Glycated Hemoglobin and Outcomes of Heart Failure (from Get With the Guidelines-Heart Failure)

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Glycated hemoglobin (HbA_{1C}) is a risk factor for new onset heart failure (HF). There is however a paucity of data evaluating its association with outcomes in patients with established HF. We assessed the relation of HbA_{1C} with outcomes among hospitalized HF patients. Among 41,776 HF patients from 263 hospitals participating to the Get with the Guidelines-HF registry between January 2009 and March 2016, we related HbA_{1C} to outcomes (in-hospital mortality, length of hospital stay, discharge to home, 30-day mortality, 30-day readmission, and 1-year mortality), using generalized estimating equation to account for within-hospital clustering and potential confounders. There were 68% of HF patients with diabetes and median HbA_{1C} was 7.1%. Each percent change in HbA_{1C} was associated with higher odds of discharge to home for HbA_{1C} levels <6.5% (covariate-adjusted odds ratio [OR] 1.13 [95% confidence interval 1.04 to 1.12]) or ≥6.5% (OR 1.05 [1.02 to 1.07]). After stratification by diabetes status, this association remained significant only among patients with diabetes (ORs for HbA_{1C} levels <6.5%: 1.17 [1.07 to 1.27]; and ≥6.5%: 1.06 [1.03 to 1.09]). Compared with the lowest HbA_{1C} tertile (HbA_{1C} ≤6.1%), patients in the highest HbA_{1C} tertile (HbA_{1C} 7.3% to 19%) were more likely to have a length of hospital stay >4 days (OR 1.10 [1.02 to 1.18]) and to be discharged home (OR 1.23 [1.14 to 1.33]). There were no significant association between HbA_{1C} and the following outcomes: in-hospital mortality, 30-day mortality, 30-day readmission, and 1-year mortality. In conclusion, among hospitalized HF patients, HbA_{1C} was associated with prolonged hospital stay and home discharge, but not with readmission, short-term, or intermediate-term mortality. **(Am J Cardiol 2019;123:618−626)**

Heart failure (HF) is common and affects ∼6.5 million of Americans.[1] Diabetes increases HF risk by several-fold.[2] Glycated hemoglobin (HbA_{1C}) reflects the average glycemia over 3 months and thus glucose control among patients with diabetes. Extant evidence suggests that elevated HbA_{1C} might increase HF risk,[3] although the evidence is conflicting.[4] It is therefore logical to explore whether HbA_{1C} adversely influences HF outcomes. Studies of glycemic status and HF outcomes have mainly accounted for diabetes status as a binary predictor and reported variable results.[5−8] Diabetes was independently associated with length of hospital stay (LOS), but not with in-hospital mortality or postdischarge mortality in HF.[5,6] Studies assessing HbA_{1C} and HF outcomes have focused on diabetic patients, reported discrepant results,[9−12] and were small in size.[9,10] Additional studies are needed to better characterize the relation of HbA_{1C} and HF outcomes across the glycemic spectrum, and in clinically important subgroups.[13]

Using Get with the Guidelines (GWTG)-HF registry data, we assessed the association between HbA_{1C} and outcomes of HF. We hypothesized that increased HbA_{1C} will be associated with worse outcomes in HF patients with and without diabetes.

Methods

The study cohort originated formed from GWTG-HF, a national prospective registry and quality improvement program sponsored by the American Heart Association. Details of the design and conduct of the GWTG-HF registry have been previously described.[14,15] Patients enrolled in the GWTG-HF registry are those hospitalized with HF, or patients who developed significant HF symptoms such that HF was the primary discharge diagnosis.

For the assessment of mortality at 1-year after discharge, the in-hospital GWTG-HF registry data were linked to Centers for Medicare & Medicaid Services (CMS) claims data. The linked clinical and claims data set was created by matching on a series of indirect identifiers, including

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admission date, discharge date, patient age or date of birth, and gender. The Medicare claims for outpatient and skilled nursing facilities data were limited to fee-for-service Medicare patients aged ≥65 years at the time of the index HF admission. In case multiple HF admission records were linked for a single patient, we used the earliest record for this analysis.

A total of 393,472 HF patients from GWTG-HF participating hospitals (419 sites) were admitted between January 1, 2009 and March 21, 2016. From this pool of patients, we excluded those discharged to hospice, with missing discharge status, those who left against medical advice, those with discharge disposition not documented or undetermined, or transferred out (N = 27,145, from 3 sites). We then excluded patients without HbA_{1C} (N = 324,551, from 153 sites). GWTG-HF is primarily a HF quality improvement program and sites are not required to assess HbA_{1C} as part of the program. Instead, sites report the most recent results obtained at their facility closest to the time of admission, if available. The final study sample included 41,776 patients from 263 sites, enrolled between January 1, 2009 and March 21, 2016. The subsample of participants with data on 1-year mortality obtained by linkage to the CMS data, included 10,119 patients (aged ≥65 years) from 204 sites, enrolled between January 1, 2009 and October 31, 2014.

Each participating hospital received either human research approval to enroll cases without individual patient consent under the common rule or a waiver of authorization and exemption from subsequent review by their institutional review board. The Duke Clinical Research Institute (Durham, North Carolina) serves as the data analysis center.

Glycosylated hemoglobin was assessed during the index hospitalization. The diabetes mellitus status was defined by previous medical history of diabetes or new clinical diagnosis of diabetes during the index hospitalization. The primary outcomes were in-hospital mortality, LOS (categorized as >4 days vs ≤4 days), and discharge home. The secondary outcomes included 30-day mortality, 30-day readmission, and 1-year mortality. Postdischarge mortality was ascertained based on death dates from the CMS vital status files, and admission was based on subsequent Medicare inpatient claims.

Patients were categorized by HbA_{1C} tertiles (tertile 1: HbA_{1C} ≤6.1%, tertile 2: HbA_{1C} 6.2% to 7.2%; tertile 2: HbA_{1C} 7.3% to 19%). We compared patient (demographic and clinical) and hospital characteristics among patients across HbA_{1C} groups. Categorical variables were presented as proportions and continuous variables were presented as median (interquartile range). Percent standardized differences were provided for variables between the groups, and a standardized difference >10% was considered clinically meaningful. We used multivariable logistic or Cox proportional hazard regression models to examine the association of HbA_{1C} and each clinical outcome, using generalized estimating equation to account for the within-hospital clustering of patients. The covariates included in the multivariable models were patients (age, gender, race [white, black, and other], medical history [anemia, coronary artery disease {CAD} and/or previous myocardial infarction, cerebrovascular disease and/or transient ischemic attack, diabetes, hyperlipidemia, hypertension, chronic obstructive pulmonary disease and/or asthma, PVD, renal insufficiency, cigarette smoking in the past year], vital signs on admission [systolic blood pressure, heart rate, sodium, blood urea nitrogen, and left ventricular ejection fraction]) and hospital (region, hospital type, number of beds, rural vs urban, heart transplant center) characteristics. We performed stratified analyses by diabetes status. We also assessed the association between HbA_{1C} (HbA_{1C} ≥6.5% vs <6.5%) and outcomes.

For missing covariates, we performed multiple imputation using Markov chain Monte Carlo and regression methods. Final estimates and associated standard errors reflect the combined analysis over 25 imputed datasets. Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina). All p values are 2-sided tests considered statistically significant at <0.05.

Results

The baseline patients (demographic and clinical) and hospitals characteristics by HbA_{1C} categories are shown in Table 1. Compared with those in the lowest tertile (HbA_{1C} ≤6.1%—reference group), participants in the highest tertile (HbA_{1C} 7.3% to 19%) were more likely to be older, Hispanic, to have a high body mass index, diabetes, hyperlipidemia, a history of CAD, previous coronary artery bypass grafting, or myocardial infarction, and to be on dialysis. Compared with patients in the reference group (HbA_{1C} ≤6.1%), patients in the middle HbA_{1C} tertile (HbA_{1C} 6.2% to 7.2%) were more likely to be black patients, uninsured, or on dialysis, as well as to have a higher body mass index, diabetes, hyperlipidemia, a history of COD, or previous coronary artery bypass grafting. Of the patients with data on 1-year mortality (aged ≥65 years and linked to CMS data), 51.8% (n = 5,239) had a new diagnosis of diabetes based on an HbA_{1C} ≥6.5% at the index visit.

The estimates of the association between HbA_{1C}, as a continuous variable, and the various outcomes (in-hospital mortality, LOS, discharge to home, 30-day mortality, 30-day readmission, and 1-year mortality) are shown in Table 2. The shape of the associations between HbA_{1C} and the various outcomes are displayed in Supplementary Figures 1 to 6. For the in-hospital mortality, 30-day mortality, 30-day readmission, and 1-year mortality outcomes, there was a nonsignificant association with HbA_{1C} in the multivariable adjusted models. The exception was among patients with an HbA_{1C} <6.5%, in whom a 1% increase in HbA_{1C} was associated with lower 30-day readmission (adjusted odds ratio [OR] 0.73 [95% confidence interval {CI} 0.59 to 0.90]) or 30-day mortality (OR 0.89 [95% CI 0.81 to 0.97]). Similar significant associations were observed after stratification by diabetes status (Table 2).

After multivariable adjustment for relevant patient characteristics (Table 2), a 1% change in HbA_{1C} was associated with a higher likelihood of being discharged home, both for HbA_{1C} levels <6.5% (OR 1.13 [95% CI 1.04 to 1.12]), and ≥6.5% (OR 1.05 [95% CI 1.02 to 1.07]). This association remained significant when the population was restricted to those with diabetes (OR for HbA_{1C} levels <6.5%: 1.17 [95% CI 1.07 to 1.27]; OR for HbA_{1C} levels ≥6.5%: 1.06 [95% CI 1.03 to 1.09]), but was nonsignificant among

Table 1
Baseline characteristics of heart failure patients by tertiles of HbA_{1C} in the GWTG-Heart Failure registry

Variable	Overall (N = 41776)	Tertile 1 of HbA_{1C} (0 − 6.2%) (N = 14042)	Tertile 2 of HbA_{1C} (6.3-7.2%) (N = 13445)	Tertile 3 of HbA_{1C} (7.3-19%) (N = 14289)	Standardized difference tertile 2 vs tertile 1	Standardized difference tertile 3 vs tertile 1
Age (years)	69 (58, 79)	70 (58, 81)	7 (61, 81)	66 (57, 75)	6.8%	21.2%
Age ≥65 years	25354 (60.8%)	8721 (62.1%)	8924 (66.5%)	7709 (54.1%)	8.9%	16.6
Men	19248 (46.1%)	6549 (46.6%)	6154 (45.9) %	6545(45.8%)	1.7%	1.7%
Asian	578 (1.4%)	179 (1.3)	196 (1.5%)	203 (1.2%)	1.6%	1.3%
Hispanic	5307 (12.7)	1386 (9.9%)	1634 (12.2%)	2287 (16.0%)	7.3%	18.4%
Black	10503 (25.2%)	3924 (28.0%)	3107 (23.2%)	3472 (24.3%)	11.1%	8.3%
White	24128 (57.9%)	8175 (58.3%)	8085 (60.3%)	7868 (55.2%)	4.0%	6.7%
Other race/ethnicity	1188 (2.9%)	357 (2.6%)	396 (3.0%)	435 (3.1%)	2.6%	3.1%
Insurance status						
No insurance/not documented	2912 (7.3%)	1189 (8. 8%)	737 (5.7%)	986 (7.2%)	12.0%	5.8%
Medicare	20119 (50.1%)	6629 (49.0%)	6890 (53. 2%)	6600 (48.2%)	8.5%	1.5%
Medicaid	6286 (15.7%)	2148 (15.9%)	1874 (14.5%)	2264 (16.5%)	3.9%	1.8%
Other type of insurance	10857 (27.0%)	3572 (26.4%)	3445 (26.6%)	3840 (28.1%)	0.5%	3.7%
Atrial fibrillation or flutter	13021 (31.2%)	4621 (33.0%)	4628 (34.4%)	3772 (26.4%)	3.2%	14.3%
COPD or asthma	14436 (34.6%)	4733 (33.8%)	4742 (35.3%)	4961 (34.7%)	3.3%	2.1%
Diabetes	28708 (68.8%)	5888 (42.0%)	9685 (72.1%)	13135 (92.0%)	63.8%	125.5%
Hyperlipidemia	23645 (56.6%)	7036 (50.2%)	7827 (58.3%	8782 (61.5%)	16.3%	23.0%
Hypertension	35505 (85.1%)	11555 (82.4%)	11454 (85.2%)	12496 (87.5%)	7.8%	14.3%
Peripheral vascular disease	5512 (13.2%)	1651 (11.8%)	1848 (13.8%)	2013 (14.1%)	5.9%	6.9%
Coronary disease	20587 (49.3%)	6074 (43.3%)	6794 (50. 6%)	7719 (54.1%)	14.6%	21.6%
Prior CABG	8645 (20.7%)	2332 (16.6%)	3015 (22.4%)	3298 (23.1%)	14.7%	16.3%
Previous MI	8912 (21.4%)	2659 (19.0%)	2867 (21.3%)	3386 (23.7%)	5.9%	11.6%
CVA/TIA	6501 (15.6%)	2126 (15.2%)	2161 (16.1%)	2214 (15.5%)	2.5%	1.0%
Dialysis	1467 (3.5%)	716 (5.1%)	365 (2.7%)	386 (2.7%)	12.4%	12.4%
Renal insufficiency (serum creatinine >2)	9795 (23.5%)	3217 (22.9%)	3139 (23.4%)	3439 (24.1%)	1.0%	2.7%
Smoking	8465 (20.3%)	3240 (23.1%)	2498 (18.6%)	2727 (19.1%)	11.1%	9.8%
Medication prior to admission						
Lipid lowering agent	23021 (59.0%)	6913 (52.2%)	7683 (61.1%)	8425 (63.9%)	17.9%	23.8%
Diabetes medication	20193 (89.6%)	3540 (75.3%)	6696 (91.9%)	9957 (94.5%)	45.8%	55.5%
Ace inhibitor	15157 (38.9%)	4702 (35.5%)	4923 (39.1%)	5532 (42.0%)	7.5%	13.2%
Angiotensin receptor blocker	5906 (15.1%)	1761 (13.3%)	1984 (15.8%)	2161 (16.4%)	7.0%	8.7%
Aldosterone antagonist	5282 (13.5%)	1537 (11.6%)	1804 (14.3) %	1941(14.7%)	8.1%	9.2%
Beta-blocker	26343 (67. 6%)	8467 (64.0%)	8710 (69.3%)	9166 (69.5%)	11.2%	11.7%
Digoxin	4256 (10.9%)	1282 (9.7%)	1412 (11.2%)	1562 (11.8%)	5.0%	7.0%
Loop diuretics	23455 (60.2%)	7214 (54.5%)	7906 (62.9%)	8335 (63.2%)	17.0%	17.7%
Nitrate	7406 (19.0%)	2191 (16.6%)	2444 (19.4%)	2771 (21.0%)	7.5%	11.4%
Hydralazine	4635 (11. 9%)	1600 (12.1%)	1441 (11.5%)	1594 (12.1%)	2.0%	0.01%
Hydralazine/nitrate	9573 (24.6%)	2989 (22.6%)	3091 (24.6%)	3493 (26.5%)	4.7%	9.1%
statin	21245 (54.5%)	6394 (48.3%)	7098 (56.4%)	7753 (58.8%)	16.3%	21.1%
In-hospital procedures						
CRT-D	675 (1.7%)	225 (1.6%)	240 (1.8%)	210 (1.5%)	1.5%	1.0%
ICD only	440 (1.1%)	148 (1.1%)	150 (1.1%)	142 (1.0%)	0.6%	0.6%
Vital signs at admission						
Weight change (discharge weight - admission weight) (kg)	-2.0 (-5, 0)	-2.0 (-5, 0)	-2.0 (-5.4, 0)	-2.0 (-5.4, 0)	0.9%	1.9%
BMI	30.39 (25.9, 36.4)	29.4 (24.3, 34.3)	30.5 (26.2, 36.7)	31.24 (27.7, 38.5)	20.7%	35.6%
Systolic blood pressure (mmHg)	142 (122, 164)	142 (122, 165)	140 (120, 162)	145 (125, 167)	5.9%	8.4%
Diastolic blood pressure (mmHg)	78 (66, 92)	79 (66, 93)	76 (65, 89)	79 (68, 92)	12.3%	1.5%
BNP at admission pg/mL	731 (318, 1513)	836 (393, 1715)	719 (308, 1498)	637 (273, 1337)	9.8%	17.9%
Heart rate (bpm)	85 (72, 99)	85 (72, 100)	84 (71, 98)	85 (73, 99)	7.9%	3.2%
LVEF	40 (25, 55)	40 (25, 55)	40 (25, 55)	40 (25, 55)	1.1%	1.0%
LVEF <40	19233 (48.2%)	6474 (48.0%)	6102 (47.5%)	6657 (49.0%)	0.1%	1.9%
Vital signs at discharge						
BMI (kg/m^2)	30.4 (25.4, 37.3)	28.37 (23.84, 34.87)	30.56 (25.7, 37.5)	32.29 (27.1, 39.3)	22.7%	38.9%
Systolic blood pressure (mmHg)	123 (110, 140)	122 (108. 138)	123 (109, 139)	125 (111, 140)	3.1%	11.8%
Diastolic blood pressure (mmHg)	68 (60, 76)	67 (59, 77)	67 (59, 75)	68 (60, 77)	6.7%	4.5%

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Table 1 (***Continued***)

Variable	Overall (N = 41776)	Tertile 1 of HbA_{1C} (0 − 6.2%) (N = 14042)	Tertile 2 of HbA_{1C} (6.3-7.2%) (N = 13445)	Tertile 3 of HbA_{1C} (7.3-19%) (N = 14289)	Standardized difference tertile 2 vs tertile 1	Standardized difference tertile 3 vs tertile 1
Heart rate (bpm)	75 (66, 84)	75.0 (66.0, 84. 0)	74 (66, 84)	75 (67, 85)	1.6%	2.0%
BNP at discharge pg/mL	528.0 (233.0, 1140.0)	582.0 (274.0, 1252.0)	533.0 (231.3, 1174.6)	469.5 (202.5, 995.0)	5.4%	13.9%
Laboratory values at admission						
Hemoglobin (g/dL)	11.9 (10.3, 13.4)	11.8 (10.2, 13.30)	11.80 (10.3, 13.3)	12.0 (10.5, 13.4)	1.4%	6.8%
Sodium (mEq/L)	138.0 (135.0, 140.0)	139.0 (136.0, 141.0)	138.0 (136.0, 141.0)	138.0 (135.0, 140.0)	5.3%	14.8%
BUN (mg/dL)	25 (17, 38)	23 (16, 35)	25 (18, 39)	25 (18, 39)	12.9%	10.9%
Serum creatinine (mg/dL)	1.30 (1.00, 1.90)	1.3 (1.0, 1.9)	1.3 (1.0, 1.9)	1.30 (1.00, 1.90)	1.8%	0.9%
Laboratory values at discharge						
Sodium (mEq/L)	138.0 (135.0, 140.0)	138.0 (135.0, 140.0)	138.0 (135.0, 140.0)	138.0 (135.0, 140.0)	3.2%	6.8%
BUN (mg/dL)	29.0 (20.0, 43.0)	27.0 (19.0, 40.0)	29.0 (21.0, 44.0)	30.0 (21.0, 45.0)	13.1%	16.5%
Serum creatinine (mg/dL)	1.30 (1.0, 1.9)	1.30 (1.0, 1.90)	1.3 (1.0, 1.9)	1.4 (1.0, 1.9)	4.1	3.2%
Risk interventions						
Referred to outpatient cardiac rehabilitation program						
Not applicable	6013 (20.6%)	1930 (19.4%)	2000 (21.3%)	2083 (21.0%)	4.8%	3.9%
Not documented	6008 (20.5%)	1832 (18.4%)	1903 (20.3%)	2273 (22.9%)	4.8%	11.1%
Yes	3796 (13.0%)	1266 (12.7%)	1247 (13.3%)	1283 (12.9%)	1.7%	0.6%
No	13438 (45.9%)	4921 (49.5%)	4221 (45.0%)	4296 (43.2%)	8.9%	12.5%
Discharge information						
Discharge disposition						
Expired	1006 (2.4%)	343 (2.4%)	358 (2.7%)	305 (2.1%)	1.4%	2.1%
Other health care facility	6702 (16.0%)	2464 (17.7%)	2326 (17.3%)	1912 (13.4%)	0.7%	11.5%
Home	34068 (81.6%)	11235 (80.0%)	10761 (80.0) %	12072 (84.5%)	0.1%	11.7%
Outcomes						
In hospital mortality	1006 (2.4%)	343 (2.4%)	358 (2.8%)	305 (2.1%)	1.4%	2.1%
Length of hospital stay	4.00 (3, 7)	4.00 (3, 7)	4 (3, 7)	4 (3, 7)	3.3%	0.7%
Achievement measures						
ACEI/ARB at discharge	13608 (95.6%)	4630 (95.4%)	4235 (96.1%)	4743 (95.4%)	3.5%	0.4%
Any beta blocker at discharge	17124 (97.8%)	5706 (97.9%)	5376 (97.8%)	6042 (97.8%)	0.3%	0.4%
Smoking cessation counseling	7917 (96.2%)	2991 (95.1%)	2360 (97.4%)	2566 (96.4%)	12.1%	6.4%
Quality measures						
Aldosterone antagonist at discharge	6684 (44.5%)	2125 (41.6) %	2159 (45.8%)	2400 (46.1%)	8.5%	9.1%
Anticoagulation for atrial fibrillation	9197 (80.9%)	3055 (78.7) %	3341 (82.7%)	2801 (81.4%)	9.9%	6.7%
DVT prophylaxis	12753 (86.8%)	4393 (86.7%)	4144 (86.3)	4216 (87.4%)	1.2%	2.0%
Evidence-based specific beta blockers	15440 (90.3%)	5144 (90.2%)	4830 (90.0)	5466 (90.7%)	0.7%	1.4%
Medications at discharge						
Beta blocker						
Contraindicated	3069 (7.5%)	1200 (8.8%)	1013 (7.7%)	856 (6.1%)	3.7%	10.1%
Prescribed	2694 (6.6%)	954 (7.0%)	866 (6.6%)	874 (6.3%)	1.4%	2.9%
Prescribed	34999 (85.9%)	11541 (84.3%)	11209 (85.6%)	12249 (87.6%)	3.8%	9.7%
ACEI						
Contraindicated	11645 (28.6%)	3897 (28.5%)	3821 (29.2%)	3927 (28.1%)	1.6%	0.8%
Not prescribed	8802 (21.6%)	2880 (21.0%)	2937 (22.5%)	2985 (21.4%)	3.4%	0.8%
Prescribed	20294 (49.8%)	6911 (50.5%)	6327 (48.4%)	7056 (50.5%)	4.3%	0.1%
ARB						
Contraindicated	11527 (28.3%)	3939 (8. 8)	3725 (28.5)	3863 (27.7)	0.7%	2.5%
Not prescribed	23056 (56.6%)	7951 (58.1)	7286 (55.7)	7819 (56.0)	4.9%	4.2%
Prescribed	6133 (15.1%)	1791 (13.1)	2068 (15.8)	2274 (16.3)	7.7%	9.1%
ACEI/ARB						
Contraindicated	10021 (24.6%)	3417 (25.0%)	3281 (25.1%)	3323 (23.8%)	0.3%	2.7%
Prescribed	4664 (11.5%)	1673 (12.2%)	1531 (11.7%)	1460 (10.5%)	1.6%	5.6%
Prescribed	26057 (4.0%)	8600 (62.8%)	8273 (63.2%)	9184 (65.8%)	0.8%	6.1%
Aldosterone antagonist						
Contraindicated	7126 (17.5%)	2393 (17.5%)	2238 (17.1%)	2495 (17.9%)	1.0%	1.0%
Not prescribed	24021 (59.0%)	8290 (60.6%)	7691 (58.8%)	8040 (57.6%)	3.6%	6.2%
Prescribed	9584 (23.5%)	2999 (21.9%)	3149 (24.1%)	3436 (24.6%)	5.1%	6.3%
Diuretic	31472 (75.3%)	10234 (72.9%)	10296 (76.6%)	10942 (76.6%)	8.5%	8.5%

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Table 1 (***Continued***)

Variable	Overall (N = 41776)	Tertile 1 of HbA_{1C} (0 − 6.2%) (N = 14042)	Tertile 2 of HbA_{1C} (6.3-7.2%) (N = 13445)	Tertile 3 of HbA_{1C} (7.3-19%) (N = 14289)	Standardized difference tertile 2 vs tertile 1	Standardized difference tertile 3 vs tertile 1
Hydralazine nitrate						
Contraindicated	2351 (5.8%)	872 (6.4%)	738 (5.7%)	741 (5.3%)	3.1%	4.6%
Not prescribed	31770 (78.1%)	10609 (77.6%)	10331 (79.0%)	10830 (77.6%)	3.5%	0.03%
Prescribed	6584 (16.2%)	2193 (16.0%)	2001 (15.3%)	2390 (17.1%)	2.0%	2.9%
Other medications at discharge						
Loop diuretic	30702 (73.5%)	9979 (71.1%)	10048 (74.7%)	10675 (74.7%)	8.3%	8.2%
Digoxin	5038 (12.1%)	1633 (11.6%)	1698 (12.6%)	1707 (12.0%)	3.1%	1.0%
Hospital characteristics						
Region						
West	5019 (12.0%)	1516 (10.8%)	1666 (12.4%)	1837 (12.9%)	5.0%	6.4%
South	14624 (35.0%)	5481 (39.0%)	4458 (33.2%)	4685 (32.8%)	12.3%	13.1%
Midwest	9308 (22.3%)	2915 (20.8%)	3097 (23.0%)	3296 (23.1%)	5.5%	5.6%
Northeast	12825 (30.7%)	4130 (29.4%)	4224 (31.4%)	4471 (31.3%)	4.4%	4.1%
Hospital type (teaching)	30596 (73.4%)	10559 (75.3%)	9652 (71.9%)	10385 (72.8%)	7.7%	5.8%
Number of beds	431 (300, 610)	438.0 (311.0, 638.0)	428 (298, 601)	410.0 (298, 601)	18.7%	18.4%
Rural location (versus urban)	1649 (4.0%)	456 (3.3%)	577 (4.3%)	616 (4.3%)	5.5%	5.6%
Heart transplant hospital	6497 (17.3%)	2790 (21.9%)	1875 (15.5%)	1832 (14.4%)	16.5%	19.8%

Values are n (%) or median (interquartile range).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; BUN = blood urea nitrogen; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; CRT-D = cardiac resynchronization therapy and defibrillator; CVA = cerebrovascular accident; DVT = deep venous thrombosis; ICD = implantable cardiac defibrillator; LVEF = left ventricular ejection fraction; MI = myocardial infraction; TIA = transient ischemic attack.

Table 2
Odds or hazard ratios for the association between HbA_{1C} (continuous variable) and outcomes of heart failure

Outcome	No. of events (%)	Unadjusted OR or HR (95% CI) for 1% increase in HbA_{1C}		Adjusted OR or HR (95% CI) for 1% increase in HbA_{1C}	
HbA_{1C}		<6.5%	≥6.5 %	<6.5 %	≥6.5 %
Overall sample					
In-hospital mortality	1006 (2.4%)	1.03 (0.88, 1.22)	0.88 (0.84 - 0.93)	0.93 (0.79 - 1.10)	0.97 (0.92 - 1.03)
LOS (>4 days)	16064 (47.3%)	1.11 (1.04 - 1.18)	0.98 (0.97 - 1.00)	1.11 (1.03 - 1.19)	0.99 (0.97 - 1.01)
Discharge to home	34068 (81.6%)	1.02 (0.95 - 1.08)	1.16 (1.14 - 1.19)	1.13 (1.04 - 1.21)	1.05 (1.02 - 1.07)
30-day mortality	534 (5.5%)	0.81 (0.67 - 0.97)	0.95 (0.86 - 1.05)	0.73 (0.59- 0.90)	1.03 (0.93 - 1.14)
30-day readmission	2173 (22.9%)	0.95 (0.86 - 1.04)	1.01 (0.97 - 1.06)	0.89 (0.81 - 0.97)	1.02 (0.97 - 1.07)
1year mortality*	3074 (31.5%)	-	0.85 (0.79 - 0.92)	-	1.01 (0.96 - 1.06)
Diabetes subgroup					
In-hospital mortality	687 (2.4%)	0.83 (0.72 - 0.96)	0.88 (0.83 - 0.93)	0.79 (0.67 - 0.93)	0.97 (0.91 - 1.02)
LOS (>4 days)	11030 (47.5%)	1.00 (0.93 - 1.09)	0.99 (0.97 - 1.01)	1.02 (0.94 - 1.11)	0.99 (0.97 - 1.02)
Discharge to home	23141 (80.6%)	1.19 (1.11- 1.28)	1.19 (1.16 - 1.22)	1.17 (1.07 - 1.27)	1.06 (1.03 - 1.09)
30-day mortality	364 (5.3%)	0.69 (0.55 - 0.87)	0.96 (0.86 - 1.06)	0.62 (0.49 - 0.80)	1.04 (0.93 - 1.16)
30-day re-admission	1581 (23.8%)	0.92 (0.82 - 1.03)	0.99 (0.95 - 1.04)	0.93 (0.83 - 1.05)	1.01 (0.95 - 1.06)
1-year mortality*	2164 (31.8%)	-	0.85 (0.77- 0.93)*	-	1.01 (0.96 - 1.06)*
Non-diabetes subgroup					
In-hospital mortality	319 (2.4%)	1.38 (1.08 - 1.75)	0.96 (0.82 - 1.12)	1.15 (0.90 - 1.47)	1.05 (0.88 - 1.26)
LOS (>4 days)	5034 (46.8%)	1.21 (1.10 - 1.34)	1.01 (0.97 - 1.06)	1.18 (1.06 - 1.31)	1.03 (0.98 - 1.08)
Discharge to home	10927 (83.6%)	0.99 (0.91 - 1.09)	1.09 (1.03 - 1.15)	1.10 (0.97 - 1.24)	0.94 (0.87 - 1.02)
30-day mortality	170 (5.8%)	0.98 (0.76 - 1.27)	1.01 (0.84 - 1.21)	0.91 (0.68 - 1.21)	1.12 (0.93 - 1.35)
30-day re-admission	592 (20.7%)	0.88 (0.75 - 1.02)	1.01 (0.87 - 1.16)	0.83 (0.70 - 0.98)	1.03 (0.88 - 1.21)
1-year mortality*	910 (30.9%)	-	0.86 (0.78 - 0.95)*	-	1.03 (0.92 - 1.15)*

CI = confidence interval; HR = hazard ratio; LOS = length of hospital stay; OR = odds ratio; HbA_{1C} = glycosylated hemoglobin; HbA_{1C} tertiles: tertile 1: 0% to 6.2%; tertile 2: 6.3% to 7.2%; tertile 3: 7.3% to 19%.

* Estimates are hazard ratio.

Table 3
Odds or hazard ratios for the association between HbA_{1C} (tertiles) and outcomes of heart failure

Outcome	No. of events (%)			Effect estimates			
	HbA_{1C} tertile 1	HbA_{1C} tertile 2	HbA_{1C} tertile 3	Unadjusted OR or HR (95% CI) HbA_{1C} tertile 2 vs tertile 1	Adjusted OR or HR (95% CI) HbA_{1C} tertile 2 vs tertile 1	Unadjusted OR or HR (95% CI) HbA_{1C} tertile 3 vs tertile 1	Adjusted OR or HR (95% CI) HbA_{1C} tertile 3 vs tertile 1
In-hospital mortality	343 (2.4%)	358 (2.6%)	305 (2.1%)	1.06 (0.94 - 1.20)	1.01 (0.89 - 1.16)	0.85 (0.74 - 0.98)	0.97 (0.85 - 1.12)
LOS (>4 days)	5111 (45.5%)	5281 (48.7%)	5672 (47.6%)	1.14 (1.07 - 1.22)	1.14 (1.06 -1.22)	1.08 (1.01 - 1.15)	1.10 (1.02 - 1.18)
Discharge to home	11235(80.0%)	10761 (80.0%)	12072 (84.5%)	1.05 (0.99 - 1.12)	1.11 (1.03 - 1.20)	1.41 (1.31 - 1.53)	1.23 (1.14 - 1.33)
30-day mortality	774 (22.7%)	780 (22.9%)	619 (23.1%)	0.85 (0.69 - 1.04)	0.81 (0.64 - 1.02)	0.79 (0.64 - 0.99)	0.85 (0.67 - 1.08)
30-day re-admission	774 (22.7%)	780 (22.9%)	619 (23.1%)	1.01 (0.90 - 1.13)	0.95 (0.85 - 1.08)	1.02 (0.90 - 1.16)	0.96 (0.83 - 1.10)
1-year mortality*	1157 (32.8%)	1092 (31.2%)	825 (30.1%)	-	0.92 (0.85 - 1.00)*	-	0.94 (0.84 - 1.05)*

CI = confidence interval; HR = hazard ratio; LOS = length of hospital stay; OR = odds ratio; HbA_{1C} = glycosylated hemoglobin; HbA_{1C} tertiles: tertile 1: 0% to 6.2%; tertile 2: 6.3% to 7.2%; tertile 3: 7.3% to 19%.

* Estimates are hazard ratio.

those without diabetes (OR for HbA_{1C} levels <6.5%: 1.10 [95% CI 0.97 to 1.24]; OR for HbA_{1C} levels ≥6.5%: 0.94 [95% CI 0.87 to 1.02]).

In analyses using HbA_{1C} categorized into tertiles, we found that the risks of in-hospitalization mortality, 30-day mortality, 30-day readmission were similar across the HbA_{1C} categories (Table 3). The Kaplan-Meier curves for the 1-year mortality outcomes by tertiles of HbA_{1C} are shown in Figure 1. The multivariable adjusted hazard ratios for mortality showed no difference between the second and third tertiles and the lowest tertile of HbA_{1C} (Table 3).

Discussion

In a large, real-world population from the GWTG-HF registry, we examined the short- and intermediate-term outcomes among HF patients with or without diabetes in relation to HbA_{1C}. The HbA_{1C} levels were associated with a prolonged hospital stay and home discharge, after accounting for demographics and co-morbid conditions. HbA_{1C} levels were not associated with short-term (in-hospital mortality, 30-day mortality, and 30-day readmission) and intermediate-term (1-year postdischarge mortality) outcomes, except among those with an HbA_{1C} <6.5% in whom a 1% increase in HbA_{1C} was associated with lower 30-day mortality and 30-day readmission.

While the association of HbA_{1C} and incident HF has been described,[16−18] a limited number of studies have evaluated the association between HbA_{1C} and clinical outcomes among HF patients. The studies that examined HbA_{1C} and mortality described a positive association,[11,19] an inverse association,[9,10] a U-shaped association [12] or no association.[20] There are differences between previous studies and our investigation; the former included fewer patients (thus a less-diverse population than that of our study with respect to race, age, or gender),[9−12,19,20] examined longer-term mortality,[9−12,20] seldom examined outcomes other than mortality,[11] focused either on diabetic patients only[11] or on nondiabetic patients only,[19] or focused on HF with reduced EF only.[9,19] The difference in the results reported across studies may partly reflect the variations in HbA_{1C} assessment methods over time.[21]

Our study provides complementary information on the association of HbA_{1C} with HF outcomes. Previous studies on HbA_{1C} and HF outcomes mainly focused on the mortality outcome.[9,11,12,19] In addition to mortality, we examined LOS, discharge disposition, and readmission. Our findings of an association of HbA_{1C} with a prolonged hospital stay are consistent with previous reports relating diabetes to an LOS among HF pateints.[5] In our study, higher HbA_{1C} was associated with lower short-term mortality or readmission, especially among those with an HbA_{1C} <6.5%. This could be related to the fact that people with high HbA_{1C} and a diagnosis of diabetes may have benefited from a more aggressive HF treatment possibly because of the co-morbidities. HbA_{1C} data may have influenced clinical decision making not only concerning glucose control but also intensification of HF management. It is likely that patients with higher HbA_{1C} on admission are more likely to be discharged on evidence-based therapies for both HF and

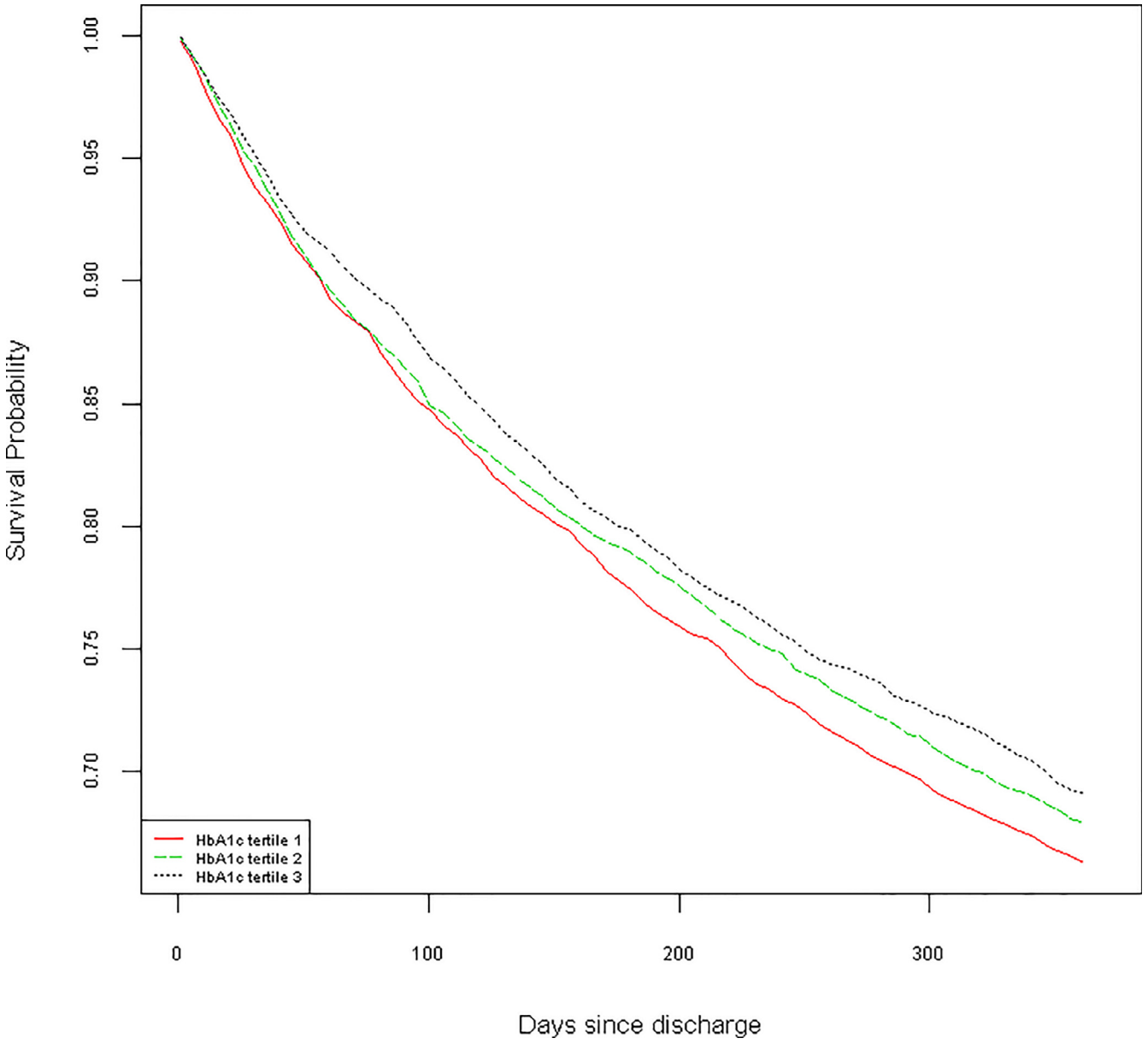

Figure 1. Kaplan-Meier curves for the 1-year mortality outcome by tertiles of HbA_{1C} (tertile 1: 0% to 6.2%; tertile 2: 6.3% to 7.2%; tertile 3: 7.3% to 19%).

diabetes. New diabetes therapies such as sodium-glucose cotransporter-2(SGLT-2) inhibitors[22] also confer cardiovascular and mortality benefits, possibly independent of glycemic control. Dipeptidyl peptidase-4 inhibitors may have an adverse influence on HF outcomes.[23–25] The short-term mortality findings in our study could have been influenced by the high use of evidence-based therapies among patients with high HbA_{1C} at discharge; with longer-term postdischarge follow-up, the influence of HbA_{1C} on prognosis may become evident. In some patients with diabetes and HF, HbA_{1C} levels may not be the most accurate index of glycemic control, especially if these patients have other co-morbidities such as anemia,[26] which would be highly prevalent among HF patients.

There are limitations to our study. First, participation to the GWTG-HF registry is voluntary. The participation to the registry may be a proxy of improved quality of HF care, thus the associations of outcomes with HbA_{1C} may be attenuated in this population. Second, for the 1-year mortality analysis, we only included HF patients aged ≥65 years, thus we were unable to assess as younger individuals. Third, we also did not account for changes in HbA_{1C} over time, which may influence the estimates of association. Furthermore, we did not investigate cause-specific mortality or readmission related to HbA_{1C}. Fourth, we did not account for glucose-lowering medications both at baseline and over time, especially as some of the novel therapies may improve HF outcomes.[22] Fifth, we did not have data on hypoglycemic episodes that may influence outcomes. We also did not have data on other markers of chronic hyperglycemia (e.g., fructosamine), which may be more representative of long-term glycemic status when HbA_{1C} is

influenced by factors such as hemoglobinopathies or anemia.[26] Indeed, anemia is not uncommon in HF patients, affecting up to a third of patients.[27] Finally, residual confounding may have affected our estimates.

In a large cohort of diabetic and nondiabetic patients with HF, glycated hemoglobin was associated with the LOS and home discharge, but not with short-term readmission or mortality. These findings point to the risks HF patients with diabetes face irrespective of HbA1c levels. This is especially important, as there is accumulating evidence on novel diabetes therapy that improve HF outcomes.

Disclosures

Dr. Fonarow reports significant consulting for Novartis, and modest consulting for Amgen, Bayer, Gambro, Medtronic, and Janssen; Dr Fonarow is a member of the GWTG Steering Committee; Dr. Fonarow holds the Eliot Corday Chair of Cardiovascular Medicine at UCLA and is also supported by the Ahmanson Foundation (Los Angeles, California).

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.amjcard.2018.11.023.

Supplementary Figure 1 Adjusted hazard ratio of 1-year mortality by percent change in HbA1C.

Supplementary Figure 2 Adjusted odds ratio of in-hospital mortality by percent change in HbA1C.

Supplementary Figure 3 Adjusted odds ratio of the length of hospital stay >4 days by percent change in HbA1C.

Supplementary Figure 4 Adjusted odds ratio of discharge home by percent change in HbA1C.

Supplementary Figure 5 Adjusted odds ratio of 30-day mortality by percent change in HbA1C.

Supplementary Figure 6 Adjusted odds ratio of 30-day readmission by percent change in HbA1C.

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