Effects of telemedicine interventions on essential hypertension: a protocol for a systematic review and meta-analysis

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ABSTRACT
Introduction Essential hypertension is a major preventable risk factor for early cardiovascular disease, premature death and disability. It has been reported that telemedicine interventions can provide an effective solution to essential hypertension to overcome the barriers that exist in traditional treatment or control. Nevertheless, this subject has not been thoroughly investigated. The goal of this study is to systematically evaluate and describe the impact of telemedicine interventions on essential hypertension.

Methods and analysis To find relevant research, we will conduct a systematic literature search of three databases (PubMed, Embase and Cochrane Library), with no language limitations, in addition to grey literature. Two reviewers will extract the data individually, and any disagreements will be resolved by discussion or by a third reviewer. The randomised controlled trials will be chosen based on predetermined inclusion criteria. Primary outcomes will include systolic blood pressure and diastolic blood pressure after the telemedicine intervention. Secondary outcomes will include medication adherence (eg, the Morisky Medication Adherence Questionnaire), quality of life (eg, the MOS item scale of the Health Survey Short Form 36 questionnaire), blood pressure control rate and adverse events (eg, stroke, chronic renal failure, aortic dissection, myocardial infarction and heart failure). The quality of the included studies will be assessed using the Cochrane risk-of-bias method. The data will be analysed using RevMan V.5.3.5 software and STATA V.16.0 software. If heterogeneity testing reveals little or no statistical heterogeneity, a fixed effect model will be used for data synthesis; otherwise, a random effect model would be employed. We will synthesise the available evidence to perform a high-quality meta-analysis.

Ethics and dissemination This project does not require ethical approval because it will be conducted using publicly available documents. The review’s findings will be published in peer-reviewed journals and publications. PROSPERO registration number CRD42021293539.

INTRODUCTION
Essential hypertension is the most common cardiovascular disease (CVD),1 and is a major preventable risk factor for premature mortality and disability worldwide.2-4 In addition, sustained increases in arterial pressure can cause damage to multiple target organs, including the heart, brain and kidneys,5 and increase the risk of hypertensive consequences such as stroke, coronary heart disease and kidney disease.6-8 Therefore, blood pressure management is essential to reduce the incidence of CVD in patients with risk factors.9 At present, there are many effective measures and methods10 that can be used to treat and regulate individual blood pressure, such as medication, diet control and activity modification. However, one study showed regional differences in hypertension control rates.11 12 Socioeconomic factors are major drivers of frequently reported poor adherence and treatment outcomes in hypertensive patients, and the efficacy of hypertension treatment depends on appropriate treatment options and active patient participation.13 Thus, hypertension remains untreated or controlled in most populations.14 So we urgently need more effective and economical general treatment/control measures.

With technological advances, telemedicine is gradually being applied to more medical fields. Telemedicine is a type of healthcare service provided through the use of telecommunications technology. Telemedicine...
provides medical services via telephone, computer, internet and videoconferencing, allowing community or home programmes. Telemedicine currently focuses on chronic diseases such as diabetes, heart failure and asthma. It has the potential to minimise length of stay and need for emergency care, as well as reduce financial burden and improve disease management. It has also been reported that remote blood pressure monitoring is widely used for the management of hypertensive patients. A meta-analysis by Zhi X et al found that remote blood pressure monitoring was more effective than routine clinic visits in the control of systolic and diastolic blood pressure in urban hypertensive patients. Chen et al found that remote management suffers from poor outcomes due to the influence of the attitudes of stakeholders (patients, families, medical staff, etc). A meta-analysis of 23 randomised controlled trials (RCTs) (7037 hypertensive patients) reported that a full range of remote blood pressure interventions resulted in a 4.71 mm Hg decrease in office systolic blood pressure and a 2.45 mm Hg decrease in diastolic blood pressure, and this was more likely to delay disease progression, reduce complications and improve prognosis. A large number of studies have also shown that telemonitoring blood pressure management models can lower blood pressure to a greater extent than management models with interventions alone. However, more studies have demonstrated that remote blood pressure interventions are more appropriate for patients with resistant or grade 2 and higher hypertension, and have a present but negligible impact in hypertensive patients with lower blood pressure values. In addition, it was not possible to demonstrate the effects and effects of sustained blood pressure reduction. Although there are many studies demonstrating the superiority of telemedicine interventions over conventional blood pressure interventions, the clinical and economic benefits derived from these studies to date are incomplete and accurate, and there is significant between-study heterogeneity. Therefore, the specific impact of telemedicine interventions in patients with essential hypertension is unknown. To our knowledge, no study has yet shown that telemedicine intervention is best for patients with essential hypertension. Furthermore, the benefits of telemedicine therapy for different levels of essential hypertension have not been explored in previous trials. Thus, the aim of this study was to evaluate the current evidence and to conduct a high-quality meta-analysis to comprehensively analyse and summarise the impact of various telemedicine on different levels of essential hypertension. This aims to provide a basis for telemedicine intervention in blood pressure practice.

Systematic review questions

► What are the different types of telemedicine interventions that benefit patients with essential hypertension?
► Which types of telemedicine interventions are most effective for patients with essential hypertension?

► Which types of telemedicine interventions are most helpful in patients with critical hypertension implementation, and what are their outcomes?
► How do the effects of various types of telemedicine interventions differ across different levels of essential hypertension?

METHODS AND ANALYSIS

Eligibility criteria
We followed the 2015 Preferred Reporting for Systematic Review and Meta-Analysis (PRISMA) Protocols Project reporting guidelines for the preparation of this protocol. Our meta-analysis will include published RCTs of telemedicine treatments for essential hypertension with unrestricted dates of publication. A flow chart of the study selection process is shown in figure 1.

Inclusion criteria
The inclusion criteria include RCTs involving patients with a diagnosis of essential hypertension or on anti-hypertensive medication, who received a telemicine intervention delivered by telecommunication technology, without language restrictions.

Exclusion criteria
The exclusion criteria include conference abstracts, research protocols, pilot studies, duplicate reports and studies with incomplete or irrelevant data.

Types of outcome measures
Primary outcome: the change in systolic and diastolic blood pressure following the intervention.
Secondary outcomes: medication compliance (eg, the Morisky Medication Adherence Questionnaire), quality of life (eg, the MOS item scale of the health survey Short Form 36 Questionnaire), blood pressure control rate and adverse events (eg, stroke, chronic renal failure, aortic dissection, myocardial infarction, heart failure).

Data sources
We will use the PubMed, Embase and Cochrane Library databases for the systematic search of published studies from the date of each database’s creation to 30 December 2022, without any language restrictions. The grey literature and review articles will be searched manually or by contacting experts in the field. The plan for our study will start on 1 January 2023 and end on 30 June 2023.

Search strategy
Two researchers (LZ and YJ) will search the PubMed, Embase and Cochrane Library databases. Relevant and regularly used phrases will be used to identify applicable keywords, except for Medical Subject Headings terms. After developing and completing a search strategy in PubMed, the same method will be used in the other databases. The following search keywords will be used: ‘hypertension’ or ‘blood pressure’ and ‘remote’ or ‘distance’ or ‘electronic’ or ‘communication’ or ‘technology’ or ‘cloud’ or ‘cloud computing’ or ‘computing’ or ‘5G’ or...
‘4G’ or ‘artificial’ or ‘intelligent’ or ‘smart’ or ‘auto’ or ‘machine’ or ‘mobile’ or ‘online’ or ‘on-line’ or ‘wireless’ or ‘data’ or ‘IoT’ or ‘connected’ or ‘AI’ or ‘network’ or ‘software’ or ‘telecom’ or ‘system’ or ‘module’ or ‘platform’ or ‘integration’ or ‘storage’ or ‘shared’ or ‘synchronized’ or ‘integrated’ or ‘development’ or ‘IT’ or ‘service’ or ‘contactless’ or ‘integration’ or ‘APP’ or ‘Android’ or ‘IOS’ or ‘Phone’ or ‘Mobile’ or ‘computer’ or ‘device’ or ‘computer’ or ‘audio’ or ‘image’ or ‘graphic’ or ‘information’ or ‘video’ or ‘conference’ or ‘training’ or ‘program’ or ‘programme’ or ‘application’ or ‘algorithm’ or ‘code’ or ‘public’ or ‘language’ and so on (the search syntax for other databases are presented in online supplemental file 1). In the search process, the main words will be combined with free word search. To find possibly relevant publications, researchers will manually search and cross-reference the reference lists of the collected studies. When issues emerge about the design or results of the studies, the corresponding authors will be contacted to confirm the information we gather from their trials or to clarify any ambiguity. We will double-check references to avoid omissions.

**Study selection**

Records will be managed using Endnote VX9.3.3 software. Following the removal of duplicates, two researchers (LZ and YJ) will conduct a double-blind examination of the titles, abstracts and other contents of the literature, excluding papers that do not fulfil the criteria and documenting the reasons for exclusion. Following that, potentially eligible literature will be read in full to further reject non-eligible material and document the grounds for exclusion. If the material in the literature cannot be properly included, it will be rescreened, which may include contacting the authors by mail, phone or other ways to collect important information. Disagreements will be settled through discussion or the opinion of a third investigator (DL). The details of the study selection and identification process will be presented in a flow chart (figure 1).
Data extraction
Two researchers (LZ and YJY) will create a uniform data extraction form that includes the following information: title, author, publication year, study nation, protocol design, sample size, inclusion criteria, patient characteristics (age, gender, height, body mass index, medical history (hypertension, diabetes, etc)), kind of remote intervention and control, intervention length, experimental period, duration, frequency, efficacy index, outcome index and study findings. The two investigators (LZ and YJY) will independently extract and enter data from the publications into a data sheet. A third investigator (DL) will review the findings of all the studies. In the event of a disagreement about the data included, the two investigators will discuss and resolve the issue, with the third investigator (DL) joining the discussion if necessary. In addition, if necessary, data are absent, incomplete or unclear in the paper, questions will be directed to the authors; otherwise, the study would be excluded.

Quality assessment
Two authors will independently assess the methodological quality and risk of bias of each included study using the Cochrane risk-of-bias tool. This tool includes random sequence generation, allocation concealing, subject and researcher blindness, insufficient outcome data, selective reporting and other biases. Each index will be assigned one of three grades: ‘low bias risk’, ‘bias uncertainty’ or ‘high bias risk’.

Publication bias analysis
STATA V.16.0 software will be used to measure reporting bias. We will use funnel plots and Egger’s test to analyse the probability of study bias in small studies if enough data are available. The degree of bias will be indicated by the asymmetry in the funnel plot; the more prominent the asymmetry, the greater the degree of bias. We will use funnel plots and Egger’s test to analyse the probability of study bias in small studies if enough data are available. The degree of bias will be indicated by the asymmetry in the funnel plot; the more prominent the asymmetry, the greater the degree of bias.

Outcome measures
RevMan V.5.3.5 software (Cochrane Collaborative, Oxford, UK) and STATA V.16.0 software (Stata) will be used to calculate mean deviations, SD, 95% CIs and p values. The χ² test will be used to compare cases, and all analyses will be considered statistically significant if p<0.05. For meta-analysis and statistical analysis, we will use standardised mean differences (SMDs) with 95% CIs for continuous variables. Certain secondary outcomes, such as adverse events, will be characterised by relative risk because they are dichotomous variables (RR).

Data synthesis
For data synthesis, the RevMan V.5.3.5 software will be used. If statistical heterogeneity tests reveal little or no statistical heterogeneity (I²<50%), the fixed effects model will be used. The random effect model will be used for data synthesis if heterogeneity tests demonstrate significant heterogeneity (I²≥50%). The meta-analysis will not be performed if the studies have a high heterogeneity. We will perform subgroup and meta-regression studies if clinical heterogeneity is present. A descriptive analysis will be performed if the source of heterogeneity is unclear.

If there is significant heterogeneity in the studies, we will perform subgroup analyses with country, age, hypertension classification and telemedicine intervention as independent variables for each study to detect their sources of heterogeneity.

To assess the stability of the analytical results, a sensitivity analysis will be performed. The procedure entails removing low-quality research and merging the data to assess the impact of sample size, research quality, missing data and statistical methodologies on meta-analysis results. The sensitivity analysis will not be applied if all of the included studies have a high risk of bias.

The final report will be written using the PRISMA criteria after the data synthesis and classification outlined above.

SUBGROUP ANALYSIS
If sufficient RCTs are included, we will perform subgroup analysis when there is significant heterogeneity in the study.

A large body of literature has discussed that specific subgroups of hypertensive patients may particularly benefit from telemedicine, and we will conduct subgroup analyses based on blood pressure levels divided into grades 1, 2 and 3 hypertension.

Mobile telemedicine interventions have been reported to be more effective than other telemedicine interventions. We will divide the telemedicine intervention into three groups according to the mode of delivery: website-based intervention, telephone-based intervention and telemedicine intervention provided by application for subgroup analysis; considering that there are also studies showing that intervention time is a factor affecting telemedicine efficacy, we will divide telemedicine intervention time into subgroups of less than 3 months, 3-6 months and more than 6 months for subgroup analysis; of course, there is evidence that BP control is associated with the level of economic development, and we will also conduct GDP (Gross Domestic Product)-based subgroup analysis. At the same time, considering age, gender, etc can also affect the acceptance and compliance of telemedicine, and then affect the effect of telemedicine intervention. We will also perform subgroup analyses for this.

DISCUSSION
Studies have shown that blood pressure control to maintain the recommended levels is effective in reducing the incidence of stroke, heart disease and heart failure. Effective control of blood pressure is therefore essential for reducing the incidence of CVD in people with hypertension. Although essential hypertension can be controlled with drugs, diet control and exercise regulation, most...
patients find hypertension control difficult. Obstacles include the following\(^2\): lack of flexibility in appointments, long distance between patients’ homes and healthcare facilities, inconvenience of protocol timing and dependence of patients on caregivers who may be preoccupied. Coupled with limited healthcare resources, as a result, hypertension remains untreated or uncontrolled in the majority of the population.\(^1\)

Telemedicine interventions are able to overcome the barriers of time and distance. Telemedicine therapies have been proven to be at least as beneficial as outpatient cardiac rehabilitation in terms of mortality, exercise, cholesterol level and smoking.\(^1\) As a result, telemedicine could be a viable choice for controlling essential hypertension.

However, the effectiveness of telemedicine in the treatment of hypertension is yet to be determined. The effects of telemedicine therapies on essential hypertension have been studied in previous reviews and meta-analyses.\(^24\)–\(^41\) Although many studies exist to support the assertion that intervention models based on remote blood pressure monitoring not only enhance the management of hypertension, but also improve patient outcomes and prognosis and reduce healthcare costs.\(^30\) At the same time, more studies have demonstrated that telemedicine blood pressure interventions are more suitable for patients with resistant or grade 2 and higher hypertension\(^39\)–\(^40\) and have a present but negligible impact in hypertensive patients with lower blood pressure values. In addition, a meta-analysis of 23 RCTs (7037 hypertensive patients) reported that all-round remote blood pressure interventions, such as patient follow-up (telephone, email, equipped health software follow-up), health education, dietary exercise and medication guidance supervision, and treatment plan reminders from professional medical teams, can lead to a 4.71 mm Hg decrease in systolic blood pressure and a 2.45 mm Hg decrease in diastolic blood pressure in the clinic, and this is more likely to delay disease progression, reduce complications and improve prognosis.\(^33\)–\(^34\) However, most studies have only looked at the effects of one or a few types of telemedicine interventions on essential hypertension, leaving it unclear which type of telemedicine intervention is best for each subgroup of essential hypertension patients and how it may be implemented effectively. This systematic review and meta-analysis will assess the impact of various telemedicine therapies on patients with essential hypertension. We hope that this meta-analysis will provide objective evidence for tailored telemedicine interventions for patients with essential hypertension.

Even with sophisticated search tactics and tools, it is not possible to include all relevant papers due to publication bias. A major constraint of systematic reviews is a lack of data, which might impair the quality of findings. Furthermore, the included studies would probably differ in sample size, participant characteristics and telemedicine intervention components and implementation techniques, potentially leading to high heterogeneity. We will perform subgroup analyses with country, age, hypertension classification and telemedicine intervention as independent variables for each study.

**Patient and public involvement**

There will be no patients or members of the public participating.

**Ethics and dissemination**

The findings of this systematic study will be shared through peer-reviewed publications. We will evaluate current literature sources; thus, no ethical assessment is required.

**Contributors**

Conceptualisation: LZ, DL and YG. Methodology: LZ, DL, YG and X-LJ. Writing original draft: FL, YL, LZ and YJ. Revised the manuscript: X-LJ, YG, XC, TL and DD. All authors have reviewed and approved the final version of this manuscript and have given consent for publication.

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**Competing interests**

None declared.

**Patient and public involvement**

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication**

Not applicable.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Supplemental material**

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