Healthy Ageing Through Internet Counselling in the Elderly: the HATICE randomised controlled trial for the prevention of cardiovascular disease and cognitive impairment

Edo Richard,1,2 Susan Jongstra,1 Hilkka Soininen,3 Carol Brayne,4 Eric P Moll van Charante,5 Yannick Meiller,6 Bram van der Groep,7 Cathrien R L Beishuizen,1 Francesca Mangialasche,8 Mariagnesè Barbera,3 Tia Ngandu,9 Nicola Coley,10,11 Juliette Guillemont,10 Stéphanie Savy,10 Marcel G W Dijkgraaf,12 Ron J G Peters,13 Willem A van Gool,1 Miia Kivipelto,3,8,9,14 Sandrine Andrieu10,11


ABSTRACT

Introduction: Cardiovascular disease and dementia share a number of risk factors including hypertension, hypercholesterolaemia, smoking, obesity, diabetes and physical inactivity. The rise of eHealth has led to increasing opportunities for large-scale delivery of prevention programmes encouraging self-management. The aim of this study is to investigate whether a multidomain intervention to optimise self-management of cardiovascular risk factors in older individuals, delivered through an coach-supported interactive internet platform, can improve the cardiovascular risk profile and reduce the risk of cardiovascular disease and cognitive decline.

Methods and analysis: HATICE is a multinational, multicentre, prospective, randomised, open-label blinded end point (PROBE) trial with 18 months intervention. Recruitment of 2600 older people (≥ 65 years) at increased risk of cardiovascular disease will take place in the Netherlands, Finland and France. Participants randomised to the intervention condition will have access to an interactive internet platform, stimulating self-management of vascular risk factors, with remote support by a coach. Participants in the control group will have access to a static internet platform with basic health information.

The primary outcome is a composite score based on the average z-score of the difference between baseline and 18 months follow-up values of systolic blood pressure, low-density-lipoprotein and body mass index. Main secondary outcomes include the effect on the individual components of the primary outcome, the effect on lifestyle-related risk factors, incident cardiovascular disease, mortality, cognitive functioning, mood and cost-effectiveness.

Strengths and limitations of this study

▪ The study proposes the assessment of a pragmatic, easily implementable, coach-supported interactive internet platform for the improvement of the cardiovascular risk profile.
▪ The strengths of the study include the large sample size, the multinational recruitment and cooperation and the relatively less investigated older target population.
▪ Limitations include the relatively short follow-up.

BACKGROUND

Despite impressive reductions of its incidence in many countries, cardiovascular diseases (CVD) continue to be a major public health issue with over 4 million deaths in Europe each year.1 In parallel, the global prevalence of dementia is likely to increase in the coming years, mainly due to increased life expectancy.2 CVD and dementia share a number of risk factors including hypertension, hypercholesterolaemia, smoking, diabetes, obesity and physical inactivity.3-7 Even small improvements of vascular risk factor management in a large...
population, can lead to a large effect on incident cardiovascular disease at the population level and substantial reductions in healthcare costs.

Although up to 30% of dementia cases are attributable to modifiable (mostly cardiovascular) risk factors, there is currently insufficient evidence from randomised controlled trials (RCTs) that treatment will also reduce dementia incidence. Vascular risk factors rarely occur in isolation. It is plausible that targeting multiple risk factors simultaneously can have an additive effect on the reduction of the risk of CVD and dementia, but RCTs targeting the older population are rare and with mixed results. However, the recently published large RCT ‘Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)’ suggests that a multidomain lifestyle intervention could improve or maintain cognitive functioning in at-risk elderly people from the general population.

In spite of clear guidelines for cardiovascular risk management mainly for younger adults, but also applied on older adults, the sobering reality of daily practice is that target values are often not reached, leaving room for a substantial improvement. Both patient and doctor factors play a role in this gap between evidence and practice. Innovative strategies to improve cardiovascular risk management are therefore urgently needed.

Patient self-management is a potentially powerful strategy to improve adherence to therapy in CVD risk reduction. Specific patient characteristics can determine the strategies applied at the individual level. Increasing knowledge about a healthy lifestyle and the possibility for tailor-made prevention programmes can empower individuals and improve adherence with pharmacological and non-pharmacological interventions.

When designing a trial on prevention of cardiovascular disease and dementia, the optimal age-range of the target population is matter of debate. The benefits of higher efficacy in midlife are counteracted by the large sample size and long follow-up required to detect an effect on incident disease. The optimal time-window depends on the peak incidence age, and is probably somewhere in late midlife or early late-life.

The internet has become a major source of information for people of all ages, and its use among older people throughout Europe has increased dramatically, making it a potentially suitable medium for the delivery of widely implementable healthcare interventions. Together with the rise of eHealth this creates opportunities for large-scale delivery of prevention programmes encouraging self-management.

In the Healthy Ageing Through Internet Counselling in the Elderly (HATICE) trial we investigate whether a coach-supported interactive internet intervention to optimise self-management of cardiovascular risk factors in older individuals can improve the cardiovascular risk profile and reduce the risk of cardiovascular disease and cognitive decline.

**METHODS**

**Study design**

HATICE is a pragmatic, multinational, multicentre, investigator initiated, prospective, randomised, open-label blinded end point (PROBE) trial with 18 months intervention and follow-up. Owing to the nature of the intervention, complete double blinding is not possible. Investigators evaluating outcome measures are blinded for the randomisation group and the primary outcome is based on objective parameters.

**Study population and recruitment**

The study population will consist of community-dwelling people aged 65 years or older who have two or more cardiovascular risk factors and/or manifest cardiovascular disease or diabetes mellitus. This leads to a mixed population with an indication for either primary or secondary prevention. Inclusion and exclusion criteria are listed in table 1.

Recruitment takes place in the Netherlands, Finland and France. Based on a pilot study (later described) and experience from previous trials we expect a response rate of ~10%. In the Netherlands recruitment will take place through registration lists of all individuals ≥65 years registered in primary care practices. In Finland recruitment will take place by inviting individuals from the population registry based on age, by selecting participants from previous population-based surveys, as was previously carried out to recruit for RCTs, and by advertisements in local media, patient organisations and their websites and healthcare centres. In France participants will be enrolled from various sources. In addition to recruitment through general practitioners (GP), prevention centres, cardiovascular risk factors consultations and the geriatrics department and memory clinics in the Toulouse area, participants will also be recruited through mailing lists and advertisements in local media, seniors clubs and conferences.

People aged ≥65 years will receive an information letter and are invited to apply through a country specific website or emailing or calling the local study centre. Those interested will receive a prescreening telephone call. If eligible, people are invited to attend the first screening visit. Recruitment started in March 2015.

**Intervention**

Participants randomised to the intervention condition will have access to an interactive internet platform, specifically designed for use by older people (figure 1). The platform is in the participants own language (Finnish, French or Dutch) and facilitates self-management of vascular and lifestyle-related risk factors, including blood pressure, overweight, physical inactivity, diet, smoking, diabetes and hypercholesterolaemia. After secure login, a participant can view his/her own cardiovascular risk profile created through baseline
measurements. At the interactive part of the platform, the participants can set a personal goal for lifestyle change, make a corresponding action plan, monitor goals by entering data (eg, blood pressure or a food diary), join lifestyle activity groups and correspond with their coach, whom they have met in person at the baseline assessment. In addition, participants can find health information in static and interactive education-modules, watch peer videos on lifestyle change, and use a programme for cognitive training.

The platform and the guidance provided by the coach are based on current European and national guidelines for cardiovascular risk management. When indicated, this is adapted to national guidelines from one of the three countries where participants are recruited. Owing to the heterogeneous population in this trial, which includes participants with elevated cardiovascular risk with or without established CVD, primary as well as secondary prevention guidelines will be applied. The HATICE intervention platform does not replace existing healthcare in any way, but is offered as an add-on.

The platform is supported by a coach trained in motivational interviewing. All coaches in all three countries work according to a coach protocol set up by the research team. Guided by the preferences of the participant, the coach provides remote support by assisting in realistic goal-setting according to the ‘specific, measurable, attainable, realistic and time bound (SMART) principle.’ Communication between the participant and the coach is through a messaging system within the platform. The coach receives automatic alerts when participants enter measurements or when a participant has not been active on the platform for more than 3 weeks. The coach advises the participant to log in at least once a week, but this is not compulsory.

There are regular national and international meetings with the coaches and the research team to discuss the intervention and to solve discrepancies between countries and coaches.

Participants randomised to the control condition will have access to an internet platform with only the static information on cardiovascular risk factors, but lacking interactive features and the support of a coach.

**Pilot**
Between September 2014 and February 2015 a pilot study was conducted in the three participating countries with a total of 41 participants, in order to test the trial procedure and the platform. We adjusted the protocol and the platform where needed, according to the feedback of the end users; for example, enlargement of electronic buttons, more guidance on the use of the platform (eg, introduction video and more instructions from the coach) and more positive tone of voice (eg, ‘health factor’ instead of ‘risk factor’).

**Primary outcome**
The primary outcome is a composite score based on the average z-score of the difference between baseline and 18 months follow-up values of systolic blood pressure.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>▶ Age ≥65 years</td>
<td>▶ Previously diagnosed dementia</td>
</tr>
<tr>
<td>▶ Available informant</td>
<td>▶ MMSE score &lt;24</td>
</tr>
<tr>
<td>▶ ≥2 Cardiovascular risk factors defined as:</td>
<td>▶ Any condition expected to limit 18 months compliance and follow-up</td>
</tr>
<tr>
<td></td>
<td>▶ Computer illiteracy, defined as unable to send an email</td>
</tr>
<tr>
<td></td>
<td>▶ Severe (visual) impairment interfering with operating a computer</td>
</tr>
<tr>
<td>▶ Hypertension, defined by any of the following:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▶ Diagnosis by specialist or GP</td>
</tr>
<tr>
<td></td>
<td>▶ Currently on antihypertensive drugs</td>
</tr>
<tr>
<td></td>
<td>▶ Baseline BP: if &lt;80 years; ≥140/90 mm Hg; If ≥80 years: systolic BP ≥160 mm Hg</td>
</tr>
<tr>
<td>▶ Dyslipidaemia, defined by any of the following:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▶ Diagnosis by specialist or GP</td>
</tr>
<tr>
<td></td>
<td>▶ Currently on lipid-lowering drugs</td>
</tr>
<tr>
<td></td>
<td>▶ Total cholesterol ≥5.0 mmol/L and/or LDL ≥2.5 mmol/L</td>
</tr>
<tr>
<td>▶ Overweight, defined by any of the following:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▶ BMI ≥30 kg/m²</td>
</tr>
<tr>
<td></td>
<td>▶ Waist circumference men ≥102 cm, women ≥88 cm</td>
</tr>
<tr>
<td>▶ Active smoking</td>
<td></td>
</tr>
<tr>
<td>▶ Lack of physical exercise defined as below the WHO norm of 30 min of intermediate exercise, 5 times a week</td>
<td></td>
</tr>
</tbody>
</table>

AND/OR

**History of cardiovascular disease:** stroke/transient ischaemic attack, myocardial infarction, angina pectoris and/or peripheral arterial disease. (diagnosis by specialist or GP)

**Diabetes mellitus** (diagnosis by specialist or GP)

BMI, body mass index; BP, blood pressure; GP, general practitioner; LDL, low-density-lipoprotein; MMSE, Mini-Mental State Examination.

Table 1 Overview of inclusion and exclusion criteria
low-density-lipoprotein (LDL) and body mass index (BMI). Several considerations have led to the decision for this outcome. First, a multidomain outcome capturing the potential effect of our multidomain intervention on a composite of risk factors was deemed appropriate. Second, no existing cardiovascular risk score can be applied to both primary and secondary prevention, whereas our pragmatic trial targets a mixed population with an indication for primary or secondary prevention. Third, we deemed it inappropriate to include any parameter based on patient-reported measures (eg, physical activity questionnaire) in our primary outcome due to the risk of reporting bias; self-reported parameters were considered insufficiently reliable for the primary outcome.

Secondary outcomes
Main secondary outcomes include the difference between baseline and month 18 on the individual components of the primary outcome, the difference in lifestyle-related risk factors (physical exercise, diet, smoking status), the difference in estimated 10-year cardiovascular disease risk based on the Framingham cardiovascular disease risk score (measured at 18 months), cardiovascular risk factors, aging and dementia risk score (CAIDE), incident cardiovascular disease, mortality, disability, cognitive functioning, incident dementia, physical fitness, mood and cost-effectiveness. The clinical outcomes stroke, myocardial infarction, angina pectoris, peripheral arterial disease, dementia and death will be adjudicated by an independent outcome committee in each country.

Study logistics
The overall study logistics are shown in figure 2. In this trial, each participant will make three visits to the study centre. After the prescreening by telephone, the first (screening) visit will take place. Informed consent will be signed by every participant. Eligibility criteria will be checked by recording blood pressure, weight, height, hip and waist circumference, cognition (Mini-Mental State Examination) and medical history. Blood pressure will be measured twice with an Omron M6 Comfort (HEM-7321-E) device in resting sitting position. After this visit the participants are requested to fill in seven online self-assessment questionnaires at home: Community Healthy Activities Model Program for Seniors physical activity questionnaire, a nutrition questionnaire (adapted from ePredice), 15-item Geriatric Depression Scale (GDS), Late Life Function and Disability Instrument (only disability part), EuroQol EQ5D-3L, Hospital Anxiety and Depression Scale (only anxiety part) and the Partners in Health scale (participant rated self-management measure). Validated versions of these questionnaires in the local languages (Finnish, French, Dutch) will be used, whenever available. If not, the validated English version of the questionnaire was translated according to the proper translation guideline into the three languages. 
Before the baseline visit, a fasting blood sample will be drawn for determining blood glucose, glycated haemoglobin, cholesterol spectrum, C-reactive protein and DNA storage. DNA will be stored locally, but is considered as one biobank. During the second (baseline) visit, which will take place ~2 weeks after the screening visit, all outcome assessment instruments will be applied. Physical functioning will be assessed using the short physical performance battery. Medication use and results of blood tests will be recorded. Cognitive function in different domains will be tested using the Stroop test, auditory verbal learning test and semantic verbal fluency test (animal naming). For the intervention group this visit will be concluded with a motivational interview by the coach and an explanation of the platform to facilitate its use.

At 12 months, the participants are requested to fill in all seven online self-assessment questionnaires again and will receive a telephone evaluation call. Participants from both groups will be called and medication lists will be checked. The participants from the intervention group will have an additional interview with a strong focus on their motivation with their own coach.

At the end of study visit at 18 months all parameters assessed during screening and baseline visits and the online questionnaires are recorded again by an independent assessor, blinded to treatment allocation.

The electronic case report forms are built into the platform and only available for the assessors and researchers. All data will be coded, to assure confidentiality. Data will be managed in one central server for all three countries.

**Randomisation and blinding**

Participants are randomised during the baseline visit in a 1:1 ratio using central randomisation according to a computer-generated randomisation sequence. We decided not to stratify for any characteristic, since the magnitude of the sample size, even within one country, renders any imbalance between the groups extremely unlikely. In case of spouse/partner participation, partners will be allocated to the same treatment arm to prevent contamination. It is explained to participants that they are randomised to one of two internet-platforms to improve lifestyle, without further details.
The coaches who support the participants in the intervention group are not blinded. Outcome assessment at the end of study at month 18 will be carried out by an independent assessor blinded to treatment allocation.

Safety
The intervention is considered low-risk, since no drugs are prescribed and only lifestyle advice and support is provided. Serious adverse events (AE) resulting from the intervention are not expected. No data safety and monitoring board is installed. AEs are however monitored using a 3-monthly questionnaire to be filled in online by the participant in both treatment arms. If the participant is not able to fill in the questionnaire due to a medical condition, the informant will be contacted to fill in the questionnaire. This questionnaire is automatically generated and concerns new cardiovascular events (myocardial infarction, stroke, transient ischaemic attack, angina pectoris, peripheral arterial disease, diabetes mellitus), GP visits and institutionalisation. A logistic algorithm was designed to optimise data collection on AEs and end point during the study (figure 3) and minimise missing data on outcomes.

STATISTICAL ANALYSES
Sample size
We originally based our power calculation on proportions. With advancing insight we decided on a continuous primary outcome, resulting in a new sample size calculation, again taking into account the effect of participants randomised as couples. We based the new sample size calculation on the effect-sizes of the HATICE primary outcome as observed in the preDIVA and FINGER trials.\textsuperscript{14}\textsuperscript{27} In the PreDIVA study the mean difference in z-score of the HATICE primary outcome between baseline and two year follow-up is 0.070 (p=0.002; intervention group −0.194 and control group −0.124). In the FINGER study this mean difference is 0.041 (p=0.11; intervention group −0.128 and control group −0.087). To avoid the risk of being underpowered since the effect was non-significant in the FINGER study, we base our sample size calculation on an effect size of 0.06.

Based on the first 1000 recruitments, we estimate that 17.5% of the participants will be recruited as a couple. Couples can be considered the smallest possible clusters (n=2). Although intra-cluster correlation coefficients (ICC) in RCTs are typically below 0.05, the ICC for vascular and lifestyle-related risk factors within small clusters of relatives may be much higher, up to 0.25.\textsuperscript{47} With 80% power, a 0.05 two-sided significance level, accounting for an estimated 14% attrition based on previous experiences in our own multi-domain prevention study,\textsuperscript{14} an ICC of 0.25\textsuperscript{47} and an effect size of 0.06 the required sample size is estimated to be 2534 participants in total. To allow for unexpected factors we raise this to 2600. Because the meaning of a difference in z-scores is difficult to interpret, we estimated the threshold for a

Figure 3  Periodic end point and adverse events check questionnaire during trial. AE, adverse event; AEQ, adverse event/end point questionnaire; C, coach or research assistant; CVD, cardiovascular disease; P, participant.
clinically relevant difference in z-score by using the follow-up data in preDIVA for clinical outcomes. For this purpose we compared preDIVA participants who did develop CVD or dementia with those who didn’t during an average follow-up of 6.7 years. In preDIVA the change in z-score after 2 years was $-0.205$ in participants who developed CVD or dementia and $-0.146$ in participants who did not develop CVD or dementia. We therefore assume that a difference of 0.059 on the composite primary outcome of HATICE can be considered as clinically relevant.

**Data analysis**

For the primary analyses we will use a univariate general linear model to assess the effect on the primary outcome. All analyses will be according to the intention-to-treat principle. No imputation of the outcome. For the primary analyses we will use a univariate general linear model to assess the effect on the primary outcome.

**Economic evaluation**

The economic evaluation of this trial will be performed as a cost-effective analysis (CEA) with the costs per patient with a reduced risk of CVD and cognitive decline as outcome parameter. Additionally, a cost-utility analysis (CUA) will be performed with the costs per quality adjusted life year (QALY) as outcome parameter. A healthcare perspective will be taken with a comparison of costs and QALYs from a lifetime perspective combines study and literature data on costs and QALYs from a lifetime perspective.

The opportunity arises if the intervention proves effective, the health states at the end of the 18 months of follow-up differ between the groups and such difference in health states is expected to have an impact on need for healthcare for the remainder of their lifetime. If so, the groups will continue to differ by their costs of healthcare and the costs per QALY may shift for the better. If the 18 months costs per QALY are already acceptable against existing standards of societal willingness to pay per QALY at the time of analysis and further improvement is expected, then no modelling scenario is needed to underpin reimbursement decisions. If the costs per QALY are unacceptable despite proven effectiveness, then modelling is needed to find out the impact of the lifetime perspective on the cost-effectiveness acceptability of the lifestyle internet platform. Modelling of costs and QALYs from a lifetime perspective combines study and literature data on costs and QALYs in different stages of cardiovascular disease and/or cognitive impairment on the one hand with literature data on risks (hazard rates) of disease progression. If modelling seems opportune, then the current study will include the design for a subsequent modelling study.

**DISCUSSION**

In HATICE, we will study the effect of an internet intervention to improve lifestyle-related risk factors for CVD, with the aim to improve the whole cardiovascular risk profile and preventing cardiovascular mortality and morbidity, including cognitive decline. The wide and still growing access and use of the internet offers an excellent possibility to deliver an eHealth intervention in a scalable and cost-effective way. By focusing on the perspective of older people during the development phase, we have built an intuitive, easy to use platform, allowing for widespread use among older adults with only limited computer skills. The pilot of this study showed that the platform was easy to use and appreciated by the participants.

Improvement in physical activity can already be reached by regular walking, exercise groups and brief exercise advice by mail in a cost-effective way.50 A Cochrane meta-analysis showed that interactive computer-based
interventions are effective for weight loss and weight maintenance. Also, support and self-management in changing lifestyle leads to improved health outcomes, and a stronger long-term effect. Using an innovative interactive approach based on the stimulation of self-management with coach support in HATICE can potentially lead to scalable and cost-effective methods to contribute to healthy ageing and the prevention of cardiovascular disease and cognitive decline.

The choice of primary outcome was carefully made. A clinically relevant outcome parameter, such as incident cardiovascular disease or dementia, would have required a longer follow-up or a significantly larger sample size, both not deemed feasible. As such HATICE can be considered a large proof-of-principle trial.

HATICE is a pragmatic trial, targeting a mixed population and delivering primary and secondary prevention. This precludes the use of one of the established cardiovascular risk scores (eg, Framingham, SCORE, which are validated for either primary or secondary prevention) as a primary outcome. Despite its limitations, a combined z-score of measurable risk factors is in our opinion the best reflection of an effect on the cardiovascular risk profile in a heterogeneous population with different risk factors present at baseline.

The different source populations will result in differences in characteristics of participants from the three countries. This resulting heterogeneity increases external validity of the results to a wider population and will allow for secondary analyses on the effect of the intervention in different populations.

The effects of the intervention can be quite different in each of the participating countries, since the implementation of cardiovascular risk management in these three countries is organised differently. The extensive experience of the research team in the different participating countries with large randomised prevention trials (FINGER, MAPT and PreDIVA) in older populations facilitates the execution of this large RCT.

Although many older people use the internet nowadays, those who feel confident enough to participate in an eHealth trial might be higher educated. This will influence the generalisability and will have to be taken into account when interpreting the results particularly when assessing effect on cognition.

In our primary outcome we have included BMI. Although this may not be the best anthropometric parameter to reflect the risk of cardiovascular disease associated with obesity, it is the least subject to bias during assessment (as opposed to waist circumference or waist-hip ratio).

In spite of the blinded outcome assessment at the final follow-up visit, a certain degree of unblinding due to participant’s expression of experiences with the platform might occur.

The pragmatic design of the intervention, independent of existing healthcare structures, will facilitate easy and wide implementation throughout Europe, if proven effective. The tailor-made character of the intervention specifically suited to the needs of older individuals fits with the current development towards a more personalised approach in medicine.

Ethical approval and dissemination

Results from this study will be published in a peer-reviewed journal electronically and in print.

Author affiliations

1Department of Neurology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
2Department of Neurology, Radboud University Medical Center, Nijmegen, The Netherlands
3Institute of Clinical Medicine/Neurology, University of Eastern Finland, Kuopio, Finland
4Department of Public Health and Primary Care, Cambridge Institute of Public Health, University of Cambridge, Cambridge, UK
5Department of General Practice, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
6Department of Information and Operations Management, ESCP Europe, Paris, France
7Vital Health Software, Ede, The Netherlands
8Aging Research Center, Karolinska Institutet/Stockholm University, Stockholm, Sweden
9Chronic Disease Prevention Unit, National Institute for Health and Welfare, Helsinki, Finland
10INSERM, University of Toulouse UMR1027, Toulouse, France
11Department of Epidemiology and Public Health, Toulouse University Hospital, Toulouse, France
12Clinical Research Unit, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
13Department of Cardiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
14Karolinska Institutet Center for Alzheimer Research, Stockholm, Sweden

Acknowledgements The authors thank the whole HATICE consortium for their contribution to this study. The authors thank the European Union Seventh Framework Programme (FP7/2007-2013) for the funding of the trial. The authors thank Pim Happel and Matthijs van Dorp for their substantial contribution in building the platform.

Collaborators On behalf of the HATICE consortium.

Contributors ER and SJ were responsible for the drafting of the manuscript. ER, MK, SA, HS, CB, WvG, EPMvC and BvG were responsible for the study conception. All authors were responsible for the study design and provided professional or statistical support. All authors approved the final version of the manuscript.

Funding The HATICE trial is funded by the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement number 305374.

Competing interests None declared.

Ethics approval Medical Ethics Committee (MEC) of the Academic Medical Center in Amsterdam, the Comité de Protection des Personnes (CPP) Sud Ouest et Outre Mer in France and the Northern Savo Hospital District Research Ethics Committee in Finland.

Provenance and peer review Not commissioned; externally peer reviewed.

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/
REFERENCES


