Region Västra Götaland, HTA-centrum
Health Technology Assessment
Regional activity-based HTA
2013:56

Renal sympathetic denervation in patients with therapy resistant hypertension.

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Renal sympathetic denervation in patients with therapy resistant hypertension. [Renal denervering vid behandlingsresistent hypertoni]

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Published January 2013
2013:56

Suggested citation: Andersson B, Herlitz H, Manhem K, Zachrisson K, Völz S[1], Daxberg EL, Holmberg Y, Samuelsson O
Renal sympathetic denervation in patients with therapy resistant hypertension. [Renal denervering vid behandlingsresistent hypertoni]. Göteborg: Västra Götalandsregionen, Sahlgrenska Universitetssjukhuset, HTA-centrum; 2013. Regional activity-based HTA 2013:56

Table of content

Summary of the Health Technology Assessment

Method and patient group

Renal sympathetic denervation (RDN) is a catheter-based technique for radiofrequency ablation (destruction) of sympathetic nerve endings within the wall of the renal arteries. The denervation reduces sympathetic nerve traffic, thereby causing a reduction in blood pressure. The primary group of patients suited for RDN are those with uncontrolled therapy resistant hypertension.

Question at issue:

Is RDN an effective and safe technique to lower the blood pressure in patients with treatment resistant hypertension, and does it result in reduced mortality and less target organ damage?

PICO

P = Patients with treatment-resistant hypertension (medical treatment with at least three antihypertensive drugs) with blood pressure ≥140/90 mm Hg
I = Catheter-based renal denervation
C = Conventional pharmacological treatment
O = Mortality
Cardiovascular morbidity
Kidney involvement
Blood pressure
Left ventricular hypertrophy/Systolic and diastolic cardiac function
Glucose metabolism
Complications

Mortality and cardiovascular morbidity

The systematic literature search did not find any published study that has reported the effects of RDN on mortality or cardiovascular morbidity (coronary heart disease, stroke, peripheral arterial obstructive disease, heart failure).

Kidney involvement

One non-randomised, controlled study analysed the effect on kidney function. It did not observe any significant effects of RDN.
Conclusion: It is uncertain whether RDN affects kidney function. Very low quality of evidence (GRADE ⊕OOO)

Blood pressure

Two randomised and three non-randomised, controlled studies analysed the effects of RDN on office blood pressure. All studies reported significant and marked reductions in blood pressure in the range of 22-31 mm Hg decrease in systolic and of 8-12 mm Hg decrease in diastolic blood pressure.
Conclusion: In comparison to patients who remain on conventional pharmacological treatment RDN markedly reduces office blood pressure.
Low quality of evidence (GRADE ⊕⊕OO)

Left ventricular hypertrophy
One non-randomised controlled study analysed the effect of RDN on left ventricular hypertrophy. It reported a significant reduction in interventricular septal thickness and in left ventricular mass.
Conclusion: In comparison to patients who remain on conventional pharmacological treatment RDN reduces left ventricular hypertrophy. Low quality of evidence (GRADE ⊕⊕OO)

Glucose metabolism
One non-randomised controlled study analysed the effect of RDN on glucose metabolism. It observed significant reductions in the serum levels of C-peptide and insulin, and a decrease in insulin resistance (measured as HOMA-IR).
Conclusion: In comparison to patients who remain on conventional pharmacological treatment RDN increases insulin sensitivity. Very low quality of evidence (GRADE ⊕OOO)

Complications
Eight studies, four controlled studies and four case series, have reported complications. The length of follow-up was 3 – 24 months. The rate of complications varied from 1 - 3 %. There were no reported procedure-related deaths, or any other type of serious adverse events.

Ethical questions
Data suggest sustained effects of RDN over 2-3 years, but the risks and benefits over longer times are unknown.
A large group of hypertensive patients are possible candidates for RDN. Therefore, this invasive method could compete with other cardiovascular interventions and resultin lead an overall shortage of interventional capacity.

Economical aspects
The cost of one RDN procedure averages 85 000 SEK, including one over-night stay in the hospital. About a third of the cost is for the devices (catheters) used for RDN. In a health economy analysis, RDN was estimated to a discounted lifetime incremental cost-effectiveness ratio of USD 3071 per QALYs (quality- adjusted life-year).

Concluding remarks
This catheter-based method, used for patients with therapy-resistant hypertension, significantly reduces blood pressure. Even though follow-up data for more than two years are lacking, present data suggest that the method may be safely used as a treatment alternative in this category of patients. The present data suggests that the method may be a valuable treatment alternative in therapy resistant hypertension.

Which health technology or method will be assessed?

1a **Who will lead the project?**
Bert Andersson, Associate professor, MD, Department of Cardiology, Sahlgrenska University Hospital, Göteborg, Sweden.

1b **Who posed the question?**
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1e **Are there any conflicts of interest for the proposer or any of the participants in the work group?**
Yes.
Bert Andersson and Sebastian Völz are presently participating in two investigator-initiated, and in two industry-sponsored trials.

Disease/disorder of Interest and Present Treatment

2a Disease of interest and its degree of severity

- **x** Risk of premature death
- **x** Risk of permanent illness or damage, or reduced quality of life
- **x** Risk of disability and health-related quality of life

High blood pressure, i.e. hypertension, is defined as a systolic blood pressure (SBP) above or equal to 140 mm Hg and/or a diastolic blood pressure above or equal to 90 mm Hg (Mancia, et al.,2007). Numerous observational studies provide evidence of a continuous association between both SBP and DBP and cardiovascular morbidity and mortality (Lewington, et al., 2002). The beneficial effect of lowering blood pressure is observed down to a level of 115/75 mm Hg. The main complications of hypertension are stroke, myocardial infarction, heart failure and kidney damage (Lewington, et al., 2002).

Hypertension is prevalent both in developed and developing countries. In 2000 it was estimated that more than a quarter of the adult population had hypertension. It is believed that it will increase to approximately 29 % of the adult population by 2025 (Kearney, et al., 2005). The beneficial effects by pharmacological antihypertensive treatment on mortality and morbidity are well documented (SBU, 2007).

Despite the benefit of blood pressure lowering in the great majority of hypertensive patients, there is still a clinical problem with a subgroup of hypertensive subjects who do not reach the blood pressure target (Hajjar and Kotchen, 2003). These individuals are categorised as having resistant hypertension (RH). It is defined as a blood pressure that is refractory to treatment by a therapeutic plan which includes both adequate lifestyle measures as well as the prescription of at least three antihypertensive drugs (including a diuretic) in adequate doses ((Mancia, et al.,2007). A commonly used definition is a SBP above 160 mm Hg (or above 150 mm Hg for patients with type 2 diabetes mellitus) despite treatment with at least three antihypertensive drugs (including a diuretic).

Dysfunction of the sympathetic nervous system is crucial in the development of primary hypertension. Increased renal sympathetic nerve activity (RSNA) causes an augmented renin secretion rate. If the renin secretion rate is high enough it will lead to an increased renal tubular sodium reabsorbtion with sodium and water retention, and even an enhanced renal vasoconstriction. Observations emphasize that a sub-vasoconstrictor effect of RSNA can produce increased renin secretion rate, and renal sodium retention (without alteration in overall renal hemodynamics), that both contribute raised to a blood pressure. Conversely, a diminished RSNA leads to renal functional responses that are opposite those following increases in RSNA.

2b **Prevalence and incidence of therapy resistant hypertension**

The prevalence of primary hypertension in the general adult population is about 20 %. However, the prevalence of RH is not known. Recent controlled hypertension outcome trials have reported a rather high frequency of treated patients who do not reach the therapeutic goals (normally SBP below 140 mm Hg and DBP below 90 mm Hg (Calhoun, et al., 2008). In these trials 20-30 % of the hypertensive patients did not reach the blood pressure goal. This would mean that up to 4 – 6 % of the general adult population may have RH.

In a recent retrospective cohort study of juvenile hypertensive patients Daugherty and co-workers identified RH in one out of 50 patients. This corresponds to a prevalence of about 2 %, one and a half years after initiation of pharmacologic treatment (Daugherty, et al., 2012). The authors state that these individuals are at an increased cardiovascular risk; 18% risk of any cardiovascular event within 4 years, as compared to 14 % in the remaining hypertensive population.

2c **Present treatment of therapy resistant hypertension**

Today, hypertensive patients are treated with lifestyle intervention and pharmacological therapy. The great majority of patients are cared for within the primary health care system.

2d **Number of patients per year who undergo current treatment regimen?**

To our knowledge, there are no reliable estimates of the number of patients with RH in Sweden. Preliminary data from ongoing research suggest that approximately 5 % of all the hypertensive patients treated in the primary health care system have RH (Manhem, et al., unpublished data).

Based on the assumptions that 20 % of the adult population has hypertension, and that the prevalence of RH is 1 %, the number of subjects with RH in Region Västra Götaland would be approximately 15 000 patients.

2e **The normal pathway of a patient with resistant hypertension through the health care system**

In Sweden the majority of patients with hypertension are cared for in the primary health care system. Patients with a suspicion of secondary hypertension or with therapy resistant hypertension are referred to specialists in internal medicine, cardiology or nephrology.

2f **Actual wait time in days for medical assessment and treatment**

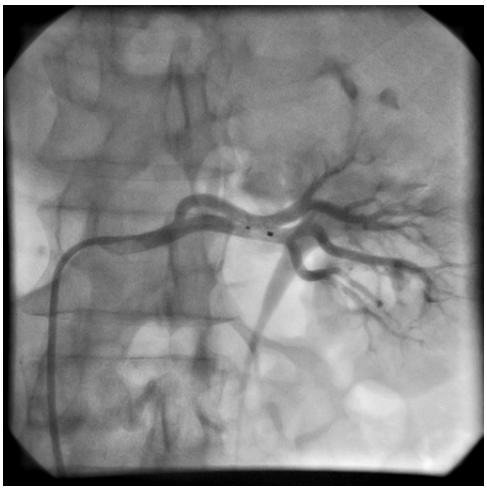
Patients with a suspicion of secondary hypertension or with therapy resistant hypertension referred to a specialist do not have to wait longer than three months for their first visit to a specialist.

Presently, the clinical problem regarding patients with RH is not that of long wait time to treatment, but the lack of effective treatment alternatives.

Present Health Technology

3a **Name and description of the health technology at issue**

Renal sympathetic denervation (RDN) is a catheter-based endovascular technique for radiofrequency ablation (destruction) of sympathetic nerve endings within the wall of the renal arteries. A special catheter is placed in the renal artery via the femoral access. Up to six radiofrequency ablations are then performed. They are separated both longitudinally and rotationally within each renal artery. The denervation reduces both the afferent and efferent sympathetic nerve traffic. Thereby, the local and the general sympathetic tone are reduced. The mid- and long-term effect is primarily a reduction in blood pressure.



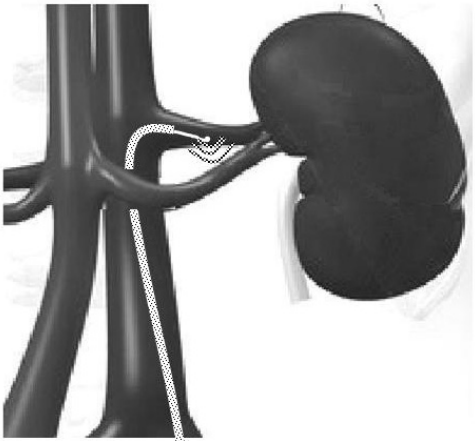


Figure. A special catheter is placed in the renal artery where it delivers high-frequency radio waves at four to six locations.

During January through September 2012, 20 patients have been treated at Sahlgrenska University Hospital. These are selected patients with RH who have been referred to the Departments of Cardiology or Nephrology. During 2013 the estimated number of cases that will be referred for RDN due to RH is 70 - 100 patients. As stated above, the numbers of patients that may be eligible for RDN are much larger.

3b **The work group's understanding of the potential value of renal denervation**

Catheter-based RDN is an interesting and promising technique. The cardiovascular risk profile of a RH patient is in most cases very disadvantageous with a high risk for major cardiovascular events. The RDN technique is therefore an awaited treatment alternative.

The first case series of treated patients indicated that RDN can lead to substantial reductions in blood pressure in patients with RH. The degree of blood pressure reduction has been reported to be much greater than would be expected if just an additional antihypertensive drug was added. Presently, there are only a few controlled trials (see below 5a). However, the general experience from clinical practice, including our own (Rundqvist, et al., 2012), indicate that the blood pressure reduction is on the average about 25 mm Hg in systolic blood pressure 3 - 6 months after

intervention. In the long-term a sustained reduction of this magnitude would have a great potential to reduce cardiovascular mortality and morbidity. However, at present there is a scarcity of data on long-term major outcome variables such as renal function, cardio- or cerebrovascular events.

Although blood pressure has been the primary outcome variable in the studies, there are several reports that suggest beneficial effects also in patients with diabetes mellitus, metabolic syndrome, cardiac arrhythmias, sleep apnea and heart failure. The potential for RDN is extensive if also these disorders can be successfully treated by this technique.

The interest in RDN is very high. Several device companies are already developing alternative techniques to the presently available radioablation procedure. This includes ultrasound-mediated heat and local pharmacological denervation.

RDN could easily be introduced in an angiographic laboratory milieu already established for cardiovascular interventions. At present, most interventions have been performed in cardiology angiographic laboratories. These laboratories do not need any further equipment or modification, besides the mobile generator for radiofrequency energy delivery.

In the selection of patients, primary care physicians and specialists in internal medicine, nephrology, interventional radiology or cardiology should be involved.

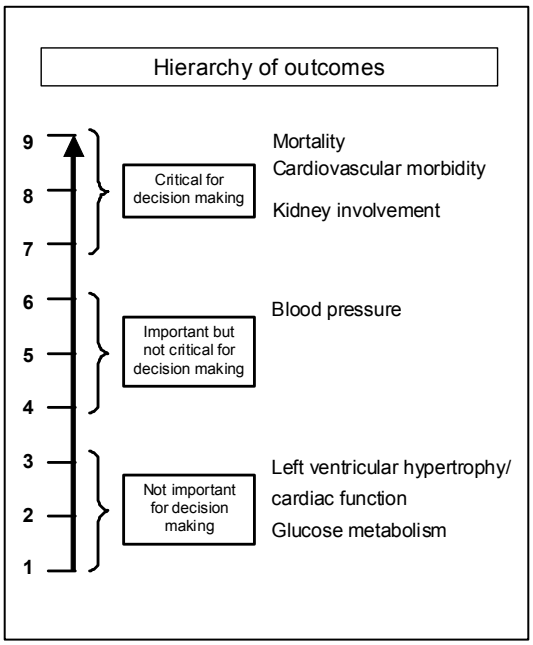
3c **The central question for the HTA project in one sentence**

Is RDN an effective and safe technique to lower the blood pressure in patients with treatment resistant hypertension, and does it result in reduced mortality and less target organ damage?

3d **PICO and hierarchy of outcomes according to importance to patients and for decision making**

P = Patients, I = Intervention, C = Comparison, O = Outcome

P = Patients with treatment-resistant hypertension (medical treatment with at least three antihypertensive drugs) with blood pressure ≥140/90 mm Hg
I = Catheter-based renal denervation
C = Conventional pharmacological treatment
O = Mortality
Cardiovascular morbidity
Kidney involvement
Blood pressure
Left ventricular hypertrophy/Systolic and diastolic cardiac function
Glucose metabolism
Complications



3e **Key words**

Swedish: Renal denervering; sympatiska nervsystemet; blodtryck

English: Renal denervation; sympathetic nervous system; blood pressure

Review of the Quality of Evidence

4 **Search strategy, study selection and references – appendix 3**

During May, 2012, with an update in August, two librarians performed systematic searches in PubMed, EMBASE, the Cochrane Library, and in a number of HTA-databases. Reference lists of relevant articles were also scanned for additional references. After removal of duplicates, a total of 1026 articles were initially identified. 959 were thereafter excluded by the librarians (YH and E-LD) after reading the abstracts. Another 51 articles were excluded by the librarians after having been read in full text. 16 articles were sent to the work group for assessment, and 15 are included in the report. Five of them are controlled studies and they have been critically appraised using checklists from SBU (Swedish Council on Health Technology Assessment) for randomized controlled trials and for cohort studies. One systematic review was checked by the AMSTAR criteria.

Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in appendix 3.

5a Present knowledge of renal denervation

The Austrian Ludwig Boltzman Institut for Health Technology Assessment published a systematic review of "Perkutane Renale Denervation bei Therepiresistenter Hypertonie" in 2011. It concluded that RDN is effective in lowering blood pressure, but there is still a lack studies on the long-term effects on mortality and morbidity (Wegmann, et al., 2011)

The systematic literature search of the present HTA identified five controlled studies of the effects of renal sympathetic denervation in patients with therapy resistant hypertension.

Mortality and cardiovascular morbidity

The literature search did not identify any published study that addressed the effects of RDN on mortality or cardiovascular morbidity (coronary heart disease, stroke, peripheral arterial obstructive disease, heart failure).

Kidney involvement (Appendix 1:1)

One non-randomised, controlled study analysed the effect of RDN on kidney function. It was an open, non-randomised study of moderate quality. The assessments of the renal outcome variables were not blinded to treatment. The time of follow-up was six months. It did not find any significant differences between study groups in any of the renal outcome variables.

Conclusion: It is uncertain whether RDN affects kidney function. Very low quality of evidence (GRADE ⊕OOO)

Blood pressure (Appendix 1:2)

Two randomised and three non-randomised controlled studies analysed the effects of RDN on office blood pressure. Three of them were of moderate, and two were of low-to-moderate study quality. Two of the non-randomised studies included some patients who also participated in a large randomised study. All the studies were open. Only one had blind assessment of blood pressure. The time of follow-up was three or six months. All studies reported significant and marked reductions in blood pressure that varied from a 22-31 mm Hg decrease in systolic and an 8-12 mm Hg decrease in diastolic blood pressure.

Conclusion: In comparison to patients who remain on conventional pharmacological treatment RDN markedly reduces office blood pressure. Low quality of evidence (GRADE ⊕⊕OO).

Left ventricular hypertrophy (Appendix 1:3)

One non-randomised, controlled study analysed the effect of RDN on left ventricular hypertrophy. It was an open study of moderate quality. The echocardiographic evaluation was performed blinded to treatment. The time of follow-up was six months.The study observed a significant reduction in interventricular septal thickness (IVS) and in left ventricular mass (LVM) in the patients treated with RDN.

Conclusion: In comparison to patients who remain on conventional pharmacological treatment RDN markedly reduces left ventricular hypertrophy. Low quality of evidence (GRADE ⊕⊕OO).

Glucose metabolism (Appendix 1:4)
One non-randomised, controlled study analysed the effect of RDN on glucose metabolism. It was an open study of moderate quality. The assessments of glucose metabolic variables were not blinded to treatment. The time of follow-up was three months. The study reported significant reductions in the serum levels of C-peptide and insulin, and a decrease in insulin resistance (measured as HOMA-IR).
Conclusion: In comparison to patients who remain on conventional pharmacological treatment RDN increases insulin sensitivity. Very low quality of evidence (GRADE ⊕OOO)

Complications (Appendix 1:5)
Eight studies, four controlled studies and four case series, have reported complication between 1 - 3 %. There were no reported procedure-related deaths, or any other type of serious adverse events.

5b **Outcome tables – appendix 1**

5c **Excluded articles – appendix 2**

5d **Ongoing research?**
A search in Clinicaltrials.gov (October 21st, 2012) using the search strategy; *renal denervation* AND *hypertension*, identified 43 registered trials in the database. Thirty-six trials include only patients with "uncontrolled" or "resistant" hypertension. Seven of them are ongoing and have completed the patient recruitment. Twenty-sex are still recruiting patients, and the remaining three studies have not yet started to recruit patients. Fourteen of the 36 studies are randomised, controlled trials, whereas 22 are either uncontrolled, safety follow-up studies or non-randomised, controlled observational studies.
No study is primarily designed to study the effects on mortality or cardiovascular morbidity. Only one protocol states that cardiovascular morbidity is a secondary outcome variable.

6 **Which medical societies or health authorities recommend renal denervation?**

Presently, there are no recommendations.

☐ **The National Board of Health and Welfare**

☐ **Medical societies**

☐ **Other health authority**

Which medical society or health authority?

Ethical aspects

7 **Ethical analysis.**
See Appendix 5.

Organisation

8a **When can this new health technology be put into practice?**
Renal sympathetic denervation has been performed at Sahlgrenska University Hospital since April 2011 (see 2d).

8b **Is renal denervation used in other hospitals in Region Västra Götaland in Sweden?**
Currently there are no other hospitals that perform RDN in Region Västra Götaland. Four other hospitals in other regions of Sweden have started to use the technique.

It is possible to set up the RDN procedure in any hospital with angiographic capacity. However, early in the development and implementation of the technique, with the present number of referred patients, it is reasonable to centralise the procedures in the region.

8c **According to the work group, will there be any consequences of the new health technology for personnel?**
It is necessary to train physicians and nurses, both at the catheterisation laboratory and at the clinics that will evaluate and follow the patients. This will require redistribution of work tasks. An angiography is necessary in order to place the radio ablation catheter in the right locations of the renal arteries. This means that all personnel who participate in the procedure of RDN will be exposed to some radiation.

8d **Will there be any consequences for other clinics or supporting functions at the hospital or in the whole Region Västra Götaland of Sweden?**
The long-term follow-up of RDN treated patients is similar to the usual care of hypertensive patients. It can be done by specialists in cardiology, internal medicine or nephrology, as well as by primary care physicians. For the limited number of patients who are expected to be treated with RDN during the next coming years this means that there is currently no need for any major reorganisation of the health care. The estimated number of patients that will be treated with RDN during 2013 at Sahlgrenska University Hospital is 70 - 100 patients.

A slight increase in the demand for functional and morphological diagnostic procedures of the renal arteries (MRI, CT, Doppler-ultrasound) is expected since this is a part of the routine protocol prior to renal denervation. There will also be an increased demand for an increase of ambulatory blood pressure measurements (24 hours registration). Furthermore, support from the Department of Anaesthesiology will be necessary since the ablation *per se* is painful.

Until now, the indication for RDN is therapy resistant hypertension. There are presently studies in progress that investigate its therapeutic efficacy in other disorders associated with elevated sympathetic nerve activity (heart failure, renal failure, arrhythmias). Depending on the outcomes of these studies the indication for RDN may in the future also include other chronic diseases. The number of patients suitable for this treatment may therefore increase even more during the next coming years.

Economy

9a Present costs of currently available treatment of resistant hypertension

The annual cost for combined antihypertensive drug treatment of RH varies between individual patients. It depends on the number of drugs needed, and the prescribed doses. A common combination of antihypertensive drugs in a RH patient could be exemplified by enalapril 20 mg o.d. combined with hydrochlorothiazide 25 mg od, metoprolol 200 mg o.d. and amlodipine 10 mg o.d. The annual cost for this specific combination is currently slightly less than 1600 SEK per year, when generic drugs are prescribed. This treatment is life-long. Thus, with a life-expectancy of about 30 years the total cost for this treatment combination is 48 000 SEK (in 2012 prices).

9b Expected costs of renal denervation

The average cost per treatment session in the Department of cardiology, Sahlgrenska University Hospital, is 85 000 SEK. This includes an average hospital stay of 1.4 days. About a third of the cost is for the devices (catheters) used for RDN. The cost for 70 - 100 patients during 2013 (see 2d and 8d) will be 6 to 8.5 million SEK. There will be no additional costs as long as the volume of patients is at the present level. However, if a larger number of patients is to be treated this will require new catheterisation laboratories as well as more personnel.

9c Total change of cost

During the first year, there will only be an increased cost for the procedure. During long-term, a reduction in the blood pressure levels will allow the withdrawal of some of the antihypertensive drugs, and thereby reduce the medication costs. Furthermore, if the blood pressure lowering is sustained during long-term, and thereby resultin less cardiovascular events, this will decrease the total costs for the health care system and the society. Such beneficial effects are presently difficult to estimate in economic terms.

9d Can renal denervation be adopted and used within the present budget (clinic budget/hospital budget)?

The present number of procedures (estimated to be about 25 patients during 2012, see 2d) has already been incorporated in the budget. A further increase to 70 -100 patients during 2013, and thereafter possibly up to one percent of all patients with hypertension (see 2d) cannot be handled without additional economic resources.

9e Are there any available analyses of health economy? Cost advantages or disadvantages?

Geisler et al.(2012) analysed the potential cost-effectiveness of RDN compared with standard care treatment in patients with RH in north America. They used a state-transition model to predict 10-year and lifetime probabilities of stroke, myocardial infarction, heart failure, end-stage renal disease and median survival. The conclusion was that RDN is potentially a cost-effective strategy in the treatment of RH, estimating a discounted lifetime incremental cost-effectiveness ratio of $ 3071 per QALYs (quality-of-life-adjusted life-year).

Unanswered Questions

10a Important gaps in scientific knowledge?

Presently, there has been no study of the effects of RDN in patients with RH with regard to long-term clinical outcomes of critical importance for decision making, such as mortality, cardiovascular morbidity and end-stage renal disease. Such data are now being collected in a recently started (February 2012) registry study, the Global SYMPLICITY Registry (ClinicalTrials.gov., 2012). The estimated enrolment is 5000 patients, and the estimated date of study completion is July 2021. The study is sponsored by Medtronic Vascular.

Currently, there is no ongoing RCT designed to evaluate the effects of RDN on mortality and cardiovascular morbidity.

There is no knowledge of the effects of RDN in early or mild forms of hypertension. Several co-morbidities and conditions associated with increased sympathetic nerve traffic could theoretically be possible candidates for RDN. Such conditions include heart failure, renal failure, metabolic syndrome, diabetes mellitus, cardiac arrhythmias, acute coronary syndrome, Takotsubo cardiomyopathy, peripheral vascular disease, obesity, and post-transplant hypertension. There are ongoing trials for many of these conditions, but only preliminary results are yet available.

It is still not known if sympathetic renal denervation has any long-term adverse effects, or whether there will be a reinnervation to such an extent that the effect on blood pressure will be diminished. It is also not known if there are significant interactions between RDN and pharmacological interventions that may affect renal hemodynamics.

Finally, we lack long-term safety aspects on how RDN treated patients can cope with conditions of salt restriction or severe hypovolemia.

10b Is there any interest in your own clinic/research group/organisation to start studies/trials within the research field at issue?

Yes. We are presently participating in two investigator-initiated, and two industry-sponsored trials.

Currently, five centres in Sweden have started to treat patients with RDN. All of them have reported scientific interest and/or have started research project associated with the procedure.

Statement from HTA-centrum of Region Västra Götaland, Sweden

Renal sympathetic denervation in patients with therapy resistant hypertension.

Question at issue

Is renal sympathetic denervation an effective and safe technique to lower blood pressure in patients with treatment resistant hypertension, and does it result in reduced mortality and less target organ damage?

PICO

P = Patients with treatment-resistant hypertension (medical treatment with at least three antihypertensive drugs) with blood pressure of ≥140/90 mm Hg
I = Catheter-based renal denervation
C = Conventional pharmacological treatment
O = Mortality, Cardiovascular morbidity, Kidney involvement, Blood pressure, Left ventricular hypertrophy/Systolic and diastolic cardiac function, Glucose metabolism, Complications

Summary of the health technology assessment

Method and patient category

Renal sympathetic denervation (RDN) is a catheter-based endovascular technique for radiofrequency ablation (destruction) of sympathetic nerve endings within the wall of the renal arteries. The denervation reduces sympathetic nerve traffic, thereby causing a reduction in blood pressure. The primary group of patients suited for RDN are those with uncontrolled therapy resistant hypertension.

Scientific documentation

Mortality and cardiovascular morbidity

The systematic literature search did not find any published study that has reported the effects of RDN on mortality or cardiovascular morbidity (coronary heart disease, stroke, peripheral arterial obstructive disease, heart failure).

Kidney involvement

One study analysed the effect on kidney function. It was an open, non-randomised, controlled study with six months follow-up. It observed no significant differences between study groups in any of the renal outcome variables.
Conclusion: It is uncertain whether RDN affects kidney function.
Very low quality of evidence (GRADE ⊕OOO).

Blood pressure

Two randomised and three non-randomised controlled studies analysed the effects of RDN on office blood pressure. All of them were open studies. The time of follow-up was three or six months. All studies reported significant and marked reductions in blood pressure that varied from a 22-31 mm Hg decrease in systolic and an 8-12 mm Hg decrease in diastolic blood pressure.
Conclusion: In comparison to patients who remain on conventional pharmacological treatment RDN markedly reduces office blood pressure. Low quality of evidence (GRADE ⊕⊕OO).

Left ventricular hypertrophy
One non-randomised, controlled study analysed the effect of RDN on left ventricular hypertrophy. It was an open study with six months follow-up. It found a significant reduction in interventricular septal thickness and in left ventricular mass in the RDN treated patients.
Conclusion: In comparison to patients who remain on conventional pharmacological treatment RDN reduces left ventricular hypertrophy. Low quality of evidence (GRADE ⊕⊕OO).

Glucose metabolism
One non-randomised, controlled analysed the effect of RDN on glucose metabolism. It was an open study with three months follow-up. The study reported significant reductions in the serum levels of C-peptide and insulin, and a decrease in insulin resistance in the RDN treated patients.
Conclusion: In comparison to patients who remain on conventional pharmacological treatment RDN increases insulin sensitivity. Very low quality of evidence (GRADE ⊕OOO).

Side effects and complications
Eight studies, four controlled studies and four case series, have reported complications. The length of follow-up were 3 – 24 months. The rate of complications varied between 1 - 3 %. No study reported any fatal or any other serious adverse event.

Ethical aspects
A large group of hypertensive patients are possible candidates for RDN. Thereby, this invasive method could compete with other cardiovascular interventions and may lead to a shortage of overall interventional capacity.
The long-term risks and benefits of RDN are still unknown. In contrast to pharmacological blood pressure lowering the effects of RDN on blood pressure cannot be reversed by withdrawal of the intervention. Is it ethically justified to introduce such treatment on a large scale in the clinical routine before possible long term risks are known?

Economical aspects
The average cost per patient treated with renal sympathetic denervation is 85 000 SEK. The annual cost of combined drug treatment varies between patients but could be exemplified by a typical 4-drug combination that costs 1600 SEK per year. During 30 years of treatment this corresponds to a total medication costs of 48 000 SEK in 2012 year's prices.
In an American health economy analysis, RDN was estimated to a discounted lifetime incremental cost-effectiveness ratio of $ 3071 per QALYs (quality-of-life-adjusted life-year), which corresponds to about 20 000 SEK.

Concluding remarks

Renal sympathetic denervation is a catheter-based endovascular technique for patients with uncontrolled therapy resistant hypertension. It reduces blood pressure and left ventricular hypertrophy significantly (GRADE⊕⊕OO), and improves insulin sensitivity (GRADE ⊕OOO). It is uncertain whether it affects renal function. Even though follow-up data for more than two years are still lacking, present data suggest that the technique may be safely used, and may be a valuable treatment alternative for patients with therapy resistant hypertension.

The Regional Health Technology Assessment Centre (HTA-centrum) of Region Västra Götaland, Sweden (VGR) has the task to make statements on HTA reports carried out in VGR. The statement should summarise the question at issue, level of evidence, efficacy, risks, and economical and ethical aspects of the particular health technology that has been assessed in the report.
HTA was accomplished during the period of
2012-04-11 – 2012-12-12. Last search updated in April 2012

On behalf of the HTA quality assurance group, in Region Västra Götaland, Sweden
Göteborg, Sweden, 2012-12-12

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Utlåtande och sammanfattande bedömning från Kvalitetssäkringsgruppen

Renal denervering vid behandlingsresistent hypertoni

Frågeställning: Är renal denervering en effektiv och säker metod att sänka blodtrycket hos patienter med behandlingsresistent hypertoni, och leder den till lägre mortalitet och mindre organskador?

PICO: (Patient, Intervention, Comparison, Outcome)

P = patienter med behandlingsresistent hypertoni (minst tre blodtryckssänkande läkemedel) och blodtryck ≥140/90 mm Hg
I = kateter-baserad renal denervering
C = konventionell farmakologisk behandling
O = mortalitet, kardiovaskulär morbiditet, njurpåverkan, blodtryck, vänsterkammarhypertrofi/systolisk och diastolisk hjärtfunktion, glukosmetabolism, komplikationer

Resultatet av HTA-processen:

Metod och målgrupp:
Renal denervering (RDN) är en kateterbaserad behandlingsteknik som innebär att sympatiska nervsignaler i njurartärens vägg blockeras med radiofrekvens (RF)-energi. RF-energin tillförs via en speciell kateter som förs in i njurartären. En följd av den reducerade sympatikusaktiviteten till och från njurarna är en sänkning av blodtrycket. De patienter som kan bli aktuella för RDN är patienter med ett inadekvat kontrollerat högt blodtryck som inte svarat tillfredsställande på medicinsk behandling.

Vetenskaplig dokumentation

Mortalitet och kardiovaskulär morbiditet
Den systematiska litteratursökningen resulterade inte i någon publicerad studie som redovisat effekter av RDN avseende mortalitet eller kardiovaskulär morbiditet (kranskärlssjukdom, stroke, perifer arteriell sjukdom, hjärtsvikt).

Njurpåverkan
En öppen, icke-randomiserad, kontrollerad studie har undersökt effekterna av RDN på olika njurfunktionsvariabler. Studien hade 6 månaders uppföljning. Inga signifikanta skillnader observerades mellan behandlingsgrupp och kontrollgrupp.
Slutsats: Det är osäkert om RDN påverkan njurfunktion. Otillräckligt vetenskapligt underlag (GRADE ⊕OOO).

Blodtryck
Två randomiserade och tre icke-randomiserade, kontrollerade studier har utvärderat effekterna av RDN på blodtrycket. Alla studierna var öppna med uppföljningstid som varierade mellan tre och sex månader. Samtliga studier rapporterade signifikant och påtaglig blodtryckssänkning som varierade mellan 22 – 31 mm Hg systoliskt och 8 – 12 mm Hg diastoliskt.
Slutsats: Jämfört med patienter som har kvar konventionell läkemedelsbehandling leder RDN till en uttalad sänkning i blodtrycket. Begränsat vetenskapligt underlag (GRADE ⊕⊕OO).

Vänsterkammarhypertrofi
En icke-randomiserad, kontrollerad studie har studerat effekterna av RDN på olika hjärtvariabler. Efter sex månaders uppföljning observerades en signifikant minskning i tjockleken av skiljeväggen mellan hjärtkamrarna (IVS) och i vänsterkammarmassan (LVM) hos patientgruppen som genomgått RDN.
Slutsats: Jämfört med patienter som har kvar konventionell läkemedelsbehandling leder RDN till en reduktion i vänsterkammarhypertrofi. Begränsat vetenskapligt underlag (GRADE ⊕⊕OO).

Glukosmetabolism
En icke-randomiserad, kontrollerad studie har undersökt effekterna av RDN på glukosmetabolismen. Efter tre månader fann man en signifikant reduktion i serumnivåer av C-peptid och insulin och en signifikant ökning i insulinkänslighet.
Slutsats: Jämfört med patienter som har kvar konventionell läkemedelsbehandling leder RDN till en förbättrad glukosmetabolism. Otillräckligt vetenskapligt underlag (GRADE ⊕⊕OO).

Biverkningar och komplikationer
Åtta studier, fyra kontrollerade och fyra fallserier, har redovisat komplikationer. Observationstiden varierade från tre till 24 månader. Komplikationsfrekvensen rapporterades vara mellan 1 – 3 %. Inga komplikationer med dödlig utgång eller av någon annan allvarlig typ har rapporterats.

Etiska aspekter:
Patienter med behandlingsresistent hypertoni är en relativ stor patientgrupp. Om en stor del av dem blir aktuella för RDN kommer den att konkurrera med andra kärlinvasiva åtgärder. Detta kan leda till en övergripande brist på kapacitet för olika typer av interventionella behandlingsmetoder. Behandlingsvinster och risker på lång sikt efter utförd RDN är okända. Till skillnad från läkemedel kan dess effekter på blodtrycket inte reverseras genom att sätta ut behandlingen. Det är därför viktigt att fråga sig om det är etiskt acceptabelt att införa RDN i stor skala i klinisk rutin innan eventuella långtidskomplikationer är klarlagda.

Ekonomiska aspekter
Den genomsnittliga kostnaden för en RDN behandling är idag 85 000 kronor per patient. Den årliga läkemedelskostnaden för en patient med behandlingsresistent hypertoni varierar beroende på kombination av blodtryckssänkande läkemedel. En vanlig kombination av fyra olika, typiska läkemedel (generika) kostar 1 600 kronor årligen. Detta innebär en total kostnad för 30 års behandling på 48 000 kronor (i 2012 års priser).
En amerikansk hälsoekonomisk analys uppskattade kostnadseffektivitet till ca 20 000 kronor per kvalitetsjusterat levnadsår (QALY).

Sammanfattning och slutsats
Renal denervering (RDN) är en kateterbaserad behandlingsteknik för patienter med behandlingsresistent hypertoni. Åtminstone upp till 6 månader efter behandling leder den till en kvarstående signifikant blodtryckssänkning (GRADE ⊕⊕OO), en minskad vänster-kammarhypertrofi (GRADE ⊕⊕OO), och en förbättrad insulinkänslighet (GRADE ⊕OOO). Det är osäkert om njurpåverkan minskar. Det saknas ännu långtidsuppföljningar av dess effekter mer än två år. Den dokumentation som för närvarande är tillgänglig talar för att metoden är säker, och kan vara ett värdefullt alternativ för patienter med ett okontrollerat, behandlingsresistent högt blodtryck.

HTA-kvalitetssäkringsgruppen har ett uppdrag att yttra sig över genomförda HTA i Västra Götalandsregionen. Yttrandet skall innefatta sammanfattning av frågeställning, samlat evidensläge, patientnytta, risker samt ekonomiska och etiska aspekter för den studerande teknologin.

Projektet har pågått under perioden 2012-04-11 – 2012-12-12.
Sista uppdatering av artikelsökning april 2012

För HTA-kvalitetssäkringsgruppen 2012-12-12

Christina Bergh
Ordförande

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Renal sympathetic denervation
Appendix 1:1
Outcome variable: Kidney involvement. GFR = glomerular filtration rate.

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention	Control		
Mahfoud, 2012	Germany	Open, non-randomised, controlled	n=88 (I) n=12 (C)	0	<u>Renal resistive index</u> Δ= -0.021 (sd 0.004) p < 0.001 between groups <u>Urinary albumine: creatinine ratio</u> Δ= -0.25 (sd 0.35) mg/mmol No significant difference between groups <u>GFR</u> Δ= -4.0 (sd 2.8) mL/min No significant difference between groups	<u>Renal resistive index</u> Δ= -0.002 (sd 0.022) <u>Urinary albumine: creatinine ratio</u> Δ= 0.17 (sd 0.29) mg/mmol <u>GFR</u> Δ= -15.1 (sd 11.1) mL/min	6 months follow-up	Moderate

Renal sympathetic denervation in therapy resistant hypertension.
Appendix 1:2
Outcome variable: Office blood pressure. SBP = systoliv blood pressure. DBP = diastolic blood pressure. NR = not reported.

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention	Control		
Symplicity HTN-2 Investigators, 2010	Australia	Open, randomised, controlled	n=52 (I) n=54 (C)	Dropouts n=3 (I) n=3 (C)	<u>SBP/DBP</u> Δ=-32/-12 mm Hg (sd 23/11) p < 0.001 between groups	<u>SBP/DBP</u> Δ=-1/0 mm Hg (sd 21/10)	6 months follow-up,	Moderate
Ukena, *et al*. 2011	Germany	Open, randomised, controlled	n=37 (I) n=9 (C)	NR	<u>SBP/DBP</u> Δ=-31/-9 mm Hg (sd 19/13) p < 0.001 between groups	<u>SBP/DBP</u> Δ= 0/-1 mm Hg (sd 17/5)	3 months follow-up	Low-moderate
Brandt, 2012	Austria	Open, non-randomised, controlled	n=46 (I) n=18 (C)	0	<u>SBP</u> Baseline: 180 (sd 18) mm Hg Follow-up: 153 (sd 22) mm Hg p=0.039 between groups	<u>SBP</u> Baseline: 184 (sd 22) mm Hg Follow-up: 183 (sd 25) mm Hg	6 months follow-up	Moderate
Mahfoud, 2012	Germany	Open, non-randomised, controlled	n=88 (I) n=12 (C)	0	<u>SBP</u> Δ=-27 (sd 3) mm Hg p < 0.001 between groups	<u>SBP</u> Δ=-4 (sd 4) mm Hg	6 months follow-up 26 (17+9) patients were also part of the HTN-2 trial	Moderate

Renal sympathetic denervation in therapy resistant hypertension.
Appendix 1:2
Outcome variable: Office blood pressure. SBP = systoliv blood pressure. DBP = diastolic blood pressure. NR = not reported.

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention	Control		
Mahfoud, Circulation 2011	Germany	Open, non-randomised, controlled	n=37 (I) n=13 (C)	0	<u>SBP</u> Δ=-32 (sd 4) mm Hg p < 0.001 between groups	<u>SBP</u> Δ=-5(sd 5) mm Hg	3 months of follow-up 26 (17+9) patients were also part of the HTN-2 trial	Low-moderate

Renal sympathetic denervation in therapy resistant hypertension
Appendix 1:3
Outcome variable: Left ventricular hypertrophy. IVS = interventricular septum, LV mass = left ventricular mass.

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention	Control		
Brandt, 2012	Austria	Open, non-randomised, controlled	n=46 (I) n=18 (C)	0	<u>IVS</u> Baseline:14.1 (sd 1.9) mm Follow-up: 12.5 (sd 1.4) mm p=0.03 between groups <u>LV mass</u> Baseline:112 (sd 34) g/m^2 Follow-up: 95 (sd 30) g/m^2 p=0.03 between groups	<u>IVS</u> Baseline:14.2 (sd 1.9) mm Follow-up: 14.2 (sd 1.9) mm <u>LV mass</u> Baseline:115 (sd 42) g/m^2 Follow-up: 119 (sd 30) g/m^2	6 months follow-up Blinded echocardiograhic assessment	Moderate

Renal sympathetic denervation in therapy resistant hypertension
Appendix 1:4
Outcome variable: Glucose metabolism. HOMA-IR = index of insulin resistance

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention	Control		
Mahfoud, 2011	Germany	Open, non-randomised, controlled	n =37 (I) n =13 (C)	0	<u>HbA1c</u> Δ= -0.1 (sd 0.4) % No significant difference between study groups <u>Insulin</u> Δ=-11.6 (sd 2.8) µIU/mL p=0.016 between study groups <u>C-peptide</u> Δ=-2.3 (sd 0.6) ng/mL p=0.031 between study groups <u>HOMA-IR</u> Δ=-3.7 (sd 0.9) p=0.003 between study groups	<u>HbA1c</u> Δ= -0.1 (sd 0.1) % <u>Insulin</u> Δ= 0.5 (sd 1.5) µIU/mL <u>C-peptide</u> Δ= 0.2 (sd 0.2) ng/mL <u>HOMA-IR</u> Δ= 0.3±0.7	3 months of follow-up	Moderate

Renal sympathetic denervation in therapy resistant hypertension
Appendix 1:5 Complications

Author, year	Country	Number of patients/ Length of follow-up (FU)	With drawals - dropouts	Complications related to the RD procedure	Comments
Krum, 2009	Australia, Europe	n =45 FU = 12 months	1 (renal artery dissection)	Renal artery dissection ; n = 1 Pseudoaneurysm at the femoral artery access site; n = 1	5 patients excluded because of anatomical criteria but were followed up in the trial. 18 patients were followed up with renal angiogram. 15 patients underwent MR angiogram after 6 months.
Mabin, 2012	South Africa	n = 11 FU = 6 months		Renal artery dissection ; n = 1	The catheter delivered ultrasound energy.
Mahfoud, 2011	Germany	n =37 FU = 3 months		Pseudoaneurysm at the femoral artery access site; n = 1	All patients treated with RDN underwent renal duplex ultrasound 3 months after the procedure, no abnormalities were found.
Prouchnau, 2012	Germany	n = 12 FU = not reported		No vascular complications.	Follow-up with renal duplex sonography.

Renal sympathetic denervation in therapy resistant hypertension
Appendix 1:5 Complications

Author, year	Country	Number of patients/ Length of follow-up (FU)	With drawals - dropouts	Complications related to the RD procedure	Comments
Simplicity HTN -1, 2011	Austarlia, Europe, USA	n = 153 FU = 24 months	1 (renal artery dissection)	Renal artery dissection ; n = 1 Pseudoaneurysm at the femoral artery access site; n = 3 Bilateral flan pain for some months; n = 1 Transient flank pain; n = 3.	Follow-up with renal angiography after 14 to 30 days in 20 patients, 81 pat underwent MR angiography , CT angio or duplex sonography after 6 months – only one of these had progression of a stenosis with no relation to the RF energy application.
Simplicity HTN-2, 2010	Australia, Europe, USA	n = 52 FU = 6 months		Pseudoaneurysm at the femoral artery access site; n = 1 Urinary tract infection; n = 1 Transient pareasthesia; n = 1 Back pain that resolved after 1 month; n = 1	6 –month follow-up with mainly Duplex ultrasound. 1 patient had a possible progression of a arteriosclerotic lesion, but intervention was not needed. The location of the stenosis was not at the site where radiofrequency had been delivered.
Voskuil, 2011	Nether-lands	n = 11 FU = 6 months		No complications.	Only one month follow-up. All patients had a postprocedural angiography, 3 were examined with IVUS.
Mahfoud, 2012	Germany	n = 88 FU = 6 months		Pseudoaneurysm at the femoral artery access site; n = 2 Allergic reaction to the contrast medium; n = 1	Postprocedural duplex ultrasound showed no abnormalities. Duplex ultrasound was performed 3 and 6 mmonths after the procedure.

Renal sympathetic denervation in therapy resistant hypertension
Appendix 1:5 Complications

Author, year	Country	Number of patients/ Length of follow-up (FU)	With drawals - dropouts	Complications related to the RD procedure	Comments
Zuern , 2012	Germany	n = 11 FU = 6 months		No periprocedural complications.	

Appendix 2. Renal sympathetic denervation in therapy resistant hypertension. Excluded articles.

Study (author, publication year)	Reason for exclusion
Ukena 2012b	Does not fulfil PICO criteria.

Appendix 3, Search strategy, study selection and references

Question(s) at issue:
Is RDN an effective and safe technique to lower blood pressure in patients with treatment resistant hypertension, and does it then result in a reduced mortality and less target organ damage?

PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)

P = Patients with treatment-resistant hypertension (medical treatment with at least three antihypertensive drugs) and blood pressure of ≥140/90 mm

I = Catheter-based percutaneous renal denervation

C = Conventional pharmacological treatment

O = Mortality
Cardiovascular morbidity
Kidney damage
Reduction of blood pressure
Left ventricular hypertrophy/Systolic and diastolic cardiac function
Glucose metabolism
Complications

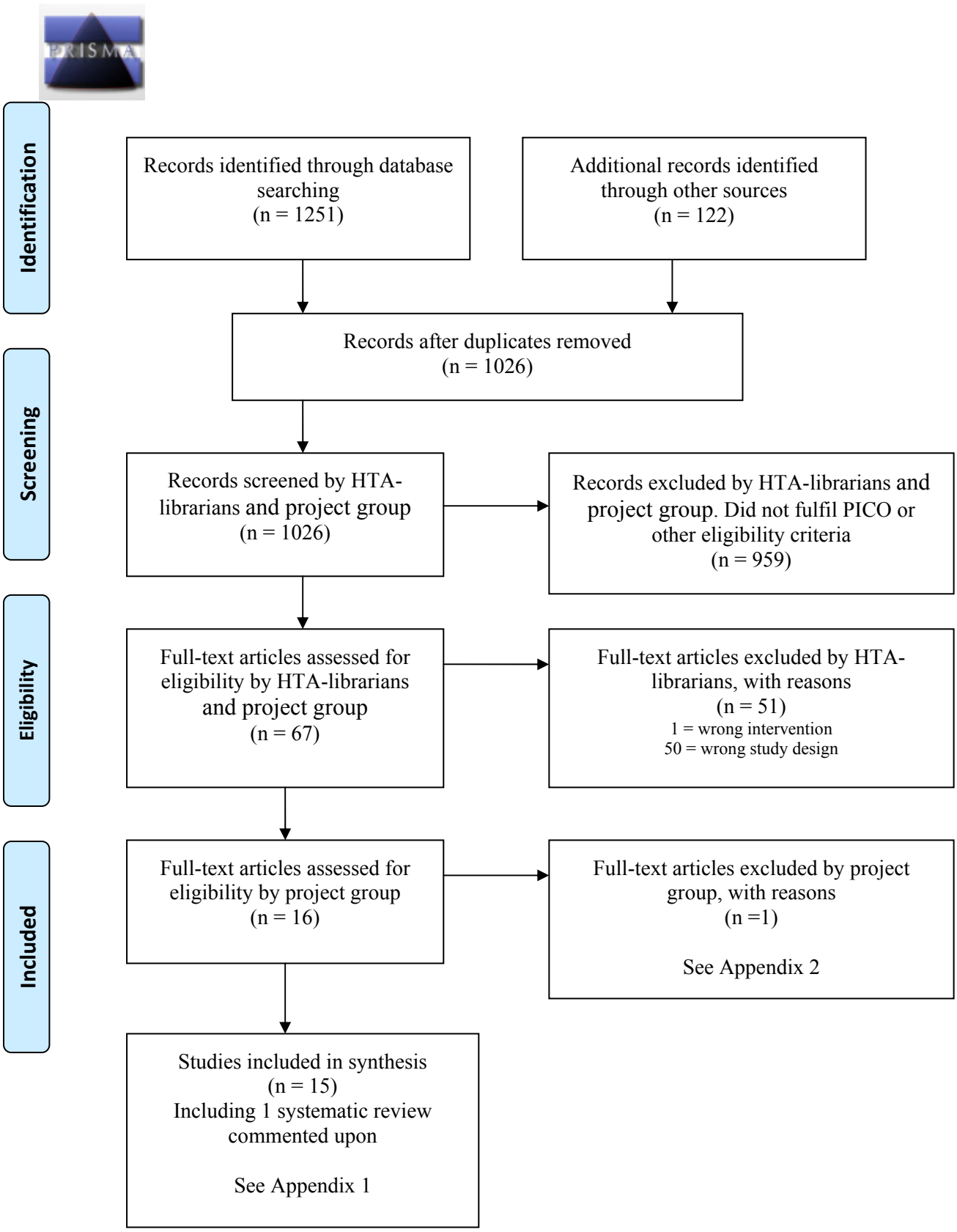
Eligibility criteria

Adult patients
Study design:
- Randomised control trials
- Systematic reviews
- Studies with some kind of control group
- Case series: ≥ 10 patients (for outcome: complications)
- No case reports or review articles

Language:
Danish, English, French, German, Norwegian, Swedish

Publication date: 2000-

Selection process – flow diagram



Search strategies

Database: PubMed
Date: 2012-04-17
No of results: 543
Search updated: 2012-08-31, **100 new results**

Search	Query	Items found
#9	**Search (#6) NOT #7 Limits: English, French, German, Danish, Norwegian, Swedish, Publication Date from 2000**	**543**
#8	Search (#6) NOT #7	1309
#7	Search (Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp])	1162530
#6	Search (#4) NOT #5	1375
#5	Search "animals"[MeSH Terms] NOT ("animals"[MeSH Terms] AND "humans"[MeSH Terms])	3662101
#4	Search ((#1) AND #2) AND #3	2680
#3	Search "hypertension"[MeSH Terms] OR "hypertension"[tiab] OR hypertensive[tiab]	334693
#2	Search "denervation"[MeSH Terms] OR "denervation"[tiab] OR "denervations"[tiab] OR sympathetic[tiab] OR "sympathectomy"[MeSH Terms] OR "sympathectomy"[tiab] OR "sympathectomies"[tiab] OR "innervation"[Subheading] OR "innervation"[tiab] OR innervations[tiab] OR "Catheter Ablation"[Mesh] OR Catheter Ablat*[tiab]	252015
#1	Search Renal[tiab] OR "kidney"[Mesh:NoExp] OR "kidney"[tiab]	646333

Database: EMBASE (OVID SP)
Date: 2012-04-17
No of results: 577

#	Searches	Results
1	kidney/ or kidney nerve/	219186
2	(kidney or renal).ti,ab,kw.	661664
3	1 or 2	744443
4	sympathectomy/	7364
5	sympathetic innervation/	2389
6	(denervation or denervations or sympathetic or sympathectomy or sympathectomies or innervation or innervations).ti,ab,kw.	117384
7	catheter ablation/	18018
8	(Catheter adj2 Ablat$).ti,ab,kw.	10088
9	4 or 5 or 6 or 7 or 8	139802
10	3 and 9	8904
11	kidney denervation/	703
12	kidney innervation/	309
13	10 or 11 or 12	9073
14	exp hypertension/	398081
15	(hypertension or hypertensive).ti,ab,kw.	362028
16	14 or 15	518442
17	13 and 16	3213
18	limit 17 to ((danish or english or french or german or norwegian or swedish) and yr="2000 -Current" and (article or "review"))	988

19	limit 18 to animals	380
20	limit 18 to animal studies	357
21	19 or 20	411
22	**18 not 21**	**577**

Database: The Cochrane Library (Wiley)
Date: 2012-04-17
No of results: 28
Cochrane reviews 0
Other reviews 0
Clinical trials 26
Technology assessments 2
Economic evaluations 0

ID	Search	Hits
#1	(renal OR kidney):ti,ab,kw	26928
#2	(Denervation OR denervations OR sympathetic OR sympathectomy OR sympathectomies OR innervation OR innervations OR Catheter NEAR/2 Ablat*):ti,ab,kw	5972
#3	(hypertension OR hypertensive):ti,ab,kw	25883
#4	(#1 AND #2 AND #3)	76
#5	**(#4), from 2000 to 2012**	**28**

Database: CRD
Date: 2012-04-17
No of results: 3
DARE 0
NHS EED 0
HTA 3

Line	Search	Hits
1	renal OR kidney	2277
2	Denervation OR denervations OR sympathetic OR sympathectomy OR sympathectomies OR innervation OR innervations	114
3	Catheter Ablation	242
4	#2 OR #3	353
5	hypertension OR hypertensive	1631
6	**#1 AND #4 AND #5**	**3**

The web-sites of **SBU, Kunnskapssenteret** and **Sundhedsstyrelsen** were visited
2012-04-17
Nothing relevant to the question at issue was found

Other HTA-databases 2012-04-18
Searches have also been made in NHS Evidence, CADTH(Canadian Agency for Drugs and Technologies in Health) and TRIP(Turning Research into Pratice as well as in the national HTA-databases in the Scandinavian countries; The Swedish Council on Health technology Assessment (SBU), Norwegian Knowledge Centre for the Health Services (NOKC), Danish Centre for Health technology Assessment (DACEHTA)
Nothing new was identified.

Reference lists
122 results

Reference lists

Included studies:

Brandt MC, Mahfoud F, Reda S, Schirmer SH, Erdmann E, Böhm M, et al. Renal sympathetic denervation reduces left ventricular hypertrophy and improves cardiac function in patients with resistant hypertension. J Am Coll Cardiol 2012; 59(10): 901-9.

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Mabin T, Sapoval M, Cabane V, Stemmett J, Lyer M. First experience with endovascular ultrasound renal denervation for the treatment of resistant hypertension. EuroIntervention. 2012; 8(1): 57-61.

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Prochnau D, Lucas N, Kuehnert H, Figulla HR, Surber R. Catheter-based renal denervation for drug-resistant hypertension by using a standard electrophysiology catheter. EuroIntervention. 2012: 7(9): 1077-80.

Symplicity HTN-1 Investigators. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. Hypertension. 2011; 57(5): 911-7.

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Ukena C, Mahfoud F, Kindermann I, Barth C, Lenski M, Kindermann M, et al. Cardiorespiratory response to exercise after renal sympathetic denervation in patients with resistant hypertension. J Am Coll Cardiol. 2011; 58(11): 1176-82.

Ukena C, Mahfoud F, Spies A, Kindermann I, Linz D, Cremers B, et al. Effects of renal sympathetic denervation on heart rate and atrioventricular conduction in patients with resistant hypertension. Int J Cardiol. 2012a Aug 20. [Epub ahead of print] 10.1016/j.ijcard.2012.07.027 [doi]

Witkowski A, Prejbisz A, Florczak E, Kadziela J, Sliwinski P, Bielen P, et al. Effects of renal sympathetic denervation on blood pressure, sleep apnea course, and glycemic control in patients with resistant hypertension and sleep apnea. Hypertension. 2011: 58(4): 559-65.

Voskuil M, Verloop WL, Blankestijn PJ, Agostini P, Stella PR, Doevendans PA. Percutaneous renal denervation for the treatment of resistant essential hypertension: the first Dutch experience. Neth Heart J. 2011; 19(7-8): 319-23.

Zuern CS, Rizas KD, Eick C, Stoleriu C, Bunk L, Barthel P, et al. Effects of Renal Sympathetic Denervation on 24-hour Blood Pressure Variability. Front Physiol. 2012; 3: 134. Epub 2012 May 10. 10.3389/fphys.2012.00134 [doi]

Systematic reviews, no appraisal done, only commented on:

Wegmann M, Thomas S, Deuber HJ. Perkutane renale denervation bei therapieresistenter hypertonie. [Renal denervation in patients with essential hypertonia] Vienna: Ludwig Boltzmann Institut fuer Health Technology Assessment (LBI-HTA). Decision Support Document No.45. 2011.

Excluded studies:

Ukena C, Bauer A, Mahfoud F, Schreieck J, Neuberger HR, Eick C, et al. Renal sympathetic denervation for treatment of electrical storm: first-in-man experience. Clin Res Cardiol. 2012b; 101(1):63-7.

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Appendix 4.
Summary of Findings: Renal sympathetic denervation in patients with therapy-resistant hypertension

Outcome variable Number of studies	Design	Study limitations	Consistency	Directness	Precision	Publication bias	Magnitude of effect	Absolute effect	Quality of evidence GRADE
Kidney involvement									
1	1 non-randomised controlled study	Some limitations[1]	No serious inconsistency	No uncertainty	Uncertain precision [2]	Unikely	Not relevant		⊕◯◯◯ Very low
Blood pressure									
5	2 RCT 3 non-randomised controlled studies	Some limitations[1]	No serious inconsistency	Some uncertainty[3]	Uncertain precision[4]	Unlikely	Not relevant		⊕⊕◯◯ Low
Left ventricular hypertrophy									
1	1 non-randomised controlled study	No serious limitations	No serious inconsistency	No uncertainty	Serious imprecision[5]	Unlikely	Large effect		⊕⊕◯◯ Low
Glucose metabolism									
1	1 non-randomised controlled study	Some limitations[1]	No serious inconsistency	No uncertainty	Serious imprecision[5]	Unlikely	Not relevant		⊕◯◯◯ Very low

Footnotes:
[1] Unblinded assessment.
[2] Few patients in the control group.
[3] Short time of follow-up.
[4] Some patients are included in more than one of the publications.
[5] Only one study of rather small sample size.

Appendix 5.

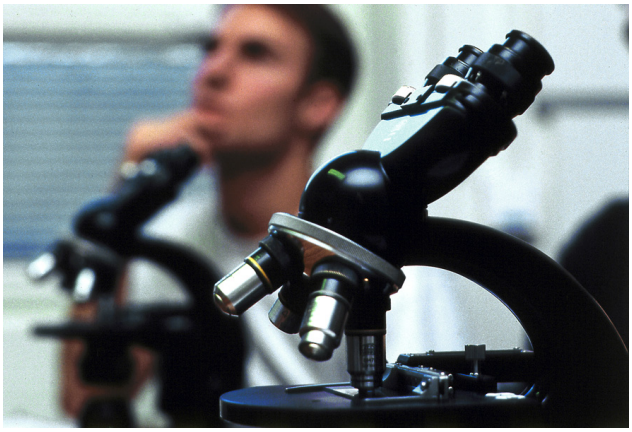
ETHICAL ANALYSIS OF RENAL SYMPATHETIC DENERVATION

Question	Answer/ comment
1. From the patient's perspective, how does renal denervation affect the patient's quality of life and life expectancy?	It is currently not known if renal denervation positively or negatively affects life expectancy. However, an extrapolation based on the observed short-term blood pressure reduction indicates that it has a great potential to increase survival.
2. How severe is the patient's need that the renal denervation must meet?	A patient with uncontrolled high blood pressure despite combination drug therapy are at high risk of stroke, myocardial infarction and cardiovascular death.
3. Does renal denervation have any influence on how others view the patient (concerning humanity and human dignity), or on how the patient views himself or herself (concerning humanity and human dignity)?	No.
4. Can renal denervation affect the patient's ability and possibility to be independent?	Yes, in a positive way. By reducing the risk of cerebrovascular damage it can potentially improve cognitive functions following long-term improvement in blood pressure, and prevent the development of conditions that may lead to dependence on other people..
5. If implemented, does renal denervation require any special steps to not compromise the patient's autonomy?	If the patient is fully informed of the procedure prior to the decision and acceptance to undergo treatment his/her autonomy will not be compromised.
6. How does renal denervation affect the patient's physical, moral and personal integrity?	There is no risk of any intrusion of the personal integrity if normally accepted administration and treatment procedures in the health care system are followed.
7. Is renal denervation cost-effective?	Yes. According to one single study.
8. How does renal denervation affect resources?	There is a definite risk that a large increase in the number of procedures will compete with other invasive procedures, such as coronary or renal angiographies, and with the overall capacity of catheterisation procedures. Furthermore, the use of other necessary investigations (ultrasound, computed tomography and magnetic resonance imaging) will also increase and require more resources. On the contrary, an improved blood pressure control has a great potential to reduce the cost and need of human resources related to treatment and care of these patients.
9. Is renal denervation in conflict with professional values?	No.

10. Does renal denervation change the role of the professional in relation to the patient?	No.
11. Does renal denervation affect, or does it put any new demands on, a third party?	Most probably not.
12. Is there any legislation of relevance with regard to renal denervation?	No.
13. Is there any risk of conflict between the procedure of renal denervation and values of the society, or values of different groups?	No.
14. Is there a risk that an introduction of renal denervation will cause a conflict with particular interests?	Since this technology is an alternative when previous non-pharmacological and pharmacological interventions have failed to achieve an adequate treatment effect, the use of this treatment modality should not pose any problem to other commercial or scientific actors.
15. Can an introduction renal denervation influence the trust of the health care system?	Most probably not.
CONCLUSIONS	There are no major ethical reasons to oppose the use of this new technology. It is important that the effects during longer term, i.e. over many years, are studied in follow-up observational studies.

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

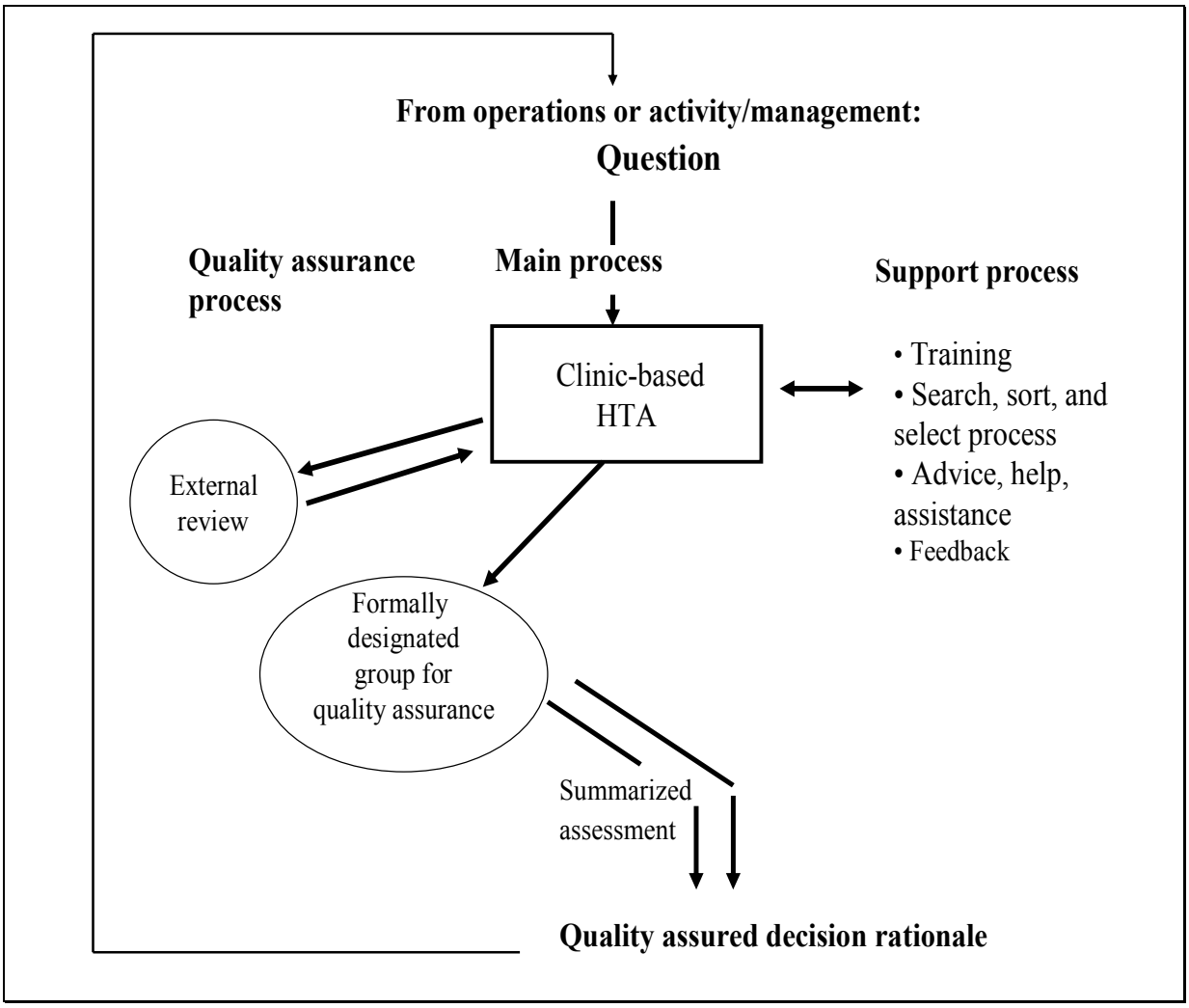
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= (GRADE⊕⊕⊕⊕)
Moderate quality of evidence	= (GRADE ⊕⊕⊕O)
Low quality of evidence	= (GRADE ⊕⊕OO)
Very low quality of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh, Professor, MD.
Head of HTA-centrum


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

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