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Trends in the Inpatient Burden of Coronary Artery Disease in Granulomatosis With Polyangiitis: A Study of a Large National Dataset

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ABSTRACT. ***Objective.*** Cardiovascular (CV) diseases are serious comorbidities in patients with granulomatosis with polyangiitis (GPA). In a sample of patients hospitalized for GPA, we sought to examine trends in the burden of coronary artery disease (CAD) and its 2 serious manifestations, acute myocardial infarction (AMI) and heart failure (HF).

Methods. We used the National Inpatient Sample to conduct a retrospective cross-sectional analysis. Our sample consisted of hospitalizations for GPA between 2005 and 2014. We examined trends in the proportion of CAD, AMI, and HF in all hospitalizations with GPA compared to those without GPA. We used logistic regression adjusted for potential confounders and included interaction terms.

Results. Among a total of 103,453 GPA hospitalizations, 20,351 (19.7%) hospitalizations had a concurrent diagnosis of CAD. GPA with CAD was associated with overall lower burden of traditional CV risk factors compared to non-GPA with CAD, with the exception of chronic kidney disease (57% vs 21%). Over the 10-year study period, there were rising trends in the inpatient burden of CAD (16.6% in 2005 to 22.7% in 2014) and CAD with HF (4.3% in 2005 to 9.9% in 2014), but not AMI (1.2% in 2005 to 1.1% in 2014), in GPA hospitalizations compared to non-GPA controls.

Conclusion. In this national sample of GPA hospitalizations, we found that the burden of CAD and CAD with HF was on the rise over the 10-year period compared to non-GPA; however, it was not the case for AMI.

Key Indexing Terms: coronary artery disease, epidemiology, granulomatosis with polyangiitis

Granulomatosis with polyangiitis (GPA, formerly Wegener granulomatosis) is a systemic necrotizing vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA) and responsible for potential severe end organ damage and frequent hospitalizations[1]. The prevalence of GPA is estimated to be 26 to 146 per million and has been increasing over the past 2 decades[2]. The advances in the management of GPA, as well as its organ-specific and treatment-related complications, have led to a significant improvement in mortality[3,4]. However, there is an uptrend in the GPA hospitalization rate over the past 2 decades which may reflect a challenge in management of its comorbidities[5].

There is a growing body of evidence suggesting increased risk of coronary artery disease (CAD), a leading global cause of mortality and morbidity[6], among patients with autoimmune diseases including GPA[7]. Two serious manifestations of CAD are acute myocardial infarction (AMI) and heart failure (HF)[8,9]. Chronic inflammation has been proposed as a unique contributor to accelerated atherosclerosis and CAD in an autoimmune disease such as GPA and this may be independent of traditional cardiovascular (CV) risk factors[10]. There is increasing awareness

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as well as increased efforts in the prevention of CAD in the general population[11]; however, the trend of the burden of CAD in GPA over the past decade is unknown.

The primary objective of this analysis is to examine temporal trends in the burden of CAD, HF, and AMI in GPA hospitalizations compared to non-GPA controls in the United States. We hypothesize that the trends in the inpatient burden of CAD are changing over time in the setting of advances in the management of and improved survival in GPA.

MATERIALS AND METHODS

Data source. In this retrospective, cross-sectional study we used the National Inpatient Sample (NIS) database. The NIS is the largest publicly available, all-payer inpatient database sponsored by the Healthcare Cost and Utilization Project (HCUP) and Agency for Healthcare Research and Quality. Unweighted, it contains data from > 7 million hospital stays each year. Weighted, it estimates > 35 million hospitalizations nationally. Prior to 2012, the NIS included all discharge data from > 1000 hospitals each year, approximating a 20% stratified sample of US community hospitals. The NIS was redesigned in 2012 and is now a sample of discharge records from all HCUP-participating hospitals rather than all discharge records from a sample of hospitals (Supplementary Methods, available with the online version of this article). The NIS represents > 95% of the US population. Inpatient stay records in the NIS include clinical and resource use information available from discharge abstracts derived from state-mandated hospital discharge reports. No unique patient identifiers are contained in the NIS, as the unit of analysis is the individual hospitalization, rather than the patient.

Analytic sample. Our analytic sample consisted of hospitalizations between 2005 and 2014. We identified diagnoses and procedures using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes. GPA was identified with ICD-9-CM primary or secondary diagnosis codes 446.4, excluding those with a concurrent diagnosis of asthma (ICD-9-CM 493.xx) or eosinophilia (ICD-9-CM 288.3). This approach has been validated with a sensitivity of 93% in previous studies for identifying GPA in healthcare administrative databases[12]. Pregnancy-related hospitalizations were excluded from our study because they contain a large sample of nonillness-related hospitalizations[13].

Study outcomes. The primary outcome was temporal trends in the proportion of CAD and its 2 serious manifestations, AMI and HF, in all GPA hospitalizations compared to non-GPA controls. Only primary diagnosis was used for identifying AMI. We used validated ICD-9-CM codes in identifying CAD, HF and AMI in hospital settings[14,15]. Thus, the CAD and HF diagnosis in our study can represent that either the patient has a history of CAD or HF or is admitted because of CAD or HF. The AMI diagnosis represents hospital admissions primarily for acute care of AMI.

Study covariates. Study covariates included demographic characteristics such as age, sex, race/ethnicity, insurance type, and the median income for the patient's zip code. We included traditional CV risk factors (hypertension [HTN], diabetes mellitus [DM], hyperlipidemia, tobacco use, obesity, chronic kidney disease [CKD], cerebrovascular disease, and peripheral vascular disease). We also included non-CV related comorbidities in the Rheumatic Disease Comorbidity Index, which were not incorporated in the CV risk factors above (lung disease; fracture of spine, hip, or leg; depression; ulcer or stomach problem; and cancer)[16]. ICD-9-CM codes used to identify diagnosis or procedures are presented in Supplementary Table 1 (available with the online version of this article).

Statistical analysis. We used descriptive statistics to compare characteristics between GPA with CAD and non-GPA with CAD. Univariable comparison between groups was performed using the Student *t*-test for continuous variables and the chi-square test for categorical variables.

We assessed differences in temporal trends using logistic regression with interaction terms. We used logistic regression with interaction terms between GPA (yes/no) and year in all hospitalizations to detect whether GPA was an effect modifier on the temporal trends of our outcomes: CAD, AMI, and CAD with HF. These models were adjusted for demographic characteristics, CV risk factors, and non-CV comorbidities as described above.

Further, we conducted 2 sensitivity analyses. To account for the possibility that the trend of CAD with HF is primarily driven by a nonischemic component of heart disease in patients with GPA (patients with concomitant CAD and nonischemic cardiomyopathy), for the trend analysis of CAD with HF in GPA, we used nonischemic heart failure (NIHF) in GPA as a comparator. Also, due to the concern that a secondary diagnosis of non-ST segment elevation myocardial infarction (NSTEMI) sometimes can represent "demand ischemia" rather than a primary coronary event, we performed a sensitivity analysis after excluding a secondary diagnosis of NSTEMI (ICD-9-CM code 410.7x) in our CAD population for the trend analysis of CAD and CAD with HF among GPA and non-GPA hospitalizations.

All analyses were performed using survey-specific analysis methods and accounted for the complex survey design, stratification, and clustering of the data per NIS database. The variable "year" was included as a stratification variable in the analysis after combining the 10-year database per HCUP recommendations. Stata software 14.0 (StataCorp) was used for statistical analyses.

Ethics. This observational study was exempt from the Hospital for Special Surgery Institutional Review Board (IRB 2018-2272) according to the institution's policy because no patient identifying information is contained in the NIS.

RESULTS

Baseline sample demographic and clinical characteristics. A total of 103,453 hospitalizations with a diagnosis of GPA were identified over the 10-year period. Approximately 19.7% (20,351) of GPA hospitalizations had a concurrent diagnosis of CAD. We identified 65,890,815 non-GPA CAD hospitalizations. Compared to non-GPA with CAD, patients with GPA and CAD were of similar age (70 vs 71), but more likely to be male sex (65% vs 56%, $P < 0.001$), White (75% vs 66%, $P < 0.001$), and insured by Medicare (77% vs 72%, $P < 0.001$). When we assessed CV risk factors, compared to non-GPA with CAD, GPA with CAD was associated with lower CV risk factors except CKD (57% vs 21%, $P < 0.001$). These include HTN (24% vs 54%, $P < 0.001$), DM (31% vs 40%, $P < 0.001$), hyperlipidemia (42% vs 50%, $P < 0.001$), smoking (6% vs 13%, $P < 0.001$), obesity (3.3% vs 4.0%, $P = 0.031$), cerebrovascular disease (11% vs 16%, $P < 0.001$), and peripheral vascular disease (1.7% vs 2.6%, $P < 0.001$). Non-CV related comorbidities were similar in the 2 groups except for a slightly higher cancer rate in non-GPA with CAD (7.1% vs 5.3%, $P < 0.001$) compared to GPA with CAD (Table 1).

Trends in prevalence of CAD over time. Over the 10-year study period, the proportion of CAD in GPA hospitalizations increased significantly (16.6% in 2005 to 22.7% in 2014) but changed minimally in non-GPA hospitalizations (19.8% in 2005 to 20.3% in 2014), with a statistically significant difference in trends (unadjusted model $P < 0.001$, adjusted model, $P = 0.010$; Table 2, Figure 1). There was no statistical significance in the difference in trends for the proportion of AMI between GPA hospitalizations (1.2% in 2005 to 1.1% in 2014)

Table 1. Characteristics of patients with GPA and CAD compared to non-GPA with CAD.

	GPA with CAD, n = 20,351	Non-GPA with CAD, n = 65,890,815	*P*
Age, yrs, mean ± SD	70 ± 12	71 ± 13	< 0.001
Male sex	65	56	< 0.001
Race/ethnicity			
White	75	66	< 0.001
Black	4	9	< 0.001
Hispanic	5	6	0.029
Asian or other	16	19	< 0.001
Primary payer			
Medicare	77	72	< 0.001
Medicaid	3	6	< 0.001
Private insurance	17	17	0.94
Other	3	5	< 0.001
Median household income for patient's ZIP code			
First (lowest) quartile	22	29	< 0.001
Second quartile	28	26	0.085
Third quartile	26	23	< 0.001
Fourth (highest) quartile	24	22	0.015
CV risk factors			
Hypertension	24	54	< 0.001
Diabetes mellitus	31	40	< 0.001
Hyperlipidemia	42	50	< 0.001
Smoking	6	13	< 0.001
Obesity	3.3	4.0	0.031
Chronic kidney disease	57	21	< 0.001
Cerebrovascular disease	10.8	15.8	< 0.001
Peripheral vascular disease	1.7	2.6	< 0.001
Non-CV–related comorbidities			
Lung disease	30	30	0.622
Fracture of spine, hip, or leg	2.9	2.6	0.322
Depression	11	11	0.675
Ulcer or stomach problem	6.3	5.3	0.461
Cancer	5.3	7.1	< 0.001

Values are in percent unless otherwise specified. CAD: coronary artery disease; CV: cardiovascular; GPA: granulomatosis with polyangiitis.

Table 2. Temporal trends of CAD in patients with and without GPA.

	GPA/Non-GPA	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Trend Difference *P*
CAD	GPA	16.6	17.1	17.1	19.1	20.4	19.9	20.9	20.6	20.7	22.7	< 0.001 (unadjusted)
	Non-GPA	19.8	20.3	19.7	20.3	20.6	19.8	20.8	20.6	20.4	20.3	0.010 (adjusted)
AMI	GPA	1.2	0.9	1.3	1.3	1.3	1.5	1.0	0.7	1.1	1.1	0.494 (unadjusted)
	Non-GPA	2.0	1.9	1.8	1.8	1.8	1.7	1.8	1.9	1.9	1.9	0.112 (adjusted)
CAD with HF	GPA	4.3	5.6	4.7	5.1	7.2	6.9	8.5	8.6	8.3	9.9	< 0.001 (unadjusted)
	Non-GPA	6.1	6.2	6.1	6.1	6.6	6.5	7.1	7.1	7.4	7.6	0.013 (adjusted)

Values are in percent unless otherwise specified. Covariates in adjusted models include demographic characteristics and comorbidities. Demographic characteristics include age, sex, race/ethnicity, insurance type, and the median income for the patients' zip code. The comorbidities include CV risk factors (hypertension, diabetes mellitus, hyperlipidemia, tobacco use, obesity, chronic kidney disease, cerebrovascular disease, and peripheral vascular disease) and non-CV–related comorbidities (lung disease, fracture of spine, hip or leg, depression, ulcer or stomach problem, and cancer). AMI: acute myocardial infarction; CAD: coronary artery disease; CV: cardiovascular; GPA: granulomatosis with polyangiitis; HF: heart failure.

and non-GPA hospitalizations (2.0% in 2005 to 1.9% in 2014; difference in trends unadjusted model $P = 0.494$, adjusted model $P = 0.112$; Table 2, Figure 2A). There was a statistically significant difference in trends in the proportion of CAD with HF in GPA hospitalizations (from 4.3% in 2005 to 9.9% in 2014) compared to non-GPA hospitalizations (from 6.1% in 2005 to 7.6% in 2014; difference in trends unadjusted model $P < 0.001$, adjusted model $P = 0.013$; Table 2, Figure 2B).

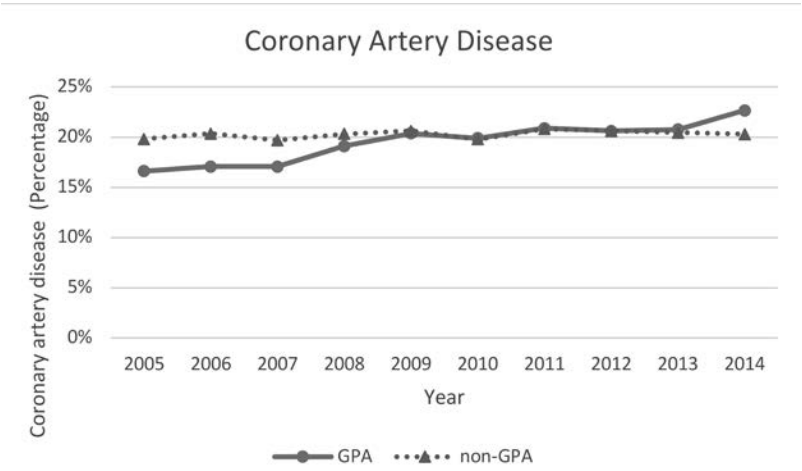

Figure 1. Temporal trends of coronary artery disease in patients with and without GPA. GPA: granulomatosis with polyangiitis.

Results from sensitivity analysis. Compared to the proportion of NIHF in GPA, there was a statistically significant difference in trends in the proportion of CAD with HF in GPA (difference in trends unadjusted model $P < 0.001$, fully adjusted model $P = 0.011$), suggesting that the rising trend of CAD with HF is not primarily driven by a nonischemic component of heart disease in GPA hospitalizations (Table 3, Figure 3)

After excluding NSTEMI cases (these are cases with potential

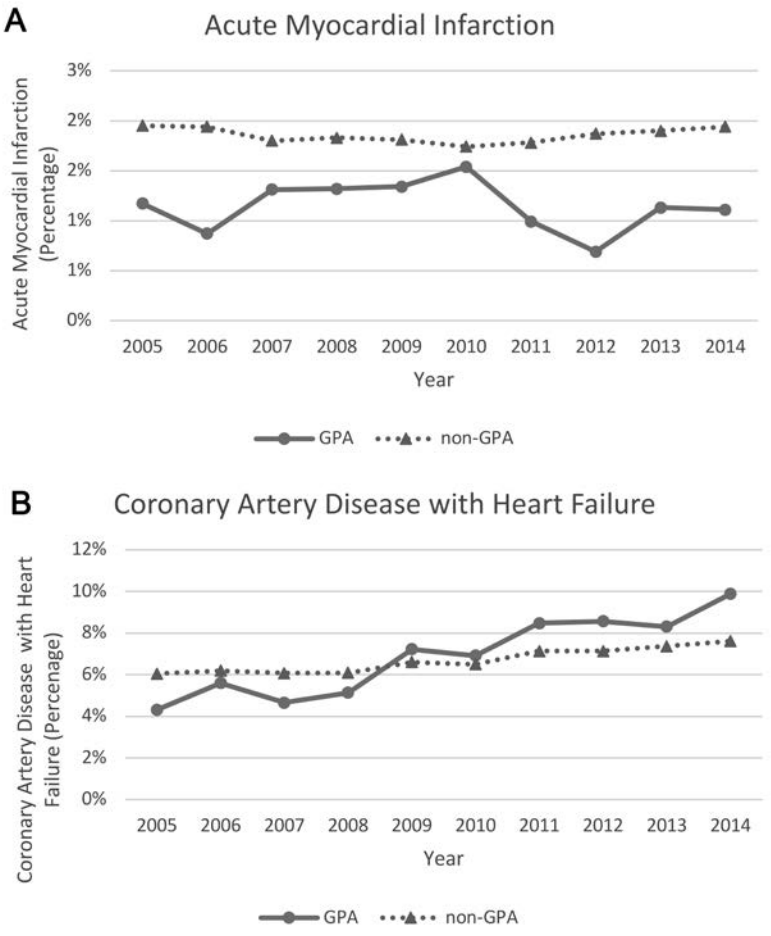

Figure 2. (A) Temporal trends of acute myocardial infarction in patients with and without GPA. (B) Temporal trends of coronary artery disease with heart failure in patients with and without GPA. GPA: granulomatosis with polyangiitis.

Table 3. Temporal trends of HF in GPA patients with and without CAD.

GPA Population	CAD/ Non-CAD	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Trend Difference *P*
HF	CAD with HF	4.3	5.6	4.7	5.1	7.2	6.9	8.5	8.6	8.3	9.9	< 0.001 (unadjusted)
	NIHF	11.5	11.4	10.2	9.5	9.9	9.9	10.4	12.4	11.5	11.5	0.011 (adjusted)

Values are in percent unless otherwise specified. Covariates in adjusted models include demographic characteristics and comorbidities. Demographic characteristics include age, sex, race/ethnicity, insurance type, and the median income for the patients' zip code. The comorbidities include CV risk factors (hypertension, diabetes mellitus, hyperlipidemia, tobacco use, obesity, chronic kidney disease, cerebrovascular disease, and peripheral vascular disease) and noncardiovascular-related comorbidities (lung disease, fracture of spine, hip or leg, depression, ulcer or stomach problem, and cancer). CAD: coronary artery disease; CV: cardiovascular; GPA: granulomatosis with polyangiitis; HF: heart failure; NIHF: non-ischemic heart failure.

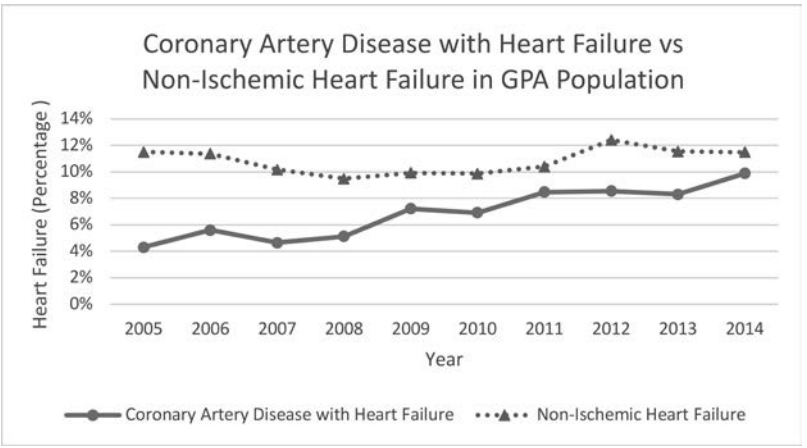

Figure 3. Temporal trends of heart failure in GPA patients with and without coronary artery disease. GPA: granulomatosis with polyangiitis.

demand ischemia but no primary coronary event) for trends of CAD and CAD with HF in GPA versus non-GPA, we found results similar to our primary analysis. The inpatient proportion of CAD was rising in GPA (15.8% in 2005 to 21.9% in 2014, Supplementary Table 2 and Supplementary Figure 1, available with the online version of this article), with significant difference in trends compared to the non-GPA population (unadjusted model $P < 0.001$, adjusted model $P = 0.003$, Supplementary Table 2). There was also an increase in the temporal trends of inpatient proportion of CAD with HF in GPA (from 3.9% in 2005 to 9.6% in 2014, Supplementary Table 3 and Supplementary Figure 2) compared to both the proportion of CAD with HF in non-GPA (difference in trends unadjusted model $P < 0.001$, adjusted model, $P < 0.001$) and the proportion of NIHF in GPA (difference in trends unadjusted model $P < 0.001$, adjusted model, $P = 0.001$, Supplementary Table 4 and Supplementary Figure 3).

DISCUSSION

In this large national sample of hospitalizations with a diagnosis of GPA between 2005 and 2014, we found that a concurrent diagnosis of CAD is prevalent and increasing over time. In all hospitalizations with a diagnosis of CAD, those with GPA are more likely to be White, male, and tend to have lower traditional CV risk factors than non-GPA controls except for CKD. The inpatient burden of CAD with HF in GPA hospitalizations is increasing but AMI is not.

There is an extensive body of evidence suggesting increased risk of CAD in GPA compared to either non-GPA controls[17,18] or the general population[19,20]. Compared to non-GPA controls, the risk of CV disease in GPA was even higher after adjusting for traditional CV risk factors[18]. Whereas most prior studies compared CV risk factors in GPA and non-GPA populations with CAD as an outcome but not necessarily as an inclusion criterion[18,21], we compared these risk factors in GPA and non-GPA in an established CAD population. Despite a high prevalence of CV risk factors having been previously described in the GPA population compared to non-GPA controls[21], our study found that in populations with CAD, GPA hospitalizations had less burden of traditional CV risk factors, except for CKD, compared to non-GPA hospitalizations. This suggests that in a large portion of patients with GPA, the development of CAD could be primarily driven by factors uniquely associated with GPA. These factors may include systemic and/or vascular inflammation[22], endothelial dysfunction[23], renal impairment[24], and hypercoagulable state[25]. Clonal hematopoiesis of indeterminate potential (CHIP) is the presence of a hematologic malignancy-associated somatic mutation in the blood and occurs in at least 10% of the general elderly population[26]. CHIP is associated with increased risk of atherosclerotic CV disease[27], possibly

mediated by the NLRP3 inflammasome[28]. A recent study found that 30.4% of patients with ANCA-associated vasculitis (AAV) have CHIP compared to 13.5% in non-AAV controls[29], which is potentially a novel mechanism for CAD in GPA.

The inpatient burden of CAD in GPA increased 37% from 2005 to 2014 and the difference in trends compared to non-GPA controls remained statistically significant even after adjusting for demographic information and comorbidities. The cause of this trend is unclear and intriguing, given that in the past 2 decades, efforts in the prevention of CAD have led to a decrease in the overall prevalence of CAD in the US general population[11], and at the same time the risk of endstage renal disease, a well-known risk factor for CAD, has also decreased in the US GPA population[30]. Longer survival of those with GPA, and inadequate recognition and management of its comorbidities, may have increased CAD prevalence and hospitalizations. A previous study in Europe showed that there was a low percentage of patients with GPA achieving optimal control of their HTN and hyperlipidemia[21]. In addition, Wallace, *et al* recently demonstrated that lipid metabolism differs among different inflammatory states of AAV[31], making it potentially more challenging for clinicians to accurately interpret the lipid measurement results. For example, CV risk may be underestimated in the setting of active inflammation, which can cause very low lipid levels but increased CV risk[32]. In addition, it has been shown that patients with GPA remained in a hypercoagulable state even if their disease was in remission[25], which may explain the increased burden of comorbidity management, including increased prevalence of CAD. Last but not least, although certain antiinflammatory therapies have been shown to reduce CV risk in high-risk populations without autoimmune diseases[33,34], the CV effects of the immunosuppressive regimens used in GPA remain largely unknown.

AMI and HF are 2 serious manifestations of CAD. There was a greater than 2-fold increase in the trend of prevalence of CAD with HF in the GPA population, with a statistically significant difference in trends compared to both CAD with HF in the non-GPA population and NIHF in the GPA population. Interestingly, the temporal trends of AMI remained unchanged over the 10-year study period. The cause of the discrepancy between the trends of CAD with HF and AMI is unclear. It was reported that patients with rheumatoid arthritis are less likely to report symptoms of angina and more likely to experience unrecognized myocardial infarction (MI)[35]. It could be a similar phenomenon in the GPA population that CAD tends to present differently from that in the general population, with a higher likelihood to manifest as HF or silent MI instead of clinically apparent AMI.

There are several limitations of our study. First, the database we used covers only hospitalized patients. The unit of observation is hospitalization and we were not able to identify individual patients with multiple hospitalizations or total number of admissions per patient. Thus, it is unknown whether the uprising trend of CAD was caused by increasing prevalence of CAD in the GPA population, or if patients with GPA and CAD were hospitalized more frequently as their survival has improved. Second, there is a risk of misclassification bias with ICD-9-CM codes in identifying GPA, CAD, and other medical conditions. The approach we used for identifying GPA is highly sensitive but with only a modest positive predictive value of 50–70%[12]. Third, it was difficult to exclude a concurrent component of nonischemic cardiomyopathy in patients with CAD and HF. Thus, the term "CAD with HF" was used in our study rather than the term "ischemic heart failure". However, a large cohort study showed that clinically significant cardiomyopathy directly caused by active GPA was rare overall[36]. Last, individual characteristics such as disease severity and activity, laboratory findings, and treatment are not available in the NIS database. The disease course of GPA is also not known in this study, such as new diagnosis or a flare, during the hospitalization with CAD.

In summary, in this large, national sample of hospitalization with a diagnosis of GPA between 2005 and 2014, we found that a concurrent diagnosis of CAD is prevalent and increasing over time. GPA hospitalizations with CAD have lower traditional CV risk factors than non-GPA controls except for CKD. There was an increasing trend in the burden of CAD and CAD with HF, but not AMI in GPA hospitalizations. Further research is warranted in identifying GPA-unique CV risk factors accounting for the discrepancy in the uprising trends of CAD observed in our study and to mitigate the CAD burden.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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