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Risk of Hospitalization among Elderly Heart Failure Patients initiating Beta-Blockers or ACE-Inhibitors

A comparative effectiveness analysis

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The original signed page can be referred in the file.

<u>Acknowledgements</u>

<u>Dedications</u>

This Dissertation work is dedicated to all my family members,

friends and my Professors.

A. <u>Executive Summary</u>

a. Overall summary of research study

Past literature suggests that for elderly Heart Failure (HF) patients, an early initiation of Beta-Blockers (BBs) can provide beneficial effects compared to Angiotensin-Converting enzyme Inhibitors (ACEI). This study compares the effect of these therapies for first HF hospitalization, recurrent HF hospitalization and for a composite outcome of HF hospitalization with death as the terminal event. The results support the effect of an early initiation of the therapies on these outcomes with a statistically non-significant effect of BBs compared to ACEI. For BBs, the class effect was tested for sub therapeutic classes of BBs, i.e. BBc1 which includes bisoprolol, metoprolol etc. and BBc3 which includes carvedilol and labetalol. The results suggest BBc1 is a preferable therapy for the elderly (age≥65 years) HF patients compared to BBc3.

b. Rationale

HF imposes major health and economic burdens. To treat the disease, guidelines recommend initiating BB for stage B HF patients, i.e. the ones with mild/moderate HF as an add-on therapy after ACEI/ARB. Despite this recommendation, some researchers argue that an early initiation on BBs could provide beneficial effects since BBs play an important role in reducing the risk of Sudden Cardiac Death (SCD) compared to ACEI.(Remme, 2007, 2008) Additionally, it has been proven that BBs have the ability for an early inhibition of cardiac remodeling, increased activation of renin-angiotensin system (RAS), greater anti-ischemic property and ability to achieve a higher dose.(Knight, Glynn, McIntyre, Mogun, & Avorn, 1999) All these findings and facts substantiate studying the impact of initiating BBs in comparison to ACEI among elderly HF patients. Although randomized controlled trials

(RCT)s such as CIBIS III and CARMEN support this hypothesis, the population included in these trials is at least 10 years younger compared to those existing in the community. These trials only concentrate on patients with EF<45% and they do not provide any class comparison of BBs with respect to ACEI. Additionally, these trials administer ACEI as a standard therapy in almost 90% of trials which creates a challenge to segregate the monotherapeutic effect of BBs from the effect of ACEI. Lastly, these trials have also been criticized for their inability to achieve optimum dose effects in the duration of follow-up. Considering these existing gaps in research, as well as cost, time and other resources required for gaining evidence from trials, motivates us to conduct this study. No other observational study has provided any such evidence in this regard.

c. Objectives

The aim of this study is to understand the impact of early initiation of different categories of BB compared to ACEI on the risk of HF hospitalization in elderly HF patients. The specific research objectives studied are:

1. To find the Baseline Predictors of receiving ACEI vs. different categories of BB or the combination of two therapies in HF patients.

2. To compare the time-to-first HF hospitalization across ACEI vs different categories of BB users or the combination therapy.

3. To compare the time-to-recurrent HF hospitalization and composite outcome of time-to-recurrent HF hospitalization with death as the terminal event across different ACEI vs different categories of BB users or the combination therapy as observed within a year of initiating a therapy.

The hypothesis for this study is that the 3 clinical outcomes (time-to-first HF hospitalization and time-to-recurrent HF hospitalization and composite outcome of time-

to-recurrent HF hospitalization with death as the terminal event) for the BB group are at least not significantly different compared to ACEI.

d. Main findings

1. An early initiation of a therapy has different predictors responsible for initiation of BBc1 or BBc3 in comparison to ACEI.

2. The effect of early initiation of BBs is not significantly different compared to ACEI for the 3 clinical outcomes.

3. For the included population patients, BBc1 seems to be a preferable therapy compared to BBc3 for the 3 clinical outcomes.

e. Conclusions

The risk of HF hospitalization varies non-significantly for BBs when compared to ACEI. There is a class effect of BBs on these outcomes with a favorable indication for BBc1 in comparison to BBc3.

f. Impact of the study.

The information from this study has multi-fold significance.

1. For patients where ACEI is not tolerated, BBs can be an alternative therapy which can be considered to prescribe to initiate the treatment. In other words, the findings guide us towards some choice of making an individual-based judgment from amongst ACEI/ BB.

2. The results are for the elderly HF patients with average age 73-75 years, as prevalent in HF community, whose frequency is less in the RCTs. In addition to this, the majority of the patients included in this study seem to have a normal Ejection Fraction

(EF). The information for this population is still a gap in the literature. Thus, the HF treatment scope is broadened in this study.

3. If the results could be validated in further studies, an early initiation of BB can be considered for achieving a rapid inhibition of cardiac remodeling and thereby providing a better HF control.

4. In addition to HF control, SCDs could decrease by an early initiation of BBs.

5. The results seem to prefer BBc1 for the included population for HF hospitalization as the outcome in comparison to BBc3. Till date only guesstimates were being made about this information. But now there is some direction in this regard.

6. The information is from real world data and has successfully teased out the effect of different categories of BBs from the influence of ACEI/ARB, which otherwise is a challenge in an RCT.

7. The study estimates once validated will diminish the need to always conduct an RCT with ACEI as the standard therapy, which at times hinder the understanding of individual effect of new drugs under study in a trial.

8. Lastly, in this study recurrent hospitalization has been estimated as a measure of Worsening of HF (WHF). This information in true sense establishes the equivalence of BBs with respect to ACEI.

g. Introduction of the journal articles to follow.

Three manuscripts discussed in the follow up journal articles are:

1. Determinants of early initiation of ACEI vs BBs among elderly HF patients

2. Risk of first HF hospitalization among elderly HF patients initiating ACEI vs BBs

3. Risk of recurrent HF hospitalization among elderly HF patients initiating ACEI vs BBs

Manuscript # 1

Determinants of early initiation of ACEI vs BBs among elderly HF patients

Finding: The identified determinants related to initiation of BBs or ACEIs is the first step to determine which class of drug leads to better patient outcomes.

Abstract

Objective: To estimate the determinants of initiating Beta-Blockers(BBs) vs. Angiotensin-Converting Enzyme Inhibitor(ACEIs) among elderly Heart Failure(HF) patients.

Methods: Using Medicare Advantage Prescription Drug Plan for 2008-2011, elderly(age≥65 years) HF patients initiating ACEI or a sub therapeutic class of BBs, defined as category 1(BBc1 e.g. Metoprolol, Bisoprolol etc.) and category 3(BBc3 i.e. BBs with combined alpha and beta blocking activity e.g. Carvedilol and Labetalol), were identified. The baseline determinants of initiating either of the drug categories were identified by Multinomial logistic regression analysis using SAS 9.3 at the p-value of 0.05.

Results: Of all 6430 eligible patients, ACEI, BBc1, BBc3, a combination of ACEI and BBc1(ABC1), a combination of ACEI and BBc3(ABC3) or a therapeutic drug other than ACEI/BBs were initiated by 1194(18.57%), 1519(23.62%), 490(7.62%), 257(4.00%), 126(1.96%) and by 2844(44.23%) patients respectively. On average, patients were more likely to initiate BBc1 compared to ACEI or BBc3. This likelihood for initiating BBc1 compared to ACEI increased statistically significantly by presence of atrial fibrillation/flutter(OR:1.348,95%CI:1.09-1.667), Age(OR:1.017,95%CI:1.005-1.028), with vasodilators(OR:1.373,95%CI:1.051-1.795) and with a missing BNP value compared to a Normal range of 0-99ng/L (OR:1.97,95%CI:1.085-3.578). For initiating BBc3 compared to ACEI the likelihood increased statistically significantly for males(OR:1.294,95%CI:1.039-1.612), for patients with chronic atherosclerosis(OR:1.502,95%CI:1.12-2.015), for those taking vasodilators(OR:1.600,1.144-2.238) or Diuretics (OR:1.306,95%CI:1.05-1.625) or having an elevated value of BNP(OR:2.465,95%CI:1.008-6.029). It decreased statistically significantly for patients taking Calcium Channel Blockers (OR:0.718,95%CI:0.547-0.942) in the washout period.

Conclusions: The identified determinants related to initiation of BBs or ACEIs is the first step to determine which class of drug leads to better patient outcomes.

Introduction

More than 5.5 million adults have heart failure (HF) in the United States, with an incidence rate of 10 per 1000 after 65 years of age and an estimated direct and indirect cost of HF of 37.2 billion for 2009.(Shafazand, Yang, Amore, O'Neal, & Brixner, 2010) To treat the disease these guidelines recommend to use Beta-Blockers (BBs) as a stage B therapy for HF patients, i.e. as an add-on therapy after Angiotensin Receptor Enzyme inhibitors (ACEI) or Angiotensin Receptor Blockers (ARB). (Hunt et al., 2009)

Contrary to this, some researchers argue that there is no need to always follow the dogmatic approach of ACEI before BB.(Cruickshank, 2000; Krum, 1999; Remme, 2008) They suggest that the reason behind ACEI being a preferable choice lies in the history of these trials. Till date, there exists ample of evidence in favor of ACEI compared to placebos which were collected decade before beta-blocker trials.(Chonchol, Benderly, & Goldbourt, 2008; de Boer & van Veldhuisen, 2008; Remme, 2007, 2008; Remme et al., 2004) As a result, ACEI became the first choice of therapy and it became an almost unethical standard to conduct a HF trial without prescribing ACEI as the standard therapy. For example, for beta-blockers, ACEI was part of approximately 90% of the trial's patient population. This makes it hard to attribute the protective effect of the trial solely to beta-blockade. This research question and similar other research questions demands to assess, if we can change the on-going custom of not conducting a Randomized clinical trial (RCT) without always prescribing ACEI as the first-therapy of choice or can it be changed with other approaches like BBs. And, while there is a lack of any guidelines for whether or not to conduct these RCTs, there is a need to take support of some alternative approaches like from observational studies that can answer these research questions.

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As per an article by Remme et al, BBs play an important role in reducing the risk of Sudden Cardiac Death (SCD) compared to ACEI, thereby, BBs can be used as an initial therapy in elderly heart failure patients.(Remme, 2007, 2008) Further, the author recommends that BBs have an early protective effect on cardiac remodeling via the sympathetic system compared to ACEI effect on renin angiotensin systems (RAS). The SOLVD trial extends an early effect of BBs on RAS activation as well.(Knight et al., 1999)

Based on these backgrounds, it becomes important to study the impact of initiating BBs before ACEI among HF patients on various clinical outcomes. If the abovementioned justifications holds true then it can be verified if BBs are more beneficial for elderly HF patients in comparison to ACEI. But before establishing this, it is of utmost importance to establish the factors that are associated with initiation of ACEI vs. BBs as monotherapy or as combination therapy. The information is crucial to establish the characteristics of sub-groups that differ in prescription of these therapies.

Evidence from Randomized Clinical Trial (RCTs) and where do they lack

The above mentioned hypothesis has been supported my many trials like CIBIS III, CARMEN trial, SENIOR trial, beta-PRESERVE trial and other RCTs like by Sliwa et al, which have proved comparable tolerability and other clinical outcomes like all-cause hospitalization, all-cause mortality etc. of different BBs with ACEI.(Flather et al., 2005; Komajda et al., 2004; Morrissey, Czer, & Shah, 2011; Remme, 2007, 2008; Remme et al., 2004; Sliwa et al., 2004; R. Willenheimer, 2009; R. Willenheimer et al., 2005; Zhou et al., 2010) These trials have established the beneficial effect of BBs mostly against Left Ventricular Ejection Fraction (LVEF). Efforts are still ongoing to establish its beneficial effect amongst patients with HF normal Ejection Fraction (HFNEF). This means, a HF

patient, irrespective of his or her Ejection fraction (EF) can be hypothesized to benefit from BBs compared to or at least for their equivalence to ACEI.

Additionally, studies have also reported that an effect of sub-therapeutic category (STC) of BBs. For example, COMET trial showed greater reduction in fatal and non-fatal MIs and SCD due to carvedilol treatment (Non-selective BB) compared to metoprolol treatment (Beta-1 selective agent).(Poole-Wilson et al., 2003) Moreover, physicians often tend to replace one drug with their therapeutic equivalent drug found in their class. This makes it important to understand this class effect. Although RCT is desirable across individual drugs, but considering its cost, time and other practical limitations, we cannot compare all BBs with all ACEI in a single trial or even in 2-3 trials. This implies that RCTs are an infeasible design approach to understand these class comparisons.

Further, as already stated RCTs are not being conducted without prescribing ACEI as the standard therapy, this makes it difficult to differentiate the protective effect of BB w.r.t. ACEI.(Flather et al., 2005; Remme, 2007, 2008) Apart from that the patients included in these trials are comparatively healthier and younger compared to real world data.(Jafar et al., 2003; Remme et al., 2004) Thus, generalization of these study findings to the community tend to be a common issue associated with these studies.(Richardson et al., 2010) And even if the population matched that of community as in CIBIS-III trial, the experimental design approach tends to lose the proximity of the design findings to that of real world data. Moreover, this trial is not considered a good design to estimate the optimum effect of BBs due to its inability of not achieving the target dose.

Evidence from the observational Studies

Few worth noting observational studies compare the effect of ACEI vs BBs, but either the ACEI group has been combined along with some drug like ARB or used as an add on therapy

with other drugs like statins.(Richardson et al., 2010; Teng, Hung, & Finn, 2010) These articles either choose some specific population like after HF discharge or do not provide a head-to-head comparison.(Austin, 2009; DiMartino, Shea, Hernandez, & Curtis, 2010; Maison et al., 2012; Wijeysundera et al., 2011) The study by Toh et al has compared ACEI/ARB vs BB for different clinical outcomes like angioedema in a sample frame different than HF. (Toh et al., 2012) Similarly, study by Galindo-Ocana et al was not just restricted to HF patients only.(Galindo-Ocaña et al., 2012) Magid et al compared ACEI vs BB for Hypertensive patients.(Magid et al., 2010) All these studies indicate towards the need to compare BBs w.r.t. ACEI, thereby bringing more evidence for BBs. And if established as a standard therapy, then it would demand an increase in utilization of the BBs. However, some of the past literature suggests an underutilization of the therapy, which raises a doubt about the factors governing the utilization of the therapy in comparison to ACEI. The current study is an attempt to fill this gap in literature.

Aim and Significance of the study

With the given background, this study therefore aims to understand the determinants of early initiation of different categories of BBs compared to ACEI or the combination of both among elderly HF patients. For this, a cross-sectional observational study design on real world data from Medicare Advantage Prescription Drug (MAPD) Plan in Texas was used. Firstly, the study provides the information from population with average age 73-75 years, as is also prevalent in HF community.(Remme, 2008) Thus, this information is directly applicable to the community elderly HF population. Secondly, as already stated the information about determinants of initiating treatment gives an idea about the differential sub-populations whereby one drug is being preferred over other. A comparative effectiveness of these sub-populations for different clinical outcomes can help to broaden the scope of HF treatment

among elderly patients for which ACEI is not tolerated. Thirdly, this study has brought evidence from real world rather than a controlled environment of a RCT and thus provides information from actual diseased patients of the community. This means a more reliable and generalizable information can be expected from the study. This shall also help us to tease out the effect of BBs from the influence of ACEI which is sometimes not possible in an RCT. In an article by Willenheimer et al, the author has suggested that the positive results of effectiveness shall provide the free choice of making an individual-based judgment from amongst ACEI/BB.(Ronnie Willenheimer, van Veldhuisen, Ponikowski, & Lechat, 2005) And thus, once there is sufficient evidence, it will not be required to always conduct an RCT with ACEI as the standard therapy, which at times hinders with the understanding of individual effect of new drugs under study in a trial. The information from this study shall also be used in future studies whereby effectiveness shall be compared across these groups to establish aforementioned hypothesis.

Thus, the specific aim of this study is to find Baseline Predictors of receiving ACEI vs. different categories of BB or the combination of two therapies in HF patients. Predicted probability of receiving treatment with either therapy was calculated based on age, sex, clinical factors (Comorbid conditions and risk indices), co-medications used and certain lab values.

__Methods__

This is a cross-sectional study on elderly (age≥65 years) HF patients enrolled in Medicare Advantage Prescription Drug Plan (MAPD) in Texas from the year 2008-2011. The data is collected by the Centers for Medicare and Medicaid Services (CMS).(Esse, Serna, Chitnis, Johnson, & Fernandez, 2013; HealthSpring, 2013). This claims data consists of several computerized data file that have information about patient membership, member summary, institutional claims, professional claims, Quest lab, CCMS and Part D Pharmacy Data.

The membership file and the member summary file contain information about demographics, CMS risk score, cost, and type of visit or admission made in each month along with membership date and date of death information available for all claims. The Institutional and Professional claims files consist of information on inpatient and outpatient claims respectively. Whereas lab tests information can be obtained from Quest lab files, the Pharmacy files consists of drug identifying and related information like fill dates, days of supply, quantity dispensed and dosing information for each prescription filled. Information like admission reason (Elective, emergency, urgent etc.) and discharge date is obtained from CCMS file.

The study is based on the CIBIS III design (R. Willenheimer, 2009; R. Willenheimer et al., 2004) modified for observational studies based on other studies and aimed to use the design in future studies to compare ACEI and BBs for hospitalization as the clinical outcome.(Abbott, Trespalacios, Agodoa, Taylor, & Bakris, 2004; Chitnis, Aparasu, Chen, & Johnson, 2012; Magid et al., 2010; Richardson et al., 2010) The pictorial representation of the study design is presented in Fig 1. As is represented in the diagram, in future studies, these patients were followed for a year to observe the outcome.

Ethical Considerations

This study is exempted from human studies review requirement by the Institutional Review Board of University of Houston.

Study Sample

The study sample includes patients from a stacked membership for the year 2008-2011 (Figure 2). All 10252 patients with CHF diagnosis were included for our study. This provides data for all HF patients in community, in long-term care facility or in hospice program and HF patients diagnosed by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 428.xx.(Richardson et al., 2010) Past literature recommends that this method has >95% specificity for the diagnosis of HF.(Birman-Deych et al., 2005; Goff, Pandey, Chan, Ortiz, & Nichaman, 2000; Richardson et al., 2010) Along with this, the ICD-9-CM codes 401.x1, 404.x1, 398.91, 402.x1 and 404.x3 are also recommended in the past literature for institutionalized Medicare beneficiaries and for those enrolled in a hospice.(DiMartino et al., 2010; Richardson et al., 2010) Based on their CHF diagnosis date, which should be prior to initiation of either of the therapeutic groups, HF patients are included in the study.

Inclusion criteria

This study included any patient who after '01Jul2008', had claimed for an ACEI or a ß-blocker as monotherapy or in combination in the Pharmacy Data File.(Richardson et al., 2010) These patients should have a diagnosis date of HF and a membership of at least 6 months prior to initiation of either therapy. These 6 months prior to initiation of therapy was defined as the ***wash out period***, whereby neither of ACEI/BB/their combination was prescribed. Although most of the past literature including CIBIS-III trial has considered a washout of 14days to 3 months; but based on a study by Shafazand et. al this study chose a washout of 6 months for severity assessment of HF based on past hospitalizations and HF

utilization.(Shafazand et al., 2010; R. Willenheimer et al., 2004) A no prescription of either therapy was defined based on proportion of days covered (PDC) which as explained later was required to be less than or equal to 0.04.

Exclusion Criteria

All the HF patients with a recorded death or taking either ACEI, or BB category 1(BBc1) or BB category 3(BBc3), or a combination of BBs with ACEI or with each other in the washout period (i.e. PDC>0.04) were excluded. This does not include any patient taking Beta-blockers category 2 (BBC2) i.e. BBs with Sympathomimetic activity for 3 months prior to and also on the index date, due to their low sample size. Further, based on CIBIS III trial recommendation, any patient taking ARB, Aliskiren or aldosterone antagonist for 3 months prior to and also on the index date (i.e. PDC>0.04) was also excluded from the study, to avoid their potential risk of biasing the study.(Rashikh, Ahmad, Pillai, & Najmi, 2012; Toh et al., 2012) Pre-existing aldosterone receptor blocker was however permitted in the trial and also in this study. All the inclusion and exclusion criteria are represented in Fig 2. The patients with records after '05Jan2011' were excluded from the study so as to include a patient with a possible 1 year record, which was used in further studies for comparative effectiveness.

The study does not exclude the patients with possible contraindications to either drug in future, because despite possibility these patients were prescribed these therapies on the index date and thus needs to be accounted for on the index date.

Index date

This is the maximum date (Dmax) for an alive patient with age≥65 years from amongst the date of first drug supply claim (first dos), date of Heart Failure diagnosis (d(HF)), the date with at least 6 months prior membership (dm-6m) or a date that allows 6 months washout

with all inclusion exclusion criteria satisfied as mentioned above or a date on or after 01Jul 2008.

Prescription Drug Use

Prescription drug use is reported in the Pharmacy Data file in the form of prescribed medication claims, with each claim corresponding to a single prescription fill for use till the recorded days of medication supply.

The study used sub-therapeutic classes (STC) from pharmacy file identified and classified different therapeutic drug categories as per JNC-7 guidelines and various generic drugs including ACEI, BBc1 and BBc3.(Verdecchia & Angeli, 2003) The generic drugs included were as follows: (i) ACEI inhibitors included benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril (ii) β-blockers included acebutolol, atenolol, betaxolol, bisoprolol, carteolol, carvedilol, labetalol, metoprolol, nadolol, penbutolol, pindolol, nebivolol, propranolol, sotalol, and timolol.(Abbott et al., 2004; DiMartino et al., 2010) The BB categories included: (1) Atenolol, betaxolol, Bisoprolol, Metaprolol, Nadolol, Propranolol and Timolol combined to define BBs as first category (BBc1). For this category no title has been defined except for Beta-Blockers. (2) Acebutalol, penbutalol, pindolol and nebivolol were classified as BBs with sympathomimetic activity (BBc2). (3) Carvedilol and Labetalol were categorized together in 3rd category of drugs with combined alpha- and beta- blocking activity (BBc3). Although ACC/AHA 2005 guidelines approve all the above mentioned BBs, but it does not specify any classification scheme for the BBs, so a classification based on JNC-7 guidelines was adopted for this study.(Anderson et al., 2007; Verdecchia & Angeli, 2003) JNC-7 guidelines, provides non-overlapping standard guidelines based therapeutic categories.(Verdecchia & Angeli, 2003) It also keeps bisoprolol/Metoprolol and carvedilol in separate groups which makes it possible to

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compare these 2 drugs in separate categories, as required for comparative effectiveness and also recommended by past literature. (Poole-Wilson et al., 2003; Remme, 2007, 2008) Another crucial point that needs to be mentioned here is the fact that ACC/AHA 2013 guidelines only recommend bisoprolol and metoprolol for BBc1 and Carvedilol forBBc3.(Yancy et al., 2013) However, considering the fact that other BB drugs are being utilized by MAPD data and additionally for various comorbidities associated with HF patients other BBs are recommended and being tested in various trials, all possible BBs mentioned above are being tested here.(Abbott et al., 2004; DiMartino et al., 2010; Hunt et al., 2009; Jessup et al., 2009; Pasternack, Pörsti, & Pöyhönen, 1982)

Finally, after applying all inclusion/exclusion criteria 6 mutually exclusive drug use groups were created: (i) ACEI only; (ii) ß-blocker category I (BBC1) only; (iii) ß-blocker category III (BBC3) only; (iv) A combination of both ACEI and BBC1; or (v) A combination of both ACEI and BBC3; or (vi) No drug use from either category also termed as other therapies considering these patients may be taking some therapy other than ACEI/BBc1/BBc3. Combination therapy was defined as if the patient was taking prescriptions for 2 drugs from 2 different categories on the index date.

Proportion of days covered

a)   Required Drugs

The prescription of a required drug i.e. ACEI, BBc1, BBc3 or their combination was defined based on the proportion of days covered (PDC) by these drugs defined by prescription date and the number of days supplied.(S. R. Leslie, Gwadry-Sridhar, Thiebaud, & Patel, 2008) Each drug was coded as '0' for no drug and '1' for the days for which the drug was prescribed. Thus, patient was defined to be on combination if the patient was coded as '1' for ACEI along with either BBc1 or BBc3 on any day. If the patient was coded as '1' for

only 1 of these drugs, then it was defined as a monotherapy of the particular drug. For example if ACEI is coded as '1' but BBc1 and BBc3 are coded as '0' then it's a monotherapy of ACEI. If the patient was coded as '0' for all these drugs, then it was defined as a patient getting some therapy other than ACEI/BBc1/BBc3. This strategy assures that patient was not misclassified as not taking a drug when he/she might have been prescribed a drug in some previous date to cover current date. Table 1 shows the respective number of drugs in each category.

For excluding these required drugs, PDC was defined for the washout period. If a PDC > 0.04 was observed, the observation was excluded from the study. For a PDC ≤ 0.04, patient was defined as taking 'no drug in washout' and thus was included in the washout.

b)   Not -Required Drugs

For excluding the not required drugs i.e. ARB and BBc2, similar strategy was adopted. Initially, all the claims date and days' supply information as available in the data set were used to define whether or not the patient received the drug on any day or not. If the PDCs covered by these drugs for 3 months within the washout period prior to the index date is ≤ 0.04 then it was considered as a 'no drug' and thus this patient was included in the study. However, if PDC was more than this cut-off of 0.04 then it was called a prescribed drug and thus this patient was excluded from the study. Both these drugs along with aldosterone antagonists, aliskiren and spironolactone, defined as not required drugs, were again coded as '0' or '1' for each day after the index date. If any of these not required drugs on the index date is coded as '1', the observation was excluded from the cohort.

c)   PDC Cut-off Point (0.04)

As stated previously, a cut-off point of 0.04 was defined to exclude patients from the washout period. This was done for a restrictive cut-off definition for not-required drugs. An

article by Chen et al suggests to keep a cut-off of 0.2 for a restrictive criteria for persistence.(Chen, Patel, Sherer, & Aparasu, 2011) This gives maximum allowable permissible days (MAPD) of 36days for 6 month washout period, which could easily include the whole month prior to the index date. To avoid this, an additional restriction was imposed on the month prior to the index date with a cut-off of 0.2. So, in all for the whole 6 month washout, a cut-off of 0.2 for 6 months and 0.2 for 1 month prior to the index date was defined. By law of multiplicative probability for independent events, this gives us a cut-off of 0.2*0.2 = 0.04.(Arora, Malhan, & ebrary Inc., 2010) This cut-off of 0.04 gives a MAPD of 7.2 days, much stricter restrictive criteria compared to previous 36 days. Additionally, the article by Funck-Brentano et al, a post-hoc analysis of CIBIS-III trial, also kept a MAPD of 7 days, thus justifying the cut-off point of this study.(Funck-Brentano et al., 2011) The patients taking any of the not required drugs in the 3 months prior to the index date and on the index date were also excluded on a similar pattern i.e. PDC(3months)*PDC(1month) = 0.2*0.2 = 0.04 which implies a MAPD of 3.6 days.

In this study, each month was defined to have 30 days for consistency. This means a 6 month wash period was of 30*6 = 180 days, 3month = 30*3 = 90 days and year of 12 months = 30*12 = 360 days.

d) Comedications

Any comedications the patient might be taking on the index date were also coded as '0' and '1' similar to each of the required drugs. However, considering the linearity distribution of the drug, if the PDC was '0' then the comedications was defined as 'No' and else 'Yes'.

Sample Characteristics

a) Socio-demographic Variables

These were obtained from member file and member summary files and included information about age, sex and county.(Ross et al., 2008) Using the frequency distribution of patients across County, patients across regions were classified as belonging to Gulf Coast, SE Texas and others. All the insurance plans were classified as healthy advantage plans which includes some form of healthy advantage plan (Healthy advantage valley, Healthy advantage preferred, Healthy advantage, Healthy advantage sadler, Healthy advantage sadler PR, and Healthy advantage select) and as total care category which includes other plans along with or apart from Healthy advantage plan (Total care, valley advantage plus Rx, advantage Plus Rx, City of Houston, Select, and Optimacare and also the ones with missing values).

b) **Severity**

The variables Disease State, fourth root of CMS risk score, log of cumulative cost observed for the treatment received in the washout period, prior hospitalization (DRG code 291-293) and duration of CHF diagnosis (<=0.25 years, 0.25-1year or > 1 year) were included as a measure of severity of the disease in the regression models.(S. M. Bernheim et al., 2010; Susannah M. Bernheim et al., 2011; "National average costs by department for heart failure and shock," 2010; Navarro-López, de Teresa, López-Sendón, & Castro-Beiras, 1997; Newhouse, Mills, Johantgen, & Pronovost, 2003; Ross et al., 2008; Suh, Hay, Johnson, & Doctor, 2012) The cumulative costs were expressed in national average annual consumer price index for year 2012 with more weightage given to recent month owing to their higher impact probability compared to services rendered 6 months back. (Statistics, 2012) The CMS score has been recommended by CMS risk adjustment methods for Heart Failure and thus has been used in this study.(S. M. Bernheim et al., 2010; Susannah M. Bernheim et al., 2011)

c) **Comorbidities**

The CMS co-morbidities as observed in the washout period were controlled using diagnosis codes from Institutional and Professional files based on their discharge date. This controls for history of Diabetes, hypertension (HTN), Coronary artery disease, Atrial fibrillation/flutter, chronic obstructive pulmonary disorder, Myocardial Infarction, Renal disease, CBVD/Stroke, Previous CABG surgery, Previous PTCA, Anemia, Peripheral vascular disease, prior percutaneous coronary intervention, pacemaker. (Susannah M. Bernheim et al., 2011; Li, Kim, & Doshi, 2010)

d) **Serum Markers**

The MAPD data also provides some of the lab values in the Quest file. Based on the recommendation by ACC/AHA guidelines and the systematic review by Ross et al, Blood urea Nitrogen (BUN), Sodium (Na), B-type Natriuretic Peptide (BNP), and Hemoglobin (Hb) as serum markers were also controlled.(Hunt et al., 2009; Jessup et al., 2009; Ross et al., 2008) For all the lab values, last observation which was carried forward (LOCF) as the observed value from the washout period was captured.(Sugihara, 2010) Additionally, BUN values were obtained from a product of BUN/Creatinine ratio and creatinine value.(Calabró, Willerson, & Yeh, 2003) For missing values of Hb, the tenth part of the product of MCH and RBC was used. If still missing, a conversion factor of 0.34 was multiplied with Htc.(Carneiro, Drakeley, Owusu-Agyei, Mmbando, & Chandramohan, 2007) All these steps were taken because the lab values are not measured frequently as also suggested by Schneeweiss et al. And thus there were many observations for which no lab values were measured in the defined interval. So, in this analysis all the missing lab values were kept in the analysis under the category of 'Missing lab value', considering they could have some important information to understand compared to a normal lab value. Therefore, all the lab values were coded as normal values, abnormal value and missing value. The normal values

for all the markers were obtained based on clinical literature.(Calabró et al., 2003; Carneiro et al., 2007; Fonarow, 2008; Smith et al., 2010; Zairis et al., 2010)

e) **Baseline Comedications**

Diuretics (thiazide, loop, potassium-sparing and aldosterone-receptor blockers), Calcium-Channel Blockers, Vasodilators and other comedications (Digoxin, cardiovascular agents, anti-arrhythmic, alpha-adrenergic agonist, alpha-blockers, Antiplatelet, Cardiac Glycoside and hypoglycemic medications) were controlled as comedications.(Ross et al., 2008; R. Willenheimer et al., 2004) As explained previously, these comedications were categorized as 'Yes' and 'No' based on their PDC values in the washout period.

f) **Type of Physician**

The study also includes whether the patient visited a physician was associated with a local Physician Organization (LPO).(Wachter & Bell, 2012) Along with this, a visit to a physician paid for its quality i.e. P4Q flagged physician was also included in the analysis as 'Yes', 'No' variable to indicate whether or not the visit was made.

All the variables were defined based on observed values for these variables in the washout period upto the index date. The transformations for CMS risk score and cumulative cost were done to bring the data distribution close to normality based on Q-Q plots for each of these variables across each treatment groups along with their respective 95% confidence interval.(LaLonde, 2012; Zhang, Chen, & Rain, 2004) For log transformation a value of '1' was added to the cost of '0' so as to make reasonable transformations.(LaLonde, 2012) For age and log transformed cumulative cost no further transformations were done.

Outcome*:*   The probability of receiving either of the required drugs i.e. either ACEI or BBc1 or BBc3 or a combination of ACEI with BBc1 (ABC1) or with BBc3(ABC3) or a

therapy other than any of these therapies was the outcome for this study. Thus, it's a multinomial outcome.

Statistical Analysis

The predictors were identified with the use of descriptive analysis and multinomial logistic regression, which aims to define the probability for prescription of ACEI/BBc1/BBc3/Combination/Other therapies. All analyses were performed using Statistical Analysis Software (SAS) version 9.3 (SAS Institute Inc., Cary, NC, USA). The final multinomial Logistic model was developed to get the final result with glogit link in Proc logistic and with statistical significance established at p-value ≤ 0.05.

Sample Size requirement

- Bisoprolol (BBC1) before Enalapril (ACE) - Monotherapy and their combination:

In CIBIS-III trial, to demonstrate non-inferiority of bisoprolol-first vs enalapril-first, 450 patients for per-protocol analysis enrollment was justified for a 95% Confidence Interval which should lie below the Hazard ratio of 1.125.(R. Willenheimer et al., 2004) The assumption made was bisoprolol-first group will reduce the primary end-point rate by at least 15% i.e. to 34%. This gives a probability of at least 92% at the 2.5% significance level (one-sided, two-sample problem, binomial distribution). And with a 10% drop-out rate, 1000 patients will be required. Further, for proving superiority of Bisoprolol (i.e. BBc1) w.r.t enalapril, to show a reduction of 25% in the bisoprolol group, the power to reduce event rate from 40% to 30% is 90% at 5% (2-sided test) significance level. In this study, with 505 patients in each group, at the end of monotherapy phase (6 months) the observed Hazard ratio (HR) for the WHF or all-cause mortality was 1.12 (95%CI: 0.77-1.64, p-value = 0.54)(R. Willenheimer, 2009) Funck-Brentano et al suggested in a post-hoc analysis of the CIBIS-III trial that being on monotherapy of either bisoprolol or

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enalapril, with an HR of 39.7 (95%CI: 26.2-60.1, p-value <0.0001) was a statistically significant predictor of mortality and CV hospitalization as combined end-point compared to their combination therapy, with higher or lower doses.(Funck-Brentano et al., 2011)

- Carvedilol (BBC3) vs. Enalapril (ACE) vs. Combination: With 159 patients on enalapril, 154 on carvedilol and 151 on combination therapy, the HR for All-cause mortality and all-cause hospitalization was 0.8403 and 0.5875 for Carvedilol and Combination therapy with enalapril as the reference category. For Carvedilol vs. combination therapy, HR was 0.7322. For WHF related hospitalization, the event rate was 8%, 6% and 4% for the enalapril, carvedilol and the combination group respectively.(Komajda et al., 2004; Remme et al., 2004)

This means a sample of at least 500 patients per group is required and for combination group at least 160 patients are required. The table 1 shows the frequencies of each of the categories.

Results

There were 6430 HF patients in the defined cohort from amongst 10302 HF patients from MAPD data. Frequency distribution of all the therapies in this cohort is represented in Table 1. The table shows that therapies other than ACEI/BBc1/BBc3 are provided to most patients (44.23%) in the cohort followed by BBc1(23.62%). The combination therapies of BBc1 and BBc3 with ACEI, defined as ABC1 and ABC3, were prescribed to only 4.00% and 1.96% of the cohort population.

Table 2 suggests that lowest mean age was 75.746 ± 6.66 for patients getting ABC3 and highest mean age was 77.386 ± 7.592 for group of patients getting therapies other than ACEI/BBc1/BBc3. The difference was statistically significant for patients initiating BBc1 and other therapies compared to ACEI. On average patients had a mean CMS risk score in the range of 1.691-2.089, with highest CMS risk score being $2.089 \pm 1.333,(0.304-8.464)$ and lowest CMS risk score being 1.691 ± 1.234 for the patients getting other therapies. This risk score was statistically significantly different for patients initiating a combination of ACEI and BBc1 and for patients initiating other therapies compared to ACEI. A long duration of CHF diagnosis with an average of $1.491\pm1.097,(0-4.977)$ may qualify a patient for ACEI prescription. The combination of ABc3 is preferred for high Count of past hospitalization $(0.119\pm0.349,(0-2))$ and high Log of cumulative cost of expenditure $(9.355\pm0.788,(7.502-11.111))$ in the washout period, which are 2 measures of patients past severity upto the index date. These were followed by BBc3 with an average past hospitalization count of $0.114\pm0.433,(0-4)$ and an average log of cumulative cost was $(9.249\pm0.797, (5.978-11.524))$. This cumulative cost was statistically significantly different for BBc3, its combination with ACEI and for other therapies. The average log of past cumulative cost was also on average high for BBc1$(9.113\pm0.783,(6.004-12.021))$ compared to ACEI$(9.088\pm0.764, (6.282-$

11.737)). However average count of past hospitalization was lowest for patients initiating BBc1(0.028±0.172,(0-2)).

Table 3 suggests that on average, the cohort included more females (53.64%) compared to males (46.36%). Most patients belonged to Gulf Coast region (79.22%), had a form of healthy advantage plan (90.84%), had hypertension (57.947%), and visited a LPO flagged Physician organization (77.086%) with HF diagnosed for more than 0.25 years prior to the index date (68.383%). A very small percentage of the cohort population was diagnosed with normal lab values of BNP(1.633%), BUN(31.742%), LDL(22.675%), Hb(22.411%) and Na(49.114%). Not many of these patients were taking any comedications in the washout period including vasodilators (7.636%), calcium channel blockers (18.523%), Diuretics (32.613%) and other comedications (28.212%).

Table 4 represents the frequency distribution of all the covariates across different treatment groups. They seem to follow the above results. Thus, apart from other therapies most males and females initiated on BBc1 on the index date and had high frequency of hypertension across all the treatment groups. Majority of patients with worsened HF hospitalization in the past initiated on some therapy other than ACEI/BBC1/BBC3(38.1%). Amongst ACEI and BBs, highest percentage of patients was initiating monotherapy of BBc3(18.45%) and BBc1(17.16%) had a worsened heart failure hospitalization in the washout period. As already stated, in all the treatment groups, majority of the patients were with LPO flagged physician during the month the drug was initiated. Of these, apart from providing therapies other than ACEI/BB(43.03%), the preference for prescribing BBc1 seem to be very high(23.89%). Even amongst patients visiting P4Q providers, the preference for initiating on BBC1 seems to be high(26.36%) compared to ACEI(22.11%) or BBC3(9.26%). Within a year of HF diagnosis,

patients were initiating other therapies. However, as the duration of HF diagnosis increases more percentage of patients were being prescribed BBc1(30.26%).

Patients who took vasodilators or diuretics in the past washout period at any time point initiated on BBc1(34.01% and 29.03% respectively). If prescribed Calcium channel blockers(CCBs) in the washout, then highest percentage of patients(32.91%) initiated on Other therapies. With other co-medications, BBc3 was prescribed to 27.01% patients as the most preferable medication. Patients initiating on ACEI, BBc1, ABC1 and other medication, diuretics was the highest prescribed co-medication in the washout period. Although the highest user percentage of diuretics was of patient initiating ABC3(61.11%), but all of these patients also received some other co-medication apart from vasodilators, CCBs or diuretics. Like ABC3 group, all of BBc3 users also received these other co-medications i.e. 100% of them got these other co-medications along with a very high percentage of diuretics(46.74%).

Table 5 represents the predictors of initiating on each of the therapies.

1) <u>BBC1 vs. ACEI</u>

- **Monotherapy (BBC1)**

The odds for initiating BBc1 therapy as opposed to ACEI increases statistically significantly amongst patients with Pneumonia (OR: 1.321; 95% CI:1.028 - 1.698), Trauma in last year (OR: 0.74; 95% CI: 0.598 - 0.917), taking Vasodilators as co-medication in the washout period (OR:1.382, 95% CI: 1.055 - 1.811) and having a Missing BNP Value vs Normal value which is in range from 0-99ng/L (OR: 1.982, 95% CI: 1.089 - 3.607). It increases by a multiple of 1.018 (95% CI: 1.006 - 1.05) for each unit increase in age.

- **Combination of BBC1 with ACEI (ABC1)**

For patients with Mental Disorder and Acute Myocardial Infarction the odds of initiating ABC1 instead of ACEI increases by 1.533(1.022 - 2.3) and 1.798(1.103 - 2.928)times. It

also increases by 1.467(1.108 - 1.943) times for patients being prescribed Diuretics in the washout period but decreases by 0.619(0.411 - 0.931) times after a year of Heart Failure (HF) diagnosis compared to if HF was diagnosed 0-3 months prior to initiation of any of these therapies on the index date.

2) BBC3 vs. ACEI

- **Monotherapy (BBC3)**

The odds of initiating BBc3 therapy as opposed to ACEI while being a male or a patient with Chronic Atherosclerosis, taking Vasodilators or Diuretics (Yes vs No) or if hospitalized with worsened HF are 1.293(1.034 - 1.617), 1.69(1.231 - 2.321), 1.625(1.156 - 2.284), 1.293(1.037 - 1.613) and 2.196(1.342 - 3.593) respectively times higher compared to their reference category. These odds of initiating BBC3 compared to ACEI decreases by 0.719(0.546 - 0.946) times if the patient was taking Calcium Channel Blockers (CCB) compared to the one not taking them.

- **Combination of BBC3 with ACEI (ABC3)**

The odds of Gender (Male vs Female), chronic atherosclerosis, Rheumatic fever (Yes vs No), Log of cumulative cost, Diuretics (Yes vs No) and if patient was hospitalized with worsened heart failure increased statistically significantly for the patient initiating ABc3 therapy as opposed to ACEI as follows: 1.817(1.213 - 2.721), 1.944(1.088 - 3.473), 2.224(1.049 - 4.712), 1.554(1.118 - 2.158), 2.675(1.802 - 3.971) and 2.568(1.233 - 5.351) respectively. The odds of CCB (Yes vs No), initiating ABc3 therapy as opposed to ACEI decreases by 0.402(0.223 - 0.725) units.

3) Other Therapies vs. ACEI

The odds of having Pneumonia (Yes vs No), Metastatic Cancer (Yes vs No) or Cardiorespiratory Failure and shock , Disease State (Disabled/ESRD/Hospice/Institutional

vs Medi/Medi), Age, LDL (Abnormal vs Optimal: <100mg/dL), LDL (Missing Value vs Optimal: <100mg/dL) for patients initiating other therapy as opposed to ACEI are 1.426(1.121 - 1.814), 2.673 (95%CI: 1.7 - 4.202), 1.61(1.246 - 2.082), 2.342(1.336 - 4.104), 1.02(1.009 - 1.032), 1.56(1.214 - 2.006) and 1.616(1.276 - 2.046) respectively.

The odds of initiating Other Therapies compared to ACEI decreases if the patient was diagnosed with Anterior Myocardial infarction (Yes vs No) or had PTCA (Yes vs No) in the washout period by 0.686(0.485 - 0.971), 0.688(0.475 - 0.997) respectively. These odds further decrease by Duration of HF (0.25-1 yr. vs <=0.25 yrs.), Duration of HF (> 1 yrs. vs <=0.25 yrs.), taking Vasodilators (Yes vs No), CCB (Yes vs No) or Diuretics (Yes vs No), or if the patient's last visit was with a physician with a P4QFlag by 0.151(0.12 - 0.189), 0.1(0.08 - 0.125), 0.526(0.384 - 0.72), 0.582(0.481 - 0.705) and 0.484(0.411 - 0.57) respectively. There is also an observed decrease on odds of initiating Other Therapies by 0.772(0.678 - 0.878) units for per unit increase in Log of Cumulative cost and by 0.52(0.428 - 0.632) for patients visiting Physicians paid for quality or by 0.612(0.419 - 0.893) if belonging to SE Texas Region vs. others.

Discussion

Although the guidelines and RCTs prefer ACEI to be a preferred therapy for Stage A HF (mild HF or patients at risk of HF), but in this study a large proportion of patients was not getting this therapy. This indicates that the cohort in this study includes patients for other HF status as well. This highlights the importance of understanding the severity state of the patient before prescribing or adding a therapy. Interestingly, against guidelines recommendation of BBs as an add-on therapy, many patients were on BBs as monotherapy (31.24%) i.e. without ACEI. Past literature suggests that BBs are an underutilized therapy but its use is increasing.(Komajda et al., 2004; Richardson et al., 2010) This could possibly explain the observation of high percentage of patients on BBs as monotherapy. And as already stated RCTs find it difficult to prescribe BBs as monotherapy, this study is a good alternative to study the factors associated with an early initiation of these therapies. And thus, the results in this study can provide good directions for future studies.

Additionally, as can be observed in the results that age variation for this study across all the treatment groups is same as that existing in the community (75-77 years) which again is a challenge for a RCT but has been captured here. Hence, these results are a better representative of the community population. The results indicate that there was a statistically significant variation in baseline age for BBc1 compared to ACEI which also proved to be a significantly high risk factor for increasing odds of initiating BBC1. For BBc3 also the likelihood was towards non-significantly high. This could be possible evidence based prescription of ACEI as per past trials like SENIOR, which recommends BBs to be safe drugs for elderlies.(Flather et al., 2005)

Since the aim of this study is to find the predictors of initiating BBs compared to ACEI, the study has focused on the results for ACEI vs BBs as monotherapy or as combination only.

These results indicate that irrespective of the gender and region, majority of the patients were initiating BBC1 as monotherapy. A combination of ACEI and BBC3 was prescribed to lowest percentage of population in any region. Probably severe cases are getting BBC3 as monotherapy or as combination as a preferable drug. And such cases are selective cases with low frequency in any region. In CARMEN trial authors have argued that BBs are under-utilized therapy being only 8%-37% in hospital setting and especially may not be a preferable choice for mild CHF patients attributable to the fear of their side-effects unknown in this population. Many other observational studies like Richardson et al and Toh et al also reported under-utilization of BBs, however all these studies included the patients with severe HF.(Richardson et al., 2010; Toh et al., 2012) This demands to further explore this population for their possible clinical risk with BBs and side-effects especially among patients with mild HF.

Although CMS risk score of the month a therapy was initiated seemed similar across all groups, on average it was highest across BBC3 initiators, which may indicate that BBc3 are prescribed in severe cases compared to ACEI. Despite this possibility, it was not a statistically significant predictor for initiation of BBc3 or BBc1 compared to ACEI. Therefore, it can be concluded that although high but not much variation w.r.t CMS risk score was observed in this study. Here, a reverse causation tendency cannot be neglected, which means because these therapies were given a high CMS risk score was observed in the month these therapies were initiated. For this further exploration of the effect of these therapies on various clinical outcomes need to be established.

The study has included other severity measures like the past hospitalization and cumulative cost in the washout period which again were found to be higher for BBc3 and ABC3 compared to ACEI and thus they again indicate plausibility that at least BBc3 are prescribed

for severe cases. Even for patients initiating BBc1, of all past hospitalization 17.16% belonged to this group compared to 18.45% for BBc3. But unlike BBc3, the likelihood of initiating BBc1 with these past hospitalizations was non-significantly low compared to ACEI. Further for all these groups, the odds ratio decreases with increasing duration of HF diagnosis, which means the odds of prescribing ACEI increases as the duration of HF increases. These contradictory results amongst different measures of severity indicate a possible lack of understanding of severity measures w.r.t. BBs not only just from current clinical point of view but also from past health status and past economic status. This could be important for exact correlation of severity measures and therapy initiation.

CIBIS III trial found a correlation between LVEF and past non-cardiovascular hospitalization and concluded it might not be of clinical significance.(R. Willenheimer et al., 2005) The trial recommends that for mild to moderate CHF patients and for those with impaired LVEF, the rates for death and all-cause hospitalization as composite outcomes were similar for bisoprolol (BBc1) and enalapril. The CARMEN trial included patients with LVEF <40% and recommended carvedilol (BBc3) as a safe therapy to initiate compared to ACEI.(Komajda et al., 2004) Similarly, in a trial by Sliwa et al, the authors recommended that carvedilol(BBc3) leads to better improvement in LVEF and reduces NYHA functional class compared to ACEI.(Sliwa et al., 2004) Another trial, Beta PRESERVE is on-going to recommend metoprolol for HF patients with normal EF.(Zhou et al., 2010) All these trials, irrespective of EF i.e. severity level, together see potential in initiating BBs compared to ACEI. Similar to these trials our study found CMS risk score, a direct indicator of severity for claims data, to be high but non-significant predictor. However, past hospitalization was significant for BBc3 and ABC3, past cumulative cost for ABC3 and duration of HF for ABC1. These varied measures of severity were not explored in the previous trials.

As stated earlier, irrespective of gender, BBc1 was being initiated in majority of population. Contrary to this, being a male has a significant positive effect on increasing the odds of initiating BBC3 or its combination with ACEI; whereas it has a non-significant negative effect on initiation of BBC1 or its combination with ACEI. The CIBIS III and CARMEN trial also included majority of males, 68.22% and 80.66% respectively.(Komajda et al., 2004; R. Willenheimer et al., 2004) However, they did not explore if that could be the reason to see beneficial effects in their population. Similar to this SENIOR trial also included majority of males(females 37%) and found that for nebivolol(BBc1) vs placebo there was no significant effect of gender on composite outcome of all-cause mortality and cardiovascular hospitalization, thereby supporting our study.(Flather et al., 2005)

The study also demonstrates the effect of comorbidities on initiation of a therapy. The results indicate that the patients diagnosed with Pneumonia and Last year Trauma preferably initiate a BBC1 therapy, with Acute Myocardial Infarction and mental disorder they prefer to initiate on a combination of ACEI and BBC1, with chronic atherosclerosis initiate BBC3 and its combination ABC3. The latter is also initiated if the patient had Rheumatic fever in the washout period. In a study by Richardson et al, the author has suggested that although previously denied recent data support the use of BBs for COPD patients provided they are up titrated carefully and dose is lowered for any observed bronchoconstriction.(Richardson et al., 2010) Interestingly, our results also indicate that although likelihood is low for initiation of BBs but despite that COPD is not a significant predictor for prescription of ACEI or BBs.

Authors from OPTIMIZE-HF trial reported Pneumonia to be one of the crucial factors for precipitating HF hospitalization with Odds ratio 1.60 and they stated that it significantly increases length of stay and in-hospital mortality.(Fonarow et al., 2008) The study by virtue

of IMPACT-HF trial, COMET trial and also from the findings of their study reported that pre-discharge initiation of beta-blockers was associated with a higher rate of β-blocker use after hospital discharge and significantly lower risk of post-discharge mortality for decompensated HF, with no increase in hospital length of stay and risk of worsening of HF.(Fonarow et al., 2008) None of these trials associate the impact of individual therapy or class therapy effect with HF hospitalization due to Pneumonia. A recent study by Soto-Gomez et al recommends the need for more studies to establish the beneficial effect of cardio protective medications for patients hospitalized with Pneumonia.(Soto-Gomez, Anzueto, Waterer, Restrepo, & Mortensen, 2013) In this regard, our study could be one of the initial evidence to establish an association between HF patients hospitalized for Pneumonia and prescribing BBc1. For post-trauma, propranolol (BBc1) is an evidence-based therapy recommended by international consensus meeting of experts for revising 2005 psychopharmacology guidelines for British Association for Psychopharmacology.(Pasternack et al., 1982) Ample of literature exist that recommend prescription of ACEI and Beta-blockers together.(Fahey, Brindle, & Ebrahim, 2005; Gupta & Aparasu, 2013; Sleight, Pouleur, & Zannad, 2006; Wald & Wald, 2010; Wise, 2005) Evidence also exists to support the use of BBc1 drugs like propranolol and timolol and bbc3 drug carvedilol for Post-MI treatment.(Gheorghiade & Goldstein, 2002) The study although did not provided a direct head-to-head comparison of the effect of type of BB on clinical outcomes, but it pooled the findings from BHAT, NORWEGIAN and CAPRICORN trial for respective drugs and reported less percentage incidence rate of all-cause mortality, sudden death and composite outcome of mortality and reinfarction for propranolol compared to carvedilol and timolol. Only Non-fatal reinfarction rate were lower for carvedilol. This could be the reason for favorable effect of ACEI with BBc1 as reported in our study. It is reported

that for mental patients the therapies for other comorbidities including cardiovascular therapies are generally underutilized.(Mitchell, Lord, & Malone, 2012) In our cohort only 19.4% had mental disorders of which 53.06% were getting either ACEI or BBs. This appears to be pretty high percentage compared to past literature which demands quality care even amongst patients with mental disorder. For atherosclerosis, HF guidelines do not state anything about treatment with BBs but recommend only for ACEI for such patients.(Yancy et al., 2013) However, an article by Fonarow et al recommends carvedilol for the atherosclerosis.(Fonarow, 2009) And in another trial by Drexel et al, the study found that bisoprolol appears to decrease the lipid mediated risk of developing or accelerating chronic atherosclerosis.(Drexel, Schmid, Follath, & Amann, 2001) Based on a brief review of past literature, a direct comparison between bisoprolol and carvedilol is not available. If that is the case, then our results again provide research direction for future research, which recommends not only a significant association between BBc3 and chronic atherosclerosis w.r.t. ACEI as monotherapy and as combination with ACEI but it also provides a non-significant association between BBc1 and chronic atherosclerosis w.r.t. ACEI thereby establishing BBC3 to be superior to BBc1 and ACEI both. For Rheumatic Fever, in a study by Shu et al, the authors attributed positive effects of bisoprolol(BBc1) to non-vasodilatory effect of the drug compared to BBc3 which has vasodilatory effect to worsen lower cardiac output.(Shu et al., 2005) Our study showed a higher non-significant odds ratio for initiation of BBc1 compared to BBc3 with ACEI as the reference drug, thus supporting the argument made by Shu et. al.(Shu et al., 2005) However, at the same time with the addition of ACEI, results reverse and thus it leads to significantly higher initiation odds ratio for BBc3 and ACEI w.r.t. ACEI.

A large portion of lab values was missing even after carrying forward the last observation (LOCF), as also suggested by Schneeweiss et al.(Schneeweiss et al., 2012) These missing values could have some reason for being missing, primarily if the physician had no reason to believe that some lab value may be high then treatment will proceed with the assumption of a normal lab value. However, logistic regression indicates that the missing values had a significant impact on prescription of these treatments. This recommends keeping a close watch on patient lab values. Deleting this information would have led to omitted variable error and this would have also tampered with the sample size of the data and hence the results would have been biased. Although, now we just are able to provide the information that missing lab values had a significant impact on prescription of these therapies but this information suggests capturing it in future as it could be an important group. Information about BNP is an important factor in increasing the odds of initiating BBc1. An elevated BNP or a missing value of BNP had a significant increasing effect on initiation of BBc1 and a non-significant high effect on odds of other BBs. This means BNP information should be captured as frequently as possible to decide if BBs are required.

While interpreting these results it is to be kept in mind that although the study has suggested that patients were initiating on certain therapy on the index date, but it is possible that patients might have been taking certain therapies other than ACEI or BBs before and also on the index date. These therapies have been defined as comedications that patient might be taking apart from the therapy initiated by him/her on the index date. The results indicate that prescribing Vasodilators and Diuretics increase the odds of prescription of BBC1 or BBC3, while CCBs tend to decrease this odds ratio. As per ACC/AHA guidelines, Diuretics and Vasodilators (Hydralazine and Nitrates) are recommended for Stage C i.e. for mild to severe HF patients.(Shafazand et al., 2010) This implies that in real world all severe patients are

being preferred BBc1 or BBc3 compared to ACEI. If this is true and also since other predictors of severity showed similar trend then an important research question that should be explored in future is that if initiating BBs in mild to moderate HF patients could be beneficial in any sense compared to ACEI. In other words, there is a need to understand if an early initiation on BBs is beneficial compared to ACEI. This is exactly what trials like Beta-PRESERVE are trying to establish and is being discussed by many authors and has been mentioned previously in this study.

An interesting observation is that although most of the physicians visited were local physician, majority of them were not P4Q flagged. This may be probably because, still there is a lot of debate on-going regarding whether or not physicians should be paid for quality as a measure of their performance. As per an article by Esse et al, various quality compensation programs although appear promising, they are yet to yield encouraging results and thus continue to hold debatable status in current scenario.(Esse et al., 2013) Both P4Q flagged physician or a LPO flagged physician (discarded during the optimization process) seems to have a non-significant effect on initiation of any of the BBs compared to ACEI. This means the initiation of any of the BBs compared to ACEI does not significantly vary across type of physician.

Limitation

1. The study is a claims database study and thus all the issues like under coding and upper coding of disease are inherent to this study.

2. The study has used Prevalent HF patients, which could be at different stages of their disease. Although, by a washout period of 6 months, only the incident drug users were included, but again the study does not discriminate if ACEI vs BB vs combination was used as first line or 2nd line or 3rd line therapy. As already stated, these patients

may not be taking these required drugs in the washout period but they may be taking some drugs defined as 'comedications' in this study. However, this study tries to control the effect of these comedications by including them as possible determinant of whether or not a patient might initiate either of the required drugs on the index date.

3. There is no direct measure of severity of HF. If ignored this could lead to differential misclassification of exposure depending on the outcome. To compensate this, the study has used several other measures like count measures, CMS risk score etc. which may contribute in explaining some portion of severity. Added advantage of using these multiple measures is that severity is explored through different viewpoints including economic factors from past treatment cost and not just from clinical aspect. This could help to provide interesting insight into severity. Further, the systematic review by Ross et al., recommends including other important predictors like age and lab measures, which have been included in this study and which has strengthened the study.(Ross et al., 2008)

4. The study has an inherent selection bias due to lack of randomly assigned treatment groups. This is accountable to the use of claims data. To confirm the findings the research question can be tested on different databases.

5. Not all ACEI/ BBs are included in the MAPD data formulary. Only JNC standardized drugs have been identified from this data. New drugs are being explored each day, whose effect needs to be tested. However, a generic based definition of all the drugs as defined in standard guidelines makes it a good approach to identify the predictors of guideline recommended therapies.

6. The estimates from this study are not national level estimates. And additionally, as stated already the results are from the claims for a 1 year follow-up period. Thus, these results should be interpreted with caution.

7. The study could not test the BBc2 category of the drug owing to their low sample size. Thus, future studies should focus on this group.

8. There could be some missing variables like race which are not available in the data. However, considering many individual level characteristics have been captured in the analysis, the information related to these missing variables must have been captured. For example, Anderson recommends that race captures socio-economic status and genetic predisposition. This study captures socio-economic status by virtue of past cumulative cost and genetic predisposition by controlling all possible associated comorbidities and lab values. Despite that future studies should try to capture this information.

Strength

1. It provides information for ACEI/BB as monotherapy and as combination both and not just of monotherapy. It also includes a category of other therapies which is a group where these required drugs are not being prescribed but any other drug may or may not be prescribed. Thus, a multiple control ensures to eliminate any possible hidden bias.

2. The sample frame includes patients with average age 70-75 years as existing in the community. Thus, the result of this study tries to explore the real world information and is not a controlled experiment of RCT which could have a biased population.

3. The operational definition for drugs, required/not required/comedications in this study are not simply based on prescription date of a drug which could lead to

misclassification error of falsely classifying a patient as not taking a drug when infact he/she might have been prescribed the drug on some previous day to cover current day being observed. This study uses the information of days' supply along with date of prescription to find the day level information of whether or not patient was prescribed a claim on that or on some day prior to the day being observed. This provides us much stronger and clearer operational definition of exposure in contrast to what is usually observed in other retrospective claims based studies.

4. A further restrictive criteria of PDC $<= 0.04$ was used to exclude or include any patient from the washout period. This again tends to decrease a misclassification error.

5. Use of Lab values including the observations with missing values minimizes confounding by indication.

6. The study provides results across different BB classes. This is essential to know because clinicians often tend to replace 1 drug with other of same class to achieve therapeutic equivalent effect.

7. The study provides evidence for all types of HF patients and not just those with Left-ventricular EF (LVEF) <35% as chosen in CIBIS III trial.(R. Willenheimer et al., 2004) As already stated, beta-PRESERVE trial is trying to target effect of using BBs in HFNEF patients too, our study provide some evidence with regard to those population and may support the need for the trial for all types of population for HF and thereafter, modification in guidelines.(Zhou et al., 2010)

8. One of the important features of this study is that although the model controls for CMS risk score but additionally comorbidities as specified by CMS for HF patients from claims data have been controlled in this study.(S. M. Bernheim et al., 2010;

Susannah M. Bernheim et al., 2011) This helps to differentiate the probable reason for

high CMS risk score instead of simply presenting the score.

Conclusion

The results indicate that many patients were getting BBs as monotherapy especially BBc1. Being male is a significant predictor for initiating BBc3 and a high age is an important predictor for initiating BBC1. Different past severity measures seem to be high among patients initiating BBs indicating a possible association of BBs with severity. Therefore, future studies need to explore the effect of an early initiation of BBs amongst HF patients. Finally, there is a need to regularly monitor the lab values especially BNP and also the history of comorbidities like Pneumonia, Trauma, mental disorders, acute myocardial infarction, chronic atherosclerosis and Rheumatic fever for these HF patients to decide whether or not to initiate on BBs and which class compared to ACEI.

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Figure 1. Study design to explain inclusion/exclusion criteria of the cohort of elderly Heart Failure patients.
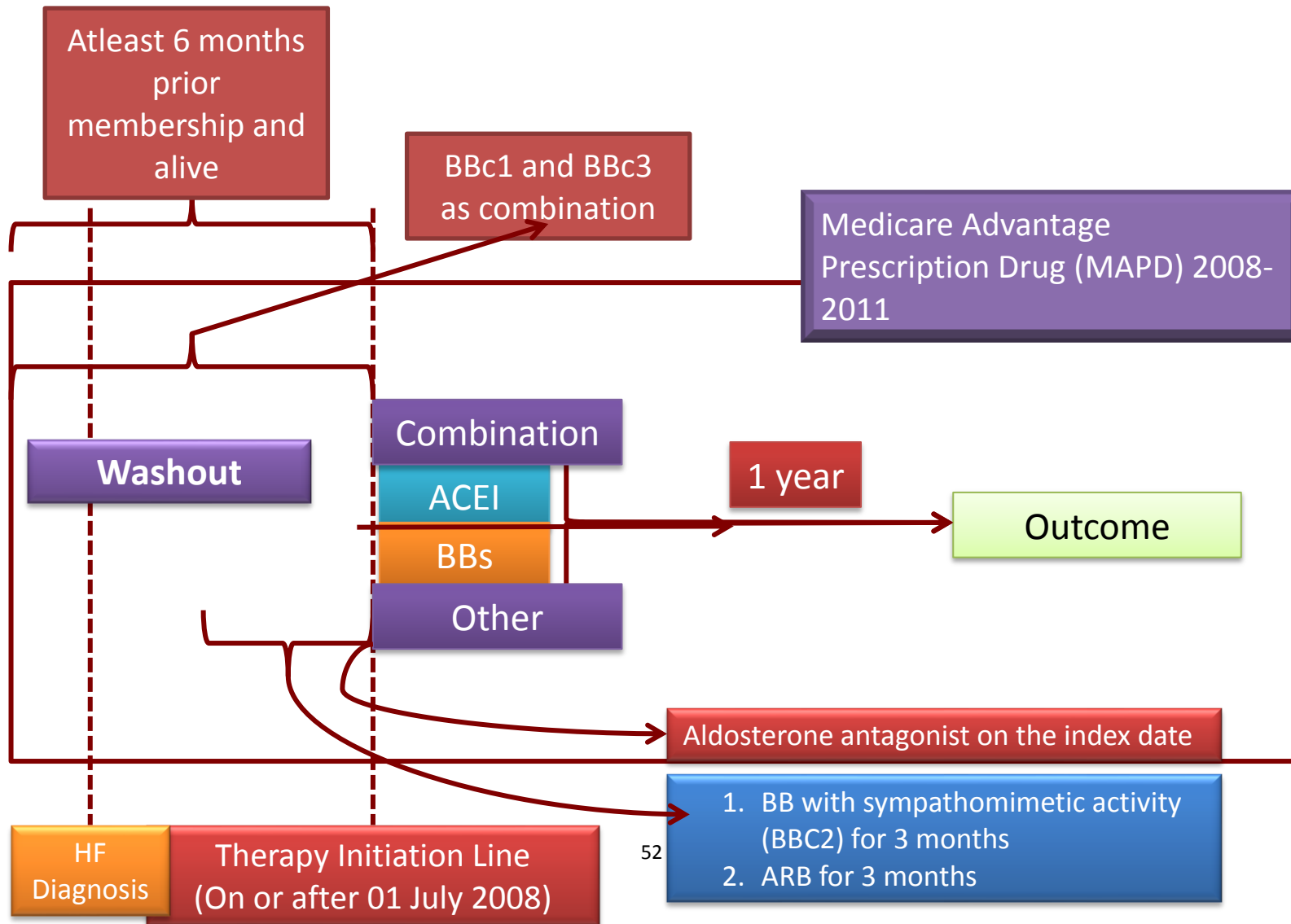
Figure 2. Flowchart to represent population included and excluded in the cohort

Define a Date=Next nearest claim to Dmax Dmax=Max (First Dos,dm-6m, 01/Jul/2008, 6 month prior washout n=672 Patients

Death month ≤ index date n=189 Patients

Patients taking ARB or BB-C2 in 3 months prior to the index date n=205 Patients

Patients after 05 Jan 2011 to prior date at least 1 year (=360 days) follow up n=2017 Patients

Patients taking aldosterone antagonist on the index date, n=65 Patients

Age < 65 years n=719 Patients

HF patients from MAPD (n=10302)

n=9630 Patients

n= 9441 Patients

n=9236 patients

n=7219 patients

n=7149 patients

n=6430 patients cohort

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Table 1. Frequency Distribution of the treatment groups being compared			
trt_1	Frequency	Percent Cohort	Percent of overall HF Patient population
ACEI	1194	18.57	11.59
bbc1 - BBs	1519	23.62	14.74
BBc3: Combined alpha and BBs	490	7.62	4.76
Combined ACEI and BBc1 (ABC1)	257	4.00	2.49
Combined ACEI and BBc3 (ABC3)	126	1.96	1.22
Other Therapies	2844	44.23	27.61

SNo	Label	ACEI	BBc1	BBc3	ABC1	ABC3	Others
	Table 2. Mean Descriptive analysis for continuous variables, Mean±SD(Minimum-Maximum Range)						
1	**Age**	76.473±6.972, (65-99)	77.33±6.956, (65-100)	76.849±6.758, (65-99)	75.872±7.066, (65-94)	75.746±6.66, (65-91)	77.386±7.592, (65-102)
2	**CMSRiskScore**	1.978±1.227, (0.277-9.804)	1.976±1.266, (0.277-9.743)	2.089±1.333, (0.304-8.464)	1.806±1.151, (0.287-5.407)	1.938±1.189, (0.277-5.429)	1.691±1.234, (0.277-9.991)
3	**Count of hospitalization**	0.039±0.228, (0-3)	0.028±0.172, (0-2)	0.114±0.433, (0-4)	0.035±0.184, (0-1)	0.119±0.349, (0-2)	0.034±0.209, (0-5)
4	**Log of cumulative cost in washout pd.**	9.088±0.764, (6.282-11.737)	9.113±0.783, (6.004-12.021)	9.249±0.797, (5.978-11.524)	9.074±0.733, (7.485-11.223)	9.355±0.788, (7.502-11.111)	9.043±1.092, (0-12.392)

Table 3. Population Characteristics of Cohort on the index Date

#	Table	Characteristics	Freq(Row%)
1	Gender	Female	3448,(53.64)
1	Gender	Male	2980,(46.36)
2	Region	Others	409(6.361)
2	Region	Gulf Coast	5094,(79.222)
2	Region	SE Texas	927,(14.417)
3	Plan type	Healthy Advantage	5841,(90.84)
3	Plan type	Total Care/Others	589,(9.16)
4	Comorbidities	No Hypertension	2704,(42.053)
4	Comorbidities	Hypertension	3726,(57.947)
5	Comorbidities	No Stroke	5038,(78.351)
5	Comorbidities	Stroke	1392,(21.649)
6	Comorbidities	No CBVD	6315,(98.212)
6	Comorbidities	CBVD	115,(1.788)
7	Comorbidities	No Renal Failure	4615,(71.773)
7	Comorbidities	Renal Failure	1815,(28.227)
8	Comorbidities	No COPD	4474,(69.58)
8	Comorbidities	COPD	1956,(30.42)
9	Comorbidities	No Pneumonia	5127,(79.736)
9	Comorbidities	Pneumonia	1303,(20.264)
10	Comorbidities	No Diabetes	4390,(68.274)
10	Comorbidities	Diabetes	2040,(31.726)
11	Comorbidities	No Protein calorie malnutrition	6025,(93.701)
11	Comorbidities	Protein calorie malnutrition	405,(6.299)
12	Comorbidities	No Dementia	5770,(89.736)
12	Comorbidities	Dementia	660,(10.264)
13	Comorbidities	No Hemiplegia & Paralysis	5495,(85.459)
13	Comorbidities	Hemiplegia & Paralysis	935,(14.541)
14	Comorbidities	No Peripheral Vascular Disease	5145,(80.016)
14	Comorbidities	Peripheral Vascular Disease	1285,(19.984)
15	Comorbidities	No Metastatic Cancer	6170,(95.956)
15	Comorbidities	Metastatic Cancer	260,(4.044)
16	Comorbidities	No Trauma in last year	4666,(72.566)
16	Comorbidities	Trauma in last year	1764,(27.434)
17	Comorbidities	No Mental disorder	5154,(80.156)
17	Comorbidities	Mental disorder	1276,(19.844)
18	Comorbidities	No Liver Disease	6136,(95.428)
18	Comorbidities	Liver Disease	294,(4.572)
19	Comorbidities	No CABG	6335,(98.523)
19	Comorbidities	CABG	95,(1.477)
20	Comorbidities	No PTCA	5982,(93.033)
20	Comorbidities	PTCA	448,(6.967)
21	Comorbidities	No unstable angina	6123,(95.226)
21	Comorbidities	Unstable Angina	307,(4.774)
22	Comorbidities	No anterior MI	6066,(94.339)
22	Comorbidities	Anterior MI	364,(5.661)
23	Comorbidities	No other MI	4299,(66.858)
23	Comorbidities	Other MI	2131,(33.142)
24	Comorbidities	No ACUTE MI	5817,(90.467)
24	Comorbidities	ACUTE MI	613,(9.533)
25	Comorbidities	No chronic atherosclerosis	3991,(62.068)
25	Comorbidities	Chronic Atherosclerosis	2439,(37.932)
26	Comorbidities	No cardiorespiratory disorder	5328,(82.862)
26	Comorbidities	Cardiorespiratory Disorder	1102,(17.138)
27	Comorbidities	No Rheumatic Fever	6188,(96.236)

		Characteristics	Freq(Row%)			Characteristics	Freq(Row%)
		Rheumatic fever	242,(3.764)	38	P4QFlag	No	5225,(81.336)
28		No Coronary Artery Disease	5768,(89.705)			Yes	1199,(18.664)
		Coronary artery Disease	662,(10.295)	39	Duration of HF	<=0.25 yrs	2033,(31.617)
29		No Atrial fibrillation & flutter	5051,(78.554)			0.25-1 yr	1634,(25.412)
		Atrial fibrillation & flutter	1379,(21.446)			> 1 yrs	2763,(42.97)
30	Whf_hos	No prior HF hos	6197,(96.376)	40		No	5939,(92.364)
		Worsened HF hos	233,(3.624)		Vasodilators	Yes	491,(7.636)
31	Disease State	Medicare/Medicaid Advantage	733,(11.4)	41	Calcium Channel Blockers	No	5239,(81.477)
		Disabled/ESRD/Hospice/Institution	191,(2.97)			Yes	1191,(18.523)
		Other/Working Age	5506,(85.63)	42		No	4333,(67.387)
32	BNP	Normal: 0-99ng/L	105,(1.633)		Diuretics	Yes	2097,(32.613)
		Elevated If, >99ng/L	153,(2.379)	43	Other Comedications	No	4616,(71.788)
		Missing Value	6172,(95.988)			Yes	1814,(28.212)
33	BUN	Normal: 8-23mg/dL	2041,(31.742)				
		Abnormal	1370,(21.306)				
		Missing Value	3019,(46.952)				
34	LDL	Optimal: <100mg/dL	1458,(22.675)				
		Abnormal	941,(14.635)				
		Missing Value	4031,(62.691)				
35	Hb*	Normal*	1441,(22.411)				
		Abnormal	1301,(20.233)				
		Missing Value	3688,(57.356)				
36	Na	Normal: 135-145mmol/L	3158,(49.114)				
		Abnormal	229,(3.561)				
		Missing Value	3043,(47.325)				
37	LPO Flag	No	1472,(22.914)				
		Yes	4952,(77.086)				

*Hb: Normal: : 13.5-17.5g/dL for males and 12.0-15.5g/dL for

female

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	Table	Characteristics	ACE Inhibitor Freq(Row%)	BBC1 Freq(Row%)	BBc3 Freq(Row%)	ABC1 Freq(Row%)	ABC3 Freq(Row%)	Other Therapies Freq(Row%)
**Table 4. Frequency distribution of Population characteristics across different treatment groups as initiated on the index Date.**
1	Gender	Female	647,(54.188)	867,(57.077)	227,(46.327)	140,(54.475)	45,(35.714)	1523,(53.495)
		Male	547,(45.812)	652,(42.923)	263,(53.673)	117,(45.525)	81,(64.286)	1324,(46.505)
2	Region	Others	62, 5.193)	86,(5.662)	22,(4.49)	8,(3.113)	7,(5.556)	226,(7.933)
		Gulf Coast	953,(79.816)	1223,(80.513)	394,(80.408)	206,(80.156)	96,(76.19)	2224,(78.062)
		SE Texas	179,(14.992)	210,(13.825)	74,(15.102)	43,(16.732)	23,(18.254)	399,(14.005)
3	Plan type	Healthy Advantage	1072,(89.782)	1368,(90.059)	445,(90.816)	233,(90.661)	116,(92.063)	2612,(91.681)
		Total Care/Others	122,(10.218)	151,(9.941)	45,(9.184)	24,(9.339)	10,(7.937)	237,(8.319)
4		No Hypertension	529,(44.305)	639,(42.067)	174,(35.51)	111,(43.191)	46,(36.508)	1215,(42.647)
		Hypertension	665,(55.695)	880,(57.933)	316,(64.49)	146,(56.809)	80,(63.492)	1634,(57.353)
5		No Stroke	957,(80.151)	1216,(80.053)	375,(76.531)	207,(80.545)	94,(74.603)	2195,(77.045)
		Stroke	237, (19.849)	303,(19.947)	115,(23.469)	50,(19.455)	32,(25.397)	654,(22.955)
6		No CBVD	1173,(98.241)	1497,(98.552)	484,(98.776)	253,(98.444)	124,(98.413)	2789,(97.894)
		CBVD	21,(1.759)	22,(1.448)	6,(1.224)	4,(1.556)	2,(1.587)	60,(2.106)
7	Comorbidities	No Renal Failure	854,(71.524)	1091,(71.824)	306,(62.449)	184,(71.595)	84,(66.667)	2103,(73.815)
		Renal Failure	340,(28.476)	428,(28.176)	184,(37.551)	73,(28.405)	42,(33.333)	746,(26.185)
8		No COPD	850,(71.189)	1079,(71.034)	337,(68.776)	184,(71.595)	83,(65.873)	1950,(68.445)
		COPD	344,(28.811)	440,(28.966)	153,(31.224)	73,(28.405)	43,(34.127)	899,(31.555)
9		No Pneumonia	1009,(84.506)	1236,(81.369)	392,(80)	227,(88.327)	99,(78.571)	2174,(76.307)
		Pneumonia	185,(15.494)	283,(18.631)	98,(20)	30,(11.673)	27,(21.429)	675,(23.693)
10		No Diabetes	796,(66.667)	1039,(68.4)	309,(63.061)	166,(64.591)	80,(63.492)	2008,(70.481)
		Diabetes	398,(33.333)	480,(31.6)	181,(36.939)	91,(35.409)	46,(36.508)	841,(29.519)
11		No Protein calorie mal.	1141,(95.561)	1451,(95.523)	467,(95.306)	249,(96.887)	119,(94.444)	2604,(91.4)
		Protein calorie mal.	53,(4.439)	68,(4.477)	23,(4.694)	8,(3.113)	7,(5.556)	245,(8.6)
12		No Dementia	1092,(91.457)	1396,(91.903)	438,(89.388)	241,(93.774)	112,(88.889)	2499,(87.715)
		Dementia	102,(8.543)	123,(8.097)	52,(10.612)	16,(6.226)	14,(11.111)	350,(12.285)

		Characteristics	ACE Inhibitor	BBC1	BBc3	ABC1	ABC3	Other Therapies
13			Freq(Row%)	Freq(Row%)	Freq(Row%)	Freq(Row%)	Freq(Row%)	Freq(Row%)
14		No Peripheral Vasc. Dis.	955,(79.983)	1208,(79.526)	372,(75.918)	206,(80.156)	98,(77.778)	2315,(81.257)
		Peripheral Vasc. Dis.	239,(20.017)	311,(20.474)	118,(24.082)	51,(19.844)	28,(22.222)	534,(18.743)
15		No Metastatic Cancer	1168,(97.822)	1473,(96.972)	479,(97.755)	254,(98.833)	124,(98.413)	2677,(93.963)
		Metastatic Cancer	26,(2.178)	46,(3.028)	11,(2.245)	3,(1.167)	2,(1.587)	172,(6.037)
16		No Trauma in last year	878,(73.534)	1156,(76.103)	359,(73.265)	190,(73.93)	92,(73.016)	1999,(70.165)
		Trauma in last year	316,(26.466)	363,(23.897)	131,(26.735)	67,(26.07)	34,(26.984)	850,(29.835)
17		No Mental disorder	981,(82.161)	1234,(81.238)	394,(80.408)	198,(77.043)	103,(81.746)	2251,(79.01)
		Mental disorder	213,(17.839)	285,(18.762)	96,(19.592)	59,(22.957)	23,(18.254)	598,(20.99)
18		No Liver Disease	1148,(96.147)	1442,(94.931)	473,(96.531)	248,(96.498)	123,(97.619)	2708,(95.051)
		Liver Disease	46,(3.853)	77,(5.069)	17,(3.469)	9,(3.502)	3,(2.381)	141,(4.949)
19		No CABG	1180,(98.827)	1494,(98.354)	480,(97.959)	252,(98.054)	122,(96.825)	2812,(98.701)
		CABG	14,(1.173)	25,(1.646)	10,(2.041)	5,(1.946)	4,(3.175)	37,(1.299)
20	Comorbidities	No PTCA	1108,(92.797)	1410,(92.824)	445,(90.816)	225, 87.549)	104,(82.54)	2696,(94.63)
		PTCA	86,(7.203)	109,(7.176)	45,(9.184)	32,(12.451)	22,(17.46)	153,(5.37)
21		No unstable angina	1133,(94.891)	1440,(94.799)	464,(94.694)	234,(91.051)	117,(92.857)	2742,(96.244)
		Unstable Angina	61,(5.109)	79,(5.201)	26,(5.306)	23,(8.949)	9,(7.143)	107,(3.756)
22		No anterior MI	1112,(93.132)	1425,(93.812)	455,(92.857)	240,(93.385)	109,(86.508)	2731,(95.858)
		Anterior MI	82,(6.868)	94,(6.188)	35,(7.143)	17,(6.615)	17,(13.492)	118,(4.142)
23		No other MI	848,(71.022)	1003,(66.03)	314,(64.082)	169,(65.759)	73,(57.937)	1902,(66.76)
		Other MI	346,(28.978)	516,(33.97)	176,(35.918)	88,(34.241)	53,(42.063)	947,(33.24)
24		No ACUTE MI	1089,(91.206)	1388,(91.376)	429,(87.551)	219,(85.214)	103,(81.746)	2596,(91.12)
		ACUTE MI	105,(8.794)	131,(8.624)	61,(12.449)	38,(14.786)	23,(18.254)	253,(8.88)
25		No chronic atherosclerosis	758,(63.484)	934,(61.488)	241,(49.184)	154,(59.922)	56,(44.444)	1860,(65.286)
		Chronic Atherosclerosis	436,(36.516)	585,(38.512)	249,(50.816)	103,(40.078)	70,(55.556)	989,(34.714)
26		No Cardiorespiratory disorder	1036,(86.767)	1312,(86.373)	404,(82.449)	221,(85.992)	103,(81.746)	2260,(79.326)

		Characteristics	ACE Inhibitor	BBC1	BBc3	ABC1	ABC3	Other Therapies
			Freq(Row%)	Freq(Row%)	Freq(Row%)	Freq(Row%)	Freq(Row%)	Freq(Row%)
		Cardiorespiratory Disorder	158,(13.233)	207,(13.627)	86,(17.551)	36,(14.008)	23,(18.254)	589,(20.674)
27		No Rheumatic Fever	1156,(96.817)	1454,(95.721)	467,(95.306)	244,(94.942)	113,(89.683)	2760,(96.876)
		Rheumatic fever	38,(3.183)	65,(4.279)	23,(4.694)	13,(5.058)	13,(10.317)	89,(3.124)
28		No Coronary Artery Disease	1068,(89.447)	1350,(88.874)	432,(88.163)	218,(84.825)	108,(85.714)	2599,(91.225)
		Coronary artery Disease	126,(10.553)	169,(11.126)	58,(11.837)	39,(15.175)	18,(14.286)	250,(8.775)
29		No Atrial fibrillation & flutter	974,(81.575)	1162,(76.498)	367,(74.898)	202,(78.599)	92,(73.016)	2265,(79.502)
		Atrial fibrillation & flutter	220,(18.425)	357,(23.502)	123,(25.102)	55,(21.401)	34,(26.984)	584,(20.498)
30	Whf hos	No prior HF hospitalization	1156,(96.817)	1479,(97.367)	448,(91.429)	248,(96.498)	112,(88.889)	2760,(96.876)
		Worsened HF hospitalization	38,(3.183)	40,(2.633)	42,(8.571)	9,(3.502)	14,(11.111)	89,(3.124)
31	DS	Medicare/Medicaid Ad.	152,(12.73)	177,(11.652)	54,(11.02)	26,(10.117)	11,(8.73)	313,(10.986)
		Disabled/ESRD/Hospice/Instit.	29,(2.429)	40,(2.633)	14,(2.857)	5,(1.946)	3,(2.381)	101,(3.545)
		Other/Working Age	1013,(84.841)	1302,(85.714)	422,(86.122)	226,(87.938)	112,(88.889)	2435,(85.469)
32	BNP	Normal: 0-99ng/L	30,(2.513)	18,(1.185)	10,(2.041)	2,(0.778)	2,(1.587)	43,(1.509)
		Elevated If, >99ng/L	29,(2.429)	36,(2.37)	29,(5.918)	7,(2.724)	6,(4.762)	46,(1.615)
		Missing Value	1135,(95.05)	1465,(96.445)	451,(92.041)	248,(96.498)	118,(93.65)	2760,(96.876)
33	BUN	Normal: 8-23mg/dL	420,(35.176)	483,(31.797)	163,(33.265)	79,(30.739)	36,(28.571)	857,(30.081)
		Abnormal	282,(23.618)	365,(24.029)	148,(30.204)	60,(23.346)	34,(26.984)	481,(16.883)
		Missing Value	492,(41.206)	671,(44.174)	179,(36.531)	118,(45.914)	56,(44.444)	1511,(53.036)
34	LDL	Optimal: <100mg/dL	341,(28.559)	380,(25.016)	151,(30.816)	68,(26.459)	36,(28.571)	480,(16.848)
		Abnormal	169,(14.154)	237,(15.602)	72,(14.694)	38,(14.786)	19,(15.079)	407,(14.286)
		Missing Value	684,(57.286)	902,(59.381)	267,(54.49)	151,(58.755)	71,(56.349)	1962,(68.866)

35		Characteristics	ACE Inhibitor	BBC1	BBc3	ABC1	ABC3	Other Therapies
			Freq(Row%)	Freq(Row%)	Freq(Row%)	Freq(Row%)	Freq(Row%)	Freq(Row%)
	Hb	Normal*	294,(24.623)	377,(24.819)	106,(21.633)	63,(24.514)	22,(17.46)	577,(20.253)
		Abnormal	268,(22.446)	309,(20.342)	145,(29.592)	48,(18.677)	33,(26.19)	498,(17.48)
		Missing Value	632,(52.931)	833,(54.839)	239,(48.776)	146,(56.809)	71,(56.349)	1774,(62.267)
36	Na	Normal: 135-145mmol/L	660,(55.276)	793,(52.205)	290,(59.184)	133,(51.751)	66,(52.381)	1213,(42.576)
		Abnormal	40,(3.35)	47,(3.094)	21,(4.286)	6,(2.335)	3,(2.381)	112,(3.931)
		Missing Value	494,(41.374)	679,(44.7)	179,(36.531)	118,(45.914)	57,(45.238)	1524,(53.492)
37	LPO	No	252,(21.106)	336,(22.12)	93,(18.98)	60,(23.346)	24,(19.048)	711,(25.009)
		Yes	942,(78.894)	1183,(77.88)	397,(81.02)	197,(76.654)	102,(80.95)	2132,(74.991)
38	P4QFlag	No	929,(77.806)	1203,(79.197)	379,(77.347)	212,(82.49)	96,(76.19)	2410,(84.77)
		Yes	265,(22.194)	316,(20.803)	111,(22.653)	45,(17.51)	30,(23.81)	433,(15.23)
39	Duration of HF	Duration of HF ≤0.25 yrs	162,(13.568)	222,(14.615)	76,(15.51)	52,(20.233)	26,(20.635)	1495,(52.56)
		Duration of HF 0.25-1 yr	342,(8.643)	461,(30.349)	155,(31.633)	77,(29.961)	33,(26.19)	566,(19.902)
		Duration of HF > 1 yrs	690,(57.789)	836,(55.036)	259,(52.857)	128,(49.805)	67,(53.175)	783,(27.532)
40	Vasodila tors	No	1093,(91.54)	1352,(89.006)	418,(85.306)	225,(87.549)	106,(84.12)	2745,(96.519)
		Yes	101,(8.459)	167,(10.994)	72,(14.694)	32,(12.451)	20,(15.873)	99,(3.481)
41	Ca Channel Blockers	No	916,(76.717)	1161,(76.432)	400,(81.633)	198,(77.043)	112,(88.88)	2452,(86.217)
		Yes	278,(23.283)	358,(23.568)	90,(18.367)	59,(22.957)	14,(11.111)	392,(13.783)
42	Diuretic s	No	719,(60.218)	906,(59.645)	261,(53.265)	132,(51.362)	49,(38.889)	2266,(79.677)
		Yes	475,(39.782)	613,(40.355)	229,(46.735)	125,(48.638)	77,(61.111)	578,(20.323)
43	Other Comedi cations	No	860,(72.027)	1108,(72.943)	0,(0)	182,(70.817)	0,(0)	2466,(86.709)
		Yes	334,(27.973)	411,(27.057)	490,(100)	75,(29.183)	126,(100)	378,(13.291)

Table 5. ODDS RATIOS for Treatment Initiation on the index date					
Effect		BBc1	BBc3	ABC1	ABC3	Other Therapy
		OR (Conf. Int.)	OR (Conf. Int.)	OR (Conf. Int.)	OR (Conf. Int.)	OR (Conf. Int.)
Gender	Male vs Female	0.894 (0.762 - 1.051)	1.293 (1.034 - 1.617)	1.008 (0.758 - 1.341)	1.817 (1.213 - 2.721)	1.019 (0.872 - 1.191)
Region	Gulf Coast vs Others	0.948 (0.64 - 1.404)	0.977 (0.548 - 1.742)	1.971 (0.861 - 4.516)	0.545 (0.211 - 1.407)	0.751 (0.519 - 1.087)
	SE Texas vs Others	0.856 (0.572 - 1.28)	1.048 (0.582 - 1.887)	1.913 (0.829 - 4.418)	0.831 (0.318 - 2.173)	0.612 (0.419 - 0.893)
Plan type	Healthy Advantage vs Total Care/Plus plan/Optimacare/Others/Missing Value	0.948 (0.71 - 1.266)	1.058 (0.701 - 1.597)	0.95 (0.564 - 1.601)	1.282 (0.6 - 2.738)	1.245 (0.934 - 1.659)
Comorbidities	Hypertension vs No Hypertension	1.109 (0.872 - 1.41)	1.173 (0.835 - 1.648)	0.806 (0.519 - 1.253)	0.797 (0.434 - 1.466)	0.819 (0.651 - 1.031)
	Stroke vs No Stroke	0.934 (0.681 - 1.281)	1.12 (0.747 - 1.678)	0.796 (0.448 - 1.416)	0.952 (0.474 - 1.912)	0.997 (0.733 - 1.356)
	CBVD vs No CBVD	0.827 (0.442 - 1.549)	0.701 (0.272 - 1.804)	0.814 (0.264 - 2.511)	0.757 (0.164 - 3.499)	0.795 (0.451 - 1.404)
	Renal Failure vs No Renal Failure	0.921 (0.743 - 1.143)	1.195 (0.895 - 1.595)	0.969 (0.66 - 1.424)	0.853 (0.511 - 1.422)	0.815 (0.661 - 1.005)
	COPD vs No COPD	0.919 (0.746 - 1.132)	0.817 (0.615 - 1.086)	0.936 (0.647 - 1.354)	0.885 (0.538 - 1.456)	1.077 (0.88 - 1.317)
	Pneumonia vs No Pneumonia	1.321 (1.028 - 1.698)	1.05 (0.751 - 1.467)	0.627 (0.385 - 1.022)	1.064 (0.602 - 1.88)	1.426 (1.121 - 1.814)
	Diabetes vs No Diabetes	0.887 (0.724 - 1.087)	0.848 (0.644 - 1.117)	1.123 (0.782 - 1.613)	0.825 (0.511 - 1.331)	0.884 (0.725 - 1.078)
	Protein calorie malnutrition vs No Protein calorie malnutrition	0.894 (0.598 - 1.339)	0.858 (0.494 - 1.493)	0.737 (0.327 - 1.663)	0.852 (0.333 - 2.177)	1.337 (0.93 - 1.923)

Dementia vs No Dementia	0.874 (0.642 - 1.189)	1.142 (0.765 - 1.705)	0.635 (0.349 - 1.158)	1.4 (0.709 - 2.765)	1.131 (0.85 - 1.506)
Hemiplegia and Paralysis vs No Hemiplegia and Paralysis	1.056 (0.741 - 1.504)	0.812 (0.511 - 1.29)	1.184 (0.624 - 2.248)	1.054 (0.48 - 2.315)	1.226 (0.871 - 1.727)
Peripheral Vascular Disease vs No Peripheral Vascular Disease	0.999 (0.79 - 1.263)	0.898 (0.66 - 1.224)	0.909 (0.599 - 1.379)	0.681 (0.396 - 1.171)	0.869 (0.691 - 1.094)
Metastatic Cancer vs No Metastatic Cancer	1.416 (0.849 - 2.361)	0.967 (0.459 - 2.036)	0.623 (0.182 - 2.13)	0.766 (0.171 - 3.434)	<mark>2.665 (1.674 - 4.243)</mark>
Trauma in last year vs No Trauma in last year	<mark>0.74 (0.598 - 0.917)</mark>	0.756 (0.566 - 1.01)	0.944 (0.647 - 1.378)	0.737 (0.442 - 1.228)	1.116 (0.909 - 1.37)
Mental disorder vs No Mental disorder	1.085 (0.855 - 1.376)	1.038 (0.753 - 1.43)	<mark>1.533 (1.022 - 2.3)</mark>	0.866 (0.492 - 1.525)	1.005 (0.8 - 1.263)
Liver Disease vs No Liver Disease	1.353 (0.914 - 2.004)	0.732 (0.405 - 1.323)	0.789 (0.368 - 1.692)	0.484 (0.142 - 1.651)	1.092 (0.738 - 1.614)
CABG vs No CABG	1.53 (0.73 - 3.205)	1.282 (0.503 - 3.268)	0.841 (0.265 - 2.669)	0.912 (0.248 - 3.351)	1.224(0.584 - 2.565)
PTCA vs No PTCA	0.933 (0.646 - 1.348)	0.967 (0.601 - 1.555)	1.279 (0.728 - 2.247)	1.581 (0.789 - 3.168)	<mark>0.688 (0.475 - 0.997)</mark>
Unstable Angina vs No unstable angina	0.95 (0.644 - 1.402)	0.83 (0.491 - 1.403)	1.346 (0.748 - 2.425)	0.667 (0.289 - 1.541)	0.761 (0.514 - 1.128)
Anterior MI vs No anterior MI	0.87 (0.619 - 1.223)	0.808 (0.514 - 1.269)	0.664 (0.361 - 1.22)	1.327 (0.687 - 2.564)	<mark>0.686 (0.485 - 0.971)</mark>
Other MI vs No other MI	1.09 (0.82 - 1.45)	0.806 (0.544 - 1.192)	1.241 (0.761 - 2.024)	1.128 (0.594 - 2.141)	1.211 (0.924 - 1.588)
ACUTE MYOCARDIAL INFARCTION vs No ACUTE MI	0.87 (0.638 - 1.187)	1.026 (0.694 - 1.517)	<mark>1.798 (1.103 - 2.928)</mark>	1.192 (0.639 - 2.222)	0.791 (0.586 - 1.068)
Chronic Atherosclerosis vs No chronic atherosclerosis	1.087 (0.862 - 1.372)	<mark>1.69 (1.231 - 2.321)</mark>	0.998 (0.654 - 1.522)	<mark>1.944 (1.088 - 3.473)</mark>	1.074 (0.858 - 1.345)
Cardiorespiratory Failure and shock vs	0.895	0.966	1.076	0.793	<mark>1.61</mark>

	No cardiorespiratory failure and shock	(0.681 - 1.177)	(0.677 - 1.38)	(0.663 - 1.746)	(0.427 - 1.474)	(1.246 - 2.082)
	Rheumatic fever vs No Rheumatic Fever	1.214 (0.788 - 1.869)	1.043 (0.591 - 1.84)	1.341 (0.669 - 2.691)	2.224 (1.049 - 4.712)	0.822 (0.53 - 1.274)
	Coronary artery disease vs No Coronary Artery disease	1.042 (0.782 - 1.389)	0.833 (0.567 - 1.224)	1.198 (0.747 - 1.919)	0.802 (0.424 - 1.517)	1.099 (0.825 - 1.463)
	Atrial fibrillation and flutter vs No Atrial fibrillation and flutter	1.33 (0.991 - 1.786)	1.388 (0.928 - 2.075)	1.082 (0.656 - 1.783)	1.132 (0.598 - 2.141)	0.955 (0.718 - 1.269)
	whf_hos YES vs NO	0.691 (0.43 - 1.111)	2.196(1.342 - 3.593)	0.895 (0.407 - 1.971)	2.568 (1.233 - 5.351)	0.757 (0.485 - 1.182)
Disease State	**Disabled/ESRD/Hospice/Institutional vs Medi/Medi**	1.322 (0.728 - 2.402)	0.985 (0.433 - 2.241)	1.054 (0.339 - 3.281)	0.993 (0.225 - 4.382)	2.342 (1.336 - 4.104)
	Other/Working Age vs Medi/Medi	1.15 (0.884 - 1.497)	1.136 (0.781 - 1.652)	1.262 (0.769 - 2.07)	1.237 (0.61 - 2.507)	1.084 (0.841 - 1.396)
	Age	1.018 (1.006 - 1.03)	1.006 (0.99 - 1.023)	0.996 (0.976 - 1.017)	0.985 (0.956 - 1.015)	1.02 (1.009 - 1.032)
	cmssqrt	0.977 (0.563 - 1.697)	0.881 (0.413 - 1.88)	0.655 (0.247 - 1.74)	0.379 (0.105 - 1.366)	1.628 (0.964 - 2.752)
Duration of HF	**0.25-1 yr. vs <=0.25 yrs.**	0.974 (0.753 - 1.261)	1.024 (0.722 - 1.454)	0.729 (0.478 - 1.111)	0.631 (0.352 - 1.13)	0.151 (0.12 - 0.189)
	> 1 yrs. vs <=0.25 yrs.	0.875 (0.683 - 1.122)	0.837 (0.595 - 1.178)	0.619 (0.411 - 0.931)	0.688 (0.394 - 1.2)	0.1 (0.08 - 0.125)
	Log of cumulative cost	1.013 (0.881 - 1.164)	1.121 (0.922 - 1.363)	1.003 (0.784 - 1.284)	1.554 (1.118 - 2.158)	0.772 (0.678 - 0.878)
	Vasodilators YES vs NO	1.382 (1.055 - 1.811)	1.625 (1.156 - 2.284)	1.424 (0.915 - 2.215)	1.718(0.985 - 2.997)	0.526 (0.384 - 0.72)
	Calcium Channel Blockers YES vs NO	0.982 (0.816 - 1.18)	0.719 (0.546 - 0.946)	0.945 (0.68 - 1.314)	0.402 (0.223 - 0.725)	0.582 (0.481 - 0.705)
	Diuretics YES vs NO	1.033 (0.88 - 1.212)	1.293 (1.037 - 1.613)	1.467 (1.108 - 1.943)	2.675 (1.802 - 3.971)	0.484 (0.411 - 0.57)

BNP	Elevated value, >99ng/L vs Normal: 0-99ng/L	1.89 (0.875 - 4.085)	2.131 (0.864 - 5.255)	3.55 (0.666 - 18.911)	2.026 (0.358 - 11.467)	0.978 (0.466 - 2.056)
	Missing Value vs Normal: 0-99ng/L	**1.982 (1.089 - 3.607)**	1.147 (0.547 - 2.404)	3.302 (0.768 - 14.198)	1.368 (0.308 - 6.074)	1.491 (0.867 - 2.566)
BUN	Abnormal vs Normal: 8-23mg/dL	1.174 (0.945 - 1.458)	1.172 (0.876 - 1.567)	1.195 (0.807 - 1.769)	1.324 (0.776 - 2.258)	1.092 (0.877 - 1.358)
	Missing Value vs Normal: 8-23mg/dL	0.522 (0.159 - 1.714)	1.627 (0.254 - 10.4)	1.581 (0.116 - 21.62)	0.282 (0.029 - 2.755)	0.784 (0.244 - 2.52)
LDL	Abnormal vs Optimal: <100mg/dL	1.231 (0.959 - 1.58)	1.017 (0.721 - 1.435)	1.11 (0.71 - 1.734)	1.134 (0.616 - 2.087)	**1.56 (1.214 - 2.006)**
	Missing Value vs Optimal: <100mg/dL	1.026 (0.81 - 1.3)	0.959 (0.699 - 1.315)	0.98 (0.636 - 1.511)	0.752 (0.415 - 1.363)	**1.616 (1.276 - 2.046)**
Hb	Abnormal vs Normal: 13.5-17.5g/dL for males and 12.0-15.5g/dL for females	0.874 (0.688 - 1.109)	1.189 (0.86 - 1.643)	0.822 (0.53 - 1.274)	1.199 (0.651 - 2.21)	0.969 (0.763 - 1.23)
	Missing Value vs Normal: 13.5-17.5g/dL for males and 12.0-15.5g/dL for females	0.942 (0.73 - 1.215)	1.15 (0.804 - 1.645)	0.946 (0.599 - 1.495)	1.402 (0.727 - 2.703)	1.048 (0.813 - 1.351)
Na	Abnormal vs Normal: 135-145mmol/L	0.927 (0.596 - 1.44)	1.044 (0.597 - 1.828)	0.657 (0.269 - 1.606)	0.529 (0.153 - 1.823)	1.331 (0.876 - 2.02)
	Missing Value vs Normal: 135-145mmol/L	2.358 (0.713 - 7.796)	0.583 (0.091 - 3.737)	0.801 (0.059 - 10.91)	5.34 (0.538 - 52.976)	1.579 (0.489 - 5.101)
LPOFlag	Y vs N	0.989 (0.774 - 1.262)	1.055 (0.743 - 1.498)	0.957 (0.63 - 1.453)	1.683 (0.918 - 3.089)	1.135 (0.898 - 1.436)
P4QFlag	Y vs N	0.902 (0.746 - 1.092)	0.973 (0.748 - 1.264)	0.733 (0.512 - 1.051)	0.978 (0.622 - 1.539)	**0.52 (0.428 - 0.632)**

Manuscript #2

Risk of First subsequent Hospitalization among Elderly Heart Failure Patients initiating Angiotensin-Converting Enzyme Inhibitors (ACEI) vs. Beta-Blockers(BBs) - a comparative effectiveness analysis

Finding: The results indicate a statistically non-significant effect of BBc1 and BBc3 in comparison to ACEI on first subsequent HF hospitalization.

Abstract

Objective: To estimate the effect of initiating Beta-Blockers(BBs) vs. Angiotensin-Converting Enzyme Inhibitors(ACEIs) among elderly Heart Failure(HF) patients on risk of first subsequent HF hospitalization.

Methods: Using elderly(age≥65 years) HF patients initiating ACEI or a category 1 BB(BBc1) and category 3 BB(BBc3 i.e. BBs with combined alpha and beta blocking activity), were identified from Medicare Advantage Prescription Drug Plan for 2008-2011. The survival probabilities of first subsequent hospitalization were obtained by inverse probability weighted count process model for a follow-up of a year using SAS 9.3 at the p-value of 0.05.

Results: There were 248 (3.86%) first subsequent hospitalizations in the cohort of 6430 elderly HF patients with 18176 person-interval observations. The hazard ratio for first subsequent hospitalizations were 0.562(95%CI:0.28- 1.13) and 1.242(95%CI:0.64- 2.43) respectively for BBc1 and BBc3 as initiation therapies with respect to ACEI.

Conclusions: The results indicate a statistically non-significant effect of BBc1 and BBc3 in comparison to ACEI on first subsequent HF hospitalization.

Introduction

Heart Failure (HF) imposes a major health and economic burdens. As per 2009 report, in US there were more than 5.5 million adults with HF of which 10 per 1000 were over 65 years of age.(Shafazand et al., 2010) That year the disease led to an estimated direct and indirect cost of 37.2 billion. American College of Cardiology and the American Heart Association (ACC/AHA) 2005 guidelines recommend angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) for stage A HF (mild HF or patients at risk of HF) patient and also for patients having vascular disease or diabetes.(Shafazand et al., 2010) These guidelines also recommend addition of Beta-Blockers (BB) for stage B HF (i.e. mild to moderate HF) patients. And for patient with mild to severe Stage C HF, additional drug therapies may include diuretics or digitalis or combination therapies with hydralazine and nitrates. Therefore, as per these guideline recommendations, BB is for stage B HF patients as an add-on therapy after ACEI/ARB.

One of possible reasons for preferring ACEI over BBs is initiation of clinical trials for ACEI much before BBs trials.(Chonchol et al., 2008; de Boer & van Veldhuisen, 2008; Remme, 2007, 2008; Remme et al., 2004) The majority of trials were conducted to compare ACEI over placebos. The ample of evidence generated in favor of ACEI against placebo made it almost unethical standard to conduct a HF trial without prescribing ACEI as the standard therapy. Even when BB trials were conducted ACEI was part of approximately 90% of the trial's patient population.(Flather et al., 2005; Remme, 2008) This makes it hard to attribute the protective effect of the trial solely to beta-blockade and thus demands to bring evidence from alternative research strategies like observational studies before planning for RCTs.

The existing past literature, suggests that BBs play an important role in reducing the risk of Sudden Cardiac Death (SCD) and ischemia compared to ACEI.(Remme, 2007) It is also easier to achieve a higher dose of BB and an early inhibition of cardiac remodeling by rapid activation of sympathetic and renin angiotensin system(RAS) compared to when ACEI is administered first. (Remme, 2007, 2008) The increased RAS activation by BBs was also justified in SOLVD trial on grounds of increased Na and water retention and thus this pre-treatment with BB was reported to diminish increased serum creatinine level following ACEI.(Knight et al., 1999) These past literature enforce us to believe in the plausible protective effect of BBs, as mentioned earlier, compared to ACEI. And it seems reasonable to hypothesize that BBs are more beneficial for elderly HF patients in comparison to ACEI.

Evidence from Randomized Clinical Trial (RCTs)

There is evidence from various RCTs that support the abovementioned hypothesis. Sliwa et al demonstrated significant improvement in Left Ventricular Ejection Fraction (LVEF) and reduction in NT-proBNP, a biomarker for HF progression, in New York Heart association functional Class (NYHA) II-III HF and patients with idiopathic dilated cardiomyopathy for carvedilol (BB) patients compared to perindopril (ACEI) group.(Sliwa et al., 2004) Both drugs were equally well tolerated. Along with established benefits of cardiac remodeling via BBs, the CARMEN trial also compared the combination therapy to monotherapy of ACEI and BBs and concluded that addition of BBs to ACEI therapy is a superior therapy to either monotherapy.(Komajda et al., 2004; Remme, 2007, 2008) The trial found more cardiovascular hospitalization in the enalapril group but found comparable tolerability in terms of adverse events and withdrawal rate for ACEI and BB groups.(Komajda et al., 2004; Remme et al., 2004) Even CIBIS III trial confirmed Bisoprolol to be a safe and efficacious drug compared to enalapril with non-significant differences in all clinical outcomes studied in

the trial. The trial reported similar all-cause mortality, all-cause hospitalization, and cardiovascular hospitalization, tolerability in both groups and worsening of CHF requiring continued hospitalization while in hospital.(R. Willenheimer, 2009) At the end of the study period, despite more discontinuation in ACEI group, comparable numbers of patients were retained in the trial who had improved 1 or more NYHA class. Despite a non-significantly higher risk of worsening Heart Failure (WHF) related hospitalization or cases while in hospital for the bisoprolol group, the trial demonstrated tendency towards less sudden death with bisoprolol group (8 versus 16 patients in the enalapril group, HR 0.50; 95% CI 0.21–1.16, p=0.11).(Remme, 2008; R. Willenheimer et al., 2005) The CIBIS III trial has been an important trial in this direction. Because the sample frame of this trial focused on the elderly population it is considered to have provided some important observations for this population. It states that enhanced sympathetic activation with age may lead to myocardial infarction (MI) or arrhythmias. However, an early start on the BBs can be used to control accelerated sympathetic responses which could otherwise lead to ischemia or arrhythmias, thereby suggesting the utility of BBs among elderly population as well.(R. Willenheimer et al., 2005) The trial therefore provided more evidence to support SENIOR trial which observed that the BBs are well tolerated among elderly population.(Flather et al., 2005)

The utility of BBs(metoprolol succinate) across various clinical outcomes is also being tested for HF with normal left ventricular ejection fraction (HFNEF) in a multicenter trial, the beta-PRESERVE trial.(Morrissey et al., 2011; Zhou et al., 2010) This study justified the need for long-term RCT on the basis of few prospective, few observational and subgroups analysis of RCTs that past literature reveals beneficial effect of BBs even in HFNEF patients for whom there is a lack of any specific therapy.(Zhou et al., 2010) This implies that the preference of the BBs or testing of their preference over ACEI should not be limited to HF

patients with depressed LVEF only. Rather, it should be extended to the patients with HFNEF as well. This means, a HF patient, irrespective of his or her Ejection fraction (EF) can be hypothesized to benefit from BBs compared to or at least for their equivalence to ACEI.

So, where do RCTs lack?

As reported previously, despite comparable clinical outcomes of bisoprolol with enalapril group in CIBIS III trial, more WHF related hospitalization or cases were reported for the bisoprolol group while in hospital.(R. Willenheimer et al., 2005) Studies have also reported that the effect of BBs varies with the type of BB under scrutiny. For example, COMET trial showed greater reduction in fatal and non-fatal MIs and SCD due to carvedilol treatment compared to metoprolol treatment (Beta-1 selective agent). Bisoprolol has a similar profile as of metoprolol. This may imply that the type of BB is an important factor in revealing the most effective BBs of all or for comparing these BBs with another class of drugs like ACEI in this case. This raises a question if it is possible to change the results of CIBIS III trial with the replacement of bisoprolol (Beta-1 selective drug) with a non-selective BB for e.g. carvedilol.(Poole-Wilson et al., 2003) Although we would like to conduct an RCT, but considering these existing gaps in research, its cost, time and other practical limitations, it is difficult to compare all or even more than 2-3 BBs with another anti-hypertensive class in a single trial. This makes RCTs as an infeasible design approach to answer the aforementioned or similar comparative effectiveness studies that require class comparisons.

There are other limitations of RCTs too, due to which there is a need of some alternative approaches. For example, in SENIORS trial for 90% of the patients in the sample frame, BB was given along with ACEI. So, it was difficult to conclude if the protective effect as observed in the BB group was solely due to BB.(Flather et al., 2005) Not just SENIOR trial, but almost all clinical trials consider it unethical to conduct a clinical trial among HF patients

without prescribing ACEI, thereby discarding the RCT as a good design for the purpose.(Remme, 2007, 2008)

Apart from that the age of patients included in these clinical trials makes it difficult to generalize the results to elderly HF patients as prevailing in community. In CARMEN trial, on average, Patients were 10 years younger than the average age of HF patients in community (73-75 years of age).(Jafar et al., 2003) And as stated earlier, ageing is an important factor that correlates with increased nor-epinephrine plasma spillover and an increase in end diastolic volume.(Remme et al., 2004) It, therefore, makes it difficult to generalize the results of CARMEN trial to elderly HF population of the community. And the trials which include elderly patients include comparatively healthy volunteers, thereby providing results on biased populations.(Richardson et al., 2010) One of the major trials for this population, the CIBIS III trial, does not address the safety and efficacy of BB for elderly patients' clinical end-points. This trial used up most of the time for initiation and up-titration of bisoprolol, so despite WHF being the phenomenon of BB introduction, the trial was not a good setting to answer if BB can be used as a first-line therapy especially for elderlies. This study population could not gain optimal clinical effects of full and prolonged BB, such as reduction in death and SCD. The positive effects of BB need some time to become evident.(R. Willenheimer et al., 2005)

Evidence from the observational Studies

Although, none of the existing observational studies have compared ACEI vs different categories of BB and their combinations (ACEI+BB) in elderly HF patients for the risk of WHF, a few interpretations are worth noting. An article by Richardson et al, compares combination of ACEI/ARB and BB as essential cardiac drugs which should be prescribed to all elderly HF patients.(Richardson et al., 2010) This study concluded that mortality rates are significantly lower for those receiving ACEI/ARB alone (OR 0.24, 0.11-0.50), BBs alone

(OR 0.17, 0.07-0.41) and with combination (OR 0.24, 0.10-0.55) compared to patients who did not receive either of these medications. Although this study was not a head-to-head comparison of ACEI/ARB with BB, but this study supports the direction of our study, since the risk of mortality was lowest among patients receiving BBs only compared to those not receiving it. This study included elderly non-hospice community dwelling Medicare patients taking ACEI/ARB, BB, combination or none at all in the concurrent year.

Similarly, the article by Teng et al, assesses the trends and predictors of prescription of cardiac medications on discharge after the index hospitalization and their subsequent effect on all-cause mortality and again this study also found a lower association of BBs with 1-year mortality (Hazard ratio, HR for ACEI/ARB = 0.71, p = 0.003 and HR for BB = 0.68, p = 0.002).(Richardson et al., 2010; Teng et al., 2010) In addition, the article also concluded that although the use of ACEI/ARB was high over the years (1996-2000), the use of BBs showed an increasing trend (from 10.5% to 51.3%). This drastic increase in the utilization of BBs signifies BBs as an upcoming choice for HF patients.

There are many other articles, where association of BBs in HF patients after discharge has been estimated. And all these articles either lack in providing a head-to-head comparison of ACEI/ARB with BB or they do not estimate the probability of observing the recurrent hospitalization.(Austin, 2009; DiMartino et al., 2010; Maison et al., 2012; Wijeysundera et al., 2011) Some articles have even compared ACEI/ARB vs BB for different clinical outcomes in a sample frame different than HF. For example, Toh et al compared the association between initiating on ACE, Arb or aliskiren compared to BB for the risk of angioedema in any adult patient (≥18 years) taking it irrespective of the disease. With BB as the reference group, initiating on ACEIs or aliskiren was associated with an approximately 3-fold higher risk for angioedema. The risk for angioedema was lower with ARBs than with

ACEIs or aliskiren. (Toh et al., 2012) Similarly, study by Galindo-Ocana et al. gives some comparative effectiveness analysis for mortality and disability progression as an outcome across ACEI/ARB vs BB vs their combination (i.e. ACE/ARB + BB). This study was not just restricted to HF patients only. The study observed that beta-blocker plus statin (HR 0.645; P=0.007), ACEI/ARB plus statin (HR 0.680; P=0.002), or combined ACEI/ARB plus statin plus beta-blocker (HR 0.541; P=0.000) prescriptions were associated with longer survival times implying BB as a preferable therapy when used as a combination with Statins and with or without ACEI/ARB. However, as monotherapy compared to no therapy, the Hazard ratios (HRs) across ACEI/ARB and across BB groups were 0.782(0.635-0.964) and 0.825(0.662-1.028) respectively, implying BB as a non-preferable therapy when used as a monotherapy. Additionally, predictive probability for patients whose Barthel index was ≥60 showed a lower risk of disability progression if treated with Beta-blockers (OR=0.704; P=0.075), or their combinations, mainly with ACEI/ARB plus statins (OR 0.563; P=0.031).(Galindo-Ocaña et al., 2012) For ACEI/ARB, the OR was 0.731, p-value 0.119. Magid et al also compared ACEI vs BB for Hypertensive patients.(Magid et al., 2010) This study concludes that ACEI and BB are equally effective in lowering Blood Pressure (BP) and preventing cardiovascular disease and related events for patients whose BP is not controlled with Thiazide Diuretics alone and who have no compelling indication for 2nd line agent.

Aim and Significance of the study

The aim of this study is to understand the impact of initiating different categories of BB compared to ACEI and the combination of both on risk of hospitalization in near future amongst HF patients. For this, a prospective observational study design on real world effectiveness data was used. The information from this study shall broaden the scope of HF treatment especially among patients for which ACEI is not tolerated and in elderly HF

patients with average age 73-75 years, as prevalent in HF community. Most importantly, the study brings evidence from real world, rather than a controlled environment of a RCT. This shall help us to tease out the effect of BBs from the influence of ACEI and other RAS inhibition. In an article by Willenheimer et al, the author has suggested that this research question is a challenge for the treatment of Heart disease against a background of ACEI and the positive result shall provide the free choice of making an individual-based judgment from amongst ACEI/ BB.(Ronnie Willenheimer et al., 2005) Additionally, the study has compared various classes of BBs compared to ACEI which is essential to decide which class of BBs to prefer compared to ACEI. Therefore, overall a better control of HF can be achieved compared to current scenario. As an indirect effect of initiating BBs before ACEI, shall also prevent many cases of SCD as has been established by the trials. Once there is valid evidence, it will not be required to always conduct an RCT with ACEI as the standard therapy, which at times hinder the understanding of individual effect of new drugs under study in a trial. This study is one step in this regard.

In short, the study is trying to compare time-to-first subsequent hospitalization across different ACEI vs different categories of BB users. The hypothesis for this study is that the time-to-first subsequent hospitalization for the BB group as monotherapy is at least not significantly different when compared to ACEI.

Methods

This is a prospective cohort study using data from patients enrolled in Texas Medicare Advantage Prescription Drug (MAPD) plan from the year 2008-2011. This claims data consists of information about patient membership, member summary, institutional claims, professional claims, Quest lab, CCMS and Part D Pharmacy Data on computerized data files. The details of this data can be referred in one of our previous article.

Ethical Considerations This study has been exempted from human studies review requirement by the Institutional Review Board of University of Houston.

Study Sample

The study sample included elderly patients (age$\geq$ 65 years) with CHF diagnosis prior to therapy initiation date from a 10252 CHF patients stacked membership in MAPD data for the year 2008-2011.

The details of the research design and its inclusion/exclusion criteria have been mentioned in one of the previous studies. In brief, this cohort has included any alive patient who after '01July2008', had claimed for an ACEI or a BB as a monotherapy or in combination in the Pharmacy Data File.(Richardson et al., 2010) These patients should have a diagnosis date of HF and a membership of at least 6 months prior to initiation of either therapy. The study has excluded patients on ARB, aldosterone antagonist or Aliskiren in the washout period which may otherwise bias the study.(Rashikh et al., 2012; Toh et al., 2012; R. Willenheimer et al., 2004; R. Willenheimer et al., 2005) Further, BBs with Sympathomimetic activity (BB category 2 or BBC2) and any combination of BBs category 1 and 3 (BBc1 and BBc3 respectively) were also excluded from the study because of its low sample size and for the risk of complicating the study design. All these 'no therapies' vs 'a prescribed therapies' in the 6 months wash out period were defined based on a cut-off of

proportion of days(PDC) being less than or equal to 0.04 for each drug. The details of these cut-off criteria, prescription drugs and the sample characteristics can be referred in the previous study.

Follow-up period

The patient was followed for 1 year from 1st Jul 2008 till the last claim on 5th Jan 2011. The follow-up time was defined as the minimum time at which either the patient switched to not-required drugs (ARB, BBc2, aldosterone antagonists or aliskiren) or had a death record on the date or reached the event time i.e. HF hospitalization or at the last record from pharmacy/Quest Lab/Institutional/Professional Claims file or 360 days.

The event time is defined as the time at which either the patient was discharged from the first subsequent hospitalization or the time at which patient switched the therapy while still hospitalized.

Outcome

The primary outcome for this study is time-to-first subsequent HF hospitalization within a year from the index date (date of initiation of a therapy). The first subsequent HF hospitalization observed after the index date is the first HF hospitalization. In case, patient was hospitalized prior to or on the index date then the next hospitalization after the index date was defined as the first subsequent hospitalization. All the HF hospitalizations were identified by the DRG codes 291, 292 and 293.("National average costs by department for heart failure and shock," 2010; "National average costs by department for heart failure and shock (revisited)," 2014; Navarro-López et al., 1997; Newhouse et al., 2003) This first subsequent HF hospitalization was defined by an event indicator variable or censor variable with value '1' for the event and value '0' for the censored time observed due to death or other

reasons of censoring including initiation of not-required drugs last claim record or completion of a year follow-up.

In order to validate the model with respect to CIBIS III trial and other trials, a secondary outcome 'mortality' has also been chosen. (CIBIS III, CARMEN etc.)

Interval observation

The whole follow-up period is divided in interval level observations, which indicates a constant status of exposure to a drug or hospitalization. The censor variable for each interval was defined separately rather than for whole follow up time. As the interval changes with a change in either of the status, a start time for the next interval and a stop time for the current interval are defined till the follow-up time is achieved. If an event is observed in an interval the censor variable was indicated as '1' else '0' with usual meaning as defined above. The assumption was made that each interval censoring or event was caused by covariates and treatment/exposure to a drug in the previous interval and the therapy initiated on the index date. The information was used to develop statistical models as explained later.

Exposure

The treatment that the patient was getting on the index date and in the previous interval was defined as the exposure to drug. It could be either ACEI or BBc1 or BBc3 or a combination of ACEI with BBc1 (ABC1) or with BBc3 (ABC3) or a therapy other than any of these therapies. Thus, it's a multinomial exposure variable. The study used a PDC based approach as was defined by Leslie for persistence using information about prescription claims and days of supply from Pharmacy file.(S. R. Leslie et al., 2008) Each day was coded as '0' and '1' for each of the respective day. Therefore, for the index date or for an interval, the PDC is 100% for a particular therapy group. The strategy was used to define exposure therapy on the index date, also defined as initiated therapy (trt_1). Additionally, same

strategy was used to define exposure to drug in an interval (dg) or in the previous interval (prdg). The day the drug code '0' was observed the interval was changed.(Powell & Bagnell, 2012)

Inverse Probability weight (IPW)

The IPW was calculated using a product of the treatment, dose and censoring weight calculated from repeated interval observation for each person-interval as follows(Chitnis et al., 2012; Faries & Kadziola, 2010; Powell & Bagnell, 2012; Sugihara, 2010):-

$$IPW = \left(\frac{Predtrt0}{Predtrt1}\right) * (Dosewt) * (Censoringwt)$$

Here, Dosewt was calculated as a time-varying variable for each person interval as follows:-

$$Dosewt = \left(\frac{ACEI0}{ACEI1}\right) * \left(\frac{BBc10}{BBc11}\right) * \left(\frac{BBc30}{ABBc31}\right)$$

The censoring weight was defined as a product of deathwt (informative censoring) and ORCwt i.e. wt for other reasons for censoring (non-informative censoring) as follows(Hernán, Hernández-Díaz, & Robins, 2004; Robins & Finkelstein, 2000; Sugihara, 2010):

$$Censoringwt = \left(\frac{Death0}{Death1}\right) * \left(\frac{ORC0}{ORC1}\right)$$

Therefore, the IPW contains a numerator for each respective term which uses the respective probabilities for each term from a model that controls for gender, baseline hospitalization status and their count and treatment in the previous interval and no. of days of previous interval as a measure of exposure history. Also the model adjusted for the therapy each patient initiated on the index date and the time from the index date as measure of initiation therapy exposure duration effect. This is defined as time-fixed model.

For the denominator of IPW, probabilities are calculated from an equation that while controlling for gender, baseline hospitalization status and their count and exposure history as stated above and a parsimonious model of all predictors defined at each interval for the observations from previous interval as time-varying covariates. This is defined as time varying model. Here, following 2 assumptions are made:

- The therapy provided in each interval effects the covariates like co-medications, cost etc. and thus varies as therapy changes with interval or time i.e. time-varying.

- These time-varying covariates in an interval further affect the treatment provided in next interval.

Here, treatment and dose are multinomial outcome and thus a proc GENMOD was used and censoring is a survival outcome and thus Phreg was used to calculate each respective numerator and denominator probability. (Flom, 2010; Van der Wal & Geskus, Sep 2011)

This IPW thus obtained was adjusted for time to represent a joint probability of having survived the previous interval thereby controlling for the history of the current observation.(Cole & Hernán, 2004; Faries & Kadziola, 2010; Hernán, Brumback, & Robins, 2000; Hernán, Brumback, & Robins, 2002; Hernán et al., 2004; Robins, Hernán, & Brumback, 2000) This past history adjusted weight was further normalized by count adjusting for sample size in respective treatment groups to obtain the final weight.(Chitnis et al., 2012; S. Leslie & Thiebaud, 2007)

Except for other categories of previous drug, for which most of the covariates were significantly different w.r.t. ACEI and continuous variables, all other categories of drug provided in the previous interval showed a balance of 41-44 categorical covariates out of 44

categorical covariates w.r.t. ACEI with final normalized IPW history weight which indicates a good balance compared to unweighted data for amongst the treatment groups w.r.t. ACEI.

Dose of drug as the time-dependent confounder

The study by Willenheimer et al used the example from different trials to emphasize that there is a controversy about the association between dose and clinical outcomes.(R. Willenheimer, 2009) The author suggests that the CIBIS III and MOCHA trial confirm the utilization of higher doses of bisoprolol for reduced mortality; however, contrary to this, the MERIT-HF and the CIBIS II trial suggested that high and low doses of bisoprolol did not brought much difference in mortality. So, this study has controlled for dose of the therapy as a covariate as well.

Average dose of ACEI, BBC1, BBc3 for previous treatment provided for each interval were calculated. As stated previously to avoid reverse causation the model explores the impact of previous interval treatment and its dose on hospitalization in current interval, provided the patient belongs to certain therapy initiation group.

The average dose or its transformation as log value or as quadratic term did not had a linear distribution, so it was categorized as No dose (<0 mg), Low dose (0-10 mg), Medium dose (10-25 mg) and Upper dose (>25 mg). These categories were used to calculate Dosewt. However, in censoring weights and also in the final model, the phreg models at various stages did not gave a good convergence with all these categories for ACEI, BBc1 and BBc3. So, a continuous dose variable for ACEI, BBc1 and BBc3 were entered in the model.

Other time varying covariates

All the covariates as defined at baseline as determinants of the treatment on the index date were redefined for each interval for the duration of previous interval. This means the covariates observed in the previous interval determines the treatment provided in that

interval. For example the lab values observed in the previous interval will determine which therapy will be provided in that interval. Apart from that other covariates as defined under IPW were also defined for each interval and entered in the IPW and final Phreg model.

Statistical Analysis

A series of models were developed to explore all possibilities. Initially, an Unadjusted Kaplan Meier curve, Schoenfeld residuals and log rank test were developed for the person-interval data to test the proportionality hazard assumption. The Univariate model here controlled for initiated therapy (trt_1) only and has been defined as Model 1 for further reference. In this model, a patient was followed for the duration as long as the patient is on one of the either treatment groups with or without switching. The model was developed to represent the effect of censoring in current interval w.r.t. the effect of therapy provided on the index date i.e. 'Initiated Therapy' (trt_1).

Similarly, another Univariate model using normalized IPW weight defined effect of initiated therapy in Model 2.(Robins & Finkelstein, 2000) The study develops a count based extended-cox-regression model to identify the time-to-first subsequent hospitalization. The article by Powell et al recommends that count process (CP) approach for time-varying covariates yields similar results compared to an extended cox model.(Powell & Bagnell, 2012) Robust estimates were obtained and COV (AGGREGATE) allowed defining the covariance structure of the repeated data.

Further a fully adjusted weighted CP model (referred as Model 3) was developed similar to model 2 by including all variables as defined above. Additionally, the therapy provided in the previous interval (prdg), its duration and average dose was also included. The model also includes the variables to define the duration of the first interval for each of the index therapy for the model and its average dose.

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It is important to note here that none of these models control for the effect of current therapy on current interval censoring to avoid the possibility of reverse causation bias. And as stated above, they represent the effect of Initiated therapy on censoring, while allowing switching of the therapy in each interval compared to previous interval.

The results of these 3 switching models were compared with the baseline Cox model with baseline covariates only and not allowing switching i.e. patients were censored as soon as they made the switch to a treatment group different than the one on the index date. This was labeled as Model 4. Additionally, the same baseline Cox model without switching and labeled as Model 5 was developed after removing patients who did not received the treatment for first 14 days after the index date, i.e. PDC ≤ 0.2 for a whole year of 360 days. For these data, a count model was not developed because log rank was non-significant for baseline Cox model without switching (p-value 0.3942 and p-value 0.4003).

For secondary outcome of mortality, a baseline Cox model with baseline covariates only and without allowing switching (Model 6) was developed along with another baseline Cox model without allowing switching (Model 7) developed after removing patients who did not received the treatment for 14 days after the index date of initiating the treatment.

All analyses were performed at a significance level of p-value ≤ 0.05 using Statistical Analysis Software (SAS) version 9.3 (SAS Institute Inc., Cary, NC, USA).

Sensitivity analysis for Change in length of follow-up

Results re-analyzed for change in follow-up time period from 1-year to 2-years. This is because, as reported previously, in the trial by Sliwa et al. as the length of follow-up increased for an additional 6 months, the results became in favor of BBs.(Sliwa et al., 2004) Further, in CIBIS-III trial also, one major limitation described was the length of follow-up

time and it was suggested that BBs take some time to show their beneficial effect. (R. Willenheimer et al., 2005)

Subgroup analysis of Ejection Fraction

A claims-based definition based of systolic dysfunction was used to identify patients in whom the EF was <45%.(Setoguchi et al., 2011) The definition required that there have been no diagnosis of atrial fibrillation (ICD-9-CM code 427.31) and had received Digoxin during the 180 days before the index date, which for this study is the therapy initiation date.(Jensen et al., 2012; Setoguchi et al., 2011) This definition had a positive predictive value of 87% for identifying patients with EF <45% in the.(Setoguchi et al., 2011)

Results

There were 248 (3.87%) first subsequent hospitalizations in the cohort of 6430 elderly HF patients. At interval level these observations gave 18176 person-interval observations in the cohort with 1.36% of event intervals of first subsequent hospitalization. Table 1 compares the frequency distribution of initiated therapy at person level as well as at interval level. Table 2 represents the censored events observations with regard to the therapy initiated at patient level. Apart from other therapeutic group, the highest percentage of censored observations was observed for BBc1 (0.92%).

The Kaplan-Meier plot for unadjusted unweighted person-interval data is represented in Fig 2. This represents maximum survival probability for patients initiating ACEI and lowest for BBc3 groups at different stop points where interval ends. None of the survival probability curves were found to follow proportional hazard assumption with respect to ACEI as also confirmed by the log rank test (p<0.0001), thereby confirming lack of proportionality hazard assumption at least for one treatment group.

Table 3 compares the result of all the Hazard Ratios and their respective 95% Confidence Interval across Model 1- 5 for the risk of first subsequent hospitalization. The results from sensitivity analysis in this regard are also demonstrated. The result demonstrates that in Model 3 after controlling for dose and other factors along with past history at a given interval the initiation on BBc1 and BBc3 gave a non-significant effect compared to initiation on ACEI. In Model 5 compared to Model 4, adjusting for covariates and ensuring at least 14 day medication removed significant variation from BBc3 and made it non-significant compared to ACEI. The therapeutic groups of BBc1 as monotherapy and as combination gave non-significant hazard ratio in all the models. Compared to Models 1-3 that allowed switching,

the hazard ratios for Model 4 and 5, that did not allowed switching, had higher hazard ratios. In model 5, no hazard ratio was obtained for the ABC3 group due to lack of observation of the event. The table also presents the results of sensitivity analysis for data followed for 2 years rather than 1 year. It provides a non-significant hazard ratio for all groups except for other therapy group. Table 4 compares the Hazard ratios for mortality and their respective 95% Confidence Interval across Model 6 and 7 along with estimates from sensitivity analysis. Neither of the models gave a significant hazard ratio for mortality for any of the initiated therapy. No Hazard ratios were obtained for a combination of ACEI and BBc1 due to lack of observation of mortality in the treated group for both models as well as for sensitivity analysis data.

Table 5 represents the data for subgroup analysis for patients with EF<45% as defined based on claims databased operational definition from past literature. It indicates that in patients with EF<45% maximum patients initiate on ACEI and these users are even higher than the other therapy group. Of all the events of first hospitalization, maximum events were observed amongst ACEI users. Of all events 38.46% were amongst ACEI users, 30.77% amongst BBc1 users, 7.69% amongst BBc3 users and 23.08% amongst other therapy users. No events were observed amongst combination therapy group. None of these groups showed mortality events except for the other therapy group which had 6 events of mortality.

Discussion

The above results indicate that for BBc1 a statistically non-significant effect was observed in all the models compared to ACEI. Thus, the results imply an observed non-significant difference in the effect of the 2 drugs for first hospitalization. These estimates of first HF hospitalization for BBs are lower than compared to those from CIBIS III trial. The trial reported a Hazard ratio for Worsening of Heart Failure (WHF) defined for events occurring while in hospital to be 1.25(95%CI: 0.87-1.81) and all-cause hospitalization was 0.95(95% CI: 0.76-1.19).(R. Willenheimer et al., 2005) These estimates appear to be close to univariate model, which despite not controlling for severity and other covariates showed BBc1 to be non-significantly different than ACEI. This observation probably could be accounted for the fact that the trial result for WHF focus only on a severe condition, which justifies this being higher than the first HF hospitalization defined here; the latter being a composite of severe and mild HF hospitalization. Similarly, all-cause hospitalization includes any possible cause of hospitalization and not just HF hospitalization, which again ought to be higher than HF hospitalization. Thus, results of our study seem to be in agreement with the CIBIS III trial.

For BBc3, Univariate models (1 and 2) along with the baseline adjusted Cox model (Model 4) gave a significantly high hazard ratio. However, with adjustment for covariates from the previous interval in the Model 3 including the treatment provided in the previous interval the difference in the effect became non-significant. This indicates the importance for controlling the history. Contrary to this in model 4 only baseline history was controlled for since throughout the follow-up time period the treatment did not changed. In this model, it is the sole effect of one treatment. This demonstrates a significantly high effect of BBc3

compared to ACEI. However, when the analysis was restricted to patients who took the drug for at least 14 days from a year follow-up then again the difference became non-significant compared ACEI. This indicates 2 possibilities. First these drugs take some time to show its effect as could be expected and also as anticipated in the CIBIS III trial.(R. Willenheimer et al., 2005) However, on comparing the estimates of model 3, i.e. 1 year data, with sensitivity analysis i.e. 2-year data, it is observed that the BBc3 estimates from both the models are close enough and thus it rules out this possibility. Second reason could be the fact that the initial 14 days were severe patients, although the history of patient was controlled for the observed duration but there could be some difference in the 2 treatment groups due to some unobserved variation. This difference was not observed in the Model 3 where similar to this model all patients were included and where by means of weighing the past history a balance in the treatment groups was achieved. So, as soon as these patients were excluded in Model 5 the difference in the hazard ratio for BBc3 and ACEI became non-significant. From the frequency distribution analysis of the hospitalization in the 2 cohorts (results not shown), it is observed that there were 7 first subsequent hospitalization for the BBc3 in Model 4 out of total 112 events i.e. 6.25% as opposed to 6 events from total 110 events i.e. 5.45% of total events in the cohort for Model 5. This means there is a decrease of 0.8% indicating a decrease in the severity in Model 5 compared to Model 4 thus supporting the possibility.

The CARMEN trial reported 10% cardiovascular hospitalization with BBc3 as opposed to 15% with ACEI.(Komajda et al., 2004) Similarly, this study found 18.15% of first HF hospitalization for ACEI compared to 16.53% of all HF hospitalization for BBc3, although little higher ratios compared to the trial but they seem to follow similar trend. The slight high percentage of HF hospitalization observed in this study could be attributed to the fact that the population included in this study is at least on average 10 years older compared to those of

the trial. This again emphasizes the need to include community population in a study unlike RCTs.

Further the hazard ratios for BBc3 are higher compared to BBc1. This is in contradiction to what previous literature predicts. However, it is possible to see some variation when a direct comparison is made. Additionally, a low sample size of BBc3 could be an issue here. However, this needs to be tested. Further, the hazard ratio for combination of ACEI and BBc3 are low or at least comparable when compared to BBc1 estimates or for BBc3 as monotherapy in Model 3, 4 and 5 and for sensitivity analysis. The combination seems to simulate a condition similar to that in a trial, where BBs are always provided with ACEI as a standard therapy and based on this trials adjudicate for providing BBc3 i.e. Carvedilol to be a better therapy. In this study, a clear distinction has been provided between a combination therapy and a monotherapy. And if as suggested earlier, the trial therapy in essence is a combination therapy of any BB with ACEI and if the results of this study are in accord with the trial then it can be inferred based on Model3-5, on sensitivity analysis and on trials that the combination of ACEI and BBc3 is a better therapy compared to the combination of ACEI and BBc1. Contrary to that this study shows that for the first hospitalization as the outcome the monotherapy of BBc1 has an upper hand compared to BBc3 in all the models, which till date has not been conveyed in the trials. The unadjusted Kaplan Meier plot also supports this observation. Further the combination of ACEI and BBc1 does not seem to provide any distinct benefit when compared to monotherapy of BBc1 for Model 3 and sensitivity analysis. For Model 4 and 5, the estimates have very wide confidence interval to justify any comment about the significant difference of BBc1 as monotherapy or as combination. So, it seems more reasonable to suggest BBc1 as monotherapy rather than as its combination with ACEI

in elderly HF patients who are already under load of polypharmacy.(Powlson, 2003; Volpe, Chin, & Paneni, 2010)

It can be argued that when in comparison to the results of Model 3 (1-year data) the estimates of BBc1 in sensitivity analysis (2-year data) increased drastically. Although the confidence intervals suggest that this difference could be non-significant; despite that it could raise a doubt if BBc1 in 2nd year is worsening the effect. On the other hand, BBc1 as monotherapy seems to provide nearly constant effect. Also it should not be overlooked that despite a questionable increase with BBc1 in 2nd year, it was still lower than that of BBc3 as monotherapy for 2nd year or at least statistically non-significant for 2nd year. This suggests that if patients initiate with BBc1 for first year the effect is comparatively better but the estimates could possibly increase slightly for second year.

The last group studied in this study was other therapy group. This group is heterogeneous in terms of patients included in this group. It includes patients who did not receive any therapy and also the patients who might have received some therapy other than ACEI or BBs as monotherapy or as combination. This group was included to cover the possibility of allowing switching to some therapy other than ACEI or BBs as monotherapy or as combination. The heterogeneity of this group from other groups was not balanced in the weighing process, which could imply unreliability of results from model 3 for this group. However despite that in any of the adjusted model hazard ratio for first subsequent hospitalization was significantly high compared to ACEI. To provide a definitive conclusion about this group it would be advisable to study varied possibilities of the treatments that could be initiated here.

The variation observed in the results for model that allow switching (Model 3) vs. the models that do not allow switching (Model 4 and 5) is also interesting. Table 3 demonstrates

the findings. It can be argued that without switching a higher hazard ratio is observed compared to when switch was permitted in the model. However, our focus of discussion is the effect of initiated therapy rather than the current therapy. As already argued and as also suggested by CIBIS III trial, the hypothesis is to prove that sooner patients start on BBs compared to ACEI, sooner protective effects may be achieved..(R. Willenheimer et al., 2004) In fact in the trial, patients initiated on one therapy for 6 months and later switched to their combination of both therapies. In Sliwa et al too, initially patients were prescribed monotherapies of ACEI and BBc3 for first 6 months and then later combination was prescribed to both groups.(Sliwa et al., 2004) Despite that the effect of group initiating with BBc3 became more prominent in favor of BBc3 group compared to ACEI even after long time after the switch was made. The authors have concluded that it's the effect of therapy that patients initiate on which plays major role in influencing current LVEF and NYHA Functional class. This is because this therapy is able to achieve optimum and a higher dose. In real world also, it is quite possible that patient will switch to another therapy. But then the effect of therapy that was initiated always imposes some influence on further course of the treatment. This study supports this hypothesis in all the models with or without switching.

The study also presented the mortality results from baseline Cox models, which again supports the possible statistically non-significant effect as is also observed in the trials. The results were generated to validate the findings from our study in comparison to the trial and other past literature. The result seems to be in agreement with the study by Richardson et al which reported an odds ratio of 0.24 (95%CI: 0.11-0.50) for ACEI vs 0.17 (95%CI: 0.07-0.41) for BBs alone and with combination it was 0.24 (95%CI: 0.10-0.55). The study by Teng et al reported a Hazard ratio for mortality of 0.71 (p-value = 0.003) for ACEI/ARB and an HR for BB of 0.68 (p-value = 0.002).(Richardson et al., 2010; Teng et al., 2010) The results

seem to be in congruence with the trial as well. The CIBIS III trial demonstrated tendency towards less sudden death (HR 0.50; 95% CI 0.21–1.16, p=0.11) and all cause death (HR 0.88; 95% CI 0.63-1.22) with bisoprolol-first group compared to enalapril-first group.(Remme, 2008; R. Willenheimer et al., 2005) The CARMEN trial did not report a hazard ratio for any of the clinical outcomes. However, it reported a rate of 7% for all-cause mortality (7%) and respective rates of 7%, 7% and 5% for cardiovascular mortality for ACEI, BBc3 and their combination; again proving a statistically non-significant difference in effect of ACEI and BBc3 and better protection from combination therapy.(Komajda et al., 2004)

An interesting observation that has been made here from 1-year data vs. 2-year data is that the estimates increased for the latter compared to 1-year data. If we recall the findings of our previous study, it was suggested that as duration of HF increases, the likelihood of initiating BBs decreases compared to ACEI. And current study suggests that as this likelihood decreases or as the duration increases the estimates of first hospitalization increases slightly. This means that the initiation therapy is important but its effect probably wears off after a year, which is a long time in itself to change many conditions.

Limitation

Some of the limitations of the cohort have already been discussed elsewhere. Briefly, there could be coding issues inherent to claims database and a lack of direct measure of severity and random assignment to different treatment groups. The study does not discriminate if ACEI vs BB vs combination was used as first line or 2nd line or 3rd line therapy, which included only JNC approved drugs.

In addition to this there is a measurement of exposure assumed to be proportionally the same in all the treatment groups for example due to insufficient follow-up time a non-differential measurement of exposure can be expected. May be all or some of the therapies

are in therapy-initiation phase and have not reached proper maintenance dose. To avoid this, patients were followed for a defined period based on past literature. The effect of strictly including patients who took the drug for at least 14 days in model 5 also assures some time on these therapy before their results can be compared. Additionally a sensitivity analysis was done to assess the effect of longer follow-up period.

The study could not provide the effect of BBs with sympathomimetic activity i.e. BBc2, effect of adherence and the effect of some important covariates like race. These should be the focus of future studies before generalizing the results to all elderly HF patients.

Strength

1. One of the greatest strengths of this study is the strong operational definition of exposure of the treatment on the index data and also during any interval. The technique used in this study based on PDC has helped to provide 100% persistence rate of a therapy on the index date as well as during an interval. This makes the comparison strong and avoids the variation in therapeutic group due to differences in adherence rate.

2. It controls for the influence of dose too. The CIBIS III trial used an open design where the titration schedule was dependent on the tolerability of each individual and their response to treatment.(R. Willenheimer et al., 2004) In real life, this situation is the driving factor for switching of the therapies.

3. It provides information for ACEI/BB as monotherapy and as combination both, and not just of monotherapy. In CIBIS III trial, the author suggested that the first initiated therapy like ACEI or BB, stands the better chance to be given long term and in adequate dose.(R. Willenheimer et al., 2004) However, our study has included patients on each therapy with doses as prescribed in real world. In real-world doses

are adjusted as per the tolerability of the patient and thus their up-titration may be different than that applied in a controlled environment of an RCT. For example, here already a minimum tolerable limit and optimum standard dose is known, so prescribers may have a different starting dose compared to that used in a RCT.

4. Sensitivity analysis tests the results for initiating ACEI/BB/combination therapies for a longer duration, which is essential as suggested by previous trials for BBs to show their optimum effect(Sliwa et al., 2004; R. Willenheimer et al., 2005).

5. The use of available lab values at various time points minimizes confounding by indication. Although there are lots of missing information in these variables, but this is expected as also suggested by Schneeweiss.(Schneeweiss et al., 2012) Further using LOCF, these possibilities of missing values was reduced. Weighing the history of the observation also helped to reduce the effect of missing information. And finally, any missing observation was not discarded from the study; rather it was included as a 'Missing value' category to extract whatever possible information could be found from the study.

6. The class effect of different BBs has been compared here, which is difficult in RCTs. This provides additional information to clinicians which look out for therapeutic equivalent drugs to replace one.

7. The study provides evidence for all types of HF patients and not just those with LVEF <35% as chosen in CIBIS III trial.(R. Willenheimer et al., 2004) As already stated, beta-PRESERVE trial is trying to target effect of using BBs in HFNEF patients too, our study provide some evidence with regard to those population and may support the need for the trial for all types of population for HF and thereafter, modification in guidelines.(Zhou et al., 2010)

8. With double weighting and Covs(aggregate) the complex nature of the treatment was incorporated in this study which often is affected by the death/switching/other causes of drop-outs as the terminal event and also by considering that measures on one person are correlated in nature. This helps to bring the data and its analysis close to reality.

9. The Inverse probability weights helped to balance various treatment groups for at least the categorical covariates with respect to the reference category, thereby strengthening the causal design.

10. By comparing the results of the switching model with models without switching, a comprehensive comparison of the effect of the treatment has been provided.

11. Further, use of multiple controls like other therapies along with nested nature of the data in the switching count process model helps to control for any overt bias. For this model, results are also obtained by cross-comparison across same patient on different treatment which provides advantages similar to cross-over designs along with cohort population.

The strength of this study is evident from the closeness of the findings with the trial. Additionally some new estimates were assessed here which were not studied previously.

<u>Conclusion</u>

The results indicate a possible statistically non-significant effect of ACEI and BBc1/BBc3 as monotherapy and as combination on first subsequent HF hospitalization and mortality. BBc1 as monotherapy seems to be a preferable therapy compared to its combination with ACEI or compared to BBc3 as monotherapy. From amongst combination therapies, combination of ACEI and BBc3 seems to be a preferable therapy. BBc1 as monotherapy or as combination showed low or none mortality events respectively compared to BBC3.

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Atleast 6 months prior membership and alive

BBc1 and BBc3 as combination

Medicare Advantage Prescription Drug (MAPD) 2008-2011

Washout

Combination

ACEI

BBs

Other

1 year

Outcome

Aldosterone antagonist on the index date

3. BB with sympathomimetic activity (BBC2) for 3 months
4. ARB for 3 months

HF Diagnosis

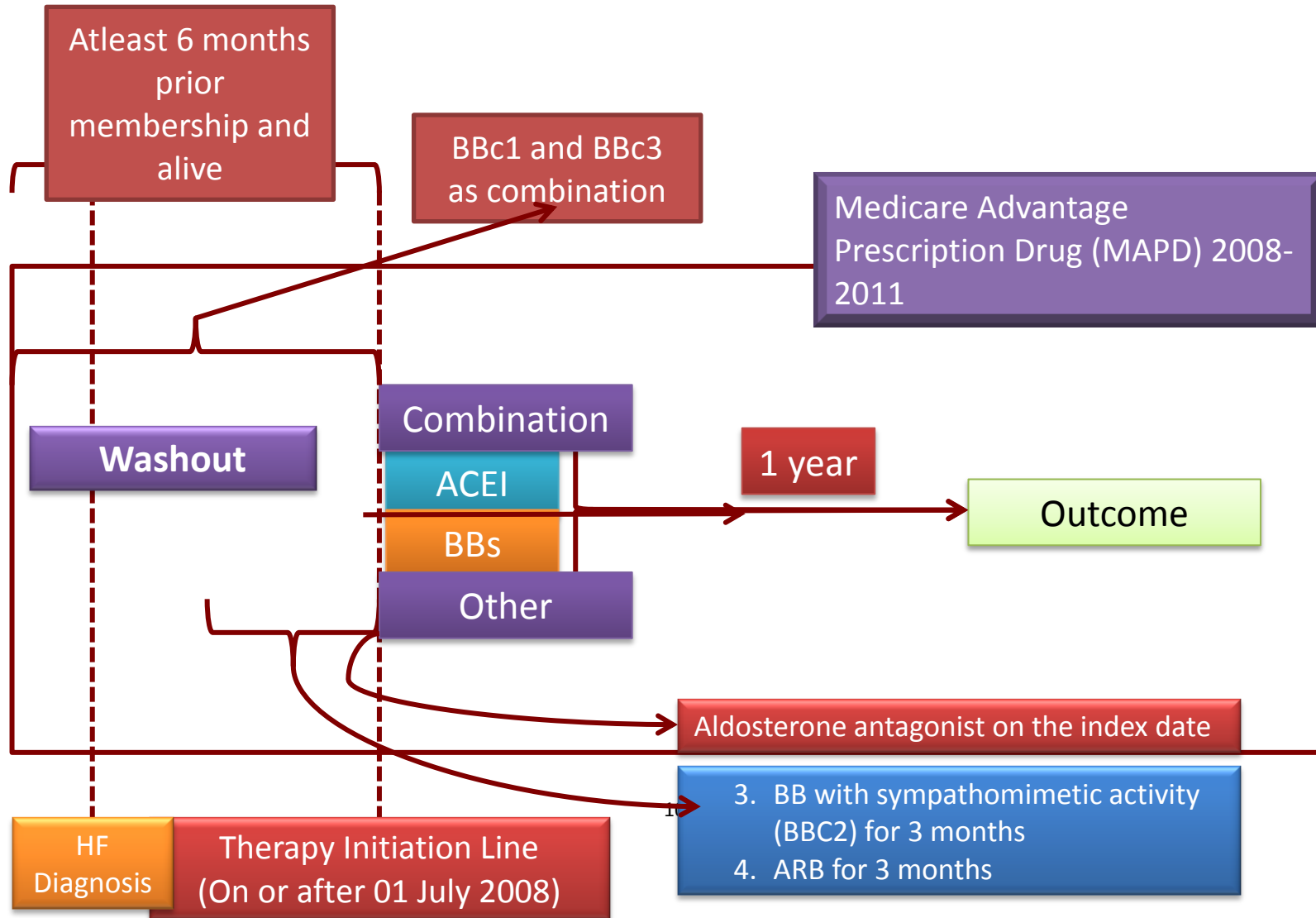Therapy Initiation Line (On or after 01 July 2008)

Figure 2. Kaplan-Meier Plot for Unadjusted unweighted survival probabilities for first hospitalization after initiating a treatment on the index date for person-interval data
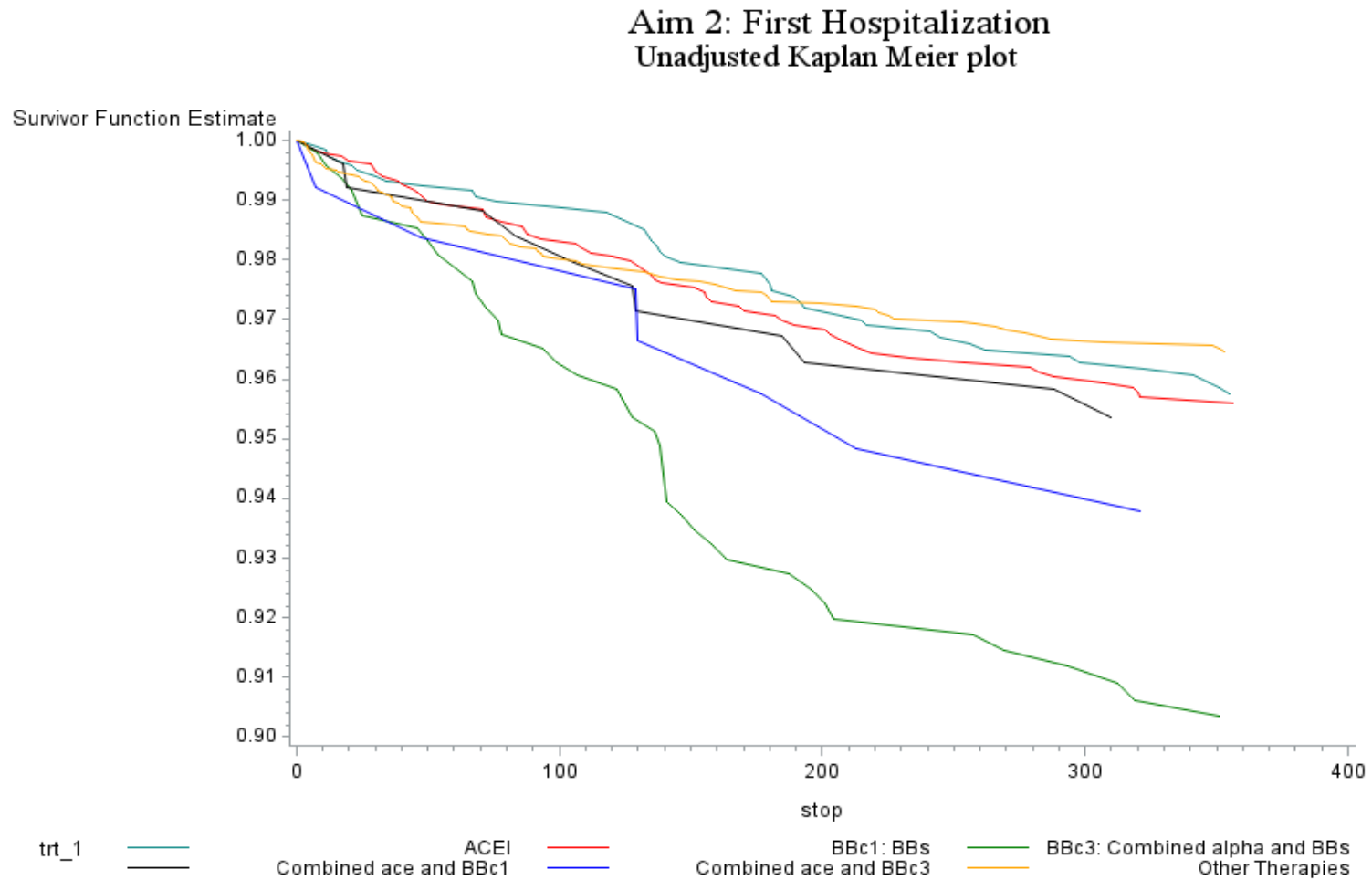

Aim 2: First Hospitalization
Unadjusted Kaplan Meier plot

Table 1. Frequency distribution of the treatment Initiated on in the cohort at patient level vs person-interval level				
Treatment Initiated (trt_1)	**Patient level**		**Person-Interval level**	
	Frequency	**Percent**	**Frequency**	**Percent**
ACEI	1194	18.57	5226	28.75
BBc1: BBs	1519	23.62	6210	34.17
BBc3: Combined alpha and BBs	490	7.62	2059	11.33
Combined ace and BBc1	257	4	1224	6.73
Combined ace and BBc3	126	1.96	528	2.9
Other Therapies	2844	44.23	2929	16.11

Table 2. Frequency distribution of all 248 Censored Observations across each initiated therapy(trt_1)		
Treatment Initiated (trt_1)	**Patient level**	
	Frequency	**Percent**
ACEI	45	0.70
BBc1: BBs	59	0.92
BBc3: Combined alpha and BBs	41	0.64
Combined ace and BBc1	11	0.17
Combined ace and BBc3	7	0.11
Other Therapies	85	1.32

		HR(95% CI: Lower CI-Upper CI)					
Table 3. Comparison of Hazard Ratios for first subsequent hospitalization due to initiation therapy across Models 1 to 5 and Sensitivity Analysis							
Obs	**Initiated Therapies**	**HR1**	**HR2**	**HR3**	**HR4**	**HR5**	**Sensitivity Analysis**
1	**BBc1: BBs**	1.054 (0.715- 1.553)	1.009 (0.651- 1.564)	0.562 (0.278- 1.134)	2.169 (0.478- 9.836)	2.171 (0.446-10.557)	0.971 (0.473- 1.994)
2	**BBc3: Combined alpha and BBs**	2.39 (1.566- 3.65)	3.501 (2.114- 5.798)	1.242 (0.636- 2.426)	5.269 (1.081- 25.679)	4.117 (0.89- 19.054)	1.303 (0.688- 2.465)
3	**Combined ace and BBc1**	1.12 (0.579- 2.165)	1.562 (0.736- 3.316)	1.052 (0.409- 2.706)	1.424 (0.22- 9.221)	1.396 (0.212- 9.171)	0.94 (0.449- 1.965)
4	**Combined ace and BBc3**	1.497 (0.675- 3.319)	2.221 (0.85- 5.802)	0.632 (0.223- 1.793)	1.155 (0.122- 10.959)		0.536 (0.19- 1.509)
5	**Other Therapies**	0.88 (0.613- 1.264)	0.469 (0.311- 0.708)	0.211 (0.114- 0.39)	3.467 (1.106- 10.866)	3.549 (1.062-11.862)	6.91 (3.137- 15.221)

HR1 = Hazard ratio for Univariate Unweighted Count Model with switching (Model 1)

HR2 = Hazard ratio for Univariate Weighted Count Model with switching (Model 2)

HR3 = Hazard ratio for Weighted Adjusted Count Model with switching (Model 3)

HR4 = Hazard ratio for Unweighted Baseline Adjusted Cox Model without switching (Model 4)

HR5 = Hazard ratio for Unweighted Baseline Adjusted Cox Model without switching for patients who took initiated therapy for at least 14 days (Model 5)

	Table 4. Comparison of Hazard Ratios of Mortality due to initiation therapy across Models 6 and 7 and for Sensitivity Analysis			
	HR(95% CI: Lower CI-Upper CI)			
Obs	Initiated Therapies	HR6	HR7	Sensitivity Analysis
1	BBc1: BBs	0.212(0.028- 1.6)	0.212(0.028- 1.598)	0.369(0.023- 6.001)
2	BBc3: Combined alpha and BBs	1.071(0.107- 10.716)	1.069(0.107- 10.701)	1.882(0.095- 37.089)
3	Combined ace and BBc1	-	-	0
4	Combined ace and BBc3	1.324(0.115- 15.209)	1.316(0.115- 15.122)	4.4(0.28- 69.249)
5	Other Therapies	1.258(0.279- 5.669)	1.252(0.277- 5.647)	1.534(0.144- 16.349)

HR6 = Hazard ratio for Unweighted Baseline Adjusted Cox Model for mortality without switching (Model 6)

HR7 = Hazard ratio for Unweighted Baseline Adjusted Cox Model for mortality without switching for patients who took initiated therapy for at least 14 days (Model 7)

	Table 5 Sub-group Analysis of the treatment groups being compared for patients with EF<45%			
S.No.	Initiated Therapy(Trt_1)	Freq (n = 160)	1st Hosp. (n = 13, 8.13%)	Mortality
1.	ACEI	52 (32.5%)	5(38.46%)	0
2.	BBc1	46 (28.75%)	4(30.77%)	0
3.	BBc3	15 (9.38%)	1 (7.69%)	0
4.	ABC1	4 (2.5%)	0	0
5.	ABC3	2 (1.25%)	0	0
6.	Other Therapies	41 (25.63%)	3 (23.08%)	6

Manuscript #3

Risk of Recurrent Hospitalization among Elderly Heart Failure Patients initiating

Angiotensin-Converting Enzyme Inhibitors(ACEI) or Beta-Blockers(BBs) - a

comparative effectiveness analysis

Finding: The results indicate a non-significant effect of BBc1 and BBc3 in comparison to ACEI on recurrent HF hospitalization and composite outcome.

Abstract

Objective: To estimate the effect of initiating Beta-Blockers(BBs) vs. Angiotensin-Converting Enzyme Inhibitors(ACEIs) among elderly Heart Failure(HF) patients for the risk of recurrent HF hospitalization and for the risk of composite outcome of HF hospitalization with death as the terminal event.

Methods: Using elderly (age≥65 years) HF patients initiating ACEI or a category 1 BB(BBc1) and category 3 BB(BBc3 i.e. BBs with combined alpha and beta blocking activity), were identified from Medicare Advantage Prescription Drug Plan(MAPD) Data 2008-2011. The survival probabilities of recurrent HF hospitalization and of composite outcome of HF hospitalization with death as the terminal event were obtained by the inverse probability weighted stratified total time and gap model and by the marginal model respectively for a follow-up of a year using SAS 9.3 at the p-value of 0.05.

Results: There were 248 (3.86%) recurrent hospitalization patients with 331 recurring events in the cohort of 6430 elderly HF patients. The hazard ratio for recurrent HF hospitalizations were 0.969(95%CI: 0.47- 1.996) and 1.32(95%CI: 0.702- 2.483) and for composite outcome were 0.871(95%CI: 0.51- 1.48) and 1.41(95%CI: 0.84- 2.36) for respective initiation therapies as BBc1 and BBc3 with respect to ACEI.

Conclusions: The results indicate a non-significant effect of BBc1 and BBc3 in comparison to ACEI on recurrent HF hospitalization and composite outcome.

Introduction

Heart Failure (HF) has been a challenge with a high prevalence rate of more than 5.5 million adults in US as per 2009 report, of which 10 per 1000 were over 65 years of age.(Shafazand et al., 2010) Treatment of the disease requires prescription of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) for requires for stage A HF (mild HF or patients at risk of HF) and if they also have vascular disease or diabetes.(Shafazand et al., 2010) For stage B HF (i.e. mild to moderate HF), Beta-Blockers (BB) may be added. These recommendations are made by the American College of Cardiology and the American Heart Association (ACC/AHA) 2005 and even by the 2013 ACC/AHA HF guidelines.(Hunt et al., 2009; Yancy et al., 2013) Despite these recommendations by the guidelines, discussion is on-going regarding the benefits of an early start of BBs even before ACEI. This has been attributed to the evidence from the recent trials which suggest that BBs plays an important role in reducing the risk of Sudden Cardiac Death (SCD), ischemia and cardiac remodeling by virtue of their rapid activation of sympathetic and renin angiotensin system (RAS) compared to when ACEI is administered first. (Remme, 2007, 2008). Additionally, a higher dose of BB can be administered and an increased RAS activation is achieved due to increased Na and water retention and a diminished level of serum creatinine.(Knight et al., 1999)

A brief review of all the important clinical trial has been presented in one of the previous studies. It demonstrates examples from trials like Sliwa et al, CARMEN trial, CIBIS III trial etc. which respectively demonstrated the beneficial or statistically non-significant effect of BBs compared to ACEI amongst patients with idiopathic dilated cardiomyopathy for carvedilol (BB category 3 drug as per JNC guideline, i.e. BBc3), for patients with increased

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cardiac remodeling for carvedilol and for patients requiring all-cause/cardiovascular hospitalization for bisoprolol (BB category 1 drug as per JNC guideline, i.e. BBc1).(Komajda et al., 2004; Remme, 2007, 2008; Remme et al., 2004).(Flather et al., 2005; Remme, 2008; R. Willenheimer, 2009; R. Willenheimer et al., 2005) At the same time, the beta-PRESERVE trial is trying to test metoprolol succinate (BBc1) across various clinical outcomes for HF with normal left ventricular ejection fraction (HFNEF) in a multicenter trial, thereby broadening the spectrum of BBs not only for patients with high LVEF but also for patients with Normal EF.(Morrissey et al., 2011; Zhou et al., 2010)

Although the existing evidence from RCTs establishes BBs as a promising therapeutic group for HF patients but there is still a need for generating the generalizable strong evidence regarding the comparative effectiveness of ACEI vs. BBs. The probable reason for this gap as suggested in past literature is that till date majority of the trials conducted so far have tried to compare only ACEI with placebos before even thinking about BBs trials.(Cruickshank, 2000; Gheorghiade, Colucci, & Swedberg, 2003; Remme, 2007; Remme et al., 2004) The ample of evidence generated in favor of ACEI against placebo made it a standard therapy for conducting a HF trial. Even when BB trials were conducted ACEI was part of approximately 90% of the trial's patient population e.g. SENIOR trial which makes it hard to attribute the protective effect of the trial solely to beta-blockade.(Flather et al., 2005; Remme, 2007, 2008) This especially poses a challenge for treating elderly patients with BBs. Although these trials target elderly HF population but the included patients are comparatively younger volunteers, thereby providing results on a biased population.(Richardson et al., 2010) The CIBIS III trial tried to include this population but the trial does not address the safety and efficacy of BB for elderly patients' clinical end-points. And this trial used up most of the time for initiation and up-titration of bisoprolol, so despite WHF being the underlying phenomenon for introducing

BBs among HF patients, the trial is not considered a good setting to answer the research question.(Remme, 2007, 2008; R. Willenheimer et al., 2005)

Further, studies have also reported that the effect of BBs varies with the type of BB under scrutiny.(Aronson, 2008) This makes it difficult to generalize the findings. For example, COMET trial showed greater reduction in fatal and non-fatal MIs and SCD due to carvedilol treatment compared to metoprolol treatment (Beta-1 selective agent or BBc1).(Poole-Wilson et al., 2003) Bisoprolol has a similar profile as of metoprolol. This may imply that the type of BB is an important factor in revealing the most effective BBs of all or for comparing these BBs with another class of drugs like ACEI in this case. Thus there exists a gap in the literature which demands us to bring more evidence in this regard. However, despite our desire for conducting a RCT, its cost, time and other practical limitations makes RCTs practically an infeasible design approach. Additionally, it is difficult to compare all or even more than 2-3 BBs with another anti-hypertensive class in a single trial. And therefore, there is a need to think of alternative research strategies like observational studies before planning for RCTs.

Till date, none of the existing observational studies have provided a direct head-to-head comparison in this regard. However, based on some observational studies like Richardson et al, Teng et al etc. which compare association of BBs with mortality or a clinical outcome other than recurrent hospitalization in HF patients after discharge, the evidence again seem to support the direction of the research hypothesis of this study.(Richardson et al., 2010; Teng et al., 2010; Toh et al., 2012) However, these studies either lack in providing a head-to-head comparison of ACEI/ARB with BB or their sample frame is different than HF for example studies like Toh et al which tests these patients for angioedema patients or study by Galindo-Ocana et al explores a cohort of any patient on these drugs.(Austin, 2009; DiMartino et al.,

2010; Maison et al., 2012; Wijeysundera et al., 2011).(Richardson et al., 2010; Teng et al., 2010) (Toh et al., 2012) Similarly, the study by Magid et al also compared ACEI vs BB for Hypertensive patients.(Magid et al., 2010) This study concludes that ACEI and BB are equally effective in lowering Blood Pressure (BP) and preventing cardiovascular disease and related events for patients whose BP is not controlled with Thiazide Diuretics alone and who have no compelling indication for 2nd line agent. None of them provide an estimate of the probability of observing the first hospitalization or recurrent hospitalization.

Based on past literature, it has been speculated that with the change in type of BB (from bisoprolol to carvedilol i.e. from BBc1 to BBc3), there is a possibility that the results of CIBIS III trial may change, especially for hospitalization due to WHF. However, to establish this difference in WHF across different BB categories compared to ACEI or their combination, the data used in this study does not have any direct measure. To deal with this issue, an approach similar to the SHIFT trial was followed. In this trial, WHF was assessed as risk of potential recurrent hospitalization as a measure of WHF and it calculated the time-to-first, second, third and subsequent repeated hospitalization, and the gap between each of these subsequently repeated hospitalizations.(Borer et al., 2012)

With these facts evident to us, this study aims to understand the impact of initiating different categories of BB compared to ACEI and the combination of both on risk of recurrent HF hospitalization in near future amongst HF patients. HF patients are at high risk of repeated hospitalization. If it can be proved that hospitalization and re-hospitalization are comparable across ACEI vs different categories of BB, then in true sense the non-significant difference of the 2 drugs can be established. But most studies as mentioned above either compare first hospitalization or they study about all-cause hospitalization. The information from this study shall overcome this gap and provide an estimate of repeated risk of

hospitalization. The information can be beneficial in situations where ACEI is not tolerated and in elderly HF patients with average age 73-75 years, as prevalent in HF community. Since the evidence in this study are from real world, rather than from a controlled environment of a RCT, the study can provide us the preliminary evidence with regard to the sole effect of BBs distinguished from the influence of ACEI and other RAS inhibition. Additionally, the study has compared various classes of BBs compared to ACEI which is essential to decide from amongst interchangeable therapeutic classes. Therefore, the study can provide a hope towards a better control of HF compared to current scenario not only by preventing hospitalizations but also by preventing many cases of SCD as has been established by the trials. Once there is sufficient evidence the results can be validated in an RCT with ACEI. This study is one step in this regard.

In short, the study is trying to compare time-to-recurrent HF hospitalization across ACEI vs different categories of BB users. The hypothesis for this study is that the time-to-recurrent hospitalization for the BB group as monotherapy is at least not significantly different when compared to ACEI.

Methods

This is a retrospective cohort study that includes elderly Medicare Advantage Prescription Drug Plan (MAPD) patients in Texas region for the year 2008-2011. The data is collected by the Centers for Medicare and Medicaid Services (CMS).

The details of this claims data have been provided elsewhere. This study has used information about patient membership and member summary for demographics, CMS risk score, cost and type of visit or admission made for each year. The Institutional and Professional claims files, Quest lab files and Pharmacy files were used to extract information on inpatient and outpatient claims, lab tests and drug identifying and related information respectively.

Ethical Considerations This study is exempted from human studies review requirement by the Institutional Review Board of University of Houston.

Study Sample

The study stacks all 10252 HF patients from MAPD 2008-2011 data as existing in community, in long-term care facility or in hospice program and HF patients diagnosed by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 428.xx, 401.x1, 404.x1, 398.91, 402.x1 and 404.x3. (Birman-Deych et al., 2005; DiMartino et al., 2010; Goff et al., 2000; Richardson et al., 2010) Of these, all the HF patients alive on the index date and those with a diagnosis date and a membership of at least 6 months prior to a claim made after '01July2008' for initiation of ACEI or BB as a monotherapy or in combination or neither of these in the Pharmacy Data File were included in the study. (Richardson et al., 2010) Further any patient claiming for ARB, aldosterone antagonist or Aliskiren in the washout period or BBs with Sympathomimetic activity (BB category 2 or BBC2) and any combination of BBs category 1 and 3 (BBc1 and BBc3 respectively) were

also excluded from the study. (Rashikh et al., 2012; Toh et al., 2012; R. Willenheimer et al., 2004; R. Willenheimer et al., 2005) A cut-off of proportion of days (PDC) being less than or equal to 0.04 for each drug was chosen to define a 'yes' and 'no' for each therapeutic category. The details of these inclusion/exclusion criteria, cut-off criteria, prescription drugs and the sample characteristics can be referred in the previous study.

Follow-up period

The patients were included from 1st Jul 2008 till 5th Jan 2011 and followed for a year of 360 days and with consistent month duration of 30 days each. The patients were censored if they initiated a claim for any of the not-required drugs (ARB, BBc2, aldosterone antagonists or aliskiren), had a death record on the date or reached the last record from pharmacy/Quest Lab/Institutional/Professional Claims file or if the follow up time of 360 days was completed.

Outcome

The primary outcome for this study is time-to-recurrent HF hospitalization within a year from the index date (date of initiation of a therapy). Recurrent hospitalization is a composite of all the HF hospitalization identified by the DRG codes 291, 292 and 293 and occurring subsequent to the index date until a year (360 days) of the index date.("National average costs by department for heart failure and shock," 2010; "National average costs by department for heart failure and shock (revisited)," 2014; Navarro-López et al., 1997; Newhouse et al., 2003) Thus, it includes -

1. A subsequent hospitalization after the index date as defined in previous study as the first subsequent hospitalization.

2. A new hospitalization event after the first subsequent hospitalization

3. A change in drug status after the hospitalization and before the discharge

The follow up does not stop at the time an event is observed; rather this was identified as an event and after changing the interval the patient was followed till the time as defined above. The censor variable is defined for each interval rather than for the whole follow up time. In every interval the drug status and hospitalization status is constant. The interval changes with a change in either of the status. If an event is observed in an interval the censor variable was indicated as '1' else '0' and continue to follow up for next interval till last claim is made. For each interval a start and a stop time are defined to indicate the duration of an interval. Each interval censoring was assumed to be caused by covariates and treatment/exposure to a drug in the previous interval and the therapy initiated on the index date. The information was used to develop statistical models as explained later.

A secondary outcome of these recurrent events with death as the terminal event was also defined. Here, censor variable was defined to indicate both the events of hospitalization and death with indicator of '1' for hospitalization, '2' for death and '0' for no event or other reasons of censoring.

Exposure

A multinomial exposure variable was defined to identify exposure to either ACEI or BBc1 or BBc3 or a combination of ACEI with BBc1 (ABC1) or with BBc3 (ABC3) or a therapy other than any of these therapies on the index date and in the previous interval. The study used a PDC based approach as defined by Leslie and used information about prescription claims and days' supply both from Pharmacy file. Each day was coded as '0' and '1' based on the pharmacy claim made on a day or if the prescription was supplied for a day.(S. R. Leslie et al., 2008) The day the drug code '0' was observed the interval was changed. Therefore, for the index date or for an interval the PDC is 100% on a particular

therapy group. Using this technique, the exposure to the index therapy (the initiated therapy or trt_1), therapy in the previous interval (prdg) or in current interval (dg) was defined.

Inverse Probability weight (IPW)

An IPW was defined as a product of the treatment, dose and censoring weights as were calculated from repeated interval observations for each person-interval.(Hernán et al., 2000; Schaubel & Zhang, 2010; Sugihara, 2010; Van der Wal & Geskus, Sep 2011) For each of these individual weights a numerator and a denominator probability was calculated by using Proc Genmod for multinomial treatment model for drug provided in the previous interval and 3 multinomial average dose (high, medium, low or none) models for ACEI, BBc1 and/or BBc3 for the same drug provided in the previous interval.(Faries & Kadziola, 2010) The Phreg models for censoring for death (Informative censoring) and other reasons for censoring (Non-informative censoring) were developed using count based approach.(Hernán et al., 2004; Robins & Finkelstein, 2000; Schaubel & Zhang, 2010; Van der Wal & Geskus, Sep 2011) Each of the numerator probability was obtained by controlling for treatment on the index date (trt_1), duration of days exposed on trt_1, time from the index date to start of current interval, dose of trt_1, treatment provided in the previous interval (prdg), days and dose of exposure on prdg. Along with these exposure history variables, time-fixed variables like gender, baseline hospitalization status and their count were defined. This was defined as time-fixed model. For denominator, all the variables of time-fixed model along with a parsimonious model of all predictors defined at each interval for the observations from previous interval as time-varying covariates were controlled. This is defined as time varying model. For each of these models following 2 assumptions are made:

- The therapy provided in each interval effects the covariates like co-medications, cost etc. and thus varies as therapy changes with interval or time i.e. time-varying.

- These time-varying covariates in an interval further affect the treatment provided in next interval.

Therefore, Dose as time-varying variable was used to calculate weight for dose at each interval as follows(Faries & Kadziola, 2010): -

$$Dosewt = \left(\frac{ACEI0}{ACEI1}\right) * \left(\frac{BBc10}{BBc11}\right) * \left(\frac{BBc30}{ABBc31}\right)$$

And the inverse probability weight (IPW) was defined as follows(Chitnis et al., 2012; Cole & Hernán, 2004, 2008; Hernán et al., 2000; Hernán et al., 2002; Hernán et al., 2004; Van der Wal & Geskus, Sep 2011): -

$$IPW = \left(\frac{Predtrt0}{Predtrt1}\right) * (Dosewt) * \left(\frac{Death0}{Death1}\right) * \left(\frac{ORC0}{ORC1}\right)$$

This IPW was adjusted for history and normalized by count to adjust for sample size in respective treatment groups to obtain the final weight.(Chitnis et al., 2012; Hernán et al., 2002; S. Leslie & Thiebaud, 2007) Except for other categories of previous drug, for which only 11 categorical covariates were balanced w.r.t. ACEI, all other categories of drug provided in the previous interval showed a balance of 41-44 categorical covariates out of 44 categorical covariates w.r.t. ACEI with final normalized IPW history weight which indicates a good balance amongst the treatment groups with respect to ACEI. For continuous variables there was still significant variation but compared to unweighted data weighing was considered a better approach as it balanced majority of the variation across treatment groups with respect to ACEI.

Further details of the method and time-varying covariates can be referred as explained in the previous study.

Statistical Analysis

The study develops a total time and gap model based conditional extended-cox-regression model to identify the time-to-recurrent hospitalization with strata across the start time of an interval.(Borer et al., 2012; Guo, Gill, & Allore, 2008; Lu & Liu, 2008; Robins & Finkelstein, 2000; Schaubel & Zhang, 2010) It was assumed that all the recurrent events are different from each other. The results were compared with unweighted and univariate model for person-interval data. A univariate Kaplan Meier curve, Schoenfeld residuals and log rank test were developed to test the proportionality hazard assumption, which was violated in this study (p-value ≤ 0.05).

For secondary outcome, a marginal model was developed which assumes a patient is at risk of all these different events i.e. hospitalization and mortality at all the times. All the conditional models and marginal models were modified to obtain robust standard errors and to indicate correlated observations for each patient using COV(Aggregate) weighted for history of the treatment, dose and likelihood of censoring using IPW weight as explained above.

In these models, a patient was followed for the duration as long as the patient is on one of the either treatment groups with or without switching to represent the effect of censoring in current interval w.r.t. the effect of therapy provided on the index date i.e. 'Initiated Therapy' (trt_1). A univariate model to test the effect of trt_1 was also developed for all the models. Additionally, the therapy provided in the previous interval (prdg) was also included in the fully adjusted models along with other fixed-effect and time varying covariates as used for

IPW weights. None of the models controlled for the effect of current therapy on current interval censoring to avoid the possibility of reverse causation bias.

For reference purpose, models were numbered as '1' for univariate unweighted crude model, '2' for weighted univariate total time model, '3' for the weighted fully adjusted total time model, '4' for weighted univariate gap time model, '5' for the weighted fully adjusted gap time model, '6' for weighted univariate marginal model, '7' for the weighted fully adjusted marginal model.

All analyses were performed using Statistical Analysis Software (SAS) version 9.3 (SAS Institute Inc., Cary, NC, USA) with a significance level defined at p-value ≤ 0.05.

Sensitivity analysis for Change in length of follow-up

As discussed in the previous study, results were re-analyzed for change in follow-up time period from 1-year to 2-years based on past literature suggestion of the effect of length of follow-up on estimates.(Sliwa et al., 2004), (R. Willenheimer et al., 2005)

Subgroup analysis of Ejection Fraction (EF)

Here, patients with EF <45% were identified using a claims-based definition based of systolic dysfunction and with a positive predictive value of 87%.(Setoguchi et al., 2011) According to this definition patients were chosen with no diagnosis of atrial fibrillation (ICD-9-CM code 427.31) and the ones who had received Digoxin during the 180 days before the index date, which for this study is the therapy initiation date.(Jensen et al., 2012; Setoguchi et al., 2011)

Results

There were 331 (5.15%) events of recurrent hospitalizations in the cohort of 6430 elderly HF patients. At interval level these observations gave 18923 person-interval observations in the cohort with 1.75% of event intervals of recurrent hospitalization. Of all the patients 55 patients (0.86% patients) observed more than one hospitalization events representing a rare event i.e. 0.29% interval observations only. Along with this there were 695 events which constitute 10.81% of cohort patients and 3.67% of person interval observations. Table 1 compares the frequency distribution of censored observations in the person-interval cohort. There were 55 recurrent events with ≥2 counts of hospital events i.e. 0.86% of all the cohort population at the patient level.

The Kaplan-Meier plot for unadjusted unweighted person-interval data is represented in Fig 2. This represents maximum survival probability for patients initiating ACEI and lowest for BBc3 groups at different stop points where interval ends. Although all the treatment groups appear to be somewhat proportional to the survival curve of ACEI for initial part of the data, but log rank test violates the proportionality hazard assumption for at least one treatment group (p-value<0.001).

Table 2 compares the result of all the Hazard Ratios from all the models and their respective 95% Confidence Interval for the risk of recurrent hospitalization. The result demonstrates that after adjusting for other covariates in Model 3 or Model 5 i.e. Total time and Gap Model, initiation on BBc1 and BBc3 gave a non-significant hazard ratio with respect to ACEI. The hazard ratio for BBc1 were 0.969(95%CI: 0.47- 1.399) and for BBc3 were 1.32(95%CI: 0.702- 2.483) from both the Models. The hazard ratios for combination therapy of BBc1 and ACEI was 0.953(95%CI: 0.457- 1.988) and it was 0.533(95% CI: 0.19- 1.496)

for a combination of ACEI and BBc3 from both the models. It is to be noted here that all the results from total time and gap model were exactly same when stratified across start time from index date. This could be probably because they both are representing the same interval when stratified by start time for an interval from the index date.

For marginal model which models the risk of recurrent hospitalization with death as the terminal event, the hazard ratio for BBc1 was 0.871(95%CI: 0.512- 1.482), for BBc3 was 1.41(95% CI: 0.843- 2.36), for combination of ACEI and BBc1 was 0.77(95%CI: 0.431- 1.376) and for combination of ACEI and BBc3 was 1.407(95%CI: 0.53- 3.736).

For other therapy group, all the models represented significantly high hazard ratios compared to ACEI except for the univariate unweighted crude model.

Table 3 presents the result of sensitivity analysis for 2 year follow up data. Contrary to 1-year follow-up data, this data gave significant p-values of BBc3 as monotherapy for both recurrent hospitalization and also for composite outcome of recurrent hospitalization with death as terminal event. The respective HR values were 2.256(95%CI: 1.154- 4.413) and 1.933(95%CI: 1.135- 3.295). For BBc3 as monotherapy also respective estimates increased compared to 1-year data. These HR estimates for recurrent hospitalization and for composite outcome were 1.132(95%CI: 0.511- 2.507) and 2.097(95%CI: 0.967- 4.55) respectively. For BBc1, the increment was within the 95%Confidence interval of 1-year data. The HR estimates for BBc1 as monotherapy were 1.265(95%CI: 0.698- 2.292) and 1.102(95%CI: 0.647- 1.877) for the 2 outcomes respectively. And they were 0.532(95%CI: 0.253- 1.119) and 1.079(95%CI: 0.611- 1.905) respectively for each outcome for BBc1 as combination therapy with ACEI.

Discussion

The above results indicate a non-significant recurrent hospitalization of BBc1 compared to ACEI. These estimates decreased for all the models, i.e. Total time, Gap time and also for Marginal model after adjustment.

The CIBIS III trial reported a slightly non-significantly high HR of 1.25 (95%CI: 0.87-1.81) for WHF while hospitalized for bisoprolol compared to ACEI.(R. Willenheimer et al., 2005) As argued previously, recurrent hospitalization can be considered a measure of WHF, the 2 results seem to have overlapping 95%CI estimates. The results also indicate that the marginal event estimates for composite outcome, i.e. for recurrent hospitalization with death as the terminal event, the estimate is slightly low with slightly narrow confidence interval. This may probably imply that the greater benefit of BBc1 lies in not just reducing the risk of recurrent hospitalization but it reduces overall risk of hospitalization with death as the terminal event and thus shows a promising therapy in comparison to ACEI. This could possibly be attributed to the ample evidence in favor of BBs being a preferable therapy to reduce SCD.

For BBc3, all the univariate models (1, 2, 4 and 6) gave a significantly high hazard ratio. However, with adjustment for covariates from the previous interval total time and gap model estimates were non-significant but slightly high compared to BBc1. The CARMEN trial did not presented any HR values but reported the 10% and 8% cases of worsening of CHF for patients on BBc3 and its combination with ACEI respectively as opposed to 10% cases for ACEI group, which similar to our study implies a no significant difference in estimate for BBc3 compared to ACEI.(Komajda et al., 2004) Surprisingly, these estimates again became significant in the sensitivity analysis indicating deterioration in their effect for the 2-year data. These estimates were worse than any of the BBc1 estimates in the second year

rendering BBc3 as the therapy as an ineffective treatment at least as monotherapy. It is important here that none of the estimates of BBc1 in this 2-year data were higher than any of the BBc3 as monotherapy or as combination estimates for the 2-year data and as BBc3 monotherapy for 1-year data.

For both the combination therapies the hazard of recurrent hospitalization was non-significantly different than ACEI. As expected the combination of BBs with ACEI gave low hazard ratio of recurrent hospitalization with more favorable results for combination of ACEI and BBc3 for 1-year data. However, these estimates although non-significant but they became unexpectedly high for the 2-year follow up data, which raises doubt regarding the utility of BBc3 even as a combination.

Overall, it appears that BBc3 has a better protective effect as combination therapy only for 1-year data followed by BBc1 as monotherapy or as combination. This leads us to recommend BBc3 combination with ACEI for better protection for the first year as also suggested by past literature.(Sliwa et al., 2004) However, the study does not support its long term utility, for which BBc1 appears to be a better alternative. Additionally, considering the estimates of BBc1 as monotherapy and as combination are close enough for the both years, it could be considered advisable to prescribe BBc1 as monotherapy rather than combination to avoid polypharmacy amongst elderly patients and for long term effect.(Fahey et al., 2005; Gupta & Aparasu, 2013; Powlson, 2003; Volpe et al., 2010)

For the secondary outcome i.e. composite outcome of recurrent hospitalization with death as the terminal event also all the BB groups gave non-significant hazard ratios with respect to ACEI. Whereas for BBc1 as monotherapy and as combination with ACEI it was non-significantly low; for BBc3 group it was non-significantly high, being highest for BBc3 as monotherapy. Therefore, for this composite outcome, it appears that although it could be a

non-significant difference nevertheless BBc1 as monotherapy or as combination both appears to be more beneficial compared to BBc3 as monotherapy or as combination. This seems justifiable because in one of our previous studies it was observed that a higher risk of mortality was observed for BBc3 as combination and as monotherapy compared to BBc1 as monotherapy or as combination. Additionally, the results of sensitivity analysis gave statistically significant high hazard ratio for BBC3 as monotherapy and non-significantly high HR values for BBc3 as combination therapy.

Although CARMEN trial did not reported a HR for all-cause mortality or all-cause hospitalization, but they reported non-significant p-values for BBc3 (0.8403) and for its combination(0.5875).(Komajda et al., 2004) The CIBIS III trial on the other hand reported a HR of 0.94 (95%CI: 0.77-1.16) for intention-to-treat analysis and a HR of 0.97 (95%CI: 0.78-1.21).(R. Willenheimer et al., 2005) The estimate from this study is slightly low for BBc1 with an HR of 0.871(95%CI: 0.512- 1.482) compared to CIBIS III trial estimate possibly because along with all-cause mortality the composite outcome in this study is specifically for HF hospitalization and not any cause hospitalization as is the case in the trial. Additionally, the composite outcome used in both these trials is not a representation of correlated repeated hospitalization; rather it counts either of the events with equal risk. This study thus provides estimates from different viewpoints as expected in real world.

In one of our previous studies, where hazard of first subsequent hospitalization was analyzed, BBc1 as monotherapy was suggested as a preferable therapy. Compared to this study, current study demonstrates that although for BBc1 as monotherapy the hazard of first hospitalization is low compared to BBc3, but for subsequent recurring hospitalizations the hazard increases slightly for monotherapy and majorly for combination of ACEI and BBc1. The hazard ratios for all the outcomes from both the studies are represented in table 4. From

these results, it is clear that BBc1 as monotherapy is a considerably more protective therapy for first hospitalization. The combination of BBc1 with ACEI, on the other hand seems to be more beneficial for mortality and for composite outcome i.e. for risk of hospitalization with death as the terminal event. For these 2 latter events, as monotherapy also, BBc1 appears to be doing a good job. And thus especially among elderly patients to avoid polypharmacy, BBc1 as monotherapy for mortality or for composite outcome can be expected to provide appreciable estimates along with reduction in risk of first hospitalization as already suggested. Further, the BBc3 as combination seems to be a therapy of choice for reducing the risk of recurrent hospitalization just for 1-year follow up. For first hospitalization also it seems to have done an appreciable job compared to monotherapy, but it definitely gives the impression of being a non-preferable therapy for mortality and for composite outcome. This contradicts the result of the COMET trial, which as suggested previously reported a greater reduction in fatal and non-fatal MIs and SCD due to carvedilol (BBc3) treatment compared to metoprolol treatment (BBc1).(Poole-Wilson et al., 2003) The possible difference could be due to the fact that the COMET trial included severe patients with EF<35% which as suggested in previous study constitutes a very small proportion of patients in this study.(Poole-Wilson et al., 2003) This possibility is supported by the fact that in subgroup analysis i.e. amongst patients with EF<45% more BBc1 users showed recurrent events compared to BBc3 users. There were 27.78% of BBc1 users compared to 11.11% of BBc3 users with recurrent events from amongst overall 18 events.

In real life, however, recurrent hospitalization is not observed as an event independent of the risk of death as the terminal event, which means there is always an existing risk of a composite recurrent hospitalization which is associated with death as the terminal event.(Lu & Liu, 2008; Schaubel & Zhang, 2010) Even with first hospitalization, recurrent

hospitalization and death seems to be associated at all points during follow up. This implies that BBc1 as combination therapy with ACEI or as monotherapy is a promising Beta-Blocker compared to BBc3. Further research in this direction shall validate the findings.

For other therapies, except for the univariate unweighted model (Model 1), all other models gave a significant high hazard ratio. However, since this group contains maximum variation in terms of exposure groups included another variables which remained unbalanced even after weighing, the estimates could be unreliable. However, considering that this group is not the focus of this study, the results are not being discussed here.

Limitation

The limitations of this study are same as discussed elsewhere. This includes coding issues inherent to claims data, lack of direct measure of severity and random assignment to different treatment groups, and no discrimination of ACEI vs BB vs their combination as first line or 2nd line or 3rd line therapy and the study included only JNC approved drugs.

In addition to this there is a measurement of exposure assumed proportionally the same in all the treatment groups. For example, due to insufficient follow-up time for these patients, a non-differential measurement of exposure can be possibly observed. May be all the therapies are in the therapy-initiation phase and have not reached proper maintenance dose, especially prevalent effect for BB-therapy. To avoid this, patients were followed for a defined period based on past literature. The effect of strictly including patients who took the drug for at least 14 days in model 5 also assures some time on these therapy before their results can be compared. Additionally a sensitivity analysis was done to assess the effect of longer follow-up period.

The study could not provide the effect of BBs with sympathomimetic activity i.e. BBc2, effect of actual adherence and the effect of some important covariates like race. These should be the focus of future studies before generalizing the results to all the elderly HF patients.

Strength

1. Unlike many other observational studies, this study controls for the influence of dose too along with other variables. The CIBIS III trial used an open design where the titration schedule was dependent on the tolerability of each individual and their response to treatment.(R. Willenheimer et al., 2004) In real life, this situation is the driving factor for switching of the therapies.

2. It provides information for ACEI/BB as monotherapy and as combination both, and not just of monotherapy. In CIBIS III trial, the author suggested that the first initiated therapy like ACEI or BB, stands the better chance to be given for a long term and in adequate dose.(R. Willenheimer et al., 2004) However, our study has included patients on each therapy with doses as prescribed in real world. In real-world doses are adjusted as per the tolerability of the patient and thus their up-titration may be different than that applied in a controlled environment of an RCT. For example, here already a minimum tolerable limit and optimum standard dose is known, so prescribers may have a different starting dose compared to that used in a RCT.

3. Sensitivity analysis tests the results for initiating ACEI/BB/combination therapies for a longer duration, which is essential as suggested by previous trials for BBs to show their optimum effect(Sliwa et al., 2004; R. Willenheimer et al., 2005).

4. The use of available lab values at various time points minimizes the confounding by indication. Although there are lots of missing information in these variables, but this is expected as also suggested by Schneeweiss.(Schneeweiss et al., 2012) Further using

LOCF, these possibilities of missing values was reduced. Weighing the history of the observation also helped to reduce the effect of missing information. And finally, any missing observation was not discarded from the study; rather it was included as a 'Missing value' category to extract whatever possible information could be found from the study.

5. The class effect of different BBs has been compared here, which is difficult in RCTs. This provides additional information to clinicians which look out for therapeutic equivalent drugs to replace one.

6. The study provides evidence for all types of HF patients and not just those with LVEF <35% as chosen in CIBIS III trial.(R. Willenheimer et al., 2004) As already stated, beta-PRESERVE trial is trying to target effect of using BBs in HFNEF patients too, our study provide some evidence with regard to those population and may support the need for the trial for all types of population for HF and thereafter may result in the modification of the guidelines.(Zhou et al., 2010)

7. With double weighting and Covs(aggregate) the complex nature of the treatment was incorporated in the study since patients are provided certain treatment by considering their possibility of death/switching/other causes of drop-outs as the terminal event and also by considering that measures on one person are correlated in nature. This helps to bring the data and its analysis close to reality.

8. The Inverse probability weights helped to balance various treatment groups for at least the categorical covariates with respect to the reference category, thereby strengthening the causal design.

9. By comparing the results of recurrent event with models of recurrent event considering death as the terminal event, a comprehensive comparison of the effect of the treatment has been provided.

10. Further, use of multiple controls like other therapies along with nested nature of the data in the switching count process model helps to control for any overt bias. For this model, results are also obtained by cross-comparison across same patient on different treatment which provides advantages similar to cross-over designs along with cohort population.

11. The use of strong operational definition of exposure on the index date and in the previous interval based on 100% persistence on a day or in an interval respectively is a major strength of the study. However, it does not confirm the actual compliance to a therapy. Despite that the current definition are good method of intention-to-treat analysis with 100% persistence rate on a day or in an interval.

The strength of this study is evident from the closeness of the findings with the trial. Additionally some new estimates were assessed here which were not studied previously.

Conclusion

The results indicate that compared to ACEI there is a possible statistically non-significant effect of BBs both as monotherapy and as combination. BBc1 seems to be a preferable therapy compared to BBc3 for first hospitalization, for composite outcome of recurrent hospitalization with death as the terminal event and for mortality as an independent event. On the other hand, BBc3 as combination rather than BBc1 appear to be more beneficial for recurrent hospitalization as a measure of WHF for 1-year follow-up after which it's effects seem to deteriorate considerably in favor of BBc1 as combination or even as monotherapy and ACEI.

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Atleast 6 months prior membership and alive

BBc1 and BBc3 as combination

Medicare Advantage Prescription Drug (MAPD) 2008-2011

Washout

Combination

ACEI

BBs

Other

1 year

Outcome

Aldosterone antagonist on the index date

5. BB with sympathomimetic activity (BBC2) for 3 months
6. ARB for 3 months

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HF Diagnosis

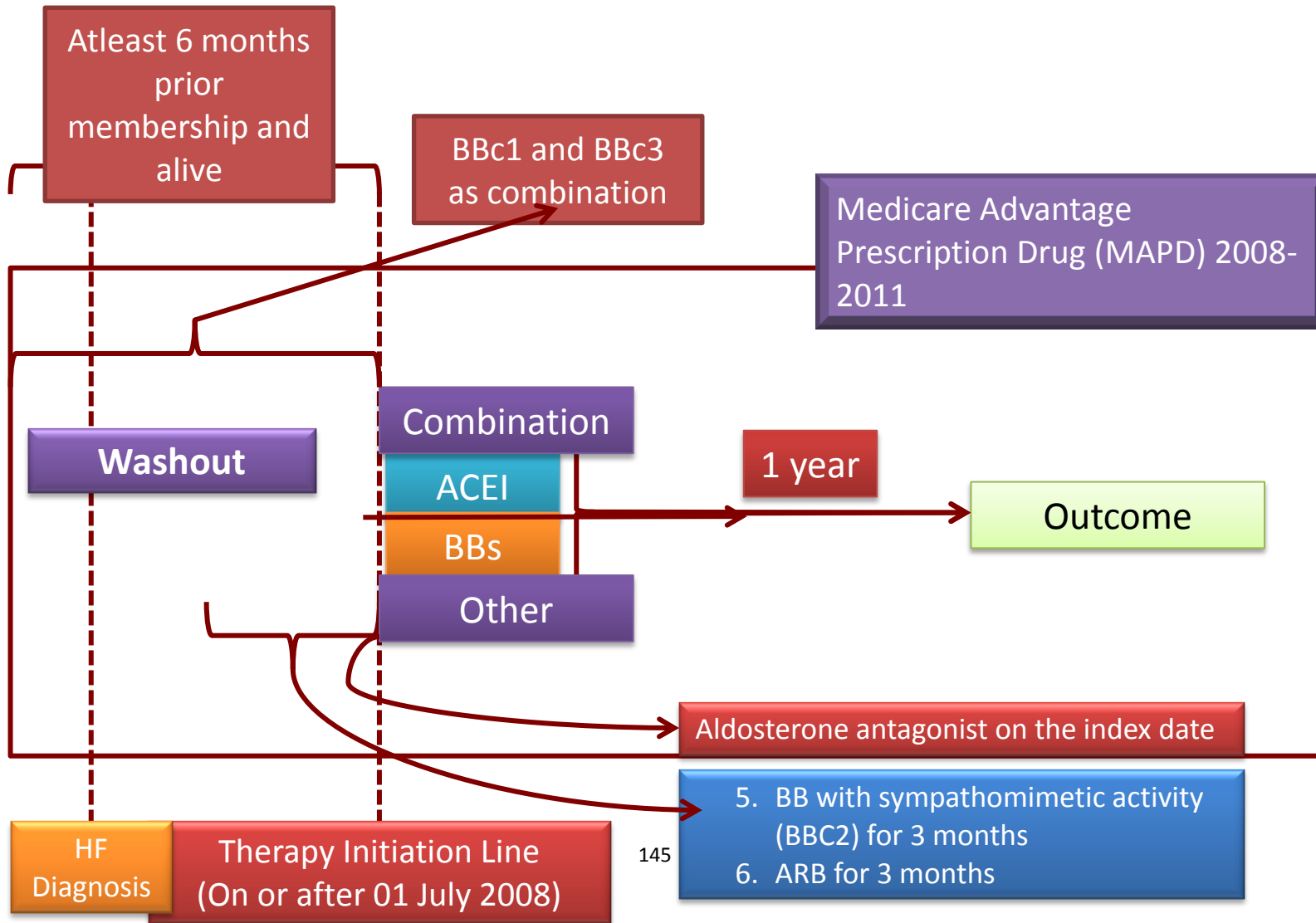Therapy Initiation Line (On or after 01 July 2008)

Fig 2. Kaplan-Meier Plot for univariate unweighted survival probabilities for recurrent hospitalization after initiating a treatment on the index date for person-interval data

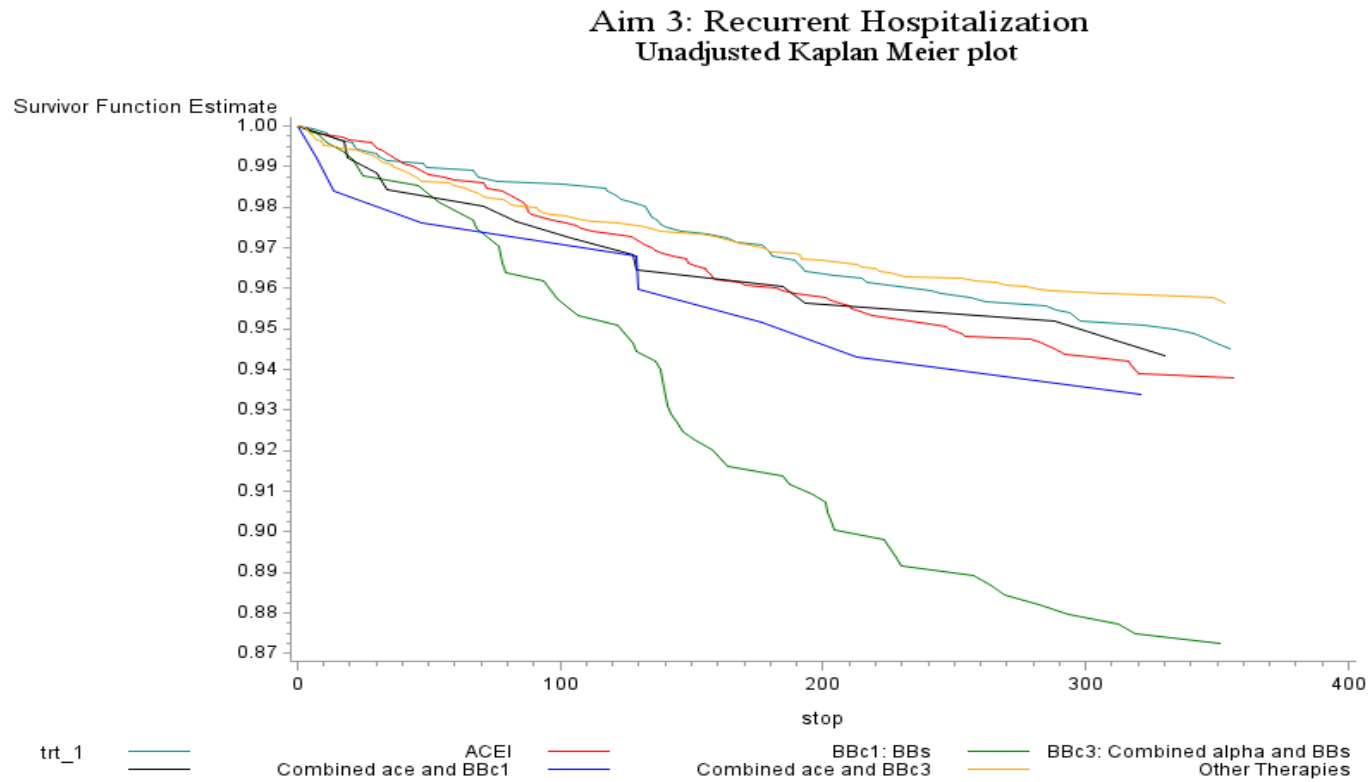| Table 1. Censored observations in the interval level cohort with death as the terminal event		
Recur	**Frequency**	**Percent**
0	17566	84.04%
1 (Hospitalization)	331	1.75%
2 (Death)	695	3.67%

Obs	Initiated Therapies	HR1	HR2 or HR4	HR3 or HR5	HR6	HR7
	Table 2. Comparison of Hazard Ratios for recurrent hospitalization due to initiation therapy across Models 1 to 7 HR(95% CI: Lower CI-Upper CI)					
1	**BBc1: BBs**	1.143 (0.824- 1.585)	1.043 (0.658- 1.655)	0.969 (0.47- 1.996)	0.985 (0.693- 1.399)	0.871 (0.512- 1.482)
2	**BBc3: Combined alpha and BBs**	2.442 (1.704- 3.498)	2.051 (1.274- 3.302)	1.32 (0.702- 2.483)	1.719 (1.133- 2.607)	1.41 (0.843- 2.36)
3	**Combined ace and BBc1**	1.052 (0.588- 1.88)	0.81 (0.381- 1.719)	0.953 (0.457- 1.988)	0.846 (0.477- 1.502)	0.77 (0.431- 1.376)
4	**Combined ace and BBc3**	1.237 (0.592- 2.585)	1.376 (0.567- 3.342)	0.533 (0.19- 1.496)	2.079 (0.839- 5.156)	1.407 (0.53- 3.736)
5	**Other Therapies**	0.823 (0.599- 1.13)	18.473 (11.419- 29.885)	6.925 (3.151- 15.218)	14.679 (9.927- 21.705)	6.311 (3.694- 10.78)

HR1 = Hazard ratio for Univariate Unweighted Count Model with switching (Model 1)

HR2 and HR4 = Hazard ratio for Weighted Univariate Model with switching– a total time or a gap model
(Model 2 and 4 respectively)

HR3 and HR5 = Hazard ratio for Weighted Adjusted Model with switching- a total time or a gap Model (Model 3 and Model 5 respectively)

HR6 = Hazard ratio for Weighted Univariate Marginal Model with switching (Model 6)

HR7 = Hazard ratio for Weighted adjusted Marginal Model with switching (Model 7)

Table 3. Sensitivity Analysis for 2-year data.

Hazard Ratios for all the HF hospitalization outcomes for BBs as monotherapy or as combination therapy with respect to ACEI

Drug	First hospitalization	Recurrent hospitalization	Composite outcome	Mortality
BBc1: BBs	0.971(0.473- 1.994)	1.265(0.698- 2.292)	1.102(0.647- 1.877)	0.369(0.023- 6.001)
BBc3: Combined alpha and BBs	1.303(0.688- 2.465)	2.256(1.154- 4.413)*	1.933(1.135- 3.295)*	1.882(0.095- 37.089)
Combined ace and BBc1	0.94(0.449- 1.965)	0.532(0.253- 1.119)	1.079(0.611- 1.905)	0.000
Combined ace and BBc3	0.536(0.19- 1.509)	1.132(0.511- 2.507)	2.097(0.967- 4.55)	4.4(0.28- 69.249)

* Significant at p-value ≤0.05

Table 4. Hazard Ratios for all the HF hospitalization outcomes for BBs as monotherapy or as combination therapy with respect to ACEI

Drug	First hospitalization	Recurrent hospitalization	Composite outcome	Mortality
BBc1: BBs	0.562 (0.278- 1.134)	0.969 (0.47- 1.996)	0.871 (0.512- 1.482)	0.212 (0.028- 1.598)
BBc3: Combined alpha and BBs	1.242 (0.636- 2.426)	1.32 (0.702- 2.483)	1.41 (0.843- 2.36)	1.069 (0.107- 10.701)
Combined ace and BBc1	1.052 (0.409- 2.706)	0.953 (0.457- 1.988)	0.77 (0.431- 1.376)	0.000
Combined ace and BBc3	0.632 (0.223- 1.793)	0.533 (0.19- 1.496)	1.407 (0.53- 3.736)	1.316 (0.115- 15.122)

Conclusion

The results indicate that -

1. Compared to ACEI there is a possible statistically non-significant effect of BBs both as monotherapy and as combination.

2. BBc1 seems to be a preferable therapy compared to BBc3 for first hospitalization, for composite outcome of recurrent hospitalization with death as the terminal event and for mortality as an independent event.

3. BBc3 rather than BBc1 seems to be more beneficial for recurrent hospitalization as a measure of WHF especially for patients with EF<45%. For general population as included in this study, BBc3 appear to be more beneficial for recurrent hospitalization as a measure of WHF just for 1-year follow-up after which it's effects seem to deteriorate considerably in favor of both ACEI and BBc1 as combination or even as monotherapy.

Final statement wrapping up the dissertation document

BBs have statistically non-significant risk of HF hospitalization in comparison to ACEI among elderly HF patients with more beneficial effects obtained for patients initiating BBc1 rather than BBc3 for a cohort of patients which includes majority of patients with normal EF i.e. patients with mild or moderate HF.