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Does Pharmaceutical Prescribing Responds to Information Shock?

Impact of Rofecoxib Withdrawal on COX-2 Inhibitors
Utilization among Rheumatoid Arthritis and
Osteoarthritis Patients

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Outlines

- Study Motivation/Background
- Objectives
- Data
- Statistical Methods
- Results
- Conclusions

Study Motivation

- Merck & Co.'s voluntary worldwide withdrawal of rofecoxib (Vioxx®, COX-2 inhibitor) on 2004/9/30
 - COX-2 inhibitor
 - New nonsteroidal anti-inflammatory drugs (NSAIDs)
 - = Selective NSAIDs (vs. nonselective NSAIDs)
 - Clinical use
 - Relief of pain/inflammation
 - Counter GI complications in nonselective NSAIDs (15%)
 - Updated drug safety information (information shock)
 - APPROVe trial (rofecoxib vs. placebo)
 - after 18 months of rofecoxib use
 - 3-fold risk (RR 2.80; 95%CI 1.44-5.45) of cardiovascular events
 - Huge market impact due to information shock?
 - Annual sales : > 2.5 billion US dollars
 - Over 80 million users

Background

Impact of information on pharmaceutical market

- Information
 - Information → demand for pharmaceutical → pharmaceutical market
 - Information and drug use
 - Patients
 - Direct-to-consumer advertising (*Spence et al, 2005*)
 - Physicians (Perceived efficacy and safety of drugs)
 - Scientific journal papers (*Azoulay, 2002*)
 - Preference/royalty to specific products (*Schneeweiss et al, 2005*)
 - Colleagues/peers (*Coumon et al, 2006*)
 - Information shock (drug safety signals)?
 - Raise uncertainty on demand for pharmaceutical
 - How patients and physicians respond to the uncertainty?
 - The market impact of information shock?

Objective

- **To investigate how information shock affect the demand for pharmaceutical?**
 - Event study: the withdrawal of rofecoxib (2004/09/30)
 - Changes of COX-2 inhibitor use in RA or OA patients after rofecoxib was withdrawn from the market
 - We specifically estimated the market impact from changes:
 - in behavior of the patient
 - in behavior (prescribing pattern) of the physician

Study Design

- Outcome
 - Volume of COX-2 inhibitor in 1st post-withdrawal RA/OA visit for each patient
 - Two stage modeling strategies
 - (1)
 - Model 1 (patient); $(Continuity_{pt}) = \alpha + \beta x + \varepsilon$
 - Model 2 (physician); $(PerceivedRisk_{py}) = \alpha + \beta x + \varepsilon$
 - (2)
 - Model 3; (patient-physician pair)
 - $(Vol_{cox2,pt}) = \beta_1 E(Continuity_{pt}) + \beta_2 E(PerceivedRisk_{py}) + \beta_3 x + \varepsilon$

Assumptions

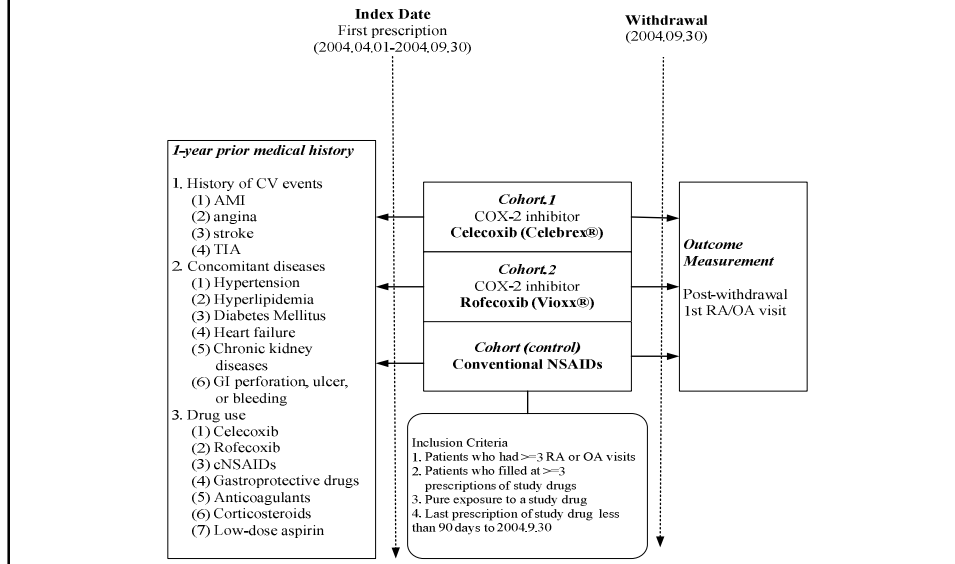
- Post-withdrawal COX-2 inhibitor utilization patterns
 - Stop use of COX-2 inhibitor
 - Shift to COX-2 inhibitor which is still available on the market
 - Celecoxib (Taiwan's NHI)

Data Source

- Our data were consisted of two parts:
 - Patient
 - 2002-2004 NHI outpatient and inpatient visit records
 - 2002-2004 NHI registry for beneficiaries
 - Physician
 - 2003-2004 NHI outpatient and inpatient visit records
 - 2003-2004 NHI hospital contract database

Two-Stage Modeling Strategy

Stage I model-patient (model 1): study subject



Two-Stage Modeling Strategy

Stage I model-patient (model 1)

■ Logistic regression:

$$\log\left(\frac{V_{raoa} = 1}{V_{raoa} = 0}\right) = \alpha + \beta C_{Pt} + \varepsilon$$

□ Dependent variable (Continuity):

- First post-withdrawal RA/OA ambulatory visit (Y=1, N=0)

□ Covariates (C_{pt}):

- Patient's characteristics
 - Demographics (gender and age) at the index date
 - 1-year prior medical history
 - CV events, gastrointestinal events and other concomitant diseases
 - 1-year prior drug use history

Results

Patients' characteristics at index date (model 1)

Table 4.1: Patient characteristics at index date (model 1)

	celecoxib n(%)	rofecoxib n(%)	cNSAIDs n(%)	P-value
	13101(100)	8763(100)	46340(100)	
Age (mean [SD])	67.41 [13.15]	68.61 [12.28]	64.02 [14.00]	<0.0001***
Women(n(%))	8949(68.31)	5983(68.28)	27890(60.19)	<0.0001***
Treatment duration (mean[SD])	122.86[54.18]	118.20[51.96]	94.97[63.04]	<0.0001***
Diagnoses in preceding year (n(%))				
Rheumatoid arthritis	3776(28.82)	1804(20.59)	5206(11.23)	<0.0001***
Osteoarthritis	7288(55.63)	5441(62.09)	23391(50.48)	<0.0001***
Any cardiovascular events	2415(18.43)	1811(20.67)	7379(15.92)	<0.0001***
Myocardial infarction	173(1.32)	131(1.49)	620(1.34)	0.489
Angina	2128(16.24)	1572(17.94)	6439(13.90)	<0.0001***
Stroke	111(0.85)	77(0.88)	287(0.62)	0.003**
Transient ischemic attack	227(1.73)	185(2.11)	688(1.48)	<0.0001***
GI events	3116(23.78)	2257(25.76)	8742(18.66)	<0.0001***
Hypertension	6113(46.66)	4286(48.91)	20439(44.11)	<0.0001***
Heart failure	533(4.07)	374(4.27)	1431(3.09)	<0.0001***
Diabetes mellitus	2263(17.27)	1565(17.86)	7627(16.46)	<0.0001***
Chronic kidney disease	586(4.47)	429(4.90)	1469(3.17)	<0.0001***
Drug use in preceding year (n(%))				
Celecoxib	8389(64.03)	2161(24.66)	4893(10.56)	<0.0001***
Rofecoxib	2180(16.64)	5421(61.86)	3680(7.94)	<0.0001***
Conventional NSAIDs	12397(94.63)	7655(87.36)	40084(86.50)	<0.0001***
Gastroprotective drugs	3938(30.06)	2868(32.73)	11776(25.41)	<0.0001***
Anticoagulants	168(1.28)	129(1.47)	348(0.75)	<0.0001***
Corticosteroids	5131(39.16)	3006(34.30)	11301(24.39)	<0.0001***
Low-dose aspirin	2825(21.56)	1911(21.81)	7827(16.89)	<0.0001***

*, p<0.05, **, p<0.01, ***, p<0.001

Results

Model 1 (logistic regression)

- **Study population**
 - 13,101 celecoxib and 8,763 rofecoxib / (control: 46,340 cNSAID)
- **Probability of patients' continuity to his/her RA or OA visits**
 - Celecoxib cohort (ref: cNSAID): OR 1.15[1.09-1.22]
 - Rofecoxib cohort (ref: cNSAID): OR 1.11[1.04-1.18]
 - Experience in use of study drugs
 - High use (ref: low use): OR 2.76[2.62-2.91]
 - Treatment duration: OR 1.01[1.01- 1.01]
 - Patient characteristics (all significant)
 - Age; Women
 - Prior medical history
 - RA; OA; GI event; hypertension
 - Prior drug use
 - Celecoxib; rofecoxib; corticosteroids

Two-Stage Modeling Strategy

Stage I model-physician (model 2) : study subject

- Study subjects
 - Physicians who ever have prescribed COX-2 inhibitors for RA or OA in their outpatient services in the preceding month of rofecoxib's withdrawal
 - Main practicing hospital: $\geq 50\%$ of a physician's patient visits were allocated
- Data collected
 - Each physician's monthly prescriptions during September (t=1) to December (t=4), 2004

Two-Stage Modeling Strategy

Stage I model-physician (model 2)

■ GLM (generalized liner model) regression; AR(1)

$$(PerceivedCVrisk)_{p,t} = \alpha + \beta_1 Pr_{cox2,p,t1} + \beta_2 V_{cox2,p,t1} + \beta_3 P_{mix,p,t1} + \beta_4 P_p + \beta_5 Time + \varepsilon$$

- Dependent variable
 - Physician's perceived CV risk of COX-2 inhibitor (t1-4)

$$(PerceivedCVrisk)_{p,t} = 1 - \left(\frac{P_{t_{cv}, COX2inhibitor}}{P_{t_{cv}}} \right)$$

- Covariates
 - Pr_{COX2} : Preference of COX-2 inhibitor, t1(baseline)
 - V_{COX2} : Volume of COX-2 inhibitor, t1(baseline)
 - P_{mix} : Pt mix, t1(baseline)
 - P : Physician characteristics
 - Time

Results

Model 2 (generalized liner regression model ; AR(1))

- **Study subjects**
 - 7,186 physicians
- **Perceived CV risk of COX-2 inhibitor**
 - Time (estimate [SD], **0.013280**[0.001676], p<0.0001)
 - Baseline
 - Perceived CV risk of COX-2 inhibitors
 - (estimate [SD], **0.260600** [0.008212], p<0.0001)
 - Peer effect
 - (estimate [SD], **0.168400** [0.019120], p<0.0001)
 - Patient mix
 - CV events (%): (estimate [SD], **-0.002350** [0.000119], p<0.0001)
 - GI events (%): (estimate [SD], **-0.000650** [0.000105], p<0.0001)
 - Hospital accreditation
 - NS

Two-Stage Modeling Strategy

Stage II model (model 3)

■ Linear regression

$$Vol_{cox2,pt} = \alpha + \beta_1 \widehat{continuity}_{pt} + \beta_2 (\widehat{PerceivedCVrisk})_p + \beta_3 Ecox2_{pt,t1} + \beta_4 C_{pt} + \varepsilon$$

- **Dependent variable: Vol_{cox2,pt}**
 - Volume of COX-2 inhibitor in 1st post-withdrawal RA/OA visit

$$Vol_{cox2,pt} = \frac{Vol_{cox2}(DDDs)}{TD(days)}$$

- **Covariates**
 - E (Continuity, pt): estimator (model 1)
 - E (PerceivedCV risk, p): estimator (model 2)
 - Ecox2: previous experience of COX-2 inhibitor, t1
 - C_{pt}: Patient characteristics

Results

Proportion of users and utilization (volume; DDDs) of COX-2 inhibitor 3 months before/after rofecoxib withdrawal

celecoxib -> celecoxib							
Category	Baseline			Post-withdrawal period			difference
	n(%)	Daily volume	Total volume	n(%)	Daily volume	Total volume	
All	13101(100.0)	1.09	356137	6748(51.5)	1.12	196113	(+2.7%;-44.9%)
Low use w/o CV risk	5966(100.0)	1.07	145055	2011(33.7)	1.10	51272	(+2.8%;-64.7%)
Low use w/ CV risk	1576(100.0)	1.02	37134	483(30.6)	1.05	11831	(+2.8%;-68.1%)
High use w/o CV risk	4720(100.0)	1.13	148981	3678(77.9)	1.15	116170	(+1.8%;-22.0%)
High use w/ CV risk	839(100.0)	1.06	24966	576(68.7)	1.07	16839	(+0.9%;-68.1%)

rofecoxib -> celecoxib							
Category	Baseline			Post-withdrawal period			difference
	n(%)	Daily volume	Total volume	n(%)	Daily volume	Total volume	
All	8763(100.0)	1.01	223326	2410(27.5)	0.98	60029	(-3.0%;-73.1%)
Low use w/o CV risk	4407(100.0)	1.01	104737	852(19.3)	0.97	19658	(-4.0%;-81.2%)
Low use w/ CV risk	1225(100.0)	1.01	29475	213(17.4)	0.95	4592	(-5.9%;-84.4%)
High use w/o CV risk	2545(100.0)	1.02	72982	1134(44.5)	0.99	30469	(-2.9%;-58.3%)
High use w/ CV risk	586(100.0)	0.98	16132	211(36.0)	0.93	5310	(-5.1%;-67.1%)

- A direct impact of information shock on use of COX-2 inhibitors
 - ↓49.5% celecoxib users ,↓72.5% rofecoxib users
 - Patient with a CV history would more likely decrease their utilization
- The withdrawal gave a clear signal of drug safety to the use of COX-2 inhibitors (*Thiebaud et al, 2006*)

Results

Model 3 (liner regression model)

- Study subjects
 - 18,276 patients (patient-physician pairs)
- Volume of COX-2 inhibitor in 1st post-withdrawal RA/OA visit (DDDs/day)
 - Adjusted patient's continuity to RA/OA treatment
 - NS
 - Adjusted physician's perceived CV risk of COX-2 inhibitor
 - (estimate [SD], -0.469000 [0.018640], p<0.0001)
 - Rofecoxib (ref: celecoxib)
 - (estimate [SD], -0.259680 [0.008180], p<0.0001)
 - High use
 - (estimate [SD], 0.221450 [0.044420], p<0.0001)
 - Patient characteristics (history of any CV event)
 - (estimate [SD], -0.027860 [0.010160], p=0.0061)

Limitations

- Limited data
 - 3 months post-withdrawal period (Oct-Dec, 2004)
- Control group in model 1: any conventional NSAIDs
 - All nonselective NSAIDs will be assumed to have equal clinical effects
- Underestimate rates of previous adverse GI events and CV events in our study subjects
 - 1 year before the index date
- Physician behavior in his/her main practicing settings only
 - One physician may practice in many settings and have different prescribing patterns in different settings.

Discussion and Conclusion

- Physicians respond more than patients to the uncertainty due to information shock of rofecoxib's withdrawal.
 - Physician characteristics could be more important than patient characteristics in determining prescribing COX-2 inhibitors (*Solomon et al, 2003; Schneeweiss et al, 2005*)
 - **Physician would implement scientific information regarding safety profile of drugs into their daily practice**
- The information shock has a diffused impact to other COX-2 inhibitor as well.
 - Rofecoxib->celecoxib

Thank you for your attention
