Cardiovascular Risk Factors and Incident Acute Renal Failure in Older Adults: The Cardiovascular Health Study

Anuja Mittalhenkle,* Catherine O. Stehman-Breen,†‡ Michael G. Shlipak,§ Linda F. Fried,‖ Ronit Katz,¶ Bessie A. Young,** Stephen Seliger,* Daniel Gillen,¶ Anne B. Newman,†† Bruce M. Psaty,†** and David Siscovick†**

**Division of Nephrology, Department of Medicine, †Department of Epidemiology, School of Public Health, ¶Department of Biostatistics, and **Department of Medicine, University of Washington, Seattle, Washington; ‡Amgen, Thousand Oaks, and §Division of General Internal Medicine, Department of Medicine, Veterans Affairs Medical Center, and Department of Epidemiology and Biostatistics, University of California, San Francisco, California; and ‖Renal Section, Veterans Affairs Pittsburgh Healthcare System, and ††Department of Epidemiology, University of Pittsburgh Graduate School of Public Health and the Division of Geriatric Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania*

Background and objectives: Although the elderly are at increased risk for acute renal failure, few prospective studies have identified risk factors for acute renal failure in the elderly.

Design, setting, participants, & measurements: The associations of cardiovascular disease risk factors, subclinical cardiovascular disease, and clinical coronary heart disease with the risk for development of acute renal failure were examined in older adults in the Cardiovascular Health Study, a prospective cohort study of community-dwelling older adults. Incident hospitalized cases of acute renal failure were identified through hospital discharge *International Classification of Diseases, Ninth Revision* codes and confirmed through physician diagnoses of acute renal failure in discharge summaries.

Results: Acute renal failure developed in 225 (3.9%) of the 5731 patients during a median follow-up period of 10.2 yr. In multivariate analyses, diabetes, current smoking, hypertension, C-reactive protein, and fibrinogen were associated with acute renal failure. Prevalent coronary heart disease was associated with incident acute renal failure, and among patients without prevalent coronary heart disease, subclinical vascular disease measures were also associated with acute renal failure: Low ankle-arm index (≤0.9), common carotid intima-media thickness, and internal carotid intima-media thickness.

Conclusions: In this large, population-based, prospective cohort study, cardiovascular risk factors and both subclinical and clinical vascular disease were associated with incident acute renal failure in the elderly.

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Acute renal failure (ARF) occurs most commonly in older adults and is associated with significant morbidity and mortality, with death rates among hospitalized patients ranging from 25 to >70% (1–4). Despite the prevalence of ARF in elderly adults, few studies have examined potential risk factors (5–7), and no studies have examined risk factors in the elderly. The limited data from small studies suggest that cardiovascular disease (CVD) risk factors, such as hypertension, diabetes, and inflammatory markers, and clinical CVD may be associated not only with chronic kidney disease (CKD) but also ARF. These associations may be particularly important in the elderly, in whom CVD is prevalent. We hypothesized that CVD risk factors and subclinical and clinical disease would be associated prospectively with the risk for development of ARF in older adults. To address these hypotheses, we evaluated the associations of these characteristics with incident ARF in the Cardiovascular Health Study (CHS), a large cohort study of older adults. If our hypotheses are correct, then prospective identification of risk factors for ARF in the elderly may suggest potential subgroups of this high-risk population that may merit additional attention or intervention.

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A.M.'s current affiliation is Division of Nephrology and Hypertension, Department of Medicine, Oregon Health and Science University, Portland, Oregon. S.S.'s current affiliation is Division of Nephrology, Department of Medicine, University of Maryland, Baltimore, Maryland. D.G.'s current affiliation is Department of Statistics, University of California, Irvine, California.

Correspondence: Dr. Anuja Mittalhenkle, Division of Nephrology & Hypertension, Mail Code MQ360, Oregon Health and Science University, 3181 S.W. Sam Jackson Park Road, Portland, OR 97239. Phone: 503-494-7880; Fax: 503-494-7695; E-mail: mittalhe@ohsu.edu

Concise Methods

Study Population

The CHS is a prospective, population-based, observational cohort study of people who were ≥65 yr of age at baseline and was initiated to evaluate risk factors for the development and progression of cardiovascular disease. The CHS cohort was identified and selected from Medicare eligibility lists from four US field centers: Forsyth County, NC; Sacramento County, CA; Allegheny County, PA; and Washington

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County, MD. An additional 687 black individuals were recruited between 1992 and 1993 using similar methods to enrich the study population with black participants. An initial cohort of 5201 were recruited between 1989 and 1990. The design, rationale, and examination details have been described elsewhere (8). Briefly, interview, examinations, and questionnaires were used at the time of enrollment and annually to obtain data on demographic characteristics, insurance status, smoking and alcohol history, body measures, medical history, seated BP, total cholesterol, and medications. Self-report of medical history and cardiovascular diseases were validated according to standardized criteria through assessment of medications, medical records, and relevant information obtained during the initial examination. Exclusion criteria were active treatment for cancer, being wheelchair-bound or institutionalized at baseline, or inability to participate in the examination. A total of 57.3% of those eligible enrolled (9). The eligible individuals were expected to remain in the defined geographic area for at least 3 yr. Comprehensive examinations and interviews were performed annually. Hospital discharge summaries and *International Classification of Diseases, Ninth Revision* (ICD-9) codes were collected for all hospitalizations. The study was approved by institutional review boards at each site. Informed consent was obtained from all participants.

Risk Factors

For each CHS participant, data from the baseline examination of CHS were used to assess the presence or level of various clinical characteristics, including CVD risk factors, subclinical disease, and clinical disease that might influence the risk for ARF. We assessed traditional CVD risk factors, including age, gender, and race (white, nonwhite) with most nonwhite individuals being black (only one nonwhite individual with ARF was not black). Diabetes was defined as the use of insulin or oral hypoglycemic medications or a fasting glucose ≥126 mg/dl; hypertension was defined as a physician's diagnosis of hypertension, the use of antihypertensive medications, or systolic BP >140 mmHg and/or diastolic >90 mmHg; smoking was defined as current smoker *versus* not and lipid levels were defined as HDL cholesterol, LDL cholesterol, and triglycerides. We also evaluated inflammatory markers, including C-reactive protein (CRP), fibrinogen, albumin, and white blood cell (WBC) count. Prevalent coronary heart disease (CHD) was defined as history of previous myocardial infarction (MI), angina, angioplasty, or cardiac bypass surgery. Subclinical cardiovascular disease measures included ankle-arm index ≤0.9, carotid intima-media thickness (IMT) defined as mean of maximum wall thickness of common carotid and mean of maximum wall thickness of internal carotid, and carotid stenosis ≥25%.

Serum chemistries, including creatinine, were performed on the Kodak Ektachem 700 Analyzer (Eastman Kodak, Rochester, NY). The Olympus Demand System (Olympus, Lake Success, NY) was used for total and HDL cholesterol and triglycerides; LDL cholesterol was calculated by the Friedewald formula (10). Fibrinogen was measured in a BBL fibrometer (Becton Dickinson, Cockeysville, MD), and CRP was measured using an ELISA (11). The interassay coefficient of variation for CRP was 5.5%. The coefficients of variation were 3.25% for albumin and 3.09% for fibrinogen. WBC count was measured in local hematology laboratories near each field center, with monitoring or internal and external assurance reports.

ARF

We identified all hospitalizations for incident ARF. Hospital discharge summaries, available on all hospitalizations for the participants, along with ICD-9 diagnosis codes were used to identify cases of ARF. Because we focused on incident cases of ARF during the course of the study, only the first discharge summary with the ICD-9 codes suggestive of ARF was identified. ICD-9 codes that were used to identify possible ARF cases included 584 (acute renal failure), 584.5 to 584.9 (acute renal failure of specified etiology), 788.9 (uremia), and 586 (renal failure, not otherwise specified). Other codes considered were 39.95 (hemodialysis), 54.98 (peritoneal dialysis), V56.8 (peritoneal). Participants were considered to have incident hospitalized ARF during the study period when the discharge record had a renal ICD-9 code of interest and there was further evidence of physician-diagnosed ARF on individual medical record review of the hospitalization record, such as short-term dialysis, renal function returning to baseline, and a rapid rise in creatinine from a normal value.

Of the 5888 participants, 5731 were included in our analysis. Individuals were excluded from this analysis when their creatinine level at baseline was missing ($n = 80$) or when baseline creatinine was ≥3.0 ($n = 21$). Furthermore, for individuals for whom there was a question of progression of CKD, we reviewed the previous discharge summary, when available, to ascertain whether the diagnosis at the identified hospitalization represented ARF or progression of CKD to ESRD. In addition, individuals with pertinent discharge documents missing ($n = 26$) and those who were identified as having ESRD ($n = 30$) from the discharge summaries were excluded. To ascertain whether ARF events had not been identified by relying on ICD-9 codes, 50 charts without ICD-9 codes of interest but with high-risk codes such as diabetes and acute MI were abstracted and none of these charts was found to have evidence of ARF (0%; 95% confidence interval 0 to 6%).

Statistical Analyses

Cox's proportional hazards models (12) were used to estimate the association of each CVD risk factor with incident ARF. Patients were considered at risk from study entry until the first date of ARF, death, or last CHS follow-up. Baseline characteristics of the study population with and without incident ARF were compared using independent t test or χ^2 test where appropriate. Each risk factor of interest was modeled before and after adjustment for the other risk factors. Creatinine, HDL, LDL, triglycerides, CRP, fibrinogen, albumin, WBC count, and carotid IMT were modeled as scaled continuous variables to estimate the risk associated with a 1-SD difference in the level of the risk factor. The distribution of creatinine was not highly skewed; therefore, no transformation was necessary. Multiplicative interactions between baseline creatinine, age, gender, and race were explored in models that included all of these covariates. Analyses also were performed with time-dependent variables for incident MI and incident congestive heart failure (CHF) added to each model to evaluate the effect of controlling for these intervening events on the association of baseline characteristics with risk for incident ARF. Analyses that were performed after exclusion of individuals with estimated GFR <30 at the baseline examination ($n = 44$ with eight in the ARF group) yielded similar results. Results are reported as hazard ratios with 95% confidence intervals and two-tailed P values. $P < 0.05$ was considered statistically significant. Formal hypothesis tests and graphic diagnostics were performed to test the proportional hazards assumption. Stata Statistical Software, Intercooled Version 8.0 (Stata Corp., College Station, TX) was used for the analyses.

Results

ARF developed in 225 (3.9%) of the 5731 community-dwelling participants during a median follow-up period of 10.2 yr. Participants who developed ARF were older and more likely male (Table 1). CVD risk factors at baseline, including hypertension, diabetes, and current smoking, were more common in partici-

Table 1. Baseline characteristics of community-dwelling elderly participants who did or did not develop ARF[a]

Variable	ARF		*P*
	Present (n = 225)	Absent (n = 5506)	
Age (yr; mean ± SD)	75 ± 6.6	73 ± 5.5	<0.01
Female gender (n [%])	83 (37)	3220 (59)	<0.01
Race (n [%])			0.65
white	186 (83)	4654 (85)	
nonwhite	38 (17)	816 (15)	
Married	127 (56)	3673 (67)	<0.01
Education			0.01
less than high school	85 (37)	1576 (29)	
high school/vocational	69 (31)	2011 (37)	
college	71 (32)	1903 (35)	
Hypertension	156 (69)	3286 (58)	0.01
Diabetic	70 (31)	841 (15)	<0.01
CHD at baseline	80 (36)	1026 (19)	<0.01
Current smoking	38 (17)	643 (12)	0.02
Diastolic BP (mmHg)	70 ± 12	71 ± 11	0.59
Systolic BP (mmHg)	142 ± 23	136 ± 22	<0.01
HDL (mg/dl)	49 ± 17	54 ± 16	<0.01
LDL (mg/dl)	126 ± 38	130 ± 36	0.18
Triglycerides (mg/dl)	162 ± 96	138 ± 76	<0.01
Creatinine	1.3 ± 0.4	1.0 ± 0.3	<0.01
Glucose (mg/dl)	130 ± 65	110 ± 34	<0.01
CRP (mg/L)	5.0 ± 6.9	3.6 ± 6.3	<0.01
Fibrinogen (mg/dl)	341 ± 76	323 ± 67	<0.01
Albumin (g/dl)	4.0 ± 0.3	4.0 ± 0.3	0.12
WBC (10^3/mm)	6.9 ± 2.6	6.3 ± 2.1	<0.01

[a]ARF, acute renal failure; CHD, coronary heart disease; CRP, C-reactive protein; WBC, white blood cell.

pants who subsequently developed ARF than among those who did not develop ARF, and participants who developed ARF had a two-fold prevalence of CHD at baseline. Participants who subsequently developed ARF also had higher baseline systolic BP and serum creatinine and triglyceride levels but lower HDL levels.

In a proportional hazards model that included demographic characteristics and baseline serum creatinine only, older age, male gender, nonwhite race, and baseline creatinine all were associated with higher risk for development of ARF (Table 2). The associations of CVD risk factors with incident ARF are presented in Table 3. Diabetes, hypertension, and current smoking were each associated with a higher risk for ARF in multivariate analysis, whereas levels of LDL cholesterol and HDL cholesterol were not associated with a greater risk for ARF. Adjusted for other traditional cardiovascular risk factors, demographics, and creatinine, diabetes and current smoking were associated with a two-fold higher risk for ARF. CRP, fibrinogen, albumin, and WBC count were each associated with a higher risk for ARF (Table 4). A 1-SD increase in fibrinogen was associated with a 20% higher risk for development of ARF beyond the risk conferred by traditional cardiovascular risk factors and demographic characteristics.

Prevalent CHD at baseline was associated with a near doubling of risk for incident ARF in multivariate analysis. In participants without prevalent CHD at baseline, markers of subclinical CVD were also strongly associated with higher risk for ARF (Table 5). Ankle-arm index of ≤0.9 was associated with a two-fold adjusted risk for ARF. For both the common carotid and the internal carotid arteries, increased carotid artery IMT was also associated with a higher ARF risk; however, carotid stenosis >25% was not associated with ARF when traditional cardiovascular risk factors were included in the model.

Of the 553 participants who experienced an MI during follow-up, 37 (7%) occurred in participants who later developed ARF. Of the 986 cases of CHF, 90 (10%) were in participants who later had an ARF event. Although incident MI and CHF both were related to the risk for incident ARF, the associations of traditional CVD risk factors, inflammatory markers, and subclinical vascular disease with risk for ARF were not meaningfully altered after further adjustment for incident MI and CHF as time-dependent covariates.

Discussion

In this prospective, community-based study of older adults, we identified several cardiovascular risk factors, including traditional risk factors, inflammatory markers, and markers of subclinical CVD, that were associated with an increased risk for

Table 2. Association between demographic variables and baseline creatinine and ARF among community-dwelling elderly adults[a]

Risk Factor	Adjusted for	HR (95% CI)
Age (per 1 yr)	Demographics + baseline creatinine	1.06 (1.03 to 1.09)
	Demographics + baseline creatinine + traditional risk factors	1.08 (1.05 to 1.10)
Gender (male *versus* female)	Demographics + baseline creatinine	1.43 (1.06 to 1.93)
	Demographics + baseline creatinine + traditional risk factors	1.33 (0.96 to 1.83)
Race (nonwhite *versus* white)	Demographics + baseline creatinine	1.56 (1.11 to 2.20)
	Demographics + baseline creatinine + traditional risk factors	1.46 (1.02 to 2.10)
Creatinine (per SD)[b]	Demographics	1.78 (1.59 to 2.00)
	Demographics + traditional risk factors	1.65 (1.48 to 1.85)

[a]Demographics: age, gender, and race; traditional risk factors: diabetes, hypertension, current smoking, HDL, LDL, and prevalent CHD. CI, confidence interval; HR, hazard ratio.
[b]Scaled variable = variable/SD of variable.

incident ARF. This is the first report to demonstrate that risk factors for ARF relate to vascular disease in the elderly.

The findings that diabetes, hypertension, and current smoking were associated prospectively with an increased risk for ARF in the elderly are novel to this study and consistent with studies that demonstrated that diabetes and hypertension are risk factors for CKD. The association between diabetes and hypertension and ARF may partially be mediated through the pathway of early CKD, because CKD likely predisposes to acute renal injury. In a multinational study of ARF in critically ill patients, almost 30% of the patients who developed ARF had CKD (13). It is possible that physiologic changes that are associated with hypertension and diabetes increase risk for acute renal injury, just as they contribute to progression of CKD to ESRD. Studies that were performed of patients who underwent cardiac surgery, including cardiac transplantation, found age and diabetes to be predictors for development of ARF requiring renal replacement therapy (14–17). This is also the first study to our knowledge that found current smoking to be associated with increased risk for incident ARF among the elderly. The relationship between smoking and ARF may be related to renal vasoconstriction, especially in the aging kidney; however, there is some evidence that smoking reduces renal plasma flow (18).

We also found an increased risk for ARF associated with

Table 3. Association between cardiovascular risk factors and incident ARF among community-dwelling elderly adults[a]

Risk Factor	Adjusted for	HR (95% CI)
Diabetes	Demographics + baseline creatinine	2.78 (2.08 to 3.71)
	Demographics + baseline creatinine + traditional risk factors	2.45 (1.79 to 3.35)
Hypertension	Demographics + baseline creatinine	1.54 (1.16 to 2.05)
	Demographics + baseline creatinine + traditional risk factors	1.45 (1.08 to 1.94)
Current smoking	Demographics + baseline creatinine	2.02 (1.40 to 2.91)
	Demographics + baseline creatinine + traditional risk factors	2.27 (1.56 to 3.31)
HDL (per SD)[b]	Demographics + baseline creatinine	0.76 (0.61 to 0.96)
	Demographics + baseline creatinine + traditional risk factors	0.91 (0.74 to 1.12)
LDL (per SD)[b]	Demographics + baseline creatinine	0.96 (0.83 to 1.11)
	Demographics + baseline creatinine + traditional risk factors	0.97 (0.84 to 1.12)

[a]Demographics: age, gender, and race; traditional risk factors: diabetes, hypertension, current smoking, HDL, LDL, and prevalent CHD.
[b]Scaled variable = variable/SD of variable.

Table 4. Association between inflammatory factors and incident ARF among community-dwelling elderly adults[a]

Risk Factor[b]	Adjusted for	HR (95% CI)
CRP (per SD)	Demographics + baseline creatinine	1.10 (1.02 to 1.18)
	Demographics + baseline creatinine + traditional risk factors	1.09 (1.02 to 1.16)
Fibrinogen (per SD)	Demographics + baseline creatinine	1.25 (1.11 to 1.41)
	Demographics + baseline creatinine + traditional risk factors	1.20 (1.06 to 1.35)
Albumin (per SD)	Demographics + baseline creatinine	0.87 (0.76 to 1.01)
	Demographics + baseline creatinine + traditional risk factors	0.86 (0.74 to 0.99)
WBC (per SD)	Demographics + baseline creatinine	1.12 (1.05 to 1.19)
	Demographics + baseline creatinine + traditional risk factors	1.08 (1.02 to 1.15)

[a]Demographics: age, gender, and race; traditional risk factors: diabetes, hypertension, current smoking, HDL, LDL, and prevalent CHD.
[b]Each variable is scaled: Scaled variable = variable/SD of variable

inflammatory markers. It is possible that high levels of inflammatory markers reflect a milieu in the kidney that place a patient at higher risk for ARF. Iglesias *et al.* (19) reported an elevated level of soluble TNF-α receptors in patients who had septic shock and developed ARF and hypothesized that the increased levels of the receptors may indicate a more proinflammatory response to renal insults. This is also consistent with a report from Shlipak *et al*. (20), who reported an association between renal insufficiency and increased levels of CRP, fibrinogen, and IL-6 in the CHS population. Elevated levels of inflammatory markers such as CRP have been associated with increased risk for CVD in patients without renal disease and in ESRD (21–25).

Inflammation contributes to the reduction in local blood flow to the kidney and has deleterious effects on tubule function. Recent work by Bonventre *et al.* (26,27) showed that resolvins and protectins, newly identified families of fatty acid metabolites, help to reduce ischemic injury and reduce fibrosis in a mouse model. These compounds may be part of kidney's endogenous mechanism to control inflammation, and perhaps dysregulation in this response may lead to permanent injury to the kidney. Whether inflammatory markers that can be measured in humans correlate with the kidney's endogenous anti-inflammatory mechanisms remains to be elucidated.

An increased risk for ARF was associated with markers of subclinical CVD, after other cardiovascular risk factors were taken into account. Both clinical and subclinical CVD reflect vascular disease burden and were associated with increased risk for ARF. Although we were not able to collect retrospectively information on potential triggers or precipitants of ARF

Table 5. Association between measurements of subclinical CVD and incident ARF among community-dwelling elderly adults[a]

Risk Factor	Adjusted for	HR (95% CI)
Low AAI	Demographics + baseline creatinine	2.43 (1.56 to 3.80)
	Demographics + baseline creatinine + traditional risk factors	2.18 (1.39 to 3.43)
Common carotid IMT (per SD)[b]	Demographics + baseline creatinine	1.35 (1.17 to 1.56)
	Demographics + baseline creatinine + traditional risk factors	1.29 (1.10 to 1.51)
Internal carotid IMT (per SD)[b]	Demographics + baseline creatinine	1.30 (1.13 to 1.49)
	Demographics + baseline creatinine + traditional risk factors	1.23 (1.06 to 1.43)
Carotid stenosis	Demographics + baseline creatinine	1.56 (1.12 to 2.18)
	Demographics + baseline creatinine + traditional risk factors	1.40 (0.99 to 1.98)

[a]Participants without CHD at baseline were included. Demographics: age, gender, and race; traditional risk factors: diabetes, hypertension, current smoking, HDL, and LDL. AAI, ankle-arm index; IMT, intima-media thickness.
[b]Scaled variable = variable/SD of variable.

in this study, it is possible that subclinical vascular disease in the kidney may make it more susceptible to injury.

Sutton *et al.* (28) demonstrated in an animal model that renal microvascular injury in endothelial cells occurs after ischemia and that it leads to increased microvascular permeability and interstitial edema. It is possible that previous vascular injury in the kidney may enhance the risk for further microvascular damage and diminution in renal function.

In contrast to previous studies, which were limited by their cross-sectional design, we were able to evaluate a wide range of CVD risk factors and markers of disease at baseline and follow individuals prospectively for the development of incident ARF. Although incident ARF was not a primary disease end point in the CHS, data previously collected in CHS offered a unique opportunity to study prospectively risk factors for ARF, because potentially important risk factors were assessed at baseline and all hospitalizations (including copies of discharge summaries and ICD-9 discharge diagnosis codes) for every patient were captured during >10 yr of follow-up.

This study has several limitations that should be considered. First, although the identification of incident ARF relied on ICD-9 codes (the ICD-9 codes were used initially to screen >16,000 hospitalizations), the diagnosis of ARF was confirmed using physician diagnoses and other clinical information from hospital discharge summaries. Some misclassification of ARF is possible, given the variability of the records. It is also possible that we missed ARF cases that were not coded with an ICD-9 code of interest. We believe that this is not likely; for testing of this, 50 charts without ICD-9 codes of interest but with high-risk codes such as diabetes and acute MI were randomly abstracted, and none had ARF. Waikar *et al.* (29) recently published a study that showed high specificity and negative predictive value of ARF ICD-9 codes when compared with diagnostic criteria of 100% change in serum creatinine.

An issue that is common to most ARF studies is the lack of consensus regarding the diagnosis of ARF in the literature. Various studies have used level of serum creatinine, change in serum creatinine, physician diagnosis alone, or a combination of these to define ARF. Whether any of these definitions accurately capture all events is a topic of debate (30). A consensus statement defined ARF (RIFLE criteria) (31) in an attempt to standardize the definition of ARF, but whether this definition will gain acceptance in the research and clinical arena remains to be seen.

Despite these limitations, this is the first large cohort study to assess prospectively risk factors for incident ARF and to describe an increased risk for incident ARF associated with a variety of markers of CVD risk and disease in the elderly. In addition, because our study is a community-based study, the results potentially could be generalized to similar, community-dwelling older adults in the United States, in contrast to previous studies from single hospitals.

Conclusions

We found prospective associations of cardiovascular risk factors, subclinical CVD, and clinical CHD with incident ARF. This constellation of predictors suggests that risk for ARF is influenced by the presence and extent of vascular disease. Further studies are needed to confirm our findings and to evaluate whether vascular risk reduction leads to a reduction in the incidence of ARF in this vulnerable population.

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Disclosures

None.

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