

**Characterization of atrial fibrillation and
bleeding risk factors in patients with CLL:
A population-based retrospective cohort study
of administrative medical claims data in the U.S.**

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Background

- Most patients with CLL have multiple chronic comorbidities (e.g., arrhythmias) and other conditions that require the use of anticoagulants and/or antiplatelet agents¹
- Understanding the frequency of use of these agents and bleeding events in routine clinical practice could provide insights on the real-world burden of anticoagulant/antiplatelet use in patients with underlying bleeding risks due to CLL-related thrombocytopenia and other comorbidities
- Some of the recently approved targeted agents may be associated with risk of cardiac arrhythmias or bleeding events
 - Mechanisms behind these events and the relations between them are largely unclear
- The purpose of this retrospective database study was to characterize the outcomes of newly diagnosed CLL patients in terms of:
 - Incidence of Afib
 - Incidence of Afib risk factors
 - Bleeding risk factors
 - Anticoagulant/antiplatelet drug usage over the course of the treatment

1. Thurmes P, et al. Leuk Lymphoma 2008;49:49–56.

Afib = atrial fibrillation; CLL = chronic lymphocytic leukemia

Study Design

- This was a retrospective, observational study using de-identified U.S. administrative healthcare claims extracted from the 2004–2015 Truven Health MarketScan® Commercial and Medicare Supplemental Databases
 - Databases contained the inpatient medical, outpatient medical, and outpatient pharmacy claims for more than 40 million people with employer-sponsored primary or Medicare supplemental insurance
- The study period was comprised of an index date (the start of the first line of therapy), a six-month pre-index period (baseline), and a variable-length post-period (follow-up)
 - Patients were followed from their index date until disenrolment from their health plan or April 30, 2015, whichever came first
- Study outcomes were evaluated during the first and second lines of therapy, as well as the gap period between therapies
- Bleeding risk factors were measured by the five-variable ATRIA risk score and the mean ATRIA bleeding risk score

Inclusion Criteria

- At least one inpatient or at least two outpatient claims with a diagnosis of CLL (ICD-9-CM diagnosis code 204.1x) between January 1, 2004 and April 30, 2015
- At least two lines of antineoplastic therapy after the index date where the second line represented a change in therapy
- Newly diagnosed CLL on the index date with no medical claims for CLL in the six months before the index date
- Continuous medical and prescription coverage for six months before the index date

Baseline Characteristics

		All patients (N = 2,335)	Age <65* (N = 1,283)	Age 65+* (N = 1,052)
Mean age, years (SD)		61.6 (18.0)	50.2 (16.5)	75.4 (6.5)
Age 65+, %		45.1	0.0	100.0
Male, %		66.2	67.9	64.1
Urban population density, %		83.5	84.2	82.7
Payer, %	Commercial	54.4%	98.9%	0.1%
	Medicare	45.6%	1.1%	99.9%
Baseline CCI, mean (SD)		2.93 (1.82)	2.78 (1.72)	3.10 (1.93)
Comorbid conditions, %	Hypertension	36.2	29.9	43.8
	Lipometabolic disorders	34.7	35.9	33.4
	Thrombocytopenia	16.4	19.8	12.4
	Neutropenia	10.1	14.2	5.1
	Thromboembolism	7.1	5.6	8.9
	Osteoarthritis	5.7	2.9	9.1
	Cerebrovascular disease	5.0	2.9	7.5
	Coronary heart disease	1.8	1.0	2.8
	Rheumatoid arthritis	1.3	1.1	1.5
Anticoagulant/antiplatelet/thrombolytic use, %		24.9	24.1	26.0
Mean follow-up time, months (SD)		35.3 (25.0)	34.5 (24.7)	36.3 (25.4)

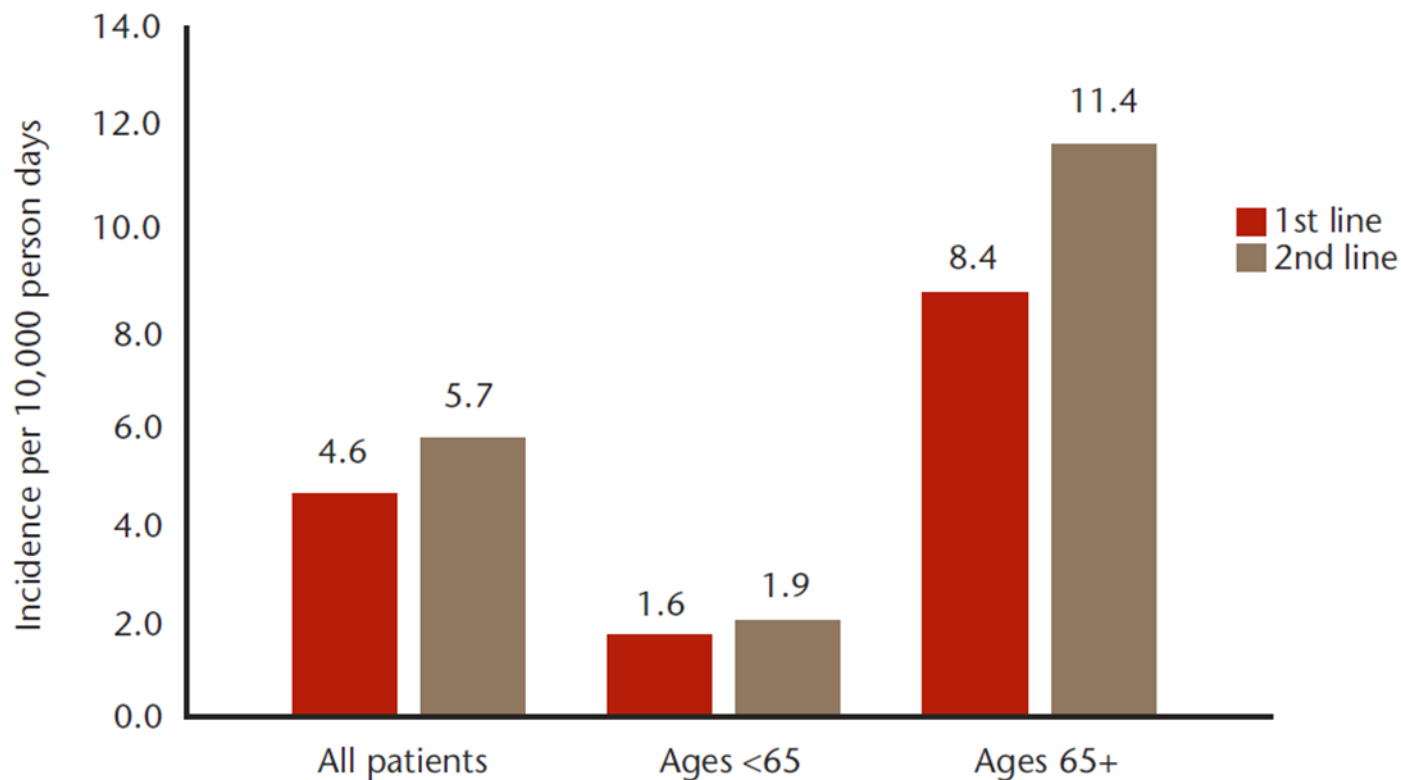
* Age as of index date (start of first-line treatment).

CCI = Deyo-Charlson Comorbidity Index score; SD = standard deviation

Study Sample

- Over the study period, a total of 2,335 patients met the study criteria
- The mean duration of treatment was 3.3 months for first-line treatment and was 4.1 months for second-line treatment

Incidence of Afib



- During follow-up, the incidence of Afib increased over time from first- to second-line treatment

Afib and Bleeding Risk Factors

	All patients			Age <65 (at index)			Age 65+ (at index)		
	1st line	Interval between 1st and 2nd line*	2nd line	1st line	Interval between 1st and 2nd line*	2nd line	1st line	Interval between 1st and 2nd line*	2nd line
	N = 2,335	N = 1,354	N = 2,335	N = 1,283	N = 659	N = 1,283	N = 1,052	N = 695	N = 1,052
Duration of therapy/ gap in therapy (months), mean (SD)	3.3 (3.1)	14.0 (15.9)	4.1 (4.2)	3.3 (2.8)	14.0 (16.3)	4.3 (4.7)	3.3 (3.4)	14.0 (15.5)	3.8 (3.7)
Anticoagulant/anti-platelet/thrombolytic use in period, %	31	28	32	34	25.6	34.5	26.7	30.6	29.8
Patients with Afib, %	4	9	7	1.6	3.5	2.3	7.7	14.1	11.8
Incidence, per 10,000 person days	4.6	2.3	5.7	1.60	0.87	1.86	8.44	3.80	11.44
95% CI of incidence	3.7–5.5	1.9–2.7	4.8–6.6	1.51–1.69	0.80–0.94	1.76–1.96	7.93–8.95	3.52–4.08	10.75–12.13

* N < study same. Patients switching immediately to 2nd line will not have an interval period between 1st and 2nd line.

Afib = atrial fibrillation; CI = confidence interval; SD = standard deviation

Afib and Bleeding Risk Factors (*cont'd*)

	All patients			Age <65 (at index)			Age 65+ (at index)		
	1st line	Interval between 1st and 2nd line*	2nd line	1st line	Interval between 1st and 2nd line*	2nd line	1st line	Interval between 1st and 2nd line*	2nd line
	N = 2,335	N = 1,354	N = 2,335	N = 1,283	N = 659	N = 1,283	N = 1,052	N = 695	N = 1,052
Patients with Afib risk factors during period, %									
Smoking	2	6	3	2.5	6.5	3.3	2.3	5.2	2.8
Alcohol consumption	0	0	0	0.1	0.2	0.4	0.2	0.4	0.4
Overweight/obesity	2	3	1	2.5	4.7	2.1	0.5	2.0	0.8
Hypertension diagnosis†	21	39	25	17.5	33.5	20.8	25.6	44.6	31.0
Hypertensive treatment	24	34	25	18.4	27.3	21.0	30.2	39.9	29.8
Diabetes	13	19	15	8.9	15.0	11.5	17.3	23.3	19.9
Electrocardiographic left ventricular hypertrophy	0	0	0	0.0	0.0	0.0	0.0	0.0	0.0
Heart failure	3	7	5	1.6	3.2	1.9	5.7	10.2	8.3
Myocardial infarction	1	1	1	0.3	0.8	0.5	1.3	1.6	1.1

Afib = atrial fibrillation; ICD-9-CM = International Statistical Classification of Diseases and Related Health Problems-9, Clinical Modification

† Hypertensive disease: ICD-9-CM diagnosis codes 401.xx – 405.xx.

Afib and Bleeding Risk Factors (*cont'd*)

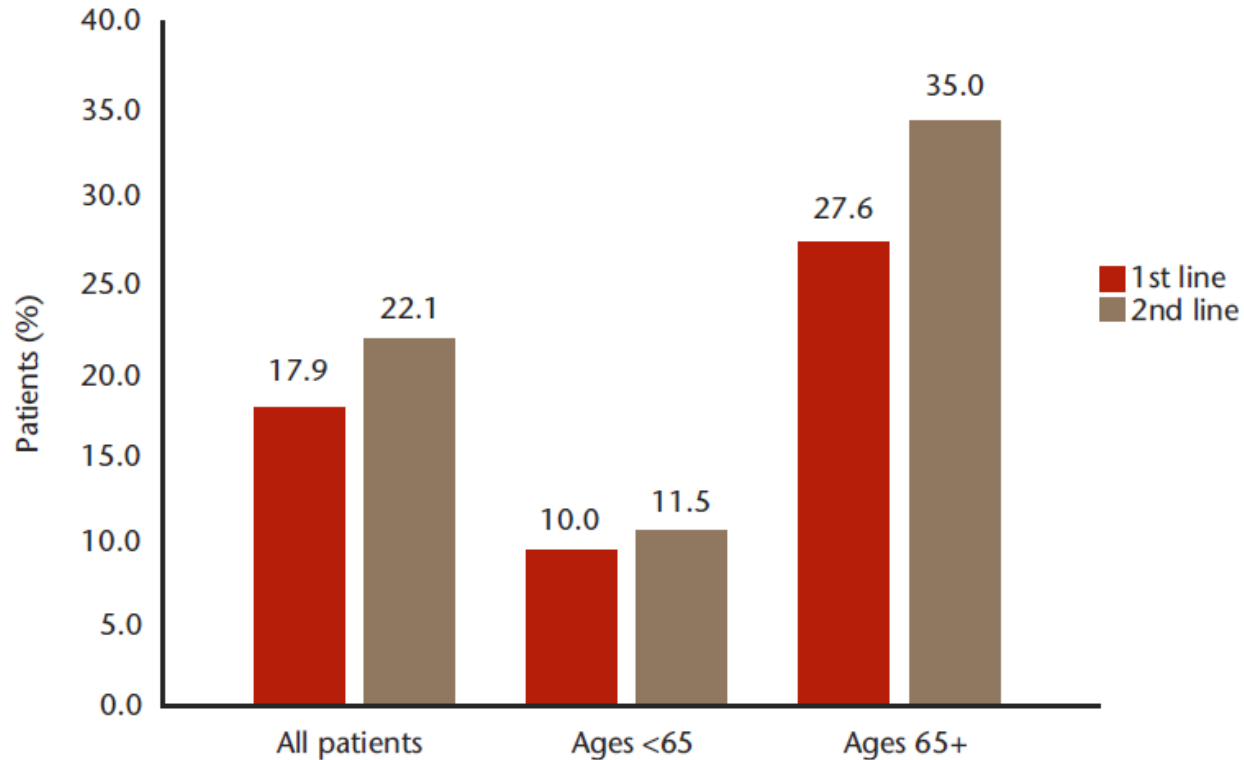
	All patients			Age <65 (at index)			Age 65+ (at index)		
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	N = 2,335	N = 1,354	N = 2,335	N = 1,283	N = 659	N = 1,283	N = 1,052	N = 695	N = 1,052
Patients with bleeding risk factors (ATRIA[‡]) during period, %									
Anemia	35	36	37	34.0	31.6	33.9	35.6	41.2	40.4
Severe renal disease	5	8	5	3.2	4.1	3.1	6.8	12.2	8.2
Age ≥75 years (as of index date)	24	31	27	0.0	0.0	0.0	54.1	59.7	59.5
Major bleeds in period	1	3	2	0.8	2.7	2.1	0.9	3.3	1.1
Hypertensive diagnosis (ATRIA definition[§])	20	39	25	17.2	33.1	20.0	24.5	43.7	30.6
ATRIA risk score, %				1.7	1.8	1.7	2.1	2.4	2.3
≤3 (low)	82	72	78	90.0	84.1	88.5	72.4	61.0	65.0
4 (moderate)	6	10	7	7.7	12.3	9.0	4.5	7.5	5.2
≥5 (high)	12	18	15	2.3	3.6	2.5	23.1	31.5	29.8

[‡] ATRIA risk factors (Fang et al. 2012).

[§] Essential hypertension (ICD-9-CM diagnosis codes 401.xx) and Hypertensive heart disease (ICD-9-CM diagnosis codes 402.xx).

Afib = atrial fibrillation; ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; ICD-9-CM = International Statistical Classification of Diseases and Related Health Problems-9, Clinical Modification

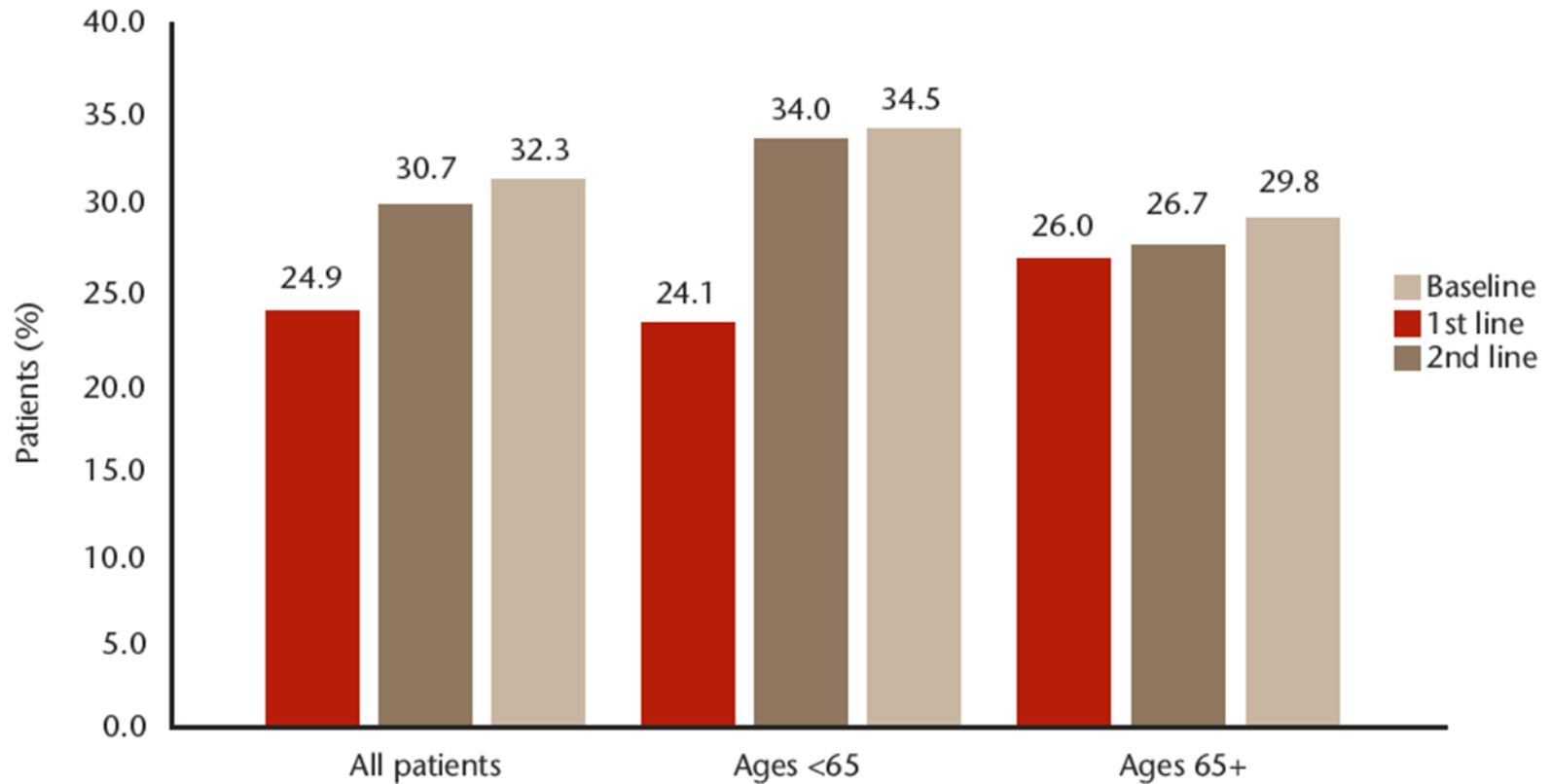
ATRIA Risk Score ≥ 4



ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation

- The proportion of patients with ATRIA scores indicating moderate to high (≥ 4) risk of bleeding increased from first- to second-line therapy
- Similar trends were observed when patients were stratified by age (<65 and ≥ 65)

Anticoagulant/Antiplatelet/Thrombolytic Use



Summary and Conclusion

- In this study, the use of anticoagulant/antiplatelet agents at diagnosis was common (25%) and increased over time from first- (30.7%) to second-line treatment (32.3%)
- Both the incidence of Afib and the ATRIA bleeding risk score increased over the course of disease progression
 - In general, the incidence of Afib and the proportion of patients with ATRIA risk scores ≥ 4 were higher among patients age ≥ 65
- Since ATRIA scores of ≥ 5 correlate with a 5.8% annual risk of major hemorrhage, understanding the characteristics of patients with CLL at diagnosis and relapse will ultimately help optimize treatment selection based on the potential risks and benefits of each treatment regimen
- These data, as well as an evaluation of cardiac status, use of concomitant medications, and potential risk factors, should be considered in the management of CLL