

Cost-Consequence Analysis of Sacubitril/Valsartan versus Enalapril in Chronic Heart Failure Patients with Reduced Ejection Fraction

Sameer Bhaskar GOKHALE^{1,*}, Saumitra RAY², Vijay Kumar CHOPRA³, Uday JADHAV⁴, Gauri BILLA⁵

¹ Health Economics and Market Access, Novartis Healthcare Private Limited. Inspire BKC, 'G' Block, 6 & 7 Floor, BKC Main Road, Bandra Kurla Complex, Bandra East, Mumbai 400051, India.

² Vivekananda Institute of Medical Sciences, 99, Sarat Bose Rd, Kolkata, West Bengal 700026, India.

³ Max Super Specialty Hospital, No. 1, 2, Press Enclave Road, Mandir Marg, Saket Institutional Area, Saket, New Delhi - 110017, India.

⁴ Cardiology Department, MGM New Bombay Hospital, Sector 4, Vashi, New Mumbai, 400702, India.

⁵ Medical Affairs, Novartis Healthcare Private Limited. Inspire BKC, 'G' Block, 6 & 7 Floor, BKC Main Road, Bandra Kurla Complex, Bandra East, Mumbai 400051, India.

E-mail(s): sameer_bhaskar.gokhale@novartis.com; drsaumitra@yahoo.co.in; chopravk@gmail.com; umjadhav@gmail.com; gauri.billa@novartis.com

* Author to whom correspondence should be addressed; Tel.: +91 9004471299

Received: March 21, 2021/Accepted: June 14, 2021/ Published online: June 28, 2021

Abstract

Purpose: The rising prevalence of heart failure (HF) in midlife years in Indians is posing an economic challenge. Sacubitril/valsartan demonstrated a significant risk reduction of cardiovascular deaths by 20% and HF rehospitalizations by 21% versus enalapril but has a higher drug cost. High cost is an impediment and poses a challenge for healthcare stakeholders to choose interventions that are more efficacious. We developed an intuitive evidence-based cost-consequence analysis (CCA) comparing sacubitril/valsartan with enalapril in chronic HF patients with reduced ejection fraction (HFrEF). *Methods:* Authors adopted HF outcome probabilities for mortality and hospitalizations from the PARADIGM-HF trial. Economic (drug acquisition and hospitalization costs, earning potential) and clinical [length of stay (LOS), rates of mortality and hospitalizations] inputs were obtained from the published literature. The tool enables the user to input patient numbers, health setting (public/private), time horizon (6-27 months), number of hospitalizations (1.42-5), LOS (5.3-9 days), and wages per day €5.61-€28.03 (INR500-INR2,500). *Results:* Hypothetical HF patient with a daily wages of €22.42 (INR 2,000) spent €420.31 (INR 37,490) for sacubitril/valsartan at a private set-up to realize an annual cost savings of €485.34 (INR 43,290). While the other patient with a lower daily wage of €11.21, at a public set-up had to spend €43.09 (INR 3,843) more to realize benefits of mortality, hospitalization, and productivity savings due to sacubitril/valsartan. *Conclusion:* Sacubitril/valsartan has the potential to improve clinical as well as economic outcomes by generating substantial cost-savings to minimize budget deficit. CCA could support healthcare stakeholders in selecting an appropriate treatment strategy for chronic HFrEF patients.

Keywords: Enalapril; Costs and Cost Analysis (CCA); Heart Failure; Medical Economics; Sacubitril/valsartan

Introduction

The rising prevalence of heart failure (HF) and an increasing economic and humanistic burden poses a socioeconomic challenge in India [1]. In the year 2010, Huffman and Prabhakaran estimated HF prevalence range in India from 1.3 million to 4.6 million [1]. From the INDUS study (INDia Ukieri Study) conducted during 2008 and 2012, authors estimated prevalence of HF in India to be around 1% of the total population (8-10 million) [2]. Heart failure develops a decade earlier in Indians as compared to developed nations, with a mean average age of 56 to 61 years at presentation [3-5]. It affects Indians in their most productive midlife years [6]. Manifestations of HF at a younger age can have a devastating effect for a patient, his/her family and the community. This includes increasing morbidity, loss of productive years of life due to early mortality and frequent hospitalizations [7-9]. Case fatality rate in HF is considerably higher in middle-income countries like India (15.9%) as compared to high-income countries (6.5%), especially in rural areas due to lack of efficient infrastructure to manage and control the disease efficiently [2, 10, 11]. Due to these factors, HF estimated as being the greatest contributor to disability and mortality in India and expected to rise significantly in the near future [12-13]. Increased risk of premature mortality (years of life lost; YLL) and increased risk of disability (years of life lost due to disability; YLD) is higher in HF affected patients in India [14]. A study reported in 2019 that the health and economic burden of CVD in various countries with low (Nigeria), middle (India), high (China, Brazil, Mexico) and very high (United States of America, Japan) human development indices. Probability of premature deaths related to CVD in India was 23.3% in the year 2016. USD \$2.17 trillion is the projected economic losses due to CVD [13].

Economic burden of HF results from direct and indirect costs. Direct costs of HF include hospitalization charges (inpatient or day-care), physician consultation charges, diagnostic procedures, multiple pharmacological therapy, and management of cardiac and non-cardiac comorbidities [7]. Indirect costs include costs associated with premature mortality, lost productivity, costs to society through morbidity, and caregivers' related costs [15]. Direct and indirect costs of HF not only affect patients and their caregivers, but also severely impacts government's state and country level budgets [16].

There have been notable advances in the pharmacological management of HFrEF patients using medications such as angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs). Despite these therapeutic interventions, premature mortality, frequent hospitalizations, and lost productivity are undesirable sequelae in chronic HFrEF patients [17-20]. In the PARADIGM-HF trial, sacubitril/valsartan (ARNI, angiotensin receptor–neprilysin inhibitors) demonstrated a significant risk reduction of cardiovascular deaths by 20% and HF related hospitalizations by 21% versus enalapril (ACEi), albeit at a higher monetary cost [21-22].

Private health insurance (PHI) companies do not reimburse HF patients in Indian healthcare setting when they often present themselves in day-care setting for their entire treatment. INDUS study reported the prevalence of HF in outpatient departments as 20.4% (102 out of 500 consecutive patients) [2]. Looking at the current scenario, there is a need for healthcare stakeholders (policy makers, insurers, physicians and hospital administrators) to make an informed decision to prioritize pharmacological interventions at a state, country or hospital level for efficient utilization of resources for chronic HFrEF patients. As per our knowledge, there is no available tool to compare costs and consequences in this subpopulation of HFrEF patients. Evidence based CCA will be of paramount importance to healthcare stakeholders in HF management.

Our study objective was to develop a user friendly and intuitive evidence-based tool that estimated the cost-consequence of sacubitril/valsartan (ARNI) compared with enalapril (ACEi) in chronic HFrEF in Indian healthcare setting. Dynamic demonstration of costs and health outcomes were presented for HFrEF patients.

Material and Method

The CCA tool was developed in MS Excel. The tool allows users to customize HF related levers as per their needs. This dynamic tool provides HF levers such as health setting, time horizon, re-hospitalizations, average length of stay (LOS), patient’s work status, and approximate wages per day. Table 1 presents options for each HF lever that were decided based on insights from the targeted literature review in addition to inputs from key medical experts.

PARADIGM-HF trial provided annual probabilities of mortality and HF related hospitalization calculations [21-22]. Local evidence from peer-reviewed journal articles included costs of HF related hospitalizations [25, 28], cost of intensive care unit (ICU) and cardiac monitoring [25-26] for HFrEF patients. The India Wage Report 2018 helped us in the estimation of earning potential of each life lost per day and loss of productivity due to HF related health events [27]. The upper four highest ranks of labor [division 1 (legislators, senior officials and managers), division 2 (professionals), division 3 (technicians and associate professionals) and division 4 (clerks)] of occupational classifications were considered for per day wage calculations. The average daily wages of the above laborers ranged from Euro; €5.61 to €16.82 (Indian Rupee; INR 500 to INR 1,500) [22]. We provided two more wage levels for highly skilled occupations, ranging from >€16.82 to €28.02 (>INR 1,500 to INR 2,500) per day.

Authors considered publicly available prices for enalapril from All India Organization of Chemists and Druggists (AIOCD) for calculations [29]. All costs are presented in Euro (€) and translated in Indian currency (INR) to suit local readers (1 Euro equals 89.17 Indian Rupees as per exchange rate as of 18th May 2021). Thus, the final CCA tool can help calculate cost per patient per time horizon for both interventions as per user options selection basis the provided HF levers. The tool dynamically presents consequences of drug interventions. The tool compares mortality, HF related hospitalizations, and productivity losses between the two interventions.

Table 1. Heart failure levers in cost-consequence analysis tool for healthcare stakeholders

HF Level	Description	Details	Ref.
Health setting	Healthcare in India is provided through public and private providers	– Private – Public	[23]
Time horizon	The time horizon for CCA is the duration over which costs and health outcomes are calculated	– 6 Months – 12 Months – 24 Months – 27 Months	NA
Number of hospitalizations	Number of HF related hospitalization during the time horizon	– 1.42 times – 2.5 – 3 – 4 – 5	[21,24]
Average length of stay (LOS)	Average length of stay per HF related hospitalization	– 5.3 days – 6 – 7 – 8	[21,25,26]
Patient’s work status	Patient’s work status as employed (working) or non-employed (not working)	– Employed – Non-employed	NA
Approximate wages per day	Earning potential of each patient is captured. Approximate wages per day are based on latest India wage report 2018	– Non-employed €0 (INR 0) – €5.61 (INR 500) – €11.21 (INR 1,000) – €16.82 (INR 1,500) – €22.42 (INR 2,000) – €28.03 (INR 2,500)	[27]

User provided inputs be interlinked with each other for HF related cost and consequence calculations. Table 2 and Table 3 exhibit costs and clinical inputs acquired by conducting a targeted literature search specifically from Indian perspective. The total average cost of HF related index hospitalization was assumed as €666.99 (INR 59,492) in a public set-up and €2,242.28 (INR 200,000) in a private set-up [25-26]. Similarly, daily cost of ICU in HF patients was considered as €52.82 (INR 4,711) in public and €205.07 (INR 18,291) in private set-up [25,28]. The hospital readmission rate in HF patients was considered as 24.3% [24]. Probabilities of hospital readmission within 6 months due to HF exacerbation was estimated to be 0.243 and 0.192 in enalapril and sacubitril/valsartan patients, respectively. Average LOS in the hospital was considered as 5.3 ± 2.9 days [25]. As per PARADIGM-HF trial, the percentage of HF patients staying in the ICU was 14.8% and 13.1% in patients taking sacubitril/valsartan and enalapril, respectively at 27 months [22]. Twenty-one percent risk reduction of ICU stay in patients taking sacubitril/valsartan treatment as compared to enalapril was considered linear irrespective of the time horizon. Cumulative mortality rates for various time horizons in HFrEF patients taking enalapril were adopted from The Trivandrum Heart Failure Registry. Mortality rates for 1 year and 2 years were 32% and 42.3% respectively [3]. Mortality rates for other time horizons (6 to 27 months) were estimated assuming a linear relationship between death rate and time. In case of premature death, employees' lost wages were estimated for the specified time horizon in the tool. Workers' real average daily wages, by occupation for upper four highest ranks of labor were adopted from the latest India wage report. Daily wage estimates were reported for the base year of 2011-12 in the India wage report. These numbers were extrapolated to year 2019-20 using similar year-on-year percentage increase from the earlier decade [27]. Costs and consequences results were collated in a waterfall chart for dynamic demonstration of results to the user/ healthcare stakeholders.

Table 2. Cost inputs for cost-consequence analysis tool

Cost Inputs	Input in € (INR)	Reference
Drug cost/ patient/ month for sacubitril/valsartan	37.77 (3,369)	[29]
Drug cost/ patient/ month for enalapril	2.75 (245)	[29]
Cost of hospitalization from a private hospital	2,242.28 (200,000)	[28]
Cost of hospitalization from Manipal Heart Registry (public set-up)	666.99 (59,492)	[25]
ICU bed cost in a private hospital in a metro city of India	205.07 (18,291)	[26]
Cost of ICU Manipal Heart Registry (public set-up)	52.82 (4,711)	[25]
Earning potential of each life lost/ productivity loss for division 1 to division 4 laborers	5.61-28.03 (500-2,500)	[27]

Table 3. Clinical inputs for cost-consequence analysis tool

Clinical Inputs	Input	Reference
Mortality risk reduction (PARADIGM-HF), %	20	[21]
Cumulative mortality rates for 1 st , 2 nd and 3 rd year (Trivandrum Heart Failure Registry)	0.32, 0.423, 0.462	[3]
HF related hospitalizations risk reduction (PARADIGM-HF), %	21	[30]
Rate of hospitalizations in India (%)	24.3	[24]
Patients staying in ICU (sacubitril/valsartan vs. enalapril) (PARADIGM-HF), %	14.8 vs. 13.1	[22]
Average LOS for public set-up in days (Manipal Heart Registry)	5.3 ± 2.9	[25]
Average LOS for private set-up in days	7 ± 5 ; 6 (4 to 9)	[3, 8]

Results

Cost-consequence analysis (CCA) tool demonstrates dynamic display of costs and health outcomes from customized inputs from user/ healthcare stakeholders. CCA tool exhibits costs and consequences (health outcomes) for HF patients in two representative HF patients (ABC and XYZ). For HF patient, ABC who is employed as a manager at a private set-up with an average daily wages of €22.42 (INR 2,000) was admitted to a private hospital for HF related treatment. Figure 1 presents the costs and health outcomes for the time horizon of 12 months. Patient ABC was hospitalized 3 times in a year due to HF related complaints with an average LOS of 6 days during each hospitalization. As shown in Figure 1, patient ABC spent €420.31 (INR 37,490) more for sacubitril/valsartan than enalapril for his/her annual HF treatment. The number of hospitalizations avoided, productivity savings and mortality benefits of sacubitril/valsartan vs. enalapril treatment in 12 months were dynamically demonstrated in a graphical form. Patient ABC on sacubitril/valsartan treatment avoided on an average 0.15 hospitalizations in a year and spent fewer days in ICU (0.12 days) as compared to patients taking enalapril. This resulted in a monetary savings of €127.32 (INR 11,356). Productivity saving of around 1 day for patient ABC resulted in an economic savings of €20.60 (INR 1,837). The most significant financial savings of €516.62 (INR 46,080) was realized in ABC, as he/she was more likely to be alive due to innovative sacubitril/ valsartan treatment. Overall patient ABC on sacubitril/valsartan treatment comprehended a savings of €485.34 (INR 43,290) when treated with sacubitril/valsartan. This cost-consequence break-up was shown systematically for user's easy understanding.

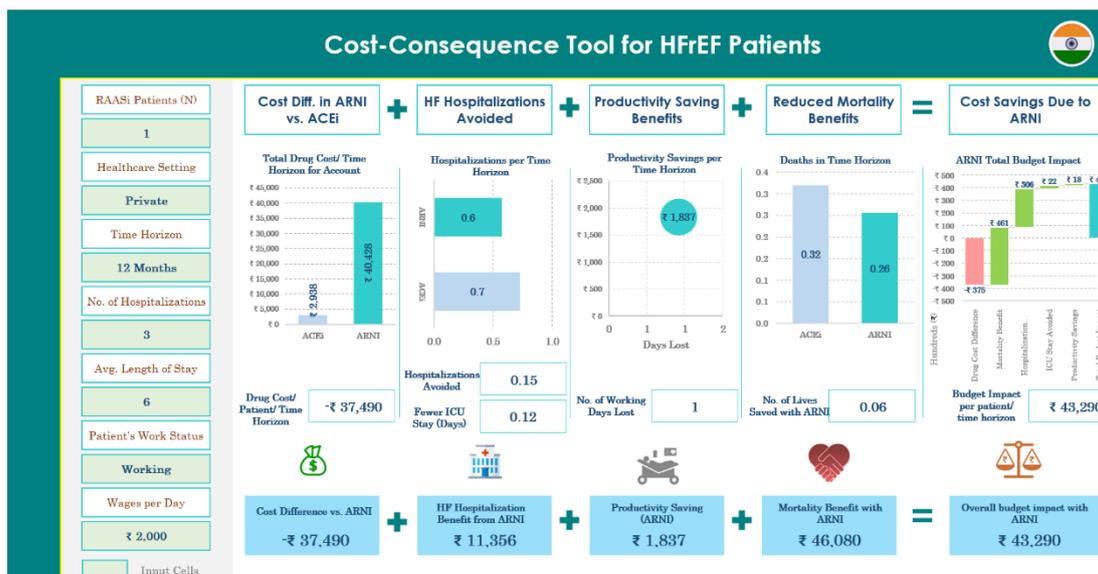


Figure 1. Cost-Consequence Representation for HF Patient ABC

Alternatively, HF patient XYZ, who is employed as a clerk at a government office with a daily wage of €11.21 (INR 1,000) was hospitalized at a government hospital for HF exacerbation. Patient XYZ was also hospitalized 3 times in a year due to HF related complaints with an average LOS of 6 days. CCA in Figure 2 demonstrates that patient XYZ spent €43.09 (INR 3,843) more for sacubitril/valsartan in comparison with enalapril in a year's time to realize benefits of mortality, hospitalization and productivity savings. Validation of the CCA tool was conducted by key medical experts across India. This tool is freely available to download as an excel file.

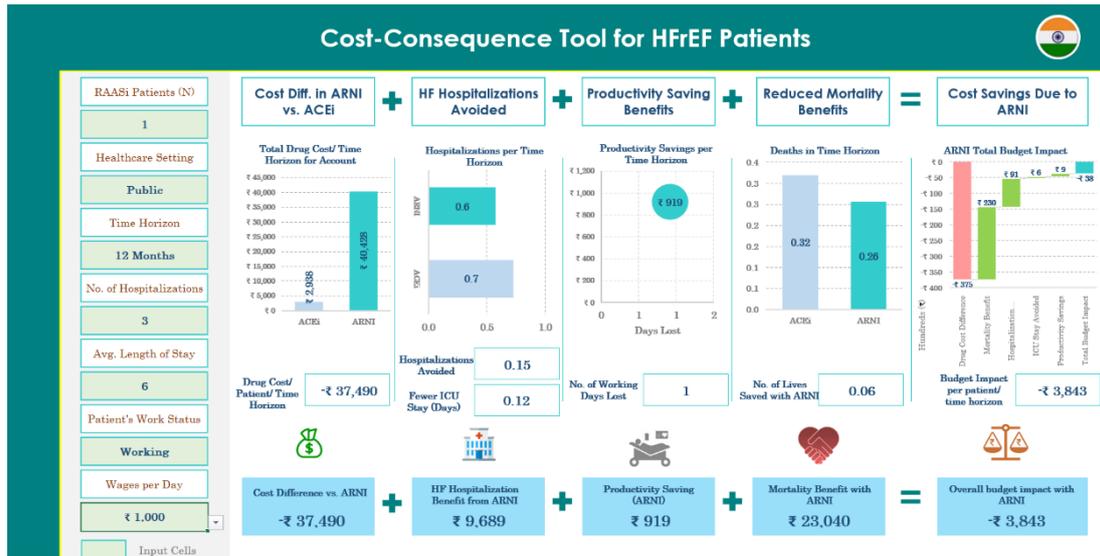


Figure 2. Cost-Consequence Representation for HF Patient XYZ

Discussion

Cost-consequence analysis (CCA) is a type of health economic evaluation; wherein all direct costs, indirect costs and relevant health outcomes are listed separately for a decision maker to form an opinion in selection of an appropriate intervention [30]. HF is an emerging health problem in India where significant health gains such as reduced premature mortality, reduced number of re-hospitalizations, and productivity gains can be experienced by carefully selecting medication interventions. This tool will be useful for understanding how effective treatments might change the direct and indirect costs in chronic HFREF patients, thereby helping healthcare stakeholders to plan health service expenditure for an individual patient or homogenous patient cohorts. This tool will equip healthcare decision makers in a specific health setting to understand which HF related levers are cost drivers that can be tweaked to reduce the economic burden of HF in society.

Overall, from the two representative cases depicted in the results section, sacubitril/valsartan can be seen as a value for money option as compared to enalapril in the HF treatment. Looking at superiority of sacubitril/valsartan over ACEi/ARBs, Mishra et al. advocated using sacubitril/valsartan instead of ACEi/ARBs if cost is not an issue [31]. The use of sacubitril/valsartan is now generally accepted, but the whole objective of this article is to develop an effective tool that gives a ready outcome of the cost-consequence analysis for a particular patient.

The Manipal Heart Failure Registry analyzed the financial burden and healthcare resource utilization across 610 HF patients and reported the total cost of HF management from index hospitalization was €0.91 million (INR 81.5 million) with an average per patient 2-year cost of €1,498.55 (INR 133,663). Every patient paid €927.92 (INR 82,766) after average health insurance coverage of €570.61 (INR 50,896). Either government (61%) or private (19%) insurance leaving behind 20% of patients' uninsured covered majority of HF patients in this registry [25]. This study also concluded that expenditure was significantly higher in HF patients with ischemic etiology, male gender, and age above 60 years. These three and additional variables such as HF patients with comorbidities, drug compliance can be studied and incorporated appropriately in the CCA tool in near future.

In a subgroup of participants suffering from coronary heart disease (N=1,509) from the Indian Human Development Survey (2011-12), participants were found to prefer private providers (74.3%) instead of government providers (25.4%) and happen to spend €44.85 (INR 4,000) more as average expenditure as compared to the government providers. In general, HF entails large medical and non-medical out-of-pocket (OOP) expenditure [32]. Low health insurance coverage and rising HF related

expenditure driven by private healthcare settings calls out for a pharmaco-economic intervention for efficient decision-making.

Often, HF patients frequently visit their physicians to titrate their prescribed medications post discharge from hospital. It is evident from data that majority of events after HF hospital admission occurs within a month's time and therefore it is recommended by HF guidelines to schedule a visit within 7 days of discharge [33-34]. Current HF guidelines (year 2017) for India recommends dose titration for ACEi/ ARBs/ ARNI in disease management [34]. Similarly, medical and non-medical OOP costs post discharge are many. Medical costs are costs of medicines, laboratory tests, doctor fees, attendant fees and hospitalization charges. Non-medical charges include cost of tips, traveling, boarding, lodging to undergo desired HF treatment [32].

HF patients often require time-off work to recover from their illness or surgery post their hospitalization. These individuals incur income losses to recover post each hospitalization. Work productivity is significantly reduced in these HF patients. In addition, use of certain medications such as beta-blockers may induce fatigue, adversely affect patient's productivity, and increase absenteeism. Employers experience substantial productivity losses associated with absenteeism (time away from work), presenteeism (reduced effectiveness at work), and early retirement from work due to underlying HF disease [35]. Due to non-availability of such data (absenteeism, presenteeism, and early retirement), we have not considered these costs in this tool. Our approach is a conservative approach but certainly is an underestimate of the socioeconomic costs associated with HF.

Conservative LOS estimates of 5.3 ± 2.9 days were considered while calculating benefits due to reduced hospitalizations but in reality this number can be higher than the one that is used [28]. Relevant LOS data from Suman et al. 2018 and Sanjay et al. 2018 was 7 ± 8 days and 4-9 days respectively [3,8].

There are limitations of this tool that should be acknowledged. The CCA tool takes into account important HF related levers to provide insights to healthcare stakeholders but does not consider other patient centric variables such as gender, etiology, age, presence of comorbidities, medication adherence etc. These variables need to be studied and incorporated into the CCA tool in near future. Additional physician visits and OOP costs post hospitalization are not considered in this tool. We believe these costs are similar in both arms (sacubitril/valsartan as well as enalapril) and hence will not make much of a difference to the CCA calculations. Despite these limitations, concept of CCA can be adapted to other disease areas with necessary clinical and cost inputs.

The importance of this article is in providing insightful information to healthcare stakeholders to make an informed decision-making for their HF patients keeping in mind the health economic perspective. It is anticipated that importance of such pharmaco-economic tools in Indian healthcare setups with resource constraints is bound to propagate.

Conclusion

Premature mortality, frequent hospitalizations, and lost productivity are some of the undesirable sequelae in chronic HFrEF patients in India. Sacubitril/valsartan treatment has the potential to improve clinical as well as economic outcomes by generating substantial cost savings to minimize budget deficit in Indian healthcare setting. CCA tool could support payers and healthcare stakeholders in selecting an appropriate treatment strategy for chronic HFrEF patients.

List of abbreviations

ACEi = Angiotensin Converting Enzyme inhibitors
AIOCD = All India Organization of Chemists and Druggists
ARBs = Angiotensin Receptor Blockers
ARNI = Angiotensin Receptor–Neprilysin Inhibitors
CCA = Cost-Consequence analysis
CVD = Cardiovascular Disease

HF = Heart Failure
HFrEF = Heart Failure with reduced Ejection Fraction
ICU = Intensive Care Unit
LOS = Length of Stay
OOP = Out-of-Pocket
PHI = Private Health Insurance
YLD = Years of Life lost due to Disability.

Conflict of Interest

Dr. Gauri Billa and Sameer Gokhale are employees of Novartis Healthcare Pvt. Ltd.

Acknowledgements

Authors would like to acknowledge Dr. Pankaj Gupta, Dr. Laboni Chatterjee and Sushant Anand, all employees of Novartis Healthcare Pvt. Ltd. for making substantial conceptual or design contributions for the CCA tool.

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