BMJ Open

The influence of hazardous drinking on psychological functioning, stress and sleep during and after treatment in patients with mental health problems: a secondary analysis of a randomised controlled intervention study

Catharina Strid,1 Claes Andersson,2 Agneta Öjehagen3

ABSTRACT

Objectives Hazardous drinking could negatively affect health and lead to alcohol use disorders, but it is unclear how hazardous drinking affects treatment outcomes of depression and anxiety and stress-related mental health problems. The aim of this study was to examine whether hazardous drinking, measured by Alcohol Use Disorders Identification Test-Consumption (AUDIT-C), influences the outcomes of repeated assessments of psychological functioning (Outcome Questionnaire-45), stress (Perceived Stress Scale) and sleep (Karolinska Sleep Questionnaire), during and after treatment in patients with mental ill health.

Methods The study was conducted within REGASSA, a randomised controlled trial aimed at comparing Internet-based cognitive–behaviour therapy and physical exercise with treatment as usual on primary care patients with mental ill health. The study involved 871 participants who completed the AUDIT at baseline and who were assessed repeatedly during and after treatment on psychological functioning, stress and sleep by interactive voice response, a computerised, automated telephone technology.

Results At baseline, hazardous drinkers were more depressed and had lower scores on psychological functioning than non-hazardous drinkers, while there were no differences on stress and sleep. During the follow-ups, hazardous drinking negatively influenced perceived stress, that is, hazardous drinkers seemed to have less treatment effect on stress, and the results remained after controlling for depression. There were no differences during the follow-ups regarding psychological functioning and sleep.

Conclusions Hazardous drinking negatively influenced perceived stress. The findings of the study emphasise the importance of screening for alcohol habits in mental ill-health patients, since risky drinking may affect the outcomes of treatment.

Trial registration number DRKS00008745; Post-results.

Strengths and limitations of this study

► This is a secondary analysis of randomised controlled trial (RCT) data and not a prospectively designed RCT, which was a limitation.
► However, the large sample of primary care patients was a strength.
► Another strength was the repeated assessments collected by automated technology, which was a convenient way of monitoring a large sample of participants.
► The high attrition in the repeated assessments was a limitation, although the analysis model compensating for the attrition was a strength and the proportion of hazardous drinkers remained almost the same.
► The Alcohol Use Disorders Identification Test-Consumption cut-off scores have not been validated in a population of mental health problems, which was a limitation.

INTRODUCTION

Hazardous or risky alcohol consumption is common in patients seeking primary care, but is often not adequately examined at the medical visit,1 2 and only some of the patients with risky consumption are advised to reduce their alcohol use.3 Hazardous drinking, including both the number of drinks consumed weekly and on a single occasion, ‘binge drinking’, is considered an alcohol drinking pattern that could lead to negative effects on health and to development of alcohol use disorders.4 5 Screening for alcohol use is a recommended intervention for patients in routine care, and patients reporting a pattern of hazardous drinking should be given advice on how to change this pattern and offered brief interventions.
Patients with alcohol use disorder or dependence should be referred for treatment.6-8

Several studies have shown higher prevalence rates for hazardous drinking in patients with common mental health problems compared with the general population.6-9,12 Eberhard and colleagues10 found a prevalence of 21% in a population of psychiatric outpatients, and Nehlin and colleagues showed a proportion of 19%,10 which was higher than that in the Swedish general population at the time (15%). However, only a few studies have examined whether concomitant hazardous drinking affects treatment outcome of mental health problems. In an extensive review by Sullivan and colleagues,12 it was found that hazardous alcohol use was associated with less antidepressant treatment effect.20 Stress is known to be linked with sleeping problems and mood disorders.16-18 In a previous primary care study, high levels of stress were commonly reported in association with symptoms of anxiety and depression,19 and high levels of perceived stress have been shown to be associated with less antidepressant treatment effect.20

In an epidemiological study of more than 30,000 individuals, Dawson et al1 found that stress resulted in increased quantities of alcohol consumption on specific drinking occasions, rather than more frequent drinking. Sher et al reported no clear results of whether alcohol reduces perceived stress, and concluded that stress is likely to be influenced by both individual and situational factors.22

Vinson and colleagues conducted a study in primary care on sleep and alcohol consumption and found no associations between hazardous drinking and sleeping problems.23 To the best of our knowledge, how hazardous drinking may affect change in psychological functioning (Outcome Questionnaire-45, OQ-45) has not yet been studied.

At baseline, patients in REGASSA completed the Alcohol Use Disorders Identification Test (AUDIT), which was developed for early detection of individuals with hazardous or harmful alcohol drinking.24 A previous cross-sectional study of REGASSA showed that the total AUDIT score, the scores of AUDIT-C and the proportions of hazardous drinkers (22%) were higher among REGASSA patients compared with the general population (15%).

This study aimed to examine whether hazardous drinking at baseline predicts the outcomes of repeated assessments of psychological functioning, stress and sleep collected by IVR during and after treatment in REGASSA.

**METHODS**

**Study design**

Study design, participants and measurements are presented in more detail in an earlier study,15 and only a brief description is given here. REGASSA was carried out in primary care in six healthcare regions in Sweden between 2011 and 2014. After giving written informed consent, patients were randomised to one of three treatment alternatives, ICBT, PE and TAU, for a 12-week intervention. At baseline, participants completed a battery of questionnaires, including measures of depression (Montgomery Åsberg Depression Rating Scale, MADRS) and alcohol use (AUDIT), and follow-ups were conducted 3 and 12 months after baseline. Secondary outcomes of psychological functioning, stress and sleep were continually collected by IVR during and after treatment.

IVR is an automated telephone system programmed to administer various questionnaires and to follow a large population over time. At baseline, the patients in REGASSA registered their personal mobile number and answered the 55 questions included in IVR using quantitative questions.
touch-tone technology. The automated system then called the patients on six measurement occasions: two during treatment, one at the end of treatment and three after treatment until 12 months after baseline. The attrition in IVR showed varying but decreasing levels over the 12-month study period (table 1). The proportion of respondents at 3-month follow-up was 54%, at 6-month 47%, at 9-month 47% and at the final 12-month follow-up the proportion of responders had fallen to 25%. The proportion of hazardous drinkers remained almost constant, 15% at 3-month follow-up, 13% at 6-months, 14% at 9-months and 15% at 12-month follow-up. The number of responders is presented in figure 1.

Participants
Participants were primary care patients with light-to-moderate depression, anxiety and stress-related mental ill health. The inclusion criteria were ≥10 points on the Patient Health Questionnaire-9, a short depression scale, and Swedish language skills due to the ICBT programme, being only delivered in Swedish. REGASSA included 945 patients, of which 879 completed the IVR baseline assessments and, of these 879 patients, 871 also completed AUDIT at baseline. Patients with a primary substance use disorder were excluded. The CONSORT diagram (figure 1) shows the flow of the participants and the number of responders at each follow-up for hazardous and non-hazardous drinkers.

Measures at baseline
AUDIT
AUDIT is a 10-item scale for measuring alcohol consumption and alcohol-related problems. The test is validated in primary care and has shown acceptable psychometric properties.24 AUDIT is in two parts: items 1–3 measuring alcohol consumption (AUDIT-C) and items 4–10 measuring alcohol problems (dependency and harm combined). In this study, we only used the abbreviated consumption subscale AUDIT-C, since the three questions in OQ-45 on negative consequences of drinking behaviour would otherwise interfere with questions 4–10 in AUDIT. The items in AUDIT-Care (1) How often do you drink alcohol? (2) How many glasses do you drink on a typical day when you drink alcohol? (3) How often do you have six or more drinks on one occasion? The scores range from 0 to 4, and maximum negative score is 12. AUDIT-C has shown high specificity and sensitivity in screening for risky alcohol habits.26 27 The cut-off score for hazardous drinking in this study was set to >5 for women and >6 for men in accordance with Swedish guidelines.28 These cut-offs are higher than in previous studies where the cut-off scores have been set to 3–4 for women and 4–5 for men, but it is recommended that cut-off scores are determined empirically in different cultures, since drinking frequency varies largely between countries.6 11 26 27

When studying the question of binge drinking separately, the cut-off was set to at least on a monthly basis for both women and men.

MADRS
In earlier REGASSA studies, MADRS was used as an outcome measure for depression but, in this study, it was
used as a baseline measurement and only for controlling results obtained with AUDIT-C. MADRS is a commonly used measure for depression that has shown good psychometric properties. It consists of 10 items with six response alternatives.29

Gender
We analysed whether there were any gender differences in terms of hazardous drinking and its influence on the outcome measures of psychological functioning, sleep and stress.

Outcome measurements in IVR
Outcome Questionnaire-45
The repeated assessments of psychological functioning were measured by OQ-45. OQ-45 was developed by Lambert and colleagues to measure psychotherapy effects.30 It consists of 45 questions with a score range
of 0–180, where 180 is the maximum negative score. OQ-45 captures the patient’s psychological functioning through questions about symptoms, interpersonal problems and social role function. Both the original and the Swedish version of OQ-45 have shown good psychometric properties.30–32

Perceived Stress Scale

Stress was repeatedly assessed by the Perceived Stress Scale (PSS), originally a 10-item scale measuring how the patient copes with stress. In this study, we used a shortened four-item version of this scale that has proved suitable for telephone assessments.33 The scores range from 0 to 4, and the maximum total negative score is 16.

Karolinska Sleep Questionnaire

A short version of the Karolinska Sleep Questionnaire (KSQ) assessed the sleep outcome. The questionnaire comprises four items capturing sleep quality, with scores ranging from 1 to 6, and the maximum negative score was 24. KSQ has shown good validity, reliability and sensitivity in various studies.34

Statistics

Differences between hazardous drinkers and non-hazardous drinkers were calculated on continuous baseline measurements using independent samples t-tests, and differences in proportions of hazardous drinkers in discrete variables were examined with X² tests. Differences in attrition between non-hazardous and hazardous drinkers were calculated with Fisher’s exact test. To examine how alcohol consumption (AUDIT-C) at baseline affected the course and outcome for psychological functioning, stress and sleep, we conducted three separate analyses with linear mixed models with a first-order autoregressive, heterogeneous rho covariance structure. Mixed models include all measures that are available at each assessment, and were therefore considered suitable for this study. We assumed that missing observations were unrelated to the observed value, that is, missing at random. Each model included six follow-ups called assessments 1, 2, 3, 4, 5 and 6; the assigned treatment groups ICBT, PE and TAU; gender; and two baseline measures, that is, hazardous drinking (AUDIT-C) and the baseline scores of one of the three outcome measures (OQ-45, PSS, KSQ). All variables were modelled as fixed effects. The outcome measure baseline scores were used as continuous covariate, and the control variable hazardous drinking (AUDIT-C) and gender as categorical covariates. AUDIT-C was a dichotomous variable, where 0 was defined as non-hazardous drinking and 1 hazardous drinking. MADRS was used as a continuous covariate for controlling for depression if AUDIT-C showed significant influence on the outcome measures. Assessment data were nominal, that is, each measurement occasion was separate and time was not a continuous linear regressor in the model. The analyses began with a full model with interaction effects of AUDIT-C × Treatment group

RESULTS

The average age of patients was 43 years, and 62% had a high level of education. Most of the patients were working and only 5% were on sick leave. In table 1, different descriptions of baseline measurements for hazardous drinkers and non-hazardous drinkers and attrition during the follow-ups are presented.

The proportion of hazardous drinkers at baseline measured by AUDIT-C was 14%, with a significantly higher proportion in men (18%) compared with women (12%), \( \chi^2 = 5.23, P = 0.022 \). The proportions of binge drinkers measured by item 3 in AUDIT-C was 13%, and the overlap between hazardous and binge drinkers was high; 90 out of the 122 hazardous drinkers were also binge drinkers, and 90 of the 110 binge drinkers were hazardous drinkers, so our analysis focused solely on the summarised score in AUDIT-C as a measure of hazardous drinking. The baseline average depression score (MADRS) showed moderate depressive problems, and hazardous drinkers were more depressed \( t (853) = -2.31, P = 0.021 \) and had lower psychological functioning (OQ-45) \( t (871) = -2.85, P = 0.004 \) than non-hazardous drinkers. There were no baseline differences between the treatment alternatives, perceived stress, sleep or age, education level, civil state and employment. The Fisher’s exact test showed no differences in attrition between non-hazardous and hazardous drinkers at any follow-up and there were no differences between the treatment alternatives.

The results of the linear mixed models showed that hazardous alcohol consumption at baseline predicted the outcome for perceived stress (PSS). The patients with hazardous drinking had a higher average score on PSS throughout the assessments, which might indicate less treatment effect for perceived stress compared with non-hazardous drinkers. To test whether this effect could be due to depression, since hazardous drinkers were more depressed than non-hazardous, we carried out a new analysis with MADRS and AUDIT-C as baseline covariates, and both MADRS \( P = 0.003 \) and AUDIT-C \( P = 0.022 \) were significant, that is, the effects of hazardous drinking remained. In the full model, we included interaction effects between hazardous alcohol consumption and treatment alternatives and hazardous alcohol consumption and the IVR assessments, but no significant interaction effects were found. The model was reduced to main effects of group, including a control for differences at baseline between hazardous and non-hazardous drinkers; the results are presented in table 2.

The main effect of group occurred after baseline, that is, during and after treatment, so hazardous drinkers
probably had less treatment effect even if no differences in how hazardous drinking predicted stress were found between the treatment alternatives. The average changes on PSS over the assessments for patients with and without hazardous drinking are presented in figure 2. The differences in stress between hazardous drinkers and non-hazardous drinkers were higher at the follow-ups conducted after the end of treatment, but these figures should be treated with some caution because of the large attrition, even if there were no differences in attrition between the two groups.

The results of the linear mixed models on psychological functioning (OQ-45) and sleep (KSQ) were not significantly influenced by the level of hazardous alcohol consumption at baseline, although there was a tendency (P=0.064) for higher average scores on OQ-45 for hazardous drinkers compared with non-hazardous drinkers (tables 3 and 4). Since the main effect of group was not significant on OQ-45 and KSQ, interaction effects between hazardous drinking and treatment group or hazardous drinking and assessments were not examined.

**DISCUSSION**

The aim of this study was to examine whether hazardous alcohol consumption predicts the outcome for psychological functioning, perceived stress and sleep, over a 12-month assessment period. The results showed that hazardous drinking predicted stress, but not psychological functioning and sleep. Patients with hazardous drinking had a higher level of stress during the follow-ups compared with non-hazardous drinkers, but not at baseline, and these results remained after controlling for depression. In a previous study in REGASSA,15 we reported that the treatment had positive effect on perceived stress, and all treatment groups showed improvements. This study adds that the improvement was negatively influenced by hazardous drinking, that is, hazardous drinkers improved less than non-hazardous drinkers irrespective of treatment alternative.

**Table 2** The influence of alcohol consumption on repeated assessments of perceived stress as the main effect of group presented in average change scores

<table>
<thead>
<tr>
<th>Variables</th>
<th>Average change</th>
<th>df</th>
<th>t</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment 1</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessment 2†</td>
<td>−0.43</td>
<td>725.65</td>
<td>−4.39***</td>
<td>(−0.63 to −0.24)</td>
</tr>
<tr>
<td>Assessment 3†</td>
<td>−1.02</td>
<td>707.27</td>
<td>−9.00***</td>
<td>(−1.25 to −0.80)</td>
</tr>
<tr>
<td>Assessment 4†</td>
<td>−1.06</td>
<td>621.12</td>
<td>−8.52***</td>
<td>(−1.30 to −0.81)</td>
</tr>
<tr>
<td>Assessment 5†</td>
<td>−1.28</td>
<td>601.23</td>
<td>−9.78***</td>
<td>(−1.53 to 1.02)</td>
</tr>
<tr>
<td>Assessment 6†</td>
<td>−1.49</td>
<td>319.69</td>
<td>1.78</td>
<td>(−1.79 to 1.19)</td>
</tr>
<tr>
<td>Gender‡</td>
<td>0.32</td>
<td>642.18</td>
<td></td>
<td>(−0.03 to 0.66)</td>
</tr>
<tr>
<td>AUDIT-C§</td>
<td>0.61</td>
<td>668.58</td>
<td>2.65***</td>
<td>(0.16 to 1.06)</td>
</tr>
</tbody>
</table>

Assessment 1 is set to zero because it is a redundant.  
†A negative score means a reduction from assessment 1.  
‡A positive score means that the average score of assessments 1–6 shows a larger reduction from assessment 1 in women as compared with men.  
§A positive score means that the average score of assessments 1–6 shows a larger reduction from assessment 1 in non-hazardous as compared with hazardous drinkers.  
P<0.05, **P<0.01, ***P<0.001.

AUDIT-C, Alcohol Use Disorders Identification Test-Consumption.

---

**Figure 2** The graph shows the course of stress during and after treatment for patients with and without hazardous drinking at baseline.
Table 3  The influence of alcohol consumption on repeated assessments of Outcome Questionnaire-45 as the main effect of group presented in average change scores

<table>
<thead>
<tr>
<th>Variables</th>
<th>Average change</th>
<th>df</th>
<th>t</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment 1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Assessment 2</td>
<td>−4.00</td>
<td>724.13</td>
<td>−7.19***</td>
<td>(−5.09 to 2.91)</td>
</tr>
<tr>
<td>Assessment 3</td>
<td>−8.50</td>
<td>694.62</td>
<td>−11.52***</td>
<td>(−9.95 to 7.05)</td>
</tr>
<tr>
<td>Assessment 4</td>
<td>−9.87</td>
<td>579.86</td>
<td>−11.15***</td>
<td>(−11.61 to 8.13)</td>
</tr>
<tr>
<td>Assessment 5</td>
<td>−10.07</td>
<td>497.79</td>
<td>−10.28***</td>
<td>(−12.00 to 8.15)</td>
</tr>
<tr>
<td>Assessment 6</td>
<td>−11.83</td>
<td>291.60</td>
<td>−10.05***</td>
<td>(−14.14 to 9.51)</td>
</tr>
</tbody>
</table>

Gender‡ 2.62 605.08 1.79 (−0.25 to 5.48)
AUDIT-C§ 3.50 627.39 1.86 (−0.20 to 7.21)

Assessment 1 is set to zero because it is a redundant.
†A negative score means a reduction from assessment 1.
‡A positive score means that the average score of assessments 1–6 shows a larger reduction from assessment 1 in non-hazardous drinkers as compared with men.
§A positive score means that the average score of assessments 1–6 shows a larger reduction from assessment 1 in women as compared with men.

*P<0.05, **P<0.01, ***P<0.001.
AUDIT-C, Alcohol Use Disorder Identification Test-Consumption.

Table 4  The influence of alcohol consumption on repeated assessments of sleep as the main effect of group presented in average change scores

<table>
<thead>
<tr>
<th>Variables</th>
<th>Average change</th>
<th>df</th>
<th>t</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment 1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Assessment 2</td>
<td>−0.44</td>
<td>710.76</td>
<td>−3.49***</td>
<td>(−0.69 to −0.19)</td>
</tr>
<tr>
<td>Assessment 3</td>
<td>−1.02</td>
<td>759.76</td>
<td>−6.47***</td>
<td>(−1.33 to −0.71)</td>
</tr>
<tr>
<td>Assessment 4</td>
<td>−1.05</td>
<td>649.15</td>
<td>−5.78***</td>
<td>(−1.41 to −0.70)</td>
</tr>
<tr>
<td>Assessment 5</td>
<td>−1.02</td>
<td>632.79</td>
<td>−5.76***</td>
<td>(−1.36 to −0.67)</td>
</tr>
<tr>
<td>Assessment 6</td>
<td>−1.31</td>
<td>338.53</td>
<td>−5.88***</td>
<td>(−1.74 to −0.87)</td>
</tr>
</tbody>
</table>

Gender‡ 0.14 635.91 0.53 (−0.37 to 0.65)
AUDIT-C§ 0.49 660.12 1.46 (−0.17 to 1.15)

Assessment 1 is set to zero because it is a redundant.
†A negative score means a reduction from assessment 1.
‡A positive score means that the average score of assessments 1–6 shows a larger reduction from assessment 1 in non-hazardous drinkers as compared with hazardous drinkers.

*P<0.05, **P<0.01, ***P<0.001.
AUDIT-C, Alcohol Use Disorder Identification Test-Consumption.

Dawson and colleagues, who separated binge drinking from other consumption measures, found that stress was associated with binge drinking and not with frequency of drinking.21 In our study, binge drinking was a part of hazardous drinking in the summarised measure of AUDIT-C, which might explain our results that hazardous drinking was associated with higher levels of stress. Hazardous drinkers seemed to get less treatment effects on stress, which is not in line with the assumption that alcohol could reduce stress. Although it is uncertain whether alcohol reduces stress, its effect on stress seems to depend on several factors.22 The focus in this study was on hazardous alcohol consumption, which may not reduce stress. The influence of alcohol use on stress seems unclear, and further investigations are required.

The finding that hazardous drinking did not affect sleep quality is in line with an earlier study conducted in primary care,23 but contradicts other findings where risky sleep quality is in line with earlier studies.24 It seems unclear, and further investigations are required.

When comparing the baseline scores of OQ-45 in our sample of depressed patients with samples of patients with alcohol use disorders, the patients in our sample showed lower psychological functioning, and this applied for both hazardous and non-hazardous drinkers.33 36 Hazardous drinkers had a significantly higher score on OQ-45 at baseline but, during follow-ups, these differences were no longer significant, although a tendency towards higher scores remained. In summary, results of our analyses were unclear about the way hazardous drinking affects psychological functioning, and more research is needed.

Several studies have concluded that alcohol use patterns should be screened in healthcare, and the AUDIT-C has been recommended as a suitable screening test.5 7 26 A common barrier for addressing alcohol habits in healthcare is lack of time, so a short screening tool such as the AUDIT-C could be a facilitator,1 7 as well as automated technology. The patients in REGASSA turned out to have higher proportions of hazardous drinking and alcohol problems than the general population,25 which emphasises the need to examine the alcohol patterns and increase the amount of advice on alcohol consumption given to patients with mental ill health. Systematic screening for alcohol use in primary care has been shown to increase the detection of hazardous drinkers, and facilitate brief interventions.7 The results in our study confirm the importance of screening for drinking habits in primary care to identify risky consumption that may have an impact on treatment effects on perceived stress for patients with common mental health problems.

**Strengths and limitations**

The large sample of mental ill-health patients in primary care is an advantage and strengthens the
results. However, the present design, a secondary analysis of RCT data, examining the prediction of alcohol consumption on psychological functioning, stress and sleep, is not powered to fully answer the question, which is a limitation. The chosen cut-off scores of AUDIT-C, which are recommended by the Swedish national guidelines, have not been validated in a population of patients with mental health problems, which is a limitation. The repeated assessments in IVR is a strength that enabled us to make reliable comparisons and to follow the patients throughout the study. The analysis model is a strength compensating for the high attrition in IVR, which is otherwise a limitation. Conclusions about differences on stress between hazardous drinkers and non-hazardous in later follow-ups should be drawn with caution due to attrition, although the attrition was not higher among hazardous drinkers during the follow-ups.

CONCLUSION

This study showed that hazardous drinkers were more depressed and had lower psychological functioning at baseline and higher level of stress during and after treatment. These results add to previous studies on the importance of screening for alcohol consumption in mental illness patients seeking primary care, since hazardous drinking may influence some treatment effects. Further research is needed on how hazardous drinking affects different treatment outcomes in patients with common mental health problems.

Acknowledgements We thank Peter Höglund in Skåne regional council for statistical advice and Lars-Gunnar Lundh at the Department of Psychology, Lund University, for valuable comments on the manuscript. Contributors CS was involved in the data collecting process, made major contributions to the data analysis and was a major contributor in writing the manuscript. CA was involved in the study design and the data collecting process. AO was vice director for the REGASSA study and was involved in the study design, made contributions to the data analysis and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Funding The REGASSA study was funded by Stockholm, Kronoberg, Västmanland and Blekinge county councils, Skåne and Västra Götaland regional councils in Sweden, and REHSAM through Vårdal Foundation.

Disclaimer The funding sources had no part in study design, data analysis or writing the manuscript.

Competing interests None declared.

Patient consent Obtained.

Ethics approval The REGASSA study was approved by the regional ethical review board at Karolinska Institutet in Stockholm (Dnr 2010/1779-31/4) and retrospectively registered in German clinical trials DRKS00008745. Before allocation, a written informed consent was obtained from each patient.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The datasets generated and/or analysed during the current study are not publicly available due to that there is no permission granted for this from the ethical review board, but are available from the corresponding author on reasonable request.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES


