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Benefits and safety of landiolol for rapid rate control in patients with atrial tachyarrhythmias and acute decompensated heart failure

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Atrial tachyarrhythmias often occur in patients with worsening heart failure (HF), and the development of atrial tachyarrhythmias in acute decompensated HF (ADHF) causes an uncontrolled heart rate (HR) and leads to further exacerbation of HF and persistence of a decompensated HF state. Landiolol, a short-acting intravenous beta-1 blocker, shows very high cardiac beta-1 selectivity and has a very short elimination half-life of approximately 4 min. As shown in several reports, the benefit of intravenous landiolol is that it lowers the ventricular rate early after the start of use without markedly deteriorating haemodynamics. After the cardiac status is stabilized by rapid control of HR, subsequent basic HF pharmacotherapy and rhythm control therapies will be effective for improving outcomes. Because of the pharmacokinetic properties of landiolol, if the patient suffers an adverse reaction such as hypotension or bradycardia, such effects can be quickly reversed by tapering the dose or discontinuing use altogether. Based on several clinical studies, this review discusses the efficacy, safety and role of intravenous landiolol in acute HR control in patients with atrial tachyarrhythmias and ADHF.

Introduction

Atrial tachyarrhythmias, including atrial fibrillation (AF), atrial flutter (AFL) and atrial tachycardia (AT), occur frequently in patients with worsening heart failure (HF).[1-4] The development of atrial tachyarrhythmias in acute decompensated HF (ADHF) causes an uncontrolled heart rate (HR) with a shortened filling time and tachycardia-induced cardiomyopathy, reduces cardiac output and further exacerbates haemodynamics, further exacerbating HF and causing a decompensated HF state to persist.[5-7]

For emergency treatment of atrial tachyarrhythmias with a high ventricular rate, it is important to restore sinus rhythm, control the ventricular rate, and improve the haemodynamics. Restoring sinus rhythm is a key to restoring normal atrioventricular excitatory processes,

regularizing and lowering HR and normalizing ventricular pumping function to improve left ventricular (LV) contractility. Therefore, the conversion and prevention of atrial tachyarrhythmias is required in the management of HF. Prompt rhythm control, for example, by electrical cardioversion, is required for persistent atrial tachyarrhythmias in the context of critical illness, but a high recurrence rate of atrial tachyarrhythmias is often observed among patients in whom initial cardioversion is successful.[8] If acute rhythm control fails to restore sinus rhythm, the management of these patients remains challenging. Prompt and reliable HR control for atrial tachyarrhythmias has a role in improving haemodynamics in the context of ADHF.

Acute rate control

In patients with ADHF, atrial tachyarrhythmias are caused by an increased sympathetic drive. Therefore, beta blockers are useful for ventricular rate reduction

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and are preferred over digoxin due to their effectiveness under the condition of high sympathetic tone.[9] The use of beta blockers clearly requires an incrementally calibrated dosage to achieve an HR that balances the need for rate control with other haemodynamic parameters. The non-dihydropyridine calcium channel blockers verapamil and diltiazem are also useful for ADHF patients with preserved LV systolic function.[9] However, beta blockers and non-dihydropyridine calcium channel blockers often show a negative inotropic effect and a blood pressure-lowering effect and, especially when administered intravenously, are of limited use in ADHF patients with reduced LV systolic function and/or low blood pressure. Meanwhile, digoxin takes time to distribute and is often unsuccessful in an acute context. Current European Society of Cardiology (ESC) guidelines recommend the use of intravenous digoxin or amiodarone exclusively in an acute setting in patients with HF and reduced LV systolic function.[10]

Landiolol as an ultra-short-acting intravenous beta-1 blocker

In the context of acute care, an intravenous beta blocker that lowers the ventricular rate by suppressing sympathetic activity but without markedly reduced blood pressure and is pharmacokinetically easy to turn on and off (start and stop) is desired.

Landiolol is a short-acting intravenous beta-1 blocker developed in Japan. Landiolol shows very high cardiac beta-1 selectivity (beta-1/beta-2 $\approx$ 250)[11] and is higher than esmolol.[12,13] Furthermore, studies using rabbits have reported that landiolol caused a less negative inotropic effect and less of a decrease in blood pressure than esmolol.[14] Regarding pharmacokinetic properties, landiolol is rapidly metabolized in plasma by pseudocholinesterase and has a very short elimination half-life of approximately 4 min.[12,13] The protein binding rate is 1.5–7.0% (in vitro), and the volume of distribution is 0.24 L/kg.[13]

In Japan, landiolol was approved in July 2002 as urgent treatment for AF, AFL and sinus tachycardia during surgery; in 2006, it was also approved for postoperative tachyarrhythmia. Furthermore, in November 2013, the indications of AF and AFL in patients with impaired LV function were added.

Acute rate control in atrial fibrillation/flutter: landiolol vs. digoxin

The J-Land study was conducted to compare the acute effect of intravenous landiolol vs. intravenous digoxin for reducing ventricular rates in patients with AF/flutter and impaired LV function.[15] This prospective randomized trial included 200 patients with ventricular rate $\geq$120 beats/min, New York Heart Association (NYHA) class III or IV and LV ejection fraction (LVEF) 25–50% who were randomized to receive either landiolol ($n = 93$) or digoxin ($n = 107$). Continuous intravenous administration of

landiolol was started at a dose of 1.0 µg/kg/min and titrated up to 10 µg/kg/min according to the patient's condition; administration lasted for $\geq$2 h and up to 72 h. Digoxin was administered intravenously at an initial dose of 0.25 mg (if treated with oral digoxin, 0.125 mg); after 2 h but no more than 72 h, more intravenous digoxin could be added according to the patient's condition. The primary endpoint was the percentage of patients with both an HR <110 beats/min and at least a 20% decrease from baseline at 2 h after administration. The mean dose of landiolol at 2 h was 6.7 $\pm$ 3.2 µg/kg/min. The primary endpoint was achieved in 48.0% of patients treated with landiolol and in 13.9% of patients treated with digoxin ($P < 0.0001$)[15] (Table 1).

Regarding safety, there was no significant difference in adverse events between the landiolol and digoxin groups (32.3% vs. 32.7%, respectively). The most common adverse events were hypotension [7 (7.5%) of 93 patients in the landiolol group vs. 4 (3.7%) of 107 patients in the digoxin group] and nausea/vomiting [7 (7.5%) vs. 1 (0.9%)]. Other common adverse events (>3%) were increased serum creatinine and urea levels, defined as an increase in values from normal to abnormal, and constipation. During the trial, three patients discontinued landiolol due to adverse events, but none discontinued digoxin. Serious adverse events were observed in two patients in the landiolol group (congestive HF and stroke) and in three patients in the digoxin group (sinus arrest, diabetes insipidus and pneumonia).[15]

This study showed that continuous intravenous landiolol, when used as an HR regulator for atrial tachyarrhythmias, can provide a more rapid HR reduction than intravenous digoxin without excessively lowering blood pressure. This effect was not affected by renal function and has been shown to be very useful in patients with AF and AF with impaired renal function.[25]

Effect of landiolol on rapid atrial tachyarrhythmias in a clinical setting

Several clinical data on the efficacy and safety of intravenous landiolol on rapid tachyarrhythmias with HF have been reported[16-24] (Table 1). These studies have focused on reductions in HR and blood pressure and adverse events, including hypotension and exacerbated HF. Although the optimal resting ventricular rate in patients with AF and HF is not certain, the ESC guidelines recommend 60–100 b.p.m. for patients with HF. In most Japanese studies, responders to landiolol have been defined as having HR decrease $\geq$ 20% or HR < 110 b.p.m. according to the criteria of the J-Land study.[15]

The effect of landiolol depends on the dose. Administration usually starts at a dose of 1.0 µg/kg/min, and the maintenance dose ranges from 1.0 to 10.0 µg/kg/min. The average dose is reported to be 3.0–5.0 µg/kg/min, and an efficacy of approximately 70% or more as the response reaches the above criteria has been obtained (Table 1). Of course, the goal of acute rate control is to stabilize haemodynamics. Interestingly, landiolol does not worsen haemodynamics even when used in

Table 1 Patient characteristics, study design and main results of landiolol studies in Japanese patients with atrial fibrillation and heart failure

	Patient characteristics	Study design	Arm	Main results
Nagai et al.[15]	200 patients with AF/AFL, HR≥120 b.p.m., NYHA FC III/IV, LVEF 25-50% (mean age 72 ± 12 years, proportion of males 53%). Ischaemic aetiology 15%.	Prospective, multicentre, single-blind, randomized controlled trial	Continuous intravenous landiolol (n = 93), intravenous digoxin (n = 107)	HR decrease ≥20% or HR < 110 b.p.m. at 2 h: landiolol (average dose of 6.7 ± 3.2 µg/kg/min) 48.0%, digoxin (0.25 mg) 13.9%. Hypotension: landiolol 7 patients, digoxin 4 patients.
Kobayashi et al.[16]	23 patients with AF, HR ≥120 b.p.m., NYHA FC III/IV (mean age 73 ± 14 years, proportion of males 61%). LVEF < 50% (n = 12), LVEF≥50% (n = 11). Ischaemic aetiology 35%.	Prospective, single-centre, non-comparative study	Continuous intravenous landiolol	At an average dose of 1.5 ± 0.4 µg/kg/min, the change in HR was −22.4% b.p.m. at 2 h; the HR decrease was greater in patients with LVEF < 50% than in patients with LVEF≥50%. No hypotension (<60 mmHg).
Adachi et al.[17]	52 patients with AF/AT, HR >100 b.p.m., NYHA FC III/IV, LVEF < 40% (mean age 65 ± 14 years, proportion of males 83%). Ischaemic aetiology 20%.	Prospective, two-centre, non-comparative study	Continuous intravenous landiolol	At an average dose of 10.8 ± 9.4 µg/kg/min, HR decreased from 133 ± 27 to 82 ± 15 b.p.m. (P < 0.01), and SBP decreased from 105 ± 21 to 101 ± 19 mmHg (P = ns). HR decrease ≥20% in all patients within 1 h. Hypotension: 3 patients.
Wada et al.[18]	39 patients with AF/AFL, HR ≥120 b.p.m. (mean age 72 ± 11 years, proportion of males 51%). Ischaemic aetiology 31%, NYHA FC III/IV 87%, mean LVEF 34 ± 16%.	Retrospective, two-centre, non-comparative study	Continuous intravenous landiolol	HR decrease ≥20% or HR < 110 b.p.m. within 3 h (responder): 29 patients (74%). The HR of responders (average dose of 4.5 ± 3.0 µg/kg/min) decreased from 152 ± 19 to 96 ± 17 b.p.m.; the HR of non-responders (average dose of 5.5 ± 4.2 µg/kg/min) decreased from 152 ± 10 to 137 ± 22 b.p.m. Hypotension (<80 mmHg): 3 patients.
Kiuchi et al.[19]	59 patients with AF/AFL, HR ≥120 b.p.m. (mean age 76 years, proportion of males 46%). Ischaemic aetiology 12%, NYHA FC III, mean LVEF 46%.	Retrospective, single-centre, comparative study	Continuous intravenous landiolol (n = 15), continuous intravenous diltiazem (n = 44)	HR decrease ≥20% or HR < 110 b.p.m. at 3 h: landiolol (average dose of 5.57 ± 4.78 µg/kg/min), 8 patients (53%); diltiazem (average dose of 2.65 ± 1.26 µg/kg/min), 14 patients (32%); P = 0.009. Latency to switch to oral beta-blockers was shorter in the landiolol groups than in the diltiazem group (median: 2 vs. 4 days, P = 0.002). BP decrease: landiolol, mean SBP from 116 to 112 mmHg, P = ns, mean DBP from 70 to 64 mmHg, P = ns; diltiazem, mean SBP from 131.1 ± 23.7 to 121.1 ± 20.3 mmHg, p < 0.001, DBP from 81.4 ± 19.0 mmHg to 69.9 ± 13.3 mmHg, P < 0.001.
Matsui et al.[20]	67 patients with AF/AFL/AT, HR ≥120 b.p.m., ADHF (mean age 67 ± 12 years, proportion of males 54%).	Retrospective, single-centre, non-comparative study	Continuous intravenous landiolol	At a median dose of 3.0 (range 1.0-12.0) µg/kg/min, HR decreased from 141 ± 17 to 99 ± 20 b.p.m. at 6 h

Continued

Table 1 Continued

	Patient characteristics	Study design	Arm	Main results
	LVEF < 50% ($n = 12$), LVEF≥50% ($n = 11$). Ischaemic aetiology 22%, NYHA FC III/IV 60%, mean LVEF 41 ± 13%.			($P < 0.001$), with no marked hypotension. 70% of discharged patients had SR, and these patients showed a lower frequency of rehospitalization due to worsening HF than patients without SR (5/41 vs. 7/18, $P = 0.019$).
Iwahashi et al.[21]	101 patients with AF, HR >120 b.p.m., NYHA FC IV, LVEF < 40% (median age 73 years, proportion of males 62%). Ischaemic aetiology 20%.	Prospective, single-centre, non-comparative study	Continuous intravenous landiolol	At an average dose of 3.8 ± 2.3 µg/kg/min, an HR decrease ≥20% or an HR < 110 b.p.m. within 24 h occurred in 95 (94%) patients. Among 37 patients who received RHC monitoring, HR decreased from 143 ± 17 to 97 ± 19 b.p.m. (p < 0.0001), and pulmonary capillary wedge pressure decreased from 23.6 ± 7.8 to 17.3 ± 6.3 ($P = 0.0008$). No bradycardia (<50 b.p.m.) nor hypotension (SBP < 80 mmHg).
Oka et al.[22]	77 patients with AF/AFL/AT, HR ≥120 b.p.m., NYHA FC III/IV, LVEF < 50% (mean age 72 ± 13 years, proportion of males 70%). Ischaemic aetiology 21%.	Retrospective, single-centre, comparative study	Continuous intravenous landiolol: AF group ($n = 65$) vs. AFL/AT group ($n = 12$)	HR decrease ≥20% or HR < 110 b.p.m. at 2 h: AF 72.3% vs. AFL/AT 16.7%, $P = 0.0004$. Maximum dose: AF 3.6 ± 2.4 µg/kg/min, AFL/AT 8.5 ± 2.4 µg/kg/min, $P < 0.001$. Alternative treatments such as intravenous amiodarone and electrical cardioversion were required in 83% of the AFL/AT patients.
Yamashita et al.[23]	1,121 patients with AF/AFL, cardiac dysfunction (mean age 73 ± 14 years, proportion of males 57%). NYHA FC III/IV 76.6%, median LVEF 40% (range 7–85%).	Prospective, multicentre, non-comparative study (post-marketing survey)	Continuous intravenous landiolol	HR decrease ≥20%: 77.5%. Adverse drug reactions: hypotension (30 events), aggravation of cardiac failure (11 events) and bradycardia (7 events).
Shinohara et al.[24]	53 patients with AF, HR ≥120 b.p.m., NYHA FC III/IV, LVEF ≤25% (mean age 67 ± 16 years, proportion of males 66%). Ischaemic aetiology 21%.	Retrospective, single-centre, comparative study	Continuous intravenous landiolol ($n = 34$), intravenous digoxin ($n = 19$)	HR decrease ≥20% or HR < 110 b.p.m. at 24 h (responders): landiolol (5.2 ± 2.7 µg/kg/min) 71.0% vs. digoxin (0.25 mg) 41.2%, $P = 0.048$. SBP was significantly decreased in the landiolol group but not in the digoxin group. Hypotension (SBP < 80 mmHg): 2 patients (landiolol).

ADHF, acute decompensated heart failure; AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; HF, heart failure; HR, heart rate; LVEF, left ventricular ejection fraction; NYHA FC, New York Heart Association functional class; SBP, systolic blood pressure.

patients with cardiac dysfunction. Kiuchi et al.[19] retrospectively evaluated that intravenous diltiazem reached the target HR less frequently than landiolol was associated with showed lower blood pressure. The benefit of intravenous landiolol is that it lowers the ventricular rate early after the start of use without markedly deteriorating haemodynamics. Because of the pharmacokinetic properties of landiolol, any adverse effects can be quickly

restored by tapering the dose or discontinuing administration altogether. These features make the drug appropriate and easy to use in acute settings.

In patients with ADHF or severe HF who are unstable hemodynamic state, landiolol is limited to use in the intensive care unit. On the other hand, in patients with mild to moderate HF who are stable hemodynamic state, it can also be used in an ordinary ward. During intravenous landiolol therapy, electrocardiographic telemetry monitoring and frequent blood pressure measurement (especially after initiation until maintenance dose) are required to assess efficacy and safety.

Dosage of landiolol

In Japan, where landiolol is most commonly used in practice, maintenance dosages of for continuous intravenous infusion of landiolol range from 1.0 to 10.0 µg/kg/min (Table 2). However, landiolol, a beta-1 blocker, does not always achieve a sufficient effect in ADHF, where sympathetic nerve activity is enhanced. Adachi et al.[17] reported that when a high dosage (up to a maximum of 20 µg/kg/min) was used with a target of 20% reduction in HR, all patients were able to reach the target HR. Three patients developed transient hypotension, and landiolol administration was discontinued, but no serious adverse events occurred.[17]

A Phase II trial in Austria, excluding HF patients of NYHA functional class III/IV, evaluated the efficacy and safety of higher dosages for rapid AF—continuous infusion at 40 µg/kg/min or a bolus dose of 100 µg/kg administered over 1 min followed by continuous infusion at 40 µg/kg/min and continuous infusion up to a maximum of 80 µg/kg/min—(maximum continuous infusion time of up to 210 min) and reported that only 3 of 20 patients developed transient hypotension; no serious adverse events occurred.[26] This study used similar doses as those used in the pharmacokinetic study in Japanese patients with supraventricular/ventricular arrhythmias (20, 40 and 80 µg/kg/min; infusion time of 5 and 15 min).[27] Additional studies conducted in different settings in Caucasian patients with supraventricular tachyarrhythmias in critical care patients[28,29] and in HF patients[30-32] showed similar dose-response with majority of patients using landiolol dose below 10 µg/kg/min (Table 3). Racial/ethnic differences in responsiveness to beta blockers have been noted[33] and genetic subtype of beta-1 receptor can lead to different HR response.[34] Although there are no racial/ethnic differences in the pharmacokinetic parameters of landiolol,[13,26,27,35] these preliminary results in Caucasians appear to confirm no difference in its pharmacodynamics. However, further studies are needed to identify the appropriate dose for acute rate control in larger cohorts.

Haemodynamics

The HR-lowering effect of landiolol persisted throughout intravenous infusion. In general, however, there was no clinically significant excessive decrease in blood pressure during intravenous landiolol therapy (Table 2). Iwahashi et al.[21] reported that among 37 patients with AF and ADHF (NYHA functional class IV, LVEF < 40%) who underwent right heart catheterization monitoring, HR decreased from 143 ± 17 to 97 ± 19 b.p.m. ($P < 0.0001$), main pulmonary artery pressure decreased from 31.1 ± 8.2 to 25.0 ± 5.3 mmHg ($P = 0.004$), pulmonary capillary wedge pressure decreased from 23.6 ± 7.8 to 17.3 ± 6.3 mmHg ($P = 0.0008$) and stroke volume increased from 25.5 ± 13.6 to 32.4 ± 11.6 mL/beat ($P = 0.02$) during continuous infusion of landiolol. However, cardiac output, right atrial pressure and systemic vascular resistance did not change during landiolol infusion. These findings suggested that landiolol improves stroke volume by improving LV filling due to lowering HR without a drop in cardiac output, since landiolol exhibits a slight negative inotropic effect.

These effects are advantageous for patients with low LVEF. Matsui et al.[20] reported that in four patients with severe systolic dysfunction (LVEF $\leq 30\%$), intravenous landiolol did not decrease blood pressure or worsen the haemodynamic state, and as a result, the LVEF values of these patients were improved after landiolol therapy.[20]

Atrial fibrillation and other atrial tachyarrhythmias (atrial flutter/atrial tachycardia)

AFL and AT are also relatively common atrial tachyarrhythmias, which are characterized by rapid, regular atrial rhythm with a regular ventricular rate. In patients with AFL/tachycardia, pharmacological rate control often has difficulty achieving adequate HR reduction.

Oka et al. reported that the magnitude of HR reduction was diminished in patients with AF compared with patients with AFL/AT despite a higher dose of landiolol (% change in HR from baseline to 12 and 24 h was only $-10.2 \pm 12.7\%$ and $-16.1 \pm 19.4\%$ in patients with AFL/AT, $-28.3 \pm 13.2\%$ and $-31.3 \pm 11.3\%$ in patients with AF ($P < 0.02$), respectively (Table 2). The prevalence of reaching the target HR (an HR decrease of $\geq 20\%$ or HR < 110 b.p.m.) with landiolol was higher in patients with AF than in patients with AFL/AT (72.3% vs. 16.7%, $P < 0.001$).[22] For AFL/AT, alternative therapies, including intravenous amiodarone or digoxin, and prompt cardioversion should be considered if intravenous landiolol fails to achieve sufficient rate control.

LVEF

The ESC guidelines state that the drug choice for acute HR control in AF depends on the LVEF; beta blockers are the first-line treatment for patients with an LVEF of $\geq 40\%$ or $< 40\%$.[9] Kobayashi et al.[16] reported that patients with an LVEF of $\geq 50\%$ experienced a much larger decrease in HR than patients with an LVEF $< 50\%$ 1-2 h after the start of landiolol treatment, although there was no difference at later time points. Ozaki et al.[36] reported that AF patients with an LVEF $\geq 40\%$ showed a much larger

Table 2 Dose and hemodynamic profiles of landiolol studies in Japanese patients with atrial fibrillation and heart failure

	Subjects (by condition)	Number	NYHA functional class	LVEF (%)	Initial dose (μg/kg/min)	Maintenance dose (μg/kg/min)	HR (b.p.m.)	SBP
Kobayashi et al.[16]	AF + ADHF	23	≥3	45.1 ± 13.5	1.0	1.5 ± 0.4	139.0 ± 14.8 ⊿−22.4%	No significant SBP change in 24 h.
Adachi et al.[17]	AF/AT + ADHF	52	≥3	32.3 ± 11.9	1.0	10.8 ± 9.4	133.3 ± 27.3 →83.0 ± 15.3	105.1 ± 20.6 mmHg→101.1 ± 19.2 mmHg. Hypotension: 3 patients.
Wada et al.[18]	AF/AFL/AT	39	≥3 (87%)	34 ± 16	1.0	4.8 ± 3.3	152 ± 19 →88 ± 29	116 ± 20 mmHg→103 ± 20 mmHg. Hypotension (SBP < 80 mmHg): 3 patients.
Kiuchi et al.[19]	AF/AFL + ADHF	15	3	42	0.5-1.0	5.57 ± 4.78	132 →98 (at 2 h)	116 mmHg→112 mmHg (at 2 h).
Matsui et al.[20]	AF/AFL/AT + ADHF	67	≥2, ≥3 (60%)	41 ± 13	1.0	Median 3.0 (range 1.0-12.0)	141 ± 17 →99 ± 20 (at 6 h)	116 ± 19 mmHg→111 ± 14 mmHg (at 6 h). Hypotension (SBP < 90 mmHg): 2 patients.
Iwahashi et al.[21]	AF + ADHF (LVEF < 40%)	101	4	22 (18-32)	1.0	3.8 ± 2.3	(n = 37) 143 ± 17 →97 ± 19	(n = 37) 127 ± 2 mmHg→116 ± 17 mmHg.
Oka et al.[22]	AF/AFL/AT + ADHF	77	≥3	33.1 ± 13.7	1.0	AFL/AT: 8.5 ± 3.0 AF: 3.6 ± 2.4	AFL/AT: 149.2 ± 10.8→139.2 ± 16.8 (at 2 h) AF: 142.0 ± 15.7→114.9 ± 17.4 b.p.m. (at 2 h). Bradycardia (HR < 50): 1 patient	Hypotension (SBP < 80 mmHg): AFL/AT 3 patients, AF 6 patients.
Shinohara et al.[24]	AF + ADHF (LVEF≤25%)	53	≥3	23.6 ± 4.0	0.5-1.0	5.2 ± 2.7	142.9 ± 15.8 →97.5 ± 17.2 (at 24 h)	122 mmHg→110 mmHg (at 24 h). Hypotension (SBP < 80 mmHg): 2 patients.

ADHF, acute decompensated heart failure; AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; HR, heart rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure.

Table 3 Patient characteristics, study design and main results of landiolol studies in Caucasian patients with atrial tachyarrhythmias and/or HF

	Patient characteristics (*group treated with landiolol)	Study design	Landiolol dosing	Main results
Stix et al.[26]	20 patients with AF/AFL, HR ≥100 b.p.m., SBP ≥100 mmHg, (mean age 67 ± 9 years, proportion of males 60%).	Prospective, single-centre, open label trial	Bolus + Infusion landiolol (n = 10) 100 µg/kg bolus administered over 1 min + 40 µg/kg/min up to a maximum of 80 µg/kg/min, Infusion landiolol (n = 10) 40 µg/kg/min up to maximum of 80 µg/kg/min.	Median HR decrease by 20.5 b.p.m., corresponding to a reduction of −17.2%, at 16 min). Overall reduction of AF/AFL symptoms at 16 min was 72%. Hypotension: 20 patients. No serious adverse events.
Weinmann et al.[28]	10 patients with AF/ST, HR 163 ± 15 b.p.m. (mean age 66 ± 15 years). MAP 68 ± 10 mmHg, LVEF 40 ± 12%. AF (90%) and ST (10%), under catecholamines (70%).	Consecutive series of patients critically ill patients with tachycardia and hypotension	Continuous intravenous landiolol (n = 10)	AF Patients showed HR decrease of 22 ± 7%, while patient with sinus tachycardia showed less HR reduction (−9%). After 2 hrs infusion hemodynamic stability (mean SBP 97 ± 12 mmHg, mean DBP 59 ± 6 mmHg, mean MAP 71 ± 10 mmHg). One septic patient with high dose catecholamine did not tolerate landiolol.
Hariri et al.[29]	15 patients with AF/AFL, HR 150 (138-150) b.p.m. [median age 70 (67-72) years, proportion of males 73%]. SOFA score 11 (7-12). LEVF 55 (50-57%), chronic AF (40%).	Consecutive series of COVD-19 patients	Continuous intravenous landiolol (n = 15). Landiolol infusion was started at 0.2 µg/kg/min and dosage reached 3.9 (1.6-7.0) µg/kg/min at 24 h.	HR reduction was 23% [115 (108-117) vs. 150 (138-160)] b.p.m. without any negative impact on global hemodynamic or tissue perfusion parameters during landiolol infusion, Norepinephrine need decreased in 9/11 patients (81%), and mean norepinephrine dose significantly decreased [0.7 (0.2-1) vs. 1.0 (0.4-1.5) µg/kg/min].
Dabrowski et al.[30]	3 patient cases with AF and ADHF, HR ≥110 b.p.m. [age 66/70/76 years, female (n = 2)/male (n = 1)]. LVEF < 25%.	3 patient cases with ADHF and treated with a combination of levosimendan and a low dose of landiolol	Continuous intravenous landiolol (10-20 µg/kg/min)	Concomitant administration of landiolol (10-20 µg/kg/min) and levosimendan (0.1 µg/kg/min) is well tolerated provides improved cardiac function improvement and stroke volume normalization, along with norepinephrine dose reduction.
Anifanti et al.[31]	19 patients* with HF and tachycardia post-extubation, LVEF 36.6 ± 7.6%, NYHA FC III (n = 32)/IV (n = 9).	Prospective, single-centre, randomized comparative study	Continuous intravenous landiolol (n = 19) (4 µg/kg/min) Continuous intravenous esmolol (n = 20) (100 µg/kg/min)	Landiolol produces a faster and deeper HR decrease compared with esmolol (−40 ± 20 vs. −30 ± 16 b.p.m.) without any hemodynamics deterioration as opposed to esmolol which was associated with a significant MAP reduction.

Continued

Table 3 Continued

	Patient characteristics (*group treated with landiolol)	Study design	Landiolol dosing	Main results
Ditali et al.[32]	2 patients with AF and ADHF. Patient A (age 44 years, male): HR 140 b.p.m., NYHA FC III, LVEF 15% Patient B (age 20 years, female): HR 120 b.p.m., NYHA FC II, LVEF 25%.	Series of 5 critically ill patients treated with a combination of inotropes and a low dose of landiolol	Continuous intravenous landiolol (6 and 9 µg/kg/min).	Patient A (9 µg/kg/min): HR decreased from 140 to 90 b.p.m. and SBP decreased from 130 to 120 mmHg. LVEF increased (LVEF 35%) and NT-proBNP decreased from 1,553 to 1,284 pg/mL. Patient B (6 µg/kg/min): HR decreased from 120 to 66 b.p.m. and SBP increased from 88 to 100 mmHg. LVEF did not change (LVEF 25%), but NT-proBNP decreased from 13 130 to 7008 pg/mL.

ADHF, acute decompensated heart failure; AF, atrial fibrillation; AFL, atrial flutter; DBP, diastolic blood pressure; HF, heart failure; HR, heart rate; LVEF, left ventricular ejection fraction; MAP, mean atrial pressure; NT-proBNP, N-terminal probrain natriuretic peptide; NYHA FC, New York Heart Association functional class; SBP, systolic blood pressure; SOFA, Sequential Organ Failure Assessment; ST, sinus tachycardia.

decrease in HR than AF patients with an LVEF < 40% after starting a similar dose of landiolol. Matsui et al.[20] also reported that there was a greater decrease in HR in patients with an LVEF ≥40% than in those with an LVEF <40% despite a similar maintenance dose of landiolol.[20] Patients with an LVEF ≥40% are more likely to experience the HR-lowering effect of landiolol than those with an LVEF <40%. Wada et al. reported that only five of nine patients with an extremely low LVEF < 25% reached the target HR (HR decrease ≥20% or HR < 110 b.p.m.), despite using a higher dose of landiolol 6.3 ± 4.6 µg/kg/min, and low LVEF was associated with the development of adverse events.[18] Shinohara et al. reported that 71% of patients with an LVEF < 25% reached the target HR (HR decrease ≥20%) during landiolol therapy.[24]

Even in patients with severe LV systolic dysfunction (LVEF≤30%), landiolol therapy could be continued without haemodynamic deterioration, and the LVEF values of these patients could improve after landiolol therapy. However, it may be important to characterize LV systolic function when administering continuous intravenous landiolol.

Outcomes

Landiolol reliably lowers the HR and improves haemodynamics in patients with atrial tachyarrhythmias and ADHF. Matsui et al.[20] reported that 22% of the patients receiving landiolol exhibited spontaneous restoration of sinus rhythm, and when defibrillation was added, 42 (63%) of the 67 patients showed a restored sinus rhythm during hospitalization.[20] Wada et al.[18] also reported that 9 (31%) of 29 patients who responded to landiolol (HR decrease ≥20% or HR < 110 b.p.m. within 3 h) exhibited

spontaneous restoration of sinus rhythm, and when defibrillation was added, 21 (54%) of the 39 patients showed a restored sinus rhythm.

In HF, sympathetic nerve activity is enhanced, and the stimulation of beta-adrenergic receptors alters the activity of several ion channels and transporters, which leads to arrhythmogenesis.[37] Landiolol may be effective in treating atrial tachyarrhythmias due to increased sympathetic drive in HF.

After landiolol therapy, further introduction or strengthening of basic pharmacotherapy for HF (such as the use of beta blockers and renin-angiotensin-aldosterone system inhibitors) and additional rhythm control strategies were provided to improve outcomes. Matsui et al.[20] reported that 41 (69%) of the 59 patients who were alive at discharge were in sinus rhythm (Figure 1). Rehospitalization due to worsening HF occurred less frequently in patients who were discharged with sinus rhythm than in those discharged with atrial tachyarrhythmias (5/41 vs. 7/18, P = 0.019).[20] Yamashita et al. also reported from a post-marketing survey that patients who were switched from landiolol to oral beta blockers had lower all-cause mortality and HF-specific mortality than those who were not switched [hazard ratio 0.39, 95% confidence interval (CI) 0.28–0.55; hazard ratio 0.40, 95% CI 0.23–0.70, respectively].[38] Kiuchi et al.[19] reported that the latency to switch to oral beta blockers was shorter in patients receiving intravenous landiolol than in patients receiving intravenous diltiazem (median: 2 vs. 4 days, P = 0.002). Adachi et al.[17] reported that 44 of 52 patients could switch from intravenous landiolol to oral beta blockers, 28 patients received additional non-pharmacological therapies such as catheter ablation, cardiac resynchronizing therapy and valve surgery, and 49 discharged patients were in NYHA functional class I/II.
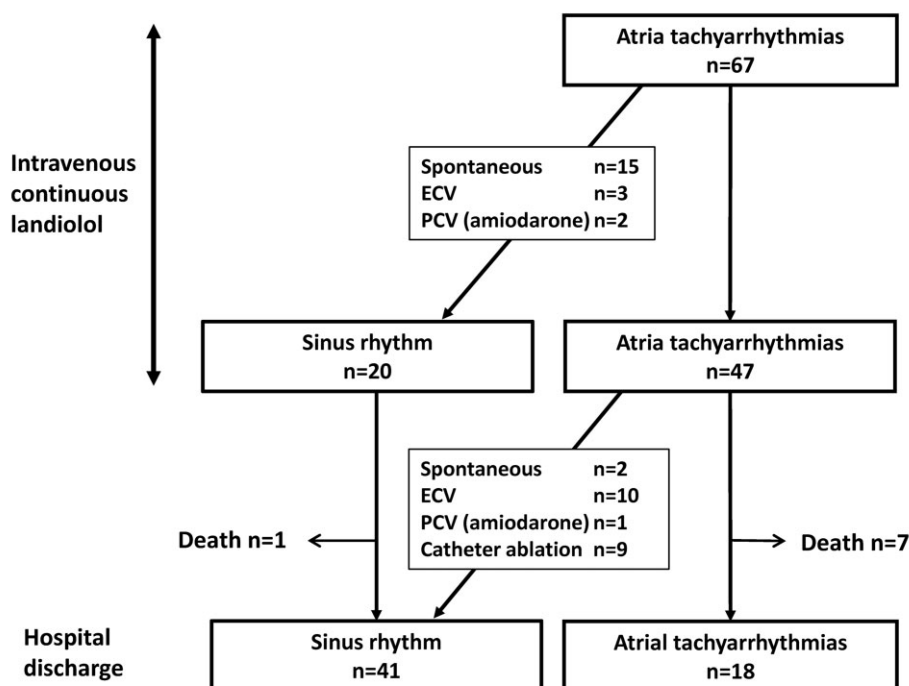
Figure 1 Sinus rhythm restoration in patients with atrial tachyarrhythmias and acute decompensated heart failure during and after intravenous landiolol infusion. Reproduced from Matsui *et al.*[20] The median maintenance dosage of intravenous landiolol was 3.0 (range 1.0–12.0) µg/kg/min, and the median treatment duration of intravenous landiolol was 5 days. ECV, electrical cardioversion; PCV, pharmacological cardioversion.

In patients with atrial tachyarrhythmias and ADHF, the restoration of sinus rhythm improves haemodynamics and cardiac function, and additional therapies for HF and the restoration and maintenance of sinus rhythm may prevent HF exacerbation and lead to a subsequent improvement in prognosis. In acute care settings, there is a high recurrence in patients in whom initial cardioversion is successful.[8] It is difficult to restore and maintain sinus rhythm in patients with deteriorated haemodynamics. In this situation, intravenous landiolol may be useful as the first-line therapy for improving the haemodynamic status by lowering the HR. After the cardiac status is stabilized, subsequent rhythm control therapy, such as cardioversion and catheter ablation, will be effective, although sinus rhythm cannot be restored during landiolol treatment. It is necessary to stabilize haemodynamics by rapidly controlling the rate of atrial tachyarrhythmias in patients with ADHF. Landiolol may reliably lower the HR during atrial tachyarrhythmias in ADHF patients without degrading their haemodynamics.

Safety

There have been no serious adverse reactions to landiolol in previous reports (*Table 1*). However, as one might expect given the pharmacological properties of the drug, hypotension, excessive bradycardia and worsening HF have been reported, although they are not frequent. These adverse drug reactions do not seem to be dose dependent. Wada *et al.*[18] reported that hypotension was observed as an adverse effect in approximately 10% of patients with atrial or ventricular tachyarrhythmias who received intravenous landiolol and that hypotension was associated with a reduced LVEF (<25%).

Due to the pharmacokinetic properties of landiolol, including a very short elimination half-life and restricted distribution, the drug is rapidly eliminated, and the patient's condition reverts quickly if administration is discontinued. This may be the main reason adverse reactions to landiolol do not lead to serious adverse events in an acute-care setting.

Conclusion

In the context of acute care, intravenous landiolol reduced the HR without markedly decreasing blood pressure in patients with atrial tachyarrhythmias and ADHF. Hypotension, excessive bradycardia and worsening HF have been observed as adverse effects but are less frequent, and the patient's condition recovers soon if administration is discontinued. Intravenous landiolol is recommended to acutely control HR in patients with atrial tachyarrhythmias and worsening HF, especially reduced LV systolic function (LVEF < 40%) in acute setting. It can also be used to reduce HR in patients with haemodynamic instability. Stabilizing the cardiac status in the early period of ADHF by rapid HR control leads into subsequent HF pharmacotherapy and rhythm control therapies and will contribute to the improvement of outcomes.

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Data availability

No new data were generated or analysed in support of this research.

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