Cardiovascular effects of irbesartan in haemodialysis patients

PhD dissertation

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Papers
This thesis is based on the following papers:

Paper I: Renal and cardiovascular effects of irbesartan in dialysis patients – a randomized controlled trial protocol (SAFIR study) (Published in Danish Medical Journal 2013; 60(4))

Paper II: Angiotensin II blockade exerts no blood pressure independent effects on intermediate cardiovascular endpoints in hemodialysis patients: A randomized, double-blinded, placebo-controlled one-year intervention trial (SAFIR study) (Submitted August 2013)

Paper III: Intradialytic central haemodynamics is not affected by angiotensin II receptor blockade: A randomised double-blinded placebo-controlled one year intervention trial (the SAFIR study) (In preparation August 2013)
Preface
The studies presented in this thesis were carried out at the Department of Renal Medicine, Aarhus University Hospital, Denmark between March 2009 and August 2013. I am indebted to my three supervisors: Bente Jespersen, Jens Dam Jensen, and Kent Lodberg Christensen. Bente Jespersen is thanked for the privilege of free hands in the ways of research as well as the financial support which enabled the studies. Jens Dam Jensen deserves a lot of credit for his original thinking, sharp analysis and extensive knowledge about haemodialysis. Early on, it was quite difficult to find a cardiologist with an interest in haemodialysis patients. Torsten Toftegaard Nielsen was the first who dared to say yes, but shortly afterwards his sudden untimely death forced me to find a replacement. Without much hesitation, Kent Lodberg Christensen undertook the challenge and he has been invaluable to have as a guide and mentor. The cardiologist’s perspective was highly treasured and your guidance and feedback improved my drafts and ideas considerably. Your support in all phases of this PhD was greatly appreciated.

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"There is no stimulus like that which comes from the consciousness of knowing that others believe in us."

Orison Swett Marden
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**List of abbreviations**

**ACEi:** ACE inhibitor  
**AIx:** Augmentation index  
**AIx@HR75:** AIx normalised to a heart rate of 75 beats per minute  
**AMBP:** Ambulatory blood pressure monitoring  
**Ang2:** Angiotensin II  
**ARB:** Angiotensin II receptor blocker  
**ASE:** American Society of Echocardiography  
**BNP:** Brain natriuretic peptide  
**BP:** Blood pressure  
**BV:** Blood volume  
**CBV:** Central blood volume  
**CCB:** Calcium channel blocker  
**CO:** Cardiac output  
**CV:** Cardiovascular  
**DDD:** Defined daily doses  
**ECG:** Electrocardiogram  
**ECV:** Extracellular volume  
**EF:** Ejection fraction  
**ESRD:** End-stage renal disease  
**E/A ratio:** The ratio of early mitral flow velocity (E) to the highest late atrial mitral flow velocity (A)  
**E/é ratio:** The ratio of early mitral flow (E) to early lateral mitral annulus velocity (e’)  
**HD:** Haemodialysis  
**HF:** Heart failure  
**LF/HF ratio:** The ratio between low frequency (LF) power and high frequency (HF) power  
**HR:** Heart rate  
**HRV:** Heart rate variability  
**IDH:** Intradialytic hypotension  
**KDOQI:** Kidney Disease Outcomes Quality Initiative  
**LV:** Left ventricular  
**LVH:** Left ventricular hypertrophy  
**LVM:** Left ventricular mass  
**MAP:** Mean arterial pressure  
**MRI:** Magnetic resonance imaging  
**MSNA:** Muscle sympathetic nerve activity  
**NT-proBNP:** N-terminal prohormone of brain natriuretic peptide  
**PP:** Pulse pressure  
**PWA:** Pulse wave analysis  
**PWV:** Pulse wave velocity  
**RAAS:** Renin-angiotensin-aldosterone system  
**RWT:** Relative wall thickness  
**SDNN:** Standard deviation of all the N-N intervals  
**SNS:** Sympathetic nervous system  
**SV:** Stroke volume  
**TPR:** Total peripheral resistance  
**UF:** Ultrafiltration
Background and introduction

Epidemiology

The number of patients with end-stage renal disease (ESRD) is rising markedly worldwide. In 2004 approximately 1.8 million ESRD patients were on renal replacement therapy with 1.4 million on dialysis and 0.4 million with a functioning renal transplant. Haemodialysis (HD) is the most common mode of dialysis therapy worldwide. Lately, incidence rates of ESRD have stabilised in most of the developed countries whereas ESRD-rates appear to be growing in the developing countries. Population dynamics, especially the aging of populations, as well as increased prevalence of diabetes are expected to increase the absolute number of ESRD patients.

In Denmark the incidence of ESRD is around 120 per million per year and approximately 2,500 patients rely on regular dialysis treatment, roughly 80%, are treated with HD. Dialysis patients have an annual mortality rate of about 20% primarily due to cardiovascular (CV) disease, which accounts for 40-50% of all deaths. Despite advances in primary and secondary prevention of CV disease, the relative risk for CV disease remains high in dialysis patients also in Denmark.

Cardiovascular disease in chronic renal failure

Until recently, it was not well recognised that CV disease is prevalent and aggressive in patients with moderate reduction in renal function such as those with chronic kidney disease stage 3-5 who had not yet reached ESRD and begun dialysis treatment. Two large studies have demonstrated the excess of CV disease in patients with chronic renal failure. A secondary analysis of the VALIANT study showed that in patients with pre-existing heart disease, the estimated risk of death from CV causes over a two year period increased markedly as glomerular filtration rate (GFR) declined and patients with an estimated GFR less than 20 mL/min were six times more likely to die than those patients with GFR above 60 mL/min. Another study including more than 1.1 million participants...
from northern California found that renal function was an independent predictor of subsequent
cardiac events, hospitalisation and overall mortality over a two year period. Accordingly, there is
a clear association between progression of CV risk and decline in renal function. Moreover, it is
often stated that the increased propensity of CV disease is caused by factors uniquely associated
with loss of renal function adding to traditional risk factors such as hypertension, diabetes,
hypercholesterolaemia, obesity and smoking. Some of the major factors include increased
arterial stiffness, increased activity of the sympathetic nervous system, impaired
endothelium-dependent vasodilation, low-grade chronic inflammation, anaemia, volume overload,
and disturbances in the calcium phosphate metabolism. The accumulated
effect of these factors is often described as early or accelerated vascular aging, and affects most
patients progressing to ESRD.

Cardiovascular risk and arterial stiffness
A hallmark of ESRD is increased arterial stiffness partly due to excessive arterial calcification as
discussed in more detail in the following. Increased arterial stiffness increases CV risk and
parameters reflecting the degree of arterial stiffness is therefore of interest in patients with
chronic renal failure, both as a prognostic indicator and when investigating interventions aiming at
reduction of arterial stiffness.

Carotid-femoral pulse wave velocity (PWV) is considered the gold standard method for assessment
of arterial stiffness and PWV has been shown to improve clinical risk assessment both in non-renal
patients as shown in the Framingham study and The Calcification Outcome in Renal Disease
(CORD) study in ESRD patients. Guerin et al. highlighted the importance of arterial stiffness for
survival in ESRD in a study that showed superior survival in ESRD patients who responded to BP-
reduction with a decrease in PWV compared to those insensitive to decreased BP. The same study
showed that prescription of an angiotensin converting enzyme inhibitor (ACEi) was associated with decreased all-cause and CV mortality\textsuperscript{28}. Recently, a Japanese study reported that long-term treatment with an angiotensin II receptor blocker (ARB) or ACEi in HD patients with increased arterial stiffness inhibited further increase in PWV independently of its BP-lowering effect\textsuperscript{29}. The central BP and central pulse wave characteristics such as augmentation index (AIx) can be obtained by analysis of peripheral pulse waves, called pulse wave analysis (PWA). The central BP and AIx have been reported to predict CV morbidity and mortality above brachial BP in patients with ESRD\textsuperscript{30,31}. Several studies have investigated the effects of antihypertensive treatments on central BP and shown that BP-lowering drugs have differential effects on central BP despite similar reductions in brachial BP\textsuperscript{32,33}. Blockade of the renin-angiotensin-aldosterone system (RAAS) is known to lower the central BP in non-uraemic patients\textsuperscript{34-36} but few studies have investigated this effect in ESRD patients\textsuperscript{37,38}.

**Cardiovascular outcome with RAAS-blockade in ESRD**

Although the cardioprotective effects of RAAS-blockade are well established by randomised controlled trials for patients with hypertension and heart failure\textsuperscript{39-42}, their effects on clinical outcomes in ESRD patients remain unclear. Traditionally, patients with chronic renal failure are excluded from large trials investigating CV outcomes. However, ACEis and ARBs are frequently used clinically in patients with ESRD and are generally suggested as agents of choice, although the evidence in support of their preferential use is limited in ESRD except for regression of left ventricular hypertrophy (LVH) and arterial stiffness (PWV) as discussed in more detail in the following\textsuperscript{29,43,44}. Concerning reduction of mortality and CV events with ACEi or ARB in ESRD, evidence is lacking in patients treated with peritoneal dialysis (PD) according to a meta-analysis from 2009\textsuperscript{45}. In HD patients, there is some evidence indicating that RAAS-blockade can counteract
the development of CV-disease. Thus, studies by Takahashi et al. 46 Suzuki et al. 47 and Cice et al. 48 found a lower CV-mortality in patients treated with ARB 46,47 or a combination of ACEi and ARB 48. However, the FOSIDIAL-study by Zannad et al. 49 found no beneficial effect on CV events in a large randomised placebo-controlled study with 397 HD patients randomised for either ACEi or placebo. Similarly, no lower risk of major CV events or death was found with BP-lowering treatment with the ARB olmesartan in the OCTOPUS-study, a recent large randomised study involving 469 HD patients 50. Overall, adequately sized intervention studies targeting CV outcome with RAAS-blockade are lacking in ESRD patients and so far results have been inconsistent.

The three papers in this thesis were based on the double-blinded multi-centre randomised placebo-controlled intervention trial “Saving Residual Renal Function Among Haemodialysis Patients Receiving Irbesartan” (SAFIR). Paper I describes design, patient recruitment, randomisation procedure, methodology, and sample size considerations for the SAFIR study. Paper II focuses on intermediate CV endpoints (BP, Central BP, Aix, PWV, LVH, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), heart rate variability (HRV), and plasma catecholamines) and paper III describes the interdialytic haemodynamic response in terms of cardiac output (CO), central blood volume (CBV), stroke volume (SV), total peripheral resistance (TPR), mean arterial pressure (MAP), and heart rate (HR).

Preservation of residual renal function was one of the primary endpoints in the SAFIR study as described in the first paper. These data were primarily handled and described by Krista Dybtved Kjærgaard and details are therefore not included in this thesis which focuses on the CV aspects of the SAFIR study.
The following sections describe in more detail 1) the concepts of arterial stiffness, wave reflection, and central blood pressure, 2) the pathophysiology of hypertension in dialysis patients including the RAAS and the sympathetic nervous system, 3) heart disease in ESRD, and finally 4) haemodynamic instability in HD patients.

**Arterial stiffness, wave reflection and pulse wave analysis**

**A brief history of the arterial pulse and pulse wave analysis**

Throughout the history of medicine, examination of the pulse has been described and used for diagnosis of disease. From ancient Chinese manuscripts allegedly written by the Yellow Emperor, Huang Ti (698-598 BC), we know that the arterial pulse was studied as early as 2,500 years ago. In ancient Greece, Praxagoras of Kos (340 BC) was the first physician credited for examining the pulse and later on Hippocrates (375 BC) described conditions of the pulse in various diseases. Erasistratus (304–250 BC) explained correctly the dilation of the arteries as a passive expansion of the vessel, but incorrectly assumed that this was caused by the moving of air within the arteries. Traces of this misconception can be found even today in the word “artery”, which originates from the Greek word for air “αρτηρ” ⁵¹. In medieval times, the pulse was regarded as an important diagnostic and prognostic sign reflecting the interplay between the four different humours blood, phlegm, yellow bile, and black bile, which determined health in medieval medicine. Counting of the pulse as we know it today was first introduced by John Floyer (1649-1734), who introduced a pulse watch that ran for sixty seconds ⁵¹. In 1831 Jules Hèrisson developed the Sphygmmometer. This was the first instrument that could display the pulse beat visually. A mobile Sphygmograph was introduced by Etienne Marey (1830-1904) in 1860. This device was attached to the wrist, one end of a lever was placed over the radial artery, and the other end of the lever depicted the magnified pulse wave on paper by an attached pen ⁵¹,⁵². Frederick Akbar Mahomed (1849-1889)
improved Mareys Sphygmograph in order to quantify the so-called "hardness of the pulse" (hypertension) in patients with Bright’s disease (renal failure). Using this improved Sphygmograph, he described changes in pulse contour with age, hypertension, and kidney disease. However, at the beginning of the 20th century interest in pulse wave analysis faded due to the introduction of the now well-known cuff based sphygmomanometer for the measurement of BP. Nevertheless, studies of arterial haemodynamics continued. In a number of papers from 1955 and onwards, Wormersly and McDonald described how the arterial system could be viewed as in a steady state of oscillations. Thus, instead of describing pulse waves in terms of obvious descriptive features used hitherto, so-called Fourier analysis was applied, which meant that the arterial system could be analysed in the frequency domain instead of the time domain. Nichols, O’Rourke and others continued in this field which led to the derivation of transfer functions, based on which central aortic pulse waves could be synthesised from recordings of peripheral pulse waves. Over the years several transfer functions have been developed, but presently only the transfer function developed by O’Rourke et al. has achieved approval by the Food and Drug Administration (FDA) in the United States. The SphygmoCor device that was used in the SAFIR study for obtaining central BP uses this transfer function.

**Arterial stiffness**

Arterial stiffness can be understood as the detectable manifestations of adverse structural and functional changes within the vessel wall. Arteriosclerosis is the term used to describe degenerative stiffness of the arterial wall, primarily media thickening with increased collagen content, calcification and hyperplasia and hypertrophy of vascular smooth muscle cells. Atherosclerosis affects the intima part of arteries and usually describes the occlusive result of endovascular inflammatory disease, lipid oxidation, and plaque formation that leads to restriction
of blood flow and ischemia or infarction of downstream tissues (e.g. ischemic heart disease, stroke, and peripheral artery disease) \(^{23,56}\). Arteriosclerosis and atherosclerosis tend to coexist and refer to a progressive, diffuse, and age-related process that occurs in all vascular beds. However, in chronic kidney disease the extent of atherosclerosis and arteriosclerosis is exceedingly high due to intima and media calcification \(^{25}\). The physiological process leading to excessive calcification in chronic renal failure is incompletely understood, but factors unique to uraemia combined with disorders in the calcium and phosphate metabolism such as hyperphosphataemia, hyperparathyroidism and vitamin D disorders are believed to be of major importance \(^{57,58}\). Medial calcification of the arteries, known as Mönckeberg's arteriosclerosis or Mönckeberg-type atherosclerosis \(^{59}\), has a different morphology from that of intimal calcification, appearing first as linear streaks along elastic lamellae, and in more severe cases, forming thick circumferential sheets of calcium apatite crystals (or even bone tissue) in the center of the medial layer, with vascular smooth muscle cells on both sides. On X-ray, the appearance of medial calcification of the arteries has been described as railroad tracks. Increased arterial stiffness is closely associated with medial calcification whereas the association with intimal calcification is less definitive \(^{60}\).

Increased arterial stiffness impairs arterial function. The aorta and its major branches, namely the brachial, radial and femoral arteries and high resistance arterioles act as elastic conduits that convert the pulsatile flow of the heart into a steady flow through the capillaries. Thus, a large part of the energy of cardiac contraction is stored as potential energy by stretching the elastic arterial wall. During diastole the elastic recoil of the arterial wall converts the potential energy into capillary flow. The aorta and its immediate branches have greater elasticity due to the presence of elastin, whereas more distal vessels become progressively stiffer, due to the predominance of collagen fibers. The tendency of the aorta to recoil toward its original dimensions upon removal of
the distending pressure is described by the elastance \( E = \Delta P/\Delta V \) or stiffness. The reciprocal of elastance is called compliance \( C \) which is defined as the change in arterial blood volume \( \Delta V \) due to a given change in arterial blood pressure \( \Delta P \) according to the formula \( C = \Delta V/\Delta P \). In contrast to compliance or elastance/stiffness, which provides information about the elasticity of the artery as a hollow structure, the elastic incremental modulus \( E_{inc} \), Young’s modulus, provides information on the intrinsic elastic properties of the biomaterials constituting the arterial wall independent of vessel geometry. The relationship between pressure and volume is non-linear. At low distending pressure, the tension is borne by distensible elastin fibers, whereas at a high distending pressure the tension is transferred and borne by less extensible collagen fibers which have 5,000 times the tensile modulus of elastin. Thus, at high BP or with advanced arterial calcification the arterial wall gets stiffer and more resistant to distension, limiting arterial blood pooling during left ventricular ejection. The most typical clinical consequence of arterial stiffening is a steep pressure volume relationship leading to increased systolic pressure during ventricular ejection and decreased diastolic pressure during diastole, resulting in high pulse pressure (PP).

**Wave reflection**

As the heart contracts in systole, the left ventricular ejection causes radial stretch of the aorta which generates a pressure wave that travels from the aortic root throughout the arterial system. However, reflected waves are also generated in places where the forward travelling wave encounters discontinuities i.e. branching points, atherosclerotic foci, lumen tapering, local areas of increased wall stiffness, and at the junctions with the resistance vessels. These multiple reflected waves converge into a single functional reflected wave and the arterial pulse wave is therefore the summation of both a forward and a reflected wave. More importantly, as seen in young persons with elastic compliant arteries, the speed of the forward and reflected wave is low,
and the reflected wave arrives in diastole, thereby augmenting the diastolic pressure and coronary perfusion pressure without increasing left ventricular afterload. In individuals with increased arterial stiffness, the amplitude of the forward pressure wave increases, and the forward and the reflected wave move faster through the arterial system. Consequently, the reflected wave arrives in systole instead of diastole and adds to the incident pulse wave. This leads to an increase in both cardiac afterload and central systolic BP, which in turn enhances the risk of stroke and left ventricular hypertrophy (LVH). Simultaneously, as coronary perfusion pressure decreases, the risk of cardiac ischaemia increases.

**Pulse wave velocity**
PWV is a regional functional measurement of arterial stiffness over a certain arterial length, whereas strain, compliance, and distensibility are local markers of arterial elasticity. PWV should not be mistaken for the blood velocity. PWV represents the transmission of energy in the arterial wall, whereas blood velocity represents the displacement of mass through the incompressible blood column. PWV varies between 4 and 5 m/s in the ascending aorta and between 9 and 12 m/s in peripheral arteries whereas blood velocity is in the order of cm/s. The so-called Moes-Korteweg equation \( PWV = \sqrt{\frac{Eh}{2\rho r}} \) describes PWV as a function of the elasticity of the arterial wall described by Young’s elastic modulus (E), wall thickness (h), blood viscosity (\( \rho \)) and the radius of the artery (r). From this equation, it can be seen that increased stiffness of the arterial wall (E) leads to increased PWV. PWV is inversely related to vascular compliance. Hence, a stiffer vessel will conduct the pulse wave faster than a more distensible and compliant vessel. Moreover, PWV is found to be closely associated with the degree of calcification within the arterial wall.

Over the years several methods have been used for assessment of PWV. These include ultrasound, magnetic resonance imaging (MRI), pressure transducers (used in the commercially available
Complior), cuff-based oscillometry (used in the commercially available Arteriograph), and applanation tonometry, which is used in the SphygmoCor device, which was used in our study \(^{67}\).

Figure A

Pulse wave velocity (PWV) = D/Δt (m/s)

Δt: Transit time; D: Distance between the carotid and femoral recording site

The assessment of PWV requires estimation of pulse transit time divided by the distance between the two recording sites (see Figure A). PWV is calculated as PWV=\(D/\Delta t\) (m/s) where \(D\) indicates the distance travelled by the waves which is usually measured as the surface distance between the two recording sites. The time delay (\(\Delta t\)) is measured between the feet of the two pulse waves. These are usually obtained at the right common carotid artery and the right femoral artery.
Carotid-femoral PWV is considered to be the gold standard measurement of arterial stiffness. It is a relatively simple and non-invasive way of assessing stiffness of the central elastic arteries, and it independently predicts CV morbidity and mortality both in low risk and high risk populations, including ESRD patients. Accordingly, in 2007 carotid-femoral PWV was included in the ESH/ESC guidelines for the management of hypertension with PWV = 12 m/s as the threshold value indicating increased arterial stiffness. Vlachopoulos et al. estimated in a recent meta-analysis, that 1 m/s increase in PWV corresponded to an age-, sex- and risk factor-adjusted risk increase with 95% confidence interval of 14(9–20)% for total CV events, a 15(9-21)% increase for CV mortality and a 15(9-21)% increase in all-cause mortality. In ESRD patients, different PWV cut-offs have been reported. Blacher et al. was the first to report a significant independent predictive value of PWV in ESRD patients for all cause and CV mortality. Thus, after adjustment for confounding factors, the odds ratio for PWV >12.0 versus <9.4 m/s with 95% confidence interval was 5.4 (2.4-11.9) for all-cause mortality and 5.9 (2.3-15.5) for CV mortality. Moreover, for each PWV increase of 1 m/s in this study population, all-cause mortality-adjusted odds ratio was 1.4 (1.2-1.6). Shoji et al. used a PWV cut-off of 8.2 m/s and confirmed that aortic stiffness was an independent predictor for overall and fatal CV events in a Japanese cohort with 265 ESRD patients. Pannier et al. found a PWV cut-off of 10.75 m/s based on receiver operating characteristic curve analysis in a study based on 305 ESRD patients. Lastly, the Calcification Outcome in Renal Disease (CORD) study based on 1084 European dialysis patients reported two-year mortality or nonfatal CV event according to tertiles of PWV and found that PWV<8.8 m/s was associated with the best outcome compared to PWV>12 m/s. As illustrated, several PWV cut-offs have emerged over the last years. Comparison between studies is difficult, due to differences in PWV-methodology including the method used for distance measurement. Accordingly, a wider
implementation of PWV into clinical practice has been hampered by the lack of a standardisation of methodology and established reference values based on a large population. In 2010, The Reference Values for Arterial Stiffness’ Collaboration group established reference and normal values for PWV based on data from 16,867 individuals after standardising results for different methods of PWV assessment. Finally in 2012, a consensus document suggested a PWV cut-off value of 10 m/s to indicate an increased risk for CV events, but it was also stated that a fixed age-and BP-independent cut-off value may not be the best predictor in different populations. Basically, this cut-off was derived from the previously mentioned cut-off value of 12 m/s from the ESH/ESC guideline by adapting it to the new recommended distance estimate (80% of the direct carotid-femoral distance) also described in this paper.

Central blood pressure
Diastolic and mean blood pressure (MAP) are practically constant as the pulse wave travels from the ascending aorta to the peripheral arteries unlike the systolic BP which increases towards the peripheral arteries. This physiological phenomenon is known as PP amplification. PP amplification is more pronounced in young individuals. With aging, PP increases more rapidly in the thoracic aorta than in peripheral arteries, thus causing an attenuation of the physiological increase in PP from central to peripheral arteries. Furthermore, when arteries become stiffer, as seen in the elderly or in subjects with hypertension and/or ESRD, the reflected waves occur earlier in the thoracic aorta within the systolic portion of the BP curve, leading to an increase in the central systolic BP. From a physiological point of view, central BP could yield prognostic information superior to brachial BP, because it more accurately reflects the BP close to vulnerable organs such as heart, brain, and kidneys. Moreover, despite a similar reduction in brachial BP, antihypertensive medications have differential effects on central BP, which makes it a relevant...
parameter in BP intervention trials. Drugs that induce arterial vasodilation have a direct influence on wave reflection and ACEi, ARB, and calcium channel blockers show greater ability to reduce central BP compared to non-vasodilating drugs such as β-blockers and diuretics. In terms of CV outcome, many studies in non-renal patients, although not all, found an independent predictive value of central BP. A recent meta-analysis based on six studies on 4,778 patients (including one study in ESRD patients) confirmed the age- and risk-factor adjusted predictive value of central systolic BP on CV outcome, but it also stated that central BP estimates were not significantly better than brachial BP. Concerning ESRD, Safar et al. found an independent predictive value of central PP for CV outcome in a study with 180 HD patients, whereas Othmane et al. found no relationship between central PP (carotid PP) and CV mortality in 98 HD patients.

**Augmentation index**

Augmentation index (Alx) describes the effect of the reflected wave on the ascending aortic pulse wave and is generally considered to be an important PWA parameter. Alx is defined as the ratio between the height of the reflected wave, known as the augmentation pressure (AP), and the central pulse pressure (Alx=AP/PP). Alx is dimensionless but is usually given as a percentage. Quantification of AP relies on identification of a shoulder or so-called inflection point on the rising limb of the central pressure wave in systole. Alx is a composite measure influenced by various factors including amplitude of the incident wave, the amplitude of the reflected wave, and duration of the cardiac cycle. The timing of the reflected wave is determined by the stiffness of the arteries. Amplitude of the incident wave is influenced by cardiac contractility and heart rate determines cardiac cycle duration. Alx is also influenced by body height and the degree of vascular smooth cell contraction in peripheral arteries. Accordingly, changes
Figure B

Pulse wave analysis (PWA)

Illustration showing the peripheral and central pulse wave and the principle of pulse wave analysis (PWA) in a 36-year-old male haemodialysis patient. PWA was obtained with the SphygmoCor device and brachial blood pressure was used for calibration of the peripheral (radial) pulse wave. Due to pulse pressure amplification a transfer function is used to convert the peripherally recorded pulse wave into the central (aortic) pulse wave, thereby enabling estimation of the central (aortic) blood pressure. AP: Augmentation pressure is the difference between the first (P1) and the second (P2) pulse wave peak, P1 is also known as the inflection point; Alx: Augmentation index; TR: Time to reflection, which is the time to return of the reflected wave from the foot of the wave to the inflection point (P1); ES: End of systole. Sp: Systolic blood pressure; Dp: Diastolic blood pressure; Mp: Mean blood pressure; PP: Pulse pressure.

in Alx may have multiple causes and do not necessarily reflect changes in arterial stiffness. The SphygmoCor system provides Alx as well as Alx adjusted to a HR of 75 (Alx@HR75) based on data from two studies by Wilkinson et al. The software uses the average value of these two studies and adjusts Alx at an inverse rate of 4.8% for each 10 beats increment in HR. Most studies use Alx and a recent Danish consensus report also recommends the use of Alx (with adjustment for HR in subsequent analysis) rather than Alx@HR75. In terms of CV outcome, the predictive value of Alx is somewhat debated. A recent meta-analysis based on 1,418 patients from six studies, including two studies with ESRD patients, found that Alx was an independent
predictor for CV outcome and all-cause mortality. However, the result of this meta-analysis has been questioned. Three large studies with more than 4,800 patients, which found no association between AIx and CV outcome, were not included in the analysis. Adding to this, AIx did not predict CV events in the Framingham Heart Study. In ESRD patients, two studies found an association between AIx and outcome but two other studies did not. Clinical use of AIx is also complicated by the lack of reference values. However, based on data from a low-risk cohort without known CV disease or diabetes consisting of 4,561 subjects, a Danish group recently published gender-specific equations including age, heart rate, and height, which enables the calculation of reference values for AIx obtained with the SphygmoCor device.

Pathophysiology of hypertension in dialysis patients

Historical perspective concerning the renin-angiotensin-aldosterone-system

Around 1827-1837 the English physician Richard Bright (1789–1858) was the first to establish a connection between renal disease, hypertension and end-organ damage such as LVH. Bright noted the presence of a hard pulse (hypertension) and the frequent autopsy finding of LVH in patients with chronic renal failure. However, it was first in 1898 that the Finnish-born medical scientist and physiologist Robert Adolph Armand Tigerstedt (1853–1923) together with his student Per Bergman at the Karolinska Institute in Stockholm observed that injection of a crude extract of rabbit kidney raised the BP in recipient rabbits. They called this new pressor substance renin and thus established the role of the kidney in BP regulation. This observation remained almost unnoticed until 1934 when the American physician Harry Goldblatt (1891-1977) demonstrated that clamping of a renal artery produced hypertension in the dog. This led to renewed interest in the hypothesis that the kidney might release a pressor substance in response to ischaemia. This discovery formed the basis for a large number of studies that led to the identification of

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Angiotensin II (Ang2), the angiotensin converting enzyme (ACE), and to the current understanding of the role of RAAS in the regulation of BP \(^{111}\).

**Hypertension in dialysis patients**

In ESRD patients undergoing dialysis hypertension is a complex multifactorial condition. Although hypertension is very frequent in the dialysis population \(^{112}\), large scale intervention studies are scarce and the optimal BP-level is debated. Some observational studies indicate that hypertensive HD patients have a better survival compared to HD patients with normal or low BP \(^{113,114}\). Other studies found a higher mortality in patients with high BP \(^{115}\) or a “U-shaped” association, with higher mortality risk at both extremes of BP \(^{116}\). Inaccurate BP measurements leading to misclassification and low BP due to heart failure, which is frequent in HD patients, is suspected to explain part of the discrepancy \(^{117-120}\). Additional factors such as age, race, and the presence of diabetes should also be considered when examining the relationship between BP and mortality in HD patients \(^{121,122}\). Although previous studies have yielded conflicting results regarding the relationship between BP-levels and outcome, hypertension is considered to be a major CV risk factor and BP-lowering is widely accepted to reduce all-cause and CV mortality in HD patients. Accordingly, the Kidney Disease Outcomes Quality Initiative (KDOQI) guideline recommends a predialytic BP below 140/90 mmHg and a postdialytic BP below 130/80 in HD patients \(^{123}\). Furthermore, recent meta-analyses based on data from randomised trials in HD patients concluded that hypertension should be treated, but no superiority of any antihypertensive medications was proven \(^{124,125}\).

**Volume overload and hypertension**

Volume overload is often mentioned as the most important contributor to hypertension in dialysis patients especially in patients without residual renal function. The regulation of body fluid volume
is dependent on the sodium excretion ability of the kidneys. Loss of renal function causes decreased ability to excrete sodium, but in the absence of renal function the thirst mechanism is still able to keep plasma osmolality normal. Thus, when entering dialysis most patients are overhydrated because their sodium intake exceeds the excretion capacity of the diseased kidneys. Dietary restrictions are usually imposed alongside dialysis treatment in order to minimise sodium intake. However, standard HD treatment (3-5 hours thrice weekly) only provides roughly 10-15% of normal kidney function. Consequently, sodium retention is hard to avoid particularly in patients without residual renal function. Retention of sodium and thereby water in order to maintain plasma osmolality causes an increase in extracellular volume (ECV). Expansion of ECV, and thereby increased blood volume (BV), will lead to an increase in venous return. The normal heart responds to this increased pre-load according to the Frank-Starling mechanism by increasing CO. Due to increased CO, BP will rise if total peripheral resistance (TPR) is unchanged (↑CO x TPR = ↑BP). Tissues will try to maintain their perfusion constant against this increased pressure by vasoconstriction, which increases BP further. Accordingly, the basic pathophysiological principle in volume dependent hypertension in ESRD patients is that the body tries to maintain fluid homeostasis at the expense of an elevated BP (ECV ↑ → BV ↑ → CO ↑ → Blood pressure ↑ → Vasoconstriction). Interestingly, it has also been shown that some ESRD patients are able to maintain normal BP despite volume overload and increased CO due to a decrease in total peripheral resistance (TPR). However, the exact mechanism behind differences in TPR response to an increase in circulating volume remains unclear. Nevertheless, augmenting fluid removal during dialysis is shown to significantly reduce BP and data collected from the Dialysis Morbidity and Mortality Study by the US Renal Data System have shown that interdialytic
weight gain and noncompliance with the dialysis regimen were independent predictors of a higher BP.  

**The renin-angiotensin-aldosterone-system**
The renin-angiotensin-aldosterone-system (RAAS) is an important regulator of BP in healthy individuals and plays an important role in the pathogenesis of hypertension in chronic renal disease. Renin is produced by specialized cells in the juxtaglomerular apparatus of the afferent arterioles of the kidney in response to a reduction in renal blood flow, low BP, low sodium concentration in the distal tubulus near the macula densa or due to activation of the sympathetic nervous system though activation of $\beta_1$ adrenoceptors $^{134,135}$. Renin then converts angiotensinogen, which is secreted by the liver, to the decapeptide angiotensin I. Angiotensin I is converted to the octapeptide Ang2 in a reaction catalysed by a metalloprotease secreted by pulmonary and renal epithelium known as angiotensin-converting enzyme (ACE). Ang2 is the principal agent of RAAS and mediates most of its effects after binding to the G-protein coupled AT$_1$ receptor $^{111,135}$. Classically, binding of Ang2 to AT$_1$ receptors causes arterial vasoconstriction, leading to increased BP and cardiac hypertrophy. Moreover, Ang2 causes volume expansion by increasing thirst sensation (dipsogenic effect), release of vasopressin (ADH), and reabsorption of sodium and water in the proximal tubules $^{135}$. Adding to this, Ang2 stimulates the release of aldosterone from the adrenal cortex. Aldosterone acts on mineralocorticoid receptors and increases renal sodium and water reabsorption in the cortical collecting duct. Vascular tone and BP is also affected by more delayed effects of Ang2. These effects include stimulation of vascular smooth muscle cell growth, fibrosis, inflammation, oxidative stress, monocyte proliferation, and vascular endothelial injury $^{136-140}$. Accordingly, RAAS-blockade may induce an anti-inflammatory and anti-fibrotic effect in addition to the vasodilating effect $^{141,142}$. Possibly by inhibiting pro-
inflammatory mediators such as interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-alpha), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappa B) \(^{143}\).

In HD patients, renin secretion by the non-functioning kidneys is not completely abolished and may sometimes be inappropriately high \(^{144}\). Aldosterone is also frequently elevated \(^{145-148}\).

Previously, before RAAS-blocking agents became available removal of excess quantities of renin and thereby Ang2 and aldosterone, was done by bilateral nephrectomy \(^{149}\). This procedure often resulted in substantial BP reduction alongside a more predictable relationship between ECV and BP \(^{150}\). However, bilateral nephrectomy also affects sympathetic activity and the BP-lowering effect of this procedure may not solely be attributed to renin \(^{13,151}\). Currently, no systematic long-term studies have addressed this subject. According to Lazarus et al. the role of excessive renin secretion in relation to the state of sodium and volume should be recognized as an important factor in the pathogenesis of hypertension in patients with ESRD \(^{150}\). However, an absence of relationship between the degree of volume overload and renin levels in HD patients has also been reported \(^{152}\). Arguments favouring a substantial role of RAAS for the maintenance of elevated BP in HD patients are mainly based on the fact that bilateral nephrectomy normalizes BP even in patients with low plasma renin levels, and the fact that in transplanted patients persistent renin secretion from the recipients own diseased kidneys contributes to hypertension \(^{126}\). On the other hand, there is evidence to suggest that the influence of RAAS is minor as long as overhydration is present \(^{153-155}\), which in turn explains why some HD patients exhibit a diminished response to RAAS-blockade \(^{154}\).

**The kidney and neurogenic factors in hypertension**

The kidneys are richly innervated with sensory afferent nerves as well as efferent nerves. The latter are involved in BP regulation through sodium reabsorption \(^{151,156}\) and activation of RAAS.
as mentioned previously. Afferent nerves convey signals about renal perfusion and metabolism from the kidney to the central nervous system. There are two main types of afferent nerves: renal baroreceptors and renal chemoreceptors. Renal baroreceptors increase their rate of firing in response to changes in intrarenal pressure or volume, whereas renal chemoreceptors are stimulated by ischemic metabolites or uraemic toxins. Stimulation of afferent nerves may lead to overactivity in the sympathetic nervous system (SNS) which in turn causes hypertension. Animal models of chronic renal disease have shown that minor kidney injury causes immediate and permanent elevation of BP, as well as increased noradrenaline secretion. Furthermore, the increase in BP associated with 5/6 nephrectomy is prevented by abrogation of afferent sensory signals from the kidneys. Recently, catheter-based renal denervation in the Symplicity HTN-2 Trial caused substantially lower BP in treatment-resistant hypertensive patients. Renal denervation also lowered BP in a case-report on a HD patient. Taken together, these findings indicate that the kidney is not only a target of the SNS but an origin and modulator of sympathetic activity. Many studies have shown that hypertension in chronic renal failure is associated with increased activity of the SNS. Moreover, part of the favourable effect of RAAS blockade may rely on inhibition of sympathetic activity. Ang2 has several stimulatory effects on the SNS both centrally and peripherally and RAAS-blockade with ACEi or ARB may reduce sympathetic activity by interfering with the effects of Ang2 on SNS transmission.

Heart rate variability and plasma catecholamines
Heart rate variability (HRV) is computed from continuous beat-to-beat analysis of HR oscillations. Thus, the behaviour of the beat-to-beat interval, the interval between adjacent R-peaks in the ECG also known as the so-called normal to normal interval (NN-interval), is considered an indirect index of adrenergic CV drive. Reduced variability (impaired HRV) is associated with autonomic
neuropathy and increased risk of arrhythmic complications and mortality\textsuperscript{184}. Variations in the beat-to-beat interval are evaluated by different methods. Time-domain analysis is the simplest to perform and includes several parameters derived from calculations performed on the beat-to-beat intervals e.g. the mean NN-interval and the standard deviation of the NN-intervals (SDNN). Spectral analysis of the beat-to-beat oscillations is another frequently used method which allows for the identification of a low frequency (LF) component, believed to result from neural mechanisms related to sympathetic and vagal activity, and a high frequency (HF) component related to vagal activity and respiration. The LF/HF ratio is often used as an index of sympatho-vagal interaction on the autonomic control of heart rate\textsuperscript{184}. Several studies have used HRV for risk stratification and impaired HRV, particularly low LF and LF/HF ratio were found to be associated with increased CV morbidity and mortality including sudden death in ESRD patients\textsuperscript{185-191}.

Measurement of the HR response during manoeuvres that triggers an autonomic response is a more simple approach for assessment of the autonomic nervous system. Often used manoeuvres include orthostatic changes (e.g. standing or passive tilt), the Valsalva manoeuvre (VM), and respiration (ratio of the maximum and minimum HR during a respiratory cycle)\textsuperscript{192-194}.

Plasma catecholamine levels (adrenaline and noradrenaline) have also been used for assessment of SNS activity. Plasma noradrenaline level in particular reflects the rate of noradrenaline spillover from the synaptic cleft and its rate of removal from plasma. Studies have generally reported increased levels of plasma noradrenaline in ESRD patients compared to controls, suggesting increased SNS activity\textsuperscript{192,195,196}. Furthermore, an increased level of noradrenaline was found to be an independent predictor of fatal and nonfatal CV events in a cohort of HD patients\textsuperscript{197}.
Heart disease in end-stage renal disease

Cardiac abnormalities in ESRD
As chronic kidney disease progresses, CV damage develops in the majority of the patients, and when entering dialysis the proportion of patients with impaired cardiac function and abnormal dimensions of the heart is very high. LVH is present in 16-86% of ESRD patients\textsuperscript{117,198-200} and the prevalence of coronary artery disease is reported to be 25-50%\textsuperscript{201}. Heart failure (HF) also accounts for 25-50%, although the latter is debated due to the high prevalence of volume overload, which may cause a falsely high number of patients with HF\textsuperscript{202}. Valvular diseases such as mitral and tricuspid regurgitation and aortic valve stenosis are also frequent in ESRD. Calcifications caused by disturbances in the calcium phosphate metabolism and cardiac dilation due to volume overload with subsequent stretching of the mitral and tricuspid annulus are believed to be important factors in the development of valvular diseases in ESRD\textsuperscript{126,203}. Lastly, fatal and non-fatal arrhythmias should be mentioned. Atrial fibrillation is seen in 10-25% of dialysis patients and sudden cardiac death caused by ventricular tachy-arrhythmias is also very frequent\textsuperscript{204,205}. According to the United States Renal Data System (USRDS), 64% of cardiac deaths (27% of all deaths) in ESRD patients are attributed to arrhythmias\textsuperscript{2}. LVH, changes in electrolyte levels, especially potassium, ischaemia, and cardiac stunning caused by dialysis-induced myocardial hypoperfusion are believed to explain the high prevalence of sudden cardiac death\textsuperscript{206,207}.

Left ventricular size and geometry
LVH is a strong risk factor for CV disease\textsuperscript{208,209}. LVH independently predicts survival in ESRD patients\textsuperscript{208,210,211} and regression of LVH is associated with better outcome\textsuperscript{212,213}. Moreover, LVH is associated with increased myocardial fibrosis and decreased capillary density, which is a major cause of diastolic functional disturbances due to increased stiffness of the ventricular wall. Briefly,
the pathogenesis of LVH in dialysis patients can be divided into factors causing increased afterload such as hypertension and increased arterial stiffness and factors causing increased preload such as fluid overload, chronic anaemia and the presence of a high output AV-fistula \textsuperscript{126,214,215}. Different methods are available for assessment of LVH. The simplest method for LVH diagnosis is the electrocardiogram (ECG) \textsuperscript{216}. However, the most frequently used electrocardiographic LVH indices are very insensitive and cannot rule out LVH according to a recent meta-analysis \textsuperscript{217}. Cardiac magnetic resonance imaging (MRI) is the gold standard technique for assessment of LVH because it accurately defines mass, volume, and pattern of LVH (concentric, eccentric, or asymmetric) independently of geometric assumptions \textsuperscript{215,218}. However, several factors limit its wider use. In most facilities it is not easily available, it is expensive, and it has some contraindications, such as claustrophobia or use of cardiac implantable devices. Cardiac computed tomography (CT) can also measure left ventricular mass (LVM) accurately but involves radiation which somewhat hampers its use. Echocardiography is used extensively \textsuperscript{117,199,208,209,212,219}, despite some shortcomings such as reduced accuracy in cases of non-standard geometry compared to the methods mentioned above, operator dependence, and reduced quality of acoustic windows due to variations in anatomy \textsuperscript{215,220}.

The basic principle for LVM estimation with echocardiography is subtraction of the calculated volume of the cavity from the total ventricular volume (delimited by the epicardial and pericardial perimeter) and correcting for the specific gravity of the myocardium (1.04-1.055 g cm\(^{-3}\)) assuming a standard geometric model for the left ventricle \textsuperscript{221,222}. LVM increases with increasing body size, which must be taken into account by indexing. Usually body surface area (BSA) or height is used for calculation of left ventricular mass index (LVM-index). Four different geometric LV patterns (normal, concentric remodelling, concentric hypertrophy, and eccentric hypertrophy) have been
identified according to the LV diameter. Calculation of wall to diameter ratio (relative wall thickness (RWT)) permits categorisation of an increase in LVM as either concentric (RWT>0.42) or eccentric (RWT<0.42) 223. These left ventricular (LV) geometry patterns have been suggested to represent anatomic adaptations, related to differences in haemodynamics, mechanical load and systolic performance 224. In patients with essential hypertension, classification of LV geometry has been shown to add prognostic information to that derived from LVM; patients with concentric hypertrophy had the highest risk of a fatal CV event, and those with normal LVM and geometry the lowest risk 225. An intermediate risk profile was found in patients with concentric remodelling and eccentric hypertrophy 225. LV geometry patterns are also relevant in ESRD. Paoletti et al. reported a greater incidence of CV events in HD patients with eccentric hypertrophy than in those with concentric hypertrophy. Furthermore, eccentric hypertrophy was less responsive to ACEi treatment compared to concentric hypertrophy 226. On the other hand, HD patients with concentric LV hypertrophy may be more predisposed to intradialytic hypotension (IDH) caused by fluid removal as suggested by de Simone 227.

**Systolic function of the left ventricle**
HF is usually classified according to the New York Heart Association (NYHA) scale I-IV 228. HF due to LV systolic dysfunction is frequent in ESRD 118,119. LV systolic function can be assessed by measuring LV ejection fraction (EF). Echocardiography is the most widely used method although cardiac MRI is more accurate 229. Currently, the American Society of Echocardiography (ASE) recommends echocardiography using a two-dimensional approach as done in our study 223. EF is frequently used as a CV endpoint in clinical trials and has also been reported as a significant independent predictor of CV death and CV events in ESRD 230,231.
**Diastolic function of the left ventricle**

Another important aspect of LVH is its impact on left ventricular diastolic function. Elevated LV filling pressure with latent or manifest HF is the main physiologic consequence of diastolic dysfunction, and HF with preserved EF and represents approximately 40–50% of all cases of HF. The flow pattern through a normal mitral valve depends on atrial systolic function and left ventricular stiffness. This flow pattern is altered when LV hypertrophy is present. Assessment of LV diastolic function includes measurement of left atrial size combined with indices of relaxation and filling patterns. Cardiac catheterization can be used to measure LV diastolic pressures directly including changes in the LV pressure-volume relationship and serves as the gold standard for LV diastolic function. Radionuclide and MRI imaging have also been used. However, the most widely used technique is echocardiography. Pulsed-wave Doppler applied in the apical four-chamber view is used for measuring mitral inflow patterns. The first (early) peak in diastolic blood velocity is designated E and the late (atrial) peak is designated A. Tissue Doppler imaging of the mitral annulus, also applied in the apical four chamber view, is used for measuring annular movements during LV filling, represented by e’ and a’ corresponding to the mitral inflow velocities mentioned previously. Two often reported ratios are the E/A ratio and the E/e’-ratio, respectively. Both ratios describe the filling pattern of the left ventricle and are used to characterize LV diastolic function.

**NT-proBNP**

Natriuretic peptides play a major role in sodium and body volume homeostasis in patients with normal kidney function. The most important of these are atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). Their primary effect is induction of natriuresis via actions on renal haemodynamics and tubular function although this effect is limited in ESRD patients. BNP
originates from left ventricular myocytes. Secretion of BNP from the endocardium occurs constantly and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) represents the inactive amino-terminal fragment from BNP released in a 1:1 ratio. The major stimulus for synthesis and secretion of BNP is increased LV systolic and diastolic wall stress, which may occur as a result of volume expansion, pressure overload, and increased wall tension \(^{238,239}\). Plasma BNP levels correlate strongly with LV size and end-diastolic pressure and BNP generally provides a better index of LV mass and load than ANP, which may be more reflective of volume status \(^{238}\). In a large cohort of dialysis patients, BNP was also found to be a better indicator of LVM than ANP \(^{240}\). The latter explains the predominant use of BNP and NT-proBNP as biomarkers for HF and LV dysfunction as a supplement to echocardiography. For diagnostic use, BNP and NT-proBNP is similar but some differences should be mentioned. NT-proBNP is cleared renally unlike BNP which is cleared by neutral endopeptidases and clearance receptors. The different routes of elimination and degradation are reflected in different circulating half-lives for BNP (20 minutes) and NT-proBNP (120 minutes). Thus, NT-proBNP levels may be more stable due to a longer half-life but have a stronger correlation with renal function than BNP levels. This should be kept in mind when comparing and interpreting results \(^{236,241}\). Roughly 10% of NT-proBNP is removed by dialysis compared to 30% of BNP \(^{236}\). In addition to LV function, there has been much interest in the use of natriuretic peptides for assessment of volume status (dryweight) in ESRD patients. Some studies have shown that BNP and NT-proBNP levels can be modified by changes in volume status \(^{242,243}\) but other studies demonstrated that BNP levels correlated better with LV function rather than with volume status and do not favour the use of BNP and NT-proBNP for determination of volume status \(^{238,244,245}\). Moreover, NT-proBNP levels have been shown to predict CV and overall mortality in ESRD patients \(^{20,243,245,246}\).
Haemodynamic instability in haemodialysis patients

Intradialytic hypotension
There is no standardised definition of intradialytic hypotension (IDH)\textsuperscript{247}. The KDOQI guideline defines IDH as a decrease in systolic BP $\geq 20$ mmHg or a decrease in mean arterial BP (MAP) by 10 mmHg associated with clinical symptoms such as abdominal discomfort, yawning, sighing, nausea, vomiting, muscle cramps, restlessness, dizziness, fainting, and anxiety\textsuperscript{123}. An improvement of this definition has been proposed by adding the need for interventions such as fluid resuscitation or termination of dialysis. Accordingly, IDH can be defined as a decrease in systolic BP $\geq 20$ mmHg or a decrease in MAP by 10 mmHg associated with clinical events and/or the need for interventions\textsuperscript{247}. Our study used the latter definition. The incidence of IDH varies between studies, and is reported to occur in 4-30\% of HD treatments\textsuperscript{248-251}. IDH may cause adverse outcome in HD patients on its own\textsuperscript{252} but IDH could also be considered as a marker of predisposing comorbid conditions such as heart disease, diabetes, and autonomous neuropathy\textsuperscript{253-255}. Avoiding IDH is important because it hinders sufficient fluid removal and causes inadequate dialysis. Moreover, episodes of IDH is suspected to cause myocardial\textsuperscript{207,256} and cerebral ischemia\textsuperscript{257} and was found to be related both to frontal lobe atrophy\textsuperscript{258} and rise in cardiac biomarkers (creatine kinase MB, troponin I)\textsuperscript{259}.

Pathophysiology of haemodynamic instability during HD
The main mechanisms involved in CV stability during HD are summarised in Figure C. HD combined with ultrafiltration (UF) leads to a decrease in blood volume. Basically, IDH develops due to hypovolaemia if vascular refilling rate from the interstitial compartment does not keep pace with the UF rate. The normal compensatory response to hypovolaemia requires activation of baroreceptors, reduction of venous compliance, increased heart rate, vasoconstriction which
Figure C

Main pathogenic factors involved in cardiovascular instability during haemodialysis

- Increases TPR, and activation of the SNS with release of catecholamines. Normally these mechanisms can maintain BP within normal range and explains why healthy individuals can tolerate a decline in circulating blood volume of 20% \(^{260}\). In HD patients, the reaction to hypovolaemia varies and a wide range of relative blood volume reductions resulting in IDH have been observed \(^{261,262}\). Thus, additional factors which impair regulatory CV mechanisms might predispose patients to develop recurrent hypotensive episodes during HD. Among these are co-morbid conditions such as heart disease (both systolic and diastolic dysfunction), diabetes,
impaired sympathetic response, old age, atherosclerosis, antihypertensive medication, and food ingestion during dialysis. Although not restricted to ESRD patients, the so-called Bezold-Jarisch reflex should also be mentioned. Severe underfilling of the left ventricle caused by hypovolaemia can cause a paradox bradycardia and release of vasoconstriction and thereby hypotension due to withdrawal of sympathetic activity as described by Converse et al. in a small group of HD patients.

Furthermore, the composition of the dialysate can markedly affect intradialytic haemodynamics. In the past, acetate was often used as dialysate buffer. However, it proved to be vasodilating and cardio-depressant and was therefore replaced by bicarbonate. Bicarbonate primarily affects sympathetic tone via correction of acidosis. However, high concentrations have been associated with poor outcome possibly due to postdialysis metabolic alkalosis. Dialysate sodium used in high concentration augments refilling from the interstitial compartment thereby reducing the risk of IDH. High calcium concentration increases cardiac contractility which in turn affects SV. Potassium affects BP though TPR and low potassium tends to decrease TPR. Thermal effects have also been investigated and use of cool dialysate (e.g. 36.5°C) or blood temperature controlled feedback prevents IDH because of increased TPR and decreased venous pooling.

Antihypertensive medications can increase IHD through impairment of the normal response to hypovolaemia. Arteriolar constriction can be blocked by vasodilators (e.g. with ARB or calcium channel blocker (CCB) treatment), β-blockers reduce an increase in HR, and an overall compensatory increase in sympathetic activity may also be reduced (e.g. with ARB or β-blocker treatment). A common approach to avoid IDH is therefore to withhold antihypertensive treatment for several hours immediately before a dialysis session in the hope that peak drug effect will not
coincide with the vasodepressor effect of HD and lead to IDH. Yet, there is limited evidence about the effect of antihypertensive drugs in terms of IDH and only few studies have investigated this aspect. Accordingly, long-term randomised controlled trials are lacking and previous studies were predominantly short-term and observational.

**Aims and hypotheses**

**Paper I**
Aims: To describe background, design, patient recruitment, randomisation procedure, methodology and sample size considerations for the double-blinded multi-centre randomised placebo-controlled intervention trial Saving Residual Renal Function Among Haemodialysis Patients Receiving Irbesartan (SAFIR).

Hypothesis: See below.

**Paper II**
Aims: To investigate the effects of RAAS-blockade with the ARB irbesartan on several important intermediate CV endpoints including central BP, Alx, PWV, LVH, NT-proBNP, and sympathetic activity (HRV and plasma catecholamines) in a group of HD patients new to dialysis using a predefined systolic BP-target of 140 mmHg in all patients.

Hypothesis: Irbesartan treatment in newly started HD patients leads to stabilization or regression of left ventricular hypertrophy and a decrease in arterial stiffness.

**Paper III**
Aims: To investigate the effects of irbesartan on intradialytic haemodynamic parameters in a group of newly started HD patients and at the same time characterise the development over a one year period.
Hypothesis: Irbesartan treatment improves intradialytic haemodynamics.

**Methods**

**Study design, participants, and inclusion criteria**
As outlined in paper I, the SAFIR study was designed as a double-blinded multicentre randomised placebo-controlled trial primarily focusing on residual renal function and intermediate CV endpoints. Patients were recruited from six Danish hospitals between May 2009 and September 2011 and followed for one year. The participating hospitals were: Skejby, Horsens, Randers, Viborg, Aalborg, and Fredericia. Block randomization was applied to ensure equal distribution of patients with diabetes. Eligibility criteria are summarised in table 1 in paper I.

Briefly, the most important inclusion criteria were: HD vintage < one year, urine volume > 300 ml/24 h, and EF > 30%. One of the primary endpoints in the SAFIR study, apart from intermediate CV endpoints, was preservation of residual renal function which explains why preserved residual renal function (urine volume > 300 ml/24 h) was mandatory at inclusion. We decided not to include patients with severe HF (EF < 30%) because we considered it unethical not to offer these patients treatment with RAAS-blockade.

Based on data from a previous intervention study with 66 HD patients by Ichihara et al. that found a decrease in arterial stiffness with either ACEi (trandolapril) or ARB (losartan) treatment after one year we calculated that a sample size of 22 patients per group would confer a power of 90% to detect a 10% reduction in PWV in ARB treated and no change in PWV in placebo treated after one year with a standard deviation of 10% in both groups and a type I error probability of 0.05.

Furthermore, using data from a previous intervention study that found a significant effect on LVH regression with an ARB (losartan) in 24 HD patients with LVH and short dialysis vintage
calculated that a sample size of 22 patients per group would confer a power of 85% to detect a reduction in LVM index of 23 g/m² in ARB treated after one year assuming a 8 g/m² decrease in LVM in the placebo treated, a standard deviation of 19 g/m² in both groups, and a type I error probability of 0.05. However, in expectation of a 40% drop-out (e.g. transplantation, adverse events), we decided to recruit a minimum of 80 patients. At the end of the recruitment period 82 eligible patients had been included in the study and randomised to ARB (irbesartan) or placebo. Last patient last visit took place in December 2012.

**Statistical methods**
Data were analysed with Stata/IC 12.1 (StataCorp LP, College Station, TX 77845 USA). Accuracy of data entry into the database was verified by at least two people by double entry verification using Epidata 3.1 (The EpiData Association, Odense, Denmark). The statistical methods used in the studies are described in detail in the papers (see papers I-III).

**Examination conditions**
All measurements were performed in the morning between 08-10 a.m. just prior to HD in the dialysis units except for echocardiography, which was performed the day after a HD session to minimise the impact of volume overload (see Table 2 in paper I). When then patient arrived in the dialysis unit at visit A-F, predialytic weight was first obtained. Afterwards the patient rested for five minutes in the dialysis chair/bed. A standard electrocardiogram (ECG) was recorded followed by BP and HRV measurements. Subsequently, needle placement was performed by the attending dialysis nurse if the patient had an AV-fistula. Blood samples at visit A-F were taken after 30 minutes of rest in supine position after placement of the dialysis needles prior to administration of heparin and start of HD. The venous/arterial line or the permanent venous catheter (in case of absence of an AV-fistula) was always used for blood sampling thereby avoiding additional venous
puncture. Movement and stress caused by fear of needles may affect catecholamine and hormone levels, which is why the patient rested 30 minutes prior to blood sampling after placement of the needles. While the patient rested PWV and PWA were obtained by applanation tonometry. HD was started immediately after blood sampling had been performed.

**Blood pressure measurements**
Validated automated oscillometric BP devices were used for all BP measurements. For the predialytic BP, the patient rested in a sitting position for five minutes with his or her legs uncrossed prior to the measurement. The cuff was positioned at heart level on the arm without an AV-fistula, with a cuff-size matching the circumference of the arm. A minimum of two measurements were performed. In case of > 5 mmHg deviation in either systolic or diastolic BP, more measurements were performed. The average of the last two was used. Intradialytic BP was obtained at the same time as the intradialytic CO measurements.

**Applanation tonometry**
The SphygmoCor device (software version 7.0 and 8.2, Atcor Medical, Sydney, Australia) that was used for PWV and PWA measurements in our study is based on applanation tonometry. This technique allows non-invasive recordings of the arterial pressure waves by use of a handheld tonometer sensor (Millar SPT-301 tonometer). When applied directly above the artery, the sensor flattens the wall of the artery which eliminates tangential forces, and the sensor records the intra-arterial pressure waves using a high-fidelity strain-gauge transducer.

**Pulse wave velocity**
As previously mentioned, PWV is defined as $PWV = \frac{D}{\Delta t}$. The pulse wave travel distance ($D$) was approximated by subtracting the distance between the suprasternal notch (SN) and CA from the distance between SN and FA. The distance was measured with a tape measure. Calculation of the
pulse wave transit time (Δt) was done by sequential applanation tonometry recordings at the
carotid and femoral artery. SphygmoCor uses the peak of the R-wave in a simultaneously recorded
ECG to identify the start of systolic contraction. With this as a reference, the time delay is
determined by the arrival of the pulse wave at the carotid and femoral arteries, respectively.
According to recommendations, the intersecting tangent algorithm was used to determine the
arrival of the pulse wave$^{67,83,277}$, and the mean of the two PWV measurements was calculated for
each patient for each visit$^{84,278}$. Measurements were always performed on the same side
throughout the study although not always by the same observer$^{279}$. After we designed our study,
a new guideline was published which recommends the use of 80% of the direct distance between
the FA and the CA recording site (CA–FA x 0.8)$^{84}$ because this has been shown to the best
approximation with the real travelled aortic path length$^{82}$. Reference and normal values for PWV
has also been established recently as previously mentioned$^{83}$. Consequently, in order to facilitate
comparison with other studies we converted all PWV measurements to the new recommended
distance by using the equation developed by Vermeersch et al.$^{280}$. This equation was also used by
The Reference Values for Arterial Stiffness’ Collaboration group$^{83}$. Thus, two different PWV-
estimates are given according to use of subtracted distance (PWV_SD) or direct distance x 0.8
(PWV). The equations used for converting PWV_SD to PWV were:

\[
D_{\text{direct}} \ (\text{m}) = 0.45 \times D_{\text{subtracted}} + 0.21 \times \text{height} + 0.08
\]

\[
\Delta t \ (\text{sec}) = \frac{D_{\text{subtracted}}}{\text{PWV}_\text{SD}}
\]

\[
\text{PWV} \ (\text{m/s}) = 0.8 \times \frac{D_{\text{direct}}}{\Delta t}
\]

**Pulse wave analysis**

PWA measurements by applanation tonometry in our study were always performed at the radial
artery. Due to BP amplification as previously described, the SphygmoCor employs a so-called
transfer function which enables synthesis of the pulse wave in the ascending aorta from pulse waves recorded at the radial artery. Pulse waves in a steady state (as in regular heart rhythm) in the time domain can be translated by a Fourier transformation into the frequency domain. Accordingly, the pulse wave is described as the sum of a set of sinusoidal waves with different amplitudes and frequencies\textsuperscript{52}. The principle of the transfer function is that for each sinusoidal harmonic of the radial pulse wave, the transfer function expresses the amplification of the wave amplitude and the changes in the phase of the wave that is required to synthesise the corresponding aortic sinusoidal wave in the frequency domain. These wave characteristics are then re-transformed to the time-domain to generate a pulse wave corresponding to the ascending aorta. The general transfer function used in the SphygmoCor was derived in 14 patients undergoing diagnostic cardiac catheterization\textsuperscript{281} and has been approved by the FDA\textsuperscript{55}. If pulse waves are obtained from the carotid artery, which is also possible with the SphygmoCor device, no transfer function is used, because BP amplification between the aorta and the carotid artery is negligible. However, this approach was not used in our study. Estimation of the central BP requires calibration of the peripherally recorded pulse wave. Predialytic systolic and diastolic BP (obtained as previously described) was used for calibration. All PWA measurements were made in duplicate. Duplicates were averaged at the end of study and only measurements with T1 (the initial peak of the wave) > 80 ms and < 150 ms, augmentation index (AIx) < 50% and operator index > 80% were accepted according to recommendations\textsuperscript{282}. Throughout the study, measurements were always performed on the arm without an AV-fistula (also used for BP measurement) although not always by the same observer.
Echocardiography
Echocardiography was performed with the patient in the left lateral position by experienced
examiners before study entry and after one year just before the end of treatment. Raw data was
stored digitally in the cineloop format defined by the R wave on the corresponding ECG for off-line
analyses using EchoPac software (GE Healthcare, Horten, Norway). Quantification of cardiac
chamber size, LV mass and function was done blinded by one experienced examiner in accordance
with current guidelines. In our study we used the regression corrected cube formula
recommended by the ASE with measurements obtained according to the ASE conventions and BSA
according to the formula developed by Dubois. The following linear measurements were
obtained from 2-dimensional M-mode in the parasternal long axis view: Inter Ventricular Septum
in diastole (IVSd), Left Ventricular Posterior Wall in diastole (LVPWd), Left Ventricular Internal
Diameter in diastole (LVIDd) and Left Ventricular Internal Diameter in systole (LVIDs). Linear
measurements were obtained thrice from the same recording. The average of these three
measurements was subsequently calculated and used for estimation of LV mass and RWT. BSA, LV
mass, LVM-index, and relative wall thickness (RWT) were calculated as:

\[
\text{BSA (m}^2\text{)} = (0.00718 \times \text{height(cm)}^{0.725}) \times (\text{weight(kg)}^{0.425})
\]

\[
\text{LV mass (g)} = 0.8 \times (1.04[(\text{LVIDd} + \text{PWTd} + \text{SWTd})^3 - (\text{LVIDd})^3]) + 0.6 \text{ g}
\]

\[
\text{LVM-index (g/m}^2\text{)} = \frac{\text{LV mass}}{\text{BSA}}
\]

\[
\text{RWT} = 2 \times \frac{\text{LVPWd}}{\text{LVIDd}}
\]

Combining gender, LVM-index and RWT allows classification of LV geometry into normal,
concentric remodelling, concentric hypertrophy and eccentric hypertrophy as previously
described. We used a partition value of 115 g/m² in men and 95 g/m² in women between normal
LV mass and LVH. LV ejection fraction (LVEF) was calculated using the modified Simpson’s
rule with biplane planimetry of the LV. The following formula was used for EF assessment:

\[
\text{Ejection fraction} = \frac{(\text{EDV} - \text{ESV})}{\text{EDV}} = \frac{\text{SV}}{\text{EDV}}
\]

EDV: End diastolic volume

ESV: End systolic volume

SV: Stroke volume

LV diastolic function was assessed by left atrial diameter and by Doppler mitral flow velocities in the apical four-chamber view and by tissue Doppler velocities obtained from the lateral corner of the mitral annulus in the apical four-chamber view. Velocities were used to calculate the E/A ratio: the ratio of highest early mitral flow velocity (E) to the highest late atrial mitral flow velocity (A) and the E/é ratio: the ratio of E to early lateral mitral annulus velocity (e').

**Heart rate variability**

Heart rate variability (HRV) was assessed under controlled conditions prior to HD using the SphygmoCor HRV-system SCOR-Hx (software version 8.2, Atcor Medical, Sydney, Australia). A standard ECG was obtained in all patients before HD at visit A-F in order to detect arrhythmias and HRV was only performed in patients with sinus rhythm. Short-term HRV methods, described in detail previously, were used. All HRV parameters obtained are shown in Table 7 in paper II. A short five minute measurement with the subject resting in a supine position provided both time domain (mean N-N: mean time between R-peaks in the ECG; SDNN: standard deviation of all the N-N intervals; pnn50: the proportion of N-N intervals having a difference of >50 ms; rmssd: the square root of the mean squared differences of successive N-N intervals) and frequency domain parameters (total power, high frequency (HF) power; low frequency (LF) power; LF/HF ratio). In addition, two manoeuvres (Valsalva and standing) selected to challenge the autonomic nervous system were used. For the Valsalva manoeuvre, the patient blew into a mouthpiece with a
constant and continuous pressure of 40 mm Hg for 15 sec. A tiny leak in the mouthpiece apparatus ensured that the patient’s glottis remained open during the blowing effort. To accept the Valsalva manoeuvre, the average pressure during blowing had to be approximately 40 mmHg. The SphymoCor records heart rate before the start of the test, during the test, and for 45 seconds after the test. The result of the Valsalva maneuver is the ratio of the highest heart rate during (or shortly after) the forced expiration (a Valsalva maneuver) to the lowest heart rate occurring after the manoeuvre. The stand manoeuvre calls for active standing from a supine position. The orthostatic change produces a compensatory response of the heart rate to maintain cardiac output. The result of the stand maneuver is the ratio of the highest heart rate to the lowest heart rate occurring due to the manoeuvre.

**NT-proBNP and catecholamines**
Venous blood samples were taken before HD in serum tubes (NT-proBNP) and EDTA-coated tubes (catecholamines) after 30 min of rest in supine position. NT-proBNP samples were centrifuged after clotting, and the separated serum was stored at −80°C. In December 2012, all samples were analysed for NT-proBNP using a sandwich immunoassay with two monoclonal antibodies against the N-terminal part of NT-proBNP and a Cobas 6000 (e601 module) analyzer (Roche Diagnostics GmbH, Mannheim, Germany) 285,286. Catecholamine samples were kept cold in ice water prior to centrifugation and the separated plasma was stored at −80°C for up to six months. Samples were analyzed for adrenaline and noradrenaline by a radioimmunoassay (2-Cat RIA, BA-1500; Labor Diagnostika Nord, Nordhorn, Germany) 287 calibrated by our own validated standards. In house inter-/intra-assay coefficient of variation was 9/6%.
Intradialytic haemodynamics
Intradialytic haemodynamic parameters are summarised in Table 3 paper 3. CO, brachial BP, and heart rate measurements were performed in duplicate within the first (HD<sub>START</sub>) and the last (HD<sub>END</sub>) 30 minutes of the dialysis session. A previously validated system for access flow and CO measurements in HD patients with an AV-fistula was used (Transonic Hemodialysis Monitor HD02/HD03, Transonic Flow-QC tubing sets, and clip-on flow/dilution sensors Transonic Systems Inc., Ithaca, NY, USA) \(^{288-290}\). The system employs a saline dilution technique based on recordings of ultrasound wave velocity obtained by sensors attached to the outside of the dialysis blood tubes (arterial and venous blood line). The velocity of ultrasound waves in blood (1560-1585 m/sec) is determined by blood protein concentration (sum of proteins in plasma and in red blood cells), temperature, and average ion concentration in plasma \(^{288,291}\). Accordingly, if a bolus of isotonic saline (ultrasound velocity: 1533 m/sec) is introduced into the blood stream it dilutes the blood which in turn causes a reduction in the ultrasound wave velocity. CO was measured by injecting a bolus of 30 mL 37°C isotonic saline into the venous blood line within 5-7 seconds. The injected bolus dilutes the blood and reduces the ultrasound velocity detected by the venous blood line sensor. The saline bolus travels into the heart, where it is mixed (diluted) into the full cardiac output. Part of this diluted indicator then reappears at the arterial sensor where it is recorded as a conventional indicator dilution curve. The concentration of the indicator recorded in the peripheral artery therefore reflects dilution in the blood and CO can be derived as:

\[
CO = \frac{I}{\int c(t) \, dt} = \frac{I}{S}
\]

I: The quantity of injected saline

c(t): Is the concentration with respect to time (dt) during the first pass of the indicator

\[\int c(t) \, dt = S = \text{the area under the first pass dilution curve}\]
Based on CO, the system also estimates the volume of blood in the heart, lungs, and the great
vessels known as the central blood volume (CBV). Thus, CBV can be calculated as:

\[ \text{CBV} = \text{CO} \times \text{MTTa} \]

MTTa represents the mean time of indicator travel from the site of injection (venous blood line) to
the site of recording (arterial blood line)\(^{289}\). Although slightly overestimated, CBV represents the
relative blood volume which responds to fluid removal by UF during HD\(^{289,292}\). We used a built-in
recirculation protocol to check for access recirculation using injection of 10 mL isotonic saline into
the venous blood line prior the first measurement. No measurements were performed if overt
access recirculation was present. If CO measurements deviated more than 15% more
measurements were performed and the two closest were averaged and subsequently used for
analysis. The mean BP (MAP), total peripheral resistance (TPR) and stroke volume (SV) were
obtained by:

\[ \text{MAP} = \text{diastolic BP} + \frac{1}{3} \times (\text{systolic BP} - \text{diastolic BP}) \]
\[ \text{CO} = \text{SV} \times \text{heart rate} = \frac{\text{mean BP}}{\text{TPR}}. \]

**Study medication**
The study medication consisted of irbesartan (known under the trade names Aprovel, Karvea, and
Avapro) 150 mg, or matching placebo. The initial dose was one tablet per day. After two weeks,
daily dose was increased to two tablets. Compliance was checked monthly by counting residual
tablets. To reach equal BP-levels in the two treatment groups, investigators were instructed to
achieve a predialytic systolic BP of 140 mmHg in all patients by adjusting dryweight and by use of
all classes of antihypertensive drugs other than RAAS-blocking agents. If patients received RAAS-
blocking agents at inclusion, this treatment was stopped one week before baseline. Irbesartan acts
as a potent, long-acting angiotensin II receptor antagonist that inhibits RAAS via selective blockade
of the type 1 receptor subtype (AT$_1$-receptor)\textsuperscript{293,294}. The selective antagonistic effect on the AT$_1$ receptors causes increased plasma renin and Ang2 levels and decreased plasma aldosterone levels. Irbesartan is a so-called nonpeptidic substituted biphenyl tetrazole with the chemical formula C$_{25}$H$_{28}$N$_6$O and a molecular weight of 428.5 g/mol developed by Sanofi and Bristol-Myers-Squib (see Figure D).

**Figure D**

![Figure D](image)

Irbesartan is almost completely absorbed after oral ingestion, with a bioavailability of 60-80% which is unaffected by food\textsuperscript{295}. Irbesartan does not require hepatic biotransformation for its pharmacologic activity\textsuperscript{296}. In plasma 90% of irbesartan is bound to plasma proteins and the volume of distribution is 53-93 litres. Irbesartan undergoes hepatic metabolism through the cytochrome P-450 enzyme system (predominantly CYP2C9), and unchanged irbesartan and metabolites are excreted primarily through bilary routes although some is excreted via the urine. Total body- and renal irbesartan clearance is 157-176 and 3-3.5 ml/min, respectively. The elimination half life is 11-15 hours and drug steady state is reached within three days when a single dose is given daily\textsuperscript{297}. The usual dosage range to achieve BP reduction is 75-300 mg. The biggest decrease in BP is reached 3-6 hours after administration and the effect lasts for at least 24 hours. Use of irbesartan in patients with chronic renal failure does not require dosage adjustment. There is no accumulation despite repeated dosing and irbesartan is not removed by HD\textsuperscript{273,298,299}.
Hepatic impairment could be a problem with irbesartan. However, in patients with hepatic cirrhosis pharmacokinetics, were unaltered and no dosage adjustment was required. Alterations in pharmacokinetics in elderly patients is another concern, but data from studies in the elderly did not show clinically significant alterations in irbesartan pharmacokinetics and no dosage adjustments are needed based on age.

**Results**

**Predialytic blood pressure**
As described in paper II there was no significant difference in overall systolic and diastolic BP between placebo and irbesartan treated (Figure 2A and table 2 in paper II). Both groups reached the pre-specified mean predialytic systolic BP-target as intended. Thus, taking all twelve months into consideration we found that predialytic systolic and diastolic BP decreased equally (test for equal levels: $P = 0.42$ (systolic BP) and $P = 0.27$ (diastolic BP)) but significantly over time (test for constant level: $P = 0.005$ (systolic BP) and $P = 0.009$ (diastolic BP)). The estimated mean decrease in systolic BP (baseline vs. 12 months) was 8.2(0.3-16.2) (placebo; $P = 0.04$) and 10.0(1.7-18.4) mmHg (irbesartan; $P = 0.02$). Mean decrease in diastolic BP was 4.0(0.2-7.9) (placebo; $P = 0.04$) and 6.3(2.3-10.4) mmHg (irbesartan; $P = 0.002$). Factors known to affect BP such as ultrafiltration volume, use of additional BP-drugs, and residual renal function were not significantly different in the two groups. However, some minor differences should be mentioned. CBV tended to be higher in the irbesartan group (e.g. test for equal levels at HDSTART: $P = 0.07$) (paper III figure 3) and during the study period mean ultrafiltration volume increased by 0.26 (-0.10 - 0.63) L in the placebo group ($P = 0.2$), whereas the increase in the irbesartan group was 0.28 (-0.08 - 0.64) L ($P = 0.1$). Predialytic weight decreased by 1.9(-0.2 - 3.9) kg in the placebo group ($P = 0.08$) and increased by 1.3(-0.5 - 3.1) kg in the irbesartan group ($P = 0.2$), whereas HD-time increased by 1.4(0.6 - 2.1)
h/week in the placebo group (P < 0.001) compared to 0.5(-1.1 - 2.1) h/week in the irbesartan group (P = 0.6). Overall, these findings suggest differences in volume overload, and some of the BP-lowering effect of irbesartan may have been outbalanced by slightly more efficient fluid removal during HD in the placebo group.

Central blood pressure and augmentation index
Changes in central BP paralleled changes in brachial BP and there was no significant difference in predialytic central BP between placebo and irbesartan treated (test for equal levels: P = 0.20 (central systolic BP); P = 0.71 (central diastolic BP)) as shown in Figure 2B and Appendix Table 5 in paper II. Central systolic BP decreased over time regardless of group (test for constant level: P = 0.004). The estimated mean decrease (baseline vs. 12 months) was 5.4(-2.3-13.0) (placebo; P = 0.17) and 10.6(4.2-17.0) mmHg (irbesartan; P = 0.001). Central diastolic BP also decreased significantly during the study regardless of treatment (test for constant level: P < 0.009). The estimated mean decrease in diastolic BP was 5.1(0.2-10.1) (placebo; P = 0.04) and 6.2(1.1-11.3) mmHg (irbesartan; P = 0.02). Overall, there was no significant change in AIx or AIx@HR75 as shown in Figure 2C and Appendix Table 5 in paper II. Thus, taking all twelve months into consideration we found that AIx and AIx@HR75 were similar in the two groups (test for equal levels: P = 0.09 (AIx) and P = 0.47 (AIx@HR75)) and stable throughout the study period without significant changes over time (test for constant level: P = 0.10 (AIx) and P = 0.09 (AIx@HR75)).

Pulse wave velocity
Mean PWV was increased in both groups at baseline (> 10 m/s) and remained stable throughout the study period (test for constant level: P = 0.42). There was no significant difference in PWV between the groups (test for equal levels: P = 0.63) although PWV tended to decrease more in the irbesartan treated (Figure 2D paper II). Mean decrease (baseline vs. 12 months) was 0.4(-0.4-1.2)
(placebo; $P = 0.31$) and $0.8(0.0-1.6)$ m/s (irbesartan; $P = 0.05$). Use of PWV based on subtracted distance gave similar results. Most patients exhibited small changes in PWV during the study period (test for constant level: $P = 0.42$), yet changes in PWV were significantly correlated with changes in BP (Figure 3 paper II). The relationship between changes in BP and changes in PWV was not significantly affected by irbesartan treatment. Thus, for a given decrease in BP virtually the same decrease occurred in PWV, regardless of treatment.

**Figure E**

A) LV: Left ventricular; (x) Placebo; (o) ARB; 1=Normal; 2=Concentric remodeling; 3=Eccentric hypertrophy; 4=Concentric hypertrophy.

B) Distribution of LV geometry pattern (0/12 months).

C) change in LV geometry with the corresponding number of patients shown as lines between 0 and 12 months. Horizontal bars indicate mean LV geometry pattern.
**Left ventricular mass, ejection fraction, and LV diastolic function**

LVM-index was similar in the two groups at baseline and there was no significant difference between the groups after one year (Table 3 in paper II). EF was also similar at baseline and there was no significant difference between the groups after one year, although EF tended to decrease more in the placebo group. Mean decrease in EF was 5.7(0.6-10.9) (placebo; P =0.03) and 3.4(-2.3-9.1) % (irbesartan; P =0.22). Comparison of changes in EF (baseline-12 months) yielded a mean difference between groups of -2.3(-9.6-5.0) % (P = 0.54). LV geometry distribution was similar in the two groups at baseline (P = 0.33) and after one year (P = 0.44) (See Figure E). Concentric hypertrophy was the predominant LV pattern accounting for 48% at baseline and 60% after one year in the placebo group and 51% at baseline and 52% after one year in the irbesartan group. Changes in LV geometry were similar in the two groups (P = 0.51). Regardless of treatment, no change was found in parameters reflecting diastolic function such as E/A ratio, E/e’ ratio, and left atrial diameter. Progression of LVM-index was significantly correlated with higher mean systolic BP (averaged from all measurements between baseline-12 months) and increase in systolic BP (Figure 4 in paper II).

**NT-proBNP**

NT-proBNP levels were elevated but not significantly different between the treatment groups at baseline (Figure 4 +Table 6 in the appendix in paper II). There was no significant difference between placebo and irbesartan treated patients during the study period (test for parallel curves: P =0.09; test for equal levels: P = 0.58) despite an initial decrease within the irbesartan group. NT-proBNP increased significantly over time regardless of treatment (test for constant level: P = 0.01). Rise in NT-proBNP in the study period was significantly correlated with increase in LVM index (Figure 3 in paper II).
**Sympathetic activity**
Both time domain and frequency domain HRV parameters were attenuated indicating increased sympathetic activity in our cohort (Figure 3 and Appendix Table 7 in paper II). There was no apparent effect of irbesartan treatment on HRV. Thus, taking all twelve months into consideration we found that HRV was similar in the two groups and stable throughout the study period without significant change over time. Concerning manoeuvres (stand and Valsalva) there was no effect of irbesartan treatment. Stand ratio was stable whereas Valsalva ratio decreased significantly regardless of treatment (test for constant level: $P = 0.03$). Median plasma catecholamine levels were elevated indicating increased sympathetic activity in line with the HRV findings (Figure 3 and Appendix Table 6 in paper II). Adrenaline levels were similar and unaffected by irbesartan treatment. Noradrenaline levels differed significantly between groups at baseline with a higher mean level in the placebo group corresponding to a mean placebo/irbesartan ratio of 1.3(1.1-1.5) ($P = 0.002$). During the study period the difference remained constant (test for parallel curves: $P = 0.50$) indicating no significant effect of irbesartan.

**Intradialytic haemodynamic parameters**
Total number of IDH episodes registered during the study period were (placebo/irbesartan) 22/25 corresponding to an annual incidence rate of 6/7% ($P = 0.65$). Regardless of the time of assessment during HD, there was no significant difference in CO, MAP, HR, TPR, and SV between placebo and ARB over time ($P > 0.22$ in all tests for parallel curves and equal levels). CBV increased significantly and equally over time (test for parallel curves: $P=0.88$ (HDSTART); $P=0.83$ (HDEND)) (test for equal levels: $P = 0.07$ (HDSTART); $P = 0.286$ (HDEND)) both when measured at HDSTART and at HDEND (test for constant levels: $P = 0.008$ (HDSTART); $P = 0.005$ (HDEND)). CO, MAP, HR, TPR, and SV were stable throughout the study period regardless of treatment and time of assessment (Figures 3-4 in
paper III). In both treatment groups, the general haemodynamic response observed during HD was that CO, SV, MAP, and CBV decreased, whereas HR increased from HD_{START} to HD_{END} (Table 3 paper III). TPR did not change significantly from HD_{START} to HD_{END}. Thus, CO decreased during HD due to a reduction in SV which was not fully compensated by an increase in heart rate. This response was unaffected by irbesartan and it was stable over time regardless of treatment (Figure 5 paper III).

**Discussion**

**Assessment of blood pressure in haemodialysis patients**

The best way to diagnose hypertension in HD patients is debated and reflects the lack of universally accepted criteria for the diagnosis of hypertension in HD patients\textsuperscript{301,302}. From an epidemiologic perspective accurate diagnosis is important and misclassification of hypertension in cohort studies may partly explain why some studies failed to demonstrate a deleterious effect of hypertension\textsuperscript{113,114}. In contrast to patients with essential hypertension, in whom BP is relatively constant from day to day, HD patients exhibit significant BP variability depending on the time of measurement. Basically, fluid removal during dialysis tends to lower BP, but afterwards BP usually increases gradually due to fluid accumulation as demonstrated in studies using interdialytic ambulatory BP monitoring (AMBP)\textsuperscript{130,303}. BP measurements obtained outside the dialysis unit can provide a better assessment of overall BP because measurements are spaced out over a variety of volume and uraemic states, avoiding the problem of extremes of BP which are typically encountered before and after dialysis. Two methods are commonly used to record BP outside the dialysis unit: AMBP and home BP measurements\textsuperscript{301}.

Routine assessment of BP in HD patients is primarily done in dialysis units before and after HD but this approach suffers from numerous sources of error which deserves attention. Measurements
are often performed by nurses according to the usual routine of the dialysis unit, and not according to guidelines. Use of proper cuff size and a five-minute rest period prior to BP measurement can easily be neglected in a busy dialysis unit. Often, a single BP measurement is obtained instead of the recommended average of two. Talking while measuring BP can raise systolic/diastolic BP with up to 10/7 mmHg. A meal can cause BP to drop, whereas ingestion of coffee and smoking can raise BP. In addition, guidelines recommend measurements of BP in both arms and subsequent use of the one with the highest BP. However, in HD patients the presence of an AV fistula limits BP measurements to one arm. A white-coat effect has also been demonstrated in many HD patients. Thus, in comparison with AMBP peridialytic BP values are of limited accuracy in predicting interdialytic BP. Measurements obtained predialytic, postdialytic, and interdialytic can differ substantially and there is poor agreement between BPs obtained in the dialysis unit and those obtained by AMBP. Post-dialytic BP is minimally better than predialytic BP, and the average of pre- and post-dialytic BP is marginally better than both. Use of BP obtained 20 minutes post dialysis has also been suggested. AMBP provides the most accurate assessment of the BP level. The relevance of AMBP in HD patients is perhaps best illustrated by the fact that roughly 80% of adult HD patients are found to be hypertensive based on routine BP measurements, whereas only 33% are hypertensive if interdialytic AMBP is used, suggesting a high proportion of falsely classified patients due to volume overload prior to HD, non-standardised measurements and white-coat effects.

Only few studies have compared the prognostic value of AMBP or home BP monitoring with BP obtained in the dialysis unit. Alborzi et al. investigated the prognostic value of peridialysis BP, home BP, and AMBP in a cohort of 150 HD patients and found that BPs obtained with AMBP or at home were stronger predictors of mortality compared with BPs obtained in the dialysis unit.
One standard deviation increase in systolic BP increased the risk of death by 1.46 (95% confidence interval: 1.09–1.94) for ambulatory, 1.35 (0.99–1.84) for home, and between 0.97 and 1.19 (P > 0.20) for dialysis unit BP. A Japanese study showed that PP derived from BPs obtained within and outside the dialysis unit when averaged over one week were predictive of CV mortality and all-cause mortality. Finally, a recent study based on 326 HD patients reported that BPs obtained with AMBP or at home were superior in predicting mortality compared to BP recorded just before and after dialysis.

Taken together, these studies indicate that one-point measurement of BP in the dialysis unit is insufficient to evaluate hypertension in HD patients. Despite its inherent shortcomings as listed above, BP obtained in the dialysis unit can be used in a qualitative sense for prediction of hypertension. Especially if the measurement technique is improved in the dialysis unit and if multiple BPs are used as in our study. According to Agarwal et al. a two-week average predialytic BP of greater than 150/85 mmHg or a postdialytic BP of greater than 130/75 mmHg has at least 80% sensitivity in diagnosing hypertension. Specificity of at least 80% can be accomplished if predialytic BP exceeds 160/90 or postdialytic BP exceeds 140/90. Use of AMBP would have strengthened our study and AMBP was considered in the planning phase. However, it was eventually abandoned because HD patients were considered not to be willing to tolerate this in addition to the time consuming investigations. BP was therefore measured in a standardised manner as previously described, in accordance with guidelines as opposed to routine BP measurements.

**Pulse wave analysis and pulse wave velocity**

PWA measurements in our study were always performed at the radial artery which is technically simple due to the support provided by the underlying radial bone. Use of the carotid artery for
PWA is more difficult especially in obese individuals in whom a stable signal can be difficult to achieve. Movements caused by respiration can also disturb signal acquisition. Furthermore, there is a small risk of baroreceptor activation when pressure is applied over the carotid artery as well as a rather theoretical risk of dislodgment of carotid plaques. Overall, these aspects favour the use of the radial artery, and pulse waves obtained by applanation tonometry at the radial artery have been shown to be very similar to invasively measured intra-arterial pressure waveforms. Estimation of the central BP requires calibration of the peripherally recorded pulse wave. In our study we used brachial systolic and diastolic BP based on the assumption of negligible amplification of the systolic BP between the brachial artery and the radial artery. When calibrated with invasively obtained intra-arterial pressures, use of the generalised transfer function resulted in a close agreement between estimated and invasively measured BPs in the ascending aorta. However, it should be mentioned that validation studies using non-invasively obtained BP for calibration generally found wide limits of agreement when estimated central BP was compared to invasively measured central BP. Perhaps of little surprise, considering the significant difference shown between indirect cuff-based brachial BP and invasively measured intra-arterial BP. In short, accuracy of the synthesized central BP is heavily influenced by the BP used for calibration although the transfer function as such is valid. However, strictly speaking this has never been tested in chronic renal failure or HD patients. However, all calibration procedures are approximations and absolute differences in central BPs are unimportant in intervention studies with repeated measurements. Consequently, the method used for BP calibration is primarily important in inter-study comparisons. In this regard, it should be kept in mind that calibration with brachial systolic and diastolic BP results in lower central systolic BP than calibration with mean and diastolic BP. Alx is not affected by BP calibration, but due to the properties of the
transfer function there are other aspects to consider. The generation of the central AIx is based on identification of the so-called inflection point. Reconstruction of pulse wave details such as the inflection point is based on higher frequency signals (i.e. above 6-8 Hz) than those used for central BP estimation. Because the transfer function is less precise at high frequencies inaccuracies arise when establishing the inflection point which in turn affects AIx. Thus, limited agreement has been reported between estimated AIx and invasively obtained AIx \(^{327-329}\). However, as for central BP, absolute differences in AIx are unimportant in intervention studies with repeated measurements as long as the same method is applied in all patients, which was the case in the SAFIR study.

Assurance of reproducibility is important when more than one individual is collecting data in a study, particularly when assessing changes over time. Reliable PWA and PWV measurements with the SphygmoCor device require training and experience as well as standardised examination conditions \(^{67,330}\). In the SAFIR study, all PWA and PWV measurements were performed by trained observers and examination conditions were similar. According to a previous study, multiple trained observers can achieve reproducible measurements of PWV and PWA with the SphygmoCor device \(^{331}\). Moreover, studies in non-renal patients reported a high reproducibility of SphygmoCor-derived PWA and PWV measurements both in terms of low intra- and inter-observer variation as well as low day-to-day variation \(^{279,330,332-334}\). Reproducibility of the SphygmoCor device has also been investigated in patients with chronic renal failure. Overall, a lower reproducibility was not shown in patients with chronic renal failure including dialysis patients, despite a higher prevalence of increased arterial stiffness \(^{335-337}\). The method used for distance measurement is a significant cause of error when measuring PWV. Thus, in patients with abdominal obesity or in women with large bust size, performing correct
straight tape measurements can be difficult causing an overestimation of the true arterial distance. A previous study found good agreement between invasively measured distance and the non-invasive distance method used in our study based on subtraction of carotid-suprasternal notch distance from suprasternal notch-femoral distance. Moreover, this method of distance measurement provided the strongest relationship with CV mortality in HD patients. However, a recent MRI-study demonstrated that use of the direct distance x 0.8 is the most accurate method when assessing PWV distance and the newest PWV guideline also recommends this distance estimation. Since measurement errors are additive, the use of one direct distance rather than the use of two distances may be favoured. Notwithstanding, both distance methods are approximations and absolute differences are unimportant in an intervention study with repeated measurements provided that the same method is used in all patients at all examinations, which was the case in the SAFIR study. However, when comparing studies, differences between methods used to assess length will be critically important. As previously mentioned, we converted all our PWV estimates based on subtracted distances to the newly recommended direct distance x 0.8 in order to facilitate inter-study comparisons including the newly proposed PWV cut-off of 10 m/s.

The timing in relation to dialysis can also affect PWA and PWV measurements. Previous studies reported significant differences in BP, PWV, central BP, and AIx when comparing measurements obtained before and after HD. Interestingly, the response following HD seems quite unpredictable, which tends to discourage the use of post-HD measurements in studies with repeated measurements. Accordingly, Georgianos et al. found a decrease in BP, central BP, and AIx and no significant change in PWV after HD, whereas Othmane et al. found an increase in BP, central BP, and PWV and a decrease in AIx after HD. PWV measured before or after HD, and PP amplification measured before HD, independently predicted CV outcome. However, neither AIx
nor central PP was related to CV outcome regardless of the time of assessment. These findings suggest that measurements obtained before and after HD are not interchangeable, although PWV may be more stable compared to PWA parameters including AIX. In the SAFIR study, measurements were always performed prior to HD in order to avoid acute effects induced by dialysis.

Use of echocardiography in haemodialysis patients
Additional awareness is required when interpreting parameters obtained by echocardiography in HD patients due to the intermittent nature of volume overload in relation to dialysis. In our study we standardised measurements in order to avoid volume overload and acute effects attributed HD by always performing echocardiography the day after a HD session. Multiple observers performed echocardiography in our study, which might be considered a weakness due to the high degree of operator dependence of this method. Although it would have been preferable to have all examinations done by the same observer it was not possible, as six different hospitals participated in the study. All observers were experienced as well as blinded in terms of treatment status (placebo/irbesartan). Subsequent analysis of all recordings was done blinded by one single trained observer in accordance with current guidelines. As recommended by the ASE, the regression corrected cube formula was used for estimation of LV mass with measurements obtained according to the ASE conventions. The primary drawback with this formula is that inaccuracies in LV dimensions are substantially magnified potentially causing poor accuracy and misclassification. To some degree, this can be rectified by use of repeated measurements. However, despite considerable intra-individual variation with single measurements, mean LVM estimates, based on all measurements within a group, have the ability to demonstrate significant
differences between groups. Accordingly, previous studies in ESRD patients demonstrated significant changes in LVM-index on a group level with fewer patients than in our study\textsuperscript{37,275,342,343}.

EF as an index of LV systolic function carries important limitations arising from its dependence on instantaneous loading conditions (volume overload), suboptimal test-retest reproducibility, and low sensitivity in detecting subtle LV systolic impairment\textsuperscript{344,345}.

The parameters used to characterise diastolic function (e.g. E/A ratio and E/é ratio) are also influenced by volume overload as well as technical pitfalls such as suboptimal gain settings and misalignment of the Doppler beam (e.g. displacement of the sample volume closer to the mitral annulus which results in underestimation of maximal velocities)\textsuperscript{346}. In addition, increased HR sometimes results in indistinguishable E and A flow velocity profiles\textsuperscript{347}. Moreover, it should be kept in mind that these methods measure the time course of left ventricular filling, which is not equivalent to diastolic function, as they do not give information about LV intracavitary pressure.

Normal values for the E/A ratio are characterised by a serial change with age\textsuperscript{232,346} as well as a progressive transformation from health through disease\textsuperscript{348}. In combination these factors create a parabolic curve function which can make interpretation of E/A ratio somewhat difficult\textsuperscript{348}. So-called pseudo-normalization of LV filling pattern (mitral flow apparently normal despite the presence of diastolic dysfunction) may be encountered because E/A ratio is strongly load-dependent\textsuperscript{349}. In the majority of HD patients the early filling (E) and the E/A ratio is decreased due to elevated end diastolic pressure resulting from decreased LV compliance caused by LVH.

However, elevated atrial pressure caused by hypervolaemia will increase early filling phase (E) causing “pseudo-normal” E/A ratio. The latter is usually revealed by re-examination after fluid removal by dialysis\textsuperscript{126,349}. Tissue Doppler velocities such as é has been shown to be less influenced
by volume overload and may therefore be better markers of LV diastolic function in HD patients. $E/e'$ ratio is dependent on both the blood flow and the tissue movement and is closely related to LV filling pressures. $E/e'$ ratio may be more accurate than other methods for estimating LV filling pressure according to previous studies in different subsets of patients. Moreover, in a cohort of 220 ESRD patients, $E/e'$ ratio provided additional long-term prognostic information above and beyond that of LVM and systolic function. Adding to this, a previous study with 125 ESRD patients reported that an $E/e'$ ratio >15 predicted invasively measured increased LV filling pressure with a sensitivity of 82% and a specificity of 88%. The correlation between $E/A$ ratio and LV filling pressure was not significant and only $E/e'$ ratio was significantly associated with increased mortality. Increased $E/e'$ ratio has also been reported to be a significant predictor of poor outcome in other ESRD studies. Overall, these findings indicate that $E/e'$ ratio is a more accurate estimate of LV filling pressure and thereby LV diastolic function in ESRD patients. Most likely, because $E/e'$ is less influenced by volume overload.

Finally, it should be mentioned that a more accurate and less operator dependent method such as MRI could have been used for assessment of cardiac status instead of echocardiography. However, although the use of MRI was considered in the planning phase, it was eventually dropped due to limited availability at most of the participating hospitals.

Assessment of sympathetic activity
Different techniques are available for assessment of SNS activity. Plasma catecholamine levels, heart rate variability (HRV), and muscle sympathetic nerve activity (MSNA) recordings are the most frequently used. An indirect marker of SNS activity such as HRV is influenced by a wide range of mechanical, chemical, and hormonal stimuli and is therefore far from perfect. Reproducibility of short-term HRV parameters and controlled manoeuvres such as Valsalva and
stand are generally reported to be high in healthy subjects \(^{193,359,360}\). In diseased individuals, reproducibility has been questioned due to impaired HRV. When HRV is impaired, all HRV parameters are lower and therefore easily influenced by even small changes leading to a large random variation within individuals \(^{361}\). Large random variation has also been found in healthy, irrespective of whether a retest was repeated immediately or with several days interruption \(^{362}\). Another major limitation of HRV is the reduced applicability in patients without normal sinus rhythm. Accordingly, a large number of measurements were discarded in our study due to arrhythmias (predominantly atrial fibrillation and multiple ectopic beats). Plasma catecholamine levels (adrenaline and noradrenaline) represent the net result of discharge, reuptake, metabolism, and clearance, which makes interpretation in terms of SNS activity difficult. Plasma measurements may therefore be regarded as a poor index of sympathetic activity \(^{363}\), although plasma noradrenaline levels respond to sympatho-inhibitory drugs including RAAS-blocking agents \(^{364,365}\). Measurement of organ-specific noradrenaline release to plasma from sympathetic nerves, also known as regional noradrenaline spillover, and MSNA recordings are generally considered to be better methods \(^{13,192,195,363}\). Noradrenaline spillover measurements requires sampling from the veins draining internal organs and isotope dilution methodology, whereas MSNA typically involves insertion of a fine electrode in the common peroneal nerve near the head of the fibula with positioning of the tip of the electrode in the sympathetic fibres. Both methods are quite complex as well as impractical in a clinical setting with a large number of patients. Noradrenaline spillover and MSNA have therefore primarily been used in studies with a relatively low number of patients \(^{13,181,366,367}\), whereas clinical studies with a large number of patients have used non-invasive techniques such as HRV \(^{186,192,368-370}\) and plasma catecholamine levels \(^{192,195-197}\). Moreover, use of
invasive methods tends to discourage patient participation in a clinical long-term study. The SAFIR study therefore used HRV and plasma catecholamines, despite the limitations listed above.

**Intradyalitic haemodynamic measurements**

One of the assumptions with the saline dilution technique used for CO measurements is that the infused bolus of saline does not diffuse out of the blood stream and into the extra-vascular compartment. This has previously been examined and is not considered a significant factor\(^{371}\). In addition, there must be no access recirculation, either pre-existing or induced by the saline injection, and second pass of the indicator must be avoided. The latter is generally considered as the biggest problem in dilution based methods\(^{289}\). The AV-fistula used for vascular access may act as peripheral arterio-venous shunt providing a fast route for blood return to the heart known as cardiopulmonary recirculation. Cardiopulmonary recirculation can be a significant source of error because it results in a second pass of the saline indicator back through the heart and lungs which follows quickly after the first pass. This second pass interferes with the indicator readings and thereby the calculation of CO. However, it can be limited by avoiding prolonged saline injection time (> 5-7 seconds)\(^{289}\). Based on the appearance of the dilution curve, the Transonic system usually recommends a new measurement if second pass or access recirculation is suspected. Access recirculation predominantly occurs if the blood flow pumped by the dialysis machine is greater than flow in the AV-fistula. In our study, the blood pump speed was kept at 200 mL/min when CO was measured, which tends to eliminate access recirculation. Accuracy of CO measurements obtained with Transonic was evaluated in pigs by comparison of invasive perivascular flow probe measurements and right atrial to left atrial bypass roller pump flows\(^{290}\). In humans, CO obtained with Transonic has been compared to the thermodilution method\(^{372}\). Both studies found good agreement between Transonic and non-Transonic derived CO. Reproducibility
(precision) is primarily influenced by access recirculation, wrong temperature and prolonged injection time. Average difference between two measurements obtained within five minutes was found to be $4.3 \pm 3.8\%$ (CO) and $4.1 \pm 3.8\%$ (CBV)\textsuperscript{289}. In our study, precision, expressed as the coefficient of variation, was $2.4\%$ based on 342 pairs of CO measurements obtained within the first 30 minutes of HD.

**Tolerability of irbesartan in haemodialysis patients**

Suspected side effects such as hypotension and hyperkalaemia were not more prevalent in the patients treated with irbesartan and irbesartan was generally well tolerated. Unlike most previous studies, our study provided long-term follow-up data on possible side effects of irbesartan in HD patients, which is novel. Previous short-term studies investigating the use of irbesartan in HD patients have reached similar conclusions\textsuperscript{273,298,299}, although one study also stated that intravascular volume depletion due to diuretic therapy and/or HD may cause an exaggerated response to irbesartan\textsuperscript{298}. The aspect of hyperkalaemia has also been investigated with other RAAS-blocking agents. Some studies found significantly higher potassium with RAAS blockade in ESRD patients\textsuperscript{373-375} but others did not\textsuperscript{376-380}. Previous studies have reported higher potassium levels in anuric compared to patients with residual renal function, which to some extent may explain the low prevalence of hyperkalaemia in our cohort\textsuperscript{380,381}. The potassium secretory capacity of the intestinal mucosa increases in chronic renal failure, leading to increased colonic potassium losses\textsuperscript{382,383}. As a result, the large intestine may contribute to the partial maintenance of potassium homeostasis as renal excretion of potassium declines. The nature of this adaptive process is poorly understood but aldosterone may act as a regulator of potassium secretion in the distal colon\textsuperscript{384}. RAAS-blockade decreases aldosterone levels, and thereby limits the action of aldosterone both in the nephron and in the intestine which in turn leads to decreased excretion of
potassium in the urine and faeces resulting in hyperkalaemia. Adding to this are factors such as excess intake of potassium through the diet, constipation, and inadequate dialysis. Thus, apart from medications such as ACEIs and ARBs, several other factors should also be considered when assessing the cause of hyperkalaemia in HD patients. In summary, results from our study, and most previous studies, indicate that side effects are negligible and should not discourage use of RAAS-blockade in HD patients. However, frequent assessment of BP, hydration status, and potassium levels is advised.

**Blood pressure**

In our study, a predialytic systolic BP-target of 140 mmHg was chosen based on the KDOQI-guideline recommendations. Both groups achieved a similar decrease in predialytic BP and the mean BP-target of 140 mmHg was reached in both groups, despite the fact that irbesartan treated patients on average received two extra defined daily doses of antihypertensive medication (300 mg irbesartan). Weekly HD-time, UF volume, hydration status, and use of additional antihypertensive medication were not significantly different in the two groups when all twelve months were considered. However, closer examination of the data indicated that there may have been some differences in fluid management in the two groups. CBV tended to be higher in the irbesartan group (when CBV was assessed at the start of HD) and predialytic weight tended to increase more in the irbesartan group compared to the placebo group from baseline to twelve months. Accordingly, some of the BP-lowering effect of irbesartan may have been offset by slightly more volume overload. Several studies in patients with essential hypertension have demonstrated the antihypertensive effects of irbesartan. Data from 2955 patients with mild to moderate hypertension enrolled in eight multicenter, randomised, double-blinded, placebo-controlled studies were pooled by Reeves et al. to analyse the integrated efficacy of irbesartan across the
dosage range of 1 mg to 900 mg\textsuperscript{387}. The study showed that antihypertensive effects increased with increasing doses and reached a plateau at $\geq$300 mg. Furthermore, irbesartan 150 mg provided placebo-subtracted reductions in trough seated systolic and diastolic BP of approximately 8 and 5 mm Hg, respectively. Kassler-Taub et al. compared the BP-lowering effect of irbesartan with the ARB losartan in a study with 567 patients with mild to moderate essential hypertension\textsuperscript{388}. Irbesartan was given as monotherapy after a placebo lead-in phase after all other antihypertensive agents were withdrawn. The study found a significant reduction in both systolic and diastolic BP after one week regardless of drug and dosage. However, after 8 weeks, reduction in systolic/diastolic BP was higher with irbesartan 300 mg (-16.4/-11.7 mmHg) than with losartan 100 mg (-11.3/-8.7 mmHg; $P < 0.01$ vs. 300 mg irbesartan). BP-lowering with 150 mg irbesartan (-12.1/-9.7) was not significantly different from 100 mg losartan. Two similar studies by Oparil et al. corroborate these findings\textsuperscript{389,390}. Although these studies did not include patients with chronic renal failure, they all clearly demonstrated a BP-lowering effect of irbesartan. In HD patients, an open-label, multicenter, randomized cross-over study found that irbesartan 150 mg significantly lowered predialytic systolic/diastolic BP from 161/83 to 151/78 over a 4-week period. This effect was similar to valsartan 80 mg\textsuperscript{273}. Accordingly, the BP-lowering effect of irbesartan is well documented also in ESRD patients treated with HD.

**Central blood pressure and augmentation index**

In our study, changes in central aortic BP were generally small and paralleled changes in brachial BP regardless of treatment with placebo or irbesartan. A tendency towards delayed wave reflection after one year was also indicated by our data (e.g. Alx, Alx@HR75, and time to reflection in Table 4 and 5 in Appendix of paper II) but this effect was not more pronounced in the irbesartan treated patients. In patients without chronic renal failure, RAAS-blockade has been reported to
cause a greater reduction in central aortic BP for the same decrease in brachial BP compared to other drugs. Two short-term studies and two long-term studies have investigated this effect in ESRD patients. All studies had a relatively low number of patients compared to studies in non-renal patients. The two short term studies found significantly reduced central BP and delayed wave reflection (Alx) with RAAS-blockade. The long-term study by London et al. based on 24 HD patients compared the effects of an ACEi (perindopril) with a CCB (nitrendipine) and found decreased central BP and Alx after one year in both groups without significant differences between the two treatment groups. Brachial BP and PWV also decreased significantly after one year in this study, but again there was no significant difference between treatments.

In another long-term study by Suzuki et al. involving 24 PD patients, there was no significant effect of ARB treatment (valsartan) after one year. Alx decreased significantly in both placebo and ARB treated patients, but the decrease was not significantly different between groups. Like the SAFIR study, this study also used a systolic BP-target of 140 mmHg and both treatment groups achieved a similar reduction in brachial BP.

In the Conduit Artery Function Evalution (CAFE) study, a substudy of the larger Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), BP-lowering treatment with a CCB and an ACEi (amlodipine+/perindopril) reduced central BP substantially more than treatment with a β-blocker and a diuretic (atenolol+/thiazide) despite a similar reduction in brachial BP in a cohort consisting of 2199 hypertensive patients. Moreover, clinical outcome (post hoc-defined composite outcome of total CV events/procedures and development of renal impairment) was found to be better with CCB and ACEi treatment possibly due to the differential effect on central BP. In our study, the majority of the patients received CCB alongside placebo/irbesartan. Accordingly, 61/63% of the patients in the placebo/irbesartan group received CCB at baseline. The relatively low number of
patients in our study prevented adequately powered analysis regarding the effect of CCB (e.g. ARB +/- CCB vs. placebo +/- CCB) and was therefore not done. However, there were no significant differences in defined daily doses or in the number of patients treated with CCB in the two treatment groups during the study period.

Central BP parameters such as PP and AIx have been linked with CV-outcome in ESRD in some 30,31 but not all studies 102, and the added value of central BP over brachial BP is debated. Nevertheless, brachial BP is not always a good surrogate for the effect of BP-lowering drugs on central arterial haemodynamics as illustrated by the CAFE study and this aspect seems relevant to investigate also in ESRD patients. A potential added effect due to the presence of CCB may be important and should be considered in future studies investigating effects of RAAS-blockade on central BP and AIx. In the near future, results from the Chronic Renal Insufficiency Cohort (CRIC) study with 2531 patients may help to clarify the added value of central BP compared to brachial BP in terms of CV outcome in patients with chronic renal failure 393.

**Arterial stiffness**
Observational studies in dialysis patients have linked RAAS-blockade to a more favourable CV outcome, possibly through reductions in PWV 28,394,395. Moreover, absence of PWV decrease in response to BP decrease constitutes a significant predictor for mortality in HD patients 28. An often used measure for the clinical relevance of the magnitude of a PWV decrease is provided by a study by Blacher et al. 12. This study involved 241 HD patients and showed that all-cause mortality odds ratio (with 95% confidence interval) increased by 1.4 (1.2-1.6) for each 1 m/s increase in PWV. In our power calculation we considered a 10% reduction in PWV to be clinically relevant which is very similar to the 1 m/s finding by Blacher et al., thus applying 10% to our baseline PWV ≈11 m/s results in ≈1.1 m/s. In addition, we also allowed for a high drop out rate as previously described.
The actual difference after one year was below 10% and dropout did not exceed 40%. Thus, although our study was based on a relatively small number of patients the power was there to detect a clinically relevant difference of ten percent in PWV after one year. A larger study could possibly have detected a small statistically significant difference, but this would hardly be clinically relevant.

Whether RAAS-blockade induces a greater decrease in PWV for the same decrease in BP is debated. Two intervention studies in dialysis patients found a BP-independent effect of RAAS-blockade on PWV, whereas our results indicate that changes in PWV, if present, were significantly correlated to changes in BP and we did not find any BP-independent effect of RAAS-blockade with irbesartan. Two intervention studies in HD patients and one in peritoneal dialysis patients reported similar results. The methods used for PWV assessment differ and may explain part of the discrepancy. Shigenaga et al. used PWV estimates obtained between the brachium and the ankle (baPWV). Ichihara et al. used baPWV together with PWV estimates obtained between the heart and the ankle (haPWV). Both baPWV and haPWV include a large proportion of muscular artery segments which may be more affected by RAAS-blockade compared to the carotid-femoral artery segment used in our study. Thus, PWV-estimates based on baPWV and haPWV may to some extent reflect peripheral vasodilatation rather than an actual decrease in arterial stiffness in the aorta. PWV measured outside the aortic track, has little predictive value according to recent guidelines. However, in retrospect including e.g. brachial-carotid PWV in our study could have elucidated this aspect fully and aided in a better comparison between studies. Ichihara et al. also reported that none of their patients were treated with RAAS-blocking agents prior to the study. In contrast, 36(44%) patients (placebo/irbesartan: 14(34%)/22(54%)) in our
study received RAAS-blocking treatment prior to the study. Although somewhat speculative, it seems plausible that ARB-treatment might have greater impact in patients never treated with RAAS-blocking agents compared to patients accustomed to RAAS-blockade. However, excluding patients treated with RAAS-blocking agents within six months prior to baseline did not change our results significantly. Overall, we cannot rule out that RAAS-blockade has a small BP-independent effect on PWV, but our study found no indication that this should be the case in HD patients.

Since all measurements in our study were performed prior to HD they represent the predialytic state of the patients and are thereby potentially highly influenced by volume overload. Use of post-HD measurements would have avoided this problem but at the expense of unpredictable acute effects caused by HD as previously mentioned. Ideally, measurements should be obtained the day after HD in order to avoid the effect of volume overload, as well as acute effects caused by HD. The logistical problems caused by attendance of patients on a non-HD day most likely discourage the use of measurements on a non-HD day and may explain the predominant use of pre- or post-HD measurements in most studies. Nevertheless, a small short-term study performed measurements on a non-HD day and found that the combined effect of fluid removal and RAAS-blockade lowered PWV and AIX substantially more than fluid removal without RAAS-blockade. Results from this study suggest, that effects of RAAS-blockade are more pronounced in a volume depleted state. The latter might to some extent explain why our study found no significant effect of ARB treatment. Awareness of the intermittent nature of volume overload in HD patients is important and this aspect should be considered both when comparing previous studies and when planning future studies.
Left ventricular hypertrophy
Regression of LVH is associated with better outcome in dialysis patients\textsuperscript{212,213} and various strategies have been proposed either as monotherapy or as combinations. Thus, effective LVH-reducing strategies include: reduction of BP either with BP lowering drugs\textsuperscript{399,400} or with improved fluid management\textsuperscript{129}, improvement of anaemia with erythropoietin (EPO) to optimise haemoglobin levels\textsuperscript{19,214}, improvements in calcium phosphate metabolism\textsuperscript{199}, and more frequent or prolonged dialysis regimens\textsuperscript{401-403}.

Concerning BP-lowering drugs and LVH regression in HD patients, several small studies reported a favourable effect of RAAS-blocking agents\textsuperscript{37,275,342,343,391,396,404-408}. Five of these studies used an ARB\textsuperscript{275,391,396,405,407} and five used an ACEi\textsuperscript{37,342,343,404,408}. Two studies compared ACEi and ARB\textsuperscript{405,406} and one study tested the combination of ACEi and ARB in addition to monotherapy with either drug\textsuperscript{406}. Two recent meta-analyses by Yang et al. and Tai et al. pooled data from several ESRD trials and found a significant effect of RAAS-blockade\textsuperscript{399,400}. Yang et al. concluded that ARB treatment was associated with a greater reduction in LVH in patients on dialysis, and ARB therapy tended to have a similar effect as ACEi, yet the combination of ARB with ACEi did not show additional benefit to LVH in HD patients\textsuperscript{400}. Tai et al. found a beneficial effect of RAAS-blockade with ACEi or ARB regarding LVH regression, but at the same time they acknowledged that their results could reflect a lack of large, high-quality trials in the HD population\textsuperscript{399}. Interestingly, large scale, randomised, double-blinded trials in non-renal patients, such as the Swedish Irbesartan In Left Ventricular Hypertrophy Investigation versus Atenolol (SILVHIA)\textsuperscript{409}, Candesartan Antihypertensive Survival Evaluation in Japan Extension (CASE-J)\textsuperscript{410} and The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial, suggested that the direct action of ARB rather than the BP-lowering effect contributed considerably to the regression of LVH. Recently, a meta-
analysis by Fagard et al. compared randomised comparative studies on regression of LVM by anti hypertensive treatment and demonstrated that the only significant difference between drug classes is a lesser regression in LVH by β-blockers than by ARB. Meta-regression analysis suggested that this effect was BP-independent \(^{411}\). The pathophysiological explanation for the proposed BP-independent effect on LVH is based on studies that investigated fibrotic, proliferative and inflammatory pathways influenced by RAAS. Accordingly, elevated levels of aldosterone, consequent to activation of RAAS, can promote cardiac fibrosis, perhaps due to increased production of transforming growth factor β (TGF-β) \(^{412-415}\). Pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6, activation of the SNS, elevated levels of cathecholamines, and excessive endothelin-1 production has also been implicated in LVH \(^{215,416}\). Inhibition of these fibrotic, proliferative, and inflammatory pathways may induce a non-BP dependent regression of both LV hypertrophy and fibrosis \(^{417-419}\). Regression of arterial stiffness with RAAS-blockade may also improve LVH in a non BP-dependent manner due to reduction of afterload. Accordingly, animal models of chronic renal failure suggest that collagen cross-linking and calcification in the aorta was inhibited with RAAS-blockade \(^{416,420}\). Overall, there is evidence suggesting that RAAS-blockade is associated with a BP-independent reduction in LVH and that RAAS-blockade is more efficient in regressing LVH than non-RAAS-blockade antihypertensive therapy in dialysis patients although our study found no such effect. Compared to previous studies \(^{400}\), our patients did not have pronounced LVH, which may partly explain the lack of additional effect of ARB on LVH in our study. Moreover, judged from the overall mean BP-level, our patients could be considered relatively normotensive and RAAS may have a limited role in the pathogenesis of mild LVH in normotensive HD patients. Accordingly, LVM-index, PWV, and AIx were not improved significantly by RAAS-
blockade with ACEi (ramipril) after twelve months in a placebo-controlled study with 45 normotensive HD patients very similar to the SAFIR study by Yu et al. ⁴⁰⁸.

Ejection fraction
In our study, EF tended to decrease over time, but the decrease was only significant in the placebo group and the decrease was not significantly different from the irbesartan group. Thus, at equal BP levels there was no effect of RAAS-blockade on EF. This finding is similar to results from a recent meta-analysis based on six randomised controlled trials with a total of 207 dialysis patients. Thus, no significant improvement in EF was found with ARB despite a significant regression of LVH as previously mentioned ⁴⁰⁰. However, this meta-analysis did not include a very large Italian study from 2010. This three-year randomised, double-blind, placebo-controlled, multi-center trial based on 332 HD patients with HF (NYHA class II to III; EF <40%), investigated the ARB (telmisartan) or placebo added to conventional antihypertensive therapy including an ACEi (enalapril or ramipril). The study found a beneficial effect of ARB treatment when added to ACEi regarding both all-cause (35.1% (ARB) vs. 54.4%; p<0.001) and CV mortality (30.3% (ARB) vs. 43.7%; p<0.001) as well as morbidity in terms of hospital admission for HF (33.9% (ARB) vs. 55.1%; p<0.0001). Moreover, both NYHA class and EF (5.8±6.7% (ARB) vs. 3.1±4.4%; p<0.0001) improved significantly in the ARB treated patients. Unfortunately, this study did not report data on LVH but a significant decrease in left ventricular internal diastolic diameter diameter (LVDd) was observed ⁴⁸. The findings from this study suggest that HD patients with reduced EF may benefit significantly from RAAS-blockade. In our study, mean EF was normal (roughly 60% regardless of group), and severe HF was an exclusion criterion. These factors combined with the absence of an ACEi may to some extent explain why our study found no effect of ARB.
Left ventricular diastolic function
Regression of LVH usually leads to an improvement in left ventricular filling dynamics \(^{421,422}\). In our study, LVM was stable over time regardless of group and parameters reflecting LV filling were also stable suggesting that changes in LV filling relies mainly on changes in LVH in line with a previous study in renal patients \(^{423}\). At baseline, mean E/A ratio was \(\approx 1\) and mean E/e’ was \(\approx 17\) in both groups, and both ratios were stable over time and unaffected by irbesartan treatment. An E/A ratio of 1 is considered normal or pseudo-normal, whereas an E/e’ ratio > 12 indicates severe diastolic dysfunction \(^{232}\). The two ratios are usually combined when assessing LV diastolic function. Accordingly, on a group level this translates into a moderate (grade 2) LV diastolic dysfunction in our cohort \(^{424}\). The above mentioned LVH reducing strategies are generally also considered to improve diastolic function in ESRD. Pharmacological interventions targeting fibrosis and arterial stiffness may in theory improve LV diastolic function independently of reductions in BP \(^{425}\).

Regarding the use of RAAS-blockade, results have been conflicting. No improvement in diastolic function or LVH was found in a previous study in HD patients using the ACEi lisinopril over a six-month period \(^{426}\). In contrast, a significant improvement in LV diastolic function was found alongside a significant reduction in LVH in a larger study with chronic renal failure patients after six and twelve months with ACEi-treatment (enalapril or captopril). However, results from this study is somewhat compromised by the lack of a placebo group \(^{423}\). In non-renal patients with hypertension and diastolic dysfunction, RAAS-blockade is considered as first-line treatment \(^{427}\) and LV diastolic function can improve with RAAS-blockade \(^{422,428-430}\). However, it may not necessarily improve overall outcome \(^{431,432}\).
**NT-proBNP**

The majority of ESRD patients have elevated levels of BNP and NT-proBNP in line with the high prevalence of LVH and LV dysfunction 20,243,245,246. Our study also found elevated levels of NT-proBNP. Moreover, patients with known heart disease had significantly higher mean NT-proBNP levels and rise in NT-proBNP tended to be associated with an increase in LVM-index. Overall, our findings support the notion that NT-proBNP is related to LV function but we cannot exclude the influence of volume overload. Mean LVM-index was generally stable regardless of treatment during the study, whereas mean NT-proBNP increased in parallel to a concomitant decrease in urine output and an increase in CBV. Accordingly, the significant increase in NT-proBNP over time may reflect an increase in volume overload combined with reduced renal clearance towards the end of the study rather than an increase in LVM. There are no established NT-proBNP cut-off values in ESRD which makes interpretation difficult, whereas in the general population the cut-off indicating heart failure is >125 pg/mL in subjects <75 years and >450 pg/mL in subjects >75 years 236. Despite the lack of cut-offs, NT-proBNP has been shown to predict CV and overall mortality in ESRD 20,243,245,246, and a substantial increase in NT-proBNP may potentially be useful for identification of high risk patients eligible for further cardiac evaluation 246,433. Moreover, improved BP 434 and volume control lowered BNP and NT-proBNP levels in ESRD patients 242,243,435. Two short-term studies in HD patients found significantly decreased levels of BNP after eight weeks of ARB treatment 436,437 and decreased BNP was also found with aliskiren treatment (a direct renin inhibitor) 434. Overall, our study found no superior effect of RAAS-blockade with irbesartan in terms of lower NT-proBNP, although a tendency towards lower levels was observed in the irbesartan treated shortly after baseline. These findings might suggest that changes in NT-proBNP are primarily BP-driven.
**Sympathetic activity**

Increased sympathetic activity was confirmed in our HD patients in terms of attenuated HRV\textsuperscript{284} and elevated plasma catecholamine levels\textsuperscript{196,197}. Thus, at baseline median SDNN (placebo/irbesartan) was 17/24 and median LF/HF ratio was 0.9/0.7. Median normal values in healthy are: 51 (SDNN) and 2.1 (LF/HF ratio)\textsuperscript{284}. However, there was no clinically relevant effect of ARB treatment on these parameters. Intervention studies targeting sympathetic activity in chronic renal failure are scarce. A sympatho-inhibitory effect of RAAS-blockade has been demonstrated in some studies\textsuperscript{181,182} but other studies found no effect\textsuperscript{438,439}. In non-renal patients, results are also conflicting with some studies reporting an effect of RAAS-blockade\textsuperscript{183,440}, whereas others did not\textsuperscript{366,441}. Different methods were used in these studies, and indirect methods such as HRV and plasma catecholamines may be insensitive to minor changes in sympathetic activity\textsuperscript{195,442}. Moreover, the sympatho-inhibitory effect of RAAS-blockade may be dosage dependent and conventional doses of ACEis or ARBs may not achieve concentrations in the brain sufficient to cause interruption of central neural Ang2 generation and blockade of central AT\textsubscript{1}-receptors. Thus, in a small study with HF patients testing low dose ARB (losartan 50 mg = 1 DDD) versus high dose ARB (losartan 200 mg = 4 DDD), only high dose ARB reduced SNS activity significantly (plasma noradrenaline and MSNA activity)\textsuperscript{183}. In comparison, the ARB dosage in our study (irbesartan 150-300 mg) corresponded to 1-2 DDDs.

**Haemodynamic parameters and the intradialytic response**

Only few studies are available on haemodynamic effects of antihypertensive drugs during HD\textsuperscript{155,247-249,271-273}, none of them being long-term, except for the study by Tisler et al.\textsuperscript{249}. This ten-month observational cohort-study found that use of long-acting nitrates and absence of CCBs increased the risk of IDH\textsuperscript{249}. Leidig et al. compared tolerability of valsartan 80 mg to irbesartan
150 mg in 67 HD patients in a short-term (2 × 5-week), open-label, multicenter, randomised cross-over study and found that occurrence of symptomatic hypotension was similar both during HD and after HD regardless of treatment. However, intradialytic haemodynamics was not measured in either of these studies. In contrast, our study provided both short and long-term results regarding the tolerability of ARB-treatment including the intradialytic haemodynamic response in comparison with placebo. Our study showed that CO decreased during HD due to a reduction in SV which was not fully compensated by an increase in HR. A similar intradialytic response was reported in previous short-term studies. At equal BP levels, this haemodynamic response to HD was not significantly affected by irbesartan and it was stable over time regardless of treatment. Apart from an increase in CBV, central haemodynamic parameters were found to be stable over time regardless of treatment and time of assessment during HD. The increase in CBV may reflect progressive volume overload due to a concomitant decrease in urine output during the study period. Interestingly, this worsening of volume overload developed despite frequent clinical assessment of hydration status and despite a significant reduction in predialytic BP in both groups.

The prevalence of symptomatic IDH was low in our study and IDH was not more frequent in irbesartan treated patients. Moreover, there was no indication of significantly lower intradialytic BP with irbesartan treatment. The low number of IDH episodes in our study probably reflects the fact that most patients were prescribed relatively low UF-volumes during HD due to preserved urine output. Anuric patients and patients with severe HF were not included in our study. Absence of these patients may have influenced our results in terms of intradialytic haemodynamics and IDH. Therefore, our results should be interpreted with some caution. Nevertheless, our findings are corroborated by observations from an audit based on 2,630 HD patients from dialysis centres in
the Great London area by Davenport et al.\textsuperscript{248}. This study found no correlation between IDH and achievement of a predialytic BP-target of 140/90 mmHg. Moreover, IDH was not made worse by the prescription of antihypertensive drugs, and RAAS-blocking agents were not superior to other drug classes in terms of reaching the predialytic BP-target\textsuperscript{248}.

**Conclusions and future perspectives**

In the SAFIR study, newly started HD patients with some residual urine output were randomised to one-year treatment with the ARB irbesartan or placebo. ARB and placebo treated achieved a similar decrease in predialytic BP and the pre-defined mean BP-target of 140 mmHg was reached in both groups, as intended. Important intermediate CV endpoints such as central BP, PWV, LVH, NT-proBNP and sympathetic activity (HRV and plasma catecholamines) were all unaffected by ARB treatment. Changes in PWV and LVH were associated with changes in BP but this relationship was not significantly altered by ARB treatment. Thus, at equal BP-levels there was no indication of additional effects due to RAAS-blockade by ARB. During HD, CO, SV, TPR, HR, and MAP remained stable and similar over a one-year period regardless of treatment and the time of assessment, whereas CBV increased equally and significantly in both groups indicating increase in volume overload over time. Intradialytic hypotension was not more frequent in ARB treated patients and there was no indication of significantly lower intradialytic BP in the ARB group. The general haemodynamic response observed during HD was a decrease in CO, SV, MAP, and CBV and an increase in HR, whereas TPR was constant. This intradialytic response was not significantly affected by ARB and it was stable over time regardless of treatment. Whether HD patients with more pronounced CV instability or larger fluid fluctuations behave similarly remains to be clarified. ARB was overall well tolerated with no excess hyperkalaemia or hypotensive episodes and can be
used in HD patients, but our study indicates that absence of ARB may serve the patient equally well thereby emphasising the importance of other factors such as volume overload and adequacy of dialysis. CV disease in HD patients is a complex condition with many interfering risk factors unique to ESRD. The lack of significant effects on intermediate CV endpoints and intradialytic central haemodynamics in the SAFIR study suggests that use of RAAS-blockade in HD patients is unlikely to improve prognosis beyond BP-lowering. Thus, to reduce the burden of CV disease in ESRD, future intervention studies should probably include a multi-facetted strategy aimed at several risk factors rather than only focusing on RAAS-blockade.
Summary

Background: Haemodialysis (HD) patients have a very high mortality rate and the most common cause of death is cardiovascular (CV) disease. Treatment that reduces blood pressure (BP) and decreases arterial stiffness and left ventricular (LV) hypertrophy may improve CV outcome. Angiotensin II receptor blocker (ARB) treatment is frequently used, but whether ARB treatment exerts beneficial CV effects beyond the BP-lowering effect in HD patients is unclear. Moreover, little is known about haemodynamic effects of ARB during HD.

Aim: To investigate the effects of the ARB irbesartan on intermediate CV endpoints and intradialytic central haemodynamics in a group of newly started HD patients.

Methods: The study was designed as a randomised, placebo-controlled, double-blinded intervention study. A total of 82 HD patients were included and 56 patients completed one year treatment with irbesartan or placebo aiming at a predialytic systolic BP-target of 140 mmHg in both groups. The primary endpoints were change in LV mass, arterial stiffness, and intradialytic haemodynamics.

Results: Predialytic BP decreased significantly in both groups but there was no significant difference between placebo and irbesartan treated. Use of additional antihypertensive medication, ultrafiltration volume, and dialysis dosage were not significantly different in the two groups. LV mass and arterial stiffness were not significantly affected by irbesartan treatment. Changes in BP during the study period correlated significantly with changes in LV mass and arterial stiffness. Intradialytic central haemodynamics were stable throughout the study except for central blood volume which increased significantly over time in both groups. The intradialytic haemodynamic response to HD was unaffected by irbesartan and it was stable over time regardless of treatment.

Conclusions: At equal BP-levels, intermediate cardiovascular endpoints and central haemodynamics during HD were not significantly affected by irbesartan treatment. The lack of significant effects suggests that ARB treatment is unlikely to improve prognosis beyond BP-lowering in HD patients.
Danish summary


Formål: At undersøge effekten af ARB behandling med irbesartan på intermediære kardiovasculære endepunkter samt hæmodynamik under dialysebehandling i en gruppe af nystartede hæmodialysepatienter.

Metoder: Studiet var designet som et randomiseret, placebo-kontrolleret, og dobbelt-blindet interventions studie. I alt 82 hæmodialysepatienter blev inkluderet, og 56 patienter fuldførte et års behandling med enten irbesartan eller placebo. I alle patienter var det målet at opnå et systolisk blodtryk på 140 mmHg før dialysestart. Størrelse af venstre ventrikel, karstivhed og hæmodynamiske ændringer under dialysebehandling udgjorde de primære endepunkter.

Resultater: Blodtryk målt før dialysestart faldt signifikant i begge grupper, men der var ingen signifikant forskel på placebo og irbesartan behandlede. I de to grupper var der ikke signifikant forskel på brug af supplerende blodtryksseducerende medicin, væsketræk (ultrafiltration) samt dialyseforskrift. Størrelse af venstre ventrikel og karstivheden var ikke signifikant påvirket af irbesartan behandling. Hæmodynamiske parametre under dialysebehandling var stabile gennem studiet fraset et signifikant øgning i det centrale blodvolumen i begge behandlingsgrupper. Det hæmodynamiske respons under dialysebehandling var upåvirket af irbesartan og desuden stabilt over tid i begge behandlingsgrupper.

Konklusion: Ved samme blodtryksniveau, var der ingen signifikant effekt af irbesartan på intermediære kardiovasculære endepunkter og hæmodynamik under dialysebehandling. Fraværer af signifikante effekter indikerer, at der næppe opnås en forbedret prognose for hæmodialysepatienter ved ARB-behandling uder den effekt, der skyldes blodtrykssænkning.
References


4. Danish Nephrology Registry Annual Report 2011
http://www.nephrology.dk/Publikationer/Landsregister/C3%85rsrapport2011.pdf.


55. SphygmoCor FDA approval http://www.accessdata.fda.gov/cdrh_docs/pdf/k002742.pdf


100. Atcor Medical *Reference values for SphygmoCor Px* http://www.atcormedical.com/technical_notes.html.


107. Bright R. Cases and observations illustrative of renal disease accompanied with the secretion of albuminous urine. 1836; 1: 338-79.


223. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; **18**(12): 1440-63.


225. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med* 1991; **114**(5): 345-52.


244. Agarwal R. B-type natriuretic peptide is not a volume marker among patients on hemodialysis. Nephrol Dial Transplant 2013.


415. Williams B. Angiotensin II and the pathophysiology of cardiovascular remodeling. *AmJCardiol* 2001; 87(8A): 10C-7C.


Appendix

Papers I-III
Renal and cardiovascular effects of irbesartan in dialysis patients – a randomized controlled trial protocol (SAFIR study)

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ABSTRACT

INTRODUCTION: Cardiovascular (CV) events are a major cause of morbidity and mortality in haemodialysis (HD) patients. Hypertension, increased arterial stiffness and left ventricular (LV) hypertrophy are highly prevalent and are often poorly controlled. Volume overload is an important factor and survival could be improved by treatment strategies that preserve residual renal function (RRF), reduce blood pressure, and decrease arterial stiffness and LV hypertrophy. Angiotensin II receptor blocker (ARB) treatment can prevent CV events in patients with hypertension and heart failure. However, few data exist in patients with chronic renal failure and it is not known whether ARB treatment improves clinical outcome in HD patients.

MATERIAL AND METHODS: This is a randomized, controlled and double-blinded intervention study. A total of 82 HD patients from six Danish HD centres will be treated for a year with an ARB (irbesartan) or placebo. The inclusion criteria are urine output > 300 ml/day, dialysis vintage < 1 year and LV ejection fraction > 30%. The primary outcomes are change in RRF, LV hypertrophy, arterial stiffness and intra-dialytic haemodynamics.

CONCLUSION: If ARB-treatment improves RRF and intermediate CV endpoints in a group of newly started HD patients, it may improve the survival for this high risk population.

FUNDING: The trial is investigator-initiated, investigator-driven and supported by the Danish Agency for Science, Technology and Innovation and several private foundations.

TRIAL REGISTRATION: Clinical Trials ID: NCT00791830.

The mortality rate in incident European dialysis patients is 192 per 1,000 person-years compared with 12 in the general population. The most common cause of death is cardiovascular (CV) disease, which accounts for 39% [1].

Dialysis patients often have an elevated blood pressure (BP) due to volume overload. In addition, chronic renal failure causes increased arterial stiffness, which is reported to be a strong independent risk factor for CV mortality [2]. The mechanisms causing increased arterial stiffness are incompletely understood. However, it is generally accepted that complete loss of renal function markedly accelerates this process, thereby potentiating traditional CV risk factors such as diabetes, hypercholesterolemia, obesity and smoking. Furthermore, the loss of kidney function leads to reduced removal and increased cytokine generation as well as impaired immune system [3]. Thus, many dialysis patients have chronic low-grade inflammation [4], which is associated with increased risk of atherosclerotic complications [5].

Various treatment strategies to preserve residual renal function (RRF) and counteract inflammation and development of CV disease have been suggested. Among these are agents blocking the renin-angiotensin-aldosterone system (RAAS).

In peritoneal dialysis (PD) patients, two Asian open-labelled studies have shown that an angiotensin-converting enzyme inhibitor (ACE-I) as well as an angiotensin II receptor blocker (ARB) can preserve RRF [6, 7]. Regarding the anti-inflammatory properties and protection against CV disease in haemodialysis (HD) patients, the results of ACE-I and ARB treatment are conflicting, both in short-term and longer follow-up studies [8, 9]. Data on large artery stiffness are scarce, whereas left ventricular hypertrophy is more frequently observed in dialysis patients [10].

ABBREVIATIONS

ACE-I = angiotensin-converting enzyme inhibitor
ARB = angiotensin II receptor blocker
AV = arterio-venous
BP = blood pressure
CA = carotid artery
CO = cardiac output
CV = cardiovascular
EEG = electrocardiogramme
FA = femoral artery
GCP = good clinical practice
HR = heart rate
HRV = heart rate variability
KDQoL-SF = Kidney Disease Quality of Life – Short Form
LV = left ventricular
LVH = left ventricular hypertrophy
PD = peritoneal dialysis
PDAUH = Pharmacy Department at Aarhus University Hospital
PWV = pulse wave velocity
QoL = quality of life
RAAS = renin-angiotensin-aldosterone system
RRF = residual renal function
SD = standard deviation
SN = suprasternal notch
SV = stroke volume
TPR = total peripheral resistance

PROTOCOL ARTICLE

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ventricular (LV) mass index is more consistently reported to be positively affected by ARB treatment [9, 10].

Further investigations on ARB treatment in HD patients would help elucidate the potential to preserve RRF and to counteract the development of CV disease.

HYPOTHESES
Irbesartan treatment in newly started HD patients leads to:

- a slower decline of RRF
- stabilization or regression of cardiac hypertrophy
- a decrease in arterial stiffness
- an improvement in intradialytic haemodynamics.

MATERIALS AND METHODS
Design, patient recruitment and randomization
This study is a double-blinded multi-centre randomized placebo-controlled intervention trial. Patients are recruited from six Danish HD centres. The eligibility criteria are summarized in Table 1. Inclusion began in May 2009. The last patient’s last visit is expected to take place in December 2012. Screened patients with a urine volume > 300 ml/24 h and a LV ejection fraction > 30% are randomized to placebo or irbesartan (1:1) by the Pharmacy Department at Aarhus University Hospital (PDAUH). Block randomization is applied according to study site and diabetic status.

STUDY DRUG
The study medication consists of the ARB irbesartan 150 mg or matching placebo. Tablets are delivered from Sanofi-Aventis in blister packages to the PDAUH, which labels blisters for all sites. Code lists, drug labelling, packaging and distribution are carried out in accordance with Good Manufacturing Practice.

The study drug is prescribed after baseline investigations are performed at visit A. The initial dose is one tablet per day. After two weeks, the daily dose is increased to two tablets, equaling 300 mg of irbesartan, which is the highest recommended dose. If side effects are unacceptable, patients are reduced to one tablet daily.

While in the study, patients cannot receive other medications influencing RAAS. Patients prescribed ACE-I, renin inhibitors or ARBs upon inclusion stop this medication one week before baseline investigations. All other classes of antihypertensive drugs are accepted. The systolic BP target is 140 mmHg in all patients.

STUDY SET-UP
The patients are investigated at baseline and after one week to elucidate acute effects of irbesartan, and thereafter every three months for one year (visits A-F). Visits A-F are carried out in the morning two days after HD. Visits after two weeks, one month, six weeks, two months and then every month are performed to ensure safety and compliance. Measurements are summarized in Table 2.

Residual renal function
Renal function is followed by measurement of glomerular filtration rate based on the mean of urinary creatinine and urea clearance. Urine is collected for 24 hours before visits A-F. To minimize the urea and creatinine post-dialysis rebound effect, blood samples for creatinine and urea analysis are drawn ten minutes after termination of the HD session two days before visits A-F. Creatinine and urea are also measured before HD at the day of visits A-F. Assuming that the inter-dialytic in-
crease in creatinine and urea concentration is linear, clearance is measured as urinary excretion of creatinine and urea related to the plasma concentrations during the same time interval, Figure 1. Clearance is standardized to a body surface area of 1.73 m².

Blood pressure
BP is measured before dialysis using validated automated oscillometric BP devices. The patient rests in a sitting position for five minutes with his or her legs uncrossed prior to the measurement. The cuff is positioned at heart level on the arm without an arterio-venous (AV) fistula, with a cuff-size matching the circumference of the arm. A minimum of two measurements are performed. In case of > 5 mmHg deviation in either systolic or diastolic BP, more measurements are performed. The average of the last two is used.

Applanation tonometry
The SphygmoCor (AtCor Medical Sydney, Australia) system is a widely used device for estimation of central aortic BP and pulse wave velocity (PWV) based on applanation tonometry and is validated for use in patients with chronic renal failure [11]. SphygmoCor applies a transfer function whereby a non-invasive recording of the pulse wave from the radial artery on the non-AV-fistula arm is transformed to approximate the central aortic pulse wave. Brachial BP is used for calibration and operator index should be > 80%. PWV is found by sequential 10-20 sec. recordings of pressure waveforms at the carotid artery (CA) and femoral artery (FA). SphygmoCor uses the R-wave in an electrocardiogramme (ECG) to determine the start of the pulse wave. It is imperative to achieve visually acceptable waveforms and equal heart rates at both sites. Length is approximated by subtracting the distance between the suprasternal notch (SN) and CA from the distance between SN and FA.

Electrocardiograms and heart rate variability
Standard ECGs are obtained before dialysis at visits A-F in order to detect arrhythmias and LV hypertrophy using the Sokolow-Lyon and Cornell criteria. In patients with sinus rhythm, heart rate variability (HRV) is assessed with the SphygmoCor HRV system SCOR-Hx using a five-minute measurement with the patient resting in a supine position and two manoeuvres (Valsalva and standing) selected to challenge the autonomic nervous system.

Echocardiography
Echocardiography is performed with the patient in the left lateral position by an experienced technician/doctor before study entry and after one year just before the end of treatment. Raw data are stored digitally in the cine-loop format defined by the R wave on the corresponding ECG for off-line analyses using EchoPac software (GE Healthcare).

Quantification of cardiac chamber size, heart valve pathology, LV mass and function are done with treatment allocation concealment by one experienced examiner in accordance with current guidelines [12].

<table>
<thead>
<tr>
<th>Blood samples</th>
<th>Visits A-F</th>
<th>Urine samples, visits A-F</th>
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<tbody>
<tr>
<td>Albumin</td>
<td>Adrenaline</td>
<td>Albumin</td>
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<tr>
<td>Calcium</td>
<td>Aldosterone</td>
<td>Creatinine</td>
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<td>CO₂/HCO₃⁻</td>
<td>Angiotensin II</td>
<td>Potassium</td>
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<td>Creatinine</td>
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<td>Potassium</td>
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<td>Sodium</td>
<td>IL⁴</td>
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<td>Urea</td>
<td>Lipids⁴</td>
<td>Liver function tests⁴</td>
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<td></td>
<td>Noradrenaline</td>
<td>NT-proBNP</td>
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<td>Renin</td>
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CRP = C-reactive protein; IL = interleukin; NT-proBNP = N-terminal pro-hormone of brain natriuretic peptide; TGF-β = transforming growth factor beta.

- a) IL-1β, IL-6, IL-8 and IL-18.
- b) Total cholesterol, low-density lipoprotein, high-density lipoprotein and triglycerides.
- c) Alanine transaminase, aspartate transaminase, alkaline phosphatase and bilirubin.
Increased arterial stiffness is common in patients with chronic renal failure and is frequently found even in young patients as illustrated by this conventional X-ray radiography of the right acetabulofemoral joint from a 30-year-old female haemodialysis patient with type 1 diabetes showing pronounced arterial calcification of the right femoral artery. Carotid-femoral pulse wave velocity (cPWV) in this patient was markedly increased (cPWV = 12 m/s) matching the radiographic findings. The image was obtained on suspicion of a hip fracture, calcification was an incidental finding.

**Intradialytic haemodynamics**

The Transonic Hemodialysis Monitor HD02/HD03 and clip-on flow/dilution sensors (Transonic Systems Inc., USA) are validated for access flow and cardiac output (CO) measurements in HD patients [13]. CO, brachial BP and heart rate measurements are performed in duplicate within the first and the last 30 minutes of a dialysis session. The mean BP, total peripheral resistance (TPR) and stroke volume (SV) are obtained assuming that mean BP = diastolic BP + 1/3 × (systolic BP – diastolic BP) and CO = SV × heart rate = mean BP/TPR.

**Quality of life questionnaire**

Quality of life (QoL) is measured at baseline, at six months and before 12 months with the validated Kidney Disease Quality of Life – Short Form (KDQoL-SF), which includes dialysis-related questions [14].

**Biochemical measurements**

Blood samples are drawn from the fistula cannula or the central venous catheter before start of the HD session. Biochemical measurements are summarized in Table 3. Blood sampling at visits A–F are drawn after at least 30 minutes of rest in a supine position with the head elevated to 20 °C. Serum and plasma are frozen immediately after centrifuging. Blood and urine from visits A–F are kept in a biobank at –80 °C for later use.

**Sample size considerations and statistical methods**

RRF: In a PD study, the annual decline in RRF was 3 ml/min/1.73 m² without ARB [6]. Assuming a RRF decline = 4 ml/min/1.73 m²/year (due to a faster decline in HD), standard deviation (SD) = 1.7, type I error = 0.05, power = 0.80, and the minimal relevant difference = 1.4 ml/min/1.73 m² (reduction in RRF decline = 35%), 24 patients per group are needed.

LV mass index: Based on Kanno et al [15], a reduction in the LV mass index of 23 g/m² in the ARB treated subjects, 8 g/m² in the placebo group and a SD of 19 g/m² in both groups are assumed. With a power = 0.85 and a type I error probability = 0.05, 22 patients per group are needed.

PWV: To detect a carotid-femoral PWV difference of 10% (ARB versus placebo) after one year, 22 patients per group are needed. The assumptions are that SD = 10% in both groups, power = 0.90 and a type I error probability = 0.05 [10]. However, in expectation of a 40% drop-out (e.g. transplantation, adverse events), we decided to recruit 80 patients.

Differences in primary endpoints (e.g. RRF, PWV, LV mass index) between treatment groups over time are investigated using an ANOVA with repeated measurements, which allows for missing values and drop-out. Two-sample/paired samples t-tests will be used for comparison between baseline and end of study. Intention to treat analyses will be performed and a p < 0.05 is considered significant.

**Ethics & good clinical practice**

The study is conducted in accordance with good clinical practice (GCP) and the ethical standards described in the Helsinki Declaration. The Central Denmark Region Committees on Biomedical Research Ethics, the Danish Medicines Agency and the Danish Data Protection Agency have approved the study protocol. All sites are monitored by a local independent GCP unit. Clinical Trials ID: NCT00791830.

**DISCUSSION**

The optimal BP level in dialysis patients is debated. Some studies indicate that hypertensive HD patients have a better survival than HD patients with a normal or low BP [16]. On the other hand, a recent meta-analysis reported better survival among HD patients on antihypertensive medications regardless of their BP levels [17]. We expect that the BP level would influence the main outcome measures investigated in this study, and a predialytic systolic BP = 140 mmHg is the treatment target in all included patients.

Volume expansion is the most important cause of hypertension in the dialysis population. Preservation of the RRF is therefore important because it allows the patient to excrete salt and water which diminishes severe fluid overload and a high BP. Furthermore, a preserved RRF may improve the QoL for the patient owing to a more liberal diet and fluid intake.
Concerning CV endpoints, the value of ARB treatment is not completely elucidated in HD patients. Several small studies indicate that RAAS blockade is beneficial regarding CV events in HD patients [9]. However, fear of elevated potassium and intradialytic hypotension often implies that ARB treatment is abandoned in patients starting HD. This aspect is thoroughly investigated in our study.

Increased sympathetic activity from the diseased kidneys is another factor that may contribute to an elevated BP. HRV is one marker of this [18] that may provide more insight into the degree of sympathetic activation and whether this is affected by ARB.

Left ventricular hypertrophy (LVH) is very common in dialysis patients, and it is reported to be a strong CV risk factor. An increased ventricular muscle mass contributes to coronary risk due to an increased oxygen demand. It is also associated with increased myocardial fibrosis and decreased capillary density, which probably serves as a substrate for arrhythmia. Arrhythmia is more frequent in patients with LVH and a common cause of death in HD patients. Briefly, the pathogenesis of LVH in dialysis patients can be divided into factors causing increased afterload such as hypertension and increased arterial stiffness and factors causing increased preload such as fluid overload, chronic anemia and AV fistula.

In the present study, the influence of ARB treatment on LVH development is investigated.

Several studies have reported that the central aortic BP may predict CV morbidity and mortality above brachial BP [19]. In addition, antihypertensive drugs seem to have differential effects on central BP despite similar reductions in brachial BP [20]. ARB is known to lower the central BP in non-uraemic patients, whereas this study investigates the effect in HD patients.

PWV reflects the stiffness of the aorta and is considered to be a strong predictor for all-cause as well as CV mortality in patients with chronic renal failure [2]. In this study, PWV is measured predialytically six times and once on a non-HD day just before termination of the study period. The aim is to clarify the influence of ARB on PWV progression in HD patients.

Moreover, effects of ARB treatment on biochemical markers reflecting inflammation, RAAS and LV function are systematically investigated.

With the present study we wish to elucidate the effects of ARB on RRF and intermediate CV end points as well as side-effects in HD patients. The overall aim is to reduce morbidity and thereby hopefully also mortality in this high-risk patient population.

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LITERATURE
12. Lang RM, Bieng M, Devereux RB et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440-63.
Angiotensin II blockade exerts no blood pressure independent effects on intermediate cardiovascular endpoints in hemodialysis patients: A randomized double-blinded placebo-controlled one-year intervention trial (SAFIR study)

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Running headline: CV effects of irbesartan in hemodialysis patients
Abstract

Agents blocking the renin-angiotensin-aldosterone system are frequently used in end-stage renal disease patients but whether they exert beneficial cardiovascular effects is unclear in this patient group. The long-term effects of the angiotensin II receptor blocker irbesartan was investigated in 82 hemodialysis patients in a double-blinded randomized placebo-controlled one year intervention trial using a pre-defined systolic blood pressure target of 140 mmHg. Patients (41 in each group) did not differ in terms of age, blood pressure, co-morbidity, antihypertensive treatment, dialysis parameters, and residual renal function. Brachial blood pressure decreased significantly in both groups but there was no significant difference between placebo and ARB. Use of additional antihypertensive medication, ultrafiltration volume, and dialysis dosage were not different. Intermediate cardiovascular endpoints such as central aortic blood pressure, carotid-femoral pulse wave velocity, left ventricular mass index, N-terminal prohormone of brain natriuretic peptide, heart rate variability, and plasma catecholamines were unaffected by irbesartan treatment. Changes in systolic blood pressure during the study period correlated significantly with changes in left ventricular mass ($P = 0.02$) and arterial stiffness ($P < 0.001$).

In conclusion, significant effects of irbesartan on intermediate cardiovascular endpoints beyond blood pressure reduction were absent in hemodialysis patients.
Introduction

Hemodialysis (HD) patients have a very high mortality rate and the most common cause of death is cardiovascular (CV) disease. Generally, blood pressure (BP) control is considered to reduce CV mortality and a recent meta-analysis recommends the use of antihypertensive medication in HD patients. Agents blocking the renin-angiotensin-aldosterone system (RAAS) are frequently used, but whether they exert beneficial CV effects beyond the BP-lowering effect in end-stage renal disease (ESRD) is unclear. In non-uremic patients, RAAS-blockade has been observed to cause a greater reduction in central aortic BP for the same decrease in brachial BP compared to other drugs. This could be important, since central aortic BP predicts CV morbidity and mortality above brachial BP in ESRD.

Apart from high BP, ESRD is also associated with increased arterial stiffness, which is a strong independent risk factor for CV mortality. Carotid femoral pulse wave velocity (PWV) reflects the stiffness of the aorta and is considered as one of the most reliable measures of arterial stiffness. A recent study in Japanese HD patients with increased arterial stiffness reported that long-term RAAS-blockade inhibited further increase in PWV independently of its BP-lowering effect.

Left ventricular hypertrophy (LVH) and elevated plasma levels of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) are common findings in ESRD due to chronic hypertension, volume overload, anemia, and RAAS activation. LVH is a strong BP independent CV risk factor and recent meta-analyses suggest a beneficial effect of RAAS-blockade in dialysis patients. Finally, increased sympathetic activity may in addition to its contribution to BP elevation also predict CV events in ESRD. Non-invasive assessment of autonomic nervous system activity can be done using heart rate variability (HRV) and plasma catecholamine levels.
In this study, we examined the effects of an angiotensin II receptor blocker (ARB) versus placebo on BP and on the above described important intermediate CV endpoints: central aortic BP, PWV, LVH, NT-proBNP, HRV, and plasma catecholamines in a group of newly started HD patients with some residual renal function using a pre-defined brachial systolic BP-target of 140 mmHg.

Results

Patient characteristics

Eighty-two patients were included in the study with forty-one in each group (Table 1). Overall, the groups were similar at baseline except that all four failing renal transplants were allocated to the ARB group. Patients (placebo/ARB) were predominantly males (63/73%) with mean age 62/61 years, body mass index 28/26 kg/m² and a relatively short median HD vintage (137/148 days). Predialytic systolic BP was 145/148 mmHg and 34/54% received RAAS-blockade prior to randomization. Diabetic nephropathy was the most common cause of ESRD in both groups. Twenty-six patients did not complete the study, eleven in the placebo and fifteen in the ARB group. Causes for drop out are listed in Figure 1. Drop out due to possible side effects (e.g. hyperkalemia, low BP and diarrhea) were low in both groups and not significantly different.

Brachial blood pressure and antihypertensive drugs

Mean values of predialytic BP are presented in Table 2 and Figure 2 (all recorded measurements). Results from multivariate repeated measurements analysis are presented in Table 4 in the appendix. Overall, there was no significant difference in systolic (test for equal levels: \( P = 0.42 \)) and diastolic BP (test for equal levels: \( P = 0.27 \)) between groups. Both systolic and diastolic BP
decreased significantly in both groups. The estimated mean decrease in systolic BP (baseline vs. 12 months) was 8.2(0.3-16.2) (placebo; \( P = 0.04 \)) and 10.0(1.7-18.4) mmHg (ARB; \( P = 0.02 \)). Mean decrease in diastolic BP was 4.0(0.2-7.9) (placebo; \( P = 0.04 \)) and 6.3(2.3-10.4) mmHg (ARB; \( P = 0.002 \)). Use of additional antihypertensive medication in the study period besides placebo/ARB was similar in the two groups and there were no significant differences in defined daily doses (DDDs), number or classes of BP-drugs.

**HD-time and ultrafiltration**

There was no significant difference in weekly HD-time between the two groups as shown in Table 2. Weekly HD-time increased significantly in the placebo group at six, nine, and 12 months, respectively. In the ARB group there was no significant change in weekly HD-time in the study period. Ultrafiltration (UF) volume was also similar in the two groups. In both groups a tendency towards increased UF volume with increasing time from baseline was found (test for constant level: \( P = 0.06 \)).

*Intermediate cardiovascular endpoints*

**Central aortic blood pressure**

There was no significant difference between placebo and ARB in predialytic central aortic BP (Figure 2). Central systolic BP decreased over time regardless of group (test for constant level: \( P = 0.004 \)). The estimated mean decrease (baseline vs. 12 months) was 5.4(-2.3-13.0) (placebo; \( P = 0.17 \)) and 10.6(4.2-17.0) mmHg (ARB; \( P = 0.001 \)). Central diastolic BP also decreased significantly during the study regardless of treatment (test for constant level: \( P < 0.009 \)). The estimated mean decrease in diastolic BP was 5.1(0.2-10.1) (placebo; \( P = 0.04 \)) and 6.2(1.1-11.3) mmHg (ARB; \( P = 0.02 \)). Overall, there was no significant change in central pulse pressure, augmentation index (Alx)
or Alx normalised to a heart rate of 75 (AlxHR75). For further details, see Table 4 and 5 in the appendix.

Pulse wave velocity

There was no significant difference in PWV between the groups (test for equal levels: \( P = 0.63 \)), although PWV tended to decrease more in the ARB-group (Figure 2). The estimated mean decrease (baseline vs. 12 months) was 0.4(-0.4-1.2) (placebo; \( P = 0.31 \)) and 0.8(0.0-1.6) m/s (ARB; \( P = 0.05 \)). Use of PWV based on subtracted distance gave similar results. Most patients exhibited small changes in PWV during the study period (test for constant level: \( P = 0.42 \)), yet changes in PWV were significantly correlated with changes in BP (Figure 3). The relationship between changes in BP and changes in PWV was not significantly affected by ARB treatment. Thus, for a given decrease in BP virtually the same decrease occurred in PWV, regardless of treatment. Mean systolic BP (averaged from all BP measurements between baseline and 12 months) was not significantly correlated with changes in PWV (data not shown).

Echocardiography

There was no significant difference between placebo and ARB in left ventricular mass index (LVM-index) and ejection fraction (EF) (Table 3). The estimated mean decrease in EF was 5.7(0.6-10.9) (placebo; \( P =0.03 \)) and 3.4(-2.3-9.1) % (ARB; \( P =0.22 \)). Regardless of treatment, no significant change was found in parameters reflecting diastolic function such as left atrial diameter, the ratio between the highest early mitral flow velocity (E) and the highest late atrial mitral flow velocity (A) and the ratio of E to early mitral annulus velocity (e’). Progression of LVM-index was significantly correlated with higher mean systolic BP (averaged from all BP measurements between baseline and 12 months) and increase in systolic BP as shown in Figure 3.
NT-proBNP
did not differ significantly between groups (test for equal levels: $P = 0.58$) despite an initial
decrease within the ARB-group (Figure 4). The raw data can be found in Table 6 in the appendix. NT-proBNP
increased significantly during the study period regardless of treatment (test for constant level: $P = 0.01$).
Patients without heart disease (n=50 at baseline; n=33 at 12 months) had lower NT-proBNP with a mean NT-proBNP ratio (no heart disease/heart disease) of 0.43(0.25-0.72) at baseline ($P = 0.002$) and 0.43(0.19-0.97) at 12 months ($P = 0.04$) (adjusted for residual renal function and systolic BP). Rise in NT-proBNP in the study period was significantly correlated with increase in LVM index (Figure 3).

HRV and plasma catecholamines

There was no significant difference between placebo and ARB in HRV-parameters (Figure 4 and Table 7 in the appendix). Time and frequency domain HRV-parameters and stand ratio were stable throughout the study period whereas Valsalva ratio decreased significantly during the study regardless of treatment (test for constant level: $P = 0.03$). Adrenaline levels were similar and unaffected by ARB treatment. Noradrenaline levels differed significantly between groups at baseline with a higher mean level in the placebo group corresponding to a mean placebo/ARB ratio of 1.3(1.1-1.5) ($P = 0.002$). During the study period the difference remained constant (test for parallel curves: $P = 0.50$) indicating no significant effect of ARB.

Pre-trial RAAS-blockade

In order to investigate potential carry-over effects of pre-trial RAAS-blockade, selected parameters (central systolic BP, AIx, PWV, LVM-index, EF, and NT-proBNP) were analysed after excluding all
Discussion

The purpose of this randomized placebo-controlled double-blinded study was to investigate effects of ARB on intermediate CV end points in combination with a predefined brachial systolic BP target of 140 mm Hg in a group of newly started HD patients with some residual renal function. Placebo or the ARB irbesartan was given as add-on to standard antihypertensive therapy and was well tolerated without significant side effects. Equal BP reduction was achieved on both placebo and ARB. Contrary to expectations, we did not find any superior effects of ARB on intermediate CV endpoints. Plasma angiotensin II levels and tablet counts documented that patients on ARB-treatment were compliant (see appendix).

Results from previous intervention studies on the effect of RAAS-blockade on CV endpoints in HD patients are conflicting. Improved CV outcome has been reported but the two largest studies (FOSIDIAL and OCTOPUS) did not find a superior effect of RAAS-blockade. Thus, our results corroborate these findings. However, HD patients with LVH and heart failure may benefit from RAAS-blockade as shown by recent studies. Compared to previous studies, our patients did not have pronounced LVH and reduced EF, which may partly explain the lack of additional effect of ARB on LVH and EF in our study.

The optimal BP-level in patients treated with HD is debated. In our study a systolic BP-target of 140 mmHg was chosen. Overall, BP-levels were similar in the two groups, except for a
slightly higher BP in the placebo group prior to six months. Residual renal function, use of additional antihypertensive drugs, and hydration according to preHD weight were similar in the two groups. However, we speculate that elimination of excess fluid and a tendency to a higher dialysis dose in the placebo group may have outbalanced some of the BP-lowering effect of ARB.

In non-uremic patients, RAAS-blockade has been reported to cause a greater reduction in central aortic BP for the same decrease in brachial BP compared to other drugs \(^{3-5}\), but few studies have investigated this effect in ESRD \(^{30-33}\). In our study, changes in central aortic BP were generally small and paralleled changes in brachial BP with both placebo and ARB. Central BP parameters such as PP and Aix have been linked with CV-outcome in ESRD in some \(^{6,34}\) but not all studies \(^{35}\) and the added value of central BP over brachial BP in HD patients remains to be fully clarified.

Observational studies in dialysis patients have linked RAAS-blockade with a more favourable CV outcome, possibly through reductions in PWV \(^{36,37}\). Absence of PWV decrease in response to BP decrease constitutes a major risk for mortality in HD patients and alternative interventions may be needed for those patients in whom antihypertensive drugs are unable to alter PWV \(^{37}\). Whether RAAS-blockade induces a greater decrease in PWV for the same decrease in BP is debated. Two intervention studies in dialysis patients found a BP-independent effect of RAAS-blockade on PWV \(^{10,38}\). However, our results indicate that changes in PWV, if present, were significantly correlated to changes in BP and we did not find any BP-independent effect of RAAS-blockade. Two intervention studies in HD patients \(^{30,39}\) and one in peritoneal dialysis patients \(^{32}\) reported similar results. To summarize, we cannot rule out that RAAS-blockade has a small BP-independent effect on PWV, but our study found no indication that this should be the case in HD patients.
NT-proBNP can predict CV and overall mortality in ESRD \(^{11-13}\) and improved BP and volume control may improve LV function and lower NT-proBNP levels \(^{13,40,41}\). In our study, NT-proBNP increased significantly over time regardless of treatment and again there was no BP independent effect of ARB treatment. Progression of LVH, reduced renal clearance of NT-proBNP over time and increased volume overload as urine output declined are possible explanations \(^{42,43}\).

Intervention studies targeting sympathetic activity in chronic renal failure are scarce, but a lowering effect of RAAS-blockade has been demonstrated \(^{44,45}\). A combination of increased activation of renal afferent nerves and increased angiotensin II levels, due to increased renin output from the diseased kidneys, is believed to enhance sympathetic activity \(^{46}\). Increased sympathetic activity was confirmed in our HD patients in terms of attenuated HRV \(^{47}\) and elevated plasma catecholamine levels \(^{19,48}\). However, we found no clinically relevant effect of RAAS-blockade on these parameters.

Overall, the ARB irbesartan was well tolerated with no excess hyperkalaemia or hypotensive episodes and can be used in HD patients, but our data indicate that absence of ARB may serve the patient equally well thereby emphasizing the importance of fluid elimination and adequacy of dialysis.

Limitations

Our study is limited by a relatively small number of patients although the power was there to detect a 10 percent difference in PWV after one year provided that the dropout percentage was less than 40% \(^{28}\). The actual difference was below 10% and dropout did not exceed 40%. A larger study could possibly have detected a statistically significant difference, but this would hardly be clinically relevant. Compliance, apart from project medication, was not monitored and patients
were not blinded to the BP-values measured during the study. Theoretically, this could have affected patients in terms of adherence and self-medication. Thus, if patients recognized an acceptable BP they might not consume all the prescribed antihypertensive drugs (study drug not included) leading to registration of false high DDDs. However, we have no reason to believe that this was the case. In order to minimize variation caused by the dialysis procedure, all measurements were performed before dialysis except for echocardiography, which was performed the day after a HD session to minimize the impact of volume overload. Consequently, our results reflect primarily the predialytic state of the patients. Ichihara et al. reported that none of their patients were treated with RAAS-blocking agents prior to the study and found a BP-independent effect of RAAS-blockade on PWV. In our study, 54% in the ARB-group received RAAS-blocking treatment prior to the study. However, a greater impact of ARB-treatment was not observed when excluding patients treated with RAAS-blocking agents prior to baseline. Thus, pre-trial RAAS-blockade did not affect our conclusions. Finally, our study was limited to a one year follow-up period. Longer follow-up could perhaps reveal positive effects of ARB treatment.

In conclusion, the SAFIR study provided results on BP-independent effects of long-term angiotensin II receptor blockade in HD patients. BP fell significantly and equally regardless of treatment as intended. Important intermediate CV endpoints such as central aortic BP, PWV, LVH, NT-proBNP and sympathetic activity (HRV and plasma catecholamines) were all unaffected by ARB treatment indicating that effects beyond BP-lowering are not present in HD patients. Nevertheless, changes in PWV and LVH were significantly correlated with changes in BP and the relationship was not significantly altered by ARB-treatment. ARB was safely used, but the lack of significant effects on intermediate CV endpoints suggest that ARB-treatment in HD patients is unlikely to improve prognosis beyond BP-lowering in this particular patient group.
Methods

Design, patient recruitment, and randomization

The study was investigator-initiated and designed as a multi-center double-blinded randomized placebo-controlled one-year intervention trial. Details regarding design, randomization, eligibility criteria, and BP-medication have been published previously. The study medication consisted of the ARB irbesartan 150 mg, or matching placebo. The initial dose was one tablet per day. After two weeks, daily dose was increased to two tablets which was maximal recommended dose.

Ethics

The study was conducted in accordance with good clinical practice (GCP) and the ethical standards described in the Helsinki Declaration. The Central Denmark Region Committees on Biomedical Research Ethics, the Danish Medicines Agency, and the Danish Data Protection Agency approved the study. All sites were monitored by a local independent GCP-Unit. Clinical Trials ID: NCT00791830.

Blood pressure

BP was measured before HD using validated automated oscillometric BP devices as previously described. A minimum of two measurements was performed. In case of deviation in systolic/diastolic BP larger than 5 mmHg, additional measurements were performed. The average of the last two was used.

Pulse wave analysis and pulse wave velocity
The SphygmoCor (version 7.0 and 8.2, Atcor Medical, Sydney, Australia) system was used for estimation of central aortic BP and PWV. The methods of pulse wave analysis (PWA) and PWV measurement has been described in detail elsewhere. All PWA measurements were made in duplicate before HD and brachial systolic and diastolic BP was used for calibration as previously described. According to recommendations only measurements with T1 (the initial peak of the wave) > 80 ms and < 150 ms, augmentation index (AIx) < 50% and operator index > 80% were accepted. At the end of study 455 mean PWA measurements were available (averaged from duplicates). Prior to code breaking, 32 were omitted due to operator index<80%, 15 due to T1<80 ms or T1>150 ms, and 4 due to AIx>50%. The PWV of the aortic segment was obtained before HD by sequential 10-20 sec. recordings of pressure waveforms at the carotid artery (CA) and femoral artery (FA). A minimum of two measurements with visually acceptable waveforms and equal heart rates at both sites were obtained using the intersecting tangent algorithm. The mean of the two PWV measurements was calculated for each patient for each visit as recommended. At the end of study 459 mean PWV values were available for analysis. However, prior to code breaking 48 were excluded from analysis due to manifest arrhythmias (e.g. atrial fibrillation or pacemaker) and 17 were dropped due to poor quality (standard deviation (SD)>20%). Mean SD (range) was 8.4% (2.7-19.5) in the remaining 394. Length was approximated by subtracting the distance between the suprasternal notch (SN) and CA from the distance between SN and FA. The distance was measured with a tape measure. The newest guideline published after we designed our study recommends the use of 80% of the direct distance between the FA and the CA recording site (CA–FA x 0.8). Consequently, PWV values were all converted using the equation developed by Vermeersch et al. and used by The Reference Values for Arterial Stiffness’ Collaboration group.
Two different PWV-estimates are given according to use of subtracted distance (PWV_SD) or direct distance x 0.8 (PWV).

Echocardiography

Echocardiography was performed the day after a HD session with the patient in the left lateral position by experienced examiners before study entry and after one year just before the end of treatment as previously described. Raw data was stored digitally in the cineloop format defined by the R wave on the corresponding ECG for off-line analyses using EchoPac software (GE Healthcare, Horten, Norway). Quantification of cardiac chamber size, LV mass and function was done blinded by one experienced examiner in accordance with current guidelines. Prior to code breaking, one patient was omitted from further analysis due to situs inversus (dextrocardia). E/A ratio was missing in nine patients at baseline and in eight patients at follow up, primarily due to increased heart rate which made E and A velocity profiles indistinguishable. e’ was missing in eight patients at baseline and in three patients at follow up.

Heart rate variability

Short-term HRV methods, described in detail previously, were used. In patients with sinus rhythm, HRV was assessed before HD with the SphygmoCor system (SCOR-Hx 8.2) using a five minute measurement with the patient resting in a supine position and two maneuvers selected to challenge the autonomic nervous system. For the Valsalva maneuver (VM), the patient blew into a mouthpiece with a constant pressure of 40 mmHg for 15 sec. The stand maneuver (SM) called for active standing from a supine position. The Valsalva/stand ratio is the ratio of the highest heart rate during (or shortly after) the VM/SM to the lowest heart rate occurring after the VM/SM. HRV was not obtained in eight patients (32 measurements) due to lack of the HRV-module. Absence of
sinus rhythm and artifacts due to muscular activity during VM and SM resulted in a high number of missing values. At the end of the study prior to code breaking the number of measurements available for analysis were 324 (five minute rest), 298 (VM) and 265 (SM).

NT-proBNP and catecholamines

Venous blood samples were taken before HD in serum tubes (NT-proBNP) and EDTA-coated tubes (catecholamines) after 30 min of rest in supine position. NT-proBNP samples were centrifuged after clotting, and the separated serum was stored at \(-80^\circ\text{C}\). In December 2012, all samples were analysed for NT-proBNP using a sandwich immunoassay with two monoclonal antibodies against the N-terminal part of NT-proBNP and a Cobas 6000 (e601 module) analyzer (Roche Diagnostics GmbH, Mannheim, Germany) \(^{58,59}\).

Catecholamine samples were kept cold in ice water prior to centrifugation and the separated plasma was stored at \(-80^\circ\text{C}\) for up to six months. Samples were analyzed for adrenaline and noradrenaline by a radioimmunoassay (2-Cat RIA, BA-1500; Labor Diagnostika Nord, Nordhorn, Germany) \(^{60}\) calibrated by our own validated standards. In house inter-/intra-assay coefficient of variation was 9/6 %.

Power calculation

Assumptions and details concerning power calculations for the primary endpoints (PWV and LVM) have been published previously \(^{28}\).

Statistics

Data were analyzed with Stata/IC 12.1 (StataCorp LP, College Station, TX 77845 USA) based on a multivariate repeated measurements model (xtmixed) which allows for missing values and drop-
out, and with visit and drug (placebo or ARB) and the interaction between them as factors (see appendix for further details). Baseline data were analyzed with chi-squared test for qualitative variables and continuous variables were analyzed with either Student’s t-test or Wilcoxon signed-rank test if data could not be assumed to be normally distributed. The latter was checked with QQ-plots and equal variance was checked with F-tests. Changes within and between groups in HD-time, number of BP-drugs, DDDs of BP-drugs and parameters obtained by echocardiography were analyzed with Student’s paired/unpaired t-test, respectively. Distribution of BP-drugs in both groups was investigated with chi-squared test at all visits. Multivariate linear regression was used to investigate the effect of placebo/ARB on changes in LVM and PWV in relation to change in BP. Intention to treat analyses were performed and $P < 0.05$ was considered significant. Values are presented as means with 95% confidence intervals unless otherwise stated.

Disclosure

No interest to disclose.

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References


55. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; 18: 1440-1463.


Inclusion and exclusion criteria have been published previously. Briefly, the inclusion criteria were urine output > 300 mL/day, dialysis vintage < 1 year and LV ejection fraction > 30%.

BP: Blood pressure; AIx: Augmentation index; PWV: Pulse wave velocity based on direct distance (see methods section for further details); *) 0.05 > $P \geq 0.01$ vs. baseline within the placebo or ARB group; **) $0.01 > P \geq 0.001$ vs. baseline within the placebo or ARB group; ***) $P < 0.001$ vs.
baseline within the placebo or ARB group

**Figure 3**

(x) Placebo

(•) ARB

(¦) Indicates regression line for placebo

(‖) Indicates regression line for ARB

Δ indicates change (12 months-baseline)

PWV: Pulse wave velocity based on direct distance; LVM-index: Left ventricular mass index; NT-proBNP: N-terminal prohormone of brain natriuretic peptide

**Figure 4**

NT-proBNP: N-terminal prohormone of brain natriuretic peptide; SDNN: The standard deviation of the N-N interval; LF/HF: Low frequency power/high frequency power

*) 0.05 > P ≥ 0.01 vs. baseline within the placebo or ARB group; **) 0.01 > P ≥ 0.001 vs. baseline within the placebo or ARB group; †) 0.05 > P ≥ 0.01 placebo vs. ARB; ‖‡) Indicates that the curves were assumed parallel (Model 2). The constant mean difference (placebo-ARB) in log(p-noradrenaline) with 95% confidence interval was 0.55(0.12-0.98) log(nmol/L); P = 0.002.
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<td>kg</td>
<td>81±17</td>
<td>50-131</td>
<td>79±17</td>
<td>52-122</td>
</tr>
<tr>
<td>Height</td>
<td>cm</td>
<td>171±10</td>
<td>148-192</td>
<td>174±9</td>
<td>152-188</td>
</tr>
<tr>
<td>Body mass index</td>
<td>kg/m²</td>
<td>28±5</td>
<td>19-40</td>
<td>26±5</td>
<td>19-39</td>
</tr>
<tr>
<td>Smokers</td>
<td>n (%)</td>
<td>11 (27)</td>
<td></td>
<td>14 (34)</td>
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<tr>
<td>Predialytic systolic BP</td>
<td>mmHg</td>
<td>145±19</td>
<td>110-203</td>
<td>148±21</td>
<td>111-197</td>
</tr>
<tr>
<td>Predialytic diastolic BP</td>
<td>mmHg</td>
<td>73±12</td>
<td>45-102</td>
<td>76±13</td>
<td>57-103</td>
</tr>
<tr>
<td>Heart rate</td>
<td>bpm</td>
<td>71±14</td>
<td>50-122</td>
<td>71±12</td>
<td>49-108</td>
</tr>
<tr>
<td><strong>Primary renal disease</strong></td>
<td></td>
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<tr>
<td>Diabetic nephropathy</td>
<td>n (%)</td>
<td>10 (24)</td>
<td></td>
<td>9 (22)</td>
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</tr>
<tr>
<td>Glomerulonephritis</td>
<td>n (%)</td>
<td>4 (10)</td>
<td></td>
<td>6 (15)</td>
<td></td>
</tr>
<tr>
<td>Hypertensive renal disease</td>
<td>n (%)</td>
<td>7 (17)</td>
<td></td>
<td>6 (15)</td>
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</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>n (%)</td>
<td>6 (15)</td>
<td></td>
<td>2 (5)</td>
<td></td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>n (%)</td>
<td>2 (5)</td>
<td></td>
<td>2 (5)</td>
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</tr>
<tr>
<td>Graft failure (previous Tx)#</td>
<td>n (%)</td>
<td>0 (0)</td>
<td></td>
<td>4 (10)</td>
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</tr>
<tr>
<td>Other</td>
<td>n (%)</td>
<td>5 (12)</td>
<td></td>
<td>7 (17)</td>
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<tr>
<td>Unknown</td>
<td>n (%)</td>
<td>7 (17)</td>
<td></td>
<td>5 (12)</td>
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<td><strong>Cardiovascular disease</strong></td>
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<tr>
<td>Heart disease (total)</td>
<td>n (%)</td>
<td>17 (41)</td>
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<td>15 (37)</td>
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<tr>
<td>Ischemic heart disease</td>
<td>n (%)</td>
<td>9 (22)</td>
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<td>8 (20)</td>
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<tr>
<td>Heart failure</td>
<td>n (%)</td>
<td>0 (0)</td>
<td></td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>n (%)</td>
<td>Heart valve disease</td>
<td>Arrhythmias</td>
<td>Co-morbidity</td>
<td>Antihypertensive treatment</td>
</tr>
<tr>
<td>---------------------------------</td>
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<td>-------------</td>
<td>--------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 (15)</td>
<td>4 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart valve disease</td>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Arrhythmias</td>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>n (%)</td>
<td>12 (29)</td>
<td>13 (32)</td>
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</tr>
<tr>
<td>Co-morbidity (conditions)</td>
<td>n</td>
<td>3.3±1.8</td>
<td>3.5±2.0</td>
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<tr>
<td>Weighted CCI-index‡</td>
<td></td>
<td>3.5±1.6</td>
<td>3.8±1.9</td>
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<tr>
<td>Diabetic</td>
<td></td>
<td></td>
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<tr>
<td>Other drugs</td>
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<tr>
<td>Antihypertensive treatment</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pre-trial RAAS-blockade</td>
<td>n (%)</td>
<td>14 (34)</td>
<td>22 (54)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP-drugs excl. Placebo/ARB</td>
<td>n</td>
<td>2.6±0.9</td>
<td>2.5±0.9</td>
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<tr>
<td>BP-drugs excl. Placebo/ARB</td>
<td>DDD</td>
<td>1.8±1.2</td>
<td>1.8±1.2</td>
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<tr>
<td>Beta-blocker</td>
<td>n (%)</td>
<td>27 (66)</td>
<td>27 (66)</td>
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<tr>
<td>Calcium channel blocker</td>
<td>n (%)</td>
<td>25 (61)</td>
<td>26 (63)</td>
<td></td>
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<tr>
<td>Alpha-blocker</td>
<td>n (%)</td>
<td>6 (15)</td>
<td>4 (10)</td>
<td></td>
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<tr>
<td>Comb. beta-alpha-blocker</td>
<td>n (%)</td>
<td>5 (12)</td>
<td>2 (5)</td>
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<tr>
<td>Other</td>
<td>n (%)</td>
<td>3 (7)</td>
<td>4 (10)</td>
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<tr>
<td>Loop diuretics</td>
<td>n (%)</td>
<td>38 (98)</td>
<td>40 (98)</td>
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<tr>
<td>Loop diuretics</td>
<td>DDD</td>
<td>6.3</td>
<td>12.5</td>
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<tr>
<td>Other drugs</td>
<td>n (%)</td>
<td>21 (51)</td>
<td>15 (37)</td>
<td></td>
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<tr>
<td>Other drugs</td>
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<tr>
<td>Chronic renal failure drugs</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPO-treatment</td>
<td>n (%)</td>
<td>40 (98)</td>
<td>38 (93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alfacalcidol</td>
<td>n (%)</td>
<td>22 (54)</td>
<td>19 (46)</td>
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</tr>
<tr>
<td>Calcium acetate</td>
<td>n (%)</td>
<td>18 (44)</td>
<td>20 (49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lanthanum</td>
<td>n (%)</td>
<td>4 (10)</td>
<td>2 (5)</td>
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</table>
**Sevelamer**

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
<th>9 (22)</th>
<th>9 (22)</th>
<th>1.00</th>
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</table>

**Dialysis parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>units</th>
<th>Placebo group</th>
<th>ARB group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time on dialysis^c</td>
<td>days</td>
<td>137</td>
<td>148</td>
<td>0.83</td>
</tr>
<tr>
<td>Urine output^a,c</td>
<td>L/24 hours</td>
<td>1.19</td>
<td>1.26</td>
<td>0.49</td>
</tr>
<tr>
<td>Glomerular filtration rate^b</td>
<td>mL/min/1.73 m^2</td>
<td>4.8±2.3</td>
<td>5.7±3.29</td>
<td>0.15</td>
</tr>
<tr>
<td>Modality (HDF/HD)</td>
<td></td>
<td>3(7)/38(93)</td>
<td>1(2)/40(98)</td>
<td>0.31</td>
</tr>
<tr>
<td>Filter (low flux)</td>
<td>n (%)</td>
<td>22(54)</td>
<td>20(49)</td>
<td>0.66</td>
</tr>
<tr>
<td>Dialysate calcium conc.</td>
<td>mmol/L</td>
<td>1.38±0.22</td>
<td>1.30±0.17</td>
<td>0.08</td>
</tr>
<tr>
<td>Frequency</td>
<td>times/week</td>
<td>2.7±0.5</td>
<td>2.8±0.5</td>
<td>0.19</td>
</tr>
<tr>
<td>HD-time</td>
<td>hours/week</td>
<td>10±2</td>
<td>11±3</td>
<td>0.14</td>
</tr>
<tr>
<td>Ultrafiltration</td>
<td>L</td>
<td>1.30</td>
<td>0.55</td>
<td>0.95</td>
</tr>
<tr>
<td>Dry weight</td>
<td>kg</td>
<td>79±16</td>
<td>78±17</td>
<td>0.64</td>
</tr>
<tr>
<td>Urea reduction ratio</td>
<td>%</td>
<td>64±8</td>
<td>62±9</td>
<td>0.31</td>
</tr>
</tbody>
</table>

**Blood samples**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>units</th>
<th>Placebo group</th>
<th>ARB group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroid hormone</td>
<td>pmol/L</td>
<td>12.5</td>
<td>17.9</td>
<td>0.28</td>
</tr>
<tr>
<td>Albumin</td>
<td>g/L</td>
<td>38±4</td>
<td>38±3</td>
<td>0.81</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>mmol/L</td>
<td>6.8±1.0</td>
<td>6.9±0.8</td>
<td>0.62</td>
</tr>
<tr>
<td>Potassium</td>
<td>mmol/L</td>
<td>4.3±0.7</td>
<td>4.2±0.5</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation or as median with range.

^#)Tx: Kidney transplantation; †)CCI: Charlson co-morbidity index: CCI score range 0-37; 0=low, 3+=high; DDD=Defined daily doses; EPO=erythropoetin; a) n=39 (Placebo group); b) n=36 (Placebo group); GFR=Glomerular filtration rate based on the mean of urinary creatinine and urea clearance as previously described; 28; bpm: beats per minute; HDF=Hemodiafiltration; HD=Hemodialysis; c) Three patients in the placebo group and two patients in the ARB group had dialysis vintage > one year and four patients (two in each group) had urine output < 300 mL/day due to delay after inclusion/screening.
<table>
<thead>
<tr>
<th>Time</th>
<th>Group</th>
<th>n</th>
<th>Systolic BP mmHg</th>
<th>Diastolic BP mmHg</th>
<th>Pulse pressure mmHg</th>
<th>Heart rate bpm</th>
<th>Additional BP-drugs n</th>
<th>Additional BP-drugs DDD</th>
<th>HD-time h/w</th>
<th>Weight (preHD) kg</th>
<th>Ultrafiltration L</th>
<th>Urine output L/24h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Placebo</td>
<td>41</td>
<td>145±19</td>
<td>73±12</td>
<td>73±17</td>
<td>71±14</td>
<td>2.6±0.9</td>
<td>1.8±1.2</td>
<td>9.8±2.3</td>
<td>80.9±17.3</td>
<td>1.30 (0-4.3)</td>
<td>1.19(0.15-2.72)</td>
</tr>
<tr>
<td></td>
<td>ARB</td>
<td>41</td>
<td>148±21</td>
<td>76±13</td>
<td>71±20</td>
<td>71±12</td>
<td>2.5±0.9</td>
<td>1.8±1.2</td>
<td>10.7±3.1</td>
<td>78.7±17.0</td>
<td>0.55 (0-3.80)</td>
<td>1.20(0.26-2.92)</td>
</tr>
<tr>
<td>1 week</td>
<td>Placebo</td>
<td>39</td>
<td>143±21</td>
<td>71±11</td>
<td>72±18</td>
<td>72±13</td>
<td>2.6±1.0</td>
<td>1.8±1.3</td>
<td>9.8±2.2</td>
<td>81.9±17.5</td>
<td>1.10 (0-4.41)</td>
<td>1.13(0.08-2.44)</td>
</tr>
<tr>
<td></td>
<td>ARB</td>
<td>40</td>
<td>138±22**</td>
<td>72±15**</td>
<td>66±20*</td>
<td>70±11</td>
<td>2.6±0.9</td>
<td>1.9±1.2</td>
<td>10.5±2.4</td>
<td>79.3±17.2</td>
<td>0.60 (0-5.00)</td>
<td>1.22(0.05-2.94)*</td>
</tr>
<tr>
<td>3 months</td>
<td>Placebo</td>
<td>37</td>
<td>144±20</td>
<td>71±13</td>
<td>73±19</td>
<td>69±11</td>
<td>2.5±1.1</td>
<td>1.8±1.3</td>
<td>10.1±2.3</td>
<td>81.8±18.1</td>
<td>1.39 (0-3.89)</td>
<td>0.88(0.03-2.66)*</td>
</tr>
<tr>
<td></td>
<td>ARB</td>
<td>35</td>
<td>140±21**</td>
<td>72±12*</td>
<td>68±21</td>
<td>72±12</td>
<td>2.4±1.1</td>
<td>1.7±1.3</td>
<td>10.5±2.6</td>
<td>80.6±17.6**</td>
<td>0.80 (0-3.51)</td>
<td>1.12(0.14-3.30)</td>
</tr>
<tr>
<td>6 months</td>
<td>Placebo</td>
<td>33</td>
<td>134±16**</td>
<td>68±11*</td>
<td>66±15**</td>
<td>73±10</td>
<td>2.3±1.1</td>
<td>1.4±1.2</td>
<td>10.5±2.2**</td>
<td>80.5±19.9</td>
<td>1.65 (0-5.70)</td>
<td>0.63(0.06-3.10)***</td>
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<tr>
<td></td>
<td>ARB</td>
<td>30</td>
<td>143±22†</td>
<td>74±15</td>
<td>70±20</td>
<td>74±13</td>
<td>2.3±1.1</td>
<td>1.4±1.3*</td>
<td>10.5±2.6</td>
<td>79.8±17.5</td>
<td>0.50 (0-4.01)†</td>
<td>1.12(0.15-3.60)†</td>
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<tr>
<td>9 months</td>
<td>Placebo</td>
<td>33</td>
<td>136±20**</td>
<td>70±13</td>
<td>66±16*</td>
<td>74±12</td>
<td>2.3±1.2</td>
<td>1.5±1.3</td>
<td>10.9±2.1***</td>
<td>81.0±19.1</td>
<td>1.33 (0-5.35)</td>
<td>0.86(0.08-3.30)***</td>
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<tr>
<td></td>
<td>ARB</td>
<td>29</td>
<td>144±20</td>
<td>73±15*</td>
<td>71±17</td>
<td>71±12</td>
<td>2.4±1.2</td>
<td>1.6±1.4</td>
<td>11.3±4.4</td>
<td>80.3±18.1*</td>
<td>1.48 (0-4.80)</td>
<td>0.96(0.04-3.05)*</td>
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<tr>
<td>12 months</td>
<td>Placebo</td>
<td>30</td>
<td>136±22*</td>
<td>68±15*</td>
<td>69±17</td>
<td>73±12</td>
<td>2.3±1.2</td>
<td>1.5±1.2</td>
<td>11.3±1.9**</td>
<td>81.6±19.5</td>
<td>1.58 (0-4.50)</td>
<td>0.73(0.00-4.30)**</td>
</tr>
<tr>
<td></td>
<td>ARB</td>
<td>26</td>
<td>138±20*</td>
<td>69±11**</td>
<td>69±18</td>
<td>72±14</td>
<td>2.3±1.2</td>
<td>1.7±1.5</td>
<td>11.5±3.9</td>
<td>80.8±18.8</td>
<td>1.11 (0-4.40)</td>
<td>1.31(0.05-2.80)†</td>
</tr>
</tbody>
</table>

Values are given as means ± standard deviation or as median with range. *) 0.05 > P ≥ 0.01 vs. baseline within the placebo or ARB group; **) 0.01 > P ≥ 0.001 vs. baseline within the placebo or ARB group; ***) P < 0.001 vs. baseline within the placebo or ARB group †) 0.05 > P ≥ 0.01 placebo vs. ARB; DDD: Defined daily dose;
BP: blood pressure; HD: Hemodialysis; bpm: beats per minute; h/w: hours per week.
Table 3

<table>
<thead>
<tr>
<th>Time</th>
<th>Group</th>
<th>n</th>
<th>g/m²</th>
<th>%</th>
<th>cm</th>
<th>LA EF</th>
<th>LV EF</th>
<th>E/A ratio</th>
<th>E/e’ ratio</th>
<th>LVM-index</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>Placebo</td>
<td>40</td>
<td>126±35</td>
<td>60±9</td>
<td>4.2±0.6</td>
<td>0.9±0.4</td>
<td>16.2±7.3</td>
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<tr>
<td></td>
<td>ARB</td>
<td>41</td>
<td>126±33</td>
<td>62±9</td>
<td>4.3±0.6</td>
<td>1.1±0.6</td>
<td>17.2±10.6</td>
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<tr>
<td>12 months</td>
<td>Placebo</td>
<td>30</td>
<td>128±38</td>
<td>55±15*</td>
<td>4.0±0.5</td>
<td>0.9±0.2</td>
<td>17.9±10.1</td>
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<tr>
<td></td>
<td>ARB</td>
<td>25</td>
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<td>58±8</td>
<td>4.2±0.4</td>
<td>1.0±0.2</td>
<td>16.5±6.2</td>
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</tbody>
</table>

Values are given as means ± standard deviation; *) P = 0.03 vs. baseline within the placebo group; a) LA diameter n=36; E/A ratio n=37; E/e’ ratio n=35; b) LA diameter n=29; E/A ratio n=26; E/e’ ratio n=26; c) LA diameter n=40; E/A ratio n=35; E/e’ ratio n=32; d) LA diameter n=25; E/A ratio n=21; E/e’ ratio n=22; LVM-index: Left ventricular mass index; LV EF: Left ventricular ejection fraction; LA: Left atrium; E: early mitral flow velocity; A: late atrial mitral flow velocity; e’: early mitral annulus velocity; LVM-index was calculated as: LV mass/body surface area; LV mass (g) = 0.8 x (1.04[(LVIDd+ PWTd+SWTd)³ – (LVIDd)³]) + 0.6 g; LVIDd: Left ventricular internal diameter; PWTd: Posterior wall thickness; SWTd: Septal wall thickness; body surface area (duBois formula) (m²) = (0.00718 x height(cm)⁰.⁷²⁵) x (weight(kg)⁰.⁴²⁵). Measurements were obtained in end-diastole from two dimensional M-mode in the parasternal long axis view.
Figure 1

Assessed for eligibility ($n=755$)

- Excluded ($n=651$)
  - Not meeting inclusion criteria ($n=265$)
  - Refused consent ($n=64$)
  - Other reasons ($n=322$)*

Enrolled ($n=104$)

- Excluded ($n=22$)
  - Not meeting inclusion criteria ($n=15$)
  - Withdrew consent ($n=4$)
  - Other reasons ($n=3$)

Randomized ($n=82$)

Allocated to placebo ($n=41$)
- Received placebo ($n=41$)
- Did not receive placebo ($n=0$)

Allocated to active ($n=41$)
- Received active ($n=41$)
- Did not receive active ($n=0$)

Follow-up

- Lost to follow-up ($n=0$)
- Discontinued intervention ($n=11$)
  - Transplantation ($n=3$)
  - Death ($n=3$)
  - Withdrew consent ($n=3$)
  - Lack of compliance ($n=2$)

- Lost to follow-up ($n=0$)
- Discontinued intervention ($n=15$)
  - Transplantation ($n=4$)
  - Withdrew consent ($n=4$)
  - Diarrhoea ($n=2$)
  - Change to PD ($n=1$)
  - Hypotension ($n=1$)
  - Myocardial infarction ($n=1$)
  - Poor general condition ($n=1$)
  - Lack of compliance ($n=1$)

Analysis

- Analyzed ($n=41$)
- Excluded from analysis ($n=0$)

- Analyzed ($n=41$)
- Excluded from analysis ($n=0$)

*) Other reasons included change to peritoneal dialysis (PD), planned transplantation, HD in relation to transplantation, patients moved to another hospital, death and unknown. It was not obligatory for the investigators to explain if a patient was not includable. When no reasons were given, it was very often because inclusion criteria were not met.
Figure 2

A. Brachial systolic & diastolic BP all visits (mean +/- SE)

B. Central aortic systolic & diastolic BP (mean +/- SE)

C. Augmentation index (mean +/- SE)

D. Pulse wave velocity (mean +/- SE)
Appendix

Statistical details

Brachial BP and heart rate, ultrafiltration, preHD weight, PWA parameters (central BP values), PWV, NT-proBNP, HRV parameters, plasma catecholamines and angiotensin II were analysed with a multivariate repeated measurements model (xtmixed), which allows for missing values and drop out with visit (baseline, 1 week, 3 months, 6 months, 9 months and 12 months) and drug (placebo or ARB) and the interaction between them as factors. An approximate test for the hypothesis of equal standard deviations and correlations in the two groups was performed and the analysis was adjusted according to whether or not equal standard deviations and correlations were achieved. Model validation was performed by comparing observed and expected within subject standard deviations and correlations and by inspecting QQ-plots. In case of skewed QQ-plots, data were log-transformed. Consequently, the two groups were compared regarding the development over time using four different models:

Model 1: Different development over time
Model 2: Parallel curves (same development over time)
Model 3: Equal levels in the two groups
Model 4: Constant curves (no change over time)

A likelihood ratio test (LR-test) was used to compare the models in order to describe the development over time. The first test compared Model 1 with Model 2. If the test was non-significant, we assumed parallel curves (same development over time). In case of parallel curves, we proceeded testing whether equal levels could be assumed. This was done by testing Model 2 versus Model 3. Finally, in case of equal levels in the two groups we tested whether there was a change over time (constant curves) by comparing Model 3 with Model 4. Pairwise comparisons between and within the placebo and ARB group were based on estimates from Model 1. HD-time and antihypertensive medication could not be analysed with this approach due to many identical values and Student’s t-test was used instead. All xtmixed results are
presented in table 4 in the appendix. The HRV time domain parameter pnn50 (the proportion of N-N intervals having a difference of >50 ms) was transformed by adding 1 to all values (pnn50+1) prior to log-transformation because many pnn50-values were equal to zero. Parameters obtained by echocardiography were analysed with Student’s t-test instead of the multivariate repeated measurements model due to fewer data (baseline and 12 months). Central BP data and PWV data were also analysed with Student’s t-test (comparison between baseline and subsequent visits) thereby excluding patients who did not complete the study. This did not alter our conclusions regarding differences between placebo and ARB (not shown).
## Table 4

### Multivariate repeated measurements analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test for parallel curves</th>
<th>Test for equal levels</th>
<th>Test for constant level</th>
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<tr>
<td><strong>Placebo vs. ARB</strong></td>
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<td><strong>Brachial BPs and HD data</strong></td>
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<td>Systolic BP</td>
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<td>Diastolic BP</td>
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<td>Pulse pressure</td>
<td><strong>0.048</strong></td>
<td>0.077&lt;sup&gt;a&lt;/sup&gt;</td>
<td><strong>0.027&lt;sup&gt;b&lt;/sup&gt;</strong></td>
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<tr>
<td>Heart rate</td>
<td>0.136</td>
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<td>PreHD weight</td>
<td>0.083</td>
<td>0.378</td>
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<td>Ultrafiltration</td>
<td>0.142</td>
<td>0.307</td>
<td>0.062</td>
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<td>Urine output</td>
<td>0.134</td>
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<td><strong>Pulse wave data</strong></td>
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<tr>
<td>Central Systolic BP</td>
<td>0.102</td>
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<td>Central Diastolic BP</td>
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<td><strong>0.009</strong></td>
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<td>Central PP</td>
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<td>0.401</td>
<td>0.473</td>
<td>0.085</td>
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<td>TR</td>
<td>0.654</td>
<td>0.992</td>
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<tr>
<td>ED</td>
<td>0.258</td>
<td>0.890</td>
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<td>ED-index</td>
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<td>0.293</td>
<td>0.780</td>
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<td>SEVR</td>
<td>0.202</td>
<td>0.654</td>
<td>0.577</td>
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<tr>
<td>PP-amp. ratio</td>
<td><strong>0.022</strong></td>
<td><strong>0.038&lt;sup&gt;a&lt;/sup&gt;</strong></td>
<td><strong>0.045&lt;sup&gt;b&lt;/sup&gt;</strong></td>
</tr>
<tr>
<td>PWV (DD)</td>
<td>0.636</td>
<td>0.627</td>
<td>0.415</td>
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<tr>
<td>PWV (SD)</td>
<td>0.572</td>
<td>0.490</td>
<td>0.516</td>
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<td><strong>Blood samples</strong></td>
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<tr>
<td>log(NT-proBNP)</td>
<td>0.093</td>
<td>0.577</td>
<td><strong>0.011</strong></td>
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<td>log(Adrenaline)</td>
<td>0.574</td>
<td>0.625</td>
<td>0.407</td>
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<tr>
<td>log(Noradrenaline)</td>
<td>0.498</td>
<td><strong>0.005&lt;sup&gt;*&lt;/sup&gt;</strong></td>
<td><strong>0.001&lt;sup&gt;c&lt;/sup&gt;</strong></td>
</tr>
<tr>
<td>log(Angiotensin II)</td>
<td>&lt;0.001&lt;sup&gt;*&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
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<td><strong>HRV-data</strong></td>
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<tr>
<td>log(Mean N-N)</td>
<td>0.373</td>
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<td>log(SDNN)</td>
<td>0.669</td>
<td>0.205</td>
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<td>log(rmssd)</td>
<td>0.249</td>
<td>0.290</td>
<td>0.900</td>
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<tr>
<td>log(pnn50+1)</td>
<td>0.894</td>
<td>0.250</td>
<td>0.626</td>
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<td>log(Total power)</td>
<td>0.654</td>
<td>0.595</td>
<td>0.506</td>
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<td>log(HF-power)</td>
<td>0.250</td>
<td>0.688</td>
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<tr>
<td>log(LF-Power)</td>
<td>0.428</td>
<td>0.296</td>
<td>0.861</td>
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<td>log(LF/HF ratio)</td>
<td>0.456</td>
<td>0.256</td>
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<td>log(Valsalva ratio)</td>
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<td>log(Stand ratio)</td>
<td>0.227</td>
<td>0.718</td>
<td>0.212</td>
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</table>
Table 4

a) Model 1 (different development over time) vs. Model 3 (equal levels)
b) Model 1 (different development over time) vs. Model 4 (no development over time)
c) Model 2 (parallel curves) vs. Model 4 (no development over time)

*) Model 2: Parallel curves with mean ratio (Placebo/ARB): 1.3(1.1-1.5); \( P = 0.002 \)

Aix: Augmentation index; AIX@HR75: Augmentation index normalized to a heart rate of 75; TR: Time to reflection; ED: Ejection duration = the duration of left ventricular systolic ejection (systolic time interval in milliseconds); ED index: Ejection duration index = ED/Time; Time: duration of systole and diastole; SEVR: Subendocardial viability index (Buckberg ratio); PP-amp. ratio: Pulse pressure (PP) amplification ratio=Brachial PP/Central PP; PWV: Pulse wave velocity based on direct distance; PWV (SD): Pulse wave velocity based on subtracted distance; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; Mean N-N: Normal to normal interval = mean interval between adjacent QRS complexes; SDNN: The standard deviation of the N-N interval; rmssd: The square root of the mean squared differences of successive N-N intervals; pnn50: The proportion of N-N intervals having a difference of \( >50 \) ms; Total power: Variance of all N-N intervals; HF-power: High frequency power; LF-power: Low frequency power.
### Table 5

**Pulse wave data**

<table>
<thead>
<tr>
<th>Time</th>
<th>Group</th>
<th>n&lt;sup&gt;PWA&lt;/sup&gt;/n&lt;sup&gt;PWV&lt;/sup&gt;</th>
<th>Central SysBP</th>
<th>Central DiaBP</th>
<th>Central PP</th>
<th>Alx</th>
<th>Alx@HR75</th>
<th>TR</th>
<th>ED</th>
<th>ED index</th>
<th>SEVR</th>
<th>PP-amp. ratio</th>
<th>PWV_SD</th>
<th>PWV</th>
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<tr>
<td>Placebo</td>
<td>29/31</td>
<td>132±16</td>
<td>76±13</td>
<td>56±12</td>
<td>28±11</td>
<td>25±11</td>
<td>140±13</td>
<td>338±24</td>
<td>38±6</td>
<td>128±29</td>
<td>1.3±0.2</td>
<td>10.0±3.3</td>
<td>11.4±3.6</td>
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<tr>
<td>ARB</td>
<td>34/36</td>
<td>134±18</td>
<td>75±13</td>
<td>58±19</td>
<td>30±8</td>
<td>26±7</td>
<td>138±11</td>
<td>336±24</td>
<td>37±5</td>
<td>132±32</td>
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<tr>
<td><strong>1 week</strong></td>
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<tr>
<td>Placebo</td>
<td>34/31</td>
<td>127±18</td>
<td>72±11</td>
<td>55±16</td>
<td>28±9</td>
<td>25±9</td>
<td>142±12</td>
<td>335±23</td>
<td>38±5*</td>
<td>127±25</td>
<td>1.3±0.1</td>
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<td>11.4±3.6</td>
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<tr>
<td>ARB</td>
<td>34/36</td>
<td>126±23*</td>
<td>73±15*</td>
<td>53±19</td>
<td>29±10</td>
<td>25±9</td>
<td>141±13</td>
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<td><strong>3 months</strong></td>
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<tr>
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<td>33/31</td>
<td>132±22</td>
<td>72±13*</td>
<td>60±20</td>
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<td>336±24</td>
<td>38±5</td>
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<tr>
<td>ARB</td>
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<td>125±21**</td>
<td>72±12*</td>
<td>54±19</td>
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<tr>
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<td>31/27</td>
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<td>68±12***</td>
<td>53±14</td>
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<tr>
<td>ARB</td>
<td>27/23</td>
<td>128±21</td>
<td>73±16</td>
<td>55±19</td>
<td>27±9*</td>
<td>24±7**</td>
<td>145±11**</td>
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<td>72±13</td>
<td>50±12*</td>
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<td>25±10</td>
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<td>123±21</td>
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<tr>
<td>ARB</td>
<td>23/22</td>
<td>125±17**</td>
<td>70±12*</td>
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<td>23±8*</td>
<td>144±13*</td>
<td>336±29</td>
<td>37±4</td>
<td>128±19</td>
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<td>9.5±2.5</td>
<td>10.7±3.0*</td>
<td></td>
</tr>
</tbody>
</table>

Table 5

Values are given as means ± standard deviation; *) 0.05 > P ≥ 0.01 vs. baseline within the placebo or ARB group; **) 0.01 > P ≥ 0.001 vs. baseline within the placebo or ARB group; ***) P < 0.001 vs. baseline within the placebo or ARB group; †) 0.05 > P ≥ 0.01 placebo vs. ARB; a) Placebo group TR at 9 months n=27; PWA: Pulse wave analysis; PWV: Pulse wave velocity; PWV_SD: PWV based on subtracted distance; SysBP: Systolic blood pressure; DiaBP: Diastolic blood pressure; Alx: Augmentation index; AIX@HR75: Alx normalised to a heart rate of 75; TR: Time to reflection; ED: Ejection duration = the duration of left ventricular systolic ejection (systolic time interval in milliseconds); ED index: Ejection duration index = ED/Total duration of systole and diastole; SEVR: Subendocardial viability index (Buckberg ratio); PP-amp. ratio: Pulse pressure (PP) amplification ratio=Brachial PP/Central PP. The equation used for converting PWV_SD to PWV was 0.8 x X<sub>direct</sub> with X<sub>direct</sub> = 0.45 x X<sub>subtracted</sub> + 0.21 x height + 0.08 (m). For further details see references in the methods section.
Table 6

Blood samples

<table>
<thead>
<tr>
<th>Time</th>
<th>Group</th>
<th>NT-proBNP</th>
<th>Adrenaline</th>
<th>Noradrenaline</th>
<th>Angiotensin II</th>
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<tr>
<td></td>
<td></td>
<td>n nmol/L</td>
<td>n nmol/L</td>
<td>n nmol/L</td>
<td>n pg/mL</td>
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<tr>
<td>Baseline</td>
<td>Placebo</td>
<td>41 0.29(0.06-1.83)</td>
<td>37 0.08 (0.01-0.31)</td>
<td>37 2.59(0.70-7.42)</td>
<td>40 11(2-117)</td>
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<td>ARB</td>
<td>41 0.28(0.02-4.13)</td>
<td>38 0.08 (0.01-0.78)</td>
<td>38 1.79(0.48-5.88)*</td>
<td>41 8(3-110)</td>
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<td>1 week</td>
<td>Placebo</td>
<td>39 0.24(0.05-2.33)</td>
<td>37 0.08 (0.01-0.32)</td>
<td>37 2.62(0.46-8.74)</td>
<td>37 9(3-44)</td>
</tr>
<tr>
<td></td>
<td>ARB</td>
<td>40 0.19(0.01-4.13)**</td>
<td>38 0.08 (0.01-0.48)</td>
<td>38 2.22(0.44-6.66)*</td>
<td>38 13(4-112)***†</td>
</tr>
<tr>
<td>3 months</td>
<td>Placebo</td>
<td>37 0.32(0.03-4.13)</td>
<td>37 0.09 (0.01-0.91)</td>
<td>37 3.06(0.94-6.12)</td>
<td>36 10(4-44)</td>
</tr>
<tr>
<td></td>
<td>ARB</td>
<td>35 0.21(0.01-4.13)**</td>
<td>35 0.09 (0.01-0.27)</td>
<td>35 2.18(0.28-7.79)†</td>
<td>34 15(4-89)***†</td>
</tr>
<tr>
<td>6 months</td>
<td>Placebo</td>
<td>33 0.37(0.06-4.13)</td>
<td>33 0.10 (0.02-1.22)</td>
<td>33 2.88(1.17-6.60)</td>
<td>32 10(4-50)</td>
</tr>
<tr>
<td></td>
<td>ARB</td>
<td>30 0.30(0.02-4.13)</td>
<td>30 0.09 (0.01-0.39)</td>
<td>30 2.31(0.67-4.86)*</td>
<td>30 14(3-180)***</td>
</tr>
<tr>
<td>9 months</td>
<td>Placebo</td>
<td>33 0.37(0.06-4.13)</td>
<td>33 0.11 (0.01-0.51)</td>
<td>33 2.97(1.10-5.98)</td>
<td>33 9(3-62)</td>
</tr>
<tr>
<td></td>
<td>ARB</td>
<td>29 0.36(0.02-3.76)</td>
<td>29 0.10 (0.01-0.44)</td>
<td>29 2.32(0.50-4.56)*</td>
<td>29 12(4-236)***†</td>
</tr>
<tr>
<td>12 months</td>
<td>Placebo</td>
<td>30 0.50(0.05-4.13)*</td>
<td>30 0.11 (0.02-0.69)*</td>
<td>30 2.64(1.06-6.54)</td>
<td>28 8(2-78)</td>
</tr>
<tr>
<td></td>
<td>ARB</td>
<td>26 0.70(0.03-4.13)</td>
<td>26 0.11 (0.01-0.41)</td>
<td>26 2.09(0.60-4.68)*</td>
<td>25 12(3-250)**†</td>
</tr>
</tbody>
</table>

Table 6

Values are presented as median with range in order to facilitate interpretation. Statistical analysis was performed after logarithmic transformation due to skewed data and p-values given are based on the log-transformed data. NT-proBNP: N-terminal prohormone of brain natriuretic peptide
*) 0.05 > P ≥ 0.01 vs. baseline within the placebo or ARB group; **) 0.01 > P ≥ 0.001 vs. baseline within the placebo or ARB group; ***) P < 0.001 vs. baseline within the placebo or ARB group; †) 0.05 > P ≥ 0.01 placebo vs. ARB; ††) 0.01 > P ≥ 0.001 placebo vs. ARB
NT-proBNP: nmol/L → 1/0.000118 pg/mL
Adrenaline: nmol/L → x 1000/5.46 pg/mL
Noradrenaline: nmol/L → x 1000/5.91 pg/mL
Noradrenaline: Curves were assumed parallel (Model 2). Mean difference (Placebo-ARB) with 95% confidence interval (CI) was 0.55(0.12-0.98) log(nmol/L); P = 0.002. Consequently, mean ratio (Placebo/ARB) with 95% CI was: 1.3(1.1-1.5); P = 0.002
Table 7

Heart rate variability

<table>
<thead>
<tr>
<th>Time</th>
<th>Group</th>
<th>n/ n\textsuperscript{V}/ n\textsuperscript{S}</th>
<th>Mean N-N</th>
<th>SDNN (ms)</th>
<th>rmssd (ms)</th>
<th>pnn50 (%)</th>
<th>Total power (ms\textsuperscript{2})</th>
<th>HF power (ms\textsuperscript{2})</th>
<th>LF power (ms\textsuperscript{2})</th>
<th>LF/HF ratio</th>
<th>Valsalva ratio</th>
<th>Stand ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>30/29/27</td>
<td>863 (525-1252)</td>
<td>17 (6-103)</td>
<td>16 (2-84)</td>
<td>0.2 (0-47.9)</td>
<td>201 (15-7958)</td>
<td>48 (1-1032)</td>
<td>34 (2-3573)</td>
<td>0.9 (0.1-6.6)</td>
<td>1.1 (1.1-1.4)</td>
<td>1.0 (1.0-1.5)</td>
<td></td>
</tr>
<tr>
<td>ARB</td>
<td>32/31/25</td>
<td>882 (559-1183)</td>
<td>24 (3-55)</td>
<td>20 (2-71)</td>
<td>1.1 (0-22.3)</td>
<td>231 (3-2394)</td>
<td>47 (1-1142)</td>
<td>54 (1-1373)</td>
<td>0.7 (0.0-5.1)</td>
<td>1.2 (1.0-1.5)</td>
<td>1.1 (1.0-2.0)</td>
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<tr>
<td><strong>1 week</strong></td>
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</tr>
<tr>
<td>Placebo</td>
<td>29/27/24</td>
<td>832 (554-1151)</td>
<td>18 (6-100)</td>
<td>16 (3-75)</td>
<td>0.3 (0-45.3)</td>
<td>150 (12-6249)</td>
<td>46 (1-1210)</td>
<td>24 (1-3008)</td>
<td>0.8 (0.1-8.4)</td>
<td>1.1 (1.0-1.4)</td>
<td>1.1 (1.0-1.4)</td>
<td></td>
</tr>
<tr>
<td>ARB</td>
<td>35/32/29</td>
<td>890 (638-1255)</td>
<td>23 (4-122)</td>
<td>18 (2-179)</td>
<td>0.7 (0-17.8)</td>
<td>290 (6-5354)</td>
<td>71 (1-3367)</td>
<td>71 (1-1110)</td>
<td>0.6 (0.0-10.0)</td>
<td>1.2 (1.0-1.4)</td>
<td>1.1 (1.0-1.9)</td>
<td></td>
</tr>
<tr>
<td><strong>3 months</strong></td>
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</tr>
<tr>
<td>Placebo</td>
<td>26/25/23</td>
<td>852 (634-1165)</td>
<td>18 (6-58)</td>
<td>15 (3-85)</td>
<td>0.4 (0-20.6)</td>
<td>191 (22-3332)</td>
<td>57 (2-1606)</td>
<td>35 (1-435)</td>
<td>0.6 (0.1-8.5)</td>
<td>1.1 (1.0-1.7)</td>
<td>1.1 (1.0-1.7)</td>
<td></td>
</tr>
<tr>
<td>ARB</td>
<td>29/25/21</td>
<td>875 (610-1168)</td>
<td>24 (3-144)</td>
<td>17 (3-224)</td>
<td>0.6 (0-71.6)</td>
<td>302 (4-13632)</td>
<td>59 (2-9166)</td>
<td>55 (1-1487)</td>
<td>0.8 (0.2-6.4)</td>
<td>1.2 (1.0-2.1)</td>
<td>1.2 (1.0-2.1)</td>
<td></td>
</tr>
<tr>
<td><strong>6 months</strong></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>27/25/23</td>
<td>864 (654-1200)</td>
<td>17 (5-52)</td>
<td>14 (3-82)</td>
<td>0.0 (0-45.5)</td>
<td>153 (16-2472)</td>
<td>42 (3-2092)</td>
<td>31 (1-545)</td>
<td>0.7 (0.0-6.3)**</td>
<td>1.1 (1.1-1.5)</td>
<td>1.1 (1.0-1.6)</td>
<td></td>
</tr>
<tr>
<td>ARB</td>
<td>24/22/18</td>
<td>864 (565-1215)</td>
<td>22 (4-141)</td>
<td>14 (2-233)</td>
<td>0.5 (0-34.1)</td>
<td>203 (4-16243)</td>
<td>38 (2-7833)</td>
<td>31 (1-3187)</td>
<td>0.6 (0.1-11.0)</td>
<td>1.1 (1.0-1.7)</td>
<td>1.1 (1.0-1.3)</td>
<td></td>
</tr>
<tr>
<td><strong>9 months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>24/22/19</td>
<td>785 (654-1283)</td>
<td>18 (6-139)</td>
<td>14 (4-249)</td>
<td>0.5 (0-91.8)</td>
<td>158 (17-10143)</td>
<td>40 (3-8723)</td>
<td>27 (1-2027)</td>
<td>0.6 (0.1-5.6)*</td>
<td>1.1 (1.0-1.8)</td>
<td>1.1 (1.0-2.2)</td>
<td></td>
</tr>
<tr>
<td>ARB</td>
<td>25/23/21</td>
<td>909 (601-1213)</td>
<td>28 (5-184)</td>
<td>19 (2-325)</td>
<td>0.9 (0-84.2)</td>
<td>403 (2-24134)</td>
<td>97 (1-16157)</td>
<td>45 (0-4428)</td>
<td>0.5 (0.0-15.6)</td>
<td>1.2 (1.0-2.0)</td>
<td>1.1 (1.0-1.7)</td>
<td></td>
</tr>
<tr>
<td><strong>12 months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>23/21/20</td>
<td>826 (665-983)</td>
<td>23 (5-42)</td>
<td>14 (4-48)</td>
<td>0.2 (0-9.1)</td>
<td>223 (15-1447)</td>
<td>53 (4-580)</td>
<td>30 (1-293)</td>
<td>0.5 (0.0-3.1)*</td>
<td>1.1 (1.0-1.7)</td>
<td>1.1 (1.0-1.3)</td>
<td></td>
</tr>
<tr>
<td>ARB</td>
<td>20/16/15</td>
<td>880 (657-1062)</td>
<td>22 (5-82)</td>
<td>18 (2-122)</td>
<td>0.2 (0-64.7)</td>
<td>251 (3-19312)</td>
<td>58 (1-2700)</td>
<td>35 (1-2094)</td>
<td>0.8 (0.1-9.1)</td>
<td>1.2 (1.0-1.2)**</td>
<td>1.1 (1.0-1.5)</td>
<td></td>
</tr>
</tbody>
</table>

Table 7

Values are presented as median with range in order to facilitate interpretation. Statistical analysis was performed after logarithmic transformation due to skewed data and p-values given are based on the log-transformed data.

*) 0.05 > P ≥ 0.01 vs. baseline within the placebo or ARB group; **) 0.01 > P ≥ 0.001 vs. baseline within the placebo or ARB group; n\textsuperscript{V}: n with Valsalva ratio; n\textsuperscript{S}: n with Stand ratio; Mean N-N: Normal to normal interval = mean interval between adjacent QRS complexes; SDNN: The standard deviation of the N-N interval; rmsd: The square root of the mean squared differences of successive N-N intervals; pnn50: The proportion of N-N intervals having a difference of >50 ms; Total power: Variance of all N-N intervals; HF-power: High frequency power; LF-power: Low frequency power

Appendix 7
Table 8

Compliance based on tablet counts

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>ARB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unit</td>
<td>n Mean±SD</td>
</tr>
<tr>
<td>Non-compliance %</td>
<td>40±9</td>
<td>41 3±6</td>
</tr>
<tr>
<td>Non-compliance&gt;10% %</td>
<td>5 23±9</td>
<td>3 22±4</td>
</tr>
<tr>
<td>Intake &lt; expected %</td>
<td>32 6±8</td>
<td>26 5±7</td>
</tr>
<tr>
<td>Intake &gt; expected %</td>
<td>7 3±6</td>
<td>10 -1±2</td>
</tr>
<tr>
<td>Pause and/or change of dose n (%)</td>
<td>9(23%)</td>
<td>13(32%)</td>
</tr>
<tr>
<td>Days on 1 tablet n</td>
<td>40±9</td>
<td>41 48±83</td>
</tr>
<tr>
<td>Days on 2 tablets n</td>
<td>40±9</td>
<td>41 230±140</td>
</tr>
<tr>
<td>Tablets consumed n</td>
<td>40±9</td>
<td>41 498±254</td>
</tr>
<tr>
<td>Expected consumption n</td>
<td>40±9</td>
<td>41 508±257</td>
</tr>
<tr>
<td>Days without &lt; 2 weeks n</td>
<td>40±9</td>
<td>41 0.2±1.1</td>
</tr>
<tr>
<td>Days without &gt; 2 weeks n</td>
<td>40±9</td>
<td>41 3±8</td>
</tr>
</tbody>
</table>

Table 8

a) n=40 in the placebo group due to drop out of one patient after baseline.

Figure 5

Figure 5 legend

*) 0.05 > P ≥ 0.01 vs. baseline within the ARB group

***) P < 0.001 vs. baseline within the ARB group

†) 0.05 > P ≥ 0.01 placebo vs. ARB; ‡) 0.01 > P ≥ 0.001 placebo vs. ARB

See table 6 for raw data.
Table 9

Adverse events

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=41)</th>
<th>ARB (n=41)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious adverse events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(total number)</td>
<td>75</td>
<td>54</td>
<td>0.33</td>
</tr>
<tr>
<td>Patients with at least 1 SAE (n)</td>
<td>29</td>
<td>27</td>
<td>0.60</td>
</tr>
<tr>
<td>Death (n)</td>
<td>3</td>
<td>0</td>
<td>0.09</td>
</tr>
<tr>
<td>Infection (n)</td>
<td>23</td>
<td>23</td>
<td>1.00</td>
</tr>
<tr>
<td>Cardiovascular events (n)</td>
<td>18</td>
<td>14</td>
<td>0.90</td>
</tr>
<tr>
<td>Low blood pressure (n)</td>
<td>0</td>
<td>3</td>
<td>0.07</td>
</tr>
<tr>
<td>High blood pressure (n)</td>
<td>3</td>
<td>2</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>Adverse events (total number)</strong></td>
<td>558</td>
<td>563</td>
<td>0.80</td>
</tr>
<tr>
<td>Low blood pressure (n)</td>
<td>7</td>
<td>9</td>
<td>0.58</td>
</tr>
<tr>
<td>High blood pressure (n)</td>
<td>8</td>
<td>7</td>
<td>0.80</td>
</tr>
<tr>
<td>Hyperkalemia (p-potassium ≥ 6 mmol/L) (n)</td>
<td>5</td>
<td>8</td>
<td>0.36</td>
</tr>
<tr>
<td>Cardiopulmonary symptoms (n)</td>
<td>29</td>
<td>27</td>
<td>0.64</td>
</tr>
<tr>
<td>Headache (n)</td>
<td>7</td>
<td>10</td>
<td>0.41</td>
</tr>
<tr>
<td>Dizziness (n)</td>
<td>15</td>
<td>14</td>
<td>0.82</td>
</tr>
<tr>
<td>Gastrointestinal symptoms (n)</td>
<td>25</td>
<td>19</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Intradialytic hypotension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(total number)</td>
<td>22</td>
<td>25</td>
<td>0.65</td>
</tr>
</tbody>
</table>

**Table 9**

Serious adverse events, adverse events and intradialytic hypotension are shown as total number of events (compared by Wilcoxon rank sum test) followed by the number of patients experiencing each of the selected events (compared by Chi2 test). Indication for categorizing low or high blood pressure as an adverse event was not predefined in the protocol, but it was chosen by the investigator e.g. if an extra control visit was considered necessary. Intradialytic hypotension was defined as symptomatic hypotension requiring administration of intravenous fluid or preterm ending of the dialysis session.

SAE: Serious adverse event
Intradialytic central haemodynamics is not affected by angiotensin II receptor blockade: A randomised double-blinded placebo-controlled one year intervention trial (the SAFIR study)

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Word count: 3498
Abstract

**Background:** Haemodynamic instability occurs frequently during haemodialysis (HD) treatments. Whether intradialytic central haemodynamics improves or worsens on treatment with an angiotensin II receptor blocker (ARB) is unknown. This randomised placebo-controlled study investigated short and long-term effects of irbesartan on intradialytic haemodynamic parameters using a predialytic systolic blood pressure (BP) target of 140 mmHg.

**Methods:** Cardiac output (CO), stroke volume (SV), central blood volume (CBV), total peripheral resistance (TPR), mean arterial blood pressure (MAP), and heart rate (HR) were assessed six times within the first (HD\(_{\text{START}}\)) and last (HD\(_{\text{END}}\)) 30 minutes of HD using the saline dilution technique during a one-year follow-up period.

**Results:** Of the 82 patients randomised (placebo/ARB: 41/41), 75 (38/37) had ≥ 1 CO measurements. Predialytic systolic BP decreased similarly (P = 0.42) but significantly (P = 0.005). Total number of intradialytic hypotensive episodes were (placebo/ARB) 22/25 (P = 0.65). CO, SV, TPR, HR, and MAP were stable and similar throughout the study regardless of time of assessment, whereas CBV increased equally and significantly over time (HD\(_{\text{START}}\): P = 0.008; HD\(_{\text{END}}\): P = 0.005). CO, SV, MAP, and CBV decreased, whereas HR increased from HD\(_{\text{START}}\) to HD\(_{\text{END}}\). There was no significant change in TPR. This intradialytic haemodynamic response was unaffected by ARB and it was stable over time regardless of treatment.

**Conclusions:** CBV increased over time despite reductions in BP. At equal BP-levels, central haemodynamics during HD was not significantly affected by ARB treatment and low intradialytic BP was not more prevalent in ARB treated patients.
Keywords

- Angiotensin II receptor blocker
- Blood pressure
- Cardiac output
- Cardiovascular function
- Dialysis
- Haemodynamics
**Short summary**

Little is known about intradialytic cardiovascular (CV) effects of angiotensin II blockade in haemodialysis (HD) patients. This randomised placebo-controlled double-blinded study provides one-year follow-up data on both short and long-term effects of the angiotensin II receptor blocker irbesartan on intradialytic haemodynamic parameters. At equal blood pressure levels, CV response to HD was not significantly affected by irbesartan treatment. Apart from an increase in central blood volume, central haemodynamics were generally stable over time regardless of treatment.

**Introduction**

Haemodynamic instability is reported to occur in 4-30% of haemodialysis (HD) treatments [1-4] and remains a significant risk factor for patient morbidity and mortality [2, 5]. Hypovolaemia due to ultrafiltration (UF) is an essential factor, and pronounced intradialytic hypotension (IDH) is seldom seen with low UF volumes [6, 7]. The presence of predisposing factors such as heart disease, diabetes, old age, atherosclerosis, food ingestion during dialysis, impaired sympathetic response, and antihypertensive medication may increase the risk of instability regardless of UF and should therefore also be considered in IDH-prone patients [2, 8-10]. The renin-angiotensin-aldosterone system (RAAS) plays an important role in cardiovascular (CV) homeostasis due to its effects on vascular tone and volume. Short and long-term effects attributed RAAS include: vasoconstriction, sodium retention, cardiac hypertrophy, and arterial remodelling [11, 12]. RAAS-blockade with an angiotensin II receptor blocker (ARB) or an angiotensin-converting-enzyme inhibitor (ACEi) is known to improve CV outcome in patients without chronic renal failure [13, 14]. However, in HD patients results have been contradictory and the value of RAAS-blockade has not
been completely elucidated [15-19]. Furthermore, elevated potassium and IDH may discourage use of RAAS-blockade in some HD patients [8, 20]. To the best of our knowledge no previous studies have examined both acute and long-term effects of RAAS-blockade on intradialytic central haemodynamics in HD patients. Therefore, the aim of this study was to describe central haemodynamics during dialysis in detail in a group of newly started HD patients randomised to ARB (irbesartan) or placebo, aiming at a predialytic systolic BP-target of 140 mmHg in both groups. Intradialytic haemodynamic parameters were evaluated six times over a one-year follow-up period, allowing for description of both short and long-term effects of ARB.

**Subjects and Methods**

**Ethics**

The study was conducted in accordance with good clinical practice (GCP) and the ethical standards described in the Helsinki Declaration. The Central Denmark Region Committees on Biomedical Research Ethics, the Danish Health and Medicines Authority, and the Danish Data Protection Agency approved the study. Clinical Trials ID: NCT00791830.

**Study design**

The study design, including considerations regarding sample size, has previously been described [21]. Briefly, the SAFIR-study was designed as a double-blinded multicentre randomised placebo-controlled trial primarily focusing on residual renal function and intermediate CV endpoints. The inclusion criteria were dialysis vintage <1 year, left ventricular ejection fraction >30% (echocardiography) and urine output >300 mL/day. Block randomization was applied to ensure
equal distribution of patients with diabetes. Patients were recruited from six Danish hospitals and followed for one year. All sites were monitored by a local independent GCP-Unit.

Study medication

The study medication consisted of irbesartan 150 mg, or matching placebo. The initial dose was one tablet per day. After two weeks, daily dose was increased to two tablets. Compliance was checked monthly by counting residual tablets. To reach equal BP-levels in the two treatment groups, investigators were instructed to achieve a predialytic systolic BP of 140 mmHg in all patients by adjusting dryweight and by use of all classes of antihypertensive drugs other than RAAS-blocking agents. If patients received RAAS-blocking agents at inclusion, this treatment was stopped one week before baseline.

Blood pressure

Blood pressure (BP) was measured with validated automated oscillometric BP devices as previously described [21]. For assessment of the predialytic BP, a minimum of two measurements were performed and the average was used. Intradialytic BP was obtained at the same time as the intradialytic cardiac output (CO) measurements.

Intradialytic measurements

CO was measured in duplicate by injecting a bolus of 30 mL 37°C isotonic saline into the venous blood line within the first and the last 30 minutes of the dialysis session using a previously validated method (Hemodialysis Monitor HD02/HD03, Flow-QC tubing sets, and clip-on flow/dilution sensors Transonic Systems Inc., Ithaca, NY, USA) [22-24]. Based on CO, the system estimates the volume of blood in the heart, lungs, and great vessels known as the central blood
volume (CBV) [23]. The mean BP (MAP), total peripheral resistance (TPR), and stroke volume (SV) were obtained by:

\[
\text{MAP} = \text{diastolic BP} + \frac{1}{3} \times (\text{systolic BP}–\text{diastolic BP})
\]

\[
\text{CO} = \text{SV} \times \text{heart rate} = \frac{\text{MAP}}{\text{TPR}}
\]

Access recirculation (AR) can cause errors when measuring CO [23]. We used a built-in recirculation protocol to check for AR using injection of 10 mL isotonic saline into the venous blood line prior to the first measurement. No measurements were performed if overt AR (pre-existing or induced by injection) was present. Second pass of the indicator is usually regarded as the biggest problem in classical dilution techniques because it disrupts the recorded dilution curve [23]. Injection time is critical, and prolonged injection time increases the risk of a second pass. All injections were done within 4-7 seconds in order to minimise this error. Loss of the saline indicator from the blood and into the tissues has previously been examined and is not considered a significant factor [25]. At end of the study, seventy-five patients had at least one CO measurement. Seven patients (placebo/ARB: 3/4) had no CO measurements due to absence of an arteriovenous fistula (AV-fistula). Thus, prior to code breaking, 355 (out of 415 expected) mean CO-values within the first 30 minutes of the HD session were available for analysis. Sixty measurements were lacking due to absence of an AV-fistula (n=52), equipment failure (n=2) or because the measurements were not performed (n=6). Additional twelve measurements within the last 30 minutes of the HD session were missing due to technical problems. Hence, 343 mean CO-values within the last 30 minutes of the HD session were available for analysis. A total of 144 access flow measurements were registered during the study period (placebo/ARB: 79/65)
corresponding to at least one measurement in 21(49%)/23(56%) patients treated with placebo/ARB.

Statistics

Data were analysed with Stata/IC 12.1 (StataCorp LP, College Station, TX 77845 USA) based on a multivariate repeated measurements model (xtmixed) which allows for missing values and drop-out, and with time and drug (placebo or ARB) and the interaction between them as factors (for further details see Appendix I). HD-time and antihypertensive medication could not be analysed with this approach due to many identical values and Wilcoxon signed-rank test was used instead. Within group comparisons between start and end of HD at each visit was done with a paired Student’s t-test. Baseline data, the number of missing data, and adverse events were analysed with chi-squared test for qualitative variables and continuous variables were analysed with Student’s t-test or Wilcoxon signed-rank test if normal distribution could not be assumed. The latter was checked with QQ-plots and equal variance was checked with F-tests. Distribution of BP-drugs in the groups was compared with chi-squared test at all visits. Pearson’s $r$ was used to describe linear relationships. Intention-to-treat analyses were performed and $P < 0.05$ was considered significant. Values are presented as estimated means with 95% confidence intervals unless otherwise stated.

Results

Patient characteristics and adverse events
Eighty-two patients were included in the study with forty-one in each group (Table 1). Overall, the groups were similar at baseline. Patients (placebo/ARB) were predominantly males (63/73%) with mean age 62/61 years, all had some residual urine production with a median output of (1.19/1.26 L/24 hours), and a relatively short median dialysis vintage (137/148 days). Prevalence of CV disease (41/37%) and diabetes (29/32%) was similar in the two groups. Twenty-six patients did not complete the study, eleven in the placebo and fifteen in the ARB group. Reasons for drop out are listed in Figure 1. Drop out due to possible side effect (e.g. hyperkalaemia, low BP and diarrhoea) was low in both groups and not significantly different. Adverse events such as low/high BP or hyperkalaemia were not significantly different in the two treatment groups (Appendix III). The total number of IDH episodes (defined as symptomatic hypotension requiring administration of intravenous fluid or preterm ending of the dialysis session) registered during the study period (placebo/ARB) were 22/25 \( (P = 0.65) \) corresponding to an annual incidence rate of 6/7%.

**Blood pressure, antihypertensive medication, and dialysis parameters**

Predialytic systolic and diastolic BP were similar (tests for equal levels: \( P > 0.27 \)) and decreased equally and significantly over time (tests for constant levels: \( P < 0.01 \)) as shown in Table 2 and Figure 2 (all recorded measurements). Use of additional antihypertensive medication in the study period besides placebo/ARB was similar in the two groups and there were no significant differences in defined daily doses, number or classes of additional BP-drugs. Overall, there was no significant difference in UF volume and urine output between placebo and ARB treated (test for equal levels: \( P = 0.31 \) (UF volume); \( P = 0.26 \) (urine output)). In both groups, UF volume tended to increase over time (test for constant level: \( P = 0.06 \)), whereas urine output decreased significantly...
over time (test for constant level: $P = 0.004$). HD-time, predialytic weight, and access flow did not differ significantly between groups over time.

**Intradialytic haemodynamic parameters**

Intradialytic changes within each group

Table 3 shows mean comparisons between intradialytic values obtained within the first (HD\textsubscript{START}) and last (HD\textsubscript{END}) 30 minutes of the dialysis session. In both groups CO, MAP, CBV, and SV decreased whereas HR increased from HD\textsubscript{START} to HD\textsubscript{END} although not always significantly. TPR did not change significantly. CO obtained at HD\textsubscript{START} correlated significantly with age ($r = -0.51; P < 0.001$) and plasma haemoglobin level ($r = -0.31, P = 0.01$) when combining the groups and using all baseline measurements. Mean access flow in the study period (averaged from all available measurements regardless of group) correlated significantly with mean CO at HD\textsubscript{START} ($r = 0.42; P = 0.005$). Thus, CO tended to decrease with higher age, higher haemoglobin level, and lower access flow. Use of CO obtained at HD\textsubscript{END} showed similar results.

Intradialytic haemodynamics and development over time

Measurements obtained at start of dialysis are shown in Figure 3 and measurements obtained at the end of dialysis are shown in Figure 4. Regardless of the time of assessment, there was no significant difference in CO, MAP, HR, TPR, and SV between placebo and ARB over time ($P > 0.22$ in all tests for parallel curves and equal levels). CBV increased significantly but equally (test for equal levels: $P = 0.07 \text{ (HD\textsubscript{START})}; P = 0.29 \text{ (HD\textsubscript{END})}$ during the study period both when measured at HD\textsubscript{START} (test for constant level: $P = 0.008$) and when measured at HD\textsubscript{END} (test for constant level: $P = 0.005$).
CO, MAP, HR, TPR, and SV were stable throughout the study period regardless of treatment and time of assessment.

Intradialytic changes between groups

Figure 5 shows intradialytic changes (Δ=HD_{\text{END}}-HD_{\text{START}}). Overall, there was no significant difference in ΔCO, ΔMAP, ΔTPR, ΔSV, and ΔCBV between placebo and ARB (P > 0.10 in all tests for parallel curves and equal levels). Thus, taking all twelve months into account we found no significant difference in ΔMAP between placebo and ARB (test for parallel curves: P = 0.10; test for equal levels: P = 0.13) although ΔMAP was significantly lower in the ARB group at six and nine months. Mean difference in ΔMAP was 9(3-15) and 8(0-16) mmHg (P = 0.006; P = 0.04) at six and nine months, respectively. Similarly, taking all twelve months into account we found no significant difference in ΔTPR (test for parallel curves: P = 0.21; test for equal levels: P = 0.19) although ΔTPR was significantly lower in the ARB group at six and twelve months. Mean difference in ΔTPR was 2.0(0.2-3.8) and 2.1(0.4-3.9) mmHg·min/L (P = 0.03; P = 0.02) at six and twelve months, respectively. ΔHR levels differed significantly between groups at baseline with a slightly higher mean intradialytic increase in HR in the ARB group corresponding to a mean ΔHR difference of 2.4(0.2-4.6) bpm (P = 0.03). During the study period the difference remained more or less constant (test for parallel curves: P = 0.22) indicating no significant effect of ARB.

Ultrafiltration volume and correlations with intradialytic changes

UF volume correlated significantly with all intradialytic changes, except for ΔHR, when combining the groups and using all measurements between baseline and twelve months. Accordingly, UF volume was negatively associated with ΔCO (r = -0.49; P < 0.001), ΔSV (r = -0.46; P < 0.001), ΔMAP (r = -0.16; P = 0.003), and ΔCBV (r = -0.30; P < 0.001) and positively associated with ΔTPR (r = 0.28;
and ΔHR ($r = 0.10; P = 0.08$). Lastly, ΔCO correlated significantly with age ($r = 0.28; P < 0.001$), but there was no significant correlation with access flow ($r = 0.14; P = 0.09$) or plasma haemoglobin level ($r = -0.06; P = 0.30$).

**Discussion**

To our knowledge, the present study is the first randomised placebo-controlled double-blinded study investigating both short and long-term intradialytic CV effects of ARB in newly started HD patients. Due to equal BP-levels in the two treatment groups, our study primarily provides results on BP-independent effects of RAAS-blockade. At equal BP-levels, there was no significant effect of ARB on intradialytic central haemodynamic parameters. We found no indication of negative effects of ARB including IDH over a one-year period. Moreover, our study yielded detailed one-year follow-up data on intradialytic central haemodynamics, which is novel.

Avoiding haemodynamic instability during HD is important because it hinders sufficient fluid removal, causes inadequate dialysis, and likely adds to CV risk [5, 26]. Thus, frequent episodes of IDH is suspected to cause myocardial [27, 28] and cerebral ischemia [29] and was found to be related both to frontal lobe atrophy [30] and rise in cardiac biomarkers (troponin I and creatine kinase isoenzyme MB) [31]. Only few studies are available on the tolerability of antihypertensive drugs during HD [1, 2, 32-36], none of them being long-term, except for the study by Tisler et al. [2]. This ten-month observational cohort-study found that use of long-acting nitrates and absence of calcium channel blockers increased the risk of IDH.
Other studies investigating intradialytic haemodynamic parameters have primarily focused on modifiable HD-related parameters such as dialysate calcium [37, 38] and sodium concentration [39], thermal effects [40], use of continuous blood volume monitoring [41, 42] and comparison of HD vs. haemodiafiltration [43, 44]. Several of these studies used the saline dilution technique for assessment of CO [37, 40, 43, 44]. Our study showed that CO decreased during HD due to a reduction in SV which was not fully compensated by an increase in HR. A similar intradialytic response was found in previous short-term studies [37, 40, 44]. The intradialytic response to HD was stable over a one-year period and intradialytic central haemodynamic parameters were overall unaffected by ARB treatment. CBV represents the relative blood volume responding to fluid removal by UF during HD [23, 43]. The increase in CBV within both groups during the study period may reflect progressive volume overload due to a concomitant decrease in urine output. Interestingly, this increase developed despite frequent clinical assessment of hydration status and despite reductions in BP.

Despite on average two extra defined daily doses of antihypertensive medication (300 mg irbesartan) in the ARB group, both groups achieved a similar decrease in predialytic BP and the predefined mean BP-target of 140 mmHg was reached in both groups. Intradialytic BP within the first and last 30 minutes of HD, as well as the intradialytic change in MAP were similar and constant in the two groups when all twelve months were taken into account. Beforehand, we expected a greater decrease in MAP and TPR during dialysis in ARB treated patients due to an expected vasodilatory effect of irbesartan. However, this response was not evident apart from ΔMAP at six and nine months and ΔTPR at six and twelve months, respectively. There is no obvious explanation for these findings except for the fact that BP was reduced equally in the placebo group. Weekly HD-time, UF volume, and use of additional antihypertensive medication were not
significantly different between the groups. CBV tended to be higher in the ARB group and predialytic weight decreased by 1.9(-0.2-3.9) kg in the placebo group \( (P = 0.08) \) and increased by 1.3(-0.5-3.1) kg in the irbesartan group \( (P = 0.2) \) during the study suggesting differences in volume overload. Accordingly, some of the BP-lowering effect of ARB may have been outbalanced by slightly more efficient fluid removal during HD in the placebo group.

IDH was not more frequent in ARB treated patients in our study and overall there was no indication of significantly lower intradialytic BP in the ARB group. Our results corroborate findings by Davenport et al. which found no correlation between IDH and achievement of a predialytic BP-target of 140/90 mmHg, although achievement of a postdialytic BP-target of 130/80 was significantly correlated with symptomatic IDH episodes [1]. The same study also suggested that IDH was not made worse by the prescription of antihypertensive agents and that RAAS-blocking agents were not superior to other drug classes in terms of reaching the predialytic BP-target. Symptomatic IDH is reported to occur in 4-30% of HD treatments [1, 6, 8]. In our study, symptomatic annual IDH incidence was 6-7% most likely due to relatively low UF-volumes. Co-morbid conditions known to affect regulatory CV mechanisms such as CV disease and diabetes were evenly distributed in the two groups. However, the relatively low number of patients in our study prevented adequately powered analysis regarding the effect of ARB in these subgroups.

Limitations

Previous studies have shown that formation of an AV-fistula has a significant impact on CV parameters such as CO, TPR, BP, and SV [45, 46]. All intradialytic measurements in our study were performed in patients with an AV-fistula and our results cannot be extrapolated to HD patients with permanent venous catheters. CV instability during HD might be more prevalent among the
more morbid and fragile patients. These patients are unlikely participants in a one-year trial such as ours and absence of these patients will inevitably influence our results. Due to preserved urine output in the majority of our patients relatively small UF volumes were prescribed during HD compared to other studies [2, 5]. In HD patients with more pronounced CV disease or larger fluid fluctuations, the results may be different. Thus, our results should be interpreted with some caution. Finally, our study was limited to a one-year follow-up period and a longer follow-up could perhaps reveal significant effects of ARB treatment.

In conclusion, the ARB irbesartan was well tolerated without significant side effects when given as an add-on to standard antihypertensive therapy in HD patients with some residual renal function and a relatively short dialysis vintage. At equal BP-levels, central haemodynamics during dialysis was not significantly affected by ARB treatment and low intradialytic BP was not more prevalent in ARB treated patients. Apart from an increase in CBV, there was no significant change in intradialytic CV parameters such as CO, SV, TPR, HR, and MAP over time. Whether anuric HD patients with longer HD vintage and larger UF volumes behave similarly remains to be clarified.

Acknowledgements

Nurses and nephrologists at all centres are thanked for their assistance.
# Tables

## Table 1

Baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Placebo (n = 41)</th>
<th>ARB (n = 41)</th>
<th>Range</th>
<th>Range</th>
<th>p</th>
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<td><strong>Demographic characteristics</strong></td>
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<tr>
<td>Age</td>
<td>years</td>
<td>62±14</td>
<td>61±16</td>
<td>29-83</td>
<td>36-84</td>
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<td>Gender (males)</td>
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<td>30 (73)</td>
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<td>Body weight</td>
<td>kg</td>
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<td>79±17</td>
<td>52-122</td>
<td>50-131</td>
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<td>Body mass index</td>
<td>kg/m²</td>
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<td>26±5</td>
<td>19-39</td>
<td>19-40</td>
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<td>Smokers</td>
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<td>11 (27)</td>
<td>14 (34)</td>
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<td>Predialytic systolic BP</td>
<td>mmHg</td>
<td>145±19</td>
<td>148±21</td>
<td>111-197</td>
<td>110-203</td>
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<td>Predialytic diastolic BP</td>
<td>mmHg</td>
<td>73±12</td>
<td>76±13</td>
<td>57-103</td>
<td>45-102</td>
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<td>Predialytic heart rate</td>
<td>bpm</td>
<td>71±14</td>
<td>71±12</td>
<td>49-108</td>
<td>50-122</td>
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<td>13 (32)</td>
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<td>Cardiovascular disease ‡</td>
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<td>17 (41)</td>
<td>15 (37)</td>
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<td>Ischemic heart disease</td>
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<td>9 (22)</td>
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<td>6 (15)</td>
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<td>Hypertensive renal disease</td>
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<td>6 (15)</td>
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<td>Polycystic kidney disease</td>
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<td>Pyelonephritis</td>
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<td>Other</td>
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<td>BP-drugs excl. Placebo/ARB</td>
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<td>1-5</td>
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<td>Prednisolone</td>
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<td>38 (93)</td>
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**Dialysis parameters**

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<td>1.19</td>
<td>0.16-2.72</td>
<td>1.26</td>
<td>0.27-3.19</td>
<td>0.49</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td>mL/min/1.73 m²</td>
<td>4.8±2.3</td>
<td>0.68-10.3</td>
<td>5.7±3.29</td>
<td>0.83-13</td>
<td>0.15</td>
</tr>
<tr>
<td>Modality (HDF/HD)</td>
<td>n (%)</td>
<td>3(7)/38(93)</td>
<td>1(2)/40(98)</td>
<td>0.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filter (low flux)</td>
<td>n (%)</td>
<td>22(54)</td>
<td>20(49)</td>
<td>0.66</td>
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<td></td>
</tr>
<tr>
<td>Dialysate calcium conc.</td>
<td>mmol/L</td>
<td>1.38±0.22</td>
<td>1.25-1.75</td>
<td>1.30±0.17</td>
<td>1.00-1.75</td>
<td>0.08</td>
</tr>
<tr>
<td>Frequency</td>
<td>times/week</td>
<td>2.7±0.5</td>
<td>2-3</td>
<td>2.8±0.5</td>
<td>2-4</td>
<td>0.19</td>
</tr>
<tr>
<td>HD-time</td>
<td>hours/week</td>
<td>10±2</td>
<td>6-15</td>
<td>11±3</td>
<td>6-24</td>
<td>0.14</td>
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<tr>
<td>Ultrafiltration</td>
<td>L</td>
<td>1.30</td>
<td>0-4.30</td>
<td>0.55</td>
<td>0-3.80</td>
<td>0.95</td>
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<tr>
<td>Dry weight</td>
<td>kg</td>
<td>79±16</td>
<td>51-128</td>
<td>78±17</td>
<td>52-122</td>
<td>0.64</td>
</tr>
<tr>
<td>Urea reduction ratio</td>
<td>%</td>
<td>64±8</td>
<td>46-78</td>
<td>62±9</td>
<td>40-88</td>
<td>0.31</td>
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</table>

**Blood samples**

<table>
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<tr>
<th>Parathyroid hormone</th>
<th>pmol/L</th>
<th>12.5</th>
<th>1-137</th>
<th>17.9</th>
<th>2-55</th>
<th>0.28</th>
</tr>
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<tbody>
<tr>
<td>Albumin</td>
<td>g/L</td>
<td>38±4</td>
<td>17-43</td>
<td>38±3</td>
<td>32-44</td>
<td>0.81</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>mmol/L</td>
<td>6.8±1.0</td>
<td>3.4-8.5</td>
<td>6.9±0.8</td>
<td>4.6-8.1</td>
<td>0.62</td>
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<tr>
<td>Potassium</td>
<td>mmol/L</td>
<td>4.3±0.7</td>
<td>2.8-6.6</td>
<td>4.2±0.5</td>
<td>3.3-5.4</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation or as median with range.

‡) Cardiovascular disease was defined as ≥ 1 known conditions (placebo/ARB): Ischemic heart disease (9/8); arrhythmia (6/5); valvular disease (6/3); heart failure (0/1); #) Tx: Kidney transplantation; §) Charlson co-morbidity index score range 0-37; 0=low, 3+=high; DDD=Defined daily doses; EPO: erythropoietin; a) n=39 (Placebo group); b) n=36 (Placebo group); GFR: glomerular filtration rate based on the mean of urinary creatinine and urea clearance as previously described [21]; bpm: beats per minute; HDF=Haemodiafiltration; HD=Haemodialysis; c) Three patients in the placebo group and two patients in the ARB group had dialysis vintage > one year and four patients (two in each group) had urine output < 300 mL/day due to delay after inclusion/screening.
Table 2
Predialytic blood pressure, antihypertensive medication, and dialysis data

<table>
<thead>
<tr>
<th>Time</th>
<th>Group</th>
<th>n/n</th>
<th>access flow</th>
<th>PreHD SysBP mmHg</th>
<th>PreHD DiaBP mmHg</th>
<th>PreHD heart rate bpm</th>
<th>Additional BP-drugs</th>
<th>Additional BP-drugs</th>
<th>PreHD weight kg</th>
<th>HD-time h/w</th>
<th>Ultrafiltration L</th>
<th>Urine output L/24h</th>
<th>Access flow mL</th>
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</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Placebo</td>
<td>41/12</td>
<td></td>
<td>145±19</td>
<td>73±12</td>
<td>71±14</td>
<td>2.6±0.9</td>
<td>1.8±1.2</td>
<td>80.9±17.3</td>
<td>9.8±2.3</td>
<td>1.32±1.27</td>
<td>1.30±0.71</td>
<td>1140±579</td>
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<tr>
<td></td>
<td>ARB</td>
<td>41/13</td>
<td></td>
<td>148±21</td>
<td>76±13</td>
<td>71±12</td>
<td>2.5±0.9</td>
<td>1.8±1.2</td>
<td>78.7±17.0</td>
<td>10.7±3.1</td>
<td>1.20±1.36</td>
<td>1.45±0.79</td>
<td>1356±603</td>
</tr>
<tr>
<td>1 week</td>
<td>Placebo</td>
<td>39/12</td>
<td></td>
<td>143±21</td>
<td>71±11</td>
<td>72±13</td>
<td>2.6±1.0</td>
<td>1.8±1.3</td>
<td>81.9±17.5</td>
<td>9.8±2.2</td>
<td>1.28±1.26</td>
<td>1.28±0.71</td>
<td>1180±553</td>
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<tr>
<td></td>
<td>ARB</td>
<td>40/12</td>
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<td>138±22**</td>
<td>72±15**</td>
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<td>1.9±1.2</td>
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<td>10.5±2.4</td>
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<td>3 months</td>
<td>Placebo</td>
<td>37/14</td>
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<td>71±13</td>
<td>69±11</td>
<td>2.5±1.1</td>
<td>1.8±1.3</td>
<td>81.8±18.1</td>
<td>10.1±2.3</td>
<td>1.51±1.24</td>
<td>1.09±0.74*</td>
<td>996±497</td>
</tr>
<tr>
<td></td>
<td>ARB</td>
<td>35/14</td>
<td></td>
<td>140±21**</td>
<td>72±12*</td>
<td>72±12</td>
<td>2.4±1.1</td>
<td>1.7±1.3</td>
<td>80.6±17.6**</td>
<td>10.5±2.6</td>
<td>1.28±1.25</td>
<td>1.36±0.78</td>
<td>1222±503</td>
</tr>
<tr>
<td>6 months</td>
<td>Placebo</td>
<td>33/13</td>
<td></td>
<td>134±16**</td>
<td>68±11*</td>
<td>73±10</td>
<td>2.3±1.1</td>
<td>1.4±1.2</td>
<td>80.5±19.9</td>
<td>10.5±2.2**</td>
<td>1.73±1.40</td>
<td>0.84±0.69***</td>
<td>1119±729</td>
</tr>
<tr>
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<td>ARB</td>
<td>30/8</td>
<td></td>
<td>143±22†</td>
<td>74±15</td>
<td>74±13</td>
<td>2.3±1.1</td>
<td>1.4±1.3*</td>
<td>79.8±17.5</td>
<td>10.5±2.6</td>
<td>1.00±1.15†</td>
<td>1.21±0.81†</td>
<td>1873±1000</td>
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<td>9 months</td>
<td>Placebo</td>
<td>33/15</td>
<td></td>
<td>136±20**</td>
<td>70±13</td>
<td>74±12</td>
<td>2.3±1.2</td>
<td>1.5±1.3</td>
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<td>29/10</td>
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<td>144±20</td>
<td>73±15*</td>
<td>71±12</td>
<td>2.4±1.2</td>
<td>1.6±1.4</td>
<td>80.3±18.1*</td>
<td>11.3±4.4</td>
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<td>Placebo</td>
<td>30/13</td>
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<td>2.3±1.2</td>
<td>1.5±1.2</td>
<td>81.6±19.5</td>
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<td>0.93±0.88**</td>
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<td>72±14</td>
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</tbody>
</table>

Values are given as means ± standard deviation.

*) 0.05 > P ≥ 0.01 vs. baseline within the placebo or ARB group; **) 0.01 > P ≥ 0.001 vs. baseline within the placebo or ARB group; 
****) P < 0.001 vs. baseline within the placebo or ARB group; †) 0.05 > P ≥ 0.01 placebo vs. ARB; DDD: Defined daily dose; SysBP: Systolic blood pressure; DiaBP: Diastolic blood pressure; bpm: beats per minute; h/w: hours per week
### Table 3
Intradialytic haemodynamic parameters within group comparisons of HD\textsubscript{START} vs. HD\textsubscript{END}

<table>
<thead>
<tr>
<th>Time</th>
<th>Group</th>
<th>(n_{\text{START}}/n_{\text{END}})</th>
<th>Cardiac output (\text{L/min})</th>
<th>Mean blood pressure (\text{mmHg})</th>
<th>Heart rate (\text{bpm})</th>
<th>Total peripheral resistance (\text{mmHg} \cdot \text{min/L})</th>
<th>Stroke volume (\text{mL})</th>
<th>Central blood volume (\text{L})</th>
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<tr>
<td></td>
<td>Placebo</td>
<td>35/33</td>
<td>6.2±1.6</td>
<td>5.8±1.6*</td>
<td>96±12</td>
<td>91±15*</td>
<td>69±12</td>
<td>72±12</td>
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<td>ARB</td>
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<td>6.8±1.9</td>
<td>6.3±1.5*</td>
<td>98±13</td>
<td>92±17</td>
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<td>31/30</td>
<td>6.8±2.1</td>
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<td>89±14**</td>
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<td>33/32</td>
<td>6.1±1.9</td>
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<td>88±13*</td>
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<td>86±14*</td>
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<td>6.0±1.1</td>
<td>94±16</td>
<td>88±13**</td>
<td>69±10</td>
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<tr>
<td></td>
<td>Placebo</td>
<td>28/28</td>
<td>6.2±1.7</td>
<td>5.7±1.6*</td>
<td>90±12</td>
<td>88±15</td>
<td>72±12</td>
<td>76±10*</td>
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<td>6.1±1.8</td>
<td>96±18</td>
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<td>72±12</td>
<td>76±16**</td>
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<tr>
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<td>Placebo</td>
<td>29/29</td>
<td>6.0±1.5</td>
<td>5.5±1.7</td>
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<td>73±14</td>
<td>74±15*</td>
</tr>
</tbody>
</table>

Values are given as mean ± standard deviation

*) 0.05 > \(P \geq 0.01\) vs. HD\textsubscript{START} within the placebo or ARB group; **) 0.01 > \(P \geq 0.001\) vs. HD\textsubscript{START} within the placebo or ARB group; ***) \(P < 0.001\) vs. HD\textsubscript{START} within the placebo or ARB group; HD\textsubscript{START}: Measurements performed within the first 30 minutes of the HD session; HD\textsubscript{END}: Measurements performed within the last 30 minutes of the HD session.
Legends to figures

Figure 1
Inclusion and exclusion criteria have been published previously [21]. Briefly, the inclusion criteria were urine output > 300 mL/day, dialysis vintage < 1 year and LV ejection fraction > 30%.

Figure 2
All predialytic brachial blood pressures recorded between baseline and 12 months.
BP: Blood pressure

Figure 3
*) 0.05 > P > 0.01 vs. baseline within the placebo or ARB group
HDSTART: Intradialytic measurement within the first 30 minutes of dialysis.
CO: Cardiac output; MAP: Mean arterial blood pressure; HR: Heart rate; TPR: Total peripheral resistance; SV: Stroke volume; CBV: Central blood volume (volume of blood in the heart, lungs, and the great vessels)

Figure 4
*) 0.05 > P > 0.01 vs. baseline within the placebo or ARB group
†) 0.05 > P > 0.01 vs. placebo
**Figure 5**

*) $0.05 > P > 0.01$ vs. baseline within the placebo or ARB group

†) $0.05 > P > 0.01$ vs. placebo

‡) $0.01 > P > 0.001$ vs. placebo

⚓†) Indicates that parallel curves were assumed (Model 2). The constant mean difference (placebo-ARB) with 95% confidence interval was $2.4(0.2.4.6)$ bpm ($P = 0.03$).

$\Delta = (H_{\text{END}} - H_{\text{START}})$; $H_{\text{START}}$: Intradialytic measurement within the first 30 minutes of dialysis; $H_{\text{END}}$: Intradialytic measurement within the last 30 minutes of dialysis; CO: Cardiac output; MAP: Mean arterial blood pressure; HR: Heart rate; TPR: Total peripheral resistance; SV: Stroke volume; CBV: Central blood volume (volume of blood in the heart, lungs, and the great vessels)
References


Figures

Figure 1

Assessed for eligibility (n=755)
- Excluded (n=651)
  - Not meeting inclusion criteria (n=265)
  - Refused consent (n=64)
  - Other reasons (n=322)*
- Enrolled (n=104)
  - Excluded (n=22)
    - Not meeting inclusion criteria (n=15)
    - Withdrew consent (n=4)
    - Other reasons (n=3)
- Randomised (n=82)

Allocation
- Allocated to placebo (n=41)
  - Received placebo (n=41)
  - Did not receive placebo (n=0)
- Allocated to active (n=41)
  - Received active (n=41)
  - Did not receive active (n=0)

Follow-up
- Lost to follow-up (n=9)
  - Discontinued intervention (n=11)
  - Transplantation (n=3)
  - Death (n=3)
  - Withdrew consent (n=3)
  - Lack of compliance (n=2)
- Lost to follow-up (n=9)
  - Discontinued intervention (n=15)
  - Transplantation (n=4)
  - Withdrew consent (n=4)
  - Diarrhoea (n=2)
  - Change to PD (n=1)
  - Hypotension (n=1)
  - Myocardial infarction (n=1)
  - Poor general condition (n=1)
  - Lack of compliance (n=1)

Analysis
- Analysed (n=41)
  - Excluded from analysis (n=0)
- Analysed (n=41)
  - Excluded from analysis (n=0)

* Other reasons included change to peritoneal dialysis (PD), planned transplantation, HD in relation to transplantation, patients moved to another hospital, death and unknown. It was not obligatory for the investigators to explain if a patient was not includable. When no reasons were given, it was very often because inclusion criteria were not met.
Figure 2

Predialytic systolic & diastolic BP all visits (mean +/- SE)

Blood pressure (mmHg)

Months

Placebo
ARB
Figure 3

CO at HD\textsc{start} (mean +/- SE)

MAP at HD\textsc{start} (mean +/- SE)

HR at HD\textsc{start} (mean +/- SE)

TPR at HD\textsc{start} (mean +/- SE)

SV at HD\textsc{start} (mean +/- SE)

CBV at HD\textsc{start} (mean +/- SE)
Figure 4

CO at HD_{END} (mean +/- SE)

MAP at HD_{END} (mean +/- SE)

HR at HD_{END} (mean +/- SE)

TPR at HD_{END} (mean +/- SE)

SV at HD_{END} (mean +/- SE)

CBV at HD_{END} (mean +/- SE)
Figure 5

- CO (mean +/- SE)
- MAP (mean +/- SE)
- HR (mean +/- SE)
- TPR (mean +/- SE)
- SV (mean +/- SE)
- CBV (mean +/- SE)
Appendix I

Statistical details

Intradialytic CV parameters (CO, SV, TPR, CBV, MAP, and HR) within the first and last 30 minutes of HD, changes in intradialytic CV parameters, pre-/postdialytic blood pressures and heart rate, ultrafiltration volume, preHD weight and plasma angiotensin II levels were analysed based on a multivariate repeated measurements model (xtmixed) which allows for missing values and drop-out, and with visit (baseline, 1 week, 3 months, 6 months, 9 months and 12 months) and drug (placebo or ARB) and the interaction between them as factors. An approximate test for the hypothesis of equal standard deviations and correlations in the two groups was performed and the analysis was adjusted according to whether or not equal standard deviations and correlations were achieved. Model validation was performed by comparing observed and expected within subject standard deviations and correlations and by inspecting QQ-plots. Consequently, the two groups were compared regarding the development over time using four different models:

Model 1: Different development over time; Model 2: Parallel curves (same development over time); Model 3: Equal levels in the two groups; Model 4: Constant curves (no change over time).

A likelihood ratio test (LR-test) was used to compare the models in order to describe the development over time. The first test compared Model 1 with Model 2. If the test was non-significant, we assumed parallel curves (same development over time). In case of parallel curves, we proceeded testing whether equal levels could be assumed. This was done by testing Model 2 versus Model 3. Finally, in case of equal levels in the two groups we tested whether there was a change over time (constant curves) by comparing Model 3 with Model 4. Pairwise comparisons between and within the placebo and ARB group were based on estimates from Model 1.
### Appendix II

Placebo vs. ARB multivariate repeated measurements results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test for parallel curves</th>
<th>Test for equal levels</th>
<th>Test for constant level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$P$</td>
<td>$P$</td>
<td>$P$</td>
</tr>
<tr>
<td><strong>BP and dialysis parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predialytic systolic BP</td>
<td>0.051</td>
<td>0.418</td>
<td><strong>0.005</strong></td>
</tr>
<tr>
<td>Predialytic diastolic BP</td>
<td>0.536</td>
<td>0.274</td>
<td><strong>0.009</strong></td>
</tr>
<tr>
<td>Predialytic heart rate</td>
<td>0.136</td>
<td>0.743</td>
<td>0.525</td>
</tr>
<tr>
<td>Predialytic weight</td>
<td>0.083</td>
<td>0.378</td>
<td>0.674</td>
</tr>
<tr>
<td>Ultrafiltration</td>
<td>0.142</td>
<td>0.307</td>
<td>0.062</td>
</tr>
<tr>
<td>Urine output</td>
<td>0.134</td>
<td>0.260</td>
<td><strong>0.004</strong></td>
</tr>
<tr>
<td>Postdialytic systolic BP</td>
<td>0.219</td>
<td>0.708</td>
<td>0.448</td>
</tr>
<tr>
<td>Postdialytic diastolic BP</td>
<td>0.470</td>
<td>0.936</td>
<td>0.232</td>
</tr>
<tr>
<td>Postdialytic heart rate</td>
<td><strong>0.031</strong></td>
<td><strong>0.045$^a$</strong></td>
<td>0.174$^b$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1$^{st}$ CO measurement</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac output</td>
<td>0.981</td>
<td>0.433</td>
<td>0.458</td>
</tr>
<tr>
<td>Mean blood pressure</td>
<td>0.286</td>
<td>0.580</td>
<td>0.175</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0.637</td>
<td>0.381</td>
<td>0.227</td>
</tr>
<tr>
<td>Total peripheral resistance</td>
<td>0.948</td>
<td>0.768</td>
<td>0.869</td>
</tr>
<tr>
<td>Central blood volume</td>
<td>0.875</td>
<td>0.070</td>
<td><strong>0.008</strong></td>
</tr>
<tr>
<td>Stroke volume</td>
<td>0.950</td>
<td>0.220</td>
<td>0.338</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2$^{nd}$ CO measurement</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac output</td>
<td>0.839</td>
<td>0.544</td>
<td>0.206</td>
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<tr>
<td>Mean blood pressure</td>
<td>0.833</td>
<td>0.792</td>
<td>0.515</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0.808</td>
<td>0.968</td>
<td>0.271</td>
</tr>
<tr>
<td>Total peripheral resistance</td>
<td>0.509</td>
<td>0.215</td>
<td>0.162</td>
</tr>
<tr>
<td>Central blood volume</td>
<td>0.833</td>
<td>0.286</td>
<td><strong>0.005</strong></td>
</tr>
<tr>
<td>Stroke volume</td>
<td>0.764</td>
<td>0.253</td>
<td>0.066</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta$(2$^{nd}$-1$^{st}$ CO measurement)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta$Cardiac output</td>
<td>0.620</td>
<td>0.946</td>
<td>0.423</td>
</tr>
<tr>
<td>$\Delta$Mean blood pressure</td>
<td>0.095</td>
<td>0.129</td>
<td>0.106</td>
</tr>
<tr>
<td>$\Delta$Heart rate</td>
<td>0.842$^\dagger$</td>
<td><strong>0.035</strong></td>
<td>0.221$^a$</td>
</tr>
<tr>
<td>$\Delta$Total peripheral resistance</td>
<td>0.212</td>
<td>0.189</td>
<td>0.680</td>
</tr>
<tr>
<td>$\Delta$Central blood volume</td>
<td>0.433</td>
<td>0.236</td>
<td>0.275</td>
</tr>
<tr>
<td>$\Delta$Stroke volume</td>
<td>0.707</td>
<td>0.291</td>
<td>0.262</td>
</tr>
</tbody>
</table>

BP: Blood pressure; a) Model 2 (parallel curves) vs. Model 4 (no change over time); b) Model 1 (different development over time) vs. Model 4 (no change over time); $^\dagger$ Parallel curves was assumed (Model 2) with mean difference 2.4(0.2-4.6) bpm ($P = 0.03$)
### Adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n=41)</th>
<th>ARB (n=41)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious adverse events (total number)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with at least 1 SAE (n)</td>
<td>75</td>
<td>54</td>
<td>0.33</td>
</tr>
<tr>
<td>Death (n)</td>
<td>29</td>
<td>27</td>
<td>0.60</td>
</tr>
<tr>
<td>Infection (n)</td>
<td>23</td>
<td>23</td>
<td>1.00</td>
</tr>
<tr>
<td>Cardiovascular events (n)</td>
<td>18</td>
<td>14</td>
<td>0.90</td>
</tr>
<tr>
<td>Low blood pressure (n)</td>
<td>0</td>
<td>3</td>
<td>0.07</td>
</tr>
<tr>
<td>High blood pressure (n)</td>
<td>3</td>
<td>2</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>Adverse events (total number)</strong></td>
<td>558</td>
<td>563</td>
<td>0.80</td>
</tr>
<tr>
<td>Low blood pressure (n)</td>
<td>7</td>
<td>9</td>
<td>0.58</td>
</tr>
<tr>
<td>High blood pressure (n)</td>
<td>8</td>
<td>7</td>
<td>0.80</td>
</tr>
<tr>
<td>Hyperkalaemia (p-potassium ≥ 6 mmol/L) (n)</td>
<td>5</td>
<td>8</td>
<td>0.36</td>
</tr>
<tr>
<td>Cardiopulmonary symptoms (n)</td>
<td>29</td>
<td>27</td>
<td>0.64</td>
</tr>
<tr>
<td>Headache (n)</td>
<td>7</td>
<td>10</td>
<td>0.41</td>
</tr>
<tr>
<td>Dizziness (n)</td>
<td>15</td>
<td>14</td>
<td>0.82</td>
</tr>
<tr>
<td>Gastrointestinal symptoms (n)</td>
<td>25</td>
<td>19</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Intradialytic hypotension (total number)</strong></td>
<td>22</td>
<td>25</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Serious adverse events, adverse events and intradialytic hypotension are shown as total number of events (compared by Wilcoxon rank sum test) followed by the number of patients experiencing each of the selected events (compared by Chi² test). Indication for categorizing low or high blood pressure as an adverse event was not predefined in the protocol, but it was chosen by the investigator e.g. if an extra control visit was considered necessary. Intradialytic hypotension was defined as symptomatic hypotension requiring administration of intravenous fluid or preterm ending of the dialysis session.

SAE: Serious adverse event
Appendix IV

Compliance based on tablet counts

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>ARB</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-compliance</td>
<td>%</td>
<td>n Mean±SD</td>
<td>n Mean±SD</td>
</tr>
<tr>
<td>Non-compliance&gt;10%</td>
<td>%</td>
<td>40 a 4±9</td>
<td>41 3±6</td>
</tr>
<tr>
<td>Intake &lt; expected</td>
<td>%</td>
<td>32 6±8</td>
<td>26 5±7</td>
</tr>
<tr>
<td>Intake &gt; expected</td>
<td>%</td>
<td>7 -3±6</td>
<td>10 -1±2</td>
</tr>
<tr>
<td>Pause and/or change of dose</td>
<td>n(%)</td>
<td>9(23%)</td>
<td>13(32%)</td>
</tr>
<tr>
<td>Days on 1 tablet</td>
<td>n</td>
<td>40 a 23±25</td>
<td>41 48±3</td>
</tr>
<tr>
<td>Days on 2 tablets</td>
<td>n</td>
<td>40 a 292±110</td>
<td>41 230±140</td>
</tr>
<tr>
<td>Tablets consumed</td>
<td>n</td>
<td>40 a 588±217</td>
<td>41 498±254</td>
</tr>
<tr>
<td>Expected consumption</td>
<td>n</td>
<td>40 a 608±216</td>
<td>41 508±257</td>
</tr>
<tr>
<td>Days without &lt; 2 weeks</td>
<td>n</td>
<td>40 a 0.0±0.0</td>
<td>41 0.2±1.1</td>
</tr>
<tr>
<td>Days without &gt; 2 weeks</td>
<td>n</td>
<td>40 a 1±4</td>
<td>41 3±8</td>
</tr>
</tbody>
</table>

SD: standard deviation; a) n=40 in the placebo group due to drop out of one patient after baseline.

Figure 6

Figure 6 legend

*) 0.05 > P ≥ 0.01 vs. baseline within the ARB group

****) P < 0.001 vs. baseline within the ARB group

†) 0.05 > P ≥ 0.01 placebo vs. ARB; ‡) 0.01 > P ≥ 0.001 placebo vs. ARB