Accurate diagnoses, evidence based drugs, and new devices (3 Ds) in heart failure

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Abstract
Heart failure becomes main problem in cardiology because of increasing of heart failure patients, rehospitalization rate, morbidity, and mortality rate. The main causes of increasing heart failure problems are: (1) Successful treatment of acute myocardial infarction can be life saving, but its sequelae can cause heart failure. (2) Increasing life expectancy rate grows along with incidences of ageing related heart failure. (3) High prevalence of infection in Indonesia can cause rheumatic heart disease post Streptococcal beta hemolytics infection, viral myocarditis, infective endocarditis, and tuberculoïd pericarditis. (4) Many risk factors for coronary heart disease are often found in heart failure patients, for examples smoking, diabetes, hypercholesterolemia, hypertension, and obesity. Indonesia joined international multicentered registry in 2006. Acute Decompensated HEart failure REgistry is a web based international registry to record patient with acute decompensated heart failure who was admitted at the emergency room and registered in 5 hospitals in Java and Bali island. A total of 1687 patients with Acute Decompensated Heart Failure were admitted at the emergency room and registered using web base international software, mean age was 60 years, 64.5% male. Compared to other countries (Asia Pasific, Europe, US), Indonesian patients were younger, sicker and late to seek treatment. The median hospital length of stay was 7 days and in hospital mortality rate was 6.7%. The aim of this article is to give summary about essential things in diagnosing and treating heart failure patients. 3D (accurate diagnoses, evidence based drugs, and new devices) are the most important but what to do and what not to do in dealing with heart failure is also useful for your daily practice.

Keywords: Devices, diagnostic, drugs, heart failure

Heart failure situation in Indonesia
Recently, heart failure had become the most prevalence of heart disease in Indonesia because of some reasons: (1) The success treatment of Acute Myocardial Infarction really prevent mortality but become systolic heart failure. (2) The increasing life expectancy leads to ageing heart that resulted in diastolic heart failure. (3) In Indonesia, where the infectious disease is still prominent, the prevalence of valvular heart disease also increases. Uncontrolled hypertension, bad life style including unhealthy food, viral myocarditis and other infection, also contribute in increasing number of heart failure, admission and mortality. (4) Uncontrolled CAD risk factors in Indonesia people as manifested by some trends of increasing hypertension, smokers, uncontrolled pregnancy and hypercholesterolemia.

In 2005 Siswanto et al. found that at 6 months follow up the mortality rate 12 % and the readmission rate 29 %. In 2006 Indonesia involved in the International Acute Decompensated HEart failure REgistry (ADHERE) involving 5 hospitals in Java and Bali island. A total of 1687 patients with Acute Decompensated Heart Failure were admitted at the emergency room and registered using web base international software, mean age was 60 years, 64.5% male. Compared to other countries (Asia Pasific, Europe, US), Indonesian patients were sicker, had more severe symptoms, lower ejection fraction, as well as higher in-hospital mortality (6.7%). On admission, only 68% got ACE-I/ARB and 41% got low dose beta blocker. Although the hospitalization rate keep increasing each year, only 33.5% got covered by health insurance.

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Three Ds in heart failure

The primary care physician typically care for 2000 patients. It is likely to have 40-50 patients with heart failure (more if population is elderly) and to have 5 or so new cases of heart failure diagnosed each year, with the diagnosis of suspected heart failure in perhaps 3 times as many. Clear guidance is needed on which clinical features and combination of investigations is best to rule out or rule in heart failure in patients with new symptoms. 3Ds is an easy way to remember important things when dealing with heart failure.

1. (D)iagnostic accuracy

Accurate and early diagnosis is important since it is a prerequisite before early treatment. Only 26% of patients with suspected heart failure referred to a rapid access for echocardiography and the diagnosis confirmed after investigation.

“Rule of half” in heart failure may occur. Only half of HF patients are diagnosed correctly. Half of the correctly diagnosed were treated not according to the guidelines; the drugs that had been used were not evidence-based and the dose that should be used were too low. Half of the etiology of HF are not assessed and not appropriately corrected. Half of the HF that we managed were readmitted and dead in 4 years follow up.

HF is a syndrome with typical symptoms of shortness of breath on exertion, signs of fluids retention (pulmonary congestion, ankle swelling, ascites and liver enlargement), and proven by objective evidence of abnormal structure and function (cardiomegaly, third heart sound, cardiac murmur, abnormal echocardiogram and abnormal natriuretic peptide). In a community without echocardiography, Framingham Heart Failure Criteria for diagnosis may be applied. Minor criteria are acceptable only if they can not be attributed to another medical condition (such as pulmonary hypertension, chronic lung disease, cirrhosis, ascites, or nephrotic syndrome). Clinical congestive heart failure is diagnosed when 2 major criteria present or 1 major and two minors present. The Modified Framingham Heart Study criteria are 100% sensitive and 78% specific for identifying persons with definite congestive heart failure.

Due to the low specificity of the clinical criteria, considerations must be thought for excluding differential diagnosis. An electrocardiogram should be performed in every patients with suspected heart failure. An abnormal ECG has a predictive value for the presence of HF. If the ECG is completely normal, HF, especially with systolic dysfunction is unlikely (< 10%). CXR is an essential component of the diagnostic work up in heart failure. It permits assessment of pulmonary congestion and may demonstrate important pulmonary or cardiac causes of dyspnoea. The chest X ray (in two planes) is useful to detect cardiomegaly, pulmonary congestion and pleural fluid accumulation and can demonstrate the presence of pulmonary disease or infection causing or contributing to dyspnea. Apart from congestion, findings are predictive of HF only in the context of typical signs and symptoms. In acute heart failure, cardiomegaly may be absent.

If an electrocardiogram (ECG), chest X ray and blood levels of B-natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NTproBNP) are within normal limits, an alternative cause must be considered. Unfortunately, biomarkers usage is still very limited in Indonesia, although point of care NTproBNP available. BNP/ NTproBNP accurately rule out/ rule in HF.

### Framingham criteria for the diagnosis of congestive heart failure

| Major Criteria | Minor Criteria |
|----------------|----------------|
| Paroxysmal nocturnal dyspnea or orthopnea | Ankle edema |
| Neck vein distension | Night cough |
| Crackles (±10 cm from the base of the lung) | Dyspnea on exertion |
| Cardiomegaly on chest radiograph | Hepatomegaly |
| Acute pulmonary edema | Pleural effusion |
| \( S_3 \) gallop | Tachycardia ≥120 beats/min |
| Weight loss ≥4.5 kg caused by CHF treatment | Weight loss ≥4.5 kg caused by CHF treatment where factors other than treatment of CHF could have contributed to the weight loss can be excluded |
| Venous pressure ≥16 cm H\( \text{O} \) |

*Modified from Kleber et al. The presence of 2 major or 1 major and 2 minor criteria are needed to diagnose congestive heart failure (CHF).
2. **(D)rugs that’s proven by EBM**

DO follow the guideline in treating heart failure. After accurate diagnosis, classify heart failure patients structurally (according to ACC/AHA) or by symptoms relating to functional capacity (NYHA) and treat accordingly with evidence-based drugs.6

ACE-inhibitors remain a cornerstone in the treatment of HF which can improve both morbidity and mortality in all grades of symptomatic heart failure with systolic dysfunction and can delay or prevent progression of asymptomatic to symptomatic heart failure. More recently, researches have shown the prognostic benefits of treatment with β blockers in heart failure with left ventricular systolic dysfunction. Unfortunately, heart failure is difficult to diagnose accurately on clinical grounds in some cases, so we need biomarker or echocardiography.

Figure 1 represents the guideline to classify the diagnosis of HF and table 1 and 2 show some evidence-based medications according to ACC/AHA guidelines.  

3. **(D)evice in appropriate patients**

Despite the emergence of new devices in the armamentarium of chronic heart failure management, mostly their usage is limited for those with advanced heart failure who have no improvement after optimal medical therapy, according to ESC 2008 Heart Failure guideline.4 Figure 2 depicts algorithm in the management of heart failure, including the use of some devices. Devices including CRT (Cardiac Resynchronization Therapy), ICD (Implantable Cardioverter Defibrillator), and LVAD (Left Ventricular Assited Devices)

**What’s new in 2011?**

The MADIT-II (Multicentre Automatic Defibrillator Implantation Trial II) trial was the first major study to show a survival benefit for prophylactic ICD implantation in patients with previous MI and a left ventricular ejection fraction (LVEF) of less than 30%.4 Most of the primary prevention ICD trials have focused on patients with ischaemic etiology of HF. The previous SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) study, which also enrolled patients with non-ischaemic cardiomyopathy (NICM).9 This showed a similar relative risk reduction of death of 27% in the NICM group as compared to 21% in the ischaemic group. Nevertheless, the absolute risk reduction over five years was only a modest 7.2% so this was cited as a possible reason as to why the National Institute for Health and Clinical Excellence (NICE) have not issued specific guidance on implantation of an ICD in the non-ischaemic population.

![Figure 1. ACC/AHA classification of heart failure](image)
Table 1. Cardiovascular medications useful for treatment of various stages of heart failure

| Drug                     | Stage A          | Stage B                        | Stage C          |
|--------------------------|------------------|--------------------------------|------------------|
| **ACE Inhibitors**       |                  |                                |                  |
| Captopril                | H, DN            | Post MI                        | HF               |
| Enalapril                | H, DN            | Asymptomatic LVSD              | HF               |
| Lisinopril               | H, DN            | Post MI                        | HF               |
| Perindopril              | H, CV Risk       | -                              | -                |
| Quinapril                | H                | -                              | HF               |
| Ramipril                 | H, CV Risk       | Post MI                        | Post MI          |
| Trandolapril             | H                | Post MI                        | Post MI          |
| **Angiotensin Receptor Blockers** |             |                                |                  |
| Candesartan              | H                | -                              | HF               |
| Eprosartan               | H                | -                              | -                |
| Irbesartan               | H, DN            | -                              | -                |
| Losartan                 | H, DN            | CV Risk                        | -                |
| Olmesartan               | H                | -                              | -                |
| Telmisartan              | H                | -                              | -                |
| Valsartan                | H, DN            | Post MI                        | Post MI, HF      |
| **Aldosterone Antagonists** |             |                                |                  |
| Eplerenone               | H                | Post MI                        | Post MI          |
| Spironolactone           | H                | -                              | HF               |
| **Beta Blockers**        |                  |                                |                  |
| Acebutolol               | H                | -                              | -                |
| Atenolol                 | H                | Post MI                        | -                |
| Bisoprolol               | H                | -                              | HF               |
| Carvedilol               | H                | Post MI                        | HF, Post MI      |
| Labetalol                | H                | -                              | -                |
| Metoprolol succinate     | H                | -                              | HF               |
| Metoprolol tartrate      | H                | Post MI                        | -                |
| Nadolol                  | H                | -                              | -                |
| Penbutolol               | H                | -                              | -                |
| Pindolol                 | H                | -                              | -                |
| Propranolol              | H                | Post MI                        | -                |
| Timolol                  | H                | Post MI                        | -                |
| **Digoxin**              | -                | -                              | HF               |

CV Risk indicates reduction in future cardiovascular events; DN, diabetic nephropathy; H, hypertension; HF, heart failure; Asymptomatic LVSD, Asymptomatic left ventricular systolic dysfunction; Post MI, reduction in heart failure or other cardiac events following myocardial infarction.

The CARE-HF (Cardiac Resynchronisation – Heart Failure) study was pivotal being the first to show that a CRT device without a defibrillator could reduce the risk of death from any cause by 36%, when compared to standard medical therapy. Crucially, a number of important patient groups were excluded from this seminal trial, such as those with permanent atrial fibrillation (AF), mild HF symptoms (New York Heart Association [NYHA] functional class I and II), or a narrow QRS duration (< 120 msec). The challenging task is to seek evidence for implanting CRT in these selective populations. When considering AF, a large Italian cohort study has reported improvements in LVEF, NYHA class and exercise capacity, similar to those seen in sinus rhythm, when CRT is combined with AV node ablation. Nevertheless, there is consensus that there is insufficient evidence to support a mortality benefit with this strategy, and more prospective randomised studies are necessary.

The most compelling evidence for use of CRT in patients with mild HF symptoms comes from the MADIT-CRT (Multicentre Automatic Defibrillator Implantation Trial with Cardiac Resynchronisation Therapy) study, which enrolled patients in NYHA class I and II and randomised to ICD or CRT-D. This showed a 41% reduction in the risk of HF-events in the CRT-D group, which was primarily evident in a prespecified group of patients with significant electrical dysynchrony (QRS > 150 msec). To anticipate the overwhelming wave of euphoria in device implantation for chronic heart failure, the ESC issued a focused update on device therapy for heart
Table 2. Oral diuretics recommended for use in the treatment of fluid retention in chronic heart failure

| Drug                          | Initial Daily Dose(s) | Maximum Total Daily Dose | Duration of Action |
|------------------------------|-----------------------|--------------------------|--------------------|
| **Loop diuretics**           |                       |                          |                    |
| Burnetanide                  | 0.5 to 1.0 mg once or twice | 10 mg                   | 4 to 6 hours       |
| Furosemide                   | 20 to 40 mg once or twice  | 600 mg                  | 6 to 8 hours       |
| Torsemide                    | 10 to 20 mg once       | 200 mg                  | 12 to 16 hours     |
| **Thiazide diuretics**       |                       |                          |                    |
| Chlorothiazide               | 250 to 500 mg once or twice | 1000 mg                | 6 to 12 hours      |
| Chlorthalidone               | 12.5 to 25 mg once     | 100 mg                  | 24 to 72 hours     |
| Hydrochlorothiazide          | 25 mg once or twice    | 200 mg                  | 6 to 12 hours      |
| Indapamide                   | 2.5 once               | 5 mg                    | 36 hours           |
| Metolazone                   | 2.5 mg once            | 20 mg                   | 12 to 24 hours     |
| **Potassium-sparing diuretics** |                     |                          |                    |
| Amiloride                    | 5 mg once              | 20 mg                   | 24 hours           |
| Spironolactone               | 12.5 to 25 mg once     | 50 mg*                  | 2 to 3 days        |
| Triamterene                  | 50 to 75 mg twice      | 200 mg                  | 7 to 9 hours       |
| **Sequential nephron blockade** |                     |                          |                    |
| Metolazone                   | 2.5 to 10 mg once plus loop diuretic |                  |                    |
| Hydrochlorothiazide          | 25 to 100 mg once or twice plus loop diuretic |                |                    |
| Chlorthiazide (IV)           | 500 to 1000 mg once plus loop diuretic |                |                    |

mg indicates miligrams; IV, intravenous. *Higher doses may occasionally be used with close monitoring. Eplerenone, although also a diuretic, is primarily used in chronic heart failure as a suppressor of the renin-angiotensin-aldosterone system.

Figure 2. A treatment algorithm for patients with symptomatic heart failure and reduced ejection fraction
failure in 2010, ensuring that practitioners DON’T go astray from their corridor. The update also mentioned some issues about LVAD (left ventricular assist devices).2

**Novel therapeutic strategies in heart failure in 2011**

Recently there are many new management strategies from the year 2011 onward

**Anaemia in CHF**

The need for checking haemoglobin and haematinics in patients with CHF, and correcting iron deficiency, where appropriate, was emphasised by the findings in FAIR-HF (Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure), a large multicentre study, which showed benefit in various clinical end-points such as symptom limitation and quality of life, when comparing intravenous iron to placebo.13 The use of erythropoietin stimulating agents (ESAs) in CHF is more controversial. Whilst initial studies suggested improvements in LVEF, exercise capacity and quality of life, the randomised clinical trials that followed disappointingly did not show a significant benefit. Results of RED-HF (Reduction of Events with Darbopoetin-α in Heart Failure), a large mortality driven study are eagerly awaited.14

**Heart rate: the SHIFT study**

Epidemiological and observational studies have shown that an elevated resting heart rate is a risk factor for mortality and poor cardiovascular outcomes. SHIFT (the Systolic Heart failure treatment with I inhibitor Ivabradine Trial) results showed a significant reduction in hospitalisation and death from HF when comparing ivabradine to placebo in patients with advanced HF on optimal therapy. Unsurprisingly, subgroup analysis suggested that those with higher resting heart rates derived greater benefit.15

**Sleep-disordered breathing**

Sleep-disordered breathing conditions are prevalent in a staggering 50-60% of HF patients and these conditions can have adverse haemodynamic consequences for the failing heart. Studies have shown that CHF patients suffering from obstructive sleep apnoea (OSA) treated with continuous positive airway pressure (CPAP) have improved LVEF as well as a significantly reduced risk of death and hospitalisation.

CPAP has not shown any convincing evidence in the management of central sleep apnoea (CSA) associated with CHF, however, adaptive servoventilation (ASV), a novel ventilatory therapy which provides ventilatory support on detection of Cheynes Stokes respiration may have different efficacy. A small randomised study has shown ASV to be of greater benefit than CPAP in treating CSA associated with CHF.16 SERVE-HF (Treatment of Sleep Disordered Breathing by Adaptive Servoventilation in HF patients) study, a large trial driven by mortality outcomes is still underway.

**Exercise training in heart failure**

The safety and efficacy of exercise training in heart failure as compared to usual-care was evaluated in HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training), a large, multicentre randomised controlled trial. Whilst there was no significant improvement in outcomes, a substudy of the trial did show a significant improvement in patient-reported health status as assessed using the Kansas City Cardiomyopathy Questionnaire.17 A small pilot study involving training using electrical muscle stimulation in patients with HF who lead sedentary lifestyles showed that there may be a future role for therapies directed at skeletal muscle to improve HF symptoms.18

**Future directions in HF management**

Now the uproar is all about gene therapy in HF. In the first clinical test of a gene therapy for heart failure called CUPID (Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease), administration of a gene that upregulates an enzyme involved in myocardial contraction and relaxation appeared to improve symptoms, functional status, and ventricular volumes in patients with severe systolic heart failure. The treatment entails delivery of a gene associated with an enzyme that is central to controlling the flow of calcium ions between the sarcoplasmic reticulum and cytoplasm and so plays a key role in regulating myocardial contractility. Deficiency of the enzyme, called sarcoplasmic reticulum CA²⁺ ATPase (SERCA2a), often occurs in advanced heart failure and is considered a mechanism of progressive systolic and diastolic dysfunction. The SERCA2a gene is administered using an adeno-associated viral vector in a single intracoronary dose.19

Another interest is the research of stem cell application in HF. Stem cells have an enormous potential to help millions of patients with end-stage ischemic heart failure who have no other therapeutic options.20 Both approach will have to wait a while to reach real clinical setting until the second phase trials completed.
While four major multi-center trials including TELE-HF, TIM-HF, TEN-HMS, failed to demonstrate the efficacy of remote telemonitoring systems, evaluation of device-based diagnostics is still underway and looks promising. The CHAMPION trial randomized 550 patients to therapy guided by an implantable wireless pulmonary artery pressure monitoring system versus standard of care and showed a 28% reduction in heart failure hospitalizations at 6 months and a 37% reduction in heart failure hospitalizations over the full duration of follow-up (averaging 15 months). The system used in this study was awaiting CE Mark and FDA approval. An implantable left atrial pressure monitoring system that was preliminarily shown to be effective in a small pilot study and the pivotal trial of this system, LAPTOP-HF, is now underway.

By means of strategy, the uprising of heart failure clinics and one day care will likely be accompanied by a heart failure subspecialty program in the near future. To combat the pandemic of heart failure in Indonesia, early diagnosis, appropriate evidence based drugs used, new evidence based device in appropriate patients, health insurance coverage, better community health services, health education for compliance in drugs, diet and life style are important. More effort should be emphasis on the prevention program by every health care providers.

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