

ORIGINAL ARTICLE

## Rates of Hyperkalemia after Publication of the Randomized Aldactone Evaluation Study

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### ABSTRACT

#### BACKGROUND

The Randomized Aldactone Evaluation Study (RALES) demonstrated that spironolactone significantly improves outcomes in patients with severe heart failure. Use of angiotensin-converting-enzyme (ACE) inhibitors is also indicated in these patients. However, life-threatening hyperkalemia can occur when these drugs are used together.

#### METHODS

We conducted a population-based time-series analysis to examine trends in the rate of spironolactone prescriptions and the rate of hospitalization for hyperkalemia in ambulatory patients before and after the publication of RALES. We linked prescription-claims data and hospital-admission records for more than 1.3 million adults 66 years of age or older in Ontario, Canada, for the period from 1994 through 2001.

#### RESULTS

Among patients treated with ACE inhibitors who had recently been hospitalized for heart failure, the spironolactone-prescription rate was 34 per 1000 patients in 1994, and it increased immediately after the publication of RALES, to 149 per 1000 patients by late 2001 ( $P < 0.001$ ). The rate of hospitalization for hyperkalemia rose from 2.4 per 1000 patients in 1994 to 11.0 per 1000 patients in 2001 ( $P < 0.001$ ), and the associated mortality rose from 0.3 per 1000 to 2.0 per 1000 patients ( $P < 0.001$ ). As compared with expected numbers of events, there were 560 (95 percent confidence interval, 285 to 754) additional hyperkalemia-related hospitalizations and 73 (95 percent confidence interval, 27 to 120) additional hospital deaths during 2001 among older patients with heart failure who were treated with ACE inhibitors in Ontario. Publication of RALES was not associated with significant decreases in the rates of readmission for heart failure or death from all causes.

#### CONCLUSIONS

The publication of RALES was associated with abrupt increases in the rate of prescriptions for spironolactone and in hyperkalemia-associated morbidity and mortality. Closer laboratory monitoring and more judicious use of spironolactone may reduce the occurrence of this complication.

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**H**EART FAILURE AFFECTS APPROXIMATELY 5 million persons annually in Canada and the United States.<sup>1</sup> Medications are the mainstay of therapy, and in the past two decades there has been a shift away from the use of diuretics and cardiac glycosides and toward neurohumoral manipulation with angiotensin-converting-enzyme (ACE) inhibitors, beta-adrenergic antagonists, and aldosterone antagonists.<sup>1</sup> Published in September 1999, the Randomized Aldactone Evaluation Study (RALES) demonstrated that treatment with spironolactone substantially reduced morbidity and mortality in patients with severe heart failure.<sup>2</sup> Spironolactone is inexpensive and generally well tolerated, but in these patients it can provoke life-threatening hyperkalemia when combined with ACE inhibitors.<sup>3-6</sup>

An early dose-finding study conducted by the RALES investigators found that hyperkalemia was a dose-dependent effect of spironolactone, yet hyperkalemia developed in only a few patients (2 percent) in the active-treatment group in RALES.<sup>2,7</sup> The low incidence of hyperkalemia may reflect unusually close laboratory monitoring, restriction of other drugs that cause hyperkalemia, or exclusion of patients with advanced renal disease or mild hyperkalemia at baseline.<sup>8-10</sup> However, clinicians rapidly embraced the findings of RALES and may not have applied similar restrictions in clinical practice.<sup>11,12</sup> One recent study found, for example, that many patients who received new prescriptions for spironolactone after the publication of RALES did not have severe heart failure, about a third had renal insufficiency, and more than a third simultaneously received prescriptions for potassium supplements.<sup>13</sup> Such differences between the clinical-trial setting and actual practice are particularly relevant for older patients with heart failure, most of whom would not have been included in RALES.<sup>14</sup>

Although the use of spironolactone or other potassium-sparing diuretics in conjunction with ACE inhibitors increases the risk of hyperkalemia in outpatients, the consequences of this drug interaction at the population level are unknown.<sup>15</sup> In this ecologic study, we examined trends in the rate of prescriptions for spironolactone and in the rate of hospitalization for hyperkalemia before and after the publication of RALES among older patients who were treated with ACE inhibitors.

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## METHODS

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### SETTING AND DESIGN

This study was a population-based, time-series analysis of health care databases in Ontario, Canada, from January 1, 1994, to December 31, 2001. During this period, Ontario had a population of about 12.3 million people, of whom approximately 1.3 million were 65 years of age or older and had universal access to hospital care, physicians' services, and prescription-drug coverage. Databases containing the health care records of individual patients could be linked and analyzed in an anonymous fashion with the use of their encrypted, 10-digit health-card numbers.

### SOURCES OF DATA

We examined the computerized prescription records of the Ontario Drug Benefit Program, which records prescription drugs dispensed to all Ontario residents 65 years of age or older. The overall error rate in this database is less than 1 percent.<sup>16</sup> Hospitalization records were obtained from the Canadian Institute for Health Information Discharge Abstract Database, which contains a record of all hospitalizations, including up to 16 diagnoses for each admission. Although the accuracy of coding in this database has not been established for all diagnoses, one recent study showed a positive predictive value of 90 to 96 percent for the diagnosis of heart failure.<sup>17</sup>

### IDENTIFICATION OF PATIENTS AND OUTCOMES

We divided each year of the eight-year study period into three four-month intervals (January through April, May through August, and September through December), for a total of 24 consecutive intervals. We chose to use 4-month intervals because the Ontario Drug Benefit Program will not reimburse prescriptions for medication supplies exceeding 100 days in duration. We examined the records of patients 66 years of age or older; we did not include records during patients' first year of eligibility for prescription-drug coverage (i.e., when they were 65 years of age) to avoid including data from incomplete medication records.

For each four-month interval, we identified every prescription for spironolactone, ACE inhibitors, angiotensin-receptor antagonists, beta-adrenergic

antagonists, loop diuretics, nonsteroidal antiinflammatory agents, potassium supplements, thiazide diuretics, or products containing other potassium-sparing diuretics (e.g., amiloride or triamterene). We selected these drugs because they are the most commonly prescribed medications that can influence potassium levels. For each interval we also identified all hospital admissions involving a diagnosis of hyperkalemia (*International Classification of Diseases, Ninth Revision* [ICD-9] code 276.7) or heart failure (ICD-9 code 428.0), with particular attention to the number of admissions culminating in death during hospitalization. A hospitalization involving transfer from one facility to another (e.g., for hemodialysis or other specialized care) was considered a single admission. This research was approved by the ethics review board of Sunnybrook and Women's College Health Sciences Centre.

#### STATISTICAL ANALYSIS

We used time-series analysis to examine patterns in the spironolactone-prescription rates and in the rates of hospitalization for hyperkalemia or for heart failure during the study period. Time-series analysis consists of several techniques for modeling autocorrelation in temporally sequenced data.<sup>18</sup> In the primary analysis, we examined trends in the spironolactone-prescription rates and in the rates of admission for hyperkalemia or heart failure among patients receiving ACE inhibitors who had been hospitalized for heart failure during the preceding three years. In a secondary analysis we examined these rates in all patients who were receiving ACE inhibitors, regardless of whether they had a history of heart failure.

Different approaches were used to assess immediate and delayed effects related to the publication of RALES. Immediate effects were assessed with interventional autoregressive integrated moving-average (ARIMA) models with the use of a ramp function.<sup>19</sup> An immediate change was defined as one occurring within three 4-month intervals (i.e., within 1 year) after the early release of the study's findings on the *Journal* Web site on July 19, 1999, 44 days ahead of its publication in print.<sup>2</sup> To assess delayed effects, we used ARIMA models to forecast expected rates and their 95 percent confidence intervals. We then compared observed with predicted rates of spironolactone use and health outcomes.<sup>20</sup>

To address population-wide changes in the use

of other drugs that could influence the risk of hyperkalemia, we examined prescriptions for medications of various other classes as dynamic regressors during each interval, with lag functions of up to two four-month intervals included as necessary. The autocorrelation, partial autocorrelation, and inverse autocorrelation functions were assessed for model parameter appropriateness and seasonality. Stationarity was assessed with the use of autocorrelation functions and the augmented Dickey-Fuller test.<sup>18,21</sup> The presence of white noise was assessed by examining the autocorrelations at various lags with use of the Ljung-Box chi-square statistic.<sup>19,22</sup> All P values were two-sided, and analyses were conducted with the use of SAS software (version 8.2).

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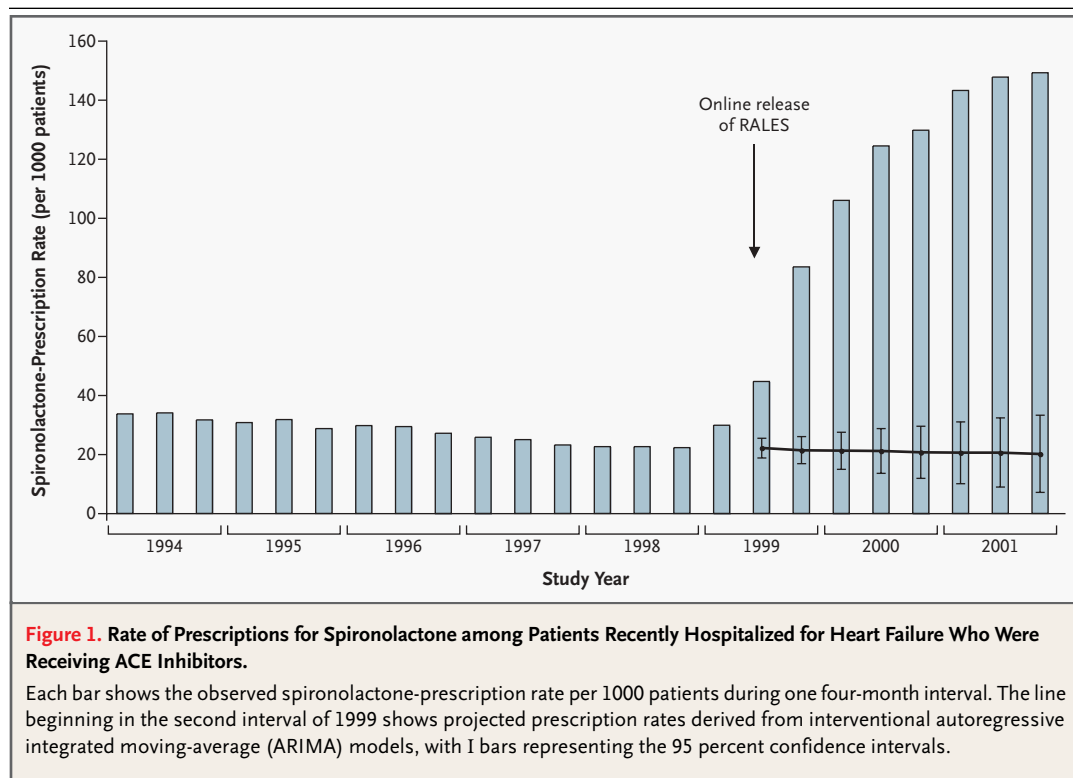
## RESULTS

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#### PATIENTS WITH HEART FAILURE

The number of patients 66 years of age or older who were treated with an ACE inhibitor after hospitalization for heart failure rose gradually over time, from 20,820 in early 1994 to 32,283 by late 2001. Among these patients, the spironolactone-prescription rate remained relatively constant from early 1994 (34 per 1000 patients) until early 1999 (30 per 1000 patients). After the publication of RALES, however, the rate of prescriptions for this drug increased by a factor of about five, to 149 per 1000 by late 2001 ( $P < 0.001$  for the comparison with the study period preceding the publication of RALES) (Fig. 1). The median dose after the publication of RALES was 25 mg per day. Patients treated with ACE inhibitors who began taking spironolactone after RALES were, on average, 13 years older than the patients who were enrolled in RALES. Men and women were equally represented. Most of the patients were also being treated with a loop diuretic, and more than half had been hospitalized for heart failure within the month before they began spironolactone therapy (Table 1).

The rate of hospital admission involving a diagnosis of hyperkalemia among these patients rose gradually from early 1994 (2.4 per 1000) to early 1999 (4.0 per 1000) but increased by a factor of about three after the publication of RALES, to 11.0 per 1000 by late 2001 ( $P < 0.001$ ) (Fig. 2). Among patients with a history of heart failure who were treated with ACE inhibitors, the rate of hyperkale-



mia-associated with in-hospital death rose gradually from early 1994 (0.3 per 1000) to early 1999 (0.7 per 1000) but increased by a factor of about three after the publication of RALES, to 2.0 per 1000 by late 2001 ( $P < 0.001$ ) (Fig. 3). The rate of hospitalization for heart failure declined gradually during the study period, with no statistically significant change in this variable after the publication of RALES ( $P = 0.78$ ) (Fig. 4). The rate of death from any cause also declined gradually during the study period (from 58 per 1000 in early 1994 to 44 per 1000 in late 2001), with no significant change after the publication of RALES.

Prescription patterns for other drugs also changed during the study period. Most of the patients who were receiving ACE inhibitors for heart failure also received prescriptions for loop diuretics, and beta-adrenergic antagonists became increasingly popular (Fig. 5). The rate of prescriptions for nonsteroidal antiinflammatory agents was relatively stable, with a slight decline when copayment became required in 1996 and a slight rise after the launch of selective cyclooxygenase-2 inhibitors in 2000. The associations among the publication of RALES, the increase in spironolactone use, and the rates of hyperkalemia-related adverse

outcomes did not change appreciably after adjustment for temporal trends in the use of these other drugs.

#### ALL PATIENTS

Because spironolactone is sometimes prescribed to patients with mild heart failure,<sup>13</sup> we repeated our analyses in all patients receiving ACE inhibitors, regardless of whether they had a history of hospitalization for heart failure. The number of patients in this group also increased steadily during the study period, from 151,305 in early 1994 to 356,657 by late 2001.

As expected, spironolactone use was infrequent among these patients, and the rate of use remained relatively constant from early 1994 until early 1999 (12 per 1000). The rate increased by a factor of almost three after the publication of RALES, rising to 32 per 1000 by late 2001. The rate of hospital admission for hyperkalemia in this group of patients rose slightly from early 1994 (0.9 per 1000) to early 1999 (1.2 per 1000) but more than doubled after the publication of RALES, to 2.8 per 1000 by late 2001 ( $P < 0.001$ ). The rate of in-hospital hyperkalemia-associated death also rose gradually, from early 1994 (0.10 per 1000) until early 1999 (0.17

**Table 1. Characteristics of Patients Recently Hospitalized for Heart Failure Who Were Receiving ACE Inhibitors and Who Began Spironolactone Therapy before or after the Publication of RALES.\***

Characteristic	Before RALES (N=4539)	After RALES (N=12,422)
Age (yr)	78.0±7.4	78.6±7.2
Male sex (%)	50	50
Residence in long-term care facility (%)	13	10
Recency of hospitalization for heart failure (%)		
Within 30 days before spironolactone	46	60
Within 180 days before spironolactone	53	65
Within 365 days before spironolactone	76	81
Diabetes mellitus (%)†	40	40
Medications used within 4 mo before spironolactone (%)		
Angiotensin-receptor antagonists	2	5
Aspirin	29	31
Nonsteroidal antiinflammatory agents other than aspirin	14	15
Beta-adrenergic antagonists	17	42
Cardiac glycosides	64	53
Loop diuretics	92	91
Potassium-sparing diuretics other than spironolactone	5	3
Thiazide diuretics	6	6
Potassium supplements	7	3

\* Plus-minus values are means ±SD.

† The presence of this diagnosis was determined with the use of the Ontario Diabetes Database, according to Hux et al.<sup>23</sup>

per 1000), but more than doubled after the publication of RALES, to 0.39 per 1000 by late 2001 ( $P < 0.001$ ). Both the rate of admission for heart failure and the rate of death from any cause in these patients declined steadily over time, with no statistically significant change after the publication of RALES.

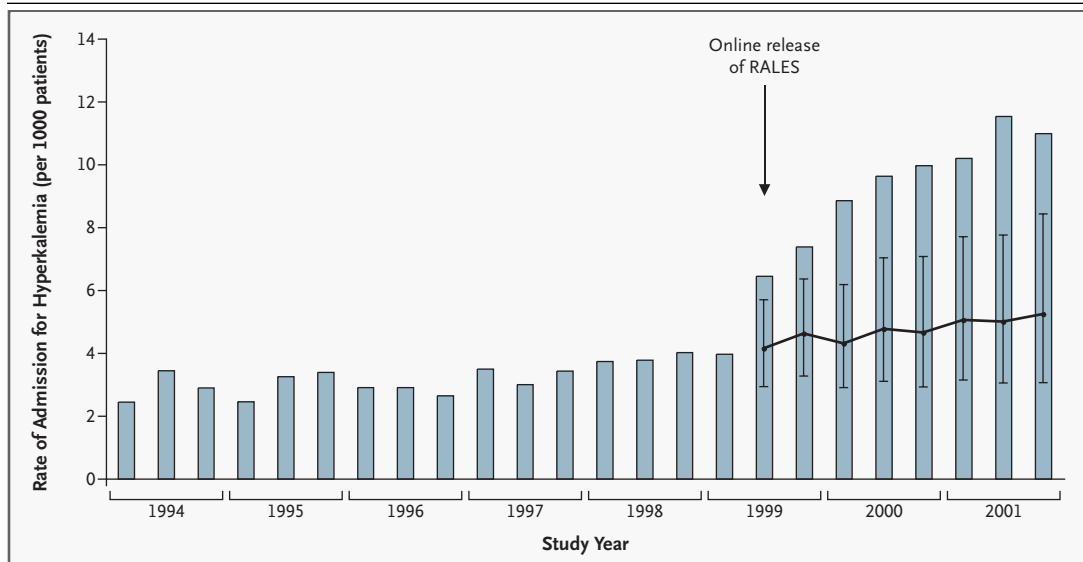
#### ADDITIONAL OBSERVATIONS

We repeated our analyses after stratification according to the use of beta-adrenergic antagonists, because these drugs may increase the risk of hyperkalemia and because their use increased substantially during the study period.<sup>24,25</sup> The publication of RALES was associated with similar increases in hospital admissions for hyperkalemia and in hyperkalemia-associated mortality among patients who were receiving beta-adrenergic antagonists and among those who were not receiving beta-adrenergic antagonists.

To explore whether increased rates of survival among patients with severe heart failure may have influenced our findings, we examined the median

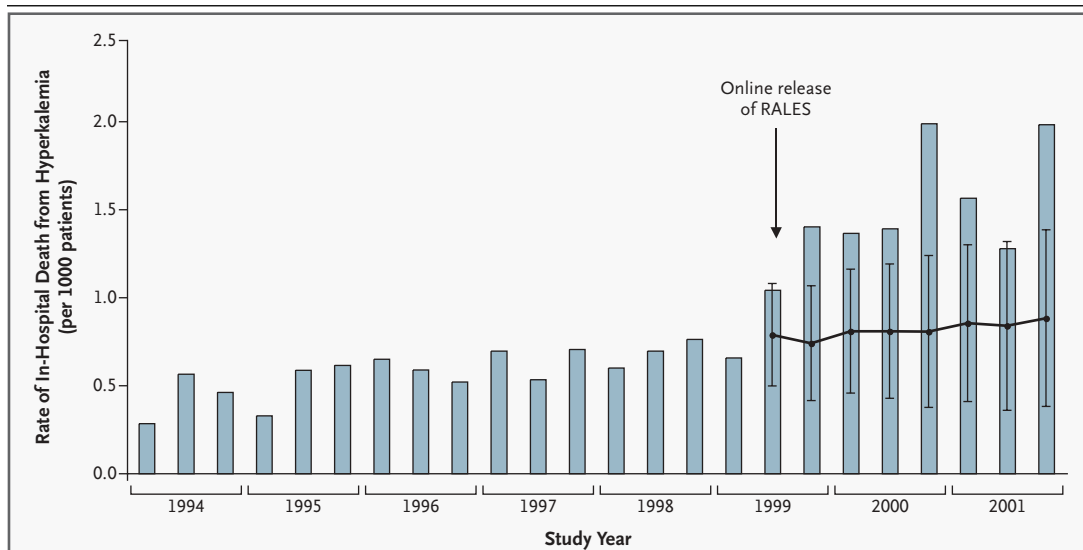
score on the Charlson comorbidity index among patients hospitalized for hyperkalemia during the study period.<sup>26,27</sup> The publication of RALES was not associated with a significant change in this score. It was, however, associated with significantly higher rates of hospital admission for renal insufficiency — a finding consistent with the known diuretic effect of spironolactone.

To estimate the excess number of admissions and in-hospital deaths associated with hyperkalemia after the publication of RALES, we compared observed annualized rates with those predicted with the use of ARIMA models. Among the patients who were treated with ACE inhibitors after hospitalization for heart failure, the publication of RALES was associated with approximately 560 (95 percent confidence interval, 285 to 754) additional hyperkalemia-related hospitalizations and at least 73 (95 percent confidence interval, 27 to 120) excess in-hospital deaths in Ontario during 2001. These estimates are conservative because spironolactone is often given to patients with less severe heart failure, many of whom may not have been



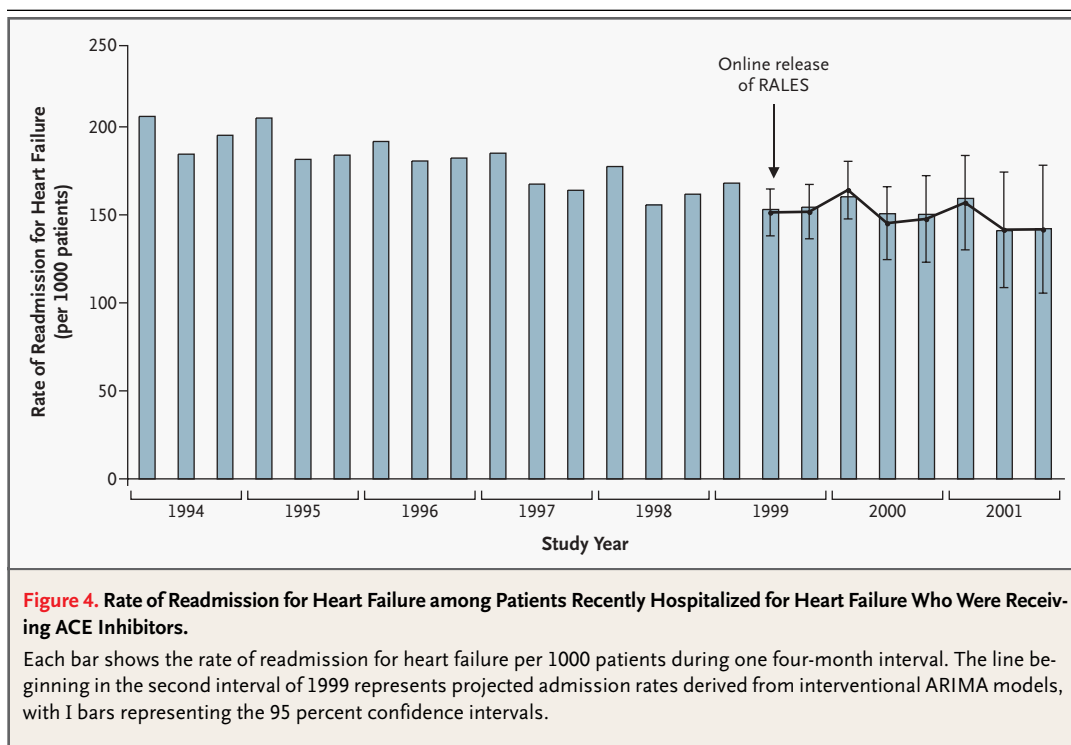
**Figure 2. Rate of Hospital Admission for Hyperkalemia among Patients Recently Hospitalized for Heart Failure Who Were Receiving ACE Inhibitors.**

Each bar shows the rate of hospital admission for hyperkalemia per 1000 patients during one four-month interval. The line beginning in the second interval of 1999 shows projected admission rates for hyperkalemia derived from interventional ARIMA models, with I bars representing the 95 percent confidence intervals.



**Figure 3. Rate of In-Hospital Death Associated with Hyperkalemia among Patients Recently Hospitalized for Heart Failure Who Were Receiving ACE Inhibitors.**

Each bar shows the rate of in-hospital death associated with hyperkalemia per 1000 patients during one four-month interval. The line beginning in the second interval of 1999 shows projected death rates derived from interventional ARIMA models, with I bars representing the 95 percent confidence intervals.



hospitalized recently.<sup>13</sup> Among the broader group of all patients 66 years of age or older who were treated with ACE inhibitors in Ontario, the publication of RALES was associated with 1485 (95 percent confidence interval, 1150 to 1802) additional hyperkalemia-related hospital admissions and 171 (95 percent confidence interval, 129 to 219) additional in-hospital deaths during 2001. These estimates correspond to approximately 37,000 additional hospitalizations and 4200 additional deaths each year in the United States, or about 100 admissions and 12 deaths each day.

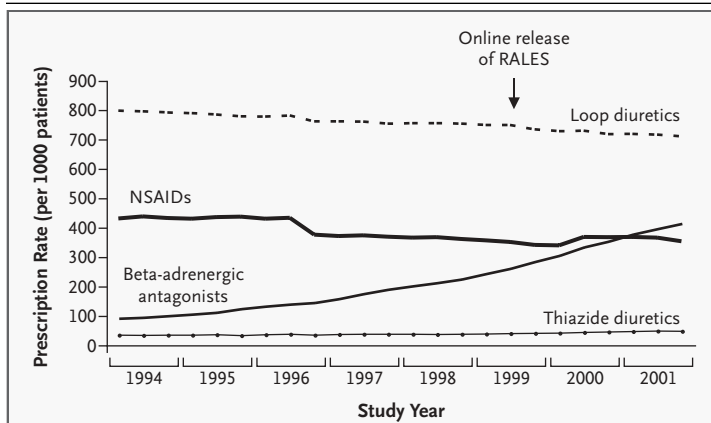
#### DISCUSSION

We found that the publication of RALES was associated with an abrupt increase in the rate of prescriptions for spironolactone among older patients in Ontario who were treated with ACE inhibitors, regardless of whether or not they had previously been hospitalized for heart failure. This finding suggests that a major clinical trial can significantly influence prescription practices in the absence of direct marketing forces from the pharmaceutical industry. We also observed considerable increases in the rates of hospital admission for hyperkalemia and subsequent in-hospital death. This excess mor-

bidity and mortality persisted after adjustment for temporal changes in the prescription rates of other commonly used drugs that can cause hyperkalemia.

Our data are population-based but exclude data related to sudden death outside the hospital or in the emergency department as well as data from patients younger than 66 years of age. As a result, our analysis probably underestimates the increase in hyperkalemia-associated morbidity and mortality after the publication of RALES. Sudden, out-of-hospital death from hyperkalemia may be erroneously attributed to underlying heart disease, and we speculate that such deaths may partly explain why no decrease in the rate of death from all causes was evident after the publication of RALES. Regardless, our findings indicate that spironolactone-related hyperkalemia is a much greater problem in everyday practice than in the setting of a clinical trial. Specifically, we estimate that every 1000 additional prescriptions for spironolactone issued after RALES led to 50 additional admissions for hyperkalemia.

We believe there are at least six reasons why hyperkalemia is a more common occurrence in clinical practice than it was in the carefully controlled setting of RALES. Physicians may not monitor potassium levels closely in patients receiving spiro-



**Figure 5. Prescription Patterns for Other Medications among Patients Recently Hospitalized for Heart Failure Who Were Receiving ACE Inhibitors.**

The curves show trends in prescription rates for various drugs per 1000 patients over the course of the eight-year study period. Patterns of use of angiotensin-receptor antagonists, potassium-sparing diuretics other than spironolactone, and potassium supplements are not shown because baseline rates of use of those medications were low. NSAIDs denotes nonsteroidal anti-inflammatory drugs.

nolactone,<sup>13</sup> may neglect baseline attributes that predispose patients to hyperkalemia (e.g., diabetes mellitus),<sup>8,9</sup> and may overlook conditions that develop during therapy (e.g., renal dysfunction). They may prescribe inappropriately high doses of spironolactone<sup>28</sup> or other medications that contribute to hyperkalemia.<sup>24</sup> Some patients may purposefully increase their dietary potassium intake, as is often recommended during treatment with diuretics such as furosemide. Finally, physicians may extend the RALES findings to patients who, unlike the patients in that study, do not have left ventricular systolic dysfunction (e.g., those with diastolic dysfunction or cor pulmonale).

Several limitations of our study should be noted. The findings may not apply to younger patients with heart failure, who may have fewer risk factors for hyperkalemia than older patients. We analyzed administrative data without direct measures of potassium or creatinine, adherence to medications, use of nonprescription drugs, and the clinical details surrounding death. Indeed, many of the patients hospitalized for hyperkalemia may have died of another illness. The diagnostic coding for

hyperkalemia has not been validated; moreover, many patients hospitalized for hyperkalemia may have also had volume contraction or renal insufficiency related to spironolactone therapy. In addition, we were unable to identify adverse outcomes that occurred before admission. Although clinicians may have been aware of the potential for spironolactone to cause hyperkalemia, detection bias is an unlikely explanation for our findings because electrolytes are routinely measured in patients with heart failure when they are admitted to the hospital. Finally, our study was observational in nature and cannot prove causality; however, the relationship between the publication of RALES, the surge in spironolactone use, and the increase in hyperkalemia-related admissions is temporally compelling, biologically plausible, and consistent with existing evidence.<sup>4-6,13,15,28</sup>

In conclusion, we found that the publication of RALES was associated with an increase in spironolactone use and hyperkalemia-associated morbidity and mortality at the population level, most likely because of an interaction between spironolactone and ACE inhibitors that is accentuated by other medications or coexisting conditions. Much of this harm probably reflects application of the findings of a landmark clinical trial to patients at increased risk for hyperkalemia, including many who would have been excluded from the trial.<sup>14</sup> We speculate that iatrogenic hyperkalemia in this setting can be avoided without withholding spironolactone from patients for whom it is appropriate. Instead, clinicians should consider other risk factors for hyperkalemia when selecting candidates for spironolactone therapy, minimize concurrent prescriptions for other medications that contribute to hyperkalemia, and closely monitor renal function and potassium levels.

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