POST TRANSPLANTATION CARDIOVASCULAR DISEASE

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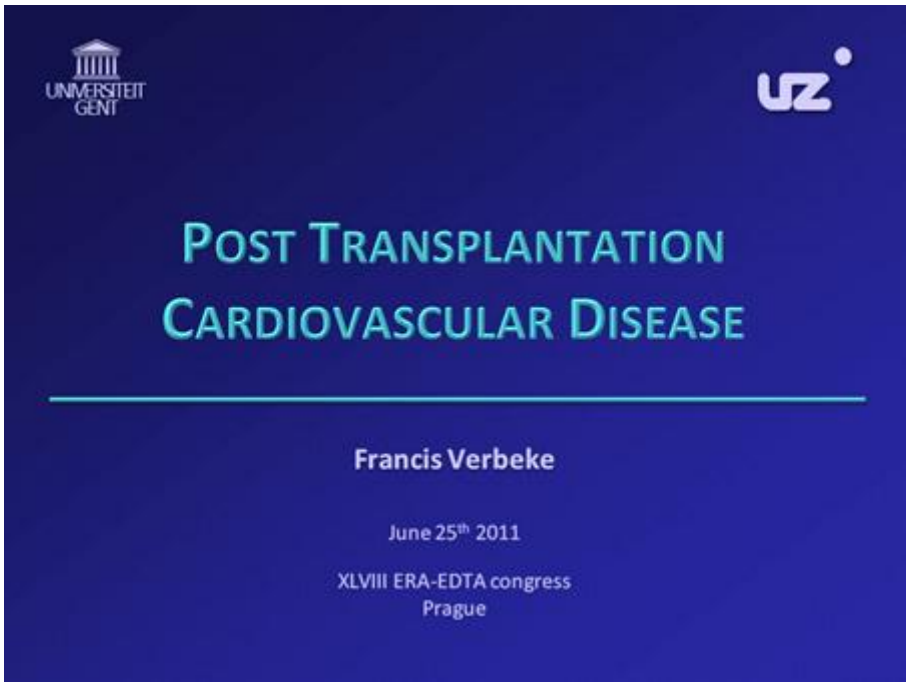
Slide 1



I'd like to thank the organisers for inviting me to talk about post-transplantation cardiovascular disease which is quite a broad topic and so in my presentation I will mainly focus on cardiovascular risk and risk estimation.

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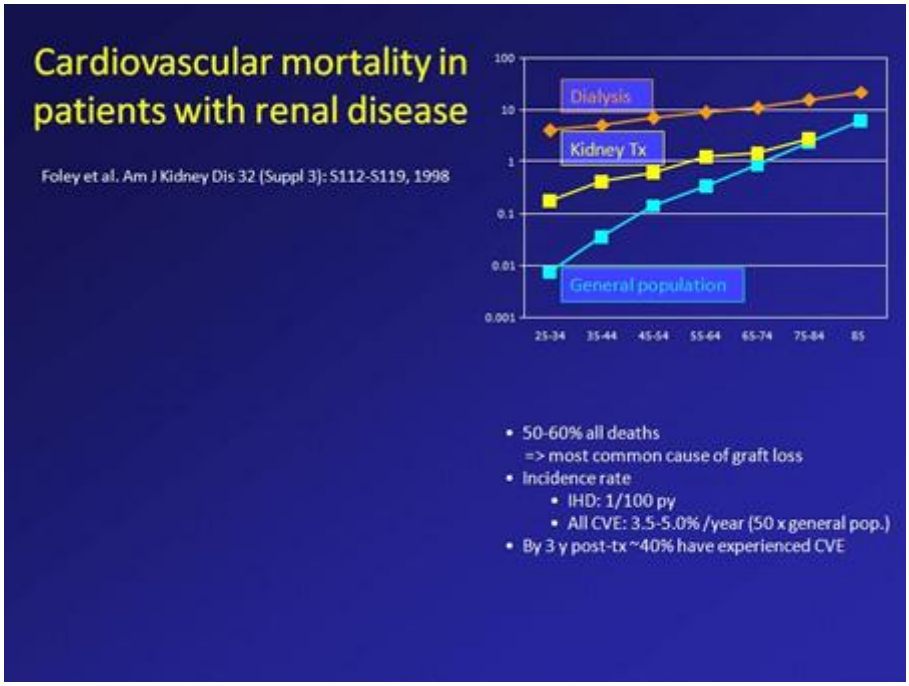

As an introduction I'll show you this very well-known graph illustrating the massively increased risk of cardiovascular disease mostly in dialysis patients but also in kidney transplants and here are a few epidemiologic data.
For instance, by 3 year post-transplant about 40% of these patients will have experienced cardiovascular events. For all events the risk is still in transplants better than in dialysis especially in the JAMA group but still about 50 times the general population.

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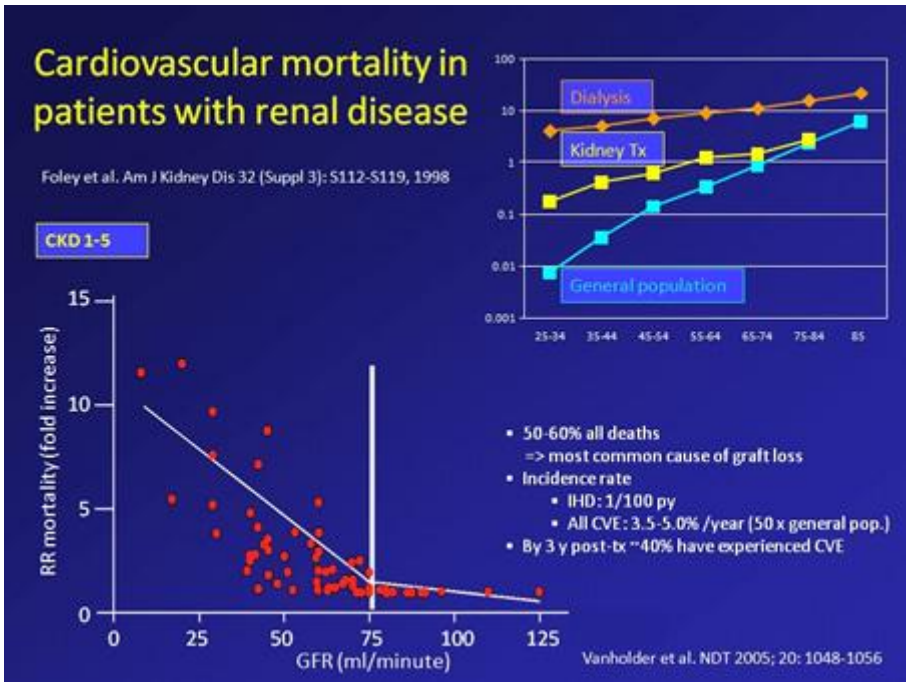

This increased cardiovascular risk is also already present in earlier stages long before renal replacement therapies such as CKD.

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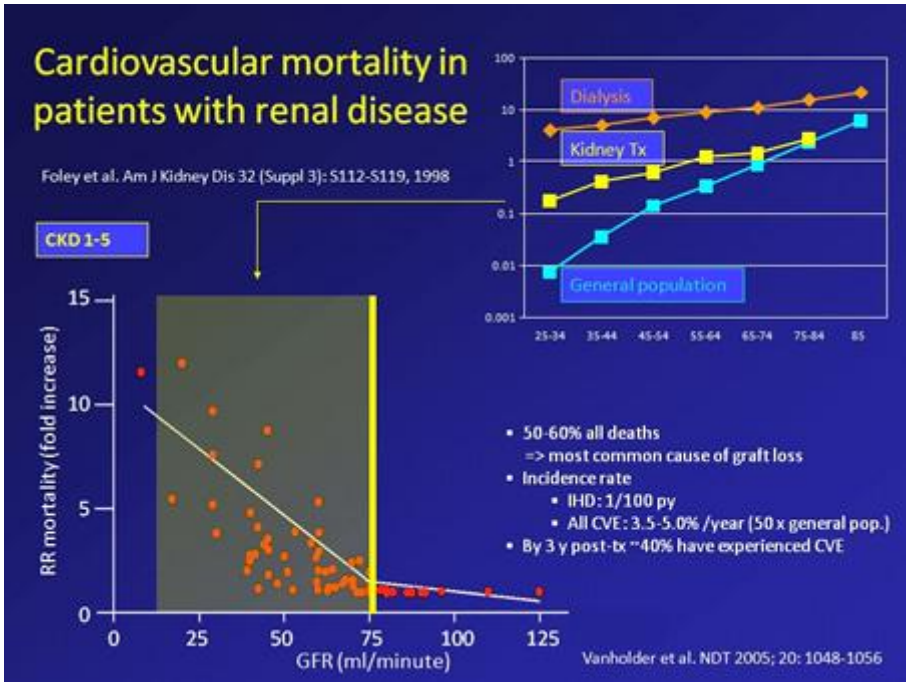

What we must realize is of course, that virtually all kidney transplant patients fall in this category of CKD patients.

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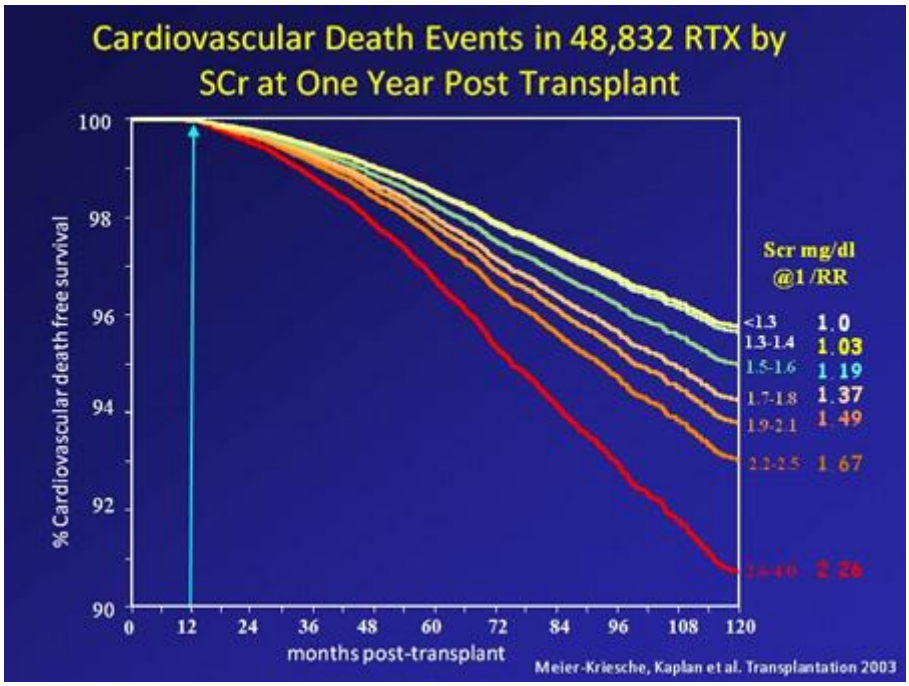

It has been shown in non-transplant CKD that the risk increases with worsening of kidney function and this actually was also shown nicely by Doctor Meier Kriesche a long time ago that serum creatinine at one year post transplant is one of the most important risk factors for survival.

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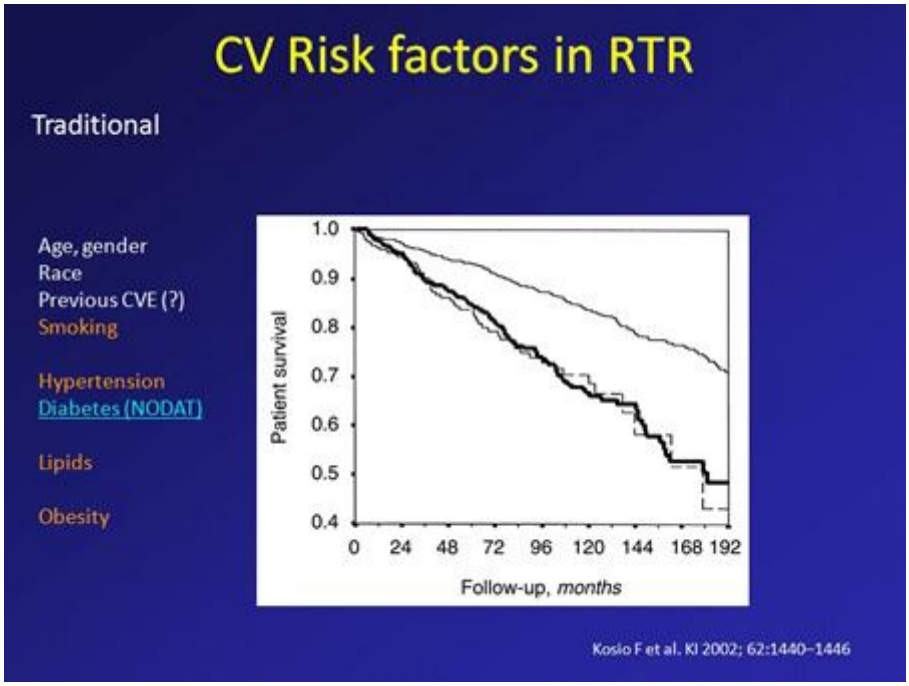

This increased risk maybe explained by several reasons and for sure there's a clear clustering of traditional risk factors like age, gender, previous cardiovascular disease, some things that are not modifiable also smoking and hypertension and here a little illustration for diabetes because I think this is a very important illustration that both pre- as well as post-transplant diabetes really have a very pronounced negative impact on the overall survival of these patients.

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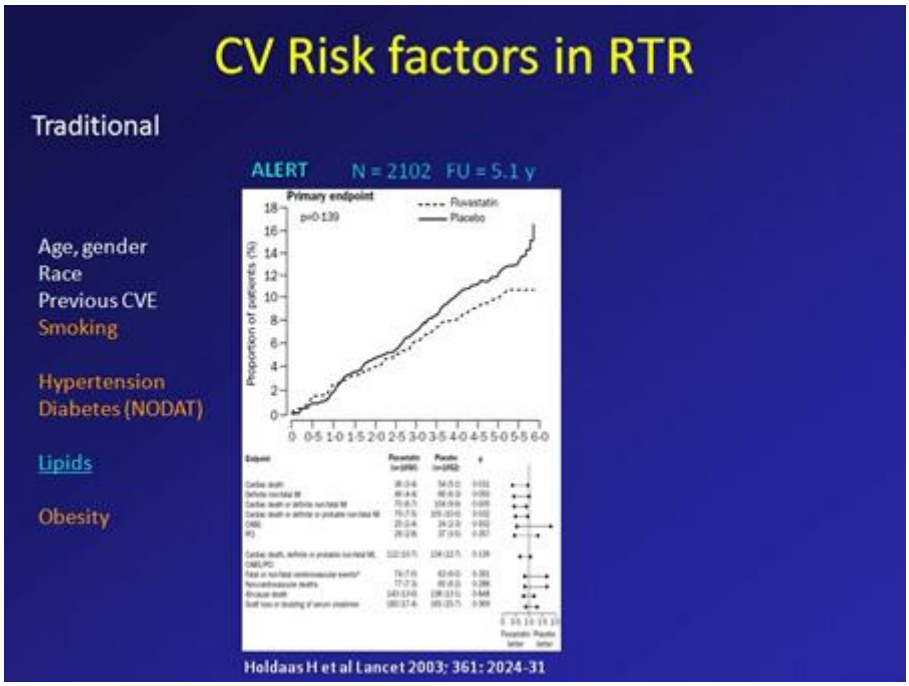

Now what about lipids? Should we treat all transplants with statins? This is one of the few large randomised trials in renal transplants where more than 2000 patients were randomised to placebo or fluvastatin and after a follow-up of 5 years the primary composite endpoint was not significant.

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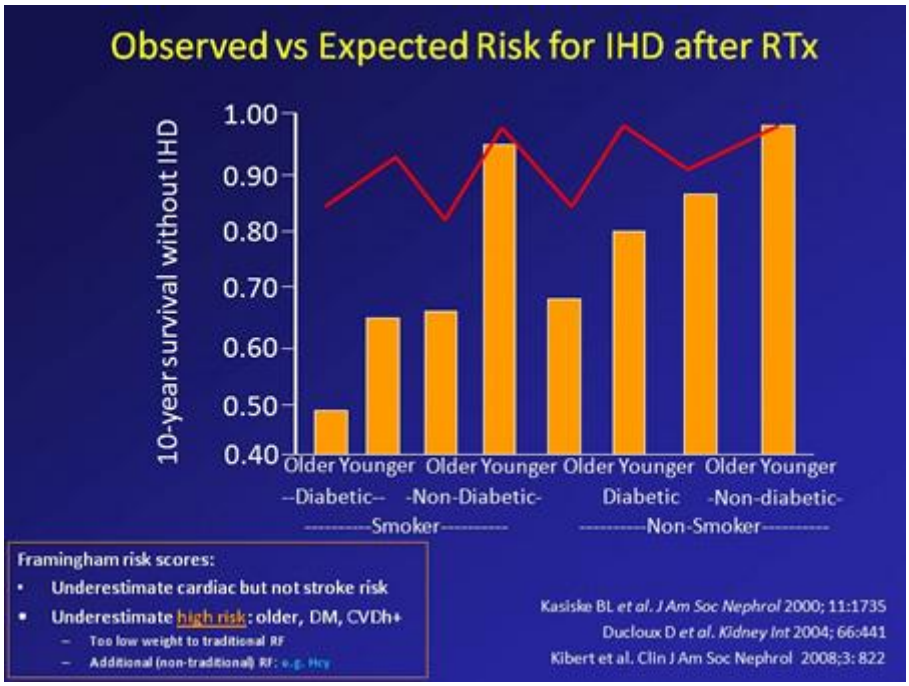

This study has been interpreted in several ways. There have been extension studies and there may be several reasons to why it didn't reach statistical significance but one of the reasons I think is that traditional risk factors as for instance, incorporated and risk scores such as the Framingham score overall underestimate cardiac risk. So they are not very accurate in predicting cardiovascular risk. This had been shown by Doctor Kasiske already in 2000 and was confirmed later on and also recently in a paper in CJASN in 2008 where it was shown in addition that the cardiac risk was underestimated but not the stroke risk so we also have to consider the type of cardiovascular event.

What is important in this slide is that the observed risk in red here is mainly underestimated in high risk patients, so older diabetics, smokers. So this is a little disappointing you could say because we have to treat these patients anyway intensively.

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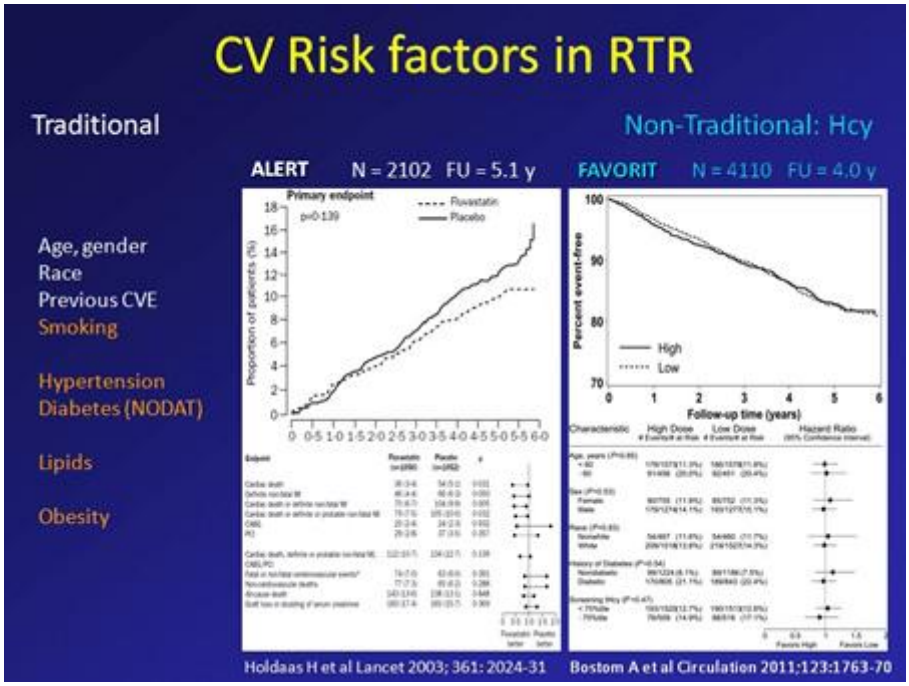

So either there is too low weight in the coefficients in the score to traditional risk factors or an alternative explanation could be that there are non-traditional risk factors present such as homocysteine that can be treated as well. Homocysteine has been demonstrated in several renal populations as a very strong and independent risk factor for outcome and therefore a second large randomised trial has then targeted this non-traditional risk factor. Again, a large number of patients and after a follow up of 4 years of intensive lowering of homocysteine with folic acid high dose, vitamin D high dose versus low dose vitamin there was no difference in survival, a study very recently published.

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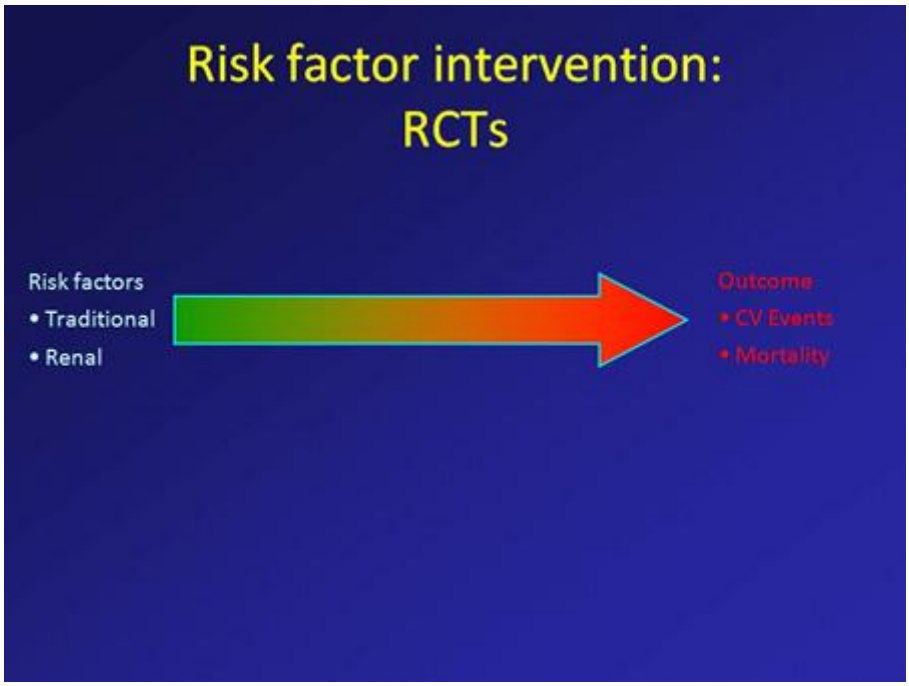

So clearly the traditional approach of randomised controlled trials in renal populations and particularly in transplants does not seem to work

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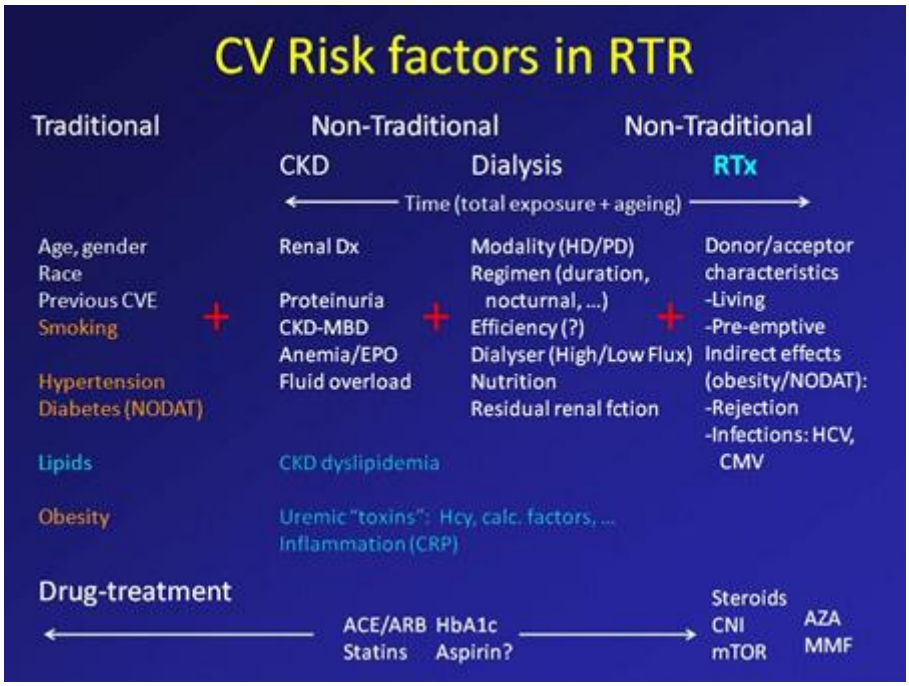

and I think this has a lot to do with the fact that renal transplants are some of the most complex and diverse populations we have to deal with when it comes to managing cardiovascular risk. They have accumulated traditional risk factors but in addition also CKD risk factors, risk factors relating to dialysis

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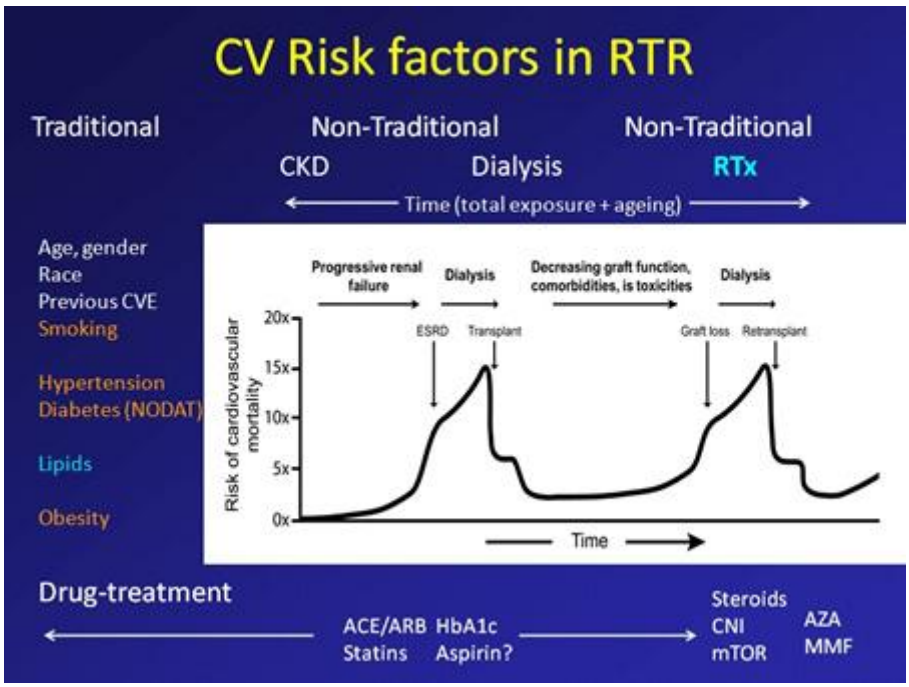

and then also on top of that typical transplants related risk factors that have been treated variably with ACE inhibitors, statins and then also by various regimens or combination of steroids. On top of that they could go then back to CKD, renal transplants, then go back to dialysis, be re-transplanted so there's a whole bunch of risk factors that also may influence

each other that makes it very difficult to know which is the one and the specific patients to treat.

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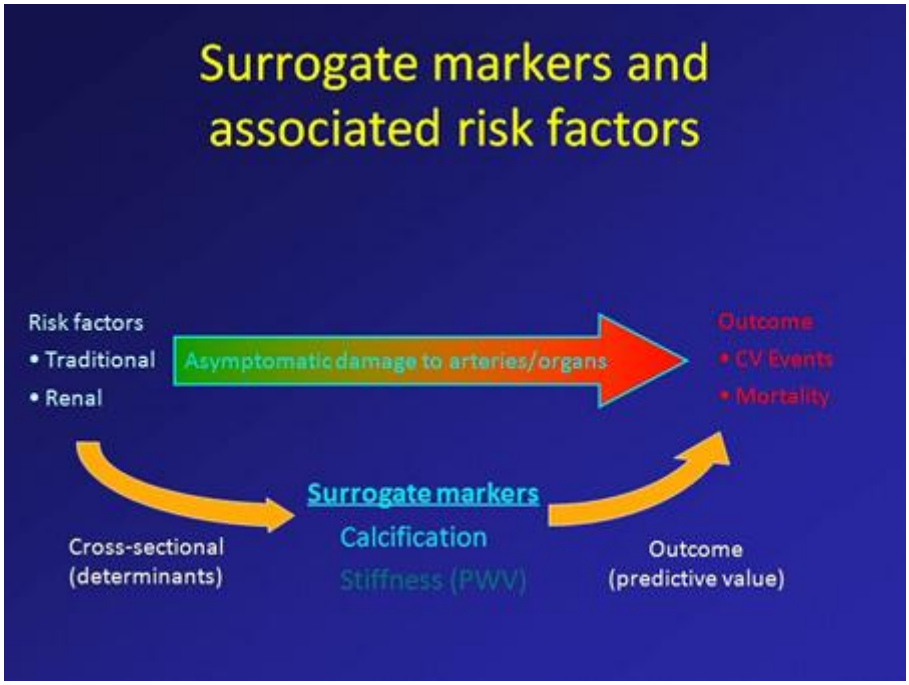

Another approach then is to look at surrogate markers. I will illustrate two important surrogate markers which are central aortic calcification and coronary calcification and stiffness as assessed by pulse wave velocity.
For surrogate markers we have to show of course that they predict outcome in transplants and then it's also interesting of course to know which of these risk factors, traditional and renal risk factors, are related to these surrogate markers.

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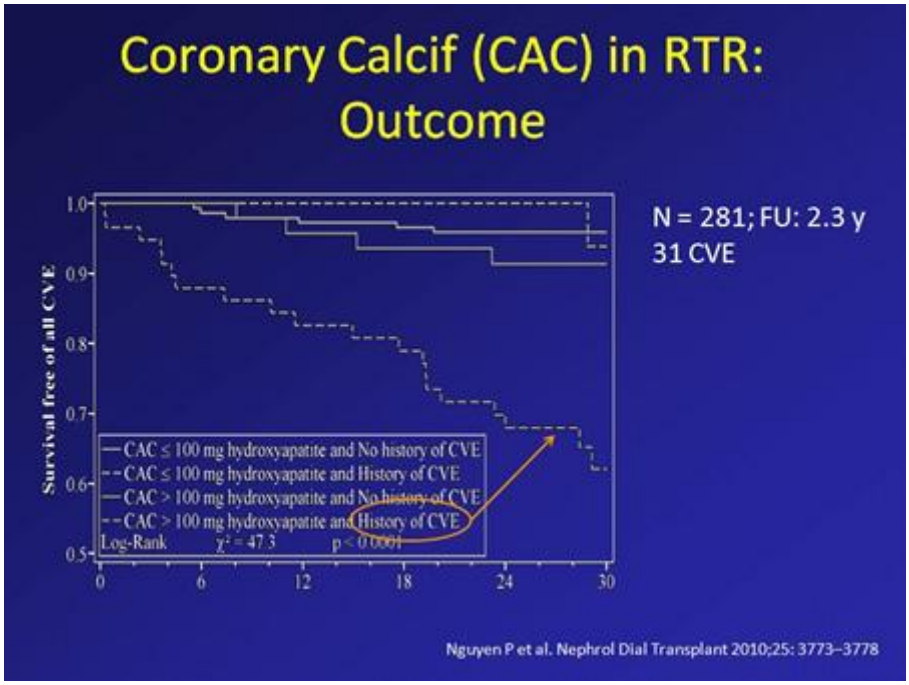

Coronary calcification had already been shown to be predictive in non-renal populations, less clear literature in dialysis patients and here the group of Brussels with whom we have also collaborated have shown recently for the first time that also indeed in transplants coronary artery calcification assessed by a standard validated methodology of EBCT really predicts outcome. But a little disappointing that the prediction mainly predicts outcome in patients who already have a history of cardiovascular disease. So a little bit – to the risk scores that underestimate high risk patients.

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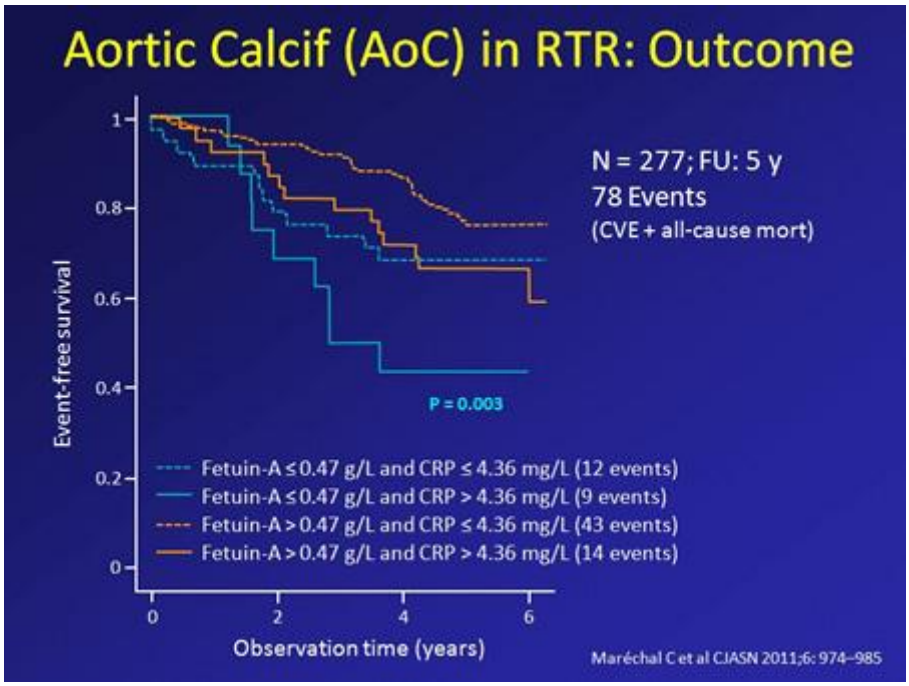

So what about aortic calcification? It also predicted outcome and what is interesting; this is the same cohort from the same study. They followed these patients longer and after 5 years 78 events were recorded and in this study they were able to demonstrate that also aortic calcification was predictive of outcome and was related to the level of calcification inhibitor, fetuin A which is the circulating inhibitor of vascular calcification. But what is also important and interesting here is that this relationship or the predictive value of fetuin was modulated by inflammation as measured by high sensitive CRP.

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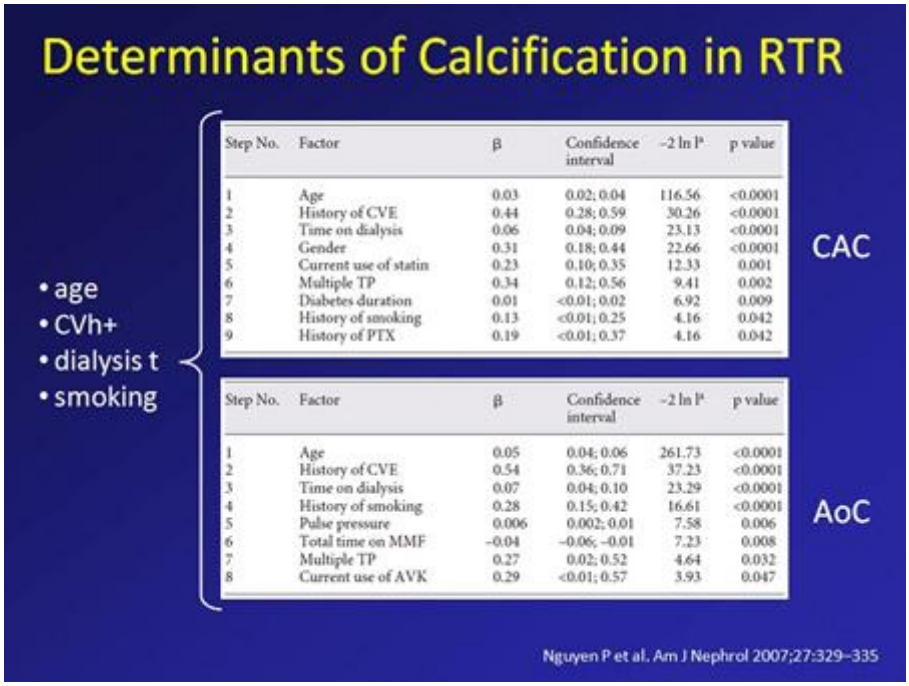

Step No.	Factor	β	Confidence interval	−2 ln l*	p value
1	Age	0.03	0.02; 0.04	116.56	<0.0001
2	History of CVE	0.44	0.28; 0.59	30.26	<0.0001
3	Time on dialysis	0.06	0.04; 0.09	23.13	<0.0001
4	Gender	0.31	0.18; 0.44	22.66	<0.0001
5	Current use of statin	0.23	0.10; 0.35	12.33	0.001
6	Multiple TP	0.34	0.12; 0.56	9.41	0.002
7	Diabetes duration	0.01	<0.01; 0.02	6.92	0.009
8	History of smoking	0.13	<0.01; 0.25	4.16	0.042
9	History of PTX	0.19	<0.01; 0.37	4.16	0.042

Step No.	Factor	β	Confidence interval	−2 ln l*	p value
1	Age	0.05	0.04; 0.06	261.73	<0.0001
2	History of CVE	0.54	0.36; 0.71	37.23	<0.0001
3	Time on dialysis	0.07	0.04; 0.10	23.29	<0.0001
4	History of smoking	0.28	0.15; 0.42	16.61	<0.0001
5	Pulse pressure	0.006	0.002; 0.01	7.58	0.006
6	Total time on MMF	−0.04	−0.06; −0.01	7.23	0.008
7	Multiple TP	0.27	0.02; 0.52	4.64	0.032
8	Current use of AVK	0.29	<0.01; 0.57	3.93	0.047

They also looked at the determinants of coronary and aortic calcifications which were not exactly the same. These were the common ones: age, cardiovascular history, time on dialysis and smoking. I'm not going to go further into detail but I'll show you here the use of anti-vitamin K was a predictor of aortic calcification but not of coronary calcification.

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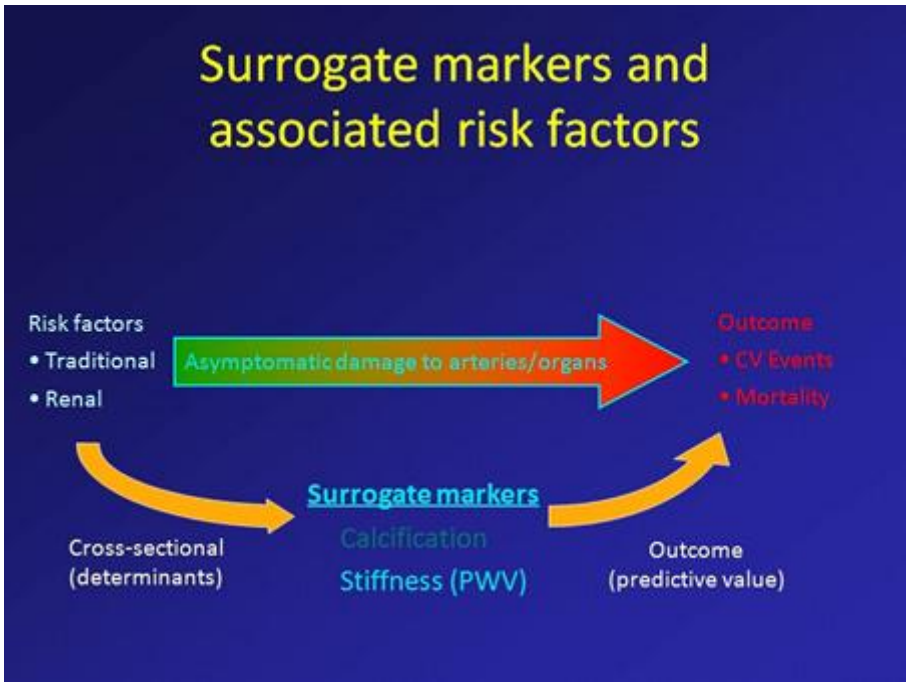

So now I come to the second surrogate marker which is pulse wave velocity.

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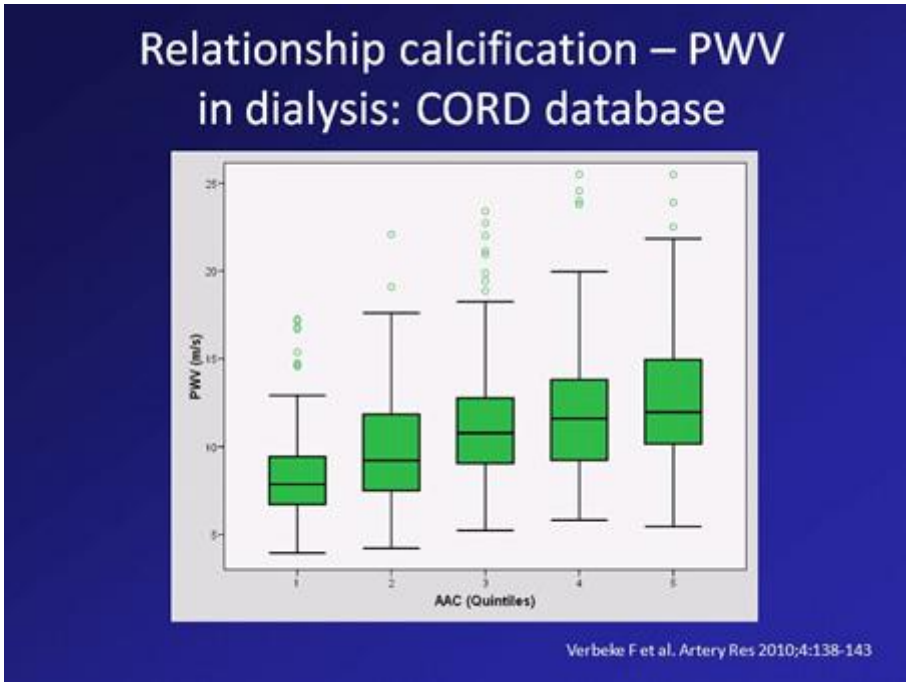

Just as a transition from calcification to pulse wave velocity I'll show you here data. This is the only slide which is not from transplant but from a large dialysis cohort showing that calcification and pulse wave velocity are also partly related which is not surprising because if calcium accumulates in the vascular wall, it can easily be seen as a factor that worsens stiffening.

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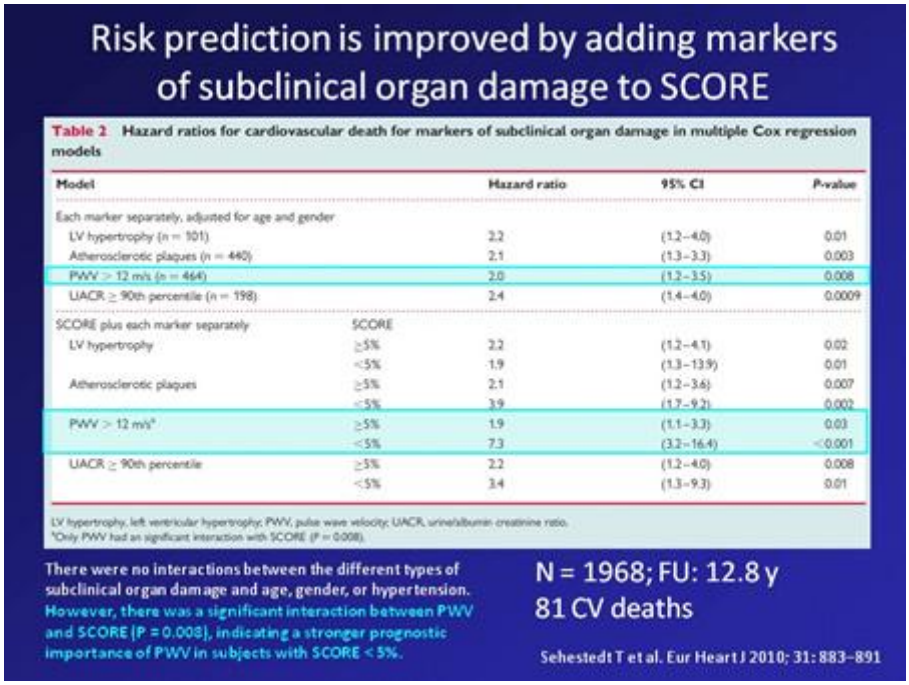

Why is pulse wave velocity interesting? Well, in a non-renal population, in the general population it is an independent predictor of outcome even after adjustment for age and gender. In using the score system in apparently healthy persons, more than 20.000 persons followers for almost than 13 years it was shown that pulse wave velocity improved the predictive value of the score system which is the European analogy of Framingham but what is more interesting is that there was an interaction between pulse wave velocity and the severity

of the score but in the inverse direction as previously. So pulse wave velocity identified mainly at risk patients in those who had a low prior probability based on the score system and that's of course an interesting parameter.

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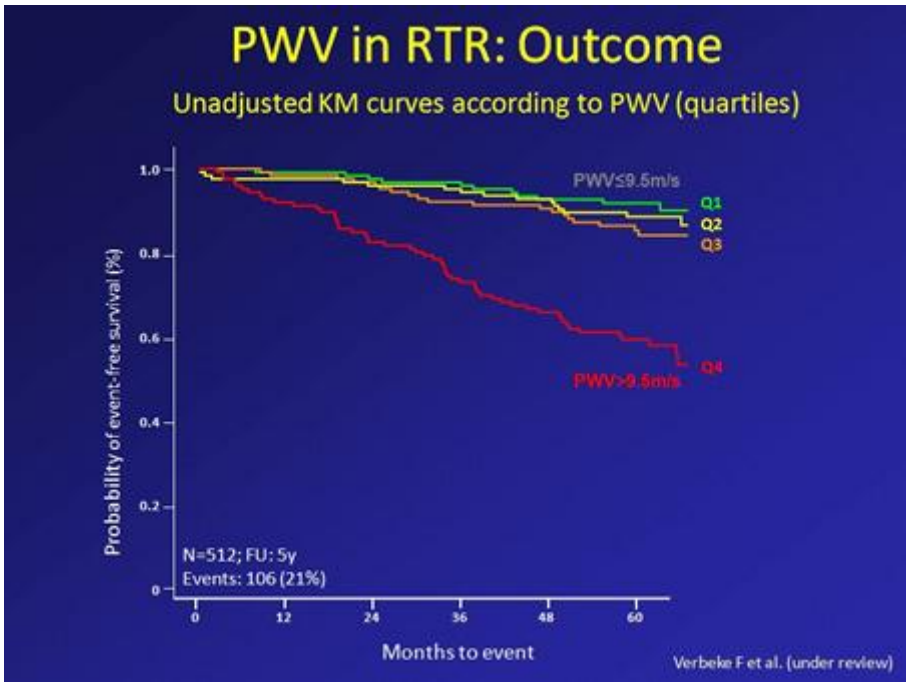

Whether this also holds true for transplants we still don't know but in any case this is work in progress, we have studied over 500 patients and measured pulse wave velocity and indeed here is a univariate predictive value for outcome. It is highly predictive and also in Cox regression models I won't show you, it remains a very strong and independent predictor of outcome.

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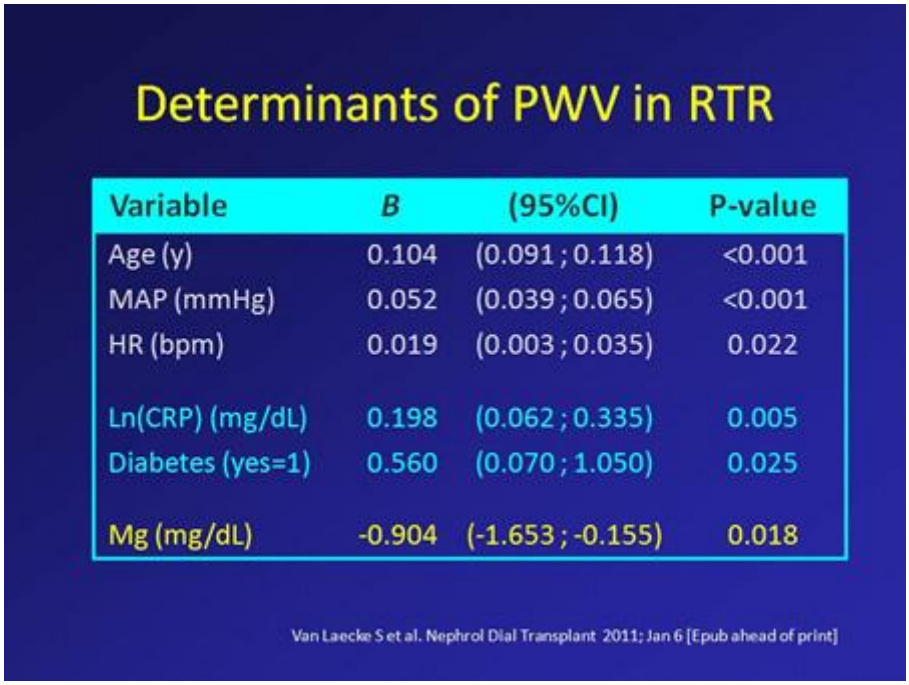

What are the determinants of pulse wave velocity? Not on expected age and some hemodynamic factors, these have been demonstrated and quite consistently been related to pulse wave velocity but here again CRP comes as a predictor and diabetes the two factors that I already highlighted previously and then as a new one low magnesium. So the higher the magnesium the lower the pulse wave velocity. The lower the magnesium the higher the pulse wave velocity. So an inverse relationship.

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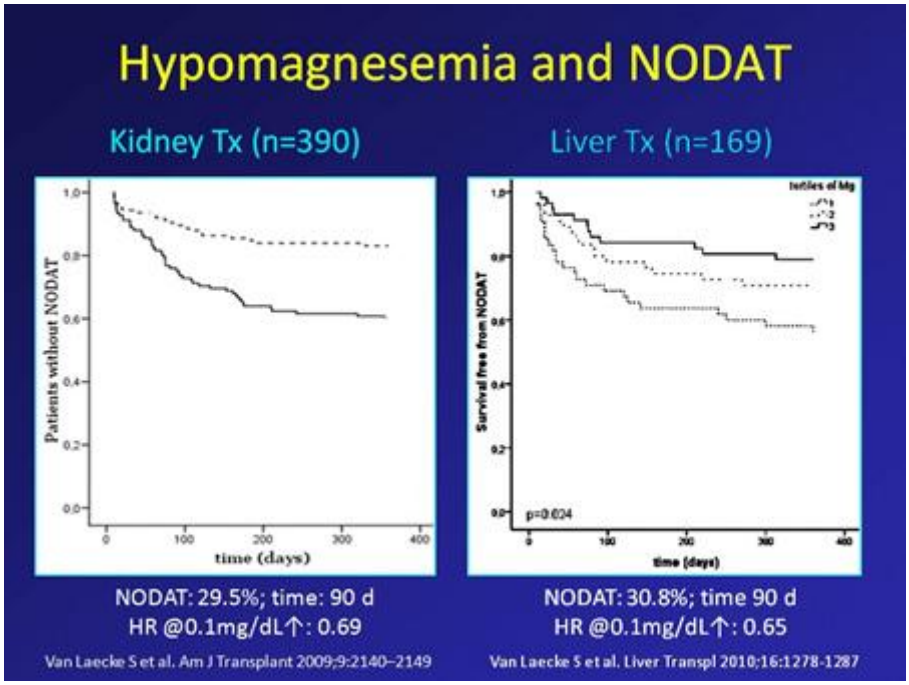

But even more important it was shown that in kidney transplants it was shown low magnesium was also a predictor for new onset diabetes and I have shown you that new onset diabetes has a very detrimental impact on the survival of transplants. This was studied in a cohort of 390 kidney transplants and even confirmed also in liver transplant. So an incidence of new onset diabetes is very comparable time to new onset diabetes almost identical and the hazards ratio per 1 mg/dl increase, the hazard decreases by 0.7. So very consistent data published by my colleague doctor Van Laecke very recently.

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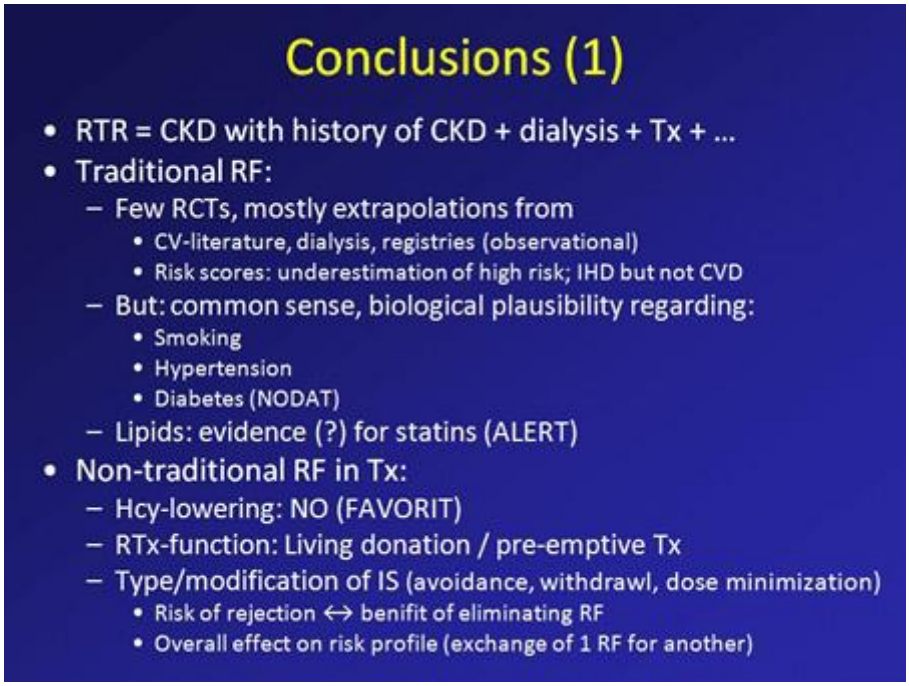
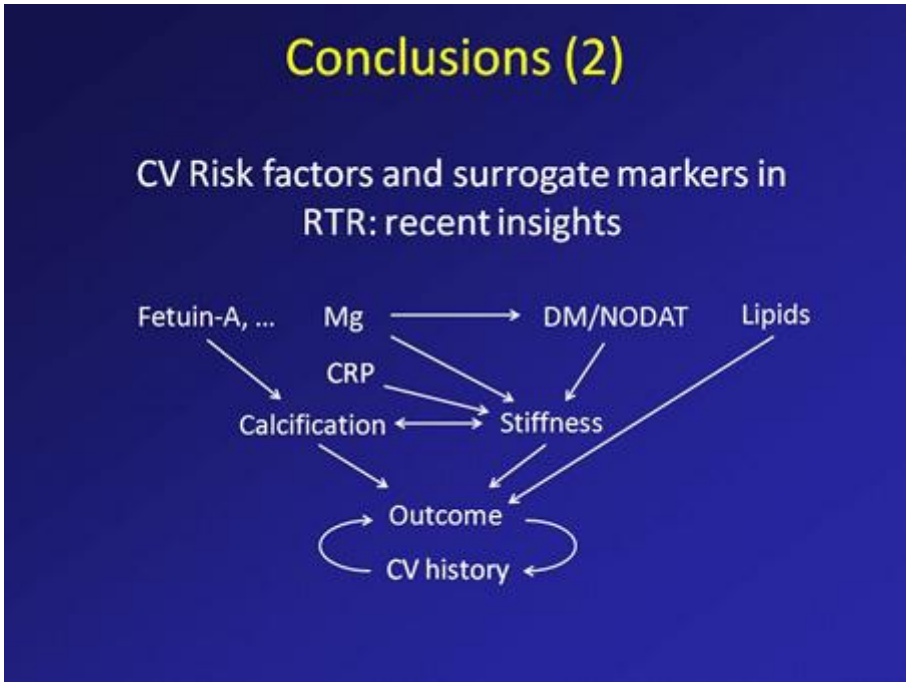


So in conclusion we should never forget that renal transplant is a complex population and should be considered as a CKD but with a history of CKD, dialysis, transplants and dialysis transplants and recurrent transplants potentially.
Traditional risk factors: there are few randomised trials mostly extrapolations from other populations, from cardiovascular literature or observational. Risk scores underestimate high risk and particularly cardiac risk but not cerebrovascular disease. There's common sense and biological plausibility for some traditional risk factors such as smoking, hypertension and diabetes be it pre-existing or new onset.
Lipids I leave the data to your own judgement. We have the ALERT study there.
Then regarding non-traditional risk factors I would say that for non-homocysteine lowering treatments definitely no evidence. Of course, everything that improves renal transplant function, living donation, pre-emptive transplant will also improve cardiovascular outcome. Modification of immune suppression risk, there are a lot of literature I have no time to review here but of course you always have to balance risk of rejection to the benefit of eliminating the risk factor and also judge the overall effect of the risk profile in that you often exchange one risk factor for another.



What we showed here regarding the relationship of cardiovascular risk factors and surrogate markers, these are recent enzymes, so calcification inhibitors indeed influence a central aortic and coronary calcification rich in turn in transplants predict outcome.

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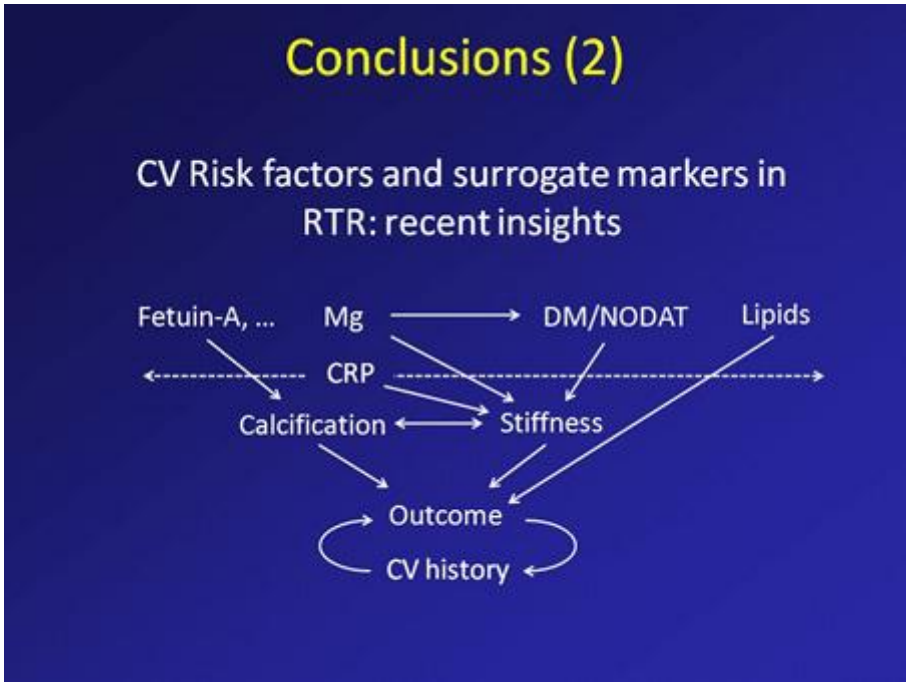

CRP also influences stiffness and magnesium both directly has an effect and also on stiffness and in turn diabetes also influences stiffness directly. So here there is a sort of clustering circle.

Regarding CRP my personal opinion is that it is rather a modulator and it's on another level regarding cardiovascular risk. These are recent insights and have to be explored in more detail in the future.

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Thank you for your attention.