Journal presentation:

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دی ماه ۱۴۰۳

The new england journal o f medicine
This article was published on November 17, 2024, at NEJM.org.

Routine Spironolactone in Acute Myocardial Infarction

Background:

Mineralocorticoid receptor antagonists have been shown to reduce **mortality** in patients after **myocardial infarction** with **congestive heart failure**.

Whether routine use of **spironolactone** is beneficial after myocardial infarction is uncertain.

Inhibition of the renin–angiotensin–aldosterone system with an **angiotensin-converting–enzyme inhibitor** improves outcomes in patients after **myocardial infarction**.

❖ **Higher aldosterone levels** have been associated with **increased mortality** after **myocardial infarction**.

Aldosterone antagonism with ***spironolactone*** has been shown to reduce **mortality** among patients with **chronic heart failure** with **reduced ejection fraction**, and is a ***cornerstone*** of therapy.

❖ **Aldosterone antagonism** also reduces **heart failure** in patients with **preserved ejection fraction** and heart Failure.

Aldosterone antagonism with **eplerenone** has been shown to improve **outcomes** in patients with **acute myocardial infarction** who have **heart failure with reduced ejection fraction.**

but whether aldosterone antagonism is beneficial in all patients after myocardial infarction remains uncertain.

A trial of routine **aldosterone antagonism** with **spironolactone** in addition to standard therapy among **1603** patients after myocardial infarction without heart failure showed no improvement in **outcomes.**

However, there was a significant reduction in **mortality** in the subgroup of **1229** patients with ST-segment elevation myocardial infarction (STEMI), a finding that highlights the need for a large trial.

Finally, an additional randomized trial involving patients with STEMI without heart failure showed that **eplerenone** reduced **B-type natriuretic peptide levels.**

We conducted the CLEAR trial to evaluate whether routine use of ***spironolactone*** is beneficial in patients after ***myocardial infarction.***

Methods:

We used a 2-by-2 factorial design in this international, investigator-initiated, prospective, randomized, placebo-controlled trial of **spironolactone** as compared with **placebo** and **colchicine** as compared with **placebo** in patients with *acute myocardial infarction*.

All patients, investigators, health care providers, data collectors, and outcome adjudicators were unaware of trial-group assignments.

Initially, patients were eligible for the trial only if they had ***STEMI*** and had undergone ***percutaneous coronary intervention***.

To increase recruitment, the steering committee modified the protocol on April 5, 2020, to enroll patients with large non–ST-segment elevation myocardial infarction (**NSTEMI**) who had undergone **percutaneous coronary intervention** and had one or more of the following risk factors:

- **a left ventricular ejection fraction of no more than 45%**;
- **diabetes mellitus**;
- **multivessel coronary artery disease**, defined by **at least 50% stenosis of a second major epicardial vessel**;
- **previous myocardial infarction**;
- **age greater than 60 years**.

Randomization:

Patients were randomly assigned in a factorial 1:1:1:1 allocation to receive **spironolactone** and **colchicine**, **colchicine** and **placebo**, **spironolactone** and **placebo**, or **placebo** only as soon as possible after the index **percutaneous coronary intervention**.

Randomization was stratified according to trial center and the type of myocardial infarction.

Outcomes:

The primary efficacy outcomes were :

- a composite of death from cardiovascular causes or
- new or worsening heart failure, evaluated as the total number of events;
- and a composite of the first occurrence of myocardial infarction,
- stroke,
- new or worsening heart failure,
- or death from cardiovascular causes, evaluated in a time-to-event analysis.

Key secondary outcomes were:

- a composite of the **first occurrence of new or worsening heart failure**,
- **clinically significant ventricular arrhythmia**,
- or **death from cardiovascular causes**;
- **death from cardiovascular causes**;
- and a composite of **the first occurrence of new or worsening heart failure**
- or **death from cardiovascular causes**;

each of these secondary outcomes was evaluated in a time-to-event analysis.

Blood pressure and safety were also assessed.

Safety outcomes included:

- ✓ **hyperkalemia** (serum potassium >5.5 mmol per liter);
- ✓ a composite of **death from renal causes**,
- ✓ **dialysis**,
- ✓ **renal transplantation**,
- ✓ or a **sustained drop in the estimated glomerular filtration rate (eGFR) of at least 40%**;

and components of the composite outcome.

A committee of clinicians who were unaware of trial-group assignments adjudicated all primary outcome events, episodes of major bleeding, and episodes of stent thrombosis.

Staff at an angiographic core laboratory at the Population Health Research Institute who were unaware of trial group assignments reviewed all ischemia-driven revascularization and stent thrombosis events.

The trial products were **spironolactone** tablets of 25 mg, **colchicine** tablets of 0.5 mg, and **placebos** matching the colchicine and spironolactone tablets.
Tiofarma provided both trial drugs and placebos, which were manufactured with raw materials produced

Statistical Analysis:

The initial calculation of sample size to provide the trial with 80% power to detect a 25% relative risk reduction was based on a time-to-event analysis of death from cardiovascular causes or new or worsening heart failure;

we anticipated a cumulative incidence of events in the placebo group of 15% at 3 years, a two-sided type I error level of 5%, a loss to follow-up of 2% of patients in both the **spironolactone** group and the **placebo** group, discontinuation of the trial regimen by 12.5% of patients, and no interaction with **colchicine**

In October 2023, blinded analysis showed an overall incidence of first events of death from cardiovascular causes or new or worsening heart failure of **4%.**

Given the lower-than-expected incidence of events,

in December 2023, we decided to proceed with two primary outcomes but preserve the type I error rate at 5%.

The type I error rate was partitioned to **4%** for the **first primary outcome** (**death from cardiovascular causes** or **new or worsening heart failure**) and 1.85% for the **second primary outcome** (a composite of the **first occurrence of myocardial infarction**, **stroke**, **new or worsening heart failure**, or **death from cardiovascular causes**), because the overall blinded data indicated an overlap of 57% of events between the two primary outcomes.

We estimate that a sample size of 7000 patients would provide the trial with 84%power to detect a relative risk reduction of 31.5% with the use of the Prentice–Williams–Peterson model for the first primary outcome, with an incidence of events in the placebo group of 6% (357 events) over 3 years.

- **The first primary outcome** (**death from cardiovascular causes** or **new or worsening heart failure**) was analyzed as the total number of events with the use of the Prentice–Williams–Peterson conditional gap-time model.

- **The second primary outcome** (a composite of **death from cardiovascular causes**, **recurrent myocardial infarction**, **stroke**, or **new or worsening heart failure**) was assessed in a time-to-first-event analysis with the log-rank test for the P value; for the effect size and 95% confidence intervals, we used a Cox proportional-hazards model with patients stratified according to whether they received **colchicine** or colchicine-matched **placebo** and whether they had **STEMI** or **NSTEMI**.

In addition,

systolic blood pressure,

diastolic blood pressure,

and **eGFR**

were analyzed with a linear mixed model with repeated measures and adjusted according to the baseline values;

Patients were divided into subgroups according to the prespecified characteristics:

- **age (≥65 vs. <65 years)**,
- **sex (female vs. male)**,
- **type of myocardial infarction (anterior STEMI vs. other myocardial infarction)**,
- **serum potassium concentration at baseline**

(<4 mmol per liter vs. ≥4 mmol per liter),

- **history of hypertension versus no history of hypertension**,
- and **timing of enrollment with respect to the coronavirus disease 2019 (Covid-19) pandemic (before ,during or after the pandemic)**

We hypothesized that the effects of the trial regimen would be consistent across the subgroups stratified according to

- ✓ **age**
- ✓ and **sex**; that the benefits would be greater in the subgroups with **anterior STEMI**,
- ✓ **a serum potassium concentration** at baseline of **less** than **4 mmol per liter**,
- ✓ and a **history of hypertension** than in the counterpart subgroups;
- ✓ and that the effects would be reduced in the subgroup **enrolled during the Covid-19 pandemic** as compared with the subgroups enrolled before or after the pandemic.
- ✓ **Geographic region** (North America vs. Europe vs. other) was added as a post hoc subgroup to demonstrate consistency.

We did not collect information about left ventricular ejection fraction, and we are unable to report results from subgroups stratified according to this characteristic.

We undertook a prespecified on-treatment analysis that excluded patients who discontinued the trial regimen on the day of randomization and censored patients **7 days** after permanent discontinuation of the trial regimen.

Results:

Between February 1, 2018, and November 8, 2022,

we enrolled **7062** patients from 104 centers in 14 countries; **3537** were assigned to receive **spironolactone** and **3525** to receive **placebo.**

Baseline characteristics of the patients appeared to be well balanced between the groups; the mean age of patients was **61 years**, and **20.4%** of patients were **women**.

A total of **9.0% of patients** had **previous myocardial infarction**,

0.8% had **a history of heart failure**, and **18.5%** had **diabetes mellitus**.

Most patients who underwent randomization had **STEMI (95.1%)**, and **4.9% had NSTEMI**.

Table 1. Demographic and Clinical Characteristics at Baseline.*

Characteristic	Spironolactone (N=3537)	Placebo (N=3525)
Demographic characteristics		
Mean age — yr	60.9±10.3	60.4±10.3
Age >75 yr — no. (%)	294 (8.3)	277 (7.9)
Female sex — no. (%)	760 (21.5)	678 (19.2)
Geographic region		
North America	1009 (28.5)	1013 (28.7)
Europe	2366 (66.9)	2349 (66.6)
Other	162 (4.6)	163 (4.6)
Clinical characteristics		
Killip class ≥II — no. (%)†	24 (0.7)	25 (0.7)
NSTEMI at presentation — no. (%)	168 (4.7)	181 (5.1)
STEMI at presentation — no. (%)	3369 (95.3)	3344 (94.9)
Myocardial area affected by STEMI — no./total no. (%)		
Anterior	1315/3369 (39.0)	1315/3344 (39.3)
Inferior	1942/3369 (57.6)	1890/3344 (56.5)
Lateral	434/3369 (12.9)	423/3344 (12.6)
Posterior	328/3369 (9.7)	332/3344 (9.9)
Multivessel coronary disease — no. (%)	1725 (48.8)	1752 (49.7)
Medical history — no. (%)		
Previous heart failure	24 (0.7)	35 (1.0)
Current smoker	1440 (40.7)	1444 (41.0)
Hypertension	1600 (45.2)	1633 (46.3)
Diabetes mellitus	630 (17.8)	673 (19.1)
Previous myocardial infarction	321 (9.1)	312 (8.9)
Previous percutaneous coronary intervention	356 (10.1)	353 (10.0)
Medications at discharge — no. (%)		
Aspirin	3417 (96.6)	3416 (96.9)
Clopidogrel	1499 (42.4)	1476 (41.9)
Ticagrelor	1596 (45.1)	1586 (45.0)
Prasugrel	393 (11.1)	401 (11.4)
Angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker	2745 (77.6)	2773 (78.7)
Statin	3408 (96.4)	3416 (96.9)
Sodium–glucose cotransporter 2 inhibitor	113 (3.2)	98 (2.8)
Initial percutaneous coronary intervention‡		
Placement of bare-metal stent — no. of stents/total no. (%)	11/4854 (0.2)	9/4841 (0.2)
Placement of ≥1 drug-eluting stent — no. of stents/total no. (%)	4667/4854 (96.1)	4646/4841 (96.0)
Angioplasty only — no. of stents/total no. (%)	149/4854 (3.1)	162/4841 (3.3)
Placement of intraaortic balloon pump — no. of patients (%)	46 (1.3)	48 (1.4)

* Plus–minus values are means ±SD. NSTEMI denotes non–ST-segment elevation myocardial infarction, and STEMI ST-segment elevation myocardial infarction.
† The Killip classification system is a tool to assess the risk of death based on the severity of heart failure in patients with acute myocardial infarction. The scale ranges from I to IV, with higher numbers indicating greater risk.
‡ The total number of stents placed was 9695, with 4854 in the spironolactone group and 4841 in the placebo group.

The median time from the onset of myocardial infarction to randomization was 26.8 hours (interquartile range, 15.9 to 42.4), and the median time from randomization to the first dose of the trial product was 2.1 hours (interquartile range, 0.7 to 9.2).

The medications provided to patients at discharge from the hospital appeared to be similar in the two groups.

The median duration of follow-up was 3.00 years (interquartile range, 2.14 to 3.71); 28.0% of patients in the **spironolactone** group and 24.4% in the **placebo** group discontinued the trial regimen.

In the case of **140** patients (4.0%) in the **spironolactone** group and **166 (4.7%) in the placebo** group, the treating physician prescribed open label spironolactone instead of the trial product.

Blood Pressure:

The least-squares mean (±SE) **systolic blood pressure** at 1 year of follow-up, adjusted according to the baseline value, was **126.9±0.3** in 2724 patients in the **spironolactone** group and **129.7±0.3** in 2672 patients in the **placebo** group, with a mean difference of −2.8 (95% confidence interval [CI], −3.6 to −2.0).

The least-squares mean **diastolic blood pressure** at 1 year of follow-up, adjusted according to the baseline value, was **77.5±0.2** in 2717 patients in the **spironolactone** group and **78.9±0.2** in 2660 patients in the **placebo** group, with a mean difference of −1.3 (95% CI, −1.8 to −0.8).

Efficacy:

For **the first primary outcome**, there were 183 events (1.7 per 100 patient-years) in the **spironolactone** group as compared with 220 events (2.1 per 100 patient-years) in the **placebo** group (hazard ratio, 0.89; 95% CI, 0.73 to 1.08; P=0.23; hazard ratio adjusted for competing risk of death from noncardiovascular causes, 0.91; 95% CI, 0.69 to 1.21; P=0.51)

With respect to the **second primary outcome**, an event occurred in 280 of 3537 patients (7.9%) in the **spironolactone** group as compared with 294 of 3525 (8.3%) in the **placebo** group.

The **colchicine** factorial had no significant effect on the primary outcomes in the trial of **spironolactone** versus **placebo** (P=0.23 and interactions with first and second primary outcomes).

Cardiovascular mortality was similar in the two groups (3.2% in the **spironolactone** group vs. 3.3% in the **placebo** group

New or worsening heart failure occurred in 58 patients (1.6%) in the **spironolactone** group as compared with 84 (2.4%) in the **placebo** group.

The baseline characteristics of the on-treatment population appeared to be well balanced between the two groups

The ontreatment analyses included 131 events (1.5 per 100 patient-years) in the **spironolactone** group versus 179 events (2.0 per 100 patient-years) in the **placebo** group for the **first primary outcome** , and **the second primary outcome** occurred in 204 patients (5.8%) in the **spironolactone** group versus 250 (7.2%) in the **placebo** group .

The incidence of the primary outcomes appeared to be consistent across all prespecified subgroups

Safety:

- **Hyperkalemia** (serum potassium **>5.5** mmol per liter) leading to discontinuation of the trial regimen occurred in 39 patients (1.1%) in the **spironolactone** group and 20 (0.6%) in the **placebo** group .
- **Death from renal causes**
- **dialysis**,
- **renal transplantation**,
- or a **sustained drop of at least 40% in the eGFR** occurred in 37 patients (1.0%) in the **spironolactone** group and 44 (1.2%) in the **placebo** group .
- **A sustained drop of at least 40% in the eGFR** occurred in 32 patients (0.9%) in the **spironolactone** group and 38 (1.1%) in the **placebo** group

The **least-squares mean (±SE) eGFR at 1 year** of follow-up, adjusted according to the baseline value, was 88.5±0.3 ml per minute per 1.73 m2 of body-surface area among 3537 patients in the **spironolactone** group and 90.2±0.3 ml per minute per 1.73 m2 among 3525 patients in the **placebo** group.

Gynecomastia was more common with ***spironolactone*** than with placebo, occurring in 81 patients (2.3%) in the **spironolactone** group as compared with 19 (0.5%) in the **placebo** group.

Table 2. Competing-Risks Analysis of Primary, Secondary, and Safety Outcomes.

Outcome	Spironolactone (N=3537)	Placebo (N=3525)	Hazard Ratio or Odds Ratio*	95% CI†	P Value
Primary outcomes					
Death from cardiovascular causes or new or worsening heart failure — total no. of events (no. per 100 patient-years)	183 (1.7)	220 (2.1)	0.91	0.69–1.21	0.51
Death from cardiovascular causes, myocardial infarction, stroke, or new or worsening heart failure — no. (%)	280 (7.9)	294 (8.3)	0.96	0.81–1.13	0.60
Components of the primary outcomes — no. (%)					
Death from cardiovascular causes	114 (3.2)	116 (3.3)	0.98	0.76–1.27	
Recurrent myocardial infarction	106 (3.0)	107 (3.0)	1.02	0.77–1.35	
Stroke	51 (1.4)	42 (1.2)	1.15	0.72–1.84	
New or worsening heart failure	58 (1.6)	84 (2.4)	0.77	0.51–1.16	
Secondary and safety outcomes — no. (%)					
Death from cardiovascular causes, new or worsening heart failure, or clinically significant arrhythmia‡	173 (4.9)	186 (5.3)	0.95	0.77–1.17	
Clinically significant arrhythmia	20 (0.6)	17 (0.5)	1.45	0.67–3.12	
Death from any cause	166 (4.7)	175 (5.0)	0.95	0.77–1.17	
Death from renal causes, dialysis, renal transplantation, or sustained drop in eGFR of ≥40%	37 (1.0)	44 (1.2)	0.84	0.54–1.30	
Death from renal causes	4 (0.1)	4 (0.1)			
Dialysis or renal transplantation	1 (<0.1)	2 (0.1)			
Persistent drop in eGFR of ≥40%	32 (0.9)	38 (1.1)	0.84	0.52–1.34	
Atrial fibrillation	93 (2.6)	87 (2.5)	1.14	0.84–1.55	

* Numbers are hazard ratios calculated in a competing-risks analysis, except for the composite renal outcome (death from renal causes, dialysis, renal transplantation, or a sustained drop in the estimated glomerular filtration rate [eGFR] of ≥40%) and the persistent drop in eGFR of at least 40%, which are odds ratios calculated with logistic regression.

† The widths of the confidence intervals (CI) have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

‡ Clinically significant arrhythmia was specified as ventricular tachycardia that led to an intervention, including electrical cardioversion, intravenous administration of antiarrhythmic agents, or chest compressions; any ventricular fibrillation; or any cardiac arrest that led to chest compressions, electrical cardioversion, or intravenous administration of antiarrhythmic agents or epinephrine.

Discussion:

After myocardial infarction, treatment with **spironolactone**, as compared with **placebo**, did not reduce the *incidence of death from cardiovascular causes or new or worsening heart failure or the incidence of composite-outcome events (death from cardiovascular causes, recurrent myocardial infarction, stroke, or new or worsening heart failure)* over a median follow-up of 3 years.

The incidence of **hyperkalemia** and **gynecomastia** was **higher** with **spirononlactone** than with placebo.

EPHESUS (**Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study**) randomly assigned **6642** patients with myocardial infarction who had an ejection fraction of less than 40% and either heart failure or diabetes mellitus to receive **eplerenone** or **placebo**.

Use of **eplerenone** was associated with a 15% relative risk reduction for both **death from any cause** and **hospitalization for heart failure**.

In contrast, **ALBATROSS (Aldosterone Lethal Effects Blockade in Acute Myocardial Infarction Treated with or without Reperfusion to Improve Outcome and Survival at Six Months Follow-Up)** trial randomly assigned 1603 patients with *myocardial infarction without heart failure* to receive **spironolactone** or **placebo** and did not show a reduction in the risk of *cardiovascular events* with spironolactone.

Finally, an additional randomized trial involving patients with *STEMI without heart failure* showed that **eplerenone** reduced *B-type natriuretic the peptide* levels, and a meta-analysis suggested benefit from ***mineralocorticoid antagonists*** in patients after *myocardial infarction without heart failure*.

A recent trial comparing **angiotensin receptor–neprilysin inhibitors** with an **angiotensinconverting–enzyme inhibitor** in 5661 patients with ***myocardial infarction*** did not show significant reductions in the incidence of ***death from cardiovascular causes or heart failure***.

However, an exploratory analysis showed that *fewer total* ***cardiovascular events*** occurred with **angiotensin receptor–neprilysin inhibitors** than with an angiotensin-converting–enzyme inhibitor

A recent trial of ***empagliflozin*** involving 3620 patients with *myocardial infarction* did not show a reduction in the risk of *death* or *hospitalization for heart failure*, but *fewer* ***heart failure events*** occurred with empagliflozin than with placebo.

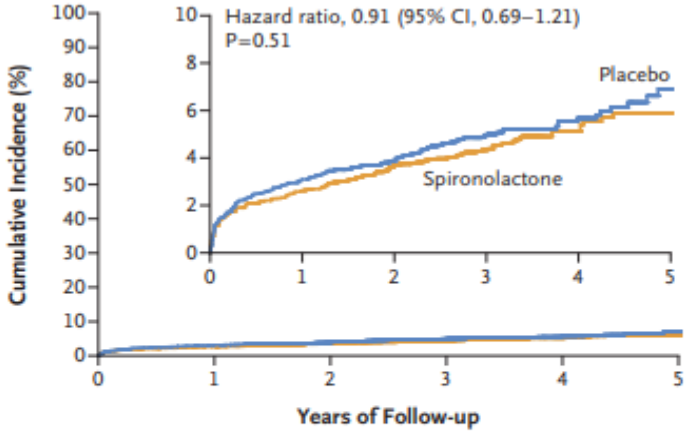
We did not demonstrate a reduction in *mortality* with **spironolactone**.

The point estimate for heart failure events in our trial was generally consistent with the findings of previous trials, which reported *reductions in heart failure events* with **spironolactone**.

The lack of an apparent reduction in cardiovascular mortality may relate to improvements in clinical care over the last two decades, which have resulted in overall lower mortality after myocardial infarction and a reduction in the power of trials to detect meaningful differences.

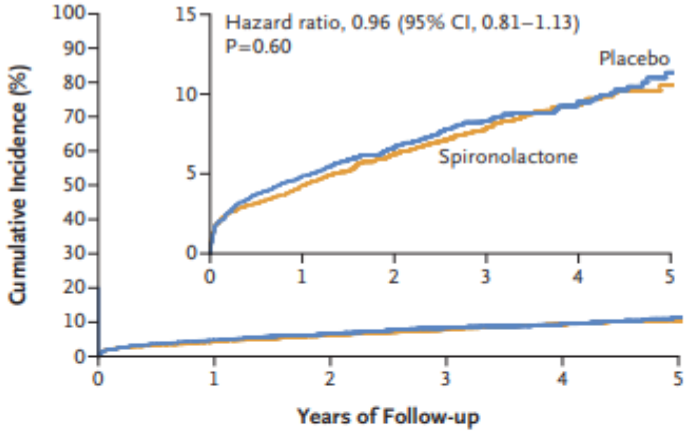
Furthermore, trials of **mineralocorticoid antagonists** in patients with *heart failure* *and* *preserved ejection fraction* have shown similar findings, with *reductions* in the **incidence of heart failure** but no effect on *mortality*.

A **Death from Cardiovascular Causes or New or Worsening Heart Failure**



No. at Risk						
Spironolactone	3537	3422	2788	1778	704	183
Placebo	3525	3392	2785	1754	735	194

B **Death from Cardiovascular Causes, Myocardial Infarction, Stroke, or New or Worsening Heart Failure**



No. at Risk						
Spironolactone	3537	3365	2712	1721	681	173
Placebo	3525	3331	2707	1695	707	184

Figure 1. Kaplan–Meier Event Curves for the Primary Outcomes.

Shown are time-to-event curves for the total number of events of death from cardiovascular causes or new or worsening heart failure (Panel A) and the composite of death from cardiovascular causes, myocardial infarction, stroke, or new or worsening heart failure (Panel B). The insets show the same data on an expanded y axis. CI denotes confidence interval.

The newer **selective nonsteroidal mineralocorticoid antagonist *finerenone*** has been examined in several trials.

In a pooled analysis of two trials comparing **finerenone** with **placebo** in 13,026 patients with **chronic kidney disease**, finerenone was associated with lower incidence of the composite outcome (**death from cardiovascular causes**, **myocardial infarction**, **stroke**, or **hospitalization for heart failure**)

a major factor in this result was ***a reduction in hospitalization for heart failure*** Furthermore, a randomized trial involving 5734 patients with established **renal disease** showed that ***finerenone*** reduced the risk of the primary composite outcome (**renal failure**, **a sustained decrease from baseline of at least 40% in the eGFR**, or **death from renal causes**)

These findings suggest that a ***selective nonsteroidal mineralocorticoid antagonist*** can be **protective of the kidneys** and **reduce heart failure.**

Our trial has limitations:

- **First**, on the basis of the 95% confidence intervals for the primary outcome results,we cannot exclude a beneficial relative risk reduction of around 30% or smaller, which could be clinically important.

- **Second**, despite the increase in sample size, the incidence of events was lower than anticipated, and we cannot rule out type II error due to reduced power.

- **Third**, women and members of some racial and ethnic groups were underrepresented in the trial as compared with the incidence of disease in these groups worldwide.

- **Fourth**, the rate of discontinuation of the trial regimen was higher than anticipated, which may have reduced the power of the trial, especially given the findings of the on-treatment analysis.

- **Fifth**, we cannot rule out that the side effects of **colchicine** in the factorial may have contributed to the discontinuation of **spironolactone** in the factorial design.

In this trial of **spironolactone** as compared with **placebo** in patients with ***myocardial infarction***, **spironolactone *did not reduce*** the incidence of a broad composite of cardiovascular outcomes.

Table 3. Adverse Events.

Event	Spironolactone (N=3537)	Placebo (N=3525)	P Value
	number (percent)		
Any serious adverse event	255 (7.2)	241 (6.8)	0.54
Hyperkalemia leading to discontinuation of trial regimen*	39 (1.1)	20 (0.6)	0.01
Any adverse event	1157 (32.7)	1086 (30.8)	0.09
Hypotension	38 (1.1)	29 (0.8)	0.28
Orthostatic hypotension	16 (0.5)	7 (0.2)	0.06
Breast tenderness	20 (0.6)	2 (0.1)	<0.001
Gynecomastia	81 (2.3)	19 (0.5)	<0.001

* Hyperkalemia was prespecified as a potassium level of greater than 5.5 mmol per liter.

Thanks for your attention