ICU

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Evidence-Based Management of Atrial Fibrillation

The 2020 ESC Guidelines and the addition of Landiolol

An overview of the updated guidelines for the diagnosis and management of atrial fibrillation, developed in association with the European Association for Cardio-Thoracic Surgery.

The European Society of Cardiology (ESC) provides a range of scientific and educational activities, such as the production and continuous updating of clinical practice guidelines for the diagnosis and treatment of cardiovascular diseases. In 2020, the ESC published new updated guidelines for the diagnosis and management of atrial fibrillation (AF), developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS) (Hindricks et al. 2020).

Rate control is an integral part of AF management and is often sufficient to improve AF-related symptoms. In these guidelines, beta-blockers are recommended as first-choice drugs to control heart rate in AF patients with left ventricular ejection fraction (LVEF) ≥40% or LVEF<40% (Class I, LoE*B) (Hindricks et al. 2020). **For the first time landiolol is included in these important guidelines. Landiolol is included as the only agent with a specific dose recommendation in patients with cardiac dysfunction (dosages of 1 µg/kg/min up to 10 µg/kg/min)** (Hindricks et al. 2020). On the other hand, intravenous amiodarone may be considered in patients with haemodynamic instability or severely depressed LVEF, for acute control of heart rate nevertheless with a lower Class of Recommendation (Class IIb, LoE B) (Hindricks et al. 2020).

Landiolol is a new ultra-short acting (T1/2=4min), intravenous, most β1 selective blocker, for the treatment of supraventricular tachyarrhythmias such as AF, atrial flutter (AFl) and non-compensatory sinus tachycardia (SmPC Rapibloc®). **Landiolol is a new kind of β-blocker, a pure S-enantiomer molecule which offers rate control with minimal negative impact on blood pressure** (Balic et al. 2018). Furthermore, landiolol has low volume distribution of 0.3 l/kg – 0.4 l/kg (SmPC Rapibloc®). This is very important because landiolol will not be stored in the tissues (DiPiro et al. 2010), thus avoiding possible toxicities (Abialbon 2019). Compared to esmolol, in experimental models, **landiolol showed very high cardioselectivity (β1/β2-selectivity = 33:1 vs. 255:1)** (Shibata et al. 2012). This translates to eightfold higher cardioselectivity for landiolol over esmolol. **Landiolol due to the highest cardioselectivity offers minimal impact on respiratory function** (Balic et al. 2018) **and unveils β2-receptor-mediated coronary hyperaemia** (Maman et al. 2017). In an experimental study, landiolol appeared to have a minimal effect on the refractory period of the action potential of a cardiomyocyte, in contrast to esmolol which dose-dependently shortened the refractory period. This is because landiolol does not affect Na+ and Ca2+ ion currents, resulting in a minimal affected cardiac contractility **(less inotropic effect)** (Shibata et al. 2012). **Landiolol also has a favourable safety profile for patients with renal and hepatic comorbidities,** due to inactive metabolites and hydrolysis by plasma esterases (Yokayama 2016).

Further statements from ESC guidelines (Hindricks et al. 2020):

- **Amiodarone** can be useful as a last resort when heart rate cannot be controlled.
- **Some antiarrhythmic drugs** (AADs) also have rate-limiting properties (e.g., amiodarone, dronedarone, sotalol) but generally they should be used only for rhythm control.
- **Intravenous administration of amiodarone** may lead to a further decrease in blood pressure in haemodynamic instable patients.
- **The "rhythm control strategy"** refers to attempts to restore and maintain sinus rhythm, and may engage a combination of treatment approaches, along with an adequate rate control.

Landiolol is the first innovative drug for acute heart rate control in cardiovascular risk patients which significantly improves the treatments options.

Landiolol is marketed by AMOMED (member of AOP Orphan Group). For more information regarding the product, please visit www.amomed.com.

LoE: Level of Evidence

References

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Summary of Rapibloc® Product Characteristics, current version.

Yokoyama H. (2016) Stabilization in Off-Pump Coronary Artery Bypass. Springer Tokyo Heidelberg New York Dordrecht London

Rapibloc®
Landiolol hydrochloride

_Rapid Rate Control.

No Compromise.

highest cardio-selectivity[3]
β1:β2
255:1

- **Ultra-rapid heart rate control**[2]
- **Limited effect** on blood pressure and inotropy[2–5]
- **Favourable safety profile**[3,5,6]
- **Precise controllability**[7]

Fast and precise management of acute atrial fibrillation.[3]
First-line also for patients with cardiac dysfunction.[1]

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MEMBER OF THE AOP ORPHAN GROUP

1 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016 Aug 27. pii: ehw2010. Available at: http:/eurheartj.oxfordjournals.org. **2** Krumpl G., et al.: Bolus application of landiolol and esmolol: comparison of the pharmacokinetic and pharmacodynamic profiles in a healthy caucasian group. Eur J Clin Pharmacol 2017; 73: 417-428. **3** Summary of Rapibloc® Product Characteristics, current version. **4** Tsuchiya H., et al.: Characteristic interactivity of landiolol, an ultra-short-acting highly selective β-1-blocker, with biomimetic membranes: comparisons with β-1-selective esmolol and non-selective propranolol and alprenolol. Front Pharmacol 2013 Dec 2; 4:150. **5** Syed Y. Y.: Landiolol: A Review in Tachyarrhythmias. Drugs 2018; 78:377–388. **6** Yamashita T., et al.: A prospective observational survey on landiolol in atrial fibrillation/ atrial flutter patients with chronic heart failure – AF-CHF landiolol survey. Journal of Cardiology 2019 Nov. Vol. 74, Issue 5: 418-425. **7** Plosker G.L.: Landiolol: a review of its use in intraoperative and postoperative tachyarrhythmias. Drugs 2013; 73:959-977.

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Rapibloc® 300 mg: Rapibloc® 300 mg powder for solution for infusion. **Composition:** A vial of 50 mL contains 300 mg landiolol hydrochloride. After reconstitution each mL contains 6 mg landiolol hydrochloride (6 mg/mL). List of excipients: Mannitol E421, sodium hydroxide (for pH adjustment). Therapeutic Indication: Landiolol hydrochloride is indicated for supraventricular tachycardia and for rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, post-operative, 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, sick sinus syndrome, severe atrioven-tricular (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. **Undesirable effects:** Common: Hypotension, bradycardia. Uncommon: Pneumonia, hyponatraemia, cerebral ischemia, headache, cardiac arrest, sinus arrest, tachycardia, hypertension, pulmonary oedema, vomiting, nausea, liver disorder, ECG: ST segment depression, cardiac index abnormal, abnormal laboratory parameters: ALT/GPT, AST/GOT, blood bilirubin, white blood cell count, red blood cell count, haemoglobin haematocrit, platelet count, blood lactate dehydrogenase, blood urea, blood creatinine, blood creatinine phosphokinase, protein total, blood albumin, blood sodium, blood potassium, blood cholesterol, blood triglycerides, protein urine present. Rare: Mediastinitis, thrombocytopenia, platelet disorder, hyperglycaemia, cerebral infarction, cerebrovascular accident, seizure, myocardial infarction, ventricular tachycardia, atrial fibrillation, low cardiac output syndrome, atrioventricular block, bundle branch block right, supraventricular extrasystole, ventricular extrasystole, shock, hot flush, asthma, respiratory distress, respiratory disorder, bronchospasm, dyspnoea, hypoxia, abdominal discomfort, oral discharge, breath odour, hyperbilirubinemia, erythema, cold sweat, muscle spasms, renal failure, acute kidney injury, oliguria, pyrexia, chills, chest discomfort, administration site pain, blood pressure increased, electrocardiogram T wave inversion, electrocardiogram: prolonged QRS complex, heart rate decreased, pulmonary arterial pressure increased, PO2 decreased, neutrophil count abnormal, blood alkaline phosphatase abnormal, leukocyte alkaline phosphatase, free fatty acids abnormal, blood chloride abnormal, glucose urine. Not known: Application site pain, injection site reaction, sensation of pressure. Prescription only/available only from pharmacy. **Date of revision of the text:** 09/2020. Marketing authorization holder: Amomed Pharma GmbH, Storchengasse 1, 1150 Wien, Austria