The role of parameters of arterial stiffness to prognose cardiovascular survival in haemodialysis patients: determinants and therapeutic options.

Ph. D. Thesis

Taha El Hadj Othmane, M.D.

Semmelweis University
School of Ph.D. Studies
Clinical Medicine

Tutor
Zoltán Járai, M.D., Ph.D.

Opponents
habil. Dénes Páll, M.D., Ph.D.
Gábor Földes, M.D., Ph.D.

Committee of Comprehensive Exam
Chairman: Prof. Dr. György Reusz, Ph.D. D.Sc.
Members: Dr. Katalin Farkas, Ph.D.
Dr. Katalin Keresztes, Ph.D.

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ABBREVIATIONS

ACE	Angiotensin converting enzyme
AGE	Advanced glycation end-product
AMP	Pulse pressure amplification
AI	Augmentation index
BMP2	Bone morphogenetic protein
Ca	Calcium
Ca X P	Calcium-phosphorus product
CCB	Calcium channel blockers
CKD	Chronic kidney disease
CPP	Carotis pulse pressure
CRP	C-reactive protein
CV	Cardiovascular
CVD	Cardiovascular disease
ESRD	End-stage renal disease
GFR	Glomerular filtration rate
HD	Haemodialysis
LV	Left ventricular
LVH	Left ventricular hypertrophy
MMPs	Matrix metalloproteinases
MGP	Matrix Gla protein
NO	Nitric oxide
OPG	Osteoprotegerin
P	Phosphate
PD	Peritoneal dialysis
pmp	per million population
PP	Pulse pressure
PWV	Pulse wave velocity
PTH	Parathyroid hormone
RAAS	Renin-angiotensin-aldosterone system
RANK	Receptor activator of NF-kB
RANKL	Receptor activator of NF-kB-ligand
RRT	Renal replacement therapy
TGF	Transforming growth factor
VSMC	Vascular smooth muscle cell

1. BACKGROUND

1.1. End-stage renal disease

There are two types of kidney failure: acute and chronic. Acute kidney failure is a temporary decline in kidney function that can most often be corrected. Chronic kidney failure, on the other hand, is a permanent condition, meaning that once it occurs, the kidneys cannot be made to function again. Patients with chronic renal failure, in whom glomerular filtration rate (GFR) is less than 15 ml/min/1.73m^2, are referred to as having end-stage renal disease (ESRD). The term indicates that the patient must rely on some type of medical treatment to help replace the loss of kidney function (i.e. dialysis or transplantation).

Simply, "ESRD is that stage of the impairment of kidney function which is irreversible, cannot be controlled by conservative therapy alone, and requires dialysis or kidney transplantation to maintain life".

The relationship between the prevalence of earlier stages of chronic kidney disease (CKD) and the incidence of ESRD is complex. Stein *et al* demonstrated that the prevalence of CKD has increased moderately while the incidence of ESRD has increased dramatically during the last decades [1]. This was probably caused by the increased prevalence of diabetes, hypertension and obesity, decreased cardiovascular (CV) mortality allowing more patients with CKD to live long enough to reach ESRD and by widened enrolling criteria for renal replacement therapy (RRT).

1.1.1. Epidemiology of ESRD

The number of patients treated for ESRD worldwide has continued to grow at an annual global average rate of 7% over the last 10 years [2,3], exceeding the growth rate of the general population. This continued growth is contributing by such factors like the universal aging of populations, multi-morbidity, higher life-expectancy of treated ESRD patients and increasing access of a generally younger patient population to treatment in countries where access was previously limited [4]. Aileen *et al* used data from 122 countries supplied by Fresenius Medical Care to provide a comprehensive overview of treated ESRD patient numbers for the year 2004, both globally and for various

geographical regions [5, 6] (Table 1.). The assessment demonstrated that almost 1.8 million patients were treated for ESRD globally at the end of 2004 and around 1.4 million were on dialysis treatment. These numbers are 20% higher than those reported in the equivalent assessment accomplished for the year 2001 [3] and represent an annual growth of about 6% compared with the year 2003. The highest prevalence values of ESRD and hemodialysis (HD) were in Japan and North America with 2045 and 1505 per million population (p.m.p.), respectively.

Table 1. Global and regional overview of ESRD, dialysis and transplant patient numbers and prevalence values per million population at year-end 2004.

patient numbers (n)					Prevalence values (p.m.p.)			
ESRD	Dialysis		Transplant		ESRD	Dialysis		Transplant
	HD	PD				HD	PD	
1783000	1222000	149000	412000	Global	280	190	25	65
492000	306000	31000	154000	North America	1505	940	95	470
473000	291000	33000	149000	Europe	585	360	40	185
261000	238000	10000	13000	Japan	2045	1865	80	100
237000	166000	30000	41000	Asia (excl. Japan)	70	50	10	10
205000	129000	41000	35000	Latin America	380	240	75	65
61000	55000	2000	5000	Africa	70	65	<5	5
54000	37000	2000	15000	Middle East	190	130	10	55

ERSD: end-stage renal disease, HD: haemodilysis, PD: peritoneal dialysis, p.m.p: per million population

(Nephrol Dial Transplant, 2005; 20: 2587–2593)

According to these calculations and taking into consideration the respective 2003–2004 growth rates, one can expect the number of dialysis patients to approach 2 million by the year 2010. Over this, the number of worldwide ERSD patients has surpassed the 2 million at the end of 2006 and around 1.55 million were on dialysis treatment (table 2.). The annual increase rate of the number of ESRD and HD patients in 2006 was about 6%, equal to rate evaluated in 2004 [7].

Table 2. **The number and annual increasing rate of ERSD with distribution of RRT in 2006.**

	number (million)	annual increasing rate (%)
general population	6500	1.2
ESRD	2.02	~ 6
HD	1.38	~ 6
PD	0.17	~ 6
transplant	0.47	~ 6

ESRD: end-stage renal disease, HD: haemodialysis, PD: peritoneal dialysis, RRT: renal replacing therapy

(EuCliD-medical registry, www.fresenius.hu/esrd/index.html)

In the *United States*, the number of patients enrolled in the ESRD Medicare-funded program has increased from approximately 10,000 in 1973 to 506,256 as of December 31, 2006 [8]. In 2006 alone, 110,854 patients entered the US ESRD program.

The average prevalence of both treated ESRD and dialysis in the *European Union* was lower than in North America and Japan (table 1.). In addition, considerable intra-regional variations were reported. In the year 2006, ERA/EDTA renal database [9] has shown that the highest ESRD prevalence rates were in Portugal, France, Spain and Italy (1371.9, 1011.5, 939 and 817 p.m.p, respectively). On the other hand Bolelaw *et al* demonstrated that epidemiology of ESRD in Central and East European countries (e.g. Hungary) seems to be similar to that in Western Europe (table 3.) [10].

Table 3. Epidemiology of ESRD in Central and East Europe (2005)

country	ERDS patients on RRT (p.m.p.)		
	incidence rate	prevalence rate	
		total	HD
Bulgaria	85	391	340
Belarus	57	174	158
Croatia	144	836	670
Hungary	134	579	509
Lithuania	95	463	343
Romania	86	321	281
Serbia	95	306	284

ERSD: end-stage renal disease, HD: haemodilysis, p.m.p: per million population (Blood Purif 2008; 26:381–385)

(Blood Purif 2008;26:381–385)

1.1.2. Etiology of ESRD

There are many potential causes of CKD leading to the development of ESRD (table 4). The major causes of ESRD in many countries are diabetes and hypertension, which together account for almost 60% of ESRD patients on dialysis.

Table 4. Major Causes of CKD leads to ESRD

Chronic tubulointerstitial nephropathies	(hypertension, nephrosclerosis)
Glomerulopathies (primary)	
Glomerulopathies associated with systemic disease	(Diabetes mellitus)
Hereditary nephropathies	(Polycystic kidney disease)
Obstructive uropathy	
Vasculopathy of renal arteries and veins	

Am J Kidney Dis 1998; 32 [Supp1]: 38-49.

In the United States, diabetes is the most frequent cause of ESRD, followed by hypertension, glomerulonephritis, others (interstitial nephritis, vasculitis, eg), unknown, cystic diseases and urological diseases [11]. In young patients (<20 years), the most common diagnoses are glomerulonephritis and cystic/hereditary/congenital diseases, whereas diabetes is rare. The incident rates of ESRD between 2000-2006 by diabetes, hypertension, glomerulonephritis and cystic kidney were 3.7 %, 6.7 %, -15.6 % and 9.9 %, respectively. In 2006 the rate of incident ESRD cases due to diabetes increased while the rate of ESRD caused by glomerulonephritis continued to fall [8].

In the *European Union* countries, the incidence of ESRD due to diabetes, hypertension and renal vascular disease nearly doubled over 10 years between 1990-1999 [12]. All European countries studied reported a much lower incidence than has been reported for the white population of the US [12]. Diabetes was a cause of ESRD in 28.8% of German patients, the percentage was considerably lower in Italy, Spain, and the UK (between 20.1 and 21.7%) and only 15.3% in France [13].

1.1.3. Cardiovascular complications in ERSD

Cardiovascular complications, including heart failure, myocardial ischaemia and infarction, stroke and peripheral artery disease, represent the leading cause of morbidity and mortality in the patients with ESRD [11] and are characterized by several cardiac and arterial disorders such as left ventricular hypertrophy (LVH), arterial stiffening, plaque formation, endothelial dysfunction and inflammation. A prospective study (Dialysis Morbidity and Mortality Study) of ESRD patients on HD found the *incidence* of acute coronary syndromes, chronic heart failure, stroke, and peripheral artery disease to be 10.2, 13.6, 2.2, and 14%, respectively [14]; that is a magnitude higher than in the general population. From large databases of ESRD patients, the *prevalence* of coronary artery disease, chronic heart failure and peripheral vascular disease are 36, 39, and 22%, respectively [14]. The high incidence and prevalence of CVD in ESRD make it primarily important to identify the significant risk factors that play a role in the development of CVD, in order to determine and apply appropriate interventions.

Risk factors for CV events in patients with ESRD can be divided into traditional and nontraditional risk factors. The latter group of risk factors is either unique to

patients with ESRD or significantly different from the general population (table 5.). The ***traditional risk factors*** (advanced age, male gender, diabetes, hypertension, dyslipidemia, tobacco consumption, obesity, sedentary lifestyle, and family history of chronic heart disease) show increased prevalence in patients with CKD, and contribute to risk in this population.

Table 5. Traditional and non-traditional risk factors of CV events in patients with ESRD.

Traditional	*Non-traditional*
Advanced age, Male gender, Diabetes mellitus, Hypertension, Dyslipidemia, Tobacco consumption, Obesity, Sedentary lifestyle, Family history of CHD	Inflammation and CRP, Oxidative stress, Nitric oxide availability, Hyperhomocysteinemia, Hyperphosphatemia, Vascular calcification, Increased vascular stiffness, Left ventricular hypertrophy, Anemia, Endothelial dysfunction, Volume overload, Electrolyte imbalance, Timing of dialysis

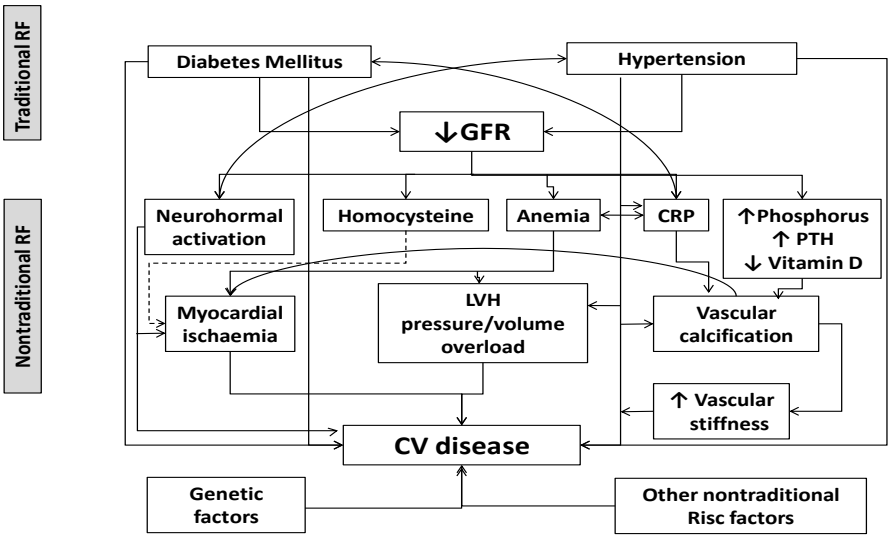
CRP: C-reactive protein, CHD: chronic heart disease

Since traditional risk factors fail to fully account for the elevated CV risk in ESRD, there has been a great deal of interest lately in emerging ***nontraditional risk factors*** that are unique to this population (vascular calcification, increased vascular stiffness, inflammation and C-reactive protein (CRP), oxidative stress, nitric oxide (NO) availability, hyperhomocysteinemia, hyperphosphatemia, LVH, anemia, endothelial dysfunction, volume overload, electrolyte imbalance, and timing of dialysis) [16], hoping that modulation of these factors might improve outcome in ESRD. The association between ERSD and CV events is demonstrated in figure 1.

Arterial calcification occurs in two distinct forms: intimal and medial calcification. Although ESRD patients have intimal atherosclerotic calcifications, they also have calcifications that involve vascular media (Mönckeberg's sclerosis) promoting arterial stiffness and progressive loss of the cushioning function of blood vessels. The increased calcium-phosphorus product (Ca X P) and parathyroid hormone (PTH) are raised as pro-calcific factors inducing and assisting ***vascular calcification*** of the coronary, central and peripheral arterial system. CRP, which is 10-fold higher in ESRD

than in normal population, may also have a role in the development of vascular calcification in ESRD by closing the loop between inflammation and atherosclerosis [17,18].

Figure 1. The association between ERSD and CV events.



CV: cardiovascular, RF: risk factor, LVH: left ventricular hypertrophy, CRP: C-reactive protein, GFR: glomerular filtration rate.

(J Am Coll Cardiol 2009;53:2129–40)

Patients with ESRD have increased prevalence of ***LVH*** [19]. Calcification and arterial stiffening predisposes to LVH by diminishing arterial distensibility and by enhancing arterial wave reflections, thus increasing the pulsatile work of the heart. Left ventricular (LV) pressure overload results from hypertension, arteriosclerosis, and aortic stenosis and causes concentric LVH. LV volume overload results from salt and water overload, anemia, and the arteriovenous fistula and causes eccentric LVH. Initially, LVH is adaptive in both types of overload, but eventually becomes maladaptive, and harmful because of myocyte death, decreased capillary density, increased myocardial fibrosis, diastolic dysfunction, and LV conduction abnormalities. These changes induce LV dilation with compensatory LVH. Eventually, beside diastolic dysfunction systolic dysfunction also occurs, which leads to ***heart failure,*** the most common CV disease in ESRD [20]. Calcification predisposes to ***ischemic heart disease*** in ESRD through impaired diastolic coronary circulation caused by early wave reflection and LVH-induced decreased subendocardial coronary perfusion [20]. Patients with ESRD have also an increased prevalence of ***complex ventricular arrhythmias*** [21], ***atrial***

fibrillation, ***mitral annular*** [22] and ***aortic valve calcification*** [23] contributing to increased CV morbidity and mortality.

1.1.4. Mortality in ESRD

Mortality in ESRD patients is staggering, reaching about 15-25% per year. The distribution of the causes of mortality is shown in table 6. Data from US Renal Data Systems has highlighted the persistent high mortality rate in ESRD patients in the first year of their life on dialysis (20-23%) [24]. In a study by Held *et al* [25] the risk of mortality for patients on HD in the United States was 15% higher than the risk in Europe and 33% higher than that in Japan. In Europe, differences in mortality suggest a north–south gradient [26]. Several reasons might be responsible for the discrepancy in mortality rates: different way in treatment, patients in the United States are older and have higher burden of comorbidities [27]. Furthermore, the sum of all the geographical, environmental, cultural, and socioeconomic effects is unique to the given area and manipulates the discrepancy between regions.

Table 6. Distribution of the causes of death in patients with ESRD in the United States between 2003 and 2005.

Cause of death	*Distribution percentage (%)*	
Cardiovascular	45	
	Myocardial Infarction	9
	Sudden Cardiac Death	26
	Cerebrovascular Disease	4
	Other Cardiovascular	6
Infection	14	
Malignancy	4	
Withdrawal from dialysis	3	
Other	34	

USRDS 2007 Annual Data Report

Cardiovascular disease is the leading cause of death both in the general and in the ESRD population. Furthermore, CV mortality in ESRD patients has been reported to be 10–20 times higher than that of the general population which is attributed to a higher prevalence of certain traditional risk factors and other causes that are unique to the ESRD. In ESRD the CV mortality accounts for 45% of all-cause mortality [28] of which sudden cardiac death constitutes 62% [24,29]. The mortality of patients with ESRD is also higher than that of patients after incident myocardial infarction, after

undergoing percutaneous coronary intervention, after coronary artery bypass grafting, even after insertion of an implantable cardiac-defibrillator or after stroke [8,30,31]. Moreover, it seems that interventions fail to improve CV mortality in ESRD.

1.2. Arterial stiffness

The arterial system consists of the large elastic arteries (thoracic aorta, carotid arteries), the more muscular conduit peripheral arteries (i.e. iliac, brachial, radial and femoral arteries) and the arterioles. The arterial wall consists of three concentric layers: the tunica adventitia, tunica media, and tunica intima. There is a single layer of endothelial cells between the blood and the vessel wall. The wall of large arteries is rich in elastin and collagen while that of small muscular arteries is rich in vascular smooth muscle. Elastin fibres play an important part in determining the mechanical strength of the vessels at lower pressures and collagen fibres bear most of the strength at the higher pressures. Large elastic arteries such as the aorta buffer flow and pressure variations generated by the intermittent LV contraction and convert pulsatile variations into steady values to the periphery. This cushioning function provides continuous oxygenation to the tissues and cardiac work. Elastic recoil of the central arteries in diastole is important for coronary perfusion and for diastolic blood flow to other organs as well. Loss of elasticity impairs coronary flow and may contribute to coronary artery disease and also leads to pulsatile stress to peripheral organs such as the brain and the kidneys.

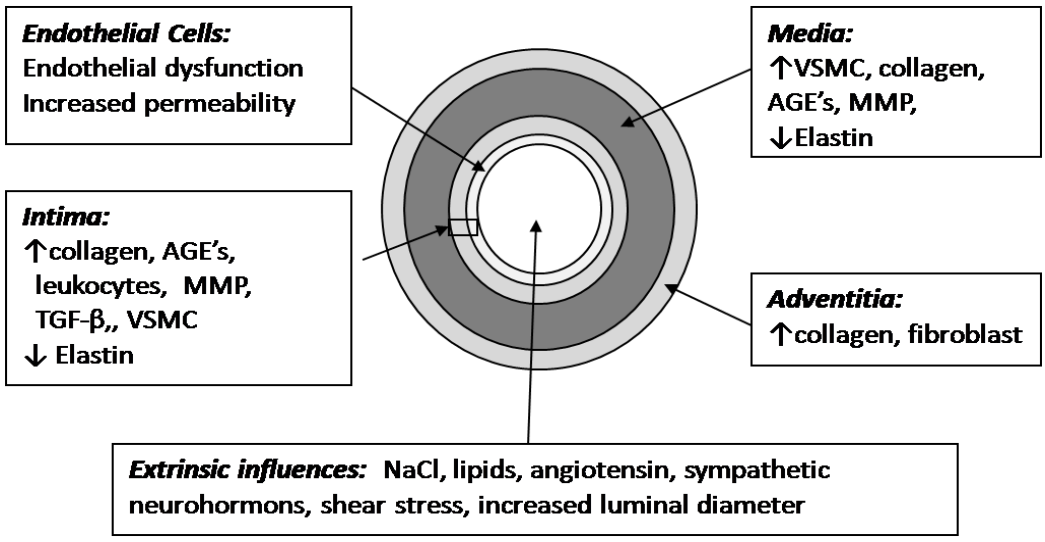
Epidemiological studies have drawn attention to the relationship of systolic pressure and pulse pressure (PP) to morbid and fatal CV events and have thus emphasized that blood pressure abnormalities characterizing hypertension and determining its CV complications originate not only from an increase in vascular resistance but also from an increase in central arterial stiffness. “Arterial stiffness” is a generic term, which simply describes the rigidity of the arterial wall. Increased central arterial stiffening is a hallmark of the aging process and the consequence of many disease states such as diabetes, atherosclerosis, CKD, also a marker for increased CVD risk, including myocardial infarction, heart failure, and total mortality, as well as stroke, dementia and worsening of kidney function.

Stiffness is not uniformly disseminated throughout the vascular tree but is often patched occurring in central and conduit vessels while sparing peripheral arteries. Diseases, such as hypertension and diabetes mellitus, or simply aging itself, amplify the vascular changes that induce artery stiffening and can do so in different, yet synergistic, ways. Aging, as one of the major determinants of arterial stiffness, has different effects on arteries. While elastic arteries (aortic, carotid) stiffen progressively with age, the stiffness of muscular arteries (radial, femoral) changes little [32]. In the media of elastic arteries, the degeneration of elastic fibers is associated with an increase in collagenous material and accompanied by calcium (Ca) deposition in ground substance [33].

1.2.1. Pathophysiology of arterial stiffness

Arterial stiffening develops from complex changes involving structural and cellular elements of the arterial wall (Figure 2). These vascular changes, occurring mainly in large arteries, are highly influenced by hemodynamic forces, as well as by several factors such as salt, hormones, the 'uremic milieu' and glucose.

Figure 2. Summary of the multiple causes of arterial stiffness.



VSMC: vascular smooth muscle cell, AGE's: advanced glycation end products, MMP: matrix metalloproteinase, TGF-β: transforming growth factor.
(*Arterioscler Thromb Vasc Biol*. 2005;25:932-943.)

Structural Components of Arterial Stiffening

The functional characteristics of the vascular wall are dependent on the balance of relative amount of ***collagen and elastin*** which is regulated by a slow, but dynamic process of production and degradation. Dysregulation of this balance, mainly by inflammation, leads to overproduction of abnormal collagen and less production of normal elastin, which contribute to vascular stiffness [34]. This leads to an impressive increase of intima-media thickness and developing of a hypertrophied smooth muscle stratum [35]. Histology of the intima of stiff arteries reveals abnormal endothelial cells, increased collagen, broken elastin, infiltration of smooth muscle cells, macrophages and mononuclear cells, and increased matrix metalloproteinases (MMPs), transforming growth factor (TGF)-β, intracellular cell adhesion molecules and cytokines [36].

Collagen molecules provide the tensile strength of the vessel wall and are enzymatically cross-linked soon after their formation to render them insoluble to hydrolytic enzymes [37]. Breaks in the integrity of these intermolecular bonds cause unraveling of the collagen matrix. Elastin is also stabilized by cross-links; disruption of which results in the weakening of the elastin array. Collagen and elastin are regulated by the catabolic effect of ***MMPs*** which degrade the extracellular matrix, resulting in structurally abnormal collagen and elastin molecules. Vascular cells and inflammatory cells produce various types of MMPs [38]. Activation of MMPs leads to frayed and broken elastin fibers which results in a predisposition to mineralization of the vessel wall due to calcium-phosphate (Ca-P) salts deposition, a phenomenon apparent at older ages and more prominent in ESRD patients [39,40]. In fact, arterial calcification is a major contributor to arterial stiffness in ESRD patients (to be discussed later).

Increased advanced glycation endproducts (***AGEs***) formation (a frequent feature of CKD and diabetes) plays a central role in arterial stiffening. Non-enzymatic glycation establishes irreversible cross-links in collagen [41] and leads to a stiffer vessel wall [42]. The elastic matrix of the vessel wall is reduced by AGE cross-linking of elastin [43]. These alterations, observed with aging, and more prominent in ESRD, where the accumulation of AGEs and their receptor is observed [44]. Through their receptor, AGEs stimulate inflammatory responses, and increase the formation of free oxygen radicals, pro-inflammatory cytokines, growth factors, nuclear factor-κB, and vascular

adhesion molecules [45]. The consequences of these alterations are endothelial dysfunction, impaired endothelial-mediated vasodilatation, elevated vascular smooth cell (VSMC) tone, angiogenesis and change in the phenotype of the VSMC [46].

Cellular Mechanism in Arterial Stiffening

In addition to structural changes, arterial stiffness is deeply influenced by ***VSMC*** tone and endothelial function. VSMC tone can be modified by mechanostimulation (as in hypertension), due to the cell stretch and changes in Ca signaling, and by paracrine mediators such as angiotensin II [47], endothelin [48], oxidative stress [49], and NO. ***Endothelial dysfunction*** is evidenced clinically by an impaired vasodilatory response to acetylcholine [50]. This stems, in part, from an imbalance between NO and endothelial-derived hyperpolarizing factor and constricting hormones, and oxygenases (eg, cyclooxygenase, NADPH, and xanthine oxidase) [51]. NO expression may itself be reduced [52], and increased expression of a natural NO synthase inhibitor, asymmetrical dimethylarginine, has been linked to vascular stiffening [53]. Bioavailability of NO is also reduced by activation of reactive oxygen species caused by stress, hormones, and likely AGEs [54].

Glucose, Insulin, and Vascular Stiffening

In patients with diabetes and metabolic syndrome, arterial stiffening is consistently observed across all age groups. A core feature appears to be insulin resistance, because central arterial stiffness and insulin resistance are positively correlated [55,56]. Chronic hyperglycemia and hyperinsulinemia increases the local activity of the renin-angiotensin-aldosterone system (RAAS) and expression of angiotensin type I receptor in vascular tissue [57], promoting development of wall hypertrophy and fibrosis [58,59]. Hyperinsulinemia itself has proliferative effects [60]. Impaired glucose tolerance also enhances nonenzymatic glycation of proteins with covalent cross-linking of collagen (AGEs) and alters the mechanical properties of interstitial tissue of the arterial wall [61]. Stiffness is further increased by endothelial dysfunction caused by high LDLs, free fatty acids [62], endothelin-l, inadequate vasodilatory effects of insulin, or decreased levels of adiponectin [63] and natriuretic peptides [64].

Genetics of Vascular Stiffening

Genetic polymorphisms have been identified to be associated with increased arterial stiffening. For example, variations in arterial stiffness have been related to gene polymorphisms in angiotensin-converting enzyme, angiotensin type I receptor [65], endothelin A and B receptor [66], collagen-Iα1 [67], fibrillin-1, and IGF-1 [68]. Importantly, these studies have been generally limited by small and preselected study populations. None of these genes seems to have a major effect in the general population, which likely reflects the polygenic and multifactorial nature of arterial stiffness [69].

Renin-Angiotensin-Aldosterone System and Salt

Many hormones are known to modulate vascular stiffness. ***Angiotensin II*** (AII) stimulates collagen formation, triggers matrix remodeling and vascular hypertrophy, depresses NO-dependent signaling, increases oxidant stress, and reduces elastin synthesis [47]. ***Aldosterone*** synthesis is primarily controlled by the action of AII on angiotensin type I receptor, and also promotes vascular stiffness and hypertension by stimulating VSMC hypertrophy, fibrosis, and fibronectin [70]. High ***NaCl*** induces VSMC hypertrophy, augments collagen and elastin production [71,72], and interacts with genetic polymorphisms for genes such as angiotensin type I receptors, NO, and aldosterone synthase [73,74]. Sodium also impairs endothelial function by reducing the production of NO by stimulating NO synthase inhibitor [75].

Hemodynamic Forces

In arteries, the impact is primarily related to changes to mechanical vascular stimulation caused by increased pulsatile shear and pressure [76,77]. Increased luminal pressure or hypertension stimulates excessive collagen production [78]. Local regions near bifurcations have more turbulent flow and suffer higher amplitude of oscillatory shear stress, magnifying endothelial dysfunction and vascular disease [79].

Pathophysiological conditions associated with increased arterial stiffness

A large number of publications and several reviews reported the various pathophysiological conditions associated with increased arterial stiffness (Table 7). The contribution of these different factors to arterial stiffness has been studied in multivariate analyses: the major parameters to be taken into account, when evaluating

the degree of arterial stiffness, are age and blood pressure and, to a lower extent, gender and classical CV risk factors [80].

Table 7. Clinical conditions associated with increased arterial stiffness and/or wave reflections

Aging	***CV risk factors***	***CVD***
Other Physiological conditions	Obesity	Coronary heart disease
Low birth weight	Smoking	Congestive heart failure
Menopausal status	Hypertension	Fatal stroke
Lack of physical activity	Hypercholesterolaemia	***Primarly non-CVD***
Genetic background	Impaired glucose tolerance	ESRD
Parental history of hypertension	Metabolic syndrome	Moderate CKD
Parental history of myocardial infarction	Type 1 diabetes	Rheumatoid arthritis
Genetic polymorphism	Type 2 diabetes	Systematic vasculitis
	Hyperhomocysteinaemia	Lupus erythematosus
	Higy CRP level	

European Heart Journal (2006) 27, 2588–2605

1.2.2. Measurement of arterial stiffness

Arterial stiffness can be measured noninvasively at the systemic (systemic compliance), regional (between two arterial sites, most frequently between the carotid–femoral arteries) or local level (common carotid artery or any peripheral artery). In contrast to systemic arterial stiffness, which can only be estimated from models of the circulation, regional and local arterial stiffness can be measured directly, and noninvasively, at various sites along the arterial tree. The commercially available, frequently used devices to measure local, regional or systemic arterial stiffness are demonstrated in table 8.

1.2.2.1. Local determination of arterial stiffness

Local arterial stiffness can be measured by using ultrasound devices in the case of superficial arteries and by magnetic resonance imaging (MRI) in the case of deep arteries. However, most of studies have used echotracking techniques.

Ultrasound-derived indices

The use of ultrasound to measure arterial stiffness (distensibility and compliance) is limited to the larger and more accessible arteries; mainly on the brachial, femoral and carotid arteries and the abdominal aorta. Several images of the vessel wall are obtained per cardiac cycle, and the maximum and minimum areas of the vessel are

calculated by wall tracking or computerized edge-finding software. Compliance calculated as ΔV (change in volume) /ΔP (change in pressure) and blood pressure is usually measured simultaneously in the brachial artery. Problems with some of this method are the limited resolution only for edge-finding! (difficult to detect small changes in vessel diameter) and the relying on the ability of the operator to image the walls. The use of ultrasound in determining arterial stiffness has been largely confined to research setting to date.

MRI-derived indices

MRI techniques also used to measure aortic distensibility and compliance in many human studies; demonstrated the inverse relationship between aortic distensibility and age. Although it has the advantage of being noninvasive, it remains expensive and the availability of scanning facilities is limited. Therefore, the role of this technique in clinical practice is doubtful, although it continues to be used in research.

Table 8. Commercially available devices to measure local, regional or systemic arterial stiffness

Device (company)	Technique	Local, regional or systemic	Outcome measure
NIUS 02 (Asulab)	Simultaneous detection of diameter and pressure waveform using the RF-signal of an ultrasound system	Local	Distensibility, elastic modulus and compliance index
WallTrack system (Pie Medical)	Simultaneous detection of diameter and pressure waveform using the RF-signal of an ultrasound system	Local	QCS
Sphygmocor (Atcor Medical)	Pressure wave detection with applanation tonometry	Regional, systemic	PWV, AI and central arterial PP
Pulse trace system (Micromedica)	Digital volume wave detection with photoplethysmography	Systemic	SI
Pulse Wave CR2000 (Hypertension Diagnostic)	Pressure wave detection with a piezoelectric sensor	Regional, systemic	C1 and C2
PulsePen (DiaTecne)	Pressure wave detection with applanation tonometry	Regional, systemic	PWV, AI and central arterial PP
PeriScope (Genesis Medical Systems)	Oscillometric pressure wave detection	Regional	PWV
Complior (ArtecMedical)	Pressure wave detection with mechanotransducer	Regional, systemic	PWV, central arterial PP and SI
AT-form PWV/ABI(Colin Co.)	Volume plethysmography	Regional	abPWV
Arteriograph (Tensiomed)	Oscillometric pressure wave detection	Regional	PWV, AI

abPWV: ankle-brachial PWV, *QCS:* quality carotid stiffness, *SI*: stiffness index, *C:* compliance, *PP:* pulse pressure

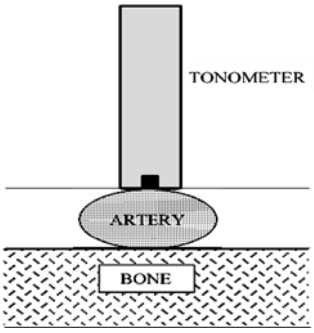
1.2.2.2. Regional measurements of arterial stiffness

The aorta is a major vessel of interest when determining regional arterial stiffness for at least two reasons: the aorta makes the largest contribution to the arterial buffering function and aortic pulse wave velocity (PWV) is an independent predictor of outcome in a variety of populations.

Arterial Tonometry:

The technique of arterial tonometry is increasingly used in clinical studies. The tonometer is similar to that used by ophthalmologists to record eyeball pressure. When applied over the examined artery so as to flatten the anterior wall, recordings of the pulse waveform are substantially similar to those recorded by a catheter within the artery (Figure 3). Clinical emphasis has been on the carotid waveform; since it is similar to the aortic waveform-be more exact-. Femoral artery tonometry is used only for the measurement of the delay in wave foot, and so to determine carotid-femoral PWV as an index of aortic stiffening.

Figure 3. Principle of applanation tonometry



The artery is gently compressed against the underlying bone, thus flattening it and equalizing circumferential pressures, allowing a high-fidelity pressure waveform to be recorded with the tonometer.
(Q J Med 2002; 95:67–74)

Carotid and femoral pulse waves can be recorded *simultaneously* by such device as Complior (Colson, Garges les Genosse, France) in which two pressure transducers are used and the transit time between the two recording points is calculated by the device. Waves can also be recorded *sequentially* by such devices as SphygmoCor (AtCor Medical, Sydney, Australia) and PulsePen (DiaTecne, Milan, Italy). Carotid–femoral PWV is measured in two steps; in the first one, carotid pulse wave and ECG, in the second one, femoral pulse wave and ECG are recorded simultaneously. ECG recording is necessary to synchronize carotid and femoral pulse wave travel times. Transit time (Δt) between the two waves is calculated using the foot-to-foot method,

while distance between the two recording sites (Δd) is measured directly on the body surface. Carotid-femoral PWV is then calculated as (Δd/Δt)

Arterial oscillometry:

The main principle of PWV estimation behind oscillometric method (i.e. Arteriograph; TensioMed, Budapest, Hungary) is to record oscillations detected on the upper-arm cuff by a special sensor. Measurements are performed when cuff pressure exceeds systolic BP by 35–40 mmHg, with a completely occluded brachial artery and pressure oscillation caused by the pressure wave during systole detected in the cuff. During systole, blood volume ejected into the aorta generates a pulse wave called '*early systolic peak'* which runs down and then reflects from the lower body creating a second wave, the *'late systolic peak'*. Return time is the difference in milliseconds between the two waves. The traveled distance is measured between the sternal notch and the pubic symphysis. Aortic PWV is calculated from pulse "return time" and the distance traveled by the pulse wave. The validity of the technique is still debated since the device detects the pressure waves at the brachial site and uses pulse wave contour analysis without the transfer function to assess aortic PWV.

Arterial Doppler probes:

Carotid–femoral PWV is calculated from waves obtained successively at a short time interval at two arterial sites (common carotid and femoral artery, for instance) by the high-definition echo-tracking devices, using the R-wave of the ECG for calculating the time delay.

1.2.2.3. Systemic determination of arterial stiffness

The simplest method used for estimating systemic arterial stiffness is the measurement of brachial PP, which is accessible by calculating the difference between systolic and diastolic blood pressure. The ratio of stroke volume to PP (***SV/PP***) is an indirect measure of total arterial compliance [81], simple enough to be used in epidemiological studies and based on the principle that in a steady-state condition, the arterial tree can be modeled as an elastic chamber with a constant compliance. De Simone *et al* have shown that a reduced value of the ratio is a predictor of CV morbidity independent of age [82].

The use of methods developed for the noninvasive determination of systemic arterial stiffness in the clinical setting have been discussed and compared with the methods used for the noninvasive determination of regional stiffness [83]. Until now, they did not provide evidence, in a longitudinal study, that systemic arterial stiffness has independent predictive value for CV events [84]. A methodology based on an ***electrical circuit*** has been developed to determine a proximal capacitive compliance and a distal oscillatory compliance (HDI/PulseWave CR-2000 Research CardioVascular Profiling System; Hypertension Diagnostics Inc., Eagan, MN, USA). This technique is based on the arterial pulse recording at the level of the radial artery and identifies the reflections in diastole as a decaying sinusoidal wave.

Systemic arterial compliance can also be determined using the ***'area method'*** [84] which requires measurement of aortic blood flow (velocimeter at the suprasternal notch) and associated driving pressure by applanation tonometry over the proximal right common carotid artery. Systemic arterial compliance is then calculated as Ad/[R(Ps-Pd)] (Ad: the area under the blood pressure diastolic decay curve from end systole to end diastole, R: the total peripheral resistance, Ps: the end-systolic blood pressure, Pd: the end-diastolic blood pressure calibrated against brachial arterial pressure).

1.2.3. Parameters of arterial stiffness

There are several different parameters of describing arterial stiffness, some of which are more widely applicable in the clinical setting than others.

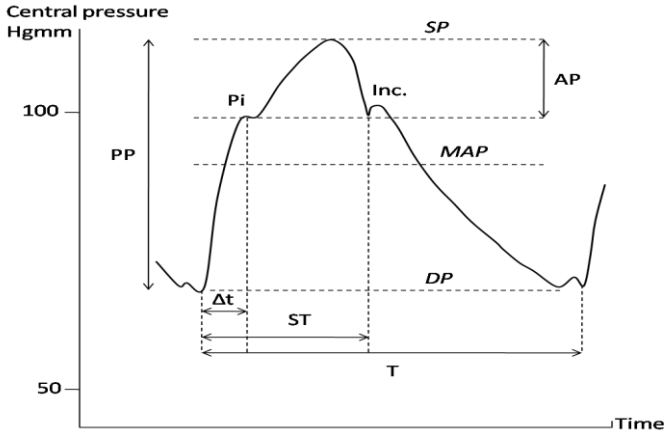
1.2.3.1. Central pulse pressure

Arterial pressure has a steady and a pulsatile component. Mean blood pressure, as the steady component of arterial pressure, provides a steady flow distribution to the tissues and organs. PP, which represents the pulsatile component of arterial pressure, is generated by intermittent ventricular ejection. The pulse wave derives from the interaction of a LV ejected forward travelling "incident" pressure wave and a late arriving reflected wave from the periphery. Thus, pulse contour is determined by the pattern of LV ejection, the magnitude of the reflected wave, the stiffness of large conduit arteries and the timing of arterial wave reflections. Wave reflection occurs

throughout the arterial tree at each branching of arteries, predominantly in the lower body at the major branches of the aorta (i.e. bifurcation) and at the border of elastic to muscular arteries: a fraction of the forward travelling pulse wave is reflected back towards the heart, where it interferes with the forward travelling wave.

A schematic representation of central (aortic, carotid) PP as a function of time is shown in figure 4. From the foot to the peak of the pressure wave two components can be distinguished: the peak forward pressure wave and the augmentation pressure. The two components are separated by inflection point (Pi), where the pressure indicates the beginning upstroke of the reflected wave. The time (Δt) to the inflection point of the first component quantifies the timing of the reflection. The characteristics of the incident wave depend mainly on LV ejection pattern and on the elastic properties of the central aorta and are not influenced by wave reflections. The characteristics of the reflected wave depend on the elastic properties of the entire arterial tree, PWV, the round-trip travel time of the wave from the heart to the periphery and back, and the distance to the major reflecting sites.

Figure 4. A schematic representation of central PP as a function of time.



***SP**, systolic pressure; **DP**, diastolic pressure; **MAP**, mean arterial pressure; **PP**, pulse pressure; **Pi**, pressure at the inflection point; **AP**, augmentation pressure (Ax = SP – Pi); **Δt**, time-to-Pi; **ST**, systolic time; **T**, heart period; **inc**, incisure (where aortic valve closes).*

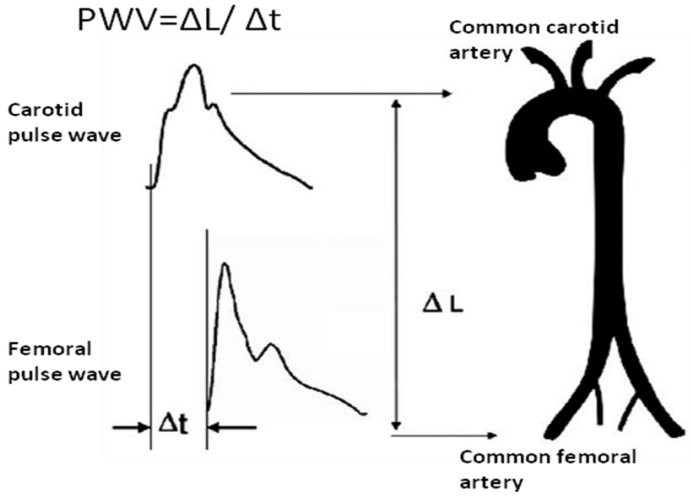
In healthy young individuals, augmentation pressure is low and weakly contributes to PP. The reflected pressure wave is rather diffuse and maintains a relatively high aortic pressure in early diastole, thus boosting coronary artery filling. In elderly individuals, the reflected pressure wave is increased and narrowed, the wave

reflection occuring mainly in systole, thus significantly contributing to PP rather than increasing early diastolic pressure. A generally accepted mechanistic view is that an increase in arterial stiffness causes a premature return of reflected waves in late systole, increasing central PP, thus systolic blood pressure. This is an effect that increases arterial wall stress, potentiates the development of atherosclerosis, elevates LV afterload, and increases LV mass and oxygen demand while decreasing stroke volume. The LV must generate more energy to overcome the increased PP with relatively less oxygen offered, leading to an increment of the development of CV events.

1.2.3.2. Pulse wave velocity

Pulse wave velocity is defined as the speed of the pressure wave travelling along an artery. PWV is calculated after arterial pressure waves have been recorded (simultaneously or sequentially) at both a proximal and a distal artery and the length of the arterial segment (*ΔL*) between the two sites has been measured with surface tape. The wave transit time (*Δt*) is obtained by using the QRS complex of a simultaneously recorded ECG as a reference frame (figure 5.).

Figure 5. Measurement of carotid-femoral PWV with the foot to foot method.



***ΔL**: distance between both measurement sites, **Δt**: transit time*

(European Heart Journal, 2006; 27, 2588–2605)

Factors that affect the value of PWV are defined by the Moens-Korteweg equation, PWV = √(Eh/2ρR), where "E" is Young's modulus of the arterial wall, "h" is wall thickness, "R" is arterial end-diastolic radius, and "ρ" is blood density [85]. Large studies proved that aortic stiffness assesed by carotid-femoral PWV is an independent

predictor for all-cause and CV mortality, coronary events, and fatal strokes in patients with uncomplicated essential hypertension, type II diabetes, ESRD, elderly subjects and general population [80,86].

In addition to carotid-femoral, other regions have also been measured for PWV, such as brachial-ankle, aortic-femoral, and femoral-tibial. Brachial-ankle PWV has brought considerable attention as a biomarker to monitor advanced clinical and subclinical atherosclosis largely based on clinical studies in Japanese populations [87]. Aortic PWV has been most widely used due to its reflection of large elastic artery stiffness in comparison of brachial-ankle PWV determined partly by peripheral artery stiffness [88]. In addition, branchial-ankle PWV measurement is closely dependent on blood pressure.

In 2006, the European expert consensus document on arterial stiffness considered the *carotid-femoral PWV as the 'gold standard'* measurement for arterial stiffness, which has the largest amount of epidemiological evidence for its predictive value for CV events, and requires little technical expertise [80].

Among physiological factors, PWV is positively associated with blood pressure and ageing [89]. The relationship between PWV and heart rate is a little less clear. Some cross-sectional studies have shown no association between the two, but others have indicated that PWV does vary with heart rate [90]. Studies using pacing to alter heart rate have also shown conflicting results.

1.2.3.3. Pulse Pressure Amplification

. While mean arterial pressure is relatively stable along the arterial tree until the level of arterioles, PP increases markedly from central (thoracic aorta, carotid arteries) to peripheral (brachial, radial) arteries [91]. It has been found, using invasive hemodynamic methods, that radial - aortic pressure difference of normotensive subjects aged 48–77 years approximates -0.8 mmHg for mean arterial pressure, -1 mmHg for diastolic blood pressure and +12 mmHg for systolic blood pressure [92]. The increase in PP is due to a significant increase in systolic blood pressure together with a small lowering of diastolic blood pressure. This phenomenon, observed both in normotensive

and hypertensive subjects, is called pulse pressure amplification (AMP). AMP is the consequence of the progressive reduction of diameter and increase in stiffness from proximal to distal arteries, and is also modified by the timing and amount of wave reflection [93]. Amplification varies with physiological maneuvers, such as change in body position, or with Valsalva maneuver and decreases with the reduction of heart rate.

Pulse pressure in younger normal subjects (≤50 years) increases markedly on going from the central to the peripheral arteries. Carotid pulse pressure (CPP), which is almost identical to aortic PP, is lower than the brachial, radial and femoral PPs, with the higher values observed at the site of femoral artery [94]. The magnitude of PP in older subjects (>50 years) is greater than that in younger subjects and tends to be quite similar in all parts of the arterial tree [92]. Indeed, CPP increases more with age than femoral PP does [32]. This disproportional increase in central PP (and hence decreased in amplification) is a consequence of decreasing of the aorta with age and more contribution of the reflected wave to central PP. According to the 'amplification phenomenon', the amplitude of the pressure wave is greater in peripheral arteries than in central arteries, and brachial PP overestimates central PP in young individuals. For opposing reasons, brachial PP underestimates central PP in some elderly individuals.

Several methods of evaluating AMP are known (Table 9). Among these, calculating the ratio of peripheral to central PP is the most frequently used one in the clinical measurements.

Table 9. Methods of evaluating AMP.

AMP		*equation*	*reference*
absolute	(mmHg)	peripheral PP – central PP	95
ratio		peripheral PP / central PP	96
absolute ratio	(%)	(peripheral PP – central PP) / peripheral PP	97
percent	(%)	(peripheral PP / central PP) – 1 * 100	98

***PP**: pulse pressure, **AMP**: pulse pressure amplification*

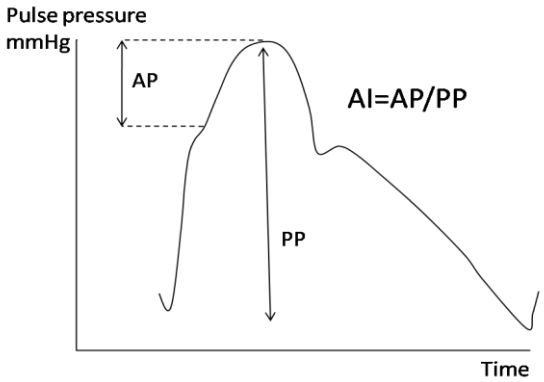
1.2.3.4. Augmentation Index (AI)

Near the aortic root, the initial pressure following LV ejection is rapidly superimposed with a reflected pressure wave returning from the periphery [99], the start of this reflected wave is visible on the measured waveform as an inflection point. AI is a

mathematical expression of the increment in pressure after the first systolic shoulder to the peak of the aortic pressure is calculated as a percentage of PP [100] (figure 6). In waveforms obtained from distensible arteries, augmentation is negative and follows an inflection in late systole close to the incisura and extends into diastole. In those obtained from stiffer arteries, the inflection occurs early in systole, the boost to pressure is positive. 2 figures should be presented for demonstration.

Augmentation index is affected by multiple factors such as LV ejection, PWV, timing of reflection, arterial tone, structure at peripheral reflecting sites, BP, age, gender, height and heart rate. McEniery et al. [101] studied normal vascular aging and found that AI increased significantly with age. The effect of alteration in heart rate on AI has been investigated. A significant linear relationship between the two parameters has been reported (r=−0.76) [102]: for every 10 beats/min increase in heart rate, AI fell by approx. 4%. This finding has been replicated in several studies.

Figure 6. Determination of the Augmentation Index (%)



***AP**: augmentation pressure, **PP**: pulse pressure*

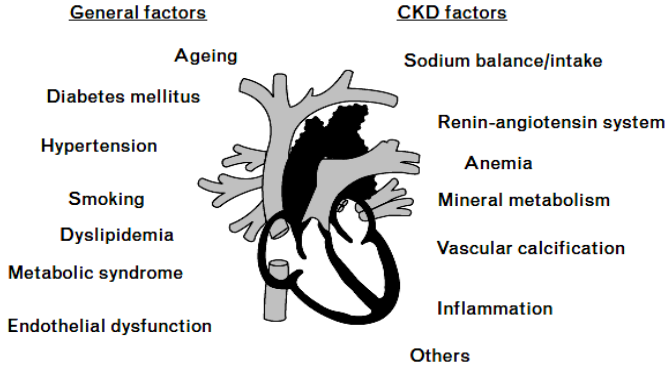
(Current Opinion in Cardiology 2005, 20:275—281)

Augmentation index must be calculated from a central arterial waveform. This may be obtained by direct carotid tonometric measurements or from analysis of pulse wave obtained at more distant sites (i.e. radial artery as used in the Sphygmocor device) by applying mathematical transfer function that transforms the peripheral pulse wave into central arterial waveform [103].

1.3. Arterial stiffness and ESRD

Increased arterial stiffness is observed in patients on HD. In ESRD arterial wall properties are influenced not only by factors such as age, genetics, hypertension, diabetes, lipid abnormalities, inflammation, or common atherosclerosis but also by factors associated with the presence of uremia (Figure 7). The most frequently observed factors associated with arterial remodeling and functional alterations in ESRD seem to be mineral metabolism modifications. In hemodialyzed patients, arterial stiffness was found to be associated with vascular calcification and worsened with the progression of calcification.

Figure 7. Factors promoting arterial stiffness in general population and in CKD



CKD: chronic renal disease.

(Curr Opin in Neph and Hypert 2007, 16:409–415)

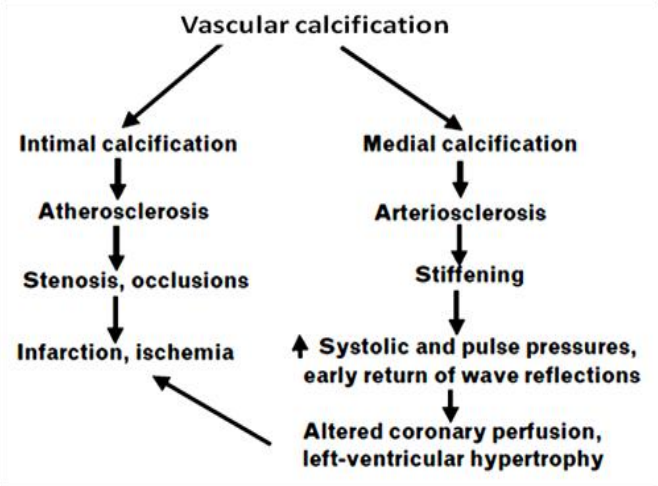
1.3.1. Mechanisms of vascular stiffness and calcification in ESRD

Mechanisms of increased arterial stiffness in ESRD include arterial calcification, chronic volume overload, increased mechanical stress by hypertension, chronic microinflammation, sympathetic overactivity, activation of the RAAS, AGEs, lipid peroxidation and abnormalities of the NO system (chapter 1.2.2.) [104]. This state is characterized by increased matrix ***collagen*** content, proliferation of ***VSMC***s and severe alteration of collagen and elastin structure by increased generation of ***AGEs*** [105]. Chronic ***overhydration*** may play an important role in dysfunction of large arteries; increased extra- to intracellular fluid ratio is associated with increased arterial stiffness [106], although volume reduction by HD is unable to decrease arterial stiffness significantly [107]. A strong relationship between stiff arteries and ***inflammation***, as assessed by serum CRP levels, has recently been found in ESRD patients [108]. The

association between abnormalities of ***lipid metabolism*** and arterial function was described in several studies; inverse correlation between PWV and HDL cholesterol levels has been reported [109, 110]. Removal of LDL cholesterol by lipid apheresis and use of vitamin E-coated HD membranes improves arterial stiffness [111]. Generalized ***endothelial dysfunction*** and decreased endothelial-dependent vasodilatation contribute significantly to arterial alterations seen in HD patients [112].

A central role among the structural changes with a strong impact on arterial stiffness in patients with ESRD is played by ***vascular calcifications***, which occurs in two distinct forms: intimal and medial calcification. ***Intimal calcification*** occurs when minerals are deposited within an atherosclerotic plaque in the intima. This progressive feature of common atherosclerosis is found in general population as well, and is not specific for ESRD. ***Medial calcification*** (Mönckeberg's sclerosis) is characterized by diffuse mineral deposits within the medial wall. While medial calcification is frequently observed with aging, it is significantly more pronounced in diabetes and ESRD. Vascular calcification leads to increased stiffening and to progressive loss of the cushioning function of the arteries, that with earlier return of the reflected pulse wave leads to increased afterload favoring LVH, and compromised coronary perfusion [113,114] contributing to increased CV morbidity and mortality in ESRD (figure 8).

Figure 8. Clinical effects of intimal and medial calcifications in ESRD

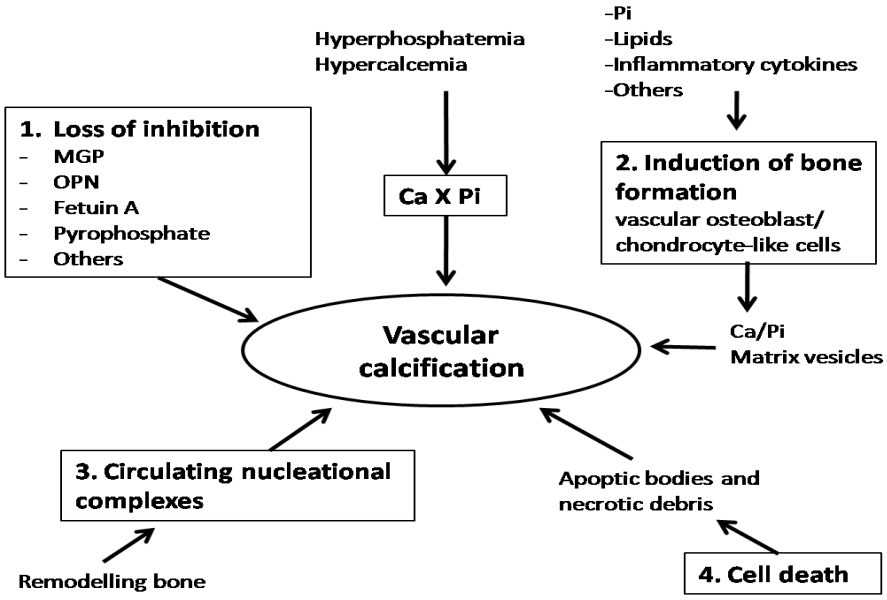


(Current Opinion in Nephrology and Hypertension 2005, 14:525–531)

Vascular calcification is the result not only of passive Ca-P deposition, but also represents an active process, similar to bone formation – 'ossification' of the vascular

wall structure [115] As shown in figure 9, four different active mechanisms for initiating vascular calcification have been proposed [116]. **First**, several study determined that blood vessels normally express inhibitors of mineralization, and that "loss of inhibition" leads to spontaneous vascular calcification [117]. **Second**, the presence of bone proteins, matrix vesicles, and bone and cartilage formation in calcified vascular lesions has suggested that osteogenic mechanisms may also play a role in vascular calcification [118]. **Third**, circulating nucleational complexes released by bone turnover have been proposed to explain the link between vascular calcification and osteoporosis in women [119]. **Fourth**, cell death (e.g. in VSMCs) can provide necrotic debris and apoptotic bodies that may serve to nucleate apatite, especially in atherosclerosis where necrosis and apoptosis are prevalent [120].

Figure 9. Schematic illustration of four theories for vascular calcification



MGP: matrix gla protein, OPN: osteopontin, Pi: phosphate, Ca: calcium.

(Cardiovascular Pathology 13 (2004) 63–70)

Finally, via "passive" mechanisms, elevated Ca, P, and Ca X P promote apatite nucleation and crystal growth and would be expected to exacerbate vascular calcification initiated by any of the other mechanisms described above. Furthermore, new evidence suggests that Ca and P may additionally have direct effects on vascular cells that predispose to mineralization. High levels of P and/or Ca are directly activating genes related to an osteoblastic phenotype in the VSMC contributing to their transformation into osteoblast like cells [115]. Increased Ca and Ca X P are important

and clinically evident contributors to vascular calcification in ESRD [121]. In the presence of a medium with high level of Ca and P, exposed VSMCs suffer rapid calcification [122] while increased intracellular P levels induce osteoblastic differentiation of vascular cells [123]. Inflammation also contributes to the calcification process [124]; pro-inflammatory cytokines have been shown to enhance in vitro calcification of vascular cells [125], suggesting a direct link between valvular calcification and inflammation in patients on dialysis [126].

Vascular calcification actually results from an imbalance between promoters and inhibitors of mineralization. Different gene products such as matrix Gla protein (MGP), fetuin-A, osteopontin, osteocalcin and the osteoprotegerin receptor activator of NF-κB (RANK)–RANK ligand (RANKL) complex may play a crucial role on modulating mineral deposition in the vessel wall [127].

Calcification promoters

Either inhibitors are deficient or absent, bone production is induced with local expression of bone proteins, circulating bone nucleation complexes settle in an arterial site or cell death occurs, all of which lead to greater Ca deposition when Ca X P is elevated [128]. Bathing cultured VSMC with increasing P concentrations in the medium leads to a loss of VSMC characteristics and to the upregulation of genes that code for the synthesis of bone tissue proteins such as ***osteopontin*** and ***osteocalcin***. This is likely mediated through the action of a cell transporter called Pit-1 which pumps sodium and P into cells. When intracellular P level rises, it triggers signal mechanisms that leads to bone protein expression [129] and osteoblastic differenciation. Elevated Ca levels appear to evoke a similar response [128].

Calcification inhibitors

In studies assessing blood vessels in ESRD, some patiens do not have evidence of coronary or aortic calcification. Several inhibitors of calcification are likely to explain this. The most important of these are MGP, fetuin-A and osteoprotegerin (OPG) [129].

Matrix Gla protein is a member of the Gla protein family requiring vitamin K-dependent γ-carboxylation in order to be activated and functions as a potent inhibitor of

cartilage and artery calcification [130]. It appears to regulate Ca deposition by binding Ca ions and crystals, inhibiting further growth, antagonizing bone morphogenetic protein-2 (BMP2), altering cell differentiation, binding to extracellular matrix components and regulating apoptosis [131]. MGP-deficient (MGP-/-) transgenic mice develop severe mediacalcinosis of the aorta predominantly localized to the elastic lamellae and contain areas of cartilaginous metaplasia [117]. This impressive phenotype is lethal, since mice suffer from "fractures" of the bone-like aorta and die of subsequent internal hemorrhage. In human atherosclerotic disease, MGP expression was found to be increased especially in lipid-rich areas of intimal plaques surrounding calcified areas [132]. The current concept explaining this apparent contradiction is that tissue MGP upregulation may be an attempt (albeit insufficient) to counteract and limit vascular calcification foci. In this regard, limited vitamin K availability by dietary deficiency or by treatment with vitamin K antagonists such as warfarin may predispose to vascular calcification by leading to the production of undercarboxylated inactive MGP. This caused the National Kidney Foundation to consider potential future recommendations toward a more careful use of vitamin K antagonists in patients on dialysis and at high risk of vascular calcification [133].

Fetuin-A is a protein secreted from the liver and consists of a heavy and a light chain joined by a connecting segment and linked by disulfide bonds. The N-terminal of the heavy chain consists of two cystatin domains, D1 and D2 and the acidic amino acids in the D1 domain appear to account for fetuin's ability to inhibit precipitation of Ca and P. In-vitro studies showed that fetuin-A accounts for up to one-half of the capacity of the serum to prevent the precipitation of Ca and P. Fetuin-A actively regulates the cell-mediated process of osteogenesis in the vessel wall. In the presence of Ca, Fetuin-A binds to cell surface proteins (annexins II and VI) of VSMC , facilitating further entry of Fetuin-A into the endosomes where it impairs apoptosis of VSMC. It is also incorporated into secreted matrix vesicles and apoptotic bodies and inhibits mineralization in a concentration-dependent manner and also enhances the phagocytosis of apoptotic bodies by viable VSMCs, which limits their ability to nucleate Ca-P. Fetuin-A also antagonizes the action of BMP2, an osteogenic protein that stimulates the first step in vascular calcification, namely the transdifferentiation of calcifying vascular cells [134]. In humans, Ketteler et al [135] reported that low serum fetuin-A levels

associate with increased calcification and CV mortality in ESRD patients on HD, suggesting that Fetuin-A could prevent the extraskeletal calcification observed in ESRD.

Osteoprotegerin is the key modulator of osteoclast activation by acting as a soluble decoy receptor scavenging the osteoclast activator, RANKL, and thus preventing binding of RANKL to its receptor RANK and preventing osteoclast activation. Nitta *et al.* demonstrated that dialysis patients have increased OPG levels when compared with the normal population and found that OPG level is independently associated with aortic calcification [136]. This situation seems similar as with MGP in that increased OPG levels may represent insufficient regulatory mechanisms of the body to prevent extraosseous calcification. The importance of OPG in ESRD patients is emphasized by my observation that OPG predicts CV survival of these patients independent of other risk factors and that this is in part mediated by increased arterial stiffness [137,138].

In summary, both intimal and medial involvement is frequent in patients on dialysis and calcification of these layers contributes to stiffening of the large arteries, producing thereby a pathophysiological link between calcification and increased CV mortality. Calcification is an active process reflected by promoters and inhibitors, among which increased serum P level seems to play an important role. Decreasing P levels in these patients for example by P binders, such as sevelamer, may influence calcification and arterial stiffness. Analysis of this question was one of the objectives of my work.

1.3.2. Cardiovascular calcification and mortality in ESRD

Cardivascular disease is the leading cause of mortality among patients with ESRD; more than half of the deaths in patients with ESRD are due to CVD. In fact, the risk of CV mortality in adult patients with ESRD is 20 to 30 times higher than that of the general population [139]. Growing evidence suggests that this increased risk of CV mortality may be partly explained by the predisposition of this population to vascular calcification.

Hemodynamic and functional changes associated with vascular calcification have significant clinical impact, that affect CV morbidity and mortality among dialysis patients. ***Aortic calcification*** is an independent predictor of all-cause mortality and CV mortality [140]. Vascular calcification, including the abdominal aorta, has been documented to be an independent predictor of vascular morbidity and mortality [141]. Blacher *et al.* showed that in ESRD the presence and degree of ***carotid artery calcification*** was a strong predictor of CV and all-cause mortality [142]. Wang *et al.* demonstrated that ***cardiac calcification*** predicts all-cause and CV mortality in HD patients [143]. Raggi *et al.* observed that ***coronary artery calcification*** was common and severe in adult HD patients, and significantly correlated with ischemic CVD [144].

Recent studies have indicated that calcification promoters and inhibitors showed association with CV calcification and mortality. ***Hyperphosphatemia*** and elevated ***Ca X P*** promote vascular calcification, and are significantly linked to all cause and CV mortality in ESRD patients [145]. Goodman *et al.* [146] found that coronary artery calcification occurred in young patients with ESRD decades before this pathology was observed in the normal population. Furthermore, progression of vascular calcification in this group was positively correlated with serum P levels, Ca X P, and daily intake of Ca. Furthermore, decreased serum levels of ***fetuin A*** were found to be associated with increased calcification and CV mortality in ESRD patients [135]. Elevated ***OPG*** levels have been associated with the progression of vascular calcification in HD patients, and a recent analysis showed that OPG is also marker of CV mortality in HD [147].

In summary, arterial calcification is a major nontraditional CV risk factor in ESRD and an independent risk factor for CV mortality in this population.

1.4. Clinical relevance of the parameters of arterial stiffness

Arterial stiffening influences morbidity and mortality by promoting a progressive loss of vascular compliance. The degree of arterial stiffening can be inferred by increases of PWV, AIx, elevated PP and decreases of AMP. Evidences for the impact of arterial stiffness on CV events come from cross-sectional studies by proving the correlation with CV risk factors. A major limitation of these studies is their nature;

they demonstrated that arterial stiffness is a ‘marker’ of CV risk, they have not shown its independent predictive value. Only longitudinal studies give a chance to estimate the predictive values of different parameters of arterial stiffness by following patients and using appropriate adjustments during analysis.

Pulse wave velocity, as a direct measure of arterial stiffness, was the most examined parameter in the last three decades. Cross-sectional studies showed that higher PWV was significantly correlated with the number of CV risk factors, the CV risk predicted by Framingham risk equations and atherosclerotic events [148]. PWV also correlates with the presence of echogenic plaques in the carotid artery [149], carotid intima–media thickness [150], endothelial dysfunction [101], decreased creatinine clearance [151] and the stage of CKD [152]. PWV is also associated with the increasing numbers of component parts of the metabolic syndrome [153] and increased in both type 1 and type 2 diabetes [154]. These studies clearly demonstrate that PWV is primarily associated with the structural changes of atherosclerosis.

The ability of PWV to predict CV events independent of other risk factors was demonstrated clearly in several prospective clinical studies. Boutouyrie *et al.* studied over 1000 subjects with hypertension for a 5.7 years follow up, and showed that a 1 m/s increase in PWV was independently associated with a relative risk of coronary or CV event of 1.42 and 1.41 respectively [155]. Multiple trials shown that increased PWV can predict CV and all-cause mortality outcomes. Willum-Hansen *el al.* demonstrated that in a general population (random sample of 1678 Danes, median follow-up of 9.4 years) PWV predicted a combined CV outcome (156). Meaume *et al.* [157] showed that, between the ages of 70 and 100 years, PWV could predict CV death. These findings were extended by the demonstration that, even among healthy older adults in their eighth decade, PWV was associated with CV mortality [158]. Increased PWV is also associated with mortality in patients with essential hypertension [159] and Type 2 diabetes mellitus [160].

In the ESRD population the ability of PWV to prognose all-cause and/or CV mortality has also been investigated. Blacher *et al.* examined 241 patients with ESRD for a mean follow up of 72 months and proved that PWV is a strong, independent predictor of all-cause and mainly CV mortality in this population, with a relative risk of

all-cause mortality being 1.39 for each 1 m/s increase in PWV [140]. Shoji *et al.* demonstrated that aortic stiffness is more pronounced in diabetic compared with nondiabetic ESRD patients and that increased aortic PWV of the diabetic ESRD patients contributes to their higher CV mortality rate [161].

PWV, a well reproducible parameter of arterial stiffness, is a relevant predictor of CV and all-cause mortality in several populations including ESRD.

Central pulse pressure, which in part indicates the degree of the buffering function of large arteries and the wave reflection, received more attention in the last decade. Several small cross-sectional studies in selected populations have documented strong relations of central PP to carotid artery intima-media thickness [162], severity of coronary artery disease and endothelial dysfunction [163]. In a large cross-sectional study, central PP was strongly related to vascular hypertrophy and the extent of atherosclerosis, as well as to incident CVD [164].

Carotid pulse pressure has been shown in several prospective studies to have predictive value for CV events and mortality. In the Strong Heart Study, 2.405 participants free of prevalent CVD were involved and followed for a mean 5.6 years, and their CPP showed a significant correlation with CV risk factors and events [165]. Matsui *et al.* studied 434 treated hypertensive patients for a follow up of 6 months and reported that the reduction in central PP was associated with a concomitant reduction in CV events, independent of the lowering of brachial BP and normalization of classical CV risk factors [166]. Jankowski *et al.* examined the prognostic significance of central BP-derived indices in 1109 patients undergoing coronary angiography for a 4.5-year follow-up and reported that central PP was related independently to CV events and death (HR 1.25) [167]. CAFE (Conduit Artery Function Evaluation) study, where 2199 patients with treated hypertension in 5 centers were followed for 4 years, reported that central PP derived from radial artery applanation tonometry independently predicted CV outcomes [168].

In subjects with ESRD, central PP is considered as a specific independent CV risk factor [169]. The ability of CPP to predict all-cause mortality in ESRD population was examined by Safar *et al.*; a cohort of 180 ESRD patient were followed up for a

mean of 52 months. This study provided evidence that in patients with ESRD CPP is a strong independent predictor of all-cause (as also CV) mortality [170].

CPP has shown to have independent predictive value for all-cause mortality in ESRD patients and CV events in the hypertensive and patients with coronary disease.

Alterations in ***augmentation index***, an indirect parameter of arterial stiffness, with diseases and CV risk factors have frequently been investigated. In cross-sectional studies a combined assessment of vascular function using AI and a measure of carotid artery intimal-medial thickness has been shown to be associated with a high CV risk, as predicted by the Framingham risk score [171]. AI was elevated in Type 1 diabetes mellitus [172] (this finding could not always be reproduced [173]), and in subjects with hypercholesterolaemia [174]. The Atherosclerosis Risk in Young Adults study measured the AI in young men and found that heavy alcohol intake, smoking and elevated LDL cholesterol levels were significantly related to AI [175]. AI is significantly and inversely related to endothelial function [101] and significantly associated with the high level of high sensitivity CRP (a possible marker of subclinical atherosclerosis) [176]. Weber *et al.* showed that AI was a strong and independent marker for premature coronary artery disease [177]. The predictive value of AI was investigated by several longitudinal studies. CAFE study reported that AI was significantly associated with the composite endpoint in all models, but after adjustment, AI was significantly associated with CV outcome only in two models [168]. Weber *et al.* reported in a follow up study that AI is a strong predictor of CV events in patients undergoing PCI [178].

The prognostic significance of AI was also assessed in ESRD patients. London *et al.* followed 180 ESRD patients for mean 52 months and AI was found to be an independent predictor of all-cause and CV mortality. After adjustment for confounders, each 10% increase in AI was associated with a risk ratio for all-cause mortality of 1.51 and 1.48 for CV mortality [179]. The study accomplished by Covic *et al.* failed to report the predictive value of AI for survival in a relatively young non-diabetic ESRD population, with minimal CVD (92 patients followed up for 61 months). Similarly the ASFAST (Cardiovascular Morbidity and Mortality in the Atherosclerosis and Folic

Acid Supplementation Trial in Chronic Renal Failure) study also failed to find AI being independently associated with CV events [180].

AI has a predictive value in some special populations but its role in predicting mortality in ESRD population is contradictive and not well studied.

Recent observational studies suggest that a lower carotid-brachial ***amplification index*** might be associated with unfavorable hemodynamic effects for the central arteries and the heart. Evidence from cross-sectional studies suggests that subjects with traditional CV risk factors such as hypertension, diabetes mellitus, hypercholesterolemia, smoking, or established CVD have lower AMP, which is independent of age, gender, height, and heart rate [181,183]. Hypertensive subjects with concomitant obesity and metabolic syndrome have exaggerated AMP [184]. Nijdam et al. reported that higher AMP reflects lower vascular risk in men between 40 and 80 years of age; lower CV risk profile, reduced common carotid intima-media thickness and lower Framingham risk of coronary heart disease [185]. In the Anglo-Cardiff Collaborative Trial II (10 613 individuals were analyzed) the major findings were that CV risk factors and atherosclerosis are independently associated with a decreased AMP in both men and women [181]. While AMP is associated with CV risk factors in cross sectional studies, data on its independent prognostic value are limited. Reduction of AMP has been shown to be an independent predictor of CV mortality in hypertensive subjects [186]. In untreated subjects with essential hypertension, regression of LV mass index after 1 year of drug treatment was independently associated with the increase of AMP [187].

The independent prognostic value of AMP in ESRD population is limited to one study. Safar *et al.* followed up 180 ESRD patients for a mean of 52 months in a cohort study. The salient findings were that in ESRD patients on HD, the disappearance of aortic brachial AMP was a significant predictor of all-cause (including CV) mortality, independent of age and other confounding factors [188].

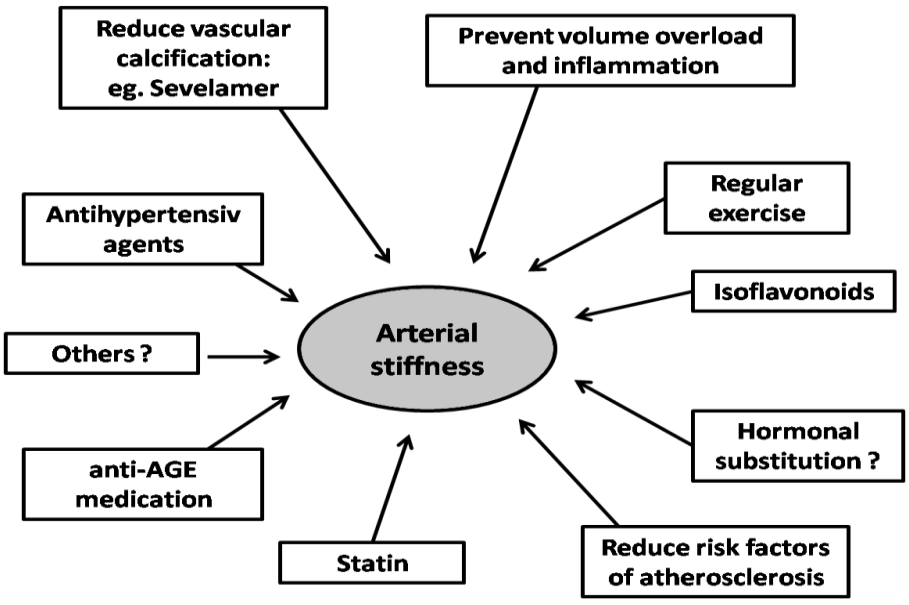
The prognostic significant of AMP is less examined compared to other arterial stiffness parameter and its predictive value in ESRD needs to be supported by further longitudinal studies.

In summary, clinicians have four parameters of arterial stiffness (PWV, AIx, CPP and AMP) to predict CV mortality in ESRD patients with HD. Prospective studies, however, evaluated the prognostic value of these parameters in ESRD in separate cohorts, and rarely examined more than one parameter. Moreover, measurements were performed at different times in relation to the dialysis procedure. Currently, it is not known which parameter predicts CV mortality in ESRD the best and when the measurements should be performed. Therefore, one of my objectives was to determine, that in one cohort of HD patients which of the four parameters of arterial stiffness predicts CV survival significantly,and whether measurements made prior to or after HD influence the results.

1.5. Therapeutic Opportunities of Arterial Stiffness

As arterial stiffness (at least some of its parameters) has been established as an independent CV risk factor, it has also emerged as a potential target for intervention. Indeed, it is clear that reduction of arterial stiffness may become a major primary goal of treatment in patients with the risk of CVD. There are a number of strategies to reduce arterial stiffness; several factors involve lifestyle issues while others are pharmacological in nature (Figure 10).

Figure 10. Present and potential therapeutic strategies for reducing arterial stiffness



(Clin Res Cardiol Suppl 2007 [supplement 1]2:S15–S21)

Stiffness of large arteries increases with age, even in healthy individuals without any CVD, but is less pronounced in those who engage in regular ***exercise*** [189]. Even once established, large artery stiffening can be diminished by a program of physical exercise [190]. In middle-aged sedentary men, 3 months of aerobic training (walking or jogging 40 minutes per day at 70% to 75% of maximum heart rate) improves the carotid artery compliance [191]. Among diet-related factors, high ***salt intake*** accelerates age-related changes in vasculature [192], and both short-term [193] and longer-term [194] sodium restriction increases arterial compliance, relatively independently from the effect on mean blood pressure. Several ***dietary supplements*** appear to influence compliance; high dietary intake of isoflavones (compound abundant in soy beans) is associated with a lower PWV in healthy volunteers [195].

There are more available evidences that arterial stiffness can be improved by ***pharmacological*** agents, such as cholesterol lowering drugs, antihypertensive treatment and therapies targeting AGEs and hyperphosphatemia.

The effect of cholesterol lowering with ***statins*** on arterial stiffness has been investigated. In *familial hypercholesterolemia* improvements in elasticity have been demonstrated in the common femoral but not the carotid artery after 1 year of simvastatin or atorvastatin [196], in the aorta after 13 months of cholesterol lowering treatment that included pravastatin [197], and in the radial artery after 2 years but not 6 months of simvastatin [198]. In *non-familial hypercholesterolemia*, simvastatin improved femoral-posterior tibial but not aortofemoral PWV, although treatment was only given for 4 weeks [199]. A reduction in small artery stiffness after 4 weeks of atorvastatin has also been reported, although this was an open study without a placebo control [200]. A placebo-controlled study in diabetic HD patients showed, after 6 months of statin therapy, that PWV was significantly reduced with fluvastatin therapy, whereas in the placebo group, arterial stiffness rose significantly [201]. In the other hand, Conduit Artery Function Evaluation Lipid-Lowering Arm (CAFE-LLA) Study demonstrated no important effects of atorvastatin on central aortic pressures or hemodynamic indices and suggested that, the benefits of statins in reducing cardiovascular events are most likely a direct consequence of lipid-lowering and/or

pleiotropic effects rather than any important action on central aortic hemodynamics [202].

Several pharmacological studies have evaluated the effects of antihypertensive drugs on arterial stiffness. The effects of organic ***nitrates*** on the central aortic waveform have been well characterized. Nitrate effectively reduces central measures of AI and PP but has little or no effect on aortic PWV [203,204]. Both ***Ca channel blockers (CCBs)*** and ***angiotensin converting enzyme (ACE) inhibitors*** also appear to have beneficial effects on arterial elasticity independent of effects on distending pressure. Perindopril reduces PWV independently of blood pressure [205]. Favorable effects on stiffness have been recorded with nitrendipine in patients with ESRD [206] and hypertension [207]. A number of studies have compared the effects of ACE inhibitors and CCBs on arterial stiffness. In ESRD treatment for 1 year with perindopril or nitrendipine similarly improved the AMP and reduced PWV and carotid AI [208]. In hypertension, 8 weeks of treatment with lisinopril more effectively reduced PWV than nifedipine [209]. ***Angiotensin II receptor antagonists*** have similar effects to ACE inhibitors on arterial stiffness in hypertension [210] and congestive heart failure [211]. In treated hypertensive nondiabetic patients, candesartan reduced the PWV more effectively than placebo [212]. In HD patients, low-dose losartan and trandolapril compared with placebo significantly decreased the PWV independently of their effect on blood pressure over [213]. Although ***β-blockers*** may reduce large artery stiffness, their effects on peripheral wave reflection and the central arterial waveform are less favorable. After 6 months of treatment in hypertensives, atenolol was as effective as the ACE inhibitor cilazapril in increasing aortic elasticity [214]. However, atenolol was less effective than either fosinopril after 8 weeks of treatment or perindopril after 1 month of treatment in lowering directly measured carotid AI [215,216]. In another study, treatment for 1 year with atenolol or perindopril/indapamide similarly reduced aortic PWV but only the ACE inhibitor/diuretic combination reduced carotid AI [217]. There are conflicting data regarding the effects of ***diuretics*** on arterial wall stiffness. However, in hypertension, perindopril was more effective than the diuretic combination in (hydrochlorothiazide and amiloride) reducing arterial stiffness [218]. The CCB felodipine more effectively improved brachial artery compliance than hydrochlorothiazide [219]. Another target, endothelin-1, leads *in vitro* to an increase in PWV and AIx; the ***endothelin receptor***

antagonist VML-88 reduces these parameters and may be another promising agent for reducing arterial stiffness [220].Treatment with endothelin-1 antagonist prevents increases in PP as well as calcification of the vessels. Remarkably, treatment of rats with endothelin-1 antagonist after calcification was established caused regression of vascular calcification and normalization of PP.

Therapeutic studies focusing on structural improvement of the vessel wall are just at the beginning. Therapies targeting ***AGEs*** have recently been developed; two main classes of drugs can attenuate the effects of AGEs. *Inhibitors of AGE formation*, such as aminoguanidine, have been used with some effect in animals. For example, treatment of normotensive rats with aminoguanidine resulted in a 20% reduction in PWV [221]. Human studies have, however, been somewhat less hopeful. The second class of compounds includes agents which *break down established AGE crosslinks*. Animal studies of the thiazolium derivative ALT-711 have shown promising results, linking the drug to an improvement in arterial stiffness [222], LV stiffness [223], SBP and proteinuria [224]. Human studies with these drugs are few. In one study, 92 humans with evidence of vascular stiffening were given ALT-711 or placebo for 56 days. ALT-711 treatment resulted in a significant rise of 15% in total arterial compliance and a significant 8% reduction in PWV [225].

Several recent studies suggest that vascular calcification may be slowed, and potentially even reversed, in humans as well as in experimental animal models. In light of the findings that elevated serum P and Ca are strongly correlated with vascular calcification and CVD mortality in ESRD, emphasis has been placed on the use of non–Ca-containing P binders, such as ***sevelamer***, to treat hyperphosphatemia in these patients [226]. Sevelamer is a not absorbable, non-Ca-containing synthetic polymer P binder. Besides its effects on P reabsorption, it is known to decrease cholesterol levels and to have anti-inflammatory properties. When sevelamer was compared to commonly used Ca-based P binders in a large HD patient group it was found that patients receiving sevelamer had unchanged median coronary artery and aorta calcification scores after one year as opposed to Ca-treated patients whose arterial calcification scores increased 28% over baseline [227]. Significantly, although both treatments controlled P levels equivalently, treatment with Ca-containing binders led to an increased frequency of

hypercalcemic episodes and greater suppression of serum PTH levels in HD patients [228,229]. Similar effects of sevelamer were also noted in a rat uremia model, where renal calcification was greatly reduced compared to Ca-carbonate treatment [230]. The impact of sevelamer treatment on the parameters of arterial stiffness in ESRD was not examined well; therefore one of my objectives was to study the influence of sevelamer on arterial stiffness.

2. OBJECTIVES

In the population of patients with ESRD structural and functional malformations and calcification in the large arteries begins early, facilitating a 20 to 30 times higher rate of cardiovascular mortality than in the age-matched general population. Cardiovascular mortality is responsible for 45% of the all-cause mortality in this population. Therefore, it is essential to investigate the predisposing risk factors of CV mortality; especially those are unique to ERSD such as vascular calcification as a strong promoter of arterial stiffness. Prospective studies demonstrated that the association between vascular calcification of the large arteries and increased risk of CV events and mortality in this population is independent of classical risk factors. Aortic wall stiffening has emerged as an independent predictor of all cause and CV mortality in patients with HD.

Arterial stiffness is described by several parameters, among which four are widely used (PWV, AI, CPP and AMP). Previous studies used separate cohorts to evaluate the prognostic value of these parameters in ESRD, while more than one parameter has rarely been analyzed. The impact of timing of the measurement on prognosis, (e.g. when these parameters were measured in relation to the dialysis procedure) has also been examined only sporadically. These parameters have not been examined in one cohort and it is not known which of them is best to used, and when to be measured. The first specific aim of my work therefore was to determine which of the four parameters of arterial stiffness predicted CV survival in HD patients the best and to determine whether the timing of measurement in relation to dialysis influenced the results.

Progressive arterial calcification and altered parameters of arterial stiffness represent a clinically relevant situation: decreasing or at least attenuating calcification may possibly lead to better patient outcome. Therefore, investigation of medications that decelerate or reverse the progression of arterial stiffness has negligible incalculable clinical value. In January 2005, sevelamer became available in Hungary with 100% reimbursement with certain indications. Sevelamer decreases aortic calcification but its effect on aortic stiffness has not been investigated previously in ESRD. My second

specific aim therefore was to determine the effect of sevelamer on PWV and AI in a prospective observational study with using concomitant controls and an appropriate follow-up period.

Measurement of arterial stiffness is increasingly included in the clinical assessment of patients. Several devices have been developed previously using different methodologies. Clinicians and researchers still report difficulties in selecting the most appropriate method for their specific use. A well validated device is needed to determine the descriptive parameters of arterial stiffness; parameters determined inadequately lead to the conclusion of false relations between examined factors and outcomes. Recently a new oscillometric device (Arteriograph) has been developed and used to measure arterial stiffness, but it has not been examined before whether the use of this device is valid in patient with high CV risks such as in ESRD. My third specific objective therefore was to determine the validity of the new Arteriograph device by comparing it to a validated tonometer in assessing PWV, AI, and predicting survival.

3. PATIENTS AND METHODS

To achieve the specific objectives, I accomplished three studies in the same cohort of patients with ESRD on HD (table 10.). To simplify detailing these studies, the first, the second and the third study abbreviation hereinafter will be used;

1. The "***first study***" where the aim was to determine which of the four parameters of arterial stiffness significantly predicted CV survival tested in one cohort of ESRD patients on HD and to determine whether measurements made prior to or after HD influenced the results.
2. The "***second study***" where the objective was to investigate the effect of sevelamer on PWV and AI in ESRD patients on HD using concomitant controls and an appropriate follow-up period.
3. The "***third study***" where the target was to compare the PWV and AI values measured by Arteriograph to those obtained by the validated PulsePen tonometer in ESRD patients on HD therapy.

3.1 Patients

ERDS patients with chronic HD (>3 months on HD) at two dialysis units of the B. Braun Avitum Nephrological Network were invited to participate (n = 126). Among them 28 patients declined participation leaving 98 patients for inclusion into the projected studies. Participants were informed about the details and objectives of the investigation. No specific exclusion criteria were applied. Patients who gave written informed consent for participation were included and had baseline clinical assessment, laboratory and arterial stiffness measurements.

All patients received HD three times a week for 4 hour duration using a dialysate calcium concentration of 1.50 mmol/L. Baseline demographic and clinical data were gathered by chart review, and laboratory parameters were measured prior to a midweek dialysis at the time of arterial stiffness assessment. The protocol of these studies was approved by the ethics committee of the Semmelweis University and the ethics committee of the dialysis network.

Table 10. The accomplished three studies in the cohort of ESRD patients on HD.

	type of study	*n*	*follow-up time*	*predictor*	*outcome*
first study	prospective follow-up	98	median of 29 months (1–35)	PWV, AI, CPP, AMP	CV mortality*
second study	prospective follow-up	26	mean 10.8 month (2.3)	PWV, AI	Improvement of aortic arterial stiffness
third study	basic cross-sectional	92		PWV, AI	relationship between PWVand AI measured by two devices**
	prospective follow-up	92	median of 29 months (1–35)	PWV, AI	CV mortality*

CV: cardiovascular, PWV: pulse wave velocity, AI: augmentation index, CPP: central pulse pressure, AMP: pulse pressure amplification index, ESRD: end-stage renal disease, HD: haemodialysis.
**CV mortality is defined as sudden cardiac death, death related to myocardial infarction, arrhythmia, heart failure or stroke as assessed by the attending physician at the dialysis center.*
***PulsePen (tonometric) and Arteriograph (oscillometric) device.*

In the *first study*, patients (n = 98) were considered to have established cardiovascular disease if they had a documented history of myocardial infarction, revascularization procedure, stroke or peripheral artery disease. Heart failure was not included in the definition of cardiovascular disease as this frequently would have been based on physician assessment only, and signs of hypervolaemia in these HD patients could have led to misclassification of heart failure. For this study patients were followed for a median of 29 (range 1–35) months. Follow-up was censored at the time of death from other causes, transplantation, transfer to an other unit or at the end of follow-up on February 29, 2008. The outcome measure was death from a CV event; CV mortality was defined as sudden cardiac death, death related to myocardial infarction, arrhythmia, heart failure or stroke as assessed by the attending physician at the dialysis center. Baseline demographic and clinical data were gathered by chart review, and laboratory parameters were measured at the time of arterial stiffness assessment.

As for participants of the *second study*: in January 2005, sevelamer became available in Hungary with 100% reimbursement through the National Health Insurance Fund for dialysis patients with the following indications: soft tissue calcifications or serum phosphorus (P) levels above 1.86 mmol/L, albumin-corrected calcium (Ca) level above 2.5 mmol/L, and Ca X P above 4.4 mmol2/L2. Based on these criteria, seventeen

patients at the two HD units commenced sevelamer treatment between March and May 2005. The starting dose of sevelamer was 2400 mg daily, with the previous calcium carbonate phosphate binder therapy withheld. The dose could be increased to 4800 mg daily at the discretion of the attending physician to achieve the treatment goals of P≤1.86 mmol/ L and Ca X P ≤4.4 mmol2/L2. These patients were involved in the second study to examine the effect of sevelamer on central arterial stiffness. During follow-up, eventually all but one patient received 4800 mg of sevelamer. Other medications, including antihypertensives and active vitamin-D treatment, were at the discretion of the treating physician. During follow-up three patients died and one was transferred to another unit, leaving thirteen sevelamer-treated patients for analysis. Thirteen control patients paired to those treated with sevelamer were also selected from the same dialysis units and matched for age, sex, presence of diabetes, and dialysis duration—all variables known to affect PWV and AI. Controls were identified by one person who was unaware of the results of baseline arterial stiffness measurements. Although highly desirable, parameters of Ca-P metabolism could not be used for selecting controls, as was the case for values of serum Ca, P, or Ca X P falling in the range of that of sevelamer treated patients, because these potential controls would have been started on sevelamer as well. This limitation should be acknowledged at all stages in evaluating my results. Control patients continued on their previous calcium carbonate therapy during follow-up.

Sevelamer-treated and control patients (n = 26) were followed for 10.8 (±2.3) months and outcome was the improvement of aortic arterial stiffness as assessed by measuring PWV and AI.

The number of participants in the *third study* was limited by the fact that PWV and AI measured by Arteriograph could not be obtained in six cases, as the Arteriograph software was not able to calculate values from the pressure wave curves in at least two out of three measurements. These patients were excluded leaving 92 patients for analyses. Similar to the first study, patients were followed for a median of 29 (range 1–35) months. Follow-up was censored at the time of death from other causes, transplantation, transfer to an other unit or at the end of follow-up on February 29, 2008. Outcome measure was death from a CV event; CV mortality was defined as

sudden cardiac death, death related to myocardial infarction, arrhythmia, heart failure or stroke as assessed by the attending physician at the dialysis center. Baseline demographic and clinical data were gathered by chart review, and laboratory parameters were measured at the time of arterial stiffness assessment.

3.2. Clinical Measurements

3.2.1 Recording of the parameters of arterial stiffness

In all studies, patients received dialysis using a bicarbonate bath, polysulphone membranes and ultrafiltration as needed based on their clinically assessed dry weight. Blood pressure and heart rate were recorded by the validated BpTru device (VSM Medtech, Vancouver, B.C., Canada) with two sequential measurements averaged manually. Mean blood pressure was calculated as diastolic brachial pressure plus one third of brachial pulse pressure. In all studies arterial stiffness was determined by tonometric method using the validated PulsePen tonometer (DiaTecne, Milan, Italy); carotid tonometric measurements were performed on the side contralateral to the fistula or tunneled jugular line and the same side was used to obtain femoral pressure waves. All femoral and carotid PP wave recordings assessed by PulsePen were evaluated for quality by a single observer. Previously, I evaluated intra- and interobserver variability of PWV measurements obtained by the PulsePen device in HD patients, and these were 4.8 and 7.3%, respectively. In another validation study of PulsePen in nonrenal patients, intra- and interobserver coefficients of variation of PWV measurements were 7.2 and 7.9%, and 15.2 and 15.8% for AI measurements, respectively [231].

For the *first study*, parameters of arterial stiffness (PWV, AI, CPP and AMP) were measured using the validated PulsePen device *before and after a midweek dialysis* session with the patient in the supine position [232]. In each subject, two sequences of measurements were performed, with the mean used for statistical analysis.

For the *second study* arterial stiffness measurements (PWV and AI) were also assessed by the PulsePen device at the start of study *before a midweek dialysis* procedure and repeated at the end of the follow-up before a midweek dialysis session with the patient in the supine position.

For the *third study*, besides the PulsePen PWV and AI measures, arterial stiffness was also assessed as calculated carotid-femoral PWV and central AI by the Arteriograph device (TensioMed, Budapest, Hungary) 3 times before a midweek dialysis treatment in the supine position (at the same time PulsePen measurements were performed). The average of at least two successful measurements was used in the calculations. When only one or none of the three measurements were successful with a given device, the patient was excluded from the analysis. The order of the measurements with the PulsePen and Arteriograph devices was randomly chosen.

PulsePen device measures the time difference between the R wave of the ECG and the 'foot' of the PP wave – obtained sequentially above the carotid and the femoral arteries using a handheld tonometer – to calculate pulse transit time between these two sites. The average signal of at least ten heart cycles was used in the measurements at both sites. The 'foot' of the pressure pulse waveform was determined by the intersection of the horizontal line tangent to the lowest point of the pressure waveform following the ECG complex with the extension of the line resulting from the mean square deviation of all points, building up the initial protosystolic rapid ascending phase of the pressure waveform (intersecting tangent method) [232]. To assess pulse wave travel distance, surface tape measurements were performed between the carotid site and the suprasternal notch, and between the suprasternal notch and the femoral site. The difference of these two distances was considered to be the pulse travel distance and was used to calculate PWV with the PulsePen software. To assure that alterations in blood pressure and heart rate do not bias the results of stiffness assessment, the software of PulsePen automatically rejected measurements in which blood pressure or heart rate changed more than 5% during the time between the sequential carotid and femoral pulse wave recordings.

Augmentation index was measured by automatic identification of the 'first shoulder' (inflection point) on the averaged carotid pulse signal by the PulsePen software. The pressure amplitude following this point divided by the PP provided the AI. CPP was determined by measuring the amplitude of the averaged carotid signal after calibration of the carotid curve to the brachial mean and diastolic blood pressures. AMP was the ratio of brachial and carotid PP-s.

Arteriograph device calculates PWV and AI, by contour analysis of the averaged oscillometric pressure curve registered on the upper arm. The principle of the oscillometric method is based on plethysmography and registers pulsatile pressure changes in an artery. Since fluctuations in pulsatile pressure in the artery beneath the inflated pressure cuff induce periodic pressure changes in the inflated cuff, the oscillometric method measures these periodic pressure changes (oscillations) as an indirect measure for the pulsatile pressure changes in the artery beneath [233]. Pressure fluctuations are detected in the blood pressure cuff inflated 35 mm Hg over the systolic pressure. The averaged pressure signal detected in the cuff is similar to the pressure changes in the brachial artery during the heart cycle on which the forward and reflected waves are identified by the Arteriograph software. The difference in time between the beginning of first wave and the beginning of reflected wave is related to the distance from the jugular notch to the symphysis, resulting in the calculated PWV in m/s.

Augmentation index corresponds to the pressure difference between the amplitude of the first (forward, P1) and second (reflected, P2) wave in relation to the PP. The Arteriograph calculates AI_A on the basis of the formula: AI = [(P2 – P1)/PP] x100, and thus provides brachial AI without applying a transfer function [233]. The Arteriograph software version 1.9.9.2 was used in this study.

3.2.2. Laboratory measurements

After arterial stiffness measurements and before dialysis, in all studies blood samples were collected for standard laboratory measurements. To accommodate for the known variability in Ca and P levels, for the second study, I also calculated time averaged Ca, P, and Ca X P values using the results of the 3, monthly blood values from before baseline and from before completion of follow-up. Reported calcium values were adjusted for albumin levels using the formula: corrected Ca (mmol/L)=measured Ca (mmol/L)*1*(40-albumin (g/L)) X 0.25. Intact PTH, osteocalcin, and β-crosslaps concentrations were determined according to the manufacturer's exact instructions using commercially available kit Roche's Elecsyss electrochemoluminescence immunoassay ''ECLIA'' (Roche Diagnostics GmbH, Mannheim, Germany). Osteoprotegerin, soluble RANKL, and Fetuin A levels in the serum were measured by

ELISA using the commercially available kits from Immundiagnostic AG Bensheim, Germany. Serum levels of human matrix GLA protein were measured according to the manufacturer's instructions using the commercially available Human MGP ELISA Kit (Biomedica, Wien, Austria).

3.3. Statistical analysis

The SAS statistical package version 6.11 (SAS Institute, Cary, NC, U.S.A.) was used for the main analyses in all three studies. For the calculation and comparison of receiver operating characteristic curves in the first study, the web-based StAR software was used [234]. Continuous variables are presented as means (standard deviation) or, in case of evidence against normal distribution, as medians (interquartile range), and categorical variables are presented as n (%). p values with a two-sided α of 0.05 were considered statistically significant. Hazard ratios are presented with their 95% confidence intervals in parentheses. Information deleted has already been stated before.

3.3.1. Analysis of the first study

To assess the relationship of arterial stiffness parameters with cardiovascular mortality, log-rank tests and Cox proportional hazards regression analyses were used. Cardiovascular mortality was defined as sudden cardiac death, death related to myocardial infarction, arrhythmia, heart failure or stroke as assessed by the attending physician at the dialysis center. Using tertiles of the pre- and postdialysis PWV, AI, CPP and AMP values, Kaplan-Meier survival curves were constructed and compared by a log-rank test. Cox regression analyses began with separate univariate models using cardiovascular mortality as the outcome and the eight stiffness values (4 before and 4 after dialysis) as continuous predictor variables. Hazard ratios (HRs) were adjusted for age, diabetes and the presence of established cardiovascular disease. Finally, stiffness parameters that showed a significant association with cardiovascular mortality were considered in the same adjusted model. I also calculated the area under the receiver operating characteristic curves of the 8 stiffness parameters for cardiovascular mortality with a pairwise comparison between them.

3.3.2. Analysis of the second study

Data are reported as mean (standard deviation) or, in case of evidence against normal distribution, as median (interquartile range). Baseline variables between sevelamer treated and control patients were compared by Student's t test for independent samples for continuous variables with no evidence against normal distribution, by the Wilcoxon rank-sum test for continuous variables with a nonnormal distribution, and by Fisher's exact test for categorical variables. Within-group changes in the parameters during follow-up were assessed by Student's t test for paired samples and by the Wilcoxon signed rank-test, as appropriate. The main analysis consisted of comparing the changes of variables during follow-up between the sevelamer-treated and control groups by Student's t test for independent samples and by the Wilcoxon rank sum test. In an attempt to identify independent predictors of changes in arterial stiffness during follow-up, I also performed univariate and multivariate linear regression analyses with the change in PWV as the dependent variable.

3.3.3. Analysis of the third study

To evaluate device validity of the arteriograph first, Pearson's correlation analysis between the readings of the test Arteriograph and "gold standard" PulsePen devices was performed. Second, I analyzed the readings according to the method proposed by Bland and Altman [235]. In this, the difference between each pair of measurement is plotted against the mean of the pair, and the number of paired differences that fall outside the ± 1 SD boundary of the mean between-device difference is also calculated. To assess clinical validity, prognostic values of the PWV and AI readings obtained by each device for CV mortality were determined by log-rank tests using tertiles of the respective parameters and also by Cox proportional hazard regression using the data as continuous variables and adjusted for age, diabetes and established CV diseases. CV mortality was defined as sudden cardiac death, death related to myocardial infarction, arrhythmia, heart failure or stroke as assessed by the attending physician at the dialysis center.

4. RESULTS

4.1. Results of the first study

Baseline demographic and laboratory chracteristics of the participants are presented in table 11. The most frequent causes for renal disease were vascular-tubulointerstitial disorders (including hypertension: 39%), diabetes mellitus (33%) and glomerulonephritis (13%). Antihypertensive treatment at baseline included β-blockers (63%), calcium-channel blockers (62%), angiotensin receptor blockers angiotensin-converting enzyme inhibitors (53%) and α-blockers (30%).

Table 11. Baseline demographic and laboratory data of the participants

Patients	*n*	98
Male	*n (%)*	60(61)
Age	*year*	63.4 (14.4)
Dialysis time*	*month*	29.6 (12.4-48.6)
Residual diuresis*	*mL/day*	600 (100-1300)
Body mass index	kg/m^2	25.3 (4.5)
Ultrafiltration	*mL*	2004 (1102)
Current smoking	*n (%)*	18 (18.4)
Diabetes	*n (%)*	40 (40.8)
Cardiovascular disease	*n (%)*	59 (60.2)
Hemoglobin	*g/L*	113.1 (15.5)
Creatinine	*µmol/L*	677 (243)
Blood urea	*mmol/L*	20.7 (6.0)
Cholesterol	*mmol/L*	4.5 (1.6)
Triglycerides	*mmol/L*	2.1 (1.5)
HDL-cholesterol	*mmol/L*	1.2 (0.4)
LDL-cholesterol	*mmol/L*	2.6 (0.9)
Sodium	*mmol/L*	137 (2.9)
Potassium	*mmol/L*	5.22 (0.86)
Calcium	*mmol/L*	2.29 (0.21)
Phosphorus	*mmol/L*	1.6 (0.54)
Albumin	*g/L*	39.4 (3.99)
Total protein	*g/L*	66.9 (4.71)
CRP*	*mg/L*	6.8 (4.2-12.4)

Data are mean (SD) or in case of evidence against normal distribution (*) median (interquartile range) for continuous variables and n (%) for categorical variables. CRP: C-reactive protein. Ultrafiltration refers to the volume of ultrafiltration during dialysis.

Of my patients, 62% were on active vitamin D therapy and 79% were on calcium carbonate. Pre- and postdialysis hemodynamic and stiffness parameters are shown in table 12.

Table 12. Stiffness and hemodynamic parameters measured predialysis and postdialysis

		Predialysis	*Postdialysis*	*p-value*
PWV	*m/s*	11.2 (3.25)	11.9 (3.75)	0.009
AI	*%*	23.3 (12.14)	21.3 (13.9)	0.033
Csys	*mmHg*	130.7 (21.8)	136.8 (26.4)	0.001
Cdias	*mmHg*	77.8 (12.9)	81.6 (11.5)	<0.0001
CPP	*mmHg*	52.9 (18.7)	55.8 (22.1)	0.064
Bsys	*mmHg*	142.2 (23.9)	148.4 (27.2)	0.001
Bdias	*mmHg*	78.0 (12.4)	81.9 (11.6)	<0.001
BPP	*mmHg*	64.2 (19.6)	66.4 (23.6)	0.187
AMP	*(ratio)*	1.24 (0.154)	1.22 (0.162)	0.247
HR	*beat/min*	72.8 (13.46)	77.03 (17.34)	<0.0001

PWV: pulse wave velocity; AI: carotid augmentation index; Csys: carotid systolic blood pressure; Cdia: carotid diastolic blood pressure; CPP: carotid pulse pressure; Bsys: brachial systolic blood pressure; Bdia: brachial diastolic blood pressure; BPP: brachial pulse pressure; AMP: carotid-brachial pulse pressure amplification; HR: heart rate

Heart rate, central and brachial systolic and diastolic blood pressures were significantly higher immediately after dialysis ($p \leq 0.001$ in all cases). CPP-s and brachial PP-s were also higher, but the differences were not statistically significant ($p = 0.064$ and 0.187, respectively). At the end of dialysis, PWV increased and AI decreased significantly ($p = 0.009$ and 0.033, respectively), while AMP did not show a significant change ($p = 0.247$). During follow-up, 40 patients died (mortality rate 20.7/100 patient-years) of which 25 were due to cardiovascular causes (myocardial infarction: 7; sudden death: 5; arrhythmia: 3; heart failure: 5; stroke: 5). Of the remainder, 8 were transplanted, 1 stopped dialysis due to improvement in renal function and 49 were censored at the end of the follow-up period. Kaplan-Meier survival curves for cardiovascular mortality using tertiles of PWV, AI, CPP and AMP are presented in figure 11, 12, 13 and 14 (log-rank p values were 0.012, 0.565, 0.256 and <0.001 for the predialysis and 0.011, 0.966, 0.867 and 0.321 for the postdialysis measurements, respectively).

In separate univariate Cox proportional hazards models, pre- and postdialysis PWV, predialysis CPP (but not postdialysis) and predialysis AMP values (but not postdialysis) were related to cardiovascular mortality. The AI was not related to the outcome, irrespective of the timing of the measurement. After adjustments for age, diabetes and established cardiovascular disease, pre- and postdialysis PWV and predialysis AMP remained significantly related to cardiovascular mortality (table 13). When included in the same adjusted model, both predialysis PWV and AMP remained significantly associated with cardiovascular survival [hazard ratios for 1 m/s higher PWV and 10% lower AMP were 1.23 (1.07–1.42) and 1.39 (1.02–1.89), respectively].

Table 13. Unadjusted and adjusted* hazard ratios for cardiovascular mortality related to the different stiffness parameters measured before and after dialysis.

		Hazard ratio before dialysis	*p-value*	*Hazard ratio after dialysis*	*p-value*
PWV (1m/s increase)	*unadjusted*	1.34 [1.17-1.53]	<0.001	1.19 [1.10-1.28]	<0.001
	adjusted	1.24 [1.07-1.44]	0.005	1.17 [1.06-1.28]	0.001
AI (1% increase)	*unadjusted*	0.99 [0.97-1.03]	0.936	1.003 [0.97-1.03]	0.850
	adjusted	1.01 [0.97-1.06]	0.531	1.02 [0.98-1.06]	0.465
CPP (1 mmHg increase)	*unadjusted*	1.02 [1.01-1.04]	0.041	1.01 [0.98-1.02]	0.925
	adjusted	1.001 [0.98-1.03]	0.922	0.99 [0.97-1.01]	0.225
AMP (10% decrease)	*unadjusted*	1.67 [1.24-2.27]	0.001	1.18 [0.90-1.56]	0.322
	adjusted	1.41 [1.03-1.89]	0.030	1.15 [0.82-1.59]	0.429

** adjusted for age, diabetes and presence of established cardiovascular disease at baseline abbreviations: PWV: carotid-femoral pulse wave velocity; AI: carotid augmentation index; CPP: carotid pulse pressure; AMP: carotid-brachial pulse pressure amplification*

Fig. 11. Kaplan-Meier survival curves for cardiovascular mortality in tertiles of PWV parameters measured before or after dialysis.

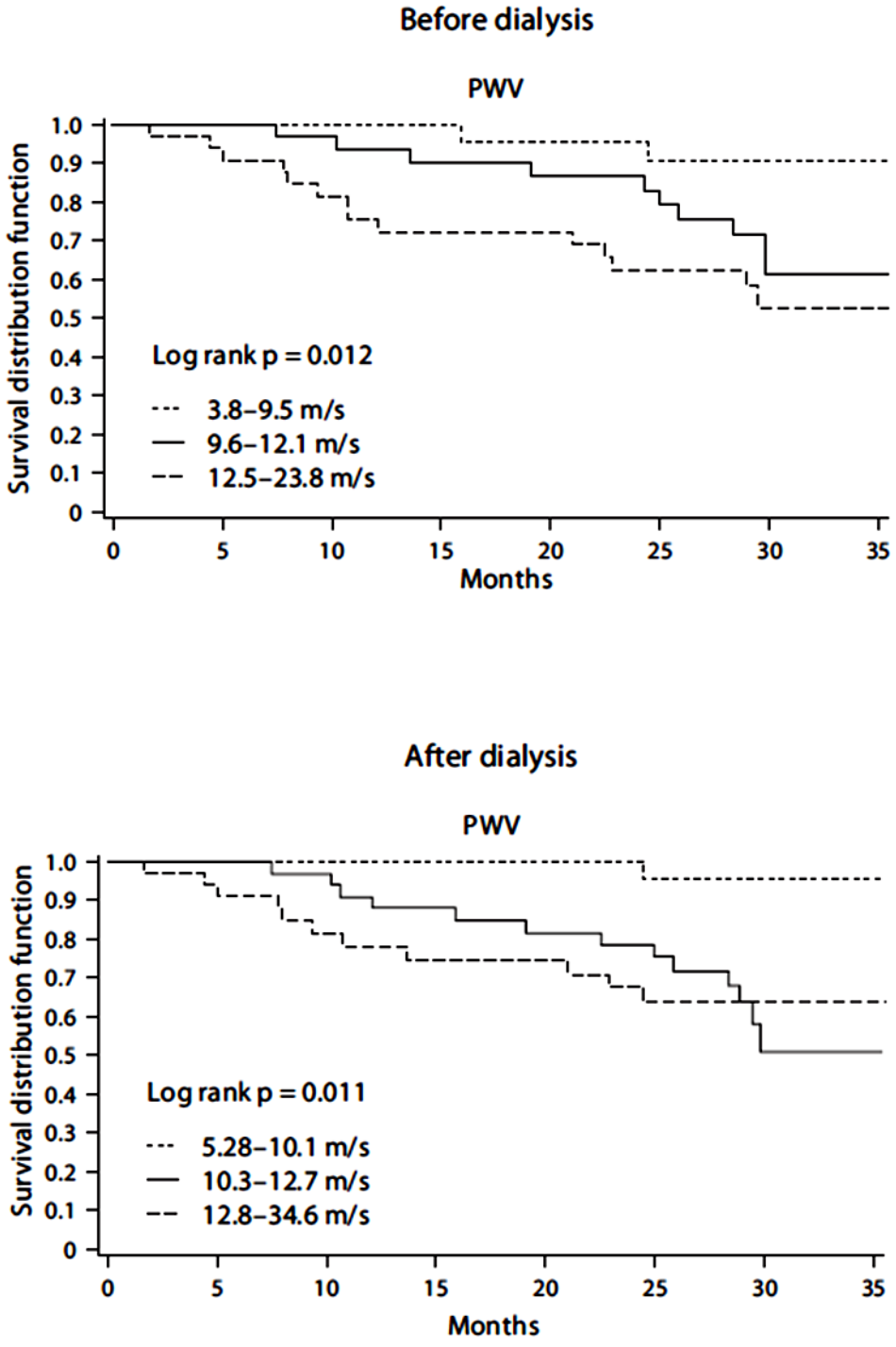


Fig. 12. Kaplan-Meier survival curves for cardiovascular mortality in tertiles of AI parameters measured before or after dialysis.

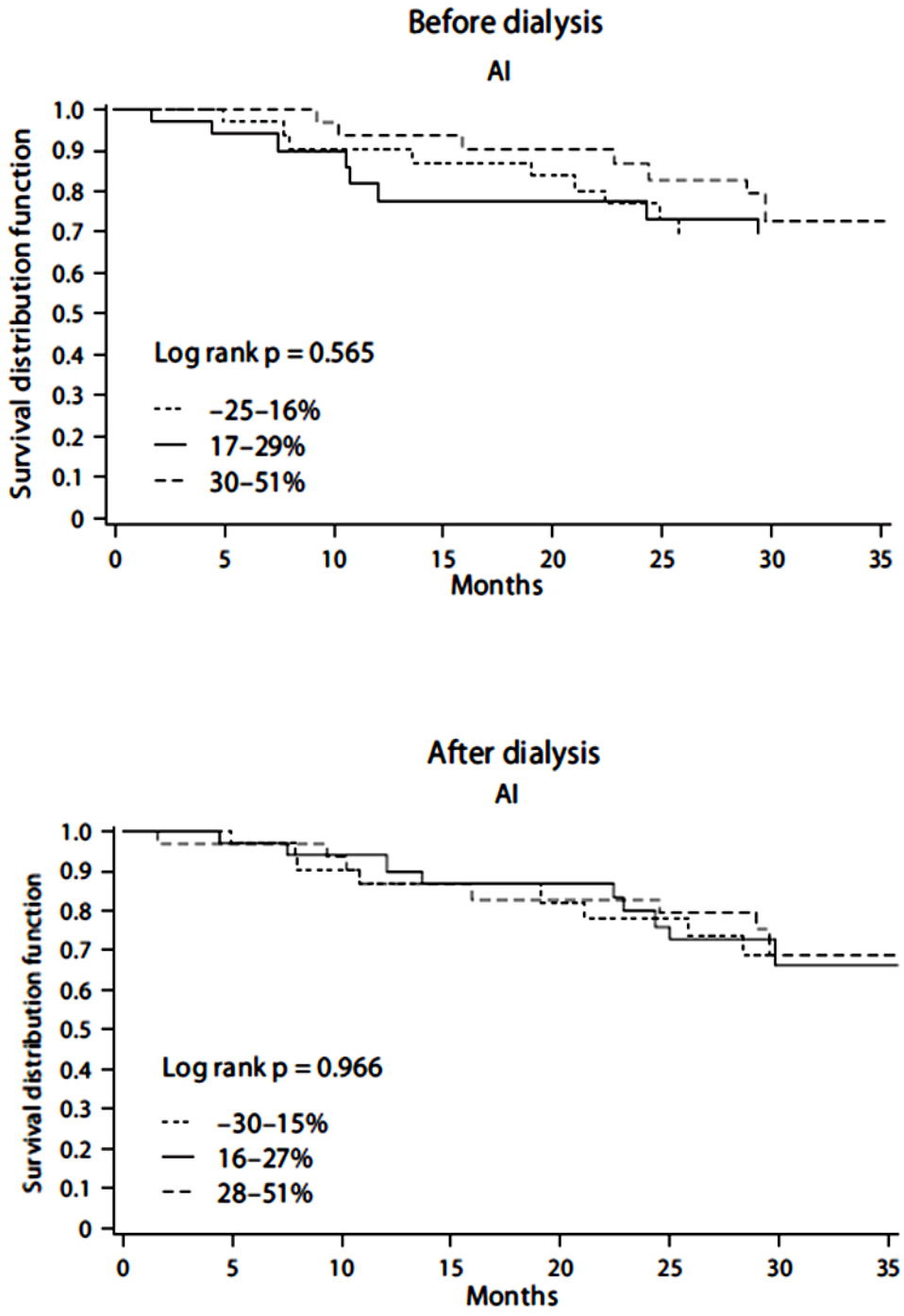


Fig. 13. Kaplan-Meier survival curves for cardiovascular mortality in tertiles of CPP parameters measured before or after dialysis.

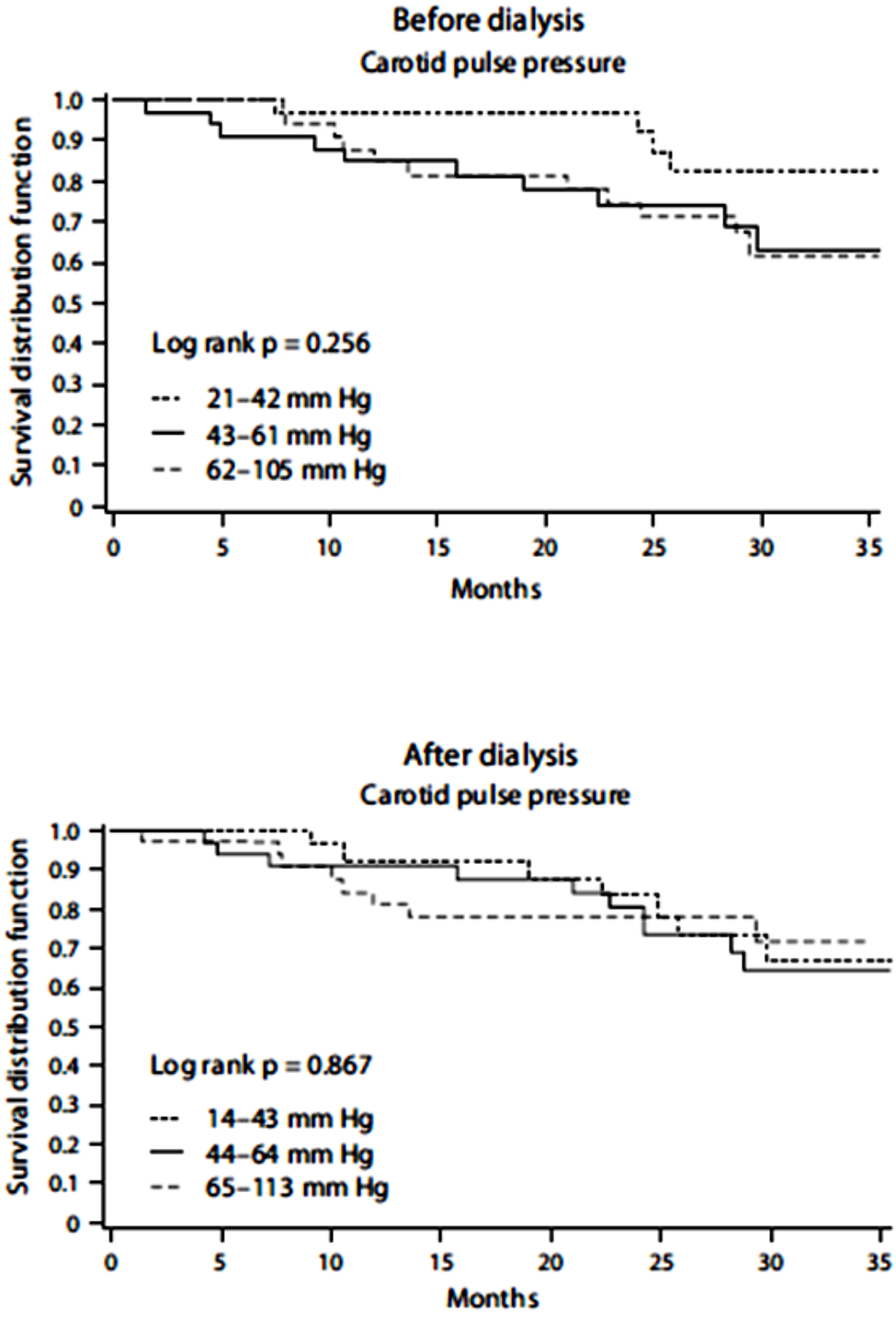
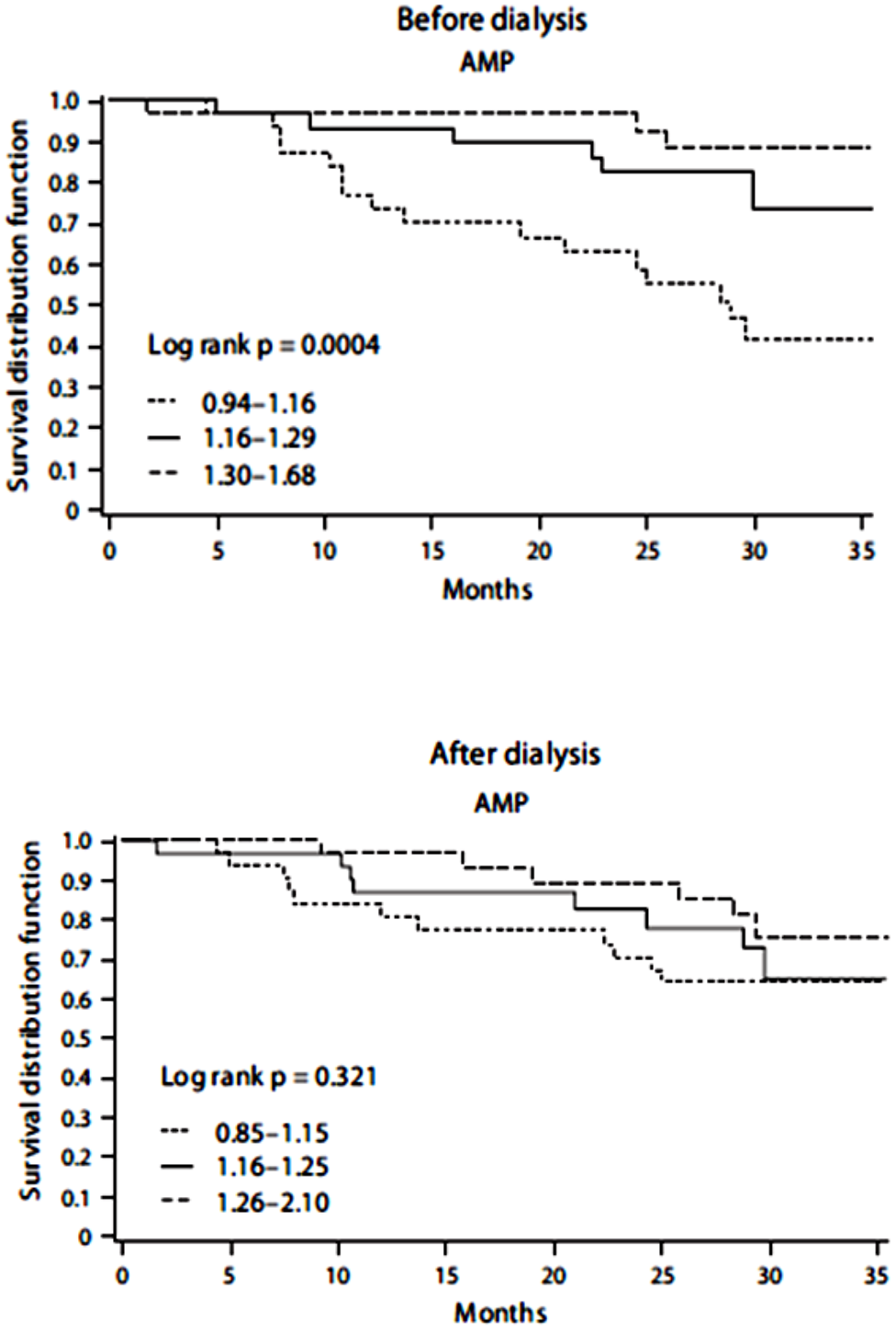


Fig. 14. Kaplan-Meier survival curves for cardiovascular mortality in tertiles of AMP parameters measured before or after dialysis.



Calculation of the area under the receiver operating characteristic curves confirmed that predialysis AMP and pre- and postdialysis PWV have the best diagnostic values for cardiovascular mortality with areas above 0.7 and no significant differences between them (table 14).

Table 14. Area under the receiver operating characteristic curves for cardiovascular mortality of the stiffness parameters measured before and after dialysis

	Before dialysis	*After dialysis*
PWV	0.724[a]	0.703[b]
AI	0.530	0.509
CPP	0.660[c]	0.538
AMP	0.746[d]	0.592

PWV: carotid-femoral pulse wave velocity; AI: carotid augmentation index; CPP: carotid pulse pressure; AMP: carotid-brachial pulse pressure amplification

[a] *p<0.05 vs. pre and postdialysis AI, postdialysis CPP*

[b] *p<0.05 vs. pre and postdialysis AI, postdialysis CPP*

[c] *p<0.05 vs. postdialysis CPP*

[d] *p<0.05 vs. pre and postdialysis AI, postdialysis CPP and AM*

4.2. Results of the second study

Baseline clinical characteristics of sevelamer-treated and control patients are presented in table 15. The groups were comparable to each other, although body mass index tended to be higher in those receiving sevelamer. Blood pressure, heart rate, PWV, AIx, and laboratory parameters, as well as their corresponding changes during follow-up, are presented in table 16. Pulse wave velocity at baseline was comparable between the two groups. By the end of follow-up, PWV decreased by 0.83 (2.27) m/s in sevelamer-treated patients while it increased by 0.93 (1.88) m/s in those continuing previous therapy (p=0.042). The direction of changes of AI was similar to that of PWV, although between-group comparison did not reach the level of statistical significance (p=0.105).

Table 15. Clinical characteristics of sevelamer-treated and control patients

		Sevelamer	*Control*	*p value*
Patients	n	13	13	
Age	(year)	54.7 (8.7)	54.0 (9.3)	0.836
Male	n (%)	10 (76.9)	10 (76.9)	1.000
Dialysis time*	(months)	38.2 (35.5)	23.9 (32.3)	0.919
Renal disease	n (%)			0.889
Glomerulonephritis		4 (30.8)	2 (15.4)	
Diabetic		1 (7.7)	2 (15.4)	
Tubulointerstitial		5 (38.5)	7 (53.8)	
Polycystic		1 (7.7)	1 (7.7)	
Other or unknown		2 (15.4)	1 (7.7)	
Weight	(kg)	81.3 (18.3)	70.0 (17.7)	0.119
Body mass index	(kg/m2)			
Baseline		27.3 (4.0)	23.7 (4.9)	0.057
Study end		26.9 (3.1)	23.7 (4.8)	0.059
Residual diuresis*	(mL)	300 (700)	300 (1500)	0.476
Current smoking,	n (%)	6 (46.2)	4 (30.8)	0.887
Diabetes	n (%)	2 (15.4)	2 (15.4)	1.000
Cardiovascular disease	n (%)	6 (46.2)	7 (53.8)	1.000
Medication	n (%)			
ACEI or ARB				
Baseline		8 (61.5)	8 (61.5)	1.000
Study end		9 (69.2)	8 (61.5)	1.000
Alpha blocker				
Baseline		4 (30.8)	5 (38.5)	1.000
Study end		4 (30.8)	5 (38.5)	1.000
β blocker				
Baseline		10 (76.9)	9 (69.2)	1.000
Study end		12 (92.3)	10 (76.9)	0.593
Ca channel blocker				
Baseline		11 (84.6)	6 (46.2)	0.097
Study end		10 (76.9)	7 (53.8)	0.411
Statin				
Baseline		3 (23.1)	2 (15.4)	1.000
Study end		3 (23.1)	2 (15.4)	1.000
Active vitamin D				
Baseline		11 (84.6)	6 (46.2)	0.097
Study end		7 (53.8)	5 (38.5)	0.695
Ca carbonate				
Baseline		11 (84.6)	9 (69.2)	0.645
Study end		3 (23.1)	9 (69.2)	0.047

Data are mean (SD) or, in case of evidence against normal distribution (*), median (interquartile range) for continuous variables and n (%) for categorical variables.

As expected, baseline P levels and Ca X P-s were higher in sevelamer-treated patients. Time-averaged P values decreased significantly during sevelamer treatment, and this change was statistically significant when compared with that in controls (p=0.008). Baseline PTH levels were higher in sevelamer-treated patients and increased in both groups during follow-up, with no significant between-group difference. Total cholesterol decreased by 0.36 (0.69) mmol/L in patients treated with sevelamer, and it increased by 0.27 (0.67) mmol/L in controls (p=0.040). We, unfortunately, had no data on LDL cholesterol levels.

Table 16. Hemodynamic, arterial stiffness and laboratory parameters at baseline and their changes during follow-up

	Sevelamer	*p within group*	*Control*	*p within group*	*p between groups*
Systolic BP (mmHg)					
Baseline	134.5 (24.0)		140.3 (19.2)		0.505
Change	1.5 (20.2)	0.786	1.8 (21.3)	0.771	0.979
Diastolic BP (mmHg)					
Baseline	81.3 (11.4)		81.0 (8.6)		0.942
Change	2.5 (12.5)	0.480	2.2 (14.2)	0.586	0.956
Heart rate (beats/min)					
Baseline	78.0 (10.2)		71.2 (12.2)		0.137
Change	-5.2 (10.4)	0.765	-0.5 (9.7)	0.855	0.222
PWV (m/sec)					
Baseline	9.93 (2.10)		9.20 (2.84)		0.464
Change	-0.83 (2.27)	0.210	0.93 (1.88)	0.088	0.042
AI (%)					
Baseline	24.2 (12.1)		28.3 (12.7)		0.415
Change	-2.4 (6.2)	0.185	3.5 (11.0)	0.257	0.105
Hemoglobin (g/L)					
Baseline	110.7 (13.2)		116.1 (19.3)		0.405
Change	-3.1 (10.4)	0.302	-3.7 (21.7)	0.546	0.924
Creatinine (mmol/L)					
Baseline	914 (233)		765 (193)		0.086
Change	-55 (192)	0.326	33 (162)	0.475	0.219
Urea nitrogen (mmol/L)					
Baseline	22.2 (5.3)		21.2 (5.8)		0.657
Change	1.9 (6.8)	0.326	0.1 (7.5)	0.956	0.532
Potassium (mmol/L)					
Baseline	5.32 (0.32)		4.99 (0.56)		0.082
Change	0.27 (0.58)	0.101	0.17 (0.60)	0.330	0.646
Bicarbonate (mmol/L)					
Baseline	20.6 (2.41)		23.7 (2.64)		0.003
Change	-1.25 (1.20)	0.028	-0.21 (2.64)	0.781	0.209

Albumin (g/L)					
Baseline	40.5 (2.6)		41.5 (2.61)		0.348
Change	-1.1 (3.5)	0.262	-0.6 (2.9)	0.489	0.673
Cholesterol (mmol/L)					
Baseline	4.52 (1.25)		3.92 (0.90)		0.066
Change	-0.36 (0.69)	0.074	0.27 (0.667)	0.182	0.040
HDL cholesterol (mmol/L)					
*Baseline**	1.0 (0.31)		0.97 (0.62)		0.878
*Change**	0.05 (0.27)	0.575	0.03 (0.19)	0.878	0.504
Triglyceride (mmol/L)					
*Baseline**	1.12(1.07)		1.18 (0.83)		0.681
*Change**	-0.22 (0.56)	0.636	-0.17 (0.82)	0.127	0.158
C-reactive protein (mg/L)					
*Baseline**	11.1 (9.9)		7.5 (5.6)		0.151
*Change**	-4.12 (11.2)	0.057	-0.8 (3.7)	0.077	0.472
Calcium (mmol/L)					
Baseline	2.30 (0.30)		2.22 (0.11)		0.370
Change	-0.03 (0.26)	0.727	0.02 (0.24)	0.729	0.620
Time-averaged calcium (mmol/L)					
Baseline	2.20 (0.26)		2.24 (0.17)		0.671
Change	0.04 (0.15)	0.328	0.01 (0.16)	0.993	0.496
Phosphorus (mmol/L)					
Baseline	2.03 (0.46)		1.49 (0.35)		0.002
Change	-0.09 (0.51)	0.560	0.06 (0.42)	0.644	0.452
Time-averaged phosphorus (mmol/L)					
Baseline	2.28 (0.46)		1.46 (0.28)		0.001
Change	-0.24 (0.36)	0.033	0.11 (0.25)	0.125	0.008
Ca-P product (mmol2/L2)					
Baseline	4.74 (1.49)		3.29 (0.78)		0.005
Change	-0.35 (1.27)	0.337	0.12 (0.86)	0.6152	0.275
Time-averaged Ca-P product (mmol2/L2)					
Baseline	5.01 (1.21)		3.26 (0.58)		0.001
Change	-0.49 (0.88)	0.068	0.25 (0.58)	0.147	0.018
PTH (pmol/L)					
*Baseline**	21.8 (29.1)		5.0 (3.8)		0.003
*Change**	4.5 (19.1)	0.040	2.0 (9.8)	0.046	0.608

Data are mean (SD) or, in case of evidence against normal distribution (*), median (interquartile range). PWV=pulse wave velocity; AIx=carotid augmentation index; Ca-P=product -calcium phosphate product; PTH=parathormone. Time averaged values were calculated using the results of 3, monthly blood values from before baseline and to end of follow-up.

Table 17 presents data on bone turnover and on serum levels of inhibitors of arterial calcification. Bone turnover at baseline was higher in patients started on sevelamer, but changes in β-crosslaps and osteocalcin levels were not significant and not different between groups during follow-up. There were no significant differences between the groups in fetuin-A, matrix GLA protein, osteoprotegerin, and soluble RANKL levels either at baseline or at the end of follow-up.

Table 17. Data on bone turnover and serum levels of inhibitors of arterial calcification

	Sevelamer	*p within group*	*Control*	*p within group*	*p between groups*
Osteocalcin (μg/L)					
*Baseline**	346 (577)		94 (206)		0.018
Change	-24 (130)	0.509	18 (53)	0.234	0.291
β crosslaps (μg/L)					
*Baseline**	3.04 (2.09)		0.85 (1.74)		0.016
*Change**	-0.04 (0.68)	0.733	0.44 (0.67)	0.034	0.440
Fetuin-A (g/L)					
*Baseline**	0.34 (0.10)		0.34 (0.08)		0.757
*Change**	-0.10 (0.06)	0.020	-0.07 (0.10)	0.203	0.588
Matix GLA protein (nmol/L)					
*Baseline**	4.99 (2.03)		3.65 (0.93)		0.086
*Change**	0.68 (2.79)	0.588	-0.15 (4.00)	0.375	0.572
Osteoprotegerin (pmol/L)					
Baseline	9.46 (5.02)		9.06 (2.65)		0.803
Change	-1.14 (1.65)	0.028	-0.18 (3.65)	0.858	0.397
Soluble RANKL (pmol/L)					
*Baseline**	145 (660)		82 (4801)		0.735
*Change**	-8.6 (200.5)	0.322	0.0 (63.6)	0.688	0.496

Data are mean (SD), or in case of evidence against normal distribution (*), median (interquartile range).

Using a forward selection procedure among baseline clinical and biochemical characteristics, baseline PWV was significantly associated with baseline CRP (p=0.008), systolic blood pressure (p=0.011), time-averaged phosphorus levels (p=0.042), and the presence of cardiovascular disease (p=0.033) (total r^2=0.625, Table 18). In a further forwardly selected multivariate model, change in PWV during follow-up as a dependent variable was determined by baseline CRP (p=0.034), sevelamer

treatment (p=0.042), diabetes (p=0.004), and baseline heart rate (p=0.016) (total r^2=0.608, Table 18).

Table 18. Parameters associated with the change in pulse wave velocity in the final multivariate linear regression model

Parameter	*β coefficient*	*p value*
Sevelamer treatment (yes vs. no)	-1.26	0.042
Diabetes (yes vs. no)	2.61	0.004
Baseline heart rate (by 1 beat/min)	-0.07	0.016
Baseline C-reactive protein (by 1 mg/L)	-0.07	0.034
Change in C-reactive protein (by 1 mg/L)	-0.04	0.388

4.3. Results of the third study

Baseline demographic, medical and laboratory information of the participants are presented in table 19.

4.3.1. Comparison of the two devices

Mean AI values measured with Arteriograph were significantly lower than those obtained by PulsePen (2.2 (25.6) % vs. 23.0 (12.1)%, p <0.001). Mean PWV values measured by Arteriograph were also significantly lower compared to PulsePen (9.9 (2.2) m/s vs. 11.1 (3.1) m/s, p < 0.01). Comparison of the AI values measured by the two methods showed statistically significant linear correlation (R = 0.527, p <0.001; fig. 13a). There was, however, no significant correlation between the PWV_A (PWV measured by Arteriograph) and PWV_P (PWV measured by PulsePen) values (R = 0.174, p = 0.097; fig. 13b). Figure 14 shows the Bland-Altman plots of the AI and PWV values measured by Arteriograph and PulsePen. For AI values, the mean between-method difference was –20.6 (21.8) %, and 27 (30) % of the 90 paired differences fall outside the ± 1 SD boundary of the mean difference. For PWV, the mean between-method difference was –1.2 (3.6) m/s, and 19 (20.6) % of the 92 paired differences fall outside the ± 1 SD boundary of the mean difference.

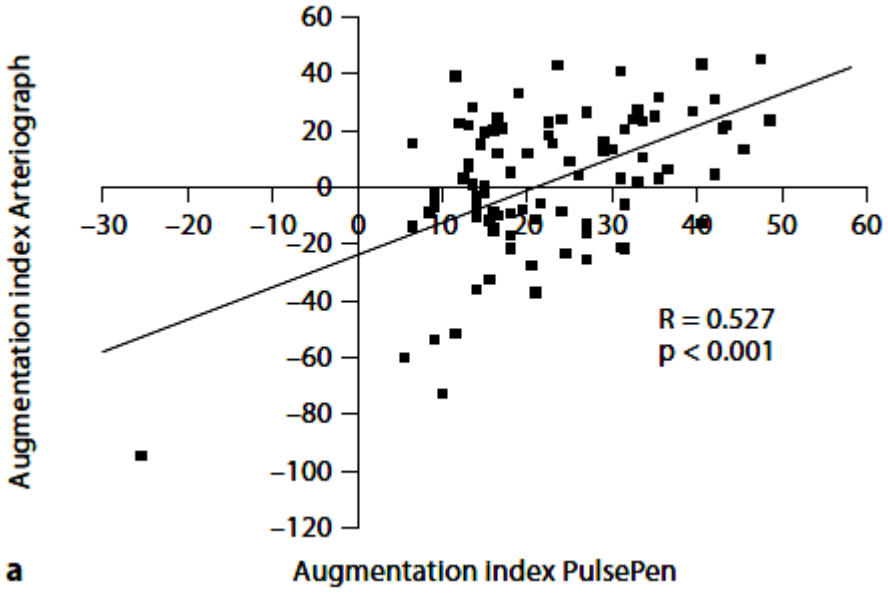
Table 19. Baseline clinical characteristics of the subjects.

patients	n	92
Age	years	62.4 (13.7)
Male n (%)	n (%)	57 (61.9)
Dialysis time*	months	29.5 (12.2-48.9)
Primary renal disease	n (%)	
Glomerulonephritis		13 (14.1)
Diabetic		32 (34.8)
Hypertensive		17 (18.5)
Tubulointerstitial		14 (15.2)
Polycystic		6 (6.5)
Other or unknown		10 (9.2)
Weight	kg	72.2 (15.7)
Body mass index	kg/m^2	25.1 (4.8)
Current smoking	n (%)	15 (16.3)
Diabetes	n (%)	37 (40.2)
Hypertension	n (%)	83 (90.2)
Cardiovascular disease**	n (%)	53 (57.6)
Medication	n (%)	
ACEI or ARB		48 (52.2)
Alpha blocker		28 (30.4)
Beta blocker		58 (63.0)
Ca-channel blocker		56 (60.9)
Active vitamin D		58 (63.0)
Ca-carbonate		73 (79.3)
Systolic blood pressure	mmHg	140.7 (23.7)
Diastolic blood pressure	mmHg	77.6 (12.1)
Heart rate	n/min	72.4 (13.1)
Hemoglobin	g/l	113 (15.7)
Albumin	g/l	39.5 (4.2)
Potassium	mmol/l	5.2 (0.89)
Creatinine	μmol/l	670 (252)
Blood urea nitrogen	mmol/l	20.4 (6.3)
Cholesterol	mmol/l	4.5 (1.2)
Trigliceride	mmol/l	2.17 (1.5)
Calcium	mmol/l	2.28 (0.2)
Phosphate	mmol/l	1.60 (0.54)
PTH	pmol/l	15.9 (26.2)
C- reactive protein*	mg/l	6.7 (4.1-12.4)

Data are mean (SD) or, in case of evidence against normal distribution (*), median (interquartile range) for continuous variables and n (%) for categorical variables.

*** Cardiovascular disease was considered to be present if there was a history of either coronary artery or cerebrovascular or peripheral artery disease.*

Fig. 13. a Linear regression of the AI values measured with the Arteriograph device versus the standard PulsePen tonometer. **b** Linear regression of the PWV values measured with the Arteriograph device versus the standard PulsePen tonometer.



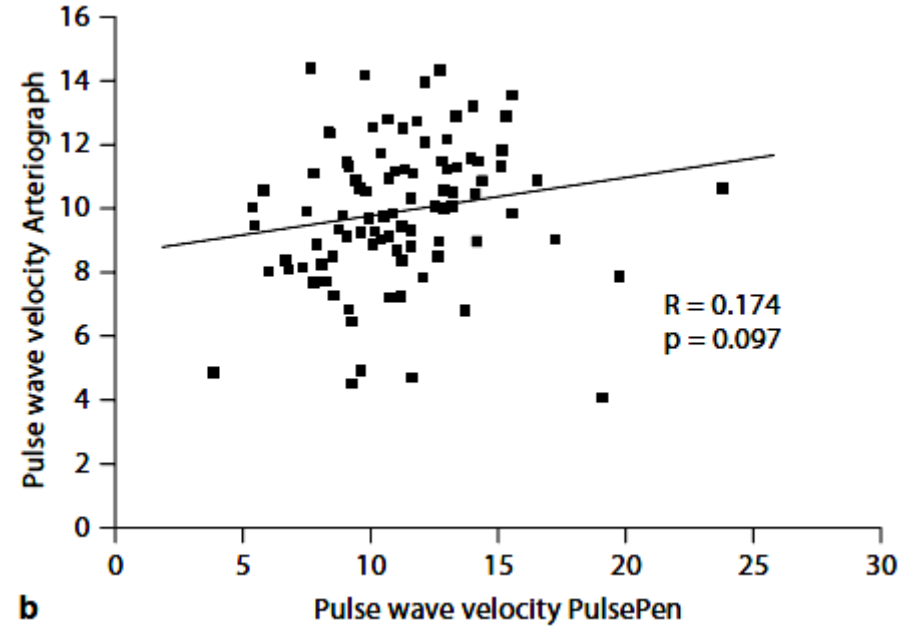
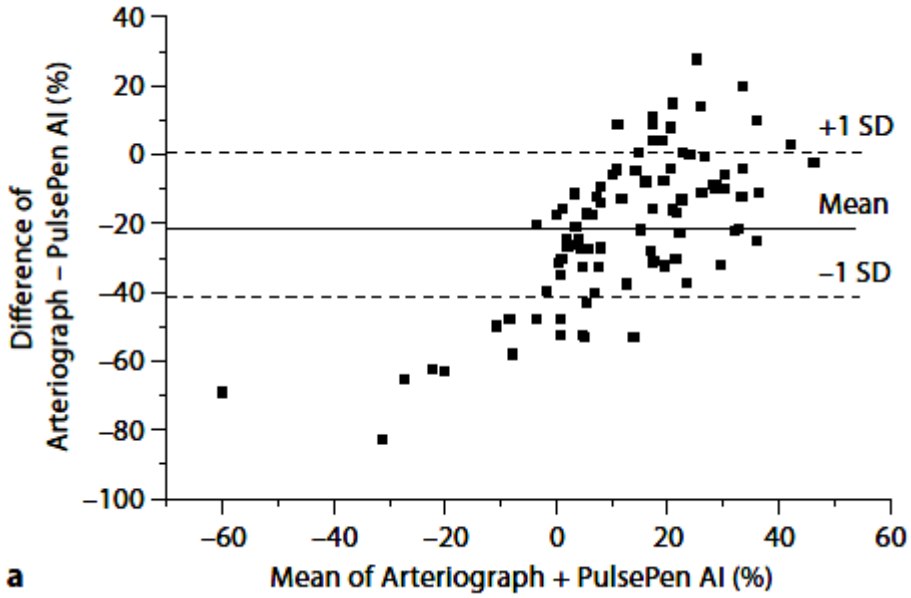
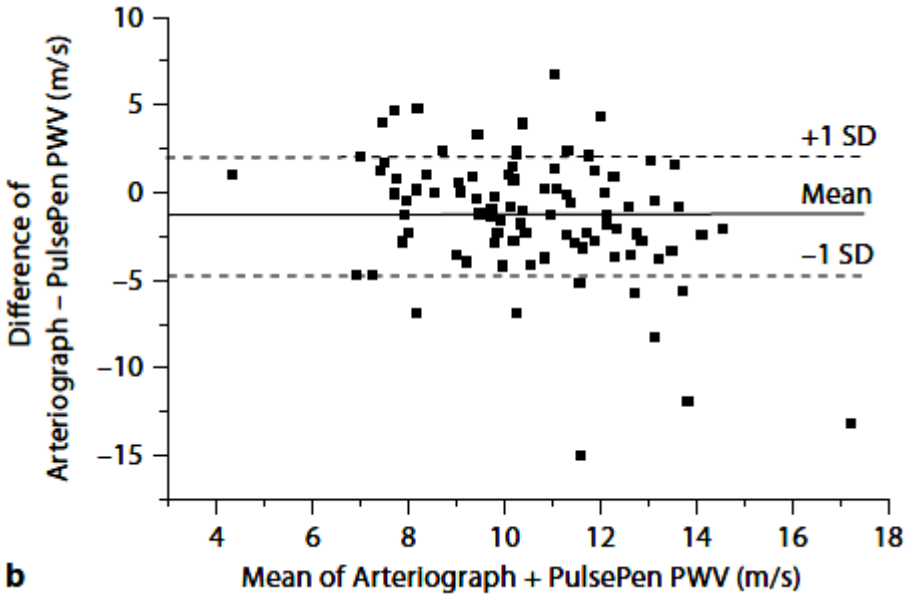


Fig. 14. Bland-Altman plots of (**a**) AI and (**b**) PWV values measured by Arteriograph and PulsePen.

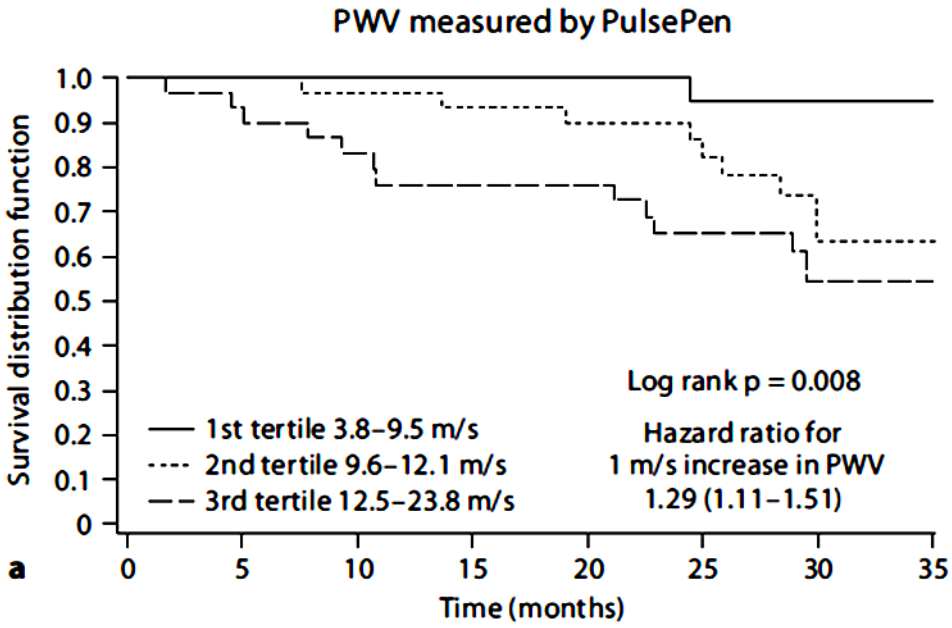




4.3.2. Survival Analysis

During follow-up, 36 of the 92 patients died (mortality rate 19.5/100 patient-years) of whom 21 died due to CV causes (myocardial infarction 7, sudden death 5, heart failure 4, stroke 3, arrhythmia 2). From the remaining 56 patients, 7 were transplanted, 1 stopped dialysis due to improvement in renal function, and data of 48 patients were censored at the end of follow-up. In separate log-rank tests, only increasing tertiles of PWV measured by PulsePen, but not that of PWV measured by Arteriograph, AI measured by PulsePen or AI measured by Arteriograph were related to CV mortality (log-rank p values 0.008, 0.135, 0.431, 0.243, respectively) (fig. 15). The results were similar in adjusted Cox-proportional hazard regression where data were considered as continuous variables: only increasing PWV measured by PulsePen, but not PWV measured by Arteriograph, AI measured by PulsePen or AI measured by Arteriograph were related to CV mortality (HRs associated with 1 m/s increase in PWV 1.29 [1.11–1.51] and 0.84 [0.62–1.14] and with 1% increase in AI 1.01 [0.96–1.05], 0.98 [0.96–1.01], respectively).

Fig. 15. Kaplan-Meier survival curves for CV mortality according to tertiles of PWV as measured by the PulsePen and Arteriograph (**a** , **b**) devices. HRs are adjusted for age, diabetes and established CV disease.



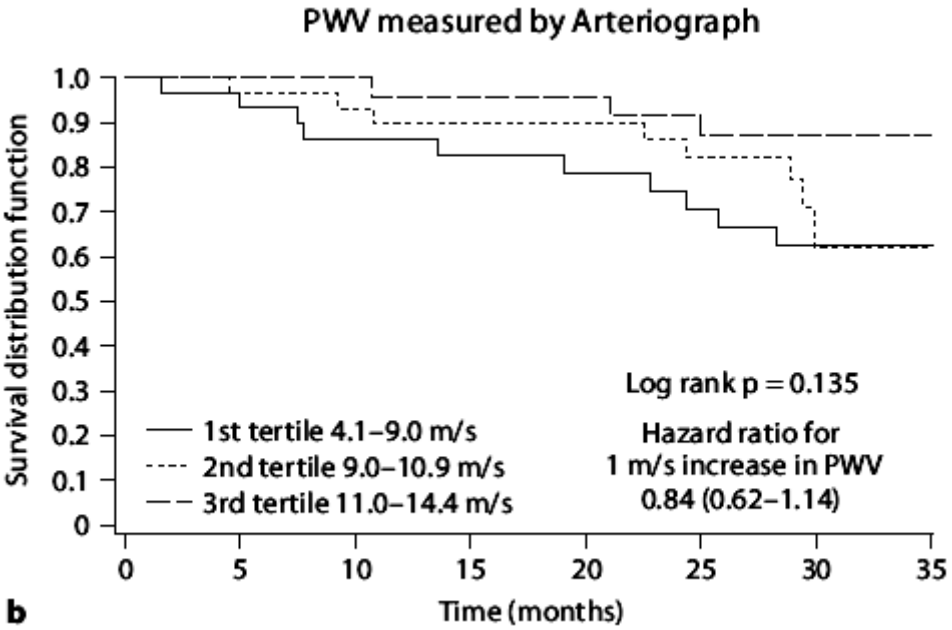
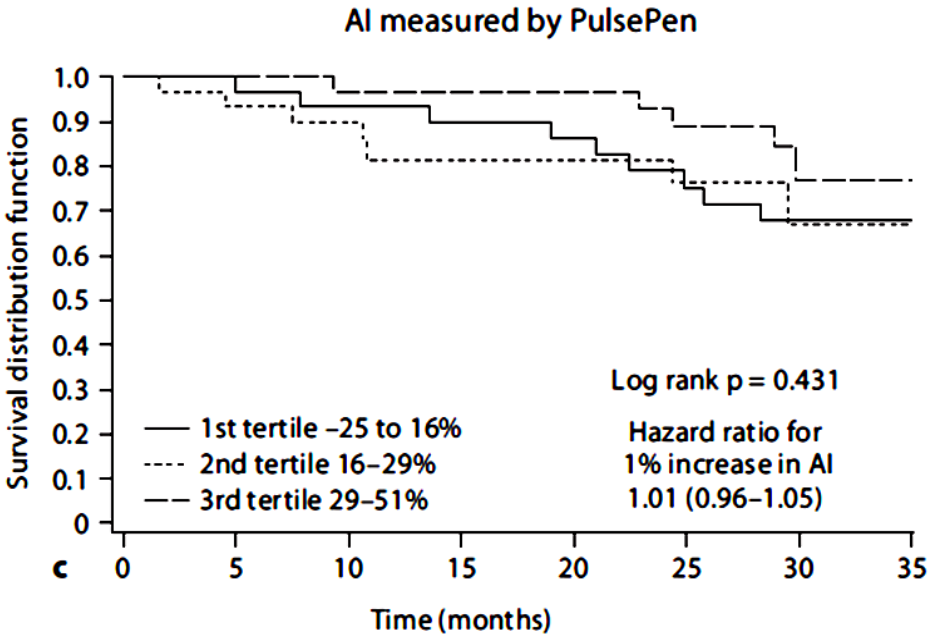
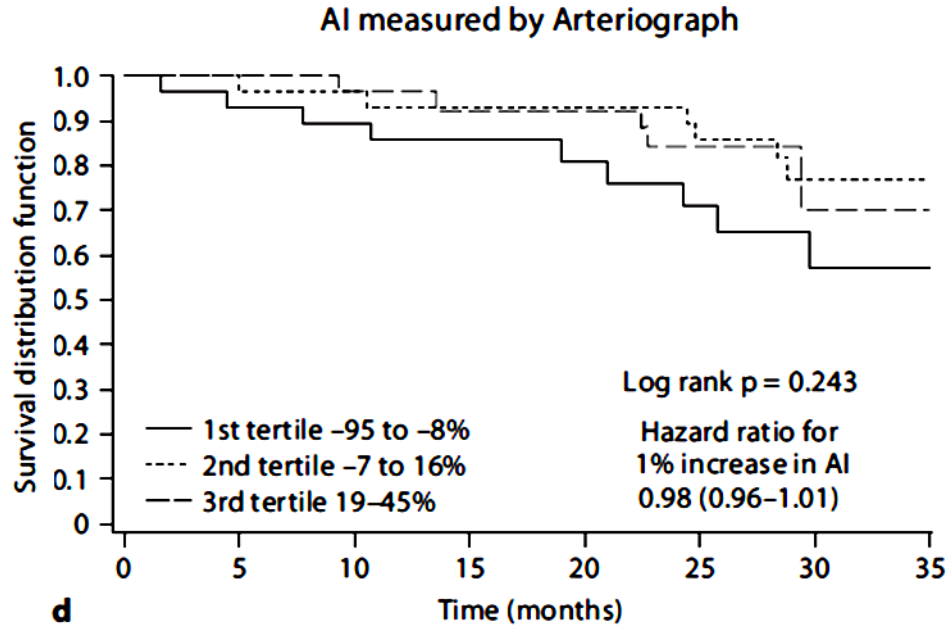


Fig. 15. Kaplan-Meier survival curves for CV mortality according to tertiles of AI as measured by the PulsePen and Arteriograph (**c** , **d**) devices. HRs are adjusted for age, diabetes and established CV disease.





5. DISCUSSION

5.1. Discussing the first study

The major findings of this follow-up study were that PWV measured before or after HD, and AMP measured before dialysis, independently and significantly predicted CV survival in ESRD patients on HD. My results, however, could demonstrate similar significant correlation between the AI or CPP and CV mortality in this population neither before nor after dialysis.

My conclusion regarding PWV confirms those of many other previous investigations in ESRD patients on HD and in other populations [236–239,156]; PWV is an arterial stiffness parameter that can strongly and independently predict CV mortality. Furthermore, to my knowledge, the association between PWV and CV mortality was not contradicted in any other previous investigations. All these observations demonstrate that PWV is the arterial stiffness parameter that adds significant prognostic information to established risk factors when assessing CV mortality risk. Indeed, it is not surprising that the European Society of Hypertension and European Society of Cardiology guidelines on hypertension management included PWV among markers of subclinical organ damage that aid physicians evaluating total CV risk [240].

The findings of my study, however, adds new prognostic information to the conclusions of previous studies in ERDS patients as I found that the relationship between CV mortality and higher PWV is significant irrespective of whether measurements are performed before or after dialysis. The effect of optimal timing of PWV measurement in relation to dialysis has not been previously evaluated or standardized. My observation suggests that the timing of PWV measurement plays a less important role in determining the prognostic power of PWV in this population. My conclusion that the predictive ability of PWV is not influenced by the time of measurement makes PWV an even more appealing and reliable measure of arterial stiffness for the assessment of CV risk in ESRD patients on HD.

My results, however, do not allow me to conclude whether high PWV was causally related to outcome or, alternatively, if it served only as a marker of underlying vascular disease affecting the aorta. For a given stroke volume, higher PWV (indicating stiffer aortic walls) would lead to the formation of a forward traveling pulse wave with higher amplitude. This, combined with a faster return of the reflected pressure wave, would result in increased central PP, increasing thereby cardiac afterload and decreasing diastolic coronary circulation [241]. Increased cardiac afterload leads to increased oxygen demand and decreased coronary artery circulation leads to decreased oxygen supply. The discrepancy between increased demand and decreased supply of oxygen could serve as a major cause of the cardiac events and complications of increased arterial stiffness which may lead to increased CV morbidity and mortality. The association between PWV and central PP was confirmed in my study; there was a significant correlation between PWV and CPP (correlation coefficient: 0.421; $p < 0.001$ for predialysis and 0.285; $p = 0.005$ for postdialysis values, respectively). Also, there was a significant relation between CPP and CV mortality when CPP was measured before dialysis and when the analysis was unadjusted ($p = 0.041$). The observation, however, that CPP was not related to CV mortality in my adjusted analysis (p-values before and after dialysis were 0.922 and 0.225, respectively) suggests that other alternative mechanisms may link PWV to the CV survival, or that PWV is simply a risk factor but not a causal player. My data do not allow me to make a distinction and this needs further study.

Augmentation index, as a relative measure of wave reflections, has widely been used to describe arterial stiffness in several investigations [80]. AI, however, is influenced by a multitude of factors not directly related to arterial stiffness (e.g. height, heart rate, small arterial and endothelial functions, etc.). This "multi-influenceability" may fade the prognostic value of AI. Indeed, only a limited number of studies have found an association between the AI and CV outcome: two were accomplished in patients with coronary heart disease [178,242] and one that was completed in ESRD patients on HD [179]. London et *al.* followed 118 ESRD patients for a mean of 52 months. At entry AI was determined by applanation tonometry on the common carotid artery. This study demonstrated that AI was a predictor of all-cause and CV mortality. After adjustment for all confounding factors, the risk ratio for each 10% increase in

augmentation index was 1.51 (95% confidence interval, 1.23 to 1.86; P<0.0001) for all-cause mortality and 1.48 (95% confidence interval, 1.16 to 1.90; P<0.0001) for CV mortality. These results provided evidence that in ESRD patients on HD increased of arterial wave reflections are independent predictor of all-cause and CV mortality [179]. The results of this latter study however were not confirmed in two subsequent studies: one was performed in younger ESRD patients on HD [243] and one was conducted among patients with CKD [236]. Covic et *al.* followed 92 ESRD patients on HD for a mean of 61 months; AI was determined by applantation tonometry using a SphygmoCor device and the outcome was all-cause mortality. In the Cox analysis AI did not reach statistical significance as an independent predictor for all-cause mortality. This study failed to support the notion that an increased effect of wave reflections on central arteries is a strong and independent predictor of mortality in all ESRD patients on haemodialysis [243]**.** In their study, Zoungas et *al.* followed 315 subjects with stages four to five CKD for a median of 3.6 years; the outcome was all-cause mortality. In this study carotid-derived AI was not proved as an independent predictor of all-cause mortality [236]. The main characteristics of these studies completed in ESRD and CKD patients are presented in table 20.

Table 20. Studies completed in ESRD and CKD patients to evaluate the predictive power of AI.

study	*year*	*follow-up (month)*	*n*	*population*	*outcome mortality*	*predictive value of AI*
London et *al.*	2001	mean 52	118	ESRD on HD	CV and all-cause	yes
Covic et *al.*	2006	mean 61	92	ESRD on HD	all-cause	no
Zoungas et *al.*	2007	median 43	315	CKD stage 4-5	all-cause	no
Othmane et *al.*	2009	median 29	98	ESRD on HD	CV	no

ESRD: end-stage renal disease, CKD: chronic kidney disease, HD: hemodialysis, AI: augmentation index.

In my study in ESRD patients, the fact that I failed to find an association between CV mortality and the AI is in line with the results of the studies accomplished by Covic et *al.* [243] and Zoungas et *al* [236] in these populations. While the explanation for the contrasting results is not clear and possibly, at least in part, relates to differences in baseline characteristics of subjects involved, these three negative studies

strongly question the widespread clinical use and importance of the AI for CV risk assessment in ESRD patients on HD.

Central PP has recently been shown to be more strongly related to CV outcome than brachial PP [164]. The popularity of central PP in predicting outcome was further strengthened by the findings of the Conduit Artery Function Evaluation Study (CAFE) in which central PP was associated with CV outcome in hypertensive patients treated with a regimen based on atenolol or amlodipine [168]. While the concept that central PP represents pressure load to the heart better than brachial PP makes this parameter an appealing one for describing central hemodynamics and associated CV risk, central PP is not entirely a direct measure of central arterial stiffness as it also depends on the amount and timing of wave reflection that augments the 'first-shoulder' of the pressure wave [244].

To my knowledge, there is only one previous publication about the prognostic value of CPP on hard outcomes in ESRD patients on HD [187] (table 21.). In this study Safar et *al* followed up a cohort of 180 patients with ESRD for a mean of 52 months, the outcome was all-cause (including CV) mortality. Adjusted hazard ratio for 1-SD increments was 1.4 (95% confidence interval 1.1 to 1.8) for CPP. This result provided evidence that in patients with ESRD, the carotid PP is a strong and independent predictor of all-cause (including CV) mortality. It must be mentioned that in this study the correlation between AI and CV mortality was not examined separately.

In my study, CPP was significantly related to CV mortality only in the unadjusted analysis and only when predialysis values were concerned; for 1 mmHg increase of CPP, unadjusted hazard ratio was 1.02 (95% confidence interval, 1.01–1.04; p=0.041). In my adjusted analysis, such a significant relation between CPP and CV mortality was not demonstrable (p-values before and after dialysis were 0.922 and 0.225, respectively). The explanation for the difference between my consequent and the previous result may be related to differences in basic patient characteristics or the fact that I assessed CV mortality as outcome, while Safar et al. analyzed all-cause mortality [187].

Table 21. Studies completed in ESRD patients to evaluate the predictive value of CPP and AMP.

study	*year*	*follow-up (month)*	*n*	*population*	*outcome mortality*	*predictive value of*	
						CPP	*AMP*
Safar et *al.*	2002	mean 52	180	ESRD on HD	all-cause	yes	yes
Othmane et *al.*	2009	median 29	98	ESRD on HD	CV	no	yes

ESRD: end-stage renal disease, HD: hemodialysis, CPP: carotid pulse pressure, CV: cardiovascular.

Pulse pressure amplification is a parameter that is intended to describe the change in vessel wall characteristics from the central elastic aorta to the more muscular and stiffer brachial artery. Amplification may be viewed as a direct measure of central arterial stiffness, as brachial artery wall characteristics change little, for example, with age. Therefore, decreased AMP between these two sites indicates stiffening of the walls of the central aorta [245]. Amplification, however, also depends on factors not directly related to the central arterial stiffness (e.g. heart rate, height, stroke volume and wave reflections).

While AMP is associated with CV risk factors in cross sectional studies [181], data on its independent prognostic value are limited. In the follow-up study accomplished by Safar et *al* [187] (table 2.), AMP was also examined as a ratio of central to peripheral pulse pressure measured by applanation tonometry; adjusted hazard ratio for 1-SD increments was 0.5 (95% confidence interval, 0.3 to 0.8) for AMP. This observation demonstrated that in patients with ESRD, AMP is a strong and independent predictor of all-cause mortality. Here, it must be mentioned that Safar *et al.* did not examine the effect of timing of the measurement in relation of the dialysis procedure on the predictive ability of AMP.

In my study, decreased AMP measured prior to dialysis was a strong determinant of CV mortality; adjusted hazard ratio for 10% decrease of AMP was 1.41 (95% confidence interval, 1.03–1.89; P=0.030). This result is in line with the study performed by Safar et *al.* [187]. My finding may suggest that in predicting CV risk, AMP is more similar to direct measures of stiffness, such as PWV, as opposed to parameters that depend more on wave reflections, such as AI and CPP.

While in my study both pre- and postdialysis PWV values were related to outcome, the strength of the association was weaker when postdialysis data were considered. Furthermore, only predialysis, but not postdialysis AMP was related to CV mortality. This suggests that the dialysis procedure elicited a compensatory response that diminished the relationship between measures of central arterial stiffness and outcome. At the end of dialysis, I noted an increase in blood pressure, heart rate and PWV. These changes are compatible with activation of the sympathetic nervous system as a compensatory response to acute fluid removal or the effects of the dialysis membrane used [246–248]. It is plausible to assume that such compensatory hemodynamic responses to the dialysis procedure temporarily mask or at least weaken the relationship between arterial stiffness and CV risk, suggesting that predialysis measurements should probably be preferred.

In summary, my findings indicate that among the different parameters of arterial stiffness PWV is the one that stands as the most robust prognostic factor with AMP providing further prognostic information.

5.2. Discussing the second study

In this follow-up study of ESRD patients on HD, I found that treatment with sevelamer was associated with improvement in aortic stiffness when compared with concomitant controls on calcium carbonate. Sevelamer treatment, however, was not associated with changes in parameters of bone turnover or/and serum levels of inhibitors of vascular calcification.

Decreased aortic compliance has recently emerged in several studies as an important independent nontraditional risk factor for CV events in ESRD patients on HD [169,249]. Aortic stiffening, however, is likely to be far more than a simple prediction tool, as mounting evidence attests to its causal role in initiating CV events through early pressure wave return with increased systolic pressure load to the heart and subsequent decrease in diastolic pressure that causes impairment in the circulation of coronary artery [250–252]. The clinical relevance of aortic stiffening and central aortic pressure is further emphasized by the results of recent therapeutic trials in ESRD patients on HD

[253] as well as hypertensive patients [168]. In these studies, brachial blood pressure independent improvement in PWV [253] and central PP [168] were associated with better patient survival and lower incidence of the composite CV outcomes, respectively.

These observations suggest that influencing aortic stiffness by therapeutic maneuvers will have relevance in the improvement of patient outcomes as well. As in my study I found that sevelamer treatment was associated with an improvement in carotid–femoral PWV, this observation holds promise that sevelamer therapy will impact on patient survival as well. Indeed, recent data published from the Dialysis Clinical Outcomes Revisited (DCOR) trial [254] and other [255] studies seem to support this notion. The DCOR trial was a multicenter, open-label study that included 2100 ESRD patients on HD from 75 American dialysis units. Patients were randomized to receive sevelamer or calcium carbonate, and were then followed for 45 months. In this study the results for the primary end point showed a 9% reduction in all-cause mortality with sevelamer relative to the calcium-binder group (p=0.30), and a significant 54% reduction in those age 65 years or older (p=0.0009).

To my knowledge, only one previous analysis has been published about the effects of sevelamer treatment on arterial stiffness, with conclusions similar to mine [256]. In this study, Takenaka et *al.* followed up fifteen ESRD patients on HD for six months without involving concomitant controls. Aorto-tibial PWV was measured using an automated polygraph device (AT Form; Nihon Colin Co. Aichi Ltd, Japan) after HD sessions when the patients had reached their own dry weights. At the end of follow-up they noted that the progressive worsening in heart-tibial PWV was attenuated by six month treatment with sevelamer. My work provided additional information as I followed sevelamer treated patients and concomitant controls for almost one year and evaluated carotid–femoral PWV as outcome. This latter parameter has been shown to be clinically more relevant among different arterial stiffness measures identified in ESRD patients on HD compared to aorto-tibial PWV [257]. The mean characteristics of the two studies are presented in table 22.

Arterial stiffening and increase in PWV is a progressive process in dialysis patients as shown in the work of Takenaka et *al.* [256] and also shown in others studies [258,213]. In my study I have observed progression of PWV in control subjects (+0.93

m/s) and an improvement in those treated with sevelamer (-0.83 m/s), the difference of changes between the two groups being statistically significant (P=0.042).

Table 22. The major differences between the two studies accomplished by Takenaka et *al.* and Othmane et *al.*

study	*device*	*n*	*control (n)*	*time of follow-up (months)*	*PWV*	*AI*	*calcification inhibitors*	*bone turover*
Takenaka *et al.*	automated polygraph	15	no	6	aorto-tibial (cm/s)	not examined	not examined	not examined
Othmane *et al.*	tonometric PulsePen	26	13	10.8	*carotid-femoral (m/s)	carotid AI (%)	Fetuin-A m GLA OPG	β crosslaps osteocalcin s RANKL

PWV: pulse wave velocity, AI: augmentation index, s RANKL: soluble RANKL, m GLA: matrix GLA protein, OPG: osteoprotegerin.
**carotid-femoral PWV measured by tonometric device is accepted as "gold standard"*

One can, however, only speculate on the potential mechanisms by which sevelamer treatment may have affected and improved PWV in this study. There are several, not mutually exclusive, explanations to this, such as a decrease in phosphate or cholesterol levels, or decreasing microinflammation. All these are known metabolic consequences of sevelamer therapy and, at the same time, are also known to influence PWV, either through affecting arterial calcification or through other functional–structural vessel wall alterations. I noted the expected changes in all these parameters, so it is difficult to discern which mechanism might have played the most relevant role in the improvement of PWV.

Total cholesterol decreased by 0.36 (0.69) mmol/L in patients treated with sevelamer, and increased by 0.27 (0.67) mmol/L in controls (p=0.040). Taking into consideration that the use of statin therapy did not change during follow-up, thereby decreased cholesterol concentration was likely to be attributed to sevelamer treatment as it is a known consequence of this therapy. The change in total cholesterol levels, however, was not related to the observed changes in arterial stiffness. This may allow me to conclude that the effect of sevelamer therapy on PWV during follow-up was not related to lowering of total cholesterol.

I have observed only minor changes in serum levels of markers of bone metabolism and concentration of the inhibitors of vascular calcification; changes did not reach the level of statistical significance (p values for osteocalcin and β crosslaps are 0.291 and 0.440, respectively). Furthermore these changes were not related to the change in PWV during follow-up.

Vascular calcification is believed to be in part regulated by inhibitors of calcification such as fetuin-A, matrix GLA protein, and osteoprotegerin [259]. While the exact mechanisms by which these proteins impact on vascular calcification in humans remain unexplained at present, measuring their serum levels has clinical relevance, as they have been shown to be independently associated with the survival of ESRD patients on HD [260,261]. The beneficial effect of sevelamer on aortic calcification raises the intriguing question of whether sevelamer treatment influenced the serum levels of these inhibitors and whether changes in PWV during therapy were related to changes in their levels.

In my study, changes observed in serum levels of fetuin-A, matrix GLA protein, osteoprotegerin, and soluble RANKL were minor, and the difference between sevelamer-treated and control patients (p-values: 0.588, 0.572, 0.397, 0.496, respectively) was not significant. Furthermore, baseline levels and changes in serum concentrations of these inhibitor proteins during follow-up were not associated with the observed change in PWV. All these suggest that sevelamer therapy has no profound effect on the serum activity of the examined inhibitors of vascular calcification, and that aortic stiffness is not strongly related to their levels in ESRD patients on HD. As for fetuin-A and osteoprotegerin, this latter conclusion is supported by recent investigations of others [262,263]. All these observations suggest that the improvement of aortic PWV induced by sevelamer therapy was mediated by such a mechanism which is independent of the process of bone turnover and/or the effect of inhibitors of vascular calcification.

Evidences suggest that Ca and P may have direct effects on vascular cells that predispose to mineralization. High levels of P and/or Ca directly activate genes related to an osteoblastic phenotype in the VSMC contributing to their transformation into osteoblast like cells [115]. Increased Ca and Ca X P are important and clinically evident contributors to vascular calcification in ESRD [121]. In the presence of a medium with

high level of Ca and P, exposed VSMCs suffer rapid calcification [122] while increased intracellular P levels induce osteoblastic differentiation of vascular cells [123]. To demonstrate if the improvement of aortic stiffness is mediated by the effect of sevelamer on P and Ca metabolism, I determined the actual and time-averaged serum levels of P, Ca, Ca X P and PTH at the start and end of follow-up. As expected, time averaged P and Ca X P decreased in the sevelamer group and the differences between sevelamer-treated and control groups were significant. While this may suggest that changes in the mineral metabolism were affecting PWV, the fact the change in PWV was not related to changes in P and Ca X P points to other mechanisms.

Microinflammation and therefore, C-reactive protein (CRP) are considered as nontraditional CV risk factor in ESRD patients on HD; CRP is 10-fold higher in these patiens than in the normal population. CRP is closing the loop between inflammation and atherosclerosis and thereby it is directly linked to vascular calcification in this population (see chapter 1.1.4.). In my study, it is tempting to speculate that decreased microinflammation by sevelamer treatment was the main responsible mechanism for the observed changes in PWV during follow-up. This assumption is supported by studies that observed improvement in CRP levels by sevelamer therapy [264] (see chapter 1.1.3.).

Decreased inflammation and serum CRP level could serve a plausible explanation for the mechanism how sevelamer influenced aortic PWV. Indeed, basic CRP and changes in PWV were significantly related in my multivariable analysis. The fact, however, that sevelamer treatment remained significant (β-coefficient: -1.26, p-value: 0.042) in the final multivariate linear regression model suggests that additional mechanisms contributed to the establishment of sevelamer effect on aortic PWV. Further studies are needed to determine by which mechanism sevelamer influences PWV.

5.3. Discussing the third study

My accomplished validation study demonstrated a significant correlation between AI measured by Arteriograph – a new oscillometric device widely used to

determine arterial stiffness – and the one measured by a (gold standard) tonometric comparator, the validated PulsePen device, in the high CV-risk ESRD patients on HD. Similar statistically significant correlation was not confirmed in the aspect of PWV in the same patient group.

Moreover, while the validation of Arteriograph has been accomplished in three previous cross-sectional studies of non-hypertensive and hypertensive patients comparing it with the tonometric Complior and SphygmoCor devices, my study is the first where the subjects were followed and the predictive value of AI and PWV measured by Arteriograph and PulsePen for CV mortality were evaluated and compared to each other. In this regard I found that only PWV-values measured by tonometric PulsePen but not the ones measured by oscillometric Arteriograph were significantly related to CV mortality. AI, measured by either method, was not related to CV mortality.

The risk of CV mortality in patients with ESRD on HD is 20 to 30 times higher than that of the general population (see chapter 1.3.2.). This observation, at least in part, is due to the fact that ESRD patients on HD have much stiffer arteries compared to the general population of the same age and blood pressure levels [265]. As a consequence of these facts, the accurate measurement of the arterial stiffness parameters has clinical significance among patients with ESRD on HD. The requirement of accurate measurement necessitates the use of devices with appropriate validation. Clearly, before new devices enter clinical application in a patient population with specific vascular wall alterations, their validity needs to be tested. In the last few years, in the line of the devices that measure arterial stiffness non-invasively, new devices using alternative procedures for the measurement of arterial stiffness were developed. For example, the 'PeriScope' device measures arterial stiffness by using oscillometric technique. The device uses automatic simultaneous limb blood pressure measurements (by placing four blood pressure cuffs placed above the ankles and on the upper arms) and ECG to calculate parameters of arterial stiffness such as brachial-ankle PWV [266]. Similarly, the operation of the new Arteriograph is based on the oscillometric theory. The difference between the two devices is represented by the automatic calculation of arterial stiffness parameters by Arteriograph, using only one cuff, a "sensor" placed on

the upper arm, which eventually makes the device less time-consuming and operator-dependent.

The Arteriograph has recently been validated against Complior and SphygmoCor devices in three studies as seen in table 23. The first validation study, comparing Arteriograph to standard devices, in patients with low CV risk, showed good validity for AI but only moderate for PWV. In the first study (Baulmann *et al*) the lower correlation coefficient between the test and standard device for PWV was explained by the fact that Arteriograph-measured aortic PWV uses a different method, with a different "theoretical and practical background" [233]. In the second study (Rajzer *et al.*) the examiners observed differences in PWV values obtained by the three devices and they attributed it to differences in calculating traveled distance [267].

Table 23. Studies completed to validate Arteriograph device vs. Complior and SphygmoCor.

study	*year*	*population*	*n*	*parameter*	*used devices*	R^2
Baulmann *et al.*	2007	healthy	51	PWV	Arteriograph vs. Complior	0.48
				PWV	Arteriograph vs. SphygmoCor	0.49
				AI	Arteriograph vs. SphygmoCor	0.85
Rajzer *et al.*	2008	longstanding hypertension	64	PWV	Arteriograph vs. Complior	0.13
				PWV	Arteriograph vs. SphygmoCor	0.09
Jatoi *et al.*	2009	untreated hypertension	254	PWV	Arteriograph vs. Complior	0.36
				AI	Arteriograph vs. SphygmoCor	0.79
Othmane *et al.*	2009	ESRD	92	PWV	Arteriograph vs. PulsePen	0.03
				AI	Arteriograph vs. PulsePen	0.28

The third study performed in a large population of untreated hypertensive patients by Jatoi *et al*. has been published shortly after my validation study was reported [268]. In this study, there was a poor agreement between Complior and Arteriograph for measuring PWV and this leaded the authors to conclude that "*Arteriograph method is not a suitable method for assessing PWV in clinical practice*". The poor agreement between PWV and AI measured by the three devices leaded to the conclusion that these techniques cannot be used interchangeably and thus "*Arteriograph device cannot be considered the 'gold standard' technique pending prospective outcome studies"*. My

study fills this gap, as I did not only completed a cross-sectional validation study with poor agreement for PWV between Arteriograph and the tonometric method but also followed the patients for hard outcomes and proved good prognostic validity only for the tonometric method, not for Arteriograph.

While the first two studies generated hesitation about the ability of Arteriograph for determining PWV, and authors tried to interpret the poor agreement by methodological differences, the third study and mine strengthen the doubt that Arteriograph is not a suitable method to measure PWV and is not a good choice for prospective outcome studies. Moreover, all three previous studies were completed in populations with low CV risk and there have been no data available about the validity of Arteriograph in a high CV risk patient population such as ESRD patients.

In my validation study the correlation coefficient between the AI values of the two devices was moderately high but statistically significant. This result is similar to that of the previous Arteriograph validation studies where a close agreement between the AI values provided by Arteriograph, Complior, and Sphygmocor was confirmed. Therefore, my finding supports the validity of Arteriograph in measuring this parameter.

Augmentation index is influenced by a multitude of factors not directly related to arterial stiffness (see chapter 1.2.3.4.). Evidence demonstrated that AI has a predictive value in some special populations but its role in predicting mortality in ESRD population is contradictive and not unequivocal (see chapter 1.4.). In my first study, no relation was found between AI and CV mortality in ESRD patients on HD. In this study AI measured by the new oscillometric method did not show associations with CV mortality either. It seems that though Arteriograph measures different AI values than Pulse Pen in ESRD patients on HD, their clinical prognostic value are equally poor.

The European expert consensus document on arterial stiffness published on 2006 considered carotid-femoral PWV as the ‘gold standard’ for arterial stiffness, which has the largest amount of epidemiological evidence for its predictive value for CV events and mortality. This parameter is confounded by less factor than AI. Prospective studies provided multitude of cumulative evidence that PWV is a relevant and independent predictor of CV and all-cause mortality in several population including ESRD (see

chapter 1.4.).As for the validity of Arteriograph, only poor and statistically not significant correlations were found between PWV-values measured by the PulsePen and Arteriograph. The difference in the results of PWV measurements is likely related to the fact that the two devices measure arterial stiffness parameters by different methods as summarized in table 24.

Table 24. Main differences between the PulsePen and Arteriograph devices.

	PulsePen device	***Arteriograph device***
method	applanation tonometry	oscillometry
ECG	used	not used
transit time (Δt)	uses QRS complex as a reference frame to determine	estimates the 'return time' of the reflected wave.
traveled distance	the *actual* distance between carotid and femoral recording sites, (measured manually)	two time of the distance between *theoretically* determined pulse wave reflecting site (symphysis) and jugulum.
parameters	carotid-femoral PWV, carotid AI, central PP	brachial PWV, brachial AI, brachial PP
prognostic value	*data* on validation and prognostic value of parameters *are widely available*	*data* on validation and prognostic value of parameters *are limited*
validation	compared with invasively determined parameters by catheter (gold standard)	compared with non invasively determined parameters by Complior and SphygmoCor
	in patients with low and high CV risk	only in patients with low CV risks
	strong PWV and AI agreement	strong AI, but poor PWV correlation
	prospective and cross-sectional study	no prospective study available

PWV: pulse wave velocity, AI: augmentation index, PP: pulse pressure, CV: cardiovascular

PulsePen uses classical ECG-guided sequential tonometric measurements to obtain carotid-femoral PWV by recording the waveforms at different sites on separate occasions and using the QRS complex of a simultaneously recorded ECG as a reference frame to determine time of transit (Δ t). Arteriograph, on the other hand, detects the pressure waves at the brachial site and uses pulse wave contour analysis without the transfer function to assess PWV. This is accomplished by estimating the 'return time' of the reflected wave (Δ t) based on the identification of the forward and reflected waves. With the measurement of the jugulum-symphysis distance to estimate aortic length (L), PWV is then calculated by the software using the PWV = 2L/ Δ t formula. Recently, it has been suggested that PWV calculated with the suprasternal notch-symphysis distance

as travel distance is unlikely to be accurate [269]. As the site of wave reflection becomes more distal to the heart with increasing arterial stiffness, PWV calculated with a fixed - and shorter - distance becomes gradually underestimated. This, in part, provides an explanation for what my Bland-Altman plot shows; Arteriograph makes a bigger mistake when measuring higher PWV values. This finding also explains why I did not find any significant association between PWV values measured by the standard tonometric and the tested oscillometric methods.

The results of the follow-up part of my study are in line with those of previous studies, where PWV measured with the standard tonometric method was found to be a predictor of CV mortality assessed either by log-rank test or by Cox proportional hazards regression [8]. PWV measured by Arteriograph, on the other hand, was not related to this outcome supporting the notion of limited validity of Arteriograph to assess this parameter in ESRD patients on HD.

While PulsePen, as well as other validated tonometric devices, can demonstrate a strong and significant relation between PWV and CV mortality and strengthen the conclusion that PWV provides a significant clinical predictive value in ESRD patients, Arteriograph seems to provide unvalid PWV results in ESRD patients. All these note me to conclude that Arteriograph can not be used for PWV and risk evaluation in patients on HD.

6. LIMITATIONS OF THE STUDIES

Discussing the reached results of the investigation gives a possibility to create an illustration about the mechanisms and relations of how the projected objective(s) could be demonstrated and proved. This created image would be unreliable and deformed without the assessment of study limitations and without focusing the light on the probable influence of limitations on the correlation between variable(s) and outcome(s). Therefore, the limitations of the performed three studies should be acknowledged in this section.

6.1. Limitations of the first study

First, the number of participants in my study was relatively small (n = 98). While this is unlikely to have influenced my positive findings, it is possible that a type two error occurred and I failed to find further significant associations, for example between CPP and CV mortality, when indeed they existed.

Second, I used only age, diabetes and established CV disease as covariates in my adjusted survival analysis. This was decided *a priori* as all of these are known determinants of CV outcome in ESRD patients on HD and inclusion of further variables could have led to overadjustment and loss of power.

Third, my explanation of the decreasing strength of association between outcome and PWV or AMP after dialysis should be viewed only as hypothesis generating and not explanatory, as I did not measure relevant hemodynamic parameters such as stroke volume, total peripheral resistance and sympathetic nervous system activity.

Finally, I indicate in my discussion that predialysis AMP may be more similar to PWV in predicting CV mortality of ESRD patients than other arterial stiffness parameters such as CPP and the AI. However, the fact that both PWV and AMP remained significantly related to the outcome in the analysis that included both of these parameters in the same adjusted model suggests that these two measures of arterial

stiffness provide, in some way, complementary prognostic information for which the explanation is not clear from my data.

6.2. Limitations of the second study

First, this was an observational study without random assignment of the participants to sevelamer treatment. As a consequence, the baseline parameters of Ca-P metabolism and markers of bone turnover were not comparable between sevelamer-treated patients and those continuing previous therapy. This was related to the fact that at the time of the beginning of the study, indications for sevelamer treatment and reimbursement in Hungary were tied to serum levels of Ca, P, and Ca-P product exceeding certain limits. I believe, however, that this limitation is unlikely to have biased my main conclusion, as in the case of comparable baseline P levels and Ca-P product in my control patients, one may have expected an even more pronounced progression in their PWV values during follow-up, further enhancing the contrast to those treated with sevelamer.

Second, while I tried to match sevelamer-treated and control patients in baseline parameters, I cannot exclude the possibility that unmeasured covariates influenced my results.

Third, the number of subjects in this study was small. While this fact is unlikely to have impacted the main conclusion, a β error might have occurred, and I may have failed to identify relevant differences between sevelamer-treated and control patients at baseline or by the end of follow-up.

Finally, the results of the linear regression modeling should be viewed with some degree of caution and regarded as hypothesis generating rather than explanatory, given the low number of subjects and the high number of variables used in these analyses.

6.3. Limitations of the third study

I used the validated PulsePen device to obtain reference values for PWV and AI. Although this device is commercially available for some years, only a limited number of publications are available about its use [21]. Nevertheless, PulsePen applies a widely accepted method for the assessment of PWV and AI and the validity of these readings has been established [10]. The fact that in my study PWV obtained by the PulsePen device showed significant association with CV survival of my ESRD patients on HD indicates that the use of PulsePen as a reference standard was, indeed, well established.

7. SUMMARY AND FUTURE DIRECTIONS

In the ***first study*** I found that in ESRD patients on HD among different parameters of arterial stiffness, PWV is consistently related to CV mortality irrespective of the timing of the measurement in relation to the dialysis. Measuring AMP before dialysis, however, seems to add further prognostic information. Parameters of arterial stiffness that depend more on the timing and amount of wave reflection were not related to the outcome. Whether these conclusions hold in other high risk populations as well needs a further study. In further studies factors that affect PWV shall be evaluated with the prospect of influencing patient-outcome.

In the ***second study*** I observed an improvement in aortic stiffness during sevelamer treatment in ESRD patients on HD. As aortic stiffness is likely to be causally related to patient outcome, this treatment holds promise to decrease the burden of CV disease in this population. Given the limitations of this study, however, the results need to be confirmed in larger randomized clinical trials. In further studies I plan to evaluate the effect of new formulation of sevelamer (sevelamer carbonate) on arterial stiffness.

In the ***third study***, although I found correlations between AI indices obtained by the reference and test devices, the lack of correlation between PWV values and the lack of prognostic value of PWV provided by the new method, as opposed to standard, limits the clinical use of Arteriograph in assessing PWV in ESRD patients on HD. Whether these conclusions about the use of Arteriograph are true for other high CV risk populations requires a further study. It seems that in ESRD population the Arteriograph has limited clinical value.

8. ABSTRACT

In end-stage renal disease (ESRD) patients, calcification of the large arteries begins early, facilitating a 20- to 30-times higher rate of cardiovascular mortality (CV) than in the age-matched general population. In ESRD patients, the prognostic value of arterial stiffness parameters (pulse wave velocity: PWV, augmentation index: AI, central pulse pressure: CPP and carotid-femoral pulse pressure amplification: AMP) in one cohort for CV survival, the effect of phosphate binder sevelamer on aortic stiffness and the validation of the oscillometric device (Arteriograph) has not previously been examined.

I have performed three studies in ESRD patients; the first examined the predictive power of different stiffness parameters for CV mortality evaluated in a single cohort. The second study assessed the effect of sevelamer on aortic stiffness, and the third evaluated the validity of Arteriograph device and the predictive value of measured parameters for CV mortality, compared to those of the reference PulsePen device.

The first study showed that, pre- and postdialysis PWV and predialysis AMP values were related to CV mortality. In the second study, by the end of follow-up, PWV decreased in sevelamer-treated patients while it increased in controls. The direction of changes of AI was similar, although it did not reach the level of statistical significance. In the third study, AI values measured by the two devices showed statistically significant linear correlation, while for PWV similar correlation was not observed. Only PWV, measured by PulsePen, was related significantly to CV mortality. AI, measured by either of the devices, did not show a relationship with CV mortality.

These results showed that in ESRD patients, among different stiffness parameters, PWV is consistently related to CV mortality, irrespective of the timing of measurement, predialysis AMP seems to provide additional prognostic information and that sevelamer treatment is associated with an improvement in aortic stiffness. Lack of correlation between PWV-values measured by the PulsePen and Arteriograph devices, and lack of prognostic significance of PWV measured by Arteriograph suggest limited validity of Arteriograph to determine PWV in patients on hemodialysis.

ÖSSZEFOGLALÓ

A végstádiumú veseelégtelenségben (ESRD) szenvedő betegben az erek kalcifikációja, a hasonló életkorú általános populációhoz képest 20-30-szor magasabb kardiovaszkuláris (CV) halálozással jár. ESRD betegeknél, az érfali tagulékonyság paraméterei (a pulzus hullám terjedési sebesség: PWV, az augmentációs index: AI, a centrális pulzusnyomás: CPP és a centrális-perifériás pulzusnyomás amplifikáció: AMP) CV halálozásra vonatkozó prediktív erejét egy közös kohorszban, a foszfátkötő sevelamer hatását az aorta érfali tágulékonyságára és a tágulékonysági paramétereket meghatározó oszcillometriás elven működő készülék (Arteriográf) hitelesítését még nem vizsgálták.

Három vizsgálatot végeztem ESRD populációban; egy közös kohorszban vizsgáltam az érfal-tágulékonysági paraméterek CV mortalitásra vonatkozó prediktív értékét, megvizsgáltam a sevelamer hatását az aortafal tágulékonyságára és megvizsgáltam az Arteriográf hitelességét és a segítségével mért paraméterek CV mortalitásra vonatkozó prediktív értékét a validált PulsePen készülékhez képest.

Az első vizsgálatban, a dialízis előtti és utáni PWV és a dialízis előtti AMP mutatott szignifikáns összefüggést a CV mortalitással. A második vizsgálatban, a követés végére a PWV csökkent a sevelamer-kezelteknél, míg a kontroll csoportban növekedett. Az AI változása nem volt szignifikáns. A harmadik vizsgálatban a két készülékkel mért AI értékek szignifikáns korrelációt mutattak, a PWV esetében hasonló összefüggés nem igazolódott. A két készülékkel mért paraméterek közül csak az PulsePen segítségével mért PWV mutatott szignifikáns összefüggést a CV mortalitással.

A vizsgálatok eredményei azt mutatták, hogy, ESRD betegeknél az érfali tágulékonyság paraméterei közül a PWV a mérés idejétől független, konzekvens összefüggést mutat a CV mortalitással, a dialízis előtti AMP értéke további prognosztikus információt nyújt és a sevelamer-kezelés javuló aortafal tágulékonysággal jár együtt. A két készülék segítségével mért PWV értékek közti korreláció hiánya, illetve az Arteriográffal meghatározott PWV prognosztikus értékének hiánya miatt az Arteriográf készülék használata korlátozott a PWV meghatározására dializált betegeknél.

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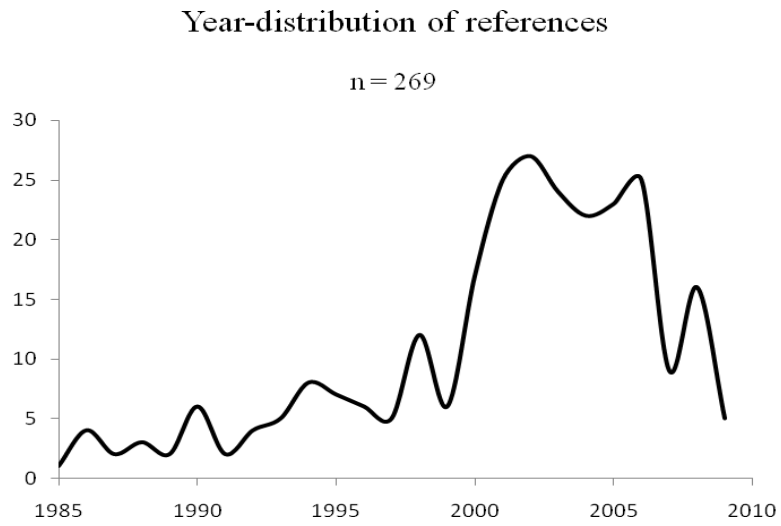

10. PUBLICATION SUMMARY

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