Event dependence in the analysis of cardiovascular readmissions postpercutaneous coronary intervention

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Accepted 14 December 2018
Published Online First 18 January 2019

To cite: Vasudevan A, Choi JW, Feghali GA, *et al*. *J Investig Med* 2019;**67**:943–949.

ABSTRACT

Recurrent hospitalizations are common in longitudinal studies; however, many forms of cumulative event analyses assume recurrent events are independent. We explore the presence of event dependence when readmissions are spaced apart by at least 30 and 60 days. We set up a comparative framework with the assumption that patients with emergency percutaneous coronary intervention (PCI) will be at higher risk for recurrent cardiovascular readmissions than those with elective procedures. A retrospective study of patients who underwent PCI (January 2008–December 2012) with their follow-up information obtained from a regional database for hospitalization was conducted. Conditional gap time (CG), frailty gamma (FG) and conditional frailty models (CFM) were constructed to evaluate the dependence of events. Relative bias (%RB) in point estimates using CFM as the reference was calculated for comparison of the models. Among 4380 patients, emergent cases were at higher risk as compared with elective cases for recurrent events in different statistical models and time-spaced data sets, but the magnitude of HRs varied across the models (adjusted HR [95% CI]: all readmissions [unstructured data]—CG 1.16 [1.09 to 1.22], FG 1.45 [1.33 to 1.57], CFM 1.24 [1.16 to 1.32]; 30-day spaced—CG1.14 [1.08 to 1.21], FG 1.28 [1.17 to 1.39], CFM 1.17 [1.10 to 1.26]; and 60-day spaced—CG 1.14 [1.07 to 1.22], FG 1.23 [1.13 to 1.34] CFM 1.18 [1.09 to 1.26]). For all of the time-spaced readmissions, we found that the values of %RB were closer to the conditional models, suggesting that event dependence dominated the data despite attempts to create independence by increasing the space in time between admissions. Our analysis showed that independent of the intercurrent event duration, prior events have an influence on future events. Hence, event dependence should be accounted for when analyzing recurrent events and challenges contemporary methods for such analysis.

Significance of this study

What is already known about this subject?
- Recurrent hospitalizations are common in longitudinal studies.
- Recurrent events are considered as independent events.
- Different models are employed for analyzing recurrent events.

What are the new findings?
- Traditional time-to-first event analysis does not measure the future events that occur following the first event and hence does not measure the actual burden of the disease.
- Emergent as compared with elective percutaneous coronary intervention patients were at higher risk for recurrent cardiovascular readmissions.
- Independent of the intercurrent event duration, prior events have an influence on future events.

How might these results change the focus of research or clinical practice?
- Event dependence should be accounted for in recurrent event analysis.

INTRODUCTION

Recurrent hospital admissions after percutaneous coronary intervention (PCI) occur between 8.9% and 22% of subjects and pose a significant burden to the hospital and healthcare system.[1] Recurrent hospitalizations are common in longitudinal studies; however, most trials employ composite endpoints based on the time to the first event, which results in a substantial loss of information on the natural course of the health condition. Use of the traditional time-to-first event analysis does not measure the future events that occur following the first event or if the intensity of the events differs. Hence, they do not account for the actual burden of the disease. Several statistical models have been proposed for the analysis of recurrent event data; however, most of these models assume that subsequent event times are independent of one another.[2] Most of these recurrent events are correlated, and the underlying data structure must be accounted for when choosing the statistical

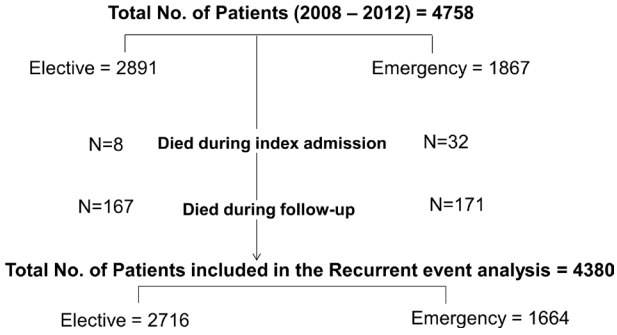

Figure 1 Patient inclusion flow chart.

model. Variance-corrected and frailty effect models, which are variants of Cox models, are employed to account for the correlation. The Andersen-Gill model, Prentice, Williamson, and Peterson conditional model, and the marginal risk Wei, Lin, and Weissfeld models are the most commonly used variance-corrected models.[3–6] The conditional model stratifies the data by event allowing the baseline hazard to vary between the events, which accounts for within-subject correlation due to event dependence.[2] The frailty effects models incorporate heterogeneity as a random effect, which captures the unobserved effects among the individuals. This model assumes that some subjects may be inherently more prone to experience repeated events than others.[7 8] The conditional frailty model proposed by Box-Steffensmeier and De Boef[9] accounts for both event dependence and heterogeneity among the subjects. Admissions within 30 days are considered to be related, and it is assumed that the dependence diminishes as the events are spaced further. However, there are instances when readmissions happen later than 30 days and are strongly related to the prior event. In this study, we explore the presence of event dependence when readmissions are spaced apart by at least 30 and 60 days. We also hypothesize that patients undergoing emergency PCI will be at higher risk for recurrent events than those undergoing elective PCI.

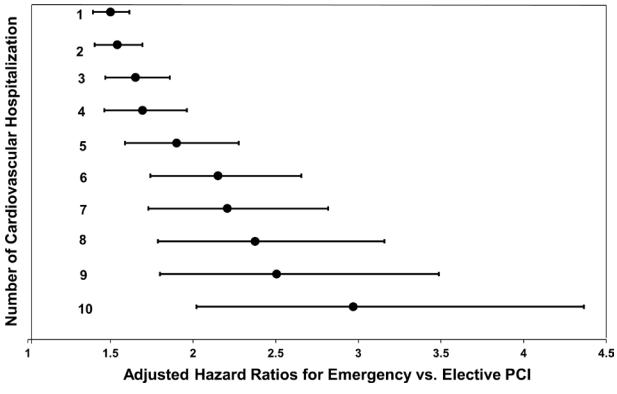

Figure 2 Adjusted HRs for emergent percutaneous coronary intervention (PCI) (event 1 through event 10). Adjusted for age, gender and comorbidities (diabetes, hypertension, cerebrovascular accident, hyperlipidemia, peripheral vascular disease, chronic lung disease and chronic heart failure).

METHODS

This is a retrospective study including all patients who underwent PCI at Baylor Heart and Vascular Hospital and Baylor University Medical Center, Dallas, Texas, from January 2008 to December 2012. The data were abstracted from the information captured for the American College of Cardiology CathPCI Registry. Readmission details for 3 years following PCI were obtained from the Dallas-Fort Worth Hospital Council Foundation. Dallas-Fort Worth Hospital Council Foundation maintains a comprehensive Regional Master Patient Index database, which maintains data on patients admitted to different hospitals in the North Texas region.[10] Only readmission due to cardiovascular (CV) reasons were included in the analysis and were restricted based on the International Classification of Diseases, Ninth Revision, Clinical Modification codes.[11] Mortality was validated by obtaining data from the Death Master File provided by the National Technical Information Service[12] for cases where vital status was uncertain. Event dependence is defined as the relationship between events indicating that the occurrence of an event influences or is related to the following event. The inclusion of the frailty term in these models indicates the heterogeneity that is caused by the unmeasured covariates and is a random-effect model for time event data analysis.

Data sets based on spacing of events

We created different data sets based on the time to the events. The first data set (all non-fatal readmissions) included all CV readmissions post-PCI that happened over the period of 3 years. We then created a data set in which the events were spaced at least over 30 days. Any event that occurred within 30 days was considered as a single event (30-day spaced readmissions). Patients with more than one event within 30 days were considered as one event and all events were systematically spaced 30 days. Another data set was created in which the events were spaced over 60 days (60-day spaced readmissions). Similar to the 30-day spacing, all events were spaced 60 days. Any event between 0 and 60 days of the prior event/index procedure was considered as a single event.

Statistical analysis

Statistical analyses were conducted using STATA V.14.2 and R V.3.2.1. Differences in baseline characteristics, procedural details, and complications between emergency and elective procedures were compared using χ^2/Fisher's exact tests for proportions and Student's t-test/Wilcoxon rank-sum test for continuous variables where applicable. The independent risk factors were identified by the multivariable analysis by including all the factors that were significant by bivariate analysis. The objective of this paper was to identify the risk factors for readmissions and to explore the dependence between events. Because we did not aim to compare hospitals or time cohorts, we did not employ a risk-standardized approach.

Fatal and non-fatal events

Including both fatal and non-fatal readmissions, we conducted a time-to-event analysis. The HRs of the different covariates were calculated separately for the first

Table 1 Demographics and clinical characteristics

	Emergent (n=1835)	Elective (n=2883)	P value
Age (years), mean±SD	61.2±12.0	64.7±10.9	<0.001
Male, n (%)	1224 (66.7)	1973 (68.4)	0.21
Diabetes mellitus, n (%)	633 (34.5)	1134 (39.3)	0.001
Hypertension, n (%)	1482 (80.8)	2600 (90.2)	<0.001
Hyperlipidemia, n (%)	1618 (88.2)	2729 (94.7)	<0.001
Cerebrovascular accident, n (%)	144 (7.9)	236 (8.2)	0.68
Peripheral vascular disease, n (%)	186 (10.1)	392 (13.6)	<0.001
Chronic lung disease, n (%)	155 (8.5)	200 (6.9)	0.06
Chronic heart failure, n (%)	283 (15.4)	443 (15.4)	0.96
Family history of coronary artery disease, n (%)	574 (31.4)	1016 (35.4)	0.005
Prior percutaneous coronary artery intervention, n (%)	532 (28.9)	1128 (39.1)	<0.001
Prior coronary artery bypass grafting, n (%)	260 (14.2)	703 (24.4)	<0.001

through the tenth subsequent events by a Cox proportional hazard survival analysis. A forest plot was constructed to represent the adjusted HRs for the emergency scheduling of the individual recurrent events.

Non-fatal readmissions

Three different models were constructed to study the details on event dependence and heterogeneity: (1) the conditional gap time model (CG) assumed the failure times were conditional on the occurrence of the prior event and thus used information about the time in between successive repeated events; (2) the frailty gamma model (FG) included heterogeneity as a random-effects term in the model which captured the unobserved effects among the individuals and thus allowed some subjects to be more prone to experiencing recurrent events; and (3) the conditional frailty model (CFM) proposed by Box-Steffensmeier and De Boef[9] accounted for both the event dependence by stratification and captured heterogeneity by including a random effect. In order to minimize the problems with convergence in the presence of many event-order strata, we set the limit of events per individual to 11. Any event greater than 10 was considered to be equal to 11 in our analysis.

Relative bias

We compared the results of the three models using the relative bias (%RB) in point estimates using the CFM as the reference.[13]

$$\%RB = (HR\ [FG\ or\ CG] - HR\ [CFM])/HR\ (CFM) \times 100$$

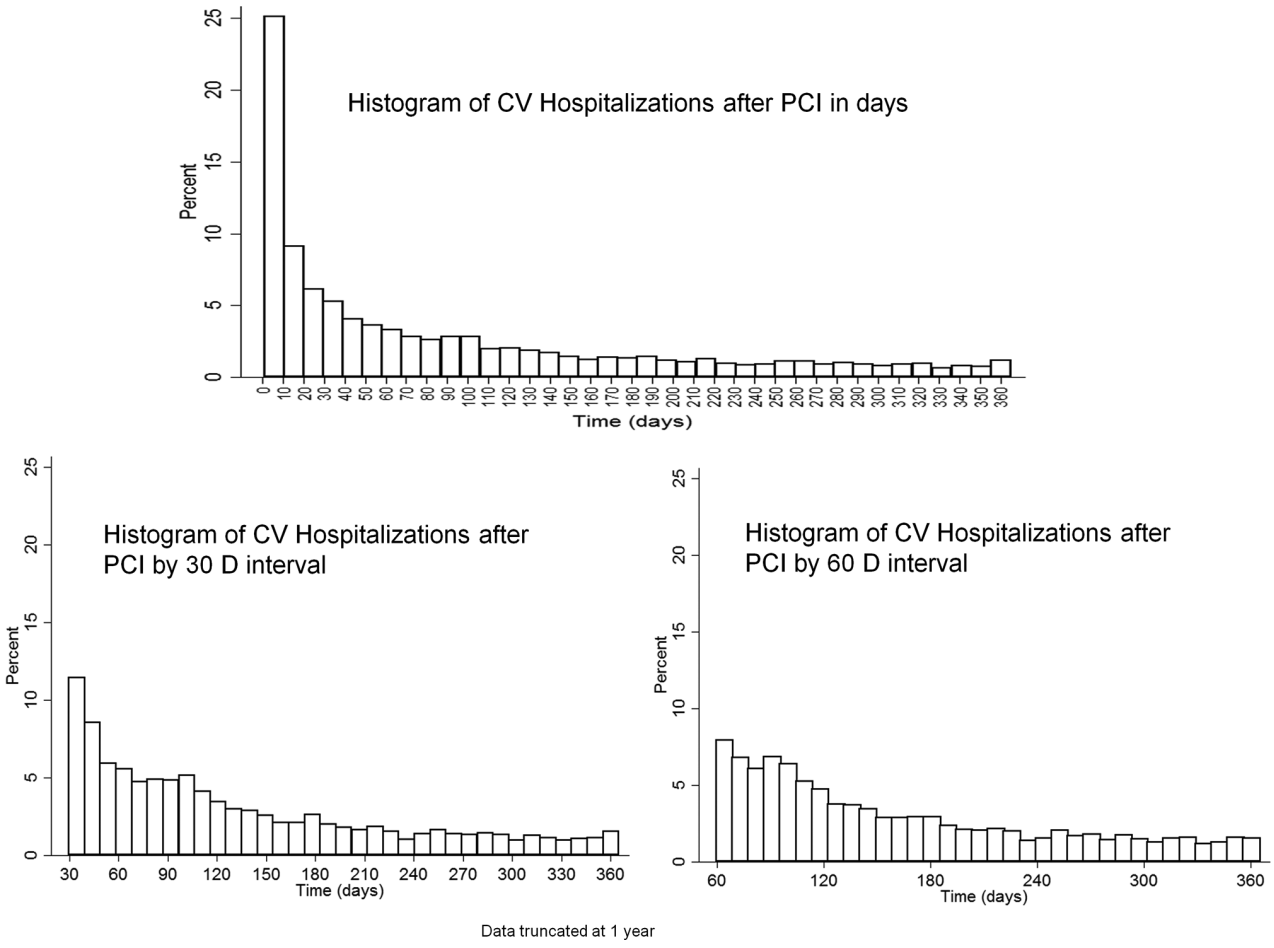

Figure 3 Distribution of events for the time-spaced readmissions. 30D, 30 days; 60D, 60 days; CV, cardiovascular; PCI, percutaneous coronary intervention.

Table 2 Adjusted HR and 95% CI for the different covariates for the different models and time-spaced readmissions

	All admissions (n=9642)			30-day spaced readmissions (n=7283)			60-day spaced readmissions (=6596)		
	Conditional gap	Frailty gamma	Conditional frailty	Conditional gap	Frailty gamma	Conditional frailty	Conditional gap	Frailty gamma	Conditional frailty
Emergency scheduling	1.16 (1.09 to 1.22)	1.45 (1.33 to 1.57)	1.24 (1.16 to 1.32)	1.14 (1.08 to 1.21)	1.28 (1.17 to 1.39)	1.17 (1.10 to 1.26)	1.14 (1.07 to 1.22)	1.23 (1.13 to 1.34)	1.18 (1.09 to 1.26)
Age ≥63	1.02 (0.96 to 1.08)	1.02 (0.94 to 1.10)	1.02 (0.96 to 1.09)	1.04 (0.98 to 1.11)	1.06 (0.98 to 1.16)	1.05 (0.99 to 1.13)	1.06 (1.00 to 1.13)	1.09 (1.00 to 1.19)	1.07 (1.00 to 1.15)
Female	1.15 (1.08 to 1.21)	1.24 (1.14 to 1.34)	1.19 (1.12 to 1.27)	1.19 (1.12 to 1.26)	1.32 (1.21 to 1.45)	1.24 (1.16 to 1.33)	1.19 (1.12 to 1.27)	1.30 (1.20 to 1.42)	1.24 (1.16 to 1.34)
Diabetes mellitus	1.15 (1.08 to 1.22)	1.34 (1.24 to 1.45)	1.23 (1.15 to 1.30)	1.20 (1.13 to 1.27)	1.33 (1.22 to 1.45)	1.25 (1.17 to 1.33)	1.22 (1.14 to 1.29)	1.31 (1.21 to 1.43)	1.26 (1.17 to 1.35)
Hypertension	1.10 (0.95 to 1.27)	1.16 (1.02 to 1.31)	1.13 (1.03 to 1.25)	1.12 (1.01 to 1.25)	1.14 (1.00 to 1.31)	1.13 (1.01 to 1.26)	1.15 (1.02 to 1.28)	1.18 (1.02 to 1.35)	1.15 (1.02 to 1.30)
Cerebrovascular accident	1.21 (1.09 to 1.34)	1.36 (1.18 to 1.57)	1.25 (1.12 to 1.38)	1.24 (1.13 to 1.36)	1.39 (1.20 to 1.61)	1.28 (1.15 to 1.43)	1.23 (1.11 to 1.35)	1.34 (1.16 to 1.55)	1.27 (1.13 to 1.43)
Hyperlipidemia	1.22 (1.08 to 1.36)	1.32 (1.13 to 1.55)	1.22 (1.08 to 1.38)	1.28 (1.12 to 1.45)	1.40 (1.17 to 1.67)	1.30 (1.13 to 1.50)	1.26 (1.10 to 1.45)	1.35 (1.13 to 1.62)	1.29 (1.11 to 1.51)
Peripheral vascular disease	1.20 (1.11 to 1.30)	1.34 (1.19 to 1.51)	1.27 (1.17 to 1.39)	1.24 (1.15 to 1.33)	1.40 (1.23 to 1.58)	1.30 (1.18 to 1.43)	1.24 (1.14 to 1.34)	1.39 (1.23 to 1.57)	1.30 (1.18 to 1.44)
Chronic lung disease	1.09 (0.99 to 1.20)	1.19 (1.02 to 1.39)	1.11 (0.99 to 1.24)	1.09 (0.99 to 1.22)	1.17 (1.00 to 1.37)	1.13 (1.00 to 1.27)	1.10 (1.00 to 1.22)	1.17 (1.00 to 1.37)	1.13 (1.00 to 1.29)
Chronic heart failure	1.19 (1.12 to 1.27)	1.36 (1.22 to 1.51)	1.27 (1.17 to 1.38)	1.25 (1.17 to 1.34)	1.46 (1.30 to 1.63)	1.33 (1.22 to 1.45)	1.25 (1.16 to 1.34)	1.42 (1.27 to 1.59)	1.33 (1.21 to 1.45)
θ		1.1	0.4		1.0	0.3		0.9	0.4
Likelihood ratio for θ		4071 (<0.001)	333 (<0.001)		1704 (<0.001)	29 (0.00001)		981 (<0.001)	8 (0.004)
Log-likelihood for model	−51,046.43	−61,834.99	−49,295.01	−35,066.19	−40,427.00	−34,071.00	−30,689.75	−34,318.12	−29,766.69

We postulated that the estimates of the conditional model would be close to the CFM in circumstances where event dependence was strong, while the estimates of the frailty model would be closer to the estimates of the CFM in situations where heterogeneity was strong.

RESULTS

There were a total of 4758 patients who had an index PCI during our study period. The mean age of the cohort was 63.4±11.5 years and 67.7% were male. Of these, 1867 (39.2%) had an emergency procedure. A total of 40 (0.8%) patients died during the index procedure and 338 (7.1%) died during the 3-year follow-up. A majority of the patients who died had undergone an emergency procedure (203/378) (figure 1). The crude mortality rate per 1000 patients was 109 deaths for emergent procedures vs 61 deaths for elective procedures. The number of readmissions ranged between 1 and 60 (median=2) for emergent procedures and between 1 and 47 (median=2) for elective procedures.

Fatal and non-fatal events

The characteristics of the patients excluding those who died (n=40, 0.8%) during the index admission are presented in table 1. By Cox proportional hazards survival analysis, adjusted HRs were calculated individually for the first through the tenth event. Those with an emergent PCI had an increased risk for CV readmission after adjusting for age, gender and comorbidities (diabetes, hypertension, cerebrovascular accident, hyperlipidemia, peripheral vascular disease, chronic lung disease and chronic heart failure).

Furthermore, this risk stochastically increased for subsequent CV readmissions. For example, those with emergent PCI were at 1.5 times higher risk of CV readmission, 1.54 times the risk of having second CV readmission, and 1.66 times the risk of third CV readmission (figure 2).

Non-fatal CV readmissions

We excluded 338 patients who died during the 3-year follow-up post-PCI. Of the 4380 patients, 1597 (36.5%) did not have a CV readmission during their follow-up. The distribution of the proportion of events for the different time-spaced admissions is presented in figure 3. Table 2 summarizes the HR estimates along with their 95% CIs of the covariates of the three different models for the different time-spaced readmissions. The adjusted HR showed that patients who underwent an emergency PCI had a consistently elevated risk of recurrent events, regardless of the model and/or time-spaced consideration. The values of RB% of the point estimates were then calculated for the different covariates and time-spaced readmissions with CFM as the reference. For example, the RB% of CG (−6.59%, −2.2%, 2.3%) was closer to CFM compared with FG (17%, 8.2%, 4.2%) for 'emergency procedure' in unstructured, 30-day and 60-day spaced readmissions, respectively, suggesting event dependence in the data. For all of the time-spaced readmissions, we found that the values of %RB were closer to the conditional models, suggesting that event dependence dominated the data (figure 4). The cumulative hazards by event number based on the CFM are presented figure 5A–C, and the cumulative hazards can be seen to vary

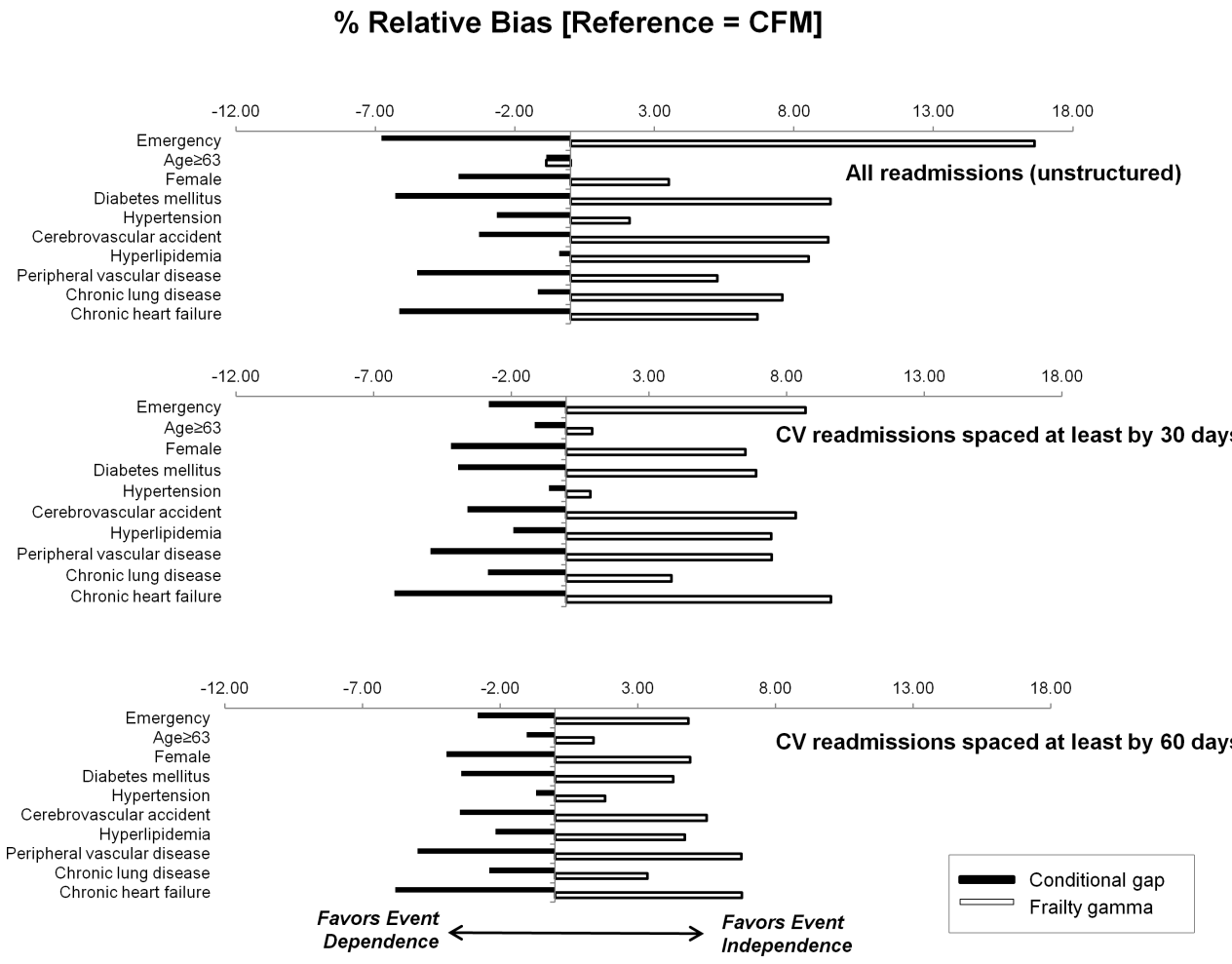

Figure 4 Relative bias of the models in reference to conditional frailty model (CFM). CV, cardiovascular.

by event number. With the spaced data (at least by 30 or 60 days), it can be seen that the cumulative hazards increase in varying magnitude for those with prior events, supporting the presence of event dependence. Including heterogeneity and event dependence, the baseline hazards seem to vary by event numbers in this graph.

DISCUSSION

Our study found emergent as compared with elective PCI patients were at higher risk for recurrent CV readmissions in all three different models and time-spaced data sets, but magnitude of the HR varied across the models. Furthermore, with both the time-spaced data sets (30-day and 60-day), the %RB of the CG model was closer to the CFM, implying the presence of strong event dependence in the data. To limit the issue of convergence (high number of strata with sparse events), we collapsed the event strata to 11.

The conditional model accounts for within-subject correlation and event dependence by stratifying the data by the events, while the frailty models capture the unobserved random effects. However, in clinical practice, it has been well recognized that there exists both heterogeneity and event dependence among the patients. Even certain patients with similar baseline characteristics as others may be more prone to adverse events compared with the others, introducing the possibility of hidden heterogeneity among individuals. This unaccounted variability between the subjects is introduced as a random effect in the frailty model. In addition, within-subject variations are complicated due to event dependence where the risk of a new event depends on the number of previous events. The CFM effectively accounts for both event dependence and heterogeneity simultaneously replicating the complex nature of the clinical data. Hence, we included CFM as the reference in our analysis to account for both event dependency and heterogeneity. It has been previously shown that use of CFMs produce unbiased results when dealing with repeated events that exhibit both heterogeneity and event dependence.[9 13–15] Further, it has been emphasized that competing risks of mortality confound the analysis of recurrent events.[16] Among patients with heart failure, it has been observed that mortality thwarts readmissions leading to skewed result.[17] Hence, we excluded those patients who died during the 3-year follow-up in our analysis in order to handle the issue of competing risk.

The traditional time-to-first event analysis results in a substantial loss of information and also does not measure the complete burden of the disease. The recurrent events must be accounted for in clinical trials to provide complete

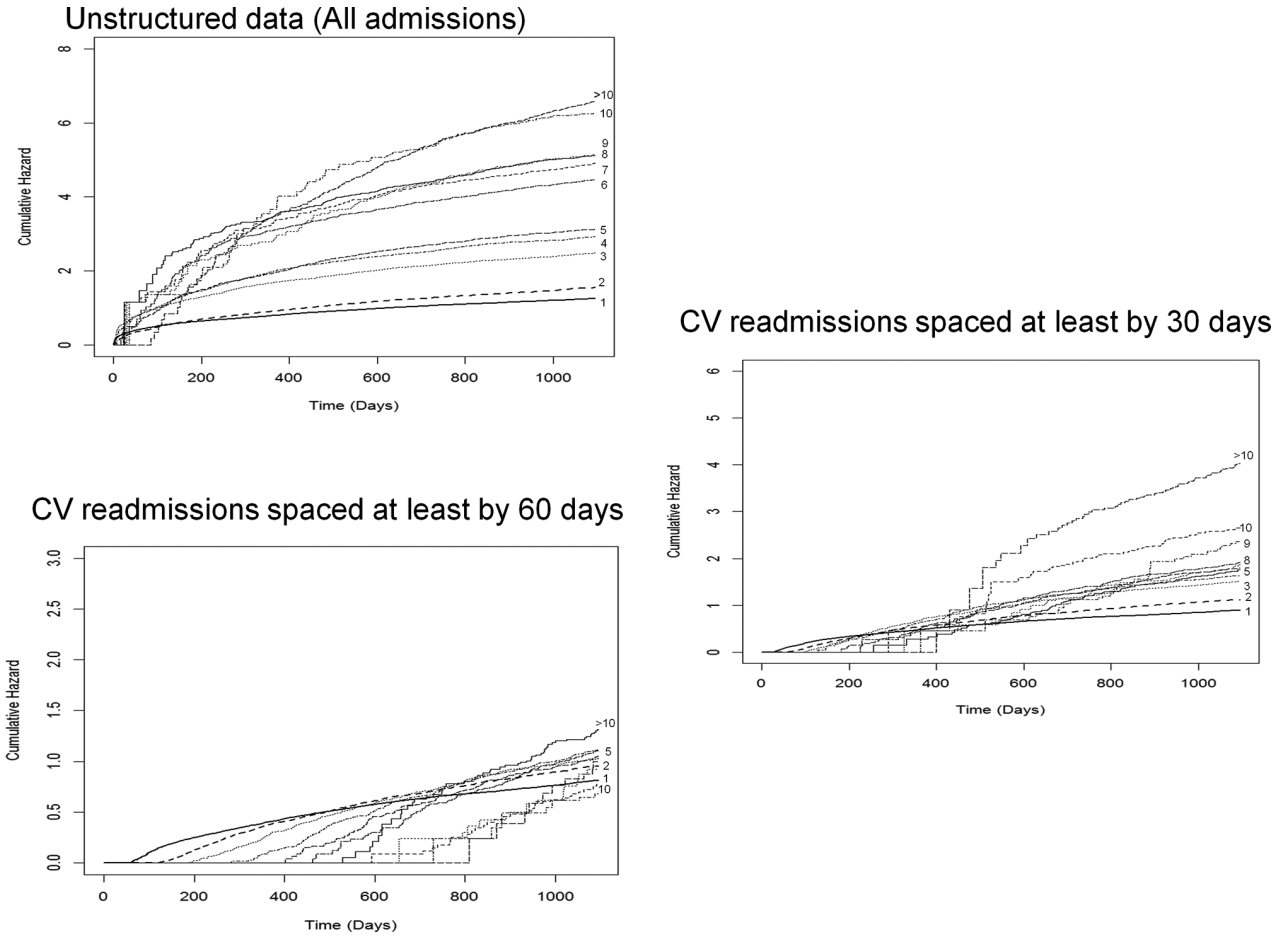

Figure 5 Estimated cumulative hazards for each event by conditional frailty model. CV, cardiovascular.

details on the progression of the disease, as well as the economic liability for the hospital and patients. It has been shown that accounting only for the first event ignored the additional 44% of heart failure hospitalizations and 42% of CV deaths in a randomized control trial.[18] It has also been emphasized that there is a need to report the effect of a drug on the non-fatal events and that the findings should not be restricted to reporting only the fatal outcomes.[19] Clinical trials in CV research have realized the importance of including recurrent events and have accounted them for in their statistical analysis plan; however, the issue of independence of subsequent events has not previously been handled.[20–22] Our results suggest that recurrent events cannot be considered independent no matter how long a period of time is inserted between the events. Thus the assumption of the Andersen-Gill model, which incorporates the Cox model into a counting process, is valid if the time between events is facilitated by time-varying covariates. The Prentice, Williamson, and Peterson conditional model stratifies the data by the event allowing for the baseline hazard to vary between events. This model can be fitted in gap time when the time index resets to zero after each recurrent event or in total time which calculates the effect of a covariate from the time of entry into the study. The marginal means/rates model assumes a baseline hazard for all events with no mention of a dependence structure or time-varying covariates and would be inappropriate if event dependence is of importance.[2]

Our study has all the limitations of retrospective studies of prospectively collected data. Importantly, we did not have time-varying covariates such as blood pressure, lipid values, and medications such as antiplatelet agents, which can vary in their intensity when a patient has progressively more events after PCI. Some of the patients included in the analysis had a prior PCI. We used %RB to ascertain the presence of dependence, while the magnitude of dependence between events was not calculated. We recognize we may have lost patients to follow-up if they were hospitalized outside of the Dallas Forth Worth metro area. We were able to obtain a complete cohort of patients who underwent PCI at our center and their corresponding CV readmissions from the Dallas-Fort Worth Hospital Council Foundation, but had no ability to capture hospitalizations beyond our region. Being a retrospective study, some bias may have been induced due to uncaptured covariates in the registry, such as procedural details, intercurrent revascularization performed at a distant center, or new important illnesses such as malignancy.

CONCLUSION

Our analysis showed that irrespective of the period between events, prior events have an influence on future events when

we analyze expected risks of hospitalization after urgent versus elective PCI. Hence, event dependence should be considered when choosing models to analyze recurrent events after PCI.

Contributors AV, PAM, LJ: substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data. AV, LJ, PAM, JWC, GAF, SRL,JMS, RCS, RCV, CEV: drafting the work or revising it critically for important intellectual content. AV, LJ, PAM, JWC, GAF, SRL,JMS, RCS, RCV, CEV: final approval of the version published. AV, PAM: agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding This study was funded by the Cardiovascular Research Review Committee.

Competing interests RCS: Medtronic: Advisory Board, Global TAVR proctor; Boston Scientific: Advisory Board, Global TAVR proctor, Others: none to report. This study was funded by the Cardiovascular Research Review Committee.

Patient consent Not required.

Ethics approval This study was approved by the Baylor Health Care System Institutional Review Board with a waiver of consent.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 National Cardiovascular Data Registry. Hospital 30-Day Risk-Standardized Readmission Rate Following Percutaneous Coronary Intervention Measure [Internet]. https://www.ncdr.com/WebNCDR/analytics/pcireadmissionmeasure.
2 Amorim LD, Cai J. Modelling recurrent events: a tutorial for analysis in epidemiology. *Int J Epidemiol* 2015;44:324–33.
3 Prentice RL, Williams BJ, Peterson AV. On the regression analysis of multivariate failure time data. *Biometrika* 1981;68:373–9.
4 Wei LJ, Lin DY, Weissfeld L. Regression analysis of multivariate incomplete failure time data by modeling marginal distributions. *J Am Stat Assoc* 1989;84:1065–73.
5 Clayton D. Some approaches to the analysis of recurrent event data. *Stat Methods Med Res* 1994;3:244–62.
6 Lin DY. Cox regression analysis of multivariate failure time data. *Stat.Med* 1994;13:2233–47.
7 Therneau TM, Grambsch PM. *Modeling Survival Data: Extending the Cox Model*. New York: Springer, 2000.
8 Oakes DA. *Frailty models for multiple event times*. Dordrecht: Survival Analysis, State of the Art, Kluwer Academic Publishers, 1992.
9 Box-Steffensmeier JM, De Boef S. Repeated events survival models: the conditional frailty model. *Stat Med* 2006;25:3518–33.
10 https://dfwhcfoundation.org/data/
11 Hicks KA, Tcheng JE, Bozkurt B, *et al*. ACC/AHA Key data elements and definitions for cardiovascular endpoint events in clinical trials: A report of the american college of cardiology/american heart association task force on clinical data standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). *J Nucl Cardiol* 2014:22:1041–144.
12 https://classic.ntis.gov/products/ssa-dmf/#
13 Torá-Rocamora I, Gimeno D, Delclos G, *et al*. Heterogeneity and event dependence in the analysis of sickness absence. *BMC Med Res Methodol* 2013;13:114.
14 Navarro A, Casanovas G, Alvarado S, *et al*. Analyzing recurrent events when the history of previous episodes is unknown or not taken into account: proceed with caution. *Gac Sanit* 2017;31:227–34.
15 Cui J, Forbes A, Kirby A, *et al*. Parametric conditional frailty models for recurrent cardiovascular events in the lipid study. *Clin Trials* 2008;5:565–74.
16 Anand IS, Win S, Rector TS, *et al*. Effect of fixed-dose combination of isosorbide dinitrate and hydralazine on all hospitalizations and on 30-day readmission rates in patients with heart failure: results from the African-American Heart Failure Trial. *Circ Heart Fail* 2014;7:759–65.
17 Claggett B, Tian L, Castagno D, *et al*. Treatment selections using risk-benefit profiles based on data from comparative randomized clinical trials with multiple endpoints. *Biostatistics* 2015;16:60–72.
18 Borer JS, Böhm M, Ford I, *et al*. Effect of ivabradine on recurrent hospitalization for worsening heart failure in patients with chronic systolic heart failure: the SHIFT Study. *Eur Heart J* 2012;33:2813–20.
19 Anker SD, McMurray JJ. Time to move on from 'time-to-first': should all events be included in the analysis of clinical trials? *Eur Heart J* 2012;33:2764–5.
20 Zsebo K, Yaroshinsky A, Rudy JJ, *et al*. Long-term effects of AAV1/SERCA2a gene transfer in patients with severe heart failure: analysis of recurrent cardiovascular events and mortality. *Circ Res* 2014;114:101–8.
21 Tikkanen MJ, Szarek M, Fayyad R, *et al*. Total cardiovascular disease burden: comparing intensive with moderate statin therapy insights from the IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) trial. *J Am Coll Cardiol* 2009:54:2353–7.
22 Abraham WT, Adamson PB, Bourge RC, *et al*. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet* 2011;377:658–66.