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

Stephan von Haehling1*, Jan Bêlohlávek2, Fikret Er3, Natig Gassanov3, Fabio Guarracino4, and Olivier Bouvet5

1Department of Cardiology and Pneumology, University of Göttingen Medical Center, Robert-Koch-Strasse 40, DE-37075 Göttingen, Germany
2Department of Internal Medicine, Cardiovascular Medicine, General Teaching Hospital and 1st Faculty of Medicine, Charles University, U Nemocnice 2, Praha 2, 128 00 Prague, Czech Republic
3Department of Cardiology, Rhythmology and Intensive Care Medicine, Klinikum Gütersloh, Germany
4Department of Anaesthesia and Critical Care Medicine, Cardiothoracic and Vascular Anaesthesia, Azienda Ospedaliero Universitaria Pisana, Via Roma n. 67, 56126 Pisa, Italy
5Department of Clinical Research and Pharmaceutical Development, Amomed Pharma GmbH Vienna, Austria

KEYWORDS
Atrial fibrillation; Beta-blockers; Landiolol; Heart failure; Supraventricular tachycardia

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 AF9 and the HF10 guidelines of the European Society of Cardiology (ESC), which have been updated in 2016. Concerning rate control, the AF guidelines9 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%).
Following the guidelines, 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.

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

Although digoxin has additional inotropic effects that may be beneficial 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. 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. 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.

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.

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.

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 euvoalaemic.’ AF Guidelines recommend that initiation of beta-blockers in patients with cardiac dysfunction should be performed at lowest dose possible and titrated as needed. Injectable beta-blockers for acute rate control include metoprolol and esmolol. 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.

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. Landiolol has also been used to prevent AF in post-cardiac surgery patients with cardiac dysfunction, which will be discussed in a review article of this supplement by Fellahi et al.

The drug’s profile has been compared to digoxin in a randomized prospective trial conducted by Nagai et al. 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.

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.](image-url)
A sub-analysis of this study published by Kinugawa et al.\textsuperscript{16} showed that the efficacy of landiolol was better than digoxin in patients with cardiac dysfunction or low baseline blood pressure (\textit{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.\textsuperscript{13} (\textit{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 \( \mu \text{g/kg/min} \). Half the patients treated with low dose landiolol (1-2 \( \mu \text{g/kg/min} \)) also received milrinone whereas the majority of patients were treated with a higher dose of landiolol (>3 \( \mu \text{g/kg/min} \)) 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% to 35% 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.\textsuperscript{15}) 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.\textsuperscript{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.\textsuperscript{9}

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

![Evolution of cardiac dysfunction status in response to treatment.](image)

\textbf{Figure 2} Evolution of cardiac dysfunction status in response to treatment.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
subgroup & Landiolol & Digoxin & Risk difference [95% CI] & \textit{P}-value \\
\hline
SBP < 120 mmHg & 45.7 (16/35) & 14.0 (6/43) & 31.1 [12.4, 49.8] & 0.001 \\
SBP \geq 120 mmHg & 51.1 (24/47) & 12.7 (7/55) & 36.3 [20.1, 52.4] & 0.001 \\
LVEF < 35% & 47.2 (17/36) & 9.3 (4/43) & 33.1 [14.7, 51.5] & 0.001 \\
LVEF \geq 35\% & 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 \\
\hline
\end{tabular}
\caption{Percentage of patients achieving the primary Endpoint according to New York Heart Association status, left ventricular ejection fraction, or systolic blood pressure at baseline}
\end{table}
### 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) | Patient condition: LVEF 36.4 ± 7.9% (Lan) 36.7 ± 7.3% (Digo) | Landiolol infusion: mean dose for 2 h 6.7 ± 3.2 mcg/kg/min mean dose after 2 h 6.3 ± 3.5 mg/kg/min mean duration 20.4 ± 20.8 h | 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) DBP 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 ± 6.3% |
| 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) HR decrease: −38 ± 12% (HFrEF) and −26 ± 13% (HFrEF) Hypotension (SBP < 80 mmHg) was not recorded in HFrEF group but in one patient with HFrEF. HR decrease: −18% (Dilt) and −26% (Lan) Blood pressure change: Unchanged for Lan. Decreased for Dilt. (−8% for SBP/−14% for DBP) |
| 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 HFrEF and 2.9 ± 1.6 mcg/kg/min in HFpEF | |
| Kuchi et al.\(^{19}\) retrospective comparative trial Landiolol (n = 15) Diltiazem (n = 44) | Patient condition: LVEF: 42% (Lan) and 47% (Dilt) BNP: 76.6 ± 436 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 | |
| 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.
Landiolol for rate control management of atrial fibrillation

Wada et al. 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, 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 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. 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.

It should be noted that in Japan, landiolol is often combined with inotropic agents (from 13% up to 83%) 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 (from 21% to up to 100% of patients). 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 or after cardiac surgery.

Conflict of interest: none declared.

References

1. Nieuwlaat R, Eurlings UW, Cleland JG, Cobbe SM, Vardas PE, Capucci A, Lopez-Sendon JL, Meeder JG, Pinto YM, Crijns HJ. Atrial fibrillation and heart failure in cardiology practice: reciprocal impact and combined management from the perspective of atrial fibrillation: results of the Euro Heart Survey on atrial fibrillation. J Am Coll Cardiol 2009;53:1690–1698.
2. Li SJ, Sartipy U, Lund LH, Dahlström U, Adiels M, Pettzold M, Fu M. Prognostic significance of resting heart rate and use of β-blockers in atrial fibrillation and sinus rhythm in patients with heart failure and reduced ejection fraction: findings from the Swedish Heart Failure Registry. Circ Heart Fail 2015;8:871–879.
3. Nielsen PB, Larsen TB, Gorst-Rasmussen A, Skjøth F, Lip GY. β-Blockers in atrial fibrillation patients with or without heart failure: association with mortality in a Nationwide Cohort Study. Circ Heart Fail 2016;9:e002597.
4. Bajaj NS, Bhatia V, Sanam K, Ather S, Hashim T, Morgan C, Fanorow GC, Nanda NC, Prabhu SD, Adamopoulos C, Kheribeik R, Aronow WS, Fletcher RD, Anker SD, Ahmed A, Deedwania P. Impact of atrial fibrillation and heart failure, independent of each other and in combination, on mortality in community-dwelling older adults. Am J Cardiol 2014;114:909–913.
5. Arrojo M, Gayat E, Parencia J, Ishihara S, Zhang J, Choi DJ, Park JJ, AlhabibKF, Sato N, Miro O, Maggioni AP, Zhang Y, Spinjär N, Cohen-Solal A, Iwashyna TJ, Mebazaa A; GREAT Network. Precipitating factors and 90-day outcome of acute heart failure: a report from the intercontinental GREAT registry. Eur J Heart Fail 2017;19:201.
6. Abualnaja S, Podder M, Hernandez AF, McMurray JJ, Starling RC, O’Connor CM, Califf RM, Armstrong PW, Ezekowitz JA. Acute heart failure and atria fibrillation: insights from the acute study of clinical effectiveness of nesiritide in decompensated heart failure (ASCEND-HF) trial. J Am Heart Assoc 2015;4:e002092.
7. Mendes FD, Atié J, García MI, Grigo ED, Sousa AS, Feijó LA, Xavier SS. Atrial fibrillation in decompensated heart failure: associated factors and in-hospital outcome. Arq Bras Cardiol 2014;103:315–322.
8. Momomura S. Acute rate control in atrial fibrillation with left ventricular dysfunction. Circ J 2013;77:893–894.
9. Kirchhof P, Benussi S, Kotechka D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hendricks G, Manolisi AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Estraison G, Buxton W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimmons D, Gorenke B, Guenoun M, Hohnloser SH, Kohl P, Lip GY, Manolisi A, McMurray J, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Swulska P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Weindecker S, Zamaronik J, Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace 2016;18:1609–1678.
10. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Cockburn I, Connolly SJ, Costiniuk P, Dean V, Dal Canto M, Delgado V, Dickstein K, Di Mario C, Druml T, Erdélyi G, Ferenc M, Filippatos GS, Franceschini N, Follath F, Gerhardt F, Gómez P, Gras D, Grothues F, Hall D, Hakim R, Han J, Heidbuchel H, Hellemans I, Hull M, Huybrechts K, Iezzi G, Inzitari D, Jirásek J, Jung M, Kahan T, Kavousi M, Keeling S, Knight B, Kober L, Krijthe B, Kwiterovich P, Lefèvre T, Lip GY, Lipiczaner A, Lindemann U, Mahfoud I, Manios Y, Mantzaris J, Marley S, Massie BM, McAllister M, McAllister A, Mihaljevic T, Mills D, Moliterni P, Morais A, Morii N, Mor photis M, Moscucci M, Muraru D, Nihoyannopoulos P, Nkomo VT, Nappi L, Nattel S, Neubauer S, Nkikkat A, Okamoto Y, Oparil S, O mestad B, O’Neill M, Perrouin-Verbe N, Perrouin-Schulte N, Pfeffer MA, Pisters S, Pisters M, Prasad A, Prasad S, Proclemer A, Rogers T, Rosano GM, Rutten FH, Ruschitzka F, Ruschitzka F, Savelieva I, Sharma S, Swulska P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Weindecker S, Zamaronik J, Zeppenfeld K. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891–975.
11. Arrojo M, Bettex D, Rudiger A. Management of atrial fibrillation in critically ill patients. Crit Care Res Pract 2013;2014:840615.
12. Czarnywojtek A, Plazinska MT, Zgorzelewicz-Stachowiak M, Wolski K, Stangierski A, Miechowicz I, Waligo’rska-Stachura J, Gut P, Krolicki L, Zlonicek W, Ruchala M. Dysfunction of the thyroid gland during amiodarone therapy: a study of 297 cases. Ther Clin Risk Manag 2016;12:505–513.
13. Adachi T, Sato A, Baba M, Hiraya D, Hasegawa T, Kuroki K, Hoshi T, Aonuma K. Novel use of the ultra-short-acting intravenous β1-selective blocker landiolol for supraventricular tachyarrhythmias in patients with congestive heart failure. Heart Vessels 2014;29:464–469.
Identify patients with non-ST elevation acute coronary syndromes at high risk for complications during intravenous beta-blocker infusion. *Acute Card Care* 2011;13:129-135.

15. Nagai R, Kinugawa K, Inoue H, Atarashi H, Seino Y, Yamashita T, Shimizu W, Alba T, Kitakaze M, Sakamoto A, Ikeda T, Imay Y, Daimon T, Fujino K, Nagano T, Okamura T, Hori M; J-Land Investigators. Urgent management of rapid heart rate in patients with atrial fibrillation/flutter and left ventricular dysfunction: comparison of the ultra-short-acting β1-selective blocker landiolol with digoxin (J-Land Study). *Circ J* 2013;77:908-916.

16. Kinugawa K, Nagai R, Inoue H, Atarashi H, Seino Y, Yamashita T, Shimizu W, Alba T, Kitakaze M, Sakamoto A, Ikeda T, Imay Y, Daimon T, Fujino K, Nagano T, Okamura T, Hori M; J-Land Investigators. Impacts of patient characteristics on the effectiveness of landiolol in AF/AFL patients complicated with LV dysfunction: Subgroup analysis of the J-Land study. *Adv Ther* 2014;31:426-439.

17. Kobayashi S, Murakami W, Myoren T, Tateishi H, Okuda S, Doi M, Nao T, Wada Y, Matsuzaki M, Yano M. A low-dose β1-blocker effectively and safely slows the heart rate in patients with acute decompen-sated heart failure and rapid atrial fibrillation. *Cardiology* 2014;127:105-113.

18. Ozaki T, Yamada T, Morita T, Furukawa Y, Tamaki S, Iwasaki Y, Kawasaki M, Kikuchi A, Kondou T, Sato Y. Urgent control of rapid atrial fibrillation using landiolol in patients with acute decompen-sated heart failure with reduced or preserved left ventricular ejec-tion fraction. *Eur Heart J* 2016;37(Abstract Supplement):1319.

19. Itochi S, Aikawa H, Hiasatake S, Kabuki T, Oka T, Dobashi S, Fujii T, Ikeda T. Efficacy of intravenous administration of landiolol in patients with acute heart failure and supraventricular tachyarrhythmia. *J Clin Med Res* 2017;9:426-432.

20. Wada Y, Alba T, Tsujita Y, Itoh H, Wada M, Nakajima I, Ishibashi K, Okamura H, Miyamoto K, Noda T, Sugano Y, Kanzaki H, Anzai T, Kusano K, Yasuda S, Horie M, Ogawa H. Practical applicability of landiolol, an ultra-short-acting β1-selective blocker, for rapid atrial and ventricular tachyarrhythmias with left ventricular dysfunction. *J Arrhythm* 2016;32:82-88.

21. Nitta D, Kinugawa K, Imamura T, Endo M, Aomiya E, Inaba T, Maki H, Hatano M, Komuro I. An experience of landiolol use for an advanced heart failure patient with severe hypotension. *Int Heart J* 2015;56:564-567.

22. Morisaki A, Hosono M, Sasaki Y, Hirai H, Sakaguchi M, Nakahira A, Seo H, Suehiro S. Very-low-dose continuous drip infusion of landiolol hydrochloride for postoperative atrial tachyarrhythmia in patients with poor left ventricular function. *Gen Thorac Cardiovasc Surg* 2012;60:386-390.

23. Miwa Y, Ikeda T, Mera H, Miyakoshi M, Hoshida K, Yanagisawa R, Ishiguro H, Tsukada T, Abe A, Yusu S, Yoshino H. Effects of landiolol, an ultra-short-acting beta1-selective blocker, on electrical storm refractory to class III antiarrhythmic drugs. *Circ J* 2010;74:856-863.

24. Yoshima S. Concomitant administration of landiolol and dobutamine in acute heart failure syndrome with atrial tachyarrhythmia. *Eur Heart J* 2017;38(Abstract Supplement):580.

25. Sezai A, Osaka S, Yaito H, Ishii Y, Arimoto M, Hata H, Shiono M. Safety and efficacy of landiolol hydrochloride for prevention of atrial fibrillation after cardiac surgery in patients with left ventricular dysfunction: Prevention of Atrial Fibrillation After Cardiac Surgery With Landiolol Hydrochloride for Left Ventricular Dysfunction (PLATON) trial. *J Thorac Cardiovasc Surg* 2015;150:957-964.

26. Fellahi JL, Heringlake M, Knotzer J, Fornier W, Cazenave L, Guerracino F. Landiolol for managing atrial fibrillation in post-cardiac. *Eur Heart J* 2018;20(Suppl A):A4-A9.