Disease-Modifying Therapy and Hospitalization Risk in Heart Failure Patients

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ABSTRACT

Objectives

To examine comorbidity and therapy use rates in a Medicaid population with heart failure (HF), evaluate hospitalization risk as a function of comorbidity and therapy use, and assess the impact of modification on costs to the Medicaid program.

Study Design

Historical prospective cohort study. Claims were from adult enrollees in Maryland Medicaid (managed care organization or fee-for-service) diagnosed with HF between 2005 and 2009.

Methods

The end point was first hospitalization after index HF. Average hazard ratios (HRs) were estimated by multivariate weighted Cox regression. Budget impact of modifications was assessed using annual number-needed-to-treat calculations and external estimate of average cost of HF hospitalization.

Results

Most patients were >45 years (71%), women (56%), and black (60%). Medication use: beta-blockers (26%), angiotensin-converting enzyme inhibitors and/or angiotensin II receptor antagonists (ACEi/ARBs) (29%), aldosterone antagonists (5%), and others including nitrates-hydralazine (37%). Nearly all (98%) were diagnosed with 1 or more comorbidities. Relative risk of hospitalization was higher with most, but not all, comorbidities investigated. ACEi/ARBs (HR, 0.77; CI, 0.73-0.81), beta-blockers (HR, 0.83; CI, 0.79-0.87), and other cardiovascular drugs (HR, 0.76; CI, 0.72-0.80) had beneficial effects. A 20% increase in the use prevalence of ACEi/ARBs and beta-blockers translated to annual Medicaid savings of at least $85 and $57 per HF patient, respectively.

Conclusions

Findings call attention to comorbidities and optimization of disease-modifying therapy in Medicaid patients with HF. Certain disease-modifying medications mitigated risk, but were used infrequently. Substantive outcome improvement and savings to Medicaid may be achieved with small changes in prescribing rates or comorbidity prevalence.

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Heart failure (HF) was estimated to affect nearly 5.7 million Americans in 2008,[1] and its prevalence has been projected to rise by 25% through 2030.[2] This rise in prevalence is accompanied by a projected 215% increase in direct medical costs over the next 20 years in the United States, from approximately $24.7 to $95.6 billion (2008 US dollars).[2] It was estimated that most (77%) medical costs following diagnosis of HF accrue during hospitalization.[3] While hospitalizations are frequent among HF patients, occurring about once per year, only one-third had HF as the primary admitting diagnosis.[4]

The clinical and corresponding economic burden of HF is often compounded by concurrent morbidities (eg, chronic obstructive pulmonary disease [COPD], renal dysfunction, psychological disorders, and stroke, among others).[5-9] Little is known on how comorbidities may affect the risk of hospitalization among patients with HF—specifically patients in expanding Medicaid plans, which have typically shown high prevalence of HF.[1,10,11] The literature has not cited many population-based studies with real-world data, which may stand to inform disease management. Much of the evidence based on clinical trial populations is invaluable in clinical practice; however, it is often difficult to interpret and apply in populations whose demographics and risk-factor profiles vary from those cited.[12,13] A case in point is the Medicaid population.[10,14-20]

Recent healthcare policy changes in the American Recovery and Reinvestment Act and the Affordable Care Act have relegated more responsibilities and expanded funding to states themselves, resulting in increased enrollment in Medicaid plans.[21,22] For instance, Medicaid enrollment grew by 9 million over the past year, increasing total enrollment to 66.5 million Americans as of October 2014, or 21.2% of the total population.[21] The projected increase in HF prevalence coupled with greater numbers of patients presenting with comorbidities are likely to place greater strain on state budgets and disease management programs.[5,23,24]

Given the high risk profile among Medicaid patients, increasing enrollment in state Medicaid programs, sparse literature on population-based HF studies, and the burden of hospitalization among HF patients, we investigated risk factors for HF in a contemporary Medicaid population and

Take-Away Points

The projected increase in heart failure prevalence coupled with greater numbers of patients presenting with comorbidities are likely to place greater strain on state Medicaid budgets and disease management programs.

- This study elucidates the impact of comorbidities on the risk of hospitalization among patients with heart failure.
- Certain disease-modifying medications mitigated the risk of hospitalization, but were used infrequently.
- Substantive outcome improvement and savings to Medicaid may be achieved with small changes in prescribing rates or comorbidity prevalence.

developed a risk score for hospitalization associated with specific medication use and comorbidities. Finally, we assessed the impact of a potential modification of risk factors on hospitalization and cost.

METHODS

This study was a historical-prospective cohort study sampling from the population of Maryland Medicaid recipients enrolled in 1 of 7 prepaid state-contracted managed care organizations (MCOs) or fee-for-service (FFS) programs. Patients between the ages of 18 and 64 years diagnosed with HF between July 1, 2005, and December 31, 2009, were enrolled in the study. We obtained all of their encounter and prescription data, and followed them from their date of enrollment through first hospitalization to end of study (June 20, 2010), or the date of disenrollment as recorded in their last Medicaid MCO or FFS encounter claim. The study design allowed for at least 6 months and for up to 5 years of follow-up post diagnosis.

We recorded demographics (age, sex, race), dates of service (physician visits, hospitalizations, medication dispensing), and primary through tertiary *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes. Pharmacy claims also included American Society of Health-System Pharmacists Pharmacologic-Therapeutic Classification (AHFS) numbers.

The date of diagnosis for HF was defined as the earliest physician visit associated with *ICD-9-CM* code 428.xx. In addition to this prevalence cohort, we built an incidence cohort to include all patients whose first HF claim was at least 6 months after their first Medicaid claim. Dates of hospitalization were derived from the first date of service on records of inpatient hospital encounters. Less than half (47%) of HF diagnoses coincided with patients' first hospitalization, in which case a second hospitalization was used as the end of follow-up. Of 24,635 HF patients identified, the final prevalence cohort included 14,149 observations and the incidence cohort included 7470 patients.

Systolic HF versus HF with preserved ejection fraction (HFpEF) was denoted if specified by secondary coding (428.2x vs 428.3x, or 428.40-428.43 combined). Although systolic HF and HFpEF share the same clinical phenotype, they are thought to differ in pathophysiology and thus tend to respond differently to treatment.[18,19,25-30] Medications that have been shown in clinical trials to produce unequivocal improvements in systolic HF have not produced similar effects in HFpEF, and the optimal treatment strategy for HFpEF has yet to be defined.[25,26,31] The type of HF was specified in only 5% of our sample; consequently, we could not distinguish which patients were considered most susceptible to disease-modifying therapy. Since it is known that about half of all patients with HF display HFpEF and the remainder systolic HF,[25] there is little reason to suspect that HF was unspecified on claims for 95% of our sample in any systematic fashion. All patients were retained, regardless of specified or unspecified HF.

Covariates included first-line disease-modifying therapies (guideline-recommended), comorbidities, age, race/ethnicity, gender, and an indicator for HF diagnosis during hospitalization. First-line therapies were ascertained using pharmacy claims with drugs dispensed between HF diagnosis and the end of follow-up. Therapies examined include ACEi/ARBs (AHFS 24:32.04 or 24:32.08); beta-blockers (AHFS 24:24); aldosterone receptor antagonists (AAs) (AHFS 24:32.20); nitrates + hydralazine combination (AHFS 24:08.20 or 24:08.20 *with* 24:12.08); "other" cardiovascular therapies, including nitrates or hydralazine alone; and all medications with AHFS 24:xx but not described above. Drugs do not include medications that are not reimbursed by Medicaid.

Diagnoses of comorbidities were determined from 3-digit *ICD-9-CM* codes recorded in the primary through tertiary fields of claims for medical encounters between the earliest claim and within 3 months after HF diagnosis. Comorbidities include COPD, stroke, renal dysfunction, diabetes, psychological disorder(s), hyperlipidemia, hypertension, and chronic ischemic heart disease (*ICD-9-CM*: 410.xx-414.xx, which includes past myocardial infarction, angina pectoris, and other forms of ischemic heart disease). An indicator for "other" cardiovascular disease captures all *ICD-9-CM* diagnosis codes between 390.xx and 459.xx, but not hypertension, ischemic heart disease, HF, or stroke. Classification of therapies and comorbidities is described in **eAppendix Table 1** (available at **www.ajmc.com**). Age (18-44 years, 45-54 years, and 55-64 years), gender, and race/

ethnicity (white, black, Hispanic, and other) were identified at HF diagnosis.

Statistical Analysis

We report the prevalence of comorbidities in the prevalence cohort as well as cross-tabulations of these comorbidities (**eAppendix Figure 1**, available at **www.ajmc.com**). Demographic distributions are examined in the prevalence cohort and across comorbidities. Kaplan-Meier estimates were used to estimate median days until hospitalization after HF diagnosis.

We built survival analysis models to assess the impact of first-line use of disease-modifying therapies with HF patients on their risk of hospitalization. We estimated the risk of hospitalization, adjusting for demographic risk factors and the presence of comorbidities. We also adjusted for the diagnosis of 1 or more comorbidities after 3 months of HF diagnosis, since new or undiagnosed morbidity might have confounded estimates for the risk of hospitalization over follow-up.

Weighted Cox regression (WCR) was used to model the average hazard ratios (HRs) of factors for hospitalization after HF diagnosis. WCR provided a simplified method for estimating HRs adjusted for covariates and averaged over the follow-up period, regardless of whether risk varies over time (ie, nonproportional hazards).[32] WCR is described in the eAppendix and was implemented using SAS version 9.2 (SAS Institute, Cary, North Carolina) macro program, WCM, provided on the Web by Heinze.[33]

Using the WCR estimates, we computed the budget impact to the Medicaid plan, given a 20% increase in the prevalence of comorbidity or therapy use in the HF cohort. The mean cost of a primary HF hospitalization among nondually enrolled Maryland Medicaid patients in 2011 was $16,341.[34] Of note, average hospitalization costs have been estimated to be up to 43% higher when HF was a secondary, rather than the primary, diagnosis for hospitalization.[35]

The numbers-needed-to-treat approach was adopted to determine the number of patients with comorbidity or using a first-line therapy associated with at least 1 hospitalization per year. We calculated the savings per patient, as attributed to the expected impact on hospitalization rates.

RESULTS

Patient characteristics and hospitalization rates for the HF sample and comorbidity cohorts are reported in **Table 1** and **eAppendix Table 2**. Most patients were 45 years or older (71%), women (56%), and black (60%); 33% were white; and Hispanics (2%) and other races (6%) represented a small portion. Nearly all HF patients (98%) were diagnosed with 1 or more other conditions. The prevalence of cardiovascular disease (78%) and hypertension (73%) was highest, followed by psychological disorder(s) (55%), ischemic heart disease (43%), diabetes (41%), hyperlipidemia (37%), COPD (27%), renal dysfunction (27%), and stroke (21%).

About two-thirds (63%) of all patients received any form of cardiovascular therapy in follow-up—mostly ACEi/ARBs (29%) or beta-blockers (26%). There were fewer AAs (5%) and others, including nitrates + hydralazine (37%). Of the only 5% of patients with specified HF, about two-thirds were diagnosed with systolic (or combined) HF. Both systolic and HFpEF patients were likely to be prescribed some form of disease-modifying therapy (70% vs 63%). The use rates of ACEi/ARBs (36% vs 32%), beta-blockers (35% vs 27%), AAs (6% vs 3%), nitrates + hydralazine (1% vs 1%), and other cardiovascular therapies (39% vs 38%) were somewhat higher in the systolic HF (vs HFpEF) patients (**eAppendix Table 3**).

Nearly 70% of all patients initially diagnosed with HF were hospitalized during follow-up, and 31% of patients were rehospitalized (since diagnosis coincided with their first hospitalization). Time to hospitalization (in median days) was shortest for those with comorbid renal failure (73 days) and longest for those with comorbid hyperlipidemia (238 days). Median time to hospitalization for the 290 patients with no comorbidity was 791 days.

Risk of Hospitalization

Figures 1 to **3** report the adjusted risk of hospitalization over the follow-up period. The following results were estimated using the prevalence cohort of HF patients—note that estimates from the incidence cohort were similar. The presence of renal failure was the strongest predictor of hospitalization (average HR, 1.43; 95% CI, 1.36-1.51), followed by other cardiovascular disease (HR, 1.40; CI, 1.31-1.50), COPD (HR, 1.33; CI, 1.26-1.40), ischemic heart disease (HR, 1.28; CI, 1.22-1.35), stroke (HR, 1.27; CI, 1.20-1.34), diabetes (HR, 1.26; CI, 1.20-1.32), and hypertension (HR, 1.11; CI, 1.05-1.17). Patients with a psychological disorder (HR, 0.77; CI, 0.73-0.81) and/or hyperlipidemia (HR, 0.81; CI, 0.77-0.85) experienced significantly lower risk of hospitalization.

Hospitalization risk was significantly reduced through the use of ACEi/ARBs (HR, 0.77; CI, 0.73-0.81), beta-blockers (HR, 0.83; CI, 0.79-0.87), and/or other cardiovascular drugs (HR, 0.76; CI, 0.72-0.80) as first-line therapies for HF. However, initiation on AA and/or nitrates + hydralazine had no significant effect on hospitalization risk.

In the adjusted models, a diagnosis of HF coinciding with hospitalization significantly increased the risk for

Table 1. Clinical and Demographic Characteristics of Heart Failure Patients (N = 14,149)

	n	(%)
HF Type at Diagnosis		
Unspecified	13,389	(95)
Systolic	397	(3)
Diastolic	274	(2)
Systolic & diastolic	89	(1)
HF Therapies[a]		
ACEi/ARBs	4097	(29)
Beta-blockers	3722	(26)
AAs	716	(5)
Nitrates + hydralazine	102	(1)
Other	5226	(37)
None	5285	(37)
Comorbidity[b]		
Chronic obstructive pulmonary disease	3869	(27)
Stroke	2900	(20)
Renal dysfunction	3750	(27)
Diabetes	5804	(41)
Psychological disorder	7786	(55)
Hyperlipidemia	5303	(37)
Chronic ischemic heart disease	6074	(43)
Hypertension	10,329	(73)
Other cardiovascular disease	10,987	(78)
Age, years		
18-44	4079	(29)
45-54	5078	(36)
55-64	4992	(35)
Race/ethnicity		
White	4608	(33)
Black	8462	(60)
Hispanic	263	(2)
Other	816	(6)
Sex		
Female	7936	(56)
Male	6213	(44)
First Hospitalized		
At HF diagnosis	5736	(41)
After HF diagnosis	9740	(69)
Days after HF diagnosis, median (25th, 75th)[c]	230	(44, 1207)

AAs indicates aldosterone receptor antagonists; ACEi/ARBs, angiotensin-converting enzyme inhibitors and/or angiotensin II receptor antagonists; HF, heart failure.
[a]First-line HF therapies are not mutually exclusive. Nitrates or hydralazine alone are included in "Other" HF therapies.
[b]All comorbidities were diagnosed prior to or within 3 months of heart failure diagnosis, and are not mutually exclusive.
[c]Estimated using Kaplan-Meier estimator to adjust for censoring.

subsequent hospitalization (HR, 1.27; CI, 1.35-1.47), as did middle age (ages 45-54 years; HR, 1.13; CI, 1.06-1.19). When adjusted for other risk factors, Hispanics (HR, 0.81; CI, 0.68-0.98) or other race groups (HR, 0.83; CI, 0.75-0.93) were at lower risk for hospitalization than white or black patients.

The predicted HRs for significant risk factors were used to estimate the 6-month, 1-year, and 2-year risks of hospitalization among Maryland Medicaid patients diagnosed with HF (eAppendix). The model's ability to correctly discriminate between individuals in the sample with high and low risk for hospitalization was good with a C statistic of 0.80 for any time horizon using both the prevalent and incident cohorts.

Cost and Savings to Maryland Medicaid

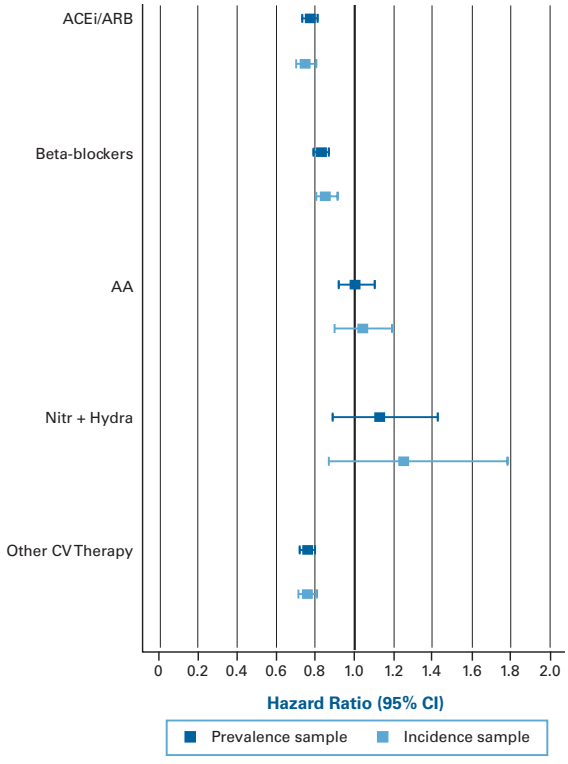
Table 2 presents the yielded annual numbers-needed-to-treat to prevent at least 1 hospitalization in the Maryland Medicaid prevalence-based HF cohort. As HF patients

may experience multiple hospitalizations per year, our relative cost/savings estimates are conservative since they are based on the first hospitalization after HF diagnosis. While not all patients are candidates for certain cardiovascular therapies,[30,31,36,37] estimates show that for every 12 patients started on ACEi/ARBs, at least 1 hospitalization can be prevented annually. A 20% increase in prescription rates in the sample resulted in savings of at least $85 (CI, $70-$101) per HF patient. Using our database of Medicaid claims to ascertain the number of non-dual-enrolled HF patients in Maryland Medicaid at any time in 2007 (12,054 patients), this estimate translated to a total annual savings of $1,024,590 (CI, $843,780-$1,217,454) for Medicaid.

For perspective, total medical expenditures by Maryland Medicaid on HF in 2007 was approximately $23.6 million.[38] Thus, Medicaid spent approximately $2200 (in 2011 dollars) per HF patient. This may be a slightly high comparator since dual-enrolled individuals were not included in our data, but comprised roughly 11% of all Maryland Medicaid enrollees in 2007.[39]

For further comparison, Table 2 also presents the reduction in the number of cases of each comorbidity that was estimated to prevent 1 hospitalization per year. For instance, for every 8 HF patients presented with concomitant renal dysfunction, at least 1 hospitalization can be expected annually. Thus, a 20% decrease in the prevalence of renal dysfunction in the HF cohort resulted in an estimated saving of at least $111 (95% CI, $96-$127) per HF patient.

Figure 1. Risk of Hospitalization Associated With First-Line Therapies for Heart Failure



AA indicates aldosterone receptor antagonist; ACEi/ARB, angiotensin-converting enzyme inhibitor and/or angiotensin II receptor antagonist; CV, cardiovascular; Nitr + Hydra, nitrates-hydralazine combination therapy. Therapies are compared only with the absence of the given therapy. Hazard ratios are adjusted for comorbidity and demographics.

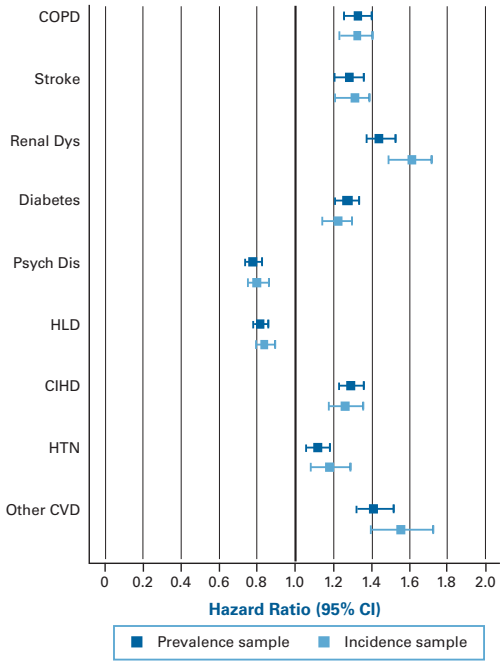
DISCUSSION

Given the high cost burden of hospitalizations and the potential ensuing complications and course of HF, our findings, in a unique Medicaid population, call for attention to strategies to attend to comorbidities and optimize use of disease-modifying therapy in such patients with HF.[10,18,19] We found that a diagnosis of COPD, stroke, renal dysfunction, diabetes, ischemic heart disease, hypertension, or other cardiovascular diseases in HF significantly increased the risk of hospitalization: by about 30% for COPD or stroke, 25% for diabetes and ischemic heart disease, 10% for hypertension, and 40% for renal dysfunction and other cardiovascular diseases. Conversely, disease-modifying therapies reduced that risk by about 20%. Medicaid patients between 45 and 54 years of age were at the highest risk of hospitalization. Interestingly, the risk was 30% greater for individuals who were diagnosed with HF upon their first recorded hospitalization, perhaps suggesting a need for more proactive differential diagnosis approaches or faster referral patterns in the first point-of-care setting.[18-20]

Medications that have been shown in clinical trials to improve systolic HF have not been shown to improve HFpEF, and prior data suggest that patients with HFpEF tend to have a history of hypertension and be older and female.[25,26,28] Thus, our results likely overestimate the impact of disease-modifying therapies on hospitalization risk in all HF patients given that the broader population of HF patients might be more heavily represented by an older population with a higher prevalence of HFpEF. Moreover, our database consisted of only non-dual-enrolled Medicaid beneficiaries; therefore, caution should be used when generalizing our findings on relative risk to a dual-enrolled population. The objective of this study was to quantify the hospitalization risk in a high-risk Medicaid population with HF and should not be generalized to the Medicare population since it is likely represented by distinctly different risk groups.

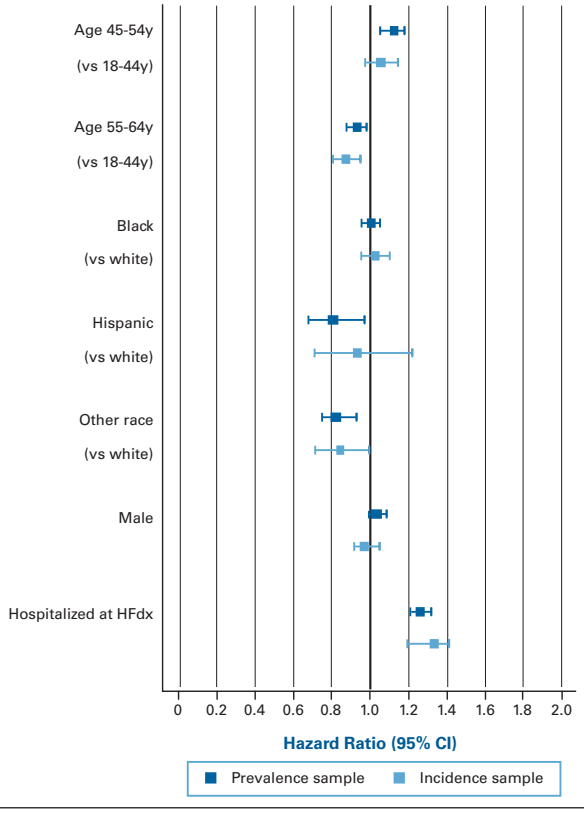
We used the WCR method to estimate the average HRs on the comorbidities and other variables to reduce the possibility of biased estimates from a proportional hazards model. Given the nature of the claims-based data, we

Figure 2. Risk of Hospitalization Associated With Heart Failure Comorbidity



CIHD indicates chronic ischemic heart disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; Dys, dysfunction; HLD, hyperlipidemia; HTN, hypertension; Psych Dis, psychological disorder.
Comorbidities are compared with the absence of the given comorbidity. Hazard ratios adjusted for first-line therapies and demographics.

Figure 3. Risk of Hospitalization Associated With Demographics and Heart Failure Diagnosed at Hospitalization



HFdx indicates heart failure diagnosis.
Adjusted for first-line heart failure therapies and comorbidity.

■ **Table 2.** Annual Numbers-Needed-to-Treat/Reduce to Prevent 1 Hospitalization, and the Annual Budget Impact of a 20% Increase in First-Line Therapy Use or of a 20% Decrease in the Prevalence of Comorbidity: Maryland Medicaid Prevalence-Based Heart Failure Population (2005-2009)

	Annual Numbers-Needed-to-Treat to Prevent 1 Hospitalization[a]		Annual Savings per HF Patient From 20% Increase in Prevalence[b]	
Disease-Modifying Therapy[c]	**Estimate**	**95% CI**	**Estimate**	**95% CI**
ACEi/ARBs	11.1	(9.4-13.5)	$85	(70-101)
Beta-blockers	15.0	(11.9-20.3)	$57	(42-72)
Other cardiovascular drugs	10.2	(8.7-12.2)	$118	(99-139)
	Annual Case Reduction Needed to Prevent 1 Hospitalization[a]		**Annual Savings per HF Patient From 20% Decrease in Prevalence[b]**	
Comorbidity	**Estimate**	**95% CI**	**Estimate**	**95% CI**
COPD	9.6	(8.2-11.7)	$93	(76-109)
Stroke	11.5	(9.3-15.2)	$58	(44-72)
Renal dysfunction	7.8	(6.8-9.0)	$111	(96-127)
Diabetes	11.8	(9.7-14.9)	$114	(90-138)
Psychological disorder	–10.4	(–12.8 to –8.8)	–$173	(–204 to –141)
Hyperlipidemia	–13.0	(–17.2 to –10.4)	–$94	(–118 to –71)
Chronic ischemic heart disease	11.0	(–9.1 to –13.8)	$128	(102-154)
Hypertension	27.0	(17.3-61.2)	$88	(39-138)
Other cardiovascular diseases	8.2	(6.8-10.3)	$309	(246-373)

ACEi/ARB indicates angiotensin-converting enzyme inhibitor and/or angiotensin II receptor antagonist; COPD, chronic obstructive pulmonary disease; HF, heart failure.
[a]Calculated using NNT formula, = 1/((S0^AHR)-(S0)), where S0 is the 1-year cumulative probability of no hospitalization, absent the comorbidity or therapy, and at the means of all other covariates observed within the respective comorbidity or therapy subpopulation.
[b]Savings based on average cost of a primary HF hospitalization (*ICD-9-CM*: 428.xx) among non-dual-enrolled Maryland Medicaid patients in 2011 (= $16,341). Estimate ascertained from 2011 discharge data from Maryland State Inpatient Databases, Healthcare Cost and Utilization Project, and Agency for Healthcare Research and Quality. Baseline sample prevalences found in Table 1. (A 10% increase in prevalence would result in exactly half the savings from a 20% increase.)
[c]Aldosterone antagonists and nitrates/hydralazine combination therapy were statistically insignificant, and therefore suppressed. Nitrates or hydralazine monotherapy were included in "Other cardiovascular drugs."

did not have access to lab values or medication logs per se, and thus could not assess disease severity nor ascertain that prescriptions filled were indeed taken by the patients. However, assuming this lack of information is systemic in the data and thus affects all comparison groups, it should not affect the risk comparisons.

To the extent that the study population was selected from among Medicaid enrollees, all study patients were, by definition, from a relatively homogeneous socioeconomic group and had the same insurance coverage, with presumably equal chance at access to medical care, medication therapy, or hospital services. Some cultural norms, beliefs and values, factors of cultural competency, literacy, self-efficacy, and other related measures may directly or indirectly affect the risk of hospitalization. We tried to adjust for these confounders indirectly, and at least partly, by adjusting for race/ethnicity. Further, we relied on the literature on the association between socioeconomic status, race/ethnicity, and socio-cultural-behavioral determinants of access to care to confirm that although worth pursuing in further research, the residual confounding due to unobservable variables may not present a notable bias in this study. We further matched samples by comorbidity in order to account for the possible imbalance of covariates across those comorbidities. Theoretically, this approach would have eliminated confounding of our estimates, to the extent possible, due to lifestyle factors or other unobservable variables that may contribute to the risk of hospitalization. The results were similar to those reported.

Perhaps physician practice styles, type of training, time in practice, or cultural competency may be concerns for bias.[40-43] However, by design, in the general Medicaid setting, particularly that of managed care and related practice, reimbursement and incentive structures somewhat limit variations in practice style. Thus, to the extent that patients are likely to see various healthcare professionals during their course of care, we do not think that the lack of information on individual physicians in our study population poses a serious validity threat.

This study is the first to address the epidemiology of comorbidities in a high-risk Medicaid population, reflect-

ing a demographic largely under-represented in large-scale studies or clinical trials.[13-15] We show the unmet needs of this population and the clinical and hospitalization issues associated with prevalent disease and therapies. The burden of comorbidity was much higher than that observed in national statistics on HF patients, and the prescribing prevalence was lower than expected given the high-risk profile of the population. These findings may point to a high-priority area for Medicaid plans. Most notably, in the context of the study's population demographic and clinical profile, we found that even small increments in disease-modifying therapies would result in significant reduction in costs to state plans. For instance, in the Maryland Medicaid program, a 20% increase in prescribing rates of ACEi/ARBs or beta-blockers would have led to an approximate annual savings of at least $85 or $57 per HF patient, respectively, or over $1 million total.

Limitations

A substantial fraction of patients had multiple comorbidities of various assortments. Thus, we modeled each comorbidity independent of the others, adjusting for concomitant conditions. While the model's ability to discriminate was good, it is still limited in its specificity; comorbidity reflects a spectrum of disease. Consider, for instance, that patients with hyperlipidemia and renal dysfunction may represent a different risk group than renal dysfunction alone or that chronic kidney disease stage 4 is different from stage 3. An obvious implication of our findings is that more work should be done to examine the management of comorbid conditions and the impact it has on HF control, hospitalizations, and costs.

First-line therapies were also modeled independently. This facilitated examining how an increase in the use prevalence of a single medication would have impacted the Medicaid budget for HF patients. However, this approach was not amenable to looking specifically at the potential budget impact of increasing the rate of 2 or more disease-modifying agents being prescribed concurrently. Certainly, not all HF patients are eligible to receive every therapy or require concomitant treatment, but the exercise may have been interesting nonetheless.

CONCLUSIONS

Healthcare reform and ongoing healthcare discussions have stimulated an interest in needs and risk assessment for target high-risk populations. In particular, the growing ranks of Medicaid plans and the rise of national health and other entitlement programs call for more deliberate, proactive, and cost-effective disease and risk management of plan enrollees.[12,13] Our study elicits the specific risk attributable to lead risk factors in HF patients enrolled in Medicaid plans and shows how disease-modifying therapies can quantifiably mitigate the risk for hospitalization in those patients. We further show the economic implications to the state by using a budget-impact approach to demonstrate the potential cost savings from a move to more optimal therapy.

Overall, our findings inform the discussions on healthcare reform by focusing on HF, which is one of the highest morbidity and cost conditions in state enrollees. The results suggest potentially parallel patterns in other highly prevalent chronic conditions, equally poised to have an impact on population health and large health program budgets. There are also important policy implications, in light of the potential outcomes of optimizing therapies on patient function, which may stimulate patients' return to work and their disenrollment from Medicaid.

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Authorship Information: Concept and design (FTS, IMB, MRM); acquisition of data (FTS, IMB); analysis and interpretation of data (FTS, IMB, MRM); drafting of the manuscript (FTS, IMB, MRM); critical revision of the manuscript for important intellectual content (FTS, IMB, MRM); statistical analysis (FTS, IMB); provision of study materials or patients (FTS); administrative, technical, or logistic support (FTS, IMB); supervision (FTS, MRM).

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eAppendix

Statistical Analysis

A multivariate weighted Cox regression (WCR) was used to assess the risk of hospitalization after diagnosis with heart failure in the Maryland Medicaid population. A weighted Schoenfeld residuals score test indicated that the hazards of the comorbidities were nonproportional over follow-up, therefore conventional Cox proportional hazards models would under- or over-estimate the hazard ratios (HRs) for hospitalization. The WCR provided a method for estimating the average risk of mortality over the follow-up period, regardless of whether that risk varied over time.[1] In general, WCR estimates HRs averaged over time using a weight function which reflects the relative importance attached to the HRs in different time periods. An average hazard ratio (AHR) is generally defined as,

$$\mathrm{AHR} = \frac{\int_{t=1}^{T} (\mathrm{h}_1(\mathrm{t})/\mathrm{h}(\mathrm{t}))\mathrm{w}(\mathrm{t})\mathrm{f}(\mathrm{t})\mathrm{dt}}{\int_{t=1}^{T} (\mathrm{h}_0(\mathrm{t})/\mathrm{h}(\mathrm{t}))\mathrm{w}(\mathrm{t})\mathrm{f}(\mathrm{t})\mathrm{dt}}, \qquad 0 \leq w(t) \leq 1$$

where $\mathrm{h}_0(\mathrm{t})$ and $\mathrm{h}_1(\mathrm{t})$ denote respective hazards of a reference group and comparison group at time t, $\mathrm{h}(\mathrm{t})$ is the sum of these hazards at time t, and $\mathrm{f}(\mathrm{t})$ is the density function for the events in time. Using censored data, the weight function $\mathrm{w}(\mathrm{t}) = \hat{\mathrm{S}}(\mathrm{t})\hat{\mathrm{G}}(\mathrm{t})^{-1}$ reflects the proportion of individuals affected by a hazard ratio at time t, where $\hat{\mathrm{S}}(\mathrm{t})$ and $\hat{\mathrm{G}}(\mathrm{t})$ denote the Kaplan-Meier estimators of the survival function and the censoring distribution, respectively. AHRs estimated under the proportional hazards assumption are obtained when $\mathrm{w}(\mathrm{t}) = 1$. For 'proportional' covariates, $\mathrm{w}(\mathrm{t}) = \hat{\mathrm{S}}(\mathrm{t})\hat{\mathrm{G}}(\mathrm{t})^{-1} \approx 1$, so there will be little difference between the hazard ratio estimated under the proportional hazards assumption and the AHR estimated using WCR. Schemper et al provide greater detail on WCR, including a description of the weighted partial likelihood for Cox's regression model and confirmation of its empirical performance.[1]

Computing Risk Scores for Hospitalization in Maryland Medicaid Patients with Heart Failure

Using the estimated hazard ratios (HRs) for significant risk factors within the prevalence-based cohort (see **Appendix Table 1** below), the binary values of the factors for a respective patient, and the corresponding baseline 1-year hazard rate ($q_1 = 0.702834$), the following risk

equation can be used to estimate the 1-year risk of hospitalization among Maryland Medicaid patients diagnosed with HF:

$$1\ year\ hospitalization\ risk = \left(1 - exp\left[-\left(q_1 \times HR^{COPD} \times HR^{stroke} \times HR^{renal} \times HR^{diabetes} \times HR^{Psych} \times HR^{Hyperlipidemia} \times HR^{heart\ disease} \times HR^{Hypertension} \times HR^{otherCVD} \times HR^{ACEi/ARB} \times HR^{beta-blocker} \times HR^{Other\ CV\ drugs} \times HR^{age\ 45-54} \times HR^{age\ 55-64} \times HR^{Hispanic} \times HR^{Other\ race} \times HR^{Hospital\ HFdx}\right)\right]\right) \times 100$$

Six-month or 2-year hospitalization risk can be calculated by substituting q_1 with $q_{.5} = 0.471884$ or $q_2 = 0.984043$, respectively. The incidence-based cohort may also be used instead by setting the HR for insignificant risk factors (ie, aged 45-54 years, Hispanic, and other race) to 1.0 in the equation above and substituting the following baseline hazards: $q_{.5}^{inc} = 0.366204$, q_1^{inc} =0.549999, and $q_2^{inc} = 0.795598$. See **Appendix Table 1** below for the relevant HR estimates to input for the prevalence and incidence based cohorts, respectively.

The model's ability to correctly discriminate between pairs of individuals in the prevalence-based sample with high- and low-risk for hospitalization was good, (ie, the C statistics were 0.80-0.81 for any time horizon). The C statistics using estimates from the incidence-based sample were 0.79-0.80 for any time horizon.

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eAppendix Table 1. Relative Risks of Heart Failure Comorbidities and Other Risk Factors for Hospitalization After Diagnosis of Heart Failure

	Prevalence-Based HF Sample HR (95% CI)	Incidence-Based HF Sample HR (95% CI)
Comorbidities[a]		
No COPD	*1.00*	*1.00*
COPD	1.33 (1.26-1.40)[b]	1.32 (1.24-1.41)[b]
No stroke	*1.00*	*1.00*
Stroke	1.27 (1.20-1.34)[b]	1.30 (1.21-1.39)[b]
No renal dysfunction	*1.00*	*1.00*
Renal dysfunction	1.43 (1.36-1.51)[b]	1.60 (1.48-1.70)[b]
No diabetes	*1.00*	*1.00*
Diabetes	1.26 (1.20-1.32)[b]	1.21 (1.13-1.29)[b]
No psychological disorder	*1.00*	*1.00*
Psychological disorder	0.77 (0.73-0.81)[b]	0.79 (0.74-0.85)[b]
No hyperlipidemia	*1.00*	*1.00*
Hyperlipidemia	0.81 (0.77-0.85)[b]	0.83 (0.78-0.89)[b]
No chronic ischemic heart disease	*1.00*	*1.00*
Chronic ischemic heart disease	1.28 (1.22-1.35)[b]	1.25 (1.17-1.34)[b]
No hypertension	*1.00*	*1.00*
Hypertension	1.11 (1.05-1.17)[b]	1.17 (1.07-1.28)[b]
No other cardiovascular disease	*1.00*	*1.00*
Other cardiovascular disease	1.40 (1.31-1.50)[b]	1.54 (1.38-1.71)[b]
First-line cardiovascular therapies		
No ACEi/ARBs	*1.00*	*1.00*
ACEi/ARBs	0.77 (0.73-0.81)[b]	0.75 (0.70-0.80)[b]
No beta-blockers	*1.00*	*1.00*
Beta-blockers	0.83 (0.79-0.87)[b]	0.85 (0.80-0.91)[b]
No aldosterone antagonists	*1.00*	*1.00*
Aldosterone antagonists	*1.00*	*1.00*
No nitrates + hydralazine	*1.00*	*1.00*
Nitrates + hydralazine	*1.00*	*1.00*
No other cardiovascular drugs	*1.00*	*1.00*
Other cardiovascular drugs	0.76 (0.72-0.80)[b]	0.76 (0.71-0.81)[b]
Demographics		
Aged 18-44 years	*1.00*	*1.00*
Aged 45-54 years	1.13 (1.06-1.19)[b]	*1.00*
Aged 55-64 years	0.94 (0.88-0.99)[c]	0.88 (0.81-0.96)[d]
White	*1.00*	*1.00*
Black	*1.00*	*1.00*
Hispanic	0.81 (0.68-0.98)‡	*1.00*

Other race	0.83 (0.75-0.93)[b]	*1.00*
Female	*1.00*	*1.00*
Male	*1.00*	*1.00*
First hospitalized		
After HF diagnosis	*1.00*	*1.00*
At HF diagnosis	1.27 (1.22-1.33)[b]	1.35 (1.2-1.43)[b]
Observations	14,149	7470
Number of hospitalizations	9740	5010

ACEi/ARBs indicates angiotensin-converting enzyme inhibitors and/or angiotensin II receptor antagonists; COPD, chronic obstructive pulmonary disease.

[a]All comorbidities were diagnosed prior to or within 3 months of diagnosis of heart failure. Model controls for diagnosis of 1 or more comorbidities after 3 months of diagnosis of heart failure (not reported). See Appendix Table 2 below for diagnoses codes defining comorbidities and American Society of Health-System Pharmacists Pharmacologic-Therapeutic Classification (AHFS) therapeutic class codes.

[b]P <.001.

[c]P <.05.

[d]P <.01.

Appendix: Reference

1. Schemper M, Wakounig S, Heinze G. The estimation of average hazard ratios by weighted Cox regression. *Stat Med*. 2009;28(19):2473-2489.

eAppendix Table 2. Comorbidity and Disease-Modifying Therapy Classification

Comorbidity	***ICD-9-CM* code (any secondary coding)**
Chronic obstructive pulmonary disease	491,492, 496
Stroke	430-438
Renal dysfunction	584-587
Diabetes	250
Psychological disorder[a]	290-298, 300, 301, 303-305, 308, 310, 311, 313, 797 (or AHFS codes 28:12, 28:16, 28:24)
Hyperlipidemia	272
Chronic ischemic heart disease	410-414
Hypertension	401, 402
Other cardiovascular disease	390-400, 403-409, 415-427, 429, 439-459
First-line disease-modifying therapies	**AHFS code**
ACEi/ARBs	24:32.04; 24:32.08
Beta-blockers	24:24
AAs	24:32.20
Nitrates-hydralazine combination	24:12.08 *with* 24:08.20; 24:08.20
Other cardiovascular drugs	24:xx (excluding drugs listed above, but including nitrates or hydralazine alone)

AAs indicates aldosterone receptor antagonists ACEi/ARBs; angiotensin-converting enzyme inhibitors and/or angiotensin II receptor antagonists; AHFS, American Society of Health-System Pharmacists Pharmacologic-Therapeutic Classification; *ICD-9-CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification*.

[a]Psychological disorders include anxiety disorders, delirium, dementia, amnestic and other cognitive disorders, mood and depressive disorders, personality disorders, schizophrenia and other psychotic disorders, alcohol/substance abuse, or use of anticonvulsants, psychotherapeutic agents, anxiolytics, sedatives, or hypnotics.

eAppendix Table 3. Clinical and Demographic Characteristics of HF Patients With Comorbidities

	COPD (N = 3869) n (%)	Stroke (N = 2900) n (%)	Renal Dysfunction (N = 3750) n (%)	Diabetes (N = 5804) n (%)	Psych Disorder (N = 7786) n (%)	HLD (N = 5303) n (%)	Ischemic Heart Disease (N = 6074) n (%)	HTN (N = 10,329) n (%)	Other CVD (N = 10,987) n (%)
HF type at diagnosis									
Unspecified	3680 (95)	2750 (95)	3548 (95)	5504 (95)	7394 (95)	4949 (93)	5722 (94)	9771 (95)	10393 (95)
Systolic	75 (2)	75 (3)	77 (2)	150 (3)	183 (2)	175 (3)	200 (3)	290 (3)	307 (3)
Diastolic	89 (2)	55(2)	101 (3)	127 (2)	162 (2)	140 (3)	111 (2)	206 (2)	213 (2)
Systolic & diastolic	25 (1)	20 (1)	24 (1)	23 (0)	47 (1)	39 (1)	41 (1)	62 (1)	74 (1)
HF therapies									
ACEi/ARBs	1080 (28)	734 (25)	869 (23)	1961 (34)	2139 (27)	1800 (34)	1841 (30)	3367 (33)	3130 (28)
Beta-blockers	847 (22)	754 (26)	1015 (27)	1644 (28)	1974 (25)	1583 (30)	1924 (32)	3031 (29)	3040 (28)
AAs	175 (5)	75 (3)	119 (3)	262 (5)	337 (4)	238 (4)	314 (5)	502 (5)	564 (5)
Nitrates + hydralazine	21 (1)	23 (1)	60 (2)	54 (1)	38 (0)	39 (1)	59 (1)	91 (1)	85 (1)
Other	1494 (39)	1198 (41)	1421 (38)	2607 (45)	2976 (38)	2665 (50)	2604 (43)	4386 (42)	4122 (38)
None	1442 (37)	1091 (62)	1560 (42)	1678 (29)	2807 (36)	1226 (23)	1952 (32)	3073 (30)	4081 (37)
Age, years									
18-44	598 (15)	578 (20)	1022 (27)	1143 (20)	2145 (28)	977 (18)	1223 (20)	2526 (24)	3119 (28)
45-54	1557 (40)	996 (34)	1372 (37)	2115 (36)	2914 (37)	1958 (37)	2244 (37)	3828 (37)	3947 (36)
55-64	1714 (44)	1326 (46)	1356 (36)	2546 (44)	2727 (35)	2368 (45)	2607 (43)	3975 (38)	3921 (36)
Race/ethnicity									
White	1813 (47)	898 (31)	972 (26)	1939 (33)	2968 (38)	2066 (39)	2152 (35)	3144 (30)	3543 (32)
Black	1861 (48)	1777 (61)	2465 (66)	3437 (59)	4353 (56)	2877 (54)	3485 (57)	6453 (62)	6611 (60)
Hispanic	30 (1)	52 (2)	102 (3)	109 (2)	95 (1)	105 (2)	108 (2)	188 (2)	206 (2)
Other	165 (4)	173 (6)	211 (6)	319 (6)	370 (5)	255 (5)	329 (5)	544 (5)	627 (6)
Sex									
Female	2296 (59)	1573 (54)	1805 (48)	3421 (59)	4543 (58)	3098 (58)	3192 (53)	5874 (57)	5945 (54)
Male	1573 (41)	1327 (46)	1945 (52)	2383 (41)	3243 (42)	2205 (42)	2882 (47)	4455 (43)	5042 (46)
Hospitalized									
At HFdx	1660 (43)	1145 (39)	1843 (49)	2357 (41)	2876 (37)	1999 (38)	2760 (45)	4196 (41)	4880 (44)
After HFdx	2971 (77)	2223 (77)	3036 (81)	4283 (74)	5320 (68)	3632 (68)	4550 (75)	7292 (71)	8023 (73)
Days after HFdx, Median (25th, 75th)[c]	141 (30, 613)	98 (24, 589)	73 (22, 387)	170 (36, 826)	201 (37, 1290)	238 (45, 1261)	136 (30, 731)	202 (40 (1073)	162 (33, 860)

AAs indicates aldosterone receptor antagonists; ACEi/ARBs, angiotensin-converting enzyme inhibitors and/or angiotensin II receptor antagonists; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease other than heart failure; HFdx, heart failure diagnosis; HLD, hyperlipidemia; HTN, hypertension.

[a]All comorbidities were diagnosed prior to or within 3 months of heart failure diagnosis. Columns are not mutually exclusive.

[b]First-line HF therapies are not mutually exclusive. Nitrates or hydralazine alone are included in "Other."

[c]Estimated using Kaplan-Meier estimator to adjust for censoring.

eAppendix Table 4. Clinical and Demographic Characteristics of Patients Where Heart Failure is Specified (5% of Prevalence Cohort)

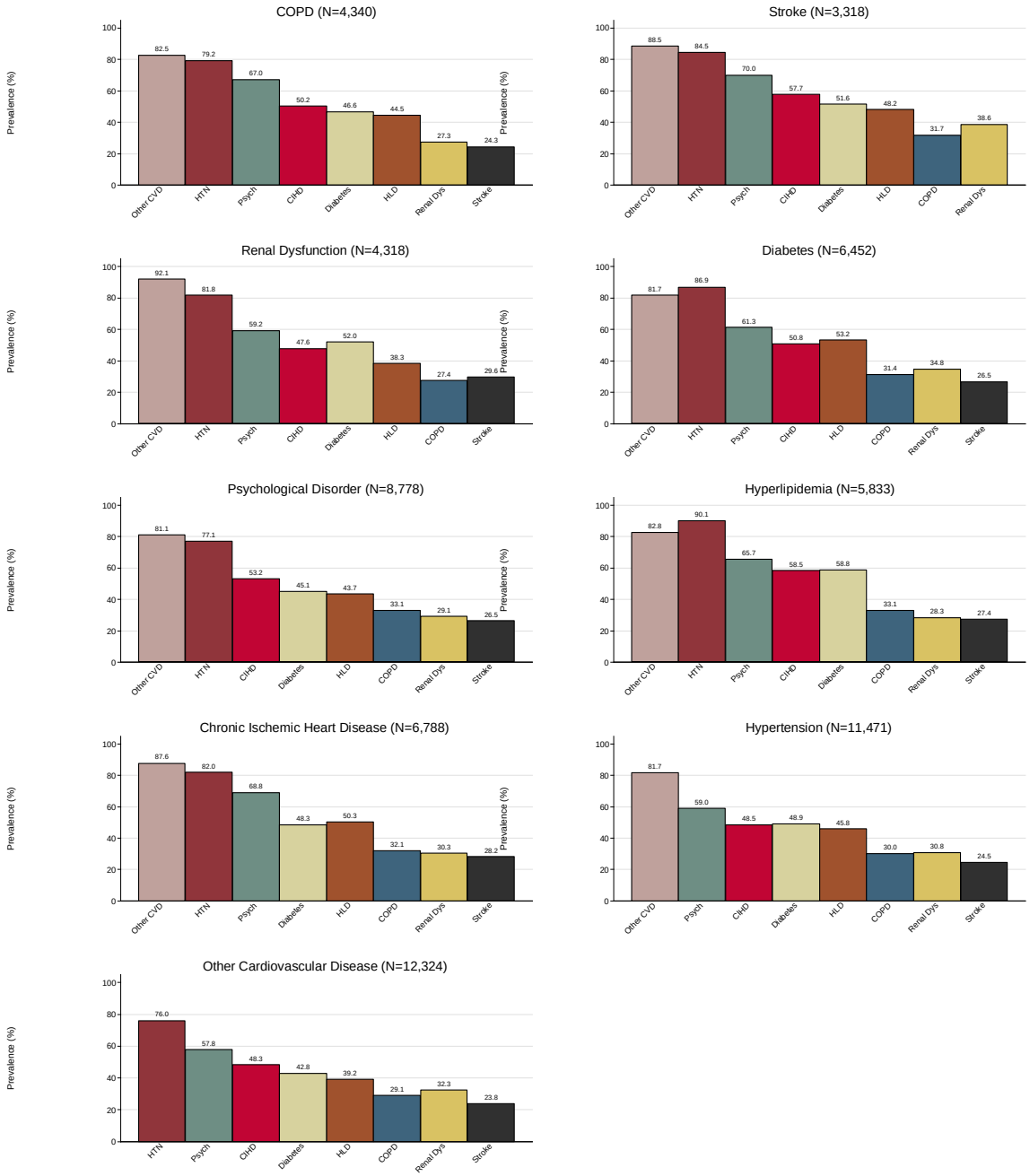
	Systolic/combined HF (N = 486) n (col%)	**HFpEF (N = 274)** n (col%)	*P*
HF therapies[a]			
ACEi/ARBs	172 (35)	87 (32)	.31
Beta-blocker	169 (35)	73 (27)	.021
AA	27 (6)	8 (3)	.096
Nitrates + Hydralazine	7(1)	3 (1)	.69
Other	104 (38)	189 (39)	.80
None	148 (30)	102 (37)	.056
Comorbidities[b]			
COPD	100 (21)	89 (32)	<.001
Stroke	95 (20)	55 (20)	.86
Renal dysfunction	101 (21)	101 (37)	<.001
Diabetes	173 (36)	127 (46)	.004
Psychological disorder	230 (47)	12 (59)	.002
HLD	214 (44)	140 (51)	.061
Chronic ischemic heart disease	241 (50)	111 (41)	.016
HTN	352 (72)	206 (75)	.41
Other CVD	381 (78)	213 (78)	.83
Age, years			
18-44	124 (26)	72 (26)	.56
45-54	187 (38)	95 (35)	
55-64	175 (36)	107 (39)	
Race/ethnicity			
White	188 (39)	104 (38)	.41
Black	258 (53)	156 (57)	
Hispanic	8 (2)	3 (1)	
Other	32 (7)	11 (4)	
Sex			
Female	213 (44)	169 (62)	<.001
Male	273 (56)	105 (38)	
First hospitalized			
At HF diagnosis	148 (30)	140 (51)	<.001
After HF diagnosis	338 (70)	134 (49)	

AA indicates aldosterone receptor antagonist; ACEi/ARBs, angiotensin-converting enzyme inhibitors and/or angiotensin II receptor antagonists; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease (other than heart failure); HFdx, heart failure diagnosis; HLD, hyperlipidemia; HTN, hypertension.

[a]First-line HF therapies are not mutually exclusive. Nitrates or hydralazine alone are included in "Other."

[b]All comorbidities were diagnosed prior to or within 3 months of heart failure diagnosis. Columns are not mutually exclusive.

eAppendix Figure 1. Cross-Prevalence of Comorbidities in Maryland Medicaid Patients With Heart Failure (2005-2010)



COPD indicates chronic obstructive pulmonary disease; CVD, cardiovascular disease (other than heart failure); HLD, hyperlipidemia; HTN, hypertension.
All comorbidities were diagnosed prior to or within 3 months of heart failure diagnosis. Columns are not mutually exclusive. Maryland Medicaid, managed care or fee-for-service, enrolled patients with a heart failure diagnosis between July 1, 2005, and December 31, 2009, aged 18-64 years, with at least 6 months follow-up; the sample was prevalence-based.