Thank you for the invitation. I should congratulate all of you because you are here rather than being outside for the risky EDTA marathon under the sunshine. So, why is it time for action?
Well, because now we have enough evidence that a high salt intake is associated with target organ damage at the level of the kidney, heart, blood vessels. Some, maybe most of these effects, are actually mediated by the increased arterial pressure. So, I will focus on the association between salt and blood pressure.

Slide 3

General Hypertensive Population

in the general population and after I will talk then about non-dialysis CKD patients.

Slide 4
What do we know at this time? In the general population, rates of hypertension are continuously climbing. Now we have, at least in the United States, more than 65 million subjects with hypertension and unfortunately, most of them still have uncontrolled blood pressure.
This occurs despite improved pharmacological therapy. But what has not changed? Actually, the salt intake has not changed. If you look at this slide over the last 10 years in the US,
that recommended to lower salt below 6 g. They actually made more restrictive recommendations (less than 4 g) in specific populations such as the elderly, hypertensives, diabetics and of course, our patients... the CKD patients.
Excess dietary sodium and inadequate potassium intake in Italy: Results of the MINISAL study

Abstract: **Objective**: As excess sodium and inadequate potassium intake are causally related to hypertension and cardiovascular disease, the MINISAL-GIRCSI Program aimed to provide reliable estimates of dietary sodium and potassium intake in representative samples of the Italian population.

**Design and methods**: Random samples of adult population were collected from 12 Italian regions, including 1168 men and 1112 women aged 35–79 yrs. Electrolyte intake was estimated from 24 hour urine collections and creatinine was measured to estimate the accuracy of the collection. Anthropometric indices were measured with standardised procedures.

**Results**: The average sodium excretion was 189 mmol (or 10.9 g of salt/day) among men and 147 mmol (or 8.5 g) among women (range 27–472 and 36–471 mmol, respectively). Ninety-seven % of men and 87% of women had a consumption higher than the WHO recommended target of 5g/day.

The picture does not change in Europe. I'm Italian, so I'll show you the results from this recent... these are actually preliminary results of the MINISAL,

which is a survey in Italy that it is now complete.
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It's a representative sample of the Italian population, adult population

and you can see that the average of salt intake is very close to that in the United States: 11g in men and 8/9 g in women. This is very important for therapeutic implications
because now we have robust meta-analysis data that actually have been published really recently in BMJ, just a few months ago,

and this meta-analysis included more than 30 randomised controlled trials for over 3,000 subjects. Authors focused on the effects of moderate salt restriction.
What they found is that a reduction of salt intake by about 4 g/day allows a reduction in systolic blood pressure of about 5mmHg in hypertensive people.

Of course, as expected, the effect is smaller in normotensive people where BP reduction is around 2mmHg.
Also in the same issue of BMJ this different meta-analysis came out addressing the effect of salt on cardiovascular risk: the association between salt intake and cardiovascular risk.
They made a definitive point on this complicated and debated issue. Authors examined 14 cohort studies and, very important, they excluded acutely ill subjects.
increased salt intake is associated with a 60% increase in stroke risk and a 30% increase in the risk for acute MI and fatal MI.
So, let's move to non-dialysis CKD patients.

All of you are well aware how difficult it is to control blood pressure in our population. These are the data from NHANES, the last survey in more than 9,000 hypertensive subjects.
You can see that in CKD patients blood pressure levels are shifted towards the right, so are higher versus non CKD, as expected I'd say!

But what is important to point out is that achievement of target blood pressure, 130/80 mmHg, is not met in 70% of CKD population.
It's also important to underline that if you examine the setting of randomised trials, the picture does not change. In these main RCTs in CKD you need an average of 3 drugs per patient to control blood pressure. Why?
Well, we all know that in CKD there is a remarkable salt sensitivity of blood pressure and there are several studies showing that. I'll show you this study because it's historical and very important study

Slide 28

- 8 normal volunteers
- 10 CKD pts (CrCl 12±4 mL/min)
by Koomans, and Dorhout Mees who studied a small group of subjects: 8 normal volunteers and 10 patients with advanced CKD.

What they found is that when after equilibrium at 1g, 12g and 67g of salt you ended up with a very small, slight increase in blood pressure in non CKD.
Conversely, in CKD for a modest increase in salt intake from 1g to 7g, matched for the residual renal function of course, you end up with a remarkable increase in blood pressure.

Slide 31

Achievement of Target Blood Pressure Levels in Chronic Kidney Disease: A Salty Question?

Also, we must not forget that if you maintain your patients at a normal salt intake, you actually reduce the efficacy of anti-hypertensive agents. When we start treatment with vasodilating drugs, we obtain an increased proximal and distal sodium reabsorption that, of course, leads to volume expansion that mainly limits the efficacy of anti-hypertensive drugs.

Slide 32
What happens when we examine those patients that are under our care? Patients we regularly see in the daily practice in renal outpatient clinics?

This is the TABLE study, which is a study that has a main peculiarity, it is a survey in patients that have at least 1 year of follow-up in nephrology before start of data collection. Actually, these more than 1,000 patients in Italy followed by 25 renal clinics have on average 2.5 years of nephrology care before baseline. What we found is that despite prolonged nephrology care we have 80% of these patients with systolic blood pressure above 130mmHg and also 50-60% of patients, independently of age, that actually have blood pressure levels above the less restrictive target of 140mmHg.
Let's see therapy. Of course,

most of these patients are under pharmacological polytherapy
and also more than 30% of them actually got 3 drugs on average. What is impressive is that despite the poor achievement of blood pressure target and despite...
the nephrological care, only 2 patients out of 10 are complaint to the prescription of a low sodium diet. So we have on the one hand refractory hypertension, that is, hypertension which is difficult to control. On the other hand, at the same time we have polytherapy.

Slide 38

Resistant Hypertension

The combination of the two factors suggests a high prevalence of resistant hypertension in our population.

Slide 39

AHA Scientific Statement

Resistant Hypertension: Diagnosis, Evaluation, and Treatment
A Scientific Statement From the American Heart Association
Professional Education Committee of the Council for
High Blood Pressure Research

DEFINITION

- Failure to achieve goal blood pressure in patients who are on optimal doses of three or more antihypertensive agents from different classes, ideally one of which is a diuretic.
- Achievement of goal blood pressure in patients treated with at least four antihypertensive agents at optimal dose

Calhoun, Hypertension 2009
Let's take a step back. What is resistant hypertension? Resistant hypertension, now considered a priority area of research by the American Heart Association, is defined as the failure to achieve goal blood pressure despite optimal treatment with full doses of at least 3 anti-hypertensive drugs one of which must be a diuretic. This definition that also includes patients that achieve the target treated with at least four anti-hypertensive drugs.

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**Exclude "Pseudoresistance"**

- Poor compliance to therapy
- **WCH-RH (in CKD: Office BP >130/80 and 24h-ABP <125/75)**

Calhoun, Hypertension 2009

It is very important to exclude false resistant hypertension or pseudo-resistance, which is characterized, either by poor compliance to therapy or white coat hypertension, that is, high blood pressure in the office but normal out of the office during the 24 hours.
Why it is a priority of research? Because the prevalence, at least in the general hypertensive population, is around 10% and, more important, having resistant hypertension actually doubles the cardiovascular risk.

Slide 42

Resistant Hypertension (RH) in CKD-ND Patients under Nephrology Care

436 hypertensive patients (stage II-V), compliant to Tx, FU 57 months (IQR 36-68)

- Control: ABP <125/75 without RH
- Pseudo-RH: ABP <125/75 with RH
- Sustained Hypertension: ABP≥125/75 without RH
- True Resistance: ABP≥125/75 with RH
We recently looked at this problem in patients with non-dialysis CKD under nephrological care. We studied 400 hypertensive patients, stages 2-5. We excluded patients that were not compliant to therapy. Aim was to gain insights into the burden of resistant hypertension in CKD in terms of prevalence and prognosis. We followed them for 5 years, some of these patients have been followed for more than 9 years. We divided patients into 4 groups: controls, normal 24-hour ambulatory blood pressure without resistant hypertension, pseudo or false resistant hypertension, that is normal blood pressure during the 24 hours but with the clinical diagnosis of resistant hypertension. The last two groups are sustained hypertension, that is, high blood pressure during the 24 hours and no resistant hypertension, and, finally, true resistant patients that are those that have high blood pressure over 24 hours and resistant hypertension.

What are the numbers? most of our patients, 70%, had high blood pressure during the 24 hours but 1 out of 3 of them, and 23% of the whole cohort have resistant hypertension which is a percentage that is actually double what has been reported for the general hypertensive population.
If we go to examine the prognosis, we find that true resistant hypertension is an independent predictor of renal death but more important it is a predictor of poor cardiovascular outcome.

Now, coming back to the specific topic of this talk, what we found is that patients with resistant hypertension have higher salt intake as testified by higher sodium excretion over the 24 hours. Only a very small percentage (about 11%) of these patients were actually compliant to our prescription of dietary salt restriction.
When we looked at the multivariable logistic regression analysis, we found that the poor adherence to low salt diet is an independent correlate of true resistance. It actually doubles the probability of having resistant hypertension.

This is very important and we need intervention studies in CKD because there is already a randomised clinical trial in resistant hypertension (no CKD) showing that if you lower the intake of salt from normal to 3 g/day, you actually lower blood pressure by 20 mmHg and 10 mmHg for systolic and diastolic blood pressure, respectively.
So how can we conclude?

Slide 49

**...Take-home messages?**

In non-dialysis CKD
- BP control still far to be optimal
- High prevalence of resistant hypertension

We have to face the problem that we still have uncontrolled blood pressure in our renal clinics. We are really far from the optimal blood pressure control. We also know that there is a high prevalence of resistant hypertension.

Slide 50
This occurs despite the main advances in the pharmacological treatment of hypertension in the past 70 years.

but in the same time frame, from the 50s to 2010, the intake of salt has not changed. Unfortunately, it is still around 9g.
So it's important to reconsider Low sodium diet as the basic intervention in the hypertensive CKD patient. Thank you.

Questions

Chairman: Thank you Doctor De Nicola for a presentation, which gave novel data to an old dilemma, salt restriction: is it effective and is it considered and taken in by the patients? The group in Naples has a long tradition of salt work and this is certainly another addition to a number of very impressive communications. It is amazing that in a cuisine which is as good as the Italian one there is still such a salt problem but we can discuss this later in the evening. Are there comments or questions here?

Question: There are recent proposals to use more sodium bicarbonate to treat the acidosis of renal insufficiency. Do you have any comments on that?

Prof. De Nicola: Sodium bicarbonate, that's another talk, it's OK but we have some data now.
showing that sodium bicarbonate may slow CKD; however, we need more data on this issue. So I suggest to use bicarbonate at least in patients with acidosis where it may improve renal outcome. Anyway, consider that the amount of sodium contained in 1 g of bicarbonate is less than that contained in 1 g of salt.

Question: Diuretic use was very common in resistant hypertension. Diuretics make sodium excretion. So would you always prefer to give a diuretic to the normal ACE and beta-blockers or calcium...?

Prof. De Nicola: thank you for the question. It's very important to point out that if you use diuretic therapy but you don't have the patient limiting salt intake, you end up with either adverse effects of diuretics because you need very high doses of diuretics or, which is more common, patients does not respond to diuretic because of the breaking phenomenon: tubules adapt functionally and structurally to the diuretic action, so you end up in greater sodium reabsorption.

Chairman: The discussion is very interesting, for time reasons we have to proceed.