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Exogenous estrogen does not attenuate the association between rofecoxib and myocardial infarction in perimenopausal women

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Abstract

Rofecoxib has been proposed to increase the risk of myocardial infarction (MI) through suppression of cyclooxygenase (COX)-2 mediated prostacyclin. Estrogen may have protective effects through augmenting COX-2 expression and subsequently increasing prostacyclin. Estrogen may attenuate the association between rofecoxib and MI. We used 1999–2002 Medicaid claims data to measure the MI-hazard ratio (HR) attributed to rofecoxib exposure in estrogen exposed and unexposed 45–65 year old women. We identified 184,169 female rofecoxib users who contributed 309,504 person-years and experienced 1217 first MIs. Estrogen exposure appeared protective (MI-HR 0.72, 95% CI 0.62–0.84) in this cohort. Rofecoxib was associated with an elevated MI-HR in both estrogen exposed (2.01, 95% CI 1.60–2.54) and estrogen unexposed women (1.69, 95% CI 1.43–1.99). The rofecoxib-estrogen interaction ratio was not significantly different from 1 (1.19, 95% CI 0.91–1.57). Although estrogen use was associated with a lower risk of MI, it did not appear to attenuate the association between rofecoxib and MI.

Keywords

myocardial infarction; hormone replacement therapy; pharmacoepidemiology; cyclooxygenase inhibitor

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) selective for cyclooxygenase (COX)-2 increase the risk of myocardial infarction (MI) by reducing the synthesis of prostacyclin in the vasculature.^{1–8} Evidence from cell biology, rodent models and clinical trials suggests that COX-2 dependent prostacyclin acts to restrain factors that promote thrombosis, atherogenesis and hypertension.^{6, 8, 9} Estrogen increases prostacyclin formation and reduces atherosclerosis in LDL-receptor deficient mice.¹⁰ Thus, estrogen is thought to augment vascular prostacyclin biosynthesis through an estrogen receptor alpha mediated increase in COX-2 gene expression. Although hormone replacement therapy, specifically conjugated equine estrogen $\pm$ medroxyprogesterone, in older, menopausal women was not protective against cardiovascular disease in the Women's Health Initiative study it may be protective in younger perimenopausal women less than ten years remote from menopause.^{11–15}

The potential cardio protective effects of estrogen and increased cardiovascular risk of COX-2 selective NSAIDs are thought to involve molecules within the same signaling cascade. Therefore, we evaluated the hypothesis that exposure to exogenous estrogen in peri- and post-menopausal 45–65 year old women may attenuate the association between rofecoxib – a COX-2 selective NSAID that was withdrawn from the market because of its cardiovascular complications - and MI. The outcome of interest was the rofecoxib-estrogen interaction ratio, defined as the rofecoxib-MI hazard ratio in estrogen exposed women divided by the rofecoxib-MI hazard ratio in estrogen unexposed women.

METHODS

Cohort study design and subject selection

We performed an observational cohort study of 45–65 year old rofecoxib users identified within administrative claims data from nearly 30 million people from the Medicaid programs of California, Florida, New York, Ohio and Pennsylvania between January 1999 and November 2002. Rofecoxib and estrogen use was common during these years. Medicare data were obtained in persons eligible for both programs to ensure complete capture of outcomes. These data have been previously described and are of high quality.^{16–18} Medicaid is a state run program providing hospital, medical, and outpatient pharmaceutical coverage for certain categories of low income and special-needs individuals. The data were obtained from the Center for Medicare and Medicaid Services.¹⁹ This study was approved by the University of Pennsylvania Institutional Review Board, which granted a waiver of informed consent and authorization under the Privacy Rule of the Health Insurance Portability and Accountability Act.

We limited this study to 45–65 year old rofecoxib users and used their prior, unexposed time to study the association between rofecoxib and incident MI in estrogen exposed and unexposed women (Figure 1). Several important design issues were relevant to this study. Claims data do not report the timing of menopause. This age group was selected to represent the likely perimenopausal period when hormone replacement therapy is common and may have a detectable beneficial cardiovascular effect. The same individuals contributed both their rofecoxib unexposed and rofecoxib exposed time to avoid studying a rofecoxib unexposed comparison group. We hypothesized that women who take rofecoxib may have different medical problems and/or lifestyles than women who never took rofecoxib. We limited the impact of many potential confounders that were not available in the claims data, including smoking status, family history, lifestyle, and body-mass index, by not having a separate unexposed comparison group and by having a short study duration over which we assumed these factors to remain relatively constant. We recognized that the pre-rofecoxib observation period constituted “immortal time”²⁰ since by design all women had to survive

to receive a rofecoxib prescription. The impact of immortal time is likely minimal because the death rate was low in this relatively young population, all subjects contributed immortal time, and any potential impact of immortal time would be likely present in both estrogen exposed and unexposed women. In the final outcome of interest, the rofecoxib-estrogen interaction ratio, any effect of immortal time would cancel out as long as there were no differences between the estrogen exposure groups.

Pre-observation covariate selection and eligibility window—Each person was required to have at least 90 days of continuous Medicaid eligibility data prior to their first rofecoxib prescription. This eligibility window was used to evaluate subjects' medical history using medication prescription claims records (National Drug Codes (NDC)) and medical diagnosis codes (ICD-9) from inpatient and outpatient visits for common conditions possibly associated with MI. People with a history of MI (defined by ICD-9 code 410.X) during or prior to this eligibility screen were excluded. Given the co-linear relationship between prescription drug claims and medical diagnoses, we defined six diagnosis categories based on either medical history or prescription claims: hypertension, diabetes, lipid disorders, vascular disease (including cerebral vascular disease, angina, and coronary atherosclerosis), heart failure, and rheumatoid arthritis. These six categories were used to adjust for baseline cardiovascular risk factors in Cox-regression. Code lists are available from the authors.

Pre-rofecoxib cohort observation window—After the eligibility observation window, subjects entered the cohort, contributing pre-rofecoxib observation time. This unexposed observation time ended with the start of a subjects' first rofecoxib prescription.

Rofecoxib-exposed cohort observation window—Rofecoxib exposure status was determined using prescription claims. If the "days' supply" field was missing, the quantity of pills was used to impute days supply assuming one per day. Subsequent prescriptions were considered to provide continuous rofecoxib exposure as long as the gap between prescription end and subsequent fill date was less than 30 days. Most (67%) subjects had consecutive rofecoxib prescriptions with no gaps between prescription end date and fill date. Among those with a gap between consecutive rofecoxib prescriptions, 96% had a gap of less than 11 days and 99% had a gap of less than 16 days.

Estrogen Exposure Status

Estrogen exposure status was determined using prescription claims data and NDCs for estrogen or estrogen/progesterone combination medications typically used for either hormone replacement therapy or oral contraception. Progestin-only medications and topical estrogen vaginal cream products were excluded. Estrogen patch formulations were included. Days' supply was determined by the "days' supply" data field or imputed from the quantity of pills dispensed. Thirty day supply was imputed for formulations dispensed as one month supply such as a patch or monthly packets. For the primary analysis, women having at least one estrogen prescription in either the pre-rofecoxib or on-rofecoxib cohort observation windows were considered estrogen exposed. We dichotomized the estrogen exposure variable as ever-exposed versus never exposed because the possible beneficial effects of exogenous estrogen may extend beyond the end of a prescription, and estrogen exposure was often not continuous throughout cohort observation time.

Using a dichotomous estrogen exposure variable for the entire cohort observation time may introduce misclassification in subjects whose estrogen status changed between the pre and on-rofecoxib exposure windows. Therefore, we performed a secondary analysis in which estrogen exposure was expressed quantitatively for both the pre- and the on-rofecoxib

exposure window. For each rofecoxib window, we measured the percent of days that were covered by an active estrogen prescription. For each pre- and on-rofecoxib window, women were considered estrogen exposed if they were covered by an active estrogen prescription for at least 50% of their pre- or on-rofecoxib window. Women were defined as estrogen unexposed if they were not exposed to estrogen during the specific pre- or on-rofecoxib observation time. Women who were exposed to estrogen for less than 50% of their specific rofecoxib defined exposure window were excluded. This secondary analysis thus excluded 14% of cohort and 8% of MI events from analysis because of low (>0% and <50%) estrogen exposure.

Outcome definition

The outcome of interest, incident MI, was defined by a hospital discharge with ICD-9 code 410.X and associated hospital stay of more than or equal to three days unless in-hospital death occurred prior to three days. Prior studies have shown that these outcome criteria for MI have a specificity of 94% and a positive predictive value of 92–95%.^{21, 22} Once a subject experienced a MI, they were excluded from further follow up. Follow up was censored when cohort members lost Medicaid eligibility, turned age 66, or died.

Baseline Covariates

The same individuals contributed both exposed and unexposed time. Subject age in years was recorded at first rofecoxib prescription. We used ICD-9 codes and prescription claims during the 90-day eligibility window to evaluate the frequency of cardiovascular disease risk factors. (Table 1) We adjusted only for baseline factors because conditioning on factors occurring subsequent to exposure can introduce bias.²³

Statistical Analysis

Between group differences in baseline characteristics were evaluated using the standardized difference approach in which the difference in means between two groups is divided by the pooled estimate of the standardized deviation.²⁴ This test provides a sense of the relative magnitude of the differences and is less sensitive to sample size than traditional approaches. Standardized differences of >0.1 are typically meaningful.²⁴ We measured the crude incidence rates of MI among female estrogen users and non-estrogen users during their pre-rofecoxib and on-rofecoxib time. We used Cox proportional hazard models to determine the hazard ratio (HR) for incident MI attributed to rofecoxib exposure.²⁵ We added a term for estrogen exposure compared to estrogen unexposed to the rofecoxib-MI hazard model. Finally, we added the rofecoxib-estrogen interaction term which corresponds to the rofecoxib-estrogen interaction ratio: the hazard ratio of MI associated with rofecoxib exposure vs. pre-rofecoxib among estrogen exposed women, divided by the hazard ratio of MI associated with rofecoxib exposure vs. pre-rofecoxib among estrogen unexposed women. In this way, we determined if estrogen modified the relative hazard of MI associated with rofecoxib.

This multivariable model was then additionally adjusted to evaluate the impact of age at first rofecoxib prescription and for the 6 cardiovascular disease groups shown in the bottom of Table 1. We performed forward stepwise inclusion of covariates that were associated with MI. Since we were primarily interested in the rofecoxib-estrogen interaction ratio, we chose to retain variables in the model only if they changed the rofecoxib-estrogen interaction-ratio by $\geq 10\%$ or were significantly associated with MI.

Confirmation that study design permits detection of rofecoxib risk of MI

We studied male 45–65 year old rofecoxib users in order to confirm that our design was able to reproduce the known association between rofecoxib and MI.^{4, 5, 26} Using this approach, we found a rofecoxib-MI hazard ratio of 1.89 (95% CI 1.61–2.22). This result is consistent with the relative risk of 1.33 for < 25 mg/day and 2.19 for >25 mg/day derived from pooled observational studies that included more than one million subjects.²⁷

RESULTS

Cohort Description

Among the nearly 30 million people in the five state Medicaid 1999–2002 dataset, we identified 1,369,325 rofecoxib prescriptions among 287,328 men (36%) and women (64%) aged 45 to 65 at the time of first rofecoxib prescription. We excluded 678 subjects who had a MI prior to cohort start date (0.2%). From this cohort, we analyzed the 184,169 female rofecoxib users, of whom 34% had an estrogen prescription. These women contributed 309,405 person-years of observation time during which we identified 1217 incident MIs. The rate of incident MI was 3.9 per 1000 person-years. On average, women were observed for 522 days pre-rofecoxib unexposed time and for 93 days of rofecoxib exposure time (Figure 1). Women exposed to estrogen had longer cohort observation times on average, including more time exposed to rofecoxib.

The baseline clinical characteristics of the cohort for women with and without estrogen exposure are described in Table 1. Most (81%) had a claim for prescription medication in the 90 day baseline window. Cardiovascular diseases, diabetes, and medications used to treat these conditions were common with similar prevalence in estrogen exposed and unexposed women (Table 1). On average, women who were never exposed to estrogen were 6 months older and more likely to have a diagnosis of heart failure.

Most rofecoxib prescriptions were for a 30 day supply of a 25 mg daily dose. Prescriptions for 50 mg dose were in the top 90th percentile and those for 12.5 mg dose were in the bottom 10th percentile. Rofecoxib exposure was short, with an average rofecoxib exposure window of 93 days.

Most estrogen-exposed women received estrogen containing formulations typically used for hormone replacement therapy (97%) with less for oral contraception (3%). Nearly half of the estrogen-exposed women were prescribed combined estrogen/progestin formulations (48%). Estrogen-exposed women filled nine prescriptions for estrogens on average, and individuals often took different formulations of estrogen over time, so type of exposure was not evaluated. Because women took estrogen at different cohort time points for variable and often non-continuous durations, we chose to dichotomize estrogen exposure as ever estrogen exposed versus never estrogen exposed. Estrogen users were exposed to estrogen for an average 51% of their observation time.

Incidence Rate (IR) of MI

In this female, presumably perimenopausal cohort, the observed crude incidence rate of MI was 3.91 per 1000 person-years (95% CI 3.69–4.16). The observed incidence rate of MI per 1000 person years was higher during rofecoxib exposure (6.75) than prior to rofecoxib exposure (3.43) and lower in estrogen exposed women (3.14) compared to those not exposed to exogenous estrogen (4.39) (Table 2). During rofecoxib exposure, estrogen-exposed women had lower IR of MI (5.78) compared to estrogen unexposed women (7.41). In a secondary analysis that used a more stringent estrogen exposure definition, the incidence rate of MI per 1000 person years remained higher on rofecoxib and lower on estrogen,

although the differences were less; the IR prior to rofecoxib was 3.78 (off estrogen) versus 3.51 (on estrogen) whereas the IR on rofecoxib was 7.21 (off estrogen) versus 6.34 (on estrogen).

Cox-Regression Analysis

In univariable Cox-regression analysis, rofecoxib exposure was associated with an increased MI-hazard (HR 1.91, 95% CI 1.67–2.20) compared to the pre-rofecoxib window. Estrogen exposure was protective (estrogen-MI HR 0.71; 95% CI 0.62–0.80) compared to never-estrogen exposed. However, the rofecoxib-MI hazard ratio was not different between estrogen exposed women (rofecoxib-HR 2.01; 95% CI 1.57–2.57) and estrogen unexposed women (rofecoxib-HR 1.89; 95% CI 1.60–2.23).

In a model with rofecoxib, estrogen, and a rofecoxib-estrogen interaction ratio term, rofecoxib was associated with a significantly elevated MI-hazard (HR 1.84; 95% CI 1.57–2.17), while estrogen was protective (HR 0.67; 95% CI 0.6–0.8). The rofecoxib-estrogen interaction ratio representing the ratio of rofecoxib-MI hazard ratios in estrogen exposed versus estrogen unexposed women was not significantly different from 1 (1.16; 95% CI 0.88–1.52). That is, estrogen exposure was not associated with an attenuation of the MI-HR associated with rofecoxib.

We then evaluated potential confounding by the age at first rofecoxib prescription and the baseline cardiovascular covariates defined by the diagnosis groups in the bottom of Table 1. The final adjusted multivariable regression model included rofecoxib, estrogen, rofecoxib-estrogen interaction ratio, age at first rofecoxib prescription and a baseline diagnosis of hypertension, diabetes, cerebral vascular disease or coronary artery disease, or heart failure. These cardiovascular risk factors were all independently associated with an increased hazard for MI. Adjustment for cardiovascular disease risk factors did not change the rofecoxib-MI HR in estrogen un-exposed women (1.69, 95% CI 1.43–1.99) or estrogen exposed women (2.01, 95% CI 1.60–2.54) (Table 3). Estrogen remained protective (HR 0.72, 95% CI 0.62–0.84). Compared to women without rofecoxib or estrogen, women on rofecoxib without estrogen had an increased MI-HR of 1.69 (95% CI 1.43–1.99) while those women on rofecoxib and estrogen had an increase MI-HR of 1.45 (95% CI 1.18–1.80) (Table 3). There remained no interaction between rofecoxib and estrogen since the rofecoxib-estrogen interaction ratio was not significantly different from 1 (1.19, 95% CI 0.91–1.57) (Table 3). This final adjusted model was then used in secondary analysis to evaluate subgroups of women based on more stringent estrogen definitions or NSAID exposure. Rheumatoid arthritis and hypercholesterolemia were not included in this final adjusted model because they were not independently associated with an increased MI-HR, nor did they change the rofecoxib-estrogen interaction ratio.

The protective effects of estrogen may be related to the duration and/or timing of estrogen exposure relative to rofecoxib exposure. We recognized that dichotomization of estrogen exposure may have led to misclassification bias. Therefore, we conducted a secondary analysis, in which estrogen exposure was defined separately for each subject's pre- and on-rofecoxib cohort time. For this analysis, the definition of estrogen exposure was restricted to those women who were exposed to estrogen a majority of days of their pre- or on-rofecoxib cohort time. We evaluated the MI-HR using the final adjusted model analysis for the 260,822 person-years and 1114 events among these more stringently defined estrogen-exposed and unexposed women. Rofecoxib maintained a similar increased MI-HR (adjusted HR 1.74; 95% CI 1.49–2.05). However, the observed protective effects of estrogen exposure were no longer significantly different from 1 (adjusted estrogen HR 0.92; 95% CI 0.77–1.10). The rofecoxib-estrogen interaction ratio remained non-significant (1.04, 95% CI 0.76–1.42), confirming the lack of interaction between rofecoxib and estrogen on MI hazard.

Many women in this cohort were exposed to other NSAIDs prior to, and less often, during their rofecoxib exposure time. We evaluated variables in the final adjusted model in the 58,031 person-years and 264 events among women without NSAID exposure. Rofecoxib remained associated with MI (HR 1.61; 95% CI 1.16–2.23) and estrogen exposure remained protective (HR 0.62; 95% CI 0.43–0.90). However, there was still no significant interaction between estrogen and rofecoxib on MI hazard (rofecoxib-estrogen interaction ratio 1.50; 95% CI 0.81–2.77).

DISCUSSION

The cardiovascular risk due to selective COX-2 inhibition has been attributed to a reduction in COX-2 derived prostacyclin production^{9, 31}. Mechanistically, the accelerated thrombotic response to perturbation of PGI₂ is explicable by its role as an endogenous platelet inhibitor⁹, and by its actions on the coagulation system²⁸ and the vessel wall.²⁹ Consistent with this mechanism, estrogen may have protective effects through augmenting COX-2 expression and subsequently increasing prostacyclin formation.¹⁰ We hypothesized that exogenous estrogen might reduce the magnitude of association between rofecoxib and MI. A clinical trial to evaluate this potential interaction would be challenging because it would require a large sample size and randomization to both a selective COX-2 drug and exogenous hormone therapy. When plausible biological mechanisms of drug interactions are proposed, administrative claims data can provide the large sample sizes needed to empirically evaluate such hypotheses. This large epidemiologic cohort study replicated the previously identified association between rofecoxib and MI. Although estrogen exposure appeared to be protective it did not attenuate the association between rofecoxib and MI.

The apparent protective effect of estrogen in this relatively young cohort was consistent with some previous studies in perimenopausal age women.^{13–15} The protective effects of estrogen were maintained in the presence of rofecoxib. One prior case-control study showed that co-administration of traditional NSAIDs was able to reverse the protective effects of hormone replacement therapy in women.³⁰ However, in this prior study, NSAIDs were not associated with an increased risk of MI in the absence of estrogen. Thus, the apparent discrepancy between the prior results and ours may be due to the fact that the prior study examined non-selective NSAIDs, while we studied a selective COX-2 inhibitor. It is possible, however, that the timing of and noncompliance with estrogen regimen may reduce any possible potential attenuation of the rofecoxib effects.

The lack of interaction between estrogen and rofecoxib may yield insight into biological mechanisms of drug associated cardiovascular risk. For example, estrogen can increase COX-2 dependent PGI₂ signaling in rodent and human tissues.³¹ Estrogen increases expression of the human prostacyclin receptor within the vasculature through an estrogen receptor alpha-dependent mechanism.³² Other cardio protective mechanisms may also play a role in patients. The mechanisms of cardiovascular risk associated with COX-2 inhibition are likely to involve other pathways in addition to PGI₂. PGE₂, which is partly formed by COX-1 and partly by COX-2, may also play a role in the acceleration of atherogenesis by inhibitors of COX-2.^{33, 34} Another route through which depression of COX-2 dependent prostaglandin formation may increase the likelihood of cardiovascular events is an elevation of blood pressure. Studies of renal COX physiology have increasingly established that inhibition of COX-2 plays the major role in the rise in blood pressure on NSAIDs³⁵ and that both PGI₂ and PGE₂ play a role in the regulation of blood pressure and salt handling.³⁶

Thus, prostaglandins other than PGI₂ or renal effects of COX-2 inhibition may modulate cardiovascular risk, but not be “rescued” by estrogen, although this remains to be addressed mechanistically. Even when prostacyclin is available to reduce thrombosis risk, alternative

prothrombotic pathways may remain active. Similarly, a potential estrogen dependent increase in COX-2 expression may not sufficiently compensate for the protein inhibitory effects of COX-2 selective drugs.

This study had a number of strengths. The use of administrative claims data allowed inclusion of 309,504 person years and 1217 MIs, much more than could be observed in an ad-hoc study. We limited our cohort to an age group representative of perimenopausal and recently menopausal aged women. Our algorithm to identify MI has been shown to have excellent specificity and positive predictive value. We used the same cohort of individuals as unexposed and exposed subjects to avoid the selection bias inherent in defining a non-rofecoxib exposed control group, and to minimize the risks of unmeasured confounding, such as aspirin use, smoking, obesity, lifestyle, and family history. Using this study design, we were able to replicate the well-known association between rofecoxib and MI.

This study also has potential limitations. The simplification of estrogen exposure into ever versus never may introduce misclassification bias. However, when we used an alternative definition of estrogen exposure defined by a majority of observed time, the results did not change. Another potential limitation is that poor adherence to estrogens, if present, would have biased our results toward the null, making it difficult to find an attenuating effect of estrogen on the association between rofecoxib and MI. Confounding is always a potential concern in non-randomized studies. Although our design inherently controlled for factors that remained constant within subject, it does not exclude the possibility of confounding by dynamic factors, such as diet, exercise, new medical conditions, or aspirin use. That said, it is difficult to envision dynamic factors that could affect estrogen users and estrogen non-users differently so as to mask an attenuating effect of estrogen on the rofecoxib-MI association. Although the pre-rofecoxib unexposed time represented immortal time, the effects of immortal time bias are likely to be minimal in this study because all subjects contributed immortal time and the death rate was low. Any effect of immortal time bias would likely be present in estrogen exposed and unexposed women and therefore cancel out in the final rofecoxib-estrogen interaction ratio. With this design we were able to detect a significant increased MI-hazard with rofecoxib exposure in both men and women that was consistent with past studies. We may be under powered to detect a smaller interaction ratio.

Conclusions

Rofecoxib was associated with an elevated hazard of MI in perimenopausal women. Exogenous estrogen did not appear to attenuate this association, despite a detectable cardio protective effect. Thus, exogenous estrogen may not be able to increase vascular prostacyclin levels in women taking rofecoxib sufficiently to mitigate its cardio toxicity or this may reflect the relative importance of other pathways in its cardio protective effect in women. While this study reflects the complexity of the biological mechanisms underlying the cardiovascular effects of estrogen treatment and COX-2 inhibition, it highlights that large pharmacoepidemiologic studies can play an important role in the exploration of biological mechanisms in human populations.

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Figure 1.

Study design includes a 90 day covariate selection window during which Medicaid eligibility is confirmed and baseline covariate information was collected. Cohort observation time began with each woman's rofecoxib unexposed time prior to first rofecoxib prescription. Their rofecoxib exposure time began with their first rofecoxib prescription and ended with last continuous rofecoxib prescription. Women who had an estrogen prescription at any time during the cohort observation time were considered estrogen exposed.

Table 1

Cohort description: Proportion of women by estrogen exposure classification with the following prescription drug claims and medical history during their baseline covariate selection window.

	Never Estrogen exposed	Ever Estrogen exposed	Standardized difference *
	N=122,286	N=61,883	
	859 events	358 events	
Age at first rofecoxib prescription	56.1 years	55.5 years	0.10 [‡]
Prescription drug claims	% of women	% of women	
ACE [§] Inhibitors	13.8	13.7	0.00
Antiarrhythmic	0.32	0.37	0.01
Calcium Channel Blocker	16.7	17	0.01
Digitalis	1.7	1.6	0.01
Thiazide	4.7	5.4	0.03
Loop Diuretics	7	7.8	0.03
All Diuretics	11.6	13	0.04
Angiotensin 2 Inhibitor	2.6	2.5	0.00
Beta Blockers	10.4	11.4	0.03
Antihypertensive combination	6.4	7.4	0.04
Anti-Anginal	5.5	5.6	0.00
Insulin	6.6	5.4	0.05
Oral Hypoglycemic	12.3	10.8	0.05
Lipid Lowering	12.8	15.3	0.07
Heparin/Coumadin	1.7	1.1	0.05
Platelet inhibitor	6.1	5.6	0.02
Anti-Rheumatoid Arthritis	1.6	2.5	0.07
Prednisone	5.3	7.4	0.09
Medical History	% of women	% of women	
Arrhythmia	2.8	2.7	0.01
Cerebrovascular Disease	2.9	2.6	0.02
Coronary Artery Disease	7.2	7.3	0.00
Diabetes	17.2	15.3	0.05
Heart Failure/Cardiomyopathy	3.5	2.9	0.18 [‡]
Hypercholesterolemia	9.4	11.6	0.07
Hypertension	27.3	26.5	0.02
Rheumatoid Arthritis	2.5	3.5	0.06
Combined diagnosis groups[‡]	% of women	% of women	
Hypertension	44.9	47.4	0.05
Diabetes	20.9	18.1	0.07
Hypercholesterolemia	17.7	21.0	0.08
Heart Failure	4.5	4.0	0.02
Cerebral vascular or Coronary Artery Disease	16.4	15.9	0.01
Rheumatoid arthritis	3.3	4.7	0.07

* Standardized difference refers to the difference in mean between two groups divided by the pooled estimate of the standard deviation.

† Standardized differences of > 0.1 are typically felt to be meaningful.

‡ Diagnosis groups determined from medical history or the use of prescription medication used to treat the medical condition.

§ ACE: Anticholinesterase

Table 2

Summary of crude incidence rates of MI per 1000 person-years and 95% confidence intervals by rofecoxib and estrogen exposure status.

Crude Incidence Rates (95% CI) of MI per 1000 person-years			
	Rofecoxib un-exposed	Rofecoxib exposed	Total
Estrogen un-exposed	3.89 (3.60–4.20)	7.41 (6.47–8.49)	4.39 (4.11–4.70)
Estrogen Exposed	2.61 (2.30–2.95)	5.78 (4.80–6.96)	3.14 (2.83–3.49)
Total	3.43 (3.21–3.66)	6.75 (6.04–7.53)	3.91 (3.69–4.16)

Table 3

Cox regression derived hazard ratios and 95% confidence intervals for MI adjusted for age at first rofecoxib prescription, baseline medical diagnosis of hypertension, diabetes, heart failure, cerebral vascular disease or coronary artery disease as defined by ICD-9 codes and prescription drug claims during baseline covariate selection window. Rofecoxib exposure significantly increased the HR for MI. Although, estrogen exposure was protective with a reduced MI-HR, it did not reduce the MI-HR associated with rofecoxib. The rofecoxib-estrogen interaction ratio was not significantly different from 1.

<u>Adjusted HR for MI (95% CI)</u>			
	<u>Rofecoxib un-exposed</u>	<u>Rofecoxib exposed</u>	<u>MI HR associated with rofecoxib exposure vs unexposed</u>
Estrogen un-exposed	1 (reference)	1.69 (1.43–1.99)	1.69 (1.43–1.99)
Estrogen exposed	0.72 (0.62–0.84)	1.45 (1.18–1.80)	2.01 (1.60–2.54)
			Interaction Ratio *
			1.19 (0.91–1.57) *

* Non-significant rofecoxib-estrogen interaction ratio defined as the rofecoxib-MI hazard ratio in estrogen exposed women relative to the rofecoxib-MI hazard ratio in non-estrogen exposed women.