ORIGINAL RESEARCH

Acute Coronary Syndrome and Suicide: A Case-Referent Study

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***Background*—**The high prevalence of acute coronary syndrome (ACS) represents a significant burden on healthcare resources. A robust association exists between depression and increased morbidity and mortality after ACS. This study examined the relationship between suicide and ACS after adjusting for depression and other comorbidities.

***Methods and Results*—**In this case-referent study conducted in Taiwan, the cases were people aged 35 years or older who died from suicide between 2000 and 2012 and 4 live referents, each matched by age, sex, and area of residence. The covariates adjusted for in the analysis were sociodemographic characteristics, physical comorbidities, and psychiatric disorders. We identified 41 050 persons who committed suicide and 164 200 referents. In the case and referent groups, 1027 (2.5%) and 2412 (1.5%) patients had ACS, respectively. After potential confounders were adjusted, ACS was significantly associated with increased odds of suicide (aOR=1.15, 95% confidence interval [CI]=1.05-1.26). The odds of suicide were highest during the initial 6 months post-ACS diagnosis (OR=3.05, 95% CI=2.55-3.65) and remained high for at least 4 years after ACS diagnosis.

***Conclusions*—**ACS patients are at an increased risk of suicide compared with otherwise healthy people. The risk of suicide is particularly high in the 6 months after ACS diagnosis. Our results suggest that we need to identify efficacious methods to recognize those at risk for suicide and to develop effective interventions to prevent such deaths. **(*J Am Heart Assoc*. 2016;5:e003998 doi: 10.1161/JAHA.116.003998)**

Key Words: acute coronary syndrome • acute myocardial infarction • suicide

Acute coronary syndrome (ACS) refers to a spectrum of clinical presentations ranging from those for ST-segment elevation myocardial infarction (STEMI) to those for non-STEMI or unstable angina.[1] Acute myocardial infarction (MI) is one of the leading causes of death in most countries,[2,3] where the high prevalence of ACS represents a significant burden on healthcare resources. Numerous meta-analyses, prospective studies, and systematic reviews have shown that depression is common in patients with ACS.[4,5] A strong association exists between depression and increased morbidity and mortality post-ACS.[6,7] Approximately 20% of patients with ACS report depressive disorders, and an even larger proportion experience subclinical levels of depressive symptoms.[5,8] Depression after an ACS event is strongly related to subsequent cardiovascular outcomes, even after adjusting for cardiac risk factors.[9,10] A recent systematic review concluded that the American Heart Association (AHA) should include depression as a risk factor for adverse medical outcomes in patients with ACS.[5] In 2008, the AHA Science Advisory recommended routine screening for depression in all patients with ACS,[11] but the actual implementation of this recommendation remains insufficient in clinical settings.

Suicide is 1 of the leading causes of death worldwide.[12,13] Coronary heart disease (CHD) and depression are 2 of the most critical causes of disability in countries with advanced economies.[14] Patients with acute life-threatening physical illnesses, such as stroke and MI, are at a significantly increased risk for both suicidal ideation and suicide attempts.[15,16] Larsen et al[17] observed an increased risk of suicide among persons with or without psychiatric illnesses following an MI. Patients with physical and psychiatric distress are not only at an increased risk of cardiovascular

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death following MI but also at a higher risk of suicide.[18] Although depression and its association with cardiac disease have been extensively investigated,[5-7] to our best knowledge, prior studies have not reported the association between ACS and suicide after adjusting for diabetes mellitus, stroke, chronic kidney disease, and psychiatric illness. Therefore, in the present study, we used longitudinal nationwide data obtained from the Health and Welfare Data Science Center (HWDC) and mortality registry data in Taiwan to determine whether ACS is associated with an increased risk of suicide.

Methods

Data Source

This case-referent study used data obtained from the HWDC of the Department of Health. The HWDC manages data for Taiwan's mandatory health insurance program, which was implemented in March 1995 and covers ~99% of the population of more than 23.7 million in Taiwan.[19] The HWDC provides medical information on inpatients and outpatients including their sex, date of birth, dates of admission and discharge, services received from medical institutions, and medication records. Disease diagnosis is based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes. This study was approved by the institutional review committee at Tri-Service General Hospital (No. 1-102-05-120). Our study protocol was also approved by the Institutional Review Board of the National Health Research Institutes. All investigators signed a confidentiality agreement before using the data set.

Study Population

Case Group

Using the National Mortality Registry (NMR) data set, we included persons who died from suicide between January 1, 2000 and December 31, 2012, in the case group. The NMR contains the records of all deaths and has been maintained by the Department of Health of Taiwan since 1981 and is maintained independent of the National Health Insurance Research Database. To ensure accuracy and credibility, the causes of individual death are validated by a committee convened by the Department of Health. The NRM uses ICD-9-CM codes for suicide (codes E950-E959) and hidden suicide (codes E980-E989, E913, and E863) and the corresponding ICD-10 codes when registering causes of death.

Referent Group

The referent group was randomly matched at a ratio of 1:4 to the study group by age, sex, and area of residence by applying the incidence density sampling method. By this matching method, the matched index date was defined as the date of suicide in the case group. Referents in the referent group included those who were still alive at the matched index date but could still become suicide cases in the following years if they committed suicide.

ACS Definition

ACS was defined according to the current 2007 American College of Cardiology/American Heart Association guidelines[20]: electrocardiographic changes consistent with ACS and serial increases in patients who received a diagnosis of STEMI, non-STEMI, or unstable angina pectoris according to standardized criteria.[1] ICD-9-CM codes 410.00 to 410.92 and 411.1 were used as the major diagnostic codes for the data on inpatient, outpatient, or emergency medical visits in the HWDC data set. Patients with ACS in this study were defined as those who received a diagnosis of ACS, including acute MI and unstable angina pectoris, before suicide in the case group and before the matching index date for the referent group. Patients younger than 35 years were excluded because we wanted to limit our study to people who have a reasonable chance of having the ACS exposure. In the case and referent groups, 1027 and 2412 persons had ACS; among them, 315 and 788, respectively, underwent coronary revascularization.

Potential Confounders

In this study we identified the following major physical diseases as potential confounders because they are potentially associated factors for suicide and ACS: hypertension (ICD-9-CM codes 401-405), diabetes (ICD-9-CM code 250), dyslipidemia (ICD-9-CM code 272), cerebrovascular disease (ICD-9-CM codes 430-438), congestive heart failure (ICD-9-CM codes 430-428), chronic kidney disease (ICD-9-CM code 585), chronic obstructive pulmonary disease (ICD-9-CM codes 490-492, 494, and 496), and cancer (ICD-9-CM codes 140-239). Furthermore, we adjusted for the following psychiatric comorbidities because of their close association with suicide: depressive disorders (ICD-9-CM code 311), substance use disorders (ICD-9-CM codes 303-305), anxiety disorders (ICD-9-CM code 300 except 300.4), mood disorders (ICD-9-CM codes 296 and 300.4), and psychotic-related disorders (ICD-9-CM codes 295, 297, and 298). Health system utilization, such as the number of outpatient visits, emergency room (ER) visits, and the number of hospitalizations, in the year before the index date was also included and adjusted for in the analysis. Information on the aforementioned comorbidities was obtained from January 1, 2000, to the index date, with the ICD-9-CM codes occurring at least 3 times during medical visits.

Statistical Analyses

We employed conditional logistic regression to investigate the association between risk factors and suicide by a matched case-referent design. Crude odds ratios (ORs), adjusted ORs (aORs), and 95% confidence intervals (CIs) were used to indicate the relative odds of suicide. ORs were also adjusted for marital status (single vs married or other). We also analyzed for intervention utilization (percutaneous coronary intervention or coronary artery bypass grafting), health system utilization (outpatient and inpatient visits vs ER visit), medical illness (hypertension, diabetes, dyslipidemia, cerebrovascular disease, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, and cancer), and psychiatric illness (depression, substance use, anxiety, mood, and psychotic-related disorders). All analyses were performed using SAS Version 9.3 (SAS Institute, Inc, 1995, Cary, NC). *P* values of <0.05 were considered statistically significant.

Results

The study population comprised 41 050 persons who died from suicide and 164 200 matched referents. As shown in Table, 68.5% and 31.5% were men and women in both the suicide group and the living referent group, respectively. Significant between-groups differences were observed in marital status. Married people were at a lower risk of suicide than those who were single, separated, divorced, and widowed. Patients with a high CCI (score >3) had a greater risk of suicide than did the referents (OR=2.10, 95% CI=2.05-2.17). In the case and referent groups, 1027 (2.5%) and 2412 (1.5%) patients had ACS, respectively. Among persons with suicide, the prevalence of ACS was significantly higher than in the reference group (OR=1.75, 95% CI=1.62-1.88).

A significant difference was also observed in health system utilization between suicide cases and referents. The mean number of outpatient visits was 5.9 (SD=12.6) and 4.7 (SD=8.9), that of hospital admissions was 0.5 (SD=1.3) and 0.1 (SD=0.6), and that of ER visits was 1.3 (SD=3.1) and 0.3 (SD=1.6) for the suicide cases and referents, respectively. Furthermore, we examined the association between the post-ACS diagnosis follow-up period and the risk of suicide. The results showed that the mean period of surveillance between the ACS and the index date (suicide vs matched date for referents) was 35.4 months (SD=33.2) for the suicide cases and 42.6 months (SD=33.5) for the referents. The elevated odds of suicide for patients with ACS were persistent throughout all time periods of follow-up, especially highest during initial diagnosis for ACS or being discharged within 0 to 6 months (OR=3.05, 95% CI=2.55-3.65).

In Table, the results of multivariable conditional logistic regression are also present. The odds of suicide are observed to be higher for patients with more than 20 outpatient visits (aOR=1.43, 95% CI=1.36-1.51), more than 5 hospital admissions (aOR=2.55, 95% CI=2.21-2.94), and for any ER visit (aOR=3.08, 95% CI=2.99-3.17). Table also reveals that most of the increased odds of suicide are more commonly observed in patients with psychiatric and physical comorbidities than in their matched referents. Among the various psychiatric disorders, patients with mood disorders (aOR=6.72, 95% CI=6.37-7.10) and psychotic-related disorders (aOR=4.33, 95% CI=3.97-4.72) were at the highest odds of suicide. In addition, most of the major physical comorbidities were associated with increased odds of suicide, such as cancer (aOR=1.85, 95% CI=1.74-1.96) and CKD (aOR=1.24, 95% CI=1.12-1.36), whereas having hypertension (aOR=0.89, 95% CI=0.86-0.92) or dyslipidemia (aOR=0.76, 95% CI=0.72-0.80) was associated with a lower odds of suicide after other factors had been adjusted.

Discussion

There is a fair amount of data on quality of life after ACS, but this paper is the first to focus on ACS and suicide using a large and revealing health care database. Among 41 050 suicide cases and 164 200 referents, 1027 (2.5%) and 2412 (1.5%) patients had ACS, respectively. After adjustment for confounders, ACS was still significantly associated with a 15% increased odds of suicide. The odds of suicide were highest during the initial 6 months post-ACS diagnosis (OR=3.05, 95% CI=2.55-3.65) and remained high for at least 4 years after ACS diagnosis. Ischemic heart disease is a public health problem worldwide.[21]

In the United States, more than 2 million people are hospitalized annually for chest pain suggestive of ACS.[22] Currently, ACS is a leading cause of mortality in the Asia-Pacific region, accounting for approximately half the global burden.[23] The personal and social ramifications of ACS have become crucial concerns worldwide. A study in Denmark reported an increased risk of suicide following an MI.[17] In the present study we observed not only MI (aOR=1.13, 95% CI=1.02-1.26) but ACS was associated with a high risk of suicide, even after adjusting for other known risk factors of suicide. This is the first case-referent study that used population-based data to investigate the association between suicide and ACS over a decade. The major finding of this study is that among persons with suicide, the prevalence of ACS was significantly higher than in the reference group, but the odds ratio of 1.75 was reduced to 1.15 after adjustment for confounders. ACS patients were at a high risk of suicide, even after potential physical and psychiatric confounders were

Table. Unadjusted Odds Ratios and Adjusted Odds Ratios of Suicide by ACS, Healthcare Utilization, and Comorbidities Identified With Conditional Logistic Regression Models

Variable	Cases (n=41 050)	Referents (n=164 200)	OR (95% CI)	aOR*	95% CI	*P* Value
Sex	n (%)	n (%)				
Male	28 131 (68.5)	112 524 (68.5)				
Female	12 919 (31.5)	51 676 (31.5)				
Age (y), mean (SD)	56.1 (14.7)	56.1 (14.7)				
35 to 44	11 174 (27.2)	44 696 (27.2)				
45 to 54	10 494 (25.6)	41 976 (25.6)				
55 to 64	7404 (18.0)	29 616 (18.0)				
65 to 74	5920 (14.4)	23 680 (14.4)				
≥75	6058 (14.8)	24 232 (14.8)				
Marital status						
Married	20 474 (49.9)	125 365 (76.4)	1.0	1.0		
Never married	6793 (16.6)	12 935 (7.9)	3.49† (3.37-3.62)	3.37†	3.24 to 3.51	<0.0001
Other‡	13 783 (33.6)	25 900 (15.8)	3.69† (3.59-3.79)	3.57†	3.45 to 3.68	<0.0001
CCI						
≤1	16 910 (41.2)	84 490 (51.5)	1.0			
2 to 3	9177 (22.4)	37 675 (22.9)	1.33† (1.29–1.37)			
>3	14 963 (36.5)	42 035 (25.6)	2.10† (2.05–2.17)			
ACS	1027 (2.5)	2412 (1.5)	1.75† (1.62-1.88)	1.15†	1.05 to 1.26	0.0022
Intervention utilization after ACS diagnosis						
PCI	288 (0.7)	712 (0.4)	1.64† (1.43-1.89)	1.11	0.94 to 1.31	0.2376
CABG	27 (0.1)	76 (0.1)	1.42 (0.92-2.21)	1.04	0.63 to 1.71	0.8770
The period of surveillance§ (months), mean (SD)	35.4 (33.2)	42.6 (33.5)				
Non-ACS	40 023 (97.5)	161 788 (98.5)	1.0			
0 to 6	209 (0.5)	283 (0.2)	3.05† (2.55-3.65)			
6 to 12	124 (0.3)	233 (0.1)	2.17† (1.75-2.71)			
12 to 24	185 (0.5)	392 (0.2)	1.92† (1.61-2.29)			
24 to 48	189 (0.5)	603 (0.4)	1.28† (1.09-1.51)			
>48	330 (0.6)	915 (0.4)	1.49† (1.31-1.69)			
Health system utilization in the preceding 1 year						
Number of outpatient visits, mean (SD)	5.9 (12.6)	4.7 (8.9)	1.01† (1.01-1.02)			
<10	33 871 (82.5)	141 244 (86.0)	1.0	1.0		
10 to 19	3817 (9.3)	15 061 (9.2)	1.08† (1.04-1.12)	0.94†	0.90 to 0.99	0.0102
>20	3362 (8.2)	7895 (4.8)	1.84† (1.76-1.93)	1.43†	1.36 to 1.51	<0.0001
Number of hospital admissions, mean (SD)	0.5 (1.3)	0.1 (0.6)	2.02† (1.98-2.06)			
0	39 661 (96.6)	163 470 (99.6)	1.0	1.0		
1 to 4	544 (1.3)	288 (0.2)	7.99† (6.91-9.24)	2.50†	2.10 to 2.98	<0.0001
>5	845 (2.1)	442 (0.3)	8.05† (7.16-9.05)	2.55†	2.21 to 2.94	<0.0001
ER visits, mean (SD)	1.3 (3.1)	0.3 (1.6)	1.59† (1.58-1.61)			
No	21 667 (52.8)	134 022 (81.6)	1.0	1.0		
Yes	19 383 (47.2)	30 178 (18.4)	4.15† (4.05-4.26)	3.08†	3.00 to 3.17	<0.0001

Continued

Table. Continued

Variable	Cases (n=41 050)	Referents (n=164 200)	OR (95% CI)	aOR*	95% CI	*P* Value
Physical comorbidity (yes vs no)						
Hypertension	10 157 (24.7)	37 264 (22.7)	1.15† (1.12-1.18)	0.89†	0.86 to 0.92	<0.0001
Diabetes mellitus	5432 (13.2)	17 116 (10.4)	1.34† (1.29-1.38)	1.21†	1.16 to 1.26	<0.0001
Dyslipidemia	2870 (7.0)	12 820 (7.8)	0.88† (0.85-0.92)	0.76†	0.72 to 0.80	<0.0001
Cerebrovascular disease	2780 (6.8)	6607 (4.0)	1.80† (1.72-1.89)	1.27†	1.20 to 1.35	<0.0001
Congestive heart failure	1031 (2.5)	2348 (1.4)	1.81† (1.68-1.95)	1.20†	1.09 to 1.31	0.0001
Chronic kidney disease	862 (2.1)	1938 (1.2)	1.81† (1.67-1.96)	1.24†	1.12 to 1.36	<0.0001
COPD	2907 (7.1)	7610 (4.6)	1.62† (1.54-1.69)	1.05	1.00 to 1.11	0.0718
Cancer	2.994 (7.3)	5366 (3.3)	2.39† (2.28-2.51)	1.85†	1.74 to 1.96	<0.0001
Psychiatric comorbidity (yes vs no)						
Depressive disorder	1461 (3.6)	573 (0.4)	10.64† (9.64-11.74)	3.22†	2.85 to 3.64	<0.0001
SUD	1123 (2.7)	509 (0.3)	9.24† (8.31-10.29)	2.42†	2.10 to 2.78	<0.0001
Anxiety disorders	6310 (15.4)	6675 (4.1)	4.42† (4.25-4.59)	2.50†	2.39 to 2.62	<0.0001
Mood disorders	7333 (17.9)	3132 (1.9)	11.52† (11.00-12.07)	6.72†	6.37 to 7.10	<0.0001
Psychotic-related disorders	2466 (6.0)	1162 (0.7)	9.04† (8.42-9.72)	4.33†	3.97 to 4.72	<0.0001

ACS indicates acute coronary syndrome; aOR, adjusted odds ratio; CABG, coronary artery bypass graft; CCI, Charlson comorbidity index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ER, emergency room; OR, unadjusted odds ratio; PCI, percutaneous coronary intervention; SD, standard deviation; SUD, substance use disorders.
*Adjusted odds ratio was obtained by using multivariable conditional logistic regression matched by sex, age, and area of residency.
†$P<0.05$.
‡Others included separated, widowed, or divorced.
§The period of surveillance means time period between the ACS and the index date (suicide vs matched date for referents).

adjusted. Furthermore, the risk of suicide was not significantly lowered by revascularization intervention. The odds of suicide were highest in the 6 months following an ACS diagnosis (OR=3.01, 95% CI=2.52-3.60). The mean age of suicide cases with a history of ACS was 68.2 years. The risk of suicide in ACS patients increased with age and the frequency of health system utilization. The risk of suicide increased 8-fold in patients older than 75 years (aOR=8.14, 95% CI=5.73-11.57).

Previous studies have reported a positive correlation between the incidence of deaths from suicide and deaths from ischemic heart disease between 1979 and 2005 in Brazil[24] and a positive association between coronary artery disease and suicide attempts in an elderly population in the south of France.[25] A population-based study in Denmark reported an increased risk of suicide after MI (aOR=3.25, 95% CI=1.61-6.56).[17] Numerous studies have reported a strong relationship between ACS and psychiatric disorders, particularly depression, anxiety, and panic attacks.[7,26,27] A growing body of evidence indicates that psychosocial factors, such as anxiety and depression, affect approximately one third of hospitalized acute MI patients.[28] Patients with MI and unstable angina may exhibit acute stress reactions.[16] Studies have reported an association among acute stress reactions, chronic physical conditions, and suicide attempts, regardless of the presence of associated mental disorders.[16,29] Although it is well recognized that depressed patients with a high level of anxiety respond poorly to treatment, and that anxiety has a negative influence on cardiac outcomes, the role of anxiety in predicting depression in the cardiac population remains unclear.[30,31]

Depression and anxiety that develop after ACS diagnosis have been associated with limited physical abilities, reduced physical function, poor health-related quality of life, and an increased risk of new cardiovascular events or mortality.[10,32,33] Somatic depressive symptoms, such as fatigue and loss of appetite, appear to indicate an increased likelihood that such individuals will respond adversely to uncontrollable major stressful life events.[34] The risk factor of depression observed in the later life of the general population is frequently associated with social isolation, lack of social support or living alone, and a low socioeconomic status.[30] In the present study although we found that ACS was associated with an increased risk of suicide, and other risk factors such as psychotic and mood disorders were also considered, the temporality of mental disorders and ACS remains unclear. Self-report measures of depression are more commonly used as the instrument than structured or semistructured interviews, with the Beck Depression Inventory-I being the most widely used measure. A recent systemic review of 53 studies and 4 meta-analyses concluded that the AHA should elevate depression to the status of a risk factor for adverse medical outcomes in patients with ACS.[5] However, there is concern about the lack of powerful randomized data providing an evidence base for treating depression post-MI. A randomized controlled trial analyzing Enhancing Recovery in Coronary Heart Disease data[35] reported that treating depression with selective serotonin reuptake inhibitors or cognitive behavioral group training (or both) achieved significant improvements in depression but did not demonstrate a benefit for mortality or morbidity related to cardiovascular events.

The major strengths of our study are the large sample, adjustment for critical covariates such as hypertension, diabetes mellitus, and psychiatric illnesses, and the use of a computerized database that is population based and highly representative, enabling a clear observation of the relationship between ACS and suicide. Our information on ACS was collected by professional cardiologists primarily based on the diagnostic criteria of ACS by AHA.[1,36] In the present study the outcome was suicide death, which was more accurate than the definition of suicide ideation or attempts. By using the single-payer nationwide healthcare registry, the study is able to consider all utilization of healthcare for ACS and other major comorbidities so that the estimation of an independent effect of ACS on suicide can be less biased.

Our findings suggest a crucial implication that ACS patients in the Asia-Pacific region are at a high risk of suicide. We suggest clinicians pay attention to patients who have multiple comorbidities, including ACS, for the potential elevated odds of suicide. The absolute risk of suicide post-ACS, however, needs to be established in a future study. In addition to the existing efforts in managing depressive symptoms and reducing suicide, all cardiologists should also be aware of the potential associations between ACS and suicide and have available necessary referrals to specialists for suicide prevention.

The present study has several limitations. First, diagnosis of ACS and suicide or any other physical comorbidity relied on administrative claims data, and misclassification is possible. However, previous studies have shown that the HWDC has acceptable quality for epidemiological estimations and can accurately represent the medical utilization of Taiwan residents. Second, bias might exist because of unmeasured or unknown confounders. Third, this is a single-country study (Taiwan), which significantly limits the global generalizability of the findings. Although this study was conducted in Taiwan, the demographics, symptom presentation, and prevalence of ACS and suicide have some similarities to previous Asian-population studies.[37,38] Fourth, we did not measure event-free survival. In our data we could not differentiate between cardiac and noncardiac causes in the frequencies of health system utilization. However, we still investigated healthcare utilization, which may indicate disease severity. Fifth, the effect size is small, and the data are retrospective and observational. The residual confounding cannot be excluded, and the findings cannot prove a causal relation.

Conclusion

We observed increased odds of suicide in ACS patients even after adjusting for physical and psychiatric illness as well as other medical utilization. The odds of suicide were particularly high in the first 6 months after ACS diagnosis. Patients with post-ACS depression exhibited poor cardiovascular outcomes and increased odds of suicide. Our results support the recommendation that screening for depression and suicidal ideation should be conducted for all patients with ACS, particularly in the early stage of new diagnosis.

Although integrating management of depression with cardiac rehabilitation makes good clinical sense, there is still enough evidence lacking on the effective identification and treatment of depression following MI. Future studies should recruit large samples of participants, such as over 15 000, to make evident the effectiveness of managing mental illness in general and depression in particular to improve various outcomes of ACS, including suicide mortality.

Author Contributions

Dr Liu: study methodology, literature review, data analysis, and manuscript writing. Professor Chang: study design, data analysis, clinical interpretation of the findings, and major manuscript revisions. Dr Wang: study design, data analysis, and clinical interpretation of the findings. Dr Weng: data collection, statistical analysis, and study methodology. Professors Chang, Yeh, and Bai: study design, interpretation of the results, and manuscript revision. All authors contributed to the manuscript and approved the final version.

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Disclosures

None.

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