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Prognostic relevance of magnesium alterations in patients with a myocardial infarction and left ventricular dysfunction: insights from the EPHESUS trial

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Abstract

***Background*:** Magnesium changes are common in myocardial infarction (MI) complicated with left ventricular systolic dysfunction (LVSD) and/or heart failure (HF). The relation between serum magnesium and clinical outcomes is insufficiently elucidated in this population.

Methods: The EPHESUS trial randomized 6632 patients to either eplerenone or placebo. Hypomagnesemia and hypermagnesemia, were defined as a serum magnesium <0.66 mmol/L and >1.10 mmol/l respectively. Linear mixed models and time-dependent Cox regression analysis were used to determine the effect of eplerenone on magnesium changes and the prognostic importance of magnesium. The co-primary outcomes were all-cause mortality and a composite of cardiovascular (CV) mortality and CV-hospitalization.

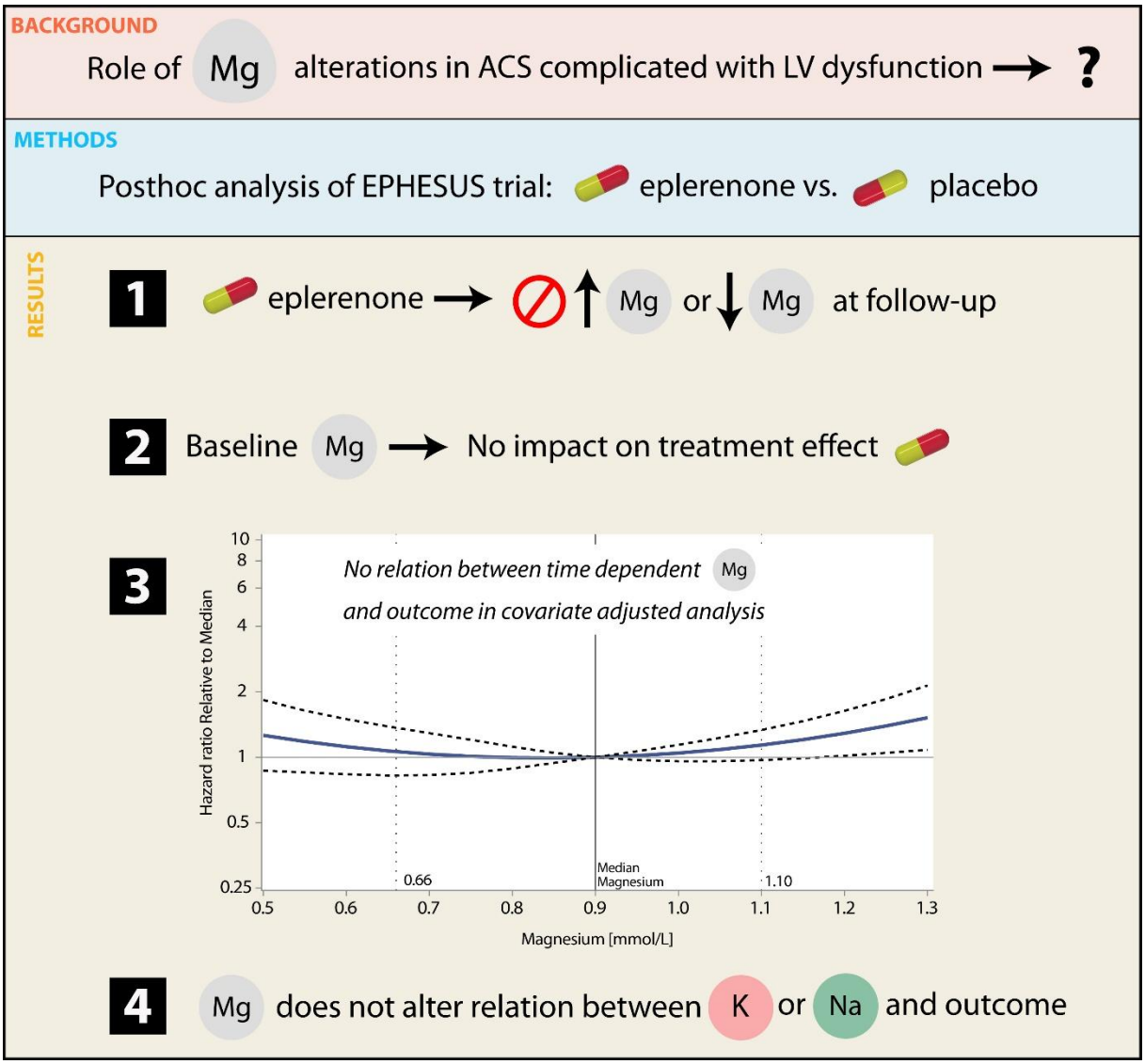
***Results*:** A total of 5371 patients had a post-baseline magnesium measurement. At baseline 231 (4.3%) patients had hypomagnesemia and 271 (5.0%) patients had hypermagnesemia. During a median follow-up of 16 months, 682 (13%) developed hypomagnesemia and 512 (9.5%) hypermagnesemia. Eplerenone treatment did not result in a different magnesium level during follow-up (p=0.14). After covariate adjustment hypo- and hypermagnesemia were not associated with a higher risk of cardiovascular events. Magnesium levels did not modulate the effect of a high potassium (>5 mmol/L) or low potassium (<4 mmol/l) on clinical outcome. Baseline magnesium levels did not influence the treatment effect of eplerenone (p-interaction> 0.1 for all primary and secondary endpoints).

***Conclusion*:** In patients with MI complicated by LVSD or HF, magnesium alterations were not associated with clinical outcomes nor did they influence the effect of eplerenone. Serum magnesium did not modulate the effect of potassium changes on clinical outcome or the treatment effect of eplerenone.

Key-words: myocardial infarction; heart failure; systolic dysfunction; eplerenone; hypomagnesemia, hypermagnesemia; electrolytes.

ClinicalTrials.gov identifier: NCT00232180

Visual abstract



Introduction

Electrolyte disturbances are common in patients with a myocardial infarction complicated with heart failure and relate to the neurohormonal changes of the disease, the older age of the patient, dietary insufficiencies and the treatment options used. Magnesium changes are common in patients with a myocardial infarction complicated with heart failure.(1) In these patients, hypomagnesemia and hypermagnesemia are associated with adverse clinical outcome in several observational studies.(2, 3) Furthermore, in animal models, hypomagnesemia was shown to potentiate the arrhythmic effect of low potassium.(4) Heart failure guidelines recommend the substitution of magnesium in patients presenting with ventricular arrhythmias.(5) Indeed, hypomagnesemia has been linked with increased ventricular arrhythmogenesis.(6) Moreover, the treatment of hypomagnesemia was associated with a reduction of ventricular ectopy after myocardial infarct in several small trials.(7, 8) However, randomized trials regarding *routine* magnesium substitution in patients with an acute coronary syndrome have shown conflicting results.(9, 10) Nevertheless, the use of magnesium supplementation remains frequent in clinical practice due to the low cost, ease of the intervention, the favorable safety profile and the association of hypomagnesemia with adverse clinical outcome in observational cohorts. However, most cohorts that established this association date back over three decades and often failed to adequately adjust for important covariates occurring in patients with magnesium alterations.(11, 12) The goal of our analysis was; (1) to determine the relation between serum magnesium and clinical outcome, (2) to determine the effect of eplerenone on serum magnesium levels, (3) to investigate whether serum magnesium levels, potentiate the adverse clinical outcome of other electrolyte disturbances (potassium and sodium), (4) to investigate the interaction between baseline serum magnesium levels and the eplerenone treatment effect in patients with an acute myocardial infarction complicated with heart failure.

Methods

Study design and population

The methodology and the results of the EPHESUS study (NCT00232180) have been previously described.(13) Briefly, Patients enrolled in EPHESUS had an acute myocardial infarction complicated

by systolic dysfunction (left ventricular ejection fraction ≤40%), heart failure (documented by at least one of the following: presence of pulmonary rales, chest radiography showing pulmonary venous congestion, or the presence of a third heart sound) or diabetes. Patients were enrolled in the trial 3-14 days after the myocardial infarction and were randomly assigned to treatment with eplerenone or placebo in a 1:1 fashion in addition to receiving standard medical therapy, which could include angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs), β-blockers, diuretics, aspirin, statins as well as coronary reperfusion therapy. EPHESUS was an event-driven study with a mean follow-up duration of 16 months. Patients with at least one post-baseline magnesium assessment were included in this analysis. The study was performed according to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all patients.

Definition of magnesium alterations

Patients were followed up after randomization at one week, four weeks, three months and every three months there-after. Magnesium analysis were performed by protocol at baseline, at 3 months, 6 months, 12 months, 18 months and 24 months of follow-up. Hypomagnesaemia was defined as a serum magnesium below 0.66 mmol/L and hypomagnesemia as a serum magnesium above 1.1 mmol/L. A normal range of magnesium was defined as between 0.66 mmol/L and 1.1 mmol/L.

Outcome endpoints and statistical analysis

In line with the original report of the EPHESUS trial, the two primary endpoints were **(1)** all-cause mortality and **(2)** a composite of cardiovascular mortality or cardiovascular hospitalization. The secondary endpoints were **(1)** cardiovascular mortality and **(2)** a composite of all-cause mortality or all-cause hospitalization. **(3)** a composite of cardiovascular mortality and non-fatal AMI, **(4)** a composite of CV-mortality and heart failure hospitalization (HFH), (**5)** HFH alone and **(6)** Sudden Cardiac Death. Because Adjudicated sudden cardiac death was relatively uncommon, this endpoint was not used in analysis determining the influence of magnesium alterations on other electrolyte abnormalities (sodium and potassium). All endpoints in the EPHESUS trial were adjudicated by an

independent and blinded endpoint committee.

Statistical analysis

Continuous variables are presented as mean ± standard deviation and categorical variables as frequencies (percentages). Between groups assessment of categorical variables were compared using Pearson's Chi-2 test or Fisher's exact, while continuous variables were compared using student t test or ANOVA as appropriate. Multivariable logistic regression models were used to determine independent predictor for the development of hypomagnesemia and hypermagnesemia during study follow-up. Univariate predictors with a $p<0.100$ were entered in the multivariable model. Linear mixed effects models with repeated measures over time were performed to assess changes in serum magnesium levels over time according to treatment group allocation (eplerenone vs. placebo). The baseline magnesium and the interaction of the treatment by time were specified as fixed effects and patient level as a random effect. Cox regression models with a time dependent covariate structures of serum magnesium were used to assess the relation between magnesium and the primary and secondary endpoints. Hazard ratios (HR) are presented with their 95% confidence interval (CI). Time dependent serum magnesium values, visualized as B-splines, were tested in outcome analysis after covariate adjustment. All outcome analyses were covariate adjusted. Covariates were chosen based on clinical relevance, prognostic importance and use in previous post-hoc analysis in the EPHESUS-trial.(14) Covariates for adjustment included: age, sex, Killip class, left ventricular ejection fraction, reperfusion therapy, hemoglobin, potassium (time dependent), systolic blood pressure, heart rate, estimated glomerular filtration rate calculated by CKD-Epi formula (time dependent), body mass index, history of diabetes, history of hypertension, history atrial fibrillation, history of chronic obstructive pulmonary disease, previous myocardial infarction, previous HFH, peripheral arterial disease, use of diuretics, ACEi/ARB, Beta-blocker, digoxin and eplerenone assignment. In addition to modeling magnesium as a continuous time-dependent variable (B-spline), baseline magnesium was also modeled (hypomagnesium, normal magnesium, hypermagnesium). To determine the impact of baseline magnesium levels on the treatment effect of eplerenone, treatment interaction was assessed for the different endpoints, using both baseline magnesium levels (pre-randomization) with reporting of p-values for interaction. All analyses were performed using SAS version 9.4.

Results

Characteristics of the study population

Of the 6632 patients included in the EPHESUS trial, 5371 patients had a post-baseline magnesium measurement and were included in the current analysis. Baseline characteristic of patients without magnesium analysis at follow-up are reflected in supplemental table 1. In comparison to patients with a post-baseline magnesium analysis, patients without a post-baseline magnesium analysis exhibited features of worse disease severity and therefore often died before the first post-baseline magnesium analysis. At baseline 231 patients (4.3%) had hypomagnesemia, 271 patients (5.0%) had hypermagnesemia and 4869 patients (90.7%) had a magnesium in the normal range. Baseline characteristics of the study population according to baseline magnesium category are reflected in table 1. Patients with hypomagnesemia were more often women and more often had a history of a myocardial infarction. Patients with hypermagnesemia had a lower estimated glomerular filtration rate. Alterations in magnesium (both hyper and hypo) were more common at baseline (table 1) in patients taking thiazides.

Magnesium changes during follow-up and independent predictors

During a median follow-up of 16 months a total of 682 (13%) patients developed hypomagnesemia , of whom 121 had hypomagnesemia at baseline. A total of 512 (9.5%) patients developed hypermagnesemia during follow-up, of whom 89 had hypermagnesemia at baseline. Supplemental table 2 lists the number of patients with multiple hypo- or hypermagnesemia events. Table 2 presents independent predictors of for the development of hypo- and hypermagnesemia during follow-up.

Magnesium levels according to treatment assignment

Figure 1 panel A illustrates the proportion of patients having a post-baseline magnesium measurement in the category of hypo- or hypermagnesemia according to treatment assignment (supplemental table 3 give further classification according to the baseline magnesium status). Treatment with eplerenone was not associated with a higher prevalence of hypo- or hypermagnesemia. Similarly, figure 1 panel B

illustrates the magnesium levels at follow-up according to treatment assignment, illustrating that eplerenone was not associated with a higher risk for hypomagnesemia (p=0.1430).

Magnesium and clinical outcome

Figure 2 illustrates the relation between the time-updated serum magnesium levels and the different primary and secondary endpoints after covariate adjustment. As visually illustrated by the horizontal incline of the curve, magnesium levels both in the hypomagnesemia range and hypermagnesemia were not associated with adverse outcome after covariate adjustment. However as indicated by the unadjusted p-value, magnesium changes were associated a borderline non-significant trend towards an elevated risk for the different primary endpoints and secondary endpoints (except the composite of cardiovascular death and myocardial infarction or sudden cardiac death). Table 3 illustrates the adjusted risk for clinical outcome according to baseline categorical magnesium ranges. Table 3 indeed shows that hypomagnesemia and hypermagnesemia at baseline were not associated with a higher risk for the different endpoints after covariate adjustment. Additionally, table 3 shows the treatment interaction with baseline magnesium values. As indicated by the p-value for interaction, baseline magnesium values did not modify the treatment effect of eplerenone.

Effect of magnesium on prognostic relevance of other electrolyte abnormalities

Figure 3 illustrates the effect of magnesium levels on the relation between high (>5 mmol/l) or low (<4 mmol/l) potassium and the different endpoints. As the blue line of low potassium is always above the green line of high potassium, this indicates that in general a low potassium is associated with a higher hazard ratio for the different endpoints. Magnesium did not influence this relationship as all the lines are flat (no inclination) over the entire magnesium range. Testing magnesium categorically as hypo and hypermagnesemia per potassium category (low or high), generated the same results (supplemental table 4). Figure 4 illustrates the same observation for sodium. In general hyponatremia was associated with a higher risk adverse outcome than hypernatremia (blue line above green line). Magnesium did not change the relationship between sodium and outcome, which was also demonstrated when testing magnesium as a categorical variable (supplemental table 5).

Discussion

Our manuscript offers novel information about the relation between eplerenone and magnesium and regarding the prognostic effect of magnesium alterations in patients with a myocardial infarction complicated with heart failure or systolic dysfunction and can be summarized as follows: (1) The use of eplerenone does not result in development of hypo- or hypermagnesemia. (2) Baseline magnesium alterations do not influence the treatment effect of eplerenone (3) In unadjusted analysis, magnesium is associated with higher risk for certain endpoints, but this relation is lost after covariate adjustment.

(4) Magnesium alterations do not potentiate or mitigate the relation between dyskalemia or dysnatremia and clinical outcome.

Most patients with a myocardial infarction complicated with heart failure or left ventricular dysfunction at baseline had normal magnesium values (> 90%). However, during follow-up, up to 13% of patients developed hypomagnesemia, while almost 10% developed hypermagnesemia. The development of hypomagnesemia is generally believed to be associated with adverse risk in patients with a myocardial infarction or heart failure.(11, 12) Numerous factors are implicated in the development of hypomagnesemia in these patients, including the use of diuretics. Previous reports indicate that the use of thiazide is associated with a higher risk for magnesium alterations.(15) Indeed, at baseline, patients using a thiazide had a higher risk for magnesium alterations. In our cohort, loop diuretic use was both an independent predictor of hypo- and hypermagnesemia. While loop diuretics generally induce more renal magnesium excretion (leading to potential hypomagnesemia), volume contraction is a known factor simulating renal magnesium reabsorption. Hereby potentially explaining the dual relation between loop diuretics and magnesium levels.(16) Little is known about the effect of a different class of diuretics (mineralocorticoid receptor antagonists) on magnesium levels.(17) In that aspect our manuscript offers novel information as it indicates that eplerenone does not induce hypomagnesemia, as illustrated by the similar magnesium levels and proportion of hypo- and hypermagnesemia during follow-up. Indeed, both thiazides and mineralocorticoid receptor antagonists such as eplerenone exert their effects in the distal nephron. However, unlike thiazides, eplerenone is not associated with the development of serum magnesium alterations in our cohort. Next to

determining the effect of eplerenone on magnesium levels, we also determined the potential effect of magnesium levels on the treatment effect of eplerenone. As older studies have implicated hypomagnesemia in the development of cardiac arrhythmias, progression of heart failure and development of cardiovascular mortality, we determined if baseline magnesium alterations led to a diminution of the treatment effect of eplerenone.(4, 11, 12) We demonstrated that baseline hypomagnesemia or hypermagnesemia does not alter the treatment effect of eplerenone. Collectively, our data argues against a causal relation between serum magnesium levels and eplerenone in a bidirectional way.

Next to determine the role of eplerenone on magnesium levels or the impact of magnesium levels on the treatment effect of eplerenone, we also investigated the prognostic relevance of magnesium alterations in a large patient cohort with myocardial infarction complicated with heart failure or systolic dysfunction. In unadjusted analysis magnesium alterations were associated with an (borderline none-significant) increased risk for most clinical outcomes (except the composite of CV-mortality and myocardial infarction and sudden cardiac death). However, after covariate adjustment this relation was lost, indicating that mainly the clinical profile of the patients with hypo- and hypermagnesemia determine this association with clinical outcome. The large sample size of our cohort might explain why in our analysis covariate adjustment resulted in a loss of the association in comparison to older studies.(2, 3, 11, 12, 18, 19) This might also explain why in the ISIS-4 (Fourth International Study of Infarct Survival) and the MAGIC (Magnesium in Coronaries) trial, routine supplementation of magnesium in patients with an acute myocardial infarction did not improve clinical outcome, however a low baseline magnesium was not a pre-requisite in these trials.(10, 20) However, in clinical practice magnesium supplementation remains common given the beneficial safety profile of magnesium and the observation that some randomized controlled trials such as the LIMIT-2 trial (second Leicester Intravenous Magnesium Intervention Trial) did suggest clinical benefit. Our analysis further strengthens the finding of the ISIS-4 and MAGIC trial regarding the routine use of magnesium supplementation, as the finding of absence of an association between serum magnesemia and clinical outcome, forms little to no premise for improvement by trials testing routine magnesium supplementation.

Additionally, we analyzed whether serum magnesium modulates the harmful association of other electrolyte disturbances such as dyskalemia or dysnatremia. Perhaps in contrast to perceptions in clinical practice, we show that a low serum magnesium does not influence the harmful association of a low or high potassium. Yet, magnesium and potassium supplementation often occur simultaneously in clinical practice, mainly to prevent electrical abnormalities such Torsade de Pointes or allow for better potassium substitution when magnesium is also co-administered.(1, 4)

Finally, an important element to highlight is that most magnesium (next to being complexed in bone tissue) is actually intracellular and only a limited amount of magnesium resides in the extracellular compartment, being measured as serum magnesium (such as in this trial). Previous studies have shown a relative poor correlation between intracellular and extracellular magnesium levels.(21) Additionally, a different study showed that spironolactone actually decreased the efflux of intracellular magnesium to the extracellular compartment.(22) As such our data should be interpreted with care as we did not measure intracellular magnesium. The absence of a relation between low serum magnesium and poor outcome in patients being treated with eplerenone could also just reflect diminished intracellular magnesium efflux. This would result in a lower serum magnesium concentration but would sustain intracellular magnesium and offset the harmful effect traditionally seen with a lower serum magnesium level. Given the poor relation between serum magnesium, intracellular magnesium and magnesium supplementation, our data should not refrain physicians from supplementing magnesium in patients who manifest with potential signs of intracellular magnesium depletion such as frequent PVCs or ventricular arrhythmias.(22)

Limitations

Several limitations need to be mentioned, first we did not measure intracellular magnesium as outline above. Second, this is a post-hoc analysis of a large randomized controlled trial and results are therefore hypothesis generating. Third, although endpoints were adjudicated uniformly by and endpoint committee, some endpoints such as sudden cardiac death were relative uncommon. Fourth, we do not have arrhythmic data from event recorder such as loop recorders, holters or implantable cardiac devices. Finally, our patient's cohort was enrolled into this trial based on inclusion and

exclusion criteria making, this cohort a relative uniform patients population, and therefore our results might not apply to a broader patients cohort encountered in daily clinical practice.

Conclusion

In patients with myocardial infarction complicated by left ventricular systolic dysfunction or heart failure, serum magnesium alterations were not associated with clinical outcome after co-variate adjustment. Serum magnesium did not modulate the effect of potassium or sodium changes on clinical outcome or the treatment effect of eplerenone. Eplerenone does not induce serum magnesium alterations.

Disclosures & funding

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Data sharing policy

Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose

proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer

Table 1: baseline characteristics of patients with or without magnesium alterations

Parameters	Baseline hypomagnesemia (N=231)	Normal baseline magnesium (N=4869)	Baseline hypermagnesemia (N=271)	p-value
Demographics and comorbidities				
Age, years	62.3±11.4	63.6±11.5	64.2±11.3	0.1700
Male gender	140 (61%)	3481 (72%)	181 (67%)	0.0006
Diabetes	89 (38%)	1519 (30%)	73 (27%)	0.0666
Hypertension	141 (61%)	2964 (61%)	176 (65%)	0.4088
Atrial fibrillation	33 (14%)	627 (13%)	30 (11%)	0.8561
COPD	24 (14%)	453 (9%)	21 (8%)	0.7017
Previous MI	62 (27%)	1324 (27%)	56 (21%)	0.0617
PAD	29 (13%)	589 (12%)	25 (10%)	0.5970
Physical features				
SBP, mmHg	121±16	119±16	120±18	0.4977
DBP, mmHg	74±10	72±11	73±11	0.1825
Heart rate, bpm	76±12	74±12	74±11	0.0795
Killip class I-II	184 (81%)	3900 (81%)	213 (79%)	0.0817
Killip clas II-III	43 (19%)	936 (19%)	57 (21%)	
Laboratory features				
Hemoglobin, g/dl	13.3±1.9	13.3±1.7	13.3±1.8	0.8886
Sodium, mmol/L	139±5	140±4	140±5	0.6127
Potassium, mmol/L	4.3±0.5	4.3±0.4	4.3±0.5	0.5040
Magnesium, mmol/L	0.53±0.13	0.88±0.10	1.35±0.29	<0.0001
eGFR, ml/min/1,73m²	70±25	70±24	60±22	<0.0001
eGFR< 60 ml/min/1,73m²	88 (38%)	1964 (40%)	142 (52%)	0.0003
Heart failure features				
LVEF, %	33±6	33±6	34±5	0.1596
Previous HFH	16 (7%)	374 (8%)	20 (7%)	0.6127
ACEi/ARB	202 (88%)	4287 (88%)	226 (83%)	0.1037
Beta-blocker	170 (74%)	3703 (76%)	200 (74%)	0.8807
Loop diuretic	126 (55%)	2611 (54%)	149 (55%)	0.5411
Thiazide use	32 (14%)	396 (8%)	35 (13%)	0.0004

Abbreviations: ACEi= angiotensin converting enzyme inhibitors, ARB= angiotensin receptor blokkers, Bpm= beats per minute, COPD= chronic obstructive pulmonary disease, DBP= diastolic blood pressure, eGFR= estimated glomerular filtration rate, HFH= heart failure hospitalization, PAD= peripheral artery disease, MI= myocardial infarction, SBP= systolic blood pressure.

Table 2: Independent predictors of hypo- and hypermagnesemia at follow-up.

Parameter	Hypomagnesemia			Hypermagnesemia		
	Odds	95% CI	p-value	Odds	95% CI	p-value
PCI	0.52	0.40-0.66	<0.001	0.40	0.29-0.54	<0.001
Reperfusion therapy	0.62	0.51-0.74	<0.001	0.59	0.47-0.73	<0.001
Type 2 DM	1.53	1.26-1.85	<0.001	0.69	0.54-0.88	0.003
History of HTN	1.49	1.23-1.81	<0.001	1.39	1.11-1.72	0.003
Diastolic BP	1.02	1.00-1.02	<0.001	1.01	1.00-1.02	0.022
LVEF	1.01	0.99-1.03	0.079	1.04	1.01-1.05	0.001
Systolic BP	1.01	1.00-1.01	0.001	1.05	0.99-1.01	0.127
Baseline Mg	0.39	0.22-0.69	0.001	0.57	0.30-1.07	0.081
eGFR	1.01	1.00-1.00	0.010	0.99	0.98-1.00	0.031
Use of loop diuretics	0.81	0.67-0.96	0.019	0.77	0.62-0.94	0.013
Beta-blockers	0.75	0.61-0.91	0.004	1.15	0.89-1.48	0.261
Baseline sodium	1.01	0.98-1.02	0.504	1.03	1.01-1.05	0.001
ACEi use	0.71	0.56-0.89	0.003	0.84	0.63-1.11	0.225
Digoxin	1.03	0.80-1.33	0.796	0.62	0.43-0.87	0.006
Age	0.99	0.98-0.99	0.010	1.01	0.99-1.01	0.584
History of AF	0.65	0.37-1.13	0.126	1.23	0.75-1.99	0.405
Previous MI	1.19	0.97-1.44	0.094	1.22	0.97-1.53	0.084
Killip class II (vs I)	1.09	0.84-1.41	0.503	1.75	1.24-2.47	0.001
Killip class III (vs I)	0.99	0.71-1.37	0.960	1.53	1.01-2.31	0.044
BMI	1.01	0.99-1.03	0.314	0.98	0.99-1.00	0.063
Heart rate	1.00	0.99-1.00	0.967	0.99	0.98-0.99	0.030
ARB use	0.94	0.55-1.59	0.834	0.39	0.15-0.95	0.039
Baseline Hb	1.01	0.95-1.06	0.834	1.07	1.00-1.13	0.045
Male Gender	0.88	0.72-1.07	0.199	0.83	0.66-1.03	0.104
Baseline potassium	1.21	0.98-1.48	0.076	0.99	0.78-1.24	0.913
Previous HFH	1.04	0.74-1.45	0.799	0.78	0.51-1.20	0.265
History of COPD	0.99	0.63-1.56	0.974	0.93	0.54-1.58	0.775
Eplerenone assignment	1.10	0.92-1.32	0.283	1.01	0.82-1.24	0.895
CABG	1.09	0.46-2.56	0.847	0.73	0.22-2.34	0.595
PAD	1.09	0.72-1.64	0.683	0.91	0.55-1.55	0.725

Explanation: results of multivariable logistic model with categories hypomagnesemia and hypermagnesemia being compared to the normal magnesium range. This table represents the final multivariate model with all predictors in a univariate screen reaching P<0.100.

Abbreviations: ACEi= angiotensin converting enzyme inhibitor, AF= atrial fibrillation, ARB= angiotensin receptor blocker, BP= blood pressure, BMI= body mass index, CABG= coronary artery bypass grafting, COPD= chronic obstructive pulmonary disease, DM= diabetes mellitus, eGFR= estimated glomerular filtration rate, Hb= haemoglobin, HFH= heart failure hospitalization, LVEF= left

ventricular ejection fraction, MI= myocardial infarction, PCI= percutaneous coronary intervention, PAD= peripheral artery disease.

Table 3: Adjusted risk of different magnesium categories and clinical outcome endpoints and

Endpoint	Magnesium category	Events (N / patients per group)	Hazard ratio between baseline magnesium category and endpoint		Treatment effect of eplerenone according to baseline magnesium category	
			HR (95% CI)	p-value	HR (95% CI)	p-interaction

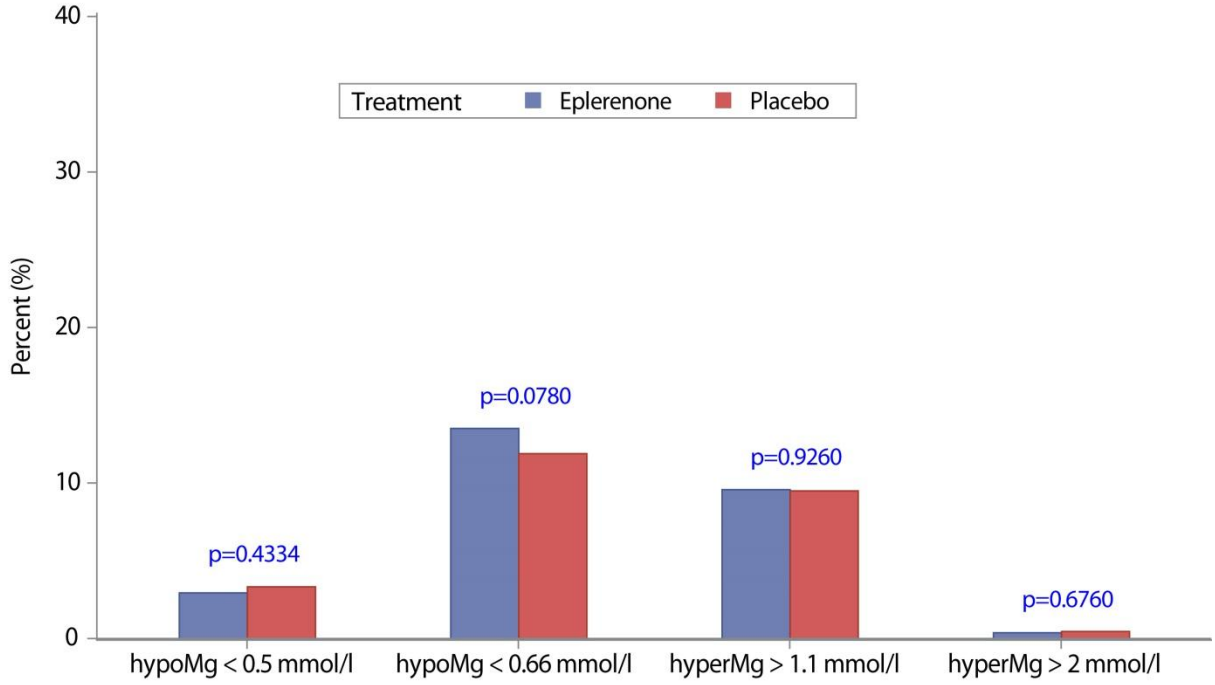
treatment effect of eplerenone according to baseline magnesium categories.

CV-mortality and CV-hospitalization	Low	63/231	1.15 (0.88 - 1.50)	0.3919	1.24 (0.71-2.08)	0.1154
	Normal	1228/4869	reference		0.87 (0.77-0.97)	
	High	60/271	0.89 (0.68 - 1.16)		0.90 (0.53-1.50)	
All-cause mortality	Low	39/231	1.41(1.00 – 1.99)	0.1376	1.24 (0.62-2.48)	0.1809
	Normal	555/4869	reference		0.83 (0.69-0.99)	
	High	32/271	0.97 (0.63 – 1.18)		1.25 (0.61-2.55)	
CV-mortality	Low	32/231	1.38 (0.68 – 1.40)	0.1968	1.41 (0.66-3.04)	0.4397
	Normal	468/4869	reference		0.80 (0.66-0.97)	
	High	25/271	0.89 (0.59 – 1.34)		1.50 (0.66-3.40)	
All-cause mortality and all cause hospitalization	Low	125/231	1.24 (1.03 – 1.50)	0.0435	0.83 (0.57-1.21)	0.6260
	Normal	2503/4869	reference		0.95 (0.88-1.03)	
	High	126/271	0.91 (0.76 – 1.09)		1.08 (0.75-1.54)	
CV-mortality or non-fatal AMI	Low	38/231	1.10 (0.78 – 1.55)	0.6266	2.00 (0.97-4.11)	0.4231
	Normal	762/4869	reference		0.86 (0.75-1.00)	
	High	36/271	0.87 (0.62 – 1.23)		0.82 (0.42-1.61)	
HFH and CV-mortality	Low	50/231	1.17 (0.87 – 1.59)	0.4651	1.02 (0.56-1.85)	0.1848
	Normal	898/4869	reference		0.82 (0.72-0.95)	
	High	45/271	0.91 (0.67 – 1.23)		1.15 (0.63-2.08)	
HFH	Low	34/231	1.24 (0.86 – 1.79)	0.5294	0.61 (0.29-1.27)	0.1288
	Normal	603/4869	reference		0.85 (0.71-1.00)	
	High	45/271	1.01 (0.70 – 1.45)		1.36 (0.67-2.76)	
Sudden Cardiac Death	Low	10/231	1.08 (0.63 – 1.85)	0.6992	1.65 (0.41-6.67)	0.2338
	Normal	222/4869	reference		0.72 (0.55-0.95)	
	High	11/271	0.80 (0.46 – 1.40)		2.51 (0.65-9.66)	

Eplanation: the hazard ratios are the result of a multivariable model with covariate adjustment as describe in the statistical section. **Abbreviations:** CV= cardiovascular, HFH= heart failure hospitalization, HR= hazard ratio, Na= sodium.

Figure 1: Magnesium levels at follow-up according to treatment assignment

PANEL A



PANEL B

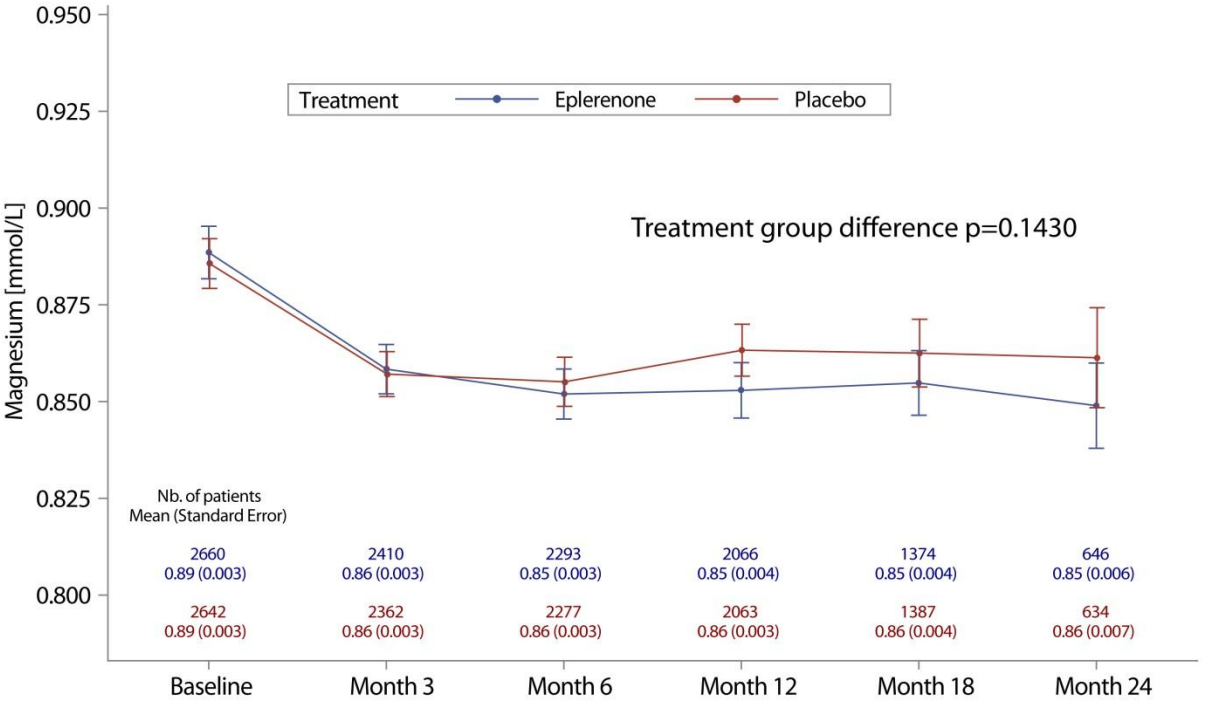
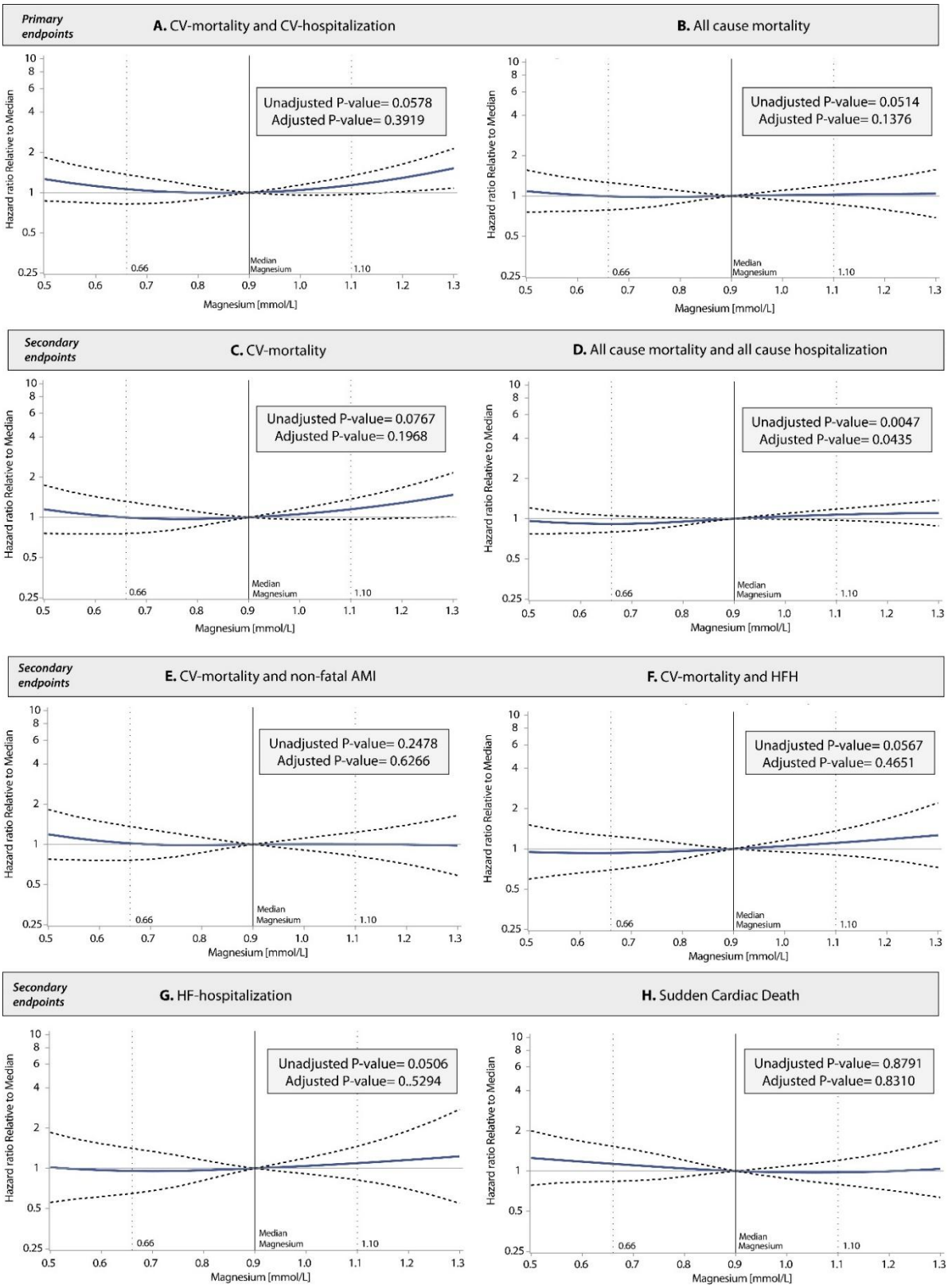
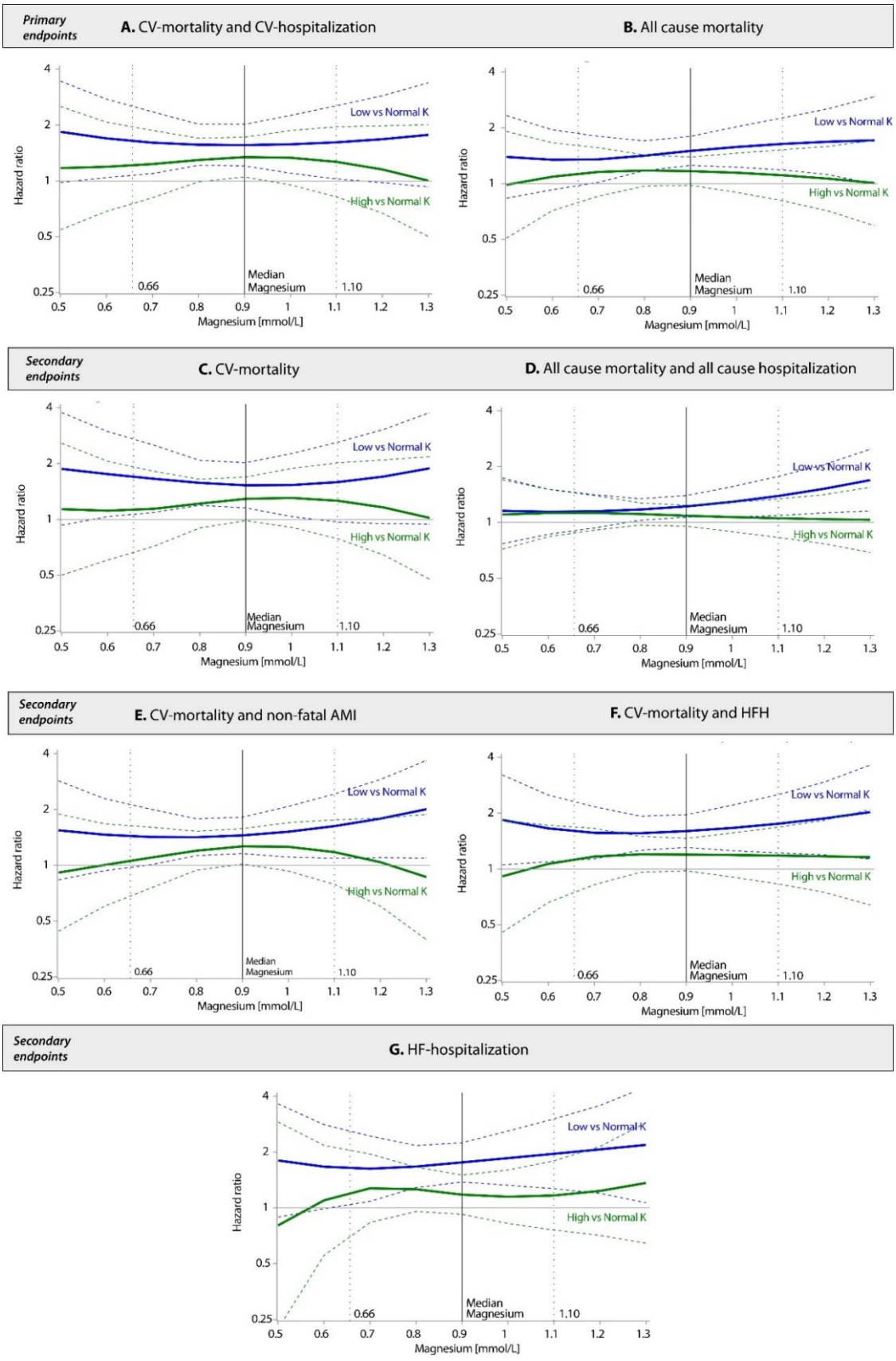


Figure 2: Splines of adjusted risk for different clinical endpoints according to baseline Mg levels



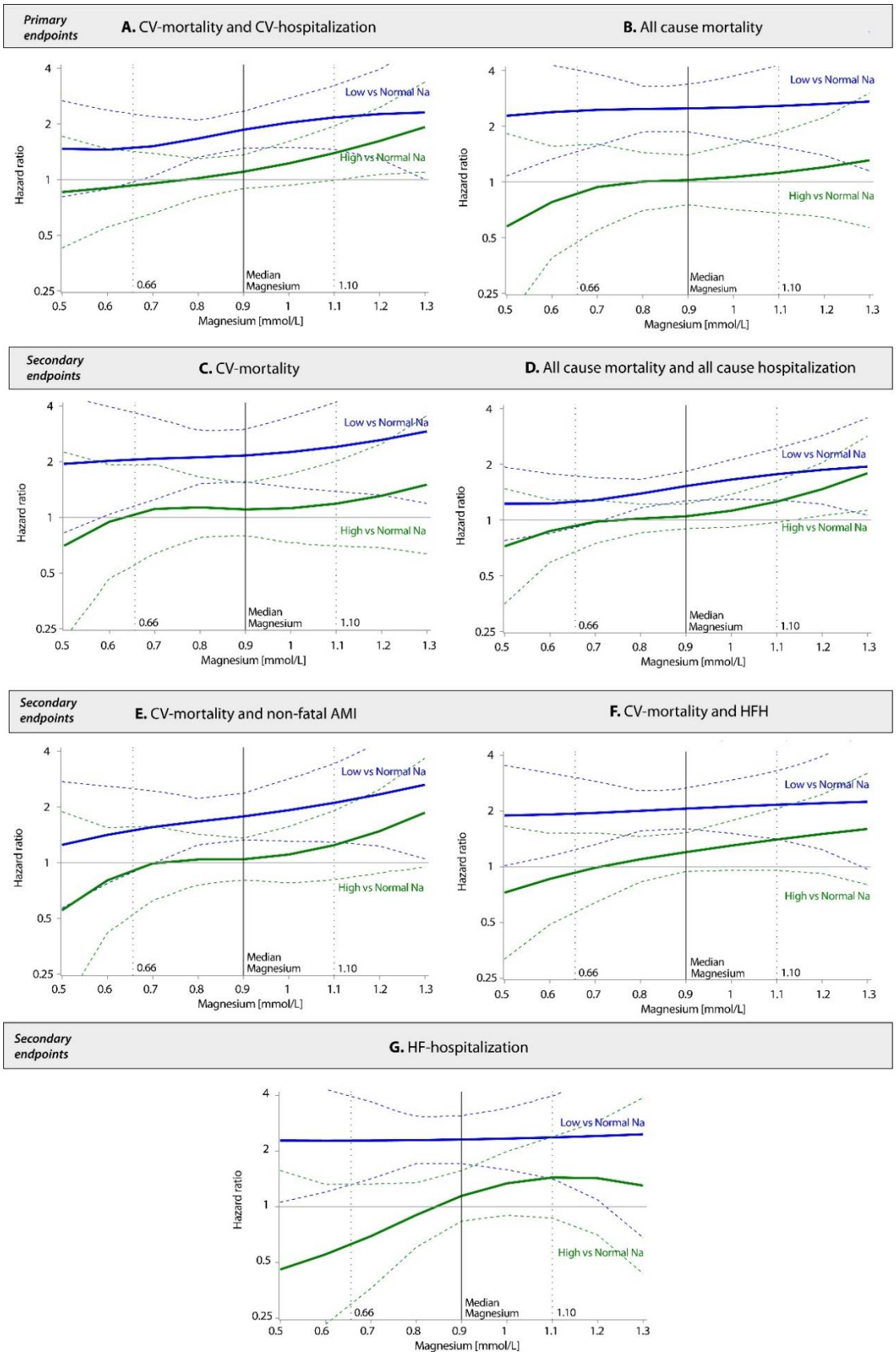
Explanation: Unadjusted P-value is model for baseline Mg-values + Mg supplementation and follow-up Mg spline. In the EPHESUS trial it was recorded at baseline which patients took Mg-supplements and we corrected for this intake to generate a fair model. Adjusted model is unadjusted model covariates corrected for covariates mentioned in statistical section. **Abbreviations:** CV = cardiovascular, HF= heart failure, HFH= HF hospitalization.

Figure 3: Interaction between time updated Mg and potassium levels on different clinical endpoints



Abbreviations: CV = cardiovascular, HF= heart failure, HFH= HF hospitalization. **Explanation**: hypokalemia was defined as serum potassium <4mmol/l and hyperkalemia as >5 mmol/l.

Figure 4: Interaction between time updated Mg and sodium levels on different clinical endpoints



Abbreviations: CV = cardiovascular, HF= heart failure, HFH= HF hospitalization. **Explanation**: hyponatremia was defined as serum sodium < 135mmol/l and hypernatremia as > 145 mmol/l.

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Supplemental table 1: Patients with or without magnesium analysis available

Baseline Characteristic	Subjects With		P-value
	Post Baseline Mg	No Post Baseline Mg	
Age (years)	63.6 ±11.5	65.4 ±11.7	<.0001
Gender Male	3802 (71%)	912 (72%)	0.2790
Gender Female	1569 (29%)	349 (28%)	0.2790
Killip class I-II	822 (15%)	190 (15%)	0.0826
Killip class III-IV	860 (16%)	235 (19%)	0.0826
Left ventricular ejection fraction	33.3 ±6.0	32.0 ±6.4	<.0001
Any reperfusion therapy Yes	2441 (45%)	565 (45%)	0.6802
Hemoglobin (g/dL)	13.3 ±1.7	13.3 ±1.8	0.9874
Potassium (mmol/L)	4.3 ±0.4	4.2 ±0.5	<.0001
Sodium (mmol/L)	139.7 ±4.4	138.5 ±4.0	<.0001
Magnesium (mmol/L)	0.89 ±0.2	0.88 ±0.2	0.6360
eGFR (mL/min/1.73m2)	66.9 ±23.7	66.3 ±24.4	0.3995
eGFR eGFR<=60	2194 (41%)	513 (42%)	0.4219
eGFR eGFR>60	3175 (59%)	705 (58%)	0.4219
Systolic blood pressure (mmHg)	119.3 ±16.4	118.1 ±16.9	0.0219
Diastolic blood pressure (mmHg)	72.3 ±10.6	71.4 ±11.1	0.0114
Heart rate (bpm)	74.3 ±11.6	76.4 ±12.3	<.0001
BMI (kg/m2)	27.4 ±4.5	27.3 ±4.4	0.5232
History of diabetes Type I	94 (2%)	49 (4%)	<.0001
History of diabetes type II	1586 (30%)	413 (33%)	<.0001
History of hypertension Yes	3281 (61%)	726 (58%)	0.0217
History of atrial fibrillation Yes, history	208 (4%)	70 (6%)	0.0275
History of atrial fibrillation Yes, currently has	482 (9%)	114 (9%)	0.0275
History of COPD Yes, history	223 (4%)	52 (4%)	0.4994
History of COPD Yes, currently has	275 (5%)	75 (6%)	0.4994
Previous myocardial infraction Yes	1442 (27%)	361 (29%)	0.2010

Baseline Characteristic	Subjects With		P-value
	Post Baseline Mg	No Post Baseline Mg	
Previous heart failure hospitalization Yes	410 (8%)	102 (8%)	0.5857
Peripheral arterial disease Yes, history	256 (5%)	64 (5%)	0.0627
Peripheral arterial disease Yes, currently has	388 (7%)	115 (9%)	0.0627
Use of diuretics Yes	3169 (59%)	815 (65%)	0.0002
Use of loop diuretics Yes	2886 (54%)	775 (62%)	<.0001
Use of other diuretics Yes	463 (9%)	77 (6%)	0.0033
Region Canada/USA	734 (14%)	124 (10%)	<.0001
Region Western Europe	1123 (21%)	606 (48%)	<.0001
Region Eastern Europe	2573 (48%)	344 (27%)	<.0001
Region Latin America	487 (9%)	84 (7%)	<.0001
Region Rest of World	454 (9%)	103 (8%)	<.0001
ACEi/ARB Yes	4655 (87%)	1096 (87%)	0.8168
ACE Inhibitors Yes	4550 (85%)	1066 (85%)	0.8744
Angiotensin II Inhibitors Yes	165 (3%)	51 (4%)	0.0800
Beta-blocker Yes	4073 (76%)	888 (70%)	<.0001
Digoxin Yes	781 (15%)	223 (18%)	0.0051
Percutaneous transluminal coronary revascularization Yes	1270 (24%)	310 (25%)	0.4816
Treatment group Placebo	2676 (50%)	637 (51%)	0.6581
Treatment group Eplerenone	2695 (50%)	624 (50%)	0.6581

Supplemental table 2: occurrence of hypo- or hypermagnesemia events according to treatment assignment and baseline magnesium status.

Hypomagnesemia

	Eplerenone	Placebo	Total
Number and Percent of Hypomagnemesia Episodes			
n	2695	2676	5371
0	2331 (86.5)	2358 (88.1)	4689 (87.3)
1	251 (9.3)	206 (7.7)	457 (8.5)
2	54 (2.0)	70 (2.6)	124 (2.3)
3	25 (0.9)	18 (0.7)	43 (0.8)
4	25 (0.9)	15 (0.6)	40 (0.7)
5	7 (0.3)	5 (0.2)	12 (0.2)
6	2 (0.1)	4 (0.1)	6 (0.1)
Number and Percent of Hypomagnemesia Episodes for Subjects With No Baseline Hypomagnemesia			
n	2578	2562	5140
0	2284 (88.6)	2295 (89.6)	4579 (89.1)
1	214 (8.3)	189 (7.4)	403 (7.8)
2	44 (1.7)	57 (2.2)	101 (2.0)
3	18 (0.7)	11 (0.4)	29 (0.6)
4	17 (0.7)	8 (0.3)	25 (0.5)
5	1 (0.0)	1 (0.0)	2 (0.0)
6	0 (0.0)	1 (0.0)	1 (0.0)

Hypermagnesemia

	Eplerenone	Placebo	Total
Number and Percent of Hypermagnemesia Episodes			
n	2695	2676	5371
0	2437 (90.4)	2422 (90.5)	4859 (90.5)
1	191 (7.1)	182 (6.8)	373 (6.9)
2	45 (1.7)	47 (1.8)	92 (1.7)
3	13 (0.5)	13 (0.5)	26 (0.5)
4	5 (0.2)	4 (0.1)	9 (0.2)
5	3 (0.1)	7 (0.3)	10 (0.2)
6	1 (0.0)	1 (0.0)	2 (0.0)
7	0 (0.0)	0 (0.0)	0 (0.0)
8	0 (0.0)	0 (0.0)	0 (0.0)
Number and Percent of Hypermagnemesia Episodes for Subjects With No Baseline Hypermagnemesia			
n	2557	2543	5100
0	2341 (91.6)	2334 (91.8)	4675 (91.7)
1	167 (6.5)	157 (6.2)	324 (6.4)
2	37 (1.4)	39 (1.5)	76 (1.5)
3	10 (0.4)	7 (0.3)	17 (0.3)
4	2 (0.1)	3 (0.1)	5 (0.1)
5	0 (0.0)	3 (0.1)	3 (0.1)
6	0 (0.0)	0 (0.0)	0 (0.0)
7	0 (0.0)	0 (0.0)	0 (0.0)
8	0 (0.0)	0 (0.0)	0 (0.0)

Supplemental table 3: Occurrence of hypo- and hypermagnesemia according to baseline status

	Post-Baseline Magnesium Levels (N=5371)		
Baseline Magnesium Levels	(a) Hypomagnesemia <0.66	(b) Hypermagnesemia >1.10	(c) Both <0.66 and >1.10
<0.66 mmol/L	121	38	20
0.66-1.10 mmol/L	529	387	62
>1.10 mmol/L	32	87	16
Total	682	512	98
Total for baseline >=0.66 mmol/L	561		
Total for baseline <=1.10 mmol/L		425	

N=5371, there are 5371 patients with post-baseline magnesium values.
(a) Patients that have at least 1 post-baseline magnesium value <0.66 mmol/L.
(b) Patients that have at least 1 post-baseline magnesium value >1.10 mmol/L.
(c) Patients that have at least 1 post-baseline magnesium value <0.66 and at least 1 post-baseline magnesium value >1.10 mmol/L.

Supplemental table 4: relation between magnesium categories according to potassium strata

		95% CI		
Magnesium Level	**Hazard Ratio**	**Lower Limit**	**Upper Limit**	**p-value (a)**
All Cause Mortality				
low vs normal magngr*at low potagr	1.259	0.628	2.523	0.516
high vs normal magngr*at low potagr	1.712	0.690	4.247	0.245
low vs normal magngr*at high potagr	1.900	0.913	3.956	0.086
high vs normal magngr*at high potagr	1.647	0.714	3.800	0.242
CV Mortality/CV Hospitalization				
low vs normal magngr*at low potagr	1.131	0.652	1.961	0.661
high vs normal magngr*at low potagr	1.403	0.686	2.866	0.353
low vs normal magngr*at high potagr	1.404	0.740	2.666	0.299
high vs normal magngr*at high potagr	1.568	0.825	2.979	0.169
CV Mortality				
low vs normal magngr*at low potagr	1.078	0.492	2.363	0.851
high vs normal magngr*at low potagr	2.144	0.859	5.349	0.102
low vs normal magngr*at high potagr	2.041	0.929	4.485	0.075
high vs normal magngr*at high potagr	1.772	0.709	4.430	0.220
All Cause Mortality/All Cause Hospitalization				
low vs normal magngr*at low potagr	1.144	0.746	1.754	0.538
high vs normal magngr*at low potagr	1.843	1.155	2.942	0.010 *

		95% CI		
Magnesium Level	**Hazard Ratio**	**Lower Limit**	**Upper Limit**	**p-value (a)**
low vs normal magngr*at high potagr	1.093	0.650	1.839	0.736
high vs normal magngr*at high potagr	1.353	0.817	2.243	0.240
CV Mortality or Non-fatal AMI				
low vs normal magngr*at low potagr	1.204	0.626	2.316	0.577
high vs normal magngr*at low potagr	1.750	0.808	3.790	0.155
low vs normal magngr*at high potagr	1.577	0.765	3.251	0.217
high vs normal magngr*at high potagr	1.756	0.813	3.796	0.151
CV Mortality or HF Hospitalization				
low vs normal magngr*at low potagr	1.082	0.582	2.014	0.803
high vs normal magngr*at low potagr	1.413	0.620	3.222	0.410
low vs normal magngr*at high potagr	1.583	0.802	3.128	0.185
high vs normal magngr*at high potagr	1.684	0.821	3.456	0.155
HF Hospitalization				
low vs normal magngr*at low potagr	1.444	0.721	2.892	0.300
high vs normal magngr*at low potagr	1.654	0.665	4.116	0.279
low vs normal magngr*at high potagr	1.474	0.596	3.649	0.401
high vs normal magngr*at high potagr	1.586	0.641	3.926	0.318

All adjusted models are stratified by region. Magngr= magnesium group potagr= potassium group
Models based on 3 levels of magnesium: hypomagnemesia (Mg<0.66), Normal (0.66<= Mg <=1.1) and hypermagnesemia (Mg>1.1).
(a) * means a significant difference.

Supplemental table 5: relation between magnesium categories according to sodium strata

		95% CI		
Magnesium Level	**Hazard Ratio**	**Lower Limit**	**Upper Limit**	**p-value (a)**
All Cause Mortality				
low vs normal magngr*at low sodmgr	1.913	0.865	4.231	0.109
high vs normal magngr*at low sodmgr	1.953	0.780	4.890	0.153
low vs normal magngr*at high sodmgr	0.865	0.312	2.400	0.781
high vs normal magngr*at high sodmgr	1.030	0.320	3.318	0.960
CV Mortality/CV Hospitalization				
low vs normal magngr*at low sodmgr	1.320	0.640	2.724	0.452
high vs normal magngr*at low sodmgr	1.520	0.663	3.481	0.322
low vs normal magngr*at high sodmgr	0.921	0.428	1.984	0.833
high vs normal magngr*at high sodmgr	2.055	1.039	4.063	0.038 *
CV Mortality				
low vs normal magngr*at low sodmgr	2.096	0.884	4.969	0.093
high vs normal magngr*at low sodmgr	2.731	1.077	6.927	0.034 *
low vs normal magngr*at high sodmgr	0.916	0.329	2.553	0.866
high vs normal magngr*at high sodmgr	1.182	0.366	3.823	0.779
All Cause Mortality/All Cause Hospitalization				
low vs normal magngr*at low sodmgr	0.988	0.535	1.826	0.970
high vs normal magngr*at low sodmgr	1.214	0.595	2.475	0.594
low vs normal magngr*at high sodmgr	0.601	0.296	1.219	0.158

		95% CI		
Magnesium Level	**Hazard Ratio**	**Lower Limit**	**Upper Limit**	**p-value (a)**
high vs normal magngr*at high sodmgr	1.806	1.085	3.008	0.023 *
CV Mortality or Non-fatal AMI				
low vs normal magngr*at low sodmgr	1.541	0.661	3.591	0.316
high vs normal magngr*at low sodmgr	2.038	0.814	5.101	0.128
low vs normal magngr*at high sodmgr	0.734	0.267	2.015	0.548
high vs normal magngr*at high sodmgr	1.438	0.578	3.577	0.434
CV Mortality or HF Hospitalization				
low vs normal magngr*at low sodmgr	1.601	0.771	3.324	0.207
high vs normal magngr*at low sodmgr	1.810	0.785	4.172	0.163
low vs normal magngr*at high sodmgr	0.876	0.381	2.013	0.755
high vs normal magngr*at high sodmgr	1.729	0.753	3.968	0.196
HF Hospitalization				
low vs normal magngr*at low sodmgr	2.129	0.968	4.686	0.060
high vs normal magngr*at low sodmgr	1.728	0.622	4.802	0.294
low vs normal magngr*at high sodmgr	0.576	0.139	2.385	0.446
high vs normal magngr*at high sodmgr	2.275	0.817	6.338	0.115

All adjusted models are stratified by region. Magngr= magnesium group sodmgr= sodium group
Models based on 3 levels of magnesium: hypomagnemesia (Mg<0.66), Normal (0.66<= Mg <=1.1) and hypermagnesemia (Mg>1.1).
(a) * means a significant difference.