Conflicts of Interest

Author	Commercial Interest
E Malangone-Monaco	Employee: IBM Watson Health, which received funding from AstraZeneca
K Ryan	Employee and shareholder: AstraZeneca
EH Marchlewicz	Employee: IBM Watson Health, which received funding from AstraZeneca
J Lo	Employee: AstraZeneca (at time of analysis)
S Huntington	Consultant: AstraZeneca, Janssen, AbbVie, Novartis, BeiGene, Flatiron Health, Genentech, Bayer, Aptitude Health, COVIA Health Solutions

Economic Burden of Cardiovascular Events in Patients with Chronic Lymphocytic Leukemia Treated with Novel Agents

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Background

- Chronic lymphocytic leukemia (CLL) is the most common leukemia among adults in Western countries, accounting for over 1/3 of all leukemias in the U.S.[1]
  - Most individuals live 5+ years with this incurable malignancy (~200,000 prevalent cases in the US)

- Since the 2013 FDA approval of ibrutinib, the first Bruton tyrosine kinase inhibitor (BTKi), there has been a shift away from cytotoxic therapies to novel agent therapies (NATs).
  - Favorable risk/benefit of NATs compared to chemotherapy has led to rapid adoption in CLL.[3,4]

- Despite the improved efficacy and tolerable safety profile compared to chemoimmunotherapy, NATs are also associated with adverse events. Previously published studies have identified several CV events associated with use of ibrutinib [5]
  - These include supraventricular arrhythmias (especially atrial fibrillation), ventricular arrhythmias, hypertension, heart failure, conduction disorders, central nervous system ischemic and hemorrhagic events.

[1] NCI SEER program. https://seer.cancer.gov/statfacts/html/clyl.html; [2] Byrd JC et al., *N Engl J Med* 2014. [3] Mato AR, et al., *Clin Lymphoma Myeloma Leuk* 2020. [4] Seymour EK, *Oncotarget* 2019. [5] Salem JE, *J Am Coll Cardiol* 2019.

BTKi: Bruton's tyrosine kinase inhibitors, CLL: chronic lymphocytic leukemia, CV: cardiovascular, NAT: novel agent treatments

Study Objectives

- To assess prevalence of CV events in CLL patients treated with NATs
- To examine real-world healthcare costs associated with CV events in real-world data

CLL: chronic lymphocytic leukemia, CV: cardiovascular, NAT: novel agent treatments

Study Design and Data Source

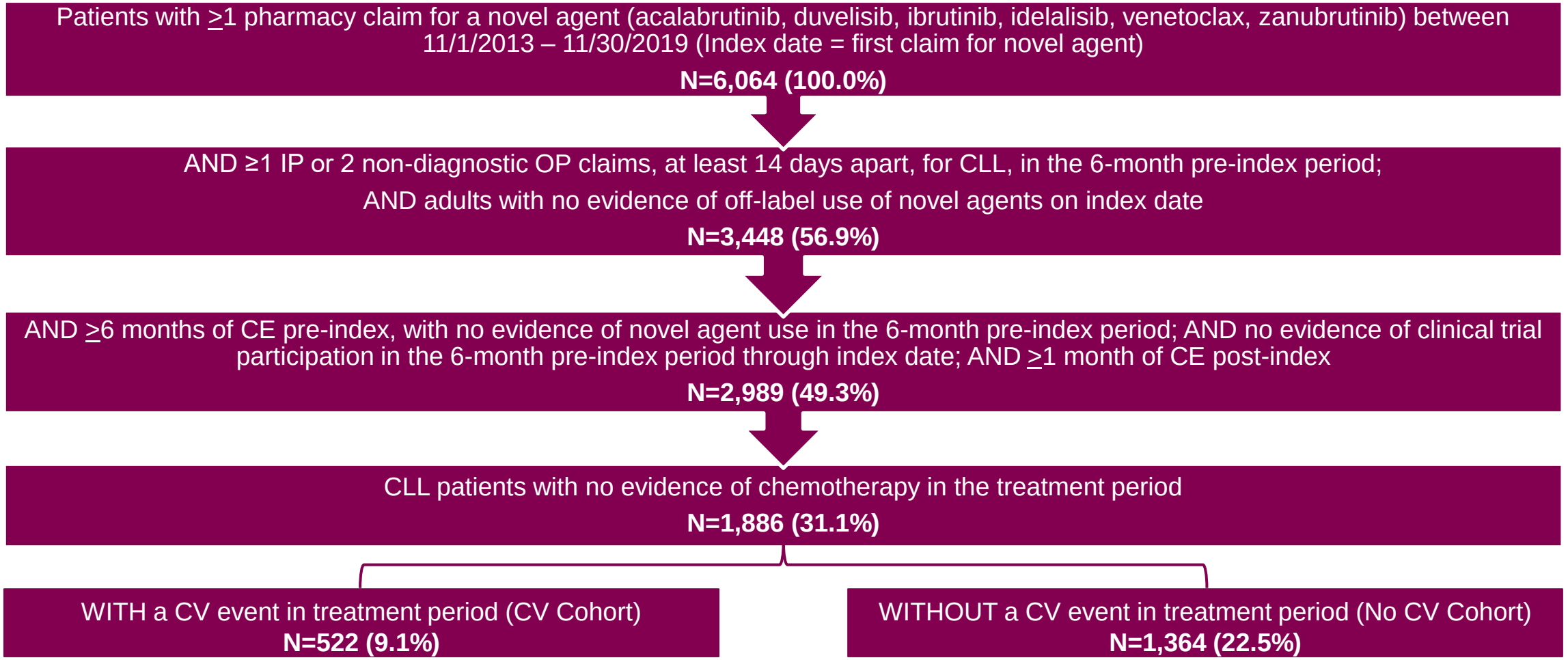
- Retrospective, observational analysis of MarketScan Commercial and Medicare Supplemental administrative claims databases covering 2013-2019.

- MarketScan Commercial database contains the inpatient, outpatient, and outpatient prescription drug experience of employees and their dependents.

- MarketScan Medicare database contains the healthcare experience retirees with Medicare supplemental insurance paid for by employers.

Results

Patient Selection



CE: continuous enrollment, CLL: chronic lymphocytic leukemia, CV: cardiovascular, IP: inpatient, OP: outpatient

Outcomes & Statistical Methods

- Previously published studies have identified several CV events associated with use of BTK inhibitors, one class of NATs.
  - These include supraventricular arrhythmias, ventricular arrhythmias, hypertension, heart failure, conduction disorders, central nervous system ischemic and hemorrhagic events.
- Annual all-cause healthcare costs (adjusted to 2019 US dollars) were compared between patients in the CV Cohort versus the No CV Cohort in two follow-up periods.
  - Variable-length follow-up (up to 12-months): days from NAT initiation to end of follow-up
  - Fixed 12-month follow-up: 365 days after NAT initiation, among patients with 12 months of post-index CE
- Per-patient, per-month (PPPM) all-cause healthcare costs were assessed in the pre-CV and post-CV event periods for patients in the CV cohort.
  - Pre-CV event period: days from NAT initiation to the day before CV event
  - Post-CV event period: days from CV event to end of follow-up

BTK: Bruton's tyrosine kinase inhibitors, CE: continuous enrollment, CLL: chronic lymphocytic leukemia, CV: cardiovascular, IP: inpatient, NAT: novel agent treatments, OP: outpatient, PPPM: per-patient-per-month

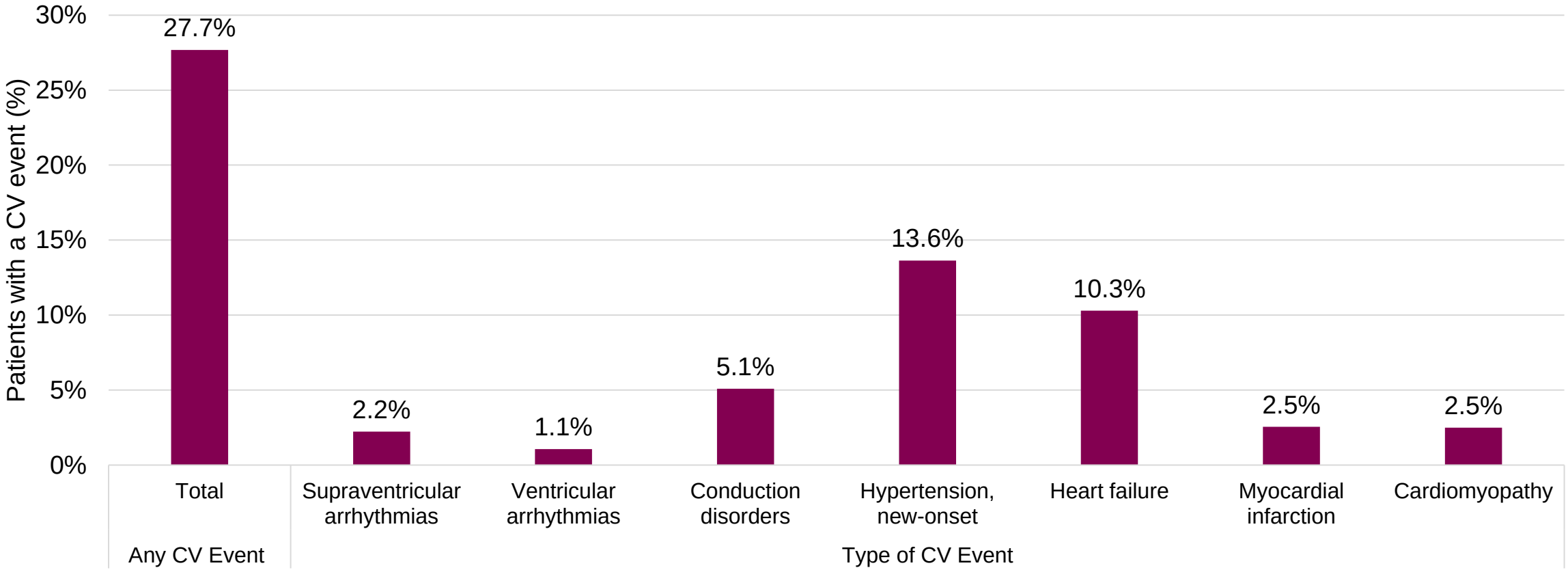
Outcomes & Statistical Methods, cont.

- Unadjusted healthcare costs were analyzed descriptively among the CV and No CV Cohorts.

- Adjusted healthcare costs were assessed via generalized linear models (GLM) with log link and gamma distribution to handle non-normal cost distributions.
  - The model adjusted for the following baseline characteristics: patient age, geographic region, index year, and baseline all-cause healthcare costs (chosen based on bivariate results and clinical significance)

CV: cardiovascular, GLM: generalized linear models

Prevalence of CV Events during Novel Agent Treatment



During a median follow-up time of 305 days, 28% (522/1886) of CLL patients experienced a CV event during treatment. CV events occurred a median 74.5 days and mean(SD) 103.0(93.9) days following NAT initiation.

CLL: chronic lymphocytic leukemia, CV: cardiovascular, NAT: novel agent treatments

Baseline Demographic & Clinical Characteristics

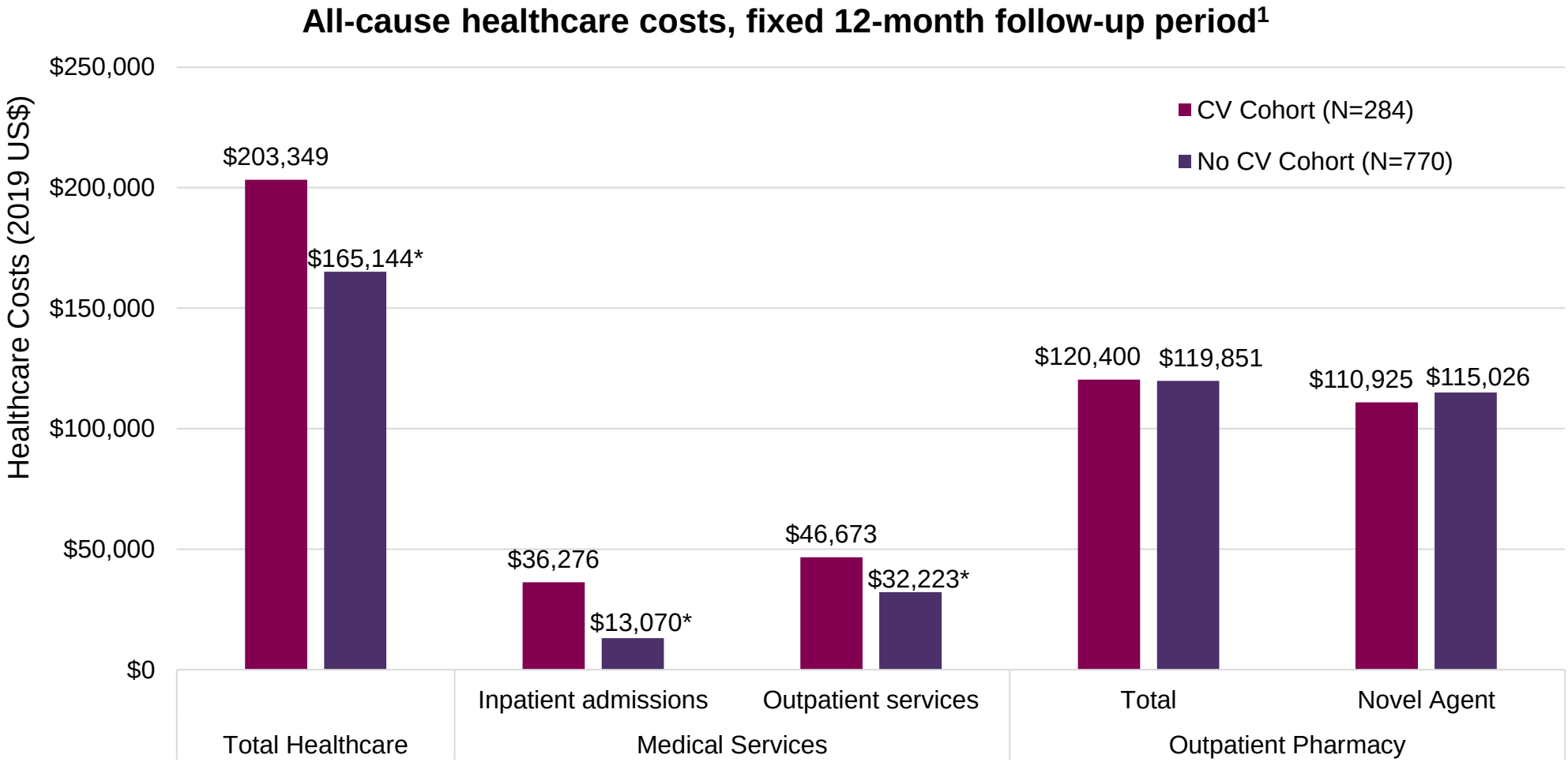
	Variable Follow-Up (up to 12M)				
	CV Cohort		No CV Cohort		CV vs. No CV
	N=522		N=1,364		p-value
Age (Mean, SD)	71.7	11.9	65.8	11.5	<0.001
Male (N, %)	352	67.4%	889	65.2%	0.355
Geographic Region (N, %)					
Northeast	168	32.2%	362	26.5%	0.054
North Central	143	27.4%	356	26.1%	
South	147	28.2%	462	33.9%	
West	62	11.9%	174	12.8%	
Unknown/Missing	2	0.4%	10	0.7%	
Insurance Type (N, %)					
Commercial	167	32.0%	723	53.0%	<0.001
Medicare	355	68.0%	641	47.0%	
Index Year (N, %)					
2013 - 2015	189	36.2%	533	39.1%	0.230
2016 - 2019	333	63.8%	831	60.9%	
Ibrutinib[2] on index date (N, %)	506	96.9%	1,323	97.0%	0.946
Baseline healthcare costs (Mean, SD)	$50,484	$99,446	$41,704	$79,208	0.046

	Variable Follow-Up (up to 12M)				
	CV Cohort		No CV Cohort		CV vs. No CV
	N=522		N=1,364		p-value
NCI-Adapted CCI (Mean, SD)	1.2	1.5	0.8	1.2	<0.001
CV-Related Comorbidities (N, %)					
Atrial fibrillation	73	14.0%	82	6.0%	<0.001
Deep vein thrombosis	16	3.1%	33	2.4%	0.430
Hyperlipidemia	162	31.0%	427	31.3%	0.910
Major bleeding	73	14.0%	113	8.3%	<0.001
Pulmonary embolism	10	1.9%	14	1.0%	0.123
Concomittant Medications[1] (N, %)					
Antiarrhythmics	39	7.5%	59	4.3%	0.006
Anticoagulants	71	13.6%	141	10.3%	0.045
Antihypertensives	320	61.3%	633	46.4%	<0.001
Antiplatelets	26	5.0%	51	3.7%	0.223
Other Primary Cancer (N, %)					
Diagnosis for other primary cancer	250	47.9%	609	44.6%	0.206
Claim for any chemotherapy agent	112	21.5%	280	20.5%	0.657

[1] Additional concomitant medications (antidepressants, antipsychotics, birth control, PDE5 inhibitors) were examined, but did not differ between cohorts (CV Cohort vs. No CV Cohort).

[2] Additional novel agents flagged on index date include: acalabrutinib, duvelisib, idelalisib, venetoclax, zanubrutinib. No patients received a CD20 monoclonal antibody (obinutuzumab, rituximab) between index date and 60 days after index.

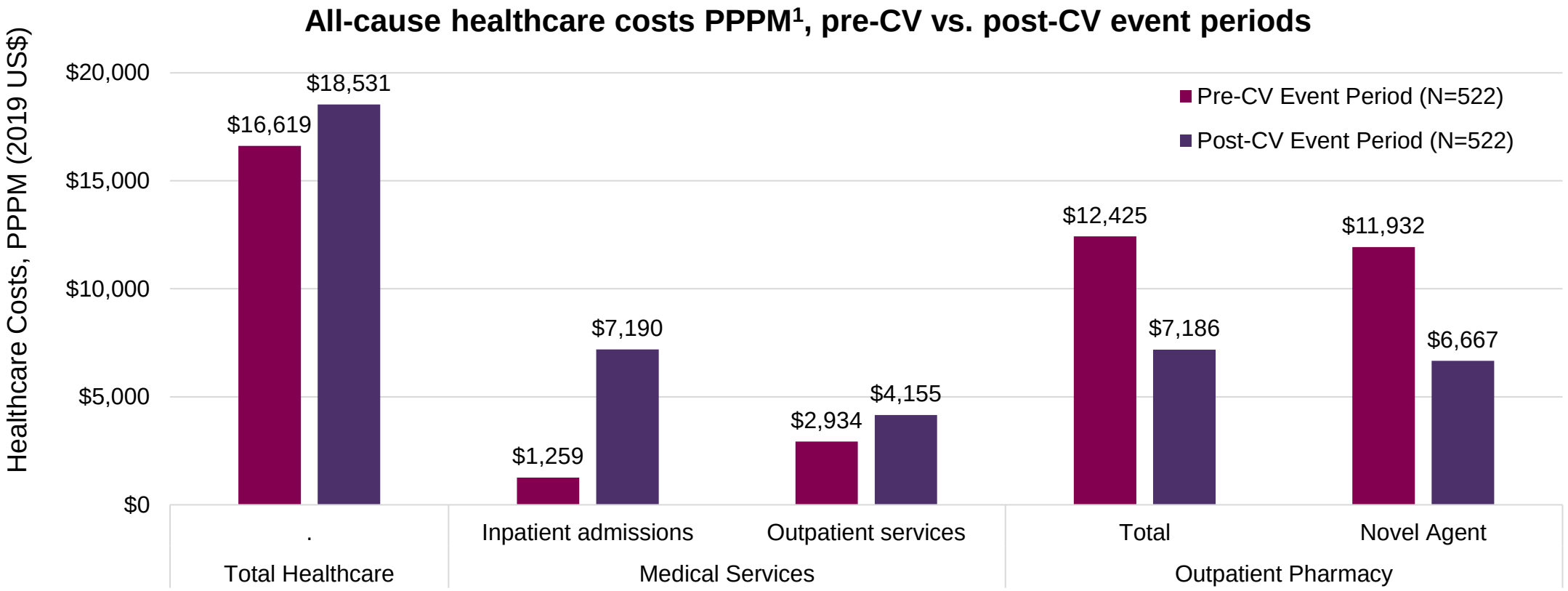
Annual all-cause healthcare costs were higher in patients with a CV event compared to those without an event.



* Denotes statistical significance, p<0.002

[1] This analysis was limited to the subset of patients with 12-months of post-index CE.

Among patients with a CV event, PPPM costs increased after the CV event, driven by greater costs for inpatient admissions and outpatient services, despite a decrease in novel agent costs.



[1] All patients with a CV event during treatment were included in this analysis. The pre-CV and post-CV event periods were variable in length, so costs are reported as per-patient-per-month (PPPM).

Adjusted Results

All-cause healthcare costs, fixed 12-month follow-up period

- On average, adjusting for patient characteristics, the 12-month all-cause costs for CLL patients with a CV event during treatment were 1.2 times the 12-month all-cause costs for CLL patients without a CV event during treatment ($p<0.0001$).

- The following factors were significant drivers of fixed 12-month all-cause healthcare costs: patient age, geographic region, index year, and baseline all-cause healthcare costs.

Limitations

- This study is subject to limitations common to all retrospective administrative claims analyses.
- Findings may not be generalizable to CLL patients with no health insurance or insurance other than Commercial or Medicare Supplemental insurance.
- Our median follow up time was 10 months, limiting our ability to capture delayed CV events due to NAT use.
- Our study period (November 2013 through December 2019) limited the ability to capture cost of CV events across all NATs now on the market.

Conclusions

- Claims for CV events were common within the first year of NAT initiation.
- CLL patients on NATs with a CV event during treatment incurred higher total all-cause healthcare costs in the first year following initiation of NAT than those without a CV event, even after adjusting for potential confounders.
- Higher costs for inpatient admissions and outpatient services compensated for decreased novel agent costs following the CV event, suggesting increased medical management and novel agent discontinuation.
- Future research should look at longer follow-up post CV events to determine the impact of CV events on CLL patients beyond the first year, including the impact to CLL treatment.

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