Editorial

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Asymmetric dymethilarginine and cardiovascular risk modelling in end stage renal disease

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SUMMARY

The Risk of disease is a multivariate problem. For example we know that several factors may induce cardiovascular damage and that these factors may be variously combined in individual patients. Observational studies in Framingham demonstrated that the risk of cardiovascular events may be satisfactorily described on the basis of 7 factors: age, sex, BP, Cholesterol, Diabetes, smoking, LVH. New factors which are suspected to influence cardiovascular risk should always be considered and tested in the context of established risk factors. To be appropriately labelled as "risk factors" any putative risk factor should increase the prediction power of standard statistical models based on "traditional" (Framingham) risk factors. In patients with ESRD, statistical models based on Framingham risk factors are unsatisfactory. The addition of factors peculiar to ESRD (hyperparathyroidism – hyperphosphatemia and anemia) and emerging risk factors (CRP and hyperhomocysteinemia) to models based on Framingham risk factors improves the models but the overall prediction power remains unsatisfactory. We suspected that Asymmetric Dimethyl Arginine (ADMA) was a cardiovascular risk factor in dialysis patients. Indeed this substance inhibits nitric oxide synthase and thereby reduces the rate of synthesis of NO. To test this hypothesis we studied the relationship between ADMA and intima media thickness (IMT) in the carotid artery and investigated whether plasma ADMA predicts survival and cardiovascular events in ESRD patients. Of note, ADMA resulted to be independently related to intima media thickness (beta=0.24, P=0.01). More importantly we found that patients with relatively higher plasma ADMA had a shorter survival in comparison to those with relatively lower plasma concentration (P<0.001).

These data clearly indicate that ADMA should be added to the list of cardiovascular risk factors in the dialysis population. We believe that the scientific data gathered on this problem represent a strong argument for not deferring intervention studies aimed at modifying plasma ADMA concentration in ESRD patients. The hypothesis that ADMA is a causal risk factor may now undergo formal experimental testing in appropriate studies.

Key-words: ADMA; cardiovascular risk; uremia; ESRD; dialysis; hypertension; atherosclerosis.

The scientific inquiry has much in common with criminal investigation. In criminal investigations the identification of the culprit of a crime is made on the basis of several witnesses and on accurate cross-checking of their testimonies. The "truth" emerges as the result of multiple source of information. In clinical research the Risk of Disease is multivariate. For example, we know that several factors may induce cardiovascular damage and that these factors may be variously combined. When risk factors are mentioned, Framingham always materialises in our minds. Framingham is internationally known for it is the basis of the best available studies in cardiovascular epidemiology. It is in Framingham that the very definition of "risk factor" was born. The beauty of observational studies in Framingham is that they demonstrated that cardiovascular risk may be satisfactorily described on the basis of 7 factors: age, sex, BP, Cholesterol, Diabetes, smoking, LVH[(1)]. In observational studies it can be ascertained if a given factor is a risk factor or not. To this end a cohort of patients is followed up for a certain time. Predictably the cohort becomes progressively smaller due to the death of a fraction of patients. If we stratify patients in this cohort according to a putative risk factor, present *vs* absent, we can conclude that the factor is a true risk factor only if the survival of those having the risk factor is less than that of those not having the risk factor (Fig. 1).

Cardiovascular risk modelling

As anticipated, risk is a multifactorial problem. Therefore any putative risk factor should be considered in the context of all know risk factors. This context is created by constructing a statistical model aimed at predicting a given outcome, for example, cardiovascular death. Any new factor suspected to be a cardiovascular risk factor should increase the prediction power of the standard statistical model based on "traditional" risk factors. The appropriate statistical model to test this problem is the Cox's model. An indicator of the likelihood of this model is the "-2LogL" of the model. The lower this indicator, the better the model. In other words if we start with a single risk factor, the –2LogL is high and it becomes smaller and smaller as we add new independent risk factors. In theory the model is perfect when predicted and observed risk are identical (Fig. 2). To exemplify, I will build a survival model based on the data of the CREED study (an observational study on cardiovascular risk in dialysis patients). To better understand how the model works we can start with a fundamental variable: age. As expected, age is a significant factor (Fig. 3). However important, age alone produces a weak model. In other words we are often right in predicting that a 70 years old man is more likely to die from cardiovascular complications than another man 10 or 20 years younger but this prediction in some cases is wrong because several individuals with multiple risk factors die prematurely while old people without other risk factors have a long survival. Previous risk is a strong predictor of future risk (those who have had cardiovascular events are at high risk of incident events). Therefore if we add to the

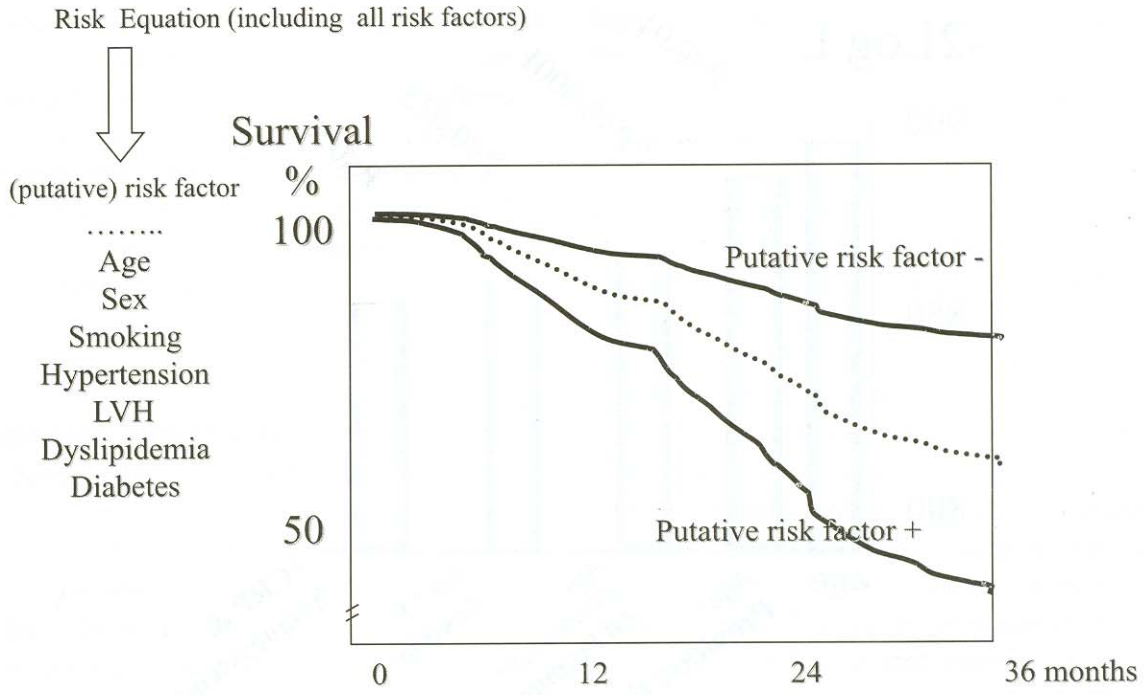

Figure 1: The figure is explained in the main text

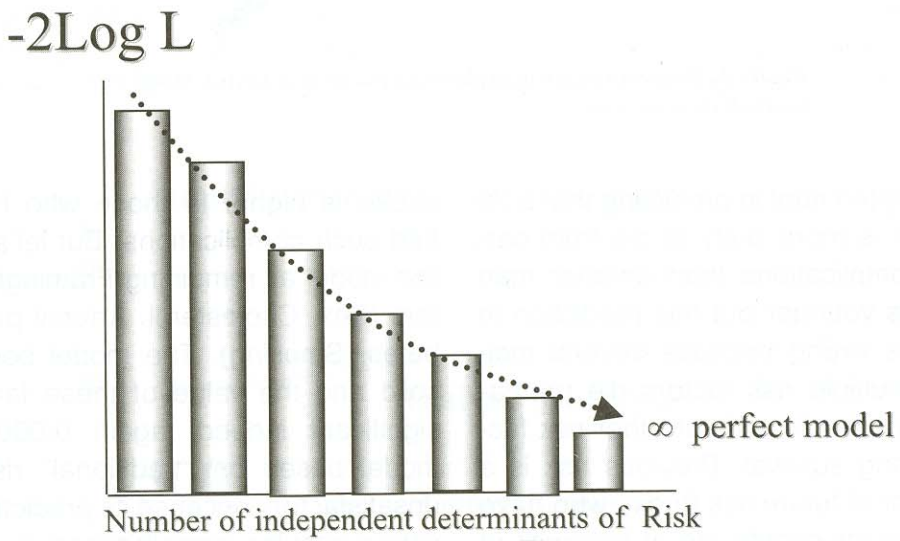

Figure 2: Progressive gain in explanatory power of a survival model

factors (Sex, Cholesterol, Arterial pressure, Diabetes, Smoking). The model becomes more solid and the value of these factors is very significant indeed, again 0.0001. Still this model based on "traditional" risk factors is unsatisfactory because its prediction power for cardiovascular complications in dialysis patients is much less precise than in the general population[2].

If the model based on Framingham risk factors is unsatisfactory we ought to go beyond Framingham. We ought to consider other risk factors which were not contemplated in the Framingham study. We may add two series of factors into the model: 1) Factors peculiar to end stage renal disease like hyperparathyroidism - hyperphosphatemia and anemia. 2) Emerging risk factors, i.e. inflammation as measured by CRP[3] and hyperhomocysteinemia[4]. As shown in Fig. 3 the addition of these factors improves the prediction power of the model.

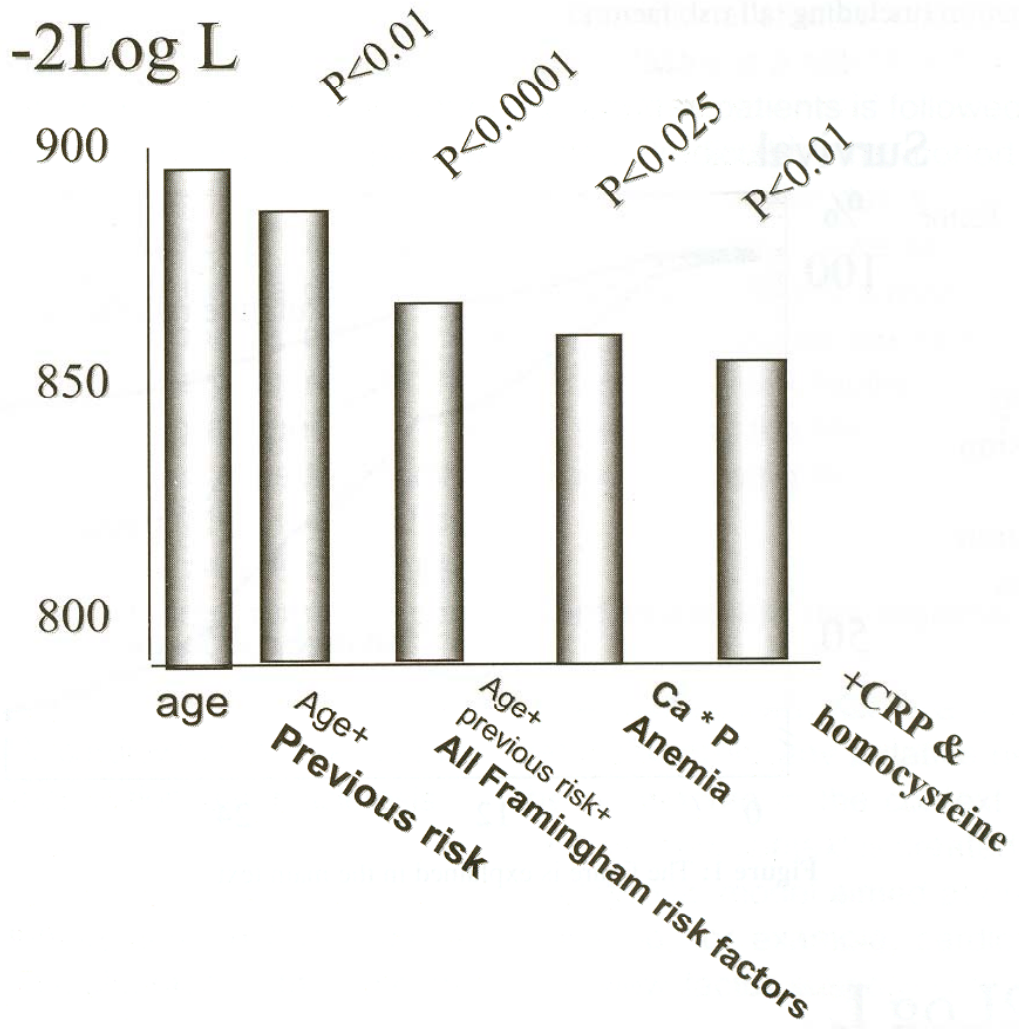

Figure 3: Progressive gain in explanatory power of a survival model in haemodialysis patients

Asymmetric Dimethyl Arginine (ADMA) as a cardiovascular risk factor

It is important to remember that the difference in cardiovascular mortality between the dialysis population and the general population in the USA is dramatic: the death rate is 5 times higher in the oldest dialysis cohort (>85 years) but 500 times higher in the youngest cohort[5] (Fig. 4). This suggests that there must be unknown factors which explain this devastating susceptibility to cardiovascular damage in patients with ESRD. We suspected that the high risk of ESRD is strongly linked to endothelial dysfunction. Indeed all the risk factors I have already mentioned, Framingham and non-Framingham, impinge upon the endothelium. This central role of the endothelium in ESRD was suggested by a study by Vallance[6]. In this study Asymmetric Dimethyl Arginine (ADMA), an endogenous inhibitor of NO synthase, was three times higher in patients with severe renal disease than in control patients. Vallance speculated that ADMA, by reducing local concentration of NO in the vascular endothelium, may cause vasoconstriction and hypertension, platelet and leucocyte adhesion and smooth muscle proliferation: all factors which are at the core of the atherosclerosis process. The paper of Vallance aroused much interest but it lost momentum after a study by the Bergstrom group[7]. In this study Anderstam and Bergstrom questioned the validity of the assay used by Vallance and noted that, although ADMA was higher in patients with advanced renal diseases and in CAPD patients than in healthy subjects, the average ADMA plasma concentration in patients with renal failure was below the threshold of biological activity. More recently a small survey by Kielstein[8] showed that ADMA is higher in dialysis patients with cardiovascular complications than in those without such complications. However in this study the definition of atherosclerosis relied on broadly defined clinical indicators.

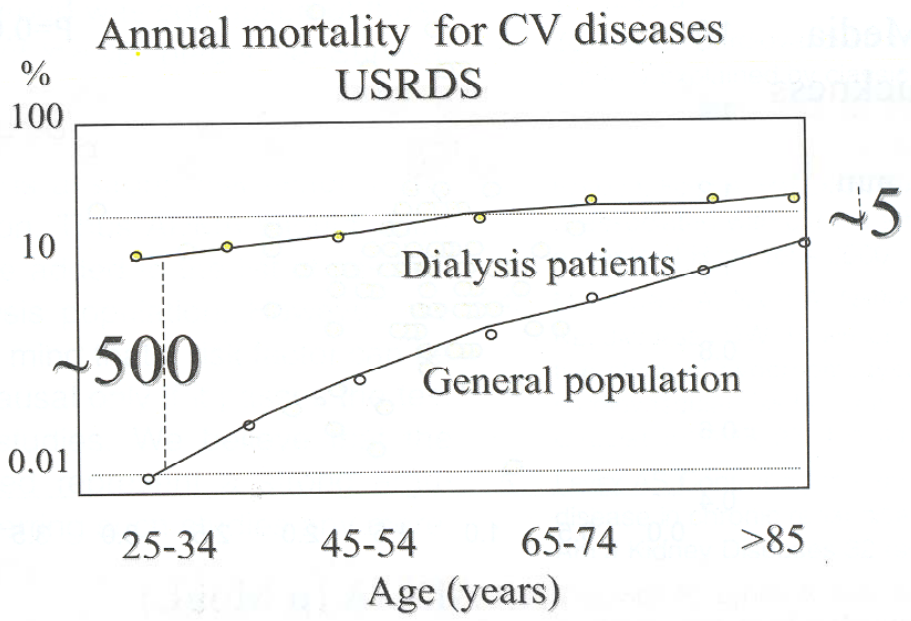

Figure 4 : Cardiovascular mortality in the USRDS and the general population in the USA

With this background in mind we decided to look into this problem in greater detail by more rigorous methodology. We established a collaboration with Dr. Boeger's laboratory to measure ADMA by a highly reliable HPLC technique. The relationship between ADMA and vascular injury was tested by relating the plasma concentration of this substance to was appropriately corrected for age and plasma homocysteine because these factors, like ADMA, were independent predictors of IMT[9]. But, however strong, this may be a mere association. For this reason it is fundamental to closely examine the relationship between ADMA and all cause and cardiovascular mortality[10]. This analysis showed that

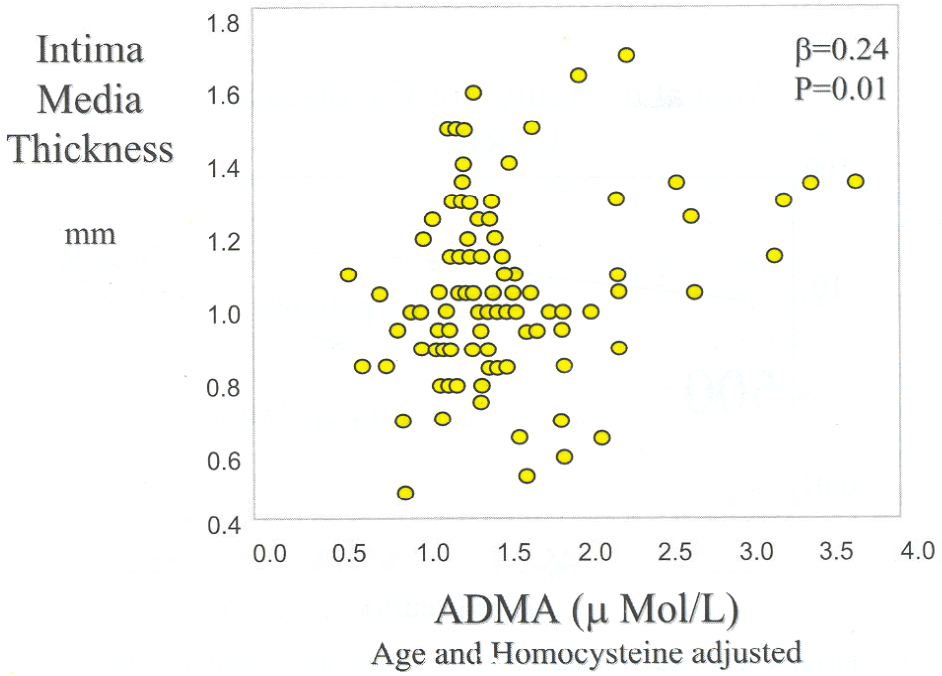

Figure 5: Relationship between ADMA and Intima Media Thickness

atherosclerosis as detected by high definition Echo-Colour Doppler and, most importantly, we also studied the relationship between ADMA and hard end-points like all-cause and cardiovascular mortality. Intima-Media thickness (IMT) is a reliable indicator of cardiovascular risk in the general population and in dialysis patients as well. Interestingly, when we related IMT to ADMA, we found a strong relationship between the two variables. The higher ADMA, the higher IMT (Fig. 5). In this analysis the plasma concentration of ADMA patients with relatively higher plasma concentration of ADMA had a shorter survival in comparison to those with relatively lower plasma concentration. The comparison of 4 groups of dialysis patients defined on the basis of their plasma ADMA is shown in Fig. 6. The first group included those with ADMA less than the 50th percentile (the median), the second those with levels between the 50th and the 70th percentile, the third those with values between the 70th and the 90th percentile and finally the fourth group was composed of those

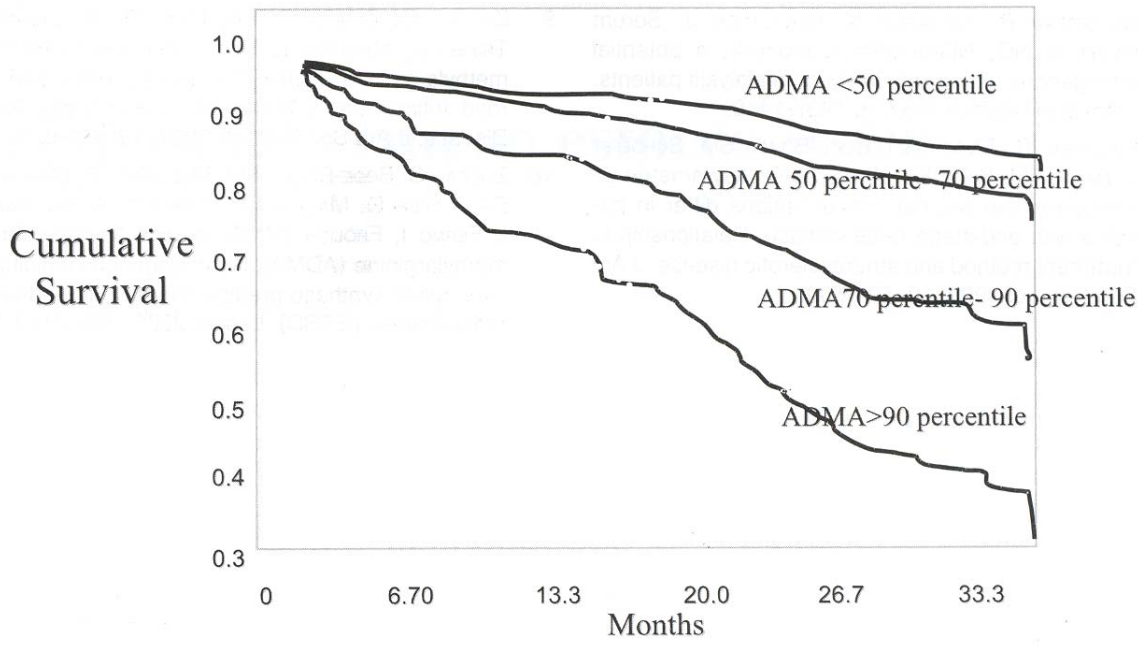

Figure 6: Relationship between ADMA and all-cause mortality

with levels beyond the 90th percentile. Survival decreased dramatically from the first to the fourth group (Fig. 6). These data clearly indicate that ADMA is a strong risk factor in the dialysis population. Thus ADMA should, without hesitation, be added to the list of risk factors in the dialysis population. However, we ought to keep in mind that a risk factor can be considered as causal only if it passes the test of intervention studies. We believe that the data we gathered represent a strong argument for not deferring such studies any more. ADMA is a modifiable risk factors and the hypothesis that it is a causal risk factor may now undergo formal experimental testing in appropriate studies.

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