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Estimating the effects of time-varying exposures in observational studies using Cox models with stabilized weights adjustment

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Summary

Purpose—Assessing the safety and effectiveness of medical products with observational electronic medical record data is challenging when the treatment is time-varying. The objective of this paper is to develop a Cox model stratified by event times with stabilized weights adjustment to examine the effect of time-varying treatment in observational studies.

Methods—Time-varying stabilized weights are calculated at unique event times and are used in a Cox model stratified by event times to estimate the effect of time-varying treatment. We applied this method in examining the effect of an anti-platelet agent, clopidogrel, on events, including bleeding, myocardial infarction (MI), and death after a Drug-Eluting Stent was implanted in coronary artery. Clopidogrel use may change over time based on patients' behavior (e.g., non-adherence) and physicians' recommendations (e.g., end of duration of therapy). We also compared the results to those from a Cox model for counting processes adjusting for all covariates used in creating stabilized weights.

Results—We demonstrate that 1) results from the stratified Cox model without stabilized weights adjustment and the Cox model for counting processes without covariate adjustment are identical in analyzing the clopidogrel data; and 2) effects of clopidogrel on bleeding, MI and death are larger in the stratified Cox model with stabilized weights adjustment compared to those from the Cox model for counting processes with covariate adjustment.

Conclusions—The Cox model stratified by event times with time-varying stabilized weights adjustment is useful in estimating the effect of time-varying treatments in observational studies while balancing for known confounders.

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Keywords

Drug-Eluting Stent; Clopidogrel; Time-varying exposure; Cox model; Stabilized weights

Introduction

In studies employing observational electronic medical record databases to assess the safety and effectiveness of medical products, propensity score based approaches are often used to balance confounders and reduce bias in making clinical inferences.¹⁻³ These approaches have included stratification or matching on propensity scores and inverse probability of treatment weighting (IPTW). More recently, propensity score based stabilized weights (SWs) were developed and used to reduce the influence of extreme outliers of IPTW.⁴⁻⁸

Hernán et al⁶ described a Cox proportional hazards model adjusted by SW to estimate the causal effect of zidovudine on the survival of men participating in the Multicenter AIDS Cohort Study. They assumed that patients remained on zidovudine therapy once they started it. In a separate study examining the long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death, SWs were calculated from a pooled logistic regression that ignored different risk sets of patients over the follow-up period.⁹ Again, they assumed patients remained on a therapy once it was started. The assumption that patients remain on therapy once started likely results in some untreated outcomes being misclassified as treated outcomes. Consequently, it may result in biased estimates for treatment effects.¹⁰ In a recent observational study examining the effects of an anti-platelet medication, clopidogrel, on subsequent risk of bleeding, myocardial infarction (MI), and death after a Drug-Eluting Stent (DES) was implanted into one or more coronary artery¹¹, clopidogrel use was a time-varying exposure variable. In a patient sample with all covariates measured and using clopidogrel dispensing data to define exposure status, 81 of 339 bleedings, 106 of 266 MIs, and 82 of 192 deaths were classified as untreated at the time of the outcome; however, if we had assumed patients remained on therapy once started, only 3 bleeds and none of the MI or death outcomes would have been classified as untreated.. This misclassification of outcomes would result in the conclusion that clopidogrel use would be associated with higher risk of MI and death, which contradicts clinical literature.¹²⁻¹⁴ Thus, when treatment is time-varying and confounders are also time-varying, it is challenging to calculate and utilize time-varying IPTW or SW to analyze outcomes.

Recently, Xu et al⁸ modeled clopidogrel therapy using separate probabilistic models for every unique event time of follow-up. The corresponding time-dependent SWs were calculated for patients at risk at those event times. A modified Kaplan-Meier method and statistical tests were developed to assess the risk and benefit of clopidogrel use after DES implantation in this observational study setting.⁸ They used stabilized weights⁴⁻⁷ to weight both the number of events and the number of subjects at risk to reduce selection bias in calculating Kaplan-Meier estimates of survival functions.

In this current paper, we use time-varying SWs at unique event times and develop a Cox model stratified by unique event times to estimate adjusted hazard ratios for time-varying exposures. This method allows for risk sets at unique events times that change not only due

to censoring and adverse events but also due to discontinuation of a treatment. The time-varying stabilized weights endeavor to balance measured covariates between treated and untreated members of the cohort at all unique event times and thus provide less biased comparisons between treated and untreated when the status of treatments is time-varying. It allows for unlimited changes of exposure status at any time during the follow-up period and also allows for recurrent events. Baseline hazard function is not considered in parameter estimation. The resulting hazard ratios represent the risk estimates for the time-varying exposure in longitudinal observational studies while balancing known time-invariant and time-varying confounders.

Methods

As foundation for the methods we propose, in this section, we provide typical formulas of partial likelihood for the Cox model with time-invariant exposure and describe two methods for Cox models with time-varying exposure, and describe calculation of SWs. We then propose a method to incorporate SWs in a Cox model stratified by unique event times.

Cox model with time-invariant exposure

The Cox model has been widely used to estimate the effect parameter of exposure in analyzing survival data.¹⁵⁻²¹ The Cox model assumes proportional hazards between two groups (e.g., exposed and unexposed) so that the underlying hazard function does not need to be considered when estimating the effect parameter of exposure. The effects of covariates and exposure are estimated by maximizing partial likelihood function; the exponentiations of coefficients are reported as hazard ratios (HR).¹⁸ The Cox model has been modified to accommodate non-proportional hazards data by stratified analyses²⁰ and inclusion of interactions between covariates and time.^{22,23} When there are no tied event times and assuming proportional hazards, the partial likelihood is calculated as a product of the likelihoods for all observed events¹⁸:

$$PL = \prod_{j=1}^J L_j = \prod_{i=1}^n \left[\frac{\lambda_0(t_j) \exp(\beta \mathbf{x}_i)}{\sum_{i \in R(t_j)} \lambda_0(t_j) \exp(\beta \mathbf{x}_i)} \right]^{y_i} = \prod_{i=1}^n \left[\frac{\exp(\beta \mathbf{x}_i)}{\sum_{i \in R(t_j)} \exp(\beta \mathbf{x}_i)} \right]^{y_i} \quad (1)$$

where J is the total number of events and L_j is the likelihood for event j at time t_j , $\lambda_0(t_j)$ is the baseline hazard function at time t_j , y_j is an indicator for individual i , equal to 1 if an event occurs and 0 if not (censored), $R(t_j)$ is the set of individuals at risk at time t_j , $\mathbf{x}_i$ is a column vector of covariates including the exposure variable, and β is a row vector of corresponding coefficients to be estimated.

With tied event times, one approximation of the partial likelihood developed by Breslow¹⁷ is

$$PL = \prod_{j=1}^r \frac{\exp(\sum_{i \in D_j} \beta \mathbf{x}_i)}{\left[\sum_{i \in R(t_j)} \exp(\beta \mathbf{x}_i) \right]^{d_j}} \quad (2)$$

where d_j is the number of events at the j th distinct event time, D_j is the event set at the j th distinct event time, r is the number of unique event times. Summation in the numerator is over all subjects who experienced event at time t_j ($i \in D(t_j)$). Summation in the denominator is over all subjects in the risk set at time t_j ($i \in R(t_j)$). We chose to only examine the Breslow method for tied event times in this study given that various methods typically provide comparable results unless tied event times are common.²⁴

Cox model with time-varying exposure

Time-varying covariates including exposures are common in survival analyses. A Cox model can be modified to allow for time-varying covariates. For example, a time-varying indicator variable for wait time to heart transplantation was included in a modified partial likelihood to estimate the effect of heart transplant on hazard of death with wait time treated as unexposed and post-transplantation time treated as exposed time.^{25,26} When the frequency of change in the covariate value is not small, a more flexible approach called Cox model for counting process²⁷⁻²⁹ can be used. This model allows for recurring events. In the counting process model, multiple observations for each individual are created. Each observation reflects a unique time interval and includes 1) the number of events an individual experiences during the time interval; 2) an indicator variable for an individual being at risk during the time interval; and 3) corresponding values of covariates including the exposure variable during the time interval. Survival data in counting processes formulation can be modeled with existing statistical software (e.g., SAS PROC PHREG).³⁰

Stratified Cox model with time-varying exposure and with SW adjustment

We briefly review the calculation for these stabilized weights here. Stabilized weights are calculated at each unique event time for those subjects at risk at the event time. They are time-varying because 1) values of some variables change over time; or 2) exposure status changes for a subject; or 3) risk sets differ due to censoring and events. We estimated the stabilized weights using logistic regression models for each unique event time, allowing intercept and covariates' coefficients to vary. Specifically, let x_{1ij} denote the indicator variable for the time-varying exposure with 1 for exposed and 0 for unexposed for subject i at event time t_j , and w_{ij} denote the SW for subject i at event time t_j . For those exposed, the propensity score π_{ij} is the probability of exposure given the observed covariates $\mathbf{z}_{ij}$ (not including the exposure variable), $\text{prob}(x_{1ij} = 1 | \mathbf{z}_{ij})$. For those not exposed, the propensity score is $1 - \text{prob}(x_{1ij} = 1 | \mathbf{z}_{ij})$.¹⁻³ At time t_j for subject i , if $x_{1ij} = 1$, the SW is calculated as

$w_{ij} = \frac{p_j}{\pi_{ij}}$, and if $x_{1ij} = 0$ it is calculated as $w_{ij} = \frac{1 - p_j}{1 - \pi_{ij}}$ where p_j is the marginal probability of treatment at time t_j without considering covariates.^{4,5,7}

We now propose a stratified Cox model with SW adjustment to estimate an average effect of treatment during follow-up. The stratification is based on unique event times where the risk set at a unique event time consists of those individuals who are at risk of events at that time. The stratified Cox model with SW adjustment has only the time-varying exposure because all confounders are adjusted through SW. We modify the partial likelihood in equations (1) and (2) to fit the stratified Cox model with SW adjustment by allowing the exposure variable to be time-varying across event times. This model assumes different baseline hazard

functions at unique event times. Because the Cox model is modeled through stratification by event times, baseline hazard functions cancel out of equations (1) and (2). We propose a partial likelihood with SWs adjustment as

$$PL_W = \prod_{j=1}^r \frac{\exp(\sum_{i \in D_j} W_{ij} \beta x_{1ij})}{\left[\sum_{i \in R(t_j)} W_{ij} \exp(\beta x_{1ij}) \right] \sum_{i \in D_j} W_{ij}} \quad (3)$$

where β is the coefficient for a time-varying exposure (e.g., clopidogrel treatment versus no treatment) and represents an average of exposure effects across event times. Because treatment status of an individual may change over time, model (3) estimates an average effect of treatment over time. This model can be modified to examine interactions between exposure and other covariates by including the interaction terms in the outcome model. Inclusion of interaction between treatment and a covariate (e.g., gender) would allow treatment effects to differ by subgroup (e.g., gender) while adjusting for other covariates through stabilized weights. Existing statistical procedures (e.g., SAS PROC PHREG) can be used in parameter estimation. To fit the newly proposed stratified Cox model with SWs adjustment in this paper, the cohort data are expanded into multiple observations reflecting the precision of the outcome measurement (e.g., daily or other time increment) and the time-dependent SWs at event times are calculated as described above. This analytic data set contains observations only for those individuals at risk at each observed event time. Those who did not experience events and who were not censored appear r times in the dataset, where r is the total number of unique event times in the study population. Similar to performing conditional logistic regression with the PHREG procedure³⁰, by assigning a fixed value to the time to event variable (e.g., surv=1) for each observation in the analytic dataset, a stratified Cox model with SWs adjustment by event times can be fit using the PHREG procedure in SAS.³¹ The number of terms in the stratified partial likelihood is the number of unique event times, r .

Results

Clopidogrel use example

We used the stratified Cox model by event times with SWs adjustment as in equation (3) to estimate the association of clopidogrel use with subsequent risk of three outcomes, bleeding, MI, and death, in an observational study of patients who received a DES.¹¹ We included the 6447 patients who had all covariate data present in analyses. Clopidogrel use was a time-varying dichotomous variable with 1 or 0 indicating clopidogrel use on a specific day. Follow up started the first day after hospital discharge following DES implantation and continued for 18 months. The stratified Cox model with SW adjustment was developed as follows: 1) fit separate logistic regression models for every unique event time of the follow-up period with treatment status as the dependent variable. 2) calculate the SWs as defined above for every unique event time of follow-up period for each individual (see further detail in the clopidogrel example below). 3) fit the stratified Cox model with SW adjustment to obtain hazard ratios of risk comparing those on clopidogrel versus those not on clopidogrel.

Calculation of SW for the clopidogrel use data

Daily SWs were calculated for the clopidogrel data as previously described by Xu et al.⁸ Briefly, in that work separate logistic regression models were fit on every unique event time of follow-up for those at risk on an event time. At this step the dichotomous variable indicating clopidogrel use each day was handled as the dependent variable and a set of known covariates⁸ were included as predictors of the probability of taking clopidogrel. Among these covariates, indicators for prior bleeding and MI were updated for each successive logistic regression model; other variables were measured at baseline. SWs were then calculated using the formulas described above on each event time of the follow-up period for those at risk. This approach balanced covariates on event times in the data set with SWs.

Fitting Cox models to the clopidogrel use data

We fit a Cox model for counting processes and a stratified Cox model by event times to the clopidogrel use data. The Cox model for counting processes was fit with time-dependent clopidogrel treatment^{28,29} adjusting for the same covariates used in creating SWs.⁸ In this model, patients' follow-up periods were partitioned into intervals with unique combination of all time-varying covariates including clopidogrel use. Multiple observations were then created for these intervals for each patient, with each interval having starting and ending time points. This data set was analyzed with a conventional Cox model.

To fit the stratified Cox model by event times with SWs adjustment for the clopidogrel use data, three outcome-specific data sets were created, including bleeding, MI, and death. The bleeding outcome dataset contained 339 bleeding events occurring on 221 unique days during the 540 follow-up days. In this analytic dataset, an individual may appear up to 221 times. The MI outcome dataset contained 266 MIs occurring on 199 unique days during 540 follow-up days. The death outcome dataset contained 192 deaths occurring on 113 unique days. The newly proposed stratified Cox models were fit to these analytic datasets as described above.

Without covariates and SWs adjustment, the Cox model for counting processes and the stratified Cox model by event times produced the same HRs and p-values for bleeding, MI and death (Table 1). The risk of bleeding increased slightly from 1.48 to 1.52 when covariates were adjusted in the Cox model for counting processes. However, HR increased to 1.92 when a stratified Cox model by event times was adjusted by SWs with a much smaller p-value (0.006 versus <0.0001). For the MI outcome, HR decreased to 0.78 from 0.81 ($p = 0.08$) with covariate adjustment in the Cox model for counting processes. HR decreased to 0.52 ($p < 0.0001$) when the stratified Cox model was adjusted by SWs. For the outcome of death, HR slightly increased from 0.64 to 0.67 when covariates were adjusted in Cox model for counting processes. In contrast, HR slightly decreased from 0.64 to 0.60 when stratified Cox model was adjusted by SWs with a smaller p-value (0.008 versus 0.0027).

Discussion

Although SWs have been used in analyses of longitudinal studies, our work detailed here extends their use to stratified Cox models. In this paper, we proposed a method to incorporate SWs in stratified Cox models by event times in a manner that allows for time-varying exposures that start and stop multiple times over the follow-up period. Unlike research that assumes patients remain on therapy once started, this work enables use of exposure status on specific event times to calculate SWs. In addition, the frequency of changes to exposure status is unlimited. Weighting by SWs balances known confounders at event times between exposed and unexposed.

While the Cox model for counting processes can analyze survival data with time-varying covariates and recurrent events, the stratified Cox model with SWs adjustment has additional potential advantages. Information on all covariates is absorbed in the SWs included in the partial likelihood (equations (1) and (2)) as weights. There is only one covariate, the exposure variable, in the partial likelihood. Combined, these attributes permit adjustment for numerous covariates while avoiding loss of degrees of freedom and focus the results on the exposure of interest.

Although we employed Breslow's approximation to the partial likelihood when there are tied event times, other approximations such as Efron's³² and Cox's or the discrete method¹⁰ can be used. Breslow approximation works well if at each distinct survival time the number of events (failures) d_j is small or/and the number of patients at risk n_j is large (i.e., the ratio d_j/n_j is small) because it is very close to the exact partial likelihood in (1). Efron suggested another approximation when the ratio d_j/n_j is not small. But often the results are comparable to Breslow's approximation in practice.²⁴ Cox's approximation or discrete method¹⁸ assumes that tied events are permissible. This method can be computationally intensive. When there are no tied events, these approximations reduce to the likelihood function in equation (1).

Similar to prior work that has compared results for conventional approaches and approaches using IPTW or SW³³, the results for the effect of clopidogrel use on MI, bleeding and death outcomes differed for the two analytic methods. The p-values for all three outcomes were smaller from the stratified Cox model with SW adjustment compared to those from the Cox model for counting processes with covariate adjustment. It appears that greater effect size (deviation from the null hypothesis $HR=1$) was the reason for smaller p-values in this example. Previous work has demonstrated that sample size and statistical inference are appropriate in SW regression models.^{7,8} In addition, p-values from the stratified Cox model with SWs adjustment were shown to be comparable to SW adjusted log rank tests in comparing survival functions in observational studies while adjusting for known confounders.⁸ Although such prior work lends support to accepting the stronger effects of the SW models, additional research contrasting the results of Cox model for counting process with covariate adjustment and stratified Cox model with SW adjustment in multiple simulation scenarios when answers are clearly known would likely improve understanding and acceptance of these models in broader research efforts.

Adjustments using propensity scores have several limitations. Propensity models can only adjust for measured covariates and exploration of potential impacts of unmeasured covariates are recommended.³⁴ Although patient medication possession can be estimated in electronic databases, actual ingestion of the drug (such as clopidogrel in this paper) on each event time cannot be confirmed, and therefore misclassification of exposure is always a concern. Sensitivity analyses that examine varied exposure definitions that may extend beyond a single day after exposure ends or that assume drug ingestion ends two weeks prior to the last pill supply date are useful in confirming consistency of results under varied assumptions. Another limitation is that response heterogeneity to treatment due to pharmacogenetic differences in patients was not considered in analyzing outcomes. If patients with potential differing drug responses are identified, treatment effects could be estimated within appropriate subgroups.

There are no studies comparing clopidogrel versus placebo after percutaneous coronary intervention (PCI) with a drug-eluting stent. However, two studies can provide some clinical context to the effect of clopidogrel as compared to placebo. The CURE trial compared clopidogrel versus placebo in addition to aspirin for patients admitted for acute coronary syndrome without ST elevation MI for 3 to 12 months.³⁵ There was a 20% relative risk reduction in the combined endpoint of death from CV cause, MI and stroke in the clopidogrel treated group. There was a 23% relative risk reduction for MI and 7% relative risk reduction for death from cardiovascular cause. For bleeding, the clopidogrel treated group had a 38% relative increase risk of major bleeding. In the PCI subgroup of the CURE trial (PCI CURE), there was a 31% relative risk reduction in death from cardiovascular cause and MI in the clopidogrel treated group.³⁶ Clinical findings in this paper are consistent with the CURE and the PCI CURE trials in direction but not in scale possibly due to difference in population and comparison group.

We conclude that this novel statistical approach has potential application in studying the effects of highly time-varying treatment when monitoring the safety of drug or medical products while adjusting for known confounders.

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Appendix: SAS codes for analyzing clopidogrel data

```
libname stent 'p:\stent';
%let interval=1; %let begin=0; %let length=539; %let outcome=bleed; %let
outcome_date=bleedDt1;
data intervaldt1;
set stent.rx_outcome1;
fup_strt=dischdt+&begin;
if bleedDt1 ne . then studyendx1=bleedDt1; **censoring bld at event;
```



```

else studyendx1=studyendx;
fup_end0=fup_strt+&length;
if&outcome_date ne . then fup_end00=min (&outcome_date, studyendx1);
else fup_end00=studyendx1;
fup_end=min (fup_end0, fup_end00);
dur=fup_end-fup_strt;
if dur>=0;
run;
data intervaldt2;
set intervaldt1;
surv=1;
do days=fup_strt to fup_end;
dis=days-fup_strt;
*assign exposed and unexposed;
if rxstrt1 ne . and rxstrt1<=days<=rxend1
or rxstrt2 ne . and rxstrt2<=days<=rxend2
or rxstrt3 ne . and rxstrt3<=days<=rxend3
or rxstrt4 ne . and rxstrt4<=days<=rxend4
or rxstrt5 ne . and rxstrt5<=days<=rxend5
or rxstrt6 ne . and rxstrt6<=days<=rxend6
or rxstrt7 ne . and rxstrt7<=days<=rxend7
or rxstrt8 ne . and rxstrt8<=days<=rxend8
or rxstrt9 ne . and rxstrt9<=days<=rxend9
or rxstrt10 ne . and rxstrt10<=days<=rxend10
or rxstrt11 ne . and rxstrt11<=days<=rxend11
or rxstrt12 ne . and rxstrt12<=days<=rxend12
or rxstrt13 ne . and rxstrt13<=days<=rxend13
or rxstrt14 ne . and rxstrt14<=days<=rxend14
or rxstrt15 ne . and rxstrt15<=days<=rxend15 then x=1; else x=0;
*assign adverse event - yes or no on a day of follow-up;
if days=&outcome_date then y=1;
else y=0;
output;
end;
run;
proc sort data=intervaldt2;
by studyid days;
*Daily stabilized weights were calculated in a separate program;
data sw;
set stent.sip_intervall1 stent.sip_interval2 stent.sip_interval3;
run;
proc sort data=sw;
by studyid days;
run;

```

```
data intervaldt3;
merge intervaldt2 (in=m) sw;
by studyid days;
if m=1;
run;
***create multiple observations based on exposure changes for each subject;
data intervaldt4;
set intervaldt3;
if bleedDt1 ne . and days>=bleedDt1 then p_bleed=1;
else p_bleed=0;
if MIdate ne . and days>=MIdate then p_MI=1;
else p_MI=0;
age1=age+dis/365;
if age1<65 then agegrp=1;
else if 65<=age1<75 then agegrp=2;
else if age1>=75 then agegrp=3;
if days<rxstrt1 then dum=1;
else if rxstrt1<=days<=rxend1 then dum=2;
else if days<rxstrt2 then dum=3;
else if rxstrt2<=days<=rxend2 then dum=4;
else if days<rxstrt3 then dum=5;
else if rxstrt3<=days<=rxend3 then dum=6;
else if days<rxstrt4 then dum=7;
else if rxstrt4<=days<=rxend4 then dum=8;
else if days<rxstrt5 then dum=9;
else if rxstrt5<=days<=rxend5 then dum=10;
else if days<rxstrt6 then dum=11;
else if rxstrt6<=days<=rxend6 then dum=12;
else if days<rxstrt7 then dum=13;
else if rxstrt7<=days<=rxend7 then dum=14;
else if days<rxstrt8 then dum=15;
else if rxstrt8<=days<=rxend8 then dum=16;
else if days<rxstrt9 then dum=17;
else if rxstrt9<=days<=rxend9 then dum=18;
else if days<rxstrt10 then dum=19;
else if rxstrt10<=days<=rxend10 then dum=20;
else if days<rxstrt11 then dum=21;
else if rxstrt11<=days<=rxend11 then dum=22;
else if days<rxstrt12 then dum=23;
else if rxstrt12<=days<=rxend12 then dum=24;
else if days<rxstrt13 then dum=25;
else if rxstrt13<=days<=rxend13 then dum=26;
else if days<rxstrt14 then dum=27;
else if rxstrt14<=days<=rxend14 then dum=28;
```

```
else if days<rxstrt15 then dum=29;
else if rxstrt15<=days<=rxend15 then dum=30;
elsedum=333;
run;
proc sort data=intervaldt4;
by studyid dum days;
data intervaldt5;
set intervaldt4;
by studyid dum;
if first.dum then do;
pt=1;
yl=y;
end;
retain pt yl;
else do;
pt+1;
yl+y;
end;
if last.dum=1;
run;
proc sort data= intervaldt5;
by studyid dum;
**data set for fitting Cox model for counting processes;
data data4counting;
set intervaldt5;
by studyid;
if first.studyid=1 then cumulative_pt=pt;
retain cumulative_pt;
else cumulative_pt=cumulative_pt+pt;
start=cumulative_pt-pt;
end=cumulative_pt;
run;
**get unique event days using DIS;
data eventdis;
keep dis;
set intervaldt2;
if y=1;
run;
proc sort data=eventdis nodupkey out=dis;
by dis;
run;
proc sort data=intervaldt2;
by dis;
run;
```

```

data disdata;
merge intervaldt2 dis (in=z);
by dis;
if z=1;
run;
proc sort data=disdata;;
by studyid days;
run;
**data set for fitting stratified Cox model;
data data4stratcox;
merge disdata (in=m) sw;
by studyid days;
if m=1;
run;
*model 1: Cox model for counting process without covariates adjustment;
proc tphreg data=data4counting;
model (start, end) * y1(0) =x;
run;
*model 2: Cox model for counting process with covariates adjustment;
proc tphreg data= data4counting;
class agegrp_mi gender bgroup prevmi prvalve diabetes rengrp cvd pvd cld
hypertn tobacco hyprchol prrevasc anychf carshock a_glyco_inhib lvfass
dstatus perimi ndes_lab1 lescomp_lab devlen1 num_lesions mPostTIMI_Complete
offlabel;
model (start, end) * y1 (0) =x agegrp p_bleed p_mi gender bgroup prevmi
prvalve diabetes rengrp cvd pvd cld hypertn tobacco hyprchol prrevasc anychf
carshock a_glyco_inhib lvfass los dstatus perimi ndes_lab1 lescomp_lab
devlen1 num_lesions mPostTIMI_Complete offlabel;
run;
*Model 3: stratified Cox model without SW adjustment;
proc sort data=data4stratcox;
by dis;
proc phreg data=data4stratcox;
model surv*y(0)= x;
strata dis;
run;
*Model 4: stratified Cox model with SW adjustment;
proc phreg data=data4stratcox;
model surv*y (0)= x;
strata dis;
weight sw;
run;

```

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Take-home messages

Assessing the safety and effectiveness of medical products with observational electronic medical record data is challenging when the treatment is time-varying. A Cox model stratified by event times was developed to estimate the effect of time-varying exposure. This model allows for unlimited changes of exposure status at any time during the follow-up period and also allows for recurrent events. Unlike other methods using propensity score based weights, it uses the exposure status of outcomes at event times in creating stabilized weights and in estimating the effect of time-varying exposure.

Table 1
Hazard ratios (95% confidence intervals) and p-values for outcomes bleeding, myocardial infarction and death from Cox model for counting processes and stratified Cox model

outcomes	Cox model for counting processes				Stratified Cox model			
	without covariates adjustment		with covariates adjustment		without SW* adjustment		with SW adjustment	
	HR*	p-value	HR	p-value	HR	p-value	HR	p-value
Bleeding	1.48 (1.12 1.96)	0.006	1.52 (1.10 2.09)	0.01	1.48 (1.12 1.96)	0.006	1.92 (1.37 2.69)	<0.0001
MI	0.81 (0.61 1.07)	0.137	0.78 (0.59 1.03)	0.08	0.81 (0.61 1.07)	0.137	0.52 (0.39 0.69)	<0.0001
Death	0.64 (0.46 0.89)	0.008	0.67 (0.48 0.93)	0.018	0.64 (0.46 0.89)	0.008	0.59 (0.43 0.84)	0.0021

* SW, stabilized weight; HR, hazard ratio; MI, myocardial infarction.