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 intradialytic 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.

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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

! 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
ECG = electrocardiogramme
FA = femoral artery
GCP = good clinical practice
HD = haemodialysis
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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TABLE 1

Eligibility criteria.

Inclusion criteria
Haemodialysis patient
Haemodialysis treatment for a maximum of 12 months
Aged 18 yrs or older
Urine volume > 300 ml/24 h
Contraception if fertile woman
Informed consent
Exclusion criteria
Allergy to angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers or renin inhibitors
Predialytic systolic blood pressure < 110 mmHg prior to admission
Left ventricular ejection fraction < 30%
Myocardial infarction or unstable angina pectoris during the last three months prior to admission
Unable to comprehend the aims of the project and follow instructions
Pregnancy

TABLE 2

Summary of study visits and measurements.

	Screening	2 + 6 weeks	Monthly	Visit pre-F[a]	Visit A-F[b]
Blood pressure	x	x	x	x	x
Heart rate, body weight		x	x	x	x
Blood sampling		x ([K^+] only)	x		x
Urine volume, 24 h, GFR	x				X
Echocardiography	x			x	
PWA + PWV				x	x
HRV					x
Cardiac output					x
ECG					x
KDQoL-SF (visits A + D + F)					x
Biobank (blood and urine)					x
Adverse events registration		x	x		x
Compliance registration		x	x		x

ECG = electrocardiogramme; GFR = glomerular filtration rate; HRV = heart rate variability; KDQoL-SF = Kidney Disease Quality of Life – Short Form; PWA = pulse wave analysis; PWV = pulse wave velocity.
a) Performed the day after a haemodialysis session between 11 months and visit F.
b) Visit A = baseline, visit B = 1 week, visit C = 3 months, visit D = 6 months, visit E = 9 months, visit F = 12 months.

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, equalling 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

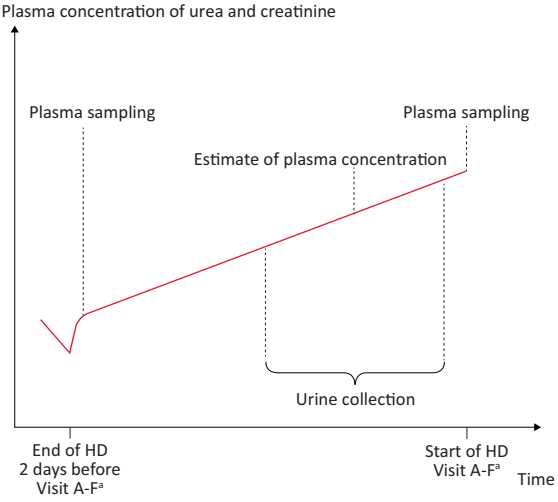
The patients are investigated at baseline and after one week to elucidate acute effects of irbesartan, and thereafter every three months for one year (visits A-F). Visits A-F are carried out in the morning two days after HD. Visits after two weeks, one month, six weeks, two months and then every month 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-

FIGURE 1

Sampling of blood and urine in relation to haemodialysis sessions.



HD = haemodialysis
a) Visit A = baseline; visit B = 1 week; visit C = 3 months, visit D = 6 months, visit E = 9 months, visit F = 12 months.

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 m^2.

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 cineloop format defined by the R wave on the corresponding ECG for off-line analyses using EchoPac software (GE Healthcare).

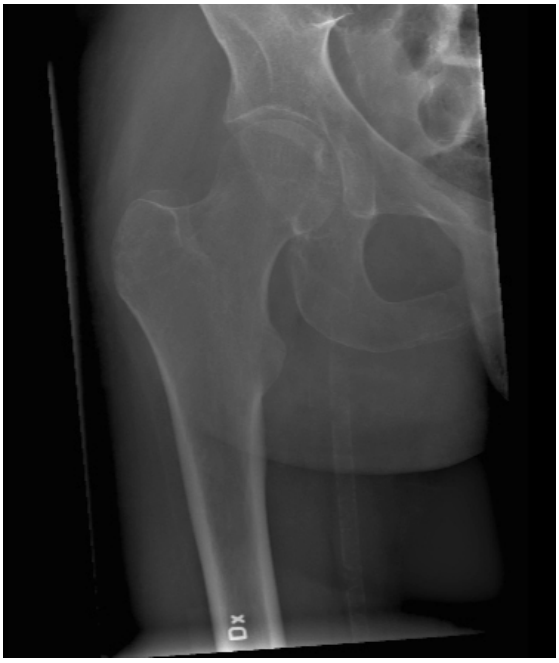
Quantification of cardiac chamber size, heart valve pathology, LV mass and function are done with treatment allocation concealment by one experienced examiner in accordance with current guidelines [12].

TABLE 3

Biochemical measurements.

Blood samples monthly and visits A-F	Visits A-F	Urine samples, visits A-F
Albumin	Adrenaline	Albumin
Calcium	Aldosterone	Creatinine
CO_2/HCO_3^-	Angiotensin II	Potassium
Creatinine	CRP	Sodium
Phosphate	Glucose	Urea
Potassium	Haemoglobin A_{1c}	
Sodium	IL[a]	
Urea	Lipids[b]	
	Liver function tests[c]	
	Noradrenaline	
	NT-proBNP	
	Renin	
	TGF-β	

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 phosphatise 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 (cfPWV) in this patient was markedly increased (cfPWV ≈ 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 m^2 without ARB [6]. Assuming a RRF decline = 4 ml/min/1.73 m^2/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 m^2 (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/m^2 in the ARB treated subjects, 8 g/m^2 in the placebo group and a SD of 19 g/m^2 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 anaemia 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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CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk.

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