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Intravenous Landiolol for Rate Control in Supraventricular Tachyarrhythmias in Patients with Left Ventricular Dysfunction: A Systematic Review and Meta-Analysis

A systematic review investigating landiolol's efficacy in non-septic or post-operated SVT patients with concomitant left ventricular dysfunction.

Managing Supraventricular Tachyarrhythmias in Heart Failure: Landiolol's Role

The coexistence of heart failure (HF) and supraventricular tachyarrhythmias (SVT) exacerbates the clinical manifestation of one another, leading to worsened cardiac function and deteriorated haemodynamic status. Atrial fibrillation (AF), the predominant SVT in HF patients, contributes to tachycardia-induced cardiomyopathy, while HF results in atrial dilatation and fibrosis. This synergy increases the risk of cardiovascular death or hospitalisation compared to HF patients maintaining sinus rhythm (Mogensen et al. 2017).

In haemodynamically unstable AF cases, rhythm control is the preferred strategy, while rate control can be considered as the initial approach in stable patients. Beta-blockers are endorsed by European Society of Cardiology guidelines for rate control in heart failure with reduced ejection fraction (HFrEF) and mildly reduced ejection fraction (HFmEF). Digoxin may be used supplementary to beta-blockers in cases of persistent high ventricular rate or in the presence of contraindication to beta-blockers. Adequate rate control is a resting heart rate of ≤110 bpm, while lower targets (<80 bpm) and sinus rhythm restoration can also be aimed for if necessary (McDonagh et al. 2021).

Landiolol, an ultra-short-acting beta-1 blocker with the highest cardio selectivity (β1/β2 selectivity ≈ 255), offers rapid and precise heart rate reduction without significant blood pressure fluctuations. Its swift onset and offset make it suitable for acute management in critical conditions, including post-operative care, intensive care, and acute decompensated HF, showing promising outcomes. This systematic review investigated landiolol's efficacy in non-septic or post-operated SVT patients with concomitant left ventricular dysfunction.

Materials and Methods

The study, registered in PROSPERO (ID: CRD42023448712), adheres to the PRISMA guidelines. A systematic search of PubMed, Cochrane, Web of Science, and Scopus databases was conducted until July 14, 2023, using solely the term "landiolol". Additionally, the reference lists of all included studies were manually searched for further relevant articles.

Inclusion criteria covered adult SVT patients with left ventricular dysfunction, excluding septic or peri-operative cases. Exclusion criteria comprised case reports, paediatric studies, and non-English publications. Two independent investigators reviewed titles, abstracts, and full texts of potentially relevant papers, resolving discrepancies through consensus or consultation with a third author.

Data extraction involved gathering study details, population characteristics, follow-up duration, outcomes, and confounding factors. The primary outcome was targeted heart rate achievement (≥20% reduction from the initial heart rate AND final heart rate <110 bpm), while secondary outcomes included sinus rhythm restoration and adverse events or symptoms leading to drug discontinuation. Other parameters included were comorbidities (diabetes mellitus, hypertension, valvular heart disease, coronary artery disease), NYHA classification, prior medication, percentage reductions in heart rate and blood pressure, demographics, and pre-and post-treatment values of relevant cardiac parameters.

Quality assessment utilised the Newcastle-Ottawa Scale for cohort studies and the Cochrane Risk of Bias tool for randomised controlled trials.

Statistical analysis pooled data on target heart rate achievement, sinus rhythm restoration, and adverse events for landiolol-treated and non-landiolol-treated groups. Dichotomous outcomes were analysed via random effects meta-analysis to generate pooled odds ratios with 95% confidence intervals. Continuous outcomes were analysed similarly to pool mean differences. Heterogeneity was assessed using I2 statistic. Meta-regression wasn't possible due to limited studies. Publication bias was visually assessed with funnel plots. Analysis was conducted using Review Manager, Version 5.4., 2020, with significance set at $p < 0.05$.

Results: Efficacy and Safety of Landiolol

Out of 2304 initially retrieved articles, 15 studies met the eligibility criteria for the systematic review, with 11 included in the meta-analysis. Four studies compared landiolol to other antiarrhythmic

drugs (Nagai et al. 2013; Shinohara et al. 2020; Kimura et al. 2016; Kiuchi et al. 2017), while seven studies were single-arm (Adachi et al. 2014; Wada et al. 2016; Matsui et al. 2019; Oka et al. 2019; Kijima et al. 2017; Sakai et al. 2019; Iwahashi et al. 2019). Quality assessment of the aforementioned studies indicated a low risk of bias. A total of 1674 patients were included.

Landiolol's therapeutic impact was evident in its ability to significantly reduce heart rate, with a mean decrease of 42 bpm, a statistically significant finding ($p < 0.01$). Additionally, 75% of patients achieved the targeted heart rate, reflecting the robust effectiveness of landiolol in heart rate control. In comparison to alternative therapies, landiolol exhibited a pronounced superiority, with a pooled odds ratio of 5.37 ($p < 0.01$), underscoring its efficacy in heart rate management.

No discernible difference in sinus rhythm restoration was observed between landiolol-treated and non-landiolol-treated cohorts. Adverse events were reported in 14.7% of landiolol-administered patients, primarily attributed to dose-dependent blood pressure reduction. Notably, only a minor proportion (6%) necessitated landiolol discontinuation, with no supplemental interventions required to counteract blood pressure effects.

The rates of adverse events and drug discontinuation did not significantly differ between landiolol and other antiarrhythmic therapies, indicating a comparable safety profile. This favourable safety profile further enhances the appeal of landiolol as a therapeutic option for supraventricular tachyarrhythmias.

"landiolol's efficacy in managing tachyarrhythmias extends to diverse clinical scenarios, including acute decompensated heart failure, ventricular arrhythmias, septic and ICU patients"

Conclusion

In this meta-analysis, landiolol treatment resulted in significant heart rate reduction and achieved targeted heart rate in 75% of SVT patients with concurrent left ventricular dysfunction. In comparison with other antiarrhythmic medications (digoxin and diltiazem), landiolol showed superior effectiveness in targeted heart rate achievement, while there was no difference in sinus rhythm restoration. Landiolol demonstrated good tolerability, with only 6% of patients requiring drug discontinuation, mainly due to hypotension. Landiolol's efficacy in managing tachyarrhythmias extends to diverse clinical scenarios, including acute decompensated heart failure, ventricular arrhythmias, septic and ICU patients. While further randomised controlled trials (RCTs) are needed to establish its superiority in sinus rhythm conversion over other antiarrhythmic drugs, landiolol presents a superior option for heart rate management in heart failure patients, with favourable safety profile. These findings support its use as a viable treatment option in clinical practice, particularly in cases where other antiarrhythmic therapies may be contraindicated or poorly tolerated.

Disclaimer

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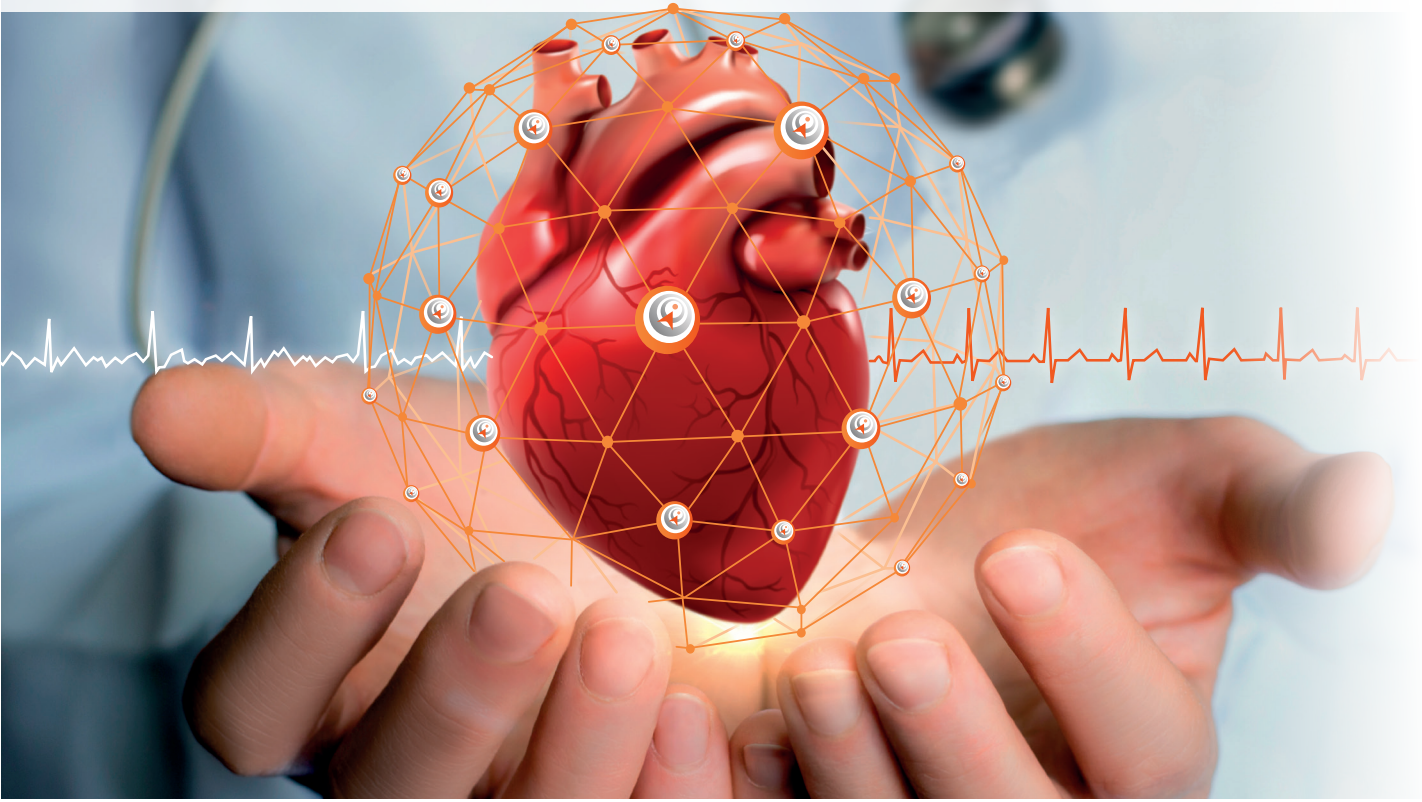

Rapid control of ventricular rate in patients with SVTs and AF[1]

First-line for patients with cardiac dysfunction[2]

- **Limited effect** on blood pressure and inotropy[3]
- **Favourable safety profile for patients with renal and hepatic comorbidities** due to inactive metabolites and hydrolysis by plasma esterases[1,4]
- **Compatible with pulmonary disorder patients** due to highest cardioselectivity (β1/β2-selectivity = 255:1) among β1-blockers[5]
- **Limited rebound and tolerance effect** due to lack of pharmacochaperoning activity[6]

Rapibloc® 300 mg: Rapibloc® 300 mg powder for solution for infusion. **Composition:** A vial of 50 mL contains 300 mg landiolol hydrochloride which is equivalent to 280 mg landiolol. After reconstitution each mL contains 6 mg landiolol hydrochloride (6 mg/mL). Excipients with known effect: Mannitol E421, sodium hydroxide (for pH adjustment). **Therapeutic Indication:** Landiolol hydrochloride is indicated for supraventricular tachycardia and for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other circumstances where short-term control of the ventricular rate with a short acting agent is desirable. Landiolol hydrochloride is also indicated for non-compensatory sinus tachycardia where, in the physician's judgment the rapid heart rate requires specific intervention. Landiolol is not intended for use in chronic settings. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients, severe bradycardia (less than 50 beats per minute), sick sinus syndrome, severe atrioventricular (AV) nodal conductance disorders (without pacemaker): 2nd or 3rd degree AV block, cardiogenic shock, severe hypotension, decompensated heart failure when considered not related to the arrhythmia, pulmonary hypertension, non-treated phaeochromocytoma, acute asthmatic attack, severe, uncorrectable metabolic acidosis. For further information on warnings and precautions for use, interaction with other medicinal products and other forms of interaction, fertility, pregnancy, lactation, effects on ability to drive and use machines, unsiderable effects, and habituation effects, please refer to the published SmPC **Prescription only/available only from pharmacy. Date of revision of the text:** 09/2021. **Marketing authorization holder:** Amomed Pharma GmbH, Leopold-Ungar-Platz 2, 1190 Vienna, Austria

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