Title page
Hypertension protocol

Study title: Efficacy and safety of Twin Precision treatment in patients with hypertension- a multicentric, open-label, randomised controlled trial

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Sponsor name: Twin Health

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Design synopsis

Study design Multicentre, open label, randomised controlled trial	**Sample size** 104 in standard care 208 in the intervention arm Allocation ratio 1:2
Number of centres Approximately 5 to 10 sites **Duration of Program** **Run in period-** 2 to 3 weeks **Duration of intervention-** 2 years **Duration of follow up-** one year	**Number of groups:** 2 **Group 1 Standard care arm** Lifestyle modifications and medications as per current guidelines **Group 2 Intervention arm** Twin Precision treatment along with the standard of care
Details of intervention (Twin Precision treatment) The platform collects data from body sensors and a mobile app to track and analyze the body's health signals to personalize patients' treatment. Individualized medicine, exercise, sleep and nutritional syntax of the Twin Precision Treatment program guided by artificial intelligence will be	**Details of standard care (as per ISH 2020 guidelines)** **Lifestyle modifications** will focus on ● Weight loss for optimal BMI, ● Physical activity of 150 min/week ● Salt reduction ● Avoid smoking, alcohol **Pharmacological therapy:** A= ACE inhibitor or ARB B = Beta blocker

administered.	C = Calcium channel blocker D = Diuretics
Study population: ● Patients with hypertension ● Monotherapy or more than one drug as well not on medications ● Well-controlled or controlled	**Key exclusion criteria** ● Uncontrolled hypertension (> 180/110 mm of Hg) ● H/o hypertensive emergency requiring admission / Resistant Hypertension ● Diabetes mellitus ● Heart failure with EF < 40%
Primary outcome Change in blood pressure* 1-year post-randomisation * Both ABPM 24 hour and at clinic BP	**Secondary outcomes** ● Change in blood pressure* 6 months and two years post-randomisation ● Requirement of antihypertensive medications ● Change in metabolic parameters ● Inflammatory markers ● Hypertension mediated organ damage (Brain, cardiac, kidney and eye) assessment ● Major adverse Cardiac outcomes

Protocol signature page

Study title: Efficacy and safety of Twin Precision treatment in patients with hypertension- a multicentric, open-label, randomised controlled trial

I have read this protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct the study as outlined therein, including all statements regarding confidentiality. I will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the device and the conduct of the study.
I will conduct the study in accordance with the protocol, the Declaration of Helsinki and applicable local requirements.

Principal Investigator :

Job title: Senior Consultant

Institution:

Address:

Signature:

Date:

2. Introduction and background

Hypertension is the leading cause of cardiovascular disease and premature deaths worldwide. (1) According to WHO, globally, 1.13 billion people have hypertension, and it was estimated in 2015 that every 1 in 4 males and 1 in 5 females had hypertension. Even worse is that fewer than 1 out of 5 patients with hypertension had control in blood pressure. (2)

Elevated blood pressure arises from a combination of genetic and environmental risk factors. (3) Some risk factors include high salt intake, low potassium intake, sedentary lifestyle, obesity, unhealthy diet and alcohol consumption. (1) Also, patients with hypertension exhibit insulin resistance and hypertriglyceridemia compared to normotensive controls. While antihypertensive medications effectively control blood pressure, they are ineffective in preventing complications and do not effectively improve insulin resistance. (4) Also, the role of insulin resistance in diabetes has shown non-diabetic hypertensive patients have significantly higher plasma insulin concentrations than normotensive subjects. (5)

Nutrition based therapy and lifestyle modifications serve as the first line of treatment for prevention as well as to control blood pressure in stage 1 hypertension. (6) Dietary modifications have been widely considered an important step in the lifestyle modification strategy for prevention of hypertension. It also has the advantage of a lesser cost requirement than pharmacological therapy and without any side effects associated with antihypertensive medications. Several dietary patterns (such as DASH diet and Mediterranean diet) and strategies in the supplementation of macro and micronutrients have been tried with varied success. (3)

DASH trial: was conducted in a subgroup of 133 patients with SBP between 140-160 mm Hg and DBP between 90-95 mm Hg. All patients were given control diet for 3 weeks followed by randomisation to receive 8 weeks of either control diet (rich in fruits and vegetables) or combination diet rich in fruits, vegetables, and low-fat dairy products, including whole grains, fish, poultry, and nuts, and reduced in fats, red meats, sweets, and sugar-containing beverages. Both the control diet and combination diet significantly reduced blood pressure with much higher effect seen with combination diet. Control diet reduced systolic BP (−7.2 mm Hg, $P < .001$) and diastolic BP (−2.8 mm Hg, $P = .013$) and combination diet reduced systolic BP (-11.4 mm Hg, $P < .001$) and diastolic BP (−5.5 mm Hg, $P < .001$). (6)

PREDIMED trial: Studied the effect of mediterranean diet in 772 participants between 55- 80 years of age. Two forms of Mediterranean diet (with extra-virgin olive oil or nuts) was compared with low fat dietary on cardiovascular disease and blood pressure. There was a significant reduction in SBP of −5.9 mm Hg (CI, −8.7 to −3.1 mm Hg) in the Mediterranean diet with olive oil group and −7.1 mmHg (CI, −10.0 to −4.1 mmHg) in the Mediterranean diet with nuts group. (7)

3. Rationale for the study

While these studies have looked at the effect of dietary intervention on reduction in blood pressure, and have not focused on the reversal of hypertension. With Digital Twin technology - powered by the Internet of Things and Artificial Intelligence - we will be studying reversal of hypertension through improvement of metabolic health.

The TPT attempts to improve blood pressure control by measuring and treating the dysfunctional metabolism in the hypertensive patient. Using Digital Twin technology powered by artificial intelligence (AI) and Internet of Things (IoT) technologies, the Whole Body Digital Twin Platform captures data on up to 174 health markers, up to 3000 daily data points to provide precision nutrition guidance to the patient that precisely balances 87 essential nutrient factors to optimize the metabolic functioning of the patient. Additionally the Whole Body Digital Twin platform also captures daily physical activity and sleep data, and provides precision guidance on activity and sleep for the patient to follow.

In an ongoing diabetic trial involving Twin nutrition, we found that the intervention was able to achieve good reduction in systolic and diastolic blood pressure along with reduction of antihypertensive medications. Hence, we intend to look at the efficacy of the program on hypertensive patients without diabetes in this trial.

4. Objectives of the study

4.1. Primary Objective

1. To compare the mean change in systolic and diastolic 24 hr blood pressure ambulatory from baseline to 1 year between the 2 groups
2. To compare the mean change in systolic and diastolic blood pressure clinic based from baseline to 1 year between the 2 groups

4.2. Secondary Objective

Blood pressure and antihypertensive medication related

1. To compare the mean change in systolic and diastolic blood pressure between the 2 groups from baseline to 6 months and 2 years post randomization
2. To compare the proportion of patients having adequate control of hypertension at end of 1 year and 2 years

3. Among those with adequate control, to compare the de-escalation of dose or reduction in the number of antihypertensive medications from baseline to 6 months, 1 year and 2 years in both the groups

4. To study the frequency of introduction of new antihypertensive medications or dose escalation of existing antihypertensive medications in both the groups

Metabolic parameters and biomarkers based

5. To study the effect of Twin Precision treatment on change on metabolic parameters

6. To study the effect of Twin Precision treatment on change in cardiac and renal biomarkers

Quality of life and Safety related

7. To study the safety of Twin Precision treatment on antihypertensive drug withdrawal

8. To compare the change in quality of life and treatment satisfaction between the 2 groups

4.3 Exploratory objective

1. To study the change in exploratory biomarkers between the 2 groups
    - Endothelial function based biomarkers
    - Stress based biomarkers
    - Inflammatory biomarkers
    - Hormones, Vitamins and minerals
2. To study the incidence of hypertension mediated organ damage (brain, heart, kidney, artery, eyes)

5. Study design: Multi centric, open label, parallel arm randomized controlled trial

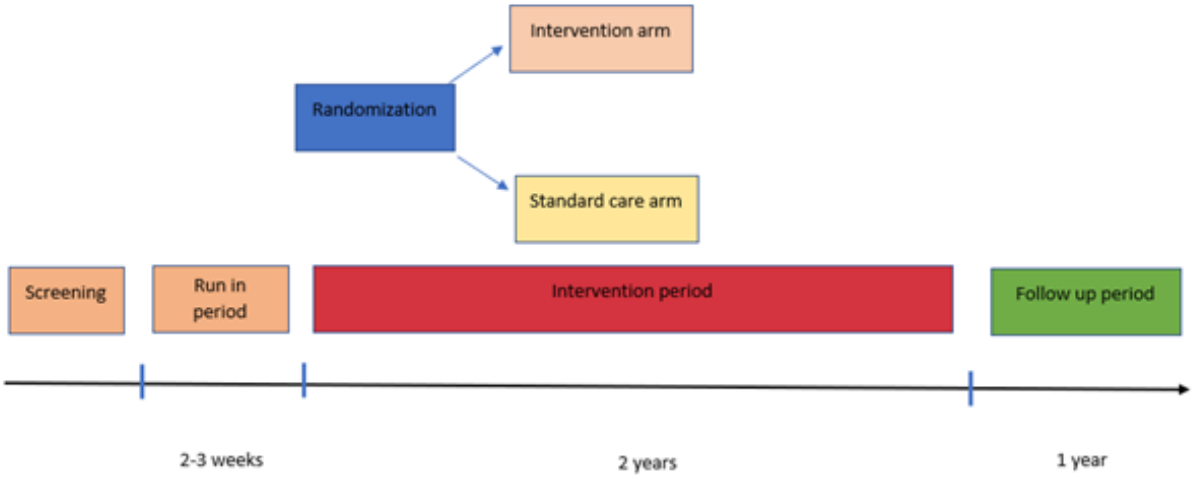

Figure-1 Study design

Study period: The total study period will be for approximately 3 years as follows:

Run in period: 2-3 weeks
Intervention period: 2 year
Passive Follow up: 1 year

After screening, all eligible patients will have a mandatory 2-3 weeks run-in period with existing therapy (standard care) for stabilization of blood pressure and for baseline continuous glucose monitoring. Patients with blood pressure >180/110 mm Hg at the end of 3 weeks run-in period will be considered as screen failure.

Number of groups:

Group A (Standard care arm): Will receive medications for hypertension along with lifestyle modifications as per existing guidelines

Group B (Intervention arm): Will receive Twin Precision Treatment along with standard care

6. Eligibility criteria

Inclusion criteria

1. Patients with diagnosis of primary hypertension (either adequately controlled or inadequately controlled with blood pressure ≤ 180/110 mm Hg); both treatment naive & on treatment (includes monotherapy or multiple drugs)
2. Age 18 years and above
3. Of either gender
4. Willing to follow study specific activities and able to handle smartphone

Exclusion criteria

Patients with the following criteria will be excluded.

1. Uncontrolled hypertension (> 180/110 mm of Hg) or history of hypertensive emergency requiring admission
2. Hypertension due to secondary causes
3. History of Diabetes mellitus (when either of the following criteria is met: on medications to control blood sugar or FBS > 126 mg/dl; RBS > 200 mg/dl; HbA1c ≥ 6.5)
4. Symptomatic heart failure or EF < 40%
5. Chronic kidney disease (eGFR less than 60 ml/min/1.73 m2) or history of any major renal anomalies like unilateral kidney, polycystic kidney
6. Any major cardiovascular event in the last 6 months (such as MI, stroke, TIA)
7. Hypertensive Retinopathy (grade 3 and above)
8. Weight loss more than 5% in 3 months
9. Arm circumference too large or small to allow accurate BP measurement with available devices
10. Special dietary requirements,or medications that would affect blood pressure (other than antihypertensive drugs) or nutrient metabolism
11. Unwilling or inability to modify current diet
12. Hypercalcemia (> 10.5 mg/dl) and Hyperkalemia.(>5.5 mmol/l)
13. Known Malignant cases < 5 years
14. Anemia (Hb < 8 gm)
15. Major Gastrointestinal diseases such as Inflammatory bowel disease, irritable bowel syndrome that can interfere with dietary intervention
16. Use of contraindicated drugs such as antacids of magnesium, calcium, steroids, lithium, anti-migraine drugs, phenytoin, antidepressants (SSRI, SNRI, and TCA), immuno-modulators, oral contraceptives, and any narcotic drugs.
17. Having received any investigational drug or device within 30 days prior to entry into the study
18. Poor compliance during screening or run in.
19. Autoimmune disorders and Connective tissue disorders
20. Total bilirubin of > 2 mg/dL or aspartate aminotransferase (AST) and alanine aminotransferase (ALT) 5 times the upper limit of normal range
21. Pregnant or planning to conceive in the next 3 years or breastfeeding
22. Psychiatric illness such as psychosis, manic depressive illness, alcohol or drug

dependence.

23. Consumption of >14 alcoholic beverages per week (for women) and > 21 for men
24. Any other condition or illness which the investigator feels would make the patient ineligible or make the patient difficult to participate in the study

7. Methodology

The study will be initiated after ethics committee approval and registration in CTRI. Eligible patients will be screened from Medicine OPD and written informed consent will be obtained before performing any study related activity. Informed consent will include consent for both screening as well as for enrolment into the study. Patients screened after informed consent but found to be eligible will be considered as screen failure.

7.1. Screening, eligibility and run-in period:

For the patient to be eligible, all inclusion criteria should be met and should not have any of the exclusion criteria.

Screening for eligibility will include

a. Medical history and clinical examination: for features of secondary hypertension if any, major cardiovascular events in the past, symptoms related to any major gastrointestinal disorders or autoimmune disorders, addiction to alcohol (AUDIT questionnaire) or other substance abuse.
b. Medication history for intake of any excluded medications, medications for conditions included in exclusion criteria
c. Blood test: Complete blood count, random blood sugar, HbA1c, electrolytes (Calcium and Potassium), liver function test, renal function test, C-Peptide
d. 2D Echo for heart failure, fundus examination for retinal changes
e. Urine pregnancy test for women in reproductive age group
f. Investigations to rule out secondary hypertension (only if clinically indicated) Doppler USG for renal artery stenosis, calcium score for ASCVD assessment, Urine/plasma metanephrines, urine cortisol, sleep apnoea questionnaire/ polysomnography for sleep apnea

Run in period

After confirming eligibility, the patient will have a 2-3 week run-in period as per standard care for stabilization of blood pressure and for assessing baseline glycaemic control using CGM. Patients not compliant during the run-in period will be excluded from the study.

Baseline assessment

- Baseline assessment will be done after completion of run-in period and before randomization. It includes
- Blood pressure monitoring both in clinic and ambulatory blood pressure
- Vital signs and anthropometric assessment (Height, weight, hip & waist circumference)
- Details of medications taken by the patient
- Quality of life assessment using: SF-36, Perceived stress questionnaire, Treatment satisfaction questionnaire, Montreal Cognitive assessment
- Blood sample for haematology, liver/ renal function test, markers of insulin resistance, HbA1c, inflammatory and other exploratory markers (detailed list included in the schedule of assessment chart
- Serum renin and aldosterone: In patients receiving potassium-wasting diuretics, the diuretic should be discontinued and potassium supplements should be administered for 1–2 weeks. If hypokalemia persists after supplementation, screening using a serum aldosterone and plasma renin activity should be performed. Ideally, antihypertensives should be stopped before testing, but that is often impractical. Aldosterone receptor antagonists, beta-adrenergic blockers, ACE inhibitors, and angiotensin receptor blockers interfere with testing and should be substituted with other antihypertensives if possible (12).
- Radiological investigations: ECG, Echo with epicardial & pericardial volume, cIMT, USG abdomen with KUB, Renal doppler, and CT Calcium score with pericardial & epicardial thickness.
- Gut microbiome analysis

Twin Health app and sensor-based assessment

Patients will be provided Bluetooth enabled body composition analysis scale, Omron blood pressure monitor, ketone meters, and Garmin wristband for tracking heart rate, footsteps, and sleep. Twin Health app will be installed in their smartphone which captures the data collected from the Bluetooth enabled devices.

7.2 Randomisation and allocation concealment:

Patients will be randomized into either standard care arm or intervention arm using central randomisation in a ratio of 1:2 (standard arm: intervention arm) Block randomisation of variable block size will be used.

Blinding: The study will be an open labelled trial.

7.3 Details of intervention:

7.3.1 Group A (Standard arm):

Will receive standard of care treatment (drugs and lifestyle modifications) as per AHA 2020 International Society of Hypertension- Global Hypertension Practice guidelines.

Counselling on lifestyle modification will be given by an exclusive study coach based on the following considerations

Salt reduction & Healthy diet	Reduce salt added when preparing foods, and at the table. Avoid or limit consumption of high salt foods such as soy sauce, fast foods and processed food including breads and cereals high in salt Advice will be given to include whole grains, fruits, vegetables, polyunsaturated fats and dairy products and Increase intake of vegetables high in nitrates known to reduce BP, such as leafy vegetables and beetroot. Other beneficial foods and nutrients include those high in magnesium, calcium and potassium such as avocados, nuts, seeds, legumes and tofu Advice to reduce food high in sugar, saturated fat and trans fats, *Dietician will guide the subjects by providing charts on the type of food to consume and the type of food to avoid based on the local availability and above recommendations
Regular physical activity	All subjects will be in the standard care arm will be advised to perform moderate intensity aerobic exercise (walking, jogging, cycling, yoga, or swimming) for 30 minutes on 5–7 days per week
Weight reduction	Subjects who are overweight will be motivated to reduce weight to reach an ideal BMI (18.5 to 24.9) or waist hip ratio < 0.5
Moderation of alcohol consumption and smoking cessation	Counselling will be provided on the importance of cessation of smoking and alcohol consumption. Habitual drinkers will be advised on the moderation of amount and to avoid binge drinking. The recommended daily limit for alcohol consumption is 2 standard drinks for men and 1.5 for women (10 g alcohol/standard drink).

Management of blood pressure in standard care arm

Medication will be started or up titrated if blood pressure is > 140/90 mm Hg and treated to reach target blood pressure

Target blood pressure control will be(10)

Office

- In <65 years < 130/80 mm Hg
- In 65 and above < 140/90 mm Hg

ABPM

- 24 hr average ≤130 and/or ≤80
- Day time average ≤135 and/or ≤85
- Night time average ≤120 and/or ≤70

HBPM ≤135 and/or ≤85

Frequency of assessment: For patients in the standard care arm, blood pressure will be assessed monthly after initiation or change in antihypertensive medication until target blood pressure is reached. Subsequently blood pressure will be monitored every 3 monthly.

Standard care home based BP monitoring: Self-measured BP monitoring be based on 2 measurements taken at least 1 minute apart in the morning and evening (ie, 4 readings per day) optimally for 7 days (ie, 28 readings total) with a minimum of 3 days (ie, 12 readings total). For each monitoring period, the average of all SBP and DBP readings should be obtained to assess BP. If the first day's readings are excluded, the preferred and minimum periods of monitoring should be 8 and 4 days, respectively. (9)

Standard care Office based BP monitoring:y 2–3 office visits at 1–4-week intervals. At each visit take 3 measurements with 1 min between them. Calculate the average of the last 2 measurements. If BP of first reading is <130/85 mmHg no further measurement is required.(10)

Stepwise approach for use of antihypertensive medications

Consider monotherapy in low risk grade 1 hypertension or in very old (> 80 yrs).

Category	**Systolic**		**Diastolic**
Normal BP	<130	and	<85
High normal BP	130-139	and/or	85-89
Grade 1 hypertension	140-159	and/or	90-99

Grade 2 hypertension	≥ 160	and/or	≥ 100

Table-1 Grades of hypertension

Classification of hypertension risk based on risk factors, end organ damage. (Table-2)

Risk factors/ Hypertension mediated organ damage	High normal blood pressure	Grade 1 hypertension	Grade 2 hypertension
No other risk factors	Low	Low	Moderate/high
1 or 2 risk factors	Low	Moderate	High
≥ 3 risk factors	Low/moderate	High	High
HMOD, CKD grade 3, diabete, CVD	High	High	High

Stepwise approach will be followed for adding antihypertensive medications as follows at each visit. (Table- 3)

Step-1 Dual low dose combination	A+C
Step-2 Dual full dose combination	A+C
Step-3 Triple combination	A+C+D
Step-4 (Resistant hypertension) Triple combination + spironolactone or other drug	A+C+D Add spironolactone

A - ACE inhibitor / ARB

C - Calcium channel blocker

D - Diuretics

Supportive references: A+C, Spironolactone, Alpha blocker, C+D

Alternatives include: Amiloride, Doxazosin, Eplerenone, Clonidine or beta-blocker

7.3.2 Group B (Intervention arm):

Will receive Twin Precision nutrition along with standard of care medications for hypertension

Details of Twin Precision Treatment (TPT)

Patients randomized to the intervention group will follow the medicine, exercise, sleep and nutritional syntax of the Twin Precision Treatment program.

Twin Health platform and sensors

The Twin Health platform uses a Whole Body Digital Twin, powered by artificial intelligence and Internet of Things technology, to precisely understand the metabolic impairment in the patient's body, which is unique to the patient. The platform collects data from body sensors and a mobile app to track and analyze the body's health signals in order to personalize patients' treatment.

The Digital Twin precisely understands metabolic dysfunction by monitoring and correlating up to 3000 health data points collected each day through sensors and by integrating with the historical and ongoing patient health data. This is done by providing blood screens and health sensors including a CGM patch, sensor watch, wireless BP meter, BHB meter and body composition scale. The platform then recommends the precision treatment needed to heal the metabolism. The precise nutrition activity and sleep recommendations are presented in the Twin mobile app, which also provides the daily health progress of the patient from day 1.

Patients enrolled in TPT according to the eligibility criteria will be analyzed retrospectively. TPT is an outpatient program. During TPT enrolment, complete information on medical history, family history related to chronic conditions, weight, height and current medication details will be captured.

Health coach: Each patient is paired with a health coach who works with the patient one-on-one to support the TPT. Upon receiving the blood test report, Twin mobile app installation, and sensor activation, the precision nutrition overview will be provided by the health coach. The sensor activation includes synchronizing the beta-hydroxybutyrate meter, body composition scale, wireless blood pressure meter and sensor watch to the Twin mobile app which was downloaded to the patient's mobile phone. As needed, the patients will be advised to perform routines of measuring beta-hydroxybutyrate (BHB) using the Ketone meter kit, measuring blood pressure using the digital Bluetooth-enabled blood pressure meter Omron 7316T, and measuring body composition parameters like weight, visceral fat, etc, using the Omron HBF 222T Bluetooth Smart Scale. Patients will be asked to wear a sensor watch (Garmin watch) to continuously record sleep parameters, heart rate, step count and other fitness parameters.

Continuous glucose monitoring (Ambulatory Glucose Profile, AGP) will be performed as needed using an FDA approved CGM patch which is integrated into the TPT web-based software.

Patients will also be asked to record their food intake and other useful markers on the Twin mobile app using voice or manual log.

Use of Machine learning

Machine learning (ML), a subtype of artificial intelligence, will use the data points that will be captured to learn what drives the glucose response to specific foods for each participant. Factors found to be involved in glycaemic response will be analysed for each participant. Participants will then be provided with a set of specific food recommendations in order to avoid glucose spikes. Using continuous glucose monitor (CGM) data, participant blood glucose values will be predicted using machine learning algorithms and data fusion techniques.

Each food item within every meal will be logged along with its weight by selecting it from a database of more than 2000 foods with nutritional values based on the USDA database and other sources that were further improved and expanded with additional items from certified sources.

The machine learning algorithm is devised to integrate these multi-dimensional data and accurately predict personalized glucose response. Dietary intake is a central determinant of blood glucose levels, and thus, in order to achieve normal glucose levels, it is imperative to make food choices that induce normal postprandial (postmeal) glycemic responses. Thus, the platform will suggest the right food to the right patient.

Meal plan

Depending on the likes and dislikes of the patient, the Twin platform will recommend a meal plan that is balanced across macro, micro and biota nutrients to reduce glucotoxicity and lipotoxicity, which helps in healing inflammation, fatty liver and damaged pancreas. This precise management of nutrition, activity and sleep ensures that the average blood glucose of the day will be consistently maintained within the optimal range. By continuously offering precision nutrition, precision sleep and precision activity recommendations, the food tolerance of the body will gradually improve. Patients will also be provided supplements to ensure sufficient micronutrients are consumed. Nutritional, activity and sleep counselling will be provided by trained health coaches through the app and via telephone.

General strategy for diet modification in Twin Precision treatment will be

- To avoid sugar(No added sugar); avoid refined oil, trans fats and substitute with healthy fats(Butter, Ghee, Olive oil, coconut oil, Sesame Oil, and Mustard oil)
- Reduce the frequency of feeding(Avoid snacks and reduce feeding window)
- Apply meal syntax vegetables first, then proteins and then carbs
- Add Non starchy vegetables in plenty(At Least five- seven servings); Adequate protein intake(1-2gms per kg of lean body weight); Green foods and supplements

Medication for blood pressure management

Blood pressure of the participants will be monitored periodically using home based, clinic based, and ambulatory blood pressure monitoring. Dose reduction or withdrawal of

antihypertensive drugs will be attempted when the patient reaches the target blood pressure.

Antihypertensive withdrawal protocol

Dose reduction or withdrawal of antihypertensive drugs will be considered when the patient reaches the target blood pressure. The dose reduction is in accordance with the protocol described by Nelson et al. i.e half dose reduction at weekly intervals with weekly assessment until the lowest dose is reached followed by withdrawal. The period of withdrawal will range from 2 weeks to 4 weeks.

Target blood pressure for our study will be considered as 130/80 mm Hg for young individuals and 140/90 mm Hg for elderly (65 and above) -2020 International Society for Hypertension Global Hypertension Practice Guidelines

Table-4 Antihypertensive medicines escalation and de-escalation protocol

Tier number	Medicines	Initial condition on enrolment	Reduction condition	Increase conditions
Tier 0	No medicine	Initial no medicine & BP < 160/100 mm Hg		Move to Tier 1, if (5d-BP > 135/85) & (after staying in this tier for 5 days)
Tier 1	Monotherapy (A)	Monotherapy	Move to Tier 0, if ((1d-BP < 135/85 for 7 consecutive days) II (1d-BP < 90/60 for 3 consecutive days) II (Symptoms of Hypotension like Postural Giddiness)) && (EOD-)	Move to Tier 2, if (5d-BP > 135/85) && (after staying in this tier for 5 days)
Tier 2	Dual low dose combination (A+C)	Dual low dose combination	Move to Tier 1, if ((1d-BP < 135/85 for 7 consecutive days) II (1d-BP < 90/60 for 3 consecutive days) II (Symptoms of Hypotension like Postural Giddiness))	Move to Tier 3, if (5d-BP > 135/85) && (after staying in this tier for 5 days)

Tier 3	Dual full dose combination (A+C)	Dual full dose combination/ Triple combination/ Triple combination + spironolactone or Alpha blocker	Move to Tier 2, if ((1d-BP < 135/85 for 7 consecutive days) II (1d-BP < 90/60 for 3 consecutive days) II (Symptoms of Hypotension like Postural Giddiness))	Move to Tier 4, if (5d-BP > 135/85) && (after staying in this tier for 5 days)
Tier 4	Triple combination (A+C+B/ D/ Alpha blocker)	Triple combination/ Triple combination + spironolactone or Alpha blocker	Move to Tier 3, if ((1d-BP < 135/85 for 7 consecutive days) II (1d-BP < 90/60 for 3 consecutive days) II (Symptoms of Hypotension like Postural Giddiness))	Consider manual change of medication or withdraw

A= ACE inhibitor or ARB
C = Calcium channel blocker
B = Beta blocker
D = Diuretics

Note:

EOD (End organ damage) + = 1. LVH present,
2. Albuminuria
3. Evidence of Heart failure
   A. Low ejection fraction
   B. High pro-BNP
   C. Clinical features
4. Hypertensive retinopathy

7.4 Monitoring for antihypertensive withdrawal

All patients will be closely monitored for sudden rise in blood pressure following dose reduction or withdrawal of antihypertensive drugs. Patients will be educated about warning symptoms such as headache, palpitations, chest pain, breathing difficulty and to immediately report to the treating physician. Also home based blood pressure monitoring will be done twice daily

7.5 Blood pressure monitoring

For the study both Home based monitoring, Ambulatory Blood pressure monitoring, and Clinic based blood pressure monitoring will be used. While ambulatory blood pressure

monitoring and clinic based blood pressure will be primarily used for end point assessment, home based blood pressure monitoring will be used for dose titration and safety monitoring.

7.5.1 Ambulatory blood pressure monitoring

For all patients ambulatory blood pressure monitoring will be done at monthly intervals for the first 3 months followed by every 3 months till the end of study and also as required by the primary treating physician.

Each measurement will be done for 24 hours. The following criteria will be used for adequacy of measurement (O'brien et al)

- 24 hr reading with > 70% of expected measurements
- 20 valid awake readings
- 7 valid readings at sleep

The frequency of measurement will be half hourly in day time and hourly at night time. Day time and sleep time will be defined based on the sleep time reported by the patient. Activity of the patient along with the time of food intake and medications will be captured during the ambulatory blood pressure monitoring.

7.5.2 Home based blood pressure monitoring

- Home based monitoring of blood pressure will be done using a calibrated Omron automatic blood pressure monitoring device. Purpose of home based BP monitoring is to ensure early detection of patients with extremes of blood pressure and to regulate the dose of antihypertensive medications.
- Blood pressure will be taken the same time each day in a comfortable room and sitting position after resting for at least 5 minutes.
- Patients will be instructed to avoid any stimulants such as coffee, tea, smoking or exercise 30 to 60 minutes before the measurement. Frequency of home-based monitoring will be twice a day daily for 5 days every week before taking medications (trough level) throughout the study period

7.5.3 Clinic based blood pressure monitoring

- Clinic based blood pressure assessment will be done by a trained nurse/doctor at the time of each study visit in both the groups.

Instructions to be followed while measuring blood pressure

- Blood pressure should be measured in a comfortable room and sitting position after resting for at least 5 minutes.
- At the time of initial evaluation measure BP in both the arms. If the difference between both the arms is > 10 mm Hg use the arm with the higher measurements. If the difference is > 20 mm Hg consider further evaluation.

- The same arm should be used preferably for all subsequent BP measurements.
- Take 3 readings at an interval of 1 min and the average of the last 2 measurements should be taken
- Patients should be instructed to avoid any stimulants such as coffee, tea, smoking or exercise 30 to 60 minutes before the measurement. Instruct the patient to empty the bladder.

7.6 Patient follow up and study period:

Patients will be followed up one month after randomisation followed by every 3 months till the end of 2 years or patient withdrawal. Details of the schedule of assessment is included in annexure

8. Schedule of activities assessment **(refer annexure)**

9. Study endpoints & outcomes

9.1 Primary endpoint

1. Primary outcome will be change in blood pressure as measured by ambulatory blood pressure monitoring at the end of 1 year
2. Primary outcome will be a change in blood pressure as measured in the clinic at the end of 1 year

Ambulatory blood pressure monitoring

Measurements will include mean 24h systolic and diastolic pressures, and daytime values (measured every 30 min from 07:00 am to 10:00 pm) and night-time values (measured every 60 min from 10:00 pm to 07:00 am). Only ambulatory BP recordings with a minimum of 70% measurements will be considered as successful.

In Clinic or office blood pressure: Average of 3 readings measured in the morning with 1 min gap at baseline and end of the study will be considered. Procedure for measurement of blood pressure is detailed under section 6.5 Blood pressure monitoring

9.2 Secondary outcome

Blood pressure and antihypertensive medication related

1. **Change in blood pressure (Clinical and ambulatory blood pressure)** from baseline to 6 months and 2 year. Ambulatory and clinic blood pressure monitoring will be done as mentioned in the primary endpoint.

2. **Adequate control of blood pressure** as measured by ambulatory blood pressure monitoring at 1 year and 2 years

Criteria for adequate control of blood pressure is

- In <65 years < 130/80 mm Hg
- In 65 and above < 140/90 mm Hg

3. Number of antihypertensive medications at 6 months, 1 year and 2 years

Among those with adequate control, the number of antihypertensive medications will be calculated at baseline (after run in period) and subsequently every 3 months. Combination pills containing more than one group (of antihypertensive medications) will be considered based on the number of groups. Example: Lotrel which is a combination of Amlodipine and benazepril will be considered as 2 drugs. Further each drug will be categorized as high dose or low dose.

Table-5 for doses of commonly used antihypertensive medications

Drug name	**Dose 1**	**Dose 2**	**Dose 3**	**Dose 4**
Losartan	25 mg	50 mg		
Telmisartan	20 mg	40 mg	80 mg	
Olmesartan	5 mg	20 mg	40 mg	
Candesartan	16 mg	32 mg		
Captopril	12.5 mg	25 mg	50 mg	100 mg
Enalapril	5 mg	10 mg	20 mg	40 mg
Lisinopril	5 mg	10 mg	20 mg	40 mg
Ramipril	1.25 mg	2.5 mg	5 mg	
Hydrochlorothiazide	12.5 mg	25 mg	50 mg	100 mg

Chlorthalidone	25 mg	50 mg	100 mg	
Indapamide	1.25 mg	2.5 mg	5 mg	
Frusemide	20 mg	40 mg		
Prazosin	1 mg	2.5 mg	5 mg	
Terazosin	1 mg	2 mg	5 mg	
Doxazosin	1 mg	2 mg	4 mg	
Propranolol	10 mg	20 mg	40 mg	
Metoprolol	25 mg	50 mg	100 mg	
Atenolol	50 mg	100 mg		
Bisoprolol	5 mg	10 mg		
Amlodipine	5 mg	10 mg		
Cilnidipine	5 mg	10 mg	20 mg	
Nicardipine	20 mg	40 mg	80 mg	
Nifedipine	30 mg	60 mg	90 mg	
Felodipine	2.5 mg	5 mg	10 mg	

4. Frequency of introduction of new antihypertensive medications or dose increment of existing antihypertensive medications will be noted across both the groups and compared.

Metabolic parameters and biomarkers based

5. Change in metabolic parameters

- Will include anthropometric assessment (Height, Weight, BMI, waist circumference, Waist hip ratio, visceral fat), lipid profile including lipoprotein (a), apolipoprotein - A1, apolipoprotein - B, insulin resistance (measured by HOMA- IR) every 3 months till end of study

6. Change in cardiac and renal biomarkers

- Cardiac biomarkers include Left ventricular hypertrophy (LVH), Ejection fraction

(EF) by Echo; Carotid intimal media thickening (cIMT) and NT pro BNP. All parameters will be measured 3 monthly except cIMT (measured 6 monthly)

- Renal biomarkers include blood urea, serum creatinine, eGFR and albumin creatinine ratio, measured every 3 months till the end of study

Quality of life and Safety related

7. **Safety assessment will** include
   - All reported adverse effects, abnormal changes in blood investigations,
   - Frequency of uncontrolled hypertension, hospital admissions due to uncontrolled blood pressure or hypertension related complications

8. Change in quality of life

- **Quality of life will be assessed using SF-36**. SF-36 is an indicator of overall health status. It has eight scaled scores under the following section (vitality, physical functioning, body pain, general health perceptions, physical, emotional and social functioning, mental health) Score ranges from 0-100 with higher score meaning less disability.
- **Physical activity** assessment using International physical activity questionnaire (IPAQ)
- **Treatment satisfaction** will be assessed using the Treatment satisfaction questionnaire for medications (TSQM). TSQM assesses four key dimensions of treatment satisfaction: Effectiveness; Side Effects; Convenience; and Global Satisfaction, enabling comparisons across medication types and diseases.
- **Stress assessment** using Perceived Stress Questionnaire

9.3. Exploratory endpoints

1. **Exploratory biomarkers (measured every 3 months)**
   - Markers of endothelial function (Endothelin, VCAM) and
   - Antioxidant stress biomarkers (cortisol, malondialdehyde, nitric oxide and glutathione).
   - Inflammatory markers: Complete blood count with ESR, hsCRP, uric acid, IL-6, AGE (advanced glycation end products)
   - Other Blood parameters: ferritin, vitamin B12, folic acid, other vitamins and minerals, electrolytes, testosterone and estradiol.

2. **Hypertension mediated organ damage (Brain, cardiac, kidney and eye)**

New onset end organ damage will be assessed as follows:

● Major adverse Cardiac outcomes such as occurrence of MI, TIA, stroke if any throughout the study period

●Hypertensive retinopathy assessed by fundus examination at baseline, 1 year and end of 2 years

● Cognitive assessment will be performed using Montreal Cognitive assessment (in patients 60 and above)

The Montreal Cognitive Assessment (MoCA) is a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal.

● Renal assessment by decline in eGFR

10. Criteria for withdrawal from study

Patients will be withdrawn from the study if they meet any of the following criteria:

- In case of hypertensive emergency or uncontrolled blood pressure
- Patient not willing to continue in the trial
- Patient not compliant with dietary instructions.
- Impaired hepatic function: AST/ALT ≥ 3.0 x ULN
- Impaired renal function: eGFR ≤ 40 mL/min/1.73 m2
- Development of any major adverse cardiac events (angina, MI, stroke etc)

11. Safety assessment

All patients will be continuously monitored for safety from the time of enrollment till the end of study. Safety will be assessed by looking for symptoms of raised blood pressure, periodic blood pressure monitoring and blood tests (liver and renal function test).

Patients will be educated to be aware of warning symptoms such as headache, palpitations, chest pain etc and immediately report to the health coach or treating physician. Patients will also be trained for home based blood pressure monitoring and contact the treating physician if the blood pressure is over 160/100 mm Hg. Blood tests for safety assessment such as liver and renal function tests will be done every 3 months.

12. Statistical considerations

12.1. Sample size calculation

Sample size is calculated based on the expected difference in mean reduction in systolic blood pressure at the end of 1 year between the 2 groups.

Based on an expected difference in mean reduction SBP from baseline to 1 year between the 2 groups as 5 mm Hg and standard deviation of 13 mm Hg, with power 80% and 5% alpha error, having 1:2 allocation ratio the estimated sample size is **83 in standard care arm and 166 in the intervention arm.** Accounting for an additional 20% drop out the final numbers are **104 in standard care and 208 in the intervention arm.**

12.2 Statistical analysis plan

All quantitative variables will be assessed for the normality by Shapiro-Wilk's test. If they follow Gaussian distribution, then they will be expressed as mean + SD. Continuous or quantitative variables which wouldn't follow normal distribution, will be transformed into logarithms or square root. Again, normality will be assessed by Shapiro-Wilk's test. Those variables which will not be following normal distribution after transformation will be represented by median (Interquartile range). Qualitative variables will be expressed as counts and percentages. Analysis will be carried out for the Intention to treat population as well per protocol population. Missing observations will be handled with imputation techniques. Comparison of quantitative data between the intervention group and control group will be done by independent sample 't' test, if they follow normal distribution. Non-normally distributed quantitative variables will be compared by Mann-Whitney U test. Comparison of categorical variables between groups was done by either Chi-square test or Fisher's Exact test based on the number of observations available. ANOVA will be used to compare the mean of normally distributed continuous variables across more than two categories. Equivalent non-parametric test viz, Kruskal Wallis H test will be used to compare non normally distributed continuous variables. Paired 't' test or Wilcoxon Signed Rank test will be used to compare pre and post continuous variables within the groups based on their normality. Exploring the possibilities of doing regression models with covariates. Data capturing and automation will be taken care of by Tableau Software. Microsoft Excel will be used to cross validate the data collected. Data validation and analysis will be carried out by IBM SPSS Statistics for Windows Ver 28.0; Armonk; NY; IBM Corporation. For statistical significance, two tailed p values <0.05 will be considered.

13. Ethical considerations

Study will be initiated after ethics committee approval and after obtaining written informed consent.

Possible benefits

The study may directly benefit the patient as well as the society. The anticipated benefits are improvement in blood pressure control, decrease in the number of antihypertensive

medications, body weight and complication rates of hypertension along with an overall improvement in the quality of life.

Risks involved

The study can have minimal risks due to tapering of antihypertensive medications. It may lead to rise in blood pressure and development of symptoms such as headache, chest pain, etc. However, since dose reduction will be done gradually and blood pressure will be closely monitored we do not anticipate any safety concerns.

14. Reporting of adverse events

Events that are both serious and unexpected for the patient population under study and that occur in participants treated with study medication will be reported to the sponsor/ Institute ethics committee. Adverse events that are not serious, but which lead to permanent discontinuation of study medication will be recorded and included in the final study report. All serious adverse events will be notified to the ethics committee and sponsor as per the timelines of the local IRB/ regulations.

An Adverse Event is any untoward medical occurrence in a patient that may or may not have a causal relationship to the study medication. It may be an unfavorable and unintended sign; symptom or medical condition occurring after the informed consent form is signed. Medical conditions/diseases present before consent is signed are considered AEs if they worsen after consent is signed. Information about every AE will be collected and recorded on the CRF. Adverse events, whether reported by the subject, information received during general discussion by the Principal Investigator, or detected through physical examination, laboratory test or other means will be recorded on the CRF and followed carefully until they resolve.

Abnormal laboratory values or test results should not generally be considered AEs, unless they induce clinical signs or symptoms or require therapeutic intervention; then, they should be recorded on the CRF with an appropriate justification.

Each AE will also be described by:

1. its duration (start and end time and date)
2. the severity grade (mild, moderate, severe)
3. its relationship to the study intervention (none, possible, probable, definite)
4. The action(s) taken by the Principal Investigator.

The severity grade of an AE provides a qualitative assessment of the extent or intensity of an AE, as determined by the investigator or as reported by the subject. The severity grade does not reflect the clinical seriousness of the event, only the degree or extent of the affliction or occurrence (e.g. severe nausea, mild seizure), and does not reflect the relationship to study supplement**.**

15. Regulatory considerations

The study does not involve use of any investigational drug product and is considered as a non regulatory trial.

The study will be conducted in accordance with the protocol and with the following:

- Applicable ICH GCP guidelines
- Applicable laws and regulations (National ethical guidelines for biomedical and health research involving human participant)

The protocol, amendments, informed consent forms and other relevant documents must be reviewed and approved by the sponsor, submitted to an IRB/IEC by the investigator, and reviewed and approved by the IRB/IEC before the study is initiated.

12.2 Insurance of study participants

All study participants in the trial will be covered under the insurance which is in line with applicable laws and/or regulations.

16. Operational considerations

16.1 Data management

All data will be de-identified for any patient identifiers and confidentiality will be maintained throughout. Each patient will be identified by a unique enrollment number. Only enrolment number, subject initials will be recorded on the CRF. If the subject's name appears on any other document collected the name will be obliterated and stored. Subjects will be informed that all personal information made available for inspection will be handled in the strictest confidence.

Data will be captured in an electronic case report form which has access restriction, password protection and backup of data.

Source documents will be maintained for all data entered in the CRF and archived for a minimum period of three years from the time of completion of trial or as per local requirements.

Data received from the sensors and data sent and received through the app will be kept secure according to requirements established by current and anticipated emerging legislation such as the Personal Data Protection Bill in India and HIPAA/HITECH in the U.S. Methods including AES 256-bit encryption for data in motion and at rest, minimum necessary disclosure and role-based security policies will be utilized.

16.2 Protocol deviation and violation

All study activities will be conducted in accordance with the protocol. No change in the protocol can be implemented without permission from the ethics committee except in scenarios to avoid an immediate hazard to trial subjects or for other medically compelling reasons and the same will be

notified to the ethics committee as early as possible. All protocol deviations will be notified to the ethics committee along with measures taken for corrective and preventive actions

16.3 Publication policy

The results of the study will be published in a peer reviewed journal. Authorship of publications of the overall study results will be determined by mutual agreement as per the International Committee of Medical Journal Editors authorship requirements. The sponsor will comply with the requirements of publication of the overall study results covering all participating sites. No data or part of the study can be published without the permission of the sponsor. Any information published will not reveal the identity of the study patients and confidentiality will be maintained.

17. References:

1. Mills, K.T., Stefanescu, A. & He, J. The global epidemiology of hypertension. *Nat Rev Nephrol* 16, 223–237
2. WHO. Hypertension. [source internet] available at https://www.who.int/news room/fact sheets/detail/hypertension#:~:text=An%20estimated%201.13%20billion%20people,cause%20of%20premature%20death%20worldwide. Last accessed November 30, 2020
3. Bazzano LA, Green T, Harrison TN, Reynolds K. Dietary approaches to prevent hypertension. *Curr Hypertens Rep*. 2013;15(6):694-702.
4. Reaven GM. Relationship between insulin resistance and hypertension. Diabetes Care 1991 Nov; 14(Supplement 4): 33-38.
5. Hu FB, Stamfer MJ. Insulin resistance and hypertension. The chicken egg question revisited. Circulation. 2005;112:1678–1680
6. Conlin PR, Chow D, Miller ER, Svetkey LP, Lin PH, Harsha DW, et al for the DASH Research Group, The effect of dietary patterns on blood pressure control in hypertensive patients: Results from the dietary approaches to stop hypertension (DASH) trial, *American Journal of Hypertension*. 2000;13(9): 949–55
7. Estruch R, Martinez Gonzalez MA, Corella D, Salas Salvado J, Ruis Guttierez V, Covas MI et al. Effects of a Mediterranean-Style Diet on Cardiovascular Risk Factors. A Randomized Trial. Annals of Internal Medicine. 2006: https://doi.org/10.7326/0003-4819-145-1-200607040-00004
8. Nelson M, Reid C, Krum H, Ryan P, Wing LMH, McNeil J et al. Short term predictors of maintenance of normotension after withdrawal of antihypertensive drugs in the second Australian National Blood Pressure study (ANBP2). American Journal of Hypertension. 2003; 16:39-45
9. Shimbo, D., Artinian, N. T., Basile, J. N., Krakoff, L. R., Margolis, K. L., Rakotz, M. K., ... & American Heart Association and the American Medical Association. (2020).

Self-measured blood pressure monitoring at home: a joint policy statement from the American Heart Association and American Medical Association. *Circulation*, *142*(4), e42-e63.

10. Unger, T., Borghi, C., Charchar, F., Khan, N. A., Poulter, N. R., Prabhakaran, D., ... & Schutte, A. E. (2020). 2020 International Society of Hypertension global hypertension practice guidelines. *Hypertension*, *75*(6), 1334-1357.
11. Shah, S. N., Munjal, Y. P., Kamath, S. A., Wander, G. S., Mehta, N., Mukherjee, S., ... & Jha, V. (2020). Indian guidelines on hypertension-IV (2019). *Journal of Human Hypertension*, *34*(11), 745-758.
12. Hypertension. Jameson J, & Fauci A.S., & Kasper D.L., & Hauser S.L., & Longo D.L., & Loscalzo J(Eds.), (2020). Harrison's Manual of Medicine, 20e. McGraw Hill.
13. Eoin O'Brien, Gianfranco Parati, George Stergiou, Ambulatory Blood Pressure Measurement What Is the International Consensus?, (Hypertension. 2013;62:988-994.)

18. List of annexures

a) Schedule of assessments and visits
b) SF-36 questionnaire
c) Perceived stress scale questionnaire
d) Montreal Cognitive assessment
e) List of green foods
f) List of supplements
g) IPAQ Questionnaire