

## Using Spironolactone in Patients with Congestive Heart Failure: Taking care when applying evidence in the real world

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References available at  
[www.tippsnetwork.ca](http://www.tippsnetwork.ca)  
“Clinical Updates” section

**Resources** on drugs and  
herbs that interfere with  
potassium homeostasis, and  
Potassium in foods handout  
for patients also available at  
[www.tippsnetwork.ca](http://www.tippsnetwork.ca),  
“Clinical Updates” section.

### BOTTOM LINE IN PRACTICE

Ensure steps are taken to minimize the risk of hyperkalemia in patients using spironolactone. Employ strategies to support best practice for spironolactone in primary care.

Heart failure is a common disease, affecting nearly one in ten over the age of 65.(1) A key goal of managing patients with heart failure in the community is to reduce symptoms and prevent heart failure episodes that require hospitalization.

The Randomized Aldactone Evaluation Study (RALES) established the clinical benefit of spironolactone therapy in patients with severe heart failure.

(2) The results of RALES led to the recommendation for the **use of low doses of spironolactone** in patients with recent or current New York Heart Association (NYHA) **Class IV symptoms**, in addition to the use of appropriate therapy with diuretics, ACE inhibitors or ARBs, a beta-blocker and digoxin.(1,3) These guidelines also advised that patients taking spironolactone therapy should have **blood potassium and creatinine levels monitored** for signs of hyperkalemia and deteriorating renal function.(1,3)

#### NYHA Class IV Symptoms

- unable to carry out any physical activity without discomfort
- symptoms of cardiac insufficiency at rest
- if any physical activity is undertaken, discomfort is increased

Recently Juurlink *et al* reported that the publication of the RALES study was associated with a large increase in the use of spironolactone, hyperkalemia-associated hospitalizations and in-hospital hyperkalemia-associated death.(4) These two studies demonstrate the challenge of applying the results of clinical trials in real life.

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## Description of RALES

(Pitt B, Zannad F, Remme WJ, Cody R, *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *NEJM* 1999;341(10):709-17)

### BOTTOM LINE

**In patients with severe heart failure, spironolactone 25mg po daily improved all-cause mortality and reduced hospitalizations for all cardiac causes including worsening heart failure, with a low incidence of serious adverse events.**

- DESIGN**
- A randomized, double-blind, placebo-controlled trial
- METHODS**
- 1663 patients (73% males) with severe heart failure (NYHA functional class IV) and a left ventricular ejection fraction of no more than 35% who were being treated with loop diuretics (100%), angiotensin converting enzyme inhibitors (95%), digoxin (74%) and beta-blockers (10%).
  - A total of 822 patients were randomly assigned to receive 25 mg of spironolactone daily, and 841 to receive placebo for 24 months.
- RESULTS**
- The spironolactone group had a relative risk of death of 0.70 (95% confidence interval 0.60 to 0.82) when compared with patients in the placebo group. This equates to a relative risk reduction of 30%, absolute risk reduction of 11.4% and number needed to treat of 9 to prevent one death over 24 months.
  - The relative risk of admission to hospital was 0.65 (0.54 to 0.77; number needed to treat = 11). There was also a significant improvement in symptoms, assessed by the New York Heart Association functional class ( $P < 0.001$ ).

Table 1. Event Rates in RALES

Outcome	RRR	ARR	NNT
Death	30%	11.4%	9
Admission to hospital	30%	9.5%	11

- Among these closely monitored patients, there was a low incidence of serious adverse events in the spironolactone group:
  - There were no significant differences between the two groups in serum sodium concentration, blood pressure, or heart rate during the study.
  - Gynecomastia or breast pain was reported more often in men taking spironolactone (10% vs 1%,  $p < 0.001$ ), causing 1% to discontinue treatment.
  - Although spironolactone increased serum potassium on average by 0.3mmol/L, the incidence of serious hyperkalemia was minimal in both groups: 14 patients on spironolactone (1.7%), 10 patients on placebo (1.2%) ( $p = 0.4$ ).

Table 2. Adverse Event Rates in RALES

Adverse Event	ARI	NNH
Gynecomastia	9%	11
Serious Hyperkalemia	1%	100

## Description of Juurlink

(Juurlink DN, Mamdani MM, Lee DS, *et al.* Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *NEJM* 2004;351(6):543-51)

### BOTTOM LINE

#### After the publication of the RALES trial:

- Spironolactone prescriptions jumped five-fold
- Rates of hospital admission for hyperkalemia increased three-fold
- Rates of in-hospital death associated with hyperkalemia increased five-to-seven fold

#### DESIGN

- A population-based time-series analysis to examine 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 ambulatory patients who were treated with ACE inhibitors.

#### METHODS

- Linked prescription claims data and hospital-admission records for more than 1.3 million adults 66 years of age or older in Ontario, for the period from 1994 through 2001.

#### RESULTS

- Patients treated were an average of 13 years older than the population in the RALES trial. The group was evenly divided between men and women. Most patients were also on a loop diuretic and more than half had been hospitalized for heart failure within the previous month.
- 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.

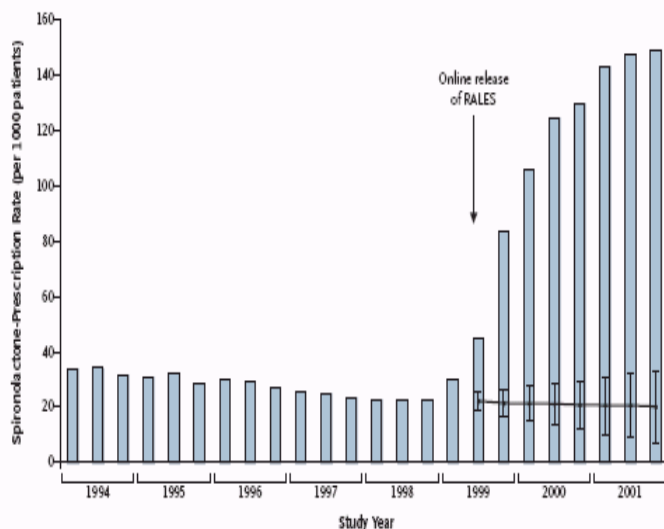


Figure 1. Rate of prescriptions for spironolactone among patients recently hospitalized for heart failure who were receiving ACE inhibitors

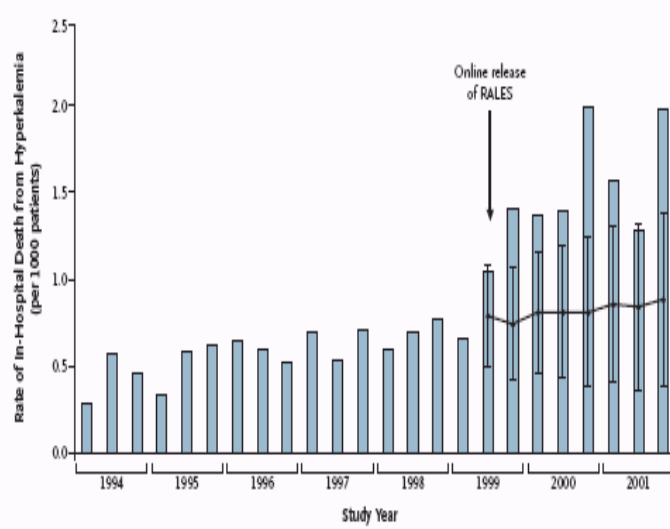


Figure 2. Rate of in-hospital death associated with hyperkalemia among patients recently hospitalized for heart failure who were receiving ACE inhibitors

## Minimizing the Risk of Hyperkalemia\*

- Measure potassium 1 week after initiating therapy or after increasing dose of spironolactone
- Calculate glomerular filtration rate (GFR) to assess specific risk of hyperkalemia
 
$$\text{GFR (ml/min/1.73 m}^2\text{)} = 186 \times \text{serum creatinine (in mg/dl)}^{-1.154} \times \text{age (in yr)}^{-0.203} \times 0.742 \text{ (if female)} \times 1.210 \text{ (if black)}$$

$$\text{Creatinine Clearance (in ml/min)} = [140 - \text{age (in yr)}] \times \text{weight (in kg)} / 72 \times \text{serum creatinine (in mg/dl)} \times 0.85 \text{ (if female)}$$
- Discontinue potassium supplements
- Whenever possible, discontinue drugs that interfere with potassium homeostasis (Table 3)
- Inquire about use of herbal preparations that effect potassium levels or that can interact with spironolactone (Table 4 and Table 5)
- Whenever possible, discontinue NSAIDs, including COX-2 inhibitors (especially in people with decreased renal function)
- Prescribe low-potassium diet; inquire about use of salt substitutes that contain potassium (visit [www.tippsnetwork.ca](http://www.tippsnetwork.ca) “Clinical Updates” for patient information you can print)
- Prescribe thiazide or loop diuretics (loop diuretics are necessary when estimated GFR is <30ml/min)
- If potassium increase to  $\geq 5.5$  mmol/litre, decrease dose of spironolactone; if patient is taking some combination of an ACE inhibitor, an angiotensin-receptor blocker, and an aldosterone-receptor blocker, discontinue one and recheck potassium
- If potassium is > 5.5 mmol/litre despite steps described above, discontinue spironolactone, and ACE inhibitor or angiotensin-receptor blocker if appropriate
- Combinations of spironolactone and an ACE inhibitor or angiotensin-receptor blocker should be avoided when the GFR is < 30 ml/min

Potassium levels may be <b>increased</b> by the following drugs	Potassium levels may be <b>decreased</b> by the following drugs
NSAIDs ACE Inhibitors Angiotensin-receptor blockers Heparin Cyclosporine Trimethoprim Beta-blockers	Thiazide diuretics Loop diuretics Corticosteroids Amphotericin B Antacids Insulin Theophylline Laxatives

Table 4: Herbs that are a source of dietary potassium	Table 5: Herbs containing digoxin-like substances †
Noni juice Alfalfa Dandelion Horsetail Nettle	Chan su Milkweed Lilly of the valley Siberian Ginseng Hawthorn berries

† When spironolactone is used with digoxin, digitalis toxicity can occur.

\* Reference: Palmer, *N Engl J Med* 2004.

## Strategies to Support Best Practice For Spironolactone in Primary Care

- Employing a preplanned potassium monitoring schedule and laboratory requisitions for all patients newly starting spironolactone.
- Providing laboratory visit reminder calls to all patients taking spironolactone.
- Screening the charts of patients with heart failure or patients who are taking spironolactone to identify patients without recent potassium levels.
- Adjusting or adding to patient education materials (in the practice or pharmacy) to reinforce the usefulness of regular potassium monitoring.
- Partnering with local pharmacies to identify patients on spironolactone and determining a mechanism for review of spironolactone use and regular potassium monitoring.
- Posting the original study or this review on a central bulletin board or common education area.