Chronic Heart Failure Guidelines: A Critique

Ramon F. Abarquez, Jr., Paul Ferdinand M. Reganit, Carmen N. Chungunco,
Jean D. Alcover, Felix Eduardo R. Punzalan and Eugenio B. Reyes

Section of Cardiology, Department of Medicine, College of Medicine and Philippine General Hospital, University of the Philippines Manila

ABSTRACT

Background. Chronic heart failure (HF) disease as an emerging epidemic has a high economic burden, hospitalization, readmission, morbidity and mortality rates despite many clinical practice guidelines recommendations.

Objective. To show that the attributed survival and hospitalization-free event rates in the reviewed chronic HF clinical practice guidelines' Class I-A recommendations as "initial HF drug therapy" is basically "add-on HF drug therapy" to the "baseline HF drug therapy" thereby under-estimating the "baseline HF drug therapy" significant contribution to the clinical outcome.

Methodology. The references cited in the chronic HF clinical practice guidelines of the American Heart Association/American College of Cardiology (AHA/ACC), the Heart Failure Society of America (HFSA), and the European Society of Cardiology (ESC) were reviewed and compared with the respective guidelines' and other countries' recommendations.

Results. The "baseline HF drug therapy" using glycosides and diuretics is 79-100% in the cited HF trials. The survival and hospitalization event-free rates attributed to the "baseline HF drug therapy" are 46-89% and 61.8- 90%, respectively. The survival and hospitalization-free event rate of the "initial HF drug therapy" is 61-92.8 % and 61.8-90 %, respectively. Thus the survival and hospitalization event-free rates of the "add-on HF drug therapy" are 0.4-15% and 4.6% to 14.7%, respectively. The extrapolated "baseline HF drug therapy" survival is 8-51% based on a 38% natural HF survival rate for the time period.

Conclusion. The contribution of "baseline HF drug therapy" is relevant in terms of survival and hospitalization event-free rates compared to the HF Class 1-A guidelines proposed "initial HF drug therapy" which is in essence an "add-on HF drug therapy" in this analysis.

Key Words: heart failure, guidelines, critique

Corresponding author: Paul Ferdinand M. Reganit, MD, MPH
Section of Cardiology
Department of Medicine
Philippine General Hospital
University of the Philippines Manila
Taft Avenue, Ermita, Manila 1000 Philippines
Telephone: +632 5548400 local 3670
Email: preganit@post.harvard.edu or preganit@netscape.net

Introduction

The prevalence of heart failure (HF) is 1-2% among adult population in developed countries and 6-10% in the elderly groups. It is rising with an estimated 660,000 new cases each year.[1-5] In China, the HF prevalence increased to 29.1% from 16.9%.[6] The US Medicare HF thirty-day unadjusted mortality rate has decreased however the post-discharge mortality rate, re-admission, and admissions to nursing home facilities have increased. The economic burden of HF remains high.[7-17]

A 2004 systematic review has shown that HF disease management programs can reduce HF hospitalizations by 27%. However, HF hospitalization costs in USA have increased by more than 175% during the last 25 years.[18-20] Incomplete implementation of trial methodology, inadequate patient education, absence of trained staff for follow-up monitoring, non-access to specialized HF clinics, application of complex adaptive systems framework or disease management programs can be plausible reasons for the continued high burden of HF.[21-29]. In a systematic review of chronic HF guidelines from Europe, 56% were consensus-based and 28% were evidenced-based advisories.[30-36]. Furthermore, guidelines recommendations do not highlight the significant contribution of baseline drug therapy. The concern is the lack of a statement describing that the Class I-A recommended "initial HF drug therapy" is in fact an "add-on HF drug therapy" to the "baseline HF drug therapy."[44-65]

Objectives

The objectives of this study are to determine the survival and hospitalization event free rate in the "baseline HF drug therapy", and "initial HF drug therapy" groups and to compute for the "add-on HF drug therapy" survival and hospitalization event-free rates.

Materials and Methods

The chronic HF trials published by the American Heart Association/American College of Cardiology (AHA/ACC), the Heart Failure Society of America (HFSA), and the European Society of Cardiology (ESC) were reviewed, summarized, collated, and compared with the guidelines' class I-A recommendations.[38-45] Other chronic HF studies and guidelines were reviewed for comparison.[46-47,91-96]

The "baseline HF drug therapy" refers to the background HF medications used as placebo in the trial. The "first line HF drug therapy" refers to the experimental drug used in the trial. The "add-on HF drug therapy" survival and hospitalization event-free rate is the difference between the "baseline HF drug therapy" and the "first line HF drug therapy" rates. The natural HF survival rate of 38% is assumed based on published literature for the time period.

Results

Table 1. Comparison of the 2005 and 2009 AHA/ACC, HFSA, and ESC Chronic HF Guidelines Final Recommendations on Drug Therapy

	AHA/ACC 2005 & 2009	ESC 2005 & 2008	HFSA 2006
ACEI	• Should be used in patients with reduced EF and no symptoms of HF, even if they have not experienced MI (I-A) • Together with a BB, should be used in all patients with a recent or remote history of MI regardless of EF or presence of HF (I-A) • Is recommended for all patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated (I-A) • 2005 recommendation remains current in 2009 update	• Is recommended as first line in all patients, with or without symptoms, who have LVEF <40-45% to improve survival, symptoms and functional capacity; and to reduce hospitalizations (I-A) • Should be given as initial therapy in the absence of fluid retention (I-B) • Should be initiated in patients with signs or symptoms of HF (even if transient) after the acute phase of MI to improve survival, reduce re-infarctions and hospitalizations for HF (I-A)	• Is recommended for routine administration to symptomatic and asymptomatic patients with LVEF <40% (A)
Diuretic	• Is indicated in patients with current or prior symptoms of HF and LVEF who have evidence of fluid retention (I-A) • 2005 recommendation remains current in 2009 update *Baseline drug recognized	• Is recommended when fluid overload is present, manifesting as pulmonary congestion or peripheral edema (I-A) • Should always be administered in combination with ACEI and BB if tolerated (I-C) *Baseline drug recognized	• Is recommended to restore and maintain normal volume status in patients with clinical evidence of fluid overload, generally manifested by congestive symptoms (orthopnea, edema, shortness of breath) or signs of elevated filling pressures (A) • Optional for symptomatic treatment
Beta Blocker	• Together with ACEI, should be used in all patients with a recent and remote history of MI regardless of EF or presence of HF (I-A) • Is indicated in all patients without history of MI who have reduced LVEF and no HF symptoms (I-C) • Bisoprolol, carvedilol or metoprolol succinate are recommended for all stable patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated (I-A) • 2005 recommendation remains current in 2009 update	• Is recommended for the treatment of all NYHA II-IV patients with stable mild, moderate, and severe HF from ischemic or non-ischemic cardiomyopathies and reduced LVEF on standard treatment, including diuretics and ACEI, unless contraindicated (I-A) • Is recommended in addition to ACEI to reduce mortality in patients with LV systolic dysfunction, with or without symptomatic HF, following an acute MI (I-B)	• BB shown to be effective in clinical trials are recommended for patients with EF<40% (A) • Combination of BB and an ACEI is recommended as routine therapy for asymptomatic patients with an LVEF<40% (C) • Recommended in the majority of patients with LV systolic dysfunction (C)
Aldosterone Antagonist	• Is reasonable in selected patients with moderately severe to severe HF symptoms and reduced LVEF who can be carefully monitored for renal function and potassium concentration (I-B) • 2005 recommendation remains current in 2009 update	• Is recommended in addition to ACEI, BB and diuretics in advanced heart failure (NYHA III-IV) to improve survival and morbidity (I-B) • Recommended in addition to ACEI and BB in HF after MI with LV systolic dysfunction and signs of HF or diabetes to reduce mortality and morbidity (I-B)	• Is recommended for patients with NYHA Class III/IV, previously Class IV, HF from LV systolic dysfunction (LVEF<35%), while receiving standard therapy, including diuretics (A) • Should be considered in patients after an acute MI, with clinical HF signs and symptoms and an LVEF<40%. Patients should be on standard therapy, including an ACEI (or ARB) and BB (A)
ARB	Recommended for current or prior symptoms of HF and reduced LVEF who are ACE inhibitor-intolerant *(Level of Evidence: A)* 2005 recommendation remains current but text modified to eliminate specific agents tested.	• Can be used as an alternative to ACEI in symptomatic patients intolerant to ACEI to improve morbidity and mortality (I-B) • Can be considered in combination with ACEI in patients who remain symptomatic to reduce mortality (IIa-B)	• Recommended for routine administration to symptomatic and asymptomatic patients with an LVEF<40% who are intolerant to ACEI for reasons other than hyperkalemia or renal insufficiency (A) • May be considered as initial therapy rather than ACEI for patients with the following conditions: HF post-MI (A), CHF and systolic dysfunction B) • Routine administration is not recommended in addition to ACEI and BB therapy in patients with recent acute MI and LV dysfunction (A)

Digoxin	• Can be beneficial to patients with current or prior symptoms of HF and reduced LVEF to decrease hospitalizations for HF (IIa-B) • 2005 recommendation remains Current in 2009 update	• Can be beneficial to patients with current or prior symptoms of HF and reduced LVEF to decrease hospitalizations for HF (IIa-B) • 2005 recommendation remains current in 2008 update	• Should be considered for patients with LV systolic dysfunction (LVEF<40%) who have signs or symptoms of HF while receiving standard therapy, including ACEI and BB (NYHA II-III [A], NYHA IV [B]) • High dose for the purpose of rate control is recommended (C)

In summary, the three chronic HF guidelines recommend the following:

(1) ACEIs - given as a routine first-line therapy" for systolic dysfunction;
(2) ARBs - as an alternative to ACEI for intolerant symptomatic HF patients;
(3) BB -used in all stable patients with systolic dysfunction and chronic HF in addition to ACEI, digitalis, and diuretics;
(4) Diuretics- recognized as baseline therapy but HFSA recommends its optional use for symptomatic HF;
(5) Aldosterone antagonists- as add-on to ACEI, BB, digitalis, and diuretics;
(6) Digitalis- "can be beneficial" as an add-on option in HF in sinus rhythm [36-48]

Table 2. Survival Rates in the "Baseline HF drug therapy", "Initial HF drug therapy" and "Add on HF drug therapy" Groups in the HF Studies Used in the Reviewed HF Clinical Practice Guidelines

NAME OF STUDY	DRUGS USED IN THE TRIAL	DRUGS IN BASELINE HF THERAPY	**"Baseline HF Therapy"** (SURVIVAL IN PLACEBO)	**"Initial HF Therapy"** (SURVIVAL IN TRIAL DRUG)	**"Add on HF Therapy"** (SURVIVAL BENEFIT OF TRIAL DRUG)	BASELINE HF THERAPY MENTIONED
V-HeFT – 1	Hydralazine + Isosorbide dinitrate	100% on digoxin and diuretics	53.1%	63.8%	10.7%	YES
SOLVD	Enalapril	85% on diuretics, 65% on digoxin, 40% on nitrates, 7% on B-blockers	60.3%	64.8%	4.5%	YES
V-HeFT-2	Enalapril	60% on vasodilators, 25% on antiarrhythmics	61.8%	67.2%	5.4%	YES
CONSENSUS	Enalapril	100% on diuretics, 94% digitalis, 50% vasodilators (mainly nitrates)	46%	61%	15%	YES
CIBIS II	Bisoprolol	99% on diuretics, 96% on ACEI or ARB, 58% on nitrates, 51% on digoxin	82.7%	88.2%	5.5%	YES
MERIT-HF	Metoprolol CR/XL	>90% on diuretics, >90% on ACEI or ARB, >60% on digitalis	89%	92.8%	3.8%	YES
COPERNICUS	Carvedilol	99% on diuretics, 97% on ACEI, 65% on digoxin	81.5%	88.6%	7.1%	YES
ELITE II	Losartan	79% on diuretics, 50% on digoxin, 21% on B-blockers, 20% on ACEI	88.3%	89.6%	1.3%	NO (but no benefit)
CHARM	Candesartan	85% on diuretics, 55% on B-blockers, 43% on digoxin, 41% on ACEI	75%	78%	3%	YES
Val-HeFT	Valsartan	93% on ACEI, 83% on diuretics, 68% on digoxin, 35% on B-blockers	80.7%	80.3%	0.4%	YES
V-HeFT III	Felodipine	97% on ACEI, 90% on diuretics, 75% on digoxin	86.2%	87.2%	1%	NO (but no benefit)
RALES	Spironolactone	100% on diuretics, 94.5% on ACEI, 74.5% on Digoxin, 10.5% on B-blockers	54%	65%	11%	YES

Legend: Dig, digoxin; BB, beta-blocker; diu, diuretic; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NO, nitrates; Mono, level of monotherapy; **CONSENSUS,** Cooperative North Scandinavian Enalapril Survival Study; **SOLVD,** Studies of Left Ventricular Dysfunction; **V-HeFT**, Vasodilator-Heart Failure Trial; **CIBIS**, Cardiac Insufficiency Bisoprolol Study; **MERIT-HF**, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; US CHF, US Carvedilol Heart Failure Study; **COPERNICUS,** Carvedilol Prospective Randomized Cumulative Survival study; **CHARM,** Candesartan in Heart Failure study; **ELITE**, Evaluation of Losartan in the Elderly trail; **Val-HeFT**, Valsartan Heart Failure Trial; **DIG**, Digoxin Investigation Group trial; **RALES**, Randomized Aldosterone Evaluation Study

In summary:

1. Proportion of HF studies with "baseline HF drug therapy" : 79% - 100%
2. Survival benefit of "baseline HF drug therapy" group: 46% - 89%
3. Survival benefit of "first-line HF drug therapy" group: 61% - 92.8%
4. Survival benefit of "add-on HF therapy" group: 0.4% - 15%.

Table 3. Proportions of Hospitalization and Computed Hospitalization Free Events in the "Baseline HF drug therapy", "Initial HF drug therapy", and "Add on HF drug therapy" Groups in the HF Studies Used in the Reviewed HF Clinical Practice Guidelines (Not hospitalized = 100% – proportion of hospitalized)

NAME OF STUDY	DRUG USED IN TRIAL	DRUGS USED IN BASELINE HF THERAPY	**"Baseline HF Therapy"** HF HOSPITALIZATIONS Among PLACEBO **(Not Hospitalized)**	**"Initial HF Therapy"** HF HOSPITALIZATIONS Among TRIAL DRUG **(Not Hospitalized)**	**"Add on HF Therapy"** HOSPITALIZATION BENEFIT OF TRIAL DRUG	BASELINE HF THERAPY MENTIONED
SOLVD	Enalapril	85% on diuretics, 65% on digoxin, 40% on nitrates, 7% on B-blockers	17.6% (82.4%)	12.5% (87.5%)	5.1%	YES
CIBIS I	Bisoprolol	100% diuretics, 100% vasodilators, 90% ACEI, 56% on digitalis	28% (72%)	19% (81%)	9%	YES
CIBIS II	Bisoprolol	99% on diuretics, 96% on ACEI or ARB, 58% on nitrates, 51% on digoxin	18% (82%)	12% (88%)	6%	YES
MERIT-HF	Metoprolol CR/XL	>90% on diuretics, >90% on ACEI or ARB, >60% on digitalis	14.7% (85.3%)	10% (90%)	4.7%	YES
COPERNICUS	Carvedilol	99% on diuretics, 97% on ACEI, 65% on digoxin	38.9% (61.1%)	26.1% (73.9%)	12.8%	YES
CHARM	Candesartan	85% on diuretics, 55% on B-blockers, 43% on digoxin, 41% on ACEI	52.9% (47.1%)	38.2% (61.8%)	14.7%	YES
Val-HeFT	Valsartan	93% on ACEI, 83% on diuretics, 68% on digoxin, 35% on B-blockers	18.5% (81.5%)	13.9% (86.1%)	4.6%	YES
RALES	Spironolactone	100% on diuretics, 94.5% on ACEI, 74.5% on Digoxin, 10.5% on B-blockers	35.6% (64.4%)	26.2% (73.8%)	9.4%	YES

Legend: Dig, digoxin; BB, beta-blocker; diu, diuretic; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NO, nitrates; Mono, level of monotherapy; **SOLVD,** Studies of Left Ventricular Dysfunction; **CIBIS**, Cardiac Insufficiency Bisoprolol Study; **MERIT-HF**, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; US CHF, US Carvedilol Heart Failure Study; **COPERNICUS**, Carvedilol Prospective Randomized Cumulative Survival study; **Val-HeFT**, Valsartan Heart Failure Trial; **COMET**, Carvedilol Or Metoprolol European Trial; **RALES**, Randomized Aldosterone Evaluation Study; **CHARM,** Candesartan in Heart Failure study

In summary:

1. The HF hospitalization free event rate of "baseline HF therapy" group: 47.1-85.3%
2. The HF hospitalization free event rate of "initial HF drug therapy" group: 61.8- 90%.
3. The HF hospitalization-free event rate of "add-on HF drug therapy" group: 4.6-14.7 %.

Discussion

The chronic HF trials referenced in the chronic HF guidelines listed the use of numerous HF medications which comprised "baseline HF drug therapy."[45-48] The extent of the survival benefit of the "baseline HF drug therapy" is 46-89% and the "first-line HF drug therapy" is 61-92.8% with a calculated "add on HF drug therapy" survival of 0.4-15%.[52,64-65] The extent of the HF hospitalization free event rates of the "baseline HF drug therapy" is 47.1-85.3% and the "first-line HF drug therapy" is 61.8-90% with a calculated "add on HF drug therapy" hospitalization free event rate of 4.6-14.7%.[52,64-65] Our review highlights a 6 times (89/15) survival rate in the "baseline HF drug therapy" compared to the "add on HF drug therapy" and a 6 to 10 times (85.3/14.7 and 47.1/4.6) HF hospitalization event-free rate in the "baseline HF drug therapy" compared to the "add on HF drug therapy"

HF Survival and Hospitalization

Hospitalization marks a fundamental change in the natural HF history. Three-fourths of all HF hospitalizations are due to symptom exacerbation with one-half of hospitalized HF patients experiencing readmissions within 6 months. Preventing HF hospitalization and re-hospitalization is important to improve patient outcomes and curb health care costs.[67-68] More importantly, avoidance of hospital admission can be equivalent to prolonging quality of life. The DIG and SHIFT studies, precisely achieved these HF management objectives.[61-71]

The RALES study showed that spironolactone reduced HF hospitalization by 30% and beta-blocker by 28-36%.[61-64] In the Cardiac Insufficiency Bisoprolol Study (CIBIS) II and III, the use of digoxin influenced the benefits of BB therapy among elderly with EF <25%.[62,70] The trial drugs in these studies were given on top of baseline HF drugs with HF hospitalization-event free rates ranging from 61.8-90% from "baseline HF drug therapy," 47.1-85.3% by "initial HF drug therapy" and 4.6-9.4% by "add on HF drug therapy."

Baseline HF Drug Therapy

A meta-analysis of loop diuretics in HF found a statistically significant survival benefit on top of baseline HF therapy.[74] A review of fourteen diuretic trials showed that ACEI or digoxin use lowered mortality (OR = 0.24, P = 0.02); reduced worsening HF (OR = 0.07, P = 0.01), and improved exercise capacity (OR 0.72, P < 0.0001).[72-75] The PROVED and the RADIANCE studies showed that worsening HF occurred 4.7% on combination digoxin, ACEI and diuretic therapy; 25% on ACEI and diuretic therapy, and 39% on diuretic alone.[76-83]

National HF practices from 1998-2011 showed HF monotherapy in 3.3% to 11.7%, dual therapy in 2.3% to 17.6%, and triple therapy in 2.0 to 11.8% in the The Netherlands. There is low digoxin use in Denmark, Australia, UK, India, and Japan.[68,85-90]

The Dutch, Scottish, South Africa, and Australian guidelines' initial treatment for HF patients consists of diuretics plus an ACEi and BB; digoxin and/or spironolactone may be added.[91-94] In France, HF take-home medications included ACE inhibitors/ARB, BB, and aldosterone inhibitors in 78%, 67%, and 27% cases, respectively. The Canadian guidelines use digoxin and diuretics as Class I recommendations for HF therapy.[95-96] Combination HF therapy adherence is approximately 83.3%.[100]

Add on HF Drug Therapy

Twenty two studies totaling 17,900 patients with LVEF <40%, showed that "ARBs did not significantly reduce total mortality (RR 0.87, 95% CI 0.76-1.00) or total hospitalizations (RR 0.94, 95% CI 0.88-1.01) compared with placebo," and total mortality or hospitalization, MI, and stroke did not differ between ARBs and ACEIs. More importantly, adverse effects resulted in increased withdrawals with combination ACEI and ARBs.[101]

In a meta-analysis of nine trials, BB therapy, on top of standard medication, does not impair quality of life parameters compared to the control. (p = 0.13).[102] Further, another meta-analysis of thirty eight HF trials showed improved survival, hospitalization and LV function with chronic use of a BB in conjunction with ACE inhibitor. It also improved dyspnea, exercise tolerance time, NYHA class and reduced death or readmission (OR=0.74), death or re-infarction (OR=0.77) or sudden death (OR=0.80).[103] Moreover, a meta-analysis of nineteen trials showed that add-on aldosterone blockade reduced all-cause mortality by 20% in both HF and post-MI patient and in nine trials, the hospitalization rate was reduced by 23%.[104]

In a review of HF trials totaling 7896 patients, digitalis compared with placebo showed an OR for mortality of 0.98 (0.89- 1.09), hospitalization of 0.68 (0.61- 0.75), and clinical HF deterioration of 0.31 (0.21- 0.43). Digoxin has no effect on long-term mortality however it reduced hospitalization and improved clinical status of symptomatic HF patients.[105]

Economic Impact of HF treatment

"The implementation of evidence-based therapy for HF treatment is not only clinically efficacious, but also economically attractive."[97] To implement cost-effective strategies and contain the HF hospitalization epidemic, optimal identification of high-risk individuals and various multi-marker risk prediction schemes have to be developed.[98] Indeed, digoxin use gave a cost saving in >50% of several higher-risk HF patient subgroups.[99] Thus, combination HF therapy is related to cost and clinical benefits such that the Class 1-A guideline recommendations maybe misconstrued as "mono-HF therapy option."

Natural History of Heart Failure

The impact of the HF natural history is important. In the 1970's, the five-year probability of dying from HF was 62% for men and 42% for women or a survival rate of 38% to 58%, respectively.[106] Three decades ago, 60% to 70% of HF patients died within 5 years. In 1990's, the Rochester Epidemiology Project showed that HF survival was 86% at 3 months, 76% at 12 months, and 35% at five years.[107-108] However, effective treatments have improved outcomes, with a relative mortality reduction of 20% to 30% in recent years.[53]

In the 2000s, the HF mortality rate among Framingham participants was higher than in the SOLVD Prevention trial (11% vs.5.1%), respectively.[50] Currently, all-cause mortality in five years is 36%. At thirty eight months of follow-up, all-cause mortality occurred in 34%.[109-111] In 2011 HF survival has improved to 70%[109] compared to 38% during the period 1970 to 1990.[109] Could we assume that the natural HF survival history is 38%?

Baseline and First line HF Therapies: Extrapolation

In the 21st century, the combination use of ACEI, ARB, BB, and aldosterone antagonist decreased hospitalizations improved survival. In Canada, ACE/ARB use averaged 43.2% after initial HF hospitalization, and BB use was 12.5%.[112] "Baseline HF drug therapy" with digoxin and diuretics is a relevant concern if the compliance with "first-line HF drug therapy is limited.

Diuretics play a role in worsening renal function and in stimulating RAAS system while inotropes improve hemodynamic parameters and relieve symptoms and functional capacity. The use of diuretics and inotropes will continue as a long as there is no other option regarding the treatment of acute HF.[113]

In a 40-month median follow-up, digoxin (SDC 0.5-0.9 ng/mL) compared to diuretic and ACEi, the mortality was 29% vs. 33%, all-cause hospitalizations was 64% vs. 67% placebo and HF hospitalizations was 23% vs. 33%.[48] Indeed, the DIG study is the only chronic HF trial with therapeutic serum digoxin levels that translated into all-cause mortality reduction.[66] Digoxin therapeutic benefit is also at par with diuretics and ACE inhibitors in symptomatic heart failure.[114]

If the recommended "initial HF drug therapy" survival rate is translated into survival rate as actually the "add-on HF drug therapy" recommended Class 1-A survival rate computed as "initial HF drug therapy survival rate minus the "baseline HF drug therapy" survival rate, then the computed "add on HF drug therapy" survival rate would be 0.4-15%. Similarly the computed "add on HF drug therapy" hospitalization free event rate would be 4.6-14.7%.

The natural HF history survival in five years prior to current evidenced-based effective therapy is assumed to be 38%.[107] Therefore, given the derived "baseline HF drug therapy" survival rate of 46 % to 89 % minus 38% assumed natural HF survival rate, the extrapolated "baseline HF drug therapy" survival rate is 8% to 51% which is higher than the "add-on HF drug therapy" Class 1-A recommendation survival rate of 0.4-15%. In view of repeated hospitalizations following initial HF diagnosis, the extrapolated "baseline HF drug therapy" survival rate versus "first-line HF drug therapy" survival rate may be speculative if not over-estimated.

Limitations

The HF studies reviewed were predominantly limited to references and our analysis depended on the published trial data cited in the AHA/ACC, HFSA, and the ESC chronic HF guidelines without uniform "chronic HF definitions" although "unstable HF state" was excluded.[38,39,41-45] A later guideline review classified HF with typical HF symptoms, physical findings and definitive EF levels.[46]

Studies did not discriminate on the duration or frequency of HF hospitalizations and HF time of death wherein death is greatest early after discharge or at re-hospitalization.[115] Duration of intervention, variability of follow-ups, withdrawal, or tolerability rates raise the possibility that shorter term studies does not reflect actual outcome rates. The limited time-frame of clinical trials, limits therapy outcome measures compared with natural history of HF disease progression. More importantly, incomplete or non-compliance to different or poly-pill HF treatment, can result in frequent acute HF re-admission, with prognostic and therapy modified outcomes.[116]

Elderly cases > 65 years old are usually not included and are in the minority as shown in peer-reviewed articles (1966-2009). Elderly patients' different proportions and concurrent co-morbidities have variable pharmacologic responses, susceptibility to adverse events, and drug-drug interactions.[49] Our analysis was limited to pharmaceutical therapy used in the trials supporting guideline recommendations and did not consider alternative drugs like eplerenone.[117] We did not also consider the positive contribution of invasive procedures and devices as well the implications of non-cardiac co-morbidity, end-of-life co-morbidities and psycho- and socio-economic determinants of outcome.

To examine critically the relative value of "baseline therapy HF therapy" compared to "add-on HF drug therapy" that is independent of the HF natural history or event-free reduction has been speculative, retrospective, post-hoc, without control of confounders. The relative value of such "baseline HF drug therapy", "add-on drug therapy" and HF natural disease progression are unclear and hard to quantify at present. Whether digoxin added cost savings and reduced mortality and hospitalization is also speculative at this time. However, other issues may affect the HF natural survival history thereby reducing the extrapolated survival benefits attributed to the baseline HF therapy such as the

following: (i) the contribution of renal failure, respiratory disease, anemia, cognitive impairment, falls and urinary incontinence as common co morbidities in the HF end of life stage;[118] (ii) the 'real world' acute HF exacerbations and re-admissions mortality of 8.2% that is independent of age, BP and creatinine levels noted in the OFICA study and Olmsted County Healthcare Expenditure and Utilization Database;[119,120] (iii) the 9.6% mortality and 19.4% re-hospitalization for CV causes at 90 days of HF admission;[121] (iv) the transition from preserved EF HF to reduced EF HF or a mixture of both pathophysiology can account for substantial mortality and HF hospitalization rates;[122] (v) the higher cost of different HF diagnostic and management options can also translate into poor outcomes;[123] (vi) the inability or poor utilization of HF biomarkers due to cost leads to 55.9% mortality compared to conventional risk scores;[124] (vii) the adaptation of HF clinical pathway;[125] (viii) the presence of socioeconomic factors that are independent of HF development and leads to adverse outcomes,[126] and finally, (ix) the interactions between multiple drugs which affects acceptance and compliance.[127] These factors impact on the natural HF history and individual and combined effects were not analyzed in this paper. Whether digoxin added cost saving and reduced mortality and hospitalization and can translate into substantial changes in the survival benefit attributable to 'baseline therapy' is also speculative at this time.

Strengths

We considered only the actual referenced trial patient population. Our analysis is supported by a systematic review of 112/2,510 eligible HF publications; only 13/46 (28%) studies showed significant outcome improvement without "baseline HF drug therapy."[100] All the chronic HF trials have baseline therapies that were continued until study end. Furthermore, poly-therapy rather than a mono-therapy is "the basis for medical treatment of chronic HF which includes diuretics, digitalis, ACE inhibitors, and beta-blockers."[129-135]

Conclusion

The contribution of "baseline HF drug therapy" is relevant in terms of survival and hospitalization-free event rates compared to the HF class 1-A guidelines proposed "initial HF drug therapy" which is in essence an "add-on HF drug therapy" in this analysis.

References

1. Hedberg P, Lönnberg I, Jonason T, Nilsson G, Pehrsson K, Ringqvist I. Left ventricular systolic dysfunction in 75-year old men and women: a population-based study. Eur Heart J. 2001 ;22(8):676–83.
2. Nielsen OW, Hilden J, Larsen CT, Hansen JF. Cross sectional study estimating prevalence of heart failure and left ventricular systolic dysfunction in community patients at risk. Heart. 2001; 86(2):172–8.
3. Cortina A, Reguero J, Segovia E, et al. Prevalence of heart failure in Asturias (a region in north of Spain). Am J Cardiol. 2001; 87(12):1417-9.
4. Ceia F, Fonseca C, Mota T, et al. Prevalence of chronic heart failure in Southwestern Europe: the EPICA study. Eur J Heart Fail. 2002; 4(4):531–9.
5. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA. 2003; 289(2):194–202.
6. Shi C, Wang LJ, Hu DF, et al. Prevalence, clinical characteristics and outcome in patients with chronic heart failure and diabetes. Chin Med J (Engl). 2010; 123(6):646-50.
7. Bueno H, Ross JS, Wang Y, et al. Trends in length of stay and short-term outcomes among Medicare patients hospitalized for heart failure, 1993–2006. JAMA. 2010; 303 (21):2141-7.
8. Mulvey GK, Wang Y, Lin Z, et al. Mortality and readmission for patients with heart failure among U.S. News & World Report's top heart hospitals. Circ Cardiovasc Qual Outcomes. 2009; 2(6):558-65.
9. Senni M, Tribouilloy CM, Rodeheffer RJ, et al. Congestive heart failure in the community: trends in incidence and survival in a 10-year period. Arch Intern Med. 1999; 159(1): 29-34.
10. Ho KK, Anderson KM, Kannel WB, Grossman, W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. Circulation. 1993; 88(1): 107-15.
11. MacIntyre K, Capewell S, Stewart S, et al. Evidence of improving prognosis in heart failure: trends in case fatality in 66 547 patients hospitalized between 1986 and 1995. Circulation. 2000; 102(10): 1126-31.
12. Fonarow GC, Heywood JT, Heidenreich PA, Lopatin M, Yancy CW; ADHERE Scientific Advisory Committee and Investigators. Temporal trends in clinical characteristics, treatments, and outcomes for heart failure hospitalizations, 2002 to 2004: findings from Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2007; 153(6):102-8.
13. Baliga V, Sapsford R. Diabetes mellitus and heart failure – an overview of epidemiology and management. Diab Vasc Dis Res. 2009; 6(3):164–71.
14. Fonarow GC, Albert NM, Curtis AB, et al. Improving evidence-based care for heart failure in outpatient cardiology practices: primary results of the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF). Circulation. 2010; 122(6):585-96.
15. Fonarow GC. Improving quality of care and outcomes for heart failure,- Role of Registries-. Circ J. 2011; 75: 1783 – 90.
16. Owens AT, Jessup M. The year in heart failure. J Am Coll Cardiol. 2012; 60 (5):359-68.
17. Szucs TD, The growing healthcare burden of CHF. J Renin Angiotensin Aldosterone Syst. 2000; 1(Suppl 1):2-6.
18. Foraker RE, Rose KM, Chang PP, Suchindran CM, McNeill AM, Rosamond WD. Hospital length of stay for incident heart failure: Atherosclerosis Risk in Communities (ARIC) Cohort: 1987-2005. J Healthc Qual. 2014; 36(1):45-51.
19. McAlister FA, Stewart S, Ferrua S, McMurray JJ. Multidisciplinary strategies for the management of heart failure patients at high risk for admission: a systematic review of randomized trials. J Am Coll Cardiol. 2004; 44(4):810–819.
20. Ng TM, Dasta JF, Durtschi AJ, McLaughlin TP, Feldman DS. Characteristics, drug therapy, and outcomes from a database of 500,000 hospitalized patients with a discharge diagnosis of heart failure. Congest Heart Fail. 2008; 14:202–10.
21. Smith DH, Johnson ES, Blough DK, et al. Predicting costs of care in heart failure patients BMC Health Serv Res. 2012;12:434.
22. Tevendale E, Baxter J. Heart failure comorbidities at the end of life. Curr Opin Support Palliat Care. 201; 5(4):322-6.
23. Leentjens AF, Burgers JS. What factors are important for the successful implementation of guidelines? Tijdschr Psychiatr. 2008; 50(6):329-35.
24. Kaul S, Diamond GA. Trial and error. How to avoid commonly encountered limitations of published clinical trials. J Am Coll Cardiol. 2010; 55:415–27.Stone GW, Pocock SJ. Randomized trials, statistics, and clinical inference. J Am Coll Cardiol. 2010; 55:428–31.
25. Granger CB, Gersh,BJ. Clinical trials and registries in cardiovascular disease: competitive or complementary? Eur Heart J. 2010; 31:520-1.

26. McMurray JJ. Clinical practice. Systolic heart failure. N Engl J Med. 2010; 362:228-38.
27. McAlister FA, Stewart S, Ferrua S, McMurray JJ. Multidisciplinary strategies for the management of heart failure patients at high risk for admission. A systematic review of randomized trials. J Am Coll Cardiol. 2004; 44(4):810–9.
28. Leykum LK, Parchman M, Pugh J, LawrenceV, Noël PH, McDaniel RR Jr. The importance of organizational characteristics for improving outcomes in patients with chronic disease: a systematic review of congestive heart failure. Implement Sci. 2010; 5:66.
29. Gonseth J, Guallar-Castillón P, Banegas JR, Rodríguez-Artalejo F. The effectiveness of disease management programmes in reducing hospital re-admission in older patients with heart failure: a systematic review and meta-analysis of published reports. Eur Heart J. 2004; 25(18):1570–95.
30. Muth C, Gensichen J, Beyer M, Hutchinson A, Gerlach FM. The systematic guideline review: method, rationale and test on chronic heart failure. BMC Health Serv Res. 2009; 9:74.
31. Clark AM, Savard LA, Thompson DR. What is the strength of evidence for heart failure disease-management programs? J Am Coll Cardiol. 2009; 54(5):397–401. Follath F. Challenging the dogma of high target doses in the treatment of heart failure: is more always better? Arch Cardiovasc Dis. 2009;102 (11):785-9.
32. Cleland JGF, Cullington D. Digoxin: quo vadis. Circ Heart Fail 2009; 2(2):81-5. Becker H, Sigmund M. Therapy of heart failure. Digitalis, diuretic plus ACE inhibitor or more? Internist (Berl). 1995; 36(12):1117-23.
33. Anguita M, Comin J, Almenar L. Comments on the ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. A report of the Task Force of the Clinical Practice Guidelines Committee of the Spanish Society of Cardiology. Rev Esp Cardiol(Engl Ed). 2012; 65(10):874-8.
34. Richter B, Koller L, Hohensinner PJ, et al. A multi-biomarker risk score improves prediction of long-term mortality in patients with advanced heart failure. Int J Cardiol. 2012; 168(2):1251-7.
35. Accad M, Fred HL. Is Jupiter also a god of primary prevention? Tex Heart Inst J. 2010; 37(1):6-7.
36. Becker H, Sigmund M. Therapy of heart failure. Digitalis, diuretic plus ACE inhibitor or more? Internist (Berl). 1995; 36(12):1117-23.
37. Accad M, Fred HL. Is Jupiter also a god of primary prevention? Tex Heart Inst J. 2010;37(1):6-7.
38. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J. 2008; 29(19):2388-442.
39. Hunt SA; American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol. 2005; 46:e1-82.
40. Williams SC, Schmaltz SP, Morton DJ, Koss RG, Loeb JM. Quality of care in U.S. hospitals as reflected by standardized measures, 2002–2004. N Engl J Med. 2005; 353(3):255-64.
41. Hunt SA, Abraham WT, Chin MH, et al. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation. 2009; 119(14):e391-e479.
42. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, et al. 2009 Writing group to review new evidence and update the 2005 guideline for the management of patients with chronic heart failure writing on behalf of the 2005 Heart Failure Writing Committee. 2009 Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation J Am Coll Cardiol 2009; 53(15);1343-82.
43. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology: developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail. 2008; 10:933-89.
44. Swedberg K, Cleland J, Dargie H, et al; Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Eur Heart J. 2005; 26:1115-1140
45. Heart Failure Society of America. Executive summary: HFSA 2006 Comprehensive Heart Failure Practice Guideline. J Card Fail. 2006; 12(1):10-38.
46. McMurray JJ, Adamopoulos S, Anker SD, et al. 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. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. Eur J Heart Fail. 2012; 14(8):803-69.
47. Kasje WN, Denig P, de Graeff PA, Haaijer-Ruskamp FM. Perceived barriers for treatment of chronic heart failure in general practice; are they affecting performance? BMC Fam Pract. 2005; 6(1):19.
48. Ahmed A, Rich MW, Love TE, et al. Digoxin and reduction in mortality and hospitalization in heart failure: a comprehensive post hoc analysis of the DIG trial. Eur Heart J. 2006; 27(2):178-86.
49. Ahmed A, Allman RM, Fonarow GC, et al. Incident Heart Failure Hospitalization and Subsequent Mortality in Chronic Heart Failure: A Propensity-Matched Study. J Card Fail. 2008; 14(3):211-8.
50. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991; 325:293–302.
51. Giamouzis G, Kalogeropoulos A, Georgiopoulou V, et al. Hospitalization epidemic in patients with heart failure: risk factors, risk prediction, knowledge gaps, and future directions. J Card Fail. 2011; 17(1):54-75.
52. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med. 1987; 316(23):1429-35.
53. Macdonald MR, Petrie MC, Varyani F, et al. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: An analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. Eur Heart J. 2008; 29(11):1377-85.
54. Pfeffer MA, Swedberg K, Granger CB, et al. CHARM Investigators and Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet. 2003; 362(9386):759-66.
55. Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial--the Losartan Heart Failure Survival Study ELITE II. Lancet. 2000; 355:1582-7.
56. Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med. 2001; 345(23):1667-75.
57. Flather MD, Shibata MC, Coats AJ, et al; SENIORS Investigators. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J. 2005; 26(3):215-25.
58. Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the

beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med. 2001; 344:1659-67.
59. Packer M, Colucci WS, Sackner-Bernstein JD, et al. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE Trial. Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise. Circulation. 1996; 94(11):2793-9.
60. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999; 353(9146):9-13.
61. Hjalmarson A, Goldstein S, Fagerberg B, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. JAMA. 2000; 283:1295-1302.
62. Colucci WS, Packer M, Bristow MR, et al. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. US Carvedilol Heart Failure Study Group. Circulation. 1996; 94(11):2800-6.
63. Eichhorn EJ, Bristow MR. The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial. Curr Control Trials Cardiovasc Med. 2001; 2(1):20-23.
64. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med. 1999; 341:709-17.
65. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med. 1997; 336:525-33.
66. Ramani GV, Uber PA, Pharm D, Mehra MR, Chronic heart failure contemporary diagnosis and management. Mayo Clin Proc. 2010; 85(2):180-95.
67. Reddy S, Bahl A, Talwar KK. Congestive heart failure in Indians: How do we improve diagnosis & management? Indian J Med Res. 2010; 132:549-60.
68. Shibata MC, Nilsson C, Hervas-Malo M, Jacobs P, Tsuyuki RT. Economic implications of treatment guidelines for congestive heart failure. Can J Cardiol. 2005; 21(14):1301-6.
69. Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomized placebo-controlled study. Lancet. 2010; 376(9744):875-85.
70. Willenheimer R, van Veldhuisen DJ, Silke B, et al. CIBIS III Investigators. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. Circulation. 2005; 112(16):2426-35.
71. Cheng JW, Nayar M. A review of heart failure management in the elderly population. Am J Geriatr Pharmacother. 2009; 5:233-49.
72. Guglin M. Diuretics as pathogenetic treatment for heart failure. Int J Gen Med. 2011; 4:91-8.
73. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: Prevalence and mortality in a populationbased cohort. J Am Coll Cardiol. 1999; 33(7):1948–55.
74. Guglin M. Reappraisal of the role of diuretics in heart failure. Cardiol Rev. 2009; 17(2):56–59.
75. Faris RF, Flather M, Purcell H, Poole-Wilson PA, Coats AJ. Diuretics for heart failure. Cochrane Database Syst Rev. 2012; 2:CD003838.
76. Uretsky BF, Young JB, Shahidi FE, Yellen LG, Harrison MC, Jolly MK. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. PROVED Investigative Group. J Am Coll Cardiol. 1993; 22(4):955-62.
77. Packer M, Gheorghiade M, Young JB, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. RADIANCE Study. N Engl J Med. 1993; 329(1):1-7.
78. Young JB, Gheorghiade M, Uretsky BF, Patterson JH, Adams KF Jr. Superiority of "triple" drug therapy in heart failure: insights from the PROVED and RADIANCE trials. Prospective Randomized Study of Ventricular Function and Efficacy of Digoxin. Randomized Assessment of Digoxin and Inhibitors of Angiotensin-Converting Enzyme. J Am Coll Cardiol. 1998; 32(3):686-92.
79. Abarquez RF Jr., Ngelangel CA, Sison VM, Morales DD, Canonigo EB. Digitalis reduces MI and LVH among uncomplicated mild hypertensive industry based cohort in a long term comparative study. Am J Hypertens. 1995; 8:4.
80. Abarquez RF Jr. Beyond the current paradigm of managing the hypertensive filipino patient. JAMA, SEA supplement. 1996; 2.3:13-19.
81. Abarquez RF Jr. The old but reliable digitalis: persistent concerns and expanded indications. Int J Clin Pract. 2001; 55(2):108-14.
82. Abarquez RF Jr. Management options for hypertension syndrome. Int J Clin Pract. 2001; 55(8):537-45.
83. Ahmed A, Pitt B, Rahimtoola SH, et al. Effects of digoxin at low serum concentrations on mortality and hospitalization in heart failure: a propensity-matched study of the DIG trial. Int J Cardiol. 2008; 123(2):138–46.
84. Jaarsma T, Haaijer-Ruskamp FM, Sturm H, Van Veldhuisen DJ. Management of heart failure in The Netherlands. Eur J Heart Fail. 2005; 7(3): 371–5.
85. Trochu JN, Gueffet JP. Experience and prospects in the treatment of heart failure. Therapie. 2009; 64(2):75-80.
86. Bosch M, Wensing M, Bakx JC, van der Weijden T, Hoes AW, Grol RP. Current treatment 16(3):644–50.
87. Driscoll A, Worrall-Carter L, Hare DL, et al. Evidence-based chronic heart-failure management programmes: reality or myth? BMJ Qual Saf. 2011; 20(1):31-7.
88. Mehta PA, McDonagh S, Poole-Wilson PA, et al. Guidelines in Heart Failure (in Dutch). Ned Tijdschr Geneeskd. 2004; 148(13):609-14.
89. Adams KF, Fonarow GC, Emerman CL, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: Rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2005; 149(2):209–16. EuroHeart Failure Survey II (2006) (Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, et al. EuroHeart Failure Survey II (EHFS II): A survey on hospitalized acute heart failure patients: Description of population. Eur Heart J. 2006; 27: 2725– 2736.
90. Tsuchihashi-Makaya M, Kinugawa S, Yokoshiki H, et al. for the JCARE-CARD. Investigators Beta-blocker use at discharge in patients hospitalized for heart failure is associated with improved survival. Circ J. 2010; 74(7):1364–1371.
91. MacKenzie E, Smith A, Angus N, Menzies S, Brulisauer F, Leslie SJ. Mixed-method exploratory study of general practitioner and nurse perceptions of a new community based nurse-led heart failure service. Rural and Remote Health 10: 1510. [Online]. 2010. Available from http://www.rrh.org.au.
92. Heart Failure clinical guideline. South African Medical Association Heart Failure Working group. S Afr Med J. 1998; 88(9 Pt 2):1133-55.
93. Krum H, Jelinek MV, Stewart S, Sindone A, Atherton JJ. on behalf of the CHF Guidelines Core Writers. Guidelines for the prevention, detection and management ofpeople with chronic heart failure in Australia 2006. Med J Aust. 2006;185(10) : 549–57.
94. Arnold JMO, Liu P, et al. Canadian Cardiovascular Society consensus conference recommendations on heart failure 2006: diagnosis and management. Can J Cardiol. 2006; 22(1):23-45.
95. Logeart D, Isnard R, Resche-Rigon M, et al. on behalf of the working group on Heart Failure of the French Society of Cardiolog. Current aspects of the spectrum of acute heart failure syndromes in a real-life setting: the OFICA study. Eur J Heart Fail. 2013; 15(4):465-76.
96. Califf RM. Translating clinical trials into practice. Tex Heart Inst J. 2006; 33:192-6.
97. Giamouzis G, Kalogeropoulos A, Georgiopoulou V, et al. Hospitalization epidemic in patients with heart failure: risk factors, risk prediction, knowledge gaps, and future directions. J Card Fail. 2011; 17(1):54-75.
98. Eisenstein EL, Yusuf S, Bindal V, et al. DIG investigators. What is the economic value of digoxin therapy in congestive heart failure patients? Results from the DIG trial. J Card Fail. 2006; 12(5):336-42.
99. Heran BS, Musini VM, Bassett K, Taylor RS, Wright JM. Angiotensin receptor blockers for heart failure. Cochrane Database Syst Rev. 2012; 4:CD003040.
100. Shaneyfelt TM, Centor RM. Reassessment of clinical practice guidelines:

go gently into that good night. JAMA. 2009; 301(8):868-9. Leykum LK, Parchman M, Pugh J, Lawrence V, Noël PH, McDaniel RR Jr. The importance of organizational characteristics for improving outcomes in patients with chronic disease. a systematic review of congestive heart failure. Implement Sci. 2010; 5:66.
101. Dobre D, van Jaarsveld CH, deJongste MJ, Haaijer Ruskamp FM, Ranchor AV. The effect of beta-blocker therapy on quality of life in heart failure patients: a systematic review and meta-analysis. Pharmacoepidemiol Drug Saf. 2007; 16(2):152-9.
102. Abdulla J, Køber L, Christensen E, Torp-Pedersen C. Effect of beta-blocker therapy on functional status in patients with heart failure - a meta-analysis. Eur J Heart Fail. 2006; 8(5):522-31.
103. Ezekowitz JA, McAlister FA. Aldosterone blockade and left ventricular dysfunction: a systematic review of randomized clinical trials. Eur J Heart Fail. 2009; 30:469–77.
104. Hood WB Jr, Dans AL, Guyatt GH, Jaeschke R, McMurray JJ. Digitalis for treatment of congestive heart failure in patients in sinus rhythm. Cochrane Database Syst Rev. 2004; 10(2):CD002901.
105. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. N Engl J Med. 1971; 285(26):1441-6.
106. Senni M, Tribouilloy CM, Rodeheffer RJ. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. Circulation. 1998; 98(21):2282-9.
107. Jhund PS, Macintyre K, Simpson CR, et al. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. Circulation. 2009; 119:515-23.
108. McMurray JJV. Systolic Heart Failure. N Engl J Med. 2010; 362:228-38.
109. Ahmed MI, Lainscak M, Mujib M. Gender-related dissociation in outcomes in chronic heart failure: reduced mortality but similar hospitalization in women. Int J Cardiol. 2011; 148(1):36-42.
110. Gambassi G, Agha SA, Sui X. Race and the Natural History of Chronic Heart Failure: A Propensity-Matched Study. J Card Fail. 2008; 14(5):373-8.
111. Ahmed A. A propensity matched study of New York Heart Association class and natural history end points in heart failure. Am J Cardiol. 2007; 99(4):549-53.
112. Whellan DJ, Hamad E. Natural history, adherence, or iatrogenic insult: repeat hospitalizations as a predictor of survival. Am Heart J. 2007; 154(2):203-5.
113. Felker GM, Benza RL, Chandler AB, et al. Heart failure etiology and response to milrinone in decompensated heart failure results from the OPTIME-CHF study. J Am Coll Cardiol. 2003; 41:997–1003.
114. Erdmann E. Digitalis--friend or foe? Eur Heart J. 1995; 16 Suppl F:16-9.
115. Chatterjee K. Congestive heart failure: what should be the initial therapy and why? Am J Cardiovasc Drugs. 2002; 2(1):1-6.
116. Fitzgerald AA, Powers JD, Ho PM, et al. Impact of medication nonadherence on hospitalizations and mortality in heart failure. J Card Fail. 2011; 17:664-9.
117. Lader E. Review: Eplerenone is not more effective for reducing mortality than other aldosterone antagonists. Ann Intern Med. 2012; 157(12):JC6-10.
118. Tevendale E, Baxter J, Heart failure comorbidities at the end of life. Curr Opin Support Palliat Care. 2011; 5(4):322-6.
119. Logeart D, Isnard R, Resche-Rigon M, et al; on behalf of the working group on Heart Failure of the French Society of Cardiology. Current aspects of the spectrum of acute heart failure syndromes in a real-life setting: the OFICA study. Eur J Heart Fail. 2013; 15(4):465-76.
120. Dunlay SM, Redfield MM, Weston SA. Hospitalizations after heart failure diagnosis: a community perspective. J Am Coll Cardiol. 2009; 54(18):1695–702.
121. Gheorghiade M, Pang P, Ambrosy A, et al. A comprehensive, longitudinal description of the in-hospital and post-discharge clinical, laboratory, and neurohormonal course of patients with heart failure who die or are re-hospitalized within 90 days: analysis from the EVEREST trial. Heart Fail Rev. 2012; 17(3):485-509.
122. Campbell RT, Jhund PS, Castagno D, Hawkins NM, Petrie MC, McMurray JJ. What have we learned about patients with heart failure and preserved ejection fraction from DIG-PEF, CHARM-Preserved, and I-PRESERVE? J Am Coll Cardiol. 2012; 60 (23); 2349-56.
123. Smith DH, Johnson ES, Blough DK, et al. Predicting costs of care in heart failure patients. BMC Health Serv Res. 2012; 12: 434.
124. Richter B, Koller L, Hohensinner PJ, et al. A multi-biomarker risk score improves prediction of long-term mortality in patients with advanced heart failure. Int J Cardiol. 2013; 168:1251-7.
125. Kul S, Barbieri A, Milan E, Montag I, Vanhaecht K, Panella M. Effects of care pathways on the in-hospital treatment of heart failure: a systematic review. BMC Cardiovasc Disord. 2012; 12:81.
126. Hawkins NM, Jhund PS, McMurray JJ, Capewell S. Heart failure and socioeconomic status: accumulating evidence of inequality. Eur J Heart Fail. 2012; 14(2):138-46.
127. Eisenstein EL, Yusuf S, Bindal V, et al.; DIG investigators. What is the economic value of digoxin therapy in congestive heart failure patients? Results from the DIG trial. J Card Fail. 2006; 12(5):336-42.
128. Ahmed A, Waagstein F, Pitt B,et al. Effectiveness of digoxin in reducing one-year mortality in chronic heart failure in the Digitalis Investigation Group Trial. Am J Cardiol. 2009; 103(1): 82–7.
129. Frohlich ED. The salt conundrum: a hypothesis. Hypertension. 2007; 50:161-6.
130. McKelvie RS. Heart Failure. Clin Evid (Online). 2011; 2011. pii: 0204.
131. McKelvie R. Heart Failure. Clin Evid. 2010; 2:204-41.
132. Cochrane Collaboration Research. BMJ. 2013; 346:f55
133. Faris RF, Flather M, Purcell H, Poole-Wilson PA, Coats AJ. Diuretics for heart failure, Cochrane Database Syst Rev. 2012; 15:2.
134. Maeda JL. Evidence-based heart failure performance measures and clinical outcomes: a systematic review. J Card Fail. 2010; 16(5):411-8.
135. Lew WYW, DeMaria AN. The divergence between guidelines and practice. J Am Coll Cardiol. 2013; 61 (1):41-3.