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Landiolol for rate control management of atrial fibrillation in patients with cardiac dysfunction

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Atrial fibrillation (AFib) is frequently associated with heart failure. Guidelines for AFib management have been recently updated and include an algorithm for acute heart rate control based on left ventricular ejection fraction and haemodynamics. Landiolol is an injectable ultra-short beta-blocker with very high beta-1 selectivity, listed in Japanese Guidelines for AFib management as potential option for rate control of patient with heart failure. Landiolol is now available in Europe with indication of controlling heart rate in AFib and supraventricular tachycardia. This review discusses existing clinical data in Japan and perspectives of landiolol use for acute rate control of AFib patients with cardiac dysfunction.

Introduction

Prevalence of atrial fibrillation (AF) in patients with heart failure (HF) is high. A European survey on AF reported that 34% of patients with AF had concomitant HF.[1] Recently, the Swedish Heart Failure Registry identified 39% of HF patients with AF and 61% were in sinus rhythm.[2]

Patients who have AF and HF are known to have a worse prognosis than patients with HF and sinus rhythm.[3,4] AF with rapid ventricular response has been identified as a precipitating factor of cardiac decompensation in 17% of patient hospitalized for acute HF (AHF),[5] but other series have reported values up to 40%.[6,7] One study identified permanent AF as the principal (73.5%)[7] type of this arrhythmia, and the presence of AF was associated with longer hospital stay and higher mortality rates.[6,7]

From the pathophysiological standpoint, tachycardic AF, because of a continuous rapid ventricular response, can induce left ventricular (LV) systolic dysfunction (i.e. tachycardia-induced cardiomyopathy). AF with rapid ventricular response impairs LV filling through loss of active atrial contraction and shortening of diastole, leading to hypotension, which can in turn lead to patient discomfort and organ dysfunction.[8]

Atrial fibrillation guidelines perspectives

The management of AF in patients with AHF has been described both in the AF[9] and the HF[10] guidelines of the European Society of Cardiology (ESC), which have been updated in 2016. Concerning rate control, the AF guidelines[9] now clearly distinguish situations with patients displaying existing cardiac dysfunction [left ventricular ejection fraction (LVEF) <40%] and those with normal or mildly compromised left ventricular function (LVEF > 40%).

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Following the guidelines,[10] it is mandatory to identify any of five triggers of cardiac decompensation, after having initiated circulatory and ventilator support: arrhythmias and conductance disturbances stand for the A, appearing in the acronym CHAMP designating potential causes to explore (C for acute coronary syndrome, H for hypertension emergency, M for acute mechanical cause, and P for pulmonary embolism). Urgent electrical cardioversion is recommended if AF is contributing to the patient's haemodynamic compromise in order to improve the patient clinical conditions, however, this is not always possible in patients with AF of unknown duration. While AF guidelines recommend to start with beta-blockers for rate control at the lowest dose possible, in patients with (LVEF < 40%), the HF guidelines remind us that oral beta-blockers may be initiated to control ventricular rate only if the patient display no worsening symptoms of HF. For patients with marked congestion with few symptoms at rest, the HF guidelines recommend digoxin orally or intravenously (IV). For patients with haemodynamic instability, IV digoxin, or amiodarone should be administered and in haemodynamic collapse, emergency electrical cardioversion is recommended.[10]

Therapeutic options for rate control in atrial fibrillation patients with cardiac dysfunction

Although digoxin has additional inotropic effects that may be benefitial in patients with HF, its negative chronotropic effect mediated through vagal stimulation is slow to develop, and its effect on the ventricular rate response decreases in presence of high adrenergic tone.[11] Amiodarone also has some limitations as its potential local toxicity may develop when injected or infused into peripheral veins and longer-term infusion of amiodarone should be delivered only by central venous access to avoid peripheral vein phlebitis.[11] Amiodarone may also trigger hypotension, and its accumulation in the body is important, potentially leading to serious adverse events (lung fibrosis, thyrotoxicosis etc . . .) when administered for longer periods.[11]

While hyperthyroidism may induce AF, the thyroid gland function is often not known during the first AF presentation, hence amiodarone must be used with caution to prevent a thyrotoxic crisis.[12]

On the other hand, in AF patient with cardiac dysfunction (LVEF < 40%), beta-blockers are to be used carefully because of their negative inotropic effects, which may depress cardiac function and further deteriorate ventricular dysfunction, thus accelerating HF decompensation.[13]

In this regard, the HF guidelines of the ESC state that 'for patients in New York Heart Association (NYHA) Class I-III, a beta-blocker, usually given orally, is safe and therefore is recommended as first-line treatment to control ventricular rate, provided the patient is euvolaemic.'

AF Guidelines recommend that initiation of beta-blockers in patients with cardiac dysfunction should be performed at lowest dose possible and titrated as needed.[10] Injectable beta-blockers for acute rate control include metoprolol and esmolol.[10] Esmolol is an injectable short acting agent whose profile enables rapid titration. However, despite such pharmacokinetic profile, in a study conducted in critical

care patients with cardiac dysfunction [B-type natriuretic peptide (BNP) > 343 pmol/mL], 44% of patients had to discontinue esmolol infusion for adverse events such as hypotension, acute dyspnea, and pulmonary congestion or severe bradycardia accompanied with hypotension. Patients with concomitant hypotension and LVEF < 50% were more likely not to tolerate esmolol infusion, with 83% (10/12) necessitating stop of the drug infusion.[14]

Landiolol in atrial fibrillation and heart failure patients: randomized study

In this context, landiolol may be more useful due to its ultra-short acting profile with faster pharmacokinetic and higher beta1 selectivity as compared to esmolol, with less hypotensive and negative inotropic effect. Landiolol has been safely used to control heart rate (HR) in patients with HF and AF, showing limited impact on blood pressure and good tolerance.[13,15-24] Landiolol has been also used to prevent AF in post-cardiac surgery patients with cardiac dysfunction,[25] which will be discussed in a review article of this supplement by Fellahi *et al.*[26]

The drug's profile has been compared to digoxin in a randomized prospective trial conducted by Nagai *et al.*[15] in 200 patients with tachycardia and cardiac dysfunction (LVEF 25-50%) to evaluate its efficacy and safety. Groups were comparable in term of HF severity. The infusion of landiolol was titrated between 1 and 10 μg/kg/min for 2 h and continued for 1 or 2 days. At 2 h, the decrease of HR was more profound, with patients achieving control more frequently with landiolol as compared with digoxin (*Figure 1*).

Tolerance of landiolol was comparable to digoxin with similar adverse event rate. However, during the 2 h infusion, blood pressure was statistically lower with landiolol compared to digoxin (*Figure 1*). Landiolol had to be discontinued in only three of 200 patients. At the end of the infusion, landiolol patients were easily transitioned to oral beta-blockers (bisoprolol or low dose carvedilol) at a mean dose of 1.8 ± 1.3 mg and 3.2 ± 2.7 mg, respectively.[15]

Controlling the HR with landiolol or digoxin throughout the study period improved the clinical status with percentage of patients displaying severe cardiac dysfunction decreasing in both group (see *Figure 2*).
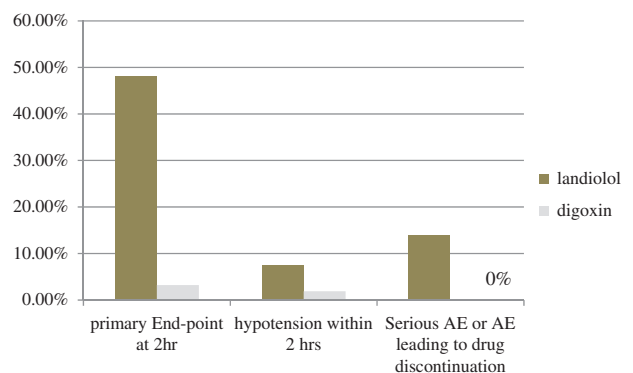

Figure 1 Percentage of patients achieving the primary Endpoint, developing hypotension or serious adverse events in response to treatment.
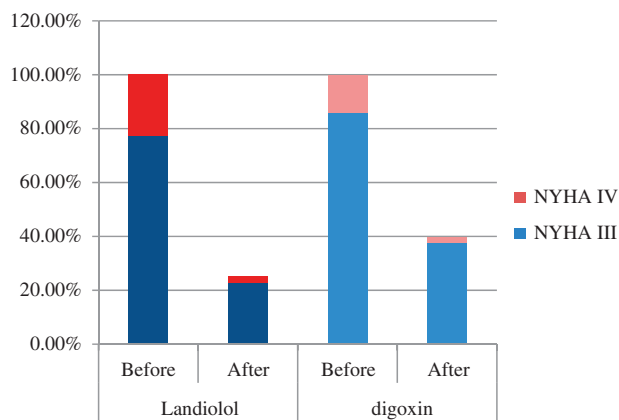
Figure 2 Evolution of cardiac dysfunction status in response to treatment.

A sub-analysis of this study published by Kinugawa et al.[16] showed that the efficacy of landiolol was better than digoxin in patients with cardiac dysfunction or low baseline blood pressure (Table 1). However, there was no difference between groups for patients with NYHA IV.

Landiolol in atrial fibrillation and heart failure patients: retrospective studies

Landiolol has also been used successfully in patients with HF with different conditions in a retrospective study by Adachi et al.[13] (Table 2). Ten patients with NYHA III and 42 patients with NYHA IV were administered an infusion of landiolol initiated at a low dose of 1 μg/kg/min. Half the patients treated with low dose landiolol (1-2 μg/kg/min) also received milrinone whereas the majority of patients were treated with a higher dose of landiolol (>3 μg/kg/min) and received a concomitant administration of dobutamine. Landiolol decreased patients' HR while their systolic blood pressure remained almost unchanged, and an improvement in LVEF was observed from $32 \pm 12\%$ to $40 \pm 6\%$.

Only three patients (5.8%) developed transient hypotension which recovered after stopping the infusion of landiolol. No other adverse effects occurred during the infusion period, and transition to oral beta-blockers was easily completed in 44 of 52 patients. The other 8 patients received

catheter ablation, cardiac resynchronization therapy or valve replacement therapy.

Another study by Kobayashi et al.[17] evaluated landiolol in 23 patients with NYHA III-IV HF status, with systolic or diastolic dysfunction. Low dose landiolol decreased patients' HR by 22.4% during AHF decompensation, without significant changes of the systolic blood pressure during 24 h of infusion. The difference in decreasing HR between systolic dysfunction and diastolic dysfunction patients became significant only at 1 h and 2 h after infusion start, with a more profound decrease in patients with diastolic dysfunction. There was no further difference thereafter, with similar HR decrease in both group. In addition, there was no blood pressure change throughout 24 h of infusion and no adverse event was observed in either subgroup. Patients with paroxysmal AF converted to sinus rhythm easily (7/8) after 12 h landiolol infusion.

A difference in HR response in function of ejection fraction status was also observed by another group of investigators (Ozaki et al.[18]) who evaluated landiolol in 33 patients with acute decompensated HF in NYHA Class III-IV. After infusing similar doses of landiolol, patients' HR decreased significantly less in patients with HF with preserved ejection fraction (HFpEF) as compared to patients with HF with reduced ejection fraction (HFrEF).

A recent retrospective study by Kiuchi et al.[19] compared 15 patients treated with landiolol to 44 patients treated with diltiazem. Although there was a trend for the landiolol group to have lower blood pressure at baseline, the degree of cardiac dysfunction was similar. Following drug infusion, a decrease in HR was observed in both groups. There was no significant drop in blood pressure in the landiolol group while diltiazem induced decreasing of patients' blood pressure. The time to transition to oral therapy was shorter in the landiolol group in patients with HFrEF, whereas there was only a trend for shorter transition in the group of patients with HFpEF. These findings confirm that beta-blockers should be preferred over calcium channel blockers for rate control in patients with LVEF < 40%, as recommended in the guidelines, even though in the acute setting a particular note of caution is warranted.[9]

Characterizing preserved or reduced ejection fraction is an important element to consider when initiating a treatment of landiolol. Indeed, another retrospective trial by

Table 1 Percentage of patients achieving the primary Endpoint according to New York Heart Association status, left ventricular ejection fraction, or systolic blood pressure at baseline

subgroup	Landiolol % (n/total)	Digoxin % (n/total)	Risk difference [95% CI]	P-value
SBP < 120 mmHg	**45.7** (16/35)	**14.0** (6/43)	31.1 [12.4, 49.8]	0.001
SBP ≥ 120 mmHg	**51.1** (24/47)	**12.7** (7/55)	36.3 [20.1, 52.4]	0.001
LVEF 25−<35%	**47.2** (17/36)	**9.3** (4/43)	33.1 [14.7, 51.5]	0.001
LVEF 35−50%	**50.0** (23/46)	**16.4** (9/55)	31.2 [14.4, 49.7]	0.001
NYHA class III	**53.2** (34/67)	**13.8** (12/87)	38.3 [25.3, 51.3]	0.001
NYHA class IV	**35.3** (6/17)	**9.1** (1/11)	24.3 [−11.3, 59.9]	**0.2**

Table 2 Patients characteristics, dosing, and haemodynamic response of landiolol in patients with atrial fibrillation and concomitant heart failure

Study	Patient characteristics	Landiolol dosing	Principal findings
Nagai *et al*[15]; Randomized Prospective Controlled Landiolol (*n* = 93) Digoxin (*n* = 107)	Patient condition:LVEF 36.4 ± 7.9% (Lan) 36.7 ± 7.3% (Digo) BNP (pg/mL) 688.0 ± 663.8 (Lan) 639.0 ± 456.6 (Digo)	Landiolol infusion: mean dose for 2 h 6.7 ± 3.2 mcg/kg/min mean dose after 2 h 6.3 ± 3.5 mcg/kg/min mean duration 20.4 ± 20.8 h Digoxin dose: Initial dose of 0.25 mg uptitrated within 72 h according to the patient's condition.	HR decrease at 2 h −27 ± 13.3 b.p.m. (Lan) −16.0 ± 13.0 b.p.m. (Digo) Patients with HR < 110 b.p.m.: 48.0% (Lan) and 13.69% (Digo) Blood pressure decrease at 30 min (Lan vs. Digo) SBP 118.1 vs. 129 mmHg, DBP 79.7 vs. 85.3 mmHg at 2 h (Lan vs. Digo) SBP 114.1 vs. 127.7 mmHg) DBP no difference
Adachi *et al*.[13] Non-comparative trial (*n* = 52)	Patient condition:ischaemic disease (19%), non-ischaemic cardiomyopathy (62%), and valvular disease (19%) Type of SVT: Paroxysmal AF (30%), persistent AF (45%), atrial tachycardia (25%) LVEF: 32.3 ± 11.9% Mean BNP: 1,017 ± 643 pg/mL	Landiolol infusion: 10.8 ± 9.4 mcg/kg/min Infusion duration: 3 ± 1 days	HR decrease: from 133.2 ± 27.3 b.p.m. to 82.0 ± 15.3 b.p.m. SBP unchanged: from 105.1 ± 20.6 to 101.1 ± 19.2 mmHg. LVEF increase from 32.3 ± 11.9% to 39.7 ± 6.5%
Kobayashi *et al*.[17] Non-comparative trial (*n* = 23)	Patient condition: systolic dysfunction (52%) and diastolic dysfunction (48%) Type of SVT: paroxysmal AF (30%) and persistent AF (45%)	Landiolol infusion: 1.0-2.0 mcg/kg/min (mean 1.5 mcg/kg/min) for 24 h	HR decrease: significant HR reduction of 22.4% within 2 h; SBP: unchanged during all 24 h Paroxysmal AF conversion (7/8)
Ozaki *et al*.[18] Non-comparative trial (*n* = 33)	Patient condition: HFrEF 22/33 (67%) and HFpEF 11/33 (33%)	Landiolol infusion: 2.6 ± 1.5 mcg/kg/min in HFpEF and 2.9 ± 1.6 mcg/kg/min in HFrEF	HR decrease: −38 ± 12% (HFpEF) and −26 ± 13% (HFrEF) Hypotension (SBP < 80 mmHg) was not recorded in HFpEF group but in one patient with HFrEF.
Kiuchi *et al*.[19] retrospective comparative trial Landiolol (*n* = 15) Diltiazem (*n* = 44)	Patient condition LVEF: 42% (Lan) and 47% (Dilt) BNP: 767.6 pg/mL (Lan) and 605.8 pg/mL (Dilt) Baseline Blood pressure (SBP/DBP) 116/70 (Lan) and 131/81 (Dilt)	Landiolol infusion: 5.6 ± 4.8 mcg/kg/min Diltiazem infusion: 2.6 ± 1.2 mcg/kg/min	HR decrease: −18% (Dilt) and −26% (Lan) Blood pressure change: Unchanged for Lan. Decreased for Dilt. (−8% for SBP/−14% for DBP)
Wada *et al*.[20] Non-comparative trial AF (*n* = 39) VT (*n* = 12)	Patient condition: Lan. responders higher LVEF (37% ± 16) lower BNP (387 pg/mL;134-663) Lan. non-responders lower LVEF (25% ± 12) higher BNP (820 pg/mL;321-1699)	Landiolol infusion: 4.5 ± 3.0 mcg/kg/min in responders 5.5 ± 4.2 mcg/kg/min in non-responders 4.4 ± 2.8 mcg/kg/min in high LVEF (40 ± 13%) 6.3 ± 4.6 mcg/kg/min in low LVEF (14 ± 4%)	HR decrease: 36.8% from 152 to 96 b.p.m. Blood pressure decrease 11% from 117 to 104 mmHg LVEF increase: From 14% to 32% in LVEF < 25% subgroup;from 40% to 45% in LVEF > 25% subgroup

HR, heart rate; LVEF, left ventricular ejection fraction; BNP, brain natriuretic peptide; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood Pressure; SVT, supraventricular tachycardia; AF, atrial fibrillation; VT, ventricular tachyarrhythmias; Lan, landiolol; Digo, digoxin; Dilt, diltiazem.

Wada et al.[20] confirmed that patient response in terms of HR reduction and tolerance differ according to LV function.

In 74% of patients, landiolol induced HR reduction of 36.8%. Non-responders have been identified by nearly unchanged HR combined with modest 10% decrease in blood pressure. However, cardiac function was improved in both groups, with a decrease in BNP and an increase in LVEF. In this study,[20] the subgroup of patients with LVEF <25% had a lower rate of patients responding (56%) and a higher proportion (22%) developed adverse events. However, this subgroup also displayed a larger improvement in LVEF after treatment whereas a subgroup with LVEF >25% experienced a modest improvement.

This study[20] also included a group of 12 patients with ventricular tachycardia and cardiac dysfunction with seven patients responded to landiolol treatment. LV dimension was found to be significantly enlarged in non-responders, with LVEF also lower than in responders. However, in contrast with AF patients, BNP was lower in non-responders.

Limitations

The data regarding efficacy and tolerance of landiolol in patients with cardiac dysfunction are quite consistent across publications but mainly result from small cohort of patients with only one large randomized trial.[15,16] There is a lack of randomized studies comparing landiolol efficacy and tolerance vs. amiodarone when used for HR control in patients with cardiac dysfunction. There is also a need for data regarding the association with other agents, such as digoxin, which is likely to be combined with beta-blockers as recommended AF Guidelines.[9]

It should be noted that in Japan, landiolol is often combined with inotropic agents (from 13% up to 83%)[13,15-17,24] such as dobutamine. In Europe, such practice may not be frequent, but the possibility of associating levosimendan (which is not available in Japan) with landiolol represents an alternative and will open to new perspectives. Similarly, carperitide was used frequently in most studies[13,15-17,20] (from 21%[20] up to 100% of patients[13]). These differences will have to be taken into consideration when interpreting results obtained in Japan.

Conclusion

In conclusion, landiolol at low dose represents a promising option to control the HR in patients with cardiac dysfunction presenting to Cardiac Intensive Care units. Landiolol has been associated with effective control of HR and seems to be well tolerated, especially in patients with preserved ejection fraction. In patients with reduced ejection fraction, titration may be conducted more cautiously, starting at low dose well below 10 μg/kg/min. Landiolol can be used in patients with AHF with arrhythmias such AF for controlling HR and as a bridge to oral beta-blocker therapy, or conducting catheter ablation, cardiac resynchronization therapy, valve replacement therapy or stabilizing patient before implanting a LV assist device[21] or after cardiac surgery.[22]

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