

# Prognostic Value of Ultrasonographic Measurement of Carotid Intima Media Thickness in Dialysis Patients

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**Abstract.** High-resolution carotid ultrasonography is considered a fundamental technique for the investigation of the vascular system. However, it is still very unclear whether ultrasonographic studies of carotid arteries are useful for the prediction of cardiovascular events in patients with end-stage renal disease. The prediction power of carotid ultrasonography for all-cause and cardiovascular mortality was tested in a cohort of 138 patients receiving chronic dialysis treatment (91 receiving hemodialysis treatment and 47 receiving continuous ambulatory peritoneal dialysis treatment; follow-up,  $29.8 \pm 15.0$  mo), and the relationship between this parameter and alterations in left ventricular mass (LVM) and geometry was examined. On univariate analysis, intima media thickness (IMT) was directly related to LVM as well as to the absolute and relative thicknesses of LV walls but independent of LV end-diastolic volume. Data analysis based on LV geometry patterns revealed that patients with concentric hypertrophy were those with the highest IMT. The internal diameter of the

common carotid artery (DCCA) was also related to concentric hypertrophy, but the strength of this relationship was of borderline significance ( $P = 0.06$ ). During the follow-up period, 63 patients died: 32 (51%) of them of cardiovascular causes. IMT was significantly higher ( $P = 0.006$ ) in patients who died of cardiovascular causes ( $1.10 \pm 0.21$  mm) than in patients who survived ( $0.99 \pm 0.24$  mm). In a Cox regression model, this parameter turned out to be an independent predictor of cardiovascular death, and it retained an independent effect in a model that included LVM. Treatment modality failed to independently predict this outcome. The risk of cardiovascular death was progressively higher from the first IMT tertile onward. DCCA failed to predict cardiovascular outcomes. IMT in dialysis patients is associated with LV concentric hypertrophy and is an independent predictor of cardiovascular death. IMT may be usefully applied for risk stratification in the dialysis population.

High-resolution carotid ultrasonography is a fundamental technique for the investigation of the vascular system (1–7). The investigation of the carotid artery with this technique is important not only for the assessment of its structural alterations but also because the extent of atherosclerosis in this vessel reflects the severity of arterial damage in other districts (6,7). Intima media thickness (IMT), particularly in the common carotid artery, is a strong predictor of cardiovascular events in the general population (8). For this reason it is now considered a valid surrogate end point that can be used in intervention studies that are aimed at modifying cardiovascular risk factors (9).

Studies that are based on carotid ultrasonography have documented the peculiar severity of arterial damage in end-stage renal disease (ESRD) (10–14). However, the question as to whether ultrasonographic studies of carotid arteries are useful for the prediction of cardiovascular events in this

population has been scarcely investigated. In the only study performed so far (15), the internal diameter of the common carotid artery (DCCA), but not IMT, predicted overall mortality and cardiovascular outcomes in a detailed analysis including the incremental modulus of elasticity, *i.e.* a marker of arterial stiffness. The issue is of relevance because parameters of arterial structure derived from carotid ultrasonography, if specifically validated in dialysis patients, may refine risk stratification in the dialysis population, which is a population that is at very high risk. We have therefore tested the prediction power of carotid-artery IMT and of the internal diameter of the carotid artery for all-cause and cardiovascular death in a cohort of patients receiving chronic dialysis treatment. Left ventricular mass (LVM) is a well-established risk factor in these patients; therefore, we also tested the relationship among IMT, DCCA, and LVM and sought to establish that they have an independent prognostic power over and above LVM for all-cause and cardiovascular mortality.

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## Materials and Methods

The protocol was in conformity with the local ethical guidelines of our institution, and informed consent was obtained from each participant.

## Patients

One hundred thirty-eight dialysis patients (81 men and 57 women; 91 receiving hemodialysis [HD] treatment and 47 receiving continuous ambulatory peritoneal dialysis [CAPD] treatment) who had been on regular dialysis treatment (RDT) for at least 6 mo and who were free of overt cardiovascular congestion or intercurrent infections (fever, infected vascular access or peritonitis, or exit-site infection) were recruited for the study. HD patients were being treated thrice weekly with standard bicarbonate dialysis ( $n = 81$ ) (138 mmol/L Na, 35 mmol/L  $\text{HCO}_3^-$ , 1.5 mmol/L K, 1.25 mmol/L Ca, 0.75 mmol/L Mg) or with high-flux HD ( $n = 10$ ) (with either polysulphone or AN69). The average urea Kt/V in these patients was  $1.29 \pm 0.30$ . The remaining 47 patients were receiving CAPD (weekly Kt/V  $1.67 \pm 0.33$ ). Patients on CAPD were all on a 4-exchange/d schedule with standard dialysis bags (132 mEq/L Na, 3.5 mEq/L Ca, 40 mEq/L acetate, 2.5 to 4.25% glucose). All HD patients were virtually anuric (24-h urine volume  $<200$  ml/d), and a minority of CAPD patients ( $n = 6$ ) had a 24-h diuresis  $>200$  ml/d. The patients who took part in this study represented approximately 70% of the dialysis population in the urban area of Reggio Calabria, Italy, during January 1997 through June 1998. The remaining 30% of patients were excluded because they had overt cardiovascular congestion or active infections or were hospitalized for intercurrent illness (approximately 20%) and/or for logistic reasons (approximately 10%). The cause of chronic renal disease was nephroangiosclerosis in 32 cases, chronic glomerulonephritis in 29, polycystic kidney disease in 13, pyelonephritis/interstitial nephritis in 11, diabetes in 9, IgA nephropathy in 5, focal glomerulosclerosis in 3, membranous nephropathy in 3, hereditary nephropathy in 2, cortical necrosis in 2, congenital renal dysplasia in 1, Wegener granulomatosis in 1, gouty nephropathy in 1. The cause was undefined in 26 cases.

Fifteen patients had a history of myocardial infarction, and 40 patients had clinical and electrocardiographic evidence of cardiac ischemia. Nine patients had had a stroke, and 14 patients had had at least one transient ischemic attack. Nineteen patients had diabetes, and 68 patients were habitual smokers. Seventy-eight patients were being treated with various antihypertensive drugs [52 on monotherapy with calcium channel blockers, angiotensin-converting enzyme inhibitors, beta-blockers, clonidine, or angiotensin II receptor antagonists and 26 on double or triple therapy with various combinations of these drugs]. Somatometric, biochemical, and hemodynamic data of the study population are reported in Table 1.

Carotid ultrasonography and echocardiography studies were performed between 9 and 12 a.m. during a midweek non-dialysis day in HD patients and on an empty abdomen in CAPD patients.

## Common Carotid Artery Ultrasonography

On all patients, ultrasonographic studies on common carotid arteries were performed bilaterally by a single observer who was unaware of the clinical and biochemical data. All studies were performed with a Hewlett Packard Sonos 1500 (Hewlett Packard, Avondale, PA) using a 7.5 MHz high resolution probe. IMT was defined as a low-level echo gray band that does not project into the arterial lumen (16) and was measured during end-diastole as the distance from the leading edge of the second echogenic line of the far walls of the distal segment of the common carotid artery, the carotid bifurcation, and the initial tract of internal carotid artery on both sides. Measurements were performed 0.5, 1, and 2 cm below the bifurcation (three measurements on each side), and the average measurement was taken as IMT. IMT measurements were always performed in plaque-free arterial segments. In our laboratory, abnormal IMT is defined as IMT  $>0.82$  mm. This value corresponds to the average value + 2 SD in a

Table 1. Somatometric, biochemical, and hemodynamic data in dialysis patients<sup>a</sup>

Somatometric data	
age (yr)	60.2 $\pm$ 15.6
duration of dialysis (mo)	46 (18 to 119)
BMI (kg/m <sup>2</sup> )	25.1 $\pm$ 4.4
Biochemical data	
hemoglobin (g/L)	104.0 $\pm$ 20.0
serum total cholesterol (mmol/L)	5.45 $\pm$ 1.41
serum triglycerides (mmol/L)	1.99 $\pm$ 1.11
serum lipoprotein(a) (mg/dl)	46.5 $\pm$ 34.1
serum albumin (g/L)	38.3 $\pm$ 6.0
serum calcium (mmol/L)	2.25 $\pm$ 0.30
serum phosphate (mmol/L)	1.90 $\pm$ 0.52
plasma homocysteine ( $\mu$ mol/L)	29.3 (20.3 to 47.0)
serum CRP (mg/L)	8.3 (3.4 to 19.1)
plasma fibrinogen (mg/dl)	567 (476 to 675)
serum LDL cholesterol (mmol/L)	3.40 $\pm$ 1.17
serum iPTH (pg/ml)	131 (56 to 343)
Hemodynamic data	
systolic pressure (mmHg)	135.4 $\pm$ 20.7
diastolic pressure (mmHg)	75.3 $\pm$ 12.5
heart rate (beats/min)	83.5 $\pm$ 10.2

<sup>a</sup> Normally distributed data are reported as mean  $\pm$  SD. Data that did not show a Gaussian distribution were expressed as median (interquartile range). BMI, body mass index; CRP, C-reactive protein; iPTH, immunoreactive parathyroid hormone.

group of 70 healthy Italian normotensive volunteers (age  $52 \pm 14$  yr) (17). DCCA was measured bilaterally 2 cm below the bifurcation during end-diastole, and the average measurement was taken as DCCA. IMT and DCCA measurements were always performed in plaque-free arterial segments.

Repeated studies of 105 dialysis patients by a blinded observer in our laboratory showed that IMT and DCCA represent reliable measurement in dialysis patients; their coefficients of variation were 5.5% and 3.2%, respectively.

## Echocardiography

All echocardiographic measurements were performed according to the recommendations of the American Society of Echocardiography (18). LVM was calculated according to the Devereux formula (19) and indexed to height<sup>2.7</sup> (LVMI) (20). The height-based indexing of LVM was specifically chosen to minimize any potential distortion that would be attributable to extracellular volume expansion (surface area indexing being weight-sensitive). Left ventricular hypertrophy (LVH) was defined by a LVMI of  $>47$  g/m<sup>2.7</sup> in women or  $>50$  g/m<sup>2.7</sup> in men. The relative wall thickness (RWT:  $2 \times$  posterior wall thickness/LV end-diastolic diameter [LVEDD]) was also calculated. Values indicative of concentric and eccentric LV geometry were established on the basis of age-specific reference standards (21). Mean wall thickness (MWT) was calculated by the standard formula ([posterior wall thickness + interventricular septum thickness]  $\div$  2).

## BP Measurements

In HD patients, we calculated the average value of all predialysis and postdialysis measurements that were taken during the month

preceding the study (12 predialysis and 12 postdialysis measurements). In CAPD patients, the average BP was calculated on the basis of a series of 10 to 20 measurements taken at home during the month preceding the study. Average dialysis BP in HD patients (22) as well as average home BP in CAPD patients (Zoccali C, unpublished data) are closely related to 24-h ambulatory arterial pressure and satisfactorily reflect the pressor burden on the cardiovascular system in these patients.

### Smoking

Smoking was estimated as packs of cigarettes/mo.

### Laboratory Measurements

Albumin (bromocresol green), parathyroid hormone (PTH), fibrinogen (Multifibre U, Dade Behring, Marburg, Germany) calcium and phosphate, total cholesterol and LDL cholesterol (Friedwald formula), and hemoglobin measurements were carried out by using standard methods in the routine clinical laboratory. For fasting HD patients, blood sampling was performed during the midweek non-dialysis day, and for CAPD patients, on an empty stomach. Serum lipoprotein(a) was measured by a commercially available enzyme-linked immunosorbent assay (Sigma Diagnostics Inc, St Louis, MO). Plasma homocysteine was determined by an HPLC method based on SBD-F (ammonium-7-fluorobenzo-2-oxa-1,3-diazole-4-sulfonate) fluorescence derivatization (23). C-reactive protein (CRP) was measured with a commercially available kit (Behring, Scoppito, L'Aquila, Italy).

### Follow-up Study

After the initial assessment, patients were followed up for  $29.8 \pm 15.0$  mo, and none of the 138 dialysis patients was lost to follow-up. Each death was reviewed and assigned an underlying cause by a panel of five physicians. As a part of the review process, all available medical information about each death was collected. This information always included study and hospitalization records. In the case of an out-of-hospital death, family members were interviewed by telephone to better ascertain the circumstances surrounding death.

### Statistical Analyses

Normally distributed data are reported as mean  $\pm$  SD. Data that did not show a Gaussian distribution were expressed as median and interquartile range. Between groups comparisons were tested by ANOVA.

The prediction power for all-cause mortality and cardiovascular outcomes of IMT and DCCA was analyzed in separate Cox proportional hazards models. In these models, variables that had an independent influence on survival were identified by a backward elimination strategy (24), starting with a standard set of covariates, including traditional risk factors (previous cardiovascular events, age, gender, diabetes, smoking, total cholesterol and LDL cholesterol, lipoprotein(a), fibrinogen, systolic BP, and antihypertensive medications), factors peculiar to ESRD (treatment modality and duration of RDT, albumin, hemoglobin, PTH, and calcium phosphate product), and emerging risk factors (CRP and homocysteine). By this strategy, we constructed models of adequate statistical power (at least 23 subjects for each variable in the final model).

The relationship between IMT and cardiovascular outcomes was further tested by stratifying patients into tertiles and adjusting for all covariates that had an independent effect on cardiovascular outcomes. To compare the statistical model based on IMT with a more extended model, including also LVM (Table 4), we used the  $-2$  log likelihood

( $-2$  Log L) statistics (25). This procedure compares different models fitted to the same set of survival data; the smaller the  $-2$  Log L value, the better the agreement between the model and the observed data. The difference between the  $-2$  Log L of the models that are being compared gives a statistical estimate as to which of them provides a better fit to the data. A 3.841 difference in  $-2$  Log L coincides with a significance level of 0.05 in a  $\chi^2$  distribution with 1 degree of freedom and indicates a better prediction of risk estimate provided by the method leading to the lowest  $-2$  log L value. Hazard ratios (HR) and their 95% confidence intervals (CI) were calculated by using the estimated regression coefficients and their standard errors in the Cox regression analysis.

All calculations were made using a standard statistical package (SPSS for Windows Version 9.0.1; SPSS, Chicago, IL).

### Results

On the whole cohort, IMT exceeded the upper limit of the normal range in 118 patients (85%) and there was no significant difference in the severity of carotid atherosclerosis between HD and CAPD patients neither in terms of IMT (HD,  $1.05 \pm 0.24$  mm; CAPD,  $1.02 \pm 0.22$  mm;  $P = \text{NS}$ ) nor in terms of DCCA (HD,  $6.79 \pm 1.00$  mm; CAPD,  $7.00 \pm 0.75$  mm;  $P = \text{NS}$ ).

One-hundred twenty-three patients (89%) displayed LVH on echocardiography, and the prevalence of LVH was identical between HD and CAPD patients (89% *versus* 89%).

### IMT, DCCA, and LV Mass and Geometry

On univariate analysis, IMT was directly related to LVM as well as to the absolute (MWT) and relative (RWT) thickness of LV walls (Figure 1) but independent of LV end-diastolic volume ( $r = -0.04$ ;  $P = \text{NS}$ ). These univariate correlations suggest that concentric hypertrophy was the geometric pattern better associated with IMT. In fact, data analysis according to LV geometry patterns reveals that patients with concentric hypertrophy were those with the highest IMT (Table 2). DCCA was directly related to LVMI ( $r = 0.32$ ;  $P = 0.0001$ ), and MWT ( $r = 0.29$ ;  $P = 0.0001$ ) was independent of RWT ( $r = 0.008$ ;  $P = \text{NS}$ ) and only slightly related to concentric hypertrophy (Table 2).

### IMT and All-Cause and Cardiovascular Mortality

During the follow-up period, 63 patients died: 32 (51%) of them of cardiovascular causes (Table 3). The cardiovascular death rate in HD patients did not differ from that in CAPD patients (15.1% yr *versus* 10.4% yr; NS).

IMT was significantly higher ( $P = 0.01$ ) in patients who died during the follow up ( $1.11 \pm 0.24$  mm) than in those who survived ( $1.00 \pm 0.22$  mm) and predicted unadjusted all-cause death (HR, 1.17; 95% CI, 1.05 to 1.30;  $P = 0.004$ ). However in a Cox regression analysis (adjusted for other risk factors) only age (HR [1 yr increase], 1.05; 95% CI, 1.03 to 1.07;  $P = 0.00001$ ) and serum CRP (HR [1 mg/dl increase], 1.01; 95% CI, 1.01 to 1.02;  $P = 0.0005$ ) were independent predictors of all-cause mortality, and IMT failed to predict this outcome in this analysis. Similarly, IMT was significantly higher ( $P = 0.006$ ) in patients who died of cardiovascular causes ( $1.10 \pm 0.21$ ) than in patients who did not have fatal cardiovascular

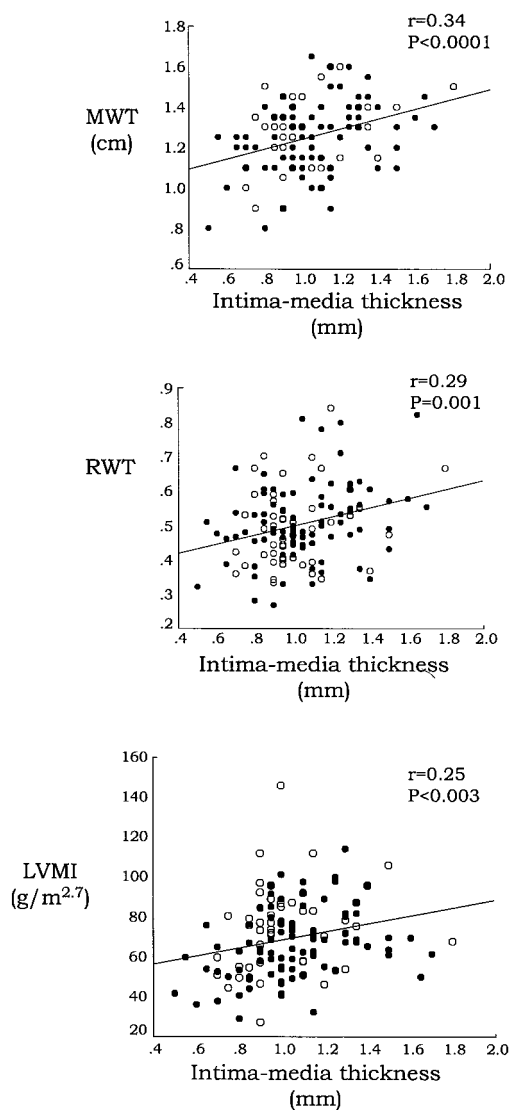


Figure 1. Relationships between intima-media thickness and mean wall thickness (MWT; top), relative wall thickness (RWT; middle), and left ventricular mass index (LVMI; bottom) in the whole group (hemodialysis and continuous ambulatory peritoneal dialysis patients). ●, hemodialysis patients; ○, continuous ambulatory peritoneal dialysis patients.

events ( $0.99 \pm 0.24$ ). In a Cox regression model that included age, male gender, calcium-phosphate product, and lipoprotein(a), IMT turned out to be an independent predictor of cardiovascular death (Table 4). Treatment modality failed to

independently predict this outcome. Interestingly, IMT retained an independent effect (HR [0.1 mm increase in IMT], 1.23; 95% CI, 1.04 to 1.45;  $P = 0.01$ ) also in an extended model that included LVMI (HR [1  $\text{g}/\text{m}^{2.7}$  increase in LVMI], 1.04; 95% CI, 1.02 to 1.07;  $P = 0.004$ ), and this extended model predicted cardiovascular death more closely ( $P < 0.005$ ) than the model that did not include LVMI (see footnote to Table 4). The risk for cardiovascular death (adjusted for the other independent predictors, [Table 4]) was progressively higher from the first tertile of IMT onward (Figure 2). The HR of patients in the third tertile was 2.40 times (95% CI, 1.04 to 5.52) higher than in those in the first tertile ( $P = 0.04$ ). DCCA was unrelated to overall and cardiovascular mortality.

*Sensitivity, Specificity, and Prediction Value of IMT for Cardiovascular Death*

The sensitivity of IMT and LVH (Table 5) for predicting cardiovascular mortality during the follow-up was high, but the specificity was low. However, due to the high frequency of abnormal IMT and LVH in this cohort, the positive prediction power of IMT and LVH was rather unsatisfactory. Yet the negative prediction power of these measurements was of a very high degree (100% and 93%). IMT coherently resulted to be a better predictor of cardiovascular death than LVH.

**Discussion**

In this study, carotid-artery IMT was strongly associated with concentric LVH and represented an independent predictor of cardiovascular death. To our knowledge, our data represent the first demonstration that carotid ultrasonography bears a prognostic value on the dialysis population.

In the general population, markers of target-organ damage, such as electrocardiographically (26) or echocardiographically determined LVH (27), have been associated with greater cardiovascular morbidity and mortality and thus have prognostic value. In recent years, additional crucial evidence has accumulated to shed light on these findings. For example, it has been shown that regression of LVH during antihypertensive treatment in part reverses the high risk associated with raised LVM (28). On these grounds, LVH is now considered a useful marker of risk in hypertensive patients, and regression of LVH is an indication that this risk has been modified by antihypertensive treatment. The relationship of structural alterations of the vascular tree with increased risk has also been studied (9). In this respect, the structural changes observed in the carotid artery, such as IMT, are especially important because they are

Table 2. Relationship between carotid atherosclerosis and heart geometry<sup>a</sup>

	Normal Geometry	Concentric Remodelling	Eccentric Hypertrophy	Concentric Hypertrophy	<i>P</i> <sup>b</sup>
IMT (mm)	0.74 ± 0.17	0.91 ± 0.18	1.03 ± 0.19	1.08 ± 0.25	0.004
DCCA (mm)	5.71 ± 0.57	6.95 ± 0.71	6.83 ± 0.97	7.01 ± 0.85	0.06

<sup>a</sup> Data are as mean ± SD. IMT, intima media thickness; DCCA, diameter of common carotid artery.

<sup>b</sup> One-way ANOVA.



Table 3. Causes of death in the study cohort<sup>a</sup>

	HD	CAPD
Cardiovascular		<i>n</i>
stroke	7	1
sudden death	2	5
heart failure	5	1
myocardial infarction	4	1
arrhythmia	2	
mesenteric infarction	2	
pulmonary embolism	2	
Total	24	8
Other causes		<i>n</i>
sepsis/infection	2	9
cachexia	4	6
hyperkalemia	4	1
neoplasia	2	1
gastrointestinal hemorrhage		1
treatment withdrawal	1	
Total	13	18

<sup>a</sup> HD, hemodialysis; CAPD, continuous ambulatory peritoneal dialysis.

common even in patients with mild hypertension and normal serum cholesterol. Furthermore, changes in the carotid artery have been correlated with a greater incidence of atherosclerosis in the coronary circulation and other large arteries. Clinical interest in IMT as a marker of vascular damage is also underscored by the fact that large arteries can be accurately, reproducibly, and noninvasively scanned by ultrasonographic means, which allows a patient's condition to be checked repeatedly during treatment.

The validation of surrogate end points is a valuable aspect in prognostic research in patients with ESRD because findings in the general population do not necessarily apply to the dialysis population. In this regard, it is worth noting that both the absolute and relative frequency of alterations in heart geometry in the uremic population differ from that in the general population (29). Due to the fact that prospective studies that are

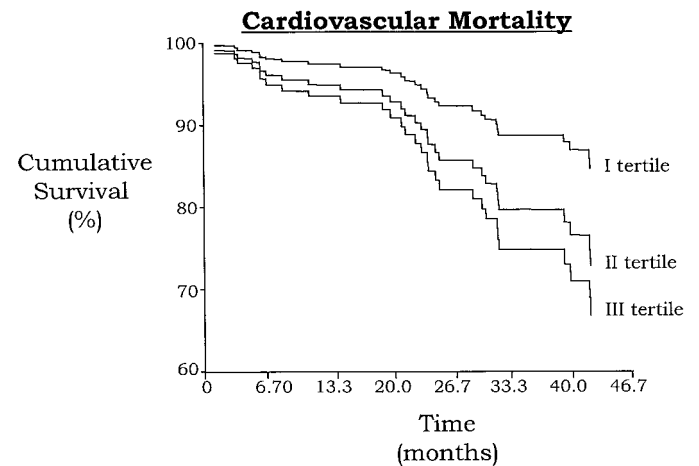


Figure 2. Cox proportional hazards survival curves for cardiovascular mortality in the study cohort. Patients were divided in relationship to the tertiles of intima-media thickness. I tertile, <0.95 mm; II tertile  $\geq 0.95$ ; III tertile,  $\geq 1.10$  mm). Data were adjusted for the other independent predictors of cardiovascular death (Table 4).

specific to the uremic population have shown that LVH and LV chamber dilation predict *de novo* ischemic heart disease, *de novo* cardiac failure, and mortality, these alterations are now considered to be important surrogate end points to target in intervention studies (29). Even more importantly, arterial damage in dialysis patients cannot be lightly equated to that observed in the general population as a result of the aging process and metabolic alterations (30).

Carotid atherosclerosis as assessed by ultrasonography in the dialysis population has been little investigated and almost exclusively in studies of cross-sectional design. Kawagishi *et al.* (10) showed that IMT was significantly higher in HD patients than in age- and gender-matched control subjects. London *et al.* (11) were the first to demonstrate that IMT is strongly associated with the thickness of the posterior wall and with LVMI. A subsequent study (12) indicated that the frequency of atherosclerotic plaques is far larger in dialysis patients not only in comparison with healthy subjects but also in

Table 4. Cox proportional hazards model for cardiovascular mortality (for comment see also Results)<sup>a</sup>

Parameter	Units of Increase	Hazard Ratio	95% CI	<i>P</i>
Age	1 yr	1.05	1.02 to 1.08	0.001
Calcium phosphate	1 mmol <sup>2</sup> /L <sup>2</sup>	1.65	1.20 to 2.26	0.002
Male gender		4.53	1.75 to 11.72	0.002
Lipoprotein(a)	1 mg/dl	1.02	1.01 to 1.03	0.004
IMT	0.1 mm	1.24	1.06 to 1.44	0.007

<sup>a</sup> IMT-based model:  $-2 \log$  likelihood = 246.463. Forcing left ventricular mass index (LVMI) into the model produced better data fitting ( $-2 \log$  likelihood = 238.215;  $P = 0.005$  versus model based on IMT only, see above). In this model, LVMI had an independent prediction power for cardiovascular death. Data are expressed as hazard ratios, 95% confidence interval (CI), and *P*. Out of the model: treatment modality ( $P = 0.10$ ), antihypertensive therapy ( $P = 0.40$ ), homocysteine ( $P = 0.44$ ), CRP ( $P = 0.47$ ), systolic BP ( $P = 0.55$ ), DCCA ( $P = 0.58$ ), duration of regular dialysis treatment ( $P = 0.63$ ), hemoglobin ( $P = 0.70$ ), albumin ( $P = 0.74$ ), smoking ( $P = 0.75$ ), fibrinogen ( $P = 0.79$ ), parathyroid hormone ( $P = 0.81$ ), LDLcholesterol ( $P = 0.83$ ), previous cardiovascular events ( $P = 0.94$ ), total cholesterol ( $P = 0.94$ ), and diabetes ( $P = 0.97$ ).

**Table 5.** Sensitivity, specificity, and positive and negative predictive values of IMT and left ventricular hypertrophy (LVH) for cardiovascular death<sup>a</sup>

	Abnormal IMT	LVH
Sensitivity	100%	97%
Specificity	19%	13%
Positive predictive power	27%	25%
Negative predictive power	100%	93%

<sup>a</sup> LVH was defined as LV mass  $>50 \text{ g/h}^{2.7}$  in men and  $>47 \text{ g/h}^{2.7}$  in women (20). Abnormal IMT was defined as IMT  $>0.82$  mm. This value corresponds to the average value + 2 SD in a group of 70 healthy Italian normotensive volunteers (age,  $52 \pm 14$  years) (17).

comparison with patients without renal diseases who are matched for traditional cardiovascular risk factors. A study by Savage *et al.* (13) documented that calcified plaques are common in dialysis patients. Finally, a more recent study has linked the severity of carotid atherosclerosis not only to traditional risk factors but also to hypoalbuminemia, *i.e.* a well-established predictor of LVH and high cardiovascular risk (14).

Whether ultrasonographic parameters of carotid atherosclerosis predict cardiovascular outcomes in dialysis patients still remains to be clarified. The issue is of importance because ultrasonography is increasingly recommended in both the high-risk and low-risk populations as a means of bettering the estimation of cardiovascular risk. Although it is well proven that IMT adds important information for the prediction of cardiovascular events beyond traditional risk factors in older adults without a history of cardiovascular disease (9), such a parameter of arterial wall structure might be noninformative in the dialysis population, which is marred with a heavy cardiovascular burden. In other words, to be prognostically useful in dialysis patients, this measurement ought to retain an independent prediction power for cardiovascular death beyond traditional and nontraditional risk factors as well as beyond previous cardiovascular events.

In this study, we have confirmed results by London *et al.* (11) that IMT is strongly related to LV concentric hypertrophy. Although the confirmation of this cardiac-arterial interaction further highlights the importance of structural alterations in large arteries in the pathogenesis of LVH in dialysis patients, it poses the problem from a clinical point of view as to whether carotid ultrasonography adds relevant information to echocardiographically measured LVM in these patients. The fact that IMT remained a consistent predictor of fatal cardiovascular events after statistical adjustment for LVM and other risk factors indicates that this measurement bears a prognostic value also on a high-risk population like the dialysis population. A 0.1-mm increase in IMT predicts a 24% higher risk for cardiovascular death. The apparent lack of prognostic power of IMT in the study by Blacher *et al.* (15) may be justified by the relatively smaller sample size and by the inherent strength of the measurement of carotid stiffness that was used (incremental elastic modulus), which in addition to cardiovascular death

also predicted all-cause mortality. DCCA failed to predict all-cause and cardiovascular death in our study. IMT, stenosis, and other carotid artery lesions, like DCCA, most likely reflect different events in the arterial wall (31) in response to aging and other risk factors and may also therefore be linked in different degrees to cardiovascular outcomes.

Two points deserve comment. First, although IMT had a prediction power for cardiovascular death independent of and superior to that of LVM, the difference was rather small. Although our study dealt with a fairly large number of patients, larger studies will probably allow a better appreciation of the relative value of these two techniques for risk stratification in dialysis patients. Second, it is well established that the primary negative effect in the arterial system is not the increase in artery thickness itself but rather the increase in the stiffness that results from increased wall thickness. Pulse wave velocity is emerging as a reliable estimate of arterial stiffness and a strong predictor of cardiovascular events in ESRD (31). Thus it may be argued that functional rather than anatomical measurements are useful for prognostic purposes in these patients. Future studies will establish the advantages and the limitations of these two approaches, which, by now, may be considered complementary rather than competitive investigations of the cardiovascular system.

## References

1. Mack WJ, Selzer RH, Hodis HN, Erickson JK, Liu CR, Liu CH, Crawford DW, Blankenhorn DH: One-year reduction and longitudinal analysis of carotid intima-media thickness associated with colestipol/niacin therapy. *Stroke* 24: 1779–1783, 1993
2. Poli A, Tremoli E, Colombo A, Sirtori M, Pignoli P, Paoletti R: Ultrasonographic measurement of the common carotid artery wall thickness in hypercholesterolemic patients: A new model for the quantification and follow-up of pre-clinical atherosclerosis in living human subjects. *Atherosclerosis* 70: 253–261, 1988
3. O'Leary DH, Polak JF, Kronmal RA, Kittner SJ, Bond MG, Wolfson Jr SK, Bommer W, Price TR, Gardin JM, Savage PJ: Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study. *Stroke* 23: 1752–1760, 1992
4. Mannami T, Konishi M, Baba S, Nishi N, Terao A: Prevalence of asymptomatic carotid atherosclerotic lesions detected by high-resolution ultrasonography and its relation to cardiovascular risk factors in the general population of a Japanese city: The Suita study. *Stroke* 28: 518–525, 1997
5. Bots ML, Breslau PJ, Briet E, de Bruyn AM, van Vliet HH, van den Ouweland FA, de Jong PT, Hofman A, Grobbee DE: Cardiovascular determinants of carotid artery disease: The Rotterdam Elderly Study. *Hypertension* 19: 717–720, 1992
6. Burke GL, Evans GW, Riley WA, Sharrett AR, Howard G, Barnes RW, Rosamond W, Crow RS, Rautaharju PM, Heiss G: Arterial wall thickness is associated with prevalent cardiovascular disease in middle-aged adults: The Atherosclerosis Risk in Communities (ARIC) Study. *Stroke* 26: 386–391, 1995
7. Allan PL, Mowbray PI, Lee AJ, Fowkes FG: Relationship between carotid intima-media thickness and symptomatic and asymptomatic peripheral arterial disease: The Edinburgh Artery Study. *Stroke* 28: 348–353, 1997
8. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson Jr SK: Carotid-artery intima and media thickness as a

- risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *N Engl J Med* 340: 14–22, 1999
9. Blankenhorn DH, Selzer RH, Crawford DW, Barth JD, Liu CR, Liu CH, Mack WJ, Alaupovic P: Beneficial effects of colestipol-niacin therapy on the common carotid artery: Two- and four-year reduction of intima-media thickness measured by ultrasound. *Circulation* 88: 20–28, 1993
  10. Kawagishi T, Nishizawa Y, Konishi T, Kawasaki K, Emoto M, Shoji T, Tabata T, Inoue T, Morii H: High-resolution B-mode ultrasonography in evaluation of atherosclerosis in uremia. *Kidney Int* 48: 820–826, 1995
  11. London GM, Guerin AP, Marchais SJ, Pannier B, Safar ME, Day M, Metivier F: Cardiac and arterial interactions in end-stage renal disease. *Kidney Int* 50: 600–608, 1996
  12. Pascasio L, Bianco F, Giorgini A, Galli G, Curri G, Panzetta G: Echo color doppler imaging of carotid vessels in hemodialysis patients: Evidence of high levels of atherosclerotic lesions. *Am J Kidney Dis* 28: 713–720, 1996
  13. Savage T, Clarke AL, Giles M, Tomson CR, Raine AE: Calcified plaque is common in the carotid and femoral arteries of dialysis patients without clinical vascular disease. *Nephrol Dial Transplant* 13: 2004–2012, 1998
  14. Malatino LS, Benedetto FA, Mallamaci F, Tripepi G, Zoccali C: Smoking, blood pressure and serum albumin are major determinants of carotid atherosclerosis in dialysis patients. CREED Investigators. Cardiovascular Risk Extended Evaluation in Dialysis patients. *J Nephrol* 12: 256–260, 1999
  15. Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME, London GM: Carotid arterial stiffness as a predictor of cardiovascular and all-cause mortality in end stage renal disease. *Hypertension* 32: 570–574, 1998
  16. Berglund GL: Ultrasound in clinical trials in atherosclerosis. *J Int Med* 236: 551–553, 1994
  17. Rossi A, Baldo-Enzi G, Calabro A, Sacchetto A, Pessina AC, Rossi GP: The renin-angiotensin-aldosterone system and carotid artery disease in mild-to-moderate primary hypertension. *J Hypertens* 18:1401–1409, 2000
  18. Sahn DJ, Demaria A, Kisslo J, Weyman A: The committee on M-mode standardization of the American Society of Echocardiography. Recommendations regarding quantification in M-mode echocardiography. Results of a survey of echocardiographic measurements. *Circulation* 58: 1072–1083, 1978
  19. Devereux B, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichelk, N: Echocardiographic assessment of left ventricular hypertrophy: Comparison to necropsy findings. *Am J Cardiol* 57: 450–458, 1986
  20. De Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, Divitiis O, Alderman MH: Left ventricular mass and body size in normotensive children and adults: Assessment of allometric relations and impact of overweight. *J Am Coll Cardiol* 20: 1251–1260, 1992
  21. Ganau A, Saba PS, Roman MJ, de Simone G, Realdi G, Devereux RB: Ageing induces left ventricular concentric remodeling in normotensive subjects. *J Hypertens* 13: 1818–1822, 1995
  22. Zoccali C, Mallamaci F, Tripepi G, Benedetto FA, Cottini E, Giaccone G, Malatino L: Prediction of left ventricular geometry by clinic, pre-dialysis and 24-h ambulatory BP monitoring in hemodialysis patients: CREED investigators. *J Hypertens* 17: 1751–1758, 1999
  23. Fermo I, Arcelloni C, Mazzola G, D'Angelo A, Paroni R: High-performance liquid chromatographic method for measuring total plasma homocysteine levels. *J Chromatogr B Biomed Sci Appl* 719: 31–36, 1998
  24. Kleinbaum DG, Kupper LL, Muller KE, Nizam A: Polynomial regression. In: *Applied Regression Analysis and Other Multivariable Methods*, 3<sup>rd</sup> edition, Pacific Grove, Duxbury Press, 1998, pp 281–316
  25. Collet D: *Modelling Survival Data in Medical Research*, London, Chapman & Hall, 1994, pp 72–85
  26. Levy D, Salomon M, D'Agostino RB, Belanger AJ, Kannel WB: Prognostic implications of baseline electrocardiographic features and their serial changes in subjects with left ventricular hypertrophy. *Circulation* 90: 1786–1793, 1994
  27. Post WS, Levy D: New developments in the epidemiology of left ventricular hypertrophy. *Curr Opin Cardiol* 9: 534–541, 1994
  28. Muiesan ML, Salvetti M, Rizzoni D, Castellano M, Donato F, Agabiti-Rosei E: Association of change in left ventricular mass with prognosis during long-term antihypertensive treatment. *J Hypertens* 13: 1091–1095, 1995
  29. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE: The prognostic importance of left ventricular geometry in uremic cardiomyopathy. *J Am Soc Nephrol* 5: 2024–2031, 1995
  30. London G, Druke TB: Atherosclerosis and arteriosclerosis in chronic renal failure. *Kidney Int* 51: 1678–1695, 1997
  31. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM: Impact of aortic stiffness on survival in end-stage renal disease. *Circulation* 99: 2434–2439, 1999