European Heart Journal Supplements (2018) **20** (Supplement A), A4–A9
The Heart of the Matter
doi:10.1093/eurheartj/sux038

ESC
European Society
of Cardiology

Landiolol for managing atrial fibrillation in post-cardiac surgery

Jean-Luc Fellahi[1]*, Matthias Heringlake[2], Johann Knotzer[3], William Fornier[1], Laure Cazenave[1], and Fabio Guarracino[4]

[1]*Service d'Anesthésie-Réanimation, Hôpital Cardiologique Louis Pradel, Hospices Civils de Lyon, 59 Boulevard Pinel, 69394 Lyon Cedex 03, France*
[2]*Department of Anesthesiology and Intensive Care Medicine, University of Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany*
[3]*Institut für Anästhesiologie und Intensivmedizin II, Klinikum Wels-Grieskirchen, Grieskirchner Str. 42, 4600 Wels, Austria*
[4]*Department of Anaesthesia and Critical Care Medicine, Cardiothoracic and Vascular Anaesthesia and Intensive Care, Azienda Ospedaliero Universitaria Pisana, Via Roma n. 67, 56126 Pisa, Italy*

KEYWORDS
Post-operative atrial fibrillation;
Cardiac surgery;
Landiolol

Landiolol is an intravenous ultra-short acting beta-blocker which has been used in Japan for many years to prevent and/or to treat post-operative atrial fibrillation following cardiac surgery. The drug is now available in Europe. This article is a systematic review of literature regarding the use of landiolol in that specific surgical setting.

Introduction

Post-operative atrial fibrillation (POAF) is a frequent complication of cardiac surgery, with recent studies still showing high incidence, ranging from 30%[1,2] up to 50%.[3,4] Time course and incidence of POAF differs with type of surgery. Post-operative atrial fibrillation following cardiac surgery has higher incidence and a peak occurring on Day 2 while in non-cardiac surgery, POAF incidence usually ranges from 10% to 20% and peak appears earlier on post-operative Day 1.[5,6] Patient displaying POAF are more likely to develop complications and are associated with prolonged intensive care unit (ICU) stay, higher mortality, and increased hospitalization cost.[7,8] Risk factors include age, history of arrhythmia, complexity and duration of surgery, cardiac hypertrophy or larger left atrial volume, bleeding, electrolyte abnormalities, and impaired renal function.[3,9,10]

Management of new-onset atrial fibrillation following cardiac surgery represent a challenge, as patients present often haemodynamic instability and increased susceptibility to adverse haemodynamic side effects in response to rate and rhythm-restoring medications, including beta-blockers.[11] Beta-blockers have potentially many roles in the management of POAF. First, Guidelines recommend that chronic treatment with beta-blocker should not be discontinued as withdrawal increase risk of POAF. Second, Guidelines propose oral beta-blockers, among other strategy, to prevent POAF. Finally, beta-blockers represent an option of choice for acute rate control in patients with POAF and elevated heart rate (HR).[12]

Landiolol is an ultra-short acting beta-blocker with high beta1-selectivity. Landiolol profile, with marked negative chronotropic effect, weaker negative inotropic effects and less hypotensive effect, compares favourably to esmolol for controlling HR in patient with cardiac dysfunction or following cardiac surgery.[13] Landiolol has been available for years in Japan where it has been extensively used in POAF following cardiac surgery. Landiolol is also recommended with Japanese AF Guidelines.[14] Landiolol has been recently approved and is now available in Europe.

We reviewed and analysed the studies already identified by the four published meta-analysis covering landiolol for prevention of atrial fibrillation, and completed the

*Corresponding author. Tel: +4 72 11 89 33, Fax: +472 357 314, Email: jean-luc.fellahi@chu-lyon.fr

literature search with an additional MEDLINE search with the term, 'landiolol', 'surgery', 'post-operative', and 'atrial fibrillation' which led to the identification of five additional studies using landiolol for treatment of Afib, after eliminating studies with non-cardiac surgery, paediatric population, patients cases, and studies including sinus tachycardia or other supra ventricular tachyarrhythmia (SVT). This review focuses on POAF. Additional data on intraoperative SVT can be found in the review by Plosker.[13]

Landiolol for treatment of post-operative atrial fibrillation post-cardiac surgery

There are limited published data available regarding the use of landiolol to treat POAF in cardiac surgery. Only one randomized controlled trial (RCT) comparing landiolol to diltiazem,[15] and two retrospective studies[16,17] provide comparative data (*Table 1*). In the RCT,[15] patients treated with landiolol showed higher response to HR control and faster return to sinus rhythm. However, the rate of conversion to sinus rhythm was not different from control group. These results are consistent with the observations provided by the two retrospective studies[16,17] and in line with results from controlled studies in non-cardiac surgery (see article by Balik *et al.*[18] from this supplement). Landiolol tolerance was better than diltiazem, displaying less hypotension, and less bradycardia.[15] In the first retrospective study,[17] landiolol tolerance was comparable to standard of care, with similar rate of hypotension and less bradycardia compared to amiodarone. In the second one,[16] no patient required discontinuation of infusion due to hypotension and no critical adverse event was observed in either group. Control of HR was rapidly obtained with a reduction of <20% of HR which was observed in 97% of patients with using landiolol doses lower than 10 mcg/kg/min.[15,16] This was confirmed by another study using similar to slightly higher doses (7.5 ± 7.6 mcg/kg/min) which showed 89% of patients controlled with minimally impact on blood pressure.[19]

The first experiences conducted in Europe with patients treated in our institution in Germany (Universitätsklinikum Schleswig-Holstein) and Austria (Institut für Anästhesiologie und Intensivmedizin II) confirm the effects of landiolol, which were published from Japan. The potency of landiolol is high with doses lower than 10 mcg/kg/min resulting in marked HR decrease. The dose response observed in Caucasian is similar to Japanese patients, in line with what was observed in Caucasian healthy volunteers or Caucasian Afib patients treated in emergency setting, although higher dose were used in this settings.[20]

Landiolol has beneficial effects on HR control and a high cardioversion rate in cardiac surgical patients with new onset SVT. Remarkable is the cardioversion effect in patients with severe diastolic dysfunction, e.g. after aortic valve replacement because of aortic stenosis.[15] In these patients, the loss of sinus rhythm comes along with a severe compromise in left ventricular filling and decrease in stroke volume. Especially in these haemodynamic compromised patients landiolol, using in our institution (Institut für Anästhesiologie und Intensivmedizin II) similar doses to doses used in Japan, shows promising first results in restoration of sinus rhythm. Thus, when landiolol is used for rate control strategy of POAF, it is associated with rapid and high response rate together with faster conversion to sinus rhythm when compared to control group.[15-17]

Table 1 Comparative studies for treatment of post-operative atrial fibrillation in cardiac surgery

References	Methodology	Landiolol % of conversion (AF/*n*)	Control % of conversion (AF/*n*)	Dose of drugs used to control heart rate	Type of surgery
Sakamoto *et al.*[15]	Prospective randomized trial	At 8 h: 54% (19/35) At 16 h: 60% (21/35) At 24 h: 74% (21/35)	At 8 h: 31% (11/36) At 16 h: 47% (17/36) At 24 h: 61% (22/36)	Landiolol 0.5-2 mcg/kg/min to a maximum rate of 40 μg/kg/min or Diltiazem 0.25 mg/kg over 2 min + infusion 3 mg/h titrated to a maximum of 15 mg/h	CABG (35%), VR (35%), CABG + VR (13%), other cardiac surgery (18%)
Nishi *et al.*[16]	Retrospective comparative study	Time to return to SR: 10.9 ± 10 h At 24 h: 74% (51/69)	Time to return to SR: 15.4 ± 29.4 h At 24 h: 57% (37/65)	Landiolol 1.6 ± 1.0 mcg/kg/min up to 3, 1 ± 5.9 mcg/kg/min or AA class I or class III and calcium blockers (doses not described) [Note: 57% of landiolol patients converting add also calcium blockers and or Class I-III AA]	CABG on-pump (80%) CABG off-pump (20%)
Shibata *et al.*[17]	Retrospective comparative study	At 24 h: 56% (18/32)	At 24 h: 43% (18/32)	Landiolol: loading dose of 30 mcg/kg/min 0.7 up to 2.5 mcg/kg/min or Amiodarone 150 mg/30 min + infusion of 25-50 mg/h	CABG (38%), VR (42%), CABG + VR (14.5%), vascular surgery (5.5%)

CABG, coronary artery bypass graft; VR, valve replacement; Combined, CABG + VR.

Recent update in AF guidelines recommend that beta-blockers or calcium blockers in patients with no cardiac dysfunction (left ventricular ejection fraction (LVEF) $>40\%$) as first line for rate control. For patients displaying LVEF $<40\%$, clinicians should only consider beta-blockers, starting with low dose, with possibility for adding digoxin. Amiodarone is now recommended as second line, for patients displaying more severe cardiac dysfunction. Landiolol potency and fast on-off profile, associated with is less negative inotropic profile may represent an option of choice to manage patients' post-cardiac surgery as alternative to amiodarone.

Landiolol for prevention of post-operative atrial fibrillation

Landiolol for preventing POAF in cardiac surgery has been extensively studied in RCTs which have been analysed in four meta-analyses (*Table 2*).[21-24]

All of these four meta-analyses retrieve similar results, with Landiolol consistently reducing the incidence of POAF, without increasing the risk of major complications. In RCTs, landiolol was found to reduce POAF incidence on average by 2.8-fold[25-32] (*Table 3*). Similar efficacy of was retrieved in five comparative retrospective studies[33-37] totalizing 373 patients which consistently reported a lower incidence of POAF in groups treated with landiolol, with a reduction of more than two-folds, as compared to standard of care. Landiolol was generally started at low dose (2-5 mcg/kg/min), except in one study that used a starting dose of 10 mcg/kg/min, and continued for at least 2 days following procedure. Landiolol was initiated at induction of anaesthesia in one case,[29] at the cardiopulmonary bypass[25,28,31] or after procedure[25,32] and at ICU admission in three occasions.[25,27,30] There are no studies comparing these different scheme of administration and meta-analyses did not conduct subanalyses to evaluate the optimal approach.

Discussion and perspectives

Beta-blockers are well-identified drugs to prevent POAF and are recommended by the guidelines.[5,12] However, beta-blockers when administered orally preoperatively must be continued as withdrawal of beta-blockers is a risk factor potentially triggering POAF.[12] Bioavailability of oral beta-blockers has been found to be decreased post-cardiac surgery and intravenous route may be a valuable option to warrant effective beta-blockade.[38]

Esmolol was once considered to be used for preventing POAF but early trials failed to show benefit with reducing POAF incidence while incidence of secondary effect such hypotension were increased.[39] Similar poor tolerance and high incidence of adverse effects was also retrieved when using esmolol for ischaemia prevention, rendering esmolol unsuitable for prophylaxis.[40,41] The landiolol ultra-short pharmacokinetic profile and high beta1-selectivity provide rapid HR control while minimally impacting blood pressure.[13] Unlike esmolol, for which early negative results precluded from conducting any further trial, landiolol benefits, and absence of complication was replicated by many trials, including one in patient with LVEF $<35\%$[31] and confirmed by meta-analysis results.[21-24] The low incidence

Table 2 Comparison of published meta-analyses of landiolol in cardiac surgery

References	Number of trials included (*n* patients)	Efficacy outcome of landiolol	Safety outcome of landiolol	Comments
Sakamoto *et al.*[21]	Six trials (560 patients): (L = 302/C = 258)	Reduce incidence of POAF vs. control OR = 0.26, 95% CI 0.17-0.40	Only two adverse events associated with landiolol (2/302, 0.7%) One hypotension One exacerbation of asthma	Included all RCT before 2014
Liu *et al.*[22]	Seven trials (543 patients): (L = 269/C = 274)	Decrease risk of POAF vs. control RR = 0.33; 95% CI: 0.23-0.48; $P<0.00001$	Not associated with an increased risk of major complications RR = 0.79; 95% CI: 0.43-1.45; $P=0.45$	Included two retrospective comparative trial (Fujiwara and Nakanishi) One RCT (Ogawa not identified/included)
Li *et al.*[23]	Seven trials (807 patients): (L = 441/C = 366)	Reduction of POAF vs. control RR = 0.41; 95% CI 0.32-0.52; $P<0.001$	No difference in incidence of major complications vs. placebo RR = 0.77; 95% CI 0.34-1.72; $P=0.52$	Same RCT as Sakamoto *et al.* and three additional abstracts
Tamura *et al.*[24]	Six trials (534 patients): (L = 268/C = 266)	Reduction of POAF vs. control OR = 0.27; 95% CI 0.18-0.42; $P<0.001$	No difference in: In-hospital mortality 0.7 vs. 3.0%; OR, 0.45; 95% CI 0.07-2.74; $P=0.39$ Complications 4.5 vs. 9.7%; OR, 0.45; 95% CI, 0.16-1.23; $P=0.12$	Same RCT as Sakamoto *et al.* except Nagaoka *et al.*[30] excluded (not vs. placebo) Sezai *et al.*[31] added

95% CI, 95% confidence interval; OR, odds ratio; RR, risk ratio.

Table 3 Comparative randomized trials for prevention of post-operative atrial fibrillation

References	Landiolol % (AF/*n*)	Control % (AF/*n*)	Dose and duration of landiolol used
Sezai *et al.*[25]	9.9% (7/71)	33.8% (24/71)	At CBP wean 2 mcg/kg/min for 2 days
Fuji *et al.*[26]	11.1% (4/36)	32.4% (11/34)	6.3 mcg/kg/min in the ICU immediately after surgery, over approximatively 50 h
Sakaguchi *et al.*[27]	20.0% (6/30)	53.0% (16/30)	Immediately at ICU admission At 10 mcg/kg/min and discontinued 72 h after surgery; mean dose 6.9 ± 2.9 mcg/kg/min
Sezai *et al.*[28]	14.7% (5/34)	35.3% (12/34)	At CBP wean 2 mcg/kg/min for 3 days
Ogawa *et al.*[29]	19.1% (13/68)	36.8% (25/68)	Started immediately after induction of anaesthesia, with adjustment of the dose between 3–5 mcg/kg/min to control HR at 60–90 b.p.m., continued for 2 days
Nagaoka *et al.*[30]	4.8% (1/21)	27.3% (6/22)	From ICU admission until the beginning of oral drug intake. Lan infusion 0.5–2 μg/kg/min for 1.6 ± 0.7 days
Subtotal of RCT[a]	13.8% (36/260)	36.3% (94/259)	
Sezai *et al.*[31]	10.0% (3/30)	40.0% (12/30)	At CBP wean 2 mcg/kg/min for 2 days LVEF = 28.6 ± 7.3 and 28.6 ± 6.0 in landiolol and control respectively
Ishigaki *et al.*[32]	16.0% (4/25)	48.0% (12/25)	After cath ablation procedure 0, 5 mckg/min and continued for 3 days after the catheter ablation
Total of RCT[b]	13.7% (43/315)	37.6% (118/314)	

[a]Subtotal not not including Sezai *et al.*[31] study (patients with LVEF < 30%) and Ishigaki *et al.*[32] (catheter ablation).
[b]Total not including landiolol/bisoprolol group (9.1% = 3/33) from Sezai *et al.*[28]

of POAF observed with landiolol in Japanese studies suggests that additional tight HR control and beta-blockade in the post-operative period, may help to reduce further POAF. Indeed, recent meta-analyses have shown that beta-blocker prophylaxis can reduce POAF incidence from 30% down to 20%.[42,43] Strategy including landiolol may enable to cut POAF incidence further down, as shown by RCTs. The last meta-analysis[43] identified landiolol/bisoprolol combination[28] as being the most effective for reducing incidence of POAF. The optimal strategy seems to initiate oral beta-blocker pre-operatively and start landiolol intra-operatively or in the ICU. One retrospective study[44] showed that preoperative oral beta-blockade associated with landiolol is superior to landiolol started alone post-operatively. On the other hand, transition to oral beta-blocker may be necessary if landiolol infusion is stopped early, with patient discharged from ICU. Sezai *et al.*[25] already identified that 57% of POAF appeared after the 48 h landiolol infusion was completed. Similar results were observed by Yoshioka *et al.*[45] who have shown that landiolol followed by carvedilol was superior to landiolol alone (limited to 2 days post-surgery) with five patients developing POAF on Days 3–4 in the landiolol group, while only two patients did in the landiolol/carvedilol group. Several mechanisms of action, such as anti-ischaemic, anti-inflammatory, anti-oxidant effects, in addition to sympatho-inhibition, seem to support landiolol benefits in cardiac surgery. Studies exploring such markers[25,28,31] reported lower troponin-I, creatinine kinase *isoenzyme Muscle-Brain* (CK-MB), and brain natriuretic peptide (BNP) levels, lower plasma interleukin 6 (IL-6), interleukin 8 (IL-8) levels post-operatively, lower level of Asymmetric DiMethylArginine (ADMA) and pentraxin-3, and stabilization of C reactive protein (CRP) at Day 3 when compared with placebo.

Conclusion

When used in cardiac surgery, landiolol provide a rapid decrease of HR with minimal impact on blood pressure, associated with faster conversion of sinus rhythm when compared to control. Landiolol, initiated at low doses during surgery or in the ICU, has been shown to decrease incidence POAF without increasing complications usually seen with beta-blockers use. Landiolol profile makes it ideal to provide tight HR control and beta-blockade during the post-operative period, and easy to transition on oral beta-blockers before discharging from ICU.

Conflict of interest: JL Fellahi received honoraria for lectures from Amomed Pharma, Orion Pharma, Masimo Incorporation, Edwards Lifesciences, and Baxter Medical. M Heringlake received honoraria for lectures from Amomed Pharma, Orion Pharma, Tenax Therapeutics, Covidien-Medtronic, Baxter Medical, and Fresenius Medical. F Guarracino received honoraria for lectures from Orion Pharma and Baxter Medical. J Knotzer received honoraria for lectures from Orion Pharma, Amomed Pharma, and Sintetica.

References

1. Gillinov AM, Bagiella E, Moskowitz AJ, Raiten JM, Groh MA, Bowdish ME, Ailawadi G, Kirkwood KA, Perrault LP, Parides MK, Smith RL 2nd, Kern JA, Dussault G, Hackmann AE, Jeffries NO, Miller MA, Taddei-Peters WC, Rose EA, Weisel RD, Williams DL, Mangusan RF, Argenziano M, Moquete EG, O'Sullivan KL, Pellerin M, Shah KJ, Gammie JS, Mayer ML, Voisine P, Gelijns AC, O'Gara PT, Mack MJ; CTSN. Rate control versus rhythm control for atrial fibrillation after cardiac surgery. *N Engl J Med* 2016;**374**:1911–1921.
2. Bonnet V, Boisselier C, Saplacan V, Belin A, Gérard JL, Fellahi JL, Hanouz JL, Fischer MO. The role of age and comorbidities in postoperative outcome of mitral valve repair: a propensity-matched study. *Medicine (Baltimore)* 2016;**95**:e3938.

3. Tsai YT, Lai CH, Loh SH, Lin CY, Lin YC, Lee CY, Ke HY, Tsai CS. Assessment of the risk factors and outcomes for postoperative atrial fibrillation patients undergoing isolated coronary artery bypass grafting. *Acta Cardiol Sin* 2015;**31**:436–443.
4. Khan J, Khan N, Loisa E, Sutinen J, Laurikka J. Increasing occurrence of postoperative atrial fibrillation in contemporary cardiac surgery. *J Cardiothorac Vasc Anesth* 2016;**30**:1302–1307.
5. Bidar E, Bramer S, Maesen B, Maessen JG, Schotten U. Post-operative atrial fibrillation—pathophysiology, treatment and prevention. *J Atr Fibrillation* 2013;**5**:781.
6. Maesen B, Nijs J, Maessen J, Allessie M, Schotten U. Post-operative atrial fibrillation: a maze of mechanisms. *Europace* 2012;**14**: 159–174.
7. LaPar DJ, Speir AM, Crosby IK, Fonner E, Jr, Brown M, Rich JB, Quader M, Kern JA, Kron IL, Ailawadi G; Investigators for the Virginia Cardiac Surgery Quality Initiative. Postoperative atrial fibrillation significantly increases mortality, hospital readmission, and hospital costs. *Ann Thorac Surg* 2014;**98**:527–533.
8. Steinberg BA, Zhao Y, He X, Hernandez AF, Fullerton DA, Thomas KL, Mills R, Klaskala W, Peterson ED, Piccini JP. Management of postoperative atrial fibrillation and subsequent outcomes in contemporary patients undergoing cardiac surgery: insights from the Society of Thoracic Surgeons CAPS-Care Atrial Fibrillation Registry. *Clin Cardiol* 2014;**37**:7–13.
9. Ismail MF, El-Mahrouk AF, Hamouda TH, Radwan H, Haneef A, Jamjoom AA. Factors influencing postoperative atrial fibrillation in patients undergoing on-pump coronary artery bypass grafting, single center experience. *J Cardiothorac Surg* 2017;**12**:40.
10. Kievišas M, Keturakis V, Vaitiekūnas E, Dambrauskas L, Jankauskienė L, Kinduris Š. Prognostic factors of atrial fibrillation following coronary artery bypass graft surgery. *Gen Thorac Cardiovasc Surg* 2017; **65**:566–574.
11. Sigurdsson MI, Body SC. Rhythm is a dancer: the immediate management of postoperative atrial fibrillation following cardiac surgery. *Ann Transl Med* 2016;**4**:S32.
12. 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. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016;**18**:1609–1678.
13. Plosker GL. Landiolol: a review of its use in intraoperative and postoperative tachyarrhythmias. *Drugs* 2013;**73**:959–977.
14. JCS Joint Working Group. Guidelines for pharmacotherapy of atrial fibrillation (JCS 2013). *Circ J* 2014;**78**:1997–2021.
15. Sakamoto A, Kitakaze M, Takamoto S, Namiki A, Kasanuki H, Hosoda S; JL-KNIGHT Study Group. Landiolol, an ultra-short-acting β_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.
16. Nishi H, Sakaguchi T, Miyagawa S, Yoshikawa Y, Fukushima S, Saito S, Ueno T, Kuratani T, Sawa Y. Efficacy of landiolol hydrochloride for atrial fibrillation after open heart surgery. *Heart Vessels* 2013;**28**: 490–496.
17. 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.
18. Balik M, Sander M, Trimmel H, Heinz G. Landiolol for managing post-operative atrial fibrillation. *Eur Heart J* 2018;**20**(Suppl A): A10–A14.
19. Wariishi S, Yamashita K, Nishimori H, Fukutomi T, Yamamoto M, Radhakrishnan G, Sasaguri S. Postoperative administration of landiolol hydrochloride for patients with supraventricular arrhythmia: the efficacy of sustained intravenous infusion at a low dose. *Interact Cardiovasc Thorac Surg* 2009;**9**:811–813.
20. Domanovits H, Michael M, Stix G. Landiolol – pharmacology and its use for rate control in Atrial Fibrillation in an emergency setting. *Eur Heart J* 2018;**20**(Suppl A):A1–A3.
21. Sakamoto A, Hamasaki T, Kitakaze M. Perioperative landiolol administration reduces atrial fibrillation after cardiac surgery: a meta-analysis of randomized controlled trials. *Adv Ther* 2014;**31**:440–450.
22. Liu S, Bian C, Zhang Y, Jian Y, Liu W. Landiolol hydrochloride for prevention of atrial fibrillation after cardiac surgery: a meta-analysis. *Pacing Clin Electrophysiol* 2014;**37**:691–696.
23. Li L, Ai Q, Lin L, Ge P, Yang C, Zhang L. Efficacy and safety of landiolol for prevention of atrial fibrillation after cardiac surgery: a meta-analysis of randomized controlled trials. *Int J Clin Exp Med* 2015;**8**: 10265–10273.
24. Tamura T, Yatabe T, Yokoyama M. Prevention of atrial fibrillation after cardiac surgery using low-dose landiolol: a systematic review and meta-analysis. *J Clin Anesth* 2017;**42**:1–6.
25. Sezai A, Minami K, Nakai T, Hata M, Yoshitake I, Wakui S, Shiono M, Hirayama A. Landiolol hydrochloride for prevention of atrial fibrillation after coronary artery bypass grafting: new evidence from the PASCAL trial. *J Thorac Cardiovasc Surg* 2011;**141**:1478–1487.
26. Fujii M, Bessho R, Ochi M, Shimizu K, Terajima K, Takeda S. Effect of postoperative landiolol administration for atrial fibrillation after off pump coronary artery bypass surgery. *J Cardiovasc Surg (Torino)* 2012;**53**:369–374.
27. Sakaguchi M, Sasaki Y, Hirai H, Hosono M, Nakahira A, Seo H, Suehiro S. Efficacy of landiolol hydrochloride for prevention of atrial fibrillation after heart valve surgery. *Int Heart J* 2012;**53**:359–363.
28. Sezai A, Nakai T, Hata M, Yoshitake I, Shiono M, Kunimoto S, Hirayama A. Feasibility of landiolol and bisoprolol for prevention of atrial fibrillation after coronary artery bypass grafting: a pilot study. *J Thorac Cardiovasc Surg* 2012;**144**:1241–1248.
29. Ogawa S, Okawa Y, Goto Y, Aoki M, Baba H. Perioperative use of a beta blocker in coronary artery bypass grafting. *Asian Cardiovasc Thorac Ann* 2013;**21**:265–269.
30. Nagaoka E, Arai H, Tamura K, Makita S, Miyagi N. Prevention of atrial fibrillation with ultra-low dose landiolol after off-pump coronary artery bypass grafting. *Ann Thorac Cardiovasc Surg* 2014;**20**: 129–134.
31. Sezai A, Osaka S, Yaoita 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.
32. Ishigaki D, Arimoto T, Iwayama T, Hashimoto N, Kutsuzawa D, Kumagai Y, Nishiyama S, Takahashi H, Shishido T, Miyamoto T, Watanabe T, Kubota I. Prevention of immediate recurrence of atrial fibrillation with low-dose landiolol after radiofrequency catheter ablation. *J Arrhythm* 2015;**31**:279–285.
33. Fujiwara H, Sakurai M, Namai A, Kawamura T. Effect of low-dose landiolol, an ultrashort-acting beta-blocker, on postoperative atrial fibrillation after CABG surgery. *Gen Thorac Cardiovasc Surg* 2009;**57**: 132–137.
34. Nakanishi K, Takeda S, Kim C, Kohda S, Sakamoto A. Postoperative atrial fibrillation in patients undergoing coronary artery bypass grafting or cardiac valve surgery: intraoperative use of landiolol. *J Cardiothorac Surg* 2013;**8**:19.
35. Sato M, Suenaga E, Fumoto H, Kawasaki H, Koga S, Maki F. Safety and efficacy of low-dose continuous infusion of landiolol, an ultra-short-acting beta-blocker, in cardiac surgery. *J Arrhythmia* 2011;**27**: 57–62.
36. Osumi M, Tashiro T, Morita Y, Kamiya S, Minematsu N, Nishimi M, Wada H. Preventive effect of intraoperative landiolol administration on atrial fibrillation after off-pump coronary artery bypass grafting. *Adv Ther* 2014;**31**:1109–1117.
37. Maisawa K, Yamazaki K, Ishitoya H, Shimamura Y. Effect of landiolol hydrochloride after off-pump coronary artery bypass. *Asian Cardiovasc Thorac Ann* 2013;**21**:170–175.
38. Valtola A, Kokki H, Gergov M, Ojanperä I, Ranta VP, Hakala T. Does coronary artery bypass surgery affect metoprolol bioavailability. *Eur J Clin Pharmacol* 2007;**63**:471–478.
39. Balcetyte-Harris N, Tamis JE, Homel P, Menchavez E, Steinberg JS. Randomized study of early intravenous esmolol versus oral beta-blockers in preventing post-CABG atrial fibrillation in high risk patients identified by signal-average ECG: results of a pilot study. *Ann Noninvasive Electrocardiol* 2002;**7**:86–91.
40. Kurian SM, Evans R, Fernandes NO, Sherry KM. The effect of an infusion of esmolol on the incidence of myocardial ischaemia during tracheal extubation following coronary artery surgery. *Anaesthesia* 2008;**56**:1163–1168.
41. Neustein SM, Bronheim DS, Lasker S, Reich DL, Thys DM. Esmolol and intraoperative myocardial ischemia: a double-blind study. *J Cardiothorac Vasc Anesth* 1994;**8**:273–277.

42. Khan MF, Wendel CS, Movahed MR. Prevention of post-coronary artery bypass grafting (CABG) atrial fibrillation: efficacy of prophylactic beta-blockers in the modern era: a meta-analysis of latest randomized controlled trials. *Ann Noninvasive Electrocardiol* 2013;**18**:58–68.
43. Ji T, Feng C, Sun L, Ye X, Bai Y, Chen Q, Qin Y, Zhu J, Zhao X. Are beta-blockers effective for preventing post-coronary artery bypass grafting atrial fibrillation? Direct and network meta-analyses. *Ir J Med Sci* 2016;**185**:503–511.
44. Yokota J, Nishi H, Sekiya N, Yamada M, Takahashi T. Atrial fibrillation following aortic valve replacement: impact of perioperative use of intravenous β-blocker. *Gen Thorac Cardiovasc Surg* 2017;**65**: 194–199.
45. Yoshioka I, Sakurai M, Namai A, Kawamura T. Postoperative treatment of carvedilol following low dose landiolol has preventive effect for atrial fibrillation after coronary artery bypass grafting. *Thorac Cardiovasc Surg* 2009;**57**:464–467.