

The role of landiolol in the management of atrial tachyarrhythmias in patients with acute heart failure and cardiogenic shock: case reports and review of literature

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KEYWORDS

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Atrial tachyarrhythmias and worsening heart failure frequently coexist and potentially progress to a life threatening condition. Therapeutic approach requires simultaneous management of rapid ventricular response and heart failure symptom relief in order to improve haemodynamic stability and cardiac function. Landiolol is an ultra-short-acting b-adrenergic receptor blocker with high b1 selectivity incorporated in 2020 European Society of Cardiology guidelines for the management of atrial fibrillation. We provide a report of two cases with atrial fibrillation treated with landiolol in the acute setting of pulmonary oedema and cardiogenic shock, respectively. Additionally, we searched the international database PUBMED (MEDLINE, PubMed Central) to retrieve scientific evidence regarding its implementation in the treatment of atrial tachyarrhythmias in patients with cardiac dysfunction. Recent studies support the use of landiolol in patients with acute heart failure and atrial tachyarrhythmias. Compared to digoxin, landiolol proved to be more effective in controlling heart rate, with minimal adverse effects. Moreover, landiolol may be helpful in the conversion of atrial tachyarrhythmia to sinus rhythm. A more potent effect has been reported in patients with heart failure with preserved or mildly reduced ejection fraction, small left ventricular volume and high blood pressure. Likewise, administration of low doses of landiolol in patients with cardiogenic shock and atrial tachyarrhythmias reduced heart rate and pulmonary capillary wedge pressure and improved cardiac contractility without reducing blood pressure. Landiolol seems to be an attractive alternative in the acute management of patients with atrial tachyarrhythmias and cardiac dysfunction, though further clinical trials are needed to establish its role.

Introduction

Atrial tachyarrhythmias and acute heart failure (AHF) are two distinct cardiovascular disorders that frequently coexist and have unfavourable impact on patients'

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prognosis. Atrial fibrillation (AF) is the most common supraventricular arrhythmia in acute decompensated heart failure (HF) patients with a prevalence of 25–40%.^{1–3} The deleterious combination of AF and AHF results in persistent symptoms, poor clinical outcomes, prolonged hospitalization and higher morbidity and mortality at 30 days.^{4,5} Interestingly, in patients with pre-existing HF, the development of AF doubles mortality and in patients with pre-existing AF the development of HF triples mortality.^{6,7}

Regarding patients with cardiogenic shock (CS) and atrial tachyarrhythmia evidence is limited and is mostly related to patients with acute coronary syndrome (ACS) complicated by CS. In these studies, whilst AF was associated with a longer time to haemodynamic stabilization, the prognostic value of AF in CS remains controversial.^{8–10}

AF and HF can induce and perpetuate each other, and their interplay may deteriorate cardiac function and haemodynamic stability. In patients with AF, loss of atrial systole, rapid ventricular response, impaired left ventricular (LV) filling and elevated left atrial pressures may decrease blood pressure, stroke volume and cardiac output and result in the development of AHF. On the other hand, in patients with HF atrial pressure overload and dilatation, atrial fibrosis, oxidative stress and inflammation may contribute to conduction abnormalities and atrial tachyarrhythmias.^{6,11}

Therefore, the rationale in the acute management of AF in patients with AHF and CS is the normalization of heart rhythm or rate in order to restore haemodynamic status and improve cardiac contractility. Although the role of β -blockers in the setting of AHF is controversial, landiolol, an ultra-short acting β_1 -receptor antagonist with a higher β_1/β_2 selectivity ratio, seems an attractive alternative. The current study describes management of AF in two patients with AHF: the first with acute

pulmonary oedema and the second one with CS. Moreover, we report the latest evidence regarding the use of landiolol in patients with AHF and CS in relation to current guidelines for the management of AHF and AF.

Case 1

The patient is a 67-year-old woman with a history of HF with mid-range ejection fraction (HFmrEF) in New York Heart Association (NYHA) Class I, with a previous medical history of coronary artery disease, arterial hypertension and chronic obstructive pulmonary disease. She was presented at the emergency department complaining of sudden onset dyspnoea that started 3 h ago. On arrival, she was hypoxaemic (oxygen saturation of 85% on room air) and tachypnoeic (respiratory rate of 29 per minute), whilst her blood pressure was 197/116 mmHg and heart rate (HR) was 145 beats/min. Arterial blood gas analysis in room air revealed hypoxaemia ($PO_2 = 65.8$ mmHg), hypercapnia ($PCO_2 = 76.6$ mmHg), acidosis ($pH = 7.110$) and bicarbonate levels in normal range ($HCO_3 = 23.8$ mmol/L). Physical examination revealed rales bilaterally, irregular heart sounds and pitting oedema bilaterally in the lower extremities.

Her electrocardiogram (ECG) showed AF of unknown onset (*Figure 1*). Focused cardiac ultrasound revealed LV ejection fraction (LVEF) of 40–45%, dilated inferior vena cava (>2 cm diameter) with diminished respiratory variation and multiple, bilateral, diffused B-lines (≥ 3 B-Lines in two chest zones on each hemithorax), findings consistent with pulmonary congestion and volume overload (*Figure 2*). Additionally, N-terminal pro hormone of brain natriuretic peptide (NT-proBNP) and troponin were slightly elevated, 2600 and 25 pg/mL, respectively.

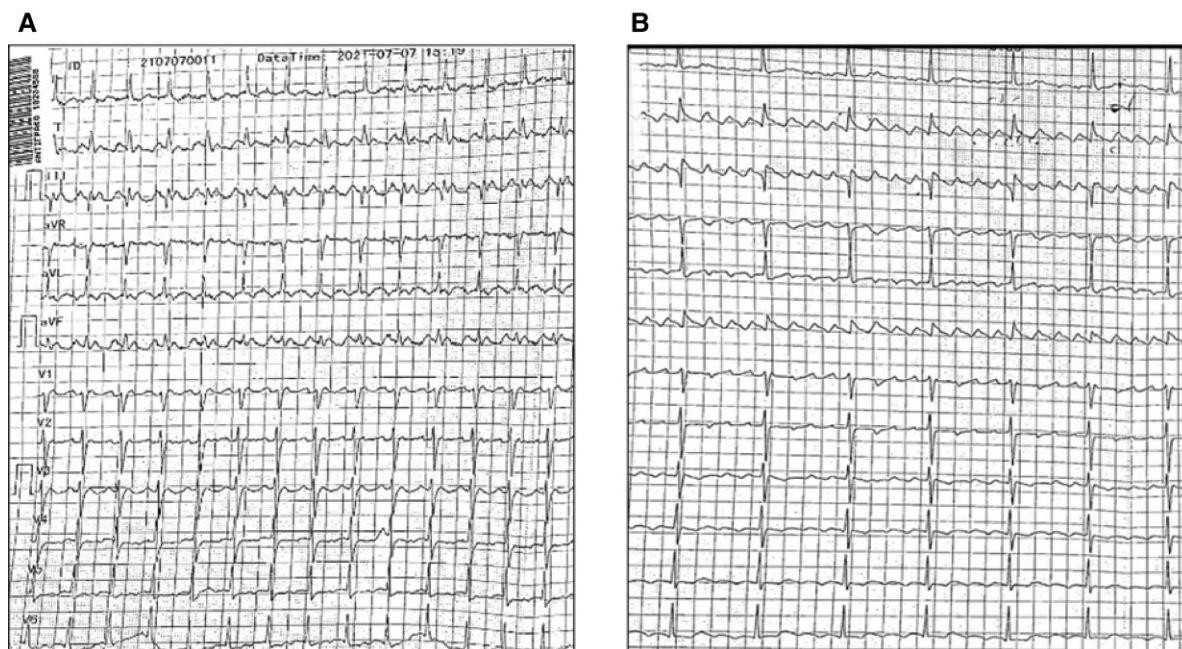


Figure 1 Electrocardiogram of case 1 before (A) and 1 h after the administration of landiolol (B). aVF, augmented vector foot; aVR, augmented vector right; ST-T, segment isoelectric section of the ECG between the end of the S wave and the beginning of the T wave.

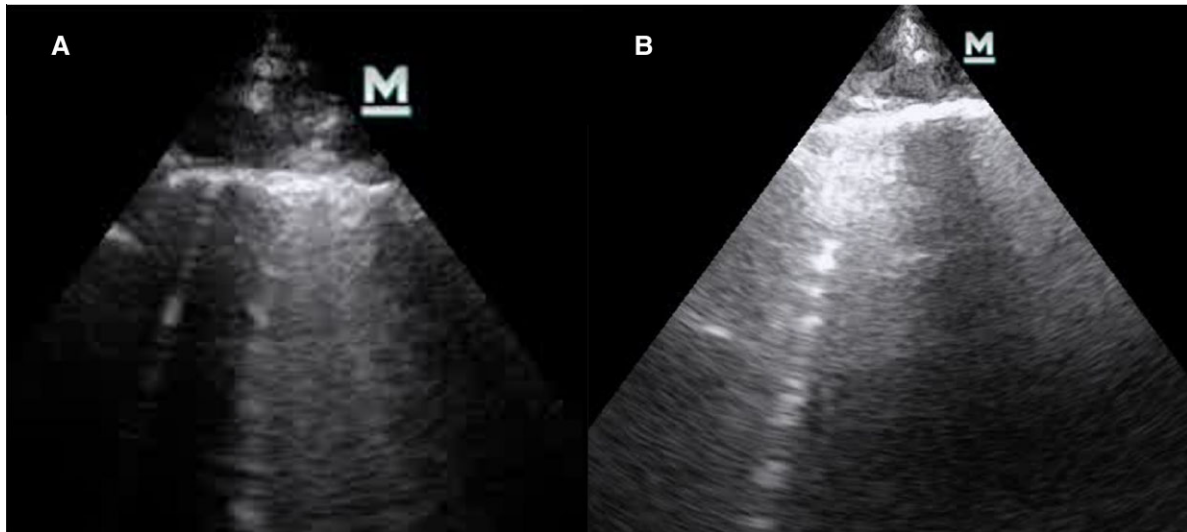


Figure 2 Lung ultrasound of case 1 showing B-lines on arrival (A) and at discharge (B).

Due to respiratory failure, non-invasive continuous positive pressure ventilation was started. Landiolol was administered intravenously at an initial dose of $2 \mu\text{g}/\text{kg}/\text{min}$ and was titrated up to $4 \mu\text{g}/\text{kg}/\text{min}$ followed by immediate rate control less than 100 beats/min and unmasked atrial flutter (AFL). Nitroglycerine $20 \mu\text{g}/\text{min}$ and furosemide at a starting dose of 40 mg were administered intravenously for blood pressure and overload control. After initial haemodynamic and clinical improvement, the patient was admitted to the cardiology care unit and 3 days later NT-proBNP decreased by $\sim 30\%$, and she was discharged.

Case 2

An 86-year-old man presented to the emergency department with progressing shortness of breath and epigastric pain over the last 3 days. He had history of Parkinson's disease without history of cardiovascular disease. Upon arrival, he was in respiratory distress with orthopnoea and cold, clammy extremities. Initial vital signs were as follows: blood pressure was 137/85 mmHg, HR was 120 b.p.m., respiratory rate 30/min and oxygen saturation was non-detectable due to peripheral vasoconstriction. Physical examination revealed a third heart sound, reduced lung sounds and coarse crackles bilaterally. Arterial blood testing on room air showed partial pressure of arterial oxygen of 60 mmHg, partial pressure of carbon dioxide of 39 mmHg, serum lactate level of 12.5 mmol/L, serum bicarbonate level of 12 mEq/L and a pH of 7.10. Initial ECG demonstrated sinus rhythm with absence of R wave in the precordial leads, segment isoelectric section of the ECG between the end of the S wave and the beginning of the Twave (ST-T) segment elevation in lead augmented vector right and ST-T segment depression in leads II, III and augmented vector foot. Echocardiography showed reduced cardiac contractility with an ejection fraction of 20% with hypokinesia of the interventricular septum and the apex, mild mitral insufficiency, dilated inferior vena

cava without respiratory variation and hepatic vein distention. Lung ultrasound showed diffuse, multiple, bilateral B-lines and pleural effusions bilaterally. Laboratory investigations revealed elevated high-sensitive troponin T 1359 pg/mL and NT-proBNP 7969 ng/L. Clinical presentation, sonographic and biomarker findings were consistent with ACS complicated by acute pulmonary oedema with signs of hypoperfusion. Non-invasive positive pressure ventilation therapy was immediately started along with furosemide 40 mg and nitroglycerin $5 \mu\text{g}/\text{min}$ intravenously, which was discontinued shortly after, due to clinical deterioration of the patient, further increase in serum lactate level and a reduction in blood pressure (100/56 mmHg). Repeated furosemide administration had no positive effect on diuresis. Due to oliguria, furosemide administration was repeated without significant effect. As CS was unmasked with further haemodynamic compromise the patient developed rapid AF (*Figure 3A*). Due to haemodynamic instability, landiolol administration was started at a dose of $10 \mu\text{g}/\text{kg}/\text{min}$ along with a bolus of intravenous amiodarone 300 mg for chemical cardioversion. Conversion to sinus rhythm was successful, and landiolol was continued to maintain sinus rhythm (*Figure 3B*). Despite a brief improvement, due to refractory haemodynamic instability, intravenous inotropes (dobutamine at a dose of $3 \mu\text{g}/\text{kg}/\text{min}$) and vasopressors (noradrenaline at a dose of $0.5 \mu\text{g}/\text{kg}/\text{min}$) were added for circulatory support. The patient was transferred urgently to the catheterization lab where coronary angiography revealed three-vessel disease and was referred for coronary artery bypass grafting.

Atrial tachyarrhythmias and acute heart failure

Patients with AHF often have atrial tachyarrhythmias, including AF, AFL and atrial tachycardia, on admission. The management of AF in patients with AHF has been

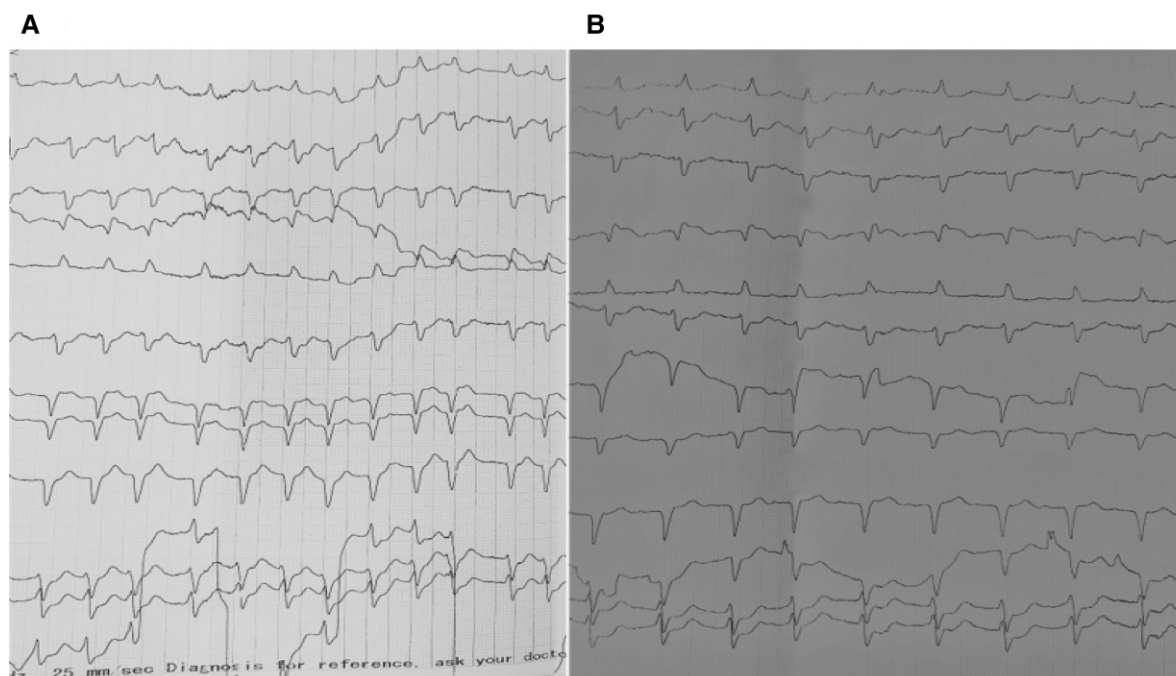


Figure 3 Electrocardiogram of case 2 before (A) and 30 min after administration of landiolol (B).

described in both HF and AF guidelines of the European Society of Cardiology (ESC). Anticoagulation is indicated in all cases according to CHA₂DS₂-VASc [congestive heart failure, hypertension, age \geq 75 (doubled), diabetes, previous stroke/transient ischemic attack/thromboembolism (doubled), vascular disease, age: 65-74, sex (female)] score evaluation in order to prevent embolic events (Class of recommendation I, Level of evidence A).^{12,13} Moreover, attention should be given in the treatment of triggers (thyrotoxicosis, electrolyte disorders, uncontrolled hypertension, valvular disease, infection) (Class of recommendation I). Management of the tachyarrhythmia itself is a more complex issue depending on the onset, on the type and on the severity of the tachyarrhythmia-related symptoms. In the acute setting it is not always straightforward to confirm whether the tachyarrhythmia is the cause or the consequence of the underlying cardiac dysfunction. Given that atrial tachyarrhythmias have been identified as precipitant factors of cardiac decompensation and have been correlated with longer hospital stay and higher mortality, rapid management and definite rate control is required. Regarding rate control, HF guidelines suggest that beta-blockers can be used in patients with heart failure with reduced ejection fraction (HFrEF) or HFmrEF due to their established safety in this subgroup of patients (Class of recommendation IIa, Level of evidence B). However, there is a lack of evidence to demonstrate their efficacy in the setting of HFpEF (HF with preserved EF).¹² AF guidelines recommend b-blockers over digoxin for rate control due to their rapid onset of action and effectiveness at high sympathetic tone. In addition, non-dihydropyridine calcium channel blockers (verapamil or diltiazem) are not suggested in patients with impaired

LV function because of their negative inotropic effects whilst b-blockers are indicated in both patients with LVEF < 40% and those with LVEF \geq 40% (Class of recommendation I, Level of evidence B).¹³

Landiolol, an ultra-short-acting, highly cardioselective intravenous beta-blocker, seems a promising option for urgent rate control in AHF patients with concomitant atrial tachyarrhythmias. Several investigations aimed to evaluate its efficacy and safety in this context (Table 1).

The landmark trial was the prospective, multicentre J-Land (Japanese landiolol versus digoxin) study which showed that continuous intravenous administration of landiolol at 1-10 μ g/kg/min was more effective compared to slow acting digoxin among 200 patients with AF/AFL and LV dysfunction (LVEF 25-50%) in NYHA Class III-IV. Successful rate control defined as \geq 20% reduction in HR together with HR < 110 beats/min from baseline at 2 h following administration was achieved in almost 50% of those treated with landiolol compared to 13.9% of those treated with digoxin. Regarding the safety of these agents, the incidence of adverse events during the 2 h treatment period was not significantly different between the two groups. After this period, two landiolol group patients experienced serious adverse events, namely congestive HF and embolic stroke.¹⁴ A subgroup analysis of J-Land study also demonstrated the superiority of landiolol over digoxin regardless of patient baseline characteristics such as age, sex, HR, systolic blood pressure, LVEF, previous use of oral b-blockers and renal function. Notably, in those with estimated glomerular filtration ratio < 30 mL/min/1.73 m² adverse events were significantly less in the landiolol arm compared to the digoxin arm, probably due to the renal excretion of digoxin.¹⁵

Table 1 Studies that aimed to evaluate the efficacy of landiolol in AHF patients with atrial tachyarrhythmia

Study	Type of study	Patients	Age (years)	LVEF (%)	Atrial tachyarrhythmia	HR (beats/min)	Landiolol dose ($\mu\text{g}/\text{kg}^{-1}/\text{min}^{-1}$)	Results
J-Land study ¹⁴	Prospective	200	71.6 \pm 11.5	36.6 \pm 7.6	AF/AFL	138.1 \pm 15.3	1-10	Landiolol was more effective than digoxin in controlling HR.
Kinugawa ¹⁵	Prospective	200	71.6 \pm 11.5	36.6 \pm 7.6	AF/AFL	138.1 \pm 15.3	1-10	Landiolol was more effective than digoxin in controlling HR, regardless of patients' characteristics.
Wada <i>et al.</i> ¹⁶	Retrospective	39	72 \pm 11	34 \pm 16	AF/AFL	152 \pm 19	1-10	Landiolol was effective in controlling HR and in nine of them, AF was spontaneously terminated.
Ozaki <i>et al.</i> ¹⁷	NA	33	HFREF: 68 \pm 13 HFpEF: 84 \pm 9	NA	AF	\geq 120	HFREF (max): 2.9 \pm 1.6 HFpEF (max): 2.6 \pm 1.5	Landiolol was more effective in HFREF patients than HfREF patients.
Kiuchi <i>et al.</i> ¹⁸	Retrospective	59	74	42	AF/AFL	132	min: 0.5-1 max: 5.57 \pm 4.78	HR decreased in both landiolol and diltiazem groups whereas a significant BP reduction was recorded only in diltiazem group. Switching to oral BB was accomplished sooner with landiolol.
Oka <i>et al.</i> ¹⁹	Retrospective	77	72.4 \pm 12.6	33.1 \pm 13.7	AF/AFL/AT	143.1 \pm 15.2	1-10	Landiolol was more effective in AF patients than AFL/AT patients.
Iwahashi <i>et al.</i> ²⁰	Prospective	101	63-81	18-32	AF	133-156	min: 1 max: 3.8 \pm 2.3	Landiolol was effective in controlling HR, especially in those with small LV volume and high BP.
Matsui <i>et al.</i> ²¹	Retrospective	67	67 \pm 12	41 \pm 13	AF/AFL/AT	141 \pm 17	1-12	Landiolol was effective in controlling HR, especially in those with LVEF \geq 40%.
Shinohara <i>et al.</i> ²²	Retrospective	53	66.7 \pm 16.1	23.8 \pm 3.9	AF	142.3 \pm 16.8	0.5-10	Landiolol was more effective than digoxin in controlling HR.

AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; BB, beta-blocker; BP, blood pressure; HFREF, heart failure with reduced ejection fraction; HR, heart rate; LV, left ventricular ejection fraction; NA, non-available.

A following retrospective multicentre survey evaluated 39 patients with decompensated HF (LVEF $34 \pm 16\%$) and atrial tachyarrhythmias (AF, AFL, atrial tachycardia). In 29 patients, intravenous landiolol induced HR reduction by about 40% from baseline and in nine of them, AF was spontaneously terminated without synchronized cardioversion or an additional antiarrhythmic treatment after landiolol administration. Patient response differed in function of LVEF. Higher LVEF at baseline was considered as a good predictor for the efficacy and safety of landiolol. Hypotension defined as systolic blood pressure reduction to less than 80 mmHg was observed only in three patients and landiolol was discontinued immediately.¹⁶ A difference in HR response according to LV function was also recorded by another group of investigators that studied landiolol in 33 patients with acute decompensated HF in NYHA Class III-IV. After administering similar doses of landiolol, HR decreased significantly greater in those with HFpEF compared to those with HFrEF. Hypotension occurred in only one patient with HFrEF.¹⁷

A retrospective study from Japan compared 15 patients treated with landiolol to 44 patients treated with the non-dihydropyridine calcium channel blocker diltiazem. All participants were hospitalized for AHF complicated with AF/AFL. Following drug infusion, a decrease in HR was noted in both groups whereas a significant reduction in blood pressure was recorded only in the diltiazem group. The infusion-to-oral β -blocker treatment commencement was accomplished sooner with landiolol in patients with HFrEF and there as a trend for shorter transition among patients with HFpEF.¹⁸

Another retrospective study from Japan of 77 patients with acute decompensated HF (LVEF $< 50\%$, NYHA Class III-IV), atrial tachyarrhythmias and HR ≥ 120 b.p.m. showed that intravenous administration of landiolol was significantly more effective for the AF group compared to the AFL/atrial tachycardia group. The magnitude of the HR decrease was $\sim 30\%$ in the AF arm about 12 h after initiating therapy whilst it was about 10% in the AFL/atrial tachycardia arm.¹⁹

A prospective single-centre study including 101 patients with acute decompensated HFrEF (LVEF $< 40\%$, NYHA Class IV) and AF revealed that landiolol decreased HR avoiding short-term major adverse events (cardiac death, worsening renal function, prolonged HF requiring hospitalization) and resulting in haemodynamic improvement. Small LV volume and high mean blood pressure at baseline were correlated with better prognosis. No serious adverse effects such as bradycardia and hypotension were noted during treatment.²⁰

A retrospective single-centre study also evaluated the effectiveness of landiolol in 67 consecutive hospitalized patients with acute decompensated HF and atrial tachyarrhythmias. Landiolol reduced the HR without decreasing blood pressure or leading to a deterioration of HF or cardiac function. Almost 70% of the discharged patients were in sinus rhythm and had a lower frequency of rehospitalizations during the following 16 ± 12 months. The magnitude of HR decrease was greater among those with LVEF $\geq 40\%$ than those

with LVEF $< 40\%$. Concerning the safety of landiolol, treatment was discontinued only in three patients because of hypotension and liver dysfunction.²¹

Finally, a recent retrospective study of 53 patients with AF and severely depressed LV dysfunction (LVEF $\leq 25\%$) demonstrated that landiolol was more effective in controlling HR compared to digoxin even in this subgroup of HF patients. Systolic blood pressure was significantly decreased within 24 h after administering landiolol, but hypotension was recorded only in two patients. Nonetheless, digoxin did not reduce systolic blood pressure over time.²²

Atrial tachyarrhythmias and cardiogenic shock

Cardiogenic shock represents the most severe manifestation of AHF. The extent and acuity of cardiac dysfunction compromises cardiac output with subsequent end-organ hypoperfusion and hypoxia resulting in multi-organ failure and death.²³ Early management of CS is crucial and demands prompt identification and treatment of the underlying cause. In parallel, management is directed to the stabilization of haemodynamic status with the administration of inotropes/vasopressors (Class of recommendation IIb, Level of evidence C) and mechanical circulatory support (Class of recommendation IIa, Level of evidence C).^{12,23} Atrial tachyarrhythmia may aggravate further haemodynamic status in patients with CS through mechanisms like impaired diastolic filling, activation of neurohormonal systems and rate-related LV impairment; thus, it demands urgent management.^{11,24}

Anticoagulation and treatment of the underlying triggers should be the first step in the therapeutic approach of patients with CS and AF. Both ESC 2021 guidelines for the diagnosis and management of acute and chronic HF and 2020 guidelines for the diagnosis and management of AF recommend urgent cardioversion in patients presenting with rapid ventricular rates and haemodynamic instability, after estimation of the thromboembolic risk (Class of recommendation I, Level of evidence C). Cardioversion is also indicated in patients who remain symptomatic after optimal medical treatment (Class of recommendation IIb, Level of evidence B). After restoration of rhythm, administration of amiodarone should be started to maintain sinus rhythm (Class of recommendation IIb).^{12,13} Rate control strategy is indicated in refractory cases and in patients who do not receive chronic therapy with an oral anticoagulant and with AF onset > 48 h. β -blockers, digoxin or amiodarone are the pharmacologic agents recommended for acute rate control in these cases to decrease ventricular rate and improve ventricular filling and stroke volume (Class of recommendation IIa).^{3,25,26} β -blockers can be used with caution in acute phases because of their rapid onset of action and of their effect on sympathetic tone.²⁷ Digoxin should be considered as second-line therapy in patients with increased ventricular rates despite β -blockers use or in case β -blockers are contraindicated or non-tolerated.^{12,28} Amiodarone is recommended as first-line

choice in patients with NYHA class IV and/or haemodynamic instability.²⁹ AFL should be managed as AF, and atrial tachycardia requires anticoagulation and management of the underlying precipitants and comorbidities.³⁰

Despite the established safety of β -blockers in patients with HFrEF, their use carries special concern in the acute phase of HF because of their negative inotropic effects.^{26,27} However, administration of β -blockade may produce a beneficial effect in the setting of sympathetic hyperactivity that usually accompanies episodes of AF with rapid ventricular rate by decreasing myocardial oxygen demand and improving ventricular diastolic filling.^{31,32}

Emerging data have shown the effectiveness and safety of landiolol as an ultra-short acting β -adrenergic receptor blocker in patients with CS (Table 2). Kobayashi *et al.*³³ reported the beneficial effect of landiolol in patients on sinus rhythm with EF < 35% and signs of HF demanding inotropic support. Low-dose landiolol (1.5 $\mu\text{g}/\text{kg}/\text{min}$) significantly reduced HR by 11% without affecting blood pressure and cardiac index (CI). At the same time, it improved cardiac function by decreasing PCWP (pulmonary capillary wedge pressure) and increased the O₂ saturation of mixed venous blood (SvO₂) and stroke volume index. Consequently, the scientific group examined the effect of landiolol on 23 patients with rapid AF. Patients were divided in two groups; 12 had systolic HF with a mean EF of $34.5\% \pm 8.6$ and 11 diastolic HF with a mean EF $56.6\% \pm 6.4$. Inotropic agents (milrinone, dopamine or dobutamine) were needed in 47.8% of patients. In both groups, low-dose landiolol reduced ventricular response significantly at and beyond the first hour after initiation of drug infusion, and 2 h after, HR was reduced significantly by 22.4% without a reduction in blood pressure. Moreover, in patients with paroxysmal AF, the rate of conversion to sinus rhythm was 88% within 24 h of landiolol administration.³⁴ In a more recent study, the team documented the dose-dependent improvement of cardiac performance in nine patients with acute decompensated HF, refractory rapid AF and 'wet and cold' phenotype who received combination therapy of landiolol at a low-dose and milrinone. Landiolol at a dose of 1.5 $\mu\text{g}/\text{kg}/\text{min}$ reduced HR significantly by 11%, which led to a decrease in PCWP and increases in stroke volume index and CI.³⁵ No changes in blood pressure, mean right atrial pressures and systemic vascular resistance were observed. However, higher doses of had a negative effect on haemodynamic parameters.

A prospective observational study assessed the acute haemodynamic response to landiolol in 52 patients with atrial tachyarrhythmia and congestive HF (EF $32 \pm 12\%$) refractory to standard treatment with diuretics, vasodilators and inotropes. An average dose of $10.8 \pm 9.4 \mu\text{g}/\text{kg}/\text{min}$ reduced HR significantly, whilst EF improved from $32.3 \pm 11.9\%$ to $39.7 \pm 6.5\%$ ($P < 0.01$). Transient asymptomatic hypotension requiring cessation of landiolol therapy occurred in three patients. Interestingly, patients receiving milrinone needed lower doses of landiolol (1-2 $\mu\text{g}/\text{kg}/\text{min}$), whilst patients receiving dobutamine required higher doses (3-20 $\mu\text{g}/\text{kg}/\text{min}$).³⁶

In addition, a retrospective observational study investigated the impact of dobutamine on the negative chronotropic action of landiolol in AHF patients with

atrial tachyarrhythmia receiving combination therapy. Maximal dose of dobutamine was $2.64 \pm 0.89 \mu\text{g}/\text{mL}/\text{kg}$, and maximal doses of landiolol were similar between groups who received either landiolol monotherapy or landiolol with dobutamine (3.53 ± 2.45 and $4.07 \pm 2.44 \mu\text{g}/\text{mL}/\text{kg}$, $P = 0.553$). Negative chronotropic action induced by landiolol appeared not to be diminished even after concomitant dobutamine administration.³⁷

Wada *et al.*¹⁶ evaluated the impact of landiolol (maximum dose of 10 $\mu\text{g}/\text{kg}/\text{min}$) on patients with rapid atrial tachyarrhythmias and LV dysfunction. They included 39 patients with a mean EF of $34 \pm 16\%$, and one-third needed inotropic support (dopamine, dobutamine, noradrenaline, combination of dopamine plus dobutamine, dopamine plus noradrenaline or dobutamine plus noradrenaline). Landiolol was successful to reduce HR in 29 patients, whilst low LVEF (<25%) was the only predictor of non-responders.

A multicentre, open-label, randomized controlled study evaluated the efficacy and safety of landiolol for the treatment of sepsis-related tachyarrhythmias receiving catecholamine support. Among 151 patients, 91% were diagnosed with septic shock and 80% presented with sinus tachycardia, 19% with AF and 1% with AFL. Patients were assigned randomly to receive either landiolol or only conventional therapies for sepsis. Significantly more patients in the landiolol group met the primary outcome (HR of 60-94 b.p.m. at 24 h) than in the control group [41 (55%) of 75 vs. 25 (33%) of 75]. Furthermore, fewer landiolol-treated patients had new-onset arrhythmia. Safety analysis concluded that landiolol was generally well tolerated; serious adverse events related to landiolol occurred in 5 (6%) of 77 patients, including blood pressure decreases in 3 patients (4%) and cardiac arrest, HR decrease and EF decrease occurred in 1 patient each (1%).³⁸

Additional data in the literature derive from case reports where landiolol has been used as an adjunctive therapy in combination with inotropes in patients with CS and AF. Nitta *et al.*³⁹ report the case of a 20-year-old patient presenting with decompensated HF and low blood pressure demanding administration of dobutamine. Landiolol at a dose of 8 $\mu\text{g}/\text{kg}/\text{min}$ proved to be a useful therapy in the setting of rapid AF refractory to digoxin. Another case series describes the beneficial effect of landiolol in three critically ill patients with rapid AF admitted in the intensive care unit either for cardiogenic or septic shock. Patients were treated with combination therapy of levosimendan plus norepinephrine, and landiolol was successfully added to reduce/restore sinus rhythm and improve cardiac output and stroke volume.⁴⁰ In another case report, a patient with septic shock treated with noradrenaline developed CS in the onset of AF, and so, she was administered continuous landiolol intravenously. Landiolol reduced rapidly HR and reversed patient's haemodynamic instability.⁴¹

Discussion

Atrial tachyarrhythmias including AF, AFL and atrial tachycardia represent precipitating clinical factors that

Table 2 Studies that aimed to evaluate the efficacy of landiolol in patients with cardiogenic shock and/atrial tachyarrhythmias

Study	Type of study	Patients	Age (years)	LVEF (%)	Rhythm	HR (beats/min)	Concomitant therapy	Landiolol dose ($\mu\text{g}/\text{kg}/\text{min}^{-1}$)	Results
Kobayashi <i>et al.</i> ³³	Prospective	20	56.2 \pm 17.8	24 \pm 7	SR	107.4 \pm 12.3	Milrinone, vasodilators, diuretics	1.5-6	Low-dose (1.5 $\mu\text{g}/\text{kg}/\text{min}$) landiolol reduced HR by 11% and PCWP and increased SVO ₂ and SVI. No changes in BP or CI were detected. Higher doses >3 $\mu\text{g}/\text{kg}/\text{min}$ tended to decrease BP and CI whilst increasing PCWP and systemic vascular resistance.
Kobayashi <i>et al.</i> ³⁴	Prospective	23	72.7 \pm 13.6	36.6 \pm 7.6	AF	142.8 \pm 18.4	Inotropes (milrinone/dobutamine), vasodilators diuretics	1.5 \pm 0.4	Landiolol reduced HR by 22.4% 2 h after its initiation with no changes in BP. Conversion to SR was seen in 88% of patients with paroxysmal AF within 24 h of landiolol administration.
Kobayashi <i>et al.</i> ³⁵	Prospective	9	65.6 \pm 15.8	27.8 \pm 7.9	AF	138 \pm 17.9	Milrinone, vasodilators, diuretics	1.5-6	Low-dose (1.5 $\mu\text{g}/\text{kg}/\text{min}$) landiolol reduced HR by 11%, decreased PCWP and increased SVI without changes in BP. Administration of more than 3 $\mu\text{g}/\text{kg}/\text{min}$ of landiolol decreased BP, CI and SVI.
Adachi <i>et al.</i> ³⁶	Prospective	52	64.8 \pm 13.5	32.3 \pm 11.9	AF/AT	133.2 \pm 27.3	Inotropes (milrinone/dobutamine), vasodilators diuretics	1-20	Landiolol at an average dose of 10.8 \pm 9.4 $\mu\text{g}/\text{kg}/\text{min}$ reduced significantly HR to 82 \pm 15 beats/min with no effect in BP. In addition, it increased LVEF significantly to 39.7 \pm 6.5% and was useful as a bridging treatment to additional therapy of oral blockade, pulmonary vein catheterization or cardiac resynchronization therapy.
Yoshima <i>et al.</i> ³⁷	Retrospective	33	NA	DB+L: 38.9 \pm 13.8 LM: 44.8 \pm 17	AF/AFL/AT	DB+L: 147.4 \pm 21.3 LM: 141.5 \pm 18.7	Dobutamine	DB+L: 3.53 \pm 2.45 LM: 4.07 \pm 2.44	Negative chronotropic action by landiolol appeared not to be diminished even under concomitant administration of DB.
Kakihana <i>et al.</i> ³⁸	Multicentre, open-label, randomized controlled trial	151	67.1	55.1	AF/AFL/SR	117.5	Conventional sepsis therapy, norepinephrine	1-20	Landiolol resulted in significantly more patients with sepsis-related tachyarrhythmia achieving a heart rate of 60-94 b.p.m. at 24 h and significantly reduced the incidence of new-onset arrhythmia.

AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; BP, blood pressure; CI, cardiac index; DB, dobutamine; HR, heart rate; L, landiolol; LM, landiolol; LV, left ventricular ejection fraction; NA, non-available; PCWP, pulmonary capillary wedge pressure; SR, sinus rhythm; SVI, stroke volume index; SVO₂, oxygen saturation of mixed venous blood.

may contribute to HF hospitalizations and have been associated with adverse in-hospital outcomes among patients with reduced, mildly reduced and preserved EF. Hence, urgent and definite rate control is of paramount importance in this context.

Landiolol is an ultra-short acting intravenous β 1 selective blocker that is available in Japan for almost two decades for the management of patients with concomitant HF and atrial tachyarrhythmias and is currently available in Europe. It shares several similarities with other b-blockers, although it exhibits weak negative inotropic, potent negative chronotropic and faster pharmacokinetics effects. Moreover, landiolol appears to have limited impact on arterial blood pressure due to its minimum negative inotropic effect. All these characteristics make it a promising choice for HR control in the setting of HF patients with atrial tachyarrhythmias especially to those with imminent or overt circulatory shock.

Furthermore, intracellular Ca^{2+} handling derangement is thought to be a common pathophysiologic mechanism in HF and arrhythmogenesis. Diastolic Ca^{2+} leak from the sarcoplasmic reticulum (SR) and decreased Ca^{2+} uptake to SR cause intracellular Ca^{2+} overload and depression of SR Ca^{2+} content eventually leading to systolic and diastolic LV dysfunction.^{42,43} In parallel, diastolic Ca^{2+} leak from SR via cardiac ryanodine receptor (RyR2) can initiate delayed after depolarization and trigger activity predisposing to arrhythmia.^{42,44} Experimental data on canine failing cardiomyocytes showed that landiolol inhibited Ca^{2+} leakage from failing RyR2 and did not suppress cardiomyocyte function. Moreover, whilst milrinone as monotherapy enhanced Ca^{2+} leakage, the addition of landiolol to milrinone

suppressed this milrinone-induced Ca^{2+} leakage leading to greater improvement of cardiomyocyte function.⁴⁵ Therefore, administration of landiolol may have a cardio-protective effect in patients with AHF and CS presenting with atrial tachyarrhythmias.

Available data demonstrate that landiolol are correlated with effective rate control particularly in patients with HFpEF, whilst a more cautious titration is recommended in those with HFrEF.

In the setting of CS where haemodynamic status is compromised, cardioversion is recommended as the first choice for the treatment of atrial tachyarrhythmias. Thus, in some cases, the clinical decision to defibrillate arises reasonable concerns due to sedation-induced hypotension, further myocardial damage induced by the cardioversion itself and adverse bradyarrhythmic events.^{46,47} Moreover, although a shock may transiently restore sinus rhythm, the expected recurrence rate in the still decompensated patient may be high.⁴⁸ Therefore, in patients with atrial tachyarrhythmias of unknown onset, in patients with history of ischaemic heart disease, in the elderly and in patients where the atrial tachyarrhythmia seems not to be the precipitating factor of haemodynamic instability, cardioversion should be used after careful assessment of the underlying risks. For patients classified as 'grey zone', landiolol could be an alternative treatment. In patients with CS, landiolol can effectively decrease HR without interfering in concurrent administration of inotropes.

Landiolol could also be useful as a bridging treatment to oral b-blocker therapy, catheter ablation, cardiac resynchronization therapy, valve replacement therapy or

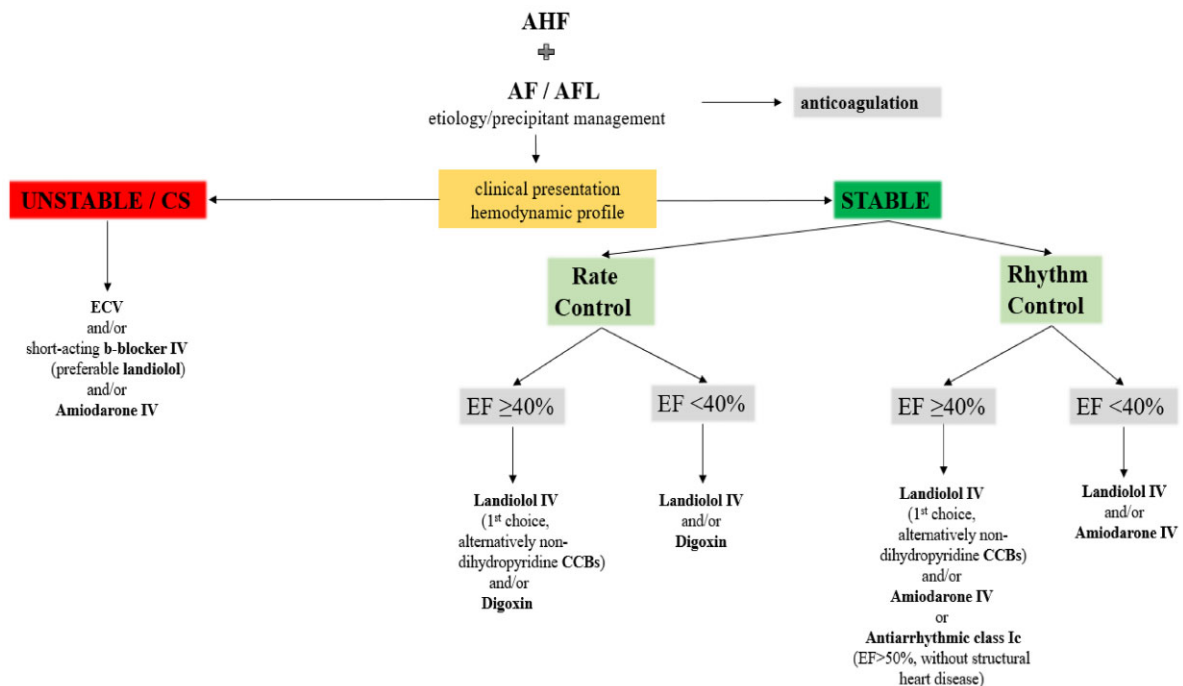


Figure 4 Proposed algorithm for the acute management of atrial tachyarrhythmias (atrial fibrillation/atrial flutter) in patients with worsening heart failure with or without haemodynamic instability. CCBs, calcium channel blockers; CS, cardiogenic shock; ECV, electrical cardioversion; IV, intravenous; EF, ejection fraction.

LV assist device implantation. A proposed algorithm for the management of patients with AHF complicated with atrial tachyarrhythmias is illustrated in *Figure 4*.

Limitations

These data are mainly retrospective single-centre observations. Thus, further studies with a large number of patients are required to confirm the findings and to investigate long-term efficacy and safety of landiolol.

Conclusion

Landiolol is effective in controlling HR without affecting cardiac contractility and serious side effects. Hence, it could be considered as a promising drug choice for the management of atrial tachyarrhythmias in the setting of patients with AHF or CS.

Conflict of interest: E.P. reported receiving honoraria for lectures from Bayer, Boehringer Ingelheim and GE Healthcare for educational events. A.B. received honoraria for lectures from Amomed pharma. J.P. received honoraria for lectures from Orion pharma, Pfizer, Servier, Astra, AOP Orphan and Roche Diagnostics. Regarding the present study all authors declare that they have no potential conflict of interest.

Data availability

Data are available upon request.

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