Drug-resistant hypertension in primary aldosteronism patients undergoing adrenal vein sampling: the AVIS-2-RH study

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Aims

We aimed at determining the rate of drug-resistant arterial hypertension in patients with an unambiguous diagnosis of primary aldosteronism (PA). Moreover, we sought for investigating the diagnostic performance of adrenal vein sampling (AVS), and the effect of adrenalectomy on blood pressure (BP) and prior treatment resistance in PA patients subtyped by AVS in major referral centres.

Methods and results

The Adrenal Vein Sampling International Study-2 (AVIS-2) was a multicentre international study that recruited consecutive PA patients submitted to AVS, according to current guidelines, during 15 years. The patients were over 18 years old with arterial hypertension and had an unambiguous diagnosis of PA. The rate of resistant hypertension was assessed at baseline and after adrenalectomy using the American Heart Association (AHA) 2018 definition. Information on presence or absence of resistant hypertension was available in 89% of the 1625 enrolled PA patients. Based on the AHA 2018 criteria, resistant hypertension was found in 20% of patients, of which about two-thirds (14%) were men and one-third (6%) women ($\chi^2 = 17.1$, $P < 1*10^{-4}$) with a higher rate of RH in men than in women (23% vs. 15% $P < 1*10^{-4}$). Of the 292 patients with resistant hypertension, 98 (34%) underwent...
unilateral AVS-guided adrenalectomy, which resolved BP resistance to antihypertensive treatment in all.

Conclusions
(i) Resistant hypertension is a common presentation in patients seeking surgical cure of PA; (ii) AVS is key for the optimal management of patients with PA due to resistant hypertension; and (iii) AVS-guided adrenalectomy allowed resolution of treatment-resistant hypertension.

Methods
Supporting methods are available in Supplementary material online. The original protocol of the AVIS-2-RH study was registered at clinicaltrials.gov (NCT01234220) in 2012.

Introduction
Notwithstanding the availability of a wide range of agents for the treatment of arterial hypertension, many patients fail to reach the optimal target blood pressure (BP) for their cardiovascular risk profile. These are high-risk patients because of their uncontrolled BP and the common co-existence of hypertension-mediated organ damage, which predicts subsequent cardiovascular events.

To draw attention to this clinical condition, the European Society of Cardiology (ESC)/European Society of Hypertension (ESH) and the American Heart Association (AHA) introduced the term ‘drug-resistant hypertension’ (RH), as a provisional case definition to be used until the cause(s) of BP resistance to treatment is (are) identified. Identifiable causes are quite common: 50% of patients recruited in a multicentre study on sympathetic renal denervation in RH could not be randomized because of a specific cause for their hypertension. Along with clinical experience, these results would support the contention that BP resistance to treatment is often due to specific forms of secondary hypertension, of which primary aldosteronism (PA) is one of the most prevalent.

A large prospective study reported that when RH patients were carefully studied for PA, about 20% had an elevated aldosterone–renin ratio (ARR). However, using spironolactone-responsiveness as the diagnostic confirmation, the estimated rate of PA fell to 11%, i.e. a rate similar to that found in the newly diagnosed hypertensive patients referred to specialized hypertension centres in the PAPY study.

At variance with this low estimate, based on relatively small single-centre studies, the Endocrine Society guidelines reported a prevalence rate of PA in RH patients ranging between 17% and 23%. Hence, although multiple lines of evidence suggest that the rate of PA in RH patients could be high, it remains unknown whether RH is common among patients with unambiguously diagnosed PA, as those selected to undergo adrenal vein sampling (AVS) and those in whom the diagnosis was confirmed by biochemical and/or clinical cure after surgery.

Accordingly, in the AVIS-2-RH study, we set out to assess the rate of RH in a large registry of individual PA patients selected to undergo AVS. Moreover, we assessed the diagnostic yield of AVS in PA with RH and on persistence/resolution of RH in these patients.

Definitions
In this study, the definition of RH was not a diagnosis per se and was used exclusively for descriptive purposes. RH was defined according to the 2018 AHA definition (RH_AHA2018). RH was held to be present when pseudo-RH was excluded and BP remained above 130/80 mmHg despite use of three antihypertensive drug classes, commonly including a long-acting calcium channel blocker, a blocker of the renin–angiotensin system (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker), and a diuretic, each drug being administered at maximum, or maximally tolerated, daily doses. This definition includes patients with ‘controlled RH’, i.e. whose BP achieved target values on ≥4 antihypertensive medications.

To gather information on the extent to which this structured definition agreed with that used in the clinical practice, the lead investigator of each centre was required to record in the collection form if the patient had RH according to the local criteria in use. This information (RH_local) was then used to assess the rate of RH and to compare this estimate with that obtained by the AHA 2018 definition.

A modified ESC/ESH definition of RH_ESC/ESH (Supplementary material online) was also used for a sensitivity analysis.

AVS was considered successful, e.g. bilaterally selective, if the selectivity index exceeded the cut-off value in use at each centre. Only bilaterally selective AVS were used to establish the presence of unilateral PA. Unilateral PA was diagnosed in the presence of a lateralization index (LI) exceeding the cut-off in use at each centre as reported (Supplementary material online, Table S1).

Based on a pilot study that showed that different experienced radiologists blind to clinical diagnosis could not consistently detect nodules smaller than 5 mm maximum diameter, adrenal nodules were defined as nodular lesions with a largest diameter ≥5 mm on imaging. Patients were classified as positive or negative imaging based on this criterion.

Adrenalectomy was defined as AVS-guided if performed on the basis of a bilaterally selective AVS study showing unilateral PA. It was classified as non-AVS-guided if performed after non-bilaterally selective AVS.
results and/or a LI below the threshold values in use at each centre as mentioned above. Supplementary material online, Table S2 shows the prespecified definitions of the BP outcome and their comparison with the PASO criteria.

Results

Baseline characteristics of the patients

Nineteen centres located in Europe (including Russia), Asia, North America, and Australia, recruited the patients undergoing AVS following the 2008 Endocrine Society guidelines. After locking the database and before starting the data analysis, 195 patients submitted to AVS before the year 2000 were excluded, out of concern that their management may not reflect current practice. Hence this analysis involved 1625 individuals who underwent AVS from 2000 to 2015 (Figure 1). The majority (76%) of patients were recruited in Europe; Caucasians (79%) were more commonly enrolled compared to Asians (16%), Africans and African-Americans (4%), and Hispanics (1%).

The presence or absence of RH could be determined in 89%, i.e. 1450, of all patients (Table 1). Their overall features did not differ significantly from those of the whole cohort and from the sub-cohort with missing information on BP resistance to treatment.

Rate of RH

RH could be ascertained by the AHA 2018 criteria (RHAHA2018) in 20% of the patients and in 49% according to centres’ lead investigators (RHlocal), indicating that the clinical definition of RH used in

![Diagram](https://example.com/diagram.png)

**Figure 1** The diagram shows the selection of the patients for this study from the original AVIS-2 Study cohort and the proportion of those with RH and without RH who had bilaterally successful AVS and then underwent adrenalectomy. Among the latter, there were also patients who underwent adrenalectomy in spite of non-lateralizing AVS results (non-AVS-guided). Please note that adrenalectomy was AVS-guided in the majority of the RH patients who had bilaterally successful AVS. For definitions of successful AVS, AVS-guided and non-AVS-guided adrenalectomy please refer to text.
centres that can perform AVS, as those participating in AVS-2-RH, markedly overestimated the rate of this condition, as compared to a structured guideline-based definition.

Table 1 shows the main features of the patients divided according to the presence/absence of RHAHA2018. The characteristics of the patients, divided according to the local Principal Investigator definition of RH (RHlocal) and to the ESC/ESH definition (RHESC/ESH) are shown in Supplementary material online, Tables S3 and S4. Briefly, the RHAHA2018 Patients had an average age of 54.3 ± 10.6 years and were mostly men (72%), with a body mass index (BMI) in the overweight range (31.1 ± 5.8 kg/m2). Their serum potassium levels and hormonal values, including Plasma aldosterone concentration (PAC) and aldosterone renin ratio (ARR) were as expected for a PA population selected to undergo AVS.

Effect of gender and ethnicity

Regardless of the definitions, the rate of RH was higher in men than in women: of the 885 men 24% were RHAHA2018 patients; of the 565 women 15% were RHAHA2018 patients (Table 1). Considering the 20% RHAHA2018 patients, about two-thirds (14%) were men and one-third (6%) were women ($\chi^2 = 17.1, P < 1 \times 10^{-4}$) (Figure 2). Amongst the RHAHA2018 females, the rate of pre-menopausal women entailed about half (11%) of the rate seen in post-menopausal women (23%, $\chi^2 = 12.73, P < 1 \times 10^{-3}$), who showed a rate of RHAHA2018 closer to that of age-matched men (28%).

Compared to the non-RH patients, the RHAHA2018 patients showed higher baseline systolic and diastolic BP values, a higher need of antihypertensive drugs, a higher rate of Caucasians and a lower proportion of Asians ($\chi^2 = 38.7, P < 1 \times 10^{-4}$). In the four centres from Asia, the rate of RHAHA2018 ranged from 0% to 1%.

Prediction of RH in PA patients

To determine if clinical and demographical variables could predict the presence of RHAHA2018, we performed discriminant and regression analyses. The first analysis showed that these variables overall permitted correct classification of 66% of the patients; the second showed that variables that were useful for the prediction of RHAHA2018 were age, BMI, gender, serum K⁺, and the ARR ($F = 40.27, P < 0.0001$). However, overall these variables explained only a small portion of the occurrence of RHAHA2018, as the adjusted $R^2$ was only 0.087.

AVS performance and allocation to treatment

Overall wash-out or switching to non-interfering drugs was undertaken before AVS in only 47% of the 1450 patients, who had information on presence/absence of resistance to anti-hypertensive drug treatment; the rest underwent AVS without adequate pharmacologic preparation. AVS was undertaken without wash-out from interfering drugs in all the patients classified with RH2018.

The rate of bilaterally successful AVS was similar in RHAHA2018 patients and non-RHAHA2018 (82% vs. 81%, NS). Adrenalectomy was also performed in similar proportions of RHAHA2018 patients and non-RHAHA2018 patients with successful AVS (56% vs. 53%, NS)

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<table>
<thead>
<tr>
<th>Variable</th>
<th>Whole cohort (n = 1450)</th>
<th>With resistant hypertension (n = 292)</th>
<th>Without resistant hypertension (n = 1158)</th>
<th>P-value for comparison between with/without resistant hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.4 ± 10.9</td>
<td>54.3 ± 10.6</td>
<td>49.2 ± 10.6</td>
<td>$&lt;10^{-4}$</td>
</tr>
<tr>
<td>Sex (male/female, %)</td>
<td>885/565 (61/39)</td>
<td>209/83 (72/28)</td>
<td>676/482 (58/42)</td>
<td>$&lt;10^{-4}$</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.6 ± 5.4</td>
<td>31.1 ± 5.8</td>
<td>28.0 ± 4.9</td>
<td>$&lt;10^{-4}$</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>154 ± 20</td>
<td>160 ± 21</td>
<td>150 ± 19</td>
<td>$&lt;10^{-4}$</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>93 ± 13</td>
<td>93 ± 13</td>
<td>92 ± 12</td>
<td>3.84*10^{-2}</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>73 ± 12</td>
<td>71 ± 11</td>
<td>73 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Serum K⁺ (mmol/L)</td>
<td>3.6 ± 0.5</td>
<td>3.6 ± 0.5</td>
<td>3.5 ± 0.5</td>
<td>3*10^{-3}</td>
</tr>
<tr>
<td>Hypokalaemia at baseline, n (%)</td>
<td>434 (36)</td>
<td>87 (36)</td>
<td>367 (38)</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma aldosterone concentration (ng/dL)</td>
<td>28.8 (25.6–31.5)</td>
<td>28.5 (25.6–31.5)</td>
<td>28.9 (27.5–30.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma renin activity (ng/mL/h)</td>
<td>0.54 (0.49–0.59)</td>
<td>0.55 (0.1–0.67)</td>
<td>0.53 (0.46–0.57)</td>
<td>NS</td>
</tr>
<tr>
<td>ARR (ng/dL)/(ng/mL/h)</td>
<td>91 (86–96)</td>
<td>95 (84–106)</td>
<td>90 (84–96)</td>
<td>NS</td>
</tr>
<tr>
<td>Antihypertensive drugs (n)</td>
<td>2.3 (2.2–2.3)</td>
<td>4.2 (4.1–4.4)</td>
<td>1.8 (1.7–1.8)</td>
<td>$&lt;10^{-4}$</td>
</tr>
<tr>
<td>Antihypertensive drugs after adrenalectomy (n)</td>
<td>1.9 (1.8–2.0)</td>
<td>2.7 (2.4–2.9)</td>
<td>1.7 (1.6–1.8)</td>
<td>$&lt;10^{-4}$</td>
</tr>
<tr>
<td>Ethnicity %</td>
<td>79/16/44/1</td>
<td>89/46/1</td>
<td>76/20/3/1</td>
<td>$&lt;10^{-4}$</td>
</tr>
</tbody>
</table>

Normal range on a Na⁺ between 100 and 300 mmol/day: PAC <15 ng/dL; PRA 0.65–2.65 ng/mL/h; ARR <26 ng/dL/ng/mL/h.

Data are presented as mean ± standard deviation or median and interquartile range.
It was AVS-guided in the majority of the RH AHA2018 and non-RH AHA2018 patients (74% and 77%, respectively, NS).

Clinical outcome
Follow-up data were provided for 80% of patients, with no difference between RH AHA2018 and non-RH AHA2018 patients. In the adrenalectomized patients, those with RH AHA2018 were less cured and mildly improved, and more markedly improved than those without RH AHA2018 (Figure 3A). After adrenalectomy, 15% of the RH AHA2018 patients were cured, 63% markedly improved, 18% mildly improved and 4% not improved. In the non-RH AHA2018 patients, the corresponding figures were 44%, 36%, 14%, and 6% ($\chi^2 = 40.6, P < 1 \times 10^{-4}$ vs. RH AHA2018 patients).

In the adrenalectomized patients, only a few were classified as 'not improved'. However, this was only because of our strict predefined criteria for outcome definition, and even in these patients, surgery resolved the treatment-resistant status.

Amongst patients with RH, there were no statistically significant differences between sexes in BP outcome after adrenalectomy ($\chi^2 = 7.71, P = 0.052$): 11% of men were cured, 69% markedly improved, 16% mildly improved and 4% not improved; 27% of women were cured, 45% markedly improved, 24% mildly improved and 3% not improved (Figure 3B).

At baseline, the number of drugs needed to control BP was greater in the RH AHA2018 than in the non-RH AHA2018 patients ($\chi^2 = 1176, P < 1 \times 10^{-4}$) (Figure 4A). After adrenalectomy, the number of antihypertensive drugs needed to control BP remained significantly higher in RH AHA2018 as compared to non-RH AHA2018 patients ($\chi^2 = 54.4, P < 1 \times 10^{-4}$; Figure 4B). Although there were more cured cases among the non-RH AHA2018 than the RH AHA2018 patients, more patients from the RH AHA2018 group were shifted to less antihypertensive drugs needed to control BP from baseline (Figure 4B).

In the RH AHA2018 group, the shift towards less antihypertensive drugs did not differ significantly between AVS-guided and non-AVS-guided adrenalectomized patients ($\chi^2 = 6.26, P = 0.281$; Figure 4C). In non-RH AHA2018 those who received an AVS-guided adrenalectomy required fewer antihypertensive drugs than those who underwent a non-AVS-guided adrenalectomy ($\chi^2 = 13.1, P = 0.022$) (Figure 4D).

Of note, among the RH AHA2018, who were adrenalectomized based on AVS performed while on potentially interfering drugs, the results were as follows: 13% of the patients with lateralized AVS were cured and 64% markedly improved; identical rates were found among those without lateralized AVS.

Outcome of RH AHA2018 in imaging-negative and -positive patients
In the 35 imaging-negative RH AHA2018 patients, i.e. where computed tomography (CT) or magnetic resonance did not identify adrenal nodules, the use of AVS for the clinical decision-making did not seem to affect the post-operative outcome: of AVS-guided
Among AVS-guided adrenalectomized patients: 14% were cured between AVS-guided and non-AVS guided adrenalectomy. Patients with drug-resistant hypertension usually have hypertension-mediated organ damage and, therefore, are exposed to imminent fatal and non-fatal cardiovascular events. This implies that they are most in need of effective and timely clinical management. In a large retrospective analysis of two integrated US health plan populations, RH was associated with a 47% covariate-adjusted hazard ratio of major cardiovascular outcomes (RH = 1.47, 95% confidence intervals: 1.33-1.62; P < 1 x 10^-3), which suggested that early identification of the causes of RH followed by implementation of targeted treatments are critical steps to improve outcomes in these patients.

The large AVIS-2 registry offered a unique opportunity to investigate the rate of RH in PA patients, who were selected to undergo AVS and to assess the diagnostic yield of AVS in PA patients with RH_AHA2018. Who, by definition, are treated with multiple medications that may confound AVS interpretation.

The most important novel finding in this study was that a considerable proportion of PA patients, i.e., one every five patients, had RH by the AHA 2018 definition and also by the ESC/ESH guidelines definition (Supplementary material online, Results) Figure 6. By looking at the issue from a different perspective than the 2016 Endocrine Society Guidelines, the present findings complement and integrate available information by showing the rate of RH in patients with PA selected to undergo AVS.

Thus, with the strength of a large sample size, this international multicentre real-life study showed evidence that RH_AHA2019 is a common clinical presentation, and likely also reason for referral of PA in patients who are candidates for surgical cure. This was by no means an unexpected finding since available guidelines list RH among the patients’ categories that should be screened for PA. What was unexpected was to discover that about half of the patients had RH by the managing physician’s definition, i.e., RHlocal, which indicates overestimation of RH, as compared to a structured guidelines-based AHA 2018 definition. This could have occurred either because the data collected in the predefined form of our study did not catch the entire clinical picture of the patients, for example the full BP profile, and/or because of lack of application of structured definitions of RH.

Tapering and/or withdrawing drug-treatment, and/or switching to non-interfering drugs, are recommended procedures during investigation of PA. This practice is justified on the grounds that multiple antihypertensive drugs can render the interpretation of tests used challenging or even impossible. However, stopping or switching medications can lead to even higher BP in RH patients, switching medications for AVS in 47% of the patients is somewhat at variance with investigations of PA in patients who are candidates for surgical cure. This was by no means an unexpected finding since available guidelines list RH among the patients’ categories that should be screened for PA. What was unexpected was to discover that about half of the patients had RH by the managing physician’s definition, i.e., RHlocal, which indicates overestimation of RH, as compared to a structured guidelines-based AHA 2018 definition. This could have occurred either because the data collected in the predefined form of our study did not catch the entire clinical picture of the patients, for example the full BP profile, and/or because of lack of application of structured definitions of RH.

Discussion

Patients with drug-resistant hypertension usually have hypertension-mediated organ damage and, therefore, are

![Figure 3](https://academic.oup.com/eurjpc/advance-article-doi/10.1093/eurjpc/zwaa108/6179010)

Figure 3 The graph shows that in patients with RH there were fewer cured or mildly improved, and more markedly improved cases than in those without RH (χ^2 = 40.571, P < 1 x 10^-5) (A); *P < 5 x 10^-3 among groups. No difference in BP outcome was seen between men and women with RH after adrenalectomy (χ^2 = 7.71, P = 5.2 x 10^-3) (B).

adrenalectomized patients 17% were cured, 63% markedly improved, 12% mildly improved and 8% not improved. In the non-AVS guided adrenalectomized patients: none was cured, 64% markedly improved, 36% mildly improved, and none not improved (χ^2 = 4.89, P = 0.179).

In the 69 imaging-positive RH_AHA2018 cases, the outcome did not differ between AVS-guided and non-AVS guided adrenalectomy. Among AVS-guided adrenalectomized patients: 14% were cured, 63% markedly improved, 21% mildly improved, and 2% not improved. Among non-AVS-guided adrenalectomized patients: 11% were cured, 72% markedly improved, 11% mildly improved, and 6% not improved (χ^2 = 1.62, P = 0.655) (Figure 5A and 8).
obtained in a smaller study where we showed that potentially interfering drugs actually did not preclude identification of unilateral PA in RH patients.\textsuperscript{27} This is a second clinically important finding since many patients with RH might be denied AVS, and thereby the opportunity for curative adrenalectomy, on account of concern that AVS may not be diagnostic if performed while on treatment.

The finding that, in RH AHA2018 patients, those who underwent AVS while on potentially interfering drugs and had AVS-guided or non-AVS-guided adrenalectomy did not seem to differ in clinical outcome might question the usefulness of AVS. However, we believe that caution should be taken in drawing this conclusion since the number of patients in this group was small thus exposing to a type 2 statistical error. The same caution should be exercised when interpreting the lack of usefulness of AVS seen in determining outcome in imaging positive and negative RH patients (Figure 5).

The third important finding of this study was to discover that overall 15% of the patients with RH, who underwent adrenalectomy, were cured, and 63% were markedly improved haemodynamically. It is worth emphasizing that although some patients could not be defined as improved by our tight predefined criteria, adrenalectomy allowed resolution of treatment-resistant status in all the RH\textsubscript{AHA2018} patients.

Limitations to be acknowledged in this study include its observational nature, the lack of 24-h ambulatory BP measurement, the impossibility to ascertain adherence to drug treatment, and the low participation of Blacks in whom RH is a common problem. Moreover, a selection bias might have occurred in that patients referred to specialized centres may represent the more severe end of the PA spectrum and a proportion of the patients could have been referred on the ground of RH, clearly a clinically overestimated phenotype, as discussed above. Although the clinical characteristics of AVIS-2-RH patients are comparable to those of newly diagnosed hypertensive patients in a previous study,\textsuperscript{8} further research can be necessary to establish the prevalence of RH in unselected PA patients in primary care. Likewise, given the AVIS-2-RH study design, we could not draw conclusions on whether RH is truly the final stage of undetected PA, as suggested by Baudrand et al.\textsuperscript{28} Finally, it should be acknowledged that our assessment of outcome was limited to the information recorded at single time points by participating centres, as the AVIS-2-RH study was not conceived as a longitudinal study to assess outcome after target treatment.

Notwithstanding these limitations, the data gathered in this study clearly demonstrated that RH is a common mode of clinical

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{The bar graphs show the number of antihypertensive drugs required to achieve control of high BP values in the RH and non-RH patients at baseline (A) and after adrenalectomy (B). The bottom panels (C) show the distribution of number of drugs required to control high BP after adrenalectomy in the patients with (C) or without RH (D) stratified according to whether they were submitted to AVS-guided surgery or not.}
\end{figure}
Conclusions

The AVIS-2-RH Study showed that one-in-five PA patients referred for AVS has RH by guidelines definitions. In such challenging patients, who receive treatment with multiple antihypertensive agents, AVS can allow identification of lateralized PA (Figure 6). In this subgroup, AVS-guided unilateral laparoscopic adrenalectomy lead to resolution of treatment-resistant status in all cases. Since a strategy of CT and AVS, alongside identification of truly RH patients by therapeutic drug monitoring (to pinpoint those adherent to their prescribed antihypertensive medications), has been reported to be cost-effective these results strongly support the conclusion that subtyping with AVS is useful for the optimal management of PA patients with resistant hypertension.

Supplementary material

Supplementary material is available at European Journal of Preventive Cardiology online.

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Conflict of interest: none declared.

Data availability

The data underlying this article cannot be shared publicly due for the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

Figure 5 The rate of cure of the RH patients submitted to adrenalectomy with a negative imaging (A), i.e. no CT/MR evidence of adrenal mass, or a positive imaging (B) was not different when surgery was guided by AVS or not.

Figure 6 Study design and main outcomes of the AVIS-2-RH.
References


