



HOT TOPICS IN CARDIOLOGIA 2023

13 e 14 Novembre 2023

Villa Doria D'Angri - Via F. Petrarca 80,
Napoli

Nuovi betabloccanti nello scompenso

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ESC GUIDELINES

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

With the special contribution of the Heart Failure Association (HFA) of the ESC

Downloaded from https://

Management of HFrEF

To reduce mortality - for all patients

ACE-I/ARNI

BB

MRA

SGLT2i

Beta-blockers

Bisoprolol	1.25 mg <i>o.d.</i>	10 mg <i>o.d.</i>
Carvedilol	3.125 mg <i>b.i.d.</i>	25 mg <i>b.i.d.</i> ^e
Metoprolol succinate (CR/XL)	12.5–25 mg <i>o.d.</i>	200 mg <i>o.d.</i>
Nebivolol ^d	1.25 mg <i>o.d.</i>	10 mg <i>o.d.</i>

Initiating factor that precipitate HF admission (%)

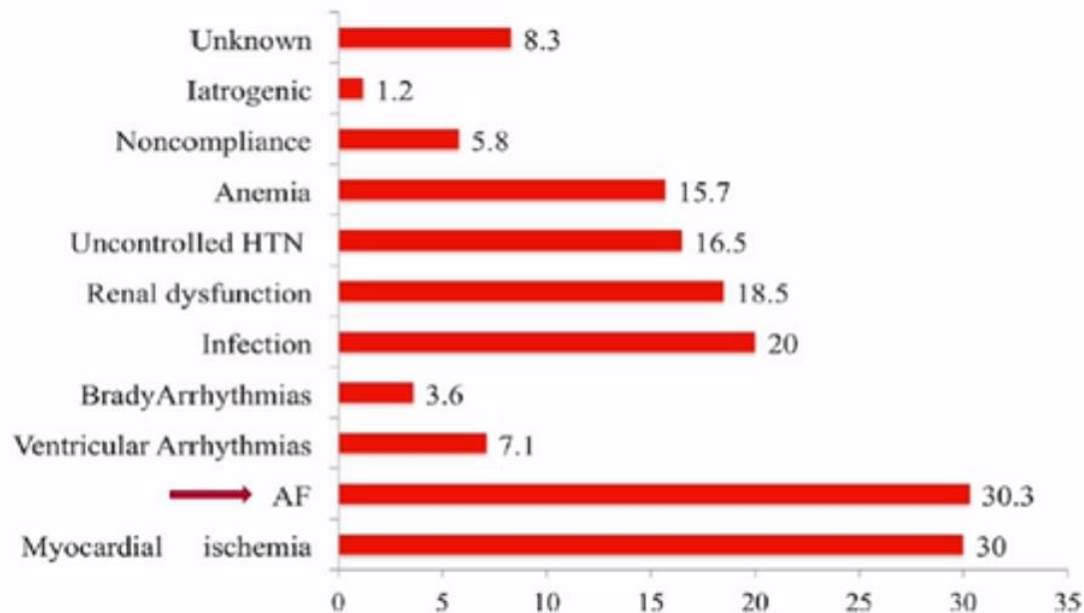
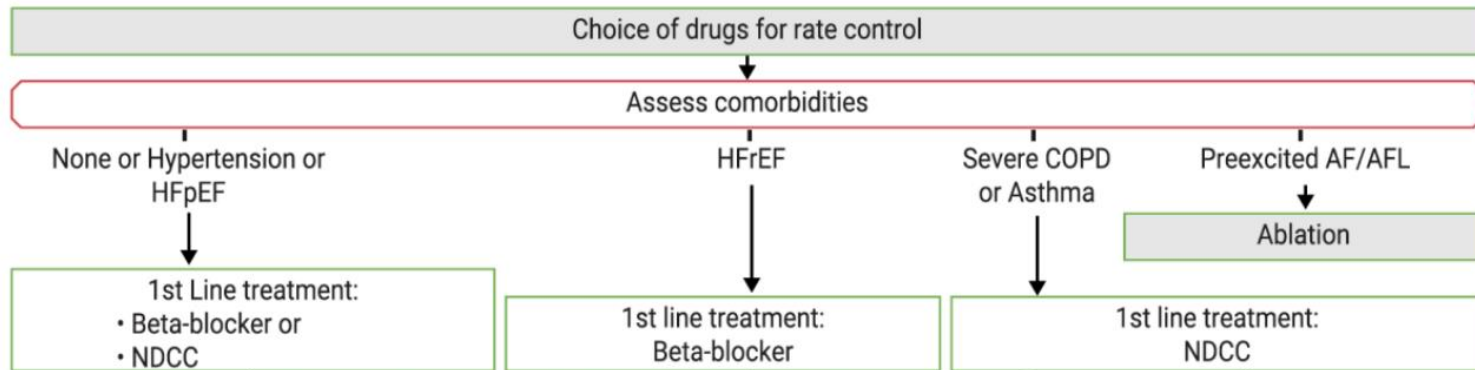


Figure 1.
Initiating factors that precipitate HF admission (5).
Abbreviations: AF=atrial fibrillation; HTN=hypertension.

ESC Guidelines 2020: β -Blockers first choice for rate control



Recommendations for ventricular rate control in patients with AF^a

Recommendations	Class ^b	Level ^c
Beta-blockers, diltiazem, or verapamil are recommended as first-choice drugs to control heart rate in AF patients with LVEF \geq 40%. ^{492,507,511,529}	I	B
Beta-blockers and/or digoxin are recommended to control heart rate in AF patients with LVEF<40%. ^{486,491,502,512,530–532}	I	B
Combination therapy comprising different rate controlling drugs ^d should be considered if a single drug does not achieve the target heart rate. ^{533,534}	IIa	B
A resting heart rate of <110 bpm (i.e. lenient rate control) should be considered as the initial heart rate target for rate control therapy. ⁴⁸⁸	IIa	B
Atrioventricular node ablation should be considered to control heart rate in patients unresponsive or intolerant to intensive rate and rhythm control therapy, and not eligible for rhythm control by LA ablation, accepting that these patients will become pacemaker dependent. ^{516,523,535,536}	IIa	B
In patients with haemodynamic instability or severely depressed LVEF, intravenous amiodarone may be considered for acute control of heart rate. ^{504,514,515}	IIb	B

Table 13 Drugs for rate control in AF^a

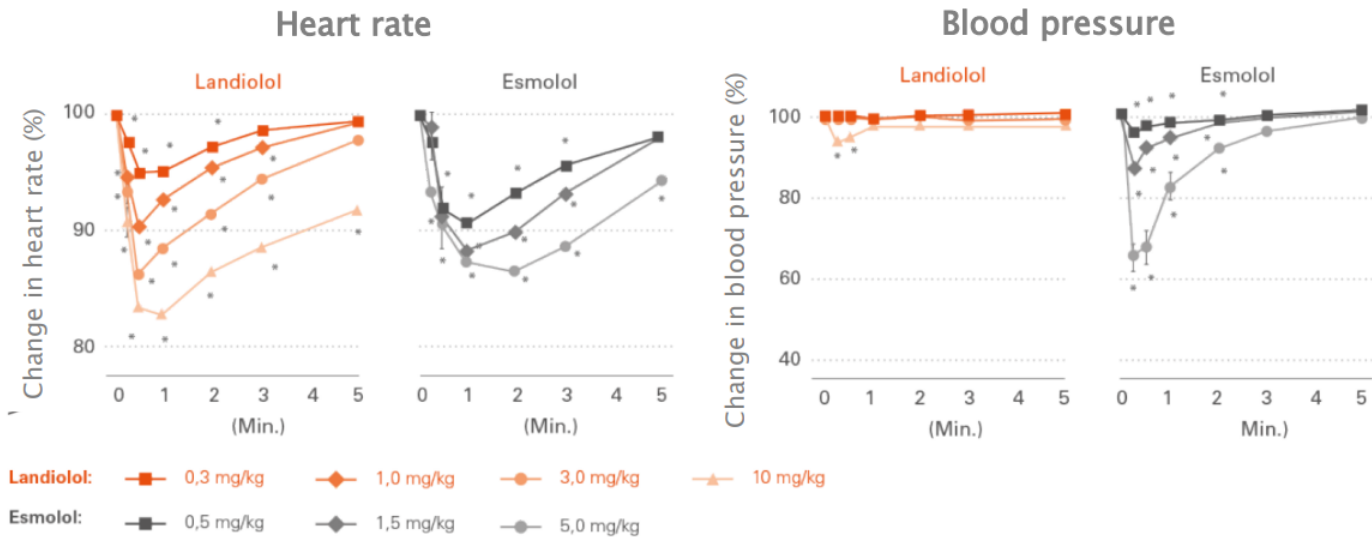
	Intravenous administration	Usual oral maintenance dose	Contraindicated
Beta-blockers^b			
Metoprolol tartrate	2.5 - 5 mg i.v. bolus; up to 4 doses	25 - 100 mg <i>b.i.d.</i>	In case of asthma use beta-1-blockers Contraindicated in acute HF and history of severe bronchospasm
Metoprolol XL (succinate)	N/A	50 - 400 mg <i>o.d.</i>	
Bisoprolol	N/A	1.25 - 20 mg <i>o.d.</i>	
Atenolol ^c	N/A	25 - 100 mg <i>o.d.</i>	
Esmolol	500 µg/kg i.v. bolus over 1 min; followed by 50 - 300 µg/kg/min	N/A	
Landiolol	100 µg/kg i.v. bolus over 1 min, followed by 10 - 40 µg/kg/min; in patients with cardiac dysfunction: 1 - 10 µg/kg/min	N/A	
Nebivolol	N/A	2.5 - 10 mg <i>o.d.</i>	
Carvedilol	N/A	3.125 - 50 mg <i>b.i.d.</i>	
Non-dihydropyridine calcium channel antagonists			
Verapamil	2.5 - 10 mg i.v. bolus over 5 min	40 mg <i>b.i.d.</i> to 480 mg (extended release) <i>o.d.</i>	Contraindicated in HFrEF Adapt doses in hepatic and renal impairment
Diltiazem	0.25 mg/kg i.v. bolus over 5 min, then 5 - 15 mg/h	60 mg <i>t.i.d.</i> to 360 mg (extended release) <i>o.d.</i>	
Digitalis glycosides			
Digoxin	0.5 mg i.v. bolus (0.75 - 1.5 mg over 24 hours in divided doses)	0.0625 - 0.25 mg <i>o.d.</i>	High plasma levels associated with increased mortality Check renal function before starting and adapt dose in CKD patients
Digitoxin	0.4 - 0.6 mg	0.05 - 0.1 mg <i>o.d.</i>	High plasma levels associated with increased mortality
Other			
Amiodarone	300 mg i.v. diluted in 250 mL 5% dextrose over 30 - 60 min (preferably via central venous cannula), followed by 900 - 1200 mg i.v. over 24 hours diluted in 500 - 1000 mL via a central venous cannula	200 mg <i>o.d.</i> after loading 3 × 200 mg daily over 4 weeks, then 200 mg daily ^{536 d} (reduce other rate controlling drugs according to heart rate)	In case of thyroid disease, only if no other options

β-Blockers in the ICU

Pharmacokinetics of β-Blockers				
	Landiolol	Esmolol	Metoprolol	Bisoprolol
Onset of Action	1 min	1-2 min	20 min	1-2 h
Half-life	2-4 min	9 min	3-4 h	9-12 h
Efficacy (β1:β2 affinity ratio)	255	33	2.3	13.5
Elimination	Pseudocholinesterase Liver carboxyesterase	Plasma esterases	Hepatic 95% Renal 5%	Hepatic 50%, renal 50%
Mode of administration	i.v.	i.v.	p.o. / i.v.	p.o.

Landiolol: lowers heart rate with neutral effects on blood pressure¹⁹

In vivo: rabbits



(n = 8 in jeder Gruppe); *p < 0,05

Landiolol: highly β -1-specific with limited negative inotropic Effects ^{1,7,11-17}

Landiolol
pure S-enantiomer structure⁷

No activity on Ca^{++} and Na^+ channels^{17,18}

High β -1-selectivity¹⁵
low negative inotropic effects¹⁶



Esmolol

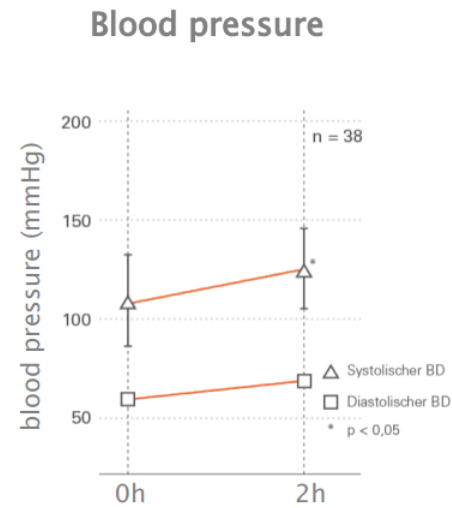
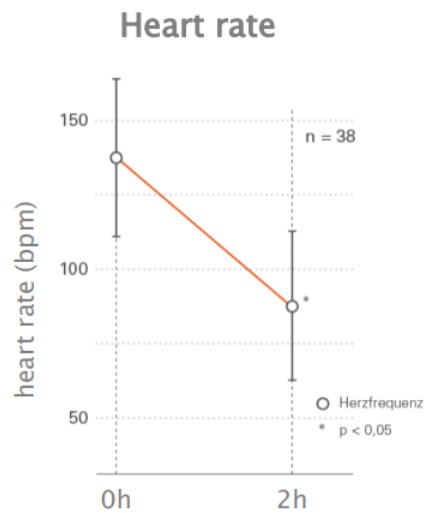
RS-enantiomers of the molecule¹⁴

Blocks L-Type $\text{Ca}^{++1,12-}$ and rapid Na^{+13-} channels

R-Esmolol lowers blood-pressure and has negative inotropy¹⁴

Landiolol - lowers heart rate with neutral effects on blood pressure

Patients with postoperative AFIB



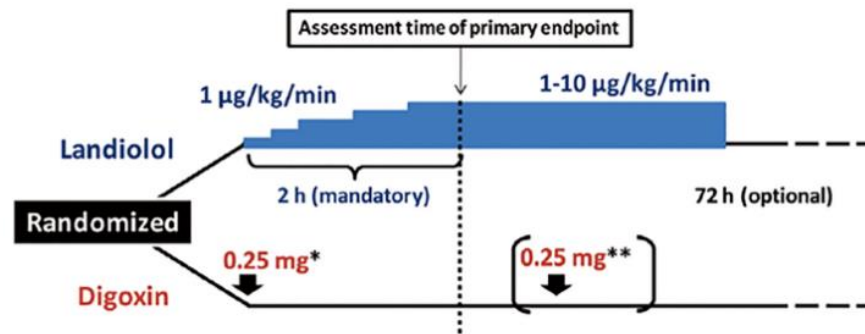
5 $\mu\text{g}/\text{kg}/\text{min}$
n=38

Landiolol infusion dosing

- Landiolol (Rapibloc) - 300 mg ampule dissolved to 50 ml solution for a perfusion pump
- Starting dose in AHF (?) – in studies from Japan 1-5 $\mu\text{g}/\text{kg}/\text{min}$ in our experience 5-20 $\mu\text{g}/\text{kg}/\text{min}$
- Adjusting dose every 15 – 20 min (?)
- Dosing in AHF should be clarified by future studies (LARISA, LANDI-UP)

<i>Kg of body weight</i>	<i>10 $\mu\text{g}/\text{kg}/\text{min}$</i>	<i>20 $\mu\text{g}/\text{kg}/\text{min}$</i>	<i>30 $\mu\text{g}/\text{kg}/\text{min}$</i>	<i>40 $\mu\text{g}/\text{kg}/\text{min}$</i>	<i>80 $\mu\text{g}/\text{kg}/\text{min}$</i>	
40	4	8	12	16	32	<i>ml/h</i>
50	5	10	15	20	40	<i>ml/h</i>
60	6	12	18	24	48	<i>ml/h</i>
70	7	14	21	28	56	<i>ml/h</i>
80	8	16	24	32	64	<i>ml/h</i>
90	9	18	27	36	72	<i>ml/h</i>
100	10	20	30	40	80	<i>ml/h</i>

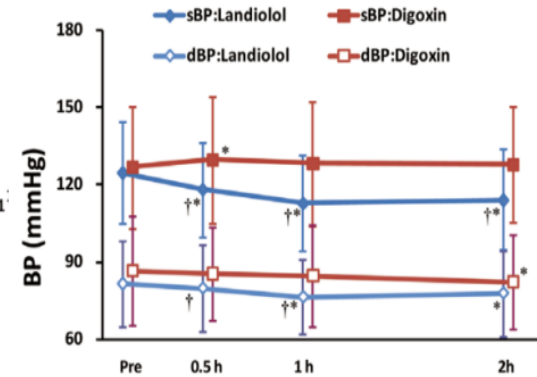
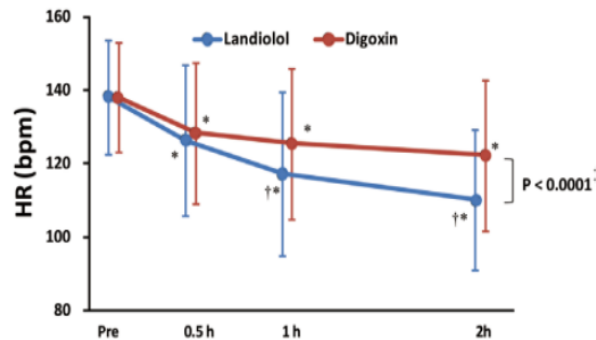
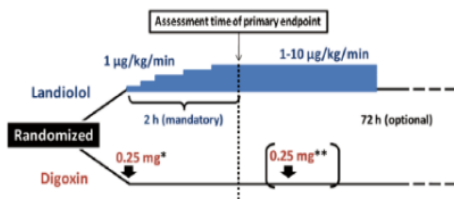
J-Land study



- 91 vs. 107 pts. with AF >120/min (mean 138/min) and LVEF 25 – 50%
- HR <110/min @2 hours: 48% with landiolol vs. 14% with digoxin (P < 0.001)
- Mean dose @2 hours: $6.7 \pm 3.2 \mu\text{g/kg/min}$
- No SAE in the landiolol group
- Key study leading to change of GL for treatment of AHF due AF in Japan (IIa B)

J-Land-Study: Landiolol in NYHA III and IV⁸

200 patients with AF/AFL
HR ≥ 120 beats/min
LV ejection fraction 25-50%

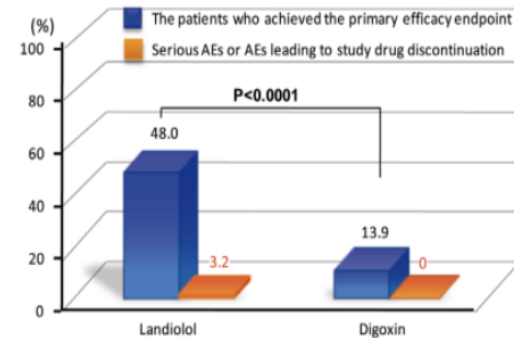


Hemodynamic parameters

HR (beats/min)	138.1±15.3	138.2±15.7	138.0±15.0	0.934
SBP (mmHg)	125.7±21.8	124.6±19.8	126.6±23.5	0.523
DBP (mmHg)	84.2±19.2	81.5±16.5	86.5±21.1	0.068
LVEF (%)	36.6±7.6	36.4±7.9	36.7±7.3	0.753
Creatinine (mg/dl)	0.98±0.32	0.98±0.33	0.97±0.32	0.883
BNP (pg/ml)	661.7±561.0	688.0±663.8	639.0±456.6	0.540

NYHA class, n (%)

III	163 (81.9)	71 (77.2)	92 (86.0)	0.108
IV	36 (18.1)	21 (22.8)	15 (14.0)	

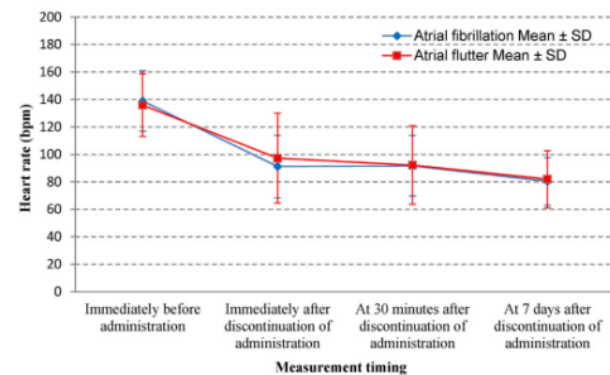


AF CHF study

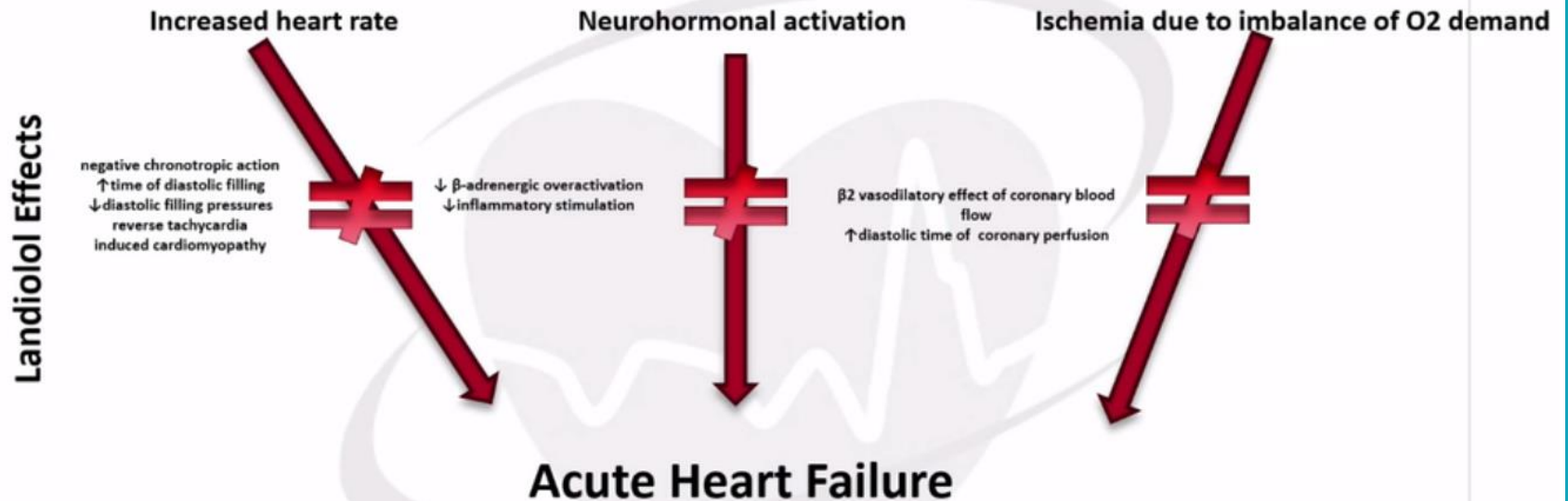
- 1121 consecutive patients
- Multicentric survey, pts. LVEF $40 \pm 16\%$
- Adverse events 5%
- Reduction of HR >20% in 78% of patients
- Median dose 3.0 ug/kg/min (max 25 ug/kg/min)

Effect of landiolol on the heart rate

b Subgroups with atrial fibrillation (N=475) or atrial flutter (N=45)



Atrial Fibrillation



Sofia Bezati, Antonios Boultadakis, John Ventoulis, Eftihia Polyzogopoulou and John Parissis. Expert Review on Cardiovascular Pharmacotherapy 2023

Recommendations for the acute management of sustained VT and electrical storm (3)

Recommendations	Class	Level
Management of electrical storm		
Mild to moderate sedation is recommended in patients with electrical storm to alleviate psychological distress and reduce sympathetic tone.	I	C
Antiarrhythmic therapy with beta-blockers (nonselective preferred) in combination with intravenous amiodarone is recommended in patients with SHD and electrical storm unless contraindicated.	I	B
Intravenous magnesium with supplementation of potassium is recommended in patients with TdP.	I	C
Isoproterenol or transvenous pacing to increase heart rate is recommended in patients with acquired LQT syndrome and recurrent TdP despite correction of precipitating conditions and magnesium.	I	C
Catheter ablation is recommended in patients presenting with incessant VT or electrical storm due to SMVT refractory to AAD.	I	B



**Efficacy and Safety of the Ultra-Short-Acting β 1-Selective
Blocker Landiolol in Patients With Recurrent
Hemodynamically Unstable Ventricular Tachyarrhythmias**
— Outcomes of J-Land II Study —

Takanori Ikeda, MD, PhD; Tsuyoshi Shiga, MD, PhD; Wataru Shimizu, MD, PhD;
Koichiro Kinugawa, MD, PhD; Atsuhiro Sakamoto, MD, PhD; Ryozo Nagai, MD, PhD;
Takashi Daimon, PhD; Kaori Oki; Haruka Okamoto; Takeshi Yamashita, MD, PhD;
The J-Land II Study Investigators

Concomitant administration of landiolol and dobutamine in acute heart failure syndrome with atrial tachyarrhythmia

Shohei Yoshima, Minoru Ichikawa, Takashi Takagi, Mitutoshi Asai, Kyungmee Lee, Kazunori Bando, Tatsuro Hashimura, Yuki Matsuoka, Yoshiyuki Kijima
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Figure 2. Changes in mean blood pressure on the first and second day from use of landiolol.

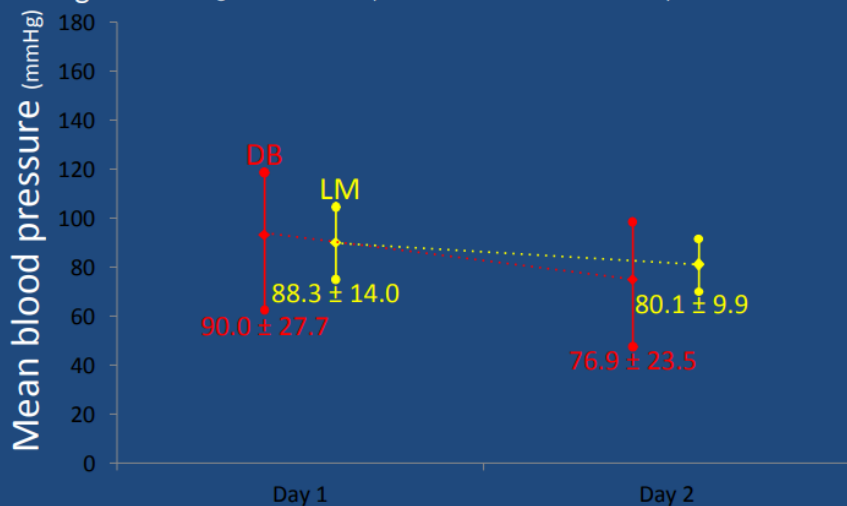
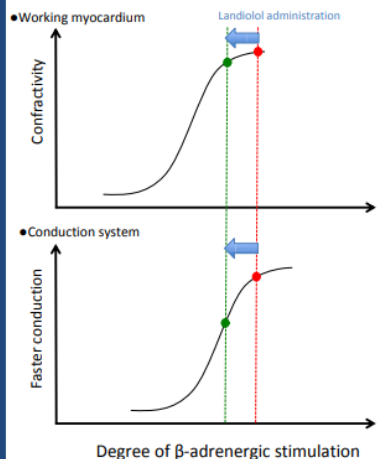
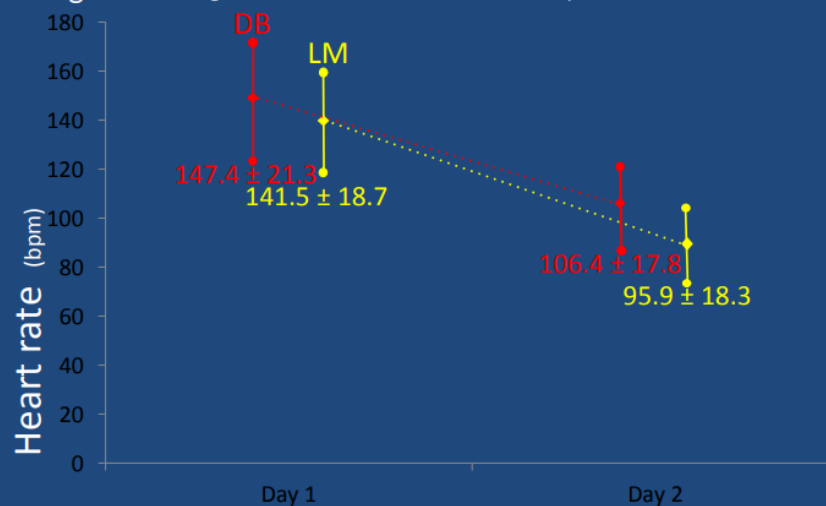


Figure 3. Changes in heart rate on the first and second day from use of landiolol.



Why did landiolol successfully reduce heart rate under concomitant use of dobutamine?

We hypothesized: differential β -adrenergic stimulation between working myocardium and conduction system (Fig.4).

Assuming the differential action of β -adrenergic stimulation between the two components of the heart, there would be an optimal window of landiolol dose, that is, it reduces heart rate but not myocardial contractility.

Degree of β -adrenergic stimulation would be a function of intrinsic plasma catecholamine, administration of β -stimulants and blockers, down-regulation of β -receptor, and desensitization of β -receptor.

References.

- (1) Nagai R et al. (2013) Urgent management of rapid heart rate in patients with atrial fibrillation/flutter and left ventricular dysfunction: comparison of the ultra-short-acting β 1-selective blocker landiolol with digoxin (β -Land Study). *Circ J* 77: 908 – 916.
- (2) Adachi T et al. (2013) Novel use of the ultra-short-acting intravenous β 1-selective blocker landiolol for supraventricular tachyarrhythmias in patients with congestive heart failure. *Heart Vessels* 29: 464-469.

Conclusion. Negative chronotropic action by landiolol appeared not to be diminished even under concomitant DB administration in AHF patients with atrial tachyarrhythmia.

Landiolol in sepsis and atrial fibrillation: high conversion rate to sinus rhythm without worsening hemodynamics

Table 1 Patients' characteristics

	Landiolol	Control
n	39	22
Age, yr	70.7 ± 12.3	70.8 ± 12.5
Underlying disease		
Cardiovascular disease	16 (41.0%)	11 (50.0%)
Malignancy	11 (28.2%)	3 (13.6%)
Immunological disorder	3 (7.7%)	2 (9.1%)
Others	9 (23.1%)	6 (27.2%)
Infected site		
Respiratory tract	17 (43.6%)	14 (63.6%)
Intra-abdominal	13 (33.3%) [†]	2 (9.1%)
Blood	5 (12.8%)	0 (0%)
Skin/soft tissue	2 (5.1%)	0 (0%)
Urinary tract	1 (2.6%) [†]	4 (18.2%)
Others	1 (2.6%)	2 (9.1%)
APACHE II	22.8 ± 5.4	22.1 ± 7.7
SOFA	8.8 ± 4.0	9.1 ± 3.9

[†]P < 0.05 vs control. APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment.

Conversion to sinus rhythm

	0 h	1 h	8 h	24 h
Landiolol		25,6% ^b	55,3% ^a	69,7% ^b
Control		0%	18,2%	36,4%

Landiolol
(µg/kg/Min.)

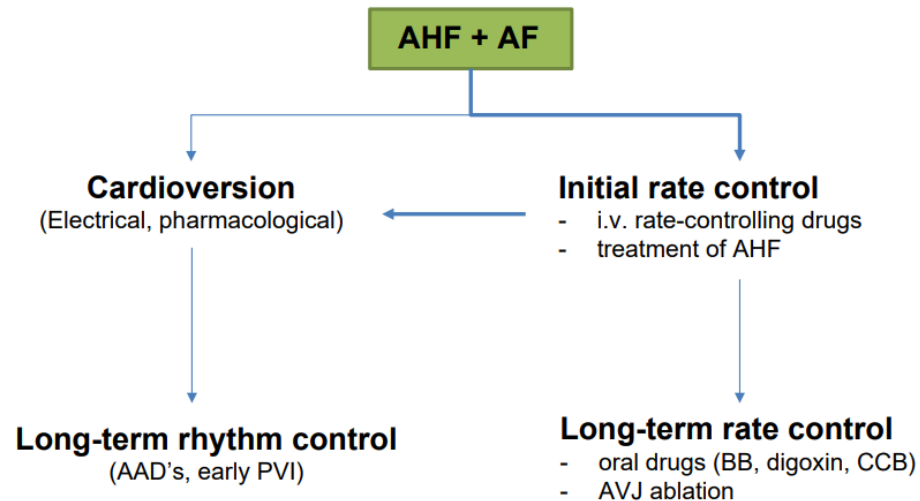
6,27 ± 5,80 6,12 ± 4,72 5,47 ± 4,10 4,17 ± 4,28

Concomitant drugs to control arrhythmia

Calcium-channel blocker	3 (8%)	5 (22%)
Other β blockers	0 (0%)	3 (14%)
Disopyramid phosphate	0 (0%)	1 (5%)
Amiodarone	0 (0%)	1 (5%)

^ap < 0,01; ^bp < 0,05 vs. Zeit 0 h

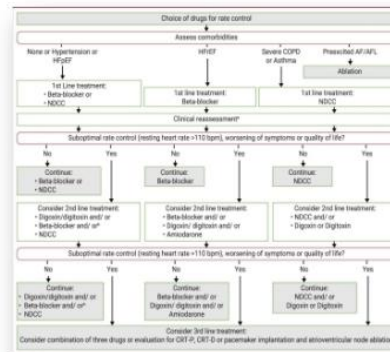
Workflow in patients with AHF and AF



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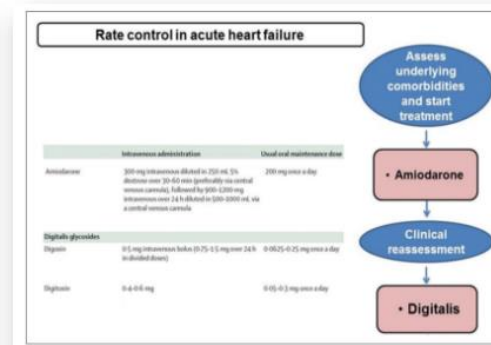
Options for acute rate control in AHF (HFrEF)

- **i.v betablockers**
 - metoprolol (?)
 - esmolol
 - landiolol
- **digoxin**
- **amiodarone**



ESC GL for AF 2020:

- BB as the 1st choice
- Digoxin as the 2nd choice
- Amiodaron as the 3rd choice



ACVC position paper on AF in AHF 2020:

- Amiodaron s the 1st choice
- Digoxin as the 2nd choice

Immediate rhythm control vs. rate control

Favours immediate (electric) cardioversion	Favours initial rhythm control
- Chronic anticoagulation, patient prepared	- Patient not fasted
- Intubated patient	- LAA thrombus
- Inadequate initial rate control	- Not tolerating TEE for pulmonary edema
- Cardiogenic shock	- Known reversible trigger of AF (sepsis, hyperkalemia, alcohol, thyroid)
- Very low LVEF/advanced CHF with limited reserves	- Orthopnea & risk of emergent intubation
	- Known permanent AF as a bystander of HF

Conclusioni

- ▶ La fibrillazione atriale o il Flutter atriale sono frequenti determinanti del peggioramento della funzione cardiaca sistolica e causa di scompenso cardiaco acuto
- ▶ Il trattamento con betabloccanti ev con breve emivita come il Landiolol è da considerarsi la prima scelta nei pazienti con scompenso cardiaco acuto e cronico e che hanno bisogno di RATE CONTROL (anche in associazione con Dig o AMIO, o inotropi +)
- ▶ Il Landiololo è il trattamento di scelta nel trattamento dei pazienti critici con tachiaritmie e disfunzione sistolica grazie alla sua breve emivita, la rapidità di azione e la selettività di azione B1, la sostanziale neutralità su pressione arteriosa e funzione contrattile. E' quindi ideale anche nel trattamento di pazienti con SEPSI



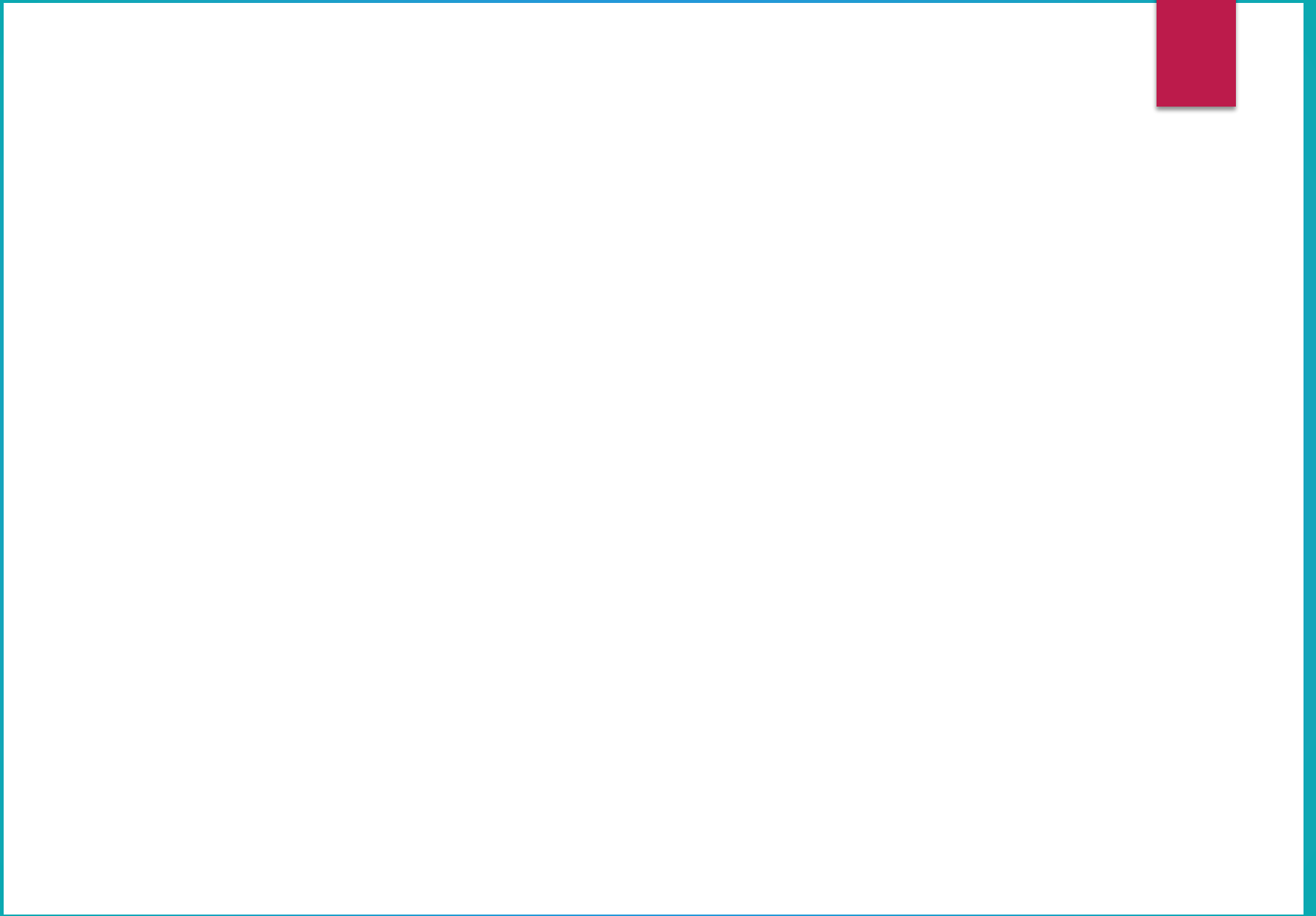












Patients with atrial fibrillation and acute decompensated heart failure

	Total (n=101)	RHC (n=37)	No RHC (n=64)
Age (years)	73 (63–81)	67 (59–79)	75 (64–82)
Male	63 (62)	22 (61)	41 (63)
BSA (m ²)	1.62 (1.5–1.84)	1.63 (1.5–1.84)	1.63 (1.5–1.84)
Systolic BP (mmHg)	125 (114–144)	123 (116–147)	126 (113–144)
Diastolic BP (mmHg)	83 (67–98)	82 (63–97)	82 (69–101)
Mean BP (mmHg)	97 (82–115)	96 (81–113)	97 (82–115)
HR (beats/min)	140 (133–156)	142 (131–150)	140 (133–156)
Echocardiography			
LVEDVI (mL/m ²)	86 (66–107)	90 (68–107)	84 (63–100)
LVESVI (mL/m ²)	66 (50–82)	68 (50–82)	62 (48–80)
LVEF (%)	22 (18–32)	22 (16–28)	23 (18–28)
E-TMF (cm/s)	102 (85–121)	100 (83.5–120)	109 (85–131)
E/e'	23.3 (16.0–31.7)	23.5 (16.3–30.7)	23.4 (15.0–32.7)
LAVI (mL/m ²)	45 (35–52)	47 (37–62)	43 (34–49)
MR>moderate	35 (35)	11 (29)	24 (37)
IVC (mm)	22 (19–24)	22 (19–25)	22 (19–24)
LVOT-VTI (cm)	10.6 (8.0–13.1)	9.4 (7.6–12.3)	10.9 (8.2–13.9)

Start dose: 1.0 µg/kg/min
 Maximum dose: 3.8+/-2.3 µg/kg/min

ESC Guidelines 2020: β -Blockers first choice for rate control

Recommendations	Class	Level
Beta-blockers, diltiazem, or verapamil are recommended as first-choice drugs to control heart rate in AF patients with LVEF \geq 40%.	I	B
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