

## 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 I-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*

### 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.<sup>1-5</sup> In China, the HF prevalence increased to 29.1% from 16.9%.<sup>6</sup> 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.<sup>7-17</sup>

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.<sup>18-20</sup> 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.<sup>21-29</sup> In a systematic review of chronic HF guidelines from Europe, 56% were consensus-based and 28% were evidenced-based advisories.<sup>30-36</sup> 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."<sup>44-65</sup>

### 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.<sup>38-45</sup> Other chronic HF studies and guidelines were reviewed for comparison.<sup>46-47,91-96</sup>

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](mailto:preganit@post.harvard.edu) or [preganit@netscape.net](mailto:preganit@netscape.net)

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
<b>ACEI</b>	<ul style="list-style-type: none"> <li>Should be used in patients with reduced EF and no symptoms of HF, even if they have not experienced MI (I-A)</li> <li>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)</li> <li>Is recommended for all patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated (I-A)</li> <li>2005 recommendation remains current in 2009 update</li> </ul>	<ul style="list-style-type: none"> <li>Is recommended as first line in all patients, with or without symptoms, who have LVEF &lt;40-45% to improve survival, symptoms and functional capacity; and to reduce hospitalizations (I-A)</li> <li>Should be given as initial therapy in the absence of fluid retention (I-B)</li> <li>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)</li> </ul>	<ul style="list-style-type: none"> <li>Is recommended for routine administration to symptomatic and asymptomatic patients with LVEF &lt;40% (A)</li> </ul>
<b>Diuretic</b>	<ul style="list-style-type: none"> <li>Is indicated in patients with current or prior symptoms of HF and LVEF who have evidence of fluid retention (I-A)</li> <li>2005 recommendation remains current in 2009 update</li> </ul> <p>*Baseline drug recognized</p>	<ul style="list-style-type: none"> <li>Is recommended when fluid overload is present, manifesting as pulmonary congestion or peripheral edema (I-A)</li> <li>Should always be administered in combination with ACEI and BB if tolerated (I-C)</li> </ul> <p>*Baseline drug recognized</p>	<ul style="list-style-type: none"> <li>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)</li> <li>Optional for symptomatic treatment</li> </ul>
<b>Beta Blocker</b>	<ul style="list-style-type: none"> <li>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)</li> <li>Is indicated in all patients without history of MI who have reduced LVEF and no HF symptoms (I-C)</li> <li>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)</li> <li>2005 recommendation remains current in 2009 update</li> </ul>	<ul style="list-style-type: none"> <li>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)</li> <li>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)</li> </ul>	<ul style="list-style-type: none"> <li>BB shown to be effective in clinical trials are recommended for patients with EF&lt;40% (A)</li> <li>Combination of BB and an ACEI is recommended as routine therapy for asymptomatic patients with an LVEF&lt;40% (C)</li> <li>Recommended in the majority of patients with LV systolic dysfunction (C)</li> </ul>
<b>Aldosterone Antagonist</b>	<ul style="list-style-type: none"> <li>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)</li> <li>2005 recommendation remains current in 2009 update</li> </ul>	<ul style="list-style-type: none"> <li>Is recommended in addition to ACEI, BB and diuretics in advanced heart failure (NYHA III-IV) to improve survival and morbidity (I-B)</li> <li>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)</li> </ul>	<ul style="list-style-type: none"> <li>Is recommended for patients with NYHA Class III/IV, previously Class IV, HF from LV systolic dysfunction (LVEF&lt;35%), while receiving standard therapy, including diuretics (A)</li> <li>Should be considered in patients after an acute MI, with clinical HF signs and symptoms and an LVEF&lt;40%. Patients should be on standard therapy, including an ACEI (or ARB) and BB (A)</li> </ul>
<b>ARB</b>	<p>Recommended for current or prior symptoms of HF and reduced LVEF who are ACE inhibitor-intolerant (<i>Level of Evidence: A</i>)</p> <p>2005 recommendation remains current but text modified to eliminate specific agents tested.</p>	<ul style="list-style-type: none"> <li>Can be used as an alternative to ACEI in symptomatic patients intolerant to ACEI to improve morbidity and mortality (I-B)</li> <li>Can be considered in combination with ACEI in patients who remain symptomatic to reduce mortality (IIa-B)</li> </ul>	<ul style="list-style-type: none"> <li>Recommended for routine administration to symptomatic and asymptomatic patients with an LVEF&lt;40% who are intolerant to ACEI for reasons other than hyperkalemia or renal insufficiency (A)</li> <li>May be considered as initial therapy rather than ACEI for patients with the following conditions: HF post-MI (A), CHF and systolic dysfunction B)</li> <li>Routine administration is not recommended in addition to ACEI and BB therapy in patients with recent acute MI and LV dysfunction (A)</li> </ul>

<b>Digoxin</b>	<ul style="list-style-type: none"> <li>• Can be beneficial to patients with current or prior symptoms of HF and reduced LVEF to decrease hospitalizations for HF (IIa-B)</li> <li>• 2005 recommendation remains Current in 2009 update</li> </ul>	<ul style="list-style-type: none"> <li>• Can be beneficial to patients with current or prior symptoms of HF and reduced LVEF to decrease hospitalizations for HF (IIa-B)</li> <li>• 2005 recommendation remains current in 2008 update</li> </ul>	<ul style="list-style-type: none"> <li>• Should be considered for patients with LV systolic dysfunction (LVEF&lt;40%) who have signs or symptoms of HF while receiving standard therapy, including ACEI and BB (NYHA II-III [A], NYHA IV [B])</li> <li>• High dose for the purpose of rate control is recommended (C)</li> </ul>
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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 <sup>(36-48)</sup>

**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
<b>V-HeFT – 1</b>	Hydralazine + Isosorbide dinitrate	100% on digoxin and diuretics	53.1%	63.8%	10.7%	YES
<b>SOLVD</b>	Enalapril	85% on diuretics, 65% on digoxin, 40% on nitrates, 7% on B-blockers	60.3%	64.8%	4.5%	YES
<b>V-HeFT-2</b>	Enalapril	60% on vasodilators, 25% on antiarrhythmics	61.8%	67.2%	5.4%	YES
<b>CONSENSUS</b>	Enalapril	100% on diuretics, 94% digitalis, 50% vasodilators (mainly nitrates)	46%	61%	15%	YES
<b>CIBIS II</b>	Bisoprolol	99% on diuretics, 96% on ACEI or ARB, 58% on nitrates, 51% on digoxin	82.7%	88.2%	5.5%	YES
<b>MERIT-HF</b>	Metoprolol CR/XL	>90% on diuretics, >90% on ACEI or ARB, >60% on digitalis	89%	92.8%	3.8%	YES
<b>COPERNICUS</b>	Carvedilol	99% on diuretics, 97% on ACEI, 65% on digoxin	81.5%	88.6%	7.1%	YES
<b>ELITE II</b>	Losartan	79% on diuretics, 50% on digoxin, 21% on B-blockers, 20% on ACEI	88.3%	89.6%	1.3%	NO (but no benefit)
<b>CHARM</b>	Candesartan	85% on diuretics, 55% on B-blockers, 43% on digoxin, 41% on ACEI	75%	78%	3%	YES
<b>Val-HeFT</b>	Valsartan	93% on ACEI, 83% on diuretics, 68% on digoxin, 35% on B-blockers	80.7%	80.3%	0.4%	YES
<b>V-HeFT III</b>	Felodipine	97% on ACEI, 90% on diuretics, 75% on digoxin	86.2%	87.2%	1%	NO (but no benefit)
<b>RALES</b>	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	Spirololactone	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.”<sup>45-48</sup> 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%.<sup>52,64-65</sup> 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%.<sup>52,64-65</sup> 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.<sup>67-68</sup> 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.<sup>61-71</sup>

The RALES study showed that spironolactone reduced HF hospitalization by 30% and beta-blocker by 28-36%.<sup>61-64</sup> 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%.<sup>62,70</sup> 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.<sup>74</sup> 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).<sup>72-75</sup> 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.<sup>76-83</sup>

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.<sup>68,85-90</sup>

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.<sup>91-94</sup> 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.<sup>95-96</sup> Combination HF therapy adherence is approximately 83.3%.<sup>100</sup>

### 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.<sup>101</sup>

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).<sup>102</sup> 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).<sup>103</sup> 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%.<sup>104</sup>

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.<sup>105</sup>

### Economic Impact of HF treatment

“The implementation of evidence-based therapy for HF treatment is not only clinically efficacious, but also economically attractive.”<sup>97</sup> 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.<sup>98</sup> Indeed, digoxin use gave a cost saving in >50% of several higher-risk HF patient subgroups.<sup>99</sup> 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.<sup>106</sup> 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.<sup>107-108</sup> However, effective treatments have improved outcomes, with a relative mortality reduction of 20% to 30% in recent years.<sup>53</sup>

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

### Baseline and First line HF Therapies: Extrapolation

In the 21<sup>st</sup> 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%.<sup>112</sup> "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 long as there is no other option regarding the treatment of acute HF.<sup>113</sup>

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%.<sup>48</sup> Indeed, the DIG study is the only chronic HF trial with therapeutic serum digoxin levels that translated into all-cause mortality reduction.<sup>66</sup> Digoxin therapeutic benefit is also at par with diuretics and ACE inhibitors in symptomatic heart failure.<sup>114</sup>

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%.<sup>107</sup> 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.<sup>38,39,41-45</sup> A later guideline review classified HF with typical HF symptoms, physical findings and definitive EF levels.<sup>46</sup>

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.<sup>115</sup> 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.<sup>116</sup>

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.<sup>49</sup> Our analysis was limited to pharmaceutical therapy used in the trials supporting guideline recommendations and did not consider alternative drugs like eplerenone.<sup>117</sup> 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;<sup>118</sup> (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;<sup>119,120</sup> (iii) the 9.6% mortality and 19.4% re-hospitalization for CV causes at 90 days of HF admission;<sup>121</sup> (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;<sup>122</sup> (v) the higher cost of different HF diagnostic and management options can also translate into poor outcomes;<sup>123</sup> (vi) the inability or poor utilization of HF biomarkers due to cost leads to 55.9% mortality compared to conventional risk scores;<sup>124</sup> (vii) the adaptation of HF clinical pathway;<sup>125</sup> (viii) the presence of socioeconomic factors that are independent of HF development and leads to adverse outcomes,<sup>126</sup> and finally, (ix) the interactions between multiple drugs which affects acceptance and compliance.<sup>127</sup> 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."<sup>100</sup> All the chronic HF trials have baseline therapies that were continued until study end. Furthermore, poly-therapy rather than a monotherapy is "the basis for medical treatment of chronic HF which includes diuretics, digitalis, ACE inhibitors, and beta-blockers."<sup>129-135</sup>

### 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.

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