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MASked-unconTrolled hypERtension management based on office BP or on ambulatory Blood Pressure measurement (MASTER) Study. A randomised controlled trial protocol

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Abstract

Introduction: Masked uncontrolled hypertension (MUCH) carries an increased risk of cardiovascular (CV) complications and can be identified through combined use of office (O) and ambulatory (A) blood pressure (BP) monitoring (M) in treated patients. However, it is still debated whether the information carried by ABPM should be considered for MUCH management. Aim of MASTER study is to assess the impact on outcome of MUCH management based on OBPM or ABPM. **Methods and Analysis.** MASTER is a 4-year prospective, randomized, open-label, blinded-endpoint investigation. A total of 1240 treated hypertensive patients from about 40 secondary care clinical centers worldwide will be included upon confirming presence of MUCH (repeated on treatment OBP<140/90mmHg, and at least one of the following: daytime ABP ≥135/85mmHg; nighttime ABP ≥120/70mmHg; 24h ABP ≥130/80mmHg), and will be randomized to a management strategy based on OBPM (Group1) or on ABPM (Group2). Patients in Group1 will have OBP measured at 0,3,6,12,18,24,30,36,42,48 months and taken as a guide for treatment; ABPM will be performed at randomization and at 12,24,36,48 months but will not be used to take treatment decisions. Patients randomized to Group2 will have ABPM performed at randomization and all scheduled visits as a guide to antihypertensive treatment. The effects of MUCH management strategy based on ABPM or on OBPM on cardiovascular and renal intermediate outcomes (changing LV mass and microalbuminuria, co-primary outcomes) at one year and on CV events at 4 years and on changes in BP-related variables, will be assessed. **Ethics and Dissemination.** MASTER study protocol has received approval by the Ethical Review Board of Istituto Auxologico Italiano. The procedures set out in this protocol, are in accordance with principles of Declaration of Helsinki and Good Clinical Practice Guidelines. Results will be published in accordance with the CONSORT statement in a peer-reviewed scientific journal. **Trial registration number:** NCT028047074.

Key words: Masked uncontrolled hypertension (MUCH); office blood pressure (OBP); ambulatory blood pressure monitoring (ABPM); treated hypertensive patients; antihypertensive treatment; hypertension management; cardiovascular and renal outcomes; hypertension control.

Word count: 3269

Introduction

The finding in untreated hypertensives of normal blood pressure (BP) levels when measured in the medical office accompanied by elevated out of office BP as assessed by either 24-hour ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM), is defined as "masked hypertension". This condition is relatively common, characterizing 10-15% of individuals in a population (1). Remarkably, even after initiation of antihypertensive treatment, a substantial number of patients continue to show elevated BP levels out of the office, despite having apparently well controlled BP levels during the medical visit. This condition has been defined as "masked uncontrolled hypertension" (MUCH), and in a population of hypertensive patients under treatment has been reported to occur in as much as 30-31% of cases (2). Moreover, there is evidence that prescription of antihypertensive treatment without adequate care of 24h BP coverage, and without implementation of ABPM in the assessment of treatment effects, may indeed be responsible for an increase in the frequency of MUCH (3). As in the case of MH, MUCH has been associated with an increased cardiovascular risk which is very similar to that of sustained hypertension and sustained uncontrolled hypertension in treated patients (i.e. persistent elevation in both office and out-of-office BP levels) (4), (3). Several hypertension guidelines have indeed included suspicion of these conditions among the key clinical indications for out-of-office BP monitoring (5), (6), (7), (8) , (9), (10). The superiority of out-of-office BP vs office BP measurements has been recently emphasized also by hypertension management guidelines, in particular by the NICE guidelines which have recommended use of a time-restricted ABPM before starting treatment in patients with elevated OBP (11). However, key evidence from randomized ad-hoc intervention trials on the benefits of using out-of-office BP measurement for assessment of blood pressure control during the follow-up of treated hypertensive patients is still lacking. With the aim to better explore this issue, the MASTER study (MASked-unconTrolled hypERtension management based on office BP or on ambulatory Blood Pressure measurement) will evaluate whether an ABPM based hypertension management strategy is superior to an OBPM based strategy in changing LV mass and

microalbuminuria (co-primary outcomes) at one year, in preventing CV events (secondary outcome) at 4 years, and in improving several BP-related variables throughout the study. The MASTER study, focusing on MUCH patients, is thus expected to provide useful information aimed at finally clarifying whether a management strategy based on out-of-office BP measurements might provide a greater benefit in terms of prevention or regression of organ damage and cardiovascular events than a management strategy based on office BP readings only, thereby assessing the actual value of using out-of-office BP in improving cardiovascular protection

Methods

Study design

The present study is a 4-year prospective, randomized, open-label, blinded-endpoint (PROBE) study aimed at comparing a management strategy for MUCH patients, based on OBPM as a guide to antihypertensive treatment (group 1) versus a management strategy based on use of ABPM for the same purpose (group 2). The study will have a period of 2 years for the enrolment of the requested number of patients; and an average 4-year follow-up period (3 to 5 years).

Study endpoints are changes in LV mass and microalbuminuria (co-primary outcomes) at one year, prevention of CV events including all-cause mortality, CV morbidity and mortality (secondary outcomes) at 4 years, and improvement of several BP-related variables throughout the study (tertiary outcome). Following a parallel group study design, patients will be randomized to one of the two management strategies by a centralized computer generated sequence with an allocation ratio of 1:1.

Sample selection

Recruitment

MASTER is a multicenter, multinational study including around 40 clinical centers from different continents: Europe (Austria, Belgium, Croatia, Georgia, Germany, Italy, Poland, Romania, Russia, Serbia, Spain, Sweden), Asia (China, India, Korea) and South America (Argentina, Brazil, Venezuela) –A list with the participating centers is provided in the table S1 in the supplemental data file.

To all participating centers, the coordinating center in Milan will supply the due study documentation, including a description of the protocol and of the expected tasks, and the files to be signed in relation to study participation agreement. In order to guarantee the necessary data quality, each participating center will be asked to submit to the coordinating center information on the available devices for collection of the data required by the protocol. They will also be asked to send a sample of the recorded files related to specific study variables for quality check and file approval by the coordinating center team. This will be specifically required for digital ECG files, for cardiac ultrasound records, for 24h ABPM files and for Home BP records. If the center fulfills all requirements and complies with study quality standards, an official agreement will be signed with the coordinating center before trial can be started. Approval by local ethics committee will also be required for each participating center.

Screening and randomization

Around 40 subjects will be enrolled in each center upon verifying the study eligibility criteria listed in **Box 1.**

Patients are to be enrolled for screening and randomization over 1 year (a maximum of 2 years will be allowed). During the screening period (1 month before randomization) eligibility of the patient will be checked and baseline measurements performed. Initial assessment of selection criteria based on subjects' clinical history will take place and, in case the subject is potentially eligible, the participation in the study will be proposed and informed consent obtained. During one or more screening visits, according to the need of the enrolling unit, the additional evaluations needed for a

complete assessment of eligibility criteria will be performed. Specifically: full medical history, physical examination, blood and urine samples, conventional BP measurements, ABPM placement for 24h recording (device to be removed on the following day). Once the diagnosis of MUCH has been made, baseline study variables will be collected. These include 7 days home BP monitoring through use of oscillometric devices validated by means of international protocols; ECG and echocardiographic examinations, and blood and urine tests. Blood samples will be obtained for assessment of eGFR, plasma creatinine, plasma glucose, HbA1c, uric acid, serum sodium and potassium and plasma lipids. Two blood samples will also be collected at follow-up visit 1, and at follow-up visit 3 in order to create a study biobank for future analyses. Spot urine samples for urine albumin/creatinine ratio will be taken twice, once in the morning before application of the ABPM device, and another time on the following morning when subjects will return to the center clinic for removing the ABPM device.

At each study site, the responsible investigator will arrange a randomization visit (within 1 month after the Screening period) during which eligible patients (i.e. those found to have masked uncontrolled hypertension) will be randomized to one of the two study groups following the dynamic allocation method for balancing baseline covariates (specifically center, age,sex, presence of diabetes and baseline Office SBP) proposed by Xhiao et al in 2012 (12). The patient's randomization number and allocation will be generated by a central computer using an online algorithm inbuilt on the e-CRF. This approach adapts the algorithm proposed by Frane et al. to obtain marginal balance for both continuous and categorical covariates, adding the Efron's biased coin method to decrease the predictability of treatment assigned to a new patient (13). This aspect is very important especially for unblinded trials. The original R code to perform this algorithm, furnished by the author, will be set on the platform managing the e-CRF.

Blinding (masking)

Because the MASTER is an open-label study, blinding will apply only for the endpoints. Thus, both participants and investigators will not be blinded to the allocated intervention. In order to guarantee the blind assessment of the co-primary end point of LVM, the personnel involved in its assessment (i.e. sonographers) will be blinded to the patient's allocated management strategy. In addition, ABPM data of patients enrolled to group 1 will be directly uploaded on the eCRF and will not be available to the investigators in charge of treatment decisions. The role of the Event Adjudicating Committee (EAC) of the MASTER study is essential in a trial such as MASTER, necessarily designed as a PROBE trial. This Committee (EAC) within the MASTER study will be responsible of verifying and adjudicating in a blinded fashion all events representing primary, secondary and tertiary outcomes of the study, as well as all serious adverse events occurring in the course of the trial. For this reason the General Coordinating Centre in Milan will insure that all outcome documentation sent to the Event Adjudicating Committee is blinded for management strategy and intensity of antihypertensive therapy. Documentation of each outcome occurring in patients will be sent (electronically or by fax) to two experts and to a third one in case the first two do not reach an agreement. Only validated outcomes will enter the final data analysis.

Interventions

Blood pressure levels in both study groups will be measured by three BP measurement techniques (office BP, home and 24-ABPM). Indications on how to measure BP in the office, at home and in ambulatory conditions over 24 hours are provided in the supplemental Operation Manual. In order to standardize ABPM and OBPM data collection and analysis as much as possible, 24h ABPM in Master Study will be preferentially performed with A&D TM2430 device and OBP levels will be measured with A&D UA-651BLE device provided by the Coordinating center thanks to a non-conditioning support given by the A&D Company (A&D Engineering, Inc. 1756 Automation Parkway San Jose, CA 95131 US). For HBPM any of the currently available validated devices can be employed. Patients randomized to be managed based on office BP (Group 1) will have their BP

measured by the office method at all scheduled visits (at 0, 3, 6, 12, 18, 24, 30, 36, 42 and 48 months). In these patients ABPM will only be performed at randomization visit and at follow-up visits 3, 5 , 7 and 9 and in case of premature discontinuation at any time. However, ABP values will not be used by the investigator to take treatment decisions, but treatment will be based on office BP only. According to the ABPM procedures manual of the MASTER study, data of these patients will not be made available to the investigators in charge of treatment decisions, but will be directly uploaded on the study website (Table 1)**.** As indicated in Table 1, additional tests and examinations will be performed at different time-points during the study follow-up. For assessment of left ventricular (LV) mass and function both, B mode and M mode 2D echocardiographic measurements and calculation of left ventricular mass (LVM) will be performed according to current American Society of Echocardiography guidelines (14), (15) (16), (17). LVM will be calculated with the formula for estimation of LVM from LV linear dimensions (17). In order to account for obesity-related LV hypertrophy (15), (16) correction of LVM will be performed both for height and for body surface area (BSA) using the Dubois and Dubois formula (14), (16). Since LVM values differ between men and women, with the latter systematically lower than the former, even when indexed for BSA, the presence of LV hypertrophy (LVH) will be defined on the basis of upper limits of normality for LVM of >115 g/m^2 (>48 $g/h^{2.7}$) in men and >95g/m^2 (>44 $g/h^{2.7}$) in women following recommendations for cardiac chamber quantification by echocardiography in adults (17). Patterns of LVH (concentric vs. eccentric) and remodeling will also be considered. LV systolic function will be estimated by calculating ejection fraction (EF) by means of the biplane method of disks summation (modified Simpson's rule), which is the recommended 2D echocardiographic method by consensus (17). Diastolic function will also be assessed by considering the following parameters: mitral inflow PW Doppler, TDI of mitral annulus, PW Doppler of pulmonary vein flow, tricuspidal valve velocity peak calculated by CW Doppler and indexed left atrial volume (biplane maximal left atrial volume will be calculated using the area-length method, and then indexed by body surface area) as indicated by current guidelines (18), (19).

Electrocardiogram recordings will also be performed at different time points of the study in order to identify the presence of ECG-LVH. This will be done by means of specific indices such as Cornell Voltage Product and Index and Sokolow-Lyon Index.

The co-primary end point of UAE will be evaluated from morning spot urine samples and expressed as albumin/creatinine ratio (UACR, mg/g). Spot urine samples will be taken twice, once in the morning before application of the ABPM device, and another time on the following morning when the ABPM device will be removed.

Blood samples will also be obtained for determination of serum creatinine, glucose, HbA1c, uric acid, Na+, K+ and lipids as well as to create a study biobank.

At each follow-up visit physicians will not only ascertain achievement of BP control and/or adjust antihypertensive treatment if needed, but they will also record the type of antihypertensive therapy, presence of concomitant medications and adverse events on the study e-CRF for study safety evaluation (Table 1).

Given that the trial inclusion criteria establish that all patients in MASTER should have OBP controlled by treatment (i.e. systolic OBP < 140 and diastolic OBP < 90 mmHg), all patients in group 1 will have their antihypertensive treatment unmodified at the randomization visit. If at any of the subsequent trial visits, SBP or DBP will exceed normal values (i.e. SBP ≥ 140 or DBP ≥ 90 mmHg) antihypertensive treatment will be intensified according to available guidelines (Figure 1).

Patients randomized to be managed based on ABPM (Group 2) will have their BP measured by the ambulatory method at all scheduled visits. OBP will also be measured at all visits, but it will not be used by the investigator to take treatment decisions. Given that the trial inclusion criteria establish that all patients in MASTER should have uncontrolled ambulatory systolic or diastolic BP values (24h or daytime or night-time), all patients in group 2 will have their antihypertensive treatment intensified at the randomization visit and at any of the subsequent trial visits, in which ambulatory

SBP or DBP will exceed normal values (i.e. 24h SBP ≥130 or 24h DBP ≥ 80 mmHg; daytime SBP ≥ 135 or Daytime DBP ≥85; night-time SBP ≥ 120 or night-time DBP ≥70 mmHg), according to available guidelines (Figure 1). In case only daytime or night-time target values are not achieved, change in timing of doses to morning or evening, respectively, should be considered. At each Follow-up visit achievement of ABP control will be ascertained and antihypertensive treatment will be adjusted if needed, according to guidelines (Figure 1).

Sample size calculation

Sample size calculation was based on the primary study end-point of changes in LVMI at 12th month. We do not know what proportion of the enrolled patients will have a diagnosis of LVH, therefore the primary end-point has not been based on categorical changes in LVH but rather on changes in LV mass as a continuous variable. As the enrolled patients are hypertensive patients with BP incompletely controlled by treatment, we expect LV mass to be often higher than in subjects with sustained BP control (normal office and ambulatory BP levels). To calculate the sample size we have assumed a difference of 5 g/m^2 in the change of LVMI with the ABP-guided (Group 2) compared to the office BP-guided (Group 1) management strategy. This has been based on the consideration that SBP will be reduced by about 8 mmHg more in the ABP-guided group, as well as on the echocardiographic data of studies such as REGAAL and CATCH in which differences in echo LVMI changes between treatments producing similar BP reductions, were lower than 3g/m^2 (20), (21) The standard deviation of ± 25 g/m^2 was also derived from data of REGAAL and CATCH as well as from previous assessment of within operator reproducibility (20), (21). Considering a LVMI difference between groups of 5.0 g/m^2 and a standard deviation of 25 g/m^2, an alpha of 0.025 (one-sided T-Test) and a power (1-beta) of 90%, with a drop-out rate of 15% during the study period, a minimum of 620 subjects per study group was deemed necessary, for a total number of 1240 subjects to be randomized. However, given the uncertainty about the true LVMI difference we might observe and/or the related standard deviation, performance of an interim

analysis has been decided aimed at a possible re-estimation of the sample size . This analysis will be carried out at 18th month when about 30% of randomized patients will achieve one year of follow-up. A re-estimation of the sample size will be calculated using the method of conditional power (22).

Outcomes

Primary, secondary and tertiary outcomes are listed in box 2.

Data collection and Data statement

All data collected locally at each enrolling unit will be recorded into an electronic e-CRF on the website of the trial (https://master.digitalcrf.eu). Clinical data to be input into the e-CRF include demographic information, results on blood and urine laboratory tests performed locally (i.e. Plasma creatinine and eGFR, fasting glucose, uric acid, Na+, K+ , Lipid profile, HbA1c, Urinary sediment), ongoing antihypertensive treatment (number and dose of antihypertensive drugs); report forms for adverse events during follow-up. Digital files containing raw data from imaging (echocardiograms) and device based examinations (ABPM, HBPM data, ECG tracings) will also be uploaded on the study website linked to the study e-CRF for further analysis by the central reading sites.

Data management

Clinical data and recordings obtained with the various technologies will be uploaded in the study e-CRF and on the study website under on-line control by the Data Management Coordinating center, which includes an Audit Trail System. The quality of data obtained with the different technologies (i.e. echocardiograms, ECG, ABPM, HBPM) will be validated by expert personnel at the Central reading sites. The occurrence of cardiovascular events (stroke; myocardial infarction, all major cardiovascular events, cardiovascular death, all cause death) and renal outcomes reported by each center and supported by clinical source documents (i.e. diagnostic tests, medical reports) will be

validated by an Adjudicating Committee of experts blinded to assigned management strategy, BP values and organ damage measurements.

Data analysis plan

Descriptive analysis. Continuous data will be summarized by means of mean value, median, minimum, maximum, standard error, standard deviation, number of observations. Moreover, a 95% confidence interval for the mean value will be provided. Categorical data will be summarized by means of absolute and relative frequencies. All these analyses will be performed per management group as well as for the study as a whole. Unpaired t-test (or U-Mann-Whitney test in case of non-normal distribution) for continuous variables or chi-square test for categorical ones in order to evaluate significant between-group differences at baseline will be applied. The incidence of adverse events will be tabulated by treatment group.

Statistical methods for co-primary endpoints analysis. We will consider two co-primary endpoints: change from baseline to 12th month in LVMI and in albumin/creatinine ratio. Each endpoint will be analyzed by means of the Analysis of Covariance (ANCOVA), adjusting the group effect for the baseline value of LVMI (or albumin/creatinine ratio) and for baseline covariates resulting significant in the comparison between groups. Moreover, to have valid inference, as suggested by several authors, we will adjust the model for all variables used in dynamic allocation scheme (13). The assumption of parallelism will be tested by introducing one or more crossproduct terms between groups and continuous covariates to the model.

Statistical methods for secondary endpoints analysis. For all secondary endpoints, except for endpoint 8, we will consider a repeated measurement approach based on mixed models which contain both fixed effects (e.g. BP technique measurements) and random effects (e.g. patient). These models are likelihood-based approaches in presence of ignorable missing data (i.e missing at random) and are a proper way to accommodate information on a patient with post-randomization

outcomes, even when such a patient's profile is incomplete (23). In particular for endpoints 1, 3, 4, 5 and 7 a repeated-measures model for dichotomous endpoints will be applied while for endpoints 2,6,9 and 10 we will consider a model for continuous outcome. In both cases the main purpose will be that to determine whether the within-person changes over time varie across levels of one or more between-person factors (e.g. BP technique measurements and for the same covariates included in the model for co-primary endpoints) (13). For endpoint 8, cumulative proportion surviving curves according Kaplan-Meier will be obtained for each group and compared with the method of log-rank test. In order to explore the group effect on the time to event of composite outcome adjusting for baseline covariates, the Cox regression model will be fitted. Though the Cox model is non-parametric to the extent that no assumptions are made about form of the baseline hazards, two important issues of non-informative censoring and proportional hazards will need to be verified. To satisfy the first assumption, the design of the underlying study must ensure that the mechanisms giving rise to censoring of individual subjects are not related to the probability of an event occurring. Care will be taken that continuation of follow-up does not depend on a participants medical condition. To satisfy the second assumption, the Chi square tests of proportional hazards assumption and the log-cumulative hazard plots will be made. If the assumption of proportionality is deemed reasonable, the assumptions of linearity and additivity, which are implicit in the linear predictor formula, will be considered. Although the composite endpoint could be misleading, we will not proceed to analyze each individual event considering the other events as competing causes of failure because also competing risk analysis can be misleading. Randomized Controlled Trials (RCTs) are frequently not powered to detect an effect of the intervention on individual components and competing risks analysis might have a low chance of detecting a true effect (24).

Statistical methods for tertiary endpoints analysis. For endpoints 1-3 we will apply mixed models proposed for secondary endpoints. For endpoints 4-12, we will apply the chi-square test for dichotomous endpoints, the T-test (or median test whenever necessary) for continuous endpoints

and, specifically for variation coefficients, the large sample Z test as suggested by Bhoj et al (25). For endpoints 13 and 14, the differences between the Person correlation coefficients of two groups will be calculated and reported with their 95% confidence intervals using the approach proposed by Zou (26). The handling of missing data will be based on a multiple imputation approach (23). All statistical tests will be interpreted at the 5% significance level considering two-sided test, unless specified otherwise. All statistical analyses will be performed by the Statistical Centre of Istituto Auxologico Italiano, Milan. Statistical packages will be used for the analyses, chosen among Stata (STATA data analysis and statistical software, Texas, USA), R (The R project for statistical computing, free software) and SAS (SAS Institute, Cary, NC, USA).

Ethical considerations

MASTER study protocol has initially received approval by the ethics committee of the Istituto Auxologico Italiano. Thus, the ethical conduct of this study will be under the control of an independent Data Safety Monitoring Board, stemming out of the Istituto Auxologico Italiano Ethical Review Board. This is an investigator generated study and as such will be performed in full independence of the study Sponsor from any other funding body. The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation, are designed to ensure that the sponsor and investigator abide by Good Clinical Practice Guidelines and follow the guiding principles detailed in the Declaration of Helsinki. All centers in this study will have to obtain approval from Ethics Review Committees and/or Institution also in their Country in order to participate, and the study should be carried out in line with applicable local law(s) and regulation(s). The need of study insurance will be determined for each participating center according to national and local laws.

Dissemination

The protocol of the MASTER study has been registered with number NCT02804074 at https://clinicaltrials.gov/ where it may be accessed and consulted. Results will be published in accordance with the CONSORT statement in peer-reviewed scientific journals regardless of the outcome.

Authors' contributions:

Parati, G; Schmieder, R; Stergiou, G; McManus, R; Redon, J; Omboni, S; Bakris, G; Mancia, G; and Zanchetti, A; contributed to the conception and design of the study.

Parati, G; Schmieder, R; Mancia, G; and Zanchetti, A; drafted and wrote the protocol in accordance to the coauthors' contributions.

Faria, T; and Wijnmaalen, P; are the study managers in charge of database management and study monitoring.

All authors: Parati, G; Agabiti-Rosei E; Bakris, G; Bilo, G; Branzi, G; Cecchi, F; Chrostowska, M; De la Sierra, A; Domenech, M; Dorobantu, M; Faria,T; Huo,Y; Jelaković, B; Kahan,T; Konradi, A; Laurent,S; Li,N; Madan, K; Mancia, G; Mcmanus, R; Modesti, PA; Ochoa, JE; Octavio, JA; Omboni, S; Palatini, P; Park, JB; Pellegrini, D; Perl, S; Podoleanu, C; Pucci,G; Redon, J; Renna, N; Rhee, MY; Rodilla Sala, E; Sanchez, R;Schmieder, R; Soranna, D; Stergiou,G; Stojanovic, M; Tsioufis, K; Valsecchi, G; Veglio, F; Waisman, G; Wang, J; Wijnmaalen, P; Zambon, A; Zanchetti, A; and Zhang, Y; contributed to the writing and the reviewing of this article, and approved the final draft of the protocol.

Roles

General Operating and Executive Committee (GOEC): Parati, G; Omboni, S; Mancia, G; and Zanchetti, A.

The General coordinator (GC) of the study: Parati, G.

Steering committee: members of the GOEC along with a selection of experts from selected centres (Parati, G; Schmieder, R; Stergiou, G; McManus, R; Redon, J; Omboni, S; Bakris, G; Mancia, G; and Zanchetti, A).

The endpoint adjudication committee (EAC): Clement, D (Ghent, Belgium), and will include experts from different centres (Agabiti Rosei, e; Palatini, P; and Waeber, B).

Data management team from the Istituto Auxologico Italiano

Data analysis: Statistical Centre (STATC) led by Zambon, A.

Data and Safety Monitoring Board (DSMB): Tsioufis, C (Athens, Greece); Cecchi F (Florence, Italy); Borghi, C (Bologna, Italy); Stéphane, L (Paris, France); Modesti, PA (Florence, Italy); and Valsecchi, G (Milan, Italy).

Acknowledgment

The names of the remaining investigators of the MASTER Study are listed in table S1, in the data supplement.

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In order to standardize ABPM and OBPM data collection and analysis as much as possible, 24h ABPM in Master Study will be preferentially performed with A&D TM2430 device and OBP levels will be measured with A&D UA-651BLE device provided by the Coordinating center thanks to a non-conditioning support given by the A&D Company (A&D Engineering, Inc. 1756 Automation Parkway San Jose, CA 95131 US).

Competing interests statement

Parati, G: honoraria as lecturer for Pfizer, Daiichi Sankyo, Menarini, Omron Healthcare. **Agabiti Rosei, E:** honoraria and/or support from Menarini, Servier, Recordati,Guidotti,Malesci,Ferrer, DOC gen, Bruno farm. **Bakris, G:** Principal investigator (FIDElio)-Bayer, Steering committee (CREDENCE(Janssen), SONAR (AbbVie)-Consultant for Merck, Relypsa, Vascular Dynamics, Elceyx, Bayer, Janssen, AbbVie. **Cecchi, F:** collaboration with Smart Solutions Technologies S.A.; AMICUS; Boston Scientific International S.A . **De la Sierra, A:** honoraria as lecturer for Abbott, Daiichi-Sankyo, Lacer, Menarini, and Pfizer. **Domenech, M:** Honoria from Recordati and Servier. **Kahan, T:** Research grants Karolinska Institutet from Amgen, Medtronic, Pfizer, and Record, all outside the presented work. **Laurent, S:** Honoraria for lecturing from Axelife, Daichi-Sankyo, Fukuda-Denshi, Menarini, Novartis, Omron, Servier, and Recordati. **Mancia, G:** honoraria as lecturer Actavis, Amgen, Boehringer Ingelheim, CVRx, Daiichi Sankyo, Ferrer, Medtronic, Menarini, Merck, Novartis, Recordati, Sanofi, Servier. **Mcmanus, R:** Has received BP Monitors for research use from Omron. **Redon, J:** has been paid as lecturer by Daiichi Sankyo, Menarini, Boehringer Ingelheim, MSD. **Rhee, M:** Lecture honoraria from Pfizer Inc., LG Life Sciences Ltd, Bayer Korea Ltd., Hanmi Pharm. Co. Ltd., Yuhan Co. Ltd., Boryung Pharmaceutical Co. Ltd., Research grant from Boryung Pharmaceutical Co. Ltd. and Dong-A Pharmaceutical Co., Ltd., CJ HealthCare Co. **Stergiou, G:** Conducted validation studies for various manufacturers; advised manufacturers on device development. **Wang, J:** lecture and consulting fees from Bayer, Daiichi-

Sankyo, Novartis, Omron, Pfizer, Sanofi, and Servier. **Zanchetti, A**: Honoraria from Menarini International

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Figure Legend

Figure 1. Randomization groups and patient flow in the study. BP: Blood Pressure, ABPM: ambulatory blood pressure monitoring; AHT: Antihypertensive treatment.

Tables and boxes

Box 1. Inclusion and exclusion criteria for enrolment

Inclusion criteria:

- Male and female subjects
- Age 40-80 years
- Diagnosis of masked uncontrolled (on treatment) hypertension: office BP <140/90 mmHg, and one or more of the following situations:
  - Ambulatory daytime BP ≥135/85 mmHg
  - Ambulatory night-time ABP ≥ 120/70 mmHg
  - Ambulatory 24h ABP ≥130/80 mmHg
- eGFR ≥45 mL/min/1.73 m2 (CKD-EPI creatinine equation 2009)

Exclusion criteria:

- eGFR <45 mL/min/1.73 m^2 (CKD-EPI creatinine equation 2009), and in particular severe chronic renal failure defined as serum creatinine > 250 µmol/l;
- One of the following conditions:
  - Persistent Atrial Fibrillation
  - Evidence of severe cardiac valve disease (i.e. >2/4 grade at echocardiographic examination)
  - Moderate and severe aortic stenosis
  - Presence of Cardiomyopathy
  - Symptomatic Heart Failure or Ejection Fraction (EF) at or below 45%
- Patients in unstable clinical conditions;

- Known secondary hypertension;
- Orthostatic hypotension (SBP fall > 20 mmHg on standing);
- Dementia (clinical diagnosis);
- Hepatic disease as determined by either AST or ALT values > 2 times the upper reference limit
- History of gastrointestinal surgery or disorders which could interfere with drug absorption
- Known allergy or contraindications to one of the drugs to be administered in the study
- History of malignancy including leukaemia and lymphoma (but not basal cell skin cancer) within the last 5 years
- History of clinically significant autoimmune disorders such as systemic lupus erythematosus.
- History of drug or alcohol abuse within the last 5 years
- History of non-compliance to medical regimens and/or patients who are considered potentially unreliable
- Inability or unwillingness to give free informed consent
- Pregnancy or planned pregnancy during study period.

Box 2. Study outcomes

Co-primary Outcomes

1. Changes from baseline to 12th month in echo LVMI (g/m^2)
2. Changes from baseline to 12th month in albumin/creatinine ratio (UACR, mg/g, morning spot sample)

Secondary Outcomes:

1. As compared to baseline, presence or absence of echo LVH (LVMI ≥ 115 g/m^2 [men] or ≥ 95 g/m^2 [women]) at 12th, 24th, 36th and 48th month
2. Changes in ECG indices of LVH (Cornell Product [main index], Cornell Voltage Index, Sokolow-Lyon Score) from baseline to 12th, 24th, 36th and 48th month
3. As compared to baseline, presence or absence of ECG LVH: (Sokolow-Lyon Index ≥ 3.5 mV or Cornell Voltage Index ≥ 2.4 mV (men) or ≥ 2.0 mV (women) or Cornell Voltage Product ≥ 244 mVms) at 12th, 24th, 36th and 48th month .
4. Increase of microalbuminuria (increase defined as increase in UACR by 100%) from baseline to 12th, 24th, 36th and 48th month .
5. Decrease of microalbuminuria (decrease defined as reduction in UACR by 50%) from baseline to 12th, 24th, 36th and 48th month .
6. Changes in eGFR (ml/min/1.73 m^2), according to CKD-EPI creatinine equation (2009) from baseline to 12th, 24th, 36th and 48th month.
7. As compared to baseline, presence or absence of CKD (eGFR < 60 ml/min/1.73 m^2) at 12th, 24th, 36th and 48th month.
8. The first occurrence of a composite endpoint of events including fatal and non-fatal stroke, acute myocardial infarction, angina, revascularization procedures (coronary, carotid, iliaco-femoral), transient ischemic attack, atrial fibrillation, CV death, hospitalization for heart failure, progression severe CKD (eGFR <30 mL/min/1.73 m^2 [CKD-EPI creatinine equation (2009)]), or doubling serum creatinine until 48th month.
9. Changes from baseline in echo LVMI at 24th, 36th and 48th month
10. Changes from baseline in UACR at 24th, 36th and 48th month

Tertiary Outcomes:

1. Changes from baseline in Office Blood Pressure (OBP) at 3rd, 6th, 12th , 24th , 36th, 48th month.
2. Changes from baseline in Ambulatory Blood Pressure (ABP; 24-hour, day-time and night-time BP) at 12th, 24th, 36th, 48th month.
3. Changes from baseline in Home Blood Pressure (HBP) at 12th and 48th month.
4. Proportions of patients with controlled BP measured with Office, Home or Ambulatory BP, respectively, at 12th month and at 48th month.
5. Proportions of patients with controlled BP measured with Office and Ambulatory BP at 3, 6, 12 and 48 month (only for ABP group). Proportions of patients with controlled BP measured with Office and HOME BP at 3, 12 and 48 month (for both groups).
6. Number of prescribed antihypertensive drugs at 3rd, 6th , 12th month and 48th month.
7. Changes over time in the diagnosis of masked uncontrolled hypertension (on the basis of

ABPM + OBP) at 12th month and at 48th month.

8. Comparison of the prevalence of masked uncontrolled hypertension (on the basis of HBPM + OBP or of ABPM + OBP, respectively) at 12th and at the 48th month.
9. Comparison between groups in visit-by-visit BP variability (SD, VC, VIM, ARV).
10. Comparison between groups in 24-hour BP variability (24h SD, 24h wSD, ARV) at 12th, 24th, 36th , 48th month.
11. Comparison between groups in day-by-day BP variability (SD, VC, ARV, MAX BP) at 12th and 48th month.
12. Comparison between groups in Smoothness index and TOVI at 12th month and at 48th month
13. Comparison between groups in the correlation between changes from baseline to 12th , 24th, 36th and 48th month in LVMI and changes from baseline to 12th , 24th, 36th and 48th month of different measures of BP (OBP, ABP and HBP).
14. Comparison between groups in the correlation between changes from baseline to 12th, 24th, 36th and 48th month in albuminuria and changes from baseline to 12th, 24th, 36th and 48th month of different measures of BP (OBP, ABP and HBP).

Table 1. Time schedule of enrolment, interventions, assessments, and visits for participants.

Assessment			Screening and randomization visits		Follow-up visits									Un-scheduled
			Period: Screening (Baseline)	Randomization	Follow-up 1	Follow-up 2	Follow-up 3	Follow-up 4	Follow-up 5	Follow-up 6	Follow-up 7	Follow-up 8	Follow-up 9 (Final)	Premature discontinuation
			Week -4 to -1	Week 0	Month 3	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36	Month 42	Month 48	
Selection criteria			X	X										
Informed consent			X											
Clinical history			X											
Physical examination			X											
BP Measures	Group 1	Office BP	X	X	X	X	X	X	X	X	X	X	X	X
		Home BP	X				X						X	X
		24h ABPM	X				X		X		X		X	X
	Group 2	Office BP	X	X	X	X	X	X	X	X	X	X	X	X
		Home BP	X				X						X	X
		24h ABPM	X		X	X	X	X	X	X	X	X	X	X
Blood sample for serum creatinine					X	X								
Blood sample for serum creatinine, glucose, HbA1c, uric acid, Na+, K+, lipids			X				X		X		X		X	X
ECG			X			X	X		X		X		X	X
Echocardiogram			X				X		X		X		X	X
Urine sample for microalbuminuria and albumin/creatinine ratio			X			X	X		X		X		X	X
Ascertain achievement of BP control/ adjust antihypertensive				X	X	X	X	X	X	X	X	X	X	X

treatment if needed												
Registration of antihypertensive therapy	X	X	X	X	X	X	X	X	X	X	X	X
Registration of concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events/ safety evaluation			X	X	X	X	X	X	X	X	X	X
Blood sample for biobank creation			X		X							

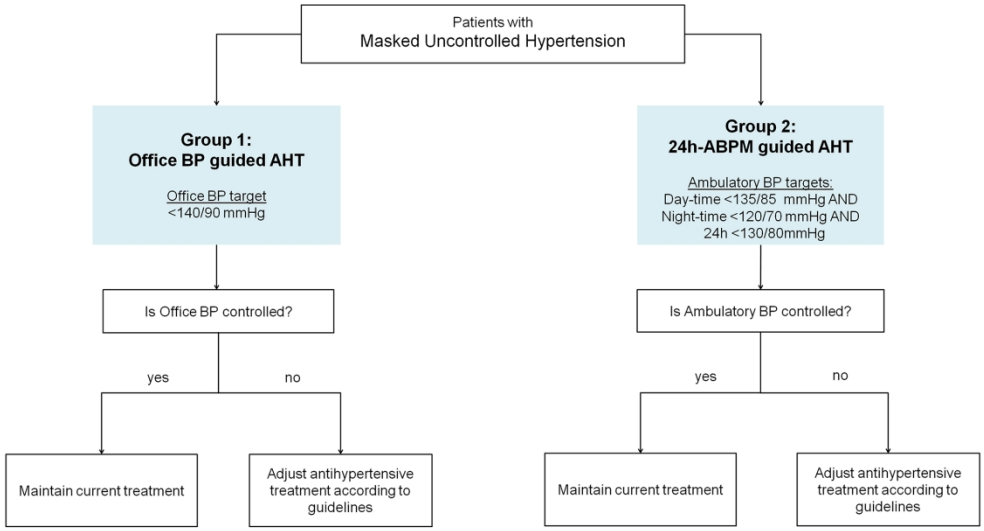


Figure 1. Randomization groups and patient flow in the study. BP: Blood Pressure, ABPM: ambulatory blood pressure monitoring; AHT: Antihypertensive treatment

199x113mm (300 x 300 DPI)

Supplemental Material

Table S1. Current List of Participating centers and investigators in the MASTER Study

	Center / Affiliation	Country	City	Principal Investigators	CO-Investigators
1	Hospital Italiano de Buenos Aires - Unit Internal Medicine Department/Hypertension Section	Argentina	Buenos aires	Waisman G	Jessica Barrochiner
2	Favaloro Foundation - Metabolic Unit, Hypertension	Argentina	Buenos aires	Sanchez R	Paula Catalano MD, Agustin J Ramirez MD, JP Manganiello MD
3	Department of Cardiology. Hospital Español de Mendoza	Argentina	Mendoza	Renna N	Alfredo Astesiano
4	Medical University Graz, Department of Cardiology	Austria	Graz	Perl S	Prof Zweiker, Dr. Niederl
5	Fu Wai Hospital, Chinese Academy of Medical Sciences & Peking Union Medical Colleges	China	Beijing	Zhang Y	Xueli Jiang, Ken Chen, Jia Ma
6	Shanghai Institute Of Hypertension	China	Shanghai	Wang J	Changyuan Liu, Yi Chen, Lei Lei, Yan Li, Shaokun Xu
7	Peking University First Hospital - Cardiology	China	Beijing , District: Xicheng	Huo Y	Zhang Yan, Gao Lan, Wang Shixuan
8	The Center of Hypertension of the Peoples Hospital of Xinjiang Uyghur Autonomous Region/Hypertension Center	China	Urumqi, Xinjiang Uygur Autonomous Region	Li N	
9	University of Zagreb School of Medicine, University Hospital Center Zagre/Dept of Nephrology, Hypertension, Dialysis and Transplantation	Croatia	Zagreb	Jelaković B	Ana Vrdoljak, Zivka Dika
10	Dharma Vira Heart Center, Sir Ganga Ram Hospital - Cardiology	India	New Delhi	Madan K	Dr. JPS Sawhney,Dr. Manish Sharma
11	Istituto Auxologico Italiano - Ospedale San Luca	Italy	Milano	Bilo G	
12	University of Padova Dipartimento di Medicina DIMED Padua	Italy	Padova	Palatini P	Dr Claudio Fania,Francesca Saladini
13	Centro Ipertensione AOU Città della Salute e della Scienza di Torino - Internal Medicine and Hypertension Division, Department of Medical 14Sciences	Italy	Torino	Veglio F	Dr. Chiara Fulcheri,Dr. Franco Rabbia
14	Ce15ntro Ipertensione Arteriosa, Sezione di Medicina Interna - Azienda Ospedaliera di Terni - Università degli Studi di Perugia	Italy	Perugia	Pucci G	

15	JB Lab and Clinic	Korea	Seoul	Park J B	
16	Dongguk University - Ilsan Hospital - Cardiovascular center	Korea	Goyang-si, Gyeonggi-do	Rhee M Y	
17	Medical University in Gdansk - Department of Hypertension and Diabetology	Poland	Gdansk	Chrostowska M	Krzysztof Narkiewicz, Anna Szyndler, Michal Hoffmann, Ewa Swierblewska, Jacek Wolf
18	Clinical County Hospital Univesity of Medicine and Pharmacy Tirgu Mures/Department of Internal Medicine	Romania	Tirgu Mures	Podoleanu C	
19	EMERGENCY CLINICAL HOSPITAL OF BUCHAREST/CARDIOLOGY	Romania	Bucharest	Dorobantu	Dr. Alexandra Paval
20	Almazov Federal North-West Medical Research Centre, Saint-Petersburg, Russia - ITMO University, Saint-Petersburg, Russia	Russia	Saint-Petersburg	Konradi. A	Zvartau N, Ionov M
21	Excellence Centre for Hypertension of the Clinical Centre of Serbia, Belgrade	Serbia	Belgrade	Stojanovic M	Obrenović-Kirćanski, Stojanov Vesna, Radivojevic Nenad, Marijanovic Marija, Simic Dragan, Parapid Biljana
22	University of Valencia and INCLIVA Research Institute, Valencia, CIBERObn, ISCIII, Madrid, Spain	Spain	Valencia	Redon J	Fernando Martinez
23	Hypertension Clinic, Hospital de Sagunto, Valencia, Spain - Universidad CEU Cardenal Herrera, Ciencias de la Salud, Valencia, Spain	Spain	Valencia	Rodilla E	
24	Hospital Mutua TerrassaUniversity of Barcelona	Spain	Barcelona	De la Sierra A	
25	Hospital Clinic of Barcelona, Spain	Spain	Barcelona	Domenech M	Dr. Javier Sobrino, Dr. Antonio Coca
26	Karolinska Institutet, Department of Clinical Sciences, Danderyd Hospital, Division of Cardiovascular Medicine, Stockholm, Sweden	Sweden	Stockholm	Kahan T	Kristina Björklund-Bodegård
27	Fundacion Venezolana de Hipertension Arterial/Instituto de Enfermedades Cardiovasculares de LUZ	Venezuela	Maracaibo	Octavio JA	Dr. Eglé Silva, Dr. Mayela Bracho, José J, Villasmil, Freddy Madueño, Carlos Esis, Greily Bermúdez, Estílita Paredes, Pablo Amair

Operators Manual MASTER Study

CLINICAL HISTORY

Past medical history (including family history, hypertension history, cardiovascular risk factors, other relevant clinical information) and drug history will be taken according to the data collection form in the eCRF. Current drug therapy will be recorded in detail giving names and daily doses of all drugs.

ANTHROPOMETRIC MEASURES

Calibrated standard equipment will be used to measure height and weight.
To determine waist circumference, the upper hip bone is located and a measuring tape will be placed around the abdomen (ensuring that the tape measure is horizontal). The tape measure should be snug and not cause compressions on the skin.
Body surface area (BSA) will be calculated from height and weight according to the Du Bois formula .
BSA [m^2] = 0.007184 × (height [cm])0.725 × (weight [kg])0.425.
Body mass index (BMI) will be calculated from height and weight according to BMI [kg/m^2] = weight [kg] / (height [m])^2 .
These calculations will be done in the data analysis phase.

PHYSICAL EXAMINATION

Physical examination will be carried out mainly in order to exclude obvious secondary causes of hypertension and to detect previously unknown heart, vascular, renal or other disease.

LABORATORY TESTS

The co-primary end point of UAE will be evaluated from morning spot urine samples and expressed as albumin/creatinine ratio (UACR, mg/g). Spot urine samples will be taken twice, once in the morning before application of the ABPM device, and another time on the following morning when the ABPM device will be removed.

Blood samples will also be obtained for determination of serum creatinine, glucose, HbA1c, uric acid, Na+, K+ and lipids as well as to create a study biobank.

HOME BLOOD PRESSURE MONITORING (HBPM)

Devices will be provided to the patients only for the duration of home monitoring period (7 days). Alternatively, patients may use their own validated BP device.

When providing the device to the patient the investigator will instruct the patient:

• On the required monitoring schedule (see below)

• To perform readings in standard conditions (after 5 minutes of rest, having abstained from smoking, exercise or caffeine intake for the past 30 minutes, in sitting position, with the arm supported on the heart level, in a quiet room, not talking during the measurement

• To obtain morning BP readings before or at the time of antihypertensive drug intake

• To register the measured BP and HR values immediately in the provided log sheet (see Figure 1). This log sheet will be provided to the centers in Word format, so that you are free to translate it in your local language.

HBPM will be performed over 7 consecutive days preceding the study visits. Two measurements should be obtained in the morning and two in the evening at 1-2 minute intervals and measurement results should be recorded in a provided log sheet (Appendix 1). This log sheet will serve as Source Document for the Home BP values.

If, on the other hand, the BP device allows export of the data as a .csv file, this csv file can be uploaded in the eCRF, according to the instructions in the eCRF manual.

Values obtained on the first day will be discarded and the average of all the remaining scheduled readings will be calculated and used in the analyses.

Figure 1. Home Blood Pressure Log

MASTER study Clinical Trials: NCT028047074

HOME BLOOD PRESSURE LOG

Section to be filled in by Investigator:

Screening ID: |__|__|__|__|__|__|__|__|__|__| Randomization ID: |__|__|__|__|

Device model: _____

Visit: O Screening 2
O Follow-up 3
O Follow-up 9
O Premature discontinuation visit

Section to be filled in by Patient:

Day	Date	Morning				Evening			
		Time	SBP	DBP	HR	Time	SBP	DBP	HR
1									
2									
3									
4									
5									
6									
7									

Notes: _____

Section to be filled in by the investigator: Mean SBP (days 2-7): |__|__|__|.|__| mmHg
Mean DBP (days 2-7): |__|__|__|.|__| mmHg
Mean HR (days 2-7): |__|__|__|.|__| /min

Note for the Investigator: This log must be filled in manually, scanned and uploaded as pdf file in the eCRF.

OFFICE BLOOD PRESSURE MEASUREMENT (OBPM)

The MASTER study requires the use of the specifically provided **A&D TM2430** device for office SBP, DBP and HR measurement.

Measurement will be performed after several minutes of rest and with the subject having abstained from smoking, strenuous exercise or caffeine intake in the period preceding the measurements.

Three blood pressure readings will be obtained at intervals of at least 1 minute with the participant being seated in a quiet room. A standard bladder (12-13 cm long, 35 cm wide) will be used, but a larger and a smaller bladder will be available for large and thin arms, respectively. All three measurements will be stored in the e-CRF, and their average will be taken to indicate office BP at each visit.

An additional measurement will be obtained with the patients standing upright for one minute (unless the patient is unable to stand).

Blood pressure will be measured on both arms during the first visit and the arm with the higher systolic value will be used again during all subsequent visits.

A&D UA-651BLE device – source data:

The supplied device UA-651BLE is equipped with Bluetooth communication which connects to the A&D connect app available for iPhone and Android devices. The data can be downloaded directly after each single measurement when the device is paired with e.g. smartphone.

Once the data are on the mobile device, access the data table and use the “share” function to export the data in **csv** format. Then remove the readings one by one (slide with the finger sideways on a single reading and a delete button will appear).

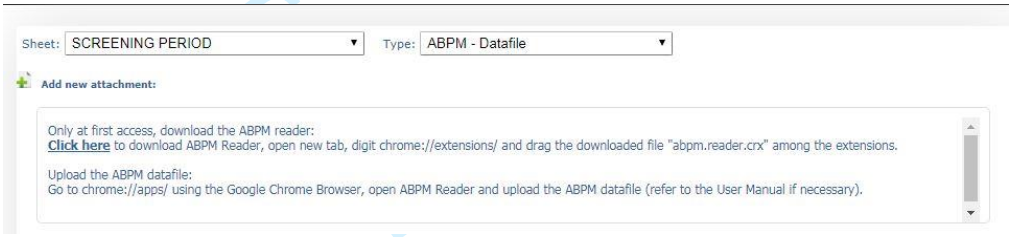
csv files should be uploaded on the eCRF as source documents.

24 H AMBULATORY BLOOD PRESSURE MONITORING (ABPM)

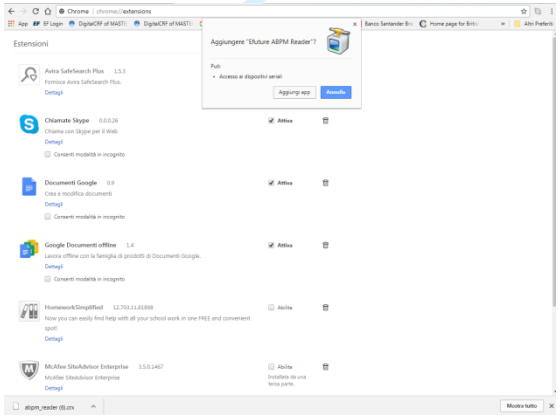
Ambulatory Blood Pressure Monitoring (ABPM) will be carried out as follows:

- The MASTER study requires the use of the specifically provided **A&D TM2430** device. This device allows direct upload of the datafile to the eCRF (see ahead).
- For more information, please check the attached TM2430 Data Sheet and Instruction Manual.
- ABPM will be performed:
    - In Group 1: during screening period, every twelve months during follow-up, and at the final visit.
    - In Group 2: during screening period, at three months, six months and every six months thereafter during follow-up, and at the final visit.
- Each monitoring should start in the morning, after the subject has taken his/her morning medication. Patients will be sent home (to perform the recording in conditions as close as possible to daily life) and asked to come back the following day for the device removal.
- The cuff will be applied on the non-dominant arm unless the patient presents a major (>10 mmHg) between arm difference in BP; in that case the arm with higher BP should be used.
- The patient will be instructed:
    - to fill the attached diary form (see Figure 1) with reference to his/her main daily activities and quality of night time sleep. This diary will be provided to the centers in Word format, so that you are free to translate it in your local language.
    - to keep the arm still and to avoid any movement during each automatic blood pressure measurement
    - to attend her/his usual daily activities (avoiding major physical activity)
    - not to remove the cuff during the recording period
- The device will be set to take automatic readings every 15 minutes at daytime (6:00 to 22:00) and every 20 minutes at night-time (22:00 to 6:00) and not to display the measured readings
- The device should be removed after 25 hours of recording to ensure a complete coverage of all hours. ABPM files, with the accompanying diary, will be uploaded on the study website for immediate quality check.

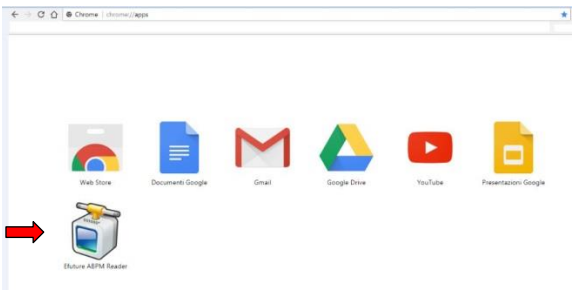
- Recordings of inadequate quality (less than 65% of the expected BP readings, 3 or more hours with no valid readings, 2 or more consecutive hours without valid readings) should be repeated by the centre in the same treatment condition.
- Attach the digital datafile to the eCRF in the “Upload attachments” section, under the heading “ABPM-datafile”:
    - Please use the **Google Chrome browser**!
    - The ABPM datafile has to be uploaded DIRECTLY from the **A&D TM2430** device to the eCRF, by an ABPM-reader APP that was specifically designed for this study.
    - At the first access: (1) download the “abpm_reader.crx” file by clicking “Click here”.



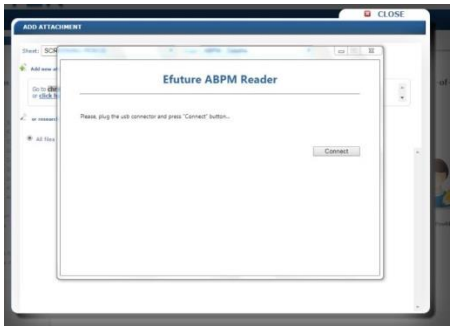
    - (2) Then drag the file among the extensions on the web page “chrome://extensions/”. (Please note that Step (1) and (2) need to be performed only once).



    - Once installed, go to “chrome://apps/ and open the ABPM reader icon.

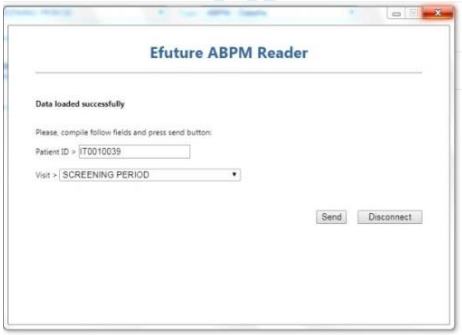


- Click on the Efuture ABPM reader icon, plug the USB connector and press “Connect”

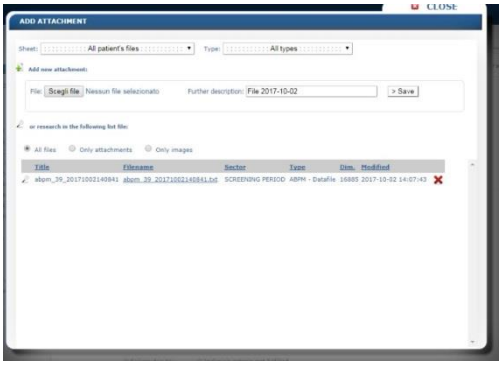


- Press red button on **A&D TM2430** device

- Fill in the patient Screening ID and corresponding visit



- “Data loaded successfully” and “Disconnect”. You will find the attached datafile in the uploaded files list



- Once the ABPM datafile has been uploaded, the raw data (including all individual measurements) of each recording will be examined by the ABPM Core Laboratory in Milan for quality control and analysis.
- ABPM data of patients randomized to group 1 (Office BP) will not be available to the investigators in charge of treatment decisions; for these patients only feedback concerning the quality of the ABPM data file will be returned. You will receive feedback from "masterdata@auxologico.it"
- ABPM data of patents randomized to group 2 (Ambulatory BP) will be available to the investigators in charge of treatment decisions; for these patients feedback concerning quality of the ABPM datafile AND mean BP values will be returned. You will receive feedback from "masterdata@auxologico.it"

- For each ABPM recording the following variables will be computed:
    - 24h, daytime and night-time average BP and heart rate (HR) values
    - SBP and DBP variability calculated as the standard deviation (SD) of the average 24h, day and night values, and as the "weighted" 24h SD, as well as Average Real Variability (AVR) and as ambulatory arterial stiffness index (AASI)
    - Nocturnal BP falls and night/day SBP and DBP ratios
    - Average morning (7-11 a.m.) SBP/DBP values and morning BP surge (defined as the difference between the lowest BP before the morning rise and the highest BP after awakening)
- Figure 1. ABPM Diary

MASTER study Clinical Trials: NCT028047074

AMBULATORY BLOOD PRESSURE MONITORING DIARY

Section to be filled in by Investigator:

Screening ID: |__|__|__|__|__|__|__|__|__|__| **Randomization ID:** |__|__|__|__|

Visit:

O Screening
O Follow-up 1 (only Group 2)
O Follow-up 2 (only Group 2)
O Follow-up 3
O Follow-up 4 (only Group 2)
O Follow-up 5
O Follow-up 6 (only Group 2)
O Follow-up 7
O Follow-up 8 (only Group 2)
O Follow-up 9
O Premature discontinuation visit

Date: |__|__| / |__|__| / |__|__|__|__| (dd/mm/yyyy)

Time recording started: |__|__|:|__|__| (hh:mm)

Section to be filled in by Patient:

Time of: sleep: |__|__|:|__|__| (hh:mm) **awakening:** |__|__|:|__|__| (hh:mm)

Morning drug intake time: |__|__|:|__|__| (hh:mm)

Quality of sleep: O Bad O Average O Good

Please record below any major event that might have affected your blood pressure

Time	Activity/posture/symptoms

Comment:_____

Note for the Investigator: This log must be filled in manually, scanned and uploaded as pdf file in the eCRF

ECHOCARDIOGRAPHIC SPECIAL PROCEDURES

1-Certification of Echo's
2-Echocardiographic Media and Data Flow
3-Instructions for Performing Echocardiograms
4-Echocardiographic Quality
5-Required Echocardiographic Views
6-Instructions for Obtaining Required Echocardiographic Views
7-Contact Information
8-References

1-Certification of Echo's:

It is essential that all sonographers at participating sites produce the highest possible quality in acquired echo images. The echo operator(s) of each participating center must perform one sample echocardiographic examination, following the instructions described in this manual. This Certification Echo must be submitted to the Core Echocardiography Laboratory (hereafter designated as "Core Echo Lab") through the eCRF (www.master.digitalcrf.eu) for assessment and subsequent certification of adequate quality.
The submitted Certification Echo must:

- be clearly labeled as a "Certification Echo"
- be of good quality and all images should be clear
- be compatible with the instructions contained within this document
- include all required views outlined in the echo protocol contained in this manual

The Core Echo Lab will provide feedback to the site within *10 business days* of receipt of the Certification Echo.
Once the Certification Echo is deemed acceptable, the Core Echo Lab will e-mail a site Certification Form to the site's Principle Investigator.

2-Echocardiographic Media and Data Flow:

The participating center must:

- save the echo data in universal DICOM format.
- unite the requested views/images for each single echocardiography examination in one single data folder.
- name this data folder, according to the patient's screening ID and follow-up visit, as follows:

Follow-Up visit	Requested folder name
Certification Echo	Certification Echo
Screening period - Baseline	ScreeningID-BA
Follow-up 3	ScreeningID-FU3
Follow-up 5	ScreeningID-FU5

Follow-up 7	ScreeningID-FU7
Follow-up 9	ScreeningID-FU9
Premature discontinuation	ScreeningID-PD

- upload the data folder directly to the electronic CRF, according to the eCRF attachment manual.
- keep a copy of the echo data folder in the Investigator Site File, for the entire duration of the study.

NOTE: If the participating site cannot upload the echo data directly to the eCRF, the site investigator(s) will need to make alternative arrangements with the Data Management team for transmitting the required echo data.

The Data Management team:

- downloads the echo data from the eCRF
- forwards the echo data to the Core Echo Lab for blinded centralized reading.
- eliminates the echo data from the eCRF, in order to free digital space in the platform.
- archives a copy of the echo data for the entire duration of the study.

3-Instructions for Performing Echocardiograms:

Recommendations on this manual have been based on the up-to date evidence and consensus provided by current guidelines listed in the reference section at the end of this manual (1-4).

A Core Echo Lab certified sonographer should obtain all study echos on a given subject. If possible, identify one or two sonographers in your Echo Lab to perform all echos related to this study.

A. Echocardiographic Equipment

Use the highest possible frequency (2.5-5.0 MHz) transducer to allow adequate penetration for endocardial border definition. It is advisable to use the same transducer frequency for all the studies on a given patient. Tissue harmonic imaging may be used, at the discretion of the sonographer and investigator, unless this worsens endocardial border definition.

B. Subject Identification on Recorded Images

The echo media (CD) and other materials received by the Core Echo Lab should not contain the subject's name or medical record number. Only the subject's assigned study screening ID should be used.

C. Subject Preparation

Electrocardiographic (ECG) leads (3-lead) should be placed and an ECG signal in which the QRS complex is clearly identifiable should be visible on the echocardiographic monitor.

4- Echocardiographic Quality

Echocardiograms should be obtained in a manner that is most consistent with good-quality subject care. However, subject comfort and safety shall always be the primary concern. Subject co-operation and comfort are essential in obtaining high quality echocardiographic images.

Importance of High Quality Echos

The Core Echo Lab relies heavily on sites performing high quality echos. Quantitative measurements entail manually tracing the endocardium and Doppler envelopes at various periods in the cardiac cycle. Even when images are of good quality, this can be extremely difficult, and it is therefore critically important that the best possible endocardial definition and Doppler signal are obtained.

Optimizing Endocardial Border Definition

Sonographers and the individual echo investigator should optimize endocardial border definition at their own discretion, using any machine-specific optimizations. Please do not use automatic border detection systems, as found on certain machines. Furthermore, adjust the transducer depth range to maximize the dimensions of the chamber of interest.

Instructions for Image Acquisition

The required echo views and echo-Doppler data should be obtained in the order outlined in the Table. Further details, specific to each echo view, can be found in the section: "Instructions for Obtaining Required Echocardiographic Views".

Recording should start once the view is optimized and end after the required number of cardiac cycles has been recorded for each required view.

At least **5 cardiac cycles** per view are required for digitally stored studies (in DICOM format).

Doppler Recordings:

With all spectral Doppler recordings, set the Nyquist limit at 50-70 cm/sec, adjusting to ensure a well-defined jet. The Nyquist limit must be documented on the image. Ensure the color sector remains as narrow as possible to obtain the best frame rate. However, the color sector should be of adequate size to capture the entire regurgitant jet.

For continuous wave and pulsed wave Doppler images, use a standardized sample volume (5 mm is recommended). Care should be taken to align the Doppler signal parallel to the presumed direction of flow. Adjust the gain to obtain a clear flow signal and the baseline and scale (80 cm/sec) to capture the peak flow velocity. Reset scale if necessary to optimize the flow signal. Record at 100 mm/sec sweep speeds for the required number of beats (as outlined above).

5- Required Echocardiographic Views

Echocardiographic Examination and Acquisition

A subset of a standard echocardiographic examination will be performed. The following table resumes the required views for each echo study:

Table. Required Echocardiographic Views

VIEW	REQUIREMENTS
A. Parasternal Long Axis View	1. 2D 2. M-mode across the LV base (where MV leaflet tips meet chordae) 3. Color flow Doppler of mitral valve 4. 2D parasternal long-axis view, which depicts the aortic root and the proximal ascending aorta
B. Parasternal Short Axis View: MV Level	1. 2D 2. M-mode across the LV base (where MV leaflet tips meet chordae)
C. Parasternal Short Axis View: Mid-papillary Level	1. 2D 2. M-Mode
D. Parasternal short Axis View: Aortic valve, RV Inflow-outflow View	1. 2 D 2. Continuous wave (CW) Doppler of tricuspid regurgitant (TR) jet if present.
E. Apical 4-Chamber View	1. 2D - include entire four cavities 2. 2D- focused on left ventricle and left atrium only 3. Color flow Doppler of mitral valve and tricuspid valve - include entire LA and RA cavity 4. CW Doppler of TR jet if present 5. Mitral inflow: PW Doppler 6. PW Doppler pulmonary vein recordings guided by color Doppler 7. Mitral annular Doppler Tissue Imaging (DTI) at the medial (septal) and at the lateral corner of the mitral annulus
F. Apical 5-Chamber View	1. 2D 2. LV outflow tract pulsed wave (PW) Doppler 3. Aortic valve color Doppler and CW Doppler
G. Apical 2-Chamber View	1. 2D - include entire LA and LV cavities 2. Color flow Doppler of mitral valve

H. Apical 3-Chamber View	1. 2D 2. Aortic valve color Doppler
I. Subcostal View	1. Four chambers view 2. Inferior vena cava - 2D (image at *rest* and with *inspiration* to assess for respiratory change in IVC diameter)

6-Instructions for Obtaining Required Echocardiographic Views:

The required echo views and echo-Doppler data should be obtained in the order outlined in the table. At least 5 cardiac cycles per view are required. For M-mode and Doppler recordings, use at least 100 mm/sec sweep speeds.

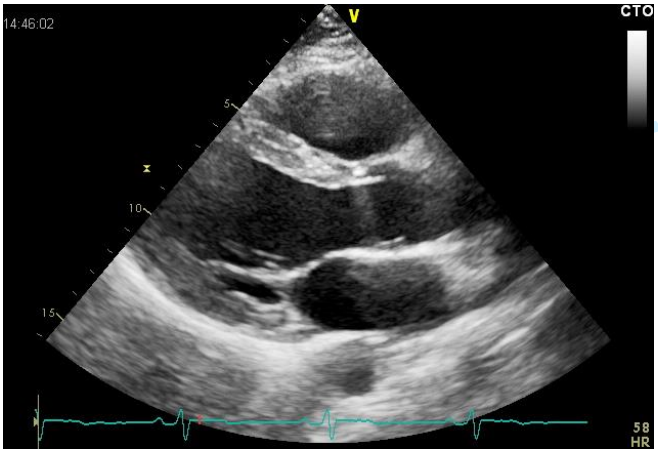
NOTE: Please record *moving* images, rather than still images, for all data except for spectral Doppler and M-mode recordings. Do NOT record measurements on the echo study submitted. The Echo Core Lab will visualize all the cardiac cycles and perform all measurements

PARASTERNAL VIEWS:

A. Parasternal Long Axis View

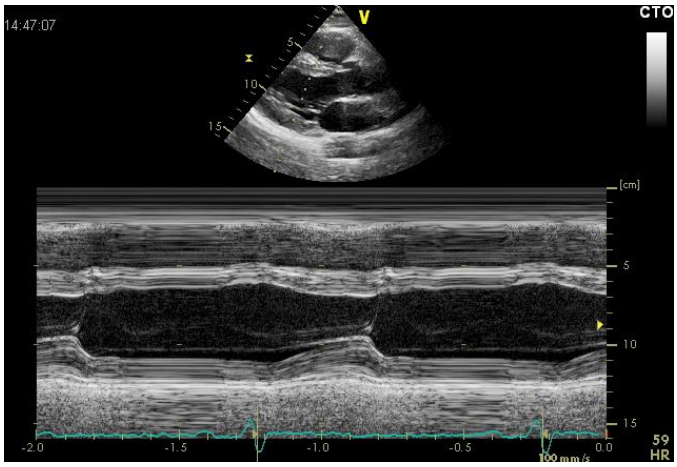
2D

This view is best obtained with the transducer positioned at the left sternal border, angled to ensure the longest apex-base view of the left ventricle (LV). It is important to acquire the true long axis of the LV and to avoid any foreshortening of the LV. The LV outflow tract should be visualized with only minimal angulation of the proximal interventricular septum (IVS) as it meets the anterior aortic wall. The anterior and posterior mitral valve (MV) leaflets and the right and non-coronary cusps of the aortic valve (AV) must also be visible.



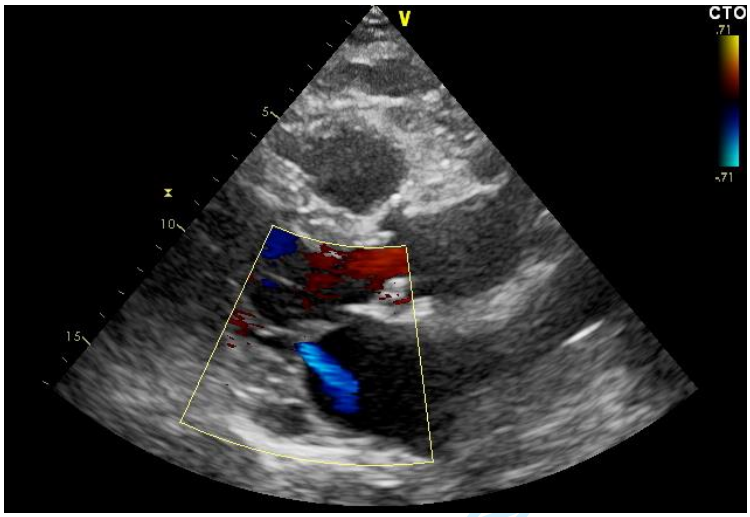
M-mode across the LV base

M-mode recording of the LV should be made with the cursor directed at or below the MV leaflet tips. The interventricular septum (IVS) and the posterior wall (PW) should be clearly visible.



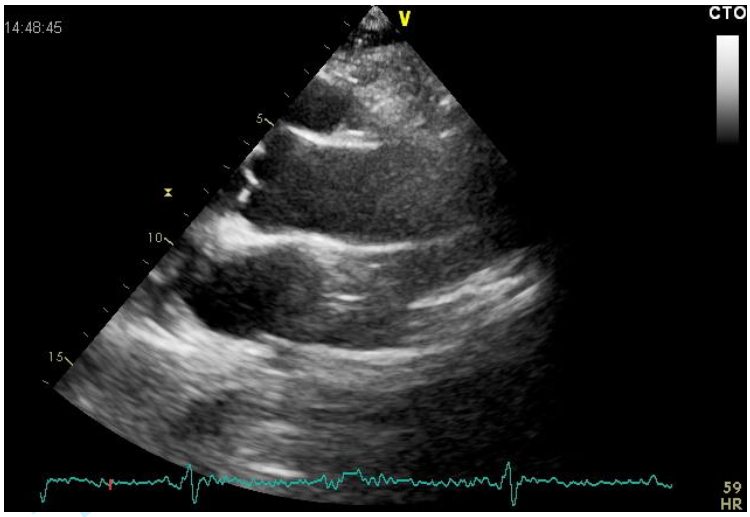
Colour flow Doppler of MV

With the optimized 2D view, place the color sector over the mitral valve, including as much of the left atrium (LA) cavity as possible.



Ascending aorta

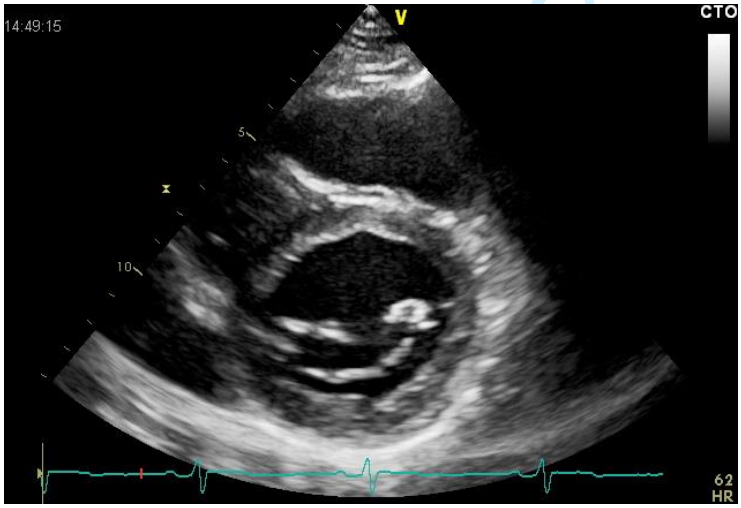
The parasternal long-axis view, which depicts the aortic root and the proximal ascending aorta. This plane is slightly different from that of the long axis of the left ventricle. Acquisition of this LV longaxis view may be performed from different intercostal spaces and at various distances from the left sternal border. The tubular ascending aorta is often not adequately visualized from a standard parasternal window. In these instances, moving the transducer closer to the sternum may allow visualization of a longer portion of the ascending aorta.



B. Parasternal Short Axis View: MV Level

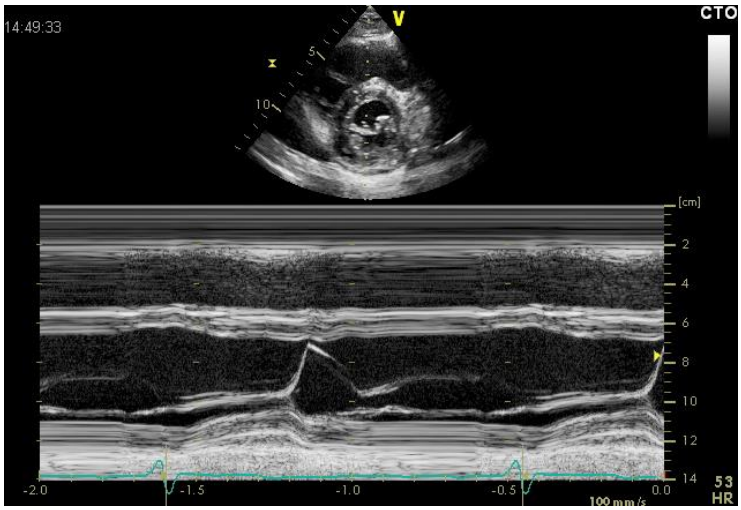
2D

This view is best obtained by 90 degree clock-wise rotation of the transducer from the parasternal long axis position and with superior or inferior angulation. The LV cavity should be visualized as a circular conformation with the depth adjusted to optimize the LV chamber dimensions. The mitral valve, with both anterior and posterior mitral valve leaflets, should be clearly visible.



M-Mode across the LV base

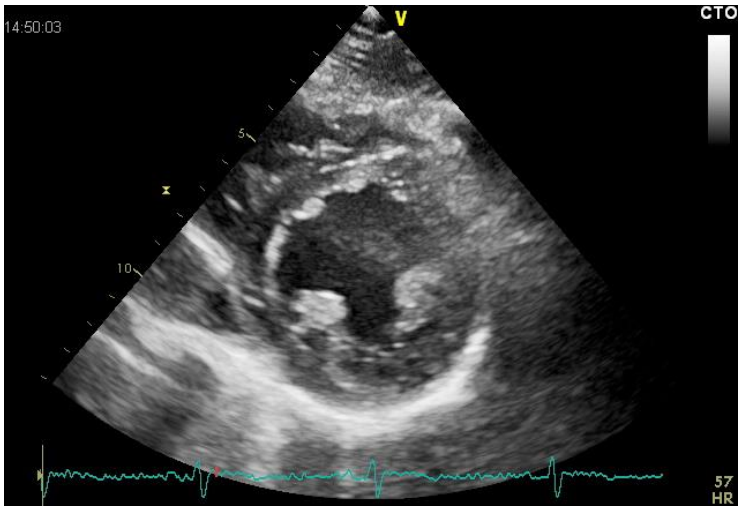
M-mode recording of the LV (for quantification of the LV mass) should be made with the cursor aligned through the middle of the circular LV, where the MV leaflet tips meet the chordae. The mitral valvular apparatus should be visible in this image.



C. Parasternal Short Axis View: Mid-papillary Level

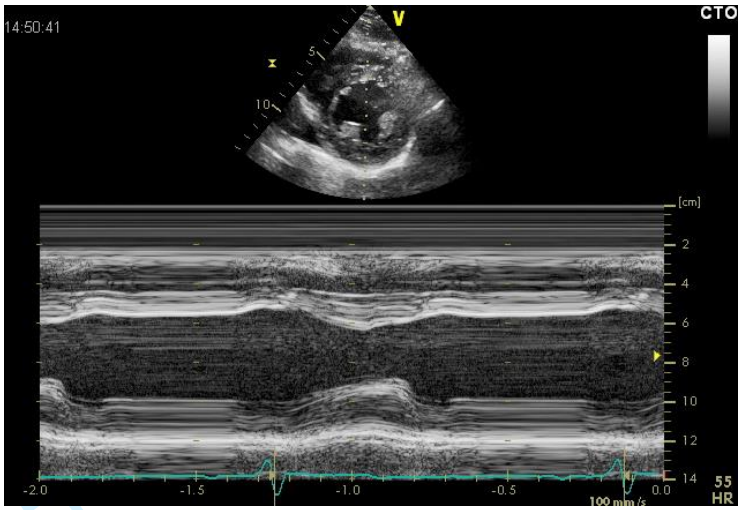
2D

This view is best obtained by 90 degree clock-wise rotation of the transducer from the parasternal long axis position and angled interiorly from the MV level. The LV should be visualized as a circular conformation with the depth adjusted to optimize the LV chamber dimensions. Both of the papillary muscles must be clearly visible.



M-Mode

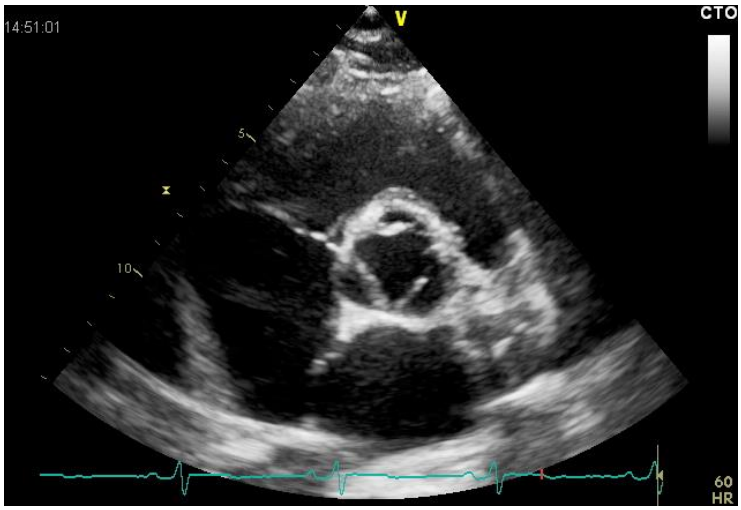
M-mode recording of the LV should be made with the cursor aligned through the middle of the circular LV.



D. Parasternal Aortic valve and Right Ventricular Inflow-outflow View

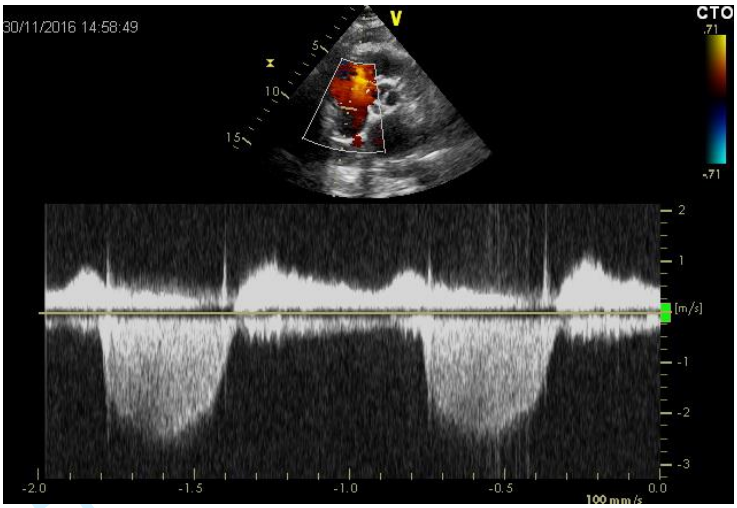
2D

This view is best obtained by 90 degree clock-wise rotation of the transducer from the parasternal long axis position and with superior angulation. The aortic valve, with its cuspids, should be clearly visible, as well as right ventricular inflow and outflow.



Continuous wave (CW) Doppler of tricuspid regurgitant (TR) jet

The cursor should be directed along the long axis of the RV and through the middle of the TV, parallel to the flow of the TR jet.



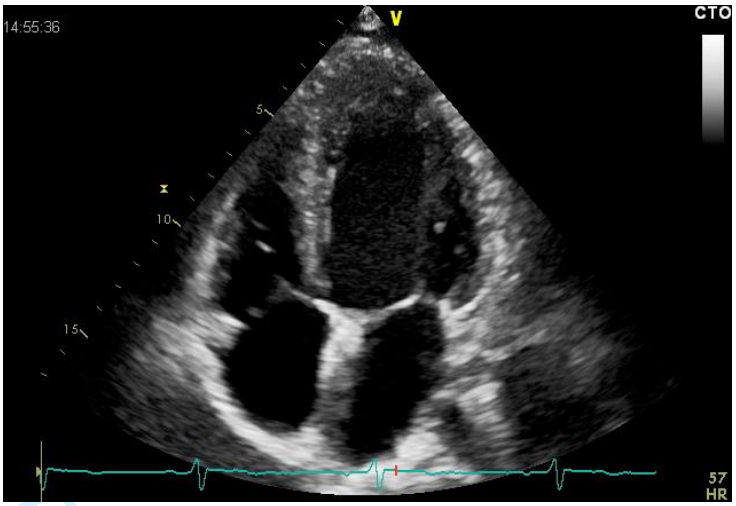
APICAL VIEWS

The apical views are obtained by placing the transducer laterally and inferiorly at the apex and moving superiorly and medially until the cardiac chambers are visualized.

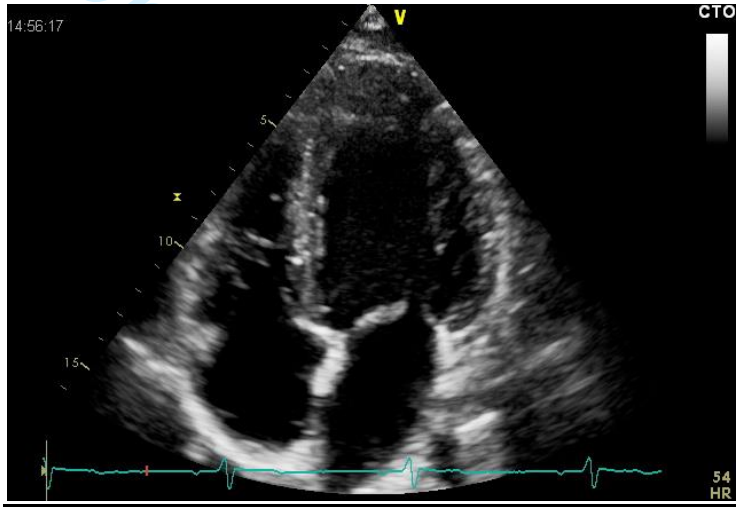
E. Apical 4-Chamber View

2D – 4 chambers

The image should be properly aligned to capture the entire four chambers. The interventricular septum should be as parallel as possible to the superior-inferior direction and the entire LV endocardium must be visualized in both systole and diastole. It is important to adequately visualize the apex and lateral LV free wall. Avoid foreshortening or elongating the RV or LV chambers.

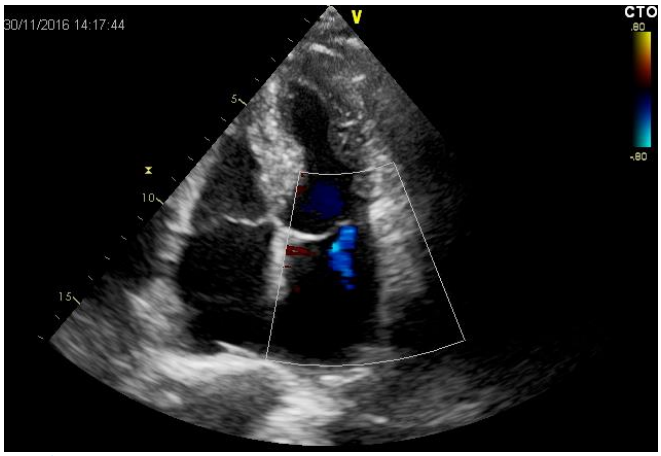


2D focusing only left chambers



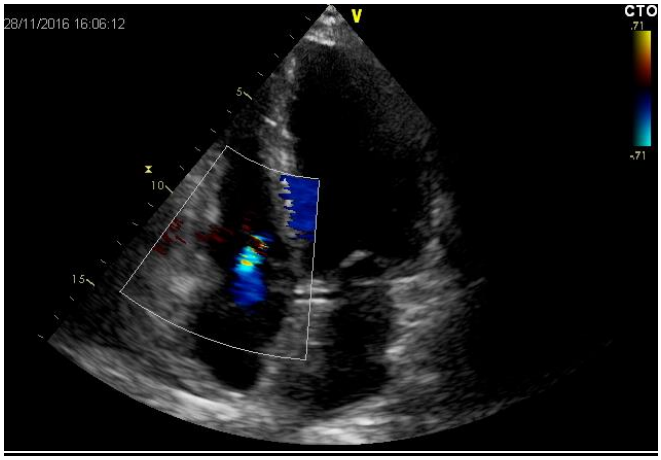
Color flow Doppler of MV

With the optimized 2D apical 4 chamber view, and the LV and LA seen in full, place the color sector over the mitral valve, including as much of the left atrium (LA) cavity as possible.



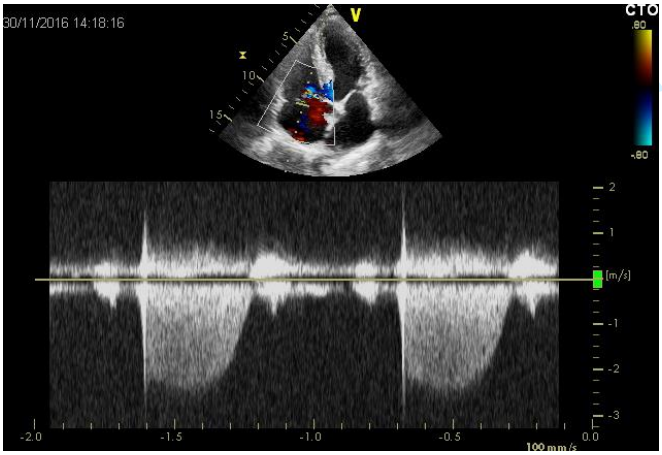
Color flow Doppler of TV

With the optimized 2D apical 4 chamber view and the entire RA seen and the tricuspid valve (TV) leaflets now clearly visible, place the color sector over the TV.



CW Doppler of TR iet

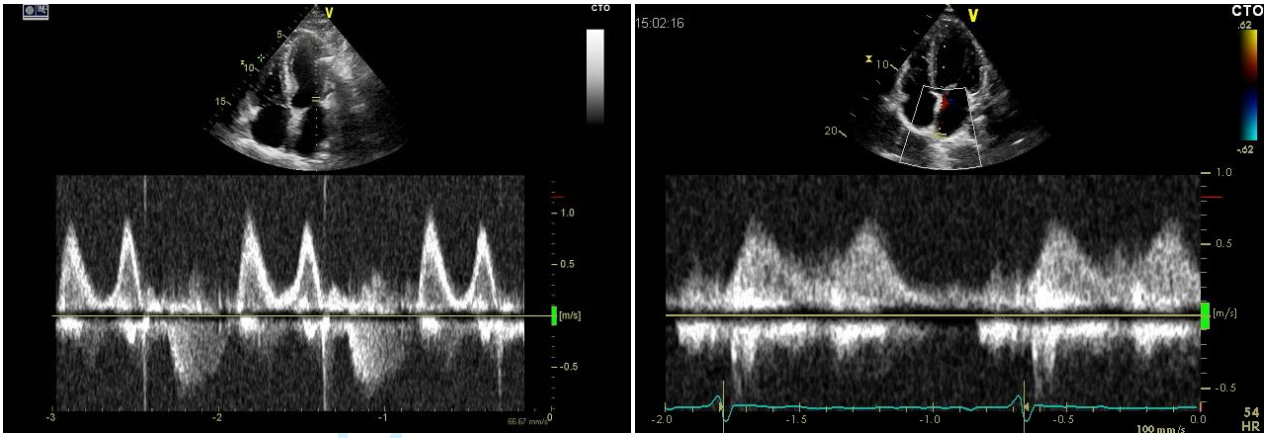
The cursor should be directed along the long axis of the right ventricle (RV) and through the middle of the TV, parallel to the TR flow.



PW Doppler

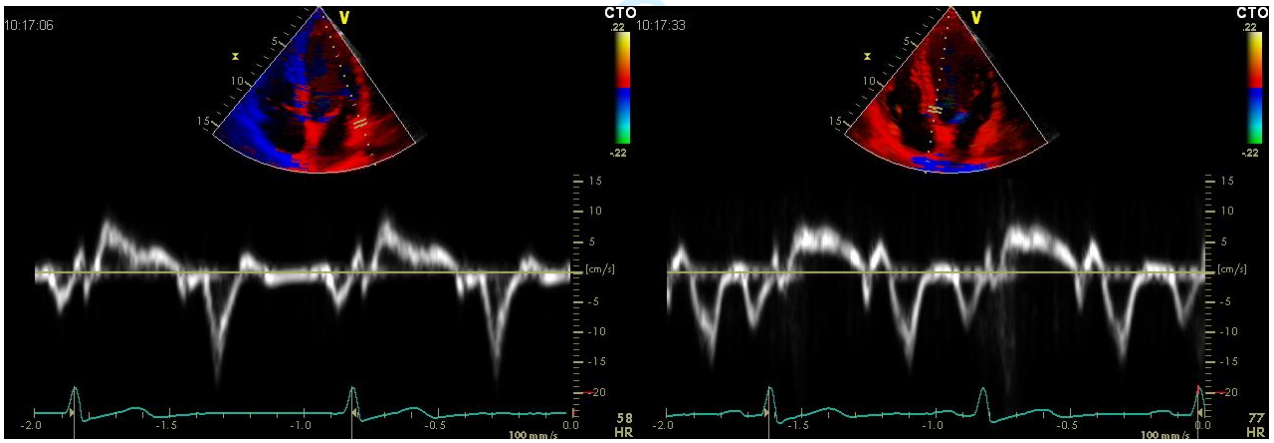
a. PW Doppler transmitral flow recordings with sample volume at leaflet tips during diastole

b. PW Doppler right superior pulmonary vein recordings guided by color Doppler



DTI PW Doppler

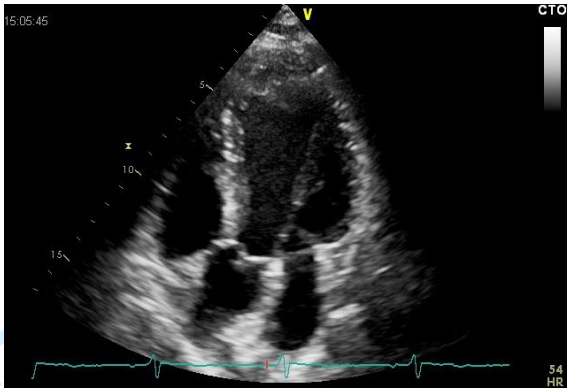
PW tissue Doppler imaging (DTI) is performed in the apical views to acquire mitral annular velocities. The sample volume should be positioned at or 1 cm within the septal and lateral insertion sites of the mitral leaflets and adjusted as necessary (usually 5–10 mm) to cover the longitudinal excursion of the mitral annulus in both systole and diastole. Record a minimum of 5 cardiac cycles at a sweep speed of 100 mm/sec.



F. Apical 5-Chamber View

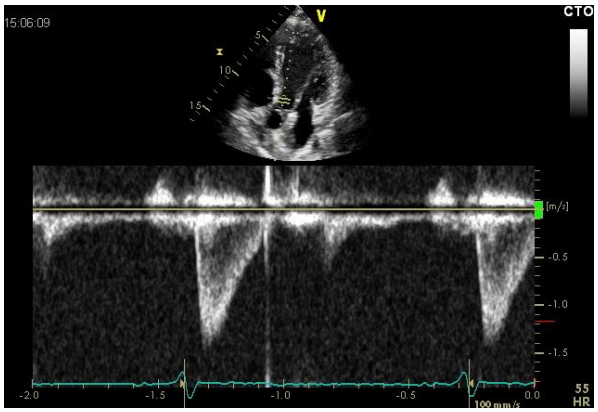
2D

Five-chamber view should include the left ventricular outflow tract (LVOT) and the aortic valve (AV) cusps. Be careful to maintain maximal LV length, to visualize all 4 cardiac chambers and to optimize endocardial definition.



LV outflow tract PW Doppler

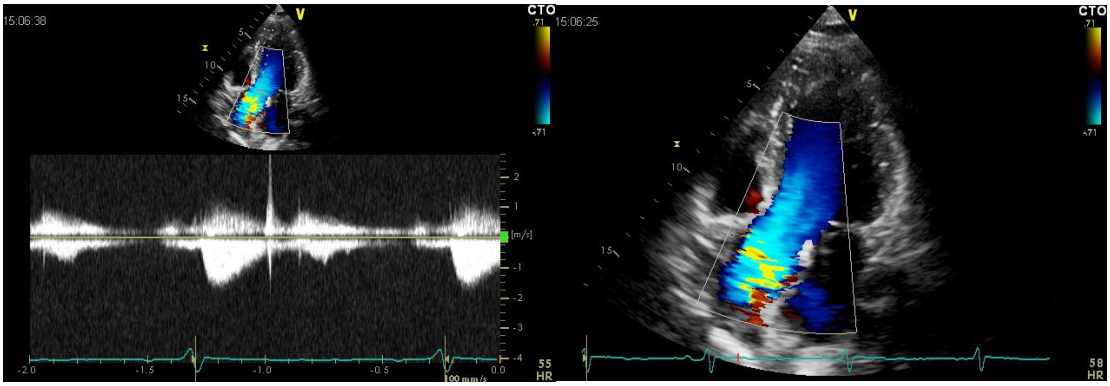
Place the color sector over the LVOT and aortic valve. Align the PW signal parallel to the direction of LVOT flow and position the PW Doppler sample (5 mm sample volume size) within the LVOT 5-10 mm proximal to the AV. Adjust the baseline and Doppler scale to visualize the peak wave velocity.



Aortic CW Doppler and color Doppler

Still in the five-chamber view, the cursor should be directed along the long axis of the LVOT and AV cusps. Adjust the gain to obtain a clear LVOT flow signal and the baseline and scale to capture the peak velocity.

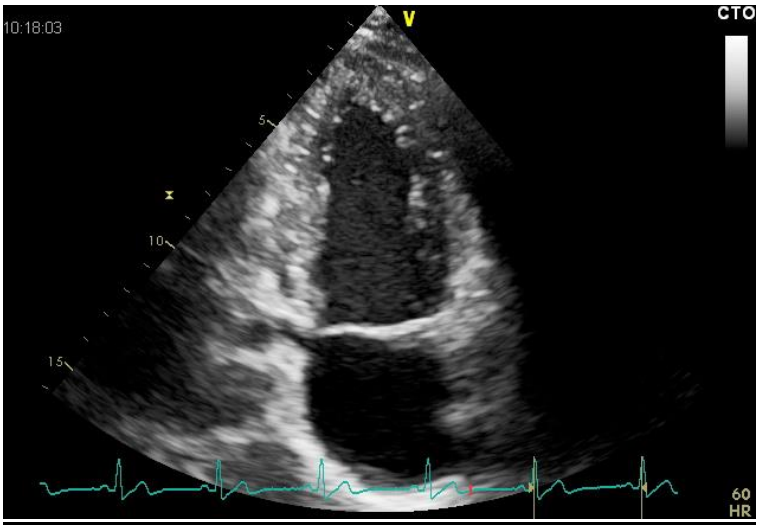
With the optimized 2D apical 5-chamber view, place the color sector over the aortic valve.



G. Apical 2-chamber view

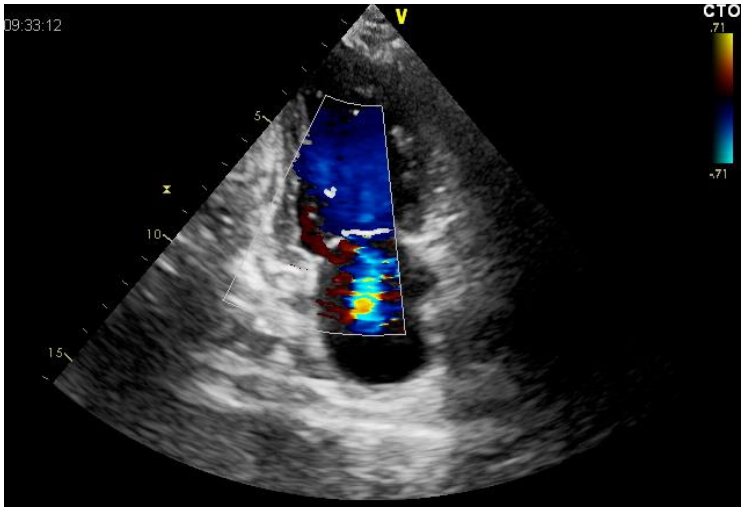
2D

LV and left atrium cavities should be entirely visualized. In particular, for LV, ensuring the entire LV endocardium is visualized in both systole and diastole. Ensure that the LV apex is not cut off.



Color flow Doppler of MV

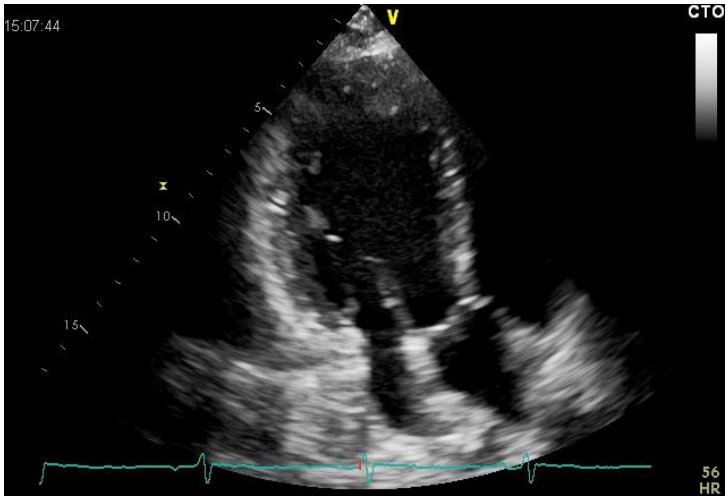
With the optimized 2D apical 2 chamber view, and the LV and LA seen in full, place the color sector over the mitral valve, including as much of the left atrium (LA) cavity as possible.



H. Apical 3-Chamber View

2D

Visualize the entire LV, as well as the MV and the LA, similar to the parasternal long axis view. Again, it is important to properly align the image and not to foreshorten the LV.



Color flow Doppler of aortic valve

With the optimized 2D apical 3-chamber view, place the color sector over the aortic valve.

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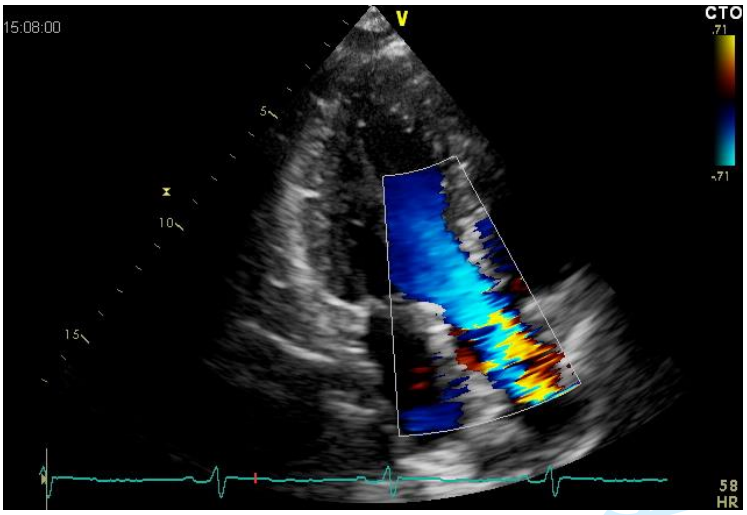
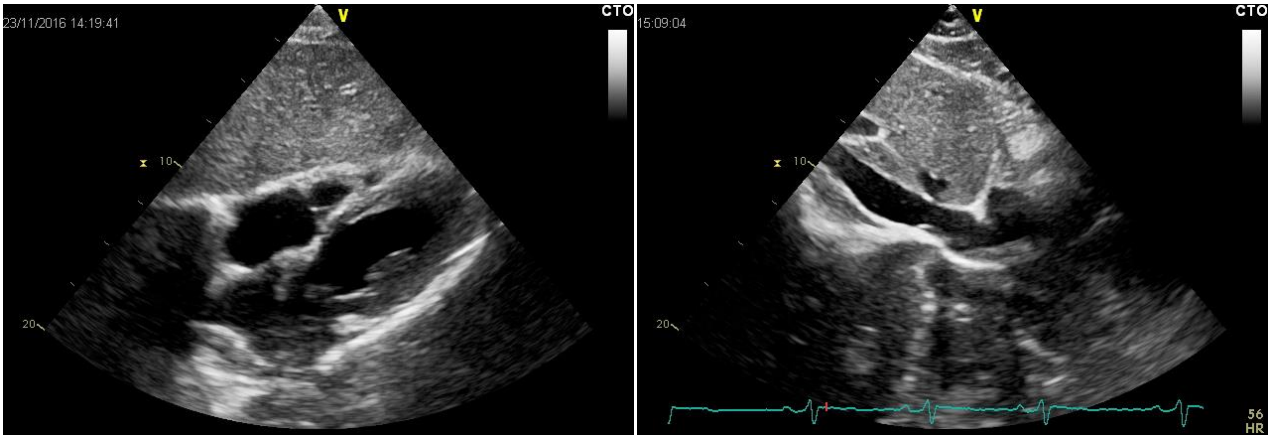


I. Subcostal View

2D

With the transducer in the subcostal position obtain a 4-chamber view.
Then, angulate the transducer to visualize the proximal inferior vena cava (IVC) where it meets the right atrium. Ask the patient to sniff or inspire - this maneuver will reveal if the IVC diameter changes with inspiration.



7-Contact Information

For technical echo-related questions, please direct all questions and inquiries to masterdata@auxologico.it

8-Supplemental References for echocardiographic procedures

1. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1-39 e14.

2. Marwick TH, Gillebert TC, Aurigemma G, Chirinos J, Derumeaux G, Galderisi M, et al. Recommendations on the Use of Echocardiography in Adult Hypertension: A Report from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE). J Am Soc Echocardiogr. 2015;28(7):727-54.

3. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009;22:107-33.

4. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016;29(4):277-314.

ELECTROCARDIOGRAPHY

Electrocardiographic assessment of LV mass

Standard 12-lead ECG will be recorded at 50 mm/s speed. There must be at least one 1 mV square calibration pulse and a time scale to facilitate analysis. Tracings must show at least 3 beats per lead and a rhythm strip of at least 10 s duration. Artefacts due to loose leads are not acceptable. Standard filter settings according to local practice should be chosen, and settings have to be recorded on the printout. The digital ECG file will be uploaded on the web based platform

Recording recommendations:

1. *Description*

The description is written for the mode "automatic system". Please read the manual of the ECG device for other modes.

2. *Installation*

The electrocardiograph is put aside the top of an examination couch of the patient's bed. The power supply comes from either the net or network-independent chargeable battery. It is important for a trouble-free operation that the power line does not go in parallel to the lines of the electrodes.
Operational check: Switching on equipment at the on-off key button.

3. *Preparations*

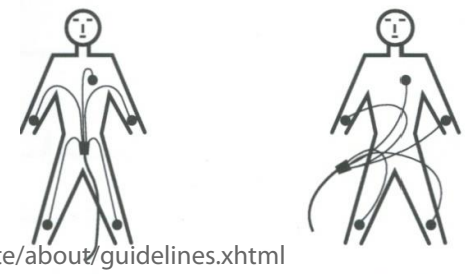
The patient/test person lies on the examination couch with undressed upper part of the body and free ankles. In males, disturbing hair-growth on the chest must be shaved off. The patient must lie relaxed, a pleasant room temperature is necessary.

4. *Attaching the electrodes for the standard derivations*

Carefully laying out the electrodes is required for an accurate ECG result. For the standard derivations 4 extremities and 6 chest wall derivations must be laid out. Contact spray on the skin (see below) is sprayed on. Important: Spray on the skin not on the electrodes.

5. *Extremity derivations*

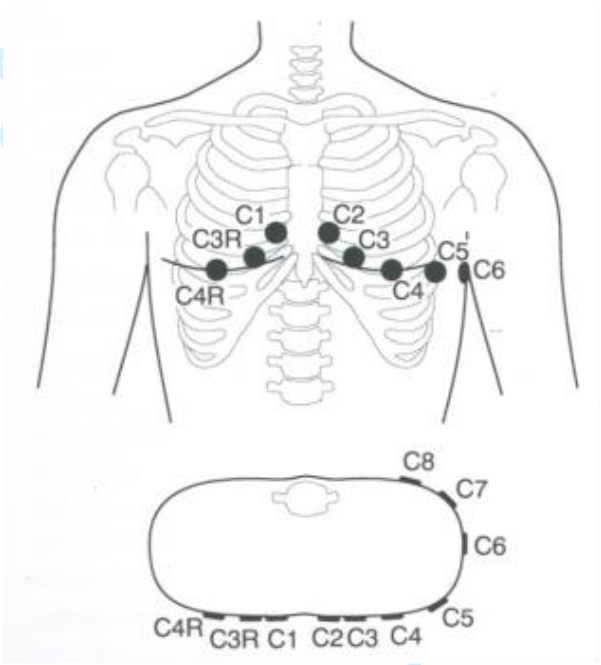
The positions of the extremity derivates are as follows:
Right arm: Red line
Left arm: Yellow line
Left leg: Green line
Right leg: Black line



6. *Chest wall derivations*

Right Wrong

C1: In the 4th Intercostal Space at the right sternal site
C2: In the 4th Intercostal Space at the left sternal site
C3: On the 5th rib between C2 and C4
C4: In the 5th Intercostal Space on the left medioclavicular line
C5: On the height of C4 (horizontal) in the front left axillary line
C6: On the height of C4 (horizontal) in the middle left axillary line



7. *Remarks:*

Laying out the chest wall electrodes, it is very important for the derivations V4-V6 proceeding on a horizontal line. So please do not follow the anatomical course of the 5th Intercostal Space as it is often misunderstood.
The 1st Intercostal Space is found directly below the clavicle; the 1st rib cannot be felt. Therefore the 1st Intercostal Space lies below the clavicle; the 2nd is the first palpable Intercostal Space.

8. *ECG writing*

Push the operating button and follow the menu for entering the patient data.
Press button "filters" for excluding muscle artefacts with the arrow keys.

The patient must lie quietly and eased and breathe normally (about 6/minutes).
Start ECG writing by pressing the suitable button.

With the control mode “Automatic” 12 derivations are taken simultaneously, analysed and the ECG distributes over a period of 10 sec. automatically.

Check the ECG tracing on the paper, provide with necessary specific data in handwriting.
If necessary: Do a copy by pressing the specific button.

Analyses:

- ECGs will be analysed for criteria of left ventricular hypertrophy by each centre; requested parameters must be inserted in the ECG sheet of the eCRF; the eCRF will automatically calculate ECG-LVH indices.

- The ECG will also be evaluated by the Central Reading Centre (Prof. R. E. Schmieder, Erlangen, Germany). In order to ascertain adequate source documents, before starting the study:

    - In case of ECG recorder with digital output, a sample file will be requested by the General Coordinating Center in Milan; this file will be checked by the Central Reading Centre
    - In case of ECG recorder without digital output, the General Coordinating Center in Milan will request a high quality scanned ECG (1200 dpi); this file will be checked by the Central Reading Centre for adequate quality.

- The source file has to be attached to the eCRF; the Central Monitoring Team will forward them to the Central Reading Centre in Germany

The following ECG indices of LVH will be calculated:

- Sokolow-Lyon Index
  SV1 + RV5 or RV6 ≥ 3.5 mV, The higher value should be documented.
- Cornell Voltage Index
  S in V3 + R in aVL > 2.4 mV (men)
  S in V3 + R in aVL > 2.0 mV (women)
- Cornell Voltage Product

(RaVL + SV3) × QRS duration	≥244.0 mVms	(men)
(RaVL + SV3 + 0.8 mV) × QRS duration	≥244.0 mVms	(women)

ECG determination of LV mass

ECG represents the most available method to evaluate LV mass in daily clinical practice. A recent meta- analysis of 26 studies comprising a large hypertensive population of 40444 subjects, found Sokolow-Lyon voltage criteria to be the most commonly used method for determination of ECG-LVH in clinical practice. However, the Cornell voltage product represented the most sensible, accurate index for detection of ECG-LVH in particular in female and obese subjects (1). Also, the recent ROADMAP study (2) found the Cornell Product to be the most accurate index of LVH; moreover, the ability to express results as continuous variables with this index allows to perform more comprehensive statistics. On the basis of these findings, the MASTER study will evaluate ECG-LVH primarily with the Cornell Voltage Product, and also with Cornell Voltage Index and Sokolow-Lyon Index.

Supplemental References for electrocardiography

1. Schillaci G, Battista F, Pucci M. A review of the role of electrocardiography in the diagnosis of left ventricular hypertrophy in hypertension. J Electrocardiol. 2012 45(6):617-23
2. Raff U, Ott C, Ruilope LM, Menne J, Haller H, Schmieder RE. Prevention of electrocardiographic left ventricular remodeling by the angiotensin receptor blocker olmesartan in patients with type 2 diabetes. J Hypertens. 2014 Nov;32(11):2267-76

BMJ Open

MASked-unconTrolled hypERtension management based on office BP or on ambulatory Blood Pressure measurement (MASTER) Study. A randomised controlled trial protocol

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine, Public health
Keywords:	Hypertension < CARDIOLOGY, Masked uncontrolled hypertension, office blood pressure, ambulatory blood pressure monitoring, treated hypertensive patients, hypertension management

MASked-unconTrolled hypERtension management based on office BP or on ambulatory Blood Pressure measurement (MASTER) Study. A randomised controlled trial protocol

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14-Departments of Pharmacology, European Georges Pompidou Hospital, Assistance Publique Hôpitaux de Paris, Inserm UMR 970 and University Paris Descartes, Paris, France

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Abstract

Introduction: Masked uncontrolled hypertension (MUCH) carries an increased risk of cardiovascular (CV) complications and can be identified through combined use of office (O) and ambulatory (A) blood pressure (BP) monitoring (M) in treated patients. However, it is still debated whether the information carried by ABPM should be considered for MUCH management. Aim of MASTER study is to assess the impact on outcome of MUCH management based on OBPM or ABPM. **Methods and Analysis.** MASTER is a 4-year prospective, randomized, open-label, blinded-endpoint investigation. A total of 1240 treated hypertensive patients from about 40 secondary care clinical centers worldwide will be included upon confirming presence of MUCH (repeated on treatment OBP<140/90mmHg, and at least one of the following: daytime ABP ≥135/85mmHg; nighttime ABP ≥120/70mmHg; 24h ABP ≥130/80mmHg), and will be randomized to a management strategy based on OBPM (Group1) or on ABPM (Group2). Patients in Group1 will have OBP measured at 0,3,6,12,18,24,30,36,42,48 months and taken as a guide for treatment; ABPM will be performed at randomization and at 12,24,36,48 months but will not be used to take treatment decisions. Patients randomized to Group2 will have ABPM performed at randomization and all scheduled visits as a guide to antihypertensive treatment. The effects of MUCH management strategy based on ABPM or on OBPM on cardiovascular and renal intermediate outcomes (changing LV mass and microalbuminuria, co-primary outcomes) at one year and on CV events at 4 years and on changes in BP-related variables, will be assessed. **Ethics and Dissemination.** MASTER study protocol has received approval by the Ethical Review Board of Istituto Auxologico Italiano. The procedures set out in this protocol, are in accordance with principles of Declaration of Helsinki and Good Clinical Practice Guidelines. Results will be published in accordance

with the CONSORT statement in a peer-reviewed scientific journal. **Trial registration number:** NCT02804074

Strengths

- *The MASTER study is the first randomized controlled study so far addressing an important and still controversial issue i.e. whether using ABPM rather than office BP measurements as a guide to antihypertensive treatment confers any benefit in terms of CV prevention.*

Limitations:

- For practical reasons, a double blind study design could not be implemented.
- Due to the multicenter nature of our study which includes hypertension centers from all over the world, there is the theoretical possibility of a dropout rate larger than expected. For this reason, however, we have implemented a strict study monitoring web-based.

Key words: Masked uncontrolled hypertension (MUCH); office blood pressure (OBP); ambulatory blood pressure monitoring (ABPM); treated hypertensive patients; antihypertensive treatment; hypertension management; cardiovascular and renal outcomes; hypertension control.

Word count: 3269

Introduction

The finding in untreated hypertensives of normal blood pressure (BP) levels when measured in the medical office accompanied by elevated out of office BP as assessed by either 24-hour ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM), is defined as "masked hypertension". This condition is relatively common, characterizing 10-15% of individuals in a population (1). Remarkably, even after initiation of antihypertensive treatment, a substantial number of patients continue to show elevated BP levels out of the office, despite having apparently well controlled BP levels during the medical visit. This condition has been defined as "masked uncontrolled hypertension" (MUCH), and in a population of hypertensive patients under treatment has been reported to occur in as much as 30-31% of cases (2). Moreover, there is evidence that prescription of antihypertensive treatment without adequate care of 24h BP coverage, and without implementation of ABPM in the assessment of treatment effects, may indeed be responsible for an increase in the frequency of MUCH (3). As in the case of MH, MUCH has been associated with an increased cardiovascular risk which is very similar to that of sustained hypertension and sustained uncontrolled hypertension in treated patients (i.e. persistent elevation in both office and out-of-office BP levels) (4), (3). Several hypertension guidelines have indeed included suspicion of these conditions among the key clinical indications for out-of-office BP monitoring (5), (6), (7), (8) , (9), (10), (11) The superiority of out-of-office BP vs office BP measurements has been recently emphasized also by hypertension management guidelines, in particular by the NICE guidelines which have recommended use of a time-restricted ABPM before

starting treatment in patients with elevated OBP (12). However, key evidence from randomized ad-hoc intervention trials on the benefits of using out-of-office BP measurement for assessment of blood pressure control during the follow-up of treated hypertensive patients is still lacking. With the aim to better explore this issue, the MASTER study (MASked-unconTrolled hypERtension management based on office BP or on ambulatory Blood Pressure measurement) will evaluate whether an ABPM based hypertension management strategy is superior to an OBPM based strategy in changing LV mass and microalbuminuria (co-primary outcomes) at one year, in preventing CV events (secondary outcome) at 4 years, and in improving several BP-related variables throughout the study. The MASTER study, focusing on MUCH patients, is thus expected to provide useful information aimed at finally clarifying whether a management strategy based on out-of-office BP measurements might provide a greater benefit in terms of prevention or regression of organ damage and cardiovascular events than a management strategy based on office BP readings only, thereby assessing the actual value of using out-of-office BP in improving cardiovascular protection

Methods

Study design

The present study is a 4-year prospective, randomized, open-label, blinded-endpoint (PROBE) study aimed at comparing a management strategy for MUCH patients, based on OBPM as a guide to antihypertensive treatment (group 1) versus a management strategy based on use of ABPM for the same purpose (group 2). The study will have a period of 2 years for the enrolment of the requested number of patients; and an average 4-year follow-up period (3 to 5 years).

Study endpoints are changes in LV mass and microalbuminuria (co-primary outcomes) at one year, prevention of CV events including all-cause mortality, CV morbidity and mortality (secondary

outcomes) at 4 years, and improvement of several BP-related variables throughout the study (tertiary outcome). Following a parallel group study design, patients will be randomized to one of the two management strategies by a centralized computer generated sequence with an allocation ratio of 1:1.

Sample selection

Recruitment

MASTER is a multicenter, multinational study including around 40 clinical centers from different continents: Europe (Austria, Belgium, Croatia, Georgia, Germany, Italy, Poland, Romania, Russia, Serbia, Spain, Sweden), Asia (China, India, Korea) and South America (Argentina, Brazil, Venezuela) A list with the participating centers is provided in the supplementary file 1.

To all participating centers, the coordinating center in Milan will supply the due study documentation, including a description of the protocol and of the expected tasks, and the files to be signed in relation to study participation agreement. In order to guarantee the necessary data quality, each participating center will be asked to submit to the coordinating center information on the available devices for collection of the data required by the protocol. They will also be asked to send a sample of the recorded files related to specific study variables for quality check and file approval by the coordinating center team. This will be specifically required for digital ECG files, for cardiac ultrasound records, for 24h ABPM files and for Home BP records. If the center fulfills all requirements and complies with study quality standards, an official agreement will be signed with the coordinating center before trial can be started. Approval by local ethics committee will also be required for each participating center.

Screening and randomization

Around 40 subjects will be enrolled in each center upon verifying the study eligibility criteria listed in **Box 1.**

Patients are to be enrolled for screening and randomization over 1 year (a maximum of 2 years will be allowed). During the screening period (1 month before randomization) eligibility of the patient will be checked and baseline measurements performed. Initial assessment of selection criteria based on subjects' clinical history will take place and, in case the subject is potentially eligible, the participation in the study will be proposed and informed consent obtained. During one or more screening visits, according to the need of the enrolling unit, the additional evaluations needed for a complete assessment of eligibility criteria will be performed. Specifically: full medical history, physical examination, blood and urine samples, conventional BP measurements, ABPM placement for 24h recording (device to be removed on the following day). Once the diagnosis of MUCH has been made, baseline study variables will be collected. These include 7 days home BP monitoring through use of oscillometric devices validated by means of international protocols; ECG and echocardiographic examinations, and blood and urine tests. Blood samples will be obtained for assessment of eGFR, plasma creatinine, plasma glucose, HbA1c, uric acid, serum sodium and potassium and plasma lipids. Two blood samples will also be collected at follow-up visit 1, and at follow-up visit 3 in order to create a study biobank for future analyses. Spot urine samples for urine albumin/creatinine ratio will be taken twice, once in the morning before application of the ABPM device, and another time on the following morning when subjects will return to the center clinic for removing the ABPM device.

At each study site, the responsible investigator will arrange a randomization visit (within 1 month after the Screening period) during which eligible patients (i.e. those found to have masked uncontrolled hypertension) will be randomized to one of the two study groups following the dynamic allocation method for balancing baseline covariates (specifically center, age,sex, presence of diabetes and baseline Office SBP) proposed by Xhiao et al in 2012 (13). The patient's randomization number and allocation will be generated by a central computer using an online algorithm inbuilt on the e-CRF. This approach adapts the algorithm proposed by Frane et al. to obtain marginal balance for both continuous

and categorical covariates, adding the Efron's biased coin method to decrease the predictability of treatment assigned to a new patient (14). This aspect is very important especially for unblinded trials. The original R code to perform this algorithm, furnished by the author, will be set on the platform managing the e-CRF.

Blinding (masking)

Because the MASTER is an open-label study, blinding will apply only for the endpoints. Thus, both participants and investigators will not be blinded to the allocated intervention. In order to guarantee the blind assessment of the co-primary end point of LVM, the personnel involved in its assessment (i.e. sonographers) will be blinded to the patient's allocated management strategy. In addition, ABPM data of patients enrolled to group 1 will be directly uploaded on the eCRF and will not be available to the investigators in charge of treatment decisions. The role of the Event Adjudicating Committee (EAC) of the MASTER study is essential in a trial such as MASTER, necessarily designed as a PROBE trial. This Committee (EAC) within the MASTER study will be responsible of verifying and adjudicating in a blinded fashion all events representing primary, secondary and tertiary outcomes of the study, as well as all serious adverse events occurring in the course of the trial. For this reason the General Coordinating Centre in Milan will insure that all outcome documentation sent to the Event Adjudicating Committee is blinded for management strategy and intensity of antihypertensive therapy. Documentation of each outcome occurring in patients will be sent (electronically or by fax) to two experts and to a third one in case the first two do not reach an agreement. Only validated outcomes will enter the final data analysis.

Interventions

Blood pressure levels in both study groups will be measured by three BP measurement techniques (office BP, home and 24-ABPM) following the recommendations issued by ESH/ESC hypertension guidelines (5) and BP monitoring groups (6) (7), (8). Indications on how to measure BP in the office, at home and in ambulatory conditions over 24 hours are provided in the supplemental Operation Manual. In order to standardize ABPM and OBPM data collection and analysis as much as possible, 24h ABPM in Master Study will be preferentially performed with A&D TM2430 device and OBP levels will be measured with A&D UA-651BLE device provided by the Coordinating center thanks to a non-conditioning support given by the A&D Company (A&D Engineering, Inc. 1756 Automation Parkway San Jose, CA 95131 US). For HBPM any of the currently available validated devices can be employed. Patients randomized to be managed based on office BP (Group 1) will have their BP measured by the office method at all scheduled visits (at 0, 3, 6, 12, 18, 24, 30, 36, 42 and 48 months). In these patients ABPM will only be performed at randomization visit and at follow-up visits 3, 5 , 7 and 9 and in case of premature discontinuation (i.e. patients' decision to withdraw, noncompliance with the study protocol) with the at any time. However, ABP values will not be used by the investigator to take treatment decisions, but treatment will be based on office BP only. According to the ABPM procedures manual of the MASTER study, data of these patients will not be made available to the investigators in charge of treatment decisions, but will be directly uploaded on the study website (Table 1). As indicated in Table 1, additional tests and examinations will be performed at different time-points during the study follow-up. For assessment of left ventricular (LV) mass and function both, B mode and M mode 2D echocardiographic measurements and calculation of left ventricular mass (LVM) will be performed according to current American Society of Echocardiography guidelines (15), (16), (17), (18). LVM will be calculated with the formula for estimation of LVM from LV linear dimensions (18). In order to account for obesity-related LV hypertrophy (16), (17) correction of LVM will be performed both for height and for body surface area (BSA) using the Dubois and Dubois formula (15), (17). Since

LVM values differ between men and women, with the latter systematically lower than the former, even when indexed for BSA, the presence of LV hypertrophy (LVH) will be defined on the basis of upper limits of normality for LVM of >115 g/m^2 (>48 g/h $^{2.7}$) in men and >95g/m^2 (>44 g/h $^{2.7}$) in women following recommendations for cardiac chamber quantification by echocardiography in adults (18). Patterns of LVH (concentric vs. eccentric) and remodeling will also be considered. LV systolic function will be estimated by calculating ejection fraction (EF) by means of the biplane method of disks summation (modified Simpson's rule), which is the recommended 2D echocardiographic method by consensus (18). Diastolic function will also be assessed by considering the following parameters: mitral inflow PW Doppler, TDI of mitral annulus, PW Doppler of pulmonary vein flow, tricuspidal valve velocity peak calculated by CW Doppler and indexed left atrial volume (biplane maximal left atrial volume will be calculated using the area-length method, and then indexed by body surface area) as indicated by current guidelines (19), (20).

Electrocardiogram recordings will also be performed at different time points of the study in order to identify the presence of ECG-LVH. This will be done by means of specific indices such as Cornell Voltage Product and Index and Sokolow-Lyon Index.

The co-primary end point of UAE will be evaluated from morning spot urine samples and expressed as albumin/creatinine ratio (UACR, mg/g). Spot urine samples will be taken twice, once in the morning before application of the ABPM device, and another time on the following morning when the ABPM device will be removed.

Blood samples will also be obtained for determination of serum creatinine, glucose, HbA1c, uric acid, Na+, K+ and lipids as well as to create a study biobank.

At each follow-up visit physicians will not only ascertain achievement of BP control and/or adjust antihypertensive treatment if needed, but they will also record the type of antihypertensive therapy,

presence of concomitant medications and adverse events on the study e-CRF for study safety evaluation (Table 1).

Given that the trial inclusion criteria establish that all patients in MASTER should have OBP controlled by treatment (i.e. systolic OBP < 140 and diastolic OBP < 90 mmHg), all patients in group 1 will have their antihypertensive treatment unmodified at the randomization visit. If at any of the subsequent trial visits, SBP or DBP will exceed normal values (i.e. SBP ≥ 140 or DBP ≥ 90 mmHg) antihypertensive treatment will be intensified according to available guidelines (Figure 1). Patients randomized to be managed based on ABPM (Group 2) will have their BP measured by the ambulatory method at all scheduled visits. OBP will also be measured at all visits, but it will not be used by the investigator to take treatment decisions. Given that the trial inclusion criteria establish that all patients in MASTER should have uncontrolled ambulatory systolic or diastolic BP values (24h or daytime or night-time), all patients in group 2 will have their antihypertensive treatment intensified at the randomization visit and at any of the subsequent trial visits, in which ambulatory SBP or DBP will exceed normal values (i.e. 24h SBP ≥130 or 24h DBP ≥ 80 mmHg; daytime SBP ≥ 135 or Daytime DBP ≥85; night-time SBP ≥ 120 or night-time DBP ≥70 mmHg), according to available guidelines (Figure 1). In case only daytime or night-time target values are not achieved, change in timing of doses to morning or evening, respectively, should be considered. At each Follow-up visit achievement of ABP control will be ascertained and antihypertensive treatment will be adjusted if needed, according to guidelines (Figure 1). Patients' adherence will also be encouraged and monitored.

Sample size calculation

Sample size calculation was based on the primary study end-point of changes in LVMI at 12th month. We do not know what proportion of the enrolled patients will have a diagnosis of LVH, therefore the

primary end-point has not been based on categorical changes in LVH but rather on changes in LV mass as a continuous variable. As the enrolled patients are hypertensive patients with BP incompletely controlled by treatment, we expect LV mass to be often higher than in subjects with sustained BP control (normal office and ambulatory BP levels). To calculate the sample size we have assumed a difference of 5 g/m^2 in the change of LVMI with the ABP-guided (Group 2) compared to the office BP-guided (Group 1) management strategy. This has been based on the consideration that SBP will be reduced by about 8 mmHg more in the ABP-guided group, as well as on the echocardiographic data of studies such as REGAAL and CATCH in which differences in echo LVMI changes between treatments producing similar BP reductions, were lower than $3g/m^2$ (20), (21) The standard deviation of ± 25 g/m^2 was also derived from data of REGAAL and CATCH as well as from previous assessment of within operator reproducibility (21), (22). Considering a LVMI difference between groups of 5.0 g/m^2 and a standard deviation of 25 g/m^2, an alpha of 0.025 (one-sided T-Test) and a power (1-beta) of 90%, with a drop-out rate of 15% during the study period, a minimum of 620 subjects per study group was deemed necessary, for a total number of 1240 subjects to be randomized. However, given the uncertainty about the true LVMI difference we might observe and/or the related standard deviation, performance of an interim analysis has been decided aimed at a possible re-estimation of the sample size . This analysis will be carried out at 18^{th} month when about 30% of randomized patients will achieve one year of follow-up. A re-estimation of the sample size will be calculated using the method of conditional power (23).

Outcomes

Primary, secondary and tertiary outcomes are listed in box 2.

Patient and Public Involvement

Neither patients nor public have been involved during the design of the MASTER Study. We only explored, in a pilot survey, how often office BP control was accompanied by persistence of elevated BP values at home in a number of patients referred to our hypertension center. Results of the MASTER study will be published in peer-reviewed scientific journals regardless of the outcome. Besides, MASTER study results will be available at https://clinicaltrials.gov/ either to patients or general public. Finally, assessment of the burden of the intervention has not been foreseen in the present study.

Data collection and Data statement

All data collected locally at each enrolling unit will be recorded into an electronic e-CRF on the website of the trial (https://master.digitalcrf.eu). Clinical data to be input into the e-CRF include demographic information, results on blood and urine laboratory tests performed locally (i.e. Plasma creatinine and eGFR, fasting glucose, uric acid, Na+, K+ , Lipid profile, HbA1c, Urinary sediment), ongoing antihypertensive treatment (number and dose of antihypertensive drugs); report forms for adverse events during follow-up. Digital files containing raw data from imaging (echocardiograms) and device based examinations (ABPM, HBPM data, ECG tracings) will also be uploaded on the study website linked to the study e-CRF for further analysis by the central reading sites.

Data management

Clinical data and recordings obtained with the various technologies will be uploaded in the study e-CRF and on the study website under on-line control by the Data Management Coordinating center, which includes an Audit Trail System. The quality of data obtained with the different technologies (i.e. echocardiograms, ECG, ABPM, HBPM) will be validated by expert personnel at the Central reading sites. The occurrence of cardiovascular events (stroke; myocardial infarction, all major cardiovascular

events, cardiovascular death, all cause death) and renal outcomes reported by each center and supported by clinical source documents (i.e. diagnostic tests, medical reports) will be validated by an Adjudicating Committee of experts blinded to assigned management strategy, BP values and organ damage measurements.

Data analysis plan

Descriptive analysis. Continuous data will be summarized by means of mean value, median, minimum, maximum, standard error, standard deviation, number of observations. Moreover, a 95% confidence interval for the mean value will be provided. Categorical data will be summarized by means of absolute and relative frequencies. All these analyses will be performed per management group as well as for the study as a whole. Unpaired t-test (or U-Mann-Whitney test in case of non-normal distribution) for continuous variables or chi-square test for categorical ones in order to evaluate significant between-group differences at baseline will be applied. The incidence of adverse events will be tabulated by treatment group.

Statistical methods for co-primary endpoints analysis. We will consider two co-primary endpoints: change from baseline to 12th month in LVMI and in albumin/creatinine ratio. Each endpoint will be analyzed by means of the Analysis of Covariance (ANCOVA), adjusting the group effect for the baseline value of LVMI (or albumin/creatinine ratio) and for baseline covariates resulting significant in the comparison between groups. Moreover, to have valid inference, as suggested by several authors, we will adjust the model for all variables used in dynamic allocation scheme (14). The assumption of parallelism will be tested by introducing one or more crossproduct terms between groups and continuous covariates to the model.

Statistical methods for secondary endpoints analysis. For all secondary endpoints, except for endpoint 8, we will consider a repeated measurement approach based on mixed models which contain both fixed effects (e.g. BP technique measurements) and random effects (e.g. patient). These models are likelihood-based approaches in presence of ignorable missing data (i.e missing at random) and are a proper way to accommodate information on a patient with post-randomization outcomes, even when such a patient's profile is incomplete (24). In particular for endpoints 1, 3, 4, 5 and 7 a repeated-measures model for dichotomous endpoints will be applied while for endpoints 2,6,9 and 10 we will consider a model for continuous outcome. In both cases the main purpose will be that to determine whether the within-person changes over time varie across levels of one or more between-person factors (e.g. BP technique measurements and for the same covariates included in the model for co-primary endpoints) (14). For endpoint 8, cumulative proportion surviving curves according Kaplan-Meier will be obtained for each group and compared with the method of log-rank test. In order to explore the group effect on the time to event of composite outcome adjusting for baseline covariates, the Cox regression model will be fitted. Though the Cox model is non-parametric to the extent that no assumptions are made about form of the baseline hazards, two important issues of non-informative censoring and proportional hazards will need to be verified. To satisfy the first assumption, the design of the underlying study must ensure that the mechanisms giving rise to censoring of individual subjects are not related to the probability of an event occurring. Care will be taken that continuation of follow-up does not depend on a participants medical condition. To satisfy the second assumption, the Chi square tests of proportional hazards assumption and the log-cumulative hazard plots will be made. If the assumption of proportionality is deemed reasonable, the assumptions of linearity and additivity, which are implicit in the linear predictor formula, will be considered. Although the composite endpoint could be misleading, we will not proceed to analyze each individual event considering the other events as competing causes of failure because also competing risk analysis can be misleading. Randomized

Controlled Trials (RCTs) are frequently not powered to detect an effect of the intervention on individual components and competing risks analysis might have a low chance of detecting a true effect (25).

Statistical methods for tertiary endpoints analysis. For endpoints 1-3 we will apply mixed models proposed for secondary endpoints. For endpoints 4-12, we will apply the chi-square test for dichotomous endpoints, the T-test (or median test whenever necessary) for continuous endpoints and, specifically for variation coefficients, the large sample Z test as suggested by Bhoj et al (26). For endpoints 13 and 14, the differences between the Person correlation coefficients of two groups will be calculated and reported with their 95% confidence intervals using the approach proposed by Zou (27). The handling of missing data will be based on a multiple imputation approach (24). All statistical tests will be interpreted at the 5% significance level considering two-sided test, unless specified otherwise. All statistical analyses will be performed by the Statistical Centre of Istituto Auxologico Italiano, Milan. Statistical packages will be used for the analyses, chosen among Stata (STATA data analysis and statistical software, Texas, USA), R (The R project for statistical computing, free software) and SAS (SAS Institute, Cary, NC, USA).

Ethical considerations

MASTER study protocol has initially received approval by the ethics committee of the Istituto Auxologico Italiano. Thus, the ethical conduct of this study will be under the control of an independent Data Safety Monitoring Board, stemming out of the Istituto Auxologico Italiano Ethical Review Board. This is an investigator generated study and as such will be performed in full independence of the study Sponsor from any other funding body. The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation, are designed to ensure that the sponsor and investigator abide

by Good Clinical Practice Guidelines and follow the guiding principles detailed in the Declaration of Helsinki. All centers in this study will have to obtain approval from Ethics Review Committees and/or Institution also in their Country in order to participate, and the study should be carried out in line with applicable local law(s) and regulation(s). The need of study insurance will be determined for each participating center according to national and local laws.

Dissemination

The protocol of the MASTER study has been registered with number NCT02804074 at https://clinicaltrials.gov/ where it may be accessed and consulted. Results will be published in accordance with the CONSORT statement in peer-reviewed scientific journals regardless of the outcome.

Authors' contributions:

Parati, G; Schmieder, R; Stergiou, G; McManus, R; Redon, J; Omboni, S; Bakris, G; Mancia, G; and Zanchetti, A; contributed to the conception and design of the study.

Parati, G; Schmieder, R; Mancia, G; and Zanchetti, A; drafted and wrote the protocol in accordance to the coauthors' contributions.

Faria, T; and Wijnmaalen, P; are the study managers in charge of database management and study monitoring.

All authors: Parati, G; Agabiti-Rosei E; Bakris, G; Bilo, G; Branzi, G; Cecchi, F; Chrostowska, M; De la Sierra, A; Domenech, M; Dorobantu, M; Faria,T; Huo,Y; Jelaković, B; Kahan,T; Konradi, A; Laurent,S; Li,N; Madan, K; Mancia, G; Mcmanus, R; Modesti, PA; Ochoa, JE; Octavio, JA; Omboni, S; Palatini, P; Park, JB; Pellegrini, D; Perl, S; Podoleanu, C; Pucci,G; Redon, J; Renna, N; Rhee, MY;

Rodilla Sala, E; Sanchez, R;Schmieder, R; Soranna, D; Stergiou,G; Stojanovic, M; Tsioufis, K; Valsecchi, G; Veglio, F; Waisman, G; Wang, J; Wijnmaalen, P; Zambon, A; Zanchetti, A; and Zhang, Y; contributed to the writing and the reviewing of this article, and approved the final draft of the protocol.

Roles

General Operating and Executive Committee (GOEC): Parati, G; Omboni, S; Mancia, G; and Zanchetti, A.

The General coordinator (GC) of the study: Parati, G.

Steering committee: members of the GOEC along with a selection of experts from selected centres (Parati, G; Schmieder, R; Stergiou, G; McManus, R; Redon, J; Omboni, S; Bakris, G; Mancia, G; and Zanchetti, A).

The endpoint adjudication committee (EAC): Clement, D (Ghent, Belgium), and will include experts from different centres (Agabiti Rosei, e; Palatini, P; and Waeber, B).

Data management team from the Istituto Auxologico Italiano

Data analysis: Statistical Centre (STATC) led by Zambon, A.

Data and Safety Monitoring Board (DSMB): Tsioufis, C (Athens, Greece); Cecchi F (Florence, Italy); Borghi, C (Bologna, Italy); Stéphane, L (Paris, France); Modesti, PA (Florence, Italy); and Valsecchi, G (Milan, Italy).

Acknowledgment

The names of the remaining investigators of the MASTER Study are listed in the supplementary file 1.

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In order to standardize ABPM and OBPM data collection and analysis as much as possible, 24h ABPM in Master Study will be preferentially performed with A&D TM2430 device and OBP levels will be measured with A&D UA-651BLE device provided by the Coordinating center thanks to a non-conditioning support given by the A&D Company (A&D Engineering, Inc. 1756 Automation Parkway San Jose, CA 95131 US).

Competing interests statement

Parati, G: honoraria as lecturer for Pfizer, Daiichi Sankyo, Menarini, Omron Healthcare. **Agabiti Rosei, E:** honoraria and/or support from Menarini, Servier, Recordati,Guidotti,Malesci,Ferrer, DOC gen, Bruno farm. **Bakris, G:** Principal investigator (FIDElio)-Bayer, Steering committee (CREDENCE(Janssen), SONAR (AbbVie)-Consultant for Merck, Relypsa, Vascular Dynamics, Elceyx, Bayer, Janssen, AbbVie. **Cecchi, F:** collaboration with Smart Solutions Technologies S.A.; AMICUS; Boston Scientific International S.A . **De la Sierra, A:** honoraria as lecturer for Abbott, Daiichi-Sankyo, Lacer, Menarini, and Pfizer. **Domenech, M:** Honoria from Recordati and Servier. **Kahan, T:** Research grants Karolinska Institutet from Amgen, Medtronic, Pfizer, and Record, all

outside the presented work. **Laurent, S:** Honoraria for lecturing from Axelife, Daichi-Sankyo, Fukuda-Denshi, Menarini, Novartis, Omron, Servier, and Recordati. **Mancia, G:** honoraria as lecturer Actavis, Amgen, Boehringer Ingelheim, CVRx, Daiichi Sankyo, Ferrer, Medtronic, Menarini, Merck, Novartis, Recordati, Sanofi, Servier. **Mcmanus, R:** Has received BP Monitors for research use from Omron. **Redon, J:** has been paid as lecturer by Daiichi Sankyo, Menarini, Boehringer Ingelheim, MSD. **Rhee, M:** Lecture honoraria from Pfizer Inc., LG Life Sciences Ltd, Bayer Korea Ltd., Hanmi Pharm. Co. Ltd., Yuhan Co. Ltd., Boryung Pharmaceutical Co. Ltd., Research grant from Boryung Pharmaceutical Co. Ltd. and Dong-A Pharmaceutical Co., Ltd., CJ HealthCare Co. **Stergiou, G:** Conducted validation studies for various manufacturers; advised manufacturers on device development. **Wang, J:** lecture and consulting fees from Bayer, Daiichi-Sankyo, Novartis, Omron, Pfizer, Sanofi, and Servier. **Zanchetti, A**: Honoraria from Menarini International

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Figure Legend

Figure 1. Randomization groups and patient flow in the study. BP: Blood Pressure, ABPM: ambulatory blood pressure monitoring; AHT: Antihypertensive treatment.

Tables and boxes

Box 1. Inclusion and exclusion criteria for enrolment

Inclusion criteria:

- Male and female subjects
- Age 40-80 years
- Diagnosis of masked uncontrolled (on treatment) hypertension: office BP <140/90 mmHg, and one or more of the following situations:
  - Ambulatory daytime BP ≥135/85 mmHg
  - Ambulatory night-time ABP ≥ 120/70 mmHg
  - Ambulatory 24h ABP ≥130/80 mmHg
- eGFR ≥45 mL/min/1.73 m2 (CKD-EPI creatinine equation 2009)

Exclusion criteria:

- eGFR <45 mL/min/1.73 m^2 (CKD-EPI creatinine equation 2009), and in particular severe chronic renal failure defined as serum creatinine > 250 µmol/l;
- One of the following conditions:
  - Persistent Atrial Fibrillation
  - Evidence of severe cardiac valve disease (i.e. >2/4 grade at echocardiographic examination)
  - Moderate and severe aortic stenosis
  - Presence of Cardiomyopathy
  - Symptomatic Heart Failure or Ejection Fraction (EF) at or below 45%
- Patients in unstable clinical conditions;

- Known secondary hypertension;
- Orthostatic hypotension (SBP fall > 20 mmHg on standing);
- Dementia (clinical diagnosis);
- Hepatic disease as determined by either AST or ALT values > 2 times the upper reference limit
- History of gastrointestinal surgery or disorders which could interfere with drug absorption
- Known allergy or contraindications to one of the drugs to be administered in the study
- History of malignancy including leukaemia and lymphoma (but not basal cell skin cancer) within the last 5 years
- History of clinically significant autoimmune disorders such as systemic lupus erythematosus.
- History of drug or alcohol abuse within the last 5 years
- History of non-compliance to medical regimens and/or patients who are considered potentially unreliable
- Inability or unwillingness to give free informed consent
- Pregnancy or planned pregnancy during study period.

Box 2. Study outcomes

Co-primary Outcomes

1. Changes from baseline to 12th month in echo LVMI (g/m^2)
2. Changes from baseline to 12th month in albumin/creatinine ratio (UACR, mg/g, morning spot sample)

Secondary Outcomes:

1. As compared to baseline, presence or absence of echo LVH (LVMI ≥ 115 g/m^2 [men] or ≥ 95 g/m^2 [women]) at 12th, 24th, 36th and 48th month
2. Changes in ECG indices of LVH (Cornell Product [main index], Cornell Voltage Index, Sokolow-Lyon Score) from baseline to 12th, 24th, 36th and 48th month
3. As compared to baseline, presence or absence of ECG LVH: (Sokolow-Lyon Index ≥ 3.5 mV or Cornell Voltage Index ≥ 2.4 mV (men) or ≥ 2.0 mV (women) or Cornell Voltage Product ≥ 244 mVms) at 12th, 24th, 36th and 48th month .
4. Increase of microalbuminuria (increase defined as increase in UACR by 100%) from baseline to 12th, 24th, 36th and 48th month .
5. Decrease of microalbuminuria (decrease defined as reduction in UACR by 50%) from baseline to 12th, 24th, 36th and 48th month .
6. Changes in eGFR (ml/min/1.73 m^2), according to CKD-EPI creatinine equation (2009) from baseline to 12th, 24th, 36th and 48th month.
7. As compared to baseline, presence or absence of CKD (eGFR < 60 ml/min/1.73 m^2) at 12th, 24th, 36th and 48th month.
8. The first occurrence of a composite endpoint of events including fatal and non-fatal stroke, acute myocardial infarction, angina, revascularization procedures (coronary, carotid, iliaco-femoral), transient ischemic attack, atrial fibrillation, CV death, hospitalization for heart failure, progression severe CKD (eGFR <30 mL/min/1.73 m^2 [CKD-EPI creatinine equation (2009)]), or doubling serum creatinine until 48th month.
9. Changes from baseline in echo LVMI at 24th, 36th and 48th month
10. Changes from baseline in UACR at 24th, 36th and 48th month

Tertiary Outcomes:

1. Changes from baseline in Office Blood Pressure (OBP) at 3rd, 6th, 12th , 24th , 36th, 48th month.
2. Changes from baseline in Ambulatory Blood Pressure (ABP; 24-hour, day-time and night-time BP) at 12th, 24th, 36th, 48th month.
3. Changes from baseline in Home Blood Pressure (HBP) at 12th and 48th month.
4. Proportions of patients with controlled BP measured with Office, Home or Ambulatory BP,

respectively, at 12th month and at 48th month.

5. Proportions of patients with controlled BP measured with Office and Ambulatory BP at 3, 6, 12 and 48 month (only for ABP group). Proportions of patients with controlled BP measured with Office and HOME BP at 3, 12 and 48 month (for both groups).
6. Number of prescribed antihypertensive drugs at 3rd, 6th , 12th month and 48th month.
7. Changes over time in the diagnosis of masked uncontrolled hypertension (on the basis of ABPM + OBP) at 12th month and at 48th month.
8. Comparison of the prevalence of masked uncontrolled hypertension (on the basis of HBPM + OBP or of ABPM + OBP, respectively) at 12th and at the 48th month.
9. Comparison between groups in visit-by-visit BP variability (SD, VC, VIM, ARV).
10. Comparison between groups in 24-hour BP variability (24h SD, 24h wSD, ARV) at 12th, 24th, 36th , 48th month.
11. Comparison between groups in day-by-day BP variability (SD, VC, ARV, MAX BP) at 12th and 48th month.
12. Comparison between groups in Smoothness index and TOVI at 12th month and at 48th month
13. Comparison between groups in the correlation between changes from baseline to 12th , 24th, 36th and 48th month in LVMI and changes from baseline to 12th , 24th, 36th and 48th month of different measures of BP (OBP, ABP and HBP).
14. Comparison between groups in the correlation between changes from baseline to 12th, 24th, 36th and 48th month in albuminuria and changes from baseline to 12th, 24th, 36th and 48th month of different measures of BP (OBP, ABP and HBP).

Table 1. Time schedule of enrolment, interventions, assessments, and visits for participants.

Assessment			Screening and randomization visits		Follow-up visits									Un-scheduled
			Period Screening (Baseline)	Randomization	Follow-up 1	Follow-up 2	Follow-up 3	Follow-up 4	Follow-up 5	Follow-up 6	Follow-up 7	Follow-up 8	Follow-up 9 (Final)	Premature discontinuation
			Week -4 to -1	Week 0	Month 3	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36	Month 42	Month 48	
Selection criteria			X	X										
Informed consent			X											
Clinical history			X											
Physical examination			X											
BP Measures	Group 1	Office BP	X	X	X	X	X	X	X	X	X	X	X	X
		Home BP	X				X						X	X
		24h ABPM	X				X		X		X		X	X
	Group 2	Office BP	X	X	X	X	X	X	X	X	X	X	X	X
		Home BP	X				X						X	X
		24h ABPM	X		X	X	X	X	X	X	X	X	X	X
Blood sample for serum					X	X								

creatinine												
Blood sample for serum creatinine, glucose, HbA1c, uric acid, Na+, K+, lipids	X				X		X		X		X	X
ECG	X			X	X		X		X		X	X
Echocardiogram	X				X		X		X		X	X
Urine sample for microalbuminuria and albumin/creatinine ratio	X			X	X		X		X		X	X
Ascertain achievement of BP control/ adjust antihypertensive treatment if needed		X	X	X	X	X	X	X	X	X	X	X
Registration of antihypertensive therapy	X	X	X	X	X	X	X	X	X	X	X	X
Registration of concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events/ safety evaluation			X	X	X	X	X	X	X	X	X	X
Blood sample for biobank creation			X		X							

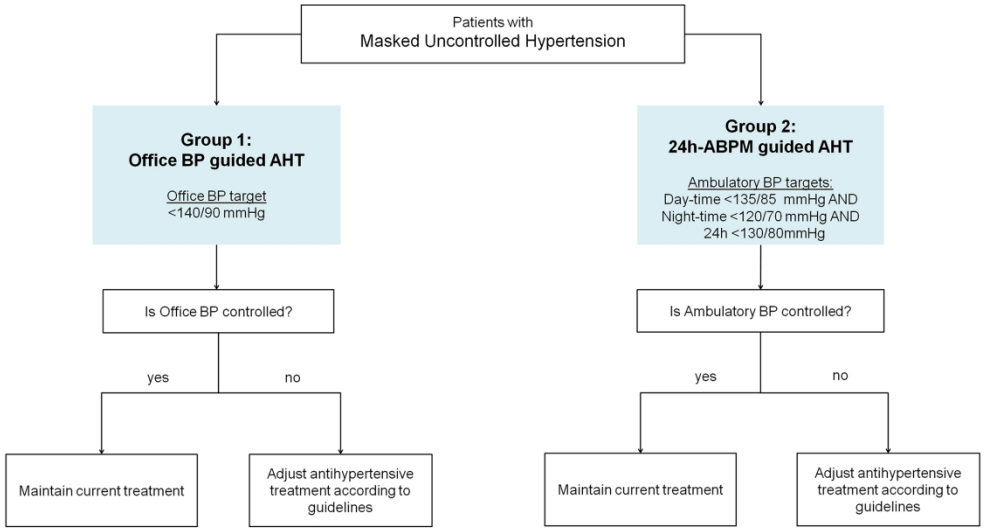


Figure 1. Randomization groups and patient flow in the study. BP: Blood Pressure, ABPM: ambulatory blood pressure monitoring; AHT: Antihypertensive treatment.

199x113mm (300 x 300 DPI)

Supplemental Material

Table S1. Current List of Participating centers and investigators in the MASTER Study

	Center / Affiliation	Country	City	Principal Investigators	CO-Investigators
1	Hospital Italiano de Buenos Aires - Unit Internal Medicine Department/Hypertension Section	Argentina	Buenos aires	Waisman G	Jessica Barrochiner
2	Favaloro Foundation - Metabolic Unit, Hypertension	Argentina	Buenos aires	Sanchez R	Paula Catalano MD, Agustin J Ramirez MD, JP Manganiello MD
3	Department of Cardiology. Hospital Español de Mendoza	Argentina	Mendoza	Renna N	Alfredo Astesiano
4	Medical University Graz, Department of Cardiology	Austria	Graz	Perl S	Prof Zweiker, Dr. Niederl
5	Fu Wai Hospital, Chinese Academy of Medical Sciences & Peking Union Medical Colleges	China	Beijing	Zhang Y	Xueli Jiang, Ken Chen, Jia Ma
6	Shanghai Institute Of Hypertension	China	Shanghai	Wang J	Changyuan Liu, Yi Chen, Lei Lei, Yan Li, Shaokun Xu
7	Peking University First Hospital - Cardiology	China	Beijing , District: Xicheng	Huo Y	Zhang Yan, Gao Lan, Wang Shixuan
8	The Center of Hypertension of the Peoples Hospital of Xinjiang Uyghur Autonomous Region/Hypertension Center	China	Urumqi, Xinjiang Uygur Autonomous Region	Li N	
9	University of Zagreb School of Medicine, University Hospital Center Zagre/Dept of Nephrology, Hypertension, Dialysis and Transplantation	Croatia	Zagreb	Jelaković B	Ana Vrdoljak, Zivka Dika
10	Dharma Vira Heart Center, Sir Ganga Ram Hospital - Cardiology	India	New Delhi	Madan K	Dr. JPS Sawhney,Dr. Manish Sharma
11	Istituto Auxologico Italiano - Ospedale San Luca	Italy	Milano	Bilo G	
12	University of Padova Dipartimento di Medicina DIMED Padua	Italy	Padova	Palatini P	Dr Claudio Fania,Francesca Saladini
13	Centro Ipertensione AOU Città della Salute e della Scienza di Torino - Internal Medicine and Hypertension Division, Department of Medical 14Sciences	Italy	Torino	Veglio F	Dr. Chiara Fulcheri,Dr. Franco Rabbia
14	Ce15ntro Ipertensione Arteriosa, Sezione di Medicina Interna - Azienda Ospedaliera di Terni - Università degli Studi di Perugia	Italy	Perugia	Pucci G	

15	JB Lab and Clinic	Korea	Seoul	Park J B	
16	Dongguk University - Ilsan Hospital - Cardiovascular center	Korea	Goyang-si, Gyeonggi-do	Rhee M Y	
17	Medical University in Gdansk - Department of Hypertension and Diabetology	Poland	Gdansk	Chrostowska M	Krzysztof Narkiewicz, Anna Szyndler, Michal Hoffmann, Ewa Swierblewska, Jacek Wolf
18	Clinical County Hospital Univesity of Medicine and Pharmacy Tirgu Mures/Department of Internal Medicine	Romania	Tirgu Mures	Podoleanu C	
19	EMERGENCY CLINICAL HOSPITAL OF BUCHAREST/CARDIOLOGY	Romania	Bucharest	Dorobantu	Dr. Alexandra Paval
20	Almazov Federal North-West Medical Research Centre, Saint-Petersburg, Russia - ITMO University, Saint-Petersburg, Russia	Russia	Saint-Petersburg	Konradi. A	Zvartau N, Ionov M
21	Excellence Centre for Hypertension of the Clinical Centre of Serbia, Belgrade	Serbia	Belgrade	Stojanovic M	Obrenović-Kirćanski, Stojanov Vesna, Radivojevic Nenad, Marijanovic Marija, Simic Dragan, Parapid Biljana
22	University of Valencia and INCLIVA Research Institute, Valencia, CIBERObn, ISCIII, Madrid, Spain	Spain	Valencia	Redon J	Fernando Martinez
23	Hypertension Clinic, Hospital de Sagunto, Valencia, Spain - Universidad CEU Cardenal Herrera, Ciencias de la Salud, Valencia, Spain	Spain	Valencia	Rodilla E	
24	Hospital Mutua TerrassaUniversity of Barcelona	Spain	Barcelona	De la Sierra A	
25	Hospital Clinic of Barcelona, Spain	Spain	Barcelona	Domenech M	Dr. Javier Sobrino, Dr. Antonio Coca
26	Karolinska Institutet, Department of Clinical Sciences, Danderyd Hospital, Division of Cardiovascular Medicine, Stockholm, Sweden	Sweden	Stockholm	Kahan T	Kristina Björklund-Bodegård
27	Fundacion Venezolana de Hipertension Arterial/Instituto de Enfermedades Cardiovasculares de LUZ	Venezuela	Maracaibo	Octavio JA	Dr. Eglé Silva, Dr. Mayela Bracho, José J, Villasmil, Freddy Madueño, Carlos Esis, Greily Bermúdez, Estílita Paredes, Pablo Amair

Operators Manual MASTER Study

CLINICAL HISTORY

Past medical history (including family history, hypertension history, cardiovascular risk factors, other relevant clinical information) and drug history will be taken according to the data collection form in the eCRF. Current drug therapy will be recorded in detail giving names and daily doses of all drugs.

ANTHROPOMETRIC MEASURES

Calibrated standard equipment will be used to measure height and weight.
To determine waist circumference, the upper hip bone is located and a measuring tape will be placed around the abdomen (ensuring that the tape measure is horizontal). The tape measure should be snug and not cause compressions on the skin.
Body surface area (BSA) will be calculated from height and weight according to the Du Bois formula .
BSA [m^2] = 0.007184 × (height [cm])0.725 × (weight [kg])0.425.
Body mass index (BMI) will be calculated from height and weight according to BMI [kg/m^2] = weight [kg] / (height [m])^2 .
These calculations will be done in the data analysis phase.

PHYSICAL EXAMINATION

Physical examination will be carried out mainly in order to exclude obvious secondary causes of hypertension and to detect previously unknown heart, vascular, renal or other disease.

LABORATORY TESTS

The co-primary end point of UAE will be evaluated from morning spot urine samples and expressed as albumin/creatinine ratio (UACR, mg/g). Spot urine samples will be taken twice, once in the morning before application of the ABPM device, and another time on the following morning when the ABPM device will be removed.

Blood samples will also be obtained for determination of serum creatinine, glucose, HbA1c, uric acid, Na+, K+ and lipids as well as to create a study biobank.

HOME BLOOD PRESSURE MONITORING (HBPM)

Devices will be provided to the patients only for the duration of home monitoring period (7 days). Alternatively, patients may use their own validated BP device.

When providing the device to the patient the investigator will instruct the patient:

• On the required monitoring schedule (see below)

• To perform readings in standard conditions (after 5 minutes of rest, having abstained from smoking, exercise or caffeine intake for the past 30 minutes, in sitting position, with the arm supported on the heart level, in a quiet room, not talking during the measurement

• To obtain morning BP readings before or at the time of antihypertensive drug intake

• To register the measured BP and HR values immediately in the provided log sheet (see Figure 1). This log sheet will be provided to the centers in Word format, so that you are free to translate it in your local language.

HBPM will be performed over 7 consecutive days preceding the study visits. Two measurements should be obtained in the morning and two in the evening at 1-2 minute intervals and measurement results should be recorded in a provided log sheet (Appendix 1). This log sheet will serve as Source Document for the Home BP values.

If, on the other hand, the BP device allows export of the data as a .csv file, this csv file can be uploaded in the eCRF, according to the instructions in the eCRF manual.

Values obtained on the first day will be discarded and the average of all the remaining scheduled readings will be calculated and used in the analyses.

Figure S1. Home Blood Pressure Log

MASTER study Clinical Trials: NCT028047074

HOME BLOOD PRESSURE LOG

Section to be filled in by Investigator:

Screening ID: |__|__|__|__|__|__|__|__|__|__| Randomization ID: |__|__|__|__|

Device model: _____

Visit: O Screening 2
O Follow-up 3
O Follow-up 9
O Premature discontinuation visit

Section to be filled in by Patient:

Day	Date	Morning				Evening			
		Time	SBP	DBP	HR	Time	SBP	DBP	HR
1									
2									
3									
4									
5									
6									
7									

Notes: _____

Section to be filled in by the investigator: Mean SBP (days 2-7): |__|__|__|.|__| mmHg
Mean DBP (days 2-7): |__|__|__|.|__| mmHg
Mean HR (days 2-7): |__|__|__|.|__| /min

Note for the Investigator: This log must be filled in manually, scanned and uploaded as pdf file in the eCRF.

OFFICE BLOOD PRESSURE MEASUREMENT (OBPM)

The MASTER study requires the use of the specifically provided **A&D TM2430** device for office SBP, DBP and HR measurement.

Measurement will be performed after several minutes of rest and with the subject having abstained from smoking, strenuous exercise or caffeine intake in the period preceding the measurements.

Three blood pressure readings will be obtained at intervals of at least 1 minute with the participant being seated in a quiet room. A standard bladder (12-13 cm long, 35 cm wide) will be used, but a larger and a smaller bladder will be available for large and thin arms, respectively. All three measurements will be stored in the e-CRF, and their average will be taken to indicate office BP at each visit.

An additional measurement will be obtained with the patients standing upright for one minute (unless the patient is unable to stand).

Blood pressure will be measured on both arms during the first visit and the arm with the higher systolic value will be used again during all subsequent visits.

A&D UA-651BLE device – source data:

The supplied device UA-651BLE is equipped with Bluetooth communication which connects to the A&D connect app available for iPhone and Android devices. The data can be downloaded directly after each single measurement when the device is paired with e.g. smartphone.

Once the data are on the mobile device, access the data table and use the “share” function to export the data in **csv** format. Then remove the readings one by one (slide with the finger sideways on a single reading and a delete button will appear).

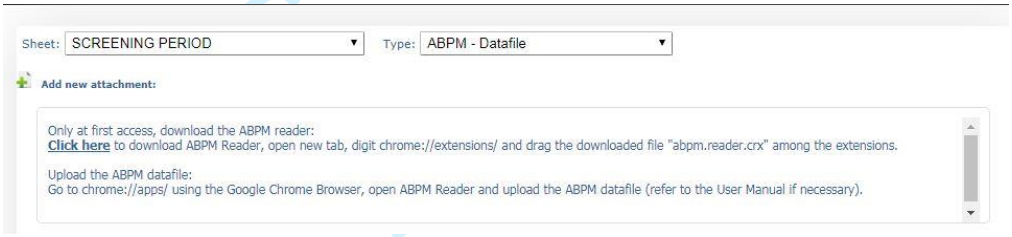
csv files should be uploaded on the eCRF as source documents.

24 H AMBULATORY BLOOD PRESSURE MONITORING (ABPM)

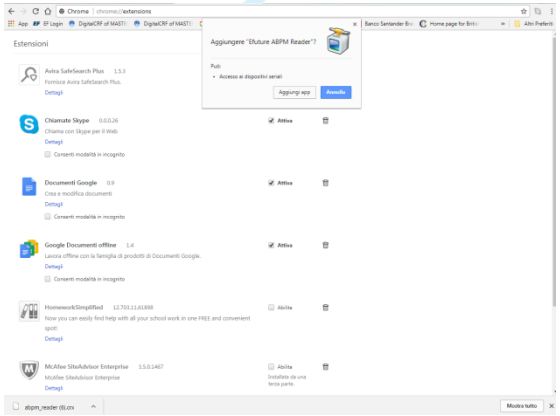
Ambulatory Blood Pressure Monitoring (ABPM) will be carried out as follows:

- The MASTER study requires the use of the specifically provided **A&D TM2430** device. This device allows direct upload of the datafile to the eCRF (see ahead).
- For more information, please check the attached TM2430 Data Sheet and Instruction Manual.
- ABPM will be performed:
    - In Group 1: during screening period, every twelve months during follow-up, and at the final visit.
    - In Group 2: during screening period, at three months, six months and every six months thereafter during follow-up, and at the final visit.
- Each monitoring should start in the morning, after the subject has taken his/her morning medication. Patients will be sent home (to perform the recording in conditions as close as possible to daily life) and asked to come back the following day for the device removal.
- The cuff will be applied on the non-dominant arm unless the patient presents a major (>10 mmHg) between arm difference in BP; in that case the arm with higher BP should be used.
- The patient will be instructed:
    - to fill the attached diary form (see Figure 1) with reference to his/her main daily activities and quality of night time sleep. This diary will be provided to the centers in Word format, so that you are free to translate it in your local language.
    - to keep the arm still and to avoid any movement during each automatic blood pressure measurement
    - to attend her/his usual daily activities (avoiding major physical activity)
    - not to remove the cuff during the recording period
- The device will be set to take automatic readings every 15 minutes at daytime (6:00 to 22:00) and every 20 minutes at night-time (22:00 to 6:00) and not to display the measured readings
- The device should be removed after 25 hours of recording to ensure a complete coverage of all hours. ABPM files, with the accompanying diary, will be uploaded on the study website for immediate quality check.

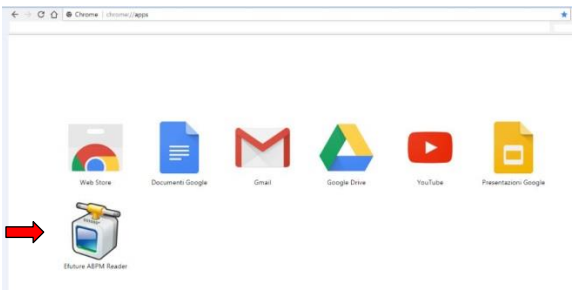
- Recordings of inadequate quality (less than 65% of the expected BP readings, 3 or more hours with no valid readings, 2 or more consecutive hours without valid readings) should be repeated by the centre in the same treatment condition.
- Attach the digital datafile to the eCRF in the “Upload attachments” section, under the heading “ABPM-datafile”:
    - Please use the **Google Chrome browser**!
    - The ABPM datafile has to be uploaded DIRECTLY from the **A&D TM2430** device to the eCRF, by an ABPM-reader APP that was specifically designed for this study.
    - At the first access: (1) download the “abpm_reader.crx” file by clicking “Click here”.



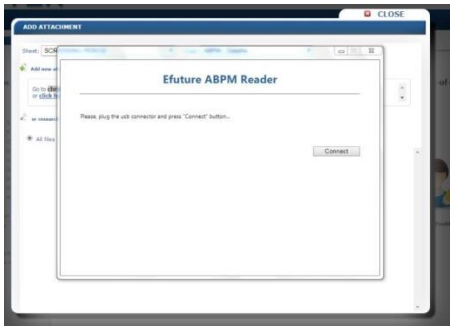
    - (2) Then drag the file among the extensions on the web page “chrome://extensions/”. (Please note that Step (1) and (2) need to be performed only once).



    - Once installed, go to “chrome://apps/ and open the ABPM reader icon.

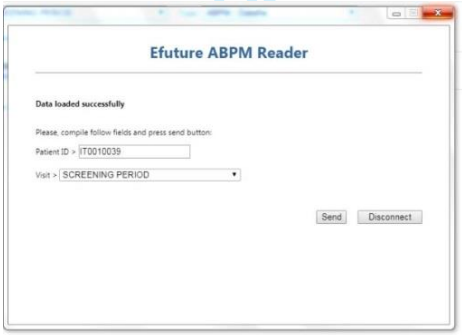


- Click on the Efuture ABPM reader icon, plug the USB connector and press “Connect”

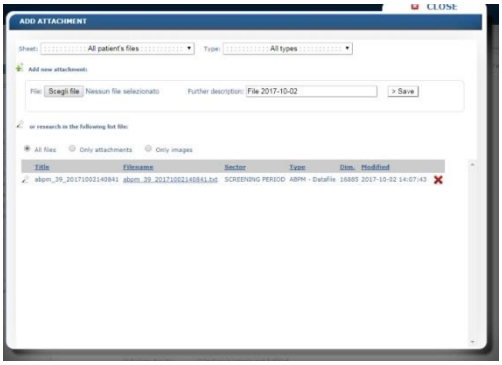


- Press red button on **A&D TM2430** device

- Fill in the patient Screening ID and corresponding visit



- “Data loaded successfully” and “Disconnect”. You will find the attached datafile in the uploaded files list



- Once the ABPM datafile has been uploaded, the raw data (including all individual measurements) of each recording will be examined by the ABPM Core Laboratory in Milan for quality control and analysis.
- ABPM data of patients randomized to group 1 (Office BP) will not be available to the investigators in charge of treatment decisions; for these patients only feedback concerning the quality of the ABPM data file will be returned. You will receive feedback from "masterdata@auxologico.it"
- ABPM data of patents randomized to group 2 (Ambulatory BP) will be available to the investigators in charge of treatment decisions; for these patients feedback concerning quality of the ABPM datafile AND mean BP values will be returned. You will receive feedback from "masterdata@auxologico.it"

- For each ABPM recording the following variables will be computed:
    - 24h, daytime and night-time average BP and heart rate (HR) values
    - SBP and DBP variability calculated as the standard deviation (SD) of the average 24h, day and night values, and as the "weighted" 24h SD, as well as Average Real Variability (AVR) and as ambulatory arterial stiffness index (AASI)
    - Nocturnal BP falls and night/day SBP and DBP ratios
    - Average morning (7-11 a.m.) SBP/DBP values and morning BP surge (defined as the difference between the lowest BP before the morning rise and the highest BP after awakening)
- Figure S2. ABPM Diary

MASTER study Clinical Trials: NCT028047074

AMBULATORY BLOOD PRESSURE MONITORING DIARY

Section to be filled in by Investigator:

Screening ID: |__|__|__|__|__|__|__|__|__|__| **Randomization ID:** |__|__|__|__|

Visit:

O Screening
O Follow-up 1 (only Group 2)
O Follow-up 2 (only Group 2)
O Follow-up 3
O Follow-up 4 (only Group 2)
O Follow-up 5
O Follow-up 6 (only Group 2)
O Follow-up 7
O Follow-up 8 (only Group 2)
O Follow-up 9
O Premature discontinuation visit

Date: |__|__| / |__|__| / |__|__|__|__| (dd/mm/yyyy)

Time recording started: |__|__|:|__|__| (hh:mm)

Section to be filled in by Patient:

Time of: sleep: |__|__|:|__|__| (hh:mm) **awakening:** |__|__|:|__|__| (hh:mm)

Morning drug intake time: |__|__|:|__|__| (hh:mm)

Quality of sleep: O Bad O Average O Good

Please record below any major event that might have affected your blood pressure

Time	Activity/posture/symptoms

Comment:_____

Note for the Investigator: This log must be filled in manually, scanned and uploaded as pdf file in the eCRF

ECHOCARDIOGRAPHIC SPECIAL PROCEDURES

1-Certification of Echo's
2-Echocardiographic Media and Data Flow
3-Instructions for Performing Echocardiograms
4-Echocardiographic Quality
5-Required Echocardiographic Views
6-Instructions for Obtaining Required Echocardiographic Views
7-Contact Information
8-References

1-Certification of Echo's:

It is essential that all sonographers at participating sites produce the highest possible quality in acquired echo images. The echo operator(s) of each participating center must perform one sample echocardiographic examination, following the instructions described in this manual. This Certification Echo must be submitted to the Core Echocardiography Laboratory (hereafter designated as "Core Echo Lab") through the eCRF (www.master.digitalcrf.eu) for assessment and subsequent certification of adequate quality.
The submitted Certification Echo must:

- be clearly labeled as a "Certification Echo"
- be of good quality and all images should be clear
- be compatible with the instructions contained within this document
- include all required views outlined in the echo protocol contained in this manual

The Core Echo Lab will provide feedback to the site within *10 business days* of receipt of the Certification Echo.
Once the Certification Echo is deemed acceptable, the Core Echo Lab will e-mail a site Certification Form to the site's Principle Investigator.

2-Echocardiographic Media and Data Flow:

The participating center must:

- save the echo data in universal DICOM format.
- unite the requested views/images for each single echocardiography examination in one single data folder.
- name this data folder, according to the patient's screening ID and follow-up visit, as follows:

Follow-Up visit	Requested folder name
Certification Echo	Certification Echo
Screening period - Baseline	ScreeningID-BA
Follow-up 3	ScreeningID-FU3
Follow-up 5	ScreeningID-FU5

Follow-up 7	ScreeningID-FU7
Follow-up 9	ScreeningID-FU9
Premature discontinuation	ScreeningID-PD

- upload the data folder directly to the electronic CRF, according to the eCRF attachment manual.
- keep a copy of the echo data folder in the Investigator Site File, for the entire duration of the study.

NOTE: If the participating site cannot upload the echo data directly to the eCRF, the site investigator(s) will need to make alternative arrangements with the Data Management team for transmitting the required echo data.

The Data Management team:

- downloads the echo data from the eCRF
- forwards the echo data to the Core Echo Lab for blinded centralized reading.
- eliminates the echo data from the eCRF, in order to free digital space in the platform.
- archives a copy of the echo data for the entire duration of the study.

3-Instructions for Performing Echocardiograms:

Recommendations on this manual have been based on the up-to date evidence and consensus provided by current guidelines listed in the reference section at the end of this manual (1-4).

A Core Echo Lab certified sonographer should obtain all study echos on a given subject. If possible, identify one or two sonographers in your Echo Lab to perform all echos related to this study.

A. Echocardiographic Equipment

Use the highest possible frequency (2.5-5.0 MHz) transducer to allow adequate penetration for endocardial border definition. It is advisable to use the same transducer frequency for all the studies on a given patient. Tissue harmonic imaging may be used, at the discretion of the sonographer and investigator, unless this worsens endocardial border definition.

B. Subject Identification on Recorded Images

The echo media (CD) and other materials received by the Core Echo Lab should not contain the subject's name or medical record number. Only the subject's assigned study screening ID should be used.

C. Subject Preparation

Electrocardiographic (ECG) leads (3-lead) should be placed and an ECG signal in which the QRS complex is clearly identifiable should be visible on the echocardiographic monitor.

4- Echocardiographic Quality

Echocardiograms should be obtained in a manner that is most consistent with good-quality subject care. However, subject comfort and safety shall always be the primary concern. Subject co-operation and comfort are essential in obtaining high quality echocardiographic images.

Importance of High Quality Echos

The Core Echo Lab relies heavily on sites performing high quality echos. Quantitative measurements entail manually tracing the endocardium and Doppler envelopes at various periods in the cardiac cycle. Even when images are of good quality, this can be extremely difficult, and it is therefore critically important that the best possible endocardial definition and Doppler signal are obtained.

Optimizing Endocardial Border Definition

Sonographers and the individual echo investigator should optimize endocardial border definition at their own discretion, using any machine-specific optimizations. Please do not use automatic border detection systems, as found on certain machines. Furthermore, adjust the transducer depth range to maximize the dimensions of the chamber of interest.

Instructions for Image Acquisition

The required echo views and echo-Doppler data should be obtained in the order outlined in the Table. Further details, specific to each echo view, can be found in the section: "Instructions for Obtaining Required Echocardiographic Views".

Recording should start once the view is optimized and end after the required number of cardiac cycles has been recorded for each required view.

At least **5 cardiac cycles** per view are required for digitally stored studies (in DICOM format).

Doppler Recordings:

With all spectral Doppler recordings, set the Nyquist limit at 50-70 cm/sec, adjusting to ensure a well-defined jet. The Nyquist limit must be documented on the image. Ensure the color sector remains as narrow as possible to obtain the best frame rate. However, the color sector should be of adequate size to capture the entire regurgitant jet.

For continuous wave and pulsed wave Doppler images, use a standardized sample volume (5 mm is recommended). Care should be taken to align the Doppler signal parallel to the presumed direction of flow. Adjust the gain to obtain a clear flow signal and the baseline and scale (80 cm/sec) to capture the peak flow velocity. Reset scale if necessary to optimize the flow signal. Record at 100 mm/sec sweep speeds for the required number of beats (as outlined above).

5- Required Echocardiographic Views

Echocardiographic Examination and Acquisition

A subset of a standard echocardiographic examination will be performed. The following table resumes the required views for each echo study:

Table S2. Required Echocardiographic Views

VIEW	REQUIREMENTS
A. Parasternal Long Axis View	1. 2D 2. M-mode across the LV base (where MV leaflet tips meet chordae) 3. Color flow Doppler of mitral valve 4. 2D parasternal long-axis view, which depicts the aortic root and the proximal ascending aorta
B. Parasternal Short Axis View: MV Level	1. 2D 2. M-mode across the LV base (where MV leaflet tips meet chordae)
C. Parasternal Short Axis View: Mid-papillary Level	1. 2D 2. M-Mode
D. Parasternal short Axis View: Aortic valve, RV Inflow-outflow View	1. 2 D 2. Continuous wave (CW) Doppler of tricuspid regurgitant (TR) jet if present.
E. Apical 4-Chamber View	1. 2D - include entire four cavities 2. 2D- focused on left ventricle and left atrium only 3. Color flow Doppler of mitral valve and tricuspid valve - include entire LA and RA cavity 4. CW Doppler of TR jet if present 5. Mitral inflow: PW Doppler 6. PW Doppler pulmonary vein recordings guided by color Doppler 7. Mitral annular Doppler Tissue Imaging (DTI) at the medial (septal) and at the lateral corner of the mitral annulus
F. Apical 5-Chamber View	1. 2D 2. LV outflow tract pulsed wave (PW) Doppler 3. Aortic valve color Doppler and CW Doppler
G. Apical 2-Chamber View	1. 2D - include entire LA and LV cavities 2. Color flow Doppler of mitral valve

H. Apical 3-Chamber View	1. 2D 2. Aortic valve color Doppler
I. Subcostal View	1. Four chambers view 2. Inferior vena cava - 2D (image at *rest* and with *inspiration* to assess for respiratory change in IVC diameter)

6-Instructions for Obtaining Required Echocardiographic Views:

The required echo views and echo-Doppler data should be obtained in the order outlined in the table. At least 5 cardiac cycles per view are required. For M-mode and Doppler recordings, use at least 100 mm/sec sweep speeds.

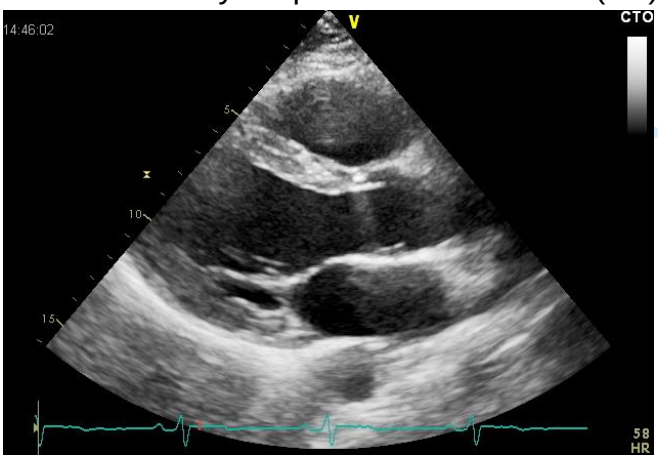
NOTE: Please record *moving* images, rather than still images, for all data except for spectral Doppler and M-mode recordings. Do NOT record measurements on the echo study submitted. The Echo Core Lab will visualize all the cardiac cycles and perform all measurements

PARASTERNAL VIEWS:

A. Parasternal Long Axis View

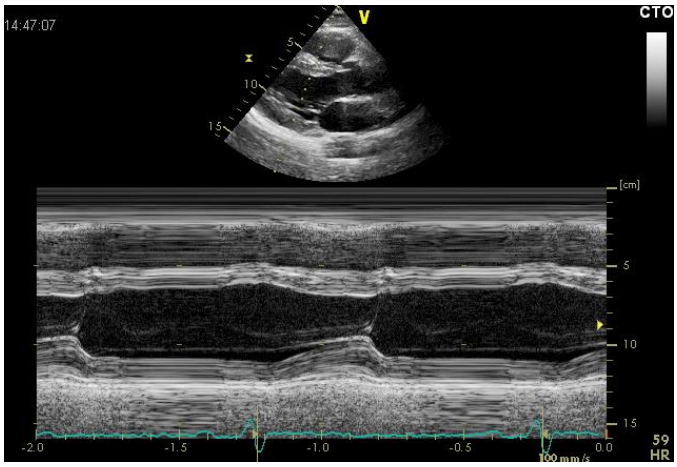
2D

This view is best obtained with the transducer positioned at the left sternal border, angled to ensure the longest apex-base view of the left ventricle (LV). It is important to acquire the true long axis of the LV and to avoid any foreshortening of the LV. The LV outflow tract should be visualized with only minimal angulation of the proximal interventricular septum (IVS) as it meets the anterior aortic wall. The anterior and posterior mitral valve (MV) leaflets and the right and non-coronary cusps of the aortic valve (AV) must also be visible.



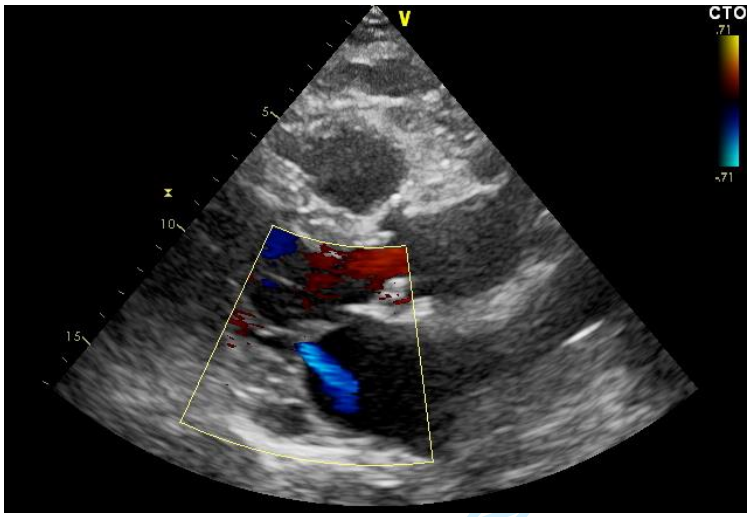
M-mode across the LV base

M-mode recording of the LV should be made with the cursor directed at or below the MV leaflet tips. The interventricular septum (IVS) and the posterior wall (PW) should be clearly visible.



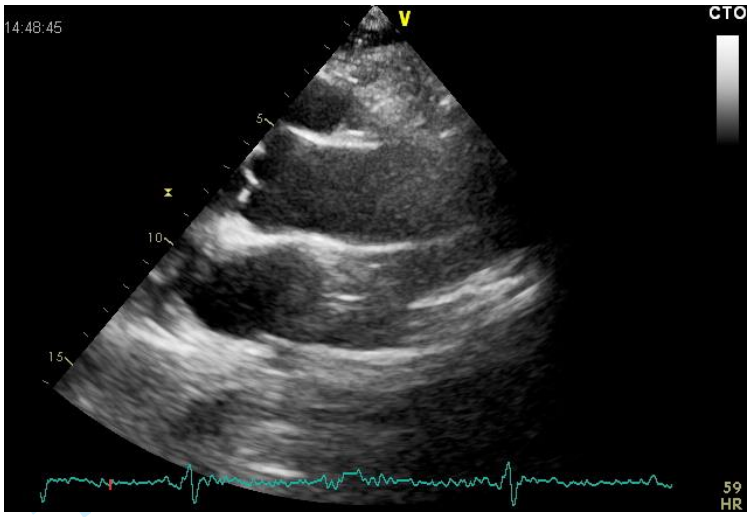
Colour flow Doppler of MV

With the optimized 2D view, place the color sector over the mitral valve, including as much of the left atrium (LA) cavity as possible.



Ascending aorta

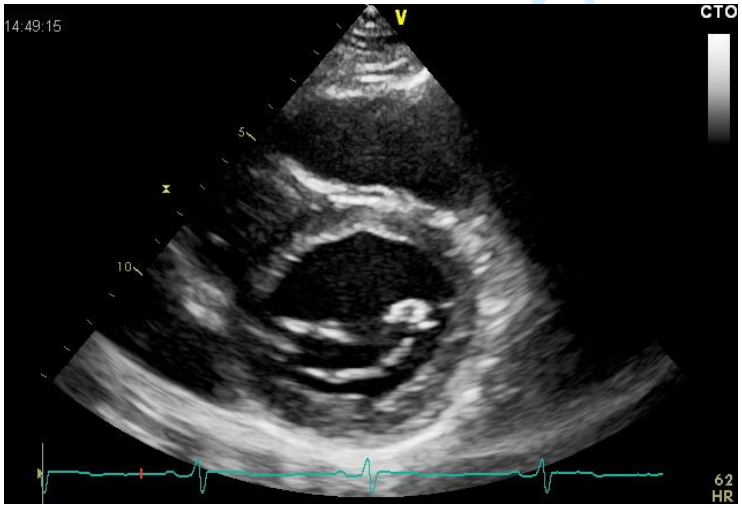
The parasternal long-axis view, which depicts the aortic root and the proximal ascending aorta. This plane is slightly different from that of the long axis of the left ventricle. Acquisition of this LV longaxis view may be performed from different intercostal spaces and at various distances from the left sternal border. The tubular ascending aorta is often not adequately visualized from a standard parasternal window. In these instances, moving the transducer closer to the sternum may allow visualization of a longer portion of the ascending aorta.



B. Parasternal Short Axis View: MV Level

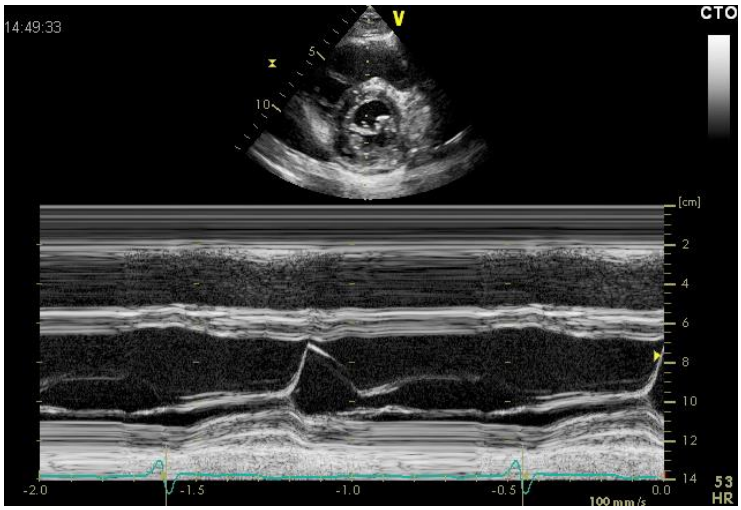
2D

This view is best obtained by 90 degree clock-wise rotation of the transducer from the parasternal long axis position and with superior or inferior angulation. The LV cavity should be visualized as a circular conformation with the depth adjusted to optimize the LV chamber dimensions. The mitral valve, with both anterior and posterior mitral valve leaflets, should be clearly visible.



M-Mode across the LV base

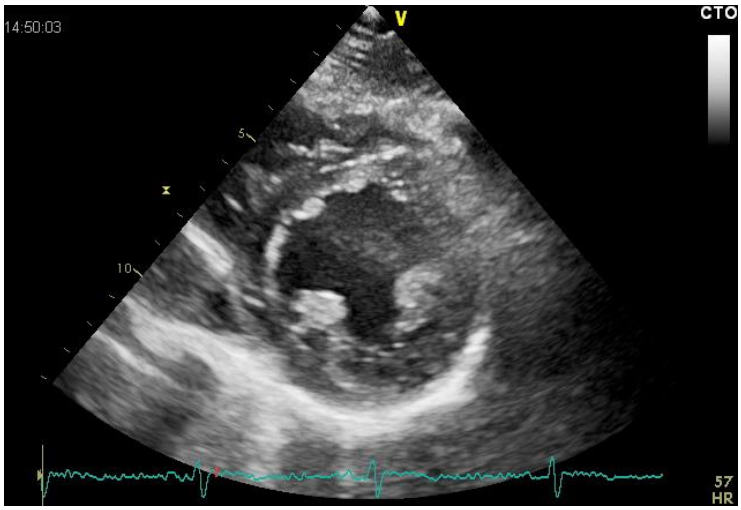
M-mode recording of the LV (for quantification of the LV mass) should be made with the cursor aligned through the middle of the circular LV, where the MV leaflet tips meet the chordae. The mitral valvular apparatus should be visible in this image.



C. Parasternal Short Axis View: Mid-papillary Level

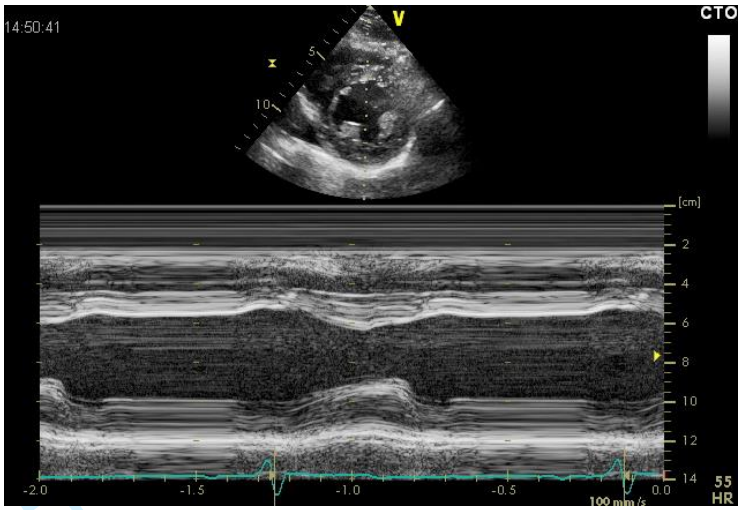
2D

This view is best obtained by 90 degree clock-wise rotation of the transducer from the parasternal long axis position and angled interiorly from the MV level. The LV should be visualized as a circular conformation with the depth adjusted to optimize the LV chamber dimensions. Both of the papillary muscles must be clearly visible.



M-Mode

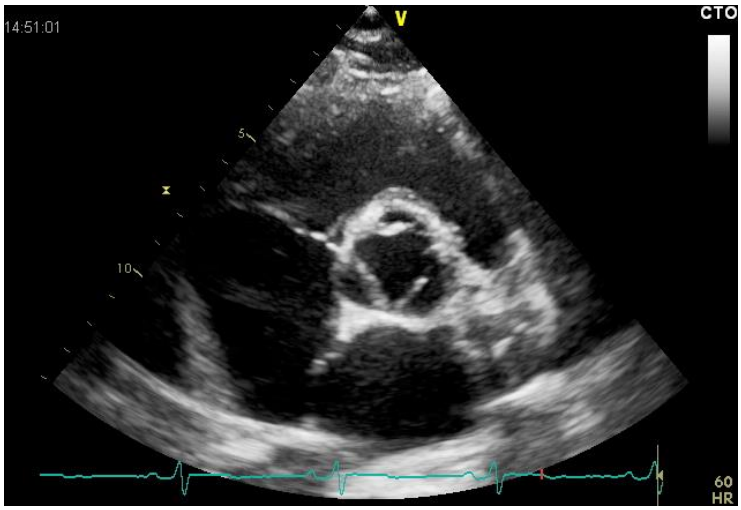
M-mode recording of the LV should be made with the cursor aligned through the middle of the circular LV.



D. Parasternal Aortic valve and Right Ventricular Inflow-outflow View

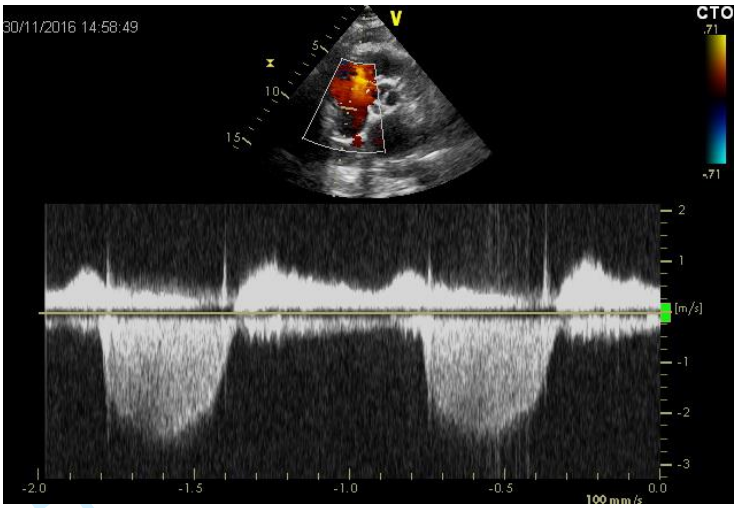
2D

This view is best obtained by 90 degree clock-wise rotation of the transducer from the parasternal long axis position and with superior angulation. The aortic valve, with its cuspids, should be clearly visible, as well as right ventricular inflow and outflow.



Continuous wave (CW) Doppler of tricuspid regurgitant (TR) jet

The cursor should be directed along the long axis of the RV and through the middle of the TV, parallel to the flow of the TR jet.



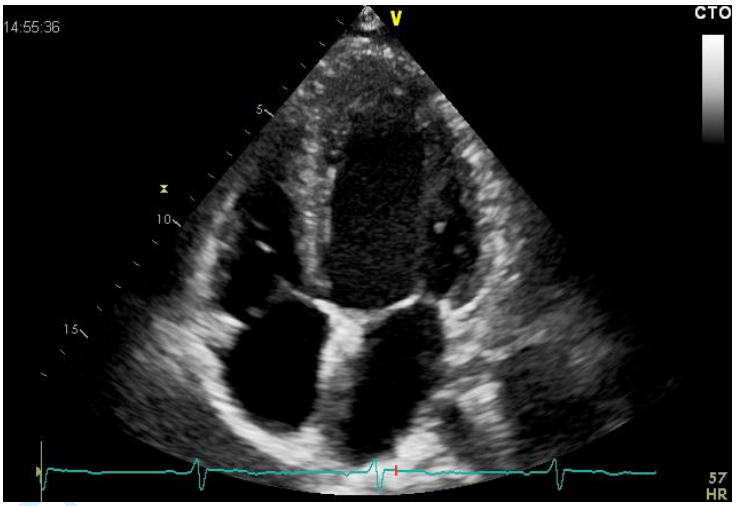
APICAL VIEWS

The apical views are obtained by placing the transducer laterally and inferiorly at the apex and moving superiorly and medially until the cardiac chambers are visualized.

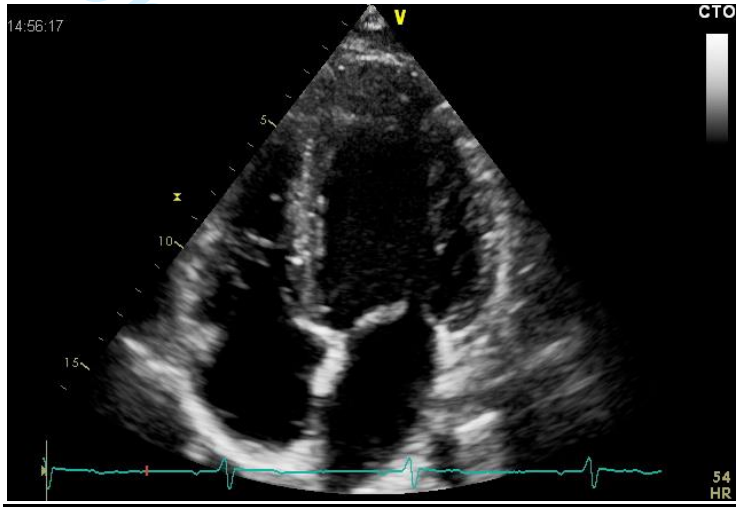
E. Apical 4-Chamber View

2D – 4 chambers

The image should be properly aligned to capture the entire four chambers. The interventricular septum should be as parallel as possible to the superior-inferior direction and the entire LV endocardium must be visualized in both systole and diastole. It is important to adequately visualize the apex and lateral LV free wall. Avoid foreshortening or elongating the RV or LV chambers.

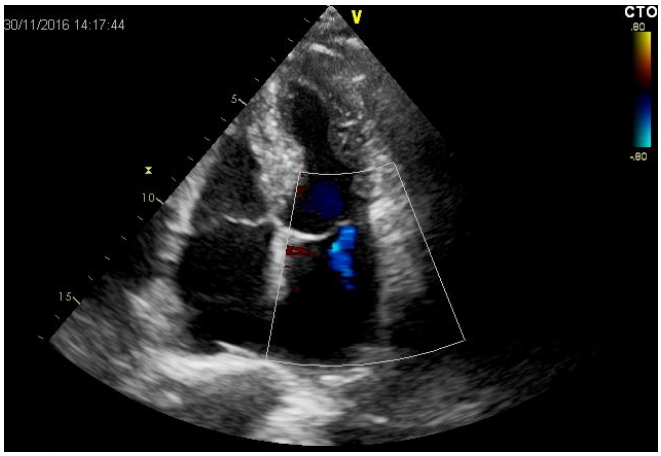


2D focusing only left chambers



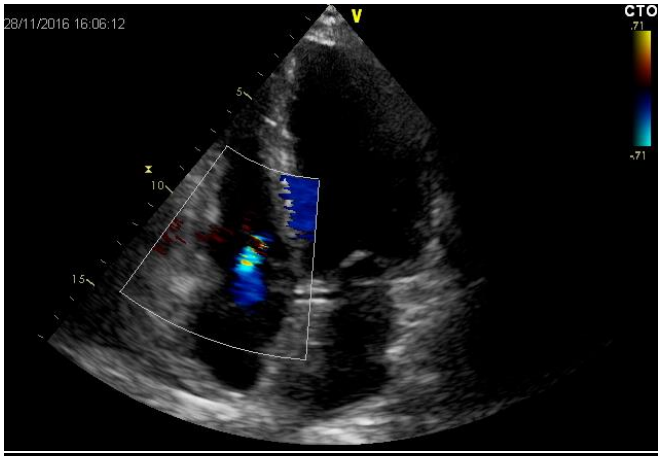
Color flow Doppler of MV

With the optimized 2D apical 4 chamber view, and the LV and LA seen in full, place the color sector over the mitral valve, including as much of the left atrium (LA) cavity as possible.



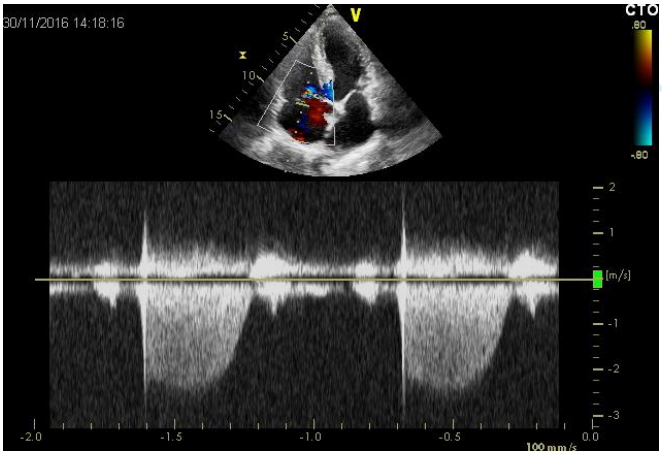
Color flow Doppler of TV

With the optimized 2D apical 4 chamber view and the entire RA seen and the tricuspid valve (TV) leaflets now clearly visible, place the color sector over the TV.



CW Doppler of TR iet

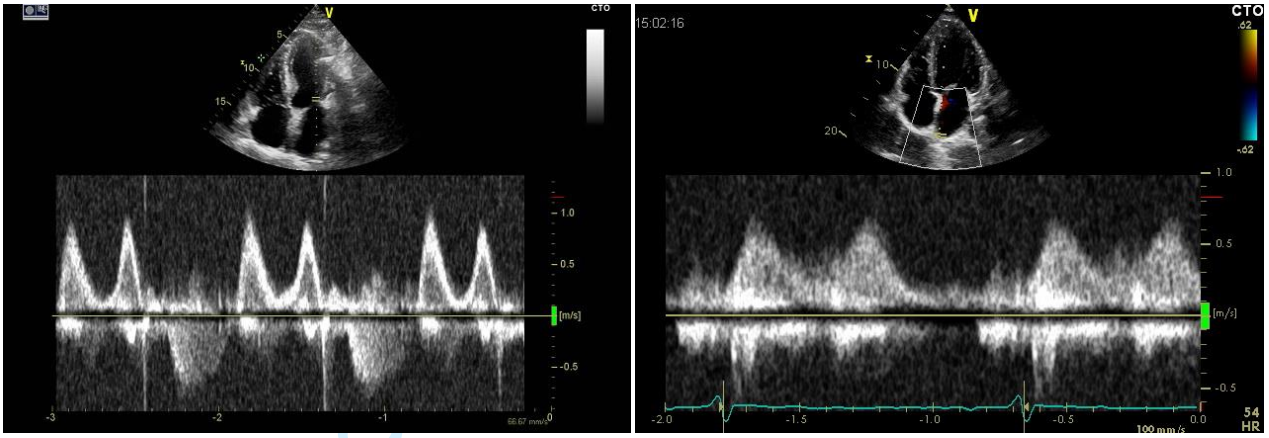
The cursor should be directed along the long axis of the right ventricle (RV) and through the middle of the TV, parallel to the TR flow.



PW Doppler

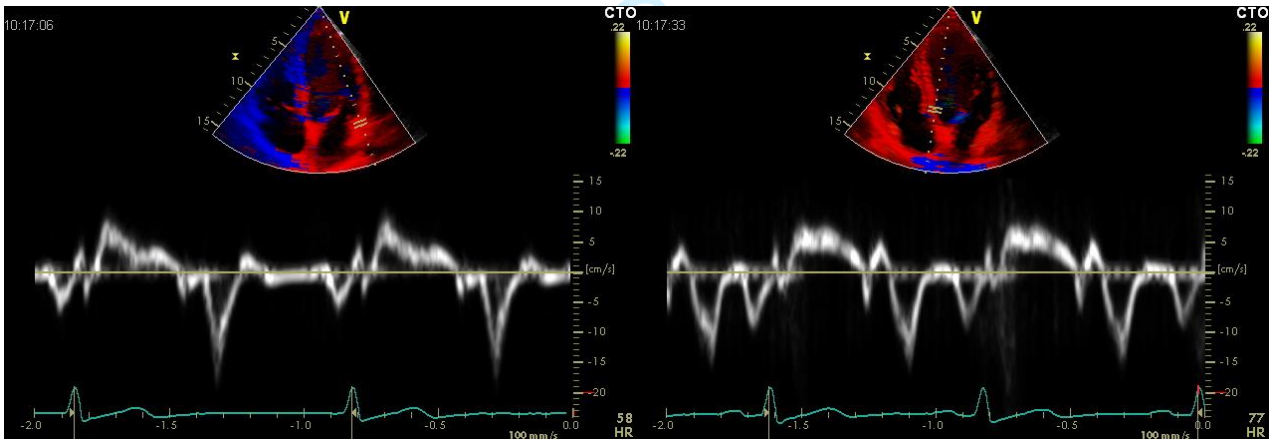
a. PW Doppler transmitral flow recordings with sample volume at leaflet tips during diastole

b. PW Doppler right superior pulmonary vein recordings guided by color Doppler



DTI PW Doppler

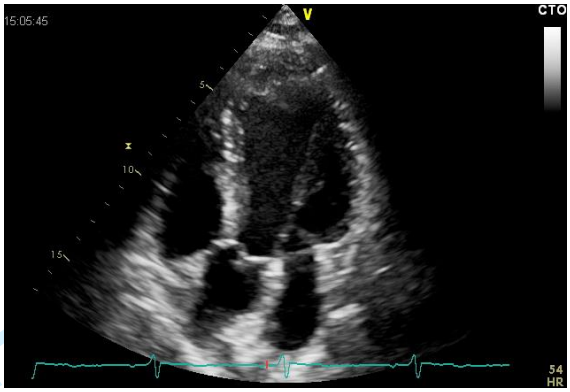
PW tissue Doppler imaging (DTI) is performed in the apical views to acquire mitral annular velocities. The sample volume should be positioned at or 1 cm within the septal and lateral insertion sites of the mitral leaflets and adjusted as necessary (usually 5–10 mm) to cover the longitudinal excursion of the mitral annulus in both systole and diastole. Record a minimum of 5 cardiac cycles at a sweep speed of 100 mm/sec.



F. Apical 5-Chamber View

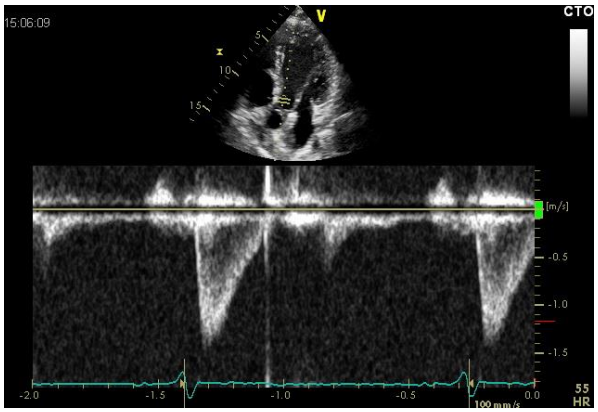
2D

Five-chamber view should include the left ventricular outflow tract (LVOT) and the aortic valve (AV) cusps. Be careful to maintain maximal LV length, to visualize all 4 cardiac chambers and to optimize endocardial definition.



LV outflow tract PW Doppler

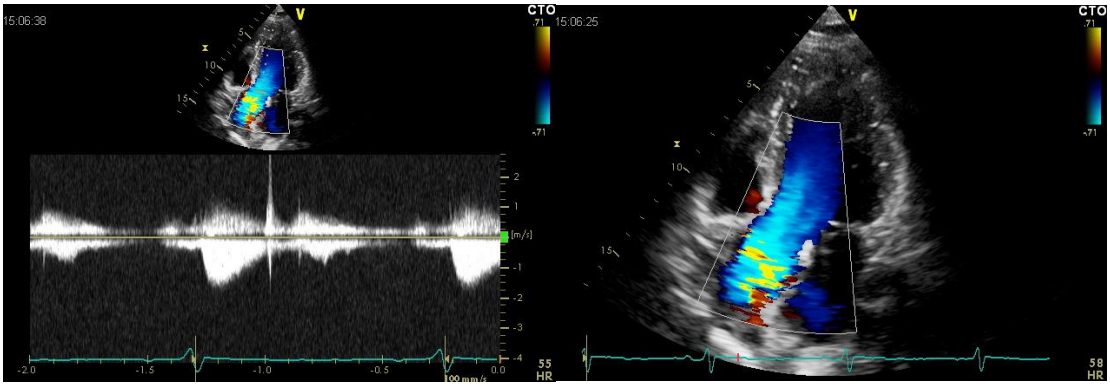
Place the color sector over the LVOT and aortic valve. Align the PW signal parallel to the direction of LVOT flow and position the PW Doppler sample (5 mm sample volume size) within the LVOT 5-10 mm proximal to the AV. Adjust the baseline and Doppler scale to visualize the peak wave velocity.



Aortic CW Doppler and color Doppler

Still in the five-chamber view, the cursor should be directed along the long axis of the LVOT and AV cusps. Adjust the gain to obtain a clear LVOT flow signal and the baseline and scale to capture the peak velocity.

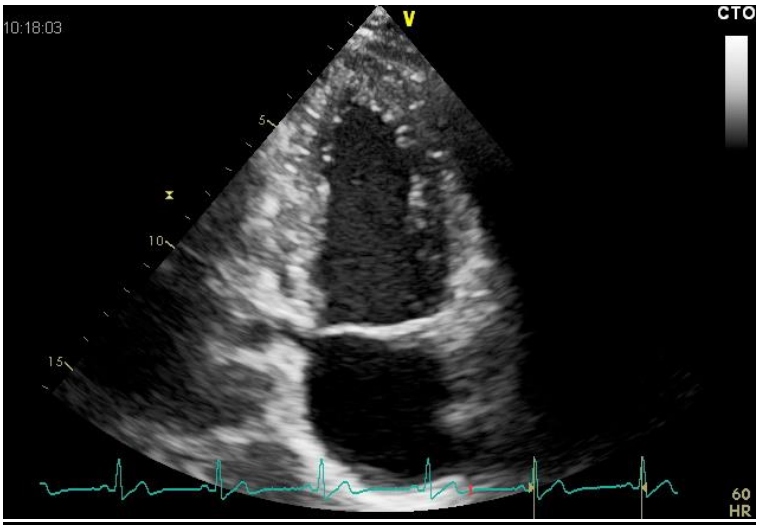
With the optimized 2D apical 5-chamber view, place the color sector over the aortic valve.



G. Apical 2-chamber view

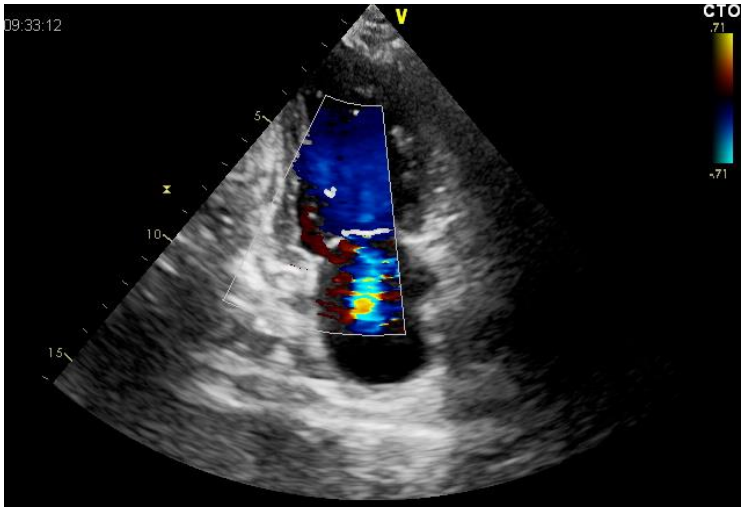
2D

LV and left atrium cavities should be entirely visualized. In particular, for LV, ensuring the entire LV endocardium is visualized in both systole and diastole. Ensure that the LV apex is not cut off.



Color flow Doppler of MV

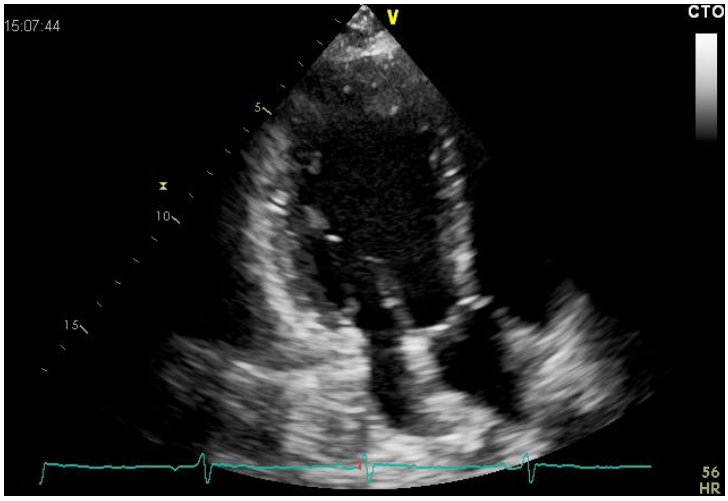
With the optimized 2D apical 2 chamber view, and the LV and LA seen in full, place the color sector over the mitral valve, including as much of the left atrium (LA) cavity as possible.



H. Apical 3-Chamber View

2D

Visualize the entire LV, as well as the MV and the LA, similar to the parasternal long axis view. Again, it is important to properly align the image and not to foreshorten the LV.



Color flow Doppler of aortic valve

With the optimized 2D apical 3-chamber view, place the color sector over the aortic valve.

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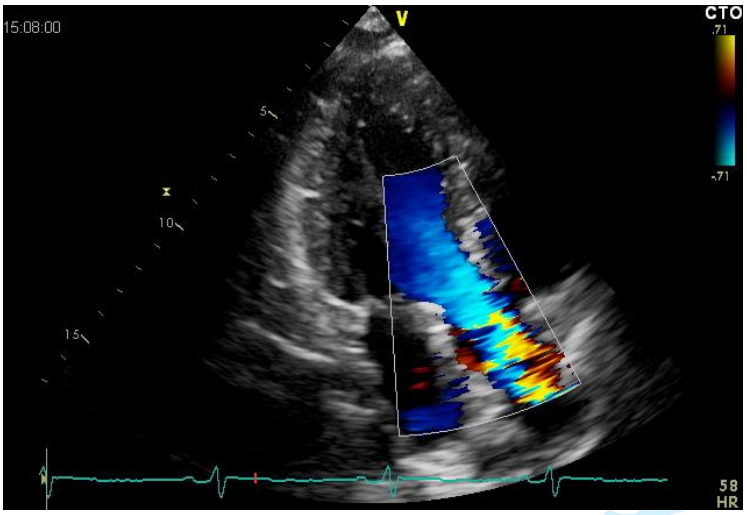
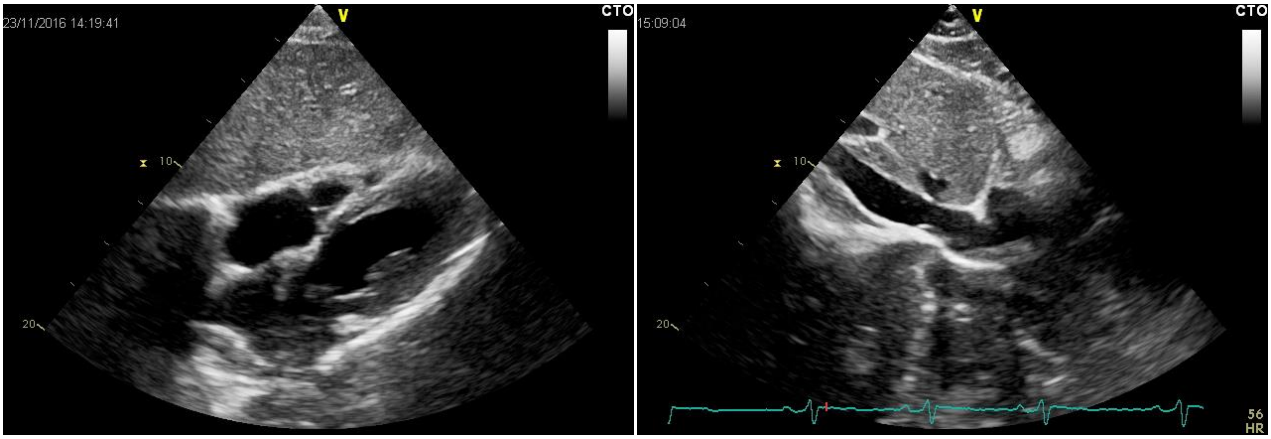


I. Subcostal View

2D

With the transducer in the subcostal position obtain a 4-chamber view.
Then, angulate the transducer to visualize the proximal inferior vena cava (IVC) where it meets the right atrium. Ask the patient to sniff or inspire - this maneuver will reveal if the IVC diameter changes with inspiration.



7-Contact Information

For technical echo-related questions, please direct all questions and inquiries to masterdata@auxologico.it

8-Supplemental References for echocardiographic procedures

1. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1-39 e14.

2. Marwick TH, Gillebert TC, Aurigemma G, Chirinos J, Derumeaux G, Galderisi M, et al. Recommendations on the Use of Echocardiography in Adult Hypertension: A Report from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE). J Am Soc Echocardiogr. 2015;28(7):727-54.

3. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009;22:107-33.

4. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016;29(4):277-314.

ELECTROCARDIOGRAPHY

Electrocardiographic assessment of LV mass

Standard 12-lead ECG will be recorded at 50 mm/s speed. There must be at least one 1 mV square calibration pulse and a time scale to facilitate analysis. Tracings must show at least 3 beats per lead and a rhythm strip of at least 10 s duration. Artefacts due to loose leads are not acceptable. Standard filter settings according to local practice should be chosen, and settings have to be recorded on the printout. The digital ECG file will be uploaded on the web based platform

Recording recommendations:

1. *Description*

The description is written for the mode "automatic system". Please read the manual of the ECG device for other modes.

2. *Installation*

The electrocardiograph is put aside the top of an examination couch of the patient's bed. The power supply comes from either the net or network-independent chargeable battery. It is important for a trouble-free operation that the power line does not go in parallel to the lines of the electrodes.
Operational check: Switching on equipment at the on-off key button.

3. *Preparations*

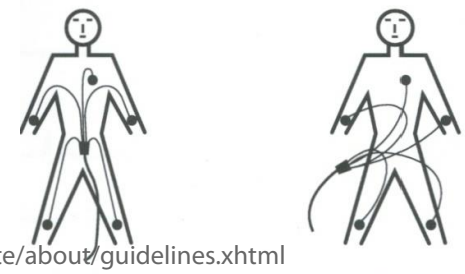
The patient/test person lies on the examination couch with undressed upper part of the body and free ankles. In males, disturbing hair-growth on the chest must be shaved off. The patient must lie relaxed, a pleasant room temperature is necessary.

4. *Attaching the electrodes for the standard derivations*

Carefully laying out the electrodes is required for an accurate ECG result. For the standard derivations 4 extremities and 6 chest wall derivations must be laid out. Contact spray on the skin (see below) is sprayed on. Important: Spray on the skin not on the electrodes.

5. *Extremity derivations*

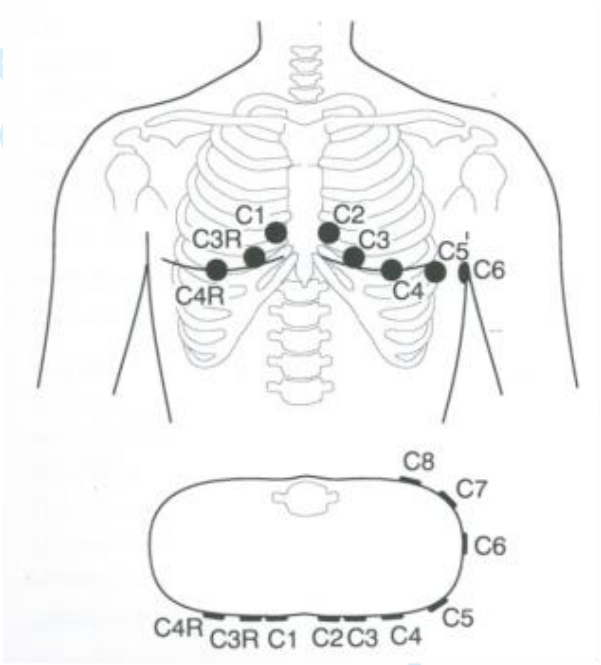
The positions of the extremity derivates are as follows:
Right arm: Red line
Left arm: Yellow line
Left leg: Green line
Right leg: Black line



6. Chest wall derivations

Right Wrong

C1: In the 4th Intercostal Space at the right sternal site
C2: In the 4th Intercostal Space at the left sternal site
C3: On the 5th rib between C2 and C4
C4: In the 5th Intercostal Space on the left medioclavicular line
C5: On the height of C4 (horizontal) in the front left axillary line
C6: On the height of C4 (horizontal) in the middle left axillary line



7. Remarks:

Laying out the chest wall electrodes, it is very important for the derivations V4-V6 proceeding on a horizontal line. So please do not follow the anatomical course of the 5th Intercostal Space as it is often misunderstood.
The 1st Intercostal Space is found directly below the clavicle; the 1st rib cannot be felt. Therefore the 1st Intercostal Space lies below the clavicle; the 2nd is the first palpable Intercostal Space.

8. ECG writing

Push the operating button and follow the menu for entering the patient data.
Press button "filters" for excluding muscle artefacts with the arrow keys.

The patient must lie quietly and eased and breathe normally (about 6/minutes).
Start ECG writing by pressing the suitable button.

With the control mode “Automatic” 12 derivations are taken simultaneously, analysed and the ECG distributes over a period of 10 sec. automatically.

Check the ECG tracing on the paper, provide with necessary specific data in handwriting.
If necessary: Do a copy by pressing the specific button.

Analyses:

- ECGs will be analysed for criteria of left ventricular hypertrophy by each centre; requested parameters must be inserted in the ECG sheet of the eCRF; the eCRF will automatically calculate ECG-LVH indices.

- The ECG will also be evaluated by the Central Reading Centre (Prof. R. E. Schmieder, Erlangen, Germany). In order to ascertain adequate source documents, before starting the study:

    - In case of ECG recorder with digital output, a sample file will be requested by the General Coordinating Center in Milan; this file will be checked by the Central Reading Centre
    - In case of ECG recorder without digital output, the General Coordinating Center in Milan will request a high quality scanned ECG (1200 dpi); this file will be checked by the Central Reading Centre for adequate quality.

- The source file has to be attached to the eCRF; the Central Monitoring Team will forward them to the Central Reading Centre in Germany

The following ECG indices of LVH will be calculated:

- Sokolow-Lyon Index
  SV1 + RV5 or RV6 ≥ 3.5 mV, The higher value should be documented.
- Cornell Voltage Index
  S in V3 + R in aVL > 2.4 mV (men)
  S in V3 + R in aVL > 2.0 mV (women)
- Cornell Voltage Product

(RaVL + SV3) × QRS duration	≥244.0 mVms	(men)
(RaVL + SV3 + 0.8 mV) × QRS duration	≥244.0 mVms	(women)

ECG determination of LV mass

ECG represents the most available method to evaluate LV mass in daily clinical practice. A recent meta- analysis of 26 studies comprising a large hypertensive population of 40444 subjects, found Sokolow-Lyon voltage criteria to be the most commonly used method for determination of ECG-LVH in clinical practice. However, the Cornell voltage product represented the most sensible, accurate index for detection of ECG-LVH in particular in female and obese subjects (1). Also, the recent ROADMAP study (2) found the Cornell Product to be the most accurate index of LVH; moreover, the ability to express results as continuous variables with this index allows to perform more comprehensive statistics. On the basis of these findings, the MASTER study will evaluate ECG-LVH primarily with the Cornell Voltage Product, and also with Cornell Voltage Index and Sokolow-Lyon Index.

Supplemental References for electrocardiography

1. Schillaci G, Battista F, Pucci M. A review of the role of electrocardiography in the diagnosis of left ventricular hypertrophy in hypertension. J Electrocardiol. 2012 45(6):617-23
2. Raff U, Ott C, Ruilope LM, Menne J, Haller H, Schmieder RE. Prevention of electrocardiographic left ventricular remodeling by the angiotensin receptor blocker olmesartan in patients with type 2 diabetes. J Hypertens. 2014 Nov;32(11):2267-76

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	1 - 29
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,2,18
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5,6
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	5, 6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7 (Box 1)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13 (Box 2), 5, 6, 9, 14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9-12 (table 1)

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12-13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8-9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8-9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9-12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13-14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14-16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14-16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14-16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16-18
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12-13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9, 11, 13, 14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16-17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	17
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	7
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	8

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.