Effect of Statin Use on Acute Kidney Injury Risk Following Coronary Artery Bypass Grafting

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Abstract

Acute kidney injury (AKI) is a serious complication of cardiovascular surgery. While some non-experimental studies suggest statin use may reduce post-surgical AKI, methodological differences in study designs leave uncertainty regarding the reality or magnitude of the effect. We estimated the effect of pre-operative statin initiation on post-coronary artery bypass graft (CABG) AKI using an epidemiologic approach more closely simulating a randomized controlled trial in a large CABG patient population. We utilized healthcare claims from large, employer-based and Medicare insurance databases for the years 2000 – 2010. To minimize healthy user bias, we identified patients undergoing non-emergency CABG who either newly initiated a statin within 20 days prior to surgery or were unexposed for 200+ days prior to CABG. AKI was identified within 15 days following CABG. We calculated multivariable adjusted risk ratios (RR) and 95% confidence intervals (CI) with Poisson regression. Analyses were repeated using propensity score methods adjusted for clinical and healthcare utilization variables. We identified 17,077 CABG patients. Post-CABG AKI developed in 3.4% of statin initiators and 6.2% of non-initiators. After adjustment, we observed a protective effect of statin initiation on AKI (RR = 0.78, 95% CI 0.63, 0.96). This effect differed by age: 65 years, RR=0.91 (95% CI: 0.68, 1.20); <65 years, RR=0.62 (95% CI: 0.45, 0.86), although AKI was more common in the older age group (7.7 vs. 4.0%). In conclusion, statin initiation immediately prior to CABG may modestly reduce the risk of post-operative AKI, particularly in younger CABG patients.

Keywords

statins; bypass; heart surgery; acute kidney injury; pharmacoepidemiology

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Introduction

Statins may have anti-inflammatory[1] and endothelial stabilizing[2] pleiotropic effects with potential benefits on kidney function[3], motivating investigation for protective effects against post-surgical kidney injury[3–15]. However, studies have employed widely varying definitions of pre-operative statin use, including: prescribed statin use at the time of surgery[4–6,8]; administration the day of or the day before surgery[11,12,15]; or pharmacy dispensing within 90 days prior to CABG[14]. Many of these definitions fail to consider history or duration of statin use, which may introduce bias due to the healthy user effect[16] whereby differences in healthy behaviors between long-term medication users and non-users may lead to exaggerated estimates of the benefits of preventive medications. These important methodological concerns limit the ability to distinguish whether observed results are direct beneficial effect of statins, or result from unmeasured behavioral differences in long-term users of statins. Yet, acute kidney injury (AKI) remains a serious complication of coronary bypass grafting (CABG), resulting in both short- and long-term consequences, including chronic kidney disease (CKD), end-stage renal disease, or death[17]. Understanding the effect of pre-operative statin use could allow clinicians to modify the risk of an outcome for which there are currently no proven interventions. In a cohort of patients undergoing planned CABG surgery, we compared post-surgery AKI risk among patients initiating a statin immediately prior to surgery to patients not initiating statins using a modern epidemiologic study design and analysis aimed at minimizing confounding bias.

Methods

Individuals undergoing CABG surgery between the years 2000 to 2010 were identified in *Thomson Reuters' MarketScan® Commercial Claims and Encounters* and *Medicare Supplemental and Coordination of Benefits* databases (Thomson Reuters (Healthcare) Inc., 2011). These databases are a compilation of insurance billing data for employees, dependents and retirees from across the United States with employer-based primary or Medicare supplemental insurance coverage (ages   65 years). Adjudicated, paid inpatient, outpatient, and pharmacy claims, as well as enrollment information, are included in the databases. This study was exempted from further review by the University of North Carolina Institutional Review Board.

All patients   18 years with inpatient procedure claims for CABG, having 200 days of continuous plan enrollment prior to hospital admission for CABG, were identified. If an individual had multiple eligible CABG surgeries, only the first was considered. The 20 days immediately prior to the date of hospital admission were considered the exposure window, during which statin initiation was assessed. The 180 days prior to the exposure window were considered the washout period, during which the absence of any statin prescription was required (see Figure 1). We required at least 1 pharmacy claim for any non-statin medication during the washout period to ensure pharmacy benefit utilization.

Patients with inpatient or outpatient diagnosis codes for AKI, unspecified renal failure, or end-stage renal disease in the 200 days before CABG surgery were excluded. To restrict to planned CABG procedures by removing individuals with emergency surgeries, we excluded patients with: inpatient claims for MI or unstable angina during the 20-day exposure period; CABG occurring after the fifth day of hospitalization; or an angiogram in the 3 days prior to CABG surgery.

Statin initiation was defined as having a pharmacy dispensing claim for any statin during the exposure window without any statin claims during the preceding baseline period. Non-users had no observable statin use during the exposure or baseline windows and were required to

have an outpatient physician's office visit during the exposure window to ensure healthcare utilization.

Baseline covariates for multivariable regression and propensity score models included claims for diagnoses, procedures, prevalent medication use, and pre-operative initiation of other, non-statin medications. Included covariates are shown in Table 1. Baseline diagnoses and procedures were assessed in the 200 days prior to hospital admission for CABG and during the hospitalization up to the day of surgery, and included: age; sex; year of surgery; number of grafts in surgery; diagnoses of cardiovascular conditions; indicators of CVD management; acute cardiovascular events and procedures; evidence of renal conditions; number of emergency department visits; and number of hospitalizations. Claims for medications during the washout period were considered prevalent medication use. If the medications were newly initiated during the exposure window without use during the washout period, the medications were considered newly-initiated and considered separately in the analysis.

Inpatient claims in the 15 days post-CABG were searched for ICD-9-CM diagnosis codes for AKI (584.5 – 584.9). Sensitivity analyses were performed employing a broader definition of kidney failure (any of the following diagnosis codes: acute renal failure, 584.5 —584.9; end stage renal disease, 585.6; or unspecified renal failure, 586).

We estimated the association between statin initiation and AKI using multivariable Poisson regression, resulting in adjusted risk ratios (RR) and 95% confidence intervals (CI)[18]. We also performed regression analyses employing stabilized inverse probability of treatment weighting (IPTW)[19]. Multivariable logistic regression was used to estimate the predicted probability of initiating a statin, or propensity score (PS), for each individual in the sample using the pre-specified covariates described above. To exclude patients treated contrary to prediction as their extreme weights may disproportionately influence the effect measure estimate[20], we trimmed individuals with a PS less than the 1st percentile of the treated, or greater than the 99th percentile of the untreated. The PS was then used to calculate the IPTW in the remaining patients, and the weights were applied to a Poisson regression model.

Lastly, we performed 1-to-1 PS matching using a greedy matching algorithm[21] where non-users were matched to statin initiators by PS to the fifth decimal place, if possible. We then estimated RR using regression models in the remaining matched individuals.

Models were run separately in the 2 databases: commercial insurance (ages 40–64 years) and Medicare supplementary insurance (ages 65 years). We also repeated the analyses in pre-specified subgroups—by gender, in those without CKD, and older age. Analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC).

Sensitivity analyses were performed by varying the length of the exposure window before CABG (10 to 30 days) to observe if the effect may be dependent on the length of time on statin prior to CABG. To estimate the extent to which medication initiation is simply a proxy for better pre-surgical care, the entire analysis was repeated considering beta-blocker initiation as a negative control exposure[22] rather than statin initiation. Beta-blockers are preventive cardiovascular medication with a similar behavioral profile and user population as statins, but they are not thought to confer a protective effect against post-operative AKI. Therefore, if a protective effect was observed among the beta-blocker initiators, it can be assumed that our study design did not adequately address the healthy user effect and other sources of confounding bias.

Results

We identified 149,696 individuals with CABG surgeries with 200 days of baseline enrollment. After applying exclusion criteria, our sample consisted of 17,077 patients: 3,085 of whom newly initiated a statin within 20 days prior to CABG admission, and 13,992 who were free of any statin use. For the distribution of day of statin initiation prior to CABG among the initiators, see Figure 2. Distributions of demographic and clinical variables by statin status are shown in Table 1. The sample was predominantly male. Statin initiators were predominantly commercially-insured, whereas statin non-initiators were as likely to be covered by Medicare or commercial insurance. Variables were generally well-balanced across treatment groups, with the notable exceptions that initiators: received more cardiac stress tests or angiograms; had more diagnoses of hyperlipidemia and ischemic heart disease; and to co-initiated more other cardiovascular medications. While these characteristics may be associated with increased CVD risk, in claims data all of these factors may also be seen as markers of better disease management, preventive healthcare utilization, or pre-operative care.

Post-CABG AKI codes occurred in 871 (6.2%) non-initiators and 104 (3.4%) initiators. Unadjusted regression models yielded a highly-protective effect measure estimate, but adjustment attenuated the estimate to RR=0.78 (95% CI: 0.63, 0.96) (see Table 2). When the analysis was repeated with trimmed IPTW weighted models and PS matching, the results were very similar (see Table 2).

However, when stratifying the effect measure estimates by age, the relative protective effect was more pronounced in individuals aged < 65 years than older individuals (see Table 3). AKI was much more common in the older age group (7.7%) than the younger age group (4.0%). No differences were seen in other subgroups.

When the length of exposure window before CABG was varied, the effect measure estimate remained constant. Additionally, when a wider definition of kidney failure was employed, the results remained essentially unchanged (see Table 2).

When the analysis was repeated considering beta-blocker initiation in the place of statin initiation, we observed no protective effect of beta blockers initiation against post-CABG AKI, with multivariable adjusted models yielding RR=0.96 (95% CI: 0.84, 1.10) and IPTW models yielding RR=1.02 (95% CI: 0.87, 1.19).

Discussion

In this cohort study of over 17,000 patients, we found that initiation of a statin prior to non-emergent CABG surgery was associated with a reduced risk of post-surgical AKI. The results were robust throughout sensitivity analyses and estimation methods.

We observed effect measure modification by age. The protective effect was much more pronounced in younger individuals. However, those under 65 years experienced many fewer post-CABG AKI events overall, suggesting that the absolute benefit of statin treatment may not be as large as the RR suggests[23].

Statins lower low-density lipoprotein cholesterol, reducing the risk of CVD. Randomized trials have also demonstrated that peri-operative statin use is associated with decreased myocardial ischemia[24] and atrial fibrillation[25], which could indirectly benefit kidney function by maintaining renal perfusion during and immediately following surgery. However, the elderly are at higher AKI risk for a variety of reasons[26], and statins' benefit may be diluted in such an at-risk population.

Other estimates of the effect of peri-operative statin use on post-operative AKI have ranged from strongly protective[8] to null[4,10,13]. Our estimate is comparable to other studies of the subject[3,14], but differs from the null result of a recent, small randomized trial[10] restricted to high-AKI risk patients. We saw little protective effect in older patients, but observed the protective effect primarily in the younger, low-risk patients, which could explain the difference in results.

Non-randomized studies of preventive medications are potentially subject to bias which can inflate protective effect measure estimates. Yet, through the implementation of a rigorous methodology, our study helps to more accurately quantify the potential benefit of statins in 4 ways. First, we adopted a design explicitly aimed at minimizing the healthy user effect, a potentially important bias in non-experimental statin studies. We restricted our study to new users who initiated a statin immediately prior to surgery and compared these with patients not initiating a statin, removing bias created by comparing long-term, adherent users to non-users.

Second, we excluded emergency CABG surgeries, resulting in a relatively homogeneous patient population of those with planned CABG surgeries. We speculated that statin initiation in these patients would be more dependent on physician preference or protocol than clinical factors or patient characteristics.

Third, we adjusted for a wide array of clinical characteristics, including complexity of surgery. Prevalent medication use and concurrent medication initiation were considered as separate covariates. Prevalent medication use was very similar between the 2 treatment groups, but statin initiators tended to co-initiate other medications more frequently. While statin initiation immediately prior to surgery may be indicative of more aggressive disease management or access to care, considering other peri-operative medication initiation allowed us to more accurately assess pre-operative care and adjust for differences which may exist between the treatment groups.

Lastly, we examined the effect of beta-blocker initiation on post-CABG AKI as a negative control. Beta blocker initiation was not associated with a reduced AKI risk, suggesting the observed effect estimate among the statin users may be a real effect, not simply unmeasured behavioral or clinical factors for which any medication initiation serves as a proxy[27].

Nevertheless, these study findings should be interpreted in the context of the following limitations. First, despite our attempts to create comparable treatment groups, we observed differences—e.g. more healthcare utilization, CVD management, and concurrent medication initiation—among the statin users which may indicate better health status, or healthcare quality and access, and thus potentially better outcomes among statin users. Although we controlled for these observed factors in our analysis, the potential for unmeasured confounding remains. For example, measures of baseline glomerular function are unavailable in claims; diagnosis codes for CKD and number of procedure claims for measures of glomerular function were used as proxies, but they may not fully capture baseline renal impairment, which is a strong risk factor for AKI[28]. However, while glomerular function is a strong predictor of AKI, it is not obviously a predictor of statin initiation, and therefore may not be a strong confounder of the association.

Secondly, some of the included variables have been shown to have poor validity, such as CKD[29] which would allow for some residual confounding by baseline renal impairment to remain. Similarly, the sensitivity AKI billing codes has been shown to be very poor, yet the specificity is very high[29]. While the insensitive AKI definition may underestimate true AKI occurrence, under the assumption of nondifferential misclassification of the outcome

between the treatment groups, relative effect measures, such as the RRs calculated in this study, should be unbiased[30].

Third, these results may not be generalizable to all CABG patients. The majority of patients undergoing CABG were prevalent statin users, and many others had urgent or emergency surgeries, thus not meeting our inclusion criteria. However, emergency CABG patients likely do not have time to initiate a statin prior to surgery. The resulting patients are those of most interest: it is among statin naive patients that statin intervention is possible and the potential benefits of initiation need to be determined.

As researchers continue to investigate and suggest additional protective and beneficial statin effects, careful consideration must be given to the designs of non-experimental studies to ensure they are not subject to common biases in studies of preventive medications. After considering the timing of statin initiation, observing the entire length of statin treatment, measuring important markers of pre-clinical care such as medication initiation, and matching non-users to users on healthcare utilization, our study supports the hypothesis that prescribing a statin prior to CABG in those not already receiving statin therapy may modestly attenuate the incidence of post-CABG AKI, particularly among younger patients. While many CABG patients will already be receiving statin therapy, those not yet receiving it may benefit from initiation prior to surgery.

Acknowledgments

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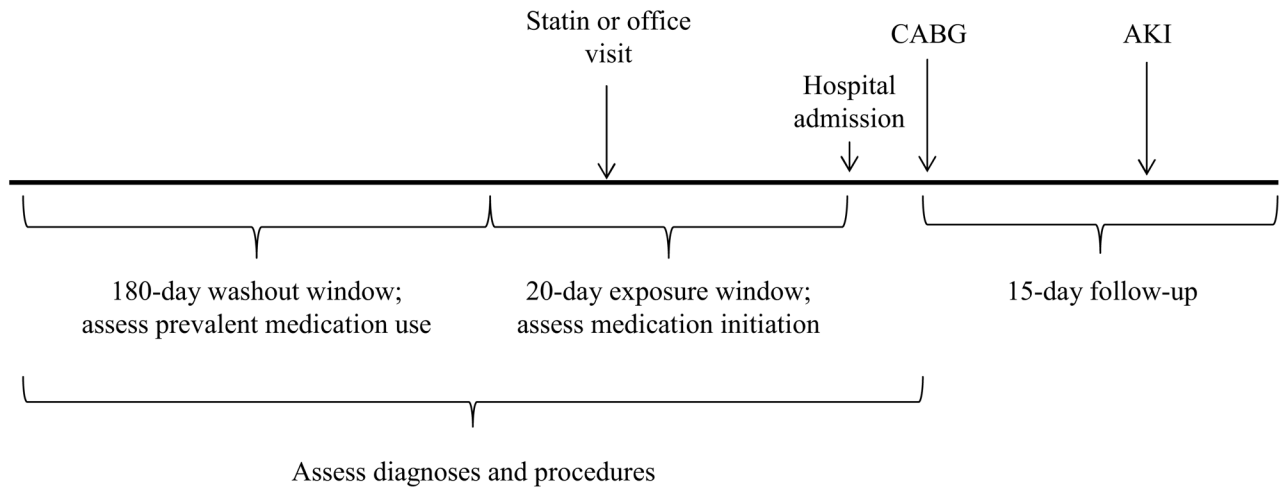
Figure 1.
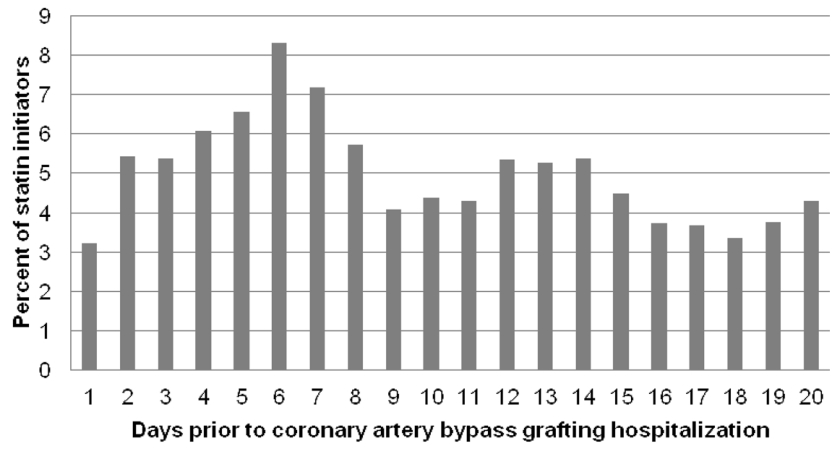Cohort schematics for pre-coronary artery bypass graft statin initiation

Figure 2.
Distribution of statin initiation by day prior to CABG surgery

Table 1

Baseline demographics and clinical characteristics by statin initiation status

Variable	Statin non-initiator (n=13,992)	Statin initiator (n=3,085)
Male	10,394 (74.3%)	2,453 (79.5%)
Mean age, standard deviation (SD)	65.4 (11.0)	(62.5) (10.0)
MarketScan Database		
Commercial Claims and Encounters Database	7,135 (51.0%)	1,978 (64.1%)
Medicare Supplementary Database	6,857 (49.0%)	1,107 (35.9%)
HEALTHCARE UTILIZATION		
Mean day of hospitalization on which CABG is performed (SD)	0.88 (1.26)	0.49 (0.99)
Mean number of lipid tests (SD) [*]	0.68 (1.11)	0.84 (1.12)
Mean number of creatinine measurements (SD) [*]	0.04 (0.37)	0.03 (0.25)
Mean number of hospitalizations (SD) [*]	0.67 (0.76)	0.47 (0.70)
Mean number of emergency department visits (SD) [*]	0.14 (0.49)	0.11 (0.43)
CARDIOVASCULAR DISEASE MANAGEMENT		
Angiography performed	10,492 (75.0%)	2,634 (85.4%)
Cardiac stress test performed	8,381 (59.9%)	2,166 (70.2%)
Echocardiograph	8,030 (57.4%)	1,723 (55.9%)
CARDIOVASCULAR & COMORBID CONDITIONS		
Number of vessels bypassed during surgery		
1–2	5,265 (37.6%)	951 (30.8%)
3–5	7,565 (54.1%)	1,779 (57.7%)
6+	862 (6.2%)	259 (8.4%)
Diabetes mellitus	4,170 (29.8%)	813 (26.4%)
Chronic kidney disease	109 (0.8%)	13 (0.4%)
Other kidney disease		
Proteinuria	70 (0.5%)	13 (0.4%)
Hypertension	7,208 (51.5%)	1,596 (51.7%)
Hyperlipidemia	4,550 (32.5%)	1,283 (41.6%)
Other ischemic heart disease	12,811 (91.6%)	2,972 (96.3%)
Atrial fibrillation	1,422 (10.2%)	163 (5.3%)
ACUTE EVENTS IN PREVIOUS 6 MONTHS		
Recent myocardial infarction [†]	484 (3.5%)	108 (3.5%)
History of myocardial infarction	364 (2.6%)	83 (2.7%)
Unstable angina [†]	1,743 (12.5%)	464 (15.0%)
Stroke	3,723 (26.6%)	746 (24.2%)
Insertion of a coronary stent	236 (1.7%)	51 (1.7%)
Angioplasty	228 (1.6%)	50 (1.6%)
PREVALENT MEDICATION USE DURING BASELINE		
Angiotensin converting enzyme inhibitors	4,349 (31.1%)	916 (29.7%)
Angiotensin receptor blockers	2,212 (15.8%)	434 (14.1%)

Variable	Statin non-initiator (n=13,992)	Statin initiator (n=3,085)
Beta blockers	4,981 (35.6%)	982 (31.8%)
Calcium channel blockers	3,219 (23.0%)	607 (19.7%)
Anti-platelet agents	1,497 (10.7%)	231 (7.5%)
Alpha blockers	1,324 (9.5%)	200 (6.5%)
Thiazide diuretics	3,215 (23.0%)	675 (21.9%)
Potassium-sparing diuretics	880 (6.3%)	124 (4.0%)
Loop diuretics	1,794 (12.8%)	210 (6.8%)
Niacin	250 (1.8%)	36 (1.2%)
Fibrates	976 (7.0%)	150 (4.9%)
Ezetimibe	637 (4.6%)	85 (2.8%)
Anti-coagulants	1,031 (7.4%)	106 (3.4%)
NSAIDs	2,612 (18.7%)	562 (18.2%)
MEDICATIONS INITIATED DURING EXPOSURE WINDOW		
Angiotensin converting enzyme inhibitors	1,410 (10.1%)	606 (19.6%)
Angiotensin receptor blockers	573 (4.1%)	189 (6.1%)
Beta blockers	2,832 (20.2%)	1,498 (48.6%)
Calcium channel blockers	928 (6.6%)	306 (9.9%)
Anti-platelet agents	549 (3.9%)	253 (8.2%)
Alpha blockers	546 (3.9%)	248 (8.0%)
Thiazide diuretics	839 (6.0%)	246 (8.0%)
Potassium-sparing diuretics	249 (1.8%)	52 (1.7%)
Loop diuretics	634 (4.5%)	106 (3.4%)
Niacin	69 (0.5%)	49 (1.6%)
Fibrates	264 (1.9%)	57 (1.9%)
Ezetimibe	143 (1.0%)	176 (5.7%)
Anti-coagulants	308 (2.2%)	47 (1.5%)
NSAIDs	456 (3.3%)	78 (2.5%)

[*] Occurring within the 200 days prior to admission for CABG surgery

[†] Not including events which occurred in the 20 days prior to hospital admission for CABG as those patients were excluded

NSAIDS – Non-steroidal anti-inflammatory drugs

Table 2

The effect of statin initiation on statin on post-coronary artery bypass grafting acute kidney injury and any renal failure

Model	Treatment Group	N	Events	Acute kidney injury Risk ratio	(95% CI)	Events	Any renal failure Risk ratio	(95% CI)
--	Non-users	13,992	871 (6.2%)	--	--	998 (7.1%)	--	--
Crude	Statin initiators	3,085	104 (3.4%)	0.54	(0.44, 0.66)	111 (3.6%)	0.50	(0.41, 0.61)
Multivariable adjusted	Statin initiators	3,085	104 (3.4%)	0.78	(0.63, 0.96)	111 (3.6%)	0.73	(0.59, 0.90)
IPTW	Non-users	13,347	777 (5.8%)	--	--	885 (6.6%)	--	--
	Statin initiators	2,866	101 (3.5%)	0.80	(0.62, 1.04)	107 (3.7%)	0.76	(0.59, 0.98)
PS matched	Non-users	2,812	134 (4.8%)	--	--	147 (5.2%)	--	--
	Statin initiators	2,812	102 (3.6%)	0.76	(0.59, 0.98)	108 (3.8%)	0.73	(0.57, 0.94)

CI: Confidence interval; IPTW: Inverse probability of treatment weighting; PS: propensity score for statin initiation

Table 3

The effect of statin initiation on statin on post-coronary artery bypass grafting acute kidney injury by age group

Model	Treatment Group	Ages <64 years				Ages 65 years			
		N	Events	Risk ratio	(95% CI)	N	Events	Risk ratio	(95% CI)
--	Non-initiator	7,201	325 (4.5%)	--	--	6,791	546 (8.0%)	--	--
Crude	Statin initiator	1,994	46 (2.3%)	0.51	(0.38, 0.70)	1,091	58 (5.3%)	0.66	(0.50, 0.87)
Multivariable adjusted				0.62	(0.48, 0.86)			0.91	(0.69, 1.20)

CI: Confidence interval