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Urinary proteomics combined with home blood pressure telemonitoring for health care reform trial: rational and protocol

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RESEARCH ARTICLE

Urinary proteomics combined with home blood pressure telemonitoring for health care reform trial: rational and protocol

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ABSTRACT

Background: Hypertension and diabetes cause chronic kidney disease (CKD) and diastolic left ventricular dysfunction (DVD) as forerunners of disability and death. Home blood pressure telemonitoring (HTM) and urinary peptidomic profiling (UPP) are technologies enabling prevention.
Methods: UPRIGHT-HTM (Urinary Proteomics Combined with Home Blood Pressure Telemonitoring for Health Care Reform [NCT04299529]) is an investigator-initiated 5-year clinical trial with patient-centred design, which will randomise 1148 patients to be recruited in Europe, sub-Saharan Africa and South America. During the whole study, HTM data will be collected and freely accessible for patients and caregivers. The UPP, measured at enrolment only, will be communicated early during follow-up to 50% of patients and their caregivers (intervention), but only at trial closure in 50% (control). The hypothesis is that early knowledge of the UPP risk profile will lead to more rigorous risk factor management and result in benefit. Eligible patients, aged 55–75 years old, are asymptomatic, but have $\geq$5 CKD- or DVD-related risk factors, preferably including hypertension, type-2 diabetes, or both. The primary endpoint is a composite of new-onset intermediate and hard cardiovascular and renal outcomes. Demonstrating that combining UPP with HTM is feasible in a multicultural context and defining the molecular signatures of early CKD and DVD are secondary endpoints.
Expected outcomes: The expected outcome is that application of UPP on top of HTM will be superior to HTM alone in the prevention of CKD and DVD and associated complications and that UPP allows shifting emphasis from treating to preventing disease, thereby empowering patients.

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Supplemental data for this article can be accessed here.

Background

The epidemiological transition is a global demographic change characterised by a longer life expectancy, but the number of years added to the human life comes at a cost of lower quality of life, i.e. a greater number of years lived with disability [1]. This demographic change represents a huge social and economic challenge. Health care will have to adjust to remain sustainable by moving emphasis from the resource-intensive and costly management of established disease to prevention. Given this context, UPRIGHT-HTM (Urinary Proteomics Combined with Home Blood Pressure Telemonitoring for Health Care Reform [NCT04299529]) focuses on chronic kidney disease (CKD) and diastolic left ventricular (LV) dysfunction (DVD), as archetypes of chronic age-related diseases, and as outlined below on two diagnostic modalities that might contribute to an improved prevention of CKD and DVD, as forerunners of premature mortality and morbidity.

Blood pressure telemonitoring

Guidelines unanimously recommend out-of-the-office monitoring as the technique of choice to assess blood pressure and to diagnose and manage hypertension [2–4]. According to expert committees, home blood pressure telemonitoring (HTM) complies with the state-of-the-art for the long-term follow-up of blood pressure [5–7]. HTM offers several of the well-recognized advantages of the more complex approach of ambulatory monitoring. The greater number of readings and the absence of the white-coat effect contribute to the higher diagnostic accuracy as compared with office blood pressure readings. If automated devices are used, the self-recorded blood pressure is free of observer bias [8]. Two randomised clinical trials, i.e. the Treatment of Hypertension Based on Home or Office Blood Pressure study (THOP) [9] and the Home Versus Office Measurement – Reduction of Unnecessary Treatment (HOMERUS) trial [10], demonstrated that adjustment of antihypertensive treatment based on the self-measured home blood pressure avoids needless treatment of white-coat hypertensive patients with no differences in general well-being or target organ damage. More recently, the HOMED-BP trial (Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure) proved that the long-term HTM was well received by hypertensive patients and that adjusting treatment based on HTM is feasible [11].

Urinary proteomics

Urine is a stable biofluid [12] and contains over 20,000 low-molecular-weight peptides, which can be analysed on a 10-ml mid-morning urine sample without additional manipulation, such as proteolysis. Approximately 60% of the total mass of urinary peptides consist of collagen fragments [13]. CKD and DVD are characterised by a disturbed balance between collagen synthesis and breakdown, leading to fibrosis and remodelling of the extracellular matrix (ECM) [14]. The urinary peptidomic profile (UPP) does not undergo significant changes when urine is stored for 6 h at room temperature [15] or for 3 days at 4°C [16]. For studies running over a long time period, urine can be stored for years at −20 °C without UPP alteration [12]. The UPP is well characterised and reference standards are available [17]. These characteristics facilitate the application of UPP in clinical practice or in clinical trials, as for instance evidenced by the PRIORITY study [18].

UPP based on capillary electrophoresis coupled to mass spectrometry (CE-MS) is a powerful technology to improve the management of chronic diseases (Figure S1). The CE-MS platform enables the separation of naturally occurring peptides in a single step, using a strong electrical field and subsequent detection by mass spectrometry [19,20]. It is a robust and operator-independent technology, allowing the high-resolution detection of several thousands of peptides ($0.8 \leq 18$ kDa) in a single urine sample. A detailed description of urine sample preparation, proteome analysis by CE-MS, data processing and sequencing of the urinary peptides allowing the identification of parental proteins has been published [19,20] and is summarised in the online only Data Supplement.

Design

UPRIGHT-HTM is an investigator-initiated randomised clinical trial, comparing UPP combined with HTM (experimental group) with HTM alone (control group) in risk profiling and as guide to starting or intensifying management of risk factors to prevent established disease. This multicentre trial will run in different countries and continents, is therefore open for patients of multiple ethnicities, who will be randomised in a 1:1 proportion to the experimental or control group. UPRIGHT-HTM complies with the Helsinkyi declaration, General Data Protection Regulations, and received or is seeking ethical approval in the countries where the study will be running (currently available ethics approvals listed at https://www.appremed.org/news).

Overview

In short, UPRIGHT-HTM consists of: (i) a run-in period of variable length (2–5 weeks or longer) during which the eligibility of patients will be checked; (ii) after stratification for centre and sex a randomised follow-up period informed by either HTM plus UPP (experimental group) or UPP alone (control group); and (iii) for patients leaving randomised follow-up prematurely a supervised follow-up period during which the incidence of the primary composite endpoint will be further monitored in consenting patients (Figure 1). The incidence of endpoints during supervised follow-up will contribute to the intention-to-treat analysis.

Inclusion and exclusion criteria

UPRIGHT-HTM aims to enrol 1148 asymptomatic patients with high-risk profile, based on their clinical history, biochemical data, and routine technical examinations as available in medical records or to be performed in compliance with current guidelines.

Inclusion criteria

Asymptomatic patients whose age ranges from 55 to 75 (inclusive) can be enrolled, after written informed consent has been obtained. In addition to age, patients must have at least five additional guideline-defined risk factors, preferably including hypertension, type-2 diabetes mellitus (T2DM), or both (Table 1). Furthermore, patients must have an email address and internet access *via* smartphone (only android will be supported), tablet, or laptop or desktop computer. Patients must be willing to engage in HTM for the duration of the study.

Exclusion criteria

Type-1 diabetic patients do not qualify for UPRIGHT-HTM. Study-specific exclusion criteria include symptoms related to renal or LV dysfunction, stage-3B CKD (i.e. eGFR >45 ml/min/1.73 m^2), a history of cardiovascular or renal disease within 1 year prior to enrolment, symptomatic patients, presence of microalbuminuria

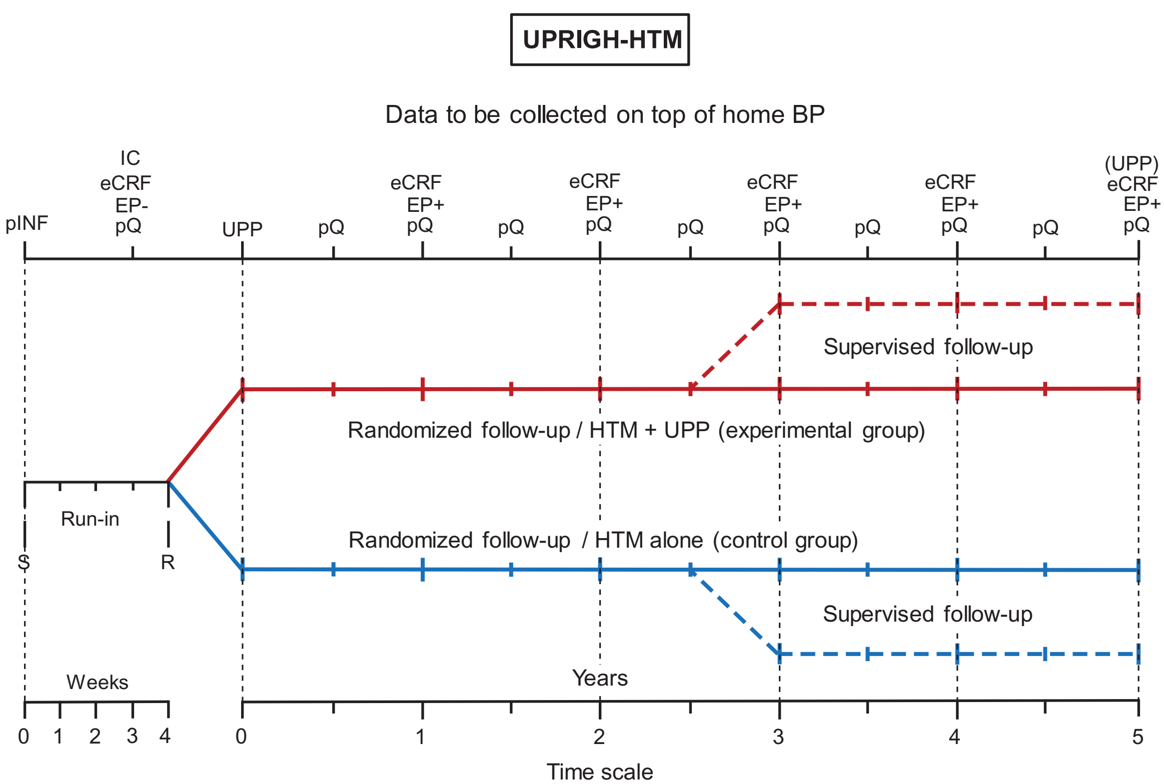

Figure 1. UPRIGHT-HTM design. eCRF: electronic report forms completed by investigators; EP: absence (-)/incidence (+) of the components of the primary endpoint during the run-in/follow-up periods, respectively; IC: written informed consent; pINF: patients received the UPRIGHT-HTM information sheet and were familiarised with operating the blood pressure monitoring devices; pQ: patient-administered questionnaires; R: randomisation after stratification for centre and sex; S: initial screening; UPP: urinary proteomic profiling (mandatory prior to randomisation – optional at the end of follow-up).

Table 1. Risk factors.

• type-2 diabetes mellitus	• *"silent"* plaques on arterial imaging
• fasting glycaemia ≥100 mg/dl	• ankle-brachial index <0.9
• random glycaemia ≥200 mg/dl	• office hypertension (≥140/≥90 mm Hg) (last of three consecutive readings)
• positive oral glucose tolerance test	• home hypertension (≥135/≥85 mm Hg)
• HOMA-IR >2.8	• 24-h ambulatory hypertension (≥120/≥80 mm Hg
• metabolic syndrome	• masked hypertension
• fasting serum insulin ≥21 μU	• tachycardia (≥80 beats per minute)
• HbA1c ≥6.5%	• Sokolow-Lyon index >3.5 mV
• body mass index 30.0-39.9 kg/m2	• Cornell product >2444 mV × ms
• waist circumference ≥88/102 cm (♀/♂/)	• peripheral ECG lead aVl >1.2 mV
• current smoking	• left ventricular mass index on echocardiography ≥95 /≥115 g/m2 (♀/♂/)
• total cholesterol >190 mg/dl	• family history of premature cardiovascular disease (women before 65 years/men before 55 years)
• high-density lipoprotein cholesterol <46/<40 mg/dl (♀/♂/)	• serum creatinine ≥1.2/≥1.3 mg/dl (♀/♂/)
• low-density lipoprotein cholesterol >115 mg/dl	• eGFR <60 ml/min/1.73 m2
• non-HDL cholesterol ≥130 mg/dl	• sedentary lifestyle
• serum triglycerides >150 mg/dl	
• aortic pulse wave velocity >10 m/s	
• Carotid intima-media thickness ≥900 μ	

Risk factors were taken from the 2018 European guideline for the management of hypertension (reference 3). To conduct an oral glucose tolerance test, WHO recommends a 75-gram orally administered dose of glucose. The fasting plasma glucose should be less than 100 mg/dl. To be normal, the 1-hour and 2-hour plasma glucose levels should be <180 mg/dl and <140 mg/dl, respectively. HOMA-IR indicates Homeostatic Model Assessment of Insulin Resistance and is computed as (fasting glucose in mg per decilitre × insulin in μU)/405 (PMID 1895955). Metabolic syndrome is the combination of an increased waist circumference, hypertriglyceridaemia (≥150 mg/dl), decreased high-density lipoprotein cholesterol (<50 mg/dl in women and <40 mg/dl in men), office hypertension (blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic), and a (fasting) plasma glucose of ≥100 mg/dl. Masked hypertension is a normal office blood pressure associated with an increased out-of-the-office blood pressure. Physical inactivity in older individuals is engaging in less than 150 min of moderate-intensity aerobic exercise (3–6 METS) throughout the week (https://www.who.int/dietphysicalactivity/physical-activity-recommendations-65years.pdf?ua=1). One metabolic equivalent (MET) is defined as the amount of oxygen consumed while sitting at rest and is equal to 3.5 ml O_2 per kilogram body weight per minute (PMID 2204507).

combined with systolic or diastolic LV dysfunction at enrolment, and hemodynamic significant valvular heart disease. Patients who during the run-in period have difficulties in completing the electronically administered questionnaires or are not adherent to HTM will not be randomised. Patients with impracticable echocardiographic window or with atrial fibrillation or flutter or frequent extrasystoles, will also be excluded, because these conditions do not allow a reliable assessment of diastolic LV function. Patients with stage-3A CKD or asymptomatic DVD at enrolment qualify for entry, but not those with DVD combined with CKD. Other exclusion criteria are common to all research in humans and include serious previous or concurrent cardiovascular or noncardiovascular disease, cancer within 5 years prior to enrolment, suspected substance abuse, psychiatric illness, or participation in other studies. However, patients who experienced a cardiovascular or noncardiovascular event or a renal complication one year or longer before being considered for randomisation qualify for entry, if they fully recovered and are symptomless.

Primary and secondary endpoints

The primary endpoint is a composite of intermediary and hard cardiovascular-renal endpoints.

Intermediary endpoints

The intermediate endpoints are: new-onset microalbuminuria, doubling of serum creatinine, a decrease in the estimated glomerular filtration rate (eGFR) by 30% or more or eGFR declining below 45 ml/min/1.73 m^2 new-onset hypertensive retinopathy (Keith-Wagener classification [21] or diabetic retinopathy [22], electrocardiographic or echocardiographic LV hypertrophy, cardiac arrhythmias (atrial fibrillation or flutter, frequent ventricular or supraventricular extrasystoles present in ≥20% of cardiac cycles [23], and DVD [24,25]. eGFR will be derived from serum creatinine, using the Chronic Kidney Disease Epidemiology Collaboration equation [26]. CKD will be staged according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guideline [27].

In line with the PRIORITY study, the presence of microalbuminuria should be confirmed in two of three morning urine samples collected on consecutive days [18]. In low-resource or primary care settings a validated dipstick test is acceptable, but a positive dipstick test should preferably be confirmed by measurment of the albumin-to-creatinine ratio [28–30]. In asymptomatic patients, atrial peptides do not provide reliable diagnostic information on the presence of silent LV dysfunction [31,32]. Diagnosis of DVD in the preclinical phase (heart failure stage B) requires echocardiography. DVD is an abnormally low age-specific transmitral E/A ratio, indicative of impaired relaxation, or a mildly-to-moderately elevated left ventricular filling pressure (E/e' >8.5) with normal or decreased age-specific E/A ratio [24,25]. The ejection fraction should be 50% or higher [24,25]. Higher e' and lower E/e’ on transmitral/tissue Doppler echocardiographic imaging, respectively, reflect faster early diastolic LV relaxation and slower LV filling pressure (Figure S2).

Hard cardiovascular-renal endpoints

The hard cardiovascular endpoints include cardiovascular mortality (ICD10: I00-I99), and nonfatal myocardial infarction (I21, I22), nonfatal hospitalised heart failure (I50), nonfatal stroke, not including transient ischaemic attack (I60-I63), and coronary or peripheral revascularisation. The hard renal outcomes include macroalbuminuria, the need for renal-replacement therapy, and death due to renal causes (N17, N18), as defined in recent outcome trials [33].

Sample size

The population [8,34–37] and patient [38–42] studies and the randomised clinical trials [18,43–49] informing the sample size calculations are summarised in the online-only Data Supplement. Sample size calculations were based on the log-rank test, using SAS software, version 9.4. We assumed a study duration of 5 years with patients being recruited over two years, an annual dropout rate of 2.5%, a 4-year primary endpoint rate of 20%, and a risk reduction of 30% in the experimental group. Under these assumptions, with the α-level set at 0.05 and power at 0.80, 1148 patients would have to be randomised in a 1:1 proportion to the experimental and control group, respectively (574 per group). Sample sizes based on alternative assumptions appear in Table S1.

Data collection

UPRIGHT-HTM will run as a patient-centred study, mainly positioned at the patients’ homes and the practices of their caregivers by implementation of modern information technology, under supervision of the patients’ own primary or specialist care providers.

Data collected by patients

Most data will be collected at the patients’ homes *via* web-based applications. For HTM, patients will use validated [50] OMRON HEM 9210-T (Europe) or OMRON HEM 9210 T-E (other regions) monitors (Omron Healthcare Co., Ltd., Kyoto, Japan) fitted with a cuff that accommodates the range of adults upper-arm circumferences. Each patient identification number will be uniquely linked with the serial number of the HTM device handed over to the patient. If a patient opts to drop out from the randomised trial or the supervised follow-up (Figure 1), the careprovider will recuperate the HTM device, check its functionality, and pass it on to another patient. Patients will be encouraged to measure their blood pressure after 5 min rest in the sitting position preferably within 1 h after awakening, before breakfast and before taking any medication, if possible, daily. Patients who fail to practice HTM at less than weekly intervals, will receive automatically generated email reminders but will not be excluded from the intention-to-treat analysis.

Other data to be collected from patients during the run-in period, at randomisation and at 6-monthly intervals during the study (Figure 1) *via* the web-based interface are the EQ-5D quality of life questionnaire (www.euroqol.org) and the World Health Organisation (G. Rose) questionnaires on chest pain, dyspnoea, claudication, cough and expectorations [51]. Both questionnaires were translated into all required local languages. Logistics will be set up in such a way that patients can collect a 10-ml mid-morning urine sample for UPP at their homes or at the practice of their caregiver. These urine samples, to be collected at baseline, will be stored locally at -20 °C and dispatched in batches to Mosaiques-Diagnostics GmbH, Hannover, Germany, for UPP analysis. Investigators will be encouraged to collect an optional 10-ml urine sample from patients, when they leave the study allowing a longitudinal UPP assessment.

Data collected by caregivers

Caregivers will be responsible for recruiting patients, obtaining informed written consent, distributing the HTM devices (one device per patient) and the UPP test kits, and for collecting depersonalised clinical data *via* web-administered electronic case report forms (eCRFs). Caregivers are free in organising the follow-up and nonpharmacological and pharmacological treatment of their patients according to current national or international guidelines. The online-only Data Supplement provides suggestions for the management of hypertension (Figure S3), antidiabetic therapy (Figure S4) and statin treatment (Table S2).

At screening, caregivers will explain the objectives of the UPRIGHT-HTM trial to patients verbally and by handing over the patient information leaflet together with the HTM monitor. They will complete an eCRF to document each patient’s anthropometrics, office blood pressure and heart rate. This information is mandatory, because it allows comparing screened patients not randomised with those randomised. Prior to randomisation, caregivers will collect informed written consent from each patient willing to be enrolled into the study. The caregivers will locally archive the consent forms, only available on paper to protect the patients' privacy. Prior to randomisation, caregivers will complete the prerandomisation eCRF showing that enrolled patients meet all eligibility criteria. Other information to be collected *via* the prerandomisation eCRF includes: (i) anthropometrics; (ii) use of antihypertensive, lipid-lowering, antidiabetic and antiplatelet medications (only by drug class); (iii) the patient's medical history; and (iv) and the presence *vs* absence of components of the primary endpoint. During follow-up, the same eCRF will be used at annual follow-up visit, the end-of-the-randomised follow-up visit, and the end-of-trial close-out visit. Thus, the contents of all follow-up eCRFs are similar to that used prior to randomisation. These eCRFS allow reporting the incidence of the components of the primary endpoint, and if applicable, the reason why a patient wishes to discontinue randomised follow-up, or the justification why a caregiver withdrew a patient from randomised or supervised follow-up (Figure 1).

On clinical indication while observing guidelines, probably at baseline and annual intervals for most patients, caregivers will collect urine samples required for the diagnosis of incident microalbuminuria and refer patients for echocardiography (Table S3) at baseline and at least once during follow-up. Routine biochemical data collected within 6 to 9 months of the due date of the eCRF qualify, so that in most cases no blood sampling for the specific purpose of the study is necessary.

Database management and statistical analysis

For data management and statistical analysis, SAS software, version 9.4, maintenance level 5 (SAS Institute, Cary, NC, USA) will be used. The HTM readings, the electronic questionnaire data collected directly from patients and the eCRFs completed by caregivers will reach the study coordinating team *via* the WiPam platform (www.wipam.net) as CSV (coma-separated values) or XML (extensible mark-up language) files. The UPP data will be emailed to study team as Excel (XLS or XLSX) email attachments. After quality control, the CSF, XML, XLS and XLSX files will be directly imported into a SAS database, using the SAS PC File Server, version 9.4.

Intention-to-treat and per-protocol analysis

The main analysis will be implemented using the intention-to-treat dataset. This analysis will address the intermediate and hard events making up the primary composite endpoint, which occurred during randomised and supervised follow-up (Figure 1). This dataset will include all randomised patients, who were free of the endpoints of interest at enrolment and who had at least one endpoint assessed after randomisation, i.e. during randomised or supervised follow-up. The per-protocol dataset is a subset of the intention-to-treat dataset excluding patients randomised, but not complying with all inclusion and exclusion criteria, patients deviating from the study protocol to such extent that they might introduce bias in the analysis, and excluding the data that accrued during supervised follow-up (Figure 1).

Stratification and randomisation

Eligible patients will be stratified by centre and sex and subsequently randomised in a 1:1 proportion within each stratum to the experimental group (HTM plus UPP) and control group (HTM alone), using a random function and permuted blocks. Stratification and randomisation will be automated *via* the WiPam platform.

Masking

Caregivers will know the group to which their patients were randomly assigned. In the two groups, both patients and caregivers will have full access to the HTM data. In both treatment groups, patients and caregivers will be informed about the UPP risk profile. However, in the experimental group, patients will be informed about their UPP risk profile shortly after randomisation and in the control group, only when they leave randomised or supervised follow-up or at the completion of the trial. As implemented in other randomised controlled trials [52,53], the central study coordinating team will run interim analyses as part of the quality control programme, excluding any component of the primary endpoint, and have these analyses published in peer-reviewed journals to report on the progress of the trial. However, the study coordinating team will remain blinded to the primary endpoint and all of its components until completion of the trial and until the statistical analysis plan has been written and all datasets have been cleaned and frozen for the final analysis.

For endpoint validation, as implemented in other investigator-initiated trials [54], each centre will appoint two junior residents and one senior supervisor, who will remain blinded to randomisation. Using a special eCRF, at annul intervals, the study coordinating team will request validation of potential endpoints, as reported *via* the follow-up eCRFs.

Statistical analysis

The primary and secondary endpoints measured on a continuous scale will be analysed using mixed models. Between-group comparisons will be executed with adjustment for baseline. The fixed effects in the model include randomisation group and, if there is imbalance between the randomised groups at baseline, confounders. To account for the correlation between a patient's repeated blood pressure and other measurements, models will also account for patient-level random effects. Centre-level random effects will be used to model the possible correlation of measurements between patients recruited at the same centre. Binary endpoints, such as the incidence of endpoints, will be analysed by means of McNemar's test and hierarchical mixed-effects regression models. All statistical tests will be two-sided.

Molecular analyses

The primary analyses will focus on the urinary markers CKD273 and HF1, which have been widely validated and for which diagnostic thresholds have been established and published in the peer-reviewed literature [18,32,55,56]. However, in pursuit of the secondary objective to gain deeper insight in the molecular pathophysiology of early CKD and DVD, the urinary peptides with known amino-acid sequence allowing identification of the parent proteins will be carried through to further analyses as summarised in Table S4. Peptides linked to a shared pathophysiological process can then be combined in novel multidimensional classifiers, which after validation can be proposed for clinical use.

Discussion

UPRIGHT-HTM is an investigator-steered, multicentre, randomised trial set up in a multicultural context. The main objective is to assess the value of UPP administered on top of HTM compared with HTM alone in risk stratification and as guide to early intervention.

Patient-centred design

UPRIGHT-HTM is a patient-centred minimally intrusive study. Giving patients access to health-related tests is a double-edged asset, because test results can cause both anxiety or enhance well feeling [57–60]. However, a literature review revealed that, in general, web-based access to personal health-related information does not increase the patients' anxiety levels, even in women with breast cancer given access to laboratory results and imaging studies [58]. What the studies revealed is that there is a great need to enhance the patients' comprehension of results [58]. HTM is a powerful instrument in educating and empowering patients [61]. In a randomised clinical trial, involving 450 patients recruited at 59 primary care practices and followed up for 12 months, self-monitoring and self-titration of antihypertensive drugs lowered systolic blood pressure 8.8 mm Hg more than usual care based on office blood pressure measurement [62]. Moreover, self-measurement of blood pressure increases adherence to antihypertensive drugs [63], allows detecting symptoms that occur between clinic visits and reduces the number of clinic visits required for optimising drug treatment [64]. However, self-titration of medication was not considered as a practicable option in UPRIGHT-HTM, because of the multi-ethnic and multicultural settings of the study sites.

Feasibility

Both CKD and DVD are associated with specific UPP profiles. The multidimensional marker CKD273 predicts progression of CKD earlier than microalbuminuria does [56]. HF1 is a marker of subclinical DVD [65]. Both CKD273 [55,56] and HF1 [65] have been extensively validated in longitudinal patient and population studies, and CKD273 also in the framework of the PRIORITY study [18]. Pharmacological treatment, including antihypertensive, lipid-lowering, antidiabetic and antiplatelet drugs and even immunosuppressive drugs in transplant patients [66], have no noticeable influence on the UPP or its association with study endpoints. As a working example, Figure 2 proposes how HF1 might be applied in clinical practice in asymptomatic high-risk individuals [32]. In the presence of clinical risk factors for DVD, in particular older age combined with overweight or abdominal obesity and hypertension (25.1% of the adult population [32]), HF1 might be used as a screening tool [32]. If its value is less than −0.350, managing risk factors over a 5-year time span is to be recommended.

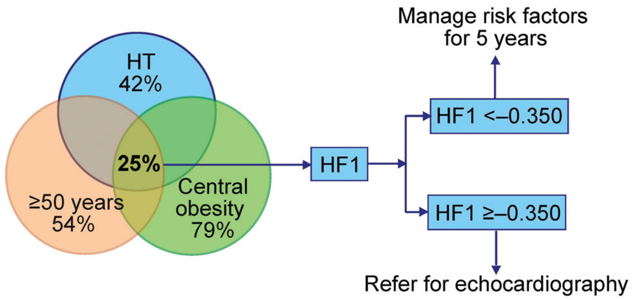

Figure 2. Proposal for the clinical application of HF1 over a 5-year horizon. In a random population sample, 25% of participants combined three major risk factors for diastolic left ventricular dysfunction. Modified and reproduced with permission from reference [32].

In contrast, if HF1 is −0.350 or higher, patients should not only have their risk factors addressed, but might be referred for echocardiography to confirm the presence of DVD [32]. An added benefit of HF1 is that the marker predicts worsening of renal function [55] and the 5-year incidence of cardiovascular and cardiac events [31]. In our studies [32,65], in line with other publications [67], N-terminal pro-B-type natriuretic peptide (NT-proBNP) did not add to the prediction of DVD over and beyond classical risk factors. Moreover, HF1 in the presence of NT-proBNP fully retained its prognostic value [32,65].

Two other considerations relate to the feasibility of URIGHT-HTM. First, drug-adherence is an important determinant of how well risk factors will be managed in the intervention and control group. Because of practicability, the clinical centres will not engage in a formal and standardised monitoring programme of drug adherence, other than the information to be collected by the caregivers and to be provided *via* the annual eCRFs. However, the home blood pressure recorded by the patients and the biochemical data, e.g. blood glucose and eGFR being mandatory fields in the eCRFs, will generate objective information on how well risk factors are being controlled. Previous experience in sub-Saharan Africa confirmed that adherence to treatment does not grossly differ compared with clinical trials in developed nations [68]. Second, UPRIGHT-HTM will be conducted in affluent communities, where drug expenses are largely covered by health insurance. However, cheap generic drugs are widely available in sub-Saharan Africa. Diuretics, the cheapest drug class, and generic long-acting calcium-channel blockers are widely available in sub-Saharan Africa and are recommended to initiate antihypertensive treatment in Blacks born and living in Africa [2–4]. This also applies to metformin, the first line agent to treat T2DM (Figure S4) [69].

Early intervention

All current guidelines state that risk factor management is the foundation for stopping progression of early towards established disease and in preventing the target organ damage and the cardiovascular-renal complications that make up the primary composite endpoint of UPRIGHT-HTM. Furthermore, guidelines concur on using angiotensin converting-enzyme inhibitors (ACEIs) in patients at risk of – or already having – CKD or heart failure with preserved ejection fraction, while angiotensin receptor blockers are indicated in ACEI-intolerant patients [5–7]. Addressing insulin resistance and glycemic control in T2DM are of primordial importance in patients at risk of DVD [24,34] and diabetic nephropathy [18]. Spironolactone did not stop progression of diabetic nephropathy in PRIORITY [18] or prevent the incidence of cardiovascular complications in patients with diastolic heart failure enrolled in the Spironolactone for Heart Failure with Preserved Ejection Fraction (TOPCAT) trial [70]. However, in the Diastolic Heart Failure (DHF) trial, a 12-month course with spironolactone improved diastolic LV function [71]. In patients with a high risk profile, such as those recruited into UPRIGHT-HTM, statins will be indicated in most (Table S2). In patients at risk of CKD, DVD or both, SGLT2-Is might be particularly indicated, if covered by health insurance. Indeed, in placebo-controlled trials of very high-risk T2DM patients, SGLT2-Is improved glycaemic control, lowered office and ambulatory blood pressure, protected against major cardiovascular and renal complications, reduced the incidence of heart failure, and lowered body weight with no risk of hypoglycaemia [33].

Molecular leads from previous studies

In stage-3 CKD [56,72], there is upregulation of mucin-1 subunit-α, a protein shed by the renal tubular epithelium [72]. Mucin-1 is a high-molecular weight (400 kDa) membrane-tethered glycoprotein [73], which normal kidneys express in the thick segment of Henle's loop and in the distal tubules and collecting ducts. The main function of mucin-1 is to shield cell surfaces by maintenance of a luminal epithelial mucobarrier [74]. Further evidence supporting mucin-1 as a marker of renal dysfunction originated from genetic studies. A frameshift mutation in the *MUC1* gene, located on chromosome 1 (1q21) [75] creates a new peptide that accumulates inside the *MUC1* expressing renal tubular cells and causes autosomal dominant medullary cystic kidney disease type-1.

With respect to DVD, the urinary proteome revealed a downregulation of WW domain-binding protein 11 [65]. The *WBP-11* gene encodes a nuclear protein, which in cell nuclei co-localises with mRNA splicing factors [76]. In cardiomyocytes, the gene product, WBP-11, interacts with the 52-amino acid integral membrane protein phospholamban (PP-1) and thereby contributes to the regulation of the trans-membrane Ca^{2+} flux *via* the Ca^{2+} pump (SERCA), which transports Ca^{2+} from the cytosol to the sarcoplasmic reticulum. Phosphorylation of PP-1 by protein kinase A and dephosphorylation by WBP-11, respectively, stimulates and inhibits SERCA [77]. Downregulation of WBP-11, as observed in DVD patients, might enhance SERCA activity and impair electromechanical coupling in the myocardium [78].

Perspectives

Governments typically invest over 95% of healthcare budgets in treatment of established disease, even though prevention generates a lower cost per additional quality-adjusted life-year [79]. If UPRIGHT-HTM fulfils the expectations underpinning its design, it will make a strong point for combining HTM with UPP as model for rigorous risk factor management to prevent target organ damage and age-related cardio-vascular-renal complications.

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