STATISTICAL ANALYSIS PLAN

Effects of Percutaneous Transluminal Renal Angioplasty of Atherosclerotic Renal Artery Stenosis in High-Risk Patients – a Danish Nationwide Randomized Sham-Controlled Study. (DAN-PTRAII)

ClinicalTrials.gov ID: NCT05834803
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This statistical analysis plan was finalised while recruitment was ongoing and prior to database lock. As specified in the protocol, participants are unblinded after completion of the 6-month follow-up, and those randomised to sham plus optimal medical therapy are offered percutaneous transluminal renal angioplasty (PTRA) if they continue to meet the eligibility criteria. Treatment allocation has therefore been revealed for some participants, but no comparative analyses of outcome data have been performed.

Item numbers in curly brackets refer to the SPIRIT 2025 checklist.

Statistical methods

Statistical methods for primary and secondary outcomes {27a}

Descriptive statistics: Baseline characteristics will be presented by treatment group. Categorical variables will be presented as numbers and percentages, and continuous variables as means with standard deviations if normally distributed, or as medians with interquartile ranges (IQR) and, where relevant, ranges if non-normally distributed. Normality will be assessed by visual inspection of histograms and Q–Q plots. In accordance with the CONSORT statement, baseline differences between groups will not be tested statistically.

Primary outcome analysis: The primary outcome is the between-group difference in the change in 24-hour ambulatory systolic BP from baseline to 6 months. This will be analysed using a linear mixed-effects model with 24-hour ambulatory systolic BP as the outcome and time (0, 3, and 6 months), treatment group, and their interaction as fixed effects, together with sex as a stratification factor used in the randomisation. Centre, also a stratification factor, will be included as a random effect. The correlation between repeated measurements within the same patient, with patients nested within centres, will be modelled using an unstructured variance–covariance matrix. The model will be fitted using restricted maximum likelihood (REML) with Kenward–Roger approximation of the degrees of freedom. Model validation will be performed by comparing observed and model-based within-subject standard deviations and correlations in each treatment group and by inspecting Q–Q plots of the residuals. If the variance–covariance structure differs between groups, as assessed by these comparisons and a likelihood ratio test, group-specific unstructured variance–covariance matrices will be used. Results will be reported as the estimated between-group difference in change from baseline to 6 months with 95% confidence interval. If model assumptions are not met, a log-transformation of the outcome will be considered, and the between-group difference will then be back-transformed and reported as the ratio of geometric mean ratios (6 months/baseline) with 95% confidence interval.

Secondary outcome analysis: Continuous secondary outcomes, including eGFR, UACR, attended and unattended automated office systolic BP, defined daily doses of antihypertensive medication, number of antihypertensive drugs, 24-hour ambulatory systolic BP corrected for changes in antihypertensive medication (1 DDD = 5 mmHg), SF-12 physical and mental component summary scores, renal ultrasound and Doppler parameters, echocardiographic parameters, split renal function assessed by renography, plasma renin, plasma aldosterone, and NT-proBNP, will be analysed using the same modelling approach, including model validation, as for the primary outcome. Time will be included according to the measurement schedule of each outcome. In patients requiring dialysis before the PTRA/sham procedure, eGFR will be set to 10 mL/min/1.73 m² at baseline and at subsequent visits for as long as dialysis is required. If patients start permanent renal replacement therapy during follow-up, eGFR will likewise be set to 10 mL/min/1.73 m² at all visits from the start of renal replacement therapy onwards. UACR, plasma renin, plasma aldosterone, and NT-proBNP will be log-transformed a priori because of their known right-skewed distributions, and the estimated between-group differences in change from baseline will be back-transformed and reported as the ratio of geometric mean ratios with 95% confidence interval. Values below or above the measuring range will be set to the lower or upper limit, respectively, before log-transformation. For other outcomes, log-transformation will be applied if model validation indicates that model assumptions are not met, in which case results will be reported in the same way. If defined daily doses of antihypertensive medication are log-transformed, the defined daily dose will be set to 0.1 in patients not receiving any antihypertensive medication to avoid missing values. Changes in renogram grade from baseline to 6 months will be presented as shift tables (cross-tabulations of baseline versus 6-month grade), and the proportion of patients with improvement in renogram grade will be compared between groups as risk differences and risk ratios with 95% confidence intervals. For clinical and adverse events during the 6-month follow-up, and separately for procedure-related (≤24 hours) and postoperative (>24 hours) adverse events within 30 days after the PTRA/sham procedure, the proportion of patients with at least one event will be calculated for each group with 95% confidence intervals. Between-group comparisons will be expressed as risk differences and risk ratios with 95% confidence intervals. All between-group comparisons of proportions will be performed using the chi-square test, or Fisher's exact test if any expected cell count is <5. Procedure-related and postoperative adverse events will additionally be presented descriptively by type and time of occurrence. Within-group (paired) comparisons regarding, for example, antihypertensive

medication use at baseline and at follow-up visits will likewise be expressed as risk differences and/or risk ratios with 95% confidence intervals and will be assessed using McNemar's method. Secondary analyses will not be adjusted for multiple comparisons and will be interpreted as supportive.

Regression analysis: Linear regression models will be used to examine the association between prespecified baseline characteristics and the changes in 24-hour ambulatory systolic BP and eGFR from baseline to 6 months. All models will include treatment group and will be adjusted for the baseline value of the respective outcome (24-hour ambulatory systolic BP or eGFR). Continuous variables will be entered as linear terms.
In the basic models, each baseline characteristic will be examined in a separate minimally adjusted model including the predictor of interest, treatment group, and the baseline value of the outcome. The predictors are age, sex, body mass index, type 2 diabetes, rapidly declining kidney function, recurrent heart failure/flash pulmonary oedema, discontinuation of ACE inhibitor/ARB due to a ≥30% increase in plasma creatinine, log-transformed UACR, log-transformed plasma renin and aldosterone, significant stenosis on Doppler ultrasound, intrarenal resistive index ≥0.80, renography with intermediate/high probability of renal artery stenosis, the invasively measured translesional pressure ratio (Pd/Pa) and mean and systolic translesional pressure gradients, CFD-derived Pd/Pa and mean and systolic translesional pressure gradients, stenosis ≥90% of at least one target renal artery, and bilateral severe renal artery stenosis or severe stenosis of a solitary functioning kidney (≥70%). In patients with bilateral renal artery stenosis, the lowest Pd/Pa value and the highest translesional pressure gradients will be used. In addition, baseline 24-hour ambulatory systolic BP will be examined as a predictor of the change in eGFR. Results from the basic models will be reported descriptively and will not be used for variable selection.
In the extended model, age, invasively measured Pd/Pa, and bilateral severe renal artery stenosis or severe stenosis of a solitary functioning kidney (≥70%) will be included simultaneously in addition to treatment group and the baseline value of the outcome. In the extended model for eGFR, baseline 24-hour ambulatory systolic BP will additionally be included. These predictors were selected a priori based on clinical relevance and evidence from previous studies, and the number of variables was restricted in accordance with the expected sample size to limit the risk of overfitting.
To explore whether the effect of PTRA differs according to the haemodynamic severity of the stenosis, an interaction term between treatment group and invasively measured Pd/Pa will be added to the basic model for Pd/Pa. Group-specific associations between Pd/Pa and the outcome in the PTRA and sham groups, as well as the difference between these associations, will be reported with 95% confidence intervals regardless of statistical significance. No other interactions will be examined. As the study is not powered to detect interactions, these analyses will be interpreted with caution.
In addition, the association between changes in echocardiographic parameters and the change in log-transformed NT-proBNP from baseline to 6 months will be examined using linear regression models adjusted for treatment group and baseline log-transformed NT-proBNP, with one echocardiographic parameter in each model.
Analyses will include patients with available data at baseline and 6 months, and the number of patients included in each model will be reported. If data on invasively measured Pd/Pa are missing in a substantial proportion of patients, the extended model will additionally be fitted without this variable. Results will be presented as regression coefficients with 95% confidence intervals, and no adjustment for multiple comparisons will be made.

Diagnostic accuracy and method agreement: Diagnostic accuracy of Doppler ultrasound and renography will be assessed as sensitivity and specificity with 95% confidence intervals, using invasive intra-arterial pressure measurements as the reference standard. Haemodynamically significant stenosis will be defined as a mean translesional pressure gradient ≥10 mmHg, a systolic translesional pressure gradient ≥20 mmHg, or Pd/Pa ≤0.80. Agreement between CFD-derived and invasively measured pressure parameters will be assessed by Bland–Altman analysis, reporting the mean difference and 95% limits of agreement. Invasively measured systolic, diastolic, mean, and pulse pressure gradients will be presented descriptively. The relationship between angiographic stenosis severity and invasively measured Pd/Pa and translesional pressure gradients will be illustrated using scatter plots and described using Spearman's rank correlation coefficient with 95% confidence interval. Proteomic analyses will be described in a separate analysis plan.

The regression, diagnostic accuracy, and method agreement analyses will be considered exploratory and hypothesis-generating. A two-sided P value <0.05 will be considered statistically significant. Data will be analysed using Stata version 19.0 (StataCorp LLC, College Station, TX, USA).

Who will be included in each analysis {27b}
The primary analysis will follow the intention-to-treat principle and include all randomised patients with at least one 24-hour ambulatory BP measurement. Participants undergoing rescue PTRA before the end of follow-up will remain in their randomised group in the intention-to-treat analysis. In addition, per-protocol and as-treated analyses will be performed as supportive sensitivity analyses. The per-protocol population will include patients who received the allocated treatment and completed the 6-month follow-up without major protocol deviations. In the as-treated analysis, patients will be analysed according to the procedure actually performed at the time of the index procedure (PTRA or sham). Measurements obtained after rescue PTRA during follow-up will be excluded and treated as missing, so that the analysis reflects the effect of the procedure in the absence of rescue PTRA. Because the number of centres is small and the distribution of patients between centres may be unequal, the primary analysis will additionally be repeated with centre included as a fixed effect, with centres with fewer than 10 included patients pooled with the second-largest centre.

How missing data will be handled in the analysis {27c}
All randomised patients with at least one measurement of the given outcome will be included in the mixed-effects analyses, which use all available observations under the assumption that data are missing at random. The regression analyses will be performed as complete-case analyses. The plausibility of the missing-at-random assumption will be assessed by comparing baseline characteristics of patients with and without complete follow-up data.

Methods for additional analyses (e.g., subgroup analyses) {27d}
In accordance with the study hypothesis, the change in eGFR will additionally be analysed in patients included on the criterion of rapidly declining kidney function. Apart from this analysis and the prespecified interaction analysis described above, no formal subgroup analyses are planned. Any additional exploratory analyses will be interpreted cautiously as hypothesis-generating.

Interim analyses {28b}
No interim analyses of efficacy are planned. Safety data will be reviewed regularly by an independent Data and Safety Monitoring Board.