COVID-19 Related Changes in Healthcare Utilization among Insured Persons in the US and its Impact on Pharmacoepidemiologic Research

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BACKGROUND

- COVID-19 containment measures affected provision and utilization of health services in the US.
- Identification of variables (e.g., exposures, confounders, outcomes) and validity of studies using real world data from this time may be impacted.
- Replication of known positive associations can help investigate the potential impact of changing healthcare utilization.

OBJECTIVE

Investigate the impact of changing healthcare utilization on ascertainment of study variables using data from before and during the COVID-19 pandemic to replicate a known positive association.

METHODS

Known positive association: Angiotensin converting enzyme inhibitors (ACEi) are known to be associated with a 3- to 5-fold increase in the risk of angioedema relative to beta blockers

Design: Retrospective active comparator new-user cohort study

Study period: January 2018 - June 2022

Data source: Five Data Partners participating in the Sentinel Distributed Database

Cohort: Adults ≥ 18 years newly initiating treatment (cohort entry) with ACEi as the primary exposure vs. beta blockers as the comparator drug with:

- 183 days of continuous medical and drug coverage,
- No evidence of other antihypertensive use, and
- No history of angioedema in the 6 months prior to cohort entry

Follow-up: Followed from cohort entry for 90 days until first occurrence of angioedema, treatment discontinuation or crossover, disenrollment, or death

Primary analysis: Propensity score (PS) methods of 1:1 matching and quintile stratification were used for confounding control. Hazard ratios (HR) for angioedema risk were estimated overall and stratified by quarter-year of cohort entry to investigate cohort changes, confounder ascertainment, and risk estimates

Secondary analyses: Assessed pre-pandemic (May 2018 - Dec. 2019) and pandemic (Sept. 2020 - Apr. 2022); altered lookback windows (365 vs. 183 days) for new user evaluation and ascertainment of covariates; included calendar time in PS model

RESULTS

- We identified 2,240,239 and 2,479,076 new users of ACEi and beta blockers, respectively, between 2018-2022, prior to any PS adjustment.
- Before PS adjustment, there were more male ACEi users, and users had a lower burden of comorbidities, allergic reaction, heart failure, and ischemic heart disease compared to beta blocker users. After PS adjustment, cohorts were balanced on all known and measured confounders.
- Figures 1 and 2 show trends in the capture of important confounders by treatment group over calendar time.
- The overall adjusted HR due to ACEi exposure was 4.44 (4.06 - 4.85) by PS matching and 4.54 (4.21 - 4.90) by stratification, which is very similar to previously published work.
- In analyses stratified by quarter-year, there were fewer new users identified in April - June 2020 (Figure 3), but there were similar distributions of demographics, measured confounders, and common chronic conditions (data not shown). The hazard ratios were similar over time (Tables 1-2).

Figure 1. Prevalence of measured confounders among ACEi new users did not vary over time

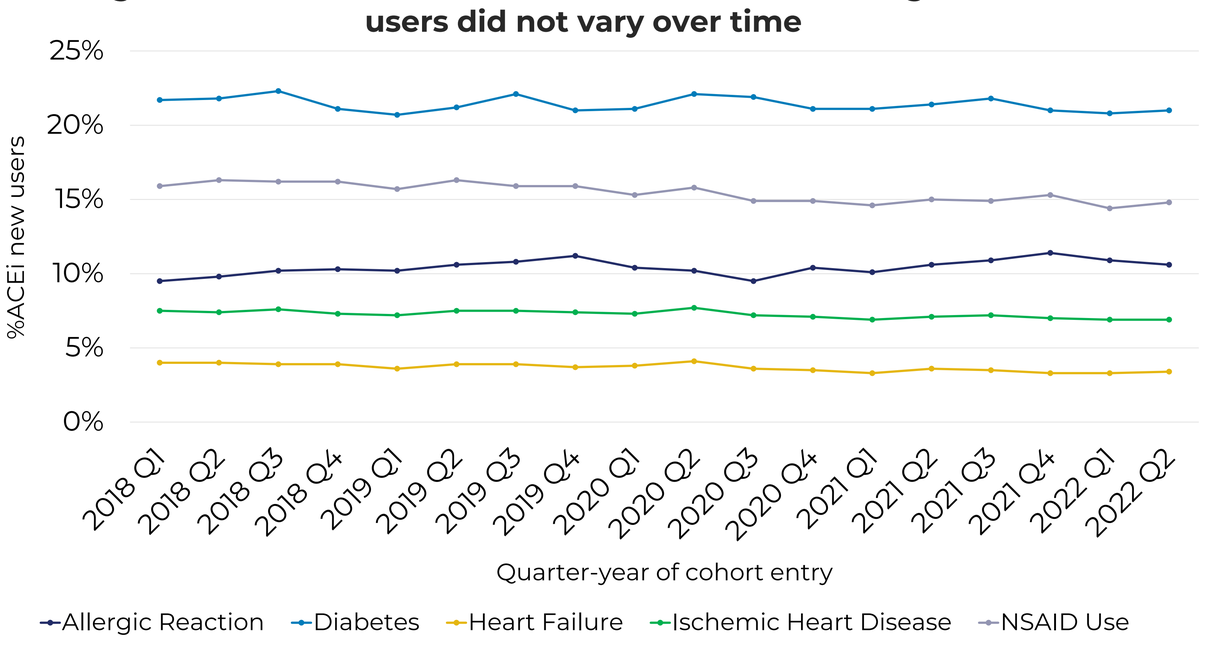

Figure 2. Prevalence of measured confounders among Beta Blocker new users did not vary over time

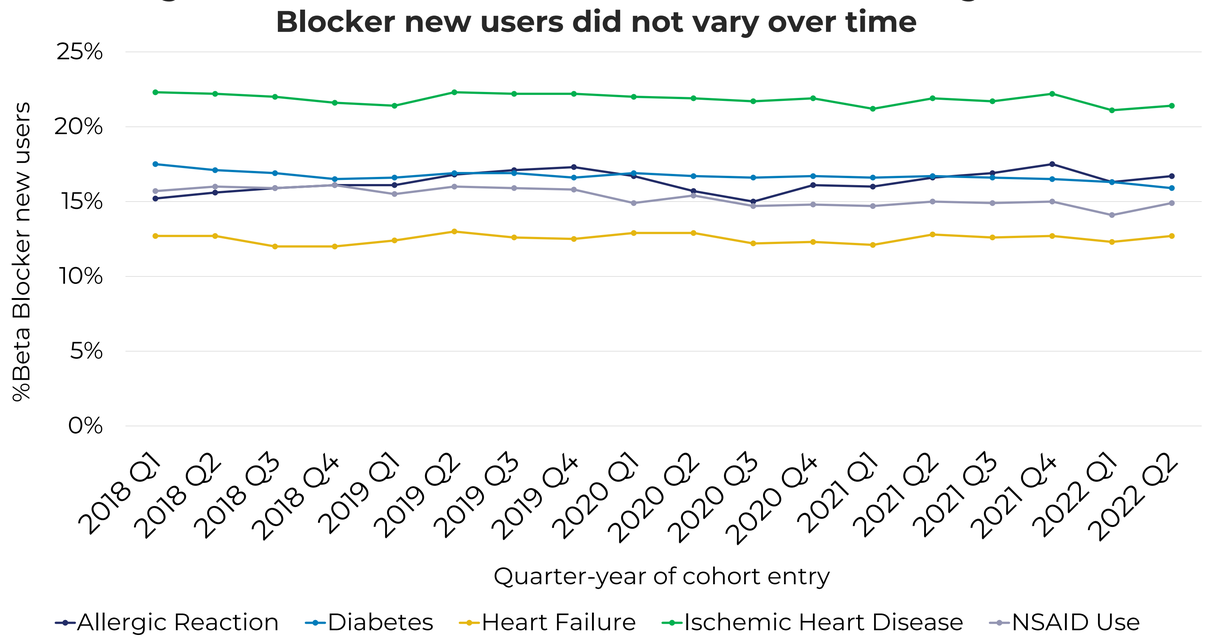

Figure 3. Fewer new users entered exposure cohorts during April - June 2020

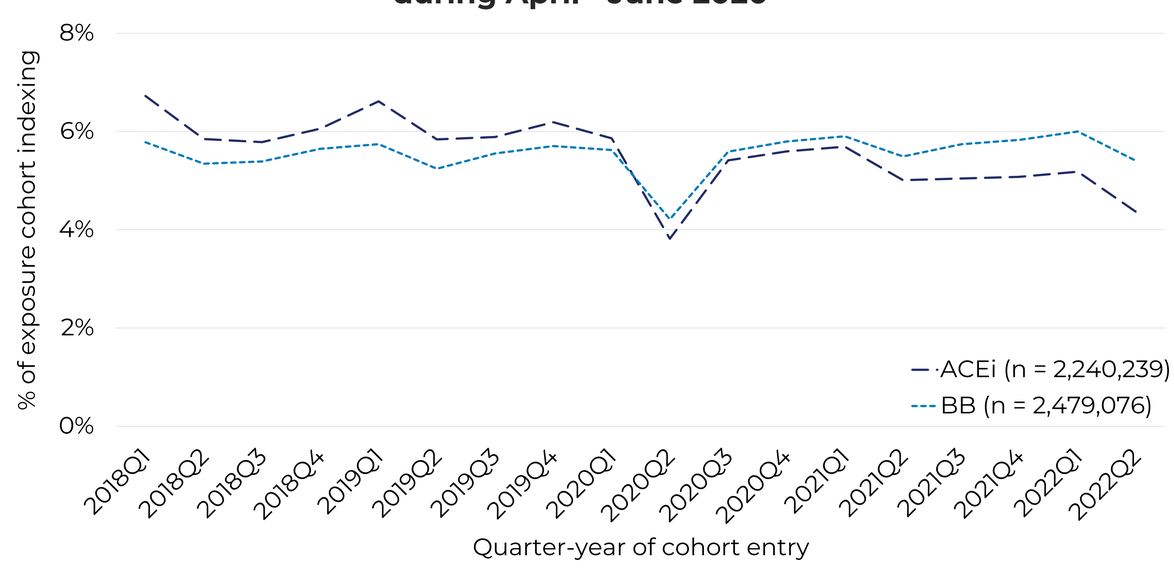

Table 1. Angioedema risk estimates from PS matched analyses

Period	New users of ACE inhibitors: New Users	Events	IR* per 1,000 PY*	New users of beta blockers (reference): New Users	Events	IR* per 1,000 PY*	HR (95% CI)
Overall	**1,511,170**	**2777**	**9.41**	**1,511,170**	**582**	**2.19**	**4.44 (4.06, 4.85)**
2018Q1	89,379	149	8.49	89,379	42	2.63	3.32 (2.36, 4.68)
2018Q2	81,331	169	10.65	81,331	28	1.93	5.65 (3.79, 8.43)
2018Q3	81,539	167	10.45	81,539	30	2.06	5.28 (3.58, 7.78)
2018Q4	85,671	160	9.71	85,671	48	3.19	3.14 (2.28, 4.34)
2019Q1	88,808	177	9.96	88,808	29	1.81	5.66 (3.82, 8.39)
2019Q2	78,958	177	11.29	78,958	30	2.1	5.47 (3.71, 8.05)
2019Q3	83,386	187	11.26	83,386	48	3.18	3.65 (2.66, 5.01)
2019Q4	85,917	180	10.78	85,917	25	1.64	6.76 (4.45, 10.28)
2020Q1	84,751	161	9.38	84,751	34	2.19	4.43 (3.06, 6.42)
2020Q2	57,908	103	8.89	57,908	22	2.08	4.39 (2.77, 6.96)
2020Q3	80,318	154	9.45	80,318	27	1.83	5.33 (3.54, 8.02)
2020Q4	83,494	130	7.90	83,494	35	2.34	3.46 (2.38, 5.02)
2021Q1	85,005	117	6.73	85,005	30	1.92	3.60 (2.41, 5.37)
2021Q2	76,001	143	9.32	76,001	30	2.16	4.44 (3.00, 6.59)
2021Q3	75,623	135	8.85	75,623	23	1.68	5.41 (3.48, 8.42)
2021Q4	76,537	116	7.68	76,537	29	2.14	3.70 (2.46, 5.56)
2022Q1	78,279	133	8.29	78,279	18	1.27	6.70 (4.10, 10.97)
2022Q2	66,264	73	9.51	66,264	19	2.72	3.59 (2.17, 5.96)

Table 2. Angioedema risk estimates from PS stratified analyses

Period	New users of ACE inhibitors: New Users	Events	IR* per 1,000 PY*	New users of beta blockers (reference): New Users	Events	IR* per 1,000 PY*	HR (95% CI)
Overall	**2,240,221**	**3771**	**8.51**	**2,479,056**	**960**	**2.23**	**4.54 (4.21, 4.90)**
2018Q1	150,587	246	8.22	143,326	59	2.33	3.68 (2.72, 4.99)
2018Q2	130,960	260	10.05	132,485	51	2.18	5.46 (3.98, 7.50)
2018Q3	129,547	246	9.57	133,610	61	2.58	4.69 (3.48, 6.32)
2018Q4	135,692	228	8.64	139,951	70	2.88	3.34 (2.51, 4.46)
2019Q1	148,132	264	8.8	142,315	56	2.21	4.82 (3.55, 6.53)
2019Q2	130,806	262	9.96	129,944	50	2.16	5.91 (4.29, 8.15)
2019Q3	131,918	269	10.11	137,620	69	2.81	4.65 (3.51, 6.16)
2019Q4	138,624	258	9.46	141,371	46	1.87	6.34 (4.56, 8.83)
2020Q1	131,318	200	7.44	139,368	52	2.07	4.11 (2.96, 5.69)
2020Q2	85,498	138	7.95	104,411	41	2.19	4.07 (2.80, 5.91)
2020Q3	121,249	207	8.3	138,511	51	2.04	4.87 (3.51, 6.75)
2020Q4	125,330	186	7.44	143,606	54	2.13	4.22 (3.05, 5.84)
2021Q1	127,499	175	6.64	146,291	64	2.43	3.21 (2.36, 4.37)
2021Q2	112,232	193	8.41	136,128	53	2.18	4.45 (3.22, 6.15)
2021Q3	112,959	191	8.27	142,254	40	1.58	6.03 (4.20, 8.67)
2021Q4	113,727	158	6.96	144,494	61	2.43	3.45 (2.50, 4.76)
2022Q1	116,065	180	7.48	148,653	47	1.78	4.87 (3.46, 6.86)
2022Q2	97,752	108	9.44	133,910	35	2.52	4.36 (2.90, 6.56)

*IR: Incidence Rate PY: Person-Year

CONCLUSION

- We replicated a known positive association using pre-pandemic and pandemic era data and saw **no notable differences in cohort composition and no meaningful qualitative differences in hazard ratios,** compared to the literature[1-3].
- **Stratifying analyses by calendar time** can help identify threats to validity of pharmacoepidemiologic studies when using data from the pandemic era.

[1] DOI: 10.1002/pds.3483; [2] DOI:10.1002/cpt.429; [3] DOI: 10.1002/pds.4550

LIMITATIONS

- This study was limited to a known association with a biological mechanism of action, a short risk window, and little measured confounding.
- Factors that may affect other drug-outcome associations that were not explored here include confounding or effect modification by COVID-19 infection, vaccination history, disease severity, and COVID-19 mortality as a competing risk.

ACKNOWLEDGEMENTS/DISCLOSURES

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- SA, CH, and MK are employees at HPHCI, an organization that conducts work for government and private organizations, including pharmaceutical companies.
- The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement by, FDA/HHS or the US government.