Diagnosis-based cohort augmentation using laboratory (lab) data in the FDA Sentinel Initiative: The case of chronic kidney disease (CKD)

David H Smith

Kaiser Permanente Northwest

Center for Health Research

Co-Investigators

- Susan Shetterly
- James Flory
- Joshua Gagne
- Kevin Haynes
- Lisa J Herrinton
- Carsie Nyirenda
- Christine Lu
- Elisabetta Patorno
- Marsha Raebel

Chronic Kidney Disease (CKD)

- Important health **outcome** of interest for drug safety studies
  - Examples include
    - Non-steroidal anti-inflammatory drugs (NSAIDS)

- Important **population** for drug safety studies
  - Examples include
    - Angiotensin converting enzyme inhibitors (ACEI)

Identification of CKD in database studies

- Diagnosis based
  - ICD9 (e.g. 585)
  - ICD10 (e.g. N18)
- Laboratory findings
  - Estimated glomerular filtration rate (eGFR)
    - Serum creatinine based and also includes age, sex, race
    - CKD-EPI equation
  - To qualify as 'Chronic' the National Kidney Foundation guidelines require 2 eGFR <60 ml/min/1.73m^2
  - Many studies use a single low eGFR

Study Context

- Incorporating laboratory findings into drug safety databases

- Objective:
  - To assess how augmenting a diagnosis-based CKD cohort with patients identified through lab results impacts cohort characteristics and outcomes.

- Data Source
  - FDA's Sentinel Distributed Database

Study Design

- Setting: Two Sentinel Data Partners with diagnosis and laboratory data
  - Kaiser Permanente Colorado and Kaiser Permanente Northern California
- Cohort Study
  - During 2012, look for first "indication" of CKD
    - ICD9 code for CKD
    - eGFR <60 ml/min/1.73m^2
  - Required 365 days of KP membership prior to first indication of CKD for collection of baseline characteristics

Study Groups

- First CKD indication in 2012 (diagnosis or eGFR<60)
- Look back 365 days (including index date) and assign mutually exclusive groups hierarchically
- 1st: DxGroup
  - N=107,607 (97% also had serum creatinine)
- 2nd: 2-LabGroup (2 or more eGFR <60)
  - N=33,542
- 3rd: 1-LabGroup (1 eGFR <60)
  - N=87,678

Statistical Analyses

- Compare pairwise standardized differences across cohorts
  - Standardized differences >0.2
- Cox regression
  - 1 year follow-up mortality = f(CKD_group, baseline characteristics)
  - P<0.05

Characteristics compared

- Age, sex, race, stage of CKD
- Comorbidity score (Gagne modification of Charlson and Elixhauser)
- Comorbidities:
  - alcohol abuse, anemia, arrhythmia, coagulation disorder, heart failure, diabetes, dementia, fluid/electrolyte disorders, HIV/AIDS, hypertension, hemiplegia, liver disease, cancer mets, psychosis, pulmonary disease, pulmonary circulation disorder, peripheral vascular disease, tumor, weight loss, myocardial infarction/stroke
- Health care utilization
  - Ambulatory visits, emergency department visits, hospital stays, institutional stays

Characteristics with Std Differences >0.2

Characteristic	DxGroup	2-LabGroup	1-LabGroup	Std Diff Dx v 2-Lab	Std Diff Dx v 1-lab
Age (years)	72.6	74.4	69.2	0.18	0.30
<65 (%)	19.4	16.7	23.9		
65-74	31.3	29.3	31.4		
75-89	49.3	54.0	44.7		
Black (%)	9.6	4.6	5.7	0.23	0.17
Stage 4 CKD (%)	10	1.8	1.7	0.38	0.39
Heart failure (%)	17.1	11.4	8.6	0.16	0.26
Diabetes* (%)	40.8	17.4	11.2	0.53	0.72
Diabetes (%)	45.6	32.1	23.1	0.28	0.49
Hypertension (%)	84.4	78.8	64.4	0.15	0.47
**complicated diabetes*					

Are there mortality differences between the CKD groups?

- Cox regression findings, adjusted for age only

Group	HR	95% CI
DxGroup	reference	
1-LabGroup	0.61	(0.59, 0.65)
2-LabGroup	0.51	(0.48, 0.55)

- Cox regression findings, fully adjusted

Group	HR	95% CI
DxGroup	reference	
1-LabGroup	0.99	(0.95, 1.06)
2-LabGroup	0.84	(0.78, 0.90)

Conclusion

- Augmenting a diagnosis-based CKD cohort with laboratory data more than doubled the population
- Our cohort with diagnosis based-CKD had a greater comorbidity load and more black patients
- Many of the 'excess' comorbidities were physiologically related to CKD
  - Stage of CKD, heart failure, diabetes and hypertension
- After adjustment, 1 year mortality was greater for the DxGroup

Conclusion

- When augmenting a diagnosis based cohort with laboratory identification, investigators should consider subgroup or stratified analysis
- Next steps:
  - Explore by-site interactions