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Hemodialysis twice versus three times a week in patients with residual kidney function: quality of life, cardiovascular outcomes and mortality

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Hemodialysis twice versus three times a week in patients with residual kidney function: quality of life, cardiovascular outcomes and mortality

[Hemodialys två eller tre gånger per vecka: livskvalitet, kardiovaskulära utfall och mortalitet]

Saeed A^{1*}, Björkander E², Carlström J³, Guron G¹, Kashioulis P¹, Kindblom JM⁴, Lönnbro Widgren J¹, Svanberg T², Strandell A⁴

¹Department of Nephrology, Sahlgrenska University Hospital, Göteborg, Sweden

²Medical Library, Sahlgrenska University Hospital, Göteborg, Sweden

³Medical advisor; Regional Executive Officer's Staff of Region Västra Götaland, Sweden

⁴HTA-centrum of Region Västra Götaland, Sweden

*Corresponding author

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Abbreviations

Ccr	= creatinine clearance (corresponding to residual kidney function)
CKD	= Chronic kidney disease
ESRD	= End stage renal disease
GFR	= Glomerular filtration rate
HD	= Hemodialysis
HRQL	= Health related quality of life
Kt/V	= Urea removal during dialysis, a measure of dialysis dose
PD	= Peritoneal dialysis
RKF	= Residual kidney function
SEK	= Swedish krona
VGR	= Region Västra Götaland

1. Summary of the Health Technology Assessment

Background

Chronic kidney disease refers to an irreversible, and usually progressive, deterioration of kidney function caused by a wide variety of diseases. A large proportion of patients with chronic kidney disease develop end stage renal disease (ESRD) with the need for dialysis or kidney transplantation. Patients on maintenance dialysis have a severalfold increase in mortality, and a lower quality of life compared to the general population. The delivered dose of dialysis is determined by measuring the amount of urea that is removed during dialysis and it is expressed as Kt/V. A typical hemodialysis (HD) prescription of three times per week for four hours at a time usually results in a standardized Kt/V above 2. This is considered an adequate weekly dose of dialysis in patients without residual kidney function and is used as a marker of good dialysis care. However, a majority of patients starting HD do have a residual kidney function and may be considered for twice-weekly treatment.

Objective

To assess whether twice-weekly HD is associated with a higher risk of mortality or cardiovascular morbidity, or compromises the health related quality of life (HRQL) as compared to standard thrice-weekly HD in patients with residual kidney function.

Main results

The systematic literature search identified four non-randomised cohort studies with controls that met the inclusion criteria. Each study reports only one of the pre-specified outcomes. All included studies were limited by differences in vital demographic and comorbidity characteristics between the studied groups.

Mortality was numerically lower in patients with twice-weekly HD as compared with those with thrice-weekly HD (RR=0.79, p=0.06). Thrice-weekly HD was associated with a significantly higher risk ratio of cardiovascular events than twice-weekly HD (p=0.034). Quality of life data showed no significant difference for patients dialysing twice versus thrice weekly. The decline in residual kidney function was slower in patients dialysing twice versus thrice weekly. Selection bias may explain the reported positive effects on several outcomes.

Complications were reported in two prospective cohort studies. In both studies, intradialytic hypotension was significantly less frequent in the twice-weekly group as compared with the thrice-weekly group. Fewer patients dialysing twice-weekly were hospitalized due to infection compared to thrice-weekly HD (31.8% vs. 62.7% respectively, p=0.012). There was no difference between the groups in the incidence of arterio-venous fistula dysfunction.

Concluding remarks

There is no data demonstrating that twice-weekly HD compromises HRQL or is associated with an increased risk of mortality or cardiovascular events in selected patients with residual kidney function, compared with thrice-weekly HD. The quality of evidence was very low for all studied outcomes (GRADE ⊕○○○). Randomised controlled studies or observational studies of high quality are needed.

2. Svensk sammanfattning – Swedish summary

Kronisk njursjukdom leder ofta till en irreversibel och progressiv försämring av njurfunktionen. En stor andel patienter med kronisk njursjukdom utvecklar terminal njursvikt och behov av dialys (hemodialys (HD) eller peritonealdialys) eller njurtransplantation. Patienter i dialys har en betydligt högre dödlighet och en påtagligt lägre livskvalitet jämfört med befolkningen i övrigt. Patienter som behandlas med HD får vanligen en dialysbehandling under fyra timmar tre gånger i veckan. Med hjälp av bestämning av urea i serum före och efter dialys kan man matematiskt beräkna avlägsnandet av urea under behandlingen, vilket betecknas Kt/V och används som ett mått på dialysdos. En dialysordination på 3 x 4 timmar/vecka resulterar vanligen i ett standardiserat Kt/V över 2,0. Detta anses vara en adekvat dialysdos för patienter med helt upphävd njurfunktion. På de allra flesta dialysenheter tar man inte hänsyn till patientens kvarvarande njurfunktion, den så kallade restfunktionen, då dialysordinationen bestäms. En majoritet av patienter som startar HD har dock en kvarvarande restfunktion och skulle därför kunna uppnå en fullgod blodrening, motsvarande ett standardiserat Kt/V över 2,0 med HD-behandling två gånger per vecka om restfunktionen togs i beaktande.

Frågeställning

Innebär behandling med hemodialys två gånger i veckan jämfört med tre gånger i veckan en försämrad livskvalitet eller ökad risk för dödlighet och kardiovaskulära händelser hos patienter med bevarad restfunktion?

Resultat

Litteratursökningen identifierade fyra icke-randomiserade, kohort-studier som uppfyllde inklusionskriterierna. Varje studie redovisade ett av de pre-specifierade utfallen. Samtliga studier begränsades av skillnader i demografiska förhållanden och samtidigt förekommande sjuklighet mellan studiegrupperna.

Mortalitet var numeriskt lägre hos patienter med två dialyser per vecka jämfört med tre ($RR=0,79$, $p=0,06$). Incidensen kardiovaskulära händelser var statistiskt signifikant lägre hos patienter med HD två gånger per vecka jämfört med tre ($p=0,034$). Avseende livskvalitet observerades inga signifikanta skillnader mellan patienter med olika dialysfrekvens. Njurfunktionen försämrades långsammare hos patienter med HD två gånger per vecka jämfört med tre.

Det är inte möjligt att avgöra om de positiva effekter som redovisas för de olika utfallen till fördel för HD två gånger per vecka förklaras av olikheten i dialysregim eller om de är resultaten av systemfel rörande patienturvalet (patienter med HD två gånger per vecka skulle kunna vara "friskare" än patienter som behandlats tre gånger per vecka).

Komplikationer rapporterades i två prospektiva kohortstudier. Blodtrycksfall under dialysbehandlingen inträffade signifikant mer sällan i gruppen som fick HD två gånger per vecka. I en prospektiv studie behövde färre patienter bland dem som fick HD två gånger per vecka läggas in på sjukhus på grund av infektion jämfört med patienterna med HD tre gånger per vecka (32% vs. 63%; $p=0,012$).

En etisk aspekt till fördel för den lägre dialysfrekvensen kan vara en förbättrad livskvalitet och stärkt personlig integritet då patienten tillbringar mindre tid på dialysenheten.

Ekonomiskt innebär den lägre dialysdosen en minskad årskostnad på ungefär 156 000 kronor per patient.

Sammanfattande bedömning

För patienter med terminal njursvikt men med en viss bevarad restfunktion finns det inga data som talar för att HD två gånger per vecka försämrar livskvaliteten eller är associerat med en ökad mortalitet eller risk för kardiovaskulära händelser. Kvaliteten på alla inkluderade studier var låg. Otillräckligt vetenskapligt underlag (GRADE ⊕○○○)

Summary of the Health Technology Assessment (1 & 2) from The Regional Health Technology Assessment Centre (HTA-centrum)

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 English summary is a concise summary of similar outline as the summaries in the Cochrane systematic reviews. The Swedish summary summarises the question at issue, results and quality of evidence regarding efficacy and risks, and economical and ethical aspects of the particular health technology that has been assessed in the report, and is ended with a final statement/concluding remark from HTA-centrum.

Christina Bergh, Professor, MD

Head of HTA-centrum of Region Västra Götaland, Sweden, 2014-12-17

Christina Bergh

MD, Professor

Elisabeth Hansson-Olofsson

PhD, Senior lecturer

Magnus Hakeberg

OD, Professor

Lennart Jivegård

MD, Senior university lecturer

Jenny Kindblom

MD, Associate professor

Anders Larsson

MD, PhD

Christian Rylander

MD, PhD

Ola Samuelsson

MD, Associate professor

Ninni Sernert

Associate professor

Henrik Sjövall

MD, Professor

Petteri Sjögren

DDS, PhD

Maria Skogby

RN, PhD

Annika Strandell

MD, Associate professor

Therese Svanberg

HTA-librarian

Kjell-Arne Ung

MD, Associate professor

Summary of Findings - table

Outcomes	Study design Number of studies Total number of patients	Relative effect (95%CI) Twice vs. thrice weekly	Absolute effect Twice vs. thrice weekly	Quality of evidence GRADE
Mortality	1 retrospective cohort study n=4888	RR=0.79, P=0.06	Not presented	⊕○○○ Very low ¹
Cardiovascular events	1 prospective cohort study n=143	aHR 2.05, 95% CI 1.14–4.44	8/103 (7.8%) vs 9/40 (23%) p=0.034	⊕○○○ Very low ²
Health related quality of life	1 cross-sectional study n=1286	See Appendix 4.3	SF12 Physical component 36.7(9.5) vs 36.1(9.1) SF12 Mental component 43.4(9.0) vs 43.8(9.5)	⊕○○○ Very low ³
Residual kidney function	1 cohort study n=74		-0.057±0.103 vs. 0.355±0.266 p=0.035 Change in Ccr (ml/min)/ month	⊕○○○ Very low ⁴

RR = risk ratio, aHR = adjusted hazard ratio, SF = short form (questionnaire on quality of life), Ccr = creatinine clearance (corresponding to residual kidney function)

¹ Serious indirectness; the study is twenty years old and includes populations of mixed ethnicities, shorter duration of dialysis than used in Sweden today. No absolute values or confidence intervals presented.

² Very serious study limitations due to large baseline differences between groups. Residual renal function defined only by urine output. Very serious indirectness; one centre study from China, patients allocated according to different criteria, unclear recruitment. Very serious imprecision; few events in a small study.

³ Very serious study limitations due to large baseline differences between groups. Residual renal function defined only by urine output. Historical controls. Very serious indirectness; treatment given according to Chinese standards.

⁴ Very serious study limitations due to large baseline differences between groups. Very serious indirectness; treatment given according to Taiwanese standards, prevalent patients included. Serious imprecision; large standard deviations for residual renal function.

Quality of evidence

High quality

⊕⊕⊕⊕

We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality

⊕⊕⊕○

We are moderately confident in the effect estimate:

The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality

⊕⊕○○

Confidence in the effect estimate is limited:

The true effect may be substantially different from the estimate of the effect.

Very low quality

⊕○○○

We have very little confidence in the effect estimate:

The true effect is likely to be substantially different from the estimate of effect

3. Participants in the project

Who posed the question?

Gert Jensen, MD, PhD, Head of Department of Nephrology, Sahlgrenska University Hospital, Göteborg, Sweden

Participants in the HTA group?

Aso Saeed, MD, PhD, Senior consultant

Gregor Guron Associate Professor, MD, Senior consultant

Pavlos Kashioulis, MD

Jennie Lönnbro Widgren, MD, Senior consultant

-all from the Department of Nephrology, Sahlgrenska University Hospital, Göteborg, Sweden

Jan Carlström, MD, Medical advisor; Regional Executive Officer's Staff of Region Västra

Götaland, Sweden

From the HTA-centrum Region Västra Götaland

Annika Strandell MD, Associate Professor

Jenny Kindblom, MD, Associate Professor

Therese Svanberg, HTA-librarian

-all from HTA-centrum, Region Västra Götaland Sahlgrenska University Hospital, Göteborg, Sweden

Emil Björkander, Librarian, Medical library, Sahlgrenska University Hospital

External reviewer

Michael Breimer, Professor, MD, Senior consultant, Department of Surgery, Sahlgrenska University Hospital/Östra, Göteborg, Sweden

Are there any conflicts of interest for the proposer or any of the participants in the work group?

No

Project time

HTA was accomplished during the period of 2014-05-19 – 2014-12-17

Last search updated in July 2014.

4. Disease/disorder of interest

Chronic kidney disease

Chronic kidney disease (CKD) refers to an irreversible and usually progressive deterioration of kidney function caused by a wide variety of diseases. In clinical practice kidney function is assessed by the estimation of glomerular filtration rate (GFR). As GFR declines, a wide range of complications develops including disorders in water and electrolyte balance, metabolic acidosis, anemia, disturbances in mineral metabolism and eventually systemic manifestations due to accumulation of metabolic waste products (uremia). The management of these complications includes dietary modifications and different medications. However, as GFR falls below 10 ml/min/1.73m², renal replacement therapy with dialysis or renal transplantation is usually required.

There are two main methods of dialysis; hemodialysis (HD) and peritoneal dialysis (PD). Although dialysis is a life-sustaining therapy, patients on maintenance dialysis have a severalfold increase in mortality and significantly lower quality of life (HRQL) compared to the general population (Fukuhara et al. 2003; Collins et al. 2013).

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

Prevalence and incidence of end-stage renal disease

Chronic kidney disease is common (Hallan et al. 2006). It is associated with a poor prognosis regardless of its aetiology. A large proportion of CKD patients develops end-stage renal disease (ESRD) with a need for dialysis or kidney transplantation. According to the Swedish renal registry report (2013) there were 3,812 patients on dialysis [3,026 patients (79%) treated with HD and 786 patients (21%) with PD].

The average annual incidence of ESRD requiring dialysis treatment in Sweden is about 1,100 patients (63% starting HD and 37% PD). The corresponding annual incidence in the Region Västra Götaland of Sweden (VGR) is approximately 180 patients (approximately 2/3 of these patients start HD). The annual mortality rate in dialysis patients is around 20% in Sweden.

Present treatment of chronic kidney disease

The adequacy of dialysis is mainly determined by calculation of delivered dose of dialysis by the “Kt/V formula”. Briefly, blood urea is used as an indicator of metabolic waste products in patients with ESRD. The efficacy of dialysis in removing these waste products is estimated by the Kt/V-formula that calculates the amount of removed urea during a dialysis session. A higher Kt/V value per week reflects a higher dialysis efficacy. This is achieved mainly by longer dialysis sessions or more frequent dialysis. In patients without residual kidney function (RKF), standardized (std) Kt/V > 2.0 is used as a marker of good dialysis care in most western countries. A typical HD prescription of three times per week for four-five hours at a time (thrice weekly HD) usually results in a std Kt/V > 2.0. However, in VGR a dialysis prescription of two times per week for four-five hours at a time (twice-weekly HD) is currently used for some patients with residual kidney function (RKF > 2 ml/min/1.73m²).

Number of patients per year who undergo hemodialysis

Approximately 120 patients start HD annually in VGR. The vast majority of these patients start with thrice weekly HD. However, many of these patients have a RKF >2 ml/min/1.73m².

The normal pathway of a patient through the health care system

Patients with advanced chronic kidney disease are usually managed at nephrology clinics. Preparations for dialysis are made when kidney function declines. Although PD is the preferred initial dialysis treatment, around two thirds of patients with ESRD requiring dialysis are treated with HD. The timing of dialysis initiation is debated. Currently, dialysis is usually started as GFR falls below 10 ml/min/1.73m² and when the patient's state of health deteriorates as a consequence of uremia.

Actual wait time in days for medical assessment /treatment

There is no wait time for dialysis treatment since it is a life-sustaining therapy.

5. Present Health Technology

Name/description of the health technology at issue

Hemodialysis twice-weekly in patients with a RKF > 2 ml/min/1.73m².

The work group's understanding of the potential value of the health technology

A number of studies have shown that the RKF is an important predictor of survival in both PD and HD patients (Bargman et al. 2001 ; Shemin et al. 2001 ; Termorshuizen et al. 2004). In patients with PD, dialysis adequacy is based on both delivered dialysis dose and the RKF. However, in HD patients a std Kt/V of > 2.0 is considered, based largely on opinions (Tattersall et al. 2007), to be the adequate dose of dialysis without taking RKF into account. As a consequence HD thrice weekly is the standard prescription even in patients with RKF. In accordance with this, healthcare departments in VGR, and Sweden, use a std Kt/V > 2.0 as a quality indicator regardless of the patient's RKF.

Termorshuizen et al. (2004) showed that a low value of delivered dialysis dose (Kt/V) was associated with a high mortality rate only in anuric patients. In addition, there is no evidence that a dialysis dose above the current recommendation reduces patient morbidity or mortality (Eknoyan et al. 2002). Thus, the exclusion of RKF when calculating the required HD dose may lead to unnecessary prescription of thrice weekly dialysis in patients with significant RKF. This may in turn compromise patient HRQL as more time is spent on dialysis. Furthermore, having twice instead of thrice weekly HD results in less frequent cannulations of arteriovenous fistula, which in turn may prolong its longevity. In addition, twice-weekly HD may lead to a better preservation of RKF. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative Adequacy Guidelines, New York (2006) suggests that in patients with moderate degrees of RKF (urea clearance ≥ 2 ml/min/1.73 m²), the minimum dialysis dose (Kt/V) can be reduced (KDOQI, 2006).

We hypothesise that HD twice-weekly provides an adequate dialysis dose in patients with RKF >2 ml/min/1.73m² and that this treatment does not increase patient mortality, morbidity or compromise HRQL as compared to standard thrice-weekly HD. Importantly, RKF should be monitored regularly and considered when evaluating dialysis adequacy in these patients.

The central question for the current HTA project in one sentence

Does twice-weekly hemodialysis increase risk for mortality, cardiovascular morbidity or compromise quality of life as compared with standard thrice-weekly hemodialysis in patients with residual kidney function?

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

P= Adult patients who require regular hemodialysis and have a significant level of residual kidney function (reported as indices of glomerular filtration rate or daily urine volume)

I= Hemodialysis twice-weekly

C= Hemodialysis thrice weekly

O=

- Critical for decision making
- Mortality
- Cardiovascular events (myocardial infarction, stroke, coronary revascularization)
- Hospitalization with a need for intensive care

- Important but not critical for decision making
- Hospitalization (without a need for intensive care)
- Unplanned dialysis
- Quality of life
- Preservation of residual kidney function
- Complications

6. Review of Quality of Evidence

Search strategy, study selection and references (Appendix 1)

During July 2014 two librarians (TS, EB) performed systematic searches in PubMed, Embase, the Cochrane Library, and a number of HTA databases. Reference lists of relevant articles were also scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1. The librarians conducted the literature searches, selected the studies and independently of one another assessed the obtained abstracts and made a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved in consensus. The remaining articles were sent to the other participants of the HTA project group, who read the articles independently of one another, and then decided in consensus which articles should be included in the final assessment.

The literature search identified a total of 407 articles (after removal of duplicates). The librarians excluded 371 articles after reading their abstracts. Another nine articles were excluded by the librarians after reading the articles in full text.

The remaining 27 articles were sent to the participants of the project group, and four were finally included in the report. The included studies are presented in Appendix 2. All of the four articles are non-randomised controlled studies and they have been critically appraised using checklists from SBU (Swedish Council on Health Technology Assessment) designed for cohort studies. Excluded studies and reasons for exclusions are presented in Appendix 3. The quality of evidence was rated according to the Grade system.

Present knowledge of hemodialysis twice vs. thrice-weekly

The systematic literature search identified four articles; two prospective cohort studies, one retrospective cohort study and one registry-based cross sectional study (Appendix 2).

Outcomes, critical for decision-making

Mortality (Appendix 4.1)

Mortality was reported in one retrospective cohort study. The study was large but limited by the fact that estimates of RKF were made only at the initiation of dialysis therapy. Thus, loss of RKF during the first year of dialysis could not be evaluated. Nevertheless, after adjustment for vital demographic and comorbidity characteristics, the mortality rate was numerically lower in patients with twice-weekly HD as compared to those with thrice-weekly HD (RR=0.79, p=0.06).

Conclusion

There is no data demonstrating that twice-weekly HD is associated with an increased risk of mortality in selected patients with residual kidney function, compared with thrice-weekly HD. Very low quality of evidence (GRADE ⊕○○○)

Cardiovascular events (Appendix 4.2)

The incidence of cardiovascular (CV) events including myocardial infarction, heart failure, stroke and others (not specified) was reported in one prospective cohort study. Patients with thrice-weekly HD had significantly higher cumulative hazard ratio of CV events (p=0.034) than those with twice-weekly HD. The study was limited by baseline differences in demographic and comorbidity characteristics between the groups and no adjustments for these potentially important confounding factors were made. Adjusted hazard ratios are presented in the analyses in which intradialytic hypotension was included as a CV event (Appendix 4.2).

Conclusion

There is no data demonstrating that twice-weekly HD is associated with an increased risk of cardiovascular events in selected patients with residual kidney function, compared with thrice-weekly HD. Very low quality of evidence (GRADE ⊕○○○)

Outcomes, important for decision-making

Hospitalisation

The outcome was not studied.

Quality of life (HRQL) (Appendix 4.3)

Quality of life data were analysed in one registry-based cross-sectional study. A validated questionnaire, Kidney Disease Quality of Life-Short Form (Hays et al. 1997), was used. At baseline, 47% of patients with twice-weekly HD had no significant urine output (< 200 ml/day). Nevertheless, there was no statistically significant difference in reported HRQL for patients dialysing twice versus thrice-weekly. The study was limited by major differences between the groups for vital demographic and comorbidity characteristics.

Conclusion

There is no data demonstrating that twice-weekly HD compromises HRQL in selected patients with residual kidney function, compared with thrice-weekly HD. Very low quality of evidence (GRADE ⊕○○○)

Preservation of residual kidney function (RKF) (Appendix 4.4)

The effect of twice-weekly HD on preservation of RKF was analysed in one prospective single centre cohort study. Patients dialysing twice-weekly had significantly slower decline in RKF during a mean follow up of 18 months as compared with patients with thrice-weekly HD. However, the study had major limitations, including large baseline differences and serious imprecision.

Conclusion

There is no data demonstrating that twice-weekly HD leads to an accelerated decline in renal function in selected patients with residual kidney function, compared with thrice-weekly HD. In contrast, data suggest a slower decline in RKF in the twice-weekly HD group.

Very low quality of evidence (GRADE ⊕○○○)

Complications (Appendix 4.5)

Complications were reported in two prospective cohort studies (n=217).

Intradialytic hypotension (IDH) incidence was significantly lower in the twice-weekly group as compared to the thrice-weekly group in both studies.

In one prospective single centre cohort study (n=74) fewer patients dialysing twice-weekly compared to thrice-weekly HD were hospitalized due to any infection (31.8% vs. 62.7% respectively, p=0.012). There was no difference between the groups regarding the incidence of arterio-venous fistula dysfunction.

Conclusion

There is no data demonstrating that twice-weekly HD leads to more complications in selected patients with residual kidney function, compared with thrice-weekly HD. In contrast, data suggest fewer dialysis related complications in the twice-weekly HD group.

Ongoing research?

A search in www.clinicaltrials.gov (2014-09-24) using the search terms (renal dialysis OR hemodialysis OR hemodialyses OR haemodialysis OR haemodialyses) AND (twice-weekly OR bi-weekly OR biweekly) identified seventy-two trials. None of these trials included hemodialysis frequency twice-weekly.

Which medical societies or health authorities recommend the new health technology?

Twice-weekly HD is not recommended by any health authorities or medical society in Sweden.

7. Ethical consequences

(Appendix 5)

Ethical consequences

Given that mortality and complication rates are not increased during HD twice-weekly compared with three times a week, the patients HRQL might increase. Patients will save one day per week for other activities than in-hospital HD treatment. A reduced dialysis frequency may also increase the patient's independence and personal integrity. In a broader view, the reduced cost of twice-weekly HD would make it possible to spend more money on other healthcare activities where needed.

8. Organisation

When can twice-weekly hemodialysis be put into practice?

The technology is available at present and is already put into practice in some dialysis units in VGR.

Is twice-weekly hemodialysis used in other hospitals in Region Västra Götaland of Sweden?

Yes, it is used in a minority of patients in VGR and in the rest of the country. However, the indications for the use of twice-weekly HD are yet to be defined. There are large regional differences in the use of the technology.

According to the work group, will there be any consequences of the twice-weekly hemodialysis for personnel?

No.

Will there be any consequences for other clinics or supporting functions at the hospital or in the whole Region Västra Götaland of Sweden?

No, there will not be any consequences for clinics outside of the hemodialysis units.

9. Economy aspects

Present costs of hemodialysis

The total cost for one hemodialysis (HD) treatment in the hospital is approximately 3,000 SEK. Based on a standard treatment of 3 HD sessions per week this gives an annual cost per patient of 468,000 SEK (3,000 x 3 x 52).

Expected costs of twice-weekly hemodialysis?

Based on a treatment frequency of 2 HD sessions per week this gives an annual cost per patient of 312,000 SEK (3,000 x 2 x 52).

Total change of cost

A reduction in HD frequency from three to two sessions per week in incident HD patients with RKF will reduce the annual cost with 156, 000 SEK per patient.

Approximately 120 patients start HD every year in VGR. If 50 % of these patients (i.e. 60 patients) during the first year were treated with two, instead of three HD sessions per week, this would lead to a cost reduction with 9,360,000 SEK (156,000 x 60).

Can twice-weekly hemodialysis be adopted and used within the present budget (clinic budget/hospital budget)?

Yes. Budget costs will be reduced.

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

No.

10. Unanswered questions

Important gaps in scientific knowledge?

The main conclusion of this systematic review is that there is a lack of evidence that twice-weekly hemodialysis is inferior to thrice-weekly. Further studies addressing this issue are needed.

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

Yes, there is an interest in performing studies.

A well-designed observational study should be considered. Such an observational study could be performed based on the data in the Swedish renal registry (SNR). However, SNR presently does not include measurements of RKF.

Ideally, a randomised controlled trial should be performed on incident hemodialysis patients with a residual GFR > 2 ml/min/1.73m², randomised to either two or three HD sessions per week with mortality and/or cardiovascular events as well as HRQL as endpoints.

Question at issue:

Does twice-weekly hemodialysis increase risk for mortality, cardiovascular morbidity or compromise quality of life as compared with standard thrice-weekly hemodialysis in patients with residual kidney function?

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

P	Adult patients who require regular hemodialysis and have a significant level of residual kidney function (reported as indices of glomerular filtration rate or daily urine volume)
I	Hemodialysis twice weekly
C	Hemodialysis thrice weekly
O	<p><u>Critical for decision making</u> Mortality Cardiovascular events (myocardial infarction, stroke, coronary revascularization) Hospitalization with a need for intensive care</p> <p><u>Important but not critical for decision making</u> Hospitalization (without the need for intensive care) Unplanned dialysis Quality of life Preservation of residual kidney function Complications</p>

Eligibility criteria**Study design:**

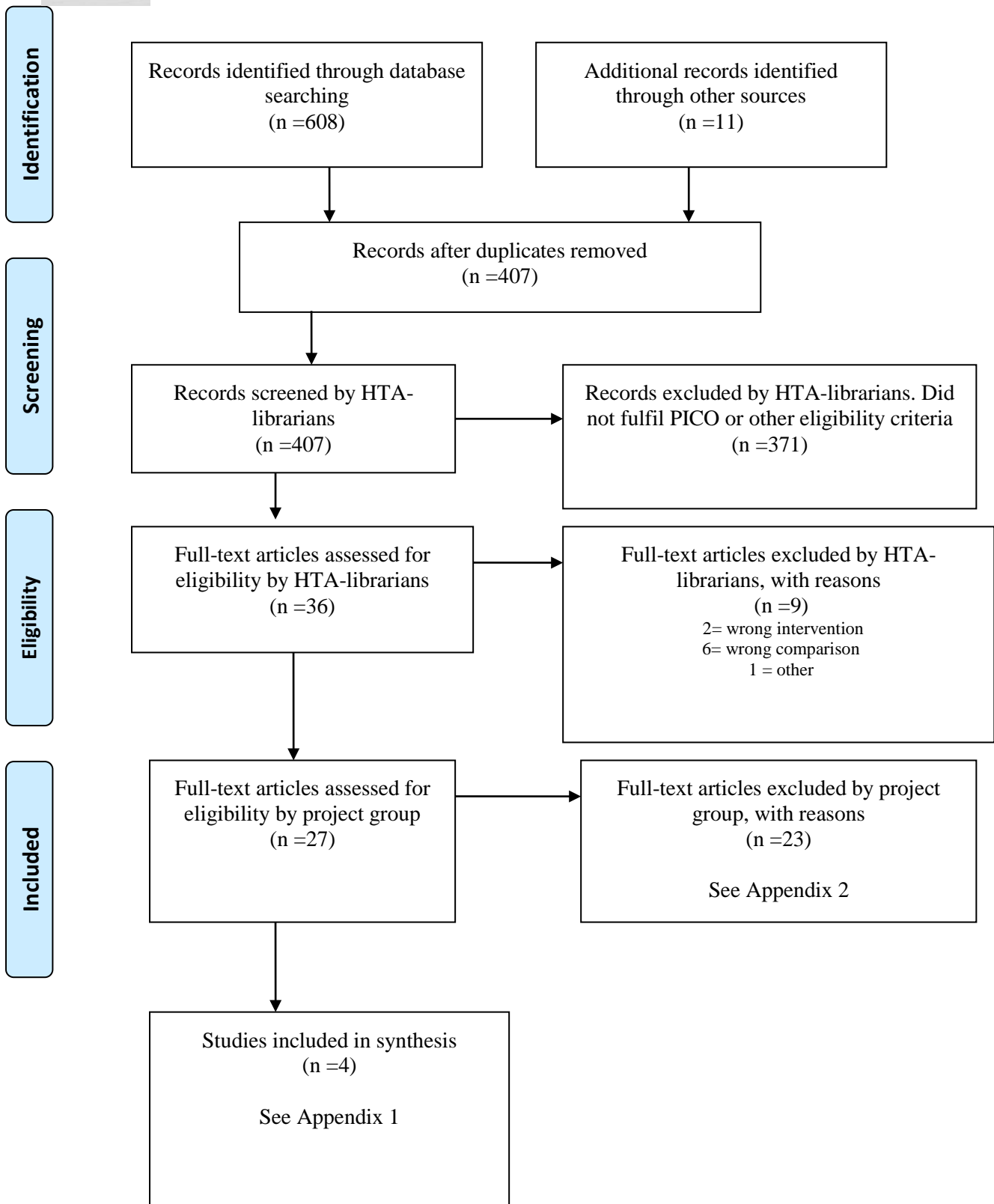
Systematic reviews
Randomized controlled trials
Non-randomized controlled studies
Case series
No case reports or review articles

Language:

English, German, Swedish, Norwegian, Danish

Publication date: -

Selection process – flow diagram



Search strategies

Database: PubMed

Date: 2014-07-02

No of results: 352

Search	Query	Result
#15	Select 352 document(s)	352
#14	Search #11 NOT #12 Filters: Danish; English; German; Norwegian; Swedish	352
#13	Search #11 NOT #12	394
#12	Search ((child[mh]) NOT (child[mh] AND adult[mh]))	954164
#11	Search #7 NOT #10	410
#10	Search #8 OR #9	5183257
#9	Search ((animals[mh]) NOT (animals[mh] AND humans[mh]))	3902103
#8	Search Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp]	1331378
#7	Search #1 AND #6	430
#6	Search #2 OR #5	30761
#5	Search #3 AND #4	26667
#4	Search week[tiab] OR weekly[tiab]	397071
#3	Search twice[tiab] OR two-times[tiab]	145245
#2	Search twice-weekly[tiab] OR bi-weekly[tiab] OR biweekly[tiab]	10364
#1	Search renal dialysis[mesh] OR renal dialysis[tiab] OR hemodialysis[tiab] OR hemodialyses[tiab] OR haemodialysis[tiab] OR haemodialyses[tiab]	105486

Database: EMBASE (OVID SP)

Date: 2014-07-02

No of results: 174

#	Searches	Results
1	hemodialysis/	68730
2	(h?emodialys\$2 or renal dialysis).ti,ab.	71767
3	1 or 2	95205
4	(twice weekly or bi-weekly or biweekly).ti,ab.	13829
5	((twice or two-times) adj5 (week or weekly)).ti,ab.	19925
6	4 or 5	25706
7	3 and 6	323
8	limit 7 to (embase and (danish or english or german or norwegian or swedish) and (article or conference paper or note or "review"))	177
9	(animal not (animal and human)).sh.	1182221
10	(child not (child and adult)).sh.	816209
11	9 or 10	1998422
12	8 not 11	174

Database: The Cochrane Library

Date: 2014-07-02

No of results: 81

Clinical Trials: 80

EED: 1

ID	Search	Hits
#1	MeSH descriptor: [Renal Dialysis] explode all trees	4290
#2	h*modialys?s or (renal next dialysis):ti,ab,kw (Word variations have been searched)	6305
#3	#1 or #2	6964
#4	twice-weekly or bi-weekly or biweekly:ti,ab,kw (Word variations have been searched)	2662
#5	(twice or two-times) near/5 (week or weekly):ti,ab,kw (Word variations have been searched)	5755
#6	#4 or #5	6678
#7	#3 and #6	81

Database: CRD

Date: 2014-07-02

No of results: 1

ID	Search	Hits
#1	(hemodialysis OR hemodialyses OR haemodialysis OR haemodialyses OR renal dialysis)	565
#2	(twice-weekly OR bi-weekly OR biweekly)	142
#3	((twice OR two-times) near5 (week OR weekly))	184
#4	#2 OR #3	266
#5	#1 AND #4	1

Reference lists

A comprehensive review of reference lists brought 11 new records

Reference lists

Included studies:

Bieber B, Qian J, Anand S, Yan Y, Chen N, Wang M, et al. Two-times weekly hemodialysis in China: frequency, associated patient and treatment characteristics and quality of life in the China dialysis outcomes and practice patterns study. *Nephrol Dial Transplant*. 2013 Dec 8. [Epub ahead of print]

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Project: Hemodialysis twice versus three times a week
 Appendix 2 – Included studies – design and patient characteristics.

Author, year,	Country	Study Design	No of participants	Measure of residual renal function	Outcomes
Bieber, 2013	China	Registry-based cross-sectional	1,286	Urine output >200ml/day	Quality of Life
Cheng, 2014	China	Prospective cohort	143	Urine output (ml/24h)	Cardiovascular events Complication (IDH)
Hanson, 1999	USA	Retrospective cohort	15,067 4,888 incident	Estimated GFR	Mortality
Lin, 2009	Taiwan	Cohort	74	Renal GFR Urine output/3 days	Preservation of residual kidney function Complications

GFR = glomerular filtration rate, IDH = intradialytic hypotension

Project: Hemodialysis twice versus three times a week
Appendix 3. Excluded articles

Study author, publication, year	Reason for exclusion
Agrawal RK, 1998	Case series, do not report complications
Casino FG, 1996	PICO not applicable (no comparison of relevant outcomes)
Charra B, 1983	PICO not applicable (no data on residual renal function, long dialysis duration 12 hrs./session)
Cheng Y, 2004	PICO not applicable (anuric patients included)
Delmez JA, 1992	PICO not applicable (anuric patients included, no outcome analysis)
Dukanovic L,1990	PICO not applicable (no control group and no relevant outcome)
Elamin S, 2012	PICO not applicable (included anuric patients and no otherwise data on residual renal function)
Guney I, 2012	PICO not applicable (no data on residual renal function)
Ivanovich P, 1977	PICO not applicable. (no comparison of relevant outcomes)
Kalantar-Zadeh K	Not original study, review article
Krairittichai U, 2006	PICO not applicable. (no comparison between twice weekly vs. thrice weekly hemodialysis)
Kwan JT, 1991	Case series, do not report complications
Lei G, 2014	Duplicate (subgroup analysis presented by Chen Y 2014)
Lin X, 2012	PICO not applicable (no data on residual renal function)
Manotham K, 2006	Case series do not report complications
Nemati E, 2008	PICO not applicable (no data on residual renal function, no relevant outcomes)
Rahman H, 1997	PICO not applicable (no data on residual renal function)
Sobh MA, 1998	PICO not applicable (no data on residual renal function, no relevant outcomes)
Stankuviene A, 2010	PICO not applicable (no data on residual renal function)
Sultania P, 2009	Case series do not report complications
Supasyndh O, 2009	PICO not applicable (no data on residual renal function, no relevant outcome)
Tang HL, 2004	PICO not applicable (no data on residual renal function, no relevant outcome)
Valek A, 1978	PICO not applicable (no data on residual renal function, no longer valid dialysis modality)

Project: Hemodialysis twice versus three times a week
 Appendix 4.1 Outcome variable: Mortality

* + No problem
 ? Some problems
 - Major problems

Author, year	Country	Study design	Number of patients n=	Withdrawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Twice-weekly HD	Thrice-weekly HD				
Hanson JA, 1999	USA	Retrospective cohort	4888 incident patients	476	RR=0.79, P=0.06 vs thrice weekly		Total study population included 15067 (also prevalent patients). Two year follow-up. Absolute mortality numbers are not available	?	-	?

HD= hemodialysis

Project: Hemodialysis twice versus three times a week
 Appendix 4.2 Outcome variable: Cardiovascular events (non-fatal)

* + No problem
 ? Some problems
 - Major problems

Author, year	Country	Study design	Number of patients n=	With draws - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Twice-weekly HD	Thrice-weekly HD				
Cheng Y, 2014	China	Single center prospective cohort	143	13	<u>Analyses excluding IDH</u> 8/103 (7.8%)	<u>Analyses excluding IDH</u> 9/40 (23%) p=0.034 not adjusted for baseline characteristics. <u>Analyses including IDH:</u> HR 2.47, 95% CI 1.31-3.91 p=0.005, adjusted for demographics, comorbidities and urine output HR 2.05, 95% CI 1.14-4.44 p=0.017, adjusted also for lab measurements	CV events including myocardial infarction, heart failure, stroke and others (not specified).	-	-	-

CV = cardiovascular
 IDH = intradialytic hypotension

Project: Hemodialysis twice versus three times a week
 Appendix 4.3 Outcome variable: Health-related quality of life**

* + No problem
 ? Some problems
 - Major problems

Author, year	Country	Study design	Number of patients n=	With drawsals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Twice-weekly HD	Thrice-weekly HD				
Bieber B, 2013	China	Cross sectional study from registry data	1379 1286 included in analysis	93	<u>Physical component</u> 36.7±9.5 Adjusted β (95% CI) = -0.61 (-2.03 to 0.82) <u>Mental component</u> 43.4±9.0 Adjusted β (95% CI) = -1.13 (-2.72 to 0.45)	<u>Physical component</u> 36.1±9.1 <u>Mental component</u> 43.8±9.5 No statistically significant difference between study groups after adjustment for demographic and comorbidity characteristics	47.5% of patient in twice-weekly HD group had no significant urine output (< 200 ml/day)	-	-	?

**Kidney Disease Quality of Life-Short Form (KDQOL-SF) 12. A computer-based scoring algorithm generates a norm-based mean value of 50 with standard deviation of 10. Scores above or below 50 are above or below average physical or mental well-being, respectively.

Project: Hemodialysis twice versus three times a week
 Appendix 4.4 Outcome Residual kidney function

* + No problem
 ? Some problems
 - Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Twice-weekly HD	Thrice-weekly HD				
Lin YF, 2009	Taiwan	Single center Prospective cohort	74	0	<u>Ccr (ml/min)</u> Baseline: 3.42±1.36 vs. Study end: 2.5±1.79 Δ per month: - 0.057±0.103 p = 0.035 between study groups <u>Urine volume (ml/3-day)</u> Baseline: 1072±700 Study end: 1551±1095 Δ per month: 160±0.442 p = 0.022 between study groups	<u>Ccr (ml/min)</u> Baseline: 4.07±2.02 Study end: 0.96±1.41 Δ per month: - 0.355±0.266 <u>Urine volume(ml/3-day)</u> Baseline: 1048±703 Study end: 660±1106 Δ per month: - 21±102		-	-	-

Ccr = creatinine clearance (corresponding to residual kidney function)

Project: Hemodialysis twice versus three times a week
 Appendix 4.5 Outcome Complications

* + No problem
 ? Some problems
 - Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Twice-weekly HD	Thrice-weekly HD				
Cheng G, 2014	China	Single center Prospective cohort	143	13	<u>IDH</u> 13/103 (12.6%) OR=2.63 95% CI 1.16-4.69, p=0.033	11/40 (27.5%)		-	-	-
Lin YF, 2009	Taiwan	Single center Prospective cohort	74	0	<u>IDH (times/month)</u> 0.26±0.49 <u>Hospitalization due to infection</u> 31.82% <u>Arterio-venous fistula dysfunction</u> 17.39%	1.10±1.21, p<0.001 62.71%, p=0.012 12.77%, p=0.72		-	-	-

IDH = intradialytic hypotension

**ETHICAL ANALYSIS OF
TWICE-WEEKLY HEMODIALYSIS FOR PATIENTS WITH SIGNIFICANT RESIDUAL KIDNEY FUNCTION**

Question	Answer/ comment
1. From the patient's perspective, how does twice-weekly HD for patients with significant RKF affect the patient's quality of life and life expectancy?	Given that the twice weekly HD compared with three times a week, does not increase mortality and complication rate, an improved HRQL may be expected.
2. How severe is the patient's need that the twice-weekly HD for patients with significant RKF must meet?	Not applicable
3. Does twice-weekly HD for patients with significant RKF 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)?	Not applicable how others view the patient. However, the patient might view him or herself as considerably more healthy and independent.
4. Can twice-weekly HD for patients with significant RKF affect the patient's ability and possibility to be independent?	If a selected group can be offered this method it will improve their ability and possibility to be independent
5. If implemented, does twice-weekly HD for patients with significant RKF require any special steps to not compromise the patient's autonomy?	No
6. How does twice-weekly HD for patients with significant RKF affect the patient's physical, moral and personal integrity?	If a selected group can be offered this method it will improve their physical, moral and personal integrity.
7. Is twice-weekly HD for patients with significant RKF cost-effective?	Yes, by comparing direct costs only, given that complication rate is not increased by twice-weekly HD.
8. How does twice-weekly HD for patients with significant RKF affect resources?	Resources are made available.

9. Is twice-weekly HD for patients with significant RKF in conflict with professional values?	Presently, there are different opinions among professionals regarding the frequency of dialysis, due to the lack of evidence.
10. Does twice-weekly HD for patients with significant RKF change the role of the professional in relation to the patient?	No
11. Does twice-weekly HD affect, or does it put any new demands on, a third party?	No, it may have positive effects on relations as it results in more time spent with family and relatives.
12. Is there any legislation of relevance with regard to twice-weekly HD?	No
13. Is there any risk of conflict between the procedure of twice-weekly HD and values of the society, or values of different groups?	No
14. Is there a risk that an introduction of twice-weekly HD will cause a conflict with particular interests?	No
15. Can an introduction twice-weekly HD influence the trust of the health care system?	No
Conclusion	The purpose of this analysis is to study whether a method in use, twice-weekly HD for patients with significant residual kidney function will increase risk for mortality, cardiovascular morbidity and compromise HRQL as compared to standard thrice-weekly HD. Establishing evidence against an increased risk would make possible the continued use of this cost effective method. If a selected group can be offered this method it would also improve their ability to be independent as well as improve their physical, moral and personal integrity.

HD = hemodialysis

RKF = residual kidney function

HRQL = health related quality of life

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 ⊕⊕⊕○)
Low quality of evidence	= (GRADE ⊕⊕○○)
Very low quality of evidence	= (GRADE ⊕○○○)

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

