Sex Differences in Mortality in Children Undergoing Congenital Heart Disease Surgery
A United States Population–Based Study

Ariane Marelli, MD; Kimberlee Gauvreau, ScD; Mike Landzberg, MD; Kathy Jenkins, MD, MPH

Background—The changing demographics of the adult congenital heart disease (CHD) population requires an understanding of the factors that impact patient survival to adulthood. We sought to investigate sex differences in CHD surgical mortality in children.

Methods and Results—Children <18 years old hospitalized for CHD surgery were identified using the Kids’ Inpatient Database in 2000, 2003, and 2006. Demographic, diagnostic, and procedural variables were grouped according to RACHS-1 (Risk Adjustment for Congenital Heart Surgery) method. Logistic regression was used to determine the odds ratio of death in females versus males adjusting for RACHS-1 risk category, age, prematurity, major noncardiac anomalies, and multiple procedures. Analyses were stratified by RACHS-1 risk categories and age. Of 33 848 hospitalizations for CHD surgery, 54.7% were in males. Males were more likely than females to have CHD surgery in infancy, high-risk CHD surgery, and multiple CHD procedures. Females had more major noncardiac structural anomalies and more low-risk procedures. However, the adjusted risk of in-hospital death was higher in females (odds ratio, 1.21; 95% confidence interval, 1.08 to 1.36) on account of the subgroup with high-risk surgeries who were <1 year of age (odds ratio, 1.39; 95% confidence interval, 1.16 to 1.67).

Conclusions—In this large US population study, more male children underwent CHD surgery and had high-risk procedures. Female infants who had high-risk procedures were at higher risk for death, but this accounted for a small proportion of females and is therefore unlikely to have a major impact on the changing demographics in adults in CHD. (Circulation. 2010;122[suppl 1]:S234–S240.)

Key Words: heart defects congenital mortality sex differences

Mortality from congenital defects has declined in the United States, but congenital heart disease (CHD) remains a major cause of death.1 Even so, the demographics of CHD patients have changed over the last 2 decades2 such that at least 1 million adults with CHD are estimated to now be alive in the United States.3 Although it is likely that both females and males with CHD have benefited from the advancements that led to increased survival, the growing number of females with CHD reaching reproductive ages pose challenges in terms of pregnancy outcomes.4 Understanding the factors that govern the numbers and sex distribution of adults with CHD is important for better planning of health services targeting this growing population.

In children with CHD, little data exist on differences in health outcomes between males and females. The report of the New England Regional Infant Cardiac Registry (NERICR) showed that male infants had a 5% higher mortality than female infants.5 On the other hand, higher in-hospital mortality rates were observed from 1989 to 1999 in female children following cardiac surgery in California.6,7 A population-level mortality study in patients of all ages found higher mortality rates in males compared to females with CHD starting at 10 years of age and continuing throughout adulthood.1 Explanations for possible sex differences in adults with CHD include a reduced ratio of male to female births in industrialized countries,8 an increased incidence of severe CHD lesions in males9 requiring cardiac surgery,10 and sex differences in mortality.

We focused our attention on sex differences in CHD related surgical outcomes in children as one potential contributing factor to the changing demographics of the adult CHD population. We hypothesized that a higher proportion of male children had CHD surgery and that female sex was protective when surgical mortality was analyzed throughout childhood. We sought to investigate sex differences in mortality rates related to cardiac surgery in children during and beyond the neonatal period using a large contemporary countrywide US population–based sample. Our goals were

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Methods

Data Sources
Data were obtained from the Healthcare Cost & Utilization Project (HCUP) Kids’ Inpatient Database (KID) for the years 2000, 2003, and 2006. The KID datasets are nationwide samples of inpatient pediatric discharges developed through a federal/state/industry partnership sponsored by the Agency for Healthcare Research and Quality. American Hospital Association definitions were used to identify all nonfederal, short-term, general, and specialty hospitals. Hospital discharge data are collected by designated state agencies and compiled by HCUP; 27 states participated in 2000, 36 in 2003, and 38 in 2006. Each KID dataset contains a 10% random sample of uncomplicated in-hospital births and an 80% sample of complicated in-hospital births and other pediatric discharges for age = 20 years. Available information includes patient demographics, admission characteristics, discharge status, and up to 15 diagnosis codes and up to 15 procedure codes categorized using the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM).

Study Population
This was a retrospective cohort analysis of US population–based samples of CHD surgical hospital admissions in 3 separate years: 2000, 2003, and 2006. Cases entered the cohort at the time of hospital admission for a CHD surgical repair and were followed until discharge or in-hospital death, whichever occurred first.

Study Design
We included all cases <18 year of age with ICD-9-CM codes indicating surgical repair of CHD.10 Cardiac transplantation and catheter-based interventions were excluded, as were newborns <30 days of age or premature infants undergoing ligation of a patent ductus arteriosus only. Variables were selected to allow application of the RACHS-1 (Risk Adjustment for Congenital Heart Surgery) method.11

Outcome
The primary outcome was in-hospital mortality post-CHD surgery. In-hospital death was based on records on the patient discharge status.

Risk Adjustment
The RACHS-1 method was used to adjust for differences in case mix when comparing in-hospital mortality.11 To apply this method, cases were assigned to one of 6 predefined risk categories on the basis of the presence or absence of specific ICD-9-CM diagnosis and procedure codes; risk category 1 has the lowest risk for in-hospital death and category 6 the highest risk. Cases with combinations of cardiac surgical procedures (eg, repair of coarctation of the aorta and ventricular septal defect repair) were placed in the category of the highest risk procedure. Additional clinical variables incorporated as part of the RACHS-1 adjustment include age at surgery (<30 days, 31 days to 1 year, >1 year), prematurity, presence of a major noncardiac structural anomaly, and the presence of multiple cardiac procedures. The RACHS-1 method has been validated in 2 US datasets: the Pediatric Cardiac Care Consortium dataset (year1996) and the hospital discharge databases from 3 states (years 1994 to 1995).11 For the Pediatric Cardiac Care Consortium data, the mortality rates were 0.4% in RACHS-1 risk category 1, 3.8% in RACHS-1 risk category 2, 8.5% in RACHS-1 risk category 3, 19.4% in RACHS-1 risk category 4, and 47.7% in RACHS-1 risk category 6, and the rates were similar in the hospital discharge data.11

However, because of advancements in the care of children with CHD, we would expect an improvement in mortality in each RACHS-1 risk category. Thus, the mortality rates in this dataset should reflect the mortality in RACHS-1 risk categories in the current era.

Statistical Analysis
KID data were pooled across the three years investigated (2000, 2003 and 2006). Descriptive statistics included proportions. Differences between groups were tested using the χ² test.

We assessed the unadjusted and adjusted association between sex and in-hospital mortality using logistic regression models from which we report odds ratios (ORs) and 95% confidence intervals (CIs). In the multivariable analysis, we first applied the full RACHS-1 risk adjustment model because it has been validated as tool to adjust for case-mix in the determination of mortality for CHD surgery.11

The RACHS-1 method uses ages ≤30 days, 31 days to 1 year and ≥1 year. To remove any potential confounding by age in those older than 1 year we further adjusted for ages 1- to 5-, 6- to 12-, and 13- to 17-year-olds, using the oldest group as a reference.

We performed stratified analyses in subgroups defined by age (<1 year, ≥1 year) and RACHS-1 risk categories (risk categories 1 to 3 and 4 to 6). We created these subgroups for the stratified analysis to avoid modeling problems attributable to sparse data on account of low number of in-hospital deaths among noninfant cases with high-risk surgeries. All stratified logistic models in age <1 year were adjusted for major noncardiac anomalies, multiple procedures and prematurity.

All hypotheses were tested at a 2-tailed 0.05 significance level and were performed using SAS software Version 9.1 (SAS Institute, Cary, NC).

Results
Characteristics of Study Population
Of 33 848 hospitalization “cases” for CHD surgeries, 54.7% were in males. Males were more likely than females to have CHD surgery, high-risk CHD surgery in infancy, and multiple CHD procedures, whereas females had more major noncardiac structural anomalies. Although high-risk surgeries were relatively rare (13.2% in risk categories 4 to 6), they accounted for 40.3% of all deaths (Table and Figure 1).

There were more males among the subjects having a high-risk profile, as defined by the risk factors incorporated in the RACHS-1 method: risk category, age <1, premature births, and multiple CHD procedures (Figure 1), with the exception of major noncardiac anomalies (Figure 1). This translated into a higher proportion of males in the high RACHS-1 risk categories and a higher proportion of women in the lowest RACHS-1 risk category. The biggest gap between males and females was for hospitalizations among the 13- to 17-year-olds (60% male versus 40% females) and for high-risk surgical operations (65.0% males versus 35.0% females in RACHS-1 risk category 5 and 60.2% males versus 39.8% females in RACHS-1 risk category 6).

Mortality by RACHS-1 Risk Category and Age
The overall mortality for 2000, 2003, and 2006 of all children undergoing cardiac surgery was 4.1%. Figure 2 shows that mortality rates increased with the increasing RACHS-1 risk category and decreased with increasing age. The highest mortality rate was for the very-high-risk surgeries (23.44% for RACHS-1 risk category 5 to 6). However, these high-risk surgeries represented only 3.5% of all cases, so the absolute number of deaths in this group was low relative to the total number of surgeries (282 deaths of 33 848 surgeries; Table).
Indeed, the largest number of deaths occurred among the lower-risk groups that had more frequent surgeries (N=580 for RACHS-1 risk category 3; Table). With respect to age, both the highest proportion of in-hospital deaths and the highest absolute number of deaths were among infants (Figure 2 and Table).

**Effect of Sex on Mortality in Children After Congenital Heart Surgery**

The unadjusted risk of in-hospital death was not different between males and females (OR, 1.06; 95% CI, 0.96 to 1.19). The risk became significantly higher in females after adjustment for RACHS-1 risk category, age at surgery, multiple procedure and major noncardiac anomaly (OR, 1.21; 95% CI, 1.08 to 1.36). Adjustment for confounding using additional age groups 1 to 5 and 6 to 12 years of age had no significant effect on the odds ratios for females versus males. The adjusted risk of in-hospital death was significantly higher in females and was driven by the high risk of in-hospital death for the females in the subgroup with high RACHS-1 risk categories who were less than one year of age (OR, 1.39; 95% CI, 1.16 to 1.67; Figure 3).

**Discussion**

**Summary of Results**

This is the largest and most contemporary analysis of sex differences in CHD surgical outcomes in children, carried out in 33,848 cases in up to 38 states. Overall, in 2000, 2003, and 2006, 55% of all children having CHD surgery were males, and males were more likely than females to have high-risk CHD surgery and multiple procedures. The predominance of males having CHD surgery compared to females was most striking in neonates and in adolescent years. A predominance of females was observed in those undergoing surgery in the lowest risk category. With the exception of a minority of patients undergoing high-risk surgery, the overall surgical mortality varied from 0.6% to 8.2%. This is the largest study to document that the overall adjusted risk of in-hospital mortality was 21% higher in females but this was accounted for only by female neonates who had a RACHS-1 risk category of 4 to 6, a group that comprised less than 15% of all those undergoing cardiac surgery but accounted for as much as 40% of all CHD surgical deaths.

**Determinants of the Demographics of the CHD Population**

A population-level mortality study in the United States found higher mortality rates in males compared to females with CHD starting at age 10 and continuing throughout adulthood. From a demographic point of view, an increase over time in female-to-male ratio has been observed in Canada in a study of more than 45,000 adults with CHD, whose mean age spanned 29 to 40 years. On the other hand, studies based on hospital samples have shown conflicting results in terms of the sex distribution of hospitalized CHD patients. This can be explained by the fact that male dominance occurs in lesions that carry a greater disease burden, including transposition of great arteries, aortic coarctation, and aortic valve stenosis, whereas milder lesions like atrial septal defects are more common in women. Although sex-related differences

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N (%)</th>
<th>In-Hospital Death</th>
<th>Discharged Alive</th>
<th>P</th>
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<tr>
<td>No. observations (CHD surgeries)</td>
<td>33,848 (100.0)</td>
<td>1371 (100.0)</td>
<td>32,477 (100.0)</td>
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<td>KID cohort</td>
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<tr>
<td>2000</td>
<td>10,066 (29.7)</td>
<td>419 (30.6)</td>
<td>9,647 (29.7)</td>
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<tr>
<td>2003</td>
<td>11,360 (33.6)</td>
<td>513 (37.4)</td>
<td>10,847 (33.4)</td>
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<tr>
<td>2006</td>
<td>12,422 (36.7)</td>
<td>439 (32.0)</td>
<td>11,983 (36.9)</td>
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</tr>
<tr>
<td>Males</td>
<td>18,521 (54.7)</td>
<td>730 (53.2)</td>
<td>17,791 (57.0)</td>
<td>0.27</td>
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<tr>
<td>Age</td>
<td></td>
<td></td>
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<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>19,151 (56.6)</td>
<td>1216 (88.7)</td>
<td>17,935 (55.2)</td>
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<td>1–5 years</td>
<td>8,770 (25.9)</td>
<td>112 (8.2)</td>
<td>8,658 (26.7)</td>
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<tr>
<td>6–12 years</td>
<td>3,757 (11.1)</td>
<td>25 (1.8)</td>
<td>3,732 (11.5)</td>
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<tr>
<td>13–17 years</td>
<td>2,170 (6.4)</td>
<td>18 (1.3)</td>
<td>2,152 (6.6)</td>
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<td>RACHS-1 risk category</td>
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<td></td>
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<td>1</td>
<td>5,024 (14.8)</td>
<td>30 (2.2)</td>
<td>4,994 (15.4)</td>
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<td>2</td>
<td>12,020 (35.5)</td>
<td>209 (15.2)</td>
<td>11,811 (36.4)</td>
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<tr>
<td>3</td>
<td>12,318 (36.4)</td>
<td>580 (42.3)</td>
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<td>4</td>
<td>3,283 (9.7)</td>
<td>270 (19.7)</td>
<td>3,013 (9.3)</td>
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<td>5–6</td>
<td>1,203 (3.5)</td>
<td>282 (20.6)</td>
<td>921 (2.8)</td>
<td></td>
</tr>
<tr>
<td>Premature birth*</td>
<td>998 (2.9)</td>
<td>162 (11.8)</td>
<td>836 (2.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Major noncardiac structural anomaly</td>
<td>1,411 (4.2)</td>
<td>98 (7.1)</td>
<td>1,313 (4.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multiple CHD procedures</td>
<td>6,475 (19.1)</td>
<td>439 (32.0)</td>
<td>6,036 (18.6)</td>
<td>&lt;0.0001</td>
</tr>
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</table>

*The variable was available only for those <1 years.
in outcomes have been well documented for adult females with acquired cardiovascular lesions, data in the CHD population are sparse. In Figure 4, we propose a conceptual model to illustrate the mechanisms that may contribute to shifts in the demographics of the CHD population. We adapt our model from Hummer’s framework categorizing into primary pathways and intervening factors the mechanisms that account for the sex distribution in the adult CHD population. We start with biology of sex determination, analyze mortality, and arrive at CHD demographics (Figure 4).

Biology-based determinants may act through primary pathways, resulting in a sex-specific distribution of lesion severity in incident cases of CHD. We hypothesized that an unequal sex distribution in adults may be explained by a difference in

Figure 1. Sex distribution within categories determined by patient risk factors.

Figure 2. Hospital mortality for CHD surgery by RACHS-1 risk category and by age.
the number of males born with severe CHD requiring surgical interventions in childhood (Figure 4A). Indeed, in the present study, we observed a predominance of females in low RACHS-1 risk categories. Consistent with our findings, in the population-based surveillance system of the Metropolitan Atlanta Congenital Defects Program (MADCAP), a significantly higher male to female ratio was found for hypoplastic left heart syndrome (HLHS), complete transposition of the great arteries (d-TGA), tetralogy of Fallot (TOF) and severe left ventricular tract obstruction.9 Conversely, previous studies have observed a predominance of females born with milder lesions including isolated atrial septal defect.5,9 Consistent with our hypothesis, in this study we also observed a predominance of males undergoing CHD surgical procedures that could contribute to a differential survival to adulthood. The New England Regional Infant Cardiac Registry (NERICP) was one of the most comprehensive registries tracking outcomes of infants born with CHD.5 Confined to the first year of life, patients had to be alive and able to reach a hospital in New England able to offer definitive cardiac care between 1968 and 1974 to be included. In this series, male babies predominated at 53.7%. This was particularly evident for many defects expected to require intervention early in life. These included TGA, HPLHS, TOF and coarctation of the aorta severe enough to present in the newborn, neonatal aortic stenosis, double outlet right ventricle and single ventricle. These data are also consistent with our findings because there was a predominance of males in those undergoing cardiac surgery of whom more than half were performed in those <1 year of age.

Mortality attributable to CHD surgical outcomes is considered one of the most important intervening determinants of long-term survival resulting in an increase in prevalence of adults.17,18 With this study we performed a comprehensive population level analysis on CHD surgical outcomes in children in the US in the current era. The overall mortality in our study was 4.1%. The mortality for CHD surgery using data from the Society for Thoracic Surgeons (STS) database and stratified by complexity varied from <1% to >20%.9 In our analysis, the mortality in children undergoing cardiac surgery in 2000, 2003 and 2006 varied from 0.6% to 23% with a distribution remarkably similar to that reported with the STS database.9 Although the exact cause of death was not available, this study includes only in-hospital deaths that occurred at the time of CHD surgery. These are expected to be related to the CHD surgery. The uniformity between surgical outcomes observed with the STS data prospectively collected and the data presented with the present analysis of KID underscores the validity of the risk stratification tool we used.11,20

Sex differences in mortality of children undergoing cardiac surgery have shown conflicting data. We hypothesized that if males had more severe CHD at birth, female sex would confer a protective effect on surgical mortality and contribute to the changing demographics of the adult CHD population (Figure 4B). We found that, with and without risk adjustment using the RACHS-1 method, female sex was not protective. In fact, we observed that the overall risk-adjusted mortality was higher in females compared to males, suggesting that for the same degree of disease, males died less with CHD surgery. The NERICP data revealed a predominance of males of 53.4% at the point of case discovery, which decreased to 51.8% for 1-year survivors.5 This corroborated with a male mortality which was 5% higher than that observed in females infants.5 Contrary to these findings and consistent with our present findings, Chang and Klitzner were the first to show sex differences in hospital mortality of children undergoing cardiac CHD surgery.6,7 Using data from 1989 to 1999 in California, female sex was associated with an 18% higher risk of death, although females had a larger proportion of low-risk procedures.6 In this study using a larger dataset across the United States, we also found that the overall adjusted risk of
death in females was higher than in males but we demonstrate that this is on account of neonates with high-risk CHD surgery, a group that accounts for a small number of patients but a disproportionate number of deaths, suggesting that these numbers are not large enough to account for possible differences in sex distribution of the adult CHD population. It is noteworthy that in adult females undergoing congenital cardiac procedures, using data from the Nationwide Inpatient Sample (NIS), a trend toward increased in-hospital mortality was also documented in adult females.21 It is interesting to speculate whether the ability for females to reproduce more effectively with milder forms of CHD has provided the evolutionary drive for increased mortality of females with severe CHD relative to males.

In accordance with our conceptual model, the ideal study would include all live and still births with CHD, with longitudinal follow-up until death or adulthood, and with documentation of the causes of death. Unfortunately, no such dataset exists, so researchers need to address one piece of the puzzle at a time. In this study, we address the sex differences in in-hospital mortality following CHD surgery in children. Other intervening factors that we did not explore with the present study may potentially contribute to the sex-related differences in the demographics of the adult CHD population include prenatal sentinel health and prevention, (Figure 4C) and those related to non-CHD outcomes and health care behavior (Figure 4D). Similarly, in this study, we did not investigate the mortality attributable to CHD-related medical complications. In industrialized countries, a significant decline in the proportion of males born from 1970 to 1990 has been observed in the United States and Canada.8 The significance of this pattern and whether it constitutes a sentinel health event remain unclear.8 In Canada, in more than 45 000 adults with CHD, females accounted for 57% of patients, a proportion that was significantly higher than the proportion of females observed in the adult general population.2 The prevalence of CHD was 4.55 per 1000 for females compared to 3.61 per 1000 in males (P<0.0001).2 Prenatal intervening factors may also modify the incidence of conotruncal CHD anomalies, as has been shown for folic acid intake in pregnancy.22 Sex differences in medical healthcare outcomes and healthcare behavior may also account for demographic differences in adults. In a population-based study from the Netherlands, female adult CHD patients had a lower risk of having endocarditis and arrhythmias.23 It is interesting to speculate how female sex may confer a protective effect on mortality in CHD adults through differences in healthcare behavior. This population, whose mean age spans 29 to 40 years,2 could be indirectly benefiting from medical encounters for reproductive surveillance. In addition, a relative female advantage during the decades leading up to those years may be conferred by hormonal24 and/or favorable health behavior variables25 in girls relative to boys. Finally, socioeconomic status, a potential predictor of risk behavior impacting on survival26 was not addressed in the present study.

Limitations
Our findings need to be interpreted in light of the limitations of the study design. Administrative databases are prone to misclassification. The agreement between our surgical mortality and the mortality observed in prospectively collected Society for Thoracic Surgeons data26 supports the validity of KID data. Even so, this information bias is expected to be nondifferential between males and females, minimizing the impact on the interpretation of our findings. Our inability to access clinical information increases the potential for confounding resulting from noncardiac factors impacting on mortality. Our adjustment for prematurity, multiple cardiac procedures, and noncardiac structural anomalies variables was designed to minimize confounding caused by other comorbidities. The use of RACHS-1 method developed for CHD surgery in children, with expert consensus refined by empirical evidence and prior validation using administrative data,21 optimizes the credibility of the instrument for risk stratification. We drew on accurate demographic data using a population sample systematically drawn from across the United States. The use of administrative data sources is expected to reduce the selection bias relative to tertiary center outcome findings. The range of institutions spanned improved our ability to generalize our findings to the population at large.

Conclusions
These limitations notwithstanding, this is the largest study looking at sex-specific mortality after CHD surgery throughout childhood, in a large population-based US sample using a comprehensively validated risk adjustment tool. We sought to determine the sex distribution of children who had CHD surgery and to determine whether either sex had a protective effect on surgical mortality. Although we found that a higher proportion of females had low-risk procedures and that males underwent more CHD surgery, we observed a 21% increase in risk of death in female infants in the highest RACHS-1 risk category, a finding confined to a small group of patients unlikely to be sufficient to alter in the sex distribution of adults with CHD. Our results are expected to contribute to our understanding of the factors governing the changing demographics of the growing population of children and adults surviving with CHD.

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Disclosures
None.

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