ESC HEART FAILURE
ESC Heart Failure 2020; **7:** 2208–2213
Published online 14 July 2020 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12879

REVIEW

Novel rate control strategy with landiolol in patients with cardiac dysfunction and atrial fibrillation

Teruhiko Imamura and Koichiro Kinugawa*

Second Department of Internal Medicine, Toyama University, Toyama, Japan

Abstract

While patients with acute heart failure often have tachycardia with atrial fibrillation, there have been no established medical tools that control tachycardia safely and definitely. Digoxin has been recommended as a first choice in the former guidelines, but it takes time to affect and has a risk of adverse events particularly for those with chronic kidney disease. Landiolol is a recently innovated ultra-short-acting beta-blocker with 251-fold β1/β2 selectivity, which was originally indicated only to control peri-operative supra-ventricular tachyarrhythmia by 2013 in Japan. We aimed to review how to use landiolol in patients with cardiac dysfunction and tachycardia due to atrial fibrillation. We reviewed recently conducted randomized control trials using landiolol, recently updated guidelines, as well as current practical use of landiolol. Japan landiolol vs. Digoxin (J-Land) study demonstrated that landiolol was more effective to control tachycardia than digoxin in atrial fibrillation patients with left ventricular dysfunction in 2013. Given the result, the revised Japanese heart failure guideline recommends landiolol for rate control during atrial fibrillation in acute heart failure patients as Class IIa with evidence level B. Currently in Japan, landiolol is used for rate control, even in patients with advanced heart failure receiving continuous infusion of inotropes. The clinical use of landiolol in patients with cardiac dysfunction and tachycardia due to atrial fibrillation is increasing. Further studies are warranted to investigate the implication of faster and safer rate control using landiolol.

Keywords Haemodynamics; Beta-blocker; Atrial fibrillation

Received: 19 November 2019; Revised: 8 June 2020; Accepted: 16 June 2020
**Correspondence to: Koichiro Kinugawa, Second Department of Internal Medicine, Toyama University, 2630 Sugitani, Toyama-shi, Toyama 930-0194, Japan. Tel: +81-76-434-2281; Fax: +81-76-434-1463. Email: kinugawa-tky@umin.ac.jp*

Background

Patients with acute heart failure often have tachyarrhythmias as a history or as a present form on admission.[1,2] Particularly, approximately 30% of such cohorts have atrial fibrillation on admission as a cause of tachyarrhythmia.[3–6] A sustained rapid ventricular response further deteriorates cardiac function,[7] and rapid managements are required for such a situation.[8]

Electronic cardioversion is the first choice for cardiogenic shock, whereas in most other situations with relatively preserved haemodynamics, definite rate control tools would be a key to successful management of acute heart failure.

Former Japanese guidelines for pharmacotherapy of atrial fibrillation (Japanese Circulation Society 2008)[9] and for treatment of acute heart failure (Japanese Circulation Society 2011)[10] recommended digoxin as the first choice for rate control with reduced cardiac function, given its positive inotropic effects.[11] However, digoxin is not so fast to get sufficient reduction in heart rate, because digoxin has a slowly developing negative chronotropic effect by way of vagal stimulation.[12] Furthermore, digoxin might be proarrhythmic provoking delayed after depolarization especially in failing myocytes.[13] Amiodarone might also be considered, but it would be insufficient for rapid rate control even during the intravenous infusion.[14] We should also be cautious about its serious adverse drug effects including lung fibrosis and thyrotoxicosis.[15,16] Beta-blockers are good alternatives, but most of them had been available only as an oral form until 2010s. More definite and safer medications have been warranted.

Beta-blocker as an alternative of digoxin

Currently, there are three commercially available major intravenous forms of β-blockers in Japan: landiolol, esmolol, and

propranolol. In Europe, atenolol and metoprolol are also available as intravenous forms of β-blockers, both of which are indicated for hypertension.[17]

Propranolol has a 2 h half-life.[18] It would take a long time to be resolved once adverse events including hypotension occur. Propranolol may not be safe in patients with reduced cardiac function. As Sasao and colleagues demonstrated in rabbits,[19] both landiolol and esmolol reduced heart rate dose-dependently. However, mean blood pressure declined significantly within 1 min following the administration of esmolol, particularly when at high dose (5 mg/kg), whereas mean blood pressure remained maintained following the administration of landiolol at any doses (1, 3, and 10 mg/kg). Given very short half-time and high selectivity of β1 receptor (4 min and 251-fold β1/β2 selectivity),[20] landiolol might be theoretically the most ideal medication to control tachycardia in patients with reduced cardiac function. Nevertheless, the indication of landiolol had been restricted for the use of supra-ventricular tachyarrhythmias,[21] and its use for congestive heart failure had been contraindicated until 2013 when the result of Japan landiolol vs. Digoxin (J-Land) study was presented.[22]

J-Land study

We conducted the J-Land study to demonstrate the efficacy and safety of landiolol to control heart rate in patients with reduced cardiac function.[22] In this trial, patients with atrial fibrillation or atrial flutter who had left ventricular ejection fraction 25–50%, New York Heart Association functional Class III or IV, and heart rate ≥120 b.p.m. were randomized into the landiolol arm or digoxin arm. Digoxin was set as a control agent given it was a first choice for the rate control in patients with left ventricular systolic dysfunction at that time.[9,10] Primary end point was the percentage of patients who achieved both a heart rate <110 b.p.m. and a ≥20% reduction in heart rate at 2 h following the administration of either agent. There had been no consensus for the target heart rate in atrial fibrillation patients except for the RACE II trial,[23] and we adopted the same goal as a primary end point.

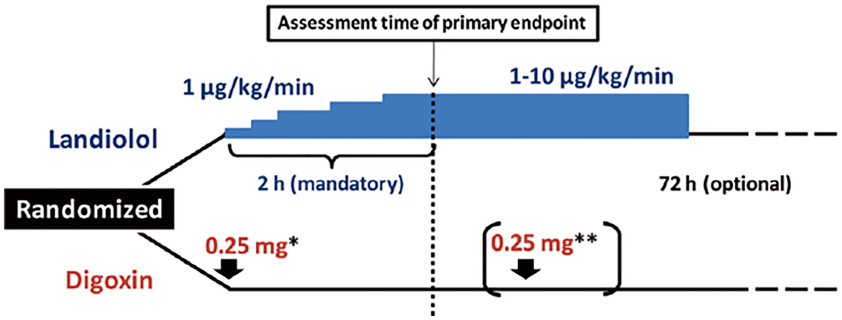
Following the randomization, the landiolol arm received landiolol at an initial dose of 1 μg/kg/min, which was titrated up to 10 μg/kg/min until the target heart rate was attained within the tolerance of patients (*Figure* 1). The digoxin arm received an intravenous bolus administration of 0.25 mg digoxin followed by an additional one if necessary. Any anti-arrhythmic agents, sympathomimetic agents, sympatholytic agents, defibrillator use, catheter ablation, or pacemaker implantation were prohibited during the first 2 h when the primary end point was assessed.

The primary end point was successfully met, and the landiolol was significantly superior for the achievement of faster heart rate control compared with the digoxin (48% vs. 14%, $P < 0.001$). The superiority of landiolol was demonstrated also in any subgroup analyses stratified by baseline characteristics including age, sex, heart rate, blood pressure, left ventricular ejection fraction, and renal function.[24] Among the patients with an estimated glomerular filtration ratio <30 mL/min/1.73 m^2, the landiolol arm had less adverse events compared with the digoxin arm, probably given that digoxin is excreted via kidney. Nevertheless, we should pay special attention to up-titrate the dose of landiolol to prevent hypotension, bradycardia, and worsening heart failure.

Post-J-Land study guidelines

Given the milestone result of J-Land study,[22] the Japanese Circulation Society updated the guideline for the atrial fibrillation rate control in 2013,[25] and landiolol has become one of the first-choice agents for rate control during atrial fibrillation with reduced cardiac function. Japanese heart failure guideline has also been updated in 2017, and landiolol is recommended for the treatment of atrial fibrillation in acute heart failure as Class IIa with evidence level B, whereas digoxin is assigned to evidence level C.[26]

Figure 1 The protocol of J-Land study (reused with permission).[22] *Dose of digoxin could be reduced down to 0.125 mg in patients being treated with oral digoxin. **Additional digoxin was administered if necessary.



DOI: 10.1002/ehf2.12879

Landiolol is not widely used for those with cardiac dysfunction in Europe thus far, although such an indication is receiving great concern.[27,28] In the current European Society of Cardiology guideline published in 2016,[29] the smallest dose of β-blocker is recommended as a first-line to achieve rate control in case of atrial fibrillation with cardiac dysfunction, followed by amiodarone and digoxin.

Practical use of landiolol in real-world practice

The post-marketing surveillance for landiolol in Japan investigated the real-world use of landiolol in atrial fibrillation or atrial flutter patients with heart failure.[30] Of 1121 patients from 209 institutes, the rate of successful heart rate control with landiolol was achieved in 77.5% with only 3% of hypotension. Other investigators reported favourable outcomes of landiolol therapy in patients with tachyarrhythmia and heart failure in small cohort, as summarized in *Table* 1.[31–34] Most of the patients included in these studies had reduced left ventricular ejection fraction, and the efficacy of landiolol in patients with preserved left ventricular ejection fraction remains future concerns. Only one retrospective study showed that heart rate reduction at 2 h following landiolol administration was greater in patients with preserved ejection fraction than those with reduced ejection fraction.[35]

In the real-world practice, we sometimes see patients with atrial tachyarrhythmia who receive continuous infusion of inotropes for their compromised haemodynamics. In Japan, we do not hesitate to add landiolol on the inotropes.[36–38] Even under inotropes administration, landiolol can effectively reduce heart rate, albeit relatively higher dose is required.

We want to present a case for better understanding of the practical use of landiolol in advanced heart failure patients with atrial fibrillation.[39] The 21-year-old male patient with non-ischaemic cardiomyopathy receiving a continuous infusion of dobutamine was referred to our institute to consider durable ventricular assist device implantation, given his progressive deterioration of cardiac function with left ventricular end-diastolic diameter of 82 mm and left ventricular ejection fraction of 34%. In Japan, we can implant durable ventricular assist devices only as bridge to transplantation, and all patients should receive careful examinations to be listed for heart transplantation before the surgery.

On admission, his haemodynamics was relatively preserved with heart rate of 110 b.p.m. with sinus rhythm and systolic blood pressure of 96 mmHg (*Figure* 2). Following the onset of atrial fibrillation, systolic blood pressure decreased down to below 80 mmHg due to >180 b.p.m. of tachycardia, which was refractory to 0.25 mg i.v. of digoxin. We initiated intravenous administration of landiolol at 2 μg/kg/min and titrated up to 8 μg/kg/min under the inotropes support, followed by immediate rate control with heart rate below 120 b.p.m. and eventual sinus conversion, leading to the successful heart transplant listing and durable ventricular assist device implantation bridged by up-titration of inotropes and intra-aortic balloon pumping support. Note that incremental dose of landiolol by itself did not result in lowering blood pressure.

A recent retrospective study in 11 patients with sinus tachycardia after on-pump cardiovascular surgery showed that concomitant use of low-dose landiolol (2.6 ± 1.3 μg/kg/min) with inotrope infusion reduced heart rate, improving stroke volume.[40] Another study in 20 patients with acute decompensated heart failure showed that low-dose landiolol therapy (1.5 μg/kg/min) in combination with milrinone reduced heart rate by 11%, maintaining haemodynamics.[41] Positive inotropic effect via β2 receptor may not be inhibited by

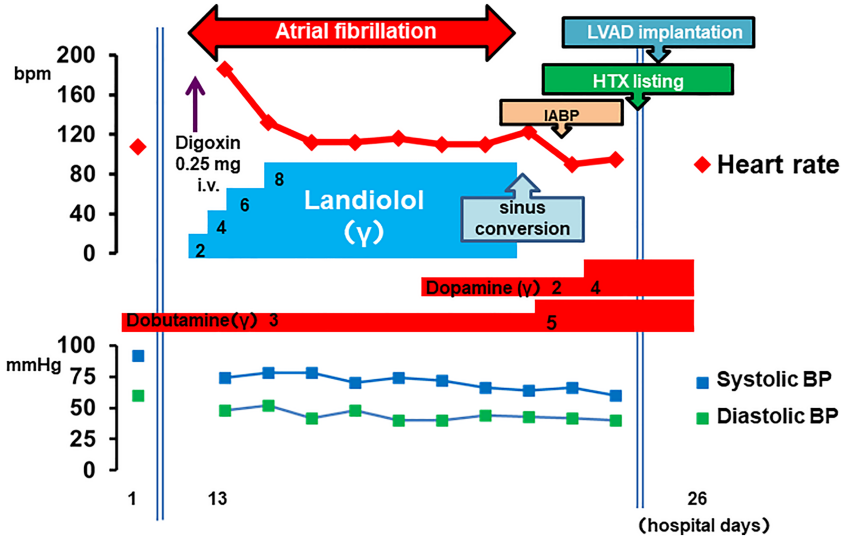
Table 1 Previous studies investigating the efficacy of landiolol in patients with heart failure and tachyarrhythmia

References	Year	Patients characteristics	Design	Control	N	LVEF
Kobayashi S[41]	2012	ADHF + milrinone	Retrospective	-	20	24 ± 7%
Nagai R (J-Land)[22]	2013	Af + LV dysfunction	Prospective	Digoxin	200	25–50%
Adachi T[37]	2014	SVT + HF	Retrospective	-	52	32 ± 12%
Kobayashi S[35]	2014	Af + ADHF	Retrospective	-	23	34.5 ± 8.6% (HFrEF, N = 12) 56.6 ± 6.4% (HFpEF, N = 11)
Wada Y[31]	2016	Af or VT + LV dysfunction	Retrospective	-	51	34 ± 16%
Kikuchi S[32]	2017	SVT + ADHF	Retrospective	Diltiazem	59	42% (landiolol) 47% (diltiazem)
Matsui Y[33]	2019	AT + ADHF	Retrospective	-	67	41 ± 13%
Yamashita T (AF-CHF landiolol survey)[30]	2019	Af + HF	Prospective	-	1,121	40.7 ± 15.9%
Oka E[34]	2019	Af/AT + LV dysfunction	Retrospective	-	77	33.1 ± 13.7%

ADHF, acute decompensated heart failure; Af, atrial fibrillation; AT, atrial tachycardia; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

DOI: 10.1002/ehf2.12879

Figure 2 A clinical course of the patient with advanced heart failure whose tachycardia due to atrial fibrillation was immediately controlled by the landiolol concomitantly administered on the inotropes support. BP, blood pressure; HTX, heart transplantation; IABP, intra-aortic balloon pumping; LVAD, left ventricular assist device.



low-dose landiolol due to its high selectivity to β1 receptor. Landiolol may rather facilitate a longer diastolic filling time, which enables heart to work in a better economic way with improved cardiac output. We have preliminary data showing more improved New York Heart Association functional class in responders with landiolol compared with those with digoxin in the sub-analysis of J-Land study (data not shown).

There are several ongoing prospective trials investigating the impact of landiolol on reducing heart rate, preventing atrial fibrillation, or conversion to sinus rhythm, in adults or paediatric patients with left ventricular dysfunction, those with septic shock, or those following cardiac surgery. Further implications of landiolol therapy on successful rate control and improved clinical outcomes in patients with heart failure or any other conditions are future concerns.

Conclusions

The J-Land study demonstrated that landiolol, an ultra-short-acting β1 super-specific blocker, achieved faster rate control targeting below 110 b.p.m. within 2 h compared with digoxin, a former guideline-recommended first choice, among acute heart failure patients with reduced cardiac function and atrial tachyarrhythmia. Faster rate control by landiolol was not associated with increased adverse events, whereas digoxin was accompanied by more adverse events among those with severe renal dysfunction.

Even though patients with advanced heart failure require inotropes infusion, landiolol can effectively reduce heart rate without interfering concomitantly used inotropes. Further studies are warranted to investigate the implication of faster and safer rate control using landiolol.

Conflict of interest

None declared.

Funding

None.

References

1. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. *Am J Cardiol* 2003; **91**: 2D–8D.
2. Nieuwlaat R, Eurlings LW, 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.
3. Sato N, Kajimoto K, Asai K, Mizuno M, Minami Y, Nagashima M, Murai K, Muanakata R, Yumino D, Meguro T, Kawana M, Nejima J, Satoh T, Mizuno

K, Tanaka K, Kasanuki H, Takano T, Investigators A. Acute decompensated heart failure syndromes (ATTEND) registry. A prospective observational multicenter cohort study: rationale, design, and preliminary data. *Am Heart J* 2010; **159**: 949–955 e1.
4. Parenica J, Spinar J, Vitovec J, Widimsky P, Linhart A, Fedorco M, Vaclavik J, Miklik R, Felsoci M, Horakova K, Cihalik C, Malek F, Spinarova L, Belohlavek J, Kettner J, Zeman K, Dusek L, Jarkovsky J, Investigators AM. Long-term survival following acute heart failure: the Acute Heart Failure Database Main registry (AHEAD Main). *Eur J Intern Med* 2013; **24**: 151–160.
5. Hamaguchi S, Yokoshiki H, Kinugawa S, Tsuchihashi-Makaya M, Yokota T, Takeshita A, Tsutsui H, Japanese Cardiac Registry of Heart Failure in Cardiology I. Effects of atrial fibrillation on long-term outcomes in patients hospitalized for heart failure in Japan: a report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). *Circ J* 2009; **73**: 2084–2090.
6. Li SJ, Sartipy U, Lund LH, Dahlstrom U, Adiels M, Petzold M, Fu M. Prognostic significance of resting heart rate and use of beta-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.
7. Clark DM, Plumb VJ, Epstein AE, Kay GN. Hemodynamic effects of an irregular sequence of ventricular cycle lengths during atrial fibrillation. *J Am Coll Cardiol* 1997; **30**: 1039–1045.
8. Rawles JM. What is meant by a "controlled" ventricular rate in atrial fibrillation? *Br Heart J* 1990; **63**: 157–161.
9. Group JCSJW. Guidelines for pharmacotherapy of atrial fibrillation (JCS 2008): digest version. *Circ J* 2010; **74**: 2479–2500.
10. Group JCSJW. Guidelines for treatment of acute heart failure (JCS 2011). *Circ J* 2013; **77**: 2157–2201.
11. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Kay GN, Le Huezey JY, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann LS. ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *J Am Coll Cardiol* 2011; **57**: e101–e198.
12. The Digitalis in Acute Atrial Fibrillation (DAAF) Trial Group. Intravenous digoxin in acute atrial fibrillation: results of a randomized, placebo-controlled multicentre trial in 239 patients. *Eur Heart J* 1997; **18**: 649–654.
13. Zeng WT, Liu ZH, Li ZY, Zhang M, Cheng YJ. Digoxin use and adverse outcomes in patients with atrial fibrillation. *Medicine* 2016; **95**: e2949.
14. Shibata SC, Uchiyama A, Ohta N, Fujino Y. Efficacy and safety of landiolol compared to amiodarone for the management of postoperative atrial fibrillation in intensive care patients. *J Cardiothorac Vasc Anesth* 2016; **30**: 418–422.
15. Arrigo M, Bettex D, Rudiger A. Management of atrial fibrillation in critically ill patients. *Crit Care Res Prac* 2014; **2014**: 840615.
16. Mechlis S, Lubin E, Laor J, Margaliot M, Strasberg B. Amiodarone-induced thyroid gland dysfunction. *Am J Cardiol* 1987; **59**: 833–835.
17. Ram CV. Beta-blockers in hypertension. *Am J Cardiol* 2010; **106**: 1819–1825.
18. Shand DG. Pharmacokinetics of propranolol: a review. *Postgrad Med J* 1976; **52**: 22–25.
19. Sasao J, Tarver SD, Kindscher JD, Taneyama C, Benson KT, Goto H. In rabbits, landiolol, a new ultra-short-acting beta-blocker, exerts a more potent negative chronotropic effect and less effect on blood pressure than esmolol. *Can J Anaesth* 2001; **48**: 985–989.
20. Shiroya T, Ichioka Y, Yoshida K, Nishijima K, Omawari N, Naka M. Pharmacological studies of ONO-1101 as a beta-blocking agent with high beta 1 selectivity and ultra-short duration of action. *Kiso To Rinsho* 1997; **31**: 2913–2923.
21. Sakamoto A, Kitakaze M, Takamoto S, Namiki A, Kasanuki H, Hosoda S, group J-Ks. Landiolol, an ultra-short-acting beta(1)-blocker, more effectively terminates atrial fibrillation than diltiazem after open heart surgery: prospective, multicenter, randomized, open-label study (JL-KNIGHT study). *Circ J* 2012; **76**: 1097–1101.
22. Nagai R, Kinugawa K, Inoue H, Atarashi H, Seino Y, Yamashita T, Shimizu W, Aiba T, Kitakaze M, Sakamoto A, Ikeda T, Imai Y, Daimon T, Fujino K, Nagano T, Okamura T, Hori M, Investigators JL. Urgent management of rapid heart rate in patients with atrial fibrillation/flutter and left ventricular dysfunction: comparison of the ultra-short-acting beta1-selective blocker landiolol with digoxin (J-Land study). *Circ J* 2013; **77**: 908–916.
23. Wyse DG. Lenient versus strict rate control in atrial fibrillation some devils in the details. *J Am Coll Cardiol* 2011; **58**: 950–952.
24. Kinugawa K, Nagai R, Inoue H, Atarashi H, Seino Y, Yamashita T, Shimizu W, Aiba T, Kitakaze M, Sakamoto A, Ikeda T, Imai Y, Daimon T, Fujino K, Nagano T, Okamura T, Hori M, Investigators JL. 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.
25. Group JCSJW. Guidelines for pharmacotherapy of atrial fibrillation (JCS 2013). *Circ J* 2014; **78**: 1997–2021.
26. Tsutsui H, Isobe M, Ito H, Ito H, Okumura K, Ono M, Kitakaze M, Kinugawa K, Kihara Y, Goto Y, Komuro I, Saiki Y, Saito Y, Sakata Y, Sato N, Sawa Y, Shiose A, Shimizu W, Shimokawa H, Seino Y, Node K, Higo T, Hirayama A, Makaya M, Masuyama T, Murohara T, Momomura SI, Yano M, Yamazaki K, Yamamoto K, Yoshikawa T, Yoshimura M, Akiyama M, Anzai T, Ishihara S, Inomata T, Imamura T, Iwasaki YK, Ohtani T, Onishi K, Kasai T, Kato M, Kawai M, Kinugasa Y, Kinugawa S, Kuratani T, Kobayashi S, Sakata Y, Tanaka A, Toda K, Noda T, Nochioka K, Hatano M, Hidaka T, Fujino T, Makita S, Yamaguchi O, Ikeda U, Kimura T, Kohsaka S, Kosuge M, Yamagishi M, Yamashina A, Japanese Circulation S, the Japanese Heart Failure Society Joint Working G. JCS 2017/JHFS 2017 Guideline on Diagnosis and Treatment of Acute and Chronic Heart Failure—Digest Version. *Circ J* 2019; **83**: 2084–2184.
27. von Haehling S, Belohlavek J, Er F, Gassanov N, Guarracino F, Bouvet O. Landiolol for rate control management of atrial fibrillation in patients with cardiac dysfunction. *Eur Heart J Suppl* 2018; **20**: A19–A24.
28. Dabrowski W, Siwicka-Gieroba D, Piasek E, Schlegel T, Jaroszynski A. Successful combination of landiolol and levosimendan in patients with decompensated heart failure—report of 3 cases. *Int Heart J* 2019 In Press.
29. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Group ESCSD. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016; **37**: 2893–2962.
30. Yamashita T, Nakasu Y, Mizutani H, Sumitani K. A prospective observational survey on landiolol in atrial fibrillation/atrial flutter patients with chronic heart failure—AF-CHF landiolol survey. *J Cardiol* 2019; **74**: 418–425.
31. Wada Y, Aiba 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 beta1-selective blocker, for rapid atrial and ventricular tachyarrhythmias with left ventricular dysfunction. *J Arrhythmia* 2016; **32**: 82–88.
32. Kiuchi S, Aikawa H, Hisatake 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.
33. Matsui Y, Suzuki A, Shiga T, Arai K, Hagiwara N. Effects of intravenous landiolol on heart rate and outcomes in patients with atrial tachyarrhythmias and acute decompensated heart failure: a single-center experience. *Drugs - Real World Outcomes* 2019; **6**: 19–26.
34. Oka E, Iwasaki YK, Maru E, Fujimoto Y, Ito-Hagiwara K, Hayashi H, Yamamoto T, Yodogawa K, Hayashi M, Shimizu W. Differential effectiveness of landiolol between atrial fibrillation and atrial flutter/atrial tachycardia patients with left ventricular dysfunction. *Circ J* 2019; **83**: 793–800.
35. Kobayashi S, Murakami W, Myoren T, Tateishi H, Okuda S, Doi M, Nao T, Wada Y, Matsuzaki M, Yano M. A low-dose beta1-blocker effectively and safely slows the heart rate in patients with acute decompensated heart failure and rapid atrial fibrillation. *Cardiology* 2014; **127**: 105–113.
36. 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.
37. Adachi T, Sato A, Baba M, Hiraya D, Hasegawa T, Kuroki K, Hoshi T, Aonuma K. Novel use of the ultra-short-acting intravenous beta1-selective blocker landiolol for supraventricular tachyarrhythmias in patients with congestive heart failure. *Heart Vessels* 2014; **29**: 464–469.
38. Hamaguchi S, Nagao M, Takahashi Y, Ikeda T, Yamaguchi S. Low dose landiolol combined with catecholamine can decrease heart rate without suppression of cardiac contraction after cardiopulmonary bypass. *Dokkyo J Med Sci* 2014; **41**: 27–33.
39. Nitta D, Kinugawa K, Imamura T, Endo M, Amiya 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.
40. Sakai M, Jujo S, Kobayashi J, Ohnishi Y, Kamei M. Use of low-dose beta1-blocker for sinus tachycardia in patients with catecholamine support following cardiovascular surgery: a retrospective study. *J Cardiothorac Surg* 2019; **14**: 145.
41. Kobayashi S, Susa T, Tanaka T, Murakami W, Fukuta S, Okuda S, Doi M, Wada Y, Nao T, Yamada J, Okamura T, Yano M, Matsuzaki M. Low-dose beta-blocker in combination with milrinone safely improves cardiac function and eliminates pulsus alternans in patients with acute decompensated heart failure. *Circ J* 2012; **76**: 1646–1653.