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MEDICATION PRESCRIBING IN HEART FAILURE: TRENDS IN DRUG TREATMENT AND EVIDENCE FROM THE PAST TEN YEARS

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BY

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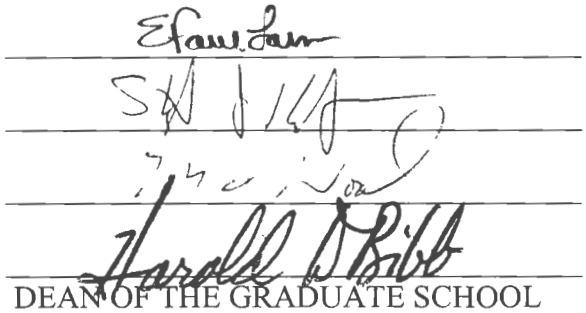

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ABSTRACT

Objective: This study assessed the macro level effects of multiple and varied forms of clinical guidance for medication based treatment for heart failure. Drug mention rates for physician visits by patients with heart failure were evaluated with respect to the dates of publication of large randomized trial evidence and guidelines.

Design: Retrospective, cross-sectional series study

Methods: We used the National Ambulatory Medical Care Survey (NAMCS) for years 1993-2000, which captures a probability sample of visits to United States physicians to provide national estimates. We examined heart failure coded visit drug mentions alongside research published during the same period to examine trends in medication prescribing and the aggregate influence of the dissemination of research findings. Multiyear estimation equations from the National Center for Health Statistics (NCHS) were used for calculation of sampling error.

Measurements: Medication mention rates were calculated for four sequential two-year periods. Relative standard errors (RSEs) were generated for measuring reliability and stability of our findings of changes in medication mention rates for beta blockers, angiotensin converting enzyme inhibitors, spironolactone, and angiotensin receptor blockers. Stratification and logistic regression models were used to provide insight into other possible predictors.

Results: The number of visits by a patient with heart failure to physicians was not statistically significantly different across the eight years of interest. The estimated medication mention rate of beta blockers, spironolactone, and angiotensin receptor blockers increased dramatically, but the number and rate of mentions was too low

for statistical reliability. There was an adequate number of drug mentions of angiotensin converting enzyme inhibitors for reliable aggregate estimates, but there were not adequate numbers of mentions to demonstrate statistically significant increases over the eight years. Logistic regression models showed strong associations between increased drug mentions and later two year periods. This association was demonstrated by progressively larger odds ratios (ORs) for subsequent periods when the first two year period is used as a referent baseline.

Discussion: The increases in medication mention rates for all medications corresponded with the findings of the major trials and evidence which we assessed. The NAMCS sample size and the low percent of drug mentions in the given therapeutic categories resulted in a lack of statistical power for determining statistical significance of the changes in medication mention rate.

Conclusion: We conclude from our collected information, and statistical analyses that the NAMCS demonstrated marked trends, but this study was inadequately powered to establish statistical significance.

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INTRODUCTION

The Institute of Medicine's 2001 report, Crossing the Quality Chasm, focused attention on the high level of unexplained variation in medical practice quality. Geographic variance, inter-provider inconsistencies, and gaps in quality highlighted the need for rational treatment. This effort for rational treatment has resulted in a major movement in the medical community to align the practice of medicine to methodically developed best practices. This broad movement is called 'Evidence Based Medicine.'

Evidence Based Medicine relies on appropriate and well-conducted studies[1]. After research results are generated, this information must be effectively disseminated to practitioners[1]. Lastly, this information must be appropriately incorporated into the medical practitioner's daily work[2]. The current healthcare system suffers from flaws at each of these stages. There are unanswered questions due to a lack of high quality studies. Distribution of knowledge is also difficult[3]. The current rate of nearly 10,000 trials annually[4] creates an enormous burden on our current information dissemination system.

Congestive Heart Failure (CHF) provides a useful subject for the investigation of the impact of evidence-based medicine for two primary reasons. The prevalence, incidence, and burden of CHF have a substantial impact on the U.S. health and healthcare. CHF affects 2-4.8 million people in the United

States[5, 6]. It has an incidence of 400,000-700,000 new cases each year, and is the leading cause of hospitalization[6]. O'Connell and Bristow estimated the U.S.'s total direct healthcare costs in 1991 for heart failure treatment to be $38.1 billion or 5.4% of 1991's total U.S. healthcare expenditure[7]. These substantial direct healthcare costs fail to capture the substantial societal costs that are attributed to heart failure's mortality and disability. This large medical burden also creates an availability of data due to the number of medical encounters recorded.

The second reason for the selection of CHF for evaluation of the impact of evidence on practice is the numerous changes in recommendations for drug treatment in recent years. Changes in our understanding of CHF have occurred frequently since the 1940's, and the subsequent evolution of recommended pharmacological interventions in the past decade are of particular interest. This could not be more clearly illustrated than the case of beta-blockers that, years ago, would be contraindicated treatment, and now are considered a cornerstone of therapy for this condition [8, 9].

This research is closely related to a broad group of guideline and research implementation studies. In 2000, Jones et al. expressed the need for "complex interventions (to be) assessed *en bloc* rather than trying to disentangle the effects of individual components of guidance..."[10] It is in the spirit of this astute observation in which this research is based. By placing emphasis on the search for the aggregate changes in medication prescribing, alongside an extensive summary of the published evidence during the period, a more complete picture can be captured.

While several guideline implementation focused studies address the prescribing rates of Angiotensin Converting Enzyme Inhibitors (ACEIs) [11-16] in heart failure, there is a lack of studies addressing the other medications with favorable supporting mortality studies. Recent studies and guidelines clearly make the case for the utilization of beta blockers, spironolactone, and Angiotensin Receptor Blockers (ARBs) depending on the type of heart failure. The association between these published findings and guidelines and medication prescribing is the primary focus of this investigation. This study examined national trends in medication prescribing rates of beta blockers, ACEIs, spironolactone, and ARBs. These changes were exhibited alongside the studies and guidelines which were expected to influence prescribing. This study also identified and tested possible demographic and medical predictors of drug mentions in the ambulatory setting for relevance to prescribing of these medications.

Our hypothesis was that we would see increases in drug mentions in the immediate and subsequent two year periods of published large trial evidence which demonstrated mortality or hospitalization benefits. We also hypothesized that guidelines would have a similar impact by magnifying previous findings.

METHODS

This study is a retrospective analysis of a series of cross sectional studies assessed in parallel with a comprehensive review of the most influential published research.

Data source

We utilized the National Ambulatory Medical Care Survey (NAMCS), using years 1993-2000 to examine changes in prescribing patterns. The NAMCS is a publicly available national probability sample survey frequently used by various leading epidemiological researchers. The study, which captures information on visits to office-based physicians, has been performed annually since 1989 (and sporadically prior). The survey instrument is reviewed and slightly altered every other year, causing minor changes in content and coding. The NAMCS is well described as a series of cross-sectional studies with visits to physicians as the unit of measure in the survey. The complex sample design is segmented into three stages. The first stage selects primary sampling units (PSUs), which consist of counties, groups of counties or equivalent areas. The second stage involves selection of physicians within the selected PSUs. Participating physicians are randomly selected from master lists maintained by the American Medical Association (AMA) and the American Osteopathic Association (AOA). From the selected physicians, the group of participants is limited to non-federally employed practitioners, and excludes the specialties of anesthesiology, radiology, and pathology. This selection comprises the in-scope number of physicians by year presented in table 1-1.

In the third stage, in-scope physicians are randomly assigned to varying one-week reporting intervals. Trained personnel provide physicians or their designee instructions on proper survey procedures and are provided the appropriate materials prior to the initiation of data collection. During this selected week, the practitioners complete a survey form for a random sample of approximately 30 visits. Visits to nurse practitioners, physician's assistants and other non-physician prescribers are not captured by this survey.

The number of in-scope selected physicians and the yearly response rates are presented in Table 1-1. Further details on the NAMCS sample design are available from published reports[17] or from the National Center for Health Statistics' (NCHS) website. To produce more stable and reliable estimates, two years of data were combined to produce each of our four periods of interest.

Sample

NAMCS databases for the corresponding years were limited to patients with an International Classification of Diseases revision 9 (ICD-9) code indicating CHF. The relevant ICD-9 codes used to identify CHF visits, as well as pertinent comorbidities are located on table 1-2. Under this disease-based sub-sample, additional data on diagnosis, treatment, and demographics were utilized for analysis.

Outcome

The NAMCS attempts to capture all current medication therapy occurring during the visit. Instruction on survey completion directs that all new or continued medications should be recorded on the survey form. The survey allowed for the

documentation of five (1993-94) or six (1995-2000) medications, which are referred to as drug mentions. The drug mention rate for CHF related medications was our surrogate outcome measure for the prescribing rate. Evaluation of the appropriateness of drug mentions was not be made in this study. The visit data found in the NAMCS can not be used to extrapolate the rate of drug usage by patient.

Analysis

Articles reviewing medication treatments for CHF were utilized to identify relevant therapeutic medication categories. Specific drug entities were identified using a comprehensive list of medications prescribed to CHF patients during the selected years. Medications that matched the previously identified therapeutic categories were recorded without regard to Food and Drug Administration (FDA) indications of individual agents. All medications recorded in the NAMCS survey were manually reviewed for inclusion as a second check to ensure that all medications used for CHF were identified. This list of relevant medications appears in table 1-3. This medication list was converted to the coding system developed by the NCHS, which is used by the NAMCS. Details on the collection and coding of this drug information by the NCHS are available.[18] Combination products, those with multiple active ingredients in one dosage form, were omitted after a preliminary analysis demonstrated that all such products accounted for very few drug mentions, and a small percent of all CHF drug mentions. Early analyses demonstrated that a majority of these medications were combinations of two diuretics, a common type of medication for symptomatic relief in CHF.

This study adopted the standards of the NCHS, which does not publish statistics on samples that are of insufficient size to rely on the central limit theorem, which states that samples of sufficient size (30 or more), approximate the value which would be found in the entire population. The NCHS utilizes relative standard errors (RSEs) to measure the reliability and precision of their sample's weighted national estimates. The RSE captures the degree sampling variability and nonsystematic biases present in the sample. NAMCS reports approximate the RSE through the use of first order Taylor approximations using SUDAAN (previously an abbreviation for Survey Data Analysis, which is no longer used as a title) statistical software. Further information on SUDAAN statistical software, which is specialized in the analysis of clustered data, is available[19]. Less precise methods for approximations of RSE for single years are published with the NAMCS advance data reports. Equations for approximation across multiple years were obtained directly from NCHS, and are located in Appendix A and B. These methods use the least reliable year being aggregated to calculate RSEs for the larger group of samples.

Predictor selection

Preliminary predictors of drug mentions were selected from among the demographic variables collected by the NAMCS. The patient's recorded sex, age, race, payment type, and comorbidities expected to influence the prescribing of the therapeutic drug categories were chosen for analysis. Age was recoded to those less than sixty, sixty to sixty-nine, seventy to seventy-nine, and eighty and older. Race was recoded to a dichotomous white and nonwhite variable due to insufficient

visits for further breakdown. Visit payment coding by the NAMCS in periods 1 and 2 allowed for multiple visit payments to be captured. Beginning in period 3, the survey form requested a single entry of only the primary expected payment. Due to this change, this information could not be recoded without substantial ambiguity in interpretation of this variable, therefore this information appears only on table 1-4 and was not included in further analysis. Health Maintenance Organization (HMO) status in periods 1 and 2 did not allow for the coding of blank or unknown HMO status. HMO status underwent no transformation, and therefore all blank and unknown entries in this variable appear in periods 3 and 4. Due to this variable change, HMO status was omitted from the logistic regression analysis.

The presence of diabetes, asthma, or hypertension would be expected to influence the rate of prescribing of medication in several of the therapeutic classes. Beta blockers would be expected to be prescribed less frequently in diabetics and asthmatics, and more frequent in hypertensive patients. ACE inhibitors would be expected to be prescribed at higher rates in diabetics. For this reason, visits involving these conditions as well as heart failure were also identified. Due to the limited number of asthmatics captured by the sample, these visits were not analyzed further.

Descriptive analyses were performed using Statistical Package for the Social Science (SPSS version 10.0 for Windows). Each visit record was flagged for drug mentions of relevant medications that affect heart failure mortality or hospitalization. These records were weighted to produce national estimates, using visit weighting by the NCHS in the NAMCS data files. These weightings take into

account the complex multi stage probability procedure and adjust for nonresponse. A weighting adjustment is also made for the physician to population ratio. Beginning in 1995, a weight smoothing technique was utilized in these weightings as well.[20] These visit based rates were considered in parallel with the published studies, as well as their statistical stability and reliability.

A list of published studies of medication usage with hospitalization or mortality outcome measures and treatment guidelines in heart failure was generated. The focus was on the larger studies which individually influenced the current standards and guidelines. This clinical trial list, organized by publication dates and medication therapeutic category, was utilized to watch for changes in practice patterns. This list descriptively outlined the outcome measure used, and the direction of the findings. Review articles, although likely influential in the aggregate, were not included due to the difficulty in determining completeness and interpretability. Guidelines that were not generally published or disseminated extensively, such as those by the American Medical Directors Association, were also excluded. These lists, by therapeutic classification, populate tables 2-1, 3-1, 4-1, and 5-1.

In measuring the degree of statistical significance and precision in our estimates, RSEs were chosen in preference to confidence intervals (CI) or statistical tests since RSEs are the standard method utilized within the NCHS for the NAMCS, providing for a "gold standard" for this type of research. Calculations of RSE were made according to previously unpublished multi-year estimate equations, which are available from the NCHS, or in the appendix of this thesis.

The complex sampling methods utilized in the NAMCS requires the calculation of cell sizes and RSEs to ensure a stable and precise estimate. The RSE can be translated to a confidence interval by multiplying the RSE by the estimate to obtain the standard error. There is a 95% confidence that the true value lies within twice the standard error of the value produced by the NAMCS, with the caveat that RSEs greater than 30% are considered unreliable by the NCHS definition.

Two different methods were utilized to assess and control for other possible influences on the drug mention rate. The first method consisted of stratification of the cases into subgroups and outcomes. This simple method was valuable for accessing the importance of individual predictors in isolation. The stratified analysis assessed the percentage of drug mentions by age, sex, race, diabetic status, and hypertensive status. The stratified analysis also listed the percent of drug mentions by those which were and were not related to an HMO. The stratified percentages on HMO status excluded those reporting blank or unknown in periods 3 and 4. These were excluded from the table to minimize potential confusion, and because a blank or unknown coding does not have a conceptual association with outcomes of interest.

The second method to control for other predictors was a multivariate standard logistic regression model to appraise the differing impact of the many suspected predictors simultaneously. In this multivariate analysis, period was our proxy measure for the impact of the evidence when in agreement with the timing and direction of the various findings. Odds ratios (OR) were used to assess each predictor's impact on prescribing where the odds of the referent category is set to 1.

An OR>1 indicates an increased association between the outcome of drug mention and the listed characteristic, while an OR<1 indicates a decreased association. Our confidence intervals represent the range that we are 95% statistically confident that our true values would fall within.

RESULTS

Limiting the records to those with a diagnosis of heart failure by the ICD-9 code listed on table 1-2 returned 1725 unweighted records for the four periods of analysis. After weighting, these surveys approximated 47 million visits over eight years. The number of visits over the four two-year periods remained relatively stable as shown on table 1-5, ranging from a high of 12.3 million in period 1 to a low of 11.2 million visits in period 3. The confidence intervals for all four periods overlap, demonstrating a lack of statistically significant difference.

Demographics of the visits are detailed on table 1-4. The sex of patients visiting for CHF was approximately evenly split with female visits in a slight majority (51.9%). Older individuals accounted for more visits than younger patients, with age 80 or older individuals accounting for the largest number of visits. Whites accounted for a majority of the visits (87.3%) as compared to non-whites. Diabetic patients comprised 14% of the sample, while asthmatics comprised only 1.3% of the estimated national visits for CHF. Hypertension was coded for the visits 18% of the time, but may have been omitted from coding more frequently if those recording information considered it less relevant in the light of a CHF coding. Recoded payment indicates a large number of Medicaid visits (55.3%) and blank or unknown status (22.8%), which likely resulted from the recoding of multi-coded payments from earlier periods to a status of "unknown".

Beta blockers

Beta blocker drug mentions were found to increase steadily and incrementally through the four periods, from 0.4 million mentions in period 1, to

1.6 million mentions in period 4. These estimates must be interpreted cautiously as the RSEs for all four periods exceed the 30% cutoff for stable and precise estimates as defined by the NCHS.

Large mortality and hospitalization studies during the four periods for beta blocker usage in heart failure were numerous, as were guidelines, as listed on table 2-1. In period 1, the Cardiac Insufficiency Bisoprolol Study (CIBIS) study was published, which was the first large trial to evaluate the impact of beta blockers on CHF mortality and hospitalization. Period 2 brought a set of trials in the US Carvedilol Heart Failure Trials Program, which consisted of five total publications. Three of the studies in the program, which measured mortality, as well as the published report that summarized them, appear on the table. The last of these reports extends into period 3. The first publication of the now widely known American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for CHF occurred during this second period of time. The third period included the last part of the US Carvediolol Heart Failure Trials Program, and one set of published guidelines. The last period brought another two large trials, one positive and one negative for beta blockers. Period 4 also produced another guideline, the first from the Heart Failure Society of America (HFSA), as well as an observational review of the Studies of Left Ventricular Dysfunction Treatment (SOLVD) trial, which was originally designed to determine the efficacy of ACE inhibitors.

Stratification of beta blocker drug mentions by various subgroups are outlined on table 2-2. Beta blocker mentions in visits by males with CHF occurred

at nearly twice the rate in women each two year period. The low number of nonwhite visits during the four periods produced sporadic mention rates. Diabetes is negatively associated with a beta blocker mention, while hypertension appears to have a positive association, as would be predicted. Those known to be in an HMO had nearly twice the rate of drug mentions as those known to not be in an HMO.

Lastly, utilizing logistic regression, we considered the relative importance of our predictors on beta blocker drug mentions. The OR and 95% CI for our predictors are found on table 2-3. In our model for beta blockers, hypertensive patients (OR 1.177, CI 1.173-1.180), and males (OR 1.945, CI 1.940-1.949) were positively associated with a drug mention for beta blockers. Diabetic patients (OR .585, CI .583-.587) and nonwhite patients (OR .690, CI .687-.692) were negatively associated with a beta blocker drug mention. The period of the visit showed the strongest association, with visits in period 4 (OR 3.754, CI 3.741-3.766) showing a dramatic difference from the referent period 1. Periods 2 (OR 1.171, CI 1.166-1.176) and 3 (OR 2.333, CI 2.325-2.341) were between the other two periods.

Angiotensin converting enzyme inhibitors (ACEIs)

ACE inhibitor drug mentions have been a recognized part of heart failure therapy for more than a decade. Their utilization rate shows that they had a moderate level of usage during the first period (3.4 million drug mentions) as shown on table 1-6. This rate increased substantially by the fourth period (4.3 million mentions). Drug mention rates in ACEIs were large enough to allow for much more stable RSEs, making for stable estimates in three of the four periods.

ACE inhibitors present a different case than the other three classes of medications in that the mortality studies were performed earlier. The first study to show clinical benefit was published in 1983 [6, 21], and mortality studies followed shortly[22]. The major studies of the efficacy of ACEIs in decreasing mortality and hospitalizations were completed before our first period of analysis as shown on table 3-1. The first such study was published in 1987, with a string of later studies in the early 1990's just prior to our period 1. Due to this earlier clinical study timing versus our other therapeutic categories, ACEI provide an opportunity to observe the impact of guidelines without simultaneous changes in research findings.

Stratification by subgroups does not show the same dramatic subgroup differences found in beta blockers. Table 3-2 documents that this sample had very similar drug mention rates by sex, race, hypertension, or HMO coverage. One exception was found among diabetics. In the last two periods the diabetic mention rates are nearly double the non-diabetic rates.

The logistic regression model for predictors of ACEI drug mentions is presented on table 3-3. ACEI prescribing varied between periods yet no strong predictors were found. In all but the first age category, the ORs were consistently similar. For sex, race, and hypertensive status, the ORs were very close to one. Only diabetics had a remarkable association (OR 1.558, CI 1.555-1.561).

Spironolactone

Spironolactone prescribing was difficult to assess due to extremely low drug mention rates for this drug, which were not statistically stable or reliable. As

would be expected from table 1-6, few mentions occurred in periods 1-3. There is a jump in reports in period 4 (to 0.4 million mentions).

There were no large mortality based clinical trials with evidence for spironolactone use in heart failure until the Randomized Aldactone Evaluation Study (RALES) [23] which occurred in period 4 as shown on table 4-1. The resulting weighted visits are stratified on table 4-2, but these numbers represent very few surveys in all periods, and should be considered with caution. The logistic regression analysis reveals the dramatic increase in association in period 4 (OR 3.542, CI 3.519-3.564) as compared to period 1. The three older age groups of the four are negatively associated with spironolactone use (ORs from .510 to.589) as compared to those younger than 60 year old, which is outlined on table 4-3.

Angiotensin receptor blockers (ARBs)

Drug mentions of ARBs increased from period 1 (173020 weighted drug mentions), to period 4 (530420 weighted drug mentions) as seen on table 1-6. The largest change occurred between periods 2 and 3 (360,878 increase in weighted estimate mentions).

ARBs differ from the previous therapeutic categories in that the evidence for their use is not based upon direct superiority against placebo, but rather based upon their equivalence to ACEI. The two studies which measured mortality and hospitalization, are the ELITE (in period 3) and ELITE II (in period 4) trials as listed on table 5-1. These studies did not show statistically significant improvements in CHF related mortality over ACE inhibitors, but ELITE did show a slight but significant decrease in all-cause mortality [24]. The first ARB to be

approved by the FDA was Losartan on April 14th, 1995 which interestingly falls during period 2 despite already having been available for coding by the NAMCS during period 1[25]. Two other ARBs were approved during the third period, Irbesartan on September 30th, 1997, and Candesartan on June 4th, 1998[25]. Valsartan was not approved until after the 4th period, but was listed by the NAMCS by period 4.

Differences shown on the stratified sample on table 5-2 are again difficult to interpret due to the poor reliability and stability of the period estimates due to low sample size and a low drug mention rate for ARBs. The evaluation of individual predictors through the logistic regression model is on table 5-3. The dramatic association with period is shown in period 3 (OR 3.115, CI 3.097-3.132) and period 4 (OR 3.767, CI 3.788) as compared to period 1.

DISCUSSION

The eight years of NAMCS data on CHF visits showed statistically insignificant increases in drug mentions for all four therapeutic categories of medications which provide benefits in survival or decreased hospitalizations. Descriptively the mention rates change with surprising similarity to expected trends, but the lack of reliability of the data precludes statistical inferences to evaluate the role of chance in our findings. Beta blockers are of particular interest as the evidence supporting the use of beta blockers mounted during our four study periods, corresponding with a large increase in drug mention rates observed in the NAMCS weighted estimates.

For beta blockers, the rate of drug mentions in period 1 is representative of the drug mention rate when only small trial and supporting theory was available to influence prescribing. If evidence were the only predictor of beta blocker use, period 2 would represent the impact of the first large randomized trial which occurred near the end of period 1. The guidelines directly reflect the prior large trials, and therefore the 1995 ACC/AHA guidelines released in period 2 discuss beta blockers cautiously. In the end of period 2 a confirmatory study was published, and the rate of drug mentions doubled from the initial rate in period 3. In period 3 and 4, more evidence is published and the drug mention rate increased further, but still only mentioned in less than 15% of visits with patients with CHF.

There are several reasons why the drug mention rate may be lower than might be expected. Some comorbidities would make a prescriber hesitant to prescribe a beta blocker, such as asthma or diabetes due to a relative

contraindication. Unlike an absolute contraindication which would always be inappropriate, a relative contraindication would discourage, but permit prescriber judgments to use the medication with the comorbidity. The NAMCS does limit the number of recorded medications to five in period 1, and six in periods 2-4. Considering a patient visiting with CHF alone, we would expect many patients to be treated with an ACEI, diuretic, digoxin, and a beta blocker or spironolactone. When one diagnosis is associated with four or more medication mentions, it is likely that a form with space for six drug mentions is not adequate to capture all medications for all visits. The NCHS plans to increase the number of drug mentions which can be listed on the survey in coming years[26]. Some medications are available as combination products, meaning that multiple active ingredients would be in one tablet. Although captured by the NAMCS, these drug mentions were not recoded in this study since early testing showed that combination products accounted for few drug mentions. In this population a majority of these combination products is for diuretics, which fall outside the scope of this investigation.

The large RSEs for this study create difficulties when using the NAMCS for analysis of specific disease states. Even with the frequently used practice of combining years [20, 27-29], limiting the number of visits by diagnosis quickly erodes the necessary power when using the approximation equations. Power is also eroded by the size of the estimate since it is related to the RSE[30]. Analysis of visits without weighting has very limited utility in describing the prescribing rate in the United States because the NAMCS is not a random sample, and therefore a

report of the raw survey reports of visits is not representative of actual practice. These concerns, taken together, demonstrate the necessity of asking large questions with this data, or by using SUDAAN to calculate the precise RSEs, which at times allows for the use of substantially fewer visits than the more conservative estimate equations.

Increases in drug mentions predicted by period are likely influenced by several factors in addition to large trials and guidelines. Over the broader period of 1985-1999, Burt was able to show an increase in drug mention rate of 59%. This rate was largely attributed to the increasing age of the population, new drugs, drug coverage, and direct to consumer advertising[29]. Increasing age, although associated with CHF, did not result in an increase in the number of visits, nor was increasing age associated with a drug mention except with ARBs. New drugs are also a minor issue in these therapeutic classes, other than the ARBs. Direct to consumer advertising is also rare in CHF. It is likely other factors are having a greater effect on CHF than those that are impacting broader prescribing trends.

ACEI mention rates appeared to increase slowly and steadily, although rates are remarkably low considering the broad agreement to the necessity of their use in CHF. Several published reports have addressed the inadequate prescribing rate of these medications in CHF[12-16]. With the majority of the studies on mortality benefits being prior to our study period, we expect that the guidelines have the greatest impact during the four periods. We find that period is a significant predictor of ACEI mentions, as is diabetic status, which is not surprising considering the great benefit of ACEIs in this population[31]. Since ACEIs and

ARBs have similar mechanisms of action and may be viewed by practitioners as being interchangeable, it is also possible that their trends should be viewed together, although guidelines and practice do firmly distinguish between the two classes.

Assessment of spironolactone mention rates provides an opportunity to determine the impact of one large randomized trial. While some prescribing of spironolactone may be attributed to its diuretic properties for symptomatic relief, we do find that the mention rate increased dramatically, but not statistically significantly, after publication of the RALES trial. The spironolactone analysis is statistically limited by its low drug mention rate, which did not allow for a reliable or precise estimate.

The increase in ARB prescribing is most pronounced in period 3. During this period we do have the first trial showing equivalence of ARBs to ACEIs. During the third period, irbesartan and candesartan were approved, joining losartan, which was the only approved ARB during the previous period. Unlike the other therapeutic categories, guidelines discourage the use of ARBs in preference to ACEIs, except where latter is not tolerated due to side effects [6, 8, 9, 32, 33]. These agents are more recent developments, and although not generally marketed directly to consumers, they certainly do have substantial sales force support from their respective manufacturers. Since the ARBs did not yet have FDA approval for the treatment of CHF during this period, this marketing influence should be a minor concern since the FDA prohibits marketing unapproved indications.

Although in this study we were able to report rates of drug mentions which corresponded with the guidance provided by the most important studies, review articles and other smaller influences can not be accounted for. The guideline update from the ACC/AHA for CHF in 2001 also falls outside the focus of this study. Further studies in the reasons behind the rates of adoption of lifesaving medication, and effective interventions to ensure appropriate use are needed.

We conclude from our collected information, and statistical analyses that the NAMCS demonstrated marked trends, but this study was inadequately powered to establish statistical significance. The trends showed dramatic increases in drug mentions which corresponded temporally with major published evidence. Beta blocker trends suggested that two studies were necessary to increase prescribing, perhaps due to prior theory which suggested the class to be contraindicated. Spironolactone, which unlike beta blockers would not have contraindication concerns, increased dramatically after only one large study. This suggesting that some prescribers are reacting quickly to new high quality evidence, but further research utilizing other data sets may offer more reliable answers in time.

Although power limitations inherent to the NAMCS limited statistical inferences, the strengths of the NAMCS should not be ignored. The NAMCS is limited by resources, versatility, and anonymity. Federal resources for the NAMCS are limited, and the survey instrument attempts to capture an enormous number of topics. Physician participation is voluntary, and therefore anonymity is necessary for high response rates, which limits the data that can be released. The strengths of

the NAMCS include persistence over multiple years, national coverage, and extensive details about visits.

Future research should be directed to establishing the degree to which these trends are statistically significant, which would require either more precise methods (notably the use of SUDAAN), or a different data source. Other data sources may involve primary data collection, or the utilization of regional data. It is important that research also be directed toward establishing optimal prescribing rates, which match the evidence to allow for benchmarking by individual health organizations. This information is necessary to evaluate the adequacy of the current evidence dissemination system.

Table 1-1: NAMCS Survey Response Rates by Year

Year	Physicians in Scope	Percent Reporting	Total Surveys Returned
1993	2464	73.0%	35,978
1994	2426	70.2%	33,598
1995	2587	72.8%	36,875
1996	2142	70.0%	29,805
1997	1801	69.2%	24,715
1998	1806	67.9%	23,339
1999	1728	62.9%	20,760
2000	2049	67.7%	27,369

Table 1-2: ICD-9 codes used to identify sample and comorbidity based subgroups

Heart Failure	Asthma	Diabetes	Hypertension
428.0	493.00	250*	401*
428.1	493.01		402.00
428.9	493.10		402.10
	493.11		402.90
	493.20		403*
	493.21		404.0
	493.90		404.2
	493.91		405*

*includes all 4th and 5th digit subclassifications

Table 1-3: List of generic names of medications captured within each therapeutic category used to prevent mortality and hospitalization in CHF

Beta Blockers	**Angiotensin Converting Enzyme Inhibitor (ACEI)**	**Spironolactone**	**Angiotensin II Receptor Blockers (ARB)**
Atenolol	Benazepril	Spironolactone	Candesartan
Bisoprolol	Captopril		Irbesartan
Carvedilol	Enalapril		Losartan
Labetalol	Fosinopril		Valsartan
Metoprolol	Lisinopril		
Nadolol	Quinapril		
Propranolol	Ramipril		
Sotalol	Trandolapril		

Table 1-4 Weighted frequency and percent occurrence of demographic characteristics of CHF visits in NAMCS for years 1993-2000

Characteristic	Weighted* Frequency n = 47,188,507	Percent of weighted* visits within subgroups
Period		
1993-94	12,329,611	26.1
1995-96	12,212,841	25.9
1997-98	11,296,468	23.9
1999-2000	11,349,587	24.1
Sex		
Female	24,491,634	51.9
Male	22,696,873	48.1
Age		
0-59	5,397,099	11.5
60-69	8,481,791	18.0
70-79	15,665,945	33.2
80+	17,643,672	37.3
Race		
White	41,179,969	87.3
Black	4,957,055	10.5
Other	1,051,483	2.2
Diagnosed diabetes visit		
Non-diabetic	40,599,823	86.0
Diabetic	6,588,684	14.0
Diagnosed asthma visit		
Non-asthmatic	46,587,112	98.7
Asthmatic	601,395	1.3
Diagnosed hypertension visit		
Non-hypertensive	38,694,590	82.0
Hypertensive	8,493,917	18.0
Visit payment		
Private insurance	6,998,833	14.8
Medicare	26,081,485	55.3
Medicaid	1,786,835	3.8
Other	590,897	1.2
Blank or unknown	10,725,545	22.8
HMO status		
HMO plan	6,877,066	14.6
Non-HMO plan	38,379,787	81.3
Blank or unknown	1,931,654	4.1

*Weighted values represent the sample adjusted to represent national visit characteristics

Table 1-5 Weighted frequency of CHF visits and aggregate multiyear relative standard error (RSE) of visits 1993-2000 by year

Visit period	Number of CHF visits*	Multi-year relative standard error for CHF visits	95% confidence intervals for number of CHF visits per 2 year period
1993-94	12,329,611	7.04	11,461,607-13,197,615
1995-96	12,212,841	7.92	11,245,584-13,180,098
1997-98	11,296,468	10.12	10,153,266-12,439,670
1999-2000	11,349,587	10.05	10,208,954-12,490,220

*weighted number of visits over period

Table 1-6 Weighted frequency and percent of medication mention rates in CHF from 1993-2000 by year

	Number of visits with one or more drug mention	Relative Standard Error for number of mentions	Percent of visits with one drug mention
Beta Blockers			
1993-94	487,601*	54.89	4.0†
1995-96	581,175*	48.37	4.8†
1997-98	1,052,052*	58.11	9.3†
1999-2000	1,617,562*	40.21	14.3†
ACEI			
1993-94	3,398,254	18.89	27.6†
1995-96	3,870,147	19.96	31.7†
1997-98	3,341,295*	30.13*	29.6†
1999-2000	4,286,231	26.68	37.8†
Spironolactone			
1993-94	126,965*	136.74	1.0†
1995-96	97,899*	135.99	0.8†
1997-98	158,048*	160.45	1.4†
1999-2000	414,960*	68.56	3.7†
ARBs			
1993-94	173,020*	88.55	1.4†
1995-96	137,381*	102.95	1.1†
1997-98	498,259*	82.94	4.4†
1999-2000	530,420*	63.76	4.7†

*Value does not meet standard of reliability or precision based upon a RSE > 30
†Value does not meet standard of reliability or precision based upon a denominator RSE ≥5 or a numerator and denominator RSE ≥ 10

Table 2-1 Summary of major trials using beta blockers in CHF which measured mortality, hospitalizations, or a combined mortality-hospitalization effect, and influential guidelines 1993-2000

Study/guideline title	Journal reference	Period	Findings
Cardiac Insufficiency Bisoprolol Study	Circulation. 1994 Oct;90(4):1765-73	1	Mortality ↓ Hospitalization ↓
ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult	Circulation 1995 Nov 1;92(9):2764-84	2	NA
The US Carvedilol Heart Failure Trials Program	N Engl J Med 1996 May 23;334(21):1349-55	2	Mortality ↓ Hospitalization ↓
Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise*	Circulation 1996 Dec 1;94(11):2793-9	2	Mortality ↓
Multicenter Oral Carvedilol Heart Failure Assessment Study*	Circulation 1996 Dec 1;94(11):2807-16	2	Mortality ↓ Hospitalizations ↓
Heart Failure guidelines of the European Society of Cardiology	Eur Heart J 1997 May;18(5):736-53	3	NA
Study of the Safety and Efficacy of Carvedilol in Severe Heart Failure*	J Card Fail 1997 Sep;3(3):173-9	3	Insufficient power to evaluate
Cardiac Insufficiency Bisoprolol Study II	Lancet 1999 Jan 2;353(9146):9-13	4	Mortality ↓
Metoprolol CR/XL Randomized Intervention Trial in Heart Failure	Lancet 1999 Jun 12;353(9169):2001-7	4	Mortality ↓ Hospitalizations ↓
HFSA Guidelines for the Management of Patients with Heart Failure Caused by Left Ventricular Systolic Dysfunction - Pharmacological Approaches.	The Journal of Cardiac Failure, 1999;5:357-382	4	NA
Retrospective Analysis of Studies of Left Ventricular Dysfunction Treatment Trial	J Am Coll Cardiol. 1999; 33:916-923	4	Mortality ↓
Beta-Blocker Survival Trial	Paper presented at: 1999 Scientific Sessions of the AHA; Nov. 7-10, 1999; Atlanta, GA	4	Mortality ↑

*indicates component study of US Carvedilol HF Trials Program
NA = Not applicable

Table 2-2 Weighted rates of one or more drug mentions in CHF for beta blocker stratified by subgroup visit demographics

Number of visits by patient age and year, and percent of the given n with a beta blockers mention.

	0-59		60-69		70-79		80+	
Year	n	%	n	%	N	%	N	%
1993-94	1229933	10.9	2069616	2.4%	4016916	4.1%	5013146	2.8%
1995-96	1223361	4.1%	2024943	2.9%	4633977	4.4%	4330560	6.2%
1997-98	1255262	8.7%	2055364	7.5%	3867993	6.8%	4117849	12.7%
1999-2000	1688543	16.6%	2331868	21.4%	3147059	12.4%	4182117	10.7%

Number of visits by sex and year, and percent of the given n with a beta blocker mention

	Female		Male	
Year	n	%	n	%
1993-94	7124629	3.2	5204982	5.0
1995-96	6282195	2.4	5930646	7.2
1997-98	5562697	5.6	5733771	12.9
1999-2000	5522113	11.3	5827474	17.0

Number of visits by race and year, and percent of the given n with a beta blocker mention

	White		Non-white	
Year	n	%	n	%
1993-94	10733051	3.4	1596560	7.7
1995-96	10776537	5.3	1436304	.6
1997-98	9926163	8.9	1370305	12.3
1999-2000	9744218	15.9	1605369	4.2

Number of visits by recorded diabetic diagnosis and year, and percent of the given n with a beta blocker mention

	Non-diabetic		Diabetic	
Year	n	%	n	%
1993-94	10772854	4.5	1556757	0
1995-96	10535885	5.4	1676956	0.5
1997-98	9727608	9.0	1568860	11.3
1999-2000	9563476	15.3	1786111	8.8

Number of visits by recorded hypertensive diagnosis and year, and percent of the given n with a beta blocker mention

	Non-hypertensive		Hypertensive	
Year	n	%	n	%
1993-94	10301868	3.7	2027743	5.0
1995-96	10349848	5.2	1862993	2.4
1997-98	8888661	9.1	2407807	10.2
1999-2000	9154213	13.4	2195374	17.8

Number of visits by HMO status and year, and percent of the given n with a beta blocker mention

	HMO plan		Non-HMO plan	
Year	n	%	n	%
1993-94	1401535	6.1	10928076	3.7
1995-96	1916046	7.3	10296795	4.3
1997-98	1645452	17.0	9176491	7.4
1999-2000	1914033	24.3	7978425	11.4

Table 2-3 Logistic regression model for identifying significant predictors of beta blocker drug mentions in CHF visits

Predictor Variables	Odds Ratio	95% Confidence Interval
Period 1, 1993-94 (referent)		
Period 2, 1995-96	1.171	1.166 - 1.176
Period 3, 1997-98	2.333	2.325 – 2.341
Period 4, 1999-2000	3.754	3.741 – 3.766
Age 0-59 (referent)		
Age 60-69	.763	.761 - .766
Age 70-79	.580	.578 - .582
Age 80+	.728	.725 - .730
Sex female (referent)		
Sex male	1.945	1.940 – 1.949
Race White (referent)		
Race Non-white	.690	.687 - .692
Non-diabetic (referent)		
Diabetic	.585	.583 - .587
Non-hypertensive (referent)		
Hypertensive	1.177	1.173 – 1.180

Table 3-1 Summary of major trials using ACE inhibitors in CHF which measured mortality, hospitalizations, or a combined mortality-hospitalization effect, and influential guidelines 1987-2000

Study/guideline title	Journal reference	Period	Findings
Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group.	N Engl J Med 1987 Jun 4;316(23):1429-35	NA	Mortality ↓
Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators.	N Engl J Med 1991 Aug 1;325(5):293-302	NA	Mortality ↓ Hospitalization ↓
A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure.	N Engl J Med 1991 Aug 1;325(5):303-10	NA	Mortality ↓
Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators.	N Engl J Med 1992 Sep 3;327(10):669-77	NA	Mortality ↓
Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigators.	N Engl J Med 1992 Sep 3;327(10):685-91	NA	Mortality ↓ Hospitalization ↓
ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult	Circulation 1995 Nov 1;92(9):2764-84	2	NA
Heart Failure guidelines of the European Society of Cardiology	Eur Heart J 1997 May;18(5):736-53	3	NA
HFSA Guidelines for the Management of Patients with Heart Failure Caused by Left Ventricular Systolic Dysfunction - Pharmacological Approaches.	The Journal of Cardiac Failure, 1999;5:357-382	4	NA

NA = Not applicable

Table 3-2 Weighted rates of one or more drug mentions in CHF for ACEIs stratified by subgroup visit demographics

Number of visits by patient age and year, and percent of the given n with an ACEI mention.

	0-59		60-69		70-79		80+	
Year	n	%	n	%	N	%	N	%
1993-94	1229933	41.7	2069616	30.1	4016916	26.1	5013146	24.2
1995-96	1223361	35.9	2024943	23.9	4633977	29.7	4330560	36.3
1997-98	1255262	28.4	2055364	29.4	3867993	35.2	4117849	24.7
1999-2000	1688543	38.0	2331868	44.5	3147059	27.8	4182117	41.4

Number of visits by sex and year, and percent of the given n with an ACEI mention

	Female		Male	
Year	n	%	N	%
1993-94	7124629	26.2	5204982	29.4
1995-96	6282195	32.5	5930646	30.9
1997-98	5562697	30.7	5733771	28.5
1999-2000	5522113	38.8	5827474	36.8

Number of visits by race and year, and percent of the given n with an ACEI mention

	White		Non-white	
Year	n	%	n	%
1993-94	10733051	27.0	1596560	31.6
1995-96	10776537	32.2	1436304	27.9
1997-98	9926163	29.1	1370305	33.2
1999-2000	9744218	37.5	1605369	39.4

Number of visits by recorded diabetic diagnosis and year, and percent of the given n with an ACEI mention

	Non-diabetic		Diabetic	
Year	n	%	n	%
1993-94	10772854	26.7	1556757	33.2
1995-96	10535885	32.6	1676956	25.7
1997-98	9727608	27.6	1568860	42.1
1999-2000	9563476	33.7	1786111	59.8

Number of visits by recorded hypertensive diagnosis and year, and percent of the given n with an ACEI mention

	Non-hypertensive		Hypertensive	
Year	n	%	n	%
1993-94	10301868	27.7	2027743	27.0
1995-96	10349848	31.5	1862993	33.0
1997-98	8888661	28.1	2407807	35.1
1999-2000	9154213	37.9	2195374	37.2

Number of visits by HMO status and year, and percent of the given n with an ACEI mention

	HMO plan		Non-HMO plan	
Year	n	%	n	%
1993-94	1401535	34.9	10928076	26.6
1995-96	1916046	32.9	10296795	31.5
1997-98	1645452	34.1	9176491	27.8
1999-2000	1914033	36.9	7978425	36.6

Table 3-3 Logistic regression model for identifying significant predictors of ACEI drug mentions in CHF visits

Predictor Variables	Odds Ratio	95% Confidence Interval
Period 1, 1993-94 (referent)		
Period 2, 1995-96	1.221	1.219-1.223
Period 3, 1997-98	1.094	1.092-1.096
Period 4, 1999-2000	1.557	1.554-1.559
Age 0-59 (referent)		
Age 60-69	.852	.850-.854
Age 70-79	.812	.811-.814
Age 80+	.868	.866-.870
Sex female (referent)		
Sex male	1.010	1.009-1.012
Race White (referent)		
Race Non-white	1.051	1.049-1.053
Non-diabetic (referent)		
Diabetic	1.558	1.555-1.561
Non-hypertensive (referent)		
Hypertensive	1.087	1.086-1.089

Table 4-1 Summary of major trials using spironolactone in CHF which measured mortality, hospitalizations, or a combined mortality-hospitalization effect, and influential guidelines 1993-2000

Study/guideline title	Journal reference	Period	Findings
ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult	Circulation 1995 Nov 1;92(9):2764-84	2	NA
Heart Failure guidelines of the European Society of Cardiology	Eur Heart J 1997 May;18(5):736-53	3	NA
HFSA Guidelines for the Management of Patients with Heart Failure Caused by Left Ventricular Systolic Dysfunction - Pharmacological Approaches.	The Journal of Cardiac Failure, 1999;5:357-382	4	NA
The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators.	N Engl J Med 1999 Sep 2;341(10):709-17	4	Mortality ↓ Hospitalizations ↓

NA = Not applicable

Table 4-2 Weighted rates of one or more drug mentions in CHF for spironolactone stratified by subgroup visit demographics

Number of visits by patient age and year, and percent of the given n with a spironolactone mention.

	0-59		60-69		70-79		80+	
Year	n	%	n	%	N	%	N	%
1993-94	1229933	0.1	2069616	2.3	4016916	0	5013146	1.5
1995-96	1223361	1.2	2024943	0.3	4633977	1.0	4330560	0.7
1997-98	1255262	0.5	2055364	2.3	3867993	2.7	4117849	0
1999-2000	1688543	9.0	2331868	1.0	3147059	2.8	4182117	3.6

Number of visits by sex and year, and percent of the given n with a spironolactone mention

	Female		Male	
Year	n	%	n	%
1993-94	7124629	1.3	5204982	0.7
1995-96	6282195	1.2	5930646	0.4
1997-98	5562697	0.7	5733771	2.1
1999-2000	5522113	4.0	5827474	3.3

Number of visits by race and year, and percent of the given n with a spironolactone mention

	White		Non-white	
Year	n	%	n	%
1993-94	10733051	1.2	1596560	0.1
1995-96	10776537	0.6	1436304	2.6
1997-98	9926163	1.6	1370305	0
1999-2000	9744218	3.2	1605369	6.4

Number of visits by recorded diabetic diagnosis and year, and percent of the given n with a spironolactone mention

	Non-diabetic		Diabetic	
Year	n	%	n	%
1993-94	10772854	1.2	1556757	0
1995-96	10535885	0.9	1676956	0
1997-98	9727608	1.6	1568860	0
1999-2000	9563476	3.3	1786111	5.5

Number of visits by recorded hypertensive diagnosis and year, and percent of the given n with a spironolactone mention

	Non-hypertensive		Hypertensive	
Year	n	%	n	%
1993-94	10301868	0.8	2027743	2.4
1995-96	10349848	0.9	1862993	0.5
1997-98	8888661	0.7	2407807	3.9
1999-2000	9154213	3.8	2195374	3.2

Number of visits by HMO status and year, and percent of the given n with a spironolactone mention

	HMO plan		Non-HMO plan	
Year	n	%	n	%
1993-94	1401535	0	10928076	1.2
1995-96	1916046	0	10296795	1.0
1997-98	1645452	0	9176491	1.7
1999-2000	1914033	0	7978425	3.6

Table 4-3 Logistic regression model for identifying significant predictors of spironolactone drug mentions in CHF visits

Predictor Variables	Odds Ratio	95% Confidence Interval
Period 1, 1993-94 (referent)		
Period 2, 1995-96	.792	.786-.799
Period 3, 1997-98	1.347	1.337-1.357
Period 4, 1999-2000	3.542	3.519-3.564
Age 0-59 (referent)		
Age 60-69	.510	.506-.513
Age 70-79	.589	.586-.593
Age 80+	.537	.533-.540
Sex female (referent)		
Sex male	.884	.880-.888
Race White (referent)		
Race Non-white	1.158	1.151-1.165
Non-diabetic (referent)		
Diabetic	.780	.775-.786
Non-hypertensive (referent)		
Hypertensive	1.551	1.543-1.559

Table 5-1 Summary of major trials using ARBs in CHF which measured mortality, hospitalizations, or a combined mortality-hospitalization effect, and influential guidelines 1993-2000

Study/guideline title	Journal reference	Period	Findings
ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult	Circulation 1995 Nov 1;92(9):2764-84	2	NA
Randomized trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE)	Lancet 1997 Mar 15;349(9054):747-52	3	CHF mortality no different from ACEI, but all cause mortality ↓
Heart Failure guidelines of the European Society of Cardiology	Eur Heart J 1997 May;18(5):736-53	3	NA
HFSA Guidelines for the Management of Patients with Heart Failure Caused by Left Ventricular Systolic Dysfunction - Pharmacological Approaches.	The Journal of Cardiac Failure, 1999;5:357-382	4	NA
Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomized trial--the Losartan Heart Failure Survival Study ELITE II.	Lancet 2000 May 6;355(9215):1582-7	4	Mortality no different from ACEI

NA = Not applicable

Table 5-2 Weighted rates of one or more drug mentions in CHF for ARBs stratified by subgroup visit demographics

Number of visits by patient age and year, and percent of the given n with an ARB mention.

	0-59		60-69		70-79		80+	
Year	n	%	n	%	N	%	N	%
1993-94	1229933	2.8	2069616	0	4016916	3.0	5013146	0.3
1995-96	1223361	1.8	2024943	2.4	4633977	0.8	4330560	0.7
1997-98	1255262	2.0	2055364	3.6	3867993	7.2	4117849	2.9
1999-2000	1688543	2.7	2331868	1.8	3147059	7.9	4182117	4.6

Number of visits by sex and year, and percent of the given n with an ARB mention

	Female		Male	
Year	n	%	n	%
1993-94	7124629	1.8	5204982	0.9
1995-96	6282195	1.2	5930646	1.0
1997-98	5562697	5.0	5733771	3.8
1999-2000	5522113	5.4	5827474	4.0

Number of visits by race and year, and percent of the given n with an ARB mention

	White		Non-white	
Year	n	%	n	%
1993-94	10733051	1.0	1596560	4.4
1995-96	10776537	1.1	1436304	1.3
1997-98	9926163	3.8	1370305	8.9
1999-2000	9744218	5.0	1605369	2.8

Number of visits by recorded diabetic diagnosis and year, and percent of the given n with an ARB mention

	Non-diabetic		Diabetic	
Year	n	%	n	%
1993-94	10772854	1.5	1556757	1.1
1995-96	10535885	1.3	1676956	0
1997-98	9727608	5.0	1568860	0.7
1999-2000	9563476	5.0	1786111	2.7

Number of visits by recorded hypertensive diagnosis and year, and percent of the given n with an ARB mention

	Non-hypertensive		Hypertensive	
Year	n	%	n	%
1993-94	10301868	0.3	2027743	7.2
1995-96	10349848	0.9	1862993	2.5
1997-98	8888661	3.9	2407807	6.3
1999-2000	9154213	4.1	2195374	7.1

Number of visits by HMO status and year, and percent of the given n with an ARB mention

	HMO plan		Non-HMO plan	
Year	n	%	n	%
1993-94	1401535	0	10928076	1.6
1995-96	1916046	1.2	10296795	1.1
1997-98	1645452	3.7	9176491	4.7
1999-2000	1914033	3.0	7978425	5.3

Table 5-3 Logistic regression model for identifying significant predictors of ARB drug mentions in CHF visits

Predictor Variables	Odds Ratio	95% Confidence Interval
Period 1, 1993-94 (referent)		
Period 2, 1995-96	.794	.788-.799
Period 3, 1997-98	3.115	3.097-3.132
Period 4, 1999-2000	3.767	3.746-3.788
Age 0-59 (referent)		
Age 60-69	.991	.984-.999
Age 70-79	2.275	2.260-2.289
Age 80+	1.058	1.050-1.065
Sex female (referent)		
Sex male	.673	.670-.675
Race White (referent)		
Race Non-white	1.259	1.253-1.264
Non-diabetic (referent)		
Diabetic	.375	.373-.378
Non-hypertensive (referent)		
Hypertensive	2.512	2.503-2.521

Appendix A: List of Definitions

ICD-9 = The International Classification of Diseases Revision 9 is a coding system which enables payers and providers of health services to efficiently communicate diagnoses.

NAMCS = The National Ambulatory Medical Care Survey is an annually performed national probability survey which records an extensive and varied list of characteristics regarding visits to physicians in the United States. The survey is designed to describe the use of ambulatory services in the US.

NCHS = The National Center for Health Statistics is a branch of the Centers for Disease Control (CDC), which falls under the U.S. Department of Health and Human Services (HHS). This department provides key health surveillance information which is utilized by a diverse set of stakeholders to identify issues and direct policy.

RSE = The Relative Standard Error is used to measure the reliability and precision of a sample by capturing the degree sampling variability and nonsystematic biases present in the sample. The RSE can be translated to a confidence interval by multiplying the RSE by the estimate to obtain the standard error. There is a 95% confidence that the true value lies within twice the standard error of the estimated value.

SPSS = The Statistical Package for the Social Sciences is a analytical software product with a broad statistical capabilities to aid in decision making. It

utilizes a graphical user interface, which often facilitates intuitive data manipulation and analysis.

SUDAAN = A statistical software package, formerly named Survey Data Analysis, which specializes in the analysis of cluster-correlated data. SUDAAN takes into account the complex sampling design of the NAMCS, eliminating the need of less powerful approximation equations.

Appendix B: Excerpt from NCHS internal memo on RSE estimation for aggregate measures using multiyear NAMCS data

by I.M. Shimizu,
December 9, 1993

Sampling Errors for Estimates Based on Multi-Years of NAMCS Data

This document presents procedures which one may use to approximate sampling errors of estimates based on NAMCS data collected across multiple years.

1. Variance of estimated aggregate across years

For discussion purposes, let:

$\hat{Y}_i$ = estimated total based on data from the individual year i.

$\hat{Y} = \sum_{i=1}^{k} \hat{Y}_i$ be the estimated aggregate NAMCS total across k years of NAMCS data.

F be that year in which NAMCS had the fewest number of responding physicians among the years included in the study ($1 \leq F \leq k$). (Table 1 gives numbers of respondents for 1989-92.)

Var ($\hat{Y}_f$) = Variance of $\hat{Y}_f$ derived from the appropriate NAMCS error curve for year F.

Then the variance of $\hat{Y}$ may be approximated with

$\hat{Var}(\hat{Y}) = Var(\hat{Y}_f)[k(2/I - 1) - 2/I + 2]$,

where

I = 0.9 for statistic for all physicians (without regard to specialty), for pediatricians only, or for OB/GYNs only.
1 for statistics for internal medicine specialty only.
0.8 for all other physician groups.

The approximation formulated in this equation is believed to be conservative. That is, the approximation should overstate, rather than understate, the variance for most multi-year aggregate estimates based on NAMCS data.

Appendix C: Excerpt from NCHS internal memo on RSE estimation for proportions using multiyear NAMCS data

by David A. Woodwell,
November 4, 2002

Question: Is there a recommended procedure for estimating the variance of a proportion when combining several years of NAMCS data?

Response:
FIRST SOME NOTATION:
Let x(i) and y(i) be binomial characteristics of interest for the ith sample unit.
x(i) = 1 or 0 and y(i) = 0 or 1.

Let X = sum of x(i) over the sample units. Let Y = sum of y(i) over the sample units.

Let R = X/Y.

If x(i) = 1 only when y(i) = 1, then R = X/Y is a proportion [the x(i)=1 units are a subset of the y(i)=1 units]

THEN
When both X and Y are estimated from the same survey, then a crude approximation typically used by NCHS analysts for the RSE of the proportion is:

RSE(R) = RSE(X/Y) = square root of [square RSE(X) - square RSE(Y)]

provided RSE(Y) < 0.05 or both RSE(X) <0.10 AND RSE(Y) < 0.10. If the conditions fail, your estimate is not stable. The RSE(X) and RSE(Y) are approximated in the same way as any other multi-year aggregate statistic. The A and B parameters of error curves for X and Y should be taken from the same year to prevent negative results.

If the X and Y are estimated from different surveys, then

RSE(R) = RSE(X/Y) = square root of [square RSE(X) + square RSE(Y)],

again provided the conditions are satisfied.

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