Master protocol and parallel approach to analyze angioedema in patients with heart failure identified in an integrated care delivery system compared to administrative claims

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Introduction

- Angiotensin-converting-enzyme inhibitors (ACEi) is a risk factor for angioedema, particularly in Black patients.
- Angioedema is generally a rare event. Most clinical cohorts do not have sufficient sample size to examine differences in risk across multiple racial strata.
- Master protocols for parallel analyses across multiple sites have been used to study rare and novel events.(1, 2)
- Key to such analyses is an understanding of differences across data sources and transparent reporting.

Objective

To address sample size issues, the Innovation in Medical Evidence Development and Surveillance (IMEDS) Network and Cardiovascular Research Network (CVRN) collaborated to adapt a protocol originally developed for electronic health record (EHR) data linked to administrative claims (claims) to one using claims only to assess angioedema risk in HF patients on angiotensin receptor-neprilysin inhibitor (ARNi) vs. ACEi. We describe the use of a master protocol and parallel analysis in a real-world regulatory safety study.

Methods

- The planned study is a population-based, retrospective, multicenter cohort study of adult patients with HF identified from two networks:
  1. IMEDS, a subset of the US Food and Drug Administration Sentinel System Network, using data from January 1, 2008 through September 30, 2019.
  2. CVRN, which includes patients seen at five integrated healthcare delivery systems across the US, using data from July 1, 2005 through May 30, 2019.
- Both networks provide broad representation across the U.S., including a diverse population of patients with commercial insurance coverage.
- Outcomes and exposures are identified through claims in both networks. Primary outcomes included: any (any setting) and serious (inpatient setting) angioedema.
- To adapt an integrated EHR+claims-based protocol to claims only, we:
  1. Held frequent and transparent discussions to understand the existing protocol;
  2. Made *apriori* decisions to adapt the existing protocol to the IMEDS database, aligning with existing protocol where possible;
  3. Conducted an interim analysis to describe exposure and outcome rates and compared results with those in CVRN. Select results for the Standard of Care group (ACEi) are presented here;
  4. Divergent results motivated the need to understand differences in approach and further protocol alignment in advance of the final analysis (*results pending*).

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Results

- In the interim analysis, IMEDS identified a total of 41,521 HF patients with exposure to ACE-i; and CVRN identified 14,241 patients.
- Population characteristics were similar in IMEDS and CVRN, except time to treatment initiation and duration of medication exposure (Table 1)
- Serious angioedema rates were consistently higher in the IMEDS vs. CVRN cohorts (Table 2)
- Divergent results point to different approaches:
  1. **Measurement of medication exposure.** Although both networks leveraged pharmacy dispensing data to define exposure, medication exposure was consistently longer in the CVRN. Subsequent conversations revealed that different experiences/perspectives contributed to different foci in operationalization of drug exposure – where the difficulty is in finding the balance between capturing only relevant safety events and not dismissing real events. From a safety perspective, a primary focus is on attributing acute onset events to the use of the drug. As such, allowable gaps in dispensing (accounting for days supply) tend to be short, with a focus on true safety events. In contrast, approaches that focus on the ascertainment of intentional medication cessation consider (more heavily) healthcare-seeking behavior to define drug exposure, and as such, stock-piling of medications.
  2. **Different look-back periods for HF identification** in IMEDS (365 days prior to index) and CVRN (as fare back as July 2005) yielded differences in the average time from HF identification to drug initiation (Table 1).
  3. **Measurement of angioedema.** "Any angioedema" and "serious angioedema" were operationalized by looking at the setting in which the angioedema occurred (i.e. any setting vs. inpatient, respectively). The existing protocol was silent on whether the serious angioedema outcome should be a subset of angioedema outcomes in any care setting or treated as an entirely separate analysis. As such, one group allowed these groups to be mutually exclusive and the other did not.
- **Upon review of interim results and many frank conversations:**
  1. IMEDS and CVRN **aligned on an approach for the final analysis to define medication exposure** that considered the clinical context (acute onset adverse events). We agreed to an allowable gap in medication that was data adaptive (i.e. half the days supply of the most recent dispensing), which was different than the standard approach taken in IMEDS and Sentinel, and shorter than what CVRN initially proposed.
  2. IMEDS **aligned with CVRN on the approach for the final analysis to measure angioedema**. IMEDS felt there was a reasonable clinical case to alter our standard approach to limit identification of angioedema to the first occurrence across both settings because a physician would likely discontinue medication use in the event of angioedema regardless of care setting, and thus events > 3 days after the first event would be outside the exposure window.
- **We have a better understanding that:**
  1. **Aligning code lists across groups using different source data** requires reconciliation and removal of duplicates prior to clinical review; an extra step not required in single-center studies.
  2. **Prior experience and resources drive an approach.** IMEDS' current focus on safety outcomes and use of Sentinel modular programs impacted our operationalization of medication exposure and angioedema occurrence. Sentinel tools tend to focus on safety endpoints and thus define medication exposure conservatively by dispensing data, with minor allowance for variable utilization factors. Sentinel tools are created to treat occurrence of events in different settings as different analyses. Only after further conversation, did we understand clinical implications that would inform the need to censor after the first event.
  3. **Potential changes to protocols that have been approved by the regulator** forces prioritization of factors strongly associated with potential bias and outcome identification; whereas deviations in definitions for secondary covariates motivated little desire for change. The impact of these decisions will be described and explored in future analyses.

Table 1. Selected characteristics for patients with heart failure on ACEi.

	IMEDS			CVRN		
	Total patients N=41,521	*Black* patients N=8.426	*Non-black* patients N=33,095	Total patients N=14,241	*Black* patients N=2,105	*Non-black* patients N=12,136
Days from HF identification to ACEi initiation, *mean (std dev)*	158.6 (124.7)	172.4 (124.6)	155.1 (124.5)	499.63 (888.61)	507.60 (935.50)	498.25 (880.25)
Female, *n (%)*	20,077 (48.4)	4,537 (53.8)	15,540 (47.0)	6,156 (43.2)	981 (46.6)	5,175 (42.6)
Age (years) at ACEi initiation, *mean (std dev)*	74.1 (11.2)	70.7 (11.9)	74.9 (10.8)	70.35 (14.29)	65.13 (14.81)	71.25 (14.01)
Mean number of pharmacy fills (std dev), *fills*	3.0 (2.9)	2.6 (2.6)	3.0 (3.0)	3.08 (2.22)	2.95 (2.14)	3.10 (2.23)
Duration of ACEi exposure (days), *mean (std dev)*	142.0 (120.4)	126.9 (112.3)	145.9 (122.1)	202.88 (134.87)	191.65 (135.04)	204.83 (134.75)
HF hospitalizations (in the year before initiation), *n* (%)						
0	30,394 (73.2)	6,087 (72.2)	24,307 (73.4)	9,949 (69.9)	1,466 (69.6)	8,483 (69.9)
1	9,275 (22.3)	1,823 (21.6)	7,452 (22.5)	3,785 (26.6)	525 (24.9)	3,260 (26.9)
2+	1,852 (4.5)	516 (6.1)	1,336 (4.0)	507 (3.6)	114 (5.4)	393 (3.2)

Table 2. Incidence of serious and any angioedema in patients taking ACEi.

	IMEDS		*CVRN*	
Angioedema type	**Race (N)**	**IR (95% CI) per 1,000 PYs**	**Race (N)**	**IR (95% CI) per 1,000 PYs**
Serious	Total (41,521)	2.04 (1.41-2.87)	Total (14,241)	0.76 (0.28-1.65)
Serious	Black (8,426)	6.48 (3.90-10.12)	Black (2,105)	1.81 (0.22-6.54)
Serious	Non-Black (33,095)	1.06 (0.58-1.78)	Non-Black (12,136)	0.59 (0.16-1.50)
Any	Total (41,521)	6.88 (5.66-8.28)	Total (14,241)	5.44 (3.93-7.32)
Any	Black (8,426)	21.53 (16.54-27.54)	Black (2,105)	19.01 (11.77-29.06)
Any	Non-Black (33,095)	3.63 (2.68-4.81)	Non-Black (12,136)	3.23 (2.03-4.89)

Discussion

- Given similarities in the base population, we did not expect important differences in exposure or outcomes in the IMEDS vs. CVRN population.
- Divergent results motivated further examination, discussion and alignment of the protocol for future analyses.
- Multi-center studies that adopt a parallel approach to analysis require:
  1. *A detailed review of protocol and SAP (whether existing or if being developed in collaboration) to ensure understanding and alignment.*
  2. *Sufficient details about programming and data specifications should be included in the Protocol/SAP and follow FAIR (Findable, Accessible, Interoperable, Reusable) principles.(3)*
  3. *Programming specifications are key to reduced ambiguity and should be developed as early as possible in the study process.*
- Challenges were resolved through:
  1. *Close and transparent communications;*
  2. *A willingness of collaborators to act on good faith and to keep the specific clinical context and scientific question top of mind;*
  3. *Respect and appreciation of different perspectives, data provenance, data and resource constraints, and flexibility;*
  4. *Review of interim analysis to understand impact of divergent approaches; and*
  5. *The ability to agree to disagree.*

References

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