HR & Heart Failure Hospitalization : How to Break the Vicious Cycle?





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Dept. of Cardiology and Vascular Medicine Faculty of Medicine– Universitas Sebelas Maret Moewardi General Hospital – UNS Hospital Why is it important? What is wrong? Where is the problem? How to overcome? Who is Ivabradine?

Heart failure prevalence is expected to increase¹



A person at age 40 has a 1 in 5 lifetime risk of developing heart failure, and more than 1 million hospitalizations due to heart failure are reported annually in Europe.^{1,4}

MI = myocardial infarction

1. Mozaffarian D, Benjamin EJ, Go AS, et al; for American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. Girculation. 2015;131(4):e29:e322; 2; Global Burden of Disease Study 2013; Collaborators; Global regional and national incidence prevalence and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013, Lancet 2015. 3. Velagaleti RS, Vasan R. Epidemiology of heart failure. In: Mann DL, ed. Heart Failure: A Companion to Braunwald's Heart Disease. 2nd ed. St Louis: Saunders; 2011. 4. Ponikowski P, Anker SD, AlHabib KF, et al. Heart failure: preventing disease and death worldwide. ESC Heart Failure. 2014;1(1):4-25.

Why is it important...?

	ADHF	ACS
Hospitalizations/year	1,000,000	1,000,000
Inpatient Mortality	3-4%	3-4%
30-days Readmission	10-15%	6-8%
Guidelines for :		
Risk Stratification	Yes	Yes
Therapy	Sort of (Lack in HFpEF)	Yes
Largest RCT	7,141	58,050

The Most Important Thing to Remember



Guideline recommended treatment goals in heart failure^{1,2}



The goals of treatment in patients with HF are to:1

- improve clinical status, functional capacity and quality of life
- prevent hospital admission
- reduce mortality



Left Heart Failure and Pulmonary Congestion



Right-sided heart failure: Cyanosis, engorgement of jugular veins, enlargement of liver, ascites, dependent edema, elevated

Right-Sided Heart Failure in a Patient With Dilated Cardiomyopathy



Heart Failure Challenges

Unmet needs

- **Poor survival**
- Poor quality of life if symptoms not controlled
- High risk of (re)hospitalisation
- **Delivering comprehensive** services to all

Why is it important? What is wrong? Where is the problem? How to overcome? Who is Ivabradine?

Prognostic importance of resting heart rate: epidemiological evidence (in general population and hypertensives)

During 25 years - more than 155 000 patients, follow-up 8-36 years

Study	Population	Follow-up	Cardiovascular mortality RR		
Chicago Gas Company '80	1 233 M	15 y	>94 vs. ≤60 bpm	2.3	
Chicago Heart Ass.Project '80	33 781 M&W	22 у	≥90 vs. <70 bpm	M: 1.6 W: 1.1 (ns)	
Framingham '93	4 530 M&W HTN	36 y	>100 vs. <60 bpm	M: 1.5 W: 1.4 (ns)	
British Regional Heart '93	735 M	8 y	>90 vs. ≤ 90 bpm	IHD death 3.3	
Spandau '97	4 756 M&W	12 y	Sudden death	5.2 per 20 bpm	
Benetos '99	19 386 M&W	18.2 y	>100 vs. <60 bpm	M: 2.2 W: 1.1 (ns)	
Castel '99	1 938 M&W	12 y	5th vs. 3rd quintile	M: 1.6 W: 1.1	
Cordis '00	3 257 M	8 y	≥90 vs. <70 bpm	2.0	
Reunanen '00	10 717 M&W	23 у	M: 1.4 (>84 vs. <60)	W: 1.5 (>94 vs.<66)	
Thomas '01	60 343 M HTN	14 y	>80 vs. ≤ 80 bpm	<55y:1.5 >55y:1.3	
Matiss '01	2 533 M	9 y	per 20 bpm: 1.5	≥90 vs. <60 bpm: 2.7	
Ohasama '04	1 780 M&W	10 y	M: 1.2 W: 1.1 (ns) per 5 bp	m	
Okamura '04	8 800 M&W	16.5 y	per 11 bpm (1 SD) M: 1.3 W: 1.2		
Jouven '05	e n '05 5 713 M		Sudden death from AMI	3.92 (>75 bpm)	

The role of heart rate in cardiovascular disease



Heart Failure Hospitalization: a key opportunity *in view of discharge phase...*

Elevated **discharge heart rate** increases the risk of **adverse 30-day outcomes**.



Hazard ratio per 10 bpm increment Heart failure patients in sinus rhythm & heart rate \geq 75 bpm

"By targeting heart rate as a potentially modifiable risk factor in the progression of HF, the <u>SHIFT trial</u> has implicated heart rate in the causal pathway of HF progression"

> Laskey WK et al. Heart rate at hospital discharge in patients with heart failure is associated with mortality and rehospitalization. J Am Heart Assoc. 2015;4:e001626.
> 2. Habal MV et al. Association of heart rate at hospital discharge with mortality and hospitalizations in patients with heart failure. Circ Heart Fail. 2014;7(1):12-20

Evolution of Heart Failure Management



Kidney disease Back/forward story Digitalis, diuretics, rest







Neuroendocrine disease Evidence based medicine, prognosis vs. symptoms ACEi, B-Blockers, training

Epidemic syndrome Remodelling, **HEART RATE** Devices, HF/transplant centres And OPTIMIZE HF Care

TODAY

Evolution of Pharmacologic Approaches in HF



ACEI=angiotensin-converting enzyme inhibitor; Ang=angiotensin; ARB=angiotensin

receptor blocker; AT₁R=angiotensin II type 1 receptor; HF=heart failure; HFrEF=heart failure with reduced ejection fraction; MRA=mineralocorticoid receptor antagonist; NP=natriuretic peptide; NPRs=natriuretic peptide receptors; RAAS=renin-angiotensin-aldosterone system; SNS=sympathetic nervous system 1. McMurray et al. Eur J Heart Fail 2013;15:1062–73 Figure references: Levin et al. N Engl J Med 1998;339:321–8 Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42 Kemp & Conte. Cardiovascular Pathology 2012;365–71 Schrier & Abraham. N Engl J Med 2009;341:577–85

Eur J Heart Fail. 2017 Oct;19(10):1230-1241. doi: 10.1002/ejhf.902. Epub 2017 Jun 19.

Heart rate and its reduction in chronic heart failure and beyond.

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Abstract

Heart rate (HR) is associated with cardiovascular outcomes in all the stages of the cardiovascular continuum as well as in patients with pulmonary, cerebrovascular, and renal disease, sepsis, cancer, and erectile dysfunction. In patients with cardiovascular disease, but also in the general population, increased HR represents an important indicator of mortality with each acceleration of HR over 70 b.p.m. increasing the risk. In patients in sinus rhythm with chronic heart failure with reduced ejection fraction (HFrEF), a HR >70 b.p.m. increased the risk of hospitalization, and >75 b.p.m. the risk of cardiovascular death as shown in the Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial (SHIFT). Reducing HR with ivabradine by 11 b.p.m. (placebo-controlled) reduced the primary composite endpoint (cardiovascular death and hospitalization for worsening heart failure). Ivabradine was well tolerated showing benefit irrespective of age or diabetes status, and also in the presence of low systolic blood pressure and severe heart failure (SHIFT trial) Therefore, HR qualifies as a modifiable risk factor in heart failure. In patients with stable coronary disease, HR is a risk marker but HR reduction with ivabradine does not improve outcomes. The role of selective HR lowering remains unclear in patients with pulmonary, renal, cerebrovascular, and other diseases, as the potential benefit of interventions on HR has not been explored in these conditions. Future studies should scrutinize if HR reduction improve outcomes, defining HR as a potential risk factor and therapeutic target in other conditions beyond heart failure.

Why is it important? What is wrong? Where is the problem? How to overcome? Who is Ivabradine?



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Review

Heart failure across Asia: Same healthcare burden but differences in organization of care☆



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Mean length of stay are relatively similar, but mortality rate 30-days after discharge are very high

Table 2

Heart failure (HF) hospitalization and mortality in the 9 Asian countries or regions, and Europe and the USA [3,20,22-24,35-38].

Hospitalization characteristics		stics Asia								Europe	USA	
		Hong Kong	Indonesia	Malaysia	Philippines	Singapore	South Ko	orea Taiwan	Thailand	Vietnam		
Hospitalizations HF hospitalizations % of total hospitali Readmission rate	s per year Hospitalizatio	18,000 on characte	- eristics	- As	 sia	6000	-	40,000 2.2%	-	- 159	-	>1M -
By 30 days Hospital stay				Н	ong Kong	Indonesia Malay:		alaysia Philippines		Singapore		25%
Mean (days) Median (range) (Mortality Inpatient Within 30 days of Annual cost of HF (l	Hospitalizatio HF hospital % of total h Readmission	ons lizations pe ospitalizat rate	er year ions	18 -	3,000	-	-	- 9%	6000 -)	- 8 6% -	- 5 4% 10%
Cost of hospitaliza Missing data are not av	By 30 days Hospital stay	5		-	10	7%	8%	-	17.6% (9	0 days)	-	23,077
	Mean (days) Median (range) (days) Mortality			6-	-10	5	9.24 7 (4–11)	10 7 (1–133)	5.1 -			
	Inpatient Within 30 Annual cost of	days of dis of HF (US\$)	charge million)	- -	016 4960	3% 17%	6% 1%	7% 10%	1.1% -			
	Annual cost of Cost of hos	of HF (US \$) pitalization	million) n (US \$ per	pt) 29	916-4860	813	-	-	-			

Under-usage of guideline-recommended HF pharmacological therapies in Indonesian patients

Table 3

Pharmacological treatment of HF in 9 Asian countries or regions, and Europe and the USA [26,28,35,39].

Pharmacological treatment of HF		Asia									Europe	USA
		Hong Kong	Indonesia	Malaysia	Philippines	Singapore	South Korea	Taiwan	Thailand	Vietnan	1	
RAAS	inhibitor	52%	78%	67%	70%	74%	65%	61%	77%	90%	89%	66%
Beta-b	olocker	39%	32%	72%	38%	65%	44%	57%	78%	41%	87%	81%
Calciu	m channel blocker	-	-	17%	12%	-		12%	-	-	10%	-
Ivabra	dine	-	-	-	0%	-		-	6%	21%	-	-
Diure	tic	84%	78%	99%	76%	87%		80%	92%	-	83%	-
Dige -	Pharmacological tre	atment of L	JE Acia									62%
Anti	Fild Inacological tre	atment of i		1								65%
Missin			Hor	ıg Kong	Indonesia	Malays	sia Philip	pines	Singapor	re So	outh Korea	
	RAAS inhibitor		52%		78%	67%	70%		74%	65	5%	
	Beta-blocker		39%		32%	72%	38%		65%	44	1%	
	Calcium channel blo	cker	-		-	17%	12%		-			
	Ivabradine		-		-	-	0%		-			
	Diuretic		84%		78%	99%	76%		87%			
	Digoxin		11%		21%	44%	53%		27%			
	Lipid-lowering agen	t	-		-	76%	-		72%			
	Anticoagulant		-		-	25%	26%		12%			
	Ainsing data and mater											-

Missing data are not available.

Why is it important? What is wrong? Where is the problem? How to overcome? Who is Ivabradine? Initiating therapy during hospitalization is suggested to reduce the risk of adverse outcomes. At discharge, patients can be considered to be in a stable chronic heart failure state at high risk for adverse outcomes.

- "Initiating therapies in patients who are stabilized in the hospital and continued long-term provides a potent option to improve long-term clinical outcomes."
- "Delaying initiation of potentially effective therapies for weeks to months post discharge risks unabated high risk for adverse events in the meantime."

Gheorghiade M et al. Heart Failure Clin. 2013.9;285-290.

Adherence to guidelines

Compliance with evidence-based clinical practice guidelines is associated with an improvement of heart failure patients' outcomes.

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

Authors/Task Force Members: Piotr Ponikowski^{*} (Chairperson) (Poland), Adriaan A. Voors^{*} (Co-Chairperson) (The Netherlands), Stefan D. Anker (Germany), Héctor Bueno (Spain), John G. F. Cleland (UK), Andrew J. S. Coats (UK), Volkmar Falk (Germany), José Ramón González-Juanatey (Spain), Veli-Pekka Harjola (Finland), Ewa A. Jankowska (Poland), Mariell Jessup (USA), Cecilia Linde (Sweden), Petros Nihoyannopoulos (UK), John T. Parissis (Greece), Burkert Pieske (Germany), Jillian P. Riley (UK), Giuseppe M. C. Rosano (UK/Italy), Luis M. Ruilope (Spain), Frank Ruschitzka (Switzerland), Frans H. Rutten (The Netherlands), Peter van der Meer (The Netherlands)



Therapeutic algorithm for a patient with symptomatic HF with reduced ejection fraction.





www.escardio.org/guidelines

Available online on Eur J Heart Fail

Therapeutic algorithm for a patient with symptomatic HF with reduced ejection fraction. (cont..)





Heart Failure Pathway Writing C, Yancy et al. Journal of the American College of Cardiology. 2017.

Panduan Praktek Klinik PP PERKI

Rekomendasi

Pemberian ACEi direkomendasikan , bagi semua pasien dengan $EF \le 40\%$, untuk menurunkan risiko hospitalisasi akibat gagal jantung dan kematian dini

Pemberian penyekat β , setelah pemberian ACEi atau ARBs pada semua pasien dengan EF \leq 40% untuk menurunkan risiko hospitalisasi akibat gagal jantung dan kematian prematur

MRA direkomendasikan bagi semua pasien dengan gejala gagal jantung yang persisten dan $EF \le 35$, walaupun sudah diberikan dengan ACEi dan penyekat β

Rekomendasi

Angiotensin Receptor Blockers (ARB)

 Direkomendasikan untuk menurunkan risiko hospitalisasi gagal jantung dan kematian dini pada pasien dengan EF ≤ 40 % dan tidak toleran dengan ACEi, dikarenakan batuk (pasien tetap sudah harus mendapat β blocker dan MRA)

Ivabradine

Harus dipertimbangkan, untuk menurunkan risiko hospitalisasi gagal jantung pada pasien dengan irama sinus, $EF \le 35$ % dan laju nadi tetap ≥ 70 x/ menit, dan simtom (NYHA II-IV) yang persisten walaupun sudah mendapatkan terapi dengan ACE/ ARB, β blocker dan MRA yang optimal

Dapat dipertimbangkan untuk menurunkan risiko hospitalisasi gagal jantung pada pasien dengan irama sinus, $EF \le 35$ % dan laju nadi ≥ 70 x/ menit, yang tidak toleran terhadap β blocker. Pasien harus sudah mendapatkan terapi dengan ACE/ ARB dan MRA Why is it important? What is wrong? Where is the problem? How to overcome? Who is Ivabradine?



- 30% reduction of diastolic slope
- other currents maintain pacemaker activity
- safety factor of ivabradine

SELG Mean heart rate reduction

Mean ivabradine dose: 6.4 mg bid at 1 month



Reduces heart rate depending on baseline heart rate



Ivabradine in the management of heart failure

optimization of the treatment...

Improves Stroke Volume RAPIDly





for patients who are **stabilized in the hospital** and continued **long term**

Early treatments matters for the treatment of HF

Böhm M. et al,



Böhm M. et al, EJHF(2017): in preparation

Early treatments matters for the treatment of HF

Böhm M. et al,



Böhm M. et al, EJHF(2017): in preparation

Ivabradine : Ensure Survival Patients



adding more life to years

Heart rate \geq 75 bpm n=4150 Hazard rate=0.61 p=0.0006

Recognize by :





Ivabradine :

Reduces re-hospitalization RAPIDLY



HF patients are protected during the vulnerable phase

Ivabradine

Re-assess that beta blockers are adjusted to maximally tolerated doses and/or target doses



Heart Failure Pathway Writing C, Yancy et al. Journal of the American College of Cardiology. 2017.

KEY-POINTS

- Heart Failure is the ending of any cardiovascular diseases.
- Mortality due to HF still high despite medical therapies.
- Targeting heart rate as a potentially modifiable risk factor.
- Early co-administration of Ivabradine (and BB), or on top of optimal tolerated dose of GDMT is safe and be an integral part of all HF guidelines.



End of Presentation

Association between high heart rate and cardiovascular risk

High heart rate as an independent risk factor

Increased ventricular wall stress Reduced arterial compliance Increased mean blood pressure Increased pulsatile pressure Decreased arrhythmic threshold Increased risk for atheroslerotic plaque instability High heart rate as a risk indicator of adrenergic hyperactivity

Left ventricular hypertrophy Insulin resistance Lower arrhythmic threshold Lower exercise capacity Increased risk for coronary thrombosis

The burden of heart failure hospitalization **Overview in figures...**

- Heart failure is a life-threatening disease estimated to be present in 1% to 2% of the general population.
- The prevalence of the disease is tending to increase due to aging of the population and improved survival in many diseases. This global pandemic is known to have a survival rate that is worse than that of some cancers.



more likely to worsen the patient's overall health status

1. McMurray J et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2012;14(8):803-869. 2. Ambrosy PA et al. The Global Health and Economic Burden of Hospitalizations for Heart Failure. Lessons Learned From Hospitalized Heart Failure Registries, J Am Coll Cardiol, 2014;63:1123–1133, 3, Butler J. Braunwald E. Gheorghiade M. Recognizing worsening chronic heart failure as an entity and an end point in clinical trials, JAMA, 2014;312(8):789-790, 4, van Deursen VM et al. Comorbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey. Eur J Heart Fail. 2014;16:103-111.

The burden of heart failure hospitalization from the society's perspective ...

Increase in health care expenses

3 X higher **by 2030**

The 2030 projected cost estimates of treating patients with heart failure will be 3 fold higher than in 2010, mainly due to the aging of the population

The burden of heart failure hospitalization Overview in figures...



Heart failure is the leading cause of hospitalization in patients aged over 65 years with average length of hospital stay 5-10 days

> HF Hospitalization Impact : Psychological, social, relational and physical capacity

1. Cowie MR et al. Improving care for patients with acute heart failure. 2014. Oxford PharmaGenesis. ISBN 978-1-903539-12-5. Available at: <u>http://www.oxfordhealthpolicyforum.org/reports/acute-heart-failure/</u> improving-care-for-patients-with-acute-heart-failure. 2. Solomon SD et al. Inluence of Nonfatal Hospitalization for Heart Failure on Subsequent Mortality in Patients With Chronic Heart Failure. Circulation. 2007;116:1482-1487.

Heart Failure Hospitalization: a key opportunity in view of the early post discharge phase ...

Re-hospitalization is particularly high in the early phase after hospitalization:



Almost 1 out of 4 heart failure readmissions (24%) will happen in the first 30 days post-discharge

The vulnerable phase is a critical determinant of prognosis. In order to avoid adverse outcomes, patients should be discharged "<u>when they are hemodynamically stable for at least 24-48 hours, euvolemic,</u> <u>and managed on evidence-based oral medication,</u> <u>and when they have stable organ function, including the kidney and liver"</u>

HEART RATE as PREDICTOR of CV Death, Hospitalization HF

1. Butler J, Braunwald E, Gheorghiade M. Recognizing worsening chronic heart failure as an entity and an end point in clinical trials. JAMA. 2014 ;312:789-790. 2. AbrahamssonP. Risk following hospitalization in stable chronic systolic heart failure. Eur J Heart Fail. 2013;15(8):885-891. 3. O'Connor CM et al. Causes of death and rehospitalization in patients hospitalized with worsening heart failure and reduce left ventricular ejection fraction: results from eficacy of vasopressin antagonism in heart failure outcome stuy with tolvaptan (EVEREST) program. Am Heart J. 2010;159:841-849.e1. 4. Krumholz HM. Post-hospital Syndrome – An acquired, Transient Condition of Generalized Risk. N Engl J Med. 2013;368;2. 5. Marti NC et al. Timing and duration of interventions in clinical trials for patients with hospitalized heart failure. Circ Heart Fail. 2013;6:1095-1101. 6. Yilmaz MB, Mebazaa A. Deinition and characteristics of the vulnerable phase in heart failure. Medicographia. 2015;37(2):144-148. 7. Mebazaa A et al. Recommendations on pre-hospital & early hospital management of acute heart failure: a consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergency Medicine. Eur J Heart Fail. 2015;17(6):544-558

There is a close relationship between heart rate and life expectancy

 Heart Rate is a marker for metabolic rate and energetic needs

7 HR Pendothelial stress **7** NO vasodilatation 7 O2 and substrates delivered metabolic rate

Life expectancy is predetermined by the basic energetics of living cells

The less the energy is needed, the longer the life span

Ref : Azbel MY. Universal biological scaling and mortality. Proc Nat Acad Sci USA 1994;91:12453-7

Heart Failure Hospitalization: a key opportunity key success factor ...

OPTIMIZATION OF TREATMENT

Hospitalization is the key moment to optimize heart failure care

Hospitalization implies several phases: an acute phase and a stable phase.

By initiating therapies in patients who are stabilized in the hospital and continued long-term, It improves long-term clinical outcomes.

It is also important to prevent heart failure progression and to take into consideration the comorbidities of heart failure patients.

• Adherence to guidelines

Compliance with evidence-based clinical practice guidelines is associated with an improvement of heart failure patients' outcomes.



Heart Failure Hospitalization: a key opportunity key success factor ...

PATIENT EDUCATION

• Knowledge associated with self-care for people suffering from heart failure

Increasing patient knowledge about self-care has a positive influence on health and well-being by respecting exercise

and dietary, interpreting symptoms to seek appropriate care, and complying with treatments prescribed

• Involvement of health care professionals in terms of availability, continuity, and quality

The positive involvement of health care professionals helps patients and their families timely care, improve confidence, and maintain self-care practice.



Heart Failure Hospitalization: a key opportunity key success factor ...

Continuity of care

Establishment of a discharge plan

Discharge plans are defined in several recommendations (2010 NICE guidance, 2013 ACCF/AHA guidelines) in order to follow up patients carefully, particularly during the post-discharge phase, which is a period of vulnerability



