ORIGINAL RESEARCH

Patterns of Use of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers Among Patients With Acute Myocardial Infarction in China From 2001 to 2011: China PEACE-Retrospective AMI Study

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Background—Chinese and U.S. guidelines recommend angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) for all patients with acute myocardial infarction (AMI) in the absence of contraindications as either a Class I or Class IIa recommendation. Little is known about the use and trends of ACEI/ARB therapy in China over the past decade.

Methods and Results—Using nationally representative data from the China Patient-centered Evaluative Assessment of Cardiac Events Retrospective Study of Acute Myocardial Infarction (China PEACE-Retrospective AMI Study), we assessed use of ACEI/ARB therapy in 2001, 2006, and 2011, overall and across geographic regions and strata of estimated mortality risk, and predictors of ACEI/ARB therapy, among patients with Class I indication by Chinese guidelines. The weighted rate of ACEI/ARB therapy increased from 62.0% in 2001 to 71.4% in 2006, decreasing to 67.6% in 2011. Use was low across all 5 geographic regions. By strata of estimated mortality risk, in 2001, rates of therapy increased with increasing risk; however, by 2011, this reversed and those at higher risk were less likely to be treated (70.7% in lowest-risk quintile vs. 63.5% in the highest-risk quintile; $P<0.001$).

Conclusion—One third of Chinese AMI patients with Class I indications do not receive ACEI/ARB therapy during hospitalization, with little improvement in rates over time. Patients at higher mortality risk in 2011 were less likely to be treated, highlighting important opportunities to optimize the use of this cost-effective therapy.

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Key Words: acute myocardial infarction • angiotensin-converting enzyme inhibitors • quality of care

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Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been shown to reduce the risk of mortality and major adverse cardiovascular (CV) events in patients with acute myocardial infarction (AMI) in randomized, clinical trials.[1–4] Chinese and U.S. guidelines endorse the use of these agents early after AMI.[5–11] The benefit of therapy is likely greatest in the highest-risk patients, for whom the consequences of undertreatment can be particularly significant.[5–11]

As a cost-effective, widely available therapy,[12] ACEI/ARB is particularly important in China, which faces challenges in caring for an increasing number of patients with AMI in the setting of limited resources. It is estimated that, by 2030, up to 23 million people will suffer an AMI in China.[13] Recognizing that acute CV care for patients with AMI in China is provided in diverse settings, and frequently in hospitals without advanced CV services,[14] it is critical to ensure the universal application of therapies such as ACEI/ARB. Understanding

contemporary trends in the use of ACEI/ARB in China can guide quality improvement efforts both domestically and may stimulate such studies in other low- and middle-income countries facing a similar growing burden of CV disease (CVD).

Accordingly, we analyzed a large, nationally representative sample of AMI patients admitted to Chinese hospitals in 2001, 2006, and 2011, from the China Patient-centered Evaluative Assessment of Cardiac Events Retrospective Study of Acute Myocardial Infarction (China PEACE-Retrospective AMI Study). We sought to determine: (1) rates of ACEI/ARB use among eligible patients during AMI hospitalization and trends in use over time; (2) rates and trends of use across geographic regions; (3) patient and hospital characteristics associated with ACEI/ARB therapy; and (4) rates of use stratified by estimated mortality risk, given that ideal care would preferentially target higher-risk individuals. This government-sponsored study sought to inform practice and policy, as well as serve as a prelude for quality improvement initiatives to optimize treatment of patients with AMI in China.

Methods

Design Overview of China PEACE-Retrospective AMI Study

The design of the China PEACE-Retrospective AMI Study has been published previously.[15] In brief, we created a nationally representative sample of hospitalizations for AMI during 2001, 2006, and 2011 with a 2-stage random sampling design. In the first stage, we identified hospitals using a simple random sampling procedure within each of the 5 study strata: Eastern-rural, Central-rural, Western-rural, Eastern-urban, and Central/Western-urban regions, given that hospital volumes and clinical capacities differ between urban and rural areas as well among the 3 official economic-geographic regions (Eastern, Central, and Western) of Mainland China. We grouped Central and Western urban regions together given their similar per capita income and health services capacity. In the 3 rural strata, the sampling framework consisted of the central hospital in each of the predefined rural regions (2010 central hospitals in 2010 rural regions). In the 2 urban strata, the sampling framework consisted of the highest-level hospitals in each of the predefined urban regions (833 hospitals in 287 urban regions; Figure 1). Because the majority of hospitals in China are publicly owned and administered, hospital closure is rare. We selected representative hospitals from 2011 to reflect current practice and trace this cohort backward to 2006 and 2001 to describe temporal trends. In the second stage, we drew cases based on the local hospital database for patients with AMI in each year at each sampled hospital using systematic random sampling procedures. Patients with AMI were identified using International Classification of Diseases, Clinical Modification, codes, including versions 9 (410.xx) and 10 (I21.xx), when available or through principal discharge diagnosis terms.

We sampled 175 hospitals, of which 7 did not have any admissions for AMI and 6 declined participation. Examination of patient databases from participating 162 hospitals yielded 31 601 hospitalizations for AMI in 2001, 2006, and 2011. We sampled 18 631 cases and finally acquired medical records for 18 110 (97.2%). After excluding those with noninterpretable medical charts, duplicates, not confirmed AMI, cases outside the study periods, and in-hospital AMI events, we identified 16 100 cases with available medical charts (Figure 1).

The central ethics committee at the China National Center for Cardiovascular Diseases approved the China PEACE-Retrospective AMI Study. All collaborating hospitals accepted the central ethics approval except for 5 hospitals, which obtained local approval by internal ethics committees.

Study Sample

Patients with AMI eligible for ACEI/ARB therapy were identified as follows: Only those patients with a definite discharge diagnosis of AMI were included in the study sample. We excluded patients with a hospital length of stay shorter than 24 hours because they might not have had adequate opportunity to receive ACEI/ARB. We also excluded patients who were transferred in from another hospital, given that information regarding ACEI/ARB therapy at their presenting hospital was unknown. In addition, we excluded patients with the following contraindications to ACEI/ARB: history of allergy to ACEI/ARB; hyperkalemia (serum potassium [K^+] >5.5 mmol/L); creatinine (Cr) >3 mg/dL (265 μmol/L); or pregnancy/breast feeding.[9,11,16] To capture the lab values influencing the decision-making process, we used the last lab value of K^+ and Cr before administration of the medication for patients who received ACEI/ARB, and for those who did not receive ACEI/ARB therapy, we used the highest lab value during the hospitalization. Because the Cr level influencing the decision to use ACE/ARB may vary among providers, we performed a sensitivity analysis excluding patients with Cr ≥1.5 mg/dL (133 μmol/L) during hospitalization.

To assess appropriate usage of ACEI/ARB therapy during hospitalization, we separated eligible patients according to Chinese guidelines into 2 groups: (1) Class I recommendation group (Chinese Class I), which included all patients with ST-elevation myocardial infarction (STEMI), and those patients with non-ST-elevation myocardial infarction (NSTEMI) and either heart failure (HF), left ventricular (LV) dysfunction (LV ejection fraction [LVEF] <40%), hypertension (HTN), or diabetes mellitus; (2) Class IIa recommendation group (Chinese

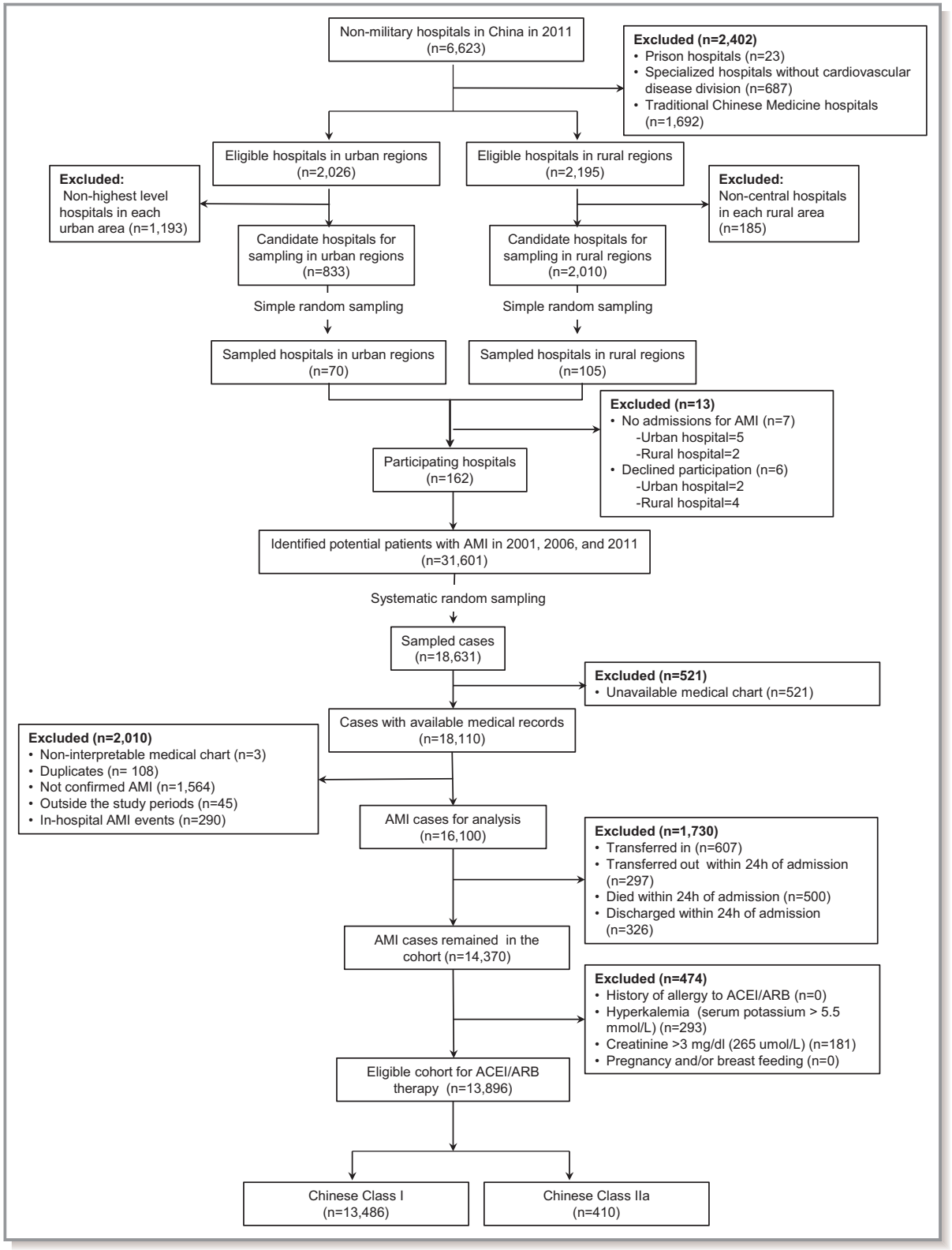

Figure 1. Study sample profile. ACEI indicates angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker.

Class IIa), which included patients with NSTEMI who do not have a Class I indication for receiving ACEI/ARB.[9–11] The diagnosis of AMI type (STEMI vs. NSTEMI) was determined by the combination of clinical discharge diagnosis terms and electrocardiogram (ECG) results. If the local diagnosis was not definitive, cardiologists at the coordinating center reviewed

the medical record and ECG to establish diagnosis. We treated left bundle branch block as a STEMI equivalent.[17]

Moreover, because doctors in China frequently refer to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, we also performed a secondary analysis by grouping patients according to ACC/AHA guidelines. The ACC/AHA Class I recommendation group included STEMI patients with LVEF ≤40%, HTN, diabetes, chronic kidney disease, HF, or anterior MI; and NSTEMI patients with LVEF ≤40%, HTN, diabetes, or HF. The ACC/AHA Class IIa recommendation group included STEMI and NSTEMI patients who do not meet a Class I recommendation for ACEI/ARB.[5–8]

Data Collection

Data were collected by centralized medical record abstraction using standardized data definitions. The following variables were collected: demographics, admission year, medical history, CV risk (CVR) factors, and clinical characteristics on admission and during hospitalization. Hospital characteristics were collected by a hospital survey. Details of these variables are shown in Table 1. We adopted rigorous monitoring at each stage to ensure data quality.[15] Data quality was monitored by randomly auditing 5% of the medical records, which demonstrated an overall variable agreement of >98%.

Outcomes

We defined the use of ACEI/ARB therapy as prescription of either agent at any point during the hospitalization, as obtained by medical record abstraction. We also assessed the specific type of ACEI/ARB used during hospitalization using the medication that was administered first.

Stratification of Patients According to Estimated Mortality Risk

We used the 7-variable risk score derived from the Cooperative Cardiovascular Project (CCP) to stratify Chinese class I patients by estimated in-hospital mortality risk.[18] This risk score incorporates age, cardiac arrest, anterior or lateral location of MI, systolic blood pressure (SBP), white blood cell (WBC) count, serum Cr, and congestive heart failure. We divided eligible patients into quintiles of estimated in-hospital mortality risk: ≤1.9%, 2.0% to 3.2%, 3.3% to 5.2%, 5.3% to 8.5%, and >8.5%. Because we only collected blood pressure (BP) at admission, we do not know whether the SBP of patients presenting with hypotension improved during hospitalization. Therefore, we performed a sensitivity analysis excluding patients with BP <90 mm Hg at admission.

Statistical Analysis

Categorical variables were reported as percentages and differences assessed using the chi-squared test. We used medians and interquartile range (IQR) to describe continuous variables. We used the Cochran-Armitage test for trend to study trends in ACEI/ARB use. To generate national estimates, we applied weights proportional to the inverse sampling fraction of patients, to account for differences in the sampling fraction for each time period.

Factors associated with the use of ACEI/ARB therapy were identified through a multilevel logistic regression model using generalized estimating equation, to account for clustering of patients within hospitals. We selected explanatory variables based on clinical judgment and review of the literature, including demographics, clinical factors, region, and year (Table 1). We transformed continuous variables, such as age and BP, into categorical variables, using a fractional polynomial approach, according to clinically meaningful cut-off values, and then created dummy variables. All selected variables were included in the multivariable model to identify predictors of not receiving ACEI/ARB therapy, which are reported as odds ratios (ORs) with 95% confidential intervals (CIs).

All comparisons were 2-sided, with a $P<0.05$ considered statistically significant. Statistical analysis was performed using SAS (version 9.2; SAS Institute Inc., Cary, NC) and R (version 3.0.2; R Foundation for Statistical Computing, Vienna, Austria) software.

Results

Study Sample

Of the 16 100 patients with AMI, after excluding patients who transferred in (n=607), transferred out (n=297), died (n=500), or were discharged within 24 hours of admission (n=326), and those with contraindications (n=474), we identified 13 896 patients eligible for ACEI/ARB therapy, which constituted the study cohort. Of these, 13 486 met Chinese Class I and 410 met Chinese Class IIa (Figure 1); by ACC/AHA guidelines, 11 839 met Class I and 2057 met Class IIa.

Among Chinese Class I patients, the median age was 66 years (IQR, 56 to 74) and 69.9% were male. CVR factors were common (HTN 52.4%, diabetes 20.6%, and current smoking 34.9%). Of the cohort, 88.2% had a STEMI (42.4% of overall cohort had an anterior STEMI) and 34.6% had HF. At admission, 4.1% presented with an SBP <90 mm Hg. Estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2 was in 16.6%. LVEF was measured only in half of the study cohort (48.6%), and among those, 14.4% had an LVEF ≤0.40 (Table 1).

Table 1. Patient and Hospital Characteristics Among Patients With a Chinese Class I Indication for ACEI/ARB, Overall and Stratified by Receipt of ACEI/ARB Therapy During Hospitalization

Characteristics	Total (%) (N=13 486)	Received ACEI/ARB (%) (N=9008)	Did not Receive ACEI/ARB (%) (N=4478)	*P* Value
Demographic				
Age, y				0.16
<55	22.2	21.6	23.4	
55 to 64	23.7	23.8	23.3	
65 to 74	30.1	30.4	29.6	
≥75	24.0	24.1	23.7	
Gender				0.30
Male	69.9	70.2	69.3	
Female	30.1	29.8	30.7	
Cardiovascular risk factors				
Hypertension	52.4	60.4	36.4	<0.001
Diabetes	20.6	22.5	16.9	<0.001
Current smoker	34.9	35.3	34.1	0.15
Medical history				
Stroke	11.5	11.9	10.8	0.07
Chronic renal insufficiency	1.9	1.9	1.8	0.68
Coronary heart disease	22.6	23.5	20.6	<0.001
Myocardial infarction	10.8	11.4	9.7	0.003
Clinical characteristics during hospitalization				
AMI type				<0.001
Anterior STEMI	42.4	44.6	37.9	
Non-anterior STEMI	45.8	42.4	52.7	
NSTEMI	11.8	13.0	9.4	
Cardiac arrest	2.8	2.6	3.1	0.09
Cardiogenic shock	6.2	5.0	8.6	<0.001
Heart failure	34.6	37.3	29.0	<0.001
Atrial fibrillation	9.4	9.5	9.3	0.63
SBP, mm Hg				<0.001
<90	4.1	2.4	7.4	
90 to 139	58.5	53.8	68.2	
≥140	37.4	43.8	24.4	
Heart rate, beats/min				<0.001
<60	12.3	10.8	15.3	
60 to 90	65.8	66.3	64.7	
>90	22.0	22.9	20.1	
eGFR, mL/min per 1.73 m^2				<0.001
<60	16.6	14.3	21.1	
60 to 89	26.1	23.7	31.1	
≥90	24.8	22.7	29.0	
Unmeasured	32.5	39.4	18.8	

Continued

Table 1. Continued

Characteristics	Total (%) (N=13 486)	Received ACEI/ARB (%) (N=9008)	Did not Receive ACEI/ARB (%) (N=4478)	*P* Value
LVEF value				<0.001
≤0.40	7.0	7.7	5.5	
>0.40	41.6	46.0	32.7	
Unmeasured	51.4	46.3	61.7	
Economic-geographic region				
Eastern	59.2	58.7	60.2	0.10
Central	21.2	21.2	21.2	
Western	19.6	20.1	18.6	
Rural/urban				
Rural	38.8	38.1	40.2	0.02
Urban	61.2	61.9	59.8	
Hospital characteristics*				
Teaching	80.3	82.3	76.3	<0.001
PCI-capable	60.8	63.4	55.5	<0.001
Year				
2001	15.1	13.9	17.7	<0.001
2006	28.5	29.9	25.9	
2011	56.3	56.3	56.4	

ACEI indicates angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction.

*The number (N) reflects the number of patients who were admitted to hospitals with this characteristic.

Use of ACEI/ARB Therapy

The weighted proportion of ACEI/ARB therapy (95% CI) in Chinese Class I was 62.0% (59.9 to 64.1) in 2001, which increased to 71.4% (70.0 to 72.8) in 2006, but subsequently decreased to 67.6% (65.5 to 68.6) in 2011 (*P*=0.01 for trend). In Chinese Class IIa, the weighted proportion of ACEI/ARB changed little over time (38.6% [32.0 to 45.3] in 2001, 38.9% [33.3 to 44.4] in 2006 and 47.9% [44.9 to 50.9] in 2011, respectively; *P*=0.1 for trend). The weighted rate of ACEI/ARB therapy in ACC/AHA Class I was 66.0% (64.8 to 67.1) in 2001, 73.8% (73.0 to 74.5) in 2006, and 70.4% (69.8 to 70.9) in 2011 (*P*=0.1 for trend), whereas in ACC/AHA Class IIa, it was 40.0% (37.4 to 42.5) in 2001, 50.4% (48.2 to 52.5) in 2006, and 45.8% (44.3 to 47.2) in 2011 (*P*=0.2 for trend; Figure 2). Baseline characteristics and use of ACEI/ARB therapy in patients with length of stay less than 24 hours are shown in Tables 2 and 3 respectively. After excluding patients with Cr ≥1.5 mg/dL during hospitalization, the weighted proportions of ACEI/ARB therapy in both Chinese Class I and IIa categories were similar to the primary cohort (Table 4).

ACEIs were more frequently used than ARBs among Chinese Class I patients across all time periods (58.9% vs. 1.7% in 2001; 65.7% vs. 3.4% in 2006; and 55.7% vs. 10.5% in

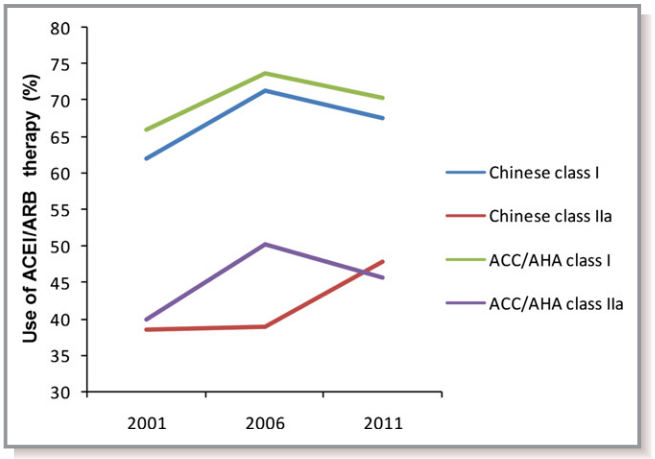

Figure 2. Temporal trends in ACEI/ARB therapy by Chinese Class I and IIa, and ACC/AHA Class I and IIa. ACC/AHA indicates American College of Cardiology/American Heart Association; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 2. Baseline Demographic and Clinical Characteristics Between Chinese Class I Patients and Patients With Length of Stay Less Than 24 Hours

Characteristics	Chinese Class I Patients (%) (N=13 486)	Patients With Length of Stay <24 Hours (%) (N=1123)	*P* Value
Demographics			
Age, y			<0.001
<55	22.2	16.7	
55 to 64	23.7	19.2	
65 to 74	30.1	31.2	
≥75	24.0	32.9	
Gender			<0.001
Male	69.9	60.6	
Female	30.1	39.4	
Cardiovascular risk factors			
Hypertension	52.4	40.7	<0.001
Diabetes	20.6	17.7	0.02
Current smoker	34.9	13.2	<0.001
Medical history			
Stroke	11.5	11.4	0.92
Chronic renal insufficiency	1.9	2.7	0.05
Coronary heart disease	22.6	19.2	0.01
Myocardial infarction	10.8	8.3	0.008
Clinical characteristics during hospitalization			
AMI type			0.001
Anterior STEMI	42.4	47.8	
Non-anterior STEMI	45.8	40.5	
NSTEMI	11.8	11.7	
Cardiac arrest	2.8	18.9	<0.001
Cardiogenic shock	6.2	35.4	<0.001
Heart failure	34.6	37.4	0.06
Atrial fibrillation	9.4	9.7	0.77
SBP, mm Hg			<0.001
<90	4.1	24.6	
90 to 139	58.5	52.2	
≥140	37.4	23.2	
Heart rate, beats/min			<0.001
<60	12.3	17.7	
60 to 90	65.8	47.8	
>90	22.0	34.5	
eGFR, mL/min per 1.73 m^2			<0.001
<60	16.6	28.6	
60 to 89	26.1	18.4	
≥90	24.8	11.1	
Unmeasured	32.5	41.9	

Continued

Table 2. Continued

Characteristics	Chinese Class I Patients (%) (N=13 486)	Patients With Length of Stay <24 Hours (%) (N=1123)	*P* Value
LVEF value			<0.001
≤0.40	7.0	1.5	
>0.40	41.6	2.5	
Unmeasured	51.4	96.0	
Economic-geographic region			
Eastern	59.2	55.8	0.03
Central	21.2	24.3	
Western	19.6	19.9	
Rural/urban			
Rural	38.8	53.8	<0.001
Urban	61.2	46.2	
Hospital characteristics*			
Teaching	80.3	72.6	<0.001
PCI-capable	60.8	48.1	<0.001
Year			
2001	15.1	9.0	<0.001
2006	28.5	27.0	
2011	56.3	64.0	

AMI indicates acute myocardial infarction; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction.
*The number (N) reflects the number of patients who were admitted to hospitals with this characteristic.

Table 3. The Proportion of Patients With Length of Stay Less Than 24 Hours Receiving ACEI/ARB Therapy

Patients	Died (N=500)	Transferred Out (N=297)	Discharged (N=326)
ACEI/ARB	20.8%	32.0%	27.6%

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

2011). The rate of dual therapy with both ACEI and ARB was low (0.6% in 2001, 0.7% in 2006, and 0.5% in 2011, respectively; Figure 3).

Over the study period, there were significant changes in the specific agents that were used among eligible patients (13 896). Among ACEIs, captopril was the dominant agent used in 2001 (68.8%). This proportion decreased to 23.6% in 2011, with an increase in use of enalapril (27.1% in 2011), benazepril (22.6%), perindopril (14.1%), and fosinopril (8.4%). Among ARBs, valsartan was the dominant agent in 2001 (67.7%), declining to 28.2% in 2011, with an increase in use of irbesartan (25.1% in 2011) and telmisartan (13.8%; Figure 4A and 4B).

Use of ACEI/ARB Across Regions

Rates of ACEI/ARB therapy in 2011 were similar across all 5 regions in China. In rural regions, ACEI/ARB use increased consistently from 2001 to 2011 (*P* for trend=0.006 for Eastern-rural and *P* for trend=0.01 and 0.009 for Central and Western-rural, respectively), whereas in urban regions, there was an increase from 2001 to 2006, but a subsequent decrease in 2011 (*P* for trend=0.32 for Eastern-urban and *P* for trend=0.04 for Central and Western-urban; Figure 5).

Factors Associated With Use of ACEI/ARB

Patient and hospital characteristics stratified by receipt of ACEI/ARB are shown in Table 1.

Significant correlates of ACEI/ARB therapy in multivariable analysis are shown in Figure 6. Women were less likely to receive ACEI/ARB therapy than men (OR, 0.83; 95% CI, 0.74 to 0.92). Patients with history of stroke (OR, 0.87; 95% CI, 0.76 to 0.99) and chronic renal insufficiency (CRI; OR, 0.72; 95% CI, 0.53 to 0.98) were also less likely to be treated with ACEI/ARB therapy. Patients with nonanterior STEMI and NSTEMI, compared with anterior STEMI, were less likely to receive this therapy (OR, 0.71; 95% CI, 0.65 to 0.78 and OR, 0.79; 95% CI 0.67 to 0.92, respectively). Patients with SBP <90 mm Hg at presentation (OR, 0.55; 95% CI, 0.42 to 0.71, compared to 90 to 139 mm Hg) and those with eGFR <60 mL/min per 1.73 m^2 (OR, 0.79; 95% CI, 0.66 to 0.96,

Table 4. The Weighted Proportion of ACEI/ARB Therapy in Patients With Creatinine <1.5 and ≤3.0 mg/dL by Year by Chinese Class I and Class IIa

Cr Value	Patients	Received ACEI/ARB, % (95% CI)			*P* for Trend
		2001	2006	2011	
Cr<1.5	Chinese Class I	62.4 (60.2 to 64.6)	72.5 (71.0 to 74.0)	68.5 (67.4 to 69.6)	<0.01
	Chinese Class IIa	36.5 (23.0 to 50.0)	37.4 (26.2 to 48.6)	48.1 (42.1 to 54.1)	0.06
Cr≤3.0	Chinese Class I	62.0 (59.9 to 64.1)	71.4 (70.0 to 72.8)	67.6 (65.5 to 68.6)	0.01
	Chinese Class IIa	38.6 (32.0 to 45.3)	38.9 (33.3 to 44.4)	47.9 (44.9 to 50.9)	0.1

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; Cr, creatinine.

compared with GFR ≥90 mL/min per 1.73 m^2) were less likely to receive ACEI/ARB. Among patients who had LV function assessed, those with an LVEF ≤0.40 were no more likely to receive ACEI/ARB therapy (OR, 0.93; 95% CI, 0.75 to 1.14), compared with LVEF >0.40. Patients without a measurement of LVEF were less likely to receive therapy, whereas those with unmeasured eGFR were more likely to be treated. The interaction between study year and unmeasured LVEF or eGFR implied that the likelihood of using ACEI/ARB in patients with unmeasured LVEF or eGFR has relatively increased during the past decade (*P* for year×LVEF interaction=0.005; *P* for year×eGFR interaction<0.001). Patients in nonteaching hospitals were less likely to be treated (OR, 0.72; 95% CI, 0.53 to 0.97, compared with teaching hospital).

Use of ACEI/ARB Stratified by Estimated Risk of In-Hospital Mortality

After excluding patients without measured WBC count or serum Cr, we identified 10 745 patients for the risk model. Among patients stratified by estimated mortality risk, a change in the risk-treatment pattern was observed over time (Figure 7A). In 2001, rates of ACE/ARB increased with increasing levels of estimated patient risk (from 62.0% in the lowest-risk quintile to 72.0% in the highest-risk quintile; *P* for trend across risk quintiles=0.006). By 2011, however, a risk-treatment paradox had emerged, with lower rates of ACEI/ARB therapy in higher-risk groups (from 70.7% in the lowest-risk quintile to 63.5% in the highest-risk quintile; *P* for trend across risk quintiles <0.001). The interaction between mortality risk and year reflects that this temporal change in treatment pattern was statistically significant (*P* for interaction <0.001). After excluding patients with BP <90 mm Hg, the results were similar (Figure 7B).

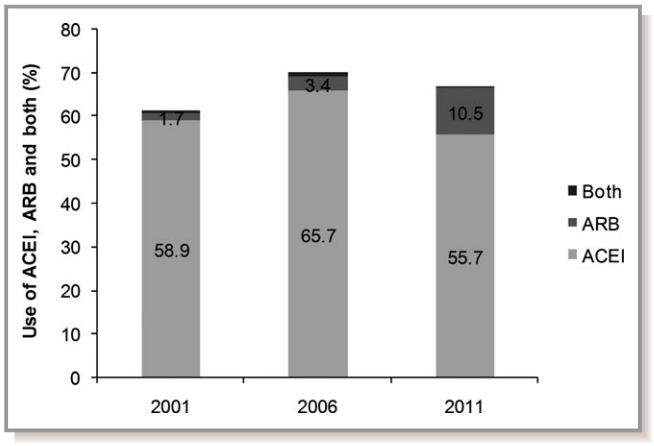

Figure 3. Use of ACEI, ARB, and both ACEI/ARB among Chinese Class I patients by year. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Discussion

In this nationally representative study of patients hospitalized with AMI in China, including both STEMI and NSTEMI, only two thirds of patients with a Class I indication received ACEI/ARB therapy in 2011. Use increased from 2001 to 2006, but subsequently declined in 2011. Use was similarly low across regions, although rural regions continued to improve their use over time. In strata of estimated mortality risk, different patterns of treatment were observed over time. Rates of therapy increased with increasing risk in 2001. However, by 2011, patients with the highest estimated risk of mortality were the least likely to be treated.

The rate of ACEI/ARB therapy for AMI in patients with Class I indications in China was lower than previous studies in China and that reported in the United States. The Clinical Pathways for Acute Coronary Syndromes in China (CPACS) study between 2004 and 2005 showed higher use of ACEI/ARB therapy (ACEI, 76%; ARB, 6.8% to 10.8%) during hospitalization among all patients with acute coronary syndrome (ACS).[19] Also, in the Bridging the Gap on Coronary Heart Disease Secondary Prevention in China (BRIG) study in 2006, the proportion of patients with ST elevation ACS receiving ACEI/ARB during hospitalization was approximately 75%.[20] However, both these studies included patients only from selected hospitals. In contrast, our cohort is a nationally

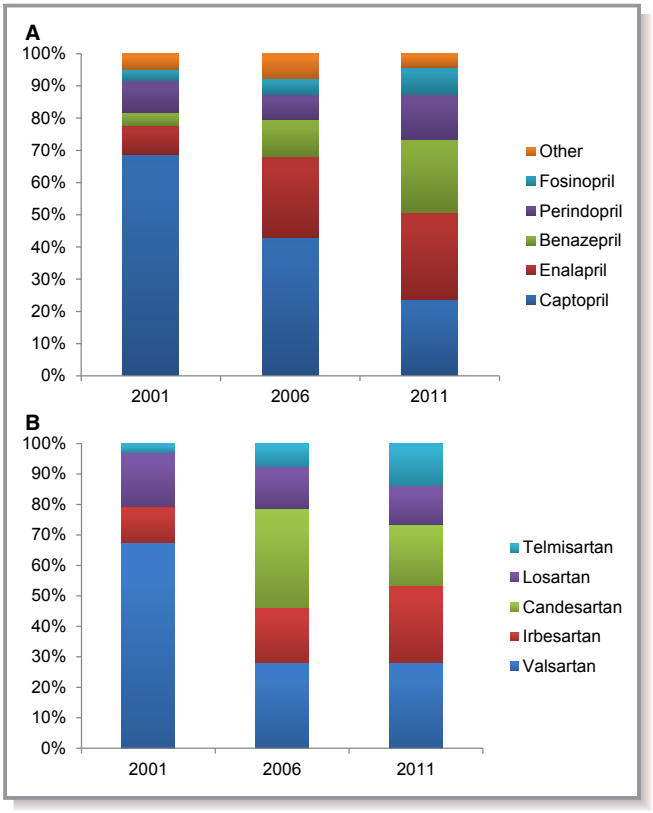

Figure 4. A, ACEI prescription among eligible patients by year. B, ARB prescription among eligible patients by year. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

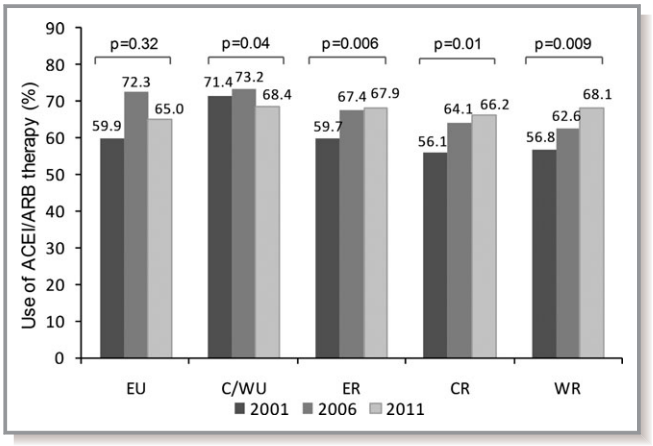

Figure 5. Regional trends in ACEI/ARB use among Chinese Class I patients by year. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; C/WU, central/western-urban; CR, central-rural; ER, eastern-rural; EU, eastern-urban; WR, western-rural.

representative sample derived through random sampling and thus provides a robust assessment of practice patterns for AMI in China. The rate of ACEI/ARB therapy in 2011 in our study is comparable to the rate in the United States in 2003 (68%).[21] By 2009, driven largely by national quality improvement efforts, the proportion of patients receiving ACEI/ARB therapy at discharge had increased to the 77% to 85% range.[22] These improvements in the United States suggests that similar initiatives in China may bolster ACEI/ARB utilization.[22,23]

Our findings show that ACEI/ARB therapy remains widely underprescribed in China, and rates of use have improved little over time. Initiation of ACEI therapy early after AMI is beneficial and saves ≈5 lives for every 1000 patients treated in the first month.[4] Both Chinese and U.S. guidelines during our study period have consistently endorsed the use of ACEI/ARB therapy early after AMI.[5–11] In China, ACEIs are both widely available and relatively inexpensive (≈$1 for a 30-day supply).[12] Moreover, since 2006, with health care reform in China, medical insurance coverage has rapidly increased and, by 2010, 90% of the entire population had some form of health insurance.[24,25] Nevertheless, we found that one third of patients did not receive either ACEI or ARB therapy.

Without significant financial constraints to ACEI/ARB use, the reasons for the widespread underuse are unclear, and additional research is needed to illuminate underlying barriers. Potential explanations include difficulties in selecting appropriate patients for ACEI/ARB, concern among providers for side effects, or a lack of practitioner knowledge.[26] Quality improvement efforts need to consider these and other potential causes, in order to stimulate wider use of ACEI/ARB for AMI in China.

Interestingly, in contrast to the trends in ACEI/ARB utilization described herein, other analyses of the China-PEACE study revealed marked improvements in the use of aspirin, clopidogrel, and statins.[17] The relative uptake of clopidogrel and statins is surprising, especially because these medicines are more expensive than ACEIs.[12] One possible explanation is that clinical considerations, such as renal dysfunction, figure more prominently in the decision to use ACEI/ARB therapy, compared to statins and antiplatelet agents. In addition, it should be noted that the evidence for statins and clopidogrel has mainly been generated in the past decade, the same time frame as our study, in contrast to the evidence supporting ACEI use, which is older. The publication of this new evidence supporting statin and antiplatelet therapy may have stimulated their uptake at all 3 time points in the China-PEACE study.

An important observation from this study was the emergence of a risk treatment paradox in China over the last decade—where high-risk patients with AMI who stand to benefit the most from treatment were the least likely to receive ACEI/ARB therapy. This pattern of care has been observed in other areas of CVD management in Canada and the United States, including both invasive[27] and preventative[28,29] interventions. A recent study using the Get With The Guidelines registry suggested that hospitals participating in

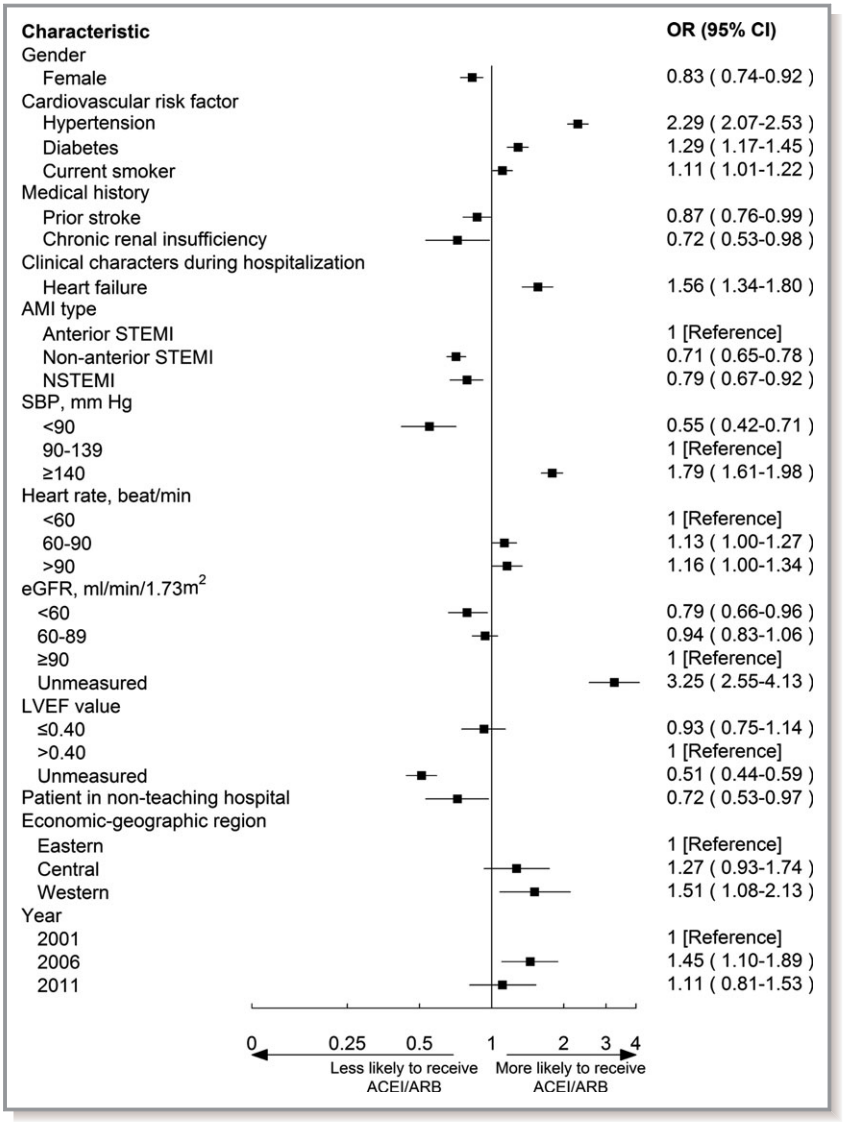

Figure 6. Factors associated with ACEI/ARB use among Chinese Class I patients in multivariable analysis. Variables associated with ACEI/ARB use are shown along the vertical axis. The strength of effect is shown along the horizontal axis with the vertical line demarcating an odds ratio (OR) of 1 (ie, no association); estimates to the right (ie, >1) are associated with a greater likelihood of ACEI/ARB use, whereas those to the left (ie, <1) indicate a reduced likelihood of ACEI/ARB use. Each dot represents the point estimate of the effect of that variable in the model, whereas the line shows the 95% confidence interval (CI). C-statistic=0.75. ACEI indicates angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction.

quality improvement programs showed improvements in risk treatment paradox over time.[30] This highlights the need for similar concerted quality improvement efforts in China to reverse this trend and ensure the delivery of evidence-based therapies to those who will benefit most.

Certain factors should be considered in the interpretation of the results of this study. First, our analysis used information based on medical record abstraction, which is dependent on the accuracy and completeness of physician documentation. However, a standardized central abstraction ensured an overall variable agreement of >98%. Second, in the same context, contraindications or intolerance to ACEI/ARB therapy may have been present, but not documented, which would have resulted in an overestimate of the ideal population for ACEI/ARB and a corresponding underestimate of the rate of ACEI/ARB use in ideal patients. Third, we only collected BP

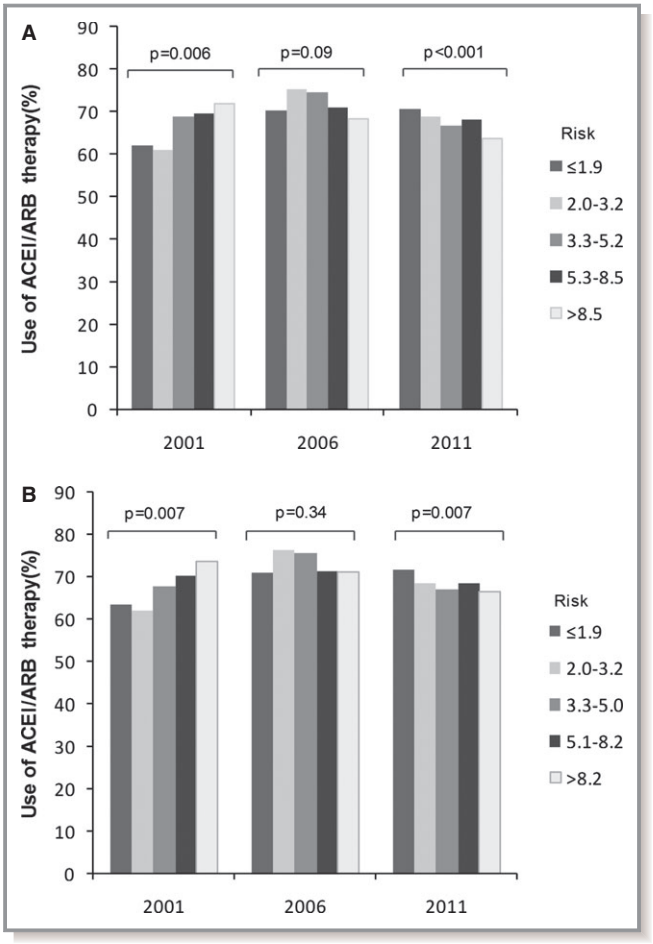

Figure 7. A, ACEI/ARB use among Chinese Class I patients by year stratified by estimated in-hospital mortality risk. *P* for trend. *P* for year×mortality risk interaction <0.001. C-statistic=0.77. B, ACEI/ARB use among Chinese Class I patients after excluding BP <90 mm Hg by year stratified by estimated in-hospital mortality risk. *P* for trend. *P* for year×mortality risk interaction <0.001. C-statistic=0.76. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure.

measurements at admission, which could have changed over the course of the hospitalization, which could influence the decision to prescribe ACEI/ARB. However, collectively, the reasons for possible underestimation of ACEI/ARB rates are insufficient to explain why nearly 3 in 10 patients did not receive this therapy. In applying stringent criteria for exclusion, we intended to isolate a study sample that most certainly would have benefited from treatment; however, we still found significant underutilization.

Conclusion

In this nationally representative study of patients hospitalized with AMI in China, we found underutilization of ACEI/ARB therapy, which extends across regions, and rates of use have not improved appreciably over the past decade. Moreover, with time, a risk treatment paradox has emerged, wherein there is considerable underuse of ACEI/ARB among subgroups at the highest risk for mortality. These findings identify important opportunities for improvement as the Chinese health-care system reengineers itself to deliver high-quality care to the rising number of people with AMI. These data can serve as a baseline against which future improvements can be measured.

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Disclosures

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