Self-testing and self-management of oral anticoagulation therapy in children

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Summary
Children and adolescents on oral anticoagulation therapy (OAT) present special challenges in terms of rapid fluctuations in International Normalised Ratio (INR) values, interruption in daily life due to frequent hospital/doctor visits, and difficulties and pain in the performance of venepuncture. Optimised management of OAT improves the quality of treatment, potentially accomplished by new methods such as patient self-testing (PST) and patient self-management (PSM). A review was performed, identifying 11 trials with children and adolescents. All studies had different methodological problems, predominantly by being non-randomised trials. A total of 284 patients were included with a mean follow-up of 22 months, finding a time within therapeutic INR target range between 63% and 84%. The coagulometers used for estimating the INR values were found to have sufficient precision and accuracy for clinical use, but external quality control is probably advisable.

It can be concluded that PST and PSM are at least as good treatment options as conventional management in highly selected children. Larger studies, preferably randomised, controlled trials using clinical endpoints, are obviously needed in order to elucidate whether these new regimens of treatment are superior to conventional management of oral anticoagulation therapy.

Keywords
Paediatric, self-testing, self-management, anticoagulation, point of care

Introduction

Oral anticoagulation therapy (OAT) with coumarins (vitamin K antagonists) is prescribed for both prophylactic and therapeutic use to patients at increased risk of thromboembolism (1). OAT has a narrow therapeutic index, and monitoring is based on the International Normalised Ratio (INR) conventionally determined on citrated plasma obtained by venepuncture. Appropriate doses of coumarins (e.g. warfarin) are based on the INR measurements.

The indications for long-term OAT in children are somewhat different from those in adults; congenital heart disease dominates followed by deep-vein thrombosis and pulmonary embolism (2). The true incidence of children prescribed long-term treatment is difficult to assess precisely, but an increasing number of children are prescribed OAT (3), especially an increased number of children with congenital heart disease (4). Furthermore, these patients have an increased long-term survival, thereby constituting a growing group of patients on OAT (5).

Despite close monitoring of therapy, thromboembolism and bleeding are common concerns and account for a large proportion of the morbidity and mortality in these patients. In adults major bleedings have an incidence ranging from 0.3 to 13.4 % per year and that of major thromboembolism ranging from 0.4 to 3.5 % per year (6, 7), though highly dependent on selection of patients and definition of events. The quality of OAT in children has improved during the last decades, and the incidence of major complications is now comparable to that in adults (2).

There are different methods of managing OAT including routine care (provided by the general practitioner), hospital outpatient clinics, highly specialised anticoagulation clinics, shared care, use of computer-assessed dosage, patient self-testing (PST) and patient self-management (PSM) (1). PSM is a concept where the patient takes an active part or even a leading role in his/her own treatment. It is the standard treatment in diabetics who measure their blood glucose using a portable apparatus and perform insulin dosage according to this (8). PSM in OAT implies that the patient analyses a drop of blood using a portable coagulometer (INR monitor) and doses coumarins accordingly. In PST the patient performs blood sampling and analysis while a health care provider decides on dosage adjustment (9).

A Cochrane review (10) concluded, that “compared to standard monitoring, patients who self-monitor or self-manage can improve the quality of their oral anticoagulation therapy. The number of thromboembolic events and mortality were decreased without increases in harms. However, self-monitoring or self-management was not feasible for up to half of the patients requiring anticoagulant therapy. Reasons included patient refusal, exclusion by their general practitioner, and inability to complete training”. Accordingly, there is evidence for using PST and PSM for selected adult patients.
In children, fluctuating INR measurements require frequent blood sampling and adjustment of doses (11). Other problems exist: concomitant medication, practical problems such as difficulties in performing venepuncture, interruption of attendance at school, interruption of parental professional engagements, problems when going abroad, and compliance (especially in puberty) (2, 5). Accordingly, PST and PSM may have potential in a paediatric setting, and the aim of this paper was to review different aspects of major importance for PST and PSM in children.

Material and methods

The definition of children and adolescent in this paper is from newborn and up to 18 years of age. When the expression pediatric is used, this is comparable to children and young adults. The involvement required by parents strongly depends on the age of the patient, but parents are always involved to some extent. When referring to the patient, therefore, this implicitly includes parental involvement.

Literature search

Publications were identified through searching the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2011, issue 3) and PubMed (start 1951 to March 2011). The search was supplemented by a review of personal files and a hand search of published reviews. The following strategy was used to search the CENTRAL and adapted appropriately for the PubMed:

(((4-Hydroxycoumarins)[MeSH]) OR (acenocoumar* OR sinkumar OR sinthrome OR sintrom OR mini-sintrom OR syn-coumar OR syncumar OR synthrom) OR (bishydroxycoumarin OR dicoumarin OR dicoumarol) OR (phenprocoumarol OR phe-nylpropylhydroxycumarine OR phenprocoumorn OR falithrom OR liquamar OR marcoumar OR marcumar) OR (bisoumacetate ethyl OR ethylidicoumarol OR carbothoxy dicoumarol OR pelenta OR tromexan) OR (warfarin potassium OR warfarin sodium OR coumadin)) OR (“Anticoagulants”[MeSH]) AND (“Administration, Oral”[MeSH] OR oral*) AND (“Self Administration”[MeSH] OR “Self Medication”[MeSH] OR home based OR self monitoring OR self monitored OR self administ* OR self medication* OR self manag* OR self care)

Based on titles and abstracts articles relevant to the topic and containing original data were selected. Additional relevant articles were identified by review of references in key publications. The final selection of relevant articles was mainly made by the first author. Only articles in English were included.

Effect parameters used in trials with oral anticoagulation therapy

The incidence of major clinical complications namely death, major thromboembolism, and bleeding events, is the best method for quality assessment, but requires many patients. Minor complications are complex to assess and are therefore generally not applicable. Surrogate parameters are often used, since they do not require a large sample. The deviation/variability of the INR measurements correlates with the number of thromboembolism and bleedings events (12). This is often displayed as the variability (standard deviation') of the INR. The number of complications increases in parallel with the time patients spends outside therapeutic INR target range, and therefore time within therapeutic INR target range is often used for assessing the quality of the OAT (12, 13). The quality of treatment can also be measured in terms of patient satisfaction (quality of life). The latter effect parameter needs to be standardised and validated in order to provide useful information (14), and this has recently been achieved (15).

Results

Trials of patient self-testing and patient self-management

Eleven trials have tested PST or PSM in children (3, 4, 13, 16–23). These studies are displayed in Table 1A (design) and Table 1B (results).

Patient self-testing (PST)

PST has been investigated in five small-scale studies (ranging from 14 to 80 patients (mean: 23 patients, median: 28 patients)) (3, 13, 16, 20, 23) with various indications for OAT and predominantly using case-series designs, except for one randomised, controlled trial (13). The mean follow-up time was 16 months (range: 2–13 months, median: 9 months). The time within therapeutic INR target range was between 63.0 and 83.9 %.

Patient self-management (PSM)

Seven studies (4, 13, 17–19, 21, 22) have assessed the feasibility of PSM in children.

The studies ranged from six to 31 patients (mean: 16 patients, median: 19 patients)) with various indications for OAT and a short follow-up (range: 7–90 months, mean: 33 months, median: 23 months). In one study (18), only 30 % (6 patients) of the children performed PSM, and no results were reported for this subgroup. Only case-series designs have been used, except for a single study (13). In

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2010, Bauman et al. (13) published a small randomised controlled trial, where 28 children were randomised to either continue with PST or commence PSM. Follow-up time was one year. There was no difference regarding time within therapeutic INR target range (83.9 and 83.0 %), but the PSM group had a higher quality of life.

### Education/training program for PST/PSM, support and use of dosage algorithms

In PSM, different settings of training are described: during an individual training period of three 2-hour (h) teaching lessons spread

#### Table 1A: Design of studies on self-management and self-testing of oral anticoagulation therapy in children. Non-reported figures are displayed as blank cells.

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Level of evidence</th>
<th>Follow-up (months)</th>
<th>Indication for OAT</th>
<th>Age in years Mean (range)</th>
<th>Method of management</th>
<th>Patients (PSM/control)</th>
<th>INR interval</th>
<th>INR measured (PSM/control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bauman 2010</td>
<td>RCT</td>
<td>Ib</td>
<td>12</td>
<td>MV, TCPC</td>
<td>10 (1 – 19)</td>
<td>PSM vs. PST</td>
<td>14/14</td>
<td>2.0–3.0, 2.5–3.5</td>
<td>Coag/Coag</td>
</tr>
<tr>
<td>Christensen 2001</td>
<td>CS</td>
<td>IV</td>
<td>18</td>
<td>MV, TCPC</td>
<td>9.7 (2.2 – 15.6)</td>
<td>PSM</td>
<td>14/</td>
<td>2.0–3.0, 2.5–3.5</td>
<td>Coag/</td>
</tr>
<tr>
<td>Christensen 2003</td>
<td>CS</td>
<td>IV</td>
<td>43</td>
<td>MV, TCPC</td>
<td>10.6 (1.8 – 18.6)</td>
<td>PSM</td>
<td>22/</td>
<td>2.0–3.0, 2.5–3.5</td>
<td>Coag/</td>
</tr>
<tr>
<td>Günther 2000</td>
<td>CS</td>
<td>IV</td>
<td>28</td>
<td>All indications</td>
<td>7.3 (1.5 – 18)</td>
<td>PSM</td>
<td>6/</td>
<td>2.5–3.5</td>
<td>Coag/</td>
</tr>
<tr>
<td>Mährönen 2004</td>
<td>CS</td>
<td>IV</td>
<td>28</td>
<td>All indications</td>
<td>6.5</td>
<td>PSM</td>
<td>28/</td>
<td>2.0–3.5</td>
<td>Coag/</td>
</tr>
<tr>
<td>Nowatzke 2003</td>
<td>CS</td>
<td>IV</td>
<td>6.5</td>
<td>All indications</td>
<td>14* (2 – 18)</td>
<td>PST</td>
<td>14/</td>
<td>2.0–3.5</td>
<td>Coag/ and Lab/</td>
</tr>
<tr>
<td>Reiss 2006</td>
<td>CS</td>
<td>IV</td>
<td>90</td>
<td>MV</td>
<td>14* (1 – 18)</td>
<td>PST</td>
<td>90/</td>
<td>2.5–3.5</td>
<td>Coag/</td>
</tr>
<tr>
<td>Bauman 2009</td>
<td>CS</td>
<td>IV</td>
<td>All indications</td>
<td>PST</td>
<td>14* (1 – 18)</td>
<td>PST</td>
<td>31/</td>
<td>2.5–3.5</td>
<td>Coag/</td>
</tr>
<tr>
<td>Marzinotto 2000</td>
<td>CS</td>
<td>IV</td>
<td>2</td>
<td>All indications</td>
<td>14* (1 – 18)</td>
<td>PST</td>
<td>23/</td>
<td>2.5–3.5</td>
<td>Coag/</td>
</tr>
<tr>
<td>Massicotte 1995</td>
<td>CS</td>
<td>IV</td>
<td>6.5</td>
<td>All indications</td>
<td>14* (1 – 18)</td>
<td>PST</td>
<td>31/</td>
<td>2.5–3.5</td>
<td>Coag/</td>
</tr>
<tr>
<td>Newall 2006</td>
<td>CS</td>
<td>IV</td>
<td>6.5</td>
<td>All indications</td>
<td>14* (1 – 18)</td>
<td>PST</td>
<td>31/</td>
<td>2.5–3.5</td>
<td>Coag/</td>
</tr>
</tbody>
</table>

Table 1B: Results from studies on self-management and self-testing of oral anticoagulation therapy in children. Non-reported figures are displayed as blank cells.

<table>
<thead>
<tr>
<th>Author</th>
<th>TTI in pct. (PSM/control)</th>
<th>TTI in pct. (PST/control)</th>
<th>Complications (PSM/control)</th>
<th>Complications (PST/control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bauman 2010</td>
<td>83.0/83.9</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Christensen 2001</td>
<td>65.5/</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Christensen 2003</td>
<td>73.1/</td>
<td>2 (death)</td>
<td>1 (major bleeding)</td>
<td>None</td>
</tr>
<tr>
<td>Günther 2000</td>
<td>69.0/</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Mährönen 2004</td>
<td>69.0/</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Nowatzke 2003</td>
<td>63.0/</td>
<td>2 (death)</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Reiss 2006</td>
<td>65.5/</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Bauman 2008</td>
<td>81.7/</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Marzinotto 2000</td>
<td>63.0/</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

out on 27 weeks, the patient gradually takes over the management of the OAT (17, 22). Bauman et al. (13, 23) did 1 h of basic training of the coagulation system and dosage adjustment followed by three months where the patients suggested the dosage, which then had to be approved by the staff in the OAT clinic. Subsequently, they were classified as self-managing. Reiss et al. educated children 6–11 days after a mechanical heart valve operation in one session and had a booster lesson six months later (24). Mähönen et al. applied two sessions on the same day (4). In PST, the education has varied between one (3, 16) and four sessions (20). Examinations have been used in both PST (3, 16, 25) and PSM (17, 22).

Two studies applied dosage algorithms (4, 13), while not in two (17, 22). The remaining studies did not provide information regarding this.

All studies advocated continuous support to the children from the OAT clinic, if questions, complications etc. should arise (e.g. [3, 24, 26]).

<table>
<thead>
<tr>
<th>Author</th>
<th>Coagulometer</th>
<th>Precision</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bauman 2008</td>
<td>CoaguChek® XS</td>
<td>CV = 5.0</td>
<td>Mean diff. = 0.13; 95 % limits of agreement: –0.22 – 0.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Conc. = 98 % (narrow) 98 % (expanded) Median deviation = 5.7 %</td>
</tr>
<tr>
<td>Christensen 2001</td>
<td>CoaguChek®</td>
<td>Median diff. = 5.3 %</td>
<td></td>
</tr>
<tr>
<td>Greenway 2009</td>
<td>CoaguChek® XS</td>
<td>CV = 5.0 – 7.4</td>
<td>Corr. coeff. = 0.81 (compared to standard laboratory)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Corr. coeff. = 0.90 (compared to WHO reference method)</td>
</tr>
<tr>
<td>Ignjatovic 2004</td>
<td>CoaguChek®</td>
<td>Corr. coeff. = 0.885</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Conc. = 88 % (Less than 0.5 INR)</td>
</tr>
<tr>
<td>Nowatzke 2003</td>
<td>CoaguChek® ProTime</td>
<td>CV = 4.9 – 8.0</td>
<td>Corr. coeff. = 0.877</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Corr. coeff. = 0.885</td>
</tr>
<tr>
<td>Marzinotto 2000</td>
<td>CoaguChek®</td>
<td>Corr. coeff. = 0.82 – 0.96</td>
<td></td>
</tr>
<tr>
<td>Mähönen 2004</td>
<td>CoaguChek®</td>
<td>Median diff. = 0.3 INR</td>
<td>Conc. = 70 % (within 0.5 INR)</td>
</tr>
<tr>
<td>Newall 2006</td>
<td>CoaguChek® S</td>
<td>Corr. coeff. = 0.949</td>
<td>95 % limits of agreement = –0.711 – 0.601</td>
</tr>
<tr>
<td>Paioni 2009</td>
<td>CoaguChek® S</td>
<td>Thromboplastin 1:</td>
<td>Mean diff. = 0.067; 95 % limits of agreement: –0.59 – 0.72</td>
</tr>
<tr>
<td></td>
<td>CoaguChek® XS</td>
<td></td>
<td>Conc. = 92 % (narrow1), 94 % (expanded2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thromboplastin 2:</td>
<td>Mean diff. = –0.105; 95 % limits of agreement: –0.67 – 0.47</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Conc. = 95 % (narrow1), 100 % (expanded2)</td>
</tr>
<tr>
<td>Williams 2007</td>
<td>CoaguChek® S</td>
<td>CoaguChek® XS</td>
<td>66 % (within 0.5 INR) 96 % (within 0.5 INR)</td>
</tr>
</tbody>
</table>

Coeff.: Coefficient, Conc.: Concordance, Corr.: Correlation, CV: Coefficient of variation in %, Diff.: Difference, INR: International Normalised Ratio, Lab: Laboratory, MRD: Mean relative difference. 1Both INR measurements are within therapeutic target range, or when both are above the therapeutic range and these pairs are within 0.8 INR units, or when both are below the therapeutic range and these pairs are within 0.4 INR units, or when one is within the therapeutic range and this pair is within 0.5 INR units. 2Both INR measurements are within therapeutic target range, when both are above the therapeutic range, when both are below the therapeutic range, or when one is within the therapeutic range and the pair is within 0.5 INR units.
Selection of patients

Approximately 80% of all adult patients can perform PST, whereas PSM is limited to not more than approximately 50% (10). In children it is difficult to estimate a number. PST is offered as standard OAT (4, 13) in some institutions so it seems reasonable to assume, that a large fraction (approximately 80%) of all children on OAT can and will perform PST. As far as PSM is concerned, no applicable estimate is available. Bauman et al. (13) found that all PST patients were able to perform PSM. It is thus difficult to draw any firm conclusion, other than extrapolating the results from that of adults with an estimated 50% children that can and will perform PSM.

Coagulometer

Several types of coagulometers are available for clinical use (9, 27). All coagulometers work in basically in the same way; a drop (10–30 µl) of capillary whole blood is released by a finger puncture device, applied on the test strip, and inserted into the coagulometer. A clotting process is initiated by thromboplastin and clot formation is subsequently detected. However, the detection of the clot is different from one coagulometer to another and there are minor differences in terms of function.

The CoaguChek® coagulometers (CoaguChek®, CoaguChek® S and CoaguChek® XS) have been intensively investigated both in terms of accuracy and precision and are the most commonly used coagulometers (28). The other types of coagulometers have been applied in only a limited number of studies including only adults.

The CoaguChek® coagulometers have been studied in 10 papers (3, 4, 17, 19, 20, 26, 29–32). The results are displayed in Table 2.

The use of external quality control to survey the performance of coagulometers has been described in a limited number of studies. Christensen et al. (17, 22) used lyophilised plasma, while Mähönen et al. used a split-sample technique (see below).

Discussion

In this review, we found that PST and PSM are feasible methods of OAT management for highly selected children, though the evidence is limited.

The studies had several limitations; no control group, lack of information regarding basic, target and sample population, no information about medication, number of patients not found suitable for PST/PSM, drop-out rate during training, a small number of patients and a relatively short follow-up time. All the studies were observational, except for one (13). This was a randomised, controlled trial where a highly selected group of children already performing PST were randomised to either continue with PST or commence PSM. The results cannot be extrapolated to a vast majority of children on conventionally managed OAT. However, it can be concluded that PSM is at least as good a treatment option as PST in selected children. In their conclusion, the authors called for studies with a larger sample size.

Since PST and PSM require an education/training program in the use of the coagulometer, dosing the coumarin etc., it will merely be applicable for children on long-term OAT (duration > 1 year). Different training schemes are available, all of which are applicable, but no studies have compared the different types of training and examination or the use of dosage algorithms.

In future trials quality of life should be incorporated as an effect parameter using the test developed and validated by Bruce and by Bauman et al. (15, 23).

Coagulometers have been shown to function well and provide acceptably accurate results compared with laboratory results, but high and low INR measurements obtained by the coagulometer should be controlled by the laboratory, since agreement between the coagulometer and laboratory decrease with INR measurements outside the therapeutic INR target range (19). Bauman et al. (5) and Newall et al. (33) have reviewed the literature and recommended the coagulometers for clinical use in children.

Laboratory INR measurements have been standardised worldwide by extensive international work and have been adapted to excessive quality control (34). This has not been the case with coagulometers. Quality control is needed in order to ensure that the coagulometer provide precise and accurate measurements over time (35). It can be done both using internal and external quality control. The former only estimates the functionality of the individual device. Therefore, as a sole quality control it is not sufficient. An external quality control checking the accuracy has been recommended (36). This can be accomplished by different methods (36–38), either by 1) using plasma (with a known INR value) sent from a central laboratory and compared with the result of the coagulometer, 2) comparing INR measured on a certified (calibrated) coagulometer with that of the patient’s coagulometer using five sets of plasma or 3) comparing INR from venous samples analysed in the laboratory with that of the coagulometer (split-sample). The latter method is dependent on the quality of the INR measured in the laboratory, accounts neither for imprecision nor accuracy, is time consuming and does not seem suitable for external quality control. The use of plasma for quality control is therefore recommendable.

Another option is a control system which is primarily aimed at detecting unforeseen incidents or irregularities in the test system or in the patient. If a patient suddenly changes in dose without notice, for example by more than 20%, this should always lead to a control visit and a parallel test with a laboratory-based INR. This will detect changes in either the patient or in test system. However, it cannot be regarded as an external quality control.

In conclusion, coagulometers used in a paediatric setting provide a precision and accuracy generally found to be adequate for clinical use. However, external quality control is advisable (35, 39, 40).

There are several limitations of this review; the design of the included studies is predominantly non-randomised, and the results should be viewed in light of this. Conclusions should be judged with caution. Publication bias is also possible, especially in case-series design.

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The future of OAT will change with more specialised OAT centres managing many patients on OAT, providing a variety of methods of managing OAT within the centre (e.g. computer-based dosing program, PST, and PSM) which will be offered on an individualised basis (1). The use of information technology will also increase in the coming years, such as interactive anticoagulant home pages, e-learning, interactive voice response systems, PST and dosage provided on-line (41, 42). These issues will be highly relevant for the pediatric population and their caregivers.

PST and PSM in these settings seem obvious, but the degree of success depends on many factors, e.g. economy, tradition, trends, and patient demands. New anticoagulant drugs are being developed, and one example are direct thrombin inhibitors (43). Initially they will predominantly be indicated for patients with a relatively low risk of thromboembolism (e.g. atrial fibrillation with a low CHADS2 score), but not for patients with a high risk, e.g. mechanical heart valve patients. Furthermore, many patients already performing PST/PSM will probably continue doing so, if they experience no complications and are satisfied with PST/PSM. Therefore, coumarins and PSM as a management option will still be relevant for many years. In order to replace OAT in children, randomised, controlled trials will have to be conducted (5). This does not seem likely to happen in the near future, because the drugs are merely on their way into the market for adults with a relative low risk of thromboembolism. It will be very difficult to recruit children for a trial who often per se have a high risk of thromboembolism. Accordingly, OAT will still be the preferred treatment for children with an increased risk of thromboembolism.

It is difficult to compare the results of the PST/PSM studies directly with other studies on OAT in children. The evidence for PST and/or PSM as a treatment option is limited, since predominantly observational studies have been published. Furthermore, these trials have only included a limited number of patients with a relatively short follow-up. It can therefore only be concluded that PST and PSM are feasible in a highly selected group of pediatric patients, and the results seem very promising. Coagulometers can be used in a paediatric clinical setting, but external quality control is advisable. Larger studies, preferably randomised, controlled trials using clinical endpoints, are obviously needed in order to elucidate whether these new regimens of treatment are superior to conventional management of OAT.

**Conflict of interest**

T. B. Larsen is a member of an advisory board in Pfizer. The authors declare no other conflict of interest.

**References**