DESIGN CONSIDERATIONS AND ALTERNATIVES FOR CLINICAL TRIALS OF MEDICAL DEVICES

FIRST ANNUAL TWIN CITIES ASA FALL RESEARCH CONFERENCE

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MEDTRONIC
OUTLINE

- Renal denervation background
- Design options
- Operational characteristics
- Power-type curves
- Summary

- 41 slides total
RENAL DENERVATION
BACKGROUND
BACKGROUND

- Renal denervation for persistent hypertension
Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study


Summary
Background Renal sympathetic hyperactivity is associated with hypertension and its progression, chronic kidney disease, and heart failure. We did a proof-of-principle trial of therapeutic renal sympathetic denervation in patients with resistant hypertension (ie, systolic blood pressure ≥160 mm Hg on three or more antihypertensive medications, including a diuretic) to assess safety and blood-pressure reduction effectiveness.

Methods We enrolled 50 patients at five Australian and European centres; 5 patients were excluded for anatomical reasons (mainly on the basis of dual renal artery systems). Patients received percutaneous radiofrequency catheter-based treatment between June, 2007, and November, 2008, with subsequent follow-up to 1 year. We assessed the effectiveness of renal sympathetic denervation with renal noradrenaline spillover in a subgroup of patients. Primary endpoints were office blood pressure and safety data before and at 1, 3, 6, 9, and 12 months after procedure. Renal angiography was done before, immediately after, and 14–30 days after procedure, and magnetic resonance angiogram 6 months after procedure. We assessed blood-pressure lowering effectiveness by repeated measures ANOVA. This study is registered in Australia and Europe with ClinicalTrials.gov, numbers NCT 00483808 and NCT 00664638.

Findings In treated patients, baseline mean office blood pressure was 177/101 mm Hg (SD 20/15), (mean 4-7 antihypertensive medications); estimated glomerular filtration rate was 81 mL/min/1.73 m² (SD 23); and mean reduction in renal noradrenaline spillover was 47% (95% CI 28–65%). Office blood pressures after procedure were reduced by −14/−10, −21/−10, −22/−11, −24/−11, and −27/−17 mm Hg at 1, 3, 6, 9, and 12 months, respectively. In the five non-treated patients, mean rise in office blood pressure was +3/−2, +2/−3, +14/−9, and +26/−17 mm Hg at 1, 3, 6, and 9 months, respectively. One intra-procedural renal artery dissection occurred before radiofrequency energy delivery, without further sequelae. There were no other renovascular complications.

Interpretation Catheter-based renal denervation causes substantial and sustained blood-pressure reduction, without serious adverse events, in patients with resistant hypertension. Prospective randomised clinical trials are needed to investigate the usefulness of this procedure in the management of this condition.

Funding Ardian Inc.
Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study

Henry Krum, Markus Schlaich, Rob Whitbourn, Paul A Sobocik, Jerzy Sadowski, Krzysztof Bartus, Boguslaw Kapel, Horst Sievert, Sukh Thambir, William T Abraham, Murray Esler

Summary
Background Renal sympathetic hyperactivity is associated with hypertension and its pro-disease, and heart failure. We did a proof-of-principle trial of therapeutic renal sympathetic denervation with resistant hypertension (i.e., systolic blood pressure ≥160 mm Hg on three or more antihypertensive medications, including a diuretic) to assess safety and blood-pressure reduction effectiveness.

Methods We enrolled 50 patients at five Australian and European centres; 5 patients were excluded for reasons (mainly on the basis of dual renal artery systems). Patients received percutaneous catheter-based treatment between June 2007 and November 2008, with subsequent follow-up of renal sympathetic denervation with renal norepinephrine spillover. Primary endpoints were office blood pressure and safety data before and after treatment, at 1, 3, 6, 9, and 12 months. Renal angiography was done before, immediately after, and 14–30 days after procedure. We assessed blood-pressure lowering effects by ANOVA. This study is registered in Australia and Europe with ClinicalTrials.gov, number: NCT0064638.

Findings In treated patients, baseline mean office blood pressure was 177/101 mm Hg (55% hypertensive medications); estimated glomerular filtration rate was 81 ml/min/1.73 m² (55% in renal norepinephrine spillover was 47% (95% CI 28–65%). Office blood pressures after 1 month were 14/10, 21/10, 22/11, 24/11, and 27/17 mm Hg at 1, 3, 6, 9, and 12 months, respectively. One intraprocedural renal artery dissection occurred before radiofrequency ablation without further sequelae. There were no other renovascular complications.

Interpretation Catheter-based renal denervation causes substantial and sustained blood-pressure reduction in patients with resistant hypertension. Prospective randomised clinical trials are needed to assess the usefulness of this procedure in the management of this condition.

Funding Ardian Inc.

Figure 2: Change in office blood pressure (95% CI) at 1, 3, 6, 9, and 12 months. Numbers in parentheses indicate patients who had attended each predefined visit at the time of submission of this article.
OBSERVATIONAL STUDY

- Observational study compares separate treatment groups, but does not intervene in the assignment of treatments.
- Potential biases could be mitigated through modeling of measured covariates; can’t adjust for unmeasured covariates.

Images: http://prehospitalresearch.eu/?p=786
Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial

Symplicity HTN-2 Investigators

Summary

Background Activation of renal sympathetic nerves is key to pathogenesis of essential hypertension. We aimed to assess effectiveness and safety of catheter-based renal denervation for reduction of blood pressure in patients with treatment-resistant hypertension.

Methods In this multicentre, prospective, randomised trial, patients who had a baseline systolic blood pressure of 160 mm Hg or more (≥150 mm Hg for patients with type 2 diabetes), despite taking three or more antihypertensive drugs, were randomly allocated in a one-to-one ratio to undergo renal denervation with previous treatment or to maintain previous treatment alone (control group) at 24 participating centres. Randomisation was done with sealed envelopes. Data analysts were not masked to treatment assignment. The primary effectiveness endpoint was change in seated office-based measurement of systolic blood pressure at 6 months. Primary analysis included all patients remaining in follow-up at 6 months. This trial is registered with ClinicalTrials.gov, number NCT00888433.

Findings 106 (56%) of 190 patients screened for eligibility were randomly allocated to renal denervation (n=52) or control (n=54) groups between June 9, 2009, and Jan 15, 2010. 49 (94%) of 52 patients who underwent renal denervation and 51 (94%) of 54 controls were assessed for the primary endpoint at 6 months. Office-based blood pressure measurements in the renal denervation group reduced by 32/12 mm Hg (SD 23/11, baseline of 178/96 mm Hg, p<0.0001), whereas they did not differ from baseline in the control group (change of 1/0 mm Hg [21/10], baseline of 178/97 mm Hg, p=0.77 systolic and p=0.83 diastolic). Between-group differences in blood pressure at 6 months were 33/11 mm Hg (p<0.0001). At 6 months, 41 (84%) of 49 patients who underwent renal denervation had a reduction in systolic blood pressure of 10 mm Hg or more, compared with 18 (35%) of 51 controls (p<0.0001). We noted no serious procedure-related or device-related complications and occurrence of adverse events did not differ between groups; one patient who had renal denervation had possible progression of an underlying atherosclerotic lesion, but required no treatment.

Interpretation Catheter-based renal denervation can safely be used to substantially reduce blood pressure in treatment-resistant hypertensive patients.

Funding Ardian.
BACKGROUND

Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial

Summary

Background Activation of renal sympathetic nerves is key to pathogenesis of essential hypertension and is important to assess effectiveness and safety of catheter-based renal denervation for reduction of blood pressure in patients with treatment-resistant hypertension.

Methods In this multicentre, prospective, randomised trial, patients who had a baseline systolic blood pressure of 160 mm Hg or more (±150 mm Hg for patients with type 2 diabetes), despite taking all available medications, were randomly allocated in a one-to-one ratio to undergo renal denervation or to receive treatment with medical therapy alone (control group) at 24 participating centres. Randomisation envelopes were not masked to treatment assignment. The primary endpoint was a change in systolic blood pressure from baseline to 6 months in all patients remaining in follow-up at 6 months. This trial is registered with number NCT00888433.

Findings 106 (56%) of 190 patients screened for eligibility were randomly allocated to control (n=54) or renal denervation (n=42) groups between June 9, 2009, and Jan 15, 2010. 49 (94%) of 52 patients in the renal denervation group and 51 (94%) of 54 controls were assessed for the primary endpoint at 6 months. Prespecified reduction in systolic blood pressure of 10 mm Hg (p=0.001). Baseline blood pressure at 6 months were 178/96 mm Hg (p<0.0001). At 6 months, 41 (84%) of 49 patients in the renal denervation group had a reduction in systolic blood pressure of 10 mm Hg or more, compared with 26 (48%) controls (p<0.0001). The incidence of new or worsened adverse events was also significantly lower in the renal denervation group.

Figure 2: Paired changes in office-based measurements of systolic and diastolic blood pressures at 1 month, 3 months, and 6 months for renal denervation and control groups

Funding Ardisan.
RANDOMIZED, CONTROLLED TRIAL

- Default design choice for most trials
- Very efficient at answering a specific question
- Usually constructed with two or more parallel, independent groups
  - Control can also be within subject (e.g., eyes, joints)

BACKGROUND

Prior unblinded studies have suggested that catheter-based renal-artery denervation reduces blood pressure in patients with resistant hypertension.

METHODS
We designed a prospective, single-blind, randomized, sham-controlled trial. Patients with severe resistant hypertension were randomly assigned in a 2:1 ratio to undergo renal denervation or a sham procedure. Before randomization, patients were receiving a stable antihypertensive regimen involving maximally tolerated doses of at least three drugs, including a diuretic. The primary efficacy end point was the change in office systolic blood pressure at 6 months; a secondary efficacy end point was the change in mean 24-hour ambulatory systolic blood pressure. The primary safety end point was a composite of death, end-stage renal disease, embolic events resulting in end-organ damage, renovascular complications, or hypertensive crisis at 1 month or new renal-artery stenosis of more than 70% at 6 months.
BACKGROUND

Prior unblinded studies have suggested that catheter-based renal-artery denervation reduces blood pressure in patients with resistant hypertension.

METHODS

We designed a prospective, single-blind, randomized, sham-controlled trial. Patients with severe resistant hypertension were randomly assigned in a 2:1 ratio to undergo renal denervation or a sham procedure. Before randomization, patients were receiving a stable antihypertensive regimen involving maximally tolerated doses of at least three drugs, including a diuretic. The primary efficacy end point was the change in office systolic blood pressure at 6 months; a secondary efficacy end point was the change in mean 24-hour ambulatory systolic blood pressure. The primary safety end point was a composite of death, end-stage renal disease, embolic events resulting in end-organ damage, renovascular complications, or hypertensive crisis at 1 month or new renal-artery stenosis of more than 70% at 6 months.
BACKGROUND

- Not yet ready to give up on billion dollar investment in therapy
- Considering issues in therapy delivery, concomitant medication for hypertension, and construction of device (among others)
- Availability of patients and physicians willing to randomize to treatment may be an important hurdle, so want to consider possibilities to reduce number of subjects needed
BACKGROUND

 We are interested in examining alternatives to a two parallel arm RCT
   Want to leverage correlation of within person measurements to reduce the number of individuals needed
   Still concerned about possible biases from patients or observers related to unblinded treatments
   Envision using sham surgery to blind treatment groups
We are interested in examining alternatives to a two parallel arm RCT

- Want to leverage correlation of within person measurements to reduce the number of individuals needed
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- Envision using sham surgery to blind treatment groups

This is more design of experiments than analysis

- What data would we want to generate to be able to examine the impact of renal denervation?
- An example of where biostatisticians can provide added value to clinical teams
Consider three potential treatment sequences

<table>
<thead>
<tr>
<th></th>
<th>Baseline; 1st treatment</th>
<th>3 month FU; 2nd treatment</th>
<th>6th month FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequence A</td>
<td>R</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>Mean of Sequence A</td>
<td>$\beta_0$</td>
<td>$\beta_1 + \beta_3$</td>
<td>$\beta_2 + \beta_4$</td>
</tr>
<tr>
<td>Sequence B</td>
<td>S</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Mean of Sequence B</td>
<td>$\beta_0$</td>
<td>$\beta_1$</td>
<td>$\beta_2 + \beta_3$</td>
</tr>
<tr>
<td>Sequence C</td>
<td>S</td>
<td>S</td>
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</tr>
<tr>
<td>Mean of Sequence C</td>
<td>$\beta_0$</td>
<td>$\beta_1$</td>
<td>$\beta_2$</td>
</tr>
</tbody>
</table>

R=RDN; S=Sham surgery
OPTIONS (TRANSITORY TREATMENT EFFECT)

- Plot of means of sequences (example)

- Sequence A (R, S)
- Sequence B (S, R)
- Sequence C (S, S)

R = RDN; S = Sham surgery
**OPTIONS**

- **Why Sequence C (two sham procedures)?**
  - Without C, observer and patient are partially unblinded
    - They both know that patient has received RDN by end of 3 months
  - Want to avoid possible bias from knowledge of RDN
    - Hiding this knowledge is why we would have sham surgery after RDN in Sequence A
  - Allows for more precision in estimate of 3 month RDN with same number of subjects
    - Presence of 3rd arm results in lower total sample size burden
Think of each sequence as a set of three observations

- $E(Y_{C0}) = \beta_0$ Common baseline mean
- $E(Y_{C1}) = \beta_1$ Common 3 month study mean
- $E(Y_{C2}) = \beta_2$ Common 6 month study mean

- $E(Y_{A0}) = \beta_0$ Common baseline mean
- $E(Y_{A1}) = \beta_1 + \beta_3$ Common 3 month study mean + 3 month RDN effect
- $E(Y_{A2}) = \beta_2 + \beta_4$ Common 6 month study mean + 6 month RDN effect
Each observation is a linear combination of $\beta$'s and 0's and 1's

- $E(Y_{A2}) = \beta_2 + \beta_4 = 0*\beta_0 + 0*\beta_1 + 1*\beta_2 + 0*\beta_3 + 1*\beta_4$

- More generally, $E(Y) = X'B$

- The expected value of the vector of responses $Y$ is obtained by left multiplying a vector of coefficients $B$ by a matrix of 0's and 1's, $X'$.

- The expected value of the vector $Y$ is composed of triplets of dependent observations, each triplet with $3x3$ covariance matrix $\Sigma$

- A triplet $Y$ is distributed as trivariate normal with mean $X'B$ and covariance $\Sigma$
OPERATIONAL CHARACTERISTICS

- With independent data, we would have $\sigma^2(X'X)^{-1}$ for the covariance of the estimated $\beta$'s, for some scalar $\sigma^2$.

- In this dependent case, the covariance of the estimated $\beta$'s is $(X'\Sigma^{-1}X)^{-1}$.

- We use maximum likelihood estimates for the $\beta$'s.
  - These are the uniformly minimum variance unbiased estimators for the $\beta$'s.

- We have estimates of $\Sigma$ from HTN-3, for both the RDN and Control arms.
### ABOUT MAXIMUM LIKELIHOOD ESTIMATES

Consider three potential treatment sequences

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For $\beta_3$, could have used averages of **D1-D3**, or **D4-D6**. Simple, but not fully efficient.

**R=**RDN; **S=**Sham surgery
Each individual from the separate sequences (A, B, and C) contributes a slightly different set of rows to $X'$

- **$X'$ for A:**
  
  \[
  \begin{array}{ccccc}
  1 & 0 & 0 & 0 & 0 \\
  0 & 1 & 0 & 1 & 0 \\
  0 & 0 & 1 & 0 & 1 \\
  \end{array}
  \]

- **$X'$ for B:**
  
  \[
  \begin{array}{ccccc}
  1 & 0 & 0 & 0 & 0 \\
  0 & 1 & 0 & 0 & 0 \\
  0 & 0 & 1 & 1 & 0 \\
  \end{array}
  \]

- **$X'$ for C:**
  
  \[
  \begin{array}{ccccc}
  1 & 0 & 0 & 0 & 0 \\
  0 & 1 & 0 & 0 & 0 \\
  0 & 0 & 1 & 0 & 0 \\
  \end{array}
  \]
OPERATIONAL CHARACTERISTICS

- Since the covariance of the estimated $\beta$'s is only a function of $\Sigma$ and the rows of $X'$, for a fixed number of subjects we can determine what allocation of subjects to sequences A, B, and C will result in the smallest variance for the estimate of the 3 month RDN effect, $\beta_3$

- The math requires that we have at least one subject with sequence A, and at least one subject with a non-A treatment sequence

- Our two different estimates of $\Sigma$ (based on Control or RDN data) give slightly different answers for optimal allocation
OPERATIONAL CHARACTERISTICS

- With 210 subjects and the observed RDN covariance, the optimal allocation is 70:70:70
- With 210 subjects and the observed Control covariance, the optimal allocation is 88:61:61
  - Note that the logistics of ensuring such a mix of arms in a randomized trial across multiple sites while maintaining blinding would be exceedingly challenging.
- This is under an assumption of transitory treatment effects

- We will look at the smallest effect size for which we have a given power (90% or 80%) using alpha=5%.
- Use both transitory and persistent effect settings
## OPTIONS (PERSISTENT TREATMENT EFFECT)

- Consider three potential treatment sequences

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R=RDN; S=Sham surgery
OPTIONS (TRANSITORY TREATMENT EFFECT)

Consider three potential treatment sequences

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R=RDN; S=Sham surgery
OPTIONS (TRANSITORY TREATMENT EFFECT)

- Plot of means of sequences (example)

![Plot of means of sequences (example)](image)

- Sequence A (R, S)
- Sequence B (S, R)
- Sequence C (S, S)

R=RDN; S=Sham surgery
OPTIONS (PERSISTENT TREATMENT EFFECT)

- Plot of means of sequences (example)

![Plot of means of sequences](image)

- Sequence A (R, S)
- Sequence B (S, R)
- Sequence C (S, S)

β₀, β₁, β₂, β₃

R=DN; S=Sham surgery
POWER-TYPE CURVES
MINIMUM DETECTABLE EFFECT SIZE

Will use minimum detectable effect multiplier to scale variance associated with observed RDN and observed Control variance estimates in different sample size configurations, and under persistent and transitory model assumptions.

Reference: “The core analytics of randomized experiments for social research”, H.S. Bloom, 2006
TRANSITORY EFFECTS, 90% POWER

Using #C=0 is effectively a crossover study, while using #B=0 is effectively a two arm parallel group study. No noticeable performance difference between these two, and both are substantially worse than either equal allocation or optimal allocation among all three arms. Equal or optimal are identical.
Similar behavior between persistent and transitory models for RDN variance, though benefit of equal or optimal allocation is lessened. With Sham variance, only crossover design is noticeable worse than the others.

A: (RDN, Sham)  B: (Sham, RDN)  C: (Sham, Sham)
TRANSITORY EFFECTS, 80% POWER

Using #C=0 is effectively a crossover study, while using #B=0 is effectively a two arm parallel group study. No noticeable performance difference between these two, and both are substantially worse than either equal allocation or optimal allocation among all three arms. Equal or optimal are identical. With lesser power, essentially just a shift downwards in curves.
PERSISTENT EFFECTS, 80% POWER

Similar behavior between persistent and transitory models for RDN variance, though benefit of equal or optimal allocation is lessened. With Sham variance, only crossover design is noticeably worse than the others. With lesser power, essentially just a shift downwards in curves.
SUMMARY, 1/2

- This work presupposes that we could run a trial with two potential sham surgeries in individual patients.
- The most efficient trials (smallest variance; fewest subjects) will use maximum likelihood estimates.
- The optimal allocation is often indistinguishable from simply using equal allocation to the three groups.
- Ultimately, team was more concerned about possible variation from medication use and adherence than optimizing number of subjects, and opted to run two separate parallel group trials (with differing medication requirements).
SUMMARY, 2/2

- This is an example where the examination of study design options was of higher utility than questions of analysis (which were relatively straightforward).
- If you are interested in contributing to the design choices of actual studies, and not simply in analyzing data that has already been generated, consider a career working with clinical trials, especially in industry (e.g., medical devices or pharmaceuticals).
THANK YOU!

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