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Increased risk of thrombotic events in cold agglutinin disease: A 10-year retrospective analysis

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Abstract

Background: Cold agglutinin disease (CAD) is a rare autoimmune hemolytic anemia mediated by IgM autoantibodies that trigger hemolysis via classical complement pathway. Increased incidence of thrombotic events (TEs) has been reported in patients with other forms of hemolysis. The incidence of TEs in patients with CAD is unknown.

Objective: Evaluate TE risk in patients with CAD.

Patients/Methods: This is a matched cohort comparison study evaluating the risk of TEs in patients with CAD and without CAD over a 10-year period. A total of 608 patients with CAD were identified in the Optum Claims–Clinical data set by reviewing clinical notes for CAD terms and matched with up to 10 patients without CAD (N = 5873). TEs were defined as the first medical claim for a TE using International Classification of Diseases, Ninth and Tenth Revision codes. Cox regression models were used to estimate time to first TE. Sensitivity analyses were conducted to estimate TE risk among patients with primary CAD.

Results: At least 1 TE occurred in 29.6% of patients with CAD and 17.6% of patients without CAD. The proportion of patients experiencing venous, arterial, and cerebral TEs were each higher among CAD patients. The overall risk of having TEs was higher in patients with CAD (adjusted hazard ratio [aHR], 1.94; 95% confidence interval [CI], 1.64-2.30). Patients with presumed primary CAD also demonstrated an increased risk of TEs (aHR, 1.80; 95% CI, 1.46-2.22). Patients with CAD with the fewest comorbidities had 2.44-fold higher risk of having a TE (95% CI, 1.70-3.52).

Conclusions: Patients with CAD have an increased risk of TEs when compared with a matched non-CAD population.

KEYWORDS

autoimmune anemia, classical complement pathway, hemolytic anemia, thrombosis, retrospective analysis

Essentials

- Thrombotic event (TE) risk in patients with cold agglutinin disease (CAD) is not well characterized.
- TE risk was assessed in 608 patients with CAD and 5873 matched patients without CAD from the Optum data set.
- There is an increased risk of venous and arterial TEs in patients with CAD.
- The increased risk of TEs in patients with CAD was noted from the time of identification through the entire follow-up period.

1 | INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is a group of disorders characterized by autoantibody-mediated hemolysis.[1] Cold agglutinin disease (CAD) is a rare form of complement-mediated AIHA in which the pathophysiology is driven by IgM autoantibodies binding to red blood cells (RBCs) at or just below core body temperature, depending on the thermal amplitude of the IgM.[2,3] These IgM antibody/antigen complexes interact with the C1 complex to activate the classical complement pathway, leading to deposition of C3b, iC3b, and C3d opsonins on the RBC membrane. The majority of the opsonin-coated RBCs are removed from the circulation by the mononuclear phagocyte system, resulting in extravascular hemolysis. Classical pathway activation may proceed to the terminal portion of the complement pathway on some RBC membranes, resulting in the formation of the membrane attack complex (C5b-9) and intravascular hemolysis. Patients with CAD may have components of both intra- and extravascular hemolysis as well as cold-induced acrocyanosis.

Patients with many types of hemolysis have been noted to have an increased incidence of thrombotic events (TEs) in both the venous and arterial systems, which can not only impact quality of life but may also lead to premature mortality.[4,5] The proposed mechanisms of hemolysis-associated thrombosis are complex and may vary depending on the specific underlying disease process. In at least 1 other form of complement-mediated hemolysis, paroxysmal nocturnal hemoglobinuria (PNH), a mechanism of thrombus generation independent of hemolysis but directly complement mediated, has been proposed.[6] In PNH, up to 44% of patients experience TEs and as many as 58% of deaths are related to TEs.[5,7] In patients with PNH, markers of hemolysis, including elevated levels of lactate dehydrogenase (LDH), have been associated with an increased risk of thrombosis.[8]

TEs can substantially increase disease burden and cost of treatment. Ten percent to 30% of patients die within 1 month of diagnosis of a venous thrombotic event (VTE), and among those who survive, 50% have long-term complications.[9] A recent study evaluating the economic impact of TEs in the United States reported an incident VTE cost between $12 000 and $15 000 in 2014, which increased to $18 000-$23 000 when including subsequent complications.[10]

Few studies have evaluated the occurrence of TEs in patients with CAD. The largest published study reporting TEs in patients with CAD is a longitudinal analysis of 29 patients seen at Stanford Health Care, in which 17% of patients had at least 1 TE.[11] In another small cohort of 13 patients with CAD observed during enrollment in a phase 2 trial, 4 (31%) patients had 7 TEs prior to treatment.[12]

The goal of this analysis was to better understand the estimated risk of TEs in patients with CAD. This analysis was performed using the Optum database, which combines electronic medical record data with adjudicated claims data, enabling evaluation of the largest cohort of patients with CAD to date.

2 | METHODS

This was a matched cohort comparison study. Patients were selected for analysis from Optum's deidentified Integrated Claims–Clinical data set. This data set links electronic medical record data with adjudicated claims data to provide deidentified information on medications, lab results, vital signs, body measurements, diagnoses, procedures, and clinical notes distilled with Natural Language Processing for approximately 55 million patients seen throughout the United States. Institutional review board waiver or approval was not required because no identifiable health information was accessed as defined by the Health Insurance Portability and Accountability Act of 1996.[13]

All patients enrolled in Optum health plans between 2006 and 2016 were eligible for inclusion. To identify patients with CAD, the clinical notes of each patient were searched for terms associated with CAD such as *cold agglutinin disease*, *cold autoimmune hemolytic anemia*, and *cold agglutinin hemoglobinuria*. If a patient had any of the CAD terms in their clinical notes on at least 3 separate dates, they were considered a true CAD case (n = 517). This method allowed us to limit the inclusion of "rule-out" diagnoses and thus ensured that physician-diagnosed patients with CAD were identified. Further, validity of this search method was tested by taking a random sample of 100 of the identified records and having 2 independent hematologists perform a manual review of the "snippets" of patient notes to evaluate for CAD status. Agreement was 95% and mention of CAD terms on 3 separate dates was considered an accurate definition. If CAD terms were found on 1 or 2 dates only, patients were included as true CAD cases only after agreement by 2 hematologists independently reviewing clinical notes for CAD status (n = 209 patients with 1 date and n = 88 patients with 2 dates). The reviewing hematologist used clinical judgment of the data available to determine if the CAD diagnosis was a valid one and not a rule-out or the result of a positive lab test only. To select a matched comparison cohort of patients without CAD, a 5% sample of Optum records was evaluated. Comparison matches were patients who did not have a CAD diagnosis but had the same sex, age (±3 years), race, region of residence, active time in the Optum health plan, and season and year of entry date into the Optum health plan. Each CAD case was matched with

as many as 10 patients without CAD. Comorbidities used to build the Charlson Comorbidity Index (CCI)[14] (Table S1) were accumulated over approximately the same period of time for the CAD and the matched patients without CAD, from date of entry into the Optum data set to the date of first mention of CAD for the diseased patient (index date). Patients with <1 year of follow-up prior to the index date were excluded due to insufficient history to assess comorbidities. Patients with <1 month of follow-up after the index date were also excluded. Patients <25 years of age at the index date were excluded from the analysis due to the high likelihood that CAD was secondary.

TEs were identified from patient data using codes from the International Classification of Diseases, Ninth and Tenth Revisions (ICD-9 and ICD-10, respectively) (Table 1). TEs were defined as the patient's first inpatient or outpatient medical claim for a TE, regardless of type (venous, arterial, and cerebral). In addition to the CCI, patient medical history was evaluated for prior history of TEs or risk factors for TEs (history of HIV/AIDS, history of malignant cancer except for nonmelanoma skin cancer, history of organ failure or organ transplantation, history of chemotherapy or radiation use, and history of anticoagulant or antiplatelet medication use) at any point between entry into the Optum data set and index date.[15] The diagnosis and procedure codes used to identify these variables are listed in Table S2.

2.1 | Statistical analyses

Descriptive analyses, including Ns, percentages, means, medians, and ranges of patients with CAD and without CAD were performed for demographic characteristics. The frequency of TEs and TE types was described.

Cox regression models adjusting for age, sex, race, region, active time in the Optum system, history of a prior TE, history of HIV/AIDS, history of malignant cancer except for nonmelanoma skin cancer, history of organ failure, history of organ transplantation (Yes/No), history of chemotherapy use, history of radiation use, history of anticoagulant medication use, history of antiplatelet medication use, cluster (matched patients with CAD and patients without CAD), and CCI score were used to estimate the hazard ratios (HRs) for all TEs, as well as for venous, cerebral, and arterial TEs, in patients with CAD. These analyses were further stratified by CCI score (CCI = 0, CCI = 1-2, CCI ≥ 3) to assess the risk for patients with no or few comorbidities. An absolute risk difference for TEs among patients with CAD and without CAD, adjusted for all covariates in the Cox model, was calculated within 1 and 5 years of the index date. Ninety-five percent confidence intervals (CIs) for the absolute risk difference were calculated using the bootstrap method.[16] *P* values <.05 were considered statistically significant. Cumulative incidence curves were constructed to illustrate the probability of developing a TE over time.

All data management and statistical analyses were carried out using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA).

TABLE 1 ICD codes used to identify TEs

Disease	ICD-9[a]	ICD-10[a]
Any venous event		
Portal vein obstruction	452	I81
Deep vein thrombosis	451	I80.1-I80.3
Pulmonary embolism	415.1x	I26
Mesenteric vein thrombosis	557.1	K55.0
Other venous events	453	I82
Any cerebral event		
Cerebral infarction, occlusion, and stenosis of cerebral and precerebral arteries	433, 434	I63, I65, I66
Vascular syndromes of brain in cerebrovascular diseases, transient cerebral ischemic attacks, and related syndromes	435	G46, G45
Any arterial event		
Arterial embolism and thrombosis	444	I74
Myocardial infarction	410	I21, I22

Abbreviations: ICD, International Classification of Diseases; ICD-10, International Classification of Disease, Tenth Revision; ICD-9, International Classification of Diseases, Ninth Revision; TE, thrombotic event.

[a]ICD codes used for groups are inclusive of all codes listed per group.

2.2 | Sensitivity analyses

As patients with both primary and secondary CAD were included in the primary analysis, sensitivity analyses were performed to evaluate the estimated risk of TEs among patients presumed to have primary CAD (not due to secondary causes) by excluding patients with CAD with a coexisting diagnosis of any type of lymphoma (except Hodgkin disease), myelomas, chronic lymphocytic leukemia, Waldenström macroglobulinemia, and certain infections known to be associated with CAD (*Mycoplasma pneumoniae*, Epstein-Barr virus, cytomegalovirus). The patients without CAD who were matched to any excluded patients with CAD were also removed. The ICD codes used to identify these diagnoses are presented in Table S3.

In another sensitivity analysis, we compared the relationship of CAD and TEs using 2 different algorithms proposed by Sanfilippo et al.[17] Since these algorithms were developed for VTEs, we limited this sensitivity analysis to assess the relationship between CAD and VTE only. The first algorithm, with a positive predictive value (PPV) of 72%, was based only on ICD codes for VTEs and was similar to both the one used in our analysis and the one used by Li et al.[15] The second algorithm improved the PPV to 91% through the addition of anticoagulant treatment or inferior vena cava (IVC) filter placement within 1 month of a VTE or death attributable to a VTE as the only outcomes. The codes for anticoagulant use and IVC filter placement are listed in Table S2. There is evidence that the identification of TEs through inpatient codes may be more sensitive than TE identification using outpatient codes.[18] As our identification of TEs included both inpatient and outpatient claims, an additional sensitivity analysis was conducted to evaluate the risk

of TEs among patients with CAD and patients without CAD for TEs identified using inpatient codes only. Further, we removed patients with any prior inpatient TE codes within a 6-month period before the admission date to reduce the potential of counting a single TE more than once.

3 | RESULTS

Between 2006 and 2016, 608 patients with CAD were identified in the Optum Claims–Clinical data set and were matched to 5873 patients without CAD. The average number of patients without CAD per patient with CAD was 9.7, with only 9.2% of patients with CAD having fewer than 10 matches. The descriptive characteristics of the 2 cohorts are presented in Table 2. Because of the matching methodology, the majority of patients with and without CAD were 65 years of age or older (~70%), female (63%), white (85%), and from the Midwest (~46%) or South (~26%). The mean active time in the Optum system for patients with CAD overall was 89.4 months (standard deviation [SD], 29.3). The patients without CAD had slightly longer active time (97.4 months; SD, 26.4). The average follow-up for patients with CAD overall was 25.0 months (SD, 23.3; median, 18; range, 0-89). The patients without CAD had longer average follow-up (35.3 months; SD, 25.7; median, 30; range, 0-113) due to higher mortality among the patients with CAD.

There were 180 patients with CAD with TEs recorded (29.6% of 608 patients with CAD) compared with 1033 non-CAD patients (17.6% of 5873 total patients without CAD) (Table 3). Subgroup analysis revealed 14.6% of patients with CAD and 5.2% of patients without CAD had venous TEs, 7.6% of patients with CAD and 3.7% of patients without CAD had arterial TEs, and 14.0% of patients with CAD and 11.6% of patients without CAD had cerebral TEs (Table 3). The incidence rate for TEs in patients with CAD was 14.2 per 100 person-years (95% CI, 12.23-16.47) compared with 6.0 per 100 person-years (95% CI, 5.62-6.35) in patients without CAD. The overall risk of having a TE was 1.9 times higher in patients with CAD than in the patients without CAD during the study period (Table 4). The adjusted absolute risk difference calculation revealed a significant excess risk of TEs for patients with CAD versus patients without CAD at 1 year (11.9 per 100 patients; 95% CI, 11.7-12.1 per 100 patients) and 5 years (11.9 per 100 patients; 95% CI, 11.6-12.2 per 100 patients) after the index date (data not shown in tables). Cumulative incidence curve demonstrated significant differences in the development of TEs in the patients with CAD as compared with patients without CAD (Figure 1).

A sensitivity analysis was done to estimate the risk of TEs among patients likely to have primary CAD. For this purpose, 183 patients with CAD and matched patients without CAD (n = 1747) were excluded due to the presence of diagnostic codes known to be associated with secondary CAD (Table S3). Among the remaining patients with CAD, 26.8% (n = 114/425) had TEs compared with 16.5% (n = 680/4126) of those in the non-CAD group. The risk of having a TE in this cohort of patients with presumed primary CAD was also significantly increased (Table 4).

TABLE 2 Characteristics of patients with CAD and patients without CAD identified in the Optum database (2006-2016)

Medical history[a]	Patients with CAD, n (%) (N = 608)	Patients without CAD, n (%) (N = 5873)
Age, y		
25-64	180 (29.6)	1896 (32.3)
≥65	428 (70.4)	3977 (67.7)
Mean (SD)	69.0 (13.5)	68.3 (13.3)
Median (range)	72.0 (26.0-89.0)	71.0 (25.0-89.0)
Sex		
Male	223 (36.7)	2138 (36.4)
Female	385 (63.3)	3735 (63.6)
Race		
White	517 (85.0)	5027 (85.6)
Black	31 (5.1)	358 (6.1)
Asian	14 (2.3)	81 (1.4)
Other/Unknown	46 (7.6)	407 (6.9)
Region		
Northeast	80 (13.2)	733 (12.5)
South	156 (25.7)	1546 (26.3)
Midwest	280 (46.1)	2754 (46.9)
West	80 (13.2)	748 (12.7)
Other/Unknown	12 (2.0)	92 (1.6)
Death	119 (19.6)	273 (4.7)
Active period, months		
Mean (SD)	89.4 (29.3)	97.4 (26.4)
Median (range)	96.0 (15.0-125.0)	106.0 (15.0-125.0)
Follow-up, months		
Mean (SD)	25.0 (23.3)	35.3 (25.7)
Median (range)	18.0 (0.0-89.0)	30.0 (0.0-113.0)
Season		
Winter	238 (39.1)	2286 (38.9)
Spring	146 (24.0)	1438 (24.5)
Summer	128 (21.1)	1219 (20.8)
Fall	96 (15.8)	930 (15.8)
Prior thrombotic event	110 (18.1)	661 (11.3)
HIV/AIDS	2 (0.3)	10 (0.2)
Malignant cancer except for nonmelanoma skin cancer	164 (27.0)	579 (9.9)
Organ failure	105 (17.3)	478 (8.1)
Organ transplantation	9 (1.5)	41 (0.7)
Chemotherapy use	80 (13.2)	187 (3.2)
Radiation use	2 (0.3)	23 (0.4)
Anticoagulant medication use	170 (28.0)	924 (15.7)
Antiplatelet medication use	34 (5.6)	601 (5.1)

Abbreviations: CAD, cold agglutinin disease; SD, standard deviation.
[a]Condition present before the index date.

The risk of TEs was stratified by CCI score category to evaluate the risk among patients with and without other comorbidities. While the risk of TEs was statistically significantly increased among patients with CAD versus patients without CAD in all categories of CCI score, the risk was strongest among patients with CAD with no comorbidities (CCI, 0) (Table 5).

Further sensitivity analyses after the algorithms proposed by Sanfilippo et al[17] based only on ICD codes for VTEs resulted in an adjusted HR of 2.95 (95% CI, 2.28-3.82) for risk of VTEs among patients with CAD in our analysis. The second algorithm, which used the same population as the first algorithm but with the outcome reclassified based on anticoagulant use, IVC filter, or death, resulted in an adjusted HR of 3.10 (95% CI, 2.24-4.30) for patients with CAD compared with patients without CAD.

An additional sensitivity analysis was conducted to compare the risk of TEs identified using only inpatient codes and excluding patients with inpatient TE codes within a 6-month window before admission. Using this definition, 10% of patients with CAD and 5.4% of patients without CAD were found to have a TE, and the risk of experiencing a TE was 1.87 times higher among patients with CAD (Table S4).

4 | DISCUSSION

To our knowledge, this is the largest cohort of patients with CAD evaluated to date and demonstrates an increased incidence of venous and arterial TEs in these patients with CAD when compared with matched patients without CAD. The risk of TEs in patients with CAD was increased over patients without CAD from the time of identification through the entire follow-up period.

There are multiple pathophysiologic mechanisms that could potentially trigger a prothrombotic state in CAD. Current theories on the interaction of hemolysis and the coagulation cascade include the release of free heme, which leads to nitric oxide scavenging.[19] Decreased nitric oxide results in vasoconstriction, platelet aggregation, and increased expression of endothelial adhesion molecules.[19] In addition, free heme results in the generation of reactive oxygen species that promote inflammation via leukocyte recruitment and enhanced cytokine excretion by monocytes and macrophages.[4,20] These cytokines may cause increased tumor necrosis factor secretion, platelet activation, endothelial injury, and exposure of the subendothelial matrix.[4] Other theories invoke enhanced tissue factor expression on endothelial cells and the presence of complement-induced tissue factor–expressing microparticles.[6]

In CAD, hemolysis is mediated by ongoing complement activation. Although there are no studies longitudinally evaluating complement activity independent of hemolysis in patients with CAD, there are a number of studies evaluating the role of complement in PNH, another complement-mediated hemolytic condition, independent of the degree of anemia.[6,21] One study demonstrated that patients with PNH and evidence of hemolysis (LDH > 1.5 × the upper limit of normal), regardless of degree of anemia, were at a significantly higher risk of developing a TE.[21] Although the exact mechanisms

TABLE 3 Number and percentage of patients with CAD and patients without CAD identified in the Optum database (2006-2016)

Disease	Patients with CAD, n (%) (N = 608)	Patients without CAD, n (%) (N = 5873)	HR[a] (95% CI)	Adjusted HR[b] (95% CI)
Any venous event	89 (14.6)	308 (5.2)	3.50 (2.76-4.43)	2.95 (2.28-3.82)
Portal vein obstruction	5 (0.8)	2 (0.03)		
Deep vein thrombosis	19 (3.1)	77 (1.3)		
Pulmonary embolism	30 (4.9)	88 (1.5)		
Mesenteric vein thrombosis	7 (1.2)	12 (0.2)		
Other venous events	56 (9.2)	205 (3.5)		
Any cerebral event	85 (14.0)	682 (11.6)	1.50 (1.20-1.88)	1.26 (1.00-1.60)
Cerebral infarction, occlusion, and stenosis of cerebral and precerebral arteries	72 (11.8)	566 (9.6)		
Vascular syndromes of brain in cerebrovascular diseases, transient cerebral ischemic attacks, and related syndromes	21 (3.5)	220 (3.7)		
Any arterial event	46 (7.6)	218 (3.7)	2.50 (1.82-3.44)	1.93 (1.37-2.72)
Arterial embolism and thrombosis	13 (2.1)	37 (0.6)		
Myocardial infarction	34 (5.6)	191 (3.3)		
Total patients with TEs	180 (29.6)	1033 (17.6)	2.36 (2.01-2.76)	1.94 (1.64-2.30)

Abbreviations: CAD, cold agglutinin disease; CI, confidence interval; HR, hazard ratio; TE, thrombotic event.

[a]Unadjusted Cox regression model.

[b]Cox regression model adjusted for age, sex, race, region, active time in the system, history of prior TEs (Yes/No), history of HIV/AIDS, history of malignant cancer except for nonmelanoma skin cancer (Yes/No), history of organ failure (Yes/No), history of organ transplantation (Yes/No), history of chemotherapy use (Yes/No), history of radiation use (Yes/No), history of anticoagulant medication use (Yes/No), history of antiplatelet medication use (Yes/No), and Charlson Comorbidity Index score.

TABLE 4 TEs in all patients with CAD and subanalysis in presumed primary CAD compared with patients without CAD

Number of TEs	Patients with CAD, n (%)	Patients without CAD, n (%)	HR[a] (95% CI)	Adjusted HR[b] (95% CI)
All CAD	N = 608	N = 5873	2.36 (2.01-2.76)	1.94 (1.64-2.30)
0	428 (70.4)	4840 (82.4)		
1+	180 (29.6)	1033 (17.6)		
Primary CAD	n = 425	n = 4126	2.25 (1.84-2.75)	1.80 (1.46-2.22)
0	311 (73.2)	3446 (83.5)		
1+	114 (26.8)	680 (16.5)		

Abbreviations: CAD, cold agglutinin disease; CI, confidence interval; HR, hazard ratio; TE, thrombotic event.

[a]Unadjusted Cox regression model.

[b]Cox regression model adjusted for age, sex, race, region, active time in the system, history of prior TEs (Yes/No), history of HIV/AIDS, history of malignant cancer except for nonmelanoma skin cancer (Yes/No), history of organ failure (Yes/No), history of organ transplantation (Yes/No), history of chemotherapy use (Yes/No), history of radiation use (Yes/No), history of anticoagulant medication use (Yes/No), history of antiplatelet medication use (Yes/No), and Charlson Comorbidity Index score.

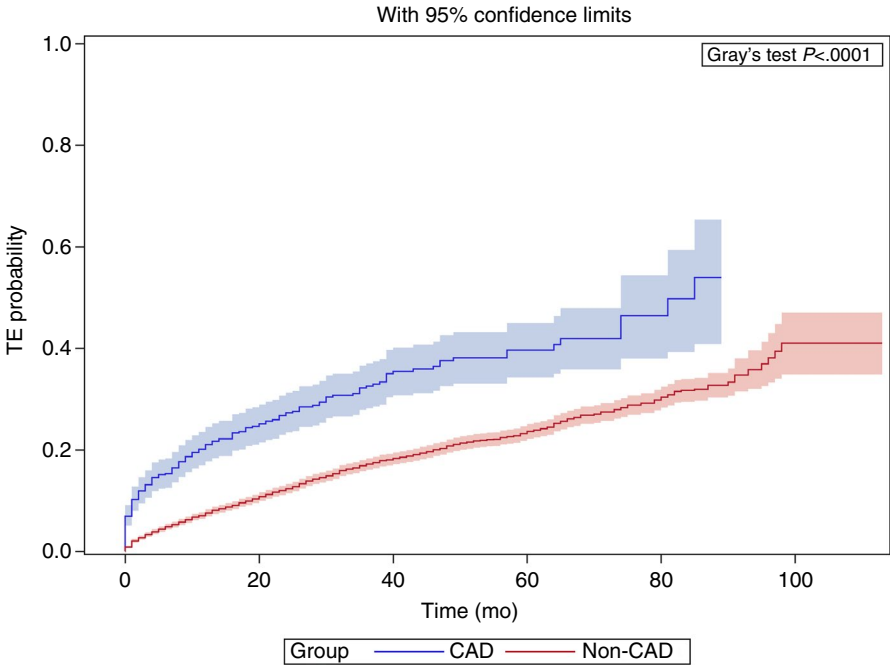

FIGURE 1 Cumulative incidence curve of first thrombotic event (TE) after index date in patients with CAD and patients without CAD. CAD, cold agglutinin disease

predisposing patients with PNH to such a high risk of TEs is complex, the role of complement in addition to the role of hemolysis seems to be supported by the multiple studies that have demonstrated the benefit of complement inhibition, in both decreasing hemolysis and decreasing TEs by up to 93% compared with the same cohort of patients on best supportive care, including anticoagulation.[8,22] Therefore, therapeutic mechanisms that could effectively control complement-mediated hemolysis in patients with CAD may help decrease their risk of TEs and should be investigated.

Identification of TEs in our data set followed the methodology used by Li et al[15] in their safety study using the US Food and Drug Administration's Sentinel Distributed Database, where ICD codes were used to identify TEs. The first TE identified in the data was used to assess TE risk. Sensitivity analyses corroborated our findings that patients with CAD were more likely to have a TE compared with patients without CAD. Reanalyzing our data for only VTE outcomes using the algorithms developed by Sanfilippo et al[17] revealed that patients with CAD were approximately 3 times more likely than patients without CAD to have a VTE. The similarity of these estimates to our original analyses for all types of TEs supports the robustness of the TE identification process used in our analysis.

There is evidence that the identification of TEs through inpatient codes is more sensitive than identification through outpatient codes.[18] As our TE identification algorithm used both inpatient and outpatient codes, there may be some misclassification in our

TABLE 5 TEs in the patients with CAD and patients without CAD stratified by CCI score

CCI score	Patients with CAD with TEs/total CAD (%)	Patients without CAD with TEs/total non-CAD (%)	HR[a] (95% CI)	Adjusted HR[b] (95% CI)
Missing	13/36 (36.1)	162/960 (16.9)	3.80 (2.10-6.88)	3.06 (1.69-5.56)
0	38/172 (22.1)	233/2202 (10.6)	2.69 (1.89-3.84)	2.44 (1.70-3.52)
1-2	73/262 (27.9)	395/1980 (20.0)	1.75 (1.36-2.25)	2.05 (1.56-2.68)
≥3	56/138 (40.6)	243/731 (33.2)	1.31 (0.98-1.76)	1.57 (1.14-2.16)

Abbreviations: CAD, cold agglutinin disease; CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; TE, thrombotic event.

[a]Unadjusted Cox regression model.

[b]Cox regression model adjusted for age, sex, race, region, active time in the system, history of prior TEs (Yes/No), history of HIV/AIDS, history of malignant cancer except for nonmelanoma skin cancer (Yes/No), history of organ failure (Yes/No), history of organ transplantation (Yes/No), history of chemotherapy use (Yes/No), history of radiation use (Yes/No), history of anticoagulant medication use (Yes/No), and history of antiplatelet medication.

analyses for TEs. However, since the misclassification would be nondifferential across both patients with CAD and patients without CAD, the relative risk difference between groups is unlikely to be affected. Additionally, our sensitivity analysis using only inpatient TE codes and excluding patients with TE codes within 6 months before admission demonstrated an HR similar to that of the primary analysis, further supporting our overall findings. The absolute number of TEs may be overestimated due to not excluding prior events in the primary analysis and using only 1 TE claim to identify patients; however, since this method was applied equally to both groups, the relative difference in TE risk between patients with CAD and patients without CAD should be an accurate estimate.

Although we were unable to determine the etiology of CAD in the current database, we conducted sensitivity analyses among patients with presumed primary disease by excluding patients with CAD diagnosed with conditions known to be associated with secondary CAD, such as lymphoma and certain infections. After excluding these patients, the risk of having a TE was still significantly increased among patients with CAD. Further, when stratified by CCI score, the risk of having a TE among patients with CAD with no comorbidities (CCI, 0) was 2.45 times higher than among patients without CAD without comorbidities. These results demonstrate that the increased risk of TEs in patients with CAD in this study cannot be solely due to the presence of underlying comorbidities or other conditions causing secondary CAD.

Clinical parameters were not available in all patients' records to identify patients with CAD using strict hemato-immunologic diagnosis criteria. However, one of the major strengths of this study is that it was conducted in a real-world setting with treating physicians defining CAD. The methodology we used to identify patients with CAD minimized the inclusion of patients that were part of a "rule-out" diagnosis or a coding error.

Study limitations include the following: (a) the use of -based data and of TE diagnostic codes (ICD-9 and ICD-10), which may be subject to coding errors; (b) the lack of data on specific CAD treatments in relation to TE development; (c) patients with both primary and secondary CAD were likely included in the main analysis, as the database did not allow for differentiation; (d) the lack of data on hereditary and acquired thrombotic risks, although we attempted to exclude patients with known risks, which may also contribute to the occurrence and severity of these events; (e) as we included only the first TE of each type, the risk of TEs may have been underestimated; and (f) there may be some selection bias, as we did not include any patient with <1 year of time in the Optum system prior to the index date. This may have excluded the most severely affected patients due to early death. Despite these limitations, the results presented provide a new insight into potential complications in a rare disease in which the ability to conduct prospective trials with sufficient numbers of patients is challenging.

This study demonstrates for the first time that CAD is associated with a significantly increased risk of TEs. The morbidity and potential mortality associated with TEs in patients with CAD should not be underestimated.

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RELATIONSHIP DISCLOSURE

CMB and JMC have received honoraria from Bioverativ, a Sanofi company. LCB, XJ, and JPF were employees of EpidStat Institute at the time of this research (currently employees of EpidStrategies, a division of ToxStrategies, Inc), and MM consults for EpidStat Institute. EpidStat Institute received funding from Bioverativ, a Sanofi company, for this research and from Amgen Inc, Merck, Genentech, Humacyte, Sanofi, and AstraZeneca for other research. AR was employed by Bioverativ, a Sanofi company, at the time of the study.

AUTHOR CONTRIBUTIONS

CMB, JMC, MM, XJ, LCB, JPF, and AR contributed to the design and execution of the study. XJ performed the statistical analysis of the data. CMB, JMC, MM, XJ, LCB, JPF, and AR assisted in analyzing and interpreting the data. MM developed the first draft of the manuscript, and CMB, JMC, MM, XJ, LCB, JPF, and AR made significant contributions to the final version of the manuscript.

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REFERENCES

1. Michel M. Classification and therapeutic approaches in autoimmune hemolytic anemia: an update. Expert Rev Hematol. 2011;4:607–18.
2. Berentsen S. Complement activation and inhibition in autoimmune hemolytic anemia: focus on cold agglutinin disease. Semin Hematol. 2018;55:141–9.
3. Brodsky RA. Complement in hemolytic anemia. Blood. 2015;126:2459–65.
4. L'Acqua C, Hod E. New perspectives on the thrombotic complications of haemolysis. Br J Haematol. 2015;168:175–85.
5. Chapin J, Terry HS, Kleinert D, Laurence J. The role of complement activation in thrombosis and hemolytic anemias. Transfus Apher Sci. 2016;54:191–8.
6. Weitz IC. Complement the hemostatic system: an intimate relationship. Thromb Res. 2014;133(Suppl 2):S117–121.
7. Hillmen P, Lewis SM, Bessler M, Luzzatto L, Dacie JV. Natural history of paroxysmal nocturnal hemoglobinuria. N Engl J Med. 1995;333:1253–8.
8. Schrezenmeier H, Muus P, Socié G, Szer J, Urbano-Ispizua A, Maciejewski JP, et al. Baseline characteristics and disease burden in patients in the International Paroxysmal Nocturnal Hemoglobinuria Registry. Haematologica. 2014;99:922–9.
9. Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public health concern. Am J Prev Med. 2010;38:S495–501.
10. Grosse SD, Nelson RE, Nyarko KA, Richardson LC, Raskob GE. The economic burden of incident venous thromboembolism in the United States: a review of estimated attributable healthcare costs. Thromb Res. 2016;137:3–10.
11. Mullins M, Jiang X, Bylsma LC, Fryzek JP, Reichert H, Chen EC, et al. Cold agglutinin disease burden: a longitudinal analysis of anemia, medications, transfusions, and health care utilization. Blood Adv. 2017;1:839–48.
12. Röth A, Bommer M, Hüttmann A, Herich-Terhürne D, Kuklik N, Rekowski J, et al. Eculizumab in cold agglutinin disease (DECADE): an open-label, prospective, bicentric, nonrandomized phase 2 trial. Blood Adv. 2018;2:2543–9.
13. United States Public Law. Patient protection and affordable care act, law 111–148 2010 [Accessed 2019 February 4] Available from https://www.michaelbartolic.com/wp-content/uploads/2014/02/patient-protection-and-affordable-care-act.pdf
14. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005;43:1130–9.
15. Li J, Panucci G, Moeny D, Liu W, Maro JC, Toh S, et al. Association of risk for venous thromboembolism with use of low-dose extended- and continuous-cycle combined oral contraceptives: a safety study using the Sentinel Distributed Database. JAMA Intern Med. 2018;178:1482–8.
16. Austin PC. Absolute risk reductions and numbers needed to treat can be obtained from adjusted survival models for time-to-event outcomes. J Clin Epidemiol. 2010;63:46–55.
17. Sanfilippo KM, Wang TF, Gage BF, Liu W, Carson KR. Improving accuracy of International Classification of Diseases codes for venous thromboembolism in administrative data. Thromb Res. 2015;135:616–20.
18. Fang MC, Fan D, Sung SH, Witt DM, Schmelzer JR, Steinhubl SR, et al. Validity of using inpatient and outpatient administrative codes to identify acute venous thromboembolism: the CVRN VTE study. Med Care. 2017;55:e137–e143.
19. Rother RP, Bell L, Hillmen P, Gladwin MT. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: a novel mechanism of human disease. JAMA. 2005;293:1653–62.
20. Zhong H, Yazdanbakhsh K. Hemolysis and immune regulation. Curr Opin Hematol. 2018;25:177–82.
21. Lee JW, Jang JH, Kim JS, Yoon SS, Lee JH, Kim YK, et al. Clinical signs and symptoms associated with increased risk for thrombosis in patients with paroxysmal nocturnal hemoglobinuria from a Korean Registry. Int J Hematol. 2013;97:749–57.
22. Hillmen P, Muus P, Dührsen U, Risitano AM, Schubert J, Luzzatto L, et al. Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal hemoglobinuria. Blood. 2007;110:4123–8.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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