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Estimating Clinical Trial Bleeding Events Using Electronic Health Record Data

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Abstract. Clinical trials conducted for regulatory approval may include outcomes that are informative but not routinely collected in clinical practice. This situation can be problematic when pragmatic clinical trials (PCT) seek to use electronic health record (EHR) data to test the effectiveness of medical products and services in actual practice settings. We use TIMI bleeding events to illustrate how a complex clinical trial endpoint can be implemented using EHR data. While we were able to demonstrate that our EHR-defined bleeding events were associated with differences in patient clinical outcomes, we are not confident that these measurements could be replicated in other locations with consistent reliability and validity. We believe the development of PCT endpoint definitions is an important issue that should be addressed by medical and informatics professional societies, regulators and the medical products industry.

Keywords. clinical trial, electronic health record, endpoint major bleed

1. Introduction

Pragmatic clinical trials have been proposed as a means for testing the effectiveness of medical products and services in actual practice settings.[1] However, clinical trials conducted for regulatory approval may include outcomes that are informative but not routinely collected in clinical practice. This situation can be problematic when pragmatic clinical trials seek to use electronic health record (EHR) data. This paper uses patient bleeding events to illustrate this issue and the problems it creates.

2. Bleeding Classification

Contemporary treatment for acute coronary syndromes (ACS), myocardial infarction or unstable angina, typically includes anti-thrombotic therapies that reduce the likelihood of a subsequent heart attack or stroke, but increase the risk of bleeding complications. [2] Because blood volume loss is not measured directly, clinical trials rely upon surrogate measures that typically use either laboratory criteria that approximate blood loss volume or clinical criteria that describe blood loss diagnosis and treatment.[3] For example, TIMI bleeding classifications emphasize laboratory criteria; whereas, GUSTO bleeding classifications emphasize clinical criteria.

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Previous research has demonstrated that data phenotypes derived from EHR diagnosis and procedure codes have limited ability to identify serious bleeding events.[4] We took an alternative approach and implemented TIMI bleeding classification definitions using actual EHR data. We then estimated the associations between index hospitalization bleeding event severity and subsequent clinical events at 24 months follow-up. The Duke University Medical Center (DUMC) Institutional Review Board approved this project with a waiver of informed consent (Protocol ID: Pro00016034).

3. Methods

3.1. Study Population

This study's population included consecutive patients with ACS undergoing percutaneous coronary intervention (PCI) procedures at Duke University Medical Center (DUMC) between June 2002 and December 2008. Patients were included if they had an ACS diagnosis (ST segment elevation myocardial infarction [STEMI]; non-ST-segment elevation myocardial infarction [NSTEMI], or unstable angina [UA]) and significant CAD (≥ 75% stenosis in ≥ 1 epicardial segment). Patients were excluded if this was not their first PCI during the study periods or they had significant (≥ 75% stenosis) left main CAD, congenital heart disease, or moderate or severe valvular heart disease.

3.2. Data Collection

Index PCI Procedure: The Duke Databank for Cardiovascular Disease (DDCD) was the primary source for baseline demographic, medical history, physical examination, catheterization, and hospitalization administrative data.[5-7] We defined three categories of ACS (STEMI, NSTEMI, and UA) using a hierarchical approach based upon *International Classification of Diseases*, 9th Edition, Clinical Modification (ICD-9-CM) codes collected in the DDCD and its associated administrative databases. DUMC's laboratory reporting database was the source for hemoglobin concentration (g/dl) and hematocrit test (%) results. Blood product usage information (number of transfusions) was obtained from the Duke Blood Bank.

TIMI Bleeding Event: We identified TIMI bleeding events using information obtained during a time window beginning at 30 days before the patient's index PCI admission and ending at that admission's discharge date. Major bleed was defined as: (a) an absolute decrease of ≥5g/dl for hemoglobin concentration; or (b) an absolute decrease of ≥15 % for hematocrit; or (c) an intracranial hemorrhage (ICD-9 diagnosis code 430-432). Minor bleed was defined as: (a) an absolute decrease of ≥3g/dl for hemoglobin concentration or (b) an absolute decrease of ≥ 10% for hematocrit. Both bleeding definitions were adjusted to account for transfusions. If a patient received 1 unit of red blood cells during the time window and that unit was before the 2nd laboratory value, we subtracted 3g/dl from hemoglobin concentration and 9% hematocrit from the 2nd value to adjust for the transfusion.

Follow-Up Clinical Events: The DDCD and DUMC administrative systems were sources for follow-up clinical event data.[8] Follow-up clinical events used in this study included: all-cause mortality, all cause readmission, and readmissions for bleeding. Death events were identified through the DDCD follow-up protocol and confirmed by

an independent physician mortality committee. However, readmission information was available only for DUHS. Readmissions were identified through administrative databases using the ICD-9-CM coding to identify bleeding events.

3.3. Statistical Analyses

Reporting of baseline characteristics and index hospitalization resource use is organized by TIMI bleeding event type (major, minor, and no bleeding event) within ACS type (STEMI, NSTEMI, and UA). Values for baseline characteristics and index hospitalization resource use are summarized as mean (standard deviation) for continuous variables and as percentages for categorical variables.

Follow-up period clinical event rates by index hospitalization bleeding event type were estimated using the Kaplan-Meier method. We used Cox proportional hazards models to estimate unadjusted and ACS-type adjusted hazard ratios comparing bleeding event types for all-cause mortality, all-cause readmission and readmission for bleeding.

4. Results

4.1. Study Population

Between June 2002 and December 2008, 3927 patients met our study's inclusion / exclusion criteria. We further excluded 802 patients: 236 with index hospitalization surgical procedures that may require transfusion, 335 with no laboratory data to determine bleeding events and 231 with limited economic data for use in another study (n=231). This resulted in 3125 patients being included in the present study.

Table 1 Patients by Acute Coronary Syndrome Group

	STEMI (n=1046)			**NSTEMI (n=931)**			**Unstable Angina (n=1148)**		
TIMI Bleed Group	**Major 6%**	**Minor 15%**	**No 79%**	**Major 3%**	**Minor 8%**	**No 89%**	**Major 2%**	**Minor 4%**	**No 95%**
Patient Characteristic									
Female	56	39	27	58	57	36	39	63	36
Age*	63(15)	62(13)	58(13)	65(14)	68(13)	62(12)	67(12)	68(12)	63(12)
Smoking	33	33	44	45	37	49	67	41	51
Diabetes	17	19	17	36	54	29	33	39	33
Hypertension	61	58	53	82	72	68	94	78	74
Heart Failure	1	8	3	33	26	12	28	17	16
Prior PCI	5	5	6	12	13	9	17	10	17
Prior CABG	3	5	4	15	19	19	11	22	29
Resource Use									
Total LOS*	10(8)	6(7)	4(2)	13(10)	8(6)	4(3)	9(7)	6(4)	3(3)
ICU LOS*	5(6)	3(4)	1(1)	6(7)	3(5)	1(1)	1(2)	1(2)	0(1)
Transfusions*	5(3)	3(1)	2(0)	6(4)	3(1)	2(0)	4(3)	3(1)	2(1)
Pacemaker	15	8	3	1	1	1	6	0	1

*mean(standard deviation), age is in years and LOS is in days.

4.2. Patient Characteristics and Resource Use

The percent of patients with bleeding events (major or minor) nearly doubled from UA (5.1%) to NSTEMI (11.3%) and again from NSTEMI to STEMI (21.0%) with a third of bleeding events being major for each ACS type (Table 1). Most differences in patient characteristics were associated with ACS type rather than bleeding type. Patients with STEMI tended to be younger and had a lower cardiac risk factor profile and fewer CAD procedures. Length of stay (LOS) and transfusion use increased with the severity of bleeding in all ACS types (Table 1).

4.3. Patient Outcomes

Half of this study's patients were readmitted by 24 months follow-up (40.2% at 12 months and 50.2% at 24 months); whereas, death (5.8% at 12 months and 9.2% at 24 months) and bleeding admissions (2.8% at 12 months and 4.1% at 24 months) were less frequent. Having an index hospitalization major or minor bleeding event was associated with worse outcomes through 24 months follow-up and this difference was more severe for patients with major versus minor bleeds.

Table 2 Patients Outcomes by Bleeding Group

	KM % (Events)		Unadjusted		Adjusted	
	12 Months	**24 Months**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Deaths	5.8 (177)	9.2 (283)				
No bleed	5.2 (142)	8.3 (226)	1.00		1.00	
Minor bleed	8.4 (21)	14.5 (36)	1.49 (1.18 – 1.88)	<0.01	1.62 (1.28 – 2.06)	<0.01
Major bleed	13.7(12)	20.6 (21)	1.91 (1.38 – 2.66)		2.02 (1.45 – 2.81)	
Readmit	40.2 (1215)	50.2 (1507)				
No bleed	38.9 (1043)	49.2 (1311)	1.00		1.00	
Minor bleed	45.2 (110)	53.2 (128)	1.13 (0.94 – 1.36)	<0.01	1.28 (1.06 – 1.53)	<0.01
Major bleed	63.1 (62)	69.5 (68)	1.95 (1.530 – 2.49)		2.16 (1.69 – 2.76)	
Bleeding	2.8 (84)	4.1 (122)				
No bleed	2.4 (64)	3.7 (96)	1.00		1.00	
Minor bleed	4.6 (11)	6.9 (16)	1.89 (1.11 – 3.20)	<0.01	1.87 (1.09 – 3.22)	<0.01
Major bleed	9.4 (9)	10.5 (10)	3.02 (1.57 – 5.80)		3.00 (1.55 – 5.79)	

5. Discussion

In this study, we implemented TIMI major and minor bleeding definitions using EHR data from a single health care system. We then demonstrated that these bleeding categories were associated with differences in major clinical events at 12 and 24 months follow-up. These results are what would be expected with a successful bleeding category implementation. However, we also encountered local data management issues related to the presence and timing of laboratory values, and the lack of detailed follow-up data for clinical events occurring at other hospitals. We found that the paired hemoglobin / hematocrit laboratory values required to detect changes and identify TIMI bleeding

events were not always available in our EHR. Some patients had none of these laboratory values during the study period and were excluded from our analyses. Other patients had only one of the laboratory values. We decided to include these patients under the assumption that the baseline laboratory values were obtained at another institution and were not entered into the EHR. We also excluded patients undergoing surgical procedures for which transfusions would be common. Our rationale was that we would not be able to determine whether a patient received a transfusion as a complication of their ACS or because of the surgical procedure. We do not know the extent to which our laboratory value assumptions were valid. Lastly, we used transfusion data to adjust observed changes in hemoglobin / hematocrit laboratory values. Our blood bank database did not contain the date the transfusion was administered. Hence, we assumed the date the transfusion was issued from the blood bank was the date of administration, a reasonable assumption given the short time between removal from controlled temperature storage and administration. Our hospitalization data also had limitations. Our EHR collected complete data on death, myocardial infarction, and revascularizations occurring at DUHS and other hospitals. However, data for other readmission types was only available for DUHS hospitalizations. Hence, our all-cause and bleeding hospitalization estimates should be considered as lower bounds for these events' actual occurrence.

Bleeding complications are important indicators of future clinical events and are relevant outcomes for both explanatory and pragmatic clinical trials. Unfortunately, the recent Bleeding Academic Research Consortium (BARC) bleeding categories recommended for explanatory clinical trials would be more difficult to implement than TIMI bleeding categories using EHR data.[9] Two solutions have been proposed: (1) adopt a common cardiovascular data model that incorporates robust bleeding event definitions or (2) use separate bleeding event definitions for explanatory and pragmatic clinical trials. The HL7 Cardiovascular Domain Analysis Model (CV DAM) has been endorsed by the US Food and Drug Administration and is being use in medical society registries. The widespread adoption of this model would enhance the likelihood that sites were collecting the correct data and would make it easier to pool data across multiple sites. However, it would be difficult to enforce conformance to this model at sites not participating in these registries. Another option would be to use transfusions as a surrogate for bleeding events? Transfusions have been shown to be an important indicator in clinical practice and have been included as a component in previous bleeding definitions. Transfusions could easily be tracked using EHR data and could serve as a marker for minor bleeding events. The issue is capturing the elements that would comprise a major vs. minor or no bleeding event. Clearly, this is an important matter that should not be left to informatics professionals alone to resolve. Whether major bleeding events can be described solely by EHR data or whether additional information from clinical site physicians will be required is a matter for future research.

6. Conclusion

As PCTs work to streamline trial data collection, care must be taken to assure that appropriate endpoint data are captured. While EHRs can be of assistance, we have demonstrated that implementation of a common explanatory trial endpoint becomes a complex process when using EHR data. We believe that the development of PCT

endpoint definitions is an important issue that should be addressed jointly by medical and informatics professional societies, regulators and the medical products industry.

7. Disclosure

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