Modeling Decisions and Heterogeneity in Defining Aortic Diseases: Implications for Observational Studies and Phenotype Characterization

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Background

The term 'Aortic diseases' has been used to collectively refer to non-ruptured aortic aneurysm (AA), aortic aneurysm rupture (AR), and aortic dissection (AD), among other pathologies that affect the aorta (1,2). In the case of degenerative causes, aortic disease pathogenesis results from a loss of elasticity of the aortic wall. This may result from normal aging, and can be exacerbated by genetic or acquired risk factors that predispose to the destruction of elastin and collagen (3). In the case of AA this results in full thickness dilation of the abdominal or thoracic aorta (with a defined cut off being >150% of the original diameter, in addition to other anatomy specific criteria). AA are at risk for subsequent rupture (i.e. AR), an event with prehospital mortality rates upwards of 85%, and only 50-70% survival in patients that do survive to hospitalization (4). AD can occur with or without an aneurysm (5), and refers to the separation of aortic wall layers, with or without communication between them (6). AD also carries high mortality rates, estimated at 40% at presentation, 50% without surgical intervention, and 5-35% perioperatively (5).

Aortic diseases have become the subject of considerable contemporary study in observational data assets. Renewed focus has been brought to these entities in view of their possible association to fluoroquinolone (FQ) use (7–11) which have been associated to other collagen related side effects (11). In this study, which is a prelude to a larger and ongoing characterization effort, we examine the different modelling decisions that have been implemented in observational studies that examine fluroquinolone exposure and vascular aneurysm outcomes, and consider the potential impact of these decisions on cohort size and sensitivity.

Methods

We undertook a review of existing phenotype definitions in observational studies examining fluoroquinolone exposure and Aortic diseases, as shown in Table 1.

	Disease	Hospitalization Required?	Primary position?	Clean window?	Definition	Database	Other
Son et al. (8)	AA, AR, AD	No	NA	365d	ICD10 I71.0-I71.9	NHIS, (Korea)	Age> 40; image codes in sensitivity analysis
Gopalakrishnan et al. (9)	AA, AR, AD	Yes	Yes	All time	ICD9 441 441.(0-7,9) 441.0(0-3)	IBM MarketScan (US)	Age >50
Newton et al. (10)	AA, AD, Iliac aneurysm, Other	No	NA	180d	ICD9, ICD10 (see reference)	IBM MarketScan (US)	Age 18-64
Pasternak et al. (11)	AA, AR, AD	Yes	Yes	All time	ICD10 I71.0-I71.9	Swedish registry (Sweden)	Age > 50
Dong et al. (12)	AA, AR, AD	Yes	No	All time	ICD-9 441.(0-7,9)	Taiwan NHIRD	Age ≥20
Lee et al. (1)	AA, AR, AD	Yes	No	All time	ICD9 441.(1-7,9) 441.0(0-3) AND imaging	Taiwan NHIRD	Age ≥ 18
Daneman et al. (13)	AA, AR, AD	Yes	Yes	365d	ICD9 441, ICD10 I710-I719, ICD9 441.(0-5), ICD10 I710-11,13, 15, 18)	Ontario Registered Persons Database (Canada)	Age ≥ 65
Lee et al. (14)	AA, AR, AD	Yes	No	All time	ICD-9CM 441.1-441.7, 441.9 or 441.0, 441.00-441.03) plus imaging	Taiwan Longitudinal Health Insurance Database	All patients

Table 1. Characteristics of prior outcome definitions used in observational studies examining the impact of fluoroquinolones on the incidence of aortic disease (and arterial aneurysms at other sites). NHIRD - National Health Insurance Research Database

Table 1 illustrates some of the identified heterogeneity in previous modelling decisions for vascular aneurysm related disease outcomes. Among others, these include differences in disease site, requirement of hospitalization, length of any 'clean' window prior to index, terminology and codes used, and the requirement that a diagnosis code be in 'primary' position. This latter requirement can serve to limit the generalizability of a definition depending on the provenance of the data and interpretation of the 'primary' position, which can vary in claims-based health records in different jurisdictions.

Cohorts that implemented some of these assumptions were then created in a public version of ATLAS (https://atlas-demo.ohdsi.org/#/home), and executed in 6 databases in CohortDiagnostics (https://ohdsi.github.io/CohortDiagnostics/). Three databases that included inpatient records are reported here: Japan Medical Data Center (JDMC), IBM Health MarketScan Commercial Claims and Encounters Database (CCAE), and Optum EHR. To aid in the interpretation of population level results for the composite outcome, we examined AA, AR, and AD separately. Cohort definitions, database related metadata (including descriptions), and results are publicly available through a CohortDiagnostics R shiny application at (https://data.ohdsi.org/SosChallengePhenotypes_Aos/).

Results

For illustrative purposes, we examine the impact of requiring a code in primary position with regards to its impact on cohort size and sensitivity error. The impact of requiring a code in the primary position on cohort size is shown in table 2.

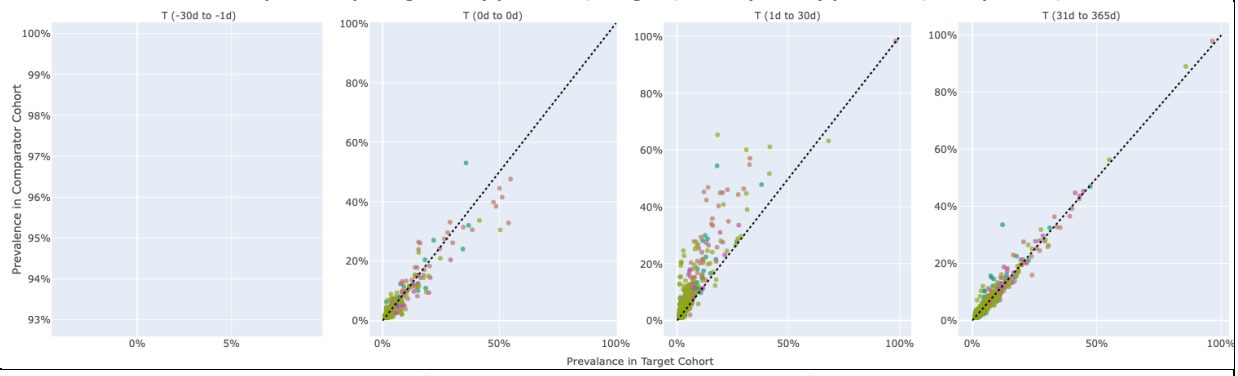
Cohort Id	Cohort Name	Cohort Size (number of people)		
		JDMC	Optum EHR	CCAE
1782546	[SOS AA] Aortic aneurysm inpatient – non-ruptured – no prior AA or AD (365)	1301	197018	67196
1782548	[SOS AA] Aortic aneurysm inpatient primary – non-ruptured – no prior AA or AD	382	36565	3957
1782633	[SOS Aar] AA rupture events inpatient - no prior AA AD or Aar	188	7560	3903
1782634	[SOS Aar] AA rupture events inpatient primary – no prior AA AD or Aar	125	5238	1140
1782655	[SOS AD] AD events inpatient – no prior AA or AD	3197	25263	17110
1782654	[SOS AD] AD events inpatient primary – no prior AA or AD	2545	14551	5773
Relative cohort size when primary position required (%)				
	Aortic Aneurysm (non-ruptured)	29%	19%	6%
	Aortic rupture	66%	69%	29%
	Aortic dissection	80%	58%	34%

Table 2. Impact of requiring a code in primary position on cohort sizes in AA (non-ruptured), AR, and AD across 3 databases with inpatient records. Cohort IDs correspond to those in the Cohort Diagnostics application and public Atlas instance. Cohort sizes are reported under the column for each database.

Table 2 illustrates that requiring a code in primary position instills a cost with regards to cohort size across each of AA, AR, and AD, in three data sources with inpatient records. The attrition is largest in the case of AA, where the cohort size is reduced to 6% of the base case (code in any position) in CCAE, to 29% (JDMC). Using this definition would result in estimates of AA incidence that are on the order of 10% of published values in comparable populations (15).

Cohort characterization results in CohortDiagnostics reveal that the epsiodes of care of patients who are in the 'primary position' cohort are enriched in concepts relating to provision of operating room, anesthesia, and critical care services in the 1-30 day post index, when compared to the 'non primary' cohort. This can be seen graphically in figure 1. These results indicate that the 'primary position' cohort is likely selecting a subset of AA cases that are undergoing surgery for AA, as opposed to all incident AA. In a pharmacovigilance context, it's the latter that is the outcome cohort of interest.

A. **Covariate plot comparing AA any position ("Target") to AA primary position ("Comparator) in CCAE**



B. Top covariate standardized differences (AA primary position – AA any position)

Covariate Name (abridged)	Concept ID	Standardized difference
Arterial catheterization or cannulation for sampling, monitoring, or transfusion	2108261	0.77
Abdominal Aortic Aneurysm	198177	0.58
Medical/surgical supplies and devices - other implants	38003162	0.56
Operating room services - general classification	38003208	0.54
Anesthesia - general classification	38003213	0.48

Figure 1. A. Covariate plot comparing AA any position, (id 1782546, "Target", x axis) and AA primary position (id 1782548, "comparator", y axis). The AA primary position cohort is enriched in many concepts that pertain to surgical care of AA cases. **B.** Top 5 covariate differences between AA primary position, and AA any position, as ranked by standardized mean difference.

Conclusion

We highlight the different modeling decisions that have been applied to aortic diseases in observational effect estimation studies that examined fluoroquinolone exposure. The heterogeneity in previous outcome definitions, such as differences in disease site, hospitalization requirement, clean window length, and the use of primary position codes, may impact the generalizability of findings. In particular, when applied in a federated network of databases, requiring a code in the primary position has a significant impact on the resultant cohort size, and may lead to underestimation of disease incidence. Furthermore, in the case of AA, the use of

primary position codes appears to enrich the cohort with a subset of cases that involve surgical care. These results do not disqualify studies that have used primary position codes, but illustrate that such approaches may not be extend to a federated network study. Population level validation with tools like CohortDiagnostics can surface the implications of modeling decisions, and should be a prelude to effect estimation or prediction studies.

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