TREATMENT

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Disclosure of Interests

None

When/who do we need to treat?

OBJECTIVES

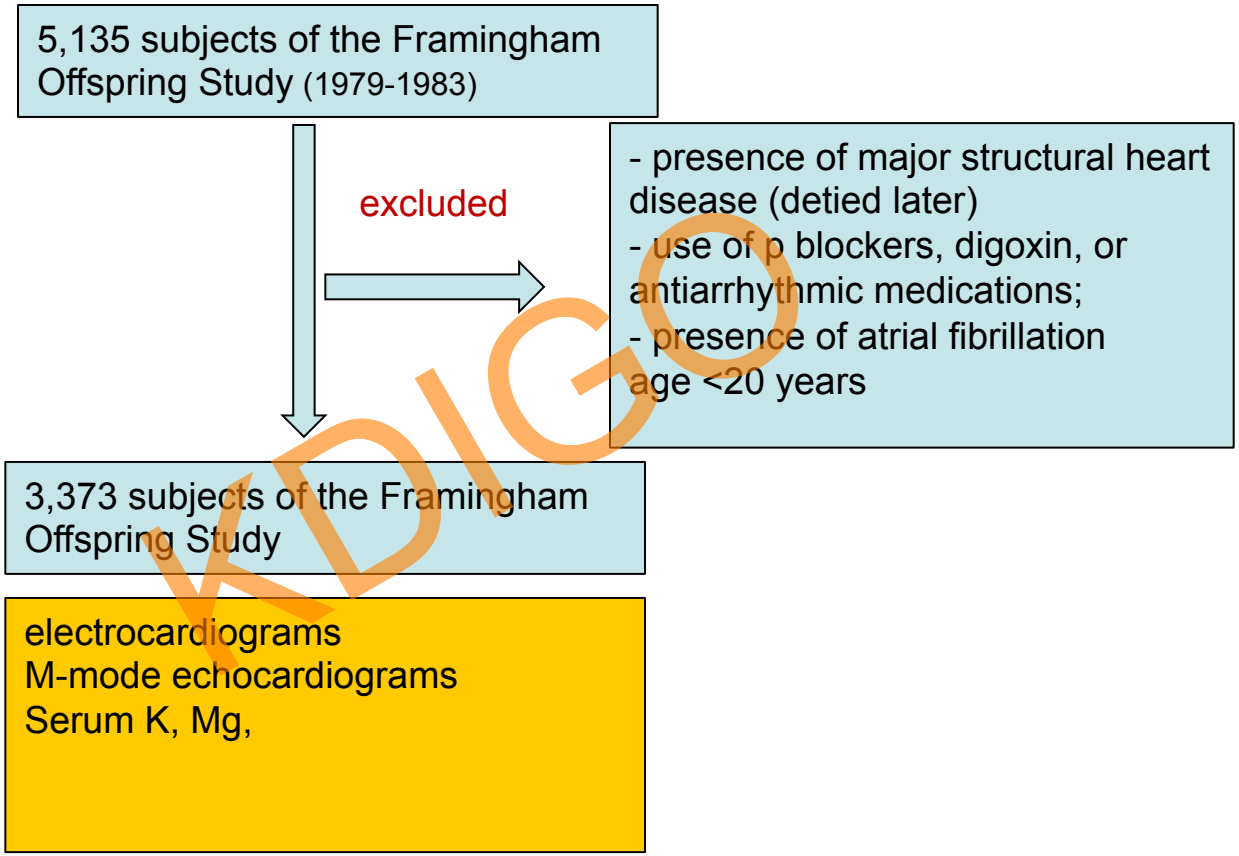
The major aim of treating potassium and/or magnesium depletion is to increase blood levels in order to avoid consequences related to potassium or magnesium depletion, including rhabdomyolysis or life-threatening ventricular ectopy and to prevent chondrocalcinosis (long-term).

- Children : catch up the growth
- Adults : improve quality of life

- Most often, no direct proof in GS : indirect evidence from patients taking TZD

When/who do we need to treat?

Link between K, Mg and cardiovascular risk in the general population :



Tsuji H et al. The associations of levels of serum potassium and magnesium with ventricular premature complexes (the Framingham Heart Study). The American journal of cardiology. 1994;74(3):232-5.

When/who do we need to treat?

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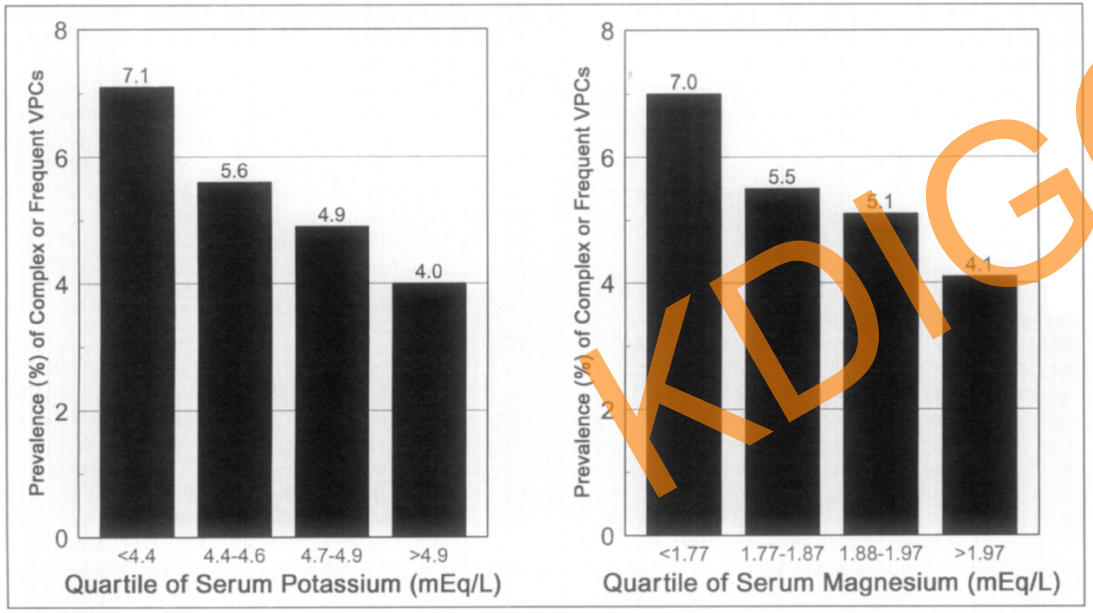

FIGURE 1. Age-adjusted prevalence (%) of ventricular arrhythmias in each quartile of serum potassium and magnesium. VPCs = ventricular premature complexes.

1 SD decrement in serum K (0.46 mEq/L) or in Mg (0.15 mEq/L) was associated with a

- **27% greater odds of ventricular premature complexes (VPC)**
- **And 20% greater frequency of VPC**

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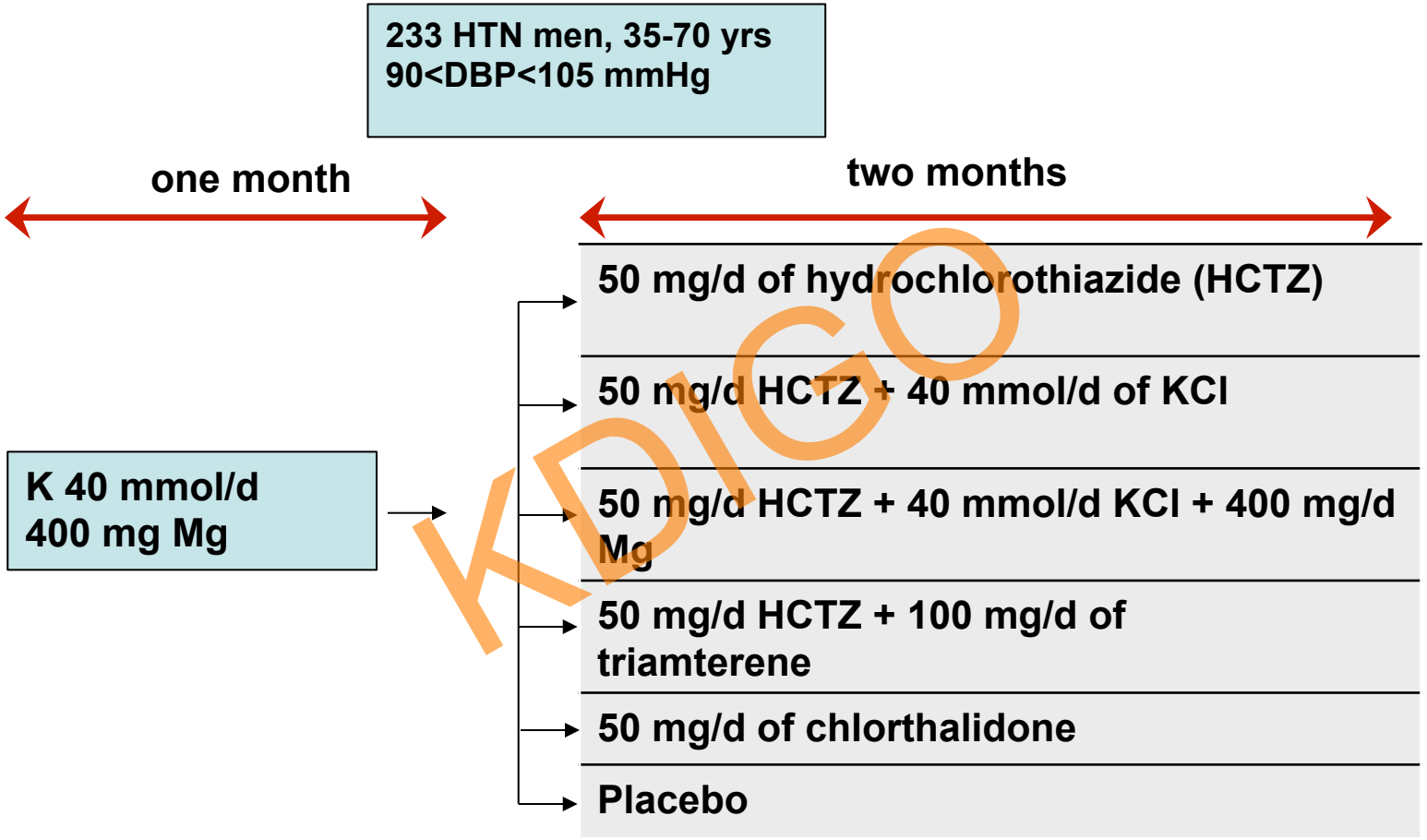
When/who do we need to treat?

Link between K, Mg and cardiovascular risk in hypertensives treated by TZD

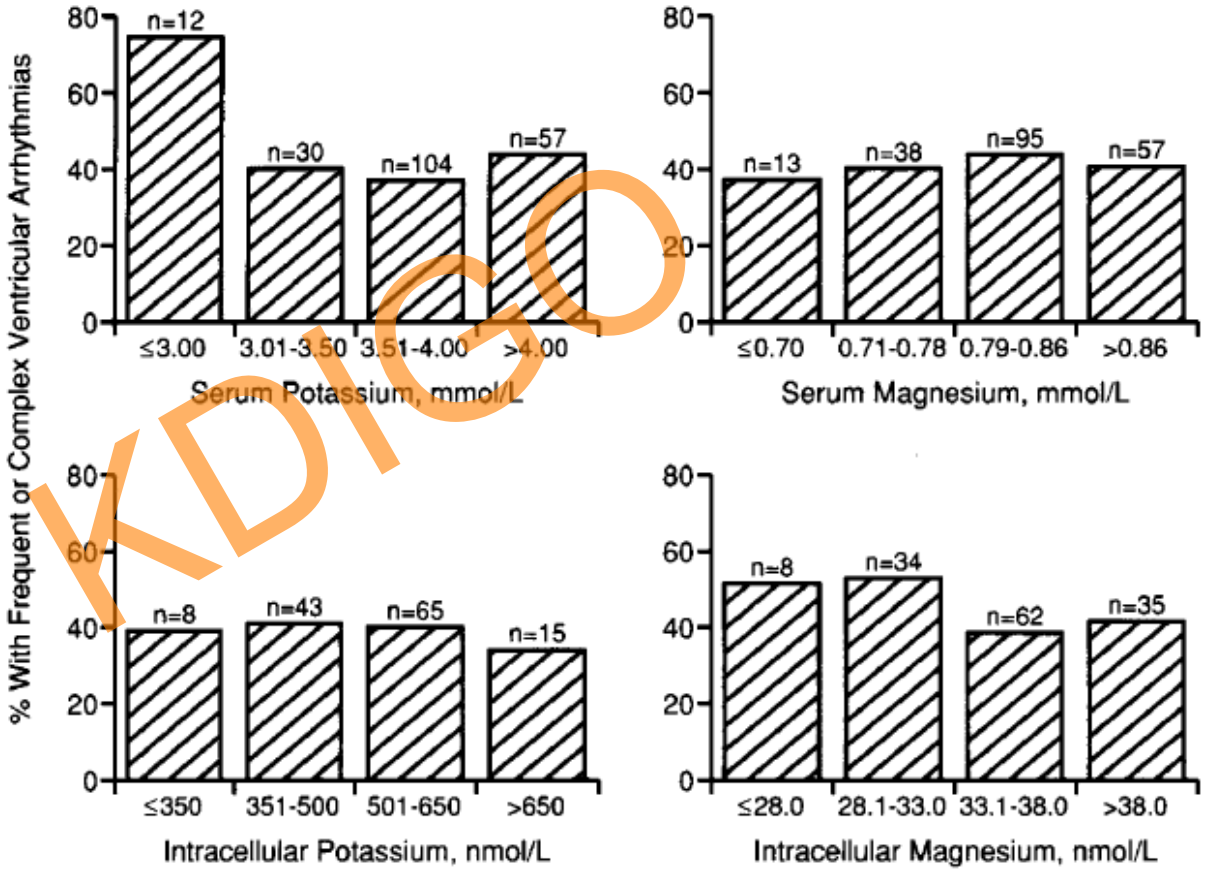


Siegel D et al. **Diuretics, serum and intracellular electrolyte levels, and ventricular arrhythmias in hypertensive men**. *Jama. 1992;267(8):1083-9*

When/who do we need to treat?

Link between K, Mg and cardiovascular risk in hypertensives treated by TZD

two-fold increase in ventricular arrhythmias (Holter monitoring) in patients in whom the serum potassium concentration fell 3.0 meq/L or bellow



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WHICH TARGET?

SEVERITY GRADE	DEFINITION	INTERVENTION
GRADE 1	Mild Transient or mild discomfort (< 48 hours)	no medical intervention/therapy required
GRADE 2	Moderate Mild to moderate limitation in activity	some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	Severe Marked limitation in activity,	some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4	Life-threatening Extreme limitation in activity,	significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

WHO Toxicity Grading Scale for Determining The Severity of Adverse Events

WHICH TARGET?

	Grade 1	Grade 2	Grade 3	Grade 4
Hypokalemia	3.0 - 3.4 mmol/L	2.5 - 2.9 mmol/L	2.0 - 2.4 mmol/L Or intensive replacement therapy or hospitalization required	< 2.0 mmol/L or abnormal potassium with paresis, ileus or life-threatening arrhythmia
Hypomagnesemia	0.60 - 0.70 mmol/L	0.45 – 0.55 mmol/L	0.30- 0.40 mmol/L	< 0.30 mmol/L or abnormal Mg with life threatening arrhythmia or tetany

Grade of hypokalemia and hypomagnesemia according to the WHO Toxicity Grading Scale for Determining The Severity of Adverse Events

OUR RECOMMENDATION (to discuss)

Any patients with moderate or severe hypokalemia and/or hypomagnesemia (grade 2 or higher)

or any patient with mild (grade 1) hypokalemia and/or hypomagnesemia AND related manifestations should be treated.

The hypokalemia should be confirmed by at least two analyses **(TO DISCUSS)**

Patients should be aware of the risk of aggravation of hypokalemia and hypomagnesemia in peculiar cases, including gastroenteritis, diarrhea and the use of certain medications such as corticosteroids, acetazolamide, or other drugs that may induce hypokalemia

Potassium supplements

Which one? Optimal dose? Precautions? Side-effects ?

Slow release potassium has been recommended in hypertensive patients at a dose ranging from 40 to 60 meq/day (3 to 5 g KCl/day) to reverse hypokalemia observed under therapy (> 2 months) with 100 mg hydrochlorothiazide : starting dose

Avoid diarrhea

In case of low dose/efficiency ratio, it is useful to monitor urinary potassium excretion to detect poor intestinal absorption due to intestinal potassium secretion and/or poor observance.

Patients likely to have delayed intestinal transit (e.g. the elderly, immobile, taking a low-volume diet or with hypokalemia induced intestinal paresia) should be given any necessary potassium supplementation in a well-diluted liquid form with or after food

Intraveinous Infusion

When? How?

When hypokalemia worsens and the patient can not take its tablets (gastroenteritis..)

when the potassium deficit is very severe and is acutely causing severe complications (grade 4) : cardiac arrhythmias, quadriplegia, respiratory failure, or rhabdomyolysis

Kim, G. H. and J. S. Han (2002). "Nephron 92 Suppl 1: 28-32.

Intraveinous Infusion

When? How?

KCl should be given in a non-dextrose-containing solution, usually in a concentration of 40 mmol/l.

No more than 50 mmol/l (4 g KCl/L) should be given through a peripheral vein at a maximum rate of 10 mmol/hour

Placing a sleeve for heating the forearm infused may limit the pain and rinse the vein at the end of infusion with isotonic saline could be helpful to prevent sclerosis of the vein used.

For central venous line the maximum concentration of 80 mmol/L and a maximum rate of 20 mmol / hour (depending hypokalemia, ECG monitoring). Beyond 10 mmol/hr, the patient should be in intensive care.

Magnesium supplements

Which one? Optimal dose? Precautions? Side-effects ?

Very important : to improve potassium repletion, to improve growth, to prevent chondrocalcinosis.

Poor bioavailability (50%) (magnesium lactate and magnesium aspartate better?). Could be impaired by Proton Pomp inhibitors

Recommended starting dose is 300 mg/day of magnesium element (5 mg/kg in children), as slow release tablets when possible. It should be then adapted accounting of intestinal tolerance, divided into two to four doses.

Utility of sequential ambulatory infusion?

Intraveinous Infusion of Mg

When? How?

In case of acute tetany, 20% $MgCl_2$ should be administered intravenously (0.1 mmol Mg/kg per dose) and can be repeated every 6 hours

Knoers, N. V. and E. N. Levtchenko (2008). "Gitelman syndrome." Orphanet J Rare Dis 3: 22.

When decrease?

In case of diarrhea induced by supplementation, it could be more efficient to decrease to dose to the maximal tolerated dose (TO DISCUSS)

DIET COUNSELLING

Salt intake

Table III. *Levels of serum sodium (mmol/l) and potassium (mmol/l), plasma renin concentration (ng/ml/h) and plasma aldosterone (ng/100 ml) before treatment, during sodium restriction and during hydrochlorothiazide with and without sodium restriction*

	Without HCT						During HCT (50 mg twice daily)							
	Sodium intake (mmol)						Sodium intake (mmol)							
	150–200[a]		50				50				150–200			
Case no.	Na	K	Na	K	PRC	PA	Na	K	PRC	PA	Na	K	PRC	PA
1	141	4.0	139	4.4	22.9	21.8	135	3.1	82.0	46.0	139	3.3	31.4	6.8
2	141	4.5	139	4.8	12.5	15.0	136	3.1	88.3	33.0	139	3.6	21.8	18.4
3	143	4.0	137	4.3	12.0	1.9	133	3.0	91.5	36.0	140	3.7	25.2	4.7
4	144	4.0	140	4.0	8.4	21.0	135	2.6	37.2	37.5	140	3.3	6.9	17.0
5	141	4.0	140	4.4	18.0	20.0	133	2.7	97.8	34.0	138	3.1	39.6	15.0
6	141	3.8	139	4.0	9.0	14.0	136	2.7	45.4	53.0	140	3.5	15.4	2.5
7[b]	139	4.0	140	4.1	10.4	8.2	135	3.1	29.9	11.6	140	3.5	—	—
8	140	3.8	139	3.8	9.0	11.6	140	2.5	43.4	11.5	140	2.8	15.0	4.5
9	140	3.9	140	3.9	7.5	6.7	137	2.9	55.8	20.0	141	3.0	32.4	8.0
Mean	141	4.0	139	4.2	12.4	14.0	136	2.9	67.7	33.9	140	3.3	23.5	9.6

van Brummelen P et al . Influence of sodium intake on hydrochlorothiazide-induced changes in blood pressure, serum electrolytes, renin and aldosterone in essential hypertension. *Acta medica Scandinavica. 1978;204(3):151-7.*

DIET COUNSELLING

HIGH K CONTENT FOOD

Nutriments	K content	Equivalent amount to provide 1 g potassium		
	mg/g	Weight (g)	glucose (g)	Kcal
KCl salt	47300	2	-	-
Dry abricot	1162	**86 (n=10)**	54	**207**
strawberry	153	654	50	216
banana	358	**279**	64	**249**
orange juce	184	**543**	65	**255**
lentils	369	271	54	314
roasted soya beans	1468	68	23	322
Green beans	370	270	65	349
fig confit	640	156	116	389
Apple juce	101	**990**	109	**455**
Chocolate Flan	184	543	125	772
hazel/nuts	755	132	24	856
coco nutz	356	281	42	994
Dark chocolate	342	**292**	175	**1 579**

***2,5**

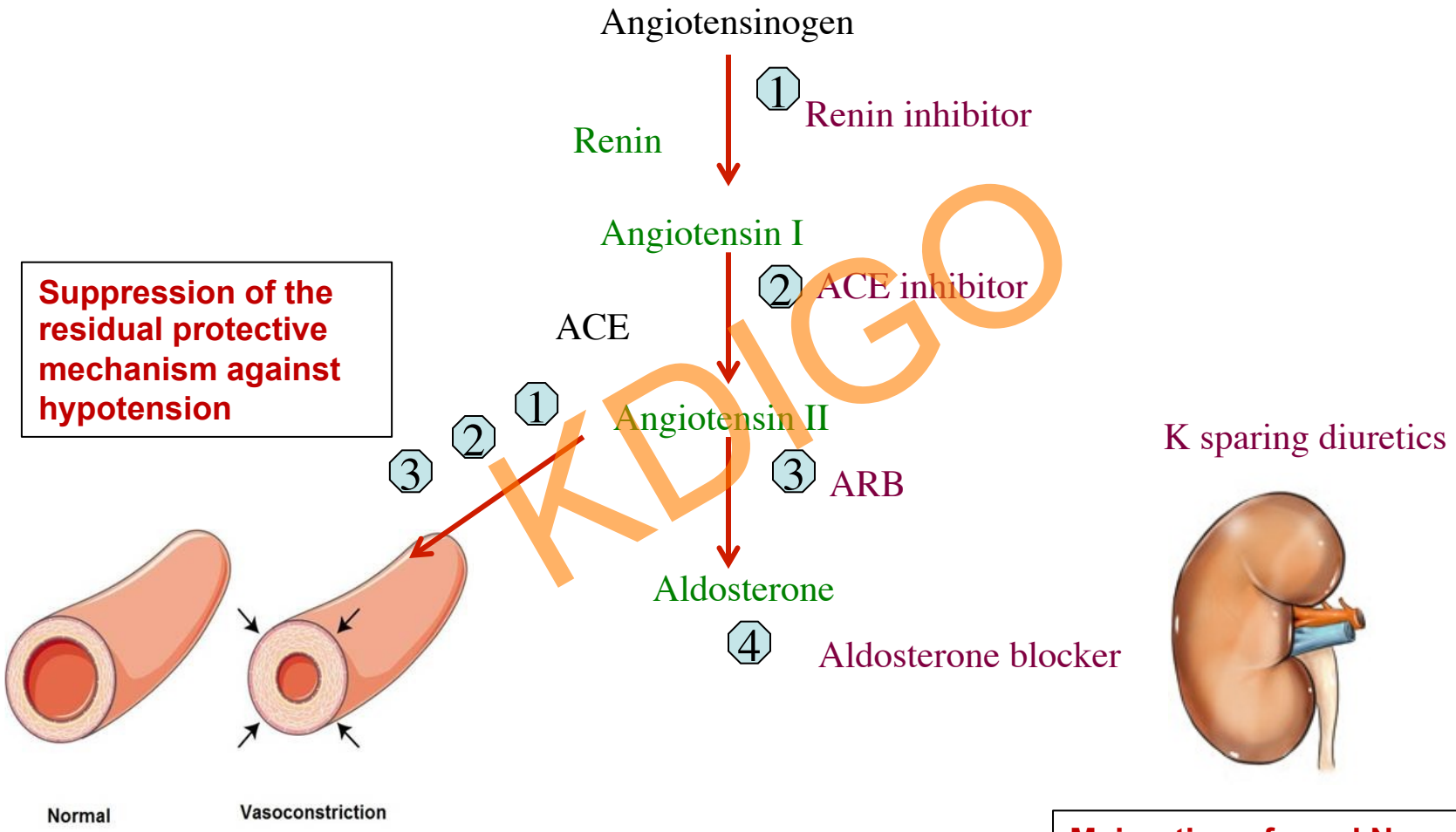
*Oral glucose test consists in acute absorption of 75 g glucose

OUR RECOMMENDATION (to discuss)

We recommend not to restrain salt intake but rather to encourage the patients to follow their appetite for salty food. In addition, any clinical extracellular dehydration should be treated.

For potassium rich food, we recommend to take into account not only the potassium content by nutriments but also the energy and glucose provided by and the amount required for a net intake of 1 g potassium.

RAAS INHIBITORS



How to scale up treatment

Role of amiloride, eplerenone, indomethacin

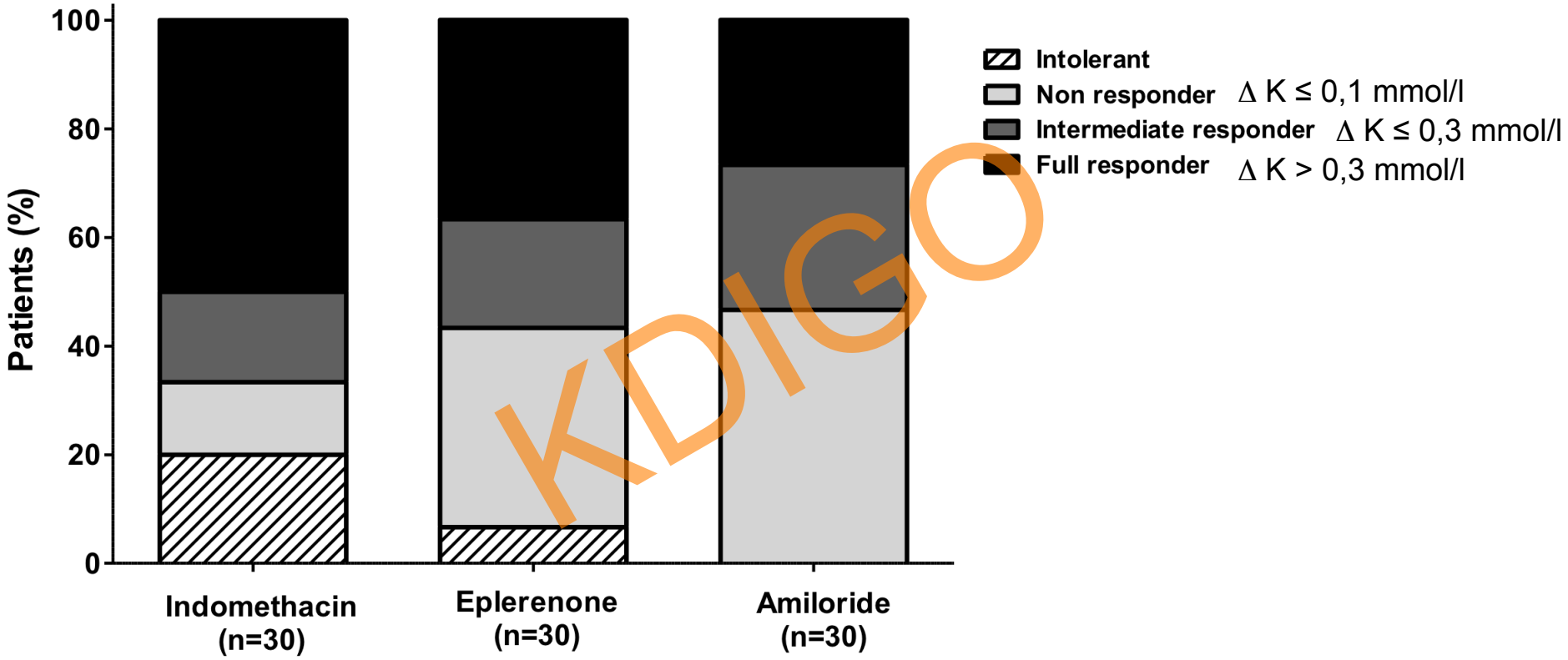
	Baseline	Chronoindocid	Eplerenone	Amiloride
Weight, kg	***69.2 ± 13.1***	**70.3 ±13.4[1]**	**66.9±12.9**	**67.1±13.0[2]**
SBP, mmHg	117±10	117±11	112±11[1]	112±10[1,2]
HR, bpm	72.5±9.6	72.9±7.5	75.8±8.0	75.0±9.2
Plasma K, mmol/L	**2.8±0.4**	**3.2±0.4**	**3.0±0.4**	**3.0±0.5**
Plasma Mg, mmol/L	0.55±0.07	0.56±0.07	0.56±0.12	0.58±0.08[1]
Plasma Na, mmol/L	139.0±1.5	139.3±1.5	138.5±1.8[1,2]	138.6±1.5[1,2]
eGFR (MDRD)	**124±30**	**115±26[1]**	**126±28[3]**	**121±31**
Plasma renin, mUI/L	**78**	**46 [1]**	**107 [1,2]**	**122 [1,2]**
Plasma aldo., pg/ml	**48**	**42**	**140 [1,2]**	**167 [1,2]**
UV Na, mmol/24h	195	187	186	201
UV K, mmol/24h	105	123	102 [	104

Data are mean ± SD or Geometric mean [IC95%]. Paired test between pre treatment (-) and post treatment (+) values : $p<0.05$ with corresponding control ([1]); or eplerenone or amiloride and indomethacin ([2]); or between eplerenone and modamide ([3])

Blanchard, A et al "Indomethacin, amiloride, or eplerenone for treating hypokalemia in Gitelman syndrome." J Am Soc Nephrol 26(2): 468-75.

How to scale up treatment

Role of amiloride, eplerenone, indomethacin?



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OUR RECOMMENDATION (to discuss)

We recommend to discuss potassium sparing inhibitors in case of symptomatic grade 2 or grade 3 to 5 hypokalemia refractory to supplementations. They should be started cautiously to avoid hypotension (amiloride 5 or 10 MG, spironolactone 25 MG or eplerenone 75 MG).

We do not recommend the use of indomethacin in first intention for the only indication of hypokalemia refractory to supplementations.

We do not recommend the use of renin inhibitors, ARB or ACE inhibitor at least until specific trial have been done in this indication.

We recommend to wean these drugs in pregnant women or preventively if pregnancy is expected

WHICH DRUGS TO EXCLUDE?

Furosemide, Drugs influencing cardiac conduction? Proton pump inhibitors?

Furosemide can worsen salt and potassium wasting but is rarely indicated in these patients

Prescription of acetazolamide for ophthalmic indication such as treatment of glaucoma or abruption of retina can be challenging. It generally dramatically worsens hypokalemia.

QT-prolonging medications should be used with caution

Dehydration in these patients can favor kidney toxicity of NSAID and of lithium salt

Proton pomp inhibitor can worsen hypomagnesemia by decreasing intestinal absorption of magnesium

PREGNANCY

During pregnancy, hypokalemia worsens and the use of renin-angiotensin II–aldosterone axis and prostaglandin synthetase inhibitors has been rarely reported

It is however not recommended because of the relatively high teratogenicity

The potassium-sparing diuretic amiloride has been proposed in case of severe hypokalemia despite supplementation, but increases the risk of oligohydramnios

Mascetti et al. Obstet Gynecol 117(2 Pt 2): 512-6.
Mathen, et al. 2013. BMJ Case Rep 2013.
Morton, et al. 2011. Nephrology (Carlton) 16(3): 349.

CHONDROCALCIOSIS

Both oral nonsteroidal anti-inflammatory drugs (NSAID) and low-dose oral colchicine are effective systemic treatment for acute CPP

Intra-articular corticosteroids may be considered in patients in whom other drugs may be contraindicated or not tolerated or few joints are involved

Basic treatment includes Mg administration combined with NSAID or colchicine that can result in an improvement or to a complete remission.

The methotrexate (MTX), which works not only as an immunosuppressant, but also as a potent anti-inflammatory agent, has been proposed as an alternative therapeutic option for patients with severe CPDD who fails to respond to standard therapy with nonsteroidal anti-inflammatory drugs and/or glucocorticoids

Zhang et al (2011). "EULAR recommendations for calcium pyrophosphate deposition. Part II: management." Ann Rheum Dis 70(4): 571-5.

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