Management of Uncontrolled Hypertension (HTN)

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Protocol

1. **Title:**

   Management of Uncontrolled Hypertension: Ambulatory Blood Pressure Monitoring and Subsequent Modification of Therapy or Shifting Anti-hypertensive Medication to Night-time Dosing

2. **Investigators:**

   Principal Investigator:

   Katherine Vogel Anderson, Pharm.D.
   Clinical Assistant Professor
   Department of Pharmacotherapy and Translational Research

   Sub-Investigators:

   Kimberly Atkinson
   Resident Pharmacist, Pharm.D.
   UF College of Pharmacy

   Ryan Nall, M.D.
   Internal Medicine Physician
   UF Health Internal Medicine – Medical Plaza

3. **Abstract:**

   Ambulatory Blood Pressure Monitoring (ABPM) and its role in clinical practice continues to evolve. ABPM allows providers to obtain blood pressure readings over a 24hour period, to assess blood pressure at night to determine "dipping" status, and to evaluate the efficacy of anti-hypertensive therapy. By utilizing ABPM in uncontrolled hypertension patients in clinical practice, modifications in drug therapy can be based on a more comprehensive and accurate depiction of the patient's overall blood pressure control throughout the day. Although, theoretically, an assessment of the 24-hour blood pressure of a patient prior to adjusting drug therapy should yield better blood pressure control, we would like to carry out a pilot study to investigate whether the modifications in therapy based on ABPM and the resulting impact on blood pressure control would be substantially different from simply switching the dosing of medication to night-time.

   In this study, we will compare chronotherapy to ABPM. Data collected will include hypertension drug therapy regimen prior to and during the study, timing of medication administration, and dose, along with the patient's office blood pressure values prior to study and one month after modification in therapy. This will enable us to explore

whether it is a practical endeavor to implement ABPM as a routine process for all uncontrolled hypertension patients or whether ABPM does not seem to provide considerable value over shifting the timing of drug administration.

4. Background:

Hypertension affects approximately 29% of the US adult population, which equates to roughly 72 million people.[1] Management of hypertension is of major importance because it is a key risk factor for heart failure, stroke, myocardial infarction, and cardiovascular disease. Another factor that has been found to correlate with the occurrence of complications in hypertension patients is dipping status. Dipping status refers to whether or not a patient's blood pressure decreases during sleep. In normotensive patients, a dip in blood pressure of around 10% of the daytime blood pressure values is seen during sleep.[2] The absence of dipping in blood pressure has been correlated with target organ damage and is associated with pseudo-resistant hypertension.[3] Without access to night-time blood pressure readings, patients may be falsely diagnosed with resistant hypertension resulting in the unnecessary addition of medications.

Ambulatory Blood Pressure Monitoring (ABPM) has garnered substantial scientific interest for its potential role in the diagnosis, management, and treatment of hypertension. Compelling indications for use of ABPM include identification of white-coat hypertension, masked hypertension, and abnormal 24-hour blood pressure patterns. In addition, ABPM may be used to assess blood pressure treatment through evaluation of 24-hour blood pressure control and, by extension, identifying truly resistant hypertension patients.[4]

ABPM is primarily used to diagnose white coat hypertension, however, ABPM may be used to assess efficacy of blood pressure treatment by evaluating the patient's blood pressure control over a 24-hour period.[5] The capability to provide night-time readings during sleep sets it apart from office blood pressure readings and home blood pressure readings, and it provides information for the determination of dipping status. Non-dipping status has been associated with target organ damage including left ventricular hypertrophy, microalbuminuria, cerebrovascular disease, congestive heart failure, vascular dementia, stroke, and myocardial infarction.[6] The frequency of non-dipper patterns tends to be higher in hypertension that is secondary to specific medical conditions such as chronic renal failure, diabetes, and autonomic nervous system dysfunction than in uncomplicated primary hypertension. A study also showed that the percentage of patients that ingest all their antihypertensive medications in the morning was significantly greater in non-dippers than the dippers suggesting that non-dipping among treated patients is partly due to lack of 24-hour therapeutic coverage when administered in the morning.[9]

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

stages hypertension as Stage 1 with pressure. Adults between the ages of 18 and 59 years old or any adult with diabetes or chronic kidney disease are considered hypertensive with three consecutive blood pressure readings above 140/90 mmHg.[7] Resistant hypertension is defined as blood pressure that remains above the goal of 130/80 mmHg despite the use of three anti-hypertensive agents at optimal doses including a diuretic, if possible, or blood pressure that is controlled with the use of four or more antihypertensive drugs.[8] Although non-adherence is a common contributing factor to pseudo-resistant hypertension, it remains difficult to apply a simple, inexpensive, and reliable method in the clinical setting to quantify this factor when investigating potential causes for resistant hypertension.[8] Additionally, seemingly resistant hypertension may be related to inadequate night-time blood pressure control leading to elevated blood pressures during sleep as well as a higher-than-normal morning rise/spike upon awakening.[6]

Chronotherapy is the purposeful timing of medications to synchronize drug concentrations with established circadian rhythms in an effort to enhance treatment outcomes and prevent adverse effects.[6] Chronotherapy of anti-hypertensive medications has been used to attenuate morning rise of systolic and diastolic blood pressure, normalize elevated daytime, nighttime, and 24-hour blood pressure means, and convert abnormal 24-hour blood pressure profiles to normal dipping patterns. Tailoring medication levels in close synchrony with known and expected day-night patterns in both systolic and diastolic blood pressure can optimize the drug's effects.[9] Given that optimal anti-hypertensive drug therapy may be dependent on circadian rhythms, dipping status, and individual 24-hour blood pressure patterns, along with the fact that ABPM serves as one of the only ways to easily evaluate a patient's blood pressure patterns throughout the day and night, we are interested in investigating whether ABPM is beneficial in clinical practice.

There are potential risks for dosing antihypertensive medications at bedtime in patients with visual field deterioration. A study which investigated 24-hour ABPM in patients with anterior ischemic optic neuropathy (AION), glaucoma, and other optic nerve head disorders have shown a 26% reduction in systolic blood pressure and 33% reduction in diastolic blood pressure at night.[12] Patients with a progressive visual field deterioration had significantly greater mean decreases in systolic blood pressure from daytime readings (46.8 ± 2.5 mmHg) compared to those without deterioration (35.0 ± 3.1 mmHg).[12] Based on these and other studies, it was hypothesized that nocturnal hypotension may lead to ischemia of the anterior ciliary artery and reduce optic nerve head blood flow below a crucial level in certain vulnerable patients triggering the precipitation of AION and blindness.[13] Therefore, patients with visual field deterioration should be excluded from the study to prevent the possibility of developing AION.

Clinical application of ABPM may lead providers to add a new drug if the patient is a dipper or shift the dosing of an existing medication to night-time, or add a dose of an existing medication to bedtime. However, it is also possible that providers could simply

move a medication to bedtime dosing, without relying on ABPM. Given that the initial cost associated with purchasing ABPM equipment ($2500-$5000) and software ($2000-$3000)[11] is not inconsequential, we propose this pilot study to determine whether ABPM in clinical practice is an investment that results in significant difference in blood pressure control when compared with chronotherapy.

5. Specific Aim:

We propose to conduct a pilot study to determine whether the incorporation of Ambulatory Blood Pressure Monitoring (ABPM) as routine procedure in clinic for uncontrolled hypertension influences how anti-hypertensive drug therapy is modified or if simply shifting the dosing of anti-hypertensive medications to night time achieves similar results. We will enroll 20 participants with uncontrolled hypertension, who are prescribed 3 anti-hypertensive medications. All twenty patients will undergo 24-hour blood pressure monitoring with ABPM at baseline and one month after change in therapy has been initiated; ten of the patients will be randomized to receive a shift in dosing schedule of anti-hypertensive medication to night-time without utilizing their ABPM results while the remaining ten will receive modifications in therapy based on their ABPM results and dipping status. The results of this study will assist in assessing the feasibility and benefits of the incorporation of ABPM into the routine management of hypertension.

6. Research Plan:

Patient eligibility

Inclusion criteria

1. Age ≥ 18 years
2. Blood pressure of >130/80 mmHg
3. Currently receiving 3 anti-hypertensive agents, one of which is a diuretic, for at least six weeks

Exclusion criteria

1. Vulnerable populations
    a. Pregnant women
    b. Prisoners
    c. Cognitively impaired persons
    d. Economically and/or educationally disadvantaged
    e. Human fetuses and neonates
    f. Patients who work night-shift
    g. Children
    h. Conditions with visual field deterioration (Anterior Ischemic Optic Neuropathy, Glaucoma, Optic Nerve Disorders)

Our target population is patients with uncontrolled hypertension. This study will recruit patients from the existing patient population assigned to a physician at the UF Health Internal Medicine Clinic at the Medical Plaza or enrolled in the Internal Medicine Interdisciplinary Hypertension Clinic. Patients that qualify/are eligible for the study will be identified by running a report through EPIC with the inclusion criteria. Either Dr. Vogel Anderson, or Kimberly Atkinson will obtain informed consent from eligible patients to enroll in the study. The informed consent form will summarize the consent discussion. Subjects, parents, or authorized representatives will be given the opportunity to consider and discuss the consent with family members and/or someone knowledgeable about the protocol. We have changed the exclusion criteria from receiving three anti-hypertensive agents for at least three months to receiving three anti-hypertensive agents for at least six weeks to broaden our target population. Ambulatory Blood Pressure Monitoring is recommended in the 2017 ACC/AHA Guidelines for patients with resistant hypertension which is defined as having elevated blood pressure while being on 3 or more anti-hypertensive agents, with one being a diuretic, however, a timeframe for how long the patient is on the medications before qualifying as resistant hypertension is not defined.[7] We chose six weeks to more closely align with the timeframe needed to see the true effect of a medication on the change in blood pressure.

A total of twenty patients will be recruited and enrolled in this study. All twenty patients will wear the Spacelabs Ambulatory Blood Pressure Monitor Model No. 90207 for 24 hours a total of two times – at baseline and following one month of the patient receiving their change in drug therapy. The randomization process to assign patients to either the group receiving chronotherapy or the group receiving therapy changes based on ABPM will be determined by placing strips of paper with the unique patient codes into an envelope and picking out numbers. One group will receive a shift in the timing of one of their antihypertensive medications to nighttime dosing without consulting their ABPM results. The other group will receive a modification in their antihypertensive medication regimen based on their ABPM results; modification in therapy would entail a shift in dosing of an existing blood pressure medication to nighttime for non-dippers while dippers would receive a change in regimen (change in strength of medication, addition of new medication, etc.) selected according to normal standard of care management of hypertension. Any specific changes to medication regimen outside of altering the timing of dose administration is not dictated by this study and will be based on usual process of treating uncontrolled hypertension patients and clinical expertise of the primary care physician. All subjects will be instructed on the operation of the ABPM and properly fitted with the monitor. Prior to leaving the office, they will undergo a minimum of one blood pressure reading to ensure adequate functioning of the monitor. They will also be given an information sheet detailing what to expect while using the ABPM as well as a diary to record the time of their meals, their medication administration, bedtime, time of awakening, any symptoms if they occur, and any period of stress or mood-altering activity that may affect the blood pressure reading. Patients will return the following day after wearing the monitor for 24 hours so that the

data can be collected, and based on the group to which the patient was assigned, drug therapy may be modified according to the analysis of the ABPM results and their diary of activity. Requirements for a satisfactory ABPM involves having a minimum of 20 valid daytime measurements, a minimum of 7 measurements while asleep, and at least 70% of the measurements obtained at least every 30 minutes or more frequently throughout the 24-hour period.[4]

Follow-up will occur for both treatment groups after one month of initiating their modified anti-hypertensive regimen to see how changes in drug therapy impact their blood pressure control. Patients will arrange for their follow-up 24-hour ABPM screening. The procedure from the first ABPM screening will be repeated, and the patient will return the following day to remove the monitor, return their ABPM diary, and submit their ABPM results for analysis.

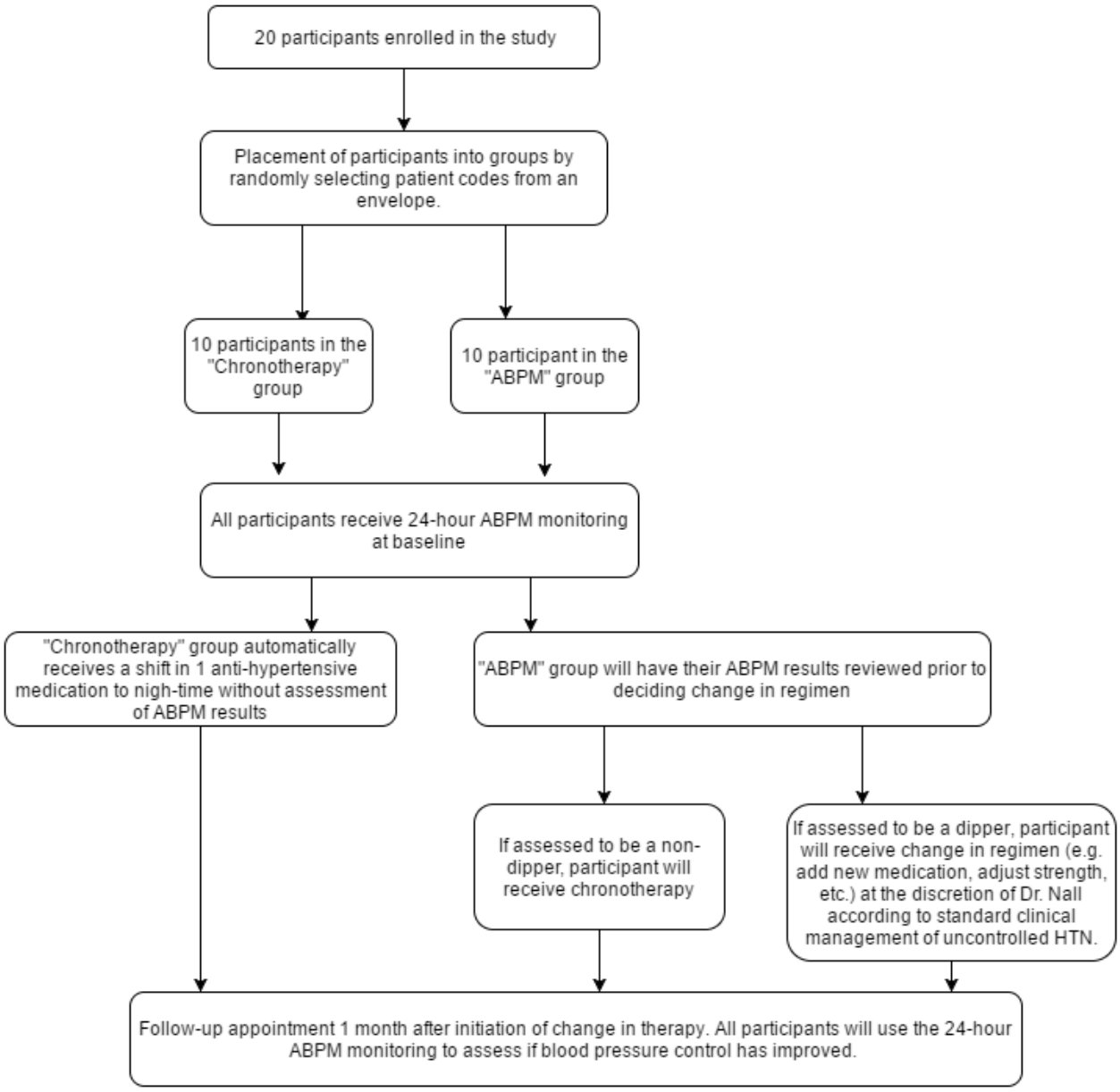

Chart 1: Flow chart demonstrating process for conducting the study

Aside from patients receiving ABPM, all patients will receive standard care in managing their hypertension involving hypertension follow-up appointments and adjustments in therapy to achieve adequate blood pressure control. For those patients who are in the group whose changes in therapy will be determined after evaluating their ABPM results, patients found to be dippers and would not benefit from the switch in dosing to nighttime will receive changes in therapy as would be expected in clinic as standard care if a dose increase/medication change is warranted. Clinical data will be obtained from standard blood pressure monitoring equipment provided by the clinic. Therefore, this study will not result in additional charges associated with the treatment and care of the patient.

Data collection will include age, sex, race, height, weight, comorbidities (Diabetes Mellitus, hyperlipidemia, history of stroke, transient ischemic attack, myocardial infarction, etc.), antihypertensive therapies including dosing schedule at baseline as well as after modification from receiving either treatment option, complete medication history including over-the-counter and herbal medications, whether or not the patient uses a home blood pressure monitor (yes or no), lifestyle history including caffeine and alcohol intake and tobacco use, number of years since HTN diagnosis, whether or not patient was at blood pressure goal at the follow-up visit at one month after initiating change in therapy (yes or no), and the blood pressure readings from the ambulatory blood pressure monitor at baseline and one month post initiation of change in drug therapy. Data will be obtained through EPIC, including the patient-recorded data such as the diary of activity during the 24 hours wearing the ABPM which will be scanned into EPIC. The results of the ABPM will be obtained from the ABPM software and may be scanned into EPIC for ease of access.

Descriptive statistics, including REDCap (Research Electronic Data Capture) will be used to analyze patient data. Unique patient codes will randomly be assigned to each patient participating in the study through REDCap, and the patient code will serve as the identity of the patient throughout the study. The master list linking the patient codes to the specific patient names will be kept as a physical copy that will remain in a locked filing cabinet in HPNP Room 3313, and only the investigators will have access. The list will be shredded at the conclusion of the study. All electronic files containing clinical information will have PHI removed, and data will be stored on encrypted, password protected files accessed on a UF server. No information will be released to any person or agency without consent of the subject except as required by law.

Analysis plan for initial questions: To determine whether there is a difference in achieving blood pressure goal by using ABPM or chronotherapy.

Descriptive statistics will be carried out using paired t test (changes in blood pressure from baseline vs after 1 month of change in drug therapy for each patient) and Chi-square test or Fisher's Exact Test (amount of subjects from each group that achieved blood pressure goal).

For researchers other than those named on the protocol, use of the data and samples procured under this study will require approval from the PIs of this study in addition to the IRB.

7. Possible Discomforts and Risks:

Risk to the patient from participation in this study is minimal. Participants will not be subjected to processes beyond what is required for obtaining a satisfactory 24-hour blood pressure evaluation and required for routine monitoring of hypertension. Risks of using the ABPM are none. Slight discomfort may occur while wearing the ABPM device throughout the 24 hours as the device periodically inflates, and there may be modest sleep disturbances at the intervals when blood pressure readings are taken. Aside from

the aforementioned, participants will not have any additional discomforts beyond those associated with routine management of their hypertension.

8. Possible Benefits:

Study subjects may experience benefits from participation in the study if modifications in therapy lead to blood pressure control and achieving patients' blood pressure goals. The results of this study may help to improve anti-hypertensive drug therapy by tailoring and individualizing drug regimens based on patient blood pressure patterns. Results may lead to increased incorporation and use of ABPM in clinical practice and may help us improve how uncontrolled hypertension is treated and managed in clinic, thus providing possible advancements and modifications of protocol in clinic. Therefore, the potential information gained from this study outweighs the minimal risk associated with study participation.

9. Data Safety Monitoring Plan:

Based on assessments of the risk-to-benefit ratio, the risk level associated with the study is minimal. All risks have been described in the consent form.

Monitoring for documentation of an adverse event, whether anticipated or unanticipated, is the responsibility of the principal investigator or co-investigators. Regarding safety monitoring, all adverse events spontaneously reported, elicited, or observed by the investigators will be recorded. All Serious Adverse Events, should they occur, whether study-related or expected, will be documented in REDCap and reported to the IRB within five (5) working days.

In addition, the principal investigator will follow the reporting requirements for serious and unexpected adverse events outlined in the UF IRB Adverse Event Evaluation and Reporting Guide. All unanticipated, serious, fatal and/or life-threatening adverse events will be reported to the UF IRB. Aggregate reports of adverse events will be prepared on an annual basis or at the end of the study, whichever may occur earlier and forwarded to the IRB at annual review.

Plan for data management: Data collection for each subject will be recorded within REDCap. To protect the participant's right of privacy, the master list linking study-assigned patient codes to the patients' personal identifiers will be stored in locked cabinets with limited access, and electronic files will be kept in secured database. A de-identified dataset from the database using a patient identification number will then be shared with statistician for analysis. During the study, data will be analyzed as it becomes available by the PI and co-investigators. No early closure is planned because of the limited scope and projected low risk of the study.

There is a prospect of direct benefit to individual subjects in that assessing ambulatory blood pressure monitoring results could lead to appropriate modifications in anti-hypertensive drug regimens that may assist in improving blood pressure control.

Nevertheless, in the absence of a direct benefit, the study may advance the fields by offering a better understanding of the capacity at which ABPM can be incorporated into routine clinical practice and standard management of hypertension.

10. Conflict of Interest:

There are no conflicts of interest involved with this study beyond the professional benefits from academic publication or presentation of research results.

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