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Evaluating the use of cheaper, less effective medications in patients with cost-based medication nonadherence

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ABSTRACT A clinical decision report using:

Sangaralingham LR, Sangaralingham SJ, Shah ND, Yao X, Dunlay SM. Adoption of Sacubitril/Valsartan for the Management of Patients With Heart Failure. *Circ Heart Fail.* 2018;11(2):e004302. https://doi.org/10.1161/circheartfailure.117.004302

for a patient with low medication adherence rates due to the high out-of-pocket costs of newer medications.

Keywords: *medication adherence, heart failure with reduced ejection fraction, out-of-pocket costs*

Clinical-Social Context

Mr. Joseph Scarillo [pseudonym] is a 55 year old man with a past medical history significant for heart failure with reduced ejection fraction (HFrEF), type 2 diabetes mellitus, hypertension and hyperlipidemia who presented for heart failure exacerbation. Mr. Scarillo is prescribed metoprolol, Entresto (sacubitril/valsartan), and Jardiance (empagliflozin) for management of his heart failure, as well as furosemide (Lasix) 20 mg as needed. Prior to presentation, he had progressive dyspnea and orthopnea for one week. Concerned about a possible exacerbation, our team asked Mr. Scarillo to further elaborate on his symptoms. “I just feel like I haven’t been able to breath as easy as usual, doc. It’s been getting worse this week and I’m concerned.” He also said he “felt like he was swollen up” and noted that he was having difficulty leaving the house due to the dyspnea: “I wanted to go to the store with my wife, but it troubles me to walk too far since I’m having a hard time breathing”. We were especially concerned when I asked if he had difficulty breathing while lying flat and he gave the answer: “It feels like I’m choking when I go to bed”. Physical examination revealed jugular venous distension, 2+ bilateral pitting edema to the knees, and bilateral lung crackles to auscultation. Mr. Scarillo was placed on furosemide while inpatient with improvement of his volemic status and symptoms.

Chart review of the patient revealed frequent admissions with similar presentations, all for heart failure exacerbations. Discussion with the patient revealed that he had not followed up with his primary provider after the exacerbations due to his inability to afford his copay. Additionally, the patient has not been able to afford his Jardiance or Entresto, which contribute to his frequent hospitalizations. He was given samples by an earlier physician, who told him that these were the latest medications that worked best to treat heart failure, and was not able to afford his medications after the first refill. He told us, “I honestly haven’t been able to afford the meds doc. These prices are crazy and I’m not working. It just costs too much money”. The patient does have a family support system in place as he lives with his wife. He is not currently employed and does live in an apartment with his wife; he has financial difficulty acquiring medication. He has reliable transportation available to and from appointments.

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Clinical Question

Should medication cost take precedence over drug efficacy when selecting a heart failure management regimen for a patient with history of financial-based medicine nonadherence?

Research Article

Sangaralingham LR, Sangaralingham SJ, Shah ND, Yao X, Dunlay SM. Adoption of Sacubitril/Valsartan for the Management of Patients With Heart Failure. *Circ Heart Fail.* 2018;11(2):e004302. https://doi.org/10.1161/circheartfailure.117.004302 [1]

Description of Related Literature

A PubMed search was conducted on the subject at hand and featured the keywords (Heart Failure), (Medication), (Cost), and (Adherence). The result of the search yielded 1100 articles. Articles were then limited to full text availability, which narrowed the results to 562. The articles were filtered to include clinical trials, randomized control trials, reviews, and systematic reviews. From there, strict exclusion/inclusion criteria were used to find articles that most appropriately addressed both Mr. Scarillo's situation and the question asked. The studies must be USA based to ensure that the findings can be applied. Additionally, the articles must discuss either a drug within the same class as those taken by Mr. Scarillo or the application of patient cost to medication adherence and its outcomes. Using these criteria, 5 articles were selected. Additionally, a PubMed search of "Medication Adherence" and "Socioeconomic status" was performed to provide additional clinical context to address the question at hand, resulting in the selection of an additional article. Other combinations of these terms and other terms, including "quality of life", "compliance", and "patient cost", "Entresto", "Jardiance" were performed to ensure no articles were missed. An additional MeSH Search with the terms "heart failure", "valsartan", "Adherence", was done to further classify the literature. The chosen 6 articles, including the one selected for critical appraisal, are discussed below.

McMurray, et al. assessed whether an angiotensin receptor – neprilysin inhibitor combination (LCZ696, comparable to Entresto) improved mortality in patients with heart failure with reduced ejection fraction compared to an ACE inhibitor (ACEi).[2] This study was a randomized, double-blinded, multi-center clinical trial that evaluated 4187 patients that were randomly assigned to receive LCZ696 and 4212 that received enalapril with an intention-to-treat analysis, with 2-8 week follow up in the first four months and then every four months after. Results of the study showed that 21.8% of the LCZ696 patients and 26.5% of the enalapril-receiving patients died from a cardiovascular outcome or in the heart failure hospitalization during the follow up period ($p<0.001$). The study concluded that the LCZ696 significantly improved mortality in patients with HFrEF compared to an ACE inhibitor. While this study provides rationale prescribing Entresto over an ACE inhibitor, it was ultimately rejected for clinical appraisal due to its lack of discussion of medication nonadherence or cost benefits.

Chernew et al. explored the effects of patient cost on health care and its relationship to socioeconomic disparities.[3] This study was a retrospective chart review of patients that met inclusion criteria for heart failure with at least 2 outpatient claims or 1 hospitalization for heart failure. Additionally, a patient's medication adherence was tracked by the medication possession ratio (MPR), which is an estimated measure of the days in a month that a patient has access to their prescribed medications. Patients were classified by income status, as well as other demographic factors, including age, sex, and race. The study results revealed that the medication adherence for ACEi/ARBs was lowest at the mean copayment in the less than $30,000 income level. While this study did show the positive correlation between medication adherence and income status, it did not discuss the patient-level decision making or discuss the AR/neprilysin inhibitors that are an increased cost.

Rao et al. performed a qualitative study in which heart failure patients discussed their experience conversing with their doctors about medication-related expenses.[4] 49 patients from outpatient heart failure clinics were interviewed and probed about their conversations with doctors about their ability to afford medication, as well as their ability to afford prescriptions. Results were analyzed via a template analytic method called MAXQDA, developed by the team. The results of the study showed that the majority (76%) of patients did report comfort discussing costs with physicians, while 49% reported difficulty paying bills. While this study comments on the need for physicians to be proactive with medication cost discussion, it was not selected for appraisal because it does not provide quantitative data on adherence rates.

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Ruppar et al. performed a systematic analysis of medication adherence and heart failure outcomes.[5] 57 eligible studies were chosen from 6665 possible. Chosen studies looked at both mortality and hospital readmissions, and their association with medication adherence. Results revealed a significant increase in both mortality and hospital readmissions with decreased medication adherence. Ultimately, this study was rejected for appraisal due to its status as a meta-analysis, as well as its lack of discussion of cost as a potential barrier to medication adherence.

Smith et al. looked at out-of-pocket cost being a driver for heart failure management decisions in the context of Entresto.[6] It was a quantitative/qualitative cross-sectional interview study of HFrEF patients. Patients were screened for LVEF less than 40% and age of greater than or equal to 18 years. 49 patients met inclusion/exclusion criteria and their results to surveyed questions regarding financial status and willingness to switch to Entresto were recorded. The study found that 92% of patients would switch to Entresto if their out-of-pocket cost was $5/month, whereas 43% would switch with a copay of $100/month. This study was ultimately rejected for appraisal due to its lack of objective data about medication adherence.

King et al. evaluated the cost effectiveness of using the sacubitril-valsartan combination compared to the cheaper, generic valsartan in patients with HFrEF.[7] This study used a Markov model to evaluate cost effectiveness in the two medication populations. The patients in this study were greater than 60 years old, and the study modeled over a 40-year lifetime. The study found that Entresto was costlier than valsartan ($60,391 compared to $21,758). It did, however, show that Entresto produced better QALY (quality-adjusted life year, where one QALY is one year in perfect health) than valsartan alone (6.49 to 5.74). This study was ultimately rejected for appraisal given that it did not focus on the clinical application of the medications.

Sangaralingham et al. assessed the out-of-pocket costs of Entresto following its FDA approval.[1] The study was a retrospective analysis of a database that collected data from all 50 states regarding prescription medication services. Two cohorts of HFrEF patients were chosen following inclusion/exclusion criteria: those taking Entresto and those eligible for Entresto but taking ACEi/ARB. Results showed that 59.1% of patients were adherent to Entresto 180 days post-initiation. Additionally, only 20% of Entresto-nonadherent patients proceeded to fill an ACEi/ARB prescription. Additionally, the median monthly out-of-pocket cost of Entresto was reported to be $40.27, compared to $2-3 for an ACEi/ARB.

This study was ultimately selected due to its relevance to Mr. Scarillo's adherence situation. Mr. Scarillo meets the inclusion/exclusion criteria, and the study directly relates to the discussion at hand of the relationship between the cost of newer heart failure drugs and adherence. There is an appropriate sample size of 2244 patients, and a comparison to a control (ACEi/ARB). The article is also recent, having been published in 2018. Per SORT criteria, Level of Evidence is grade B.[8]

Critical Appraisal

The study selected is a retrospective data analysis of adoption and prescription drug costs of Entresto compared to traditional HF regimen of ACEi/ARB in patients with HFrEF. Using SORT criteria, the study falls under the Level 2 quality of evidence.[8]

The study design was a retrospective analysis of data already compiled in a prescription database. The use of a retrospective analysis allows for analysis into patient trends with prescription fills and demographic status. It also allows for the ability to assess outcomes and then evaluate for risk factors and criteria. For example, it allows for age analysis of those who continued to take ACEi/ARB vs those who transitioned to Entresto. Additionally, retrospective analysis allows for a large study size (2244 patients), therefore allowing for a large effect size and accurate standard deviation. However, no true value on the numerical effect size was provided, despite statistical data were published suggesting rates of adherence between Entresto and ACEi/ARB as a factor of out-of-pocket costs. A further study performing a clinical trial between Entresto and ACEi/ARB would be beneficial to clarifying a true value on the numerical effect size. It is also pertinent to note that these goals also can be accomplished in a prospective trial. Doing so would allow a more cause-and-effect evaluation of the two therapies and further the literature on the topic.

Patients in this retrospective analysis study were selected using the OptomLabs Data Warehouse. Its benefits include gathering data from all 50 US states, providing a larger geographical region than a study centered in one hospital. It also provides objective, accurate data about patient demographics, pharmacy fill rates, and medication adherence levels. An additional benefit of the study design is the avoidance of participation bias. Patients were not enrolled in a study at the time of receiving the medication, thus providing a more realistic adherence rate. Additionally, the inclusion/exclusion criteria of this study ensured that patients'

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characteristics were like those of Mr. Scarillo. Patients selected had to be 18 years of age or older and be diagnosed with heart failure with an ejection fraction<45% (via billing codes for systolic HF), both applicable to Mr. Scarillo. Additionally, patients had to be clinically eligible to receive Entresto, as in our patient. While there was a sizeable amount of Entresto patients in the study (2244), this was compared to a body of 39598 ACEi/ARB patients.

The intervention group did receive Entresto, as opposed to the standard regimen of ACE/ARB therapy, which served as the control group in this study. Thus, this study was a good representation of Entresto adherence compared to the generic ACEi/ARB therapies. Out-of-pocket cost and medication refill rates were directly examined in this study, making it directly applicable to Mr. Scarillo's clinical case, with inclusion/exclusion criteria factored in. The study showed a significantly lower medication refill rate of Entresto (59.1%), thus revealing a lower 180-day medication refill rate for Entresto compared to its ACEi/ARB companions. Of note, the study does not report an adherence rate to ACEi/ARB, which is a potential limitation to the work.

In terms of the study's results, all clinically relevant outcomes were reported. The study approached medication adherence from multiple fronts. Out-of-pocket (OOP) cost mean, median, range was provided for all studied drugs, including Entresto and ACEi/ARB, revealing increased mean and median OOP costs for Entresto compared to its ACEi/ARB companions. Additionally, univariate and multivariant predictors were given for 180-day medication adherence rates for Entresto. These two different fronts suggest the correlation between adherence rates and out-of-pocket costs. However, the study did not show a direct comparison between income level and medication adherence, which would have been able to further suggest a correlation between adherence levels and financial cost in Entresto vs ACEi/ARB therapies. These results would be clinically relevant because it would provide evidence to support that physicians should address medication costs directly with patients to improve adherence rates. However, the lower rates of adherence and medication refill given via univariate and multivariate analysis in the study for the medications with higher out-of-pocket costs still suggest a correlation between the two variables, providing clinical evidence that is of use in counseling Mr. Scarillo on medication adherence and choosing the right medication regimen to manage his heart failure. Data from this article can be factored into clinical practice, as it is feasible for clinicians to extrapolate the data of this article and lead discussions with their patients about potential adherence rates and their out-of-pocket costs. This would allow for a medication regimen that is more likely to be adhered to, given the low rates of adherence to Entresto in the study. It is also interesting to note that the study revealed that patients who were on ACEi/ARB prior to initiation of Entresto had better adherence rates; the univariate and multivariable Odds ratios for Entresto adherence were 1.42 and 1.146, respectively. Mr. Scarillo was unable to recall whether he was on ACEi/ARB in the past.

Additionally, statistical analysis was considered in this study. The study performed a univariate and multivariate analysis on the acquired data, providing 95% confidence intervals on refill rates broken down by demographic within each respective medication group (receiving Entresto; receiving ACEi/ARB). Mean and median values were reported for the out-of-pocket costs of the respective studied drugs, and logistic regression was used to determine odds ratios and confidence intervals for ACEi/ARB vs Entresto groups.

While this was not a clinical study, but rather a retrospective analysis, the study did organize patients into groups and analyzed outcomes within those groups. Proper inclusion and exclusion criteria were met, and demographic criteria was detailed and randomized, suggesting a quality level of randomization amongst patients that can be analyzed in similar fashion. However, as this was not a clinical study (no variable was studied), this cannot qualify as an intention-to-treat analysis. Additionally, the patients and study personnel were not blinded in this study. As this was a retrospective analysis, patients were not enrolled in the study during the studied period. Therefore, no blinding was needed due to the nature of the study. The patients were also analyzed equally by demographic. There was no direct treatment of patients in this study, but the retrospective analysis of data broke down statistical analysis (logistic regression used) of different demographic factors (age/sex/etc.). Additionally, all patients met the same inclusion/exclusion criteria and were both eligible to receive Entresto therapy, further demonstrating equal treatment of the two groups by the study. The therapy was given to the patients in this study due to new data and guideline recommendations that favor the use of Entresto over ACE/ARB, given the improvement in mortality rates and reduced hospitalization rates seen with Entresto therapy.

The authors had no conflicts of interest to disclose with this study. The sponsor of the study was the Mayo Robert and Patricia Kern Center for the Science of Healthcare Delivery. The only other financial disclosure reported was NIH funding to Dr. Sangaralingham. No role of these funders was reported in the influence of the study design. There was no publication bias seen in this article.

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Clinical Application

Mr. Scarillo is a patient who has suffered from frequent heart failure exacerbations, resulting in repeated hospital admissions. Additionally, he was open about his inability to afford his medications, leading to decreased management of his heart failure, and this was thought to be the cause of his poorly controlled symptoms and frequent hospital admissions.

After discussing within our team, we discussed with Mr. Scarillo the possibility of switching to generic medications that would be more affordable. After sharing with him about the new medications and the risks and benefits of switching, he was open to the idea, as the frequent exacerbations had a significant effect on his quality of life and limited his ability to go about his day. We talked about how daily adherence to his medications would allow him to leave the house with his wife more, stay more active, and reduce the chances he gets admitted to the hospital.

Sangaralingham et al.[1] was used as part of our evidence to discuss a change in medication regimen with Mr. Scarillo. As Mr. Scarillo was having difficulty affording his expensive drugs that were more recently approved for the management of HFrEF, the data regarding medication adherence with Entresto was used to recommend switching the patient from Entresto to generic losartan, which was based partly from the results of this study. While studies do show improved mortality and reduced hospitalizations when comparing Entresto to ACEi/ARB, the use of ACEi/ARB still provides mortality benefits in HFrEF patients. ACEi/ARBS still show improved mortality in heart failure patients, and thus are a viable option even if there are medications that are more effective but costlier. Entresto also has a higher QALY compared to ACEi/ARB therapy; both medication therapies still increase QALY compared to no therapy. Therefore, as the patient was more likely to remain adherent to more affordable medications, the decision was made to discontinue Entresto and switch to losartan. The risk and benefit of switching to a less effective medication was explained in detail with our patient, who was agreeable to the decision.

New Knowledge Related to Clinical Decision Science

Mr. Joseph Scarillo [pseudonym] faced a challenging predicament: the decision to sacrifice a more beneficial treatment to be able to afford his medication. Therefore, it was important that Mr. Scarillo was given all the information necessary to make this decision. It is easy for us providers to look at goal-directed medical therapy and prescribe because the data tell us that this will improve mortality. This study and the context of Mr. Scarillo remind us of the other important factors we must consider before recommending a medical management: is there any barrier or cost issue with obtaining the medication? If a patient, such as Mr. Scarillo, has trouble affording his medication, then the mortality benefits that we read about may not be applied to that patient. The use of the findings of Sangaralingham et al.[1] and similar articles remind us that cost of medication is an important factor for patients that we should consider in addition to medication benefit when deciding medication options.

Using this clinical decision report, a protocol for screening and shared decision making could be developed for patients who are readmitted with chronic diseases such as congestive heart failure or COPD. Using these inclusion criteria such a protocol could confirm the prevalence of cost related non-adherence to prescribed medicine. More importantly clinicians need to learn how to manage this problem and not simply restate that the problem exists. This clinical decision report can be used as a template for a protocol to adjust therapeutic regimens based on economic realities of clinical practice. It's more important for clinicians to learn how to address the problem than to simply keep telling each other that the problem exists.

Conflict Of Interest Statement

The author declares no conflicts of interest.

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