in the bronchial tree and peripheral vasculature. Clinically, this greater selectivity is reflected in potent heart rate reduction with comparatively weaker negative inotropic effects and less interference with peripheral vascular tone. Landiolol's ultra-short half-life and high hydrophilicity provide an additional safety margin. Drug accumulation is minimal, and hemodynamic effects dissipate quickly after dose reduction or infusion discontinuation, which is reassuring when treating unstable patients whose clinical status may abruptly change [13, 14]. Compared with esmolol, landiolol provides effective heart rate reduction with a more favorable hemodynamic profile and fewer episodes of arterial hypotension in several studies, although direct comparative evidence remains heterogeneous (Table 1) [15, 16]. These pharmacological characteristics do not consistently translate into improved patient-centered outcomes, and recent analyses suggest that the overall clinical benefit remains uncertain in some populations [17].

Taken together, the available evidence suggests that landiolol can be used for acute heart rate control across a variety of clinical settings, including emergency, perioperative, cardiac, and intensive care environments.

Landiolol and supraventricular tachycardia

New-onset supraventricular tachyarrhythmia or persistent AF in critically ill patients poses a substantial clinical challenge considering that this phenomenon affects in this setting from 4 to 46% of patients. Rapid ventricular rates with elevated myocardial oxygen demand, in fact, may precipitate ischemia and hemodynamic

compromise [2]. The European Society of Cardiology (ESC) 2024 guidelines recommend that in patients with acute hemodynamic instability—defined by the presence of shock, symptomatic arterial hypotension, pulmonary edema, or ongoing myocardial ischemia—the primary therapeutic goal is rapid restoration of sinus rhythm, typically by urgent electrical cardioversion. In contrast, in hemodynamically stable but symptomatic patients, management focuses on improving hemodynamic status through either rate-control or rhythm-control strategies [18, 19]. In critically ill patients, however, clinicians frequently encounter situations characterized by relative hemodynamic vulnerability, such as vasoplegia requiring vasopressor support or severely impaired left ventricular function, without fulfilling strict criteria for immediate cardioversion. In this context, the rapid onset and high β_1-selectivity of landiolol may represent a useful option (class IIb, level B), allowing precise ventricular rate control with minimal effects on arterial pressure and myocardial contractility [18]. In such settings, landiolol has been shown to effectively reduce heart rate while maintaining a low incidence of arterial hypotension and bradycardia compared with other β-blockers. Continuous infusion, with or without an initial loading bolus, has been shown to be effective. However, bolus administration should be used with caution due to the potential risk of abrupt arterial hypotension or bradycardia. In clinical practice, continuous infusion is generally preferred: landiolol is typically initiated at low doses (e.g., 1–5 μg/kg/min) and titrated stepwise according to heart rate and hemodynamic response, up to 40 μg/kg/min if needed [14, 20, 21]. Several recent studies have investigated the efficacy and safety of landiolol. The landmark multicenter randomized J-Land 3S trial demonstrated that landiolol achieved target heart rates (60–94 bpm) significantly faster than amiodarone (median time 1 h vs. 6 h, $p < 0.01$), with fewer episodes of severe arterial hypotension (3% vs. 12%, $p = 0.02$) and without negatively impacting left ventricular ejection fraction, as confirmed by serial echocardiography assessments even in patients with heart failure with reduced ejection fraction (HFrEF) [1, 2]. Consistent with these findings, a systematic review of studies evaluating landiolol in critically ill patients with new-onset AF reported sinus rhythm restoration in approximately two-thirds to three-quarters of patients, often occurring within the first hours after treatment initiation. These findings suggest that landiolol may facilitate the spontaneous conversion of AF following effective rate control, while maintaining a favorable hemodynamic profile [19]. Meta-analyses suggest effective rate control with a favorable safety profile, although improvements in major clinical outcomes remain unproven [22, 23]. In line with these findings, a retrospective propensity score–matched case–control study by Si et al. compared landiolol and esmolol in critically ill patients and found that landiolol reduced the average heart rate over the first 72 h of infusion more than esmolol, better preserved hemodynamic profile, and was associated with shorter overall hospital and ICU stays [16]. From a health economics perspective, an analysis by Walter et al. showed that landiolol reduced ICU pharmacy costs per AF episode due to shorter infusion durations and fewer associated complications [24]. Nevertheless, in the absence of consistent improvements in patient-centered outcomes, economic considerations alone are insufficient to support broader implementation. Additionally, landiolol's rapid heart rate control and superior hemodynamic preservation may help achieve heart rate control and hemodynamic stabilization prior to planned electrical cardioversion [25].

The Italian Society of Anesthesia, Analgesia, Resuscitation and Intensive Care (SIAARTI) 2023 expert consensus on β-blocker use in critically ill patients suggests that intravenous β_1-selective agents such as landiolol may be considered for heart rate control in critically ill patients with persistent tachyarrhythmias, provided that hypovolemia and reversible causes of tachycardia have been corrected and that close hemodynamic monitoring is ensured. In patients with AF and frank hemodynamic instability, however, synchronized electrical cardioversion remains the first-line therapy [7]. In a recent post hoc analysis of 30 critically ill patients with sudden-onset supraventricular tachycardia, prior chronic oral β-blocker therapy did not attenuate the response to an intravenous bolus of landiolol. Rates of successful rate control (35–40%) and rhythm conversion (approximately 30%) appear modest and indicate that landiolol may be ineffective in a substantial proportion of patients. These findings should be interpreted in the context of critically ill populations, in whom arrhythmias are multifactorial and rhythm control is not always the primary therapeutic objective [26] (Fig. 2).

Also in the pediatric population, the use of landiolol has been explored mainly in ICU and perioperative settings, particularly in patients with congenital heart disease and supraventricular tachyarrhythmias. Available evidence remains limited and is derived from small studies and clinical trials. A monocentric study reported effective heart rate control or rhythm conversion in most cases without major adverse events, while the multicenter HEARTFUL study confirmed efficacy in children with impaired cardiac function, although arterial hypotension remained the main adverse effect [27, 28]. Similarly, the European LANDI-PED trial showed that continuous infusion with titration achieved clinically relevant heart rate control in approximately half of patients, with a low incidence of arterial hypotension [29]. In pediatric

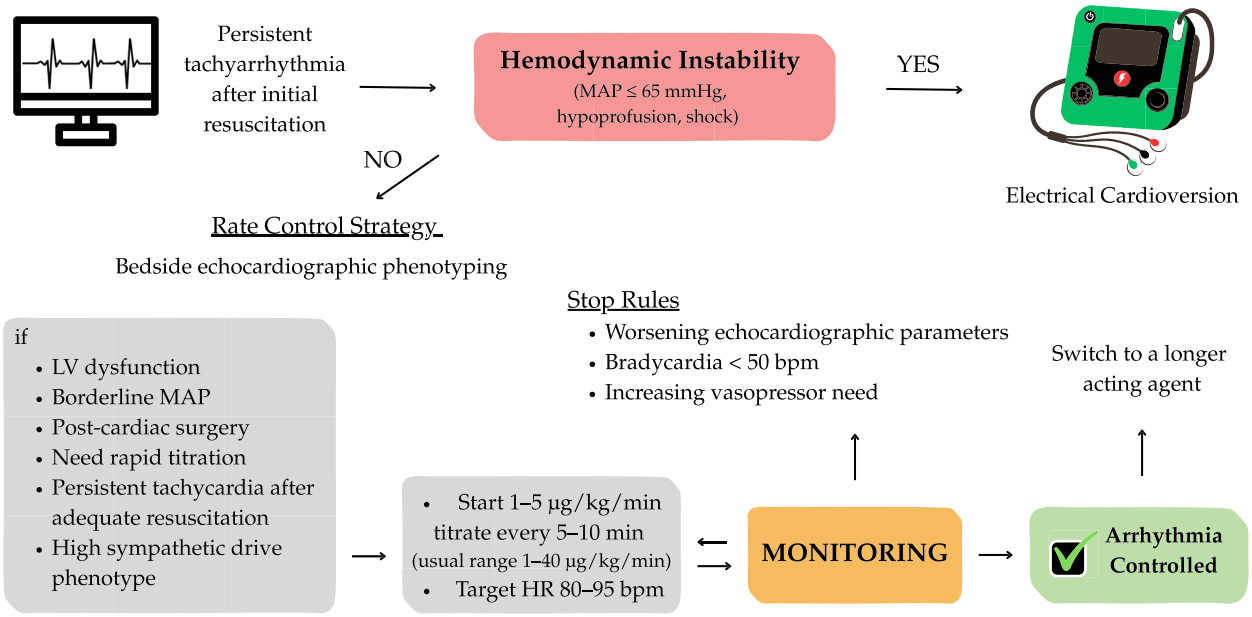

Fig. 2 Proposed expert-based algorithm for landiolol use in critically ill patients with tachyarrhythmia. Assess hemodynamic stability in patients with new-onset supraventricular tachyarrhythmia. Unstable patients require urgent electrical cardioversion. In stable patients, consider rate control after bedside echocardiographic phenotyping and adequate resuscitation. Landiolol may be used in selected cases (e.g., LV dysfunction, borderline MAP, post-cardiac surgery, need for rapid titration) under continuous invasive monitoring (continuous arterial blood pressure monitoring, minimally invasive or invasive cardiac output/stroke volume monitoring). Discontinue if worsening of echocardiographic parameters, bradycardia, or increasing vasopressor requirements occur. If effective, consider gradual weaning or transition to longer-acting agents

cardiac surgery, emerging data, including the LANDI-cardioPed study, suggest that landiolol may be useful for intra and postoperative heart rate control, improving hemodynamic parameters without clear evidence of intolerance [30]. Additional reports in postoperative junctional ectopic tachycardia suggest a potential benefit of combining landiolol with amiodarone, although with a non-negligible risk of arterial hypotension in more fragile patients [31]. However, the overall evidence remains limited and heterogeneous, and no firm conclusions can be drawn regarding its impact on clinical outcomes.

Although supported by RCTs and meta-analyses showing heart rate control with low hypotension risk even in patients with compromised left ventricular ejection fraction (LVEF) or chronic β-blocker therapy, landiolol lacks definitive evidence for reducing mortality, organ failure, ICU stays, or costs, positioning it as a safe and effective pharmacological option rather than first-line therapy pending larger confirmatory trials.

Landiolol evidence on sepsis-associated tachycardia

Persistent tachycardia in sepsis is an independent predictor of mortality [32]. It may result from two primary mechanisms: a compensatory increase in heart rate due to low stroke volume (SV), or an excessive or dysregulated sympathetic response, which may be associated with arrhythmias. In the early phase of septic shock, uncontrolled inflammation causes vasodilation, absolute and relative hypovolemia, and a consequent reduction in cardiac output (CO), which is initially compensated for by an increase in heart rate (HR). High catecholamine doses, essential for reversing vasoplegia and maintaining perfusion in septic shock, are linked to negative cardiac, immunologic, and metabolic effects, including tachyarrhythmias, increased myocardial oxygen consumption, and potential direct cardiac injury. Tachycardia itself, especially after initial resuscitation, is frequently a marker of unresolved sympathetic stress/imbalance and is independently associated with poor outcome particularly in patients with either hyperdynamic (high LVEF) or severely depressed left ventricular function [33]. Distinguishing treatable from compensatory tachycardia is crucial in septic patients, as blunting compensatory tachycardia in early/distributive shock—where it maintains cardiac output—may precipitate hemodynamic collapse due to β-blockade. Early evidence from Morelli et al. showed esmolol safely reduced HR and improved 28-day survival in resuscitated septic shock (20% vs. 40%), but significant limitations—including single-center design, lack of blinding, non-standard care practices, and underpowering for mortality—preclude definitive conclusions and highlight the need for larger confirmatory trials [32].

Table 2 Guideline comparison for β-blockers in septic shock

Key aspect	SSC (2026)	JSG (2024)
Recommendation	Not recommend routine use of β-blockers in septic shock due to low certainty evidence	Suggested
Evidence level	Very low	Weak (grade 2C)
Suggested drugs	–	Esmolol, landiolol
Timing	Not routinely recommended	After adequate initial resuscitation
Recommended heart rate target	Not specified	Individualized (80–94 bpm)
Precautions	–	Avoid if hypoperfusion Careful titration Discontinue if MAP decreases

Summary of current sepsis guidelines regarding the use of β-blockers

In this context, landiolol may help optimize the relationship between heart rate and contractile performance, thereby reducing myocardial oxygen consumption [7]. The J-Land 3S randomized open-label trial enrolled 151 adult septic patients with persistent tachycardia despite fluid optimization and vasopressor support. Compared with standard care, landiolol infusion increased the proportion of patients achieving target heart rates (60–94 bpm) at 24 h (55% vs. 33%, $p=0.003$). No increase in vasopressor requirements or arterial hypotension was observed (1). A predefined subgroup analysis suggested trends toward reduced 28-day mortality among those achieving heart rate control, although the study was not powered for mortality endpoints (2). Building on these results, the LANDI-SEP trial randomized 200 septic shock patients across 20 European ICUs to landiolol versus usual care. At 24 h, 40% of the landiolol group met heart rate goals versus 23.5% of controls ($p=0.013$), and vasopressor requirements remained stable. Importantly, no significant differences emerged in 28-day or 90-day mortality (49% vs. 47% at 28 days, $p=0.67$), nor in organ-failure–free days, reinforcing landiolol's safety but leaving its impact on hard outcomes unresolved (3). Overall, although landiolol has been shown to reduce heart rate in septic patients, current randomized evidence does not demonstrate a consistent benefit on major patient-centered outcomes, including mortality and organ-failure–free days [34]. Therefore, its use in this setting should be considered exploratory and hypothesis-generating rather than standard of care.

In contrast, the STRESS-L trial in the UK was halted early due to a non-significant trend toward higher mortality in landiolol recipients with high vasopressor dependencies (90-day mortality 43.5% vs. 28.6%, $p=0.08$), prompting caution in patients with severe vasoplegia [35]. A very recent meta-analysis by Sato et al. found no statistically significant reduction in mortality with ultra-short-acting β-blockers (esmolol or landiolol) versus standard therapy [36]. International guidelines remain cautious: the Surviving Sepsis Campaign (SSC) 2026 does not recommend the routine use of β-blockers in septic shock, reflecting the lack of consistent evidence on clinically relevant outcomes [37]. Instead the Japanese Sepsis Guidelines (updated 2024) provide a weak recommendation to consider β_1-blockade for persistent septic tachycardia in individualized, closely supervised and well-resuscitated patients under invasive hemodynamic monitoring (Table 2) [38].

An expert editorial by De Backer and Chen on the use of beta-blockers in sepsis concludes that careful patient phenotyping is crucial. Beta-blockers may benefit only a specific subset of patients, namely those with hyperkinetic left ventricular function and left ventricular outflow tract obstruction, whereas they are contraindicated in patients with left or right ventricular dysfunction or in unselected septic populations. Consequently, echocardiography should be performed to identify candidates who might benefit from beta-blockade, and, when these agents are used, the dose should be titrated cautiously with close hemodynamic monitoring (Table 3, Fig. 3) [33]. However, this echocardiography-guided approach is currently based on physiological rationale and expert opinion, and has not yet been prospectively validated in controlled clinical trials.

Landiolol effectively controls persistent tachycardia in sepsis but fails to demonstrate consistent mortality benefit across major RCTs. Current evidence supports its safety profile in well-resuscitated patients, yet optimal patient selection through hemodynamic phenotyping (echocardiography-guided) and cautious titration under invasive monitoring remain critical. In this context, the absence of consistent outcome benefit, together with the signal of possible harm in selected patients, supports a highly selective and individualized approach.

In contrast to landiolol, ivabradine—a highly selective inhibitor of the sinoatrial node's pacemaker

Table 3 Proposed expert-based echo-guided classification of patients who might benefit from beta-blockade

Phenotype	Echo findings	Landiolol suitability	Rationale
Hyperkinetic LV	LVEF > 55%, LVOT VTI > 20 cm	Potential suitability (start low dose)	Reduces O2 demand, improves diastolic filling
Depressed LV	LVEF < 40%, VTI < 15 cm	Use with caution	Negative chronotropy/inotropy effect
RV dysfunction	RV dilated, TAPSE < 17 mm, PA pressure > 35 mmHg	Not recommended	Risks RV collapse despite mild negative effects
Hypovolemic/early shock	Small cavities, IVC < 1 cm, lactate ↑	Not recommended	Compensatory HR

Proposed expert-based echo-guided classification with key parameters' suitability and rationale. *LVEF* left ventricular ejection fraction, *LVOT VTI* left ventricular outflow tract velocity-time integral, *TAPSE* tricuspid annular plane systolic excursion, *PA* pulmonary artery, *IVC* inferior vena cava

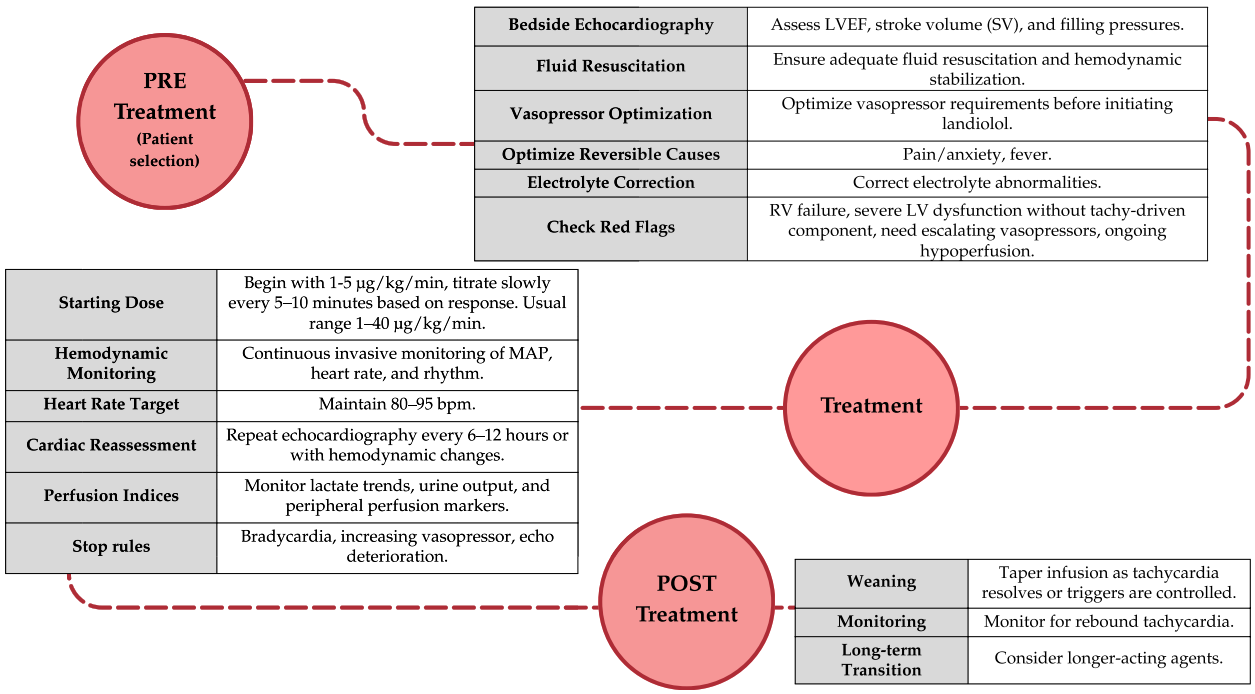

Fig. 3 Proposed expert-based practical algorithm for landiolol use in septic shock patients. Expert-based practical algorithm for landiolol initiation, titration, and discontinuation in critically ill patients. LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; SV, stroke volume

current—reduces heart rate without additional negative inotropy and may thus find a role in septic shock management. Small randomized trials and a recent systematic review suggest that ivabradine safely achieves comparable or greater heart rate reduction in septic shock while preserving or even improving stroke volume, ejection fraction, and lactate clearance, without increasing vasopressor requirements or mortality—particularly in tachycardic phenotypes with impaired or borderline ventricular function, where further β-blockade may be poorly tolerated. Nevertheless, ivabradine remains a mechanistically attractive but still investigational alternative or complement to landiolol, pending adequately powered, outcome-driven trials [39–41].

Landiolol as part of catecholamine-sparing strategies combining β1-blockade with non-adrenergic vasopressors

High-dose vasopressors are essential for reversing vasoplegia in septic shock, yet prolonged exposure carries serious adverse consequences, including myocardial stunning, increased myocardial oxygen consumption, immunologic suppression, coagulopathy, and arrhythmias. In recent years, the literature has described decatecholaminization as a strategy to reduce both endogenous and exogenous adrenergic stimulation in septic shock, recognizing that while early sympathetic activation supports hemodynamic compensation, prolonged catecholamine excess significantly contributes to organ dysfunction, tachycardia, myocardial injury,

and poor outcomes [42]. More broadly, decatecholaminization refers to a comprehensive hemodynamic strategy that includes individualized mean arterial pressure targets, a tissue perfusion–oriented approach, and the use of non-adrenergic vasopressors and inotropes, with β-blockade representing only one component of this approach [43]. A recent Italian health economics analysis demonstrated cost benefits when decatecholaminization, combining vasopressin and landiolol, is systematically implemented in septic shock management [44]. Landiolol may contribute by reducing compensatory tachycardia without causing prolonged hemodynamic depression. In theory, this may attenuate sympathetic overactivation, facilitate heart rate control without increasing vasopressor requirements, and support earlier vasopressor weaning during recovery [3, 35, 43]. This translates into reduced heart rate and lower myocardial VO_2 demand, preserved contractility, blunted inflammatory response, reduced arrhythmia risk from lowered sympathetic tone, and improved coronary perfusion through longer diastole that enhances ventricular filling and coronary blood flow.

Despite its theoretical appeal, decatecholaminization extends beyond β-blockade and should not be equated with landiolol use alone, while clinical evidence remains inconsistent. The lack of mortality benefit in recent trials, despite catecholamine-sparing effects, likely reflects significant phenotypic heterogeneity. This strategy is not limited to hyperkinetic patients with preserved LVEF, but its impact may differ across clinical profiles, potentially benefiting selected patients while being harmful in those with impaired contractility. Moreover, treatment effects appear time-dependent, with a possible therapeutic window after initial hemodynamic stabilization and before advanced organ dysfunction. Compensatory physiological mechanisms may further attenuate clinical benefits [3, 45]. Overall, in the absence of clear outcome advantages, decatecholaminization should be considered hypothesis-generating and restricted to selected phenotypes, pending results from ongoing RCTs.

Cardiac surgery and transplant settings

Landiolol has been used as an option in cardiac surgery due to its rapid onset/offset, high β_1-selectivity, and favorable hemodynamic profile, making it suitable in the immediate post-cardiopulmonary bypass and early ICU phases, when myocardial vulnerability and hemodynamic instability are prominent [46]. Its role is best established in the prevention of postoperative atrial fibrillation (POAF), with RCTs showing that low-dose continuous infusions (0.5–10 μg/kg/min), initiated intraoperatively or early after ICU admission, reduce POAF incidence without increasing adverse events such as arterial hypotension, bradycardia, pacing requirement, or heart failure [47, 48]. Beyond prophylaxis, landiolol is also used for acute management of post-cardiac-surgery FA and other tachyarrhythmias, providing effective rate control and facilitating sinus rhythm restoration in observational studies [11, 46]. Outside cardiac surgery, its use may be considered in selected cases of POAF after major non-cardiac procedures (e.g., thoracic or esophageal surgery), although evidence remains heterogeneous and insufficient to support routine application [46]. Tight heart rate control may also confer myocardial protection by reducing oxygen demand and improving the supply–demand balance [47, 48].

In solid organ transplantation, evidence is limited to case reports and small series. Landiolol's short half-life and titratability may be advantageous in highly dynamic perioperative settings, with reported use during liver transplantation, in ICU management of supraventricular arrhythmias, and in advanced heart failure patients awaiting transplantation, often combined with inotropes to preserve perfusion [49]. However, in the absence of randomized data, its impact on graft function or survival remains unclear, and its use should be considered exploratory rather than a standard indication.

Immunomodulatory signals: experimental and perioperative data

Most evidence supporting the immunomodulatory effects of landiolol derives from experimental studies and small perioperative investigations, and should therefore be interpreted with caution when extrapolated to critically ill populations. Experimental and mechanistic data suggested that landiolol may exert significant anti-inflammatory actions, particularly in critically ill and septic patients, through modulation of the complex bidirectional crosstalk between the adrenergic and immune systems. In sepsis, sustained sympathetic activation and high circulating catecholamine levels promote a dysregulated immune response by directly influencing immune-cell function via β-adrenergic receptors expressed on monocytes, macrophages, lymphocytes, and endothelial cells. Excessive adrenergic stimulation has been shown to amplify pro-inflammatory cytokine release in the early hyperinflammatory phase, while paradoxically contributing to immune exhaustion and immunoparalysis in later stages [50, 51]. Several mechanisms have been proposed to explain landiolol's anti-inflammatory effects, predominantly related to modulation of adrenergic-mediated cytokine release and attenuation of stress-induced inflammatory cascades. These include attenuation of catecholamine-driven cytokine production, partial restoration of autonomic balance, and modulation of intracellular inflammatory signaling pathways [12, 52].

Clinical evidence, however, remains limited. Small studies and perioperative trials have reported reductions in circulating inflammatory mediators. For instance, Wada et al. demonstrated that landiolol infusion significantly decreased circulating inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), within just 6 h of initiation compared to standard therapy. This rapid modulation suggests a direct impact of β_1-blockade on inflammatory mediator release independent from the heart-rate-lowering effect [53]. The PASCAL trial showed that patients receiving landiolol during cardiac surgery had significantly lower levels of inflammatory mediators and ischemic biomarkers, suggesting that sympathetic inhibition blunts the inflammatory cascade triggered by surgical trauma and cardiopulmonary bypass [54]. These findings align with experimental studies demonstrating β_1-selective blockade's capacity to downregulate the expression of pro-inflammatory cytokines and inhibit nuclear factor in the inflammation cascade [53]. In this context, the potential anti-inflammatory effects observed with landiolol are unlikely to result from direct immune-cell interaction. A more plausible explanation is that these effects are indirect and mediated through modulation of sympathetic activity and catecholamine exposure [55].

Despite these anti-inflammatory effects observed in animal models and perioperative studies, the anti-inflammatory actions of landiolol in humans remain insufficiently defined, and their true impact on hard clinical endpoints like short/medium-term mortality, organ-failure-free days, or other patient-centered outcomes is unclear. Accordingly, biomarker-level immunomodulation has not yet translated into demonstrable clinical benefit, highlighting the need for studies integrating immunologic and autonomic phenotyping with clinically relevant outcomes.

Conclusions

Landiolol represents a novel therapeutic option for precise heart rate control in critical care and perioperative medicine, owing to its ultra-short half-life and remarkable β_1-selectivity. It has shown efficacy across different scenarios, including perioperative management, septic shock, supraventricular tachyarrhythmias, and acute atrial fibrillation. Current data support its effectiveness for rate control, along with potential benefits in ICU resource utilization; however, robust health-economic analyses remain scarce, and no clear mortality advantage has been demonstrated, particularly in patients with severe vasoplegia or significant ventricular dysfunction. Consequently, landiolol should be considered a valuable but selective tool rather than a therapy for broad use in unselected critically ill populations.

Abbreviations

AF	Atrial fibrillation
cAMP	Cyclic AMP
CO	Cardiac output
ESC	European Society of Cardiology
HFrEF	Heart failure with reduced ejection fraction
HR	Heart rate
ICU	Intensive care unit
LVEF	Left ventricular ejection fraction
POAF	Postoperative atrial fibrillation
RCT	Randomized controlled trial
SIAARTI	Italian Society of Anesthesia, Analgesia, Resuscitation and Intensive Care
SSC	Surviving Sepsis Campaign
SV	Stroke volume
SVT	Supraventricular tachycardia
TNF	Tumor necrosis factor

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
CB and GC contributed equally to this study. CB and SS made substantial contributions to the conception of the manuscript. CB, GC made contributions to writing the manuscript. CB produced the tables and the figures. CA, BB, DM, FA and LS revised it critically. FF, GP, FST and SS supervised and revised the manuscript critically. All authors have read and agreed to the published version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
FA served as an advisor for AOP Pharma, which is developing products related to the research reported in this article. CB, FF and SS received speaker honoraria from AOP Pharma for a clinical case presentation. Other authors declare no competing interests.

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