Dear colleagues before starting I would like to spend a few words on how I made my selection.

Slide 2
Updating means going back one year. I put in PubMed the date of May 2011 and said at present. As a search word I used CKD, cardiac not review, I’m not interested in review. These words are not mesh terms but are simply text words.

In other words, I’ve explored how it’s said in jargon the search. Then repeated the search by substituting to cardiac, left ventricular mass index, left ventricular hypertrophy, cardiovascular risk, atherosclerosis, endothelial and progression. That is I tried to make a wide range search. This search gave over 1000 papers. I screened these papers and excluded two major trials that is the SHARP and the PRIMO-paracalcitool trial because these trials have been heard in other sessions of this meeting.
I eventually made by selection. I used clinical relevance selection criteria. This is highly subjective it means that I hope that you may believe me and this is my selection. As for cardiovascular risk I focused on ambulatory blood pressure monitoring because this is an area where we have had substantial progress. Two studies one prognostic by Minutolo in Archives of Internal Medicine and the second by Hermida in JASN about therapy guided by ambulatory blood pressure monitoring. Another cardiovascular risk study, intervention study, the effects of allopurinol on LVM and endothelial function. Progression: two papers.

Slide 5

A paper neatly showing that in some patients with hypertensive nephropathy there may be an actual partial recovery of renal function and the second which illustrates the deleterious effect of salt on the response to angiotensin II blockade and/or ACE inhibition.

Slide 6
Let’s start with the first study, the study by Minutolo. This year has been a special year for clinical research in hypertension because for the first time the nice guideline made the recommendation that hypertension should be diagnosed on the basis of 24-hour ambulatory monitoring. This is a recommendation made by the British and as you know, the British are very conservative in making apparently costly recommendations.

Slide 7

The statement of this editorial in the BMJ is that as many as 25% of people with hypertension, high blood pressure readings subsequently have normal blood pressure on ambulatory blood pressure monitoring, white coat hypertension. They say that if you use ambulatory monitoring, we can make better diagnosis and be cost effective, I underline cost effective.

What about CKD? Is it true that in CKD? The question is not trivial because hypertension is exceedingly frequent in CKD and therefore, we can say we don’t need ambulatory monitoring because the diagnosis is obvious in most cases.

Slide 8
No doubt most of our patients are hypertensive but there are problems in CKD patients, problems related to the physiology of blood pressure control over time. We know that during the night there is a physiological dipping. In CKD this dipping is abolished in most patients and in some patients there may be actual nocturnal hypertension, a net rise in blood pressure during the night.

Slide 9

In fact, the diagnosis of hypertension in CKD patients is fairly complicated because Rajiv Agarwal clearly demonstrated in about 20% of CKD patients there may be white coat type hypertension, high clinic but normal 24 hour ambulatory blood pressure monitoring. Vice versa about 20% have masked hypertension that is normal clinic but high 24-hour ambulatory monitoring blood pressure.

Slide 10
Here we have the paper by Minutolo. In this study 43% were non dippers which confirms previous reports. 14% were patients with nocturnal hypertension.

Now the cohort, the cohort was a large cohort of patients: 453. This is one of the largest studies in CKD applying 24-hour ambulatory monitoring. Patients enrolled in this study were all hypertensive with blood pressure, ambulatory monitoring greater than 130 mmHg or anti-hypertensive treatment. Let’s go to the results. This is the hazard rate, the risk of a composite of death and incident cardiovascular event.

Let’s start with office blood pressure. As you can see, across quintiles of office blood pressure there was no risk excess. This confirms that in prognostic terms in CKD blood pressure in the clinic has no prediction power. This is not the first study showing this finding. Let’s go to daytime systolic blood pressure. Here in the last quintile, systolic greater than 146 mmHg, the composite end point tripled in the last quintile as compared to the reference quintile which was the third.

Night time systolic pressure risk was even greater. Those in the fifth quintile are the quadrupling of the cardiovascular events or death.

In this study we can calculate the risk excess associated with a blood pressure, systolic blood pressure difference of 10 mmHg which is 52%. If we lower systolic blood pressure by 10 mmHg, we can expect a 52% reduction in risk.

Keep in mind this figure because I will use this figure also for commenting the subsequent paper. The same associations but somewhat weaker were found with diastolic pressure. What are the implications of this study? It’s clear that ambulatory monitoring is superior as a diagnostic marker in patients with CKD, superior to office blood pressure. Given the fact that also in the general population ambulatory monitoring is now recommended, this study supplies further support to the application of this technique in future clinical trials.

We still need cost effective analysis for recommending 24-hour ambulatory monitoring in CKD. This study can be
done as I will show in the next paper with available data.

Slide 12

The second study.
The second study is a study about therapy. Hermida, a Spanish colleague, tested the effect of giving the drugs at bedtime instead of giving them in the morning.

Slide 13

This is the paper which appeared in JASN. It was prospective open blind endpoint trial, the P.R.O.B.E. design. 661 patients, even larger than the previous one, which were randomised to antihypertensive drugs given in the morning or given at bedtime at least one drug given at bedtime.

Which drug did they use? ACE inhibitors or angiotensin II blockers, either alone or combined with calcium antagonists.

Now in the active arm of the study at least one of these drugs was given at bedtime. Patients were followed up for 5 years and ambulatory blood pressure monitoring was done at least once a year. So it was a very intensive study. The endpoint was a composite of death and cardiovascular events like in the previous study, exactly like in the previous study. In the study we had 21 deaths and 119 cardiovascular events.
Let's see the effect of the drug on blood pressure. This is the baseline. In baseline conditions, there was absolutely no difference between bedtime dosing and morning dosing for office systolic pressure. The same was for daytime blood pressure and the same was for night time blood pressure. This is baseline, look at the effect of treatment.

Slide 15

Treatment reduced systolic blood pressure both when the drugs were given in the morning or given at bedtime.

Slide 16
The same was for daytime.

Slide 17

But look at night time. When dosing was done at bedtime, there was a greater fall in blood pressure and the difference was 7 mmHg. A very important difference.

Slide 18
But now let’s look at the outcomes. There was a spectacular difference between bedtime dosing and morning dosing. The number of events was far greater when drugs were given in the day and the risk reduction obtained with bedtime dosing was spectacular, as I said 66% risk reduction. This risk reduction is very similar, is of the same order of that estimated in the previous study by Minutolo, so it’s a credible estimate.

So now let’s comment this study. Does this paper demand a change in clinical practice? Now, scientifically speaking not yet because for changing drug administration schedules confirmation is needed in another perhaps larger multi-centre trial. You’ll say why do we need another trial if this trial I so convincing? Because this trial needs what is called external validation. Doing a trial in just one centre is not sufficient for making strong recommendations. But this study supports the value of ambulatory monitoring application in CKD patients because it helps the decision. We need a cost benefit analysis and cost benefit analyses can be done probably with available data. Given the fact that the change in time of the administration of drugs is certainly safe, as this study has shown, and does not impose extra costs a change in policy seems justified. I was involved with the new version of the kidney blood pressure guideline. I must say that when we formulated the recommendation this study had not been published. Probably we would have added the recommendation which is the last line of this slide.

Slide 19

Let’s now move to the third cardiovascular study. This is a study testing the effect of allopurinol on left ventricular mass. As you know, allopurinol inhibits xanthin oxidase that is a drug that has an anti-oxidant effect.

Slide 20
The study was again published in JASN. 90 patients, not such a large trial and 67 of these had left ventricular hypertrophy at echo and were enrolled for the trial. They were split into placebo and allopurinol. Allopurinol was up titrated to 300 mg/day. Patients were followed up for 9 months.

The main study endpoints were left ventricular mass index, but left ventricular mass index measured by nuclear cardiac resonance which is a very precise way of estimating LVM unbeatable, the variability is as low as 3% in some studies.

The other endpoints were flow-mediated vasodilatation and pulse wave velocity. These studies: flow-mediated vasodilatation and pulse wave velocity were repeated at 6 and 9 moths while left ventricular mass was measured just at baseline and at 9 months.
Let's see the results.

Left ventricular mass, as you can see left ventricular mass, was less in those treated with allopurinol than with placebo.

Slide 23

The difference approached was significant, not so highly significant but significant which is quite impressive given the low number of patients that were enrolled in this study.

Slide 24
The other two endpoints: flow-mediated vasodilatation again flow-mediated vasodilatation had a favourable increase, favourable change and increase in those treated with allopurinol and this was highly significant and exactly the same was the augmentation index. The augmentation index is a sort of flow-mediated vasodilatation and endothelial function and again these had a favourable response to allopurinol.

So let’s discuss this study. What are the implications? This study is specifically confirmed in chronic kidney disease patients. Observations made with the same drugs in other populations. But does this study demand a change in clinical practice in the way we treat our patients? By now no because LVM, flow-mediated vasodilatation and the augmentation index are surrogates, these are not clinical endpoints and we can change clinical practice only when we have studies based on clinical endpoints. So the study is the basis for doing a formal clinical trial based on clinical endpoints.

Slide 25

The last two studies deal with CDK progression. The first the identification of a group of patients who actually recover partially their renal function as the time passes by.

Slide 26
This is a study, an African-American study on kidney disease people. This is a methodological study but it is important to bring this study to the attention of all nephrologists interested in the problem. In clinical practice we measure estimated GFR by MDRD formula. We put the point of the eGFR over time and calculate the slope. But this slope, which is the rate of loss of renal function over time, hardly reflects the true renal function loss because as you can see, the variability of the data points where you point the calculation of the line is based is quite large.

Slide 27

So we can calculate a slope but there is much uncertainty about which is the true slope of the individual patient. Some patients have an upward slope. The usual comment to this trend is that in reality these patients do not improve. This upward trend is not bracket and bracket statistically different from the downward trend because the variability of the two lines largely overlaps. Now there is a technique, a statistical technique the Bayesian mixed effect models that allow us to identify the two slopes that go really up and separate this from those that go down. The investigators in this study applied exactly this technique to see whether there is a group of these patients where renal function actually improves. The identification of these patients is important because if we identify these patients, we can study the factors associated with improvement. So it is scientifically very important for future research.

Slide 28
These are the results. 3%, a small group of patients had an improvement in the estimated GFR. The difference in the slope was huge in these 3% of remaining patients. 1 ml improvement per year versus 2.5 ml decrease per year. This is eGFR, MDRD formula but the investigators had also very precise measurements of the GFR by the clearance of iothalamate and these analyses with the clearance of iothalamate perfectly confirmed that this subpopulation truly exists.

Slide 29

The investigators went on to trying to find the factors associated with improvement. The factors are factors that we know very well that is a decrease in proteinuria by 50% and younger age. If you are younger patients, hypertensive patients and those who have a decrease in proteinuria during treatment have a higher probability of recovering renal function.

Slide 30
Relevance: applying this refined statistical approach may allow in the future a better study of factors that may help the kidney recover in patients with hypertensive nephropathy.

Slide 31

The last study.

Slide 32
In proteinuric nephropathy the slope of the GFR points downwards and we know that angiotensin II antagonists reduce the rate of renal function loss by about 50%.

Slide 33

But the dream of nephrologists is having no loss of GFR over time and we are far away from this dream because in reality also in patients on angiotensin II antagonists renal function often goes bad over time.

Slide 34
One factor which has been long suspected as a limiting factor for renal protection is high salt intake. We know that salt intake is quite high in the patients that we see in our clinics. No what do we do in patients with high proteinuria? We apply ACE inhibitors, then we often consider as a subsequent stage adding angiotensin II blockers and pay very little attention to salt intake. Until now there has been no study comparing salt reduction versus dual blockade. Therefore, the issue is of paramount clinical importance.

Slide 35

The issue was dealt with in this study published in the British Medical Journal Electronically last July. It’s a Dutch study by Georgiana V’s group. This group of investigators enrolled 52 non-diabetic patients with proteinuria greater than 1g that were already on maximal ACE inhibition with lisinopril: 40 mg/day and with blood pressure not perfectly controlled they say greater than 150/75 mmHg.

Slide 36
The protocol they first studied those only lisinopril, maximal ACE inhibition, on a normal and low salt diet then lisinopril plus angiotensin II blockade again on a normal and low salt diet. So 4 diet periods, ACE inhibition, dual blockade, 4 periods and these periods were randomised.

Slide 37

Let’s see the effect of low salt. On low salt, the excretion of salt reduced by about 80mmol/day demonstrating compliance to the salt diet both in those on ACE inhibition and on dual blockade. Blood pressure: blood pressure went down both when lisinopril alone was given or lisinopril plus angiotensin II blockade. But as you can see, there was no great difference in systolic blood pressure at normal or high salt intake as far as blood pressure was concerned. The additional decrease in systolic pressure achieved thanks to dual blockade was 3 mmHg. While the decrease in blood pressure achieved because of low salt was 10 mmHg. So, this is once again a confirmation that low salt is a powerful antihypertensive intervention.

Slide 38
Proteinuria.

As you can see, with low salt intake there was halving, literally halving of proteinuria both in those treated with lisinopril and in those treated with dual blockade.
As you can see, the effect of dual blockade, as compared to ACE inhibition alone, on proteinuria was statistically significant but clinically modest.

Slide 41

Look at the effect of low salt both in those on ACE inhibition alone and in those on dual blockade. Dramatic, halving of proteinuria.

Slide 42
So this study is a good lesson for clinical practice because low salt in proteinuric nephropathies resistant to full scale ACE inhibition reduces proteinuria far more effectively than dual angiotensin II blockade. The implication is that salt intake is often high in CKD patients and therefore we should make major efforts at curbing salt intake in these patients rather than rush in to dual blockade. Thank you for your attention.