Telemonitoring blood pressure in kidney disease: a feasibility study

(Oxford Heart and Renal Protection Study-I)

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Blood pressure is an important modifiable risk factor in chronic kidney disease

Patients with chronic kidney disease (CKD) face two major hazards: premature cardiovascular morbidity and mortality, and progression to end-stage renal disease (ESRD). Observational studies and randomized trials suggest that blood pressure (BP) is a modifiable risk factor for both of these outcomes, but substantial uncertainty remains about optimal BP targets among people with CKD. In order to address this uncertainty, a large randomized trial of intensive- versus standard BP lowering is required but before this can be conducted a pilot study assessing the feasibility and safety of intensive BP-lowering among people with CKD (who are frequently resistant to BP lowering) is needed to inform the planning of a randomized trial.

Telemonitoring BP may increase the efficiency of a BP lowering trial

Telemonitoring of BP (i.e. participants measure their BP at home on an electronic sphygmomanometer that automatically uploads these measurements to a central computer via the Internet where the results are checked and actioned by trained clinicians) may improve the efficiency of a BP lowering trial by more accurately measuring usual BP and implementing actions to achieve the allocated BP target more rapidly. However, the acceptability of such telemonitoring is uncertain among patients with CKD, so a feasibility study is required before such technology can be more widely implemented.

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1 SYNOPSIS

Study Title	Feasibility study of telemonitoring blood pressure in patients with chronic kidney disease
Short Title	Telemonitoring BP in CKD
Study Design	Observational
Trial Participants	Inclusion criteria: • Age ≥18 years • eGFR ≥20 <45 mL/min/1.73m^2; *or* • eGFR ≥45 <60 mL/min/1.73m^2 and urine albumin:creatinine ratio >20 mg/mmol Exclusion criteria • Mean systolic BP <130 mmHg at Screening visit • Planned change to BP lowering therapy within the next 1 month • Acute vascular event (e.g. acute coronary syndrome, transient ischaemic attack or stroke) within last month • Medical history that might limit the patient's ability to comply with study procedures for the duration of the study
Planned sample size	At least 25 participants
Duration	3 months for each participant
Primary outcome	Proportion of participants providing complete data
Other outcomes	• Acceptability of telemonitoring • Intra- and inter-individual variability in BP • Proportion of patients reaching target BP by final follow-up. • Costs of telemonitoring

2 BACKGROUND AND RATIONALE

2.1 BP is an important modifiable risk factor in CKD

2.1.1 BP and cardiovascular risk

Patients with CKD are at substantially increased risk of cardiovascular disease.[1] Patients with CKD typically have higher BP than their peers because CKD increases BP by several mechanisms including salt and water retention, over-activity of renin-angiotensin and sympathetic nervous systems and reduced concentrations of endogenous vasodilators.[2] Observational studies in the general population have demonstrated that systolic BP is positively associated with risk of vascular disease. In middle age (40-69 years), each 20 mmHg higher usual (i.e. long-term average) systolic BP is associated with a doubling in the

risk of dying from coronary heart disease.[3] Randomized trials have demonstrated that this association is causal: lowering systolic BP by 10 mmHg reduces the risk of cardiovascular events by 20% (relative risk [RR] 0.80, 95% confidence interval [CI] 0.77-0.83).[4]

Observational studies among patients with CKD are susceptible to confounding by disease, but studies which have appropriately adjusted for this find results consistent with those in the general population (although the associations are somewhat weaker, possibly due to the high prevalence of BP lowering medication use among patients with CKD).[5] Meta-analyses of randomized trials suggest that the benefits of lowering BP in terms of reducing risk of cardiovascular disease among patients with CKD are similar to those among the general population.[4, 6] However, few participants in these trials had advanced CKD (i.e. estimated glomerular filtration rate [eGFR] <45 mL/min/1.73m^2 or significant albuminuria). Further trials are therefore required to assess clinical safety and efficacy of BP-lowering treatment in this population.[7]

2.1.2 BP and risk of renal progression

Observational studies among patients with CKD suggest a positive association between BP and progression of CKD, although the association between BP and severity of CKD complicates such studies.[8] A meta-analysis of more versus less-intensive BP lowering suggests that reducing BP does slow the progression of CKD.[9] Although the effect was significant among patients with albuminuria (HR 0.73, 95% CI 0.62-0.86), among patients without albuminuria the effect was non-significant (RR 1.12, 95% CI 0.67-1.87; p for heterogeneity =0.006). However, the amount of data is small so substantial uncertainty remains. Furthermore, trials of more- versus less-intensive BP lowering in the general population (including patients with eGFR down to 45 mL/min/1.73m^2) have shown that intensive BP lowering increases the risk of acute kidney injury (which patients with CKD are more prone to) so the hazards need more careful study.[10]

2.2 Telemonitoring of BP may be a useful adjunct in trials of BP lowering

Technology now exists that allows participants to measure their BP at home and for such measurements to be automatically transferred (via Bluetooth to a phone or tablet device and then via the Internet) to a central computer where they can be reviewed and actioned as necessary.[11] Use of such technology might improve the efficiency of trials of BP lowering by providing a more accurate assessment of the participant's long-term average BP, reducing the number of clinic visits required to titrate therapy and improving the safety of participants by avoiding prolonged hypotension. Trials of home monitoring BP (in which participants measure their own BP and titrate their own treatment against an agreed action plan) have shown improved BP control,[12] but telemonitoring may provide additional advantages in complex conditions such as CKD whereby clinicians working centrally can monitor and advise a large number of participants simultaneously.

In order to address the uncertainty about the benefits and risks of intensive BP lowering in advanced CKD, a large outcomes trial is required comparing intensive versus standard BP lowering. Before nephrologists can be persuaded to enter patients in large numbers into such a trial, a pilot randomized trial is needed to test first whether it is possible to lower BP intensively in patients with advanced CKD, and second how such treatment is tolerated (and whether it is safe). Such a trial also offers the opportunity to test how useful telemonitoring could be in a larger trial, but before this pilot randomized trial can begin development of the

infrastructure to perform BP telemonitoring and information on the acceptability of telemonitoring among patients with CKD is required.

3 PLAN OF INVESTIGATION

3.1 Study aims

This study will include at least 25 participants aged at least 18 years with CKD (with either an eGFR ≥20 <45 mL/min/1.73m^2, or eGFR ≥45 <60 mL/min/1.73m^2 and urine albumin:creatinine ratio >20 mg/mmol) and whose mean systolic blood pressure is ≥130 at Screening

3.1.1 Primary aim

The primary aim is to assess the participants' acceptability of telemonitoring BP over 3 months, assessed by the proportion of patients who provide at least 90% of expected data (see below).

3.1.2 Secondary aims

Secondary aims include assessment of intra-individual variability in BP as determined by telemonitoring, participants' acceptability of titration of treatment guided by telemonitoring and the proportion of patients reaching target BP by final follow-up.

3.2 Study design

This study is primarily an observational study during which participants telemonitor their BP. In addition, after the first month, participants will have their BP lowering therapy titrated to achieve current guideline targets based on the results of telemonitoring.[13]

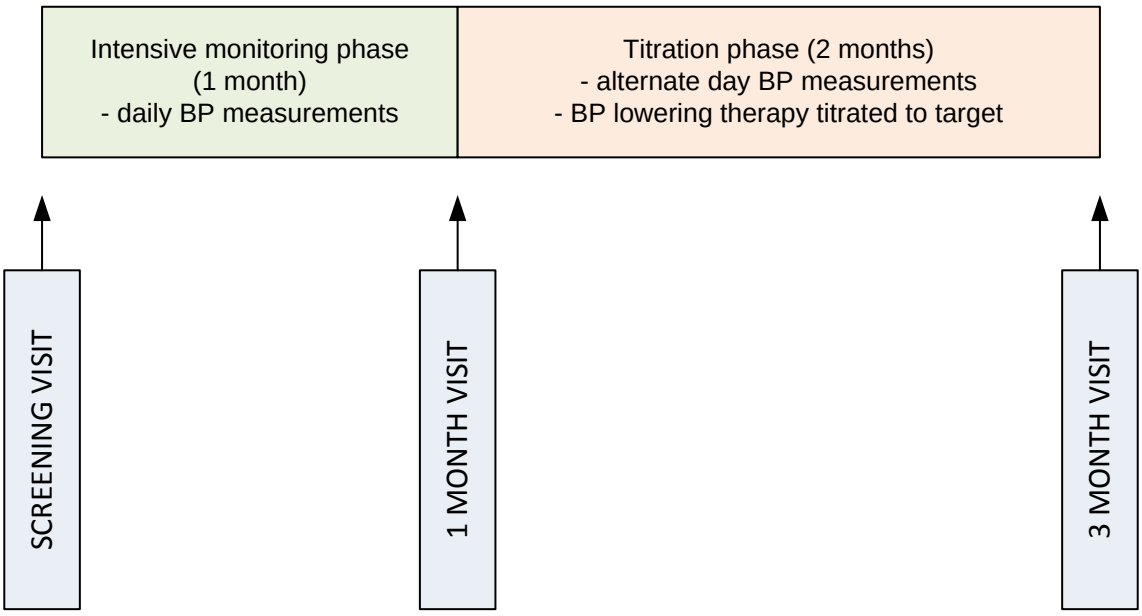

Figure 1: Study outline

3.2.1 Intensive monitoring phase (1 month)

Willing and eligible participants will be provided with telemonitoring equipment and instructed to measure their BP daily. On each occasion they will measure their BP three times whilst seated after resting for at least 5 minutes. If they have any symptoms of orthostatic hypotension they will also be asked to measure their BP after standing.

3.2.2 Titration phase (2 months)

After completing the intensive monitoring phase, participants will be instructed to reduce the frequency of their BP measurements to at least alternate daily. These measurements will be compared to current guideline targets[13] (<140 mmHg systolic if urine albumin:creatinine ratio [uACR] <3 mg/mmol or <130 mmHg systolic if uACR ≥3 mg/mmol) and if necessary, participants will be instructed to titrate their BP lowering therapy accordingly. If additional BP lowering medications are required, an appropriate agent will be selected (based on concomitant medications and comorbidities) and provided (either from the hospital pharmacy or through primary care).

At the end of this phase, participants will return for a final visit at which they will return their telemonitoring equipment.

3.3 Assessment of outcomes

The primary assessment is the completeness of BP data provided. Each participant would be expected to provide about 120 BP measurements and the proportion of patients providing at least 90% of these would be the primary outcome.

Secondary assessments include the intra-individual variability in BP and the acceptability to the participants of titration of BP lowering therapy guided by telemonitoring.

3.4 Sample size assumptions

This is a preliminary feasibility study to assess whether telemonitoring could be used in a pilot trial, so a formal sample calculation is not required. 25 participants should provide sufficient information to assess whether it is feasible to include telemonitoring in a pilot trial of intensive versus standard BP lowering. If during this study it becomes apparent that it would be useful to include more participants then more would be recruited after seeking the necessary approvals.

3.5 Overview of study organisation

The sponsor will be the University of Oxford. This study will be coordinated by the Clinical Trial Service Unit in collaboration with the Institute for Biomedical Engineering. Participants will be recruited from a single kidney unit (the Oxford Kidney Unit based at the Churchill Hospital, Oxford University Hospitals NHS Trust), where the Chief Investigator and a Local Research Coordinator (LRC) will be responsible for the identification, recruitment and follow-up of study participants.

The trial will be conducted in accordance with the principles of Good Clinical Practice (GCP), the current protocol and relevant national and local regulations.

3.5.1 Training

The LRC will be trained in the study procedures by coordinating centre staff and be provided with necessary materials detailing relevant study procedures.

3.5.2 Monitoring

This study is a low risk study and the monitoring will be based on the risk assessment. If necessary, coordinating centre staff will visit the site. The purpose of these visits will be to help the LRC resolve any local problems and ensure the study is being conducted according to the protocol. A report of any such visit would be prepared and reviewed by coordinating centre staff.

3.5.3 Data management

This study's information technology system will consist of custom-written applications including a tablet-based data capture system for use by the participants (which will include the necessary facilities to record BP measurements made on a Bluetooth-enabled electronic sphygmomanometer). All accesses by coordinating and local staff will require a username and password and any changes to data will require the user to enter their electronic signature. All data changes will be audited and the username associated to any change. Staff access will be restricted according to their role in the study.

Data will be retained electronically for at least 15 years, or longer if required by local or national regulations.

3.5.4 Biological samples

No samples of blood or urine will be required specifically for this study. However, if the participant has not had a recent (within the last 6 months) measurement of albuminuria (or proteinuria) then a urine sample may be sent at the Screening visit to the local laboratory for this.

3.5.5 End of study

Participants will be followed for 3 months (unless they withdraw consent prior to this). The end of the study is defined as the last visit of the last participant.

3.5.6 Funding

This study is funded by the British Heart Foundation, through a grant from the Oxford Centre for Research Excellence (reference).

3.5.7 Indemnity

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

3.5.8 Publications

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the British Heart Foundation. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

4 SUMMARY OF PRACTICAL PROCEDURES

POTENTIALLY ELIGIBLE

- patients with established CKD, defined by:
  - eGFR ≥20 <45 mL/min/1.73m^2; OR
  - eGFR ≥45 <60 mL/min/1.73m^2 and urine albumin:creatinine ratio >20 mg/mmol (or protein:creatinine ratio >30 mg/mmol)
- age >18 years
- mean systolic BP (at Screening) ≥130 mmHg

IDENTIFICATION AND INVITATION

- potentially eligible patients identified from local hospital database
- patients invited to attend Screening clinic appointment at local renal unit

SCREENING VISIT

- medical history, relevant current treatment and other eligibility factors recorded
- written informed consent sought from eligible and willing patients
- telemonitoring equipment and training in their use provided

INTENSIVE MONITORING PHASE (1 month)

- daily BP measurement (three times on each occasion)
- weekly symptom diary

1 MONTH FOLLOW-UP ASSESSMENT (in person or by telephone)

- equipment check and additional training provided if necessary
- current treatment record updated
- offer BPro device

TITRATION PHASE (2 months)

- BP measured at least 3 times per week
- weekly symptom diary
- BP lowering treatment titrated by coordinating centre clinician to achieve guideline targets

FINAL FOLLOW-UP VISIT (3 months after Screening)

- equipment retrieved
- participant thanked for participation

4.1 Eligibility for study

Consenting patients are eligible for this study if (a) the Chief Investigator does not believe there is a definite contraindication to telemonitoring; and (b) inclusion criteria are satisfied and no exclusion criteria applies.

4.1.1 Inclusion criteria

- Men or women aged ≥18 years (at Screening)
    - eGFR ≥20 <45 mL/min/1.73m^2; OR
    - eGFR ≥45 <60 mL/min/1.73m^2 and urine albumin:creatinine ratio >20 mg/mmol (or protein:creatinine ratio >30 mg/mmol)

4.1.2 Exclusion criteria

- Mean systolic BP <130 mmHg at Screening visit
- Planned change to BP lowering therapy within the next 1 month
- Acute vascular event (e.g. acute coronary syndrome, transient ischaemic attack or stroke) within last month
- Medical history that might limit the patient's ability to comply with study procedures for the duration of the study

4.2 Identification and invitation

Potentially eligible patients will be identified by study staff from hospital records including electronic databases. All nephrologists at the study site will be asked to give permission for their patients to be invited into the study by the Chief Investigator. They will be sent an invitation letter and Participant Information Leaflet (or provided with them during a routine clinic attendance) and asked to inform the research team if they do not wish to discuss the study. Otherwise study staff will contact them and invite them to attend a Screening visit.

4.3 Screening visit

4.3.1 Basic assessment of eligibility

At the Screening visit, the participant's eligibility will be confirmed by checking their recent laboratory results and checking other inclusion and exclusion criteria. Such data will be recorded directly onto the Screening form on the study's IT system. Any potential problems that might require further investigation or treatment will be brought to the attention of the patient's own doctor.

4.3.2 Patient consent

Patients who appear eligible will have the study explained to them by the LRC, using the Participant Information Leaflet as a basis for discussion. Patients will have the opportunity to initiate discussion and have time to think about their participation in the study, perhaps after discussing it with their family or other doctor. Patients will be discouraged from participating if it is thought unlikely that they would be willing and able to participate in all aspects of the study.

4.3.3 BP measurement and urine sample

Participants will be shown how to use the study equipment and record their BP during the Screening visit. They will be asked to measure their BP three times and the average of the second two readings will be used. (If their systolic BP is >180 mmHg their treatment will be reviewed and if necessary a recommendation made to their general practitioner to start further BP lowering therapy. If there is good reason to believe that their measurements in

clinic are significantly higher than their usual BP [i.e. “white coat hypertension”] then they will be eligible to participate.) If their BP is <130 mmHg they are not eligible to participate.

If they have not had a urine albumin:creatinine (or protein:creatinine) ratio measured in the last 6 months, participants will be asked to provide a sample so this can be measured before they enter the Titration phase.

4.4 Intensive monitoring phase

4.4.1 BP measurement

Participants will be asked to measure their BP daily during this phase. They will be asked to measure it 3 times after sitting for at least 5 minutes. In addition, if they have any symptoms of orthostatic hypotension (e.g. dizziness on standing) they will be asked to measure it once after standing. These measurements will be recorded directly into the study electronic system (using the tablet device provided). If the participant has any problems recording their measurements they will asked to contact the coordinating centre or LRC during working hours.

If the coordinating centre does not receive the measurements, they will contact the participant to enquire whether the measurements have been done or if there is a problem with the connection between the tablet device and the Internet. If any problem cannot be resolved over the phone, the participant will be asked to attend the study clinic at their earliest convenience.

4.4.2 Symptom diary

Participants will be asked to complete a simple symptom diary (on a tablet device) at least weekly during the intensive monitoring phase. This will record any problems with BP measurement and any symptoms that might be related to high or low BP.

4.5 1 month assessment

Towards the end of the intensive monitoring phase the participant will either be seen in clinic or contacted by telephone by a member of the research team. The nature of the titration phase will be explained to the participant again and the record of their current medication updated. If they attend clinic in person then their BP will be recorded in clinic. They will asked to compete a brief questionnaire on the acceptability of using the telemonitoring equipment. Participants will be offered a BPro[1] device to wear for 24 hours and a stamped addressed envelope to return it to the clinical centre.

4.6 Titration phase

4.6.1 BP measurement

Participants will be asked to record their BP at least three times per week (as in the intensive monitoring phase, each recording will comprise three measurements). In addition, if they have any symptoms of orthostatic hypotension (e.g. dizziness on standing) they will be asked to measure it once after standing. These measurements will be recorded directly into the study electronic system (using the tablet device provided). If the participant has any problems recording their measurements they will asked to contact the coordinating centre or LRC during working hours.

[1] The BPro device is an approved watch-like device that measures BP continually for a 24 hour period (CE registration HD 60077980 0001).

4.6.2 Symptom diary

Participants will be asked to complete a simple symptom diary (on a tablet device) at least weekly during the titration phase. This will record any problems with BP measurement and any symptoms that might be related to high or low BP.

4.6.3 Titration of BP lowering therapy

A clinician at the coordinating centre will review the BP measurements for each participant approximately once a week. If they are above the target recommended in current guidelines (i.e. systolic BP >140 mmHg if uACR <3 mg/mmol or >130 mmHg if uACR ≥3 mg/mmol) then their BP lowering therapy will be increased (either by increasing the dose of an existing agent or by adding another agent). If an additional agent is required, the decision will be based on their other medications, drug allergies and comorbidities and it will be prescribed by a doctor and provided either from the hospital pharmacy or general practitioner.

If the participant reports symptoms of orthostatic hypotension and their BP is at least 10 mmHg below their recommended target then their current therapy will be reduced (either by reducing the dose or stopping an existing agent entirely). The choice of agent to reduce or stop will be based on their other medications and comorbidities.

4.7 Final follow-up visit

After two months of the titration phase, the participant will be asked to attend the study clinic. Their BP will be measured and recorded and their study equipment retrieved. They will be asked to complete a questionnaire on the acceptability of the telemonitoring equipment and thanked for their participation.

If there have been any changes to the BP lowering medications their GP will be informed and asked take over management and monitoring of them as per normal clinical care.

4.8 Withdrawal from the study

Participants have the right to withdraw from the study at any time and for any reason, without prejudice to their future medical care by the physician or institution, and are not obliged to give their reason for doing so. They will be asked to return their study equipment.

4.9 Out of hours assistance

An on-call doctor is available from the coordinating centre 24 hours a day, seven days a week by calling (Freefone) 0800 585323.

5 APPENDICES

5.1 Schedule of study procedures

Procedure	Study stage				
	Screening visit	Intensive monitoring phase	1 month assessment	Titration phase	Final visit
Assess eligibility	X				
Record relevant history	X				
Record medications	X		X		X
Informed consent	X				
Collect urine sample[2]	X				
Measure BP	X	X[3]	X	X[4]	X
Provide BPro device			X[5]		
Symptom questionnaire		X	X	X	X
Titrate BP lowering therapy				X	

[2] If no result available from previous 6 months
[3] Daily
[4] At least alternate days
[5] Optional

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