Amiodarone is a cost-neutral way of preventing atrial fibrillation after surgery for lung cancer

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INTRODUCTION

Since Bailey [1] first described cardiac arrhythmias related to lung surgery in 1943, there has been only sparse research into preventing atrial fibrillation (AF), even though it is commonly known to increase the risk of mortality—especially after pneumonectomy, where the risk has been described as being as great as 25% [2]. Furthermore, the onset of atrial fibrillation often causes anxiety in patients, reduces mobility, increases medical costs and prompts more tests and examinations.

Data on the impact of AF on the length of hospital stay (LOS) have been described in retrospective studies but no convincing prospective data have yet been published [3-5].

Medical therapy to control heart rate and restore sinus rhythm has included various anti-arrhythmic drugs but most of these drugs have adverse effects [6-13]. No drug has yet shown superiority but a frequently used anti-arrhythmic drug is amiodarone (Cordarone®), in respect of which the Reduction of Atrial fibrillation Study for patients undergoing Coronary Artery Bypass Grafting (RASCA) showed that a five-day-long, high dose of oral amiodarone after an intravenous administered bolus was a feasible regime that reduced the risk of postoperative AF, without causing detectable side-effects [14]. We therefore directed our research towards the prophylactic agent amiodarone and performed the ‘Amiodarone Prophylaxis for Atrial fibrillation in patients undergoing Surgery for lung Cancer: A Controlled, Randomized, double-blinded Trial’ (PASCART trial) [15]. This study showed a 23% reduction of AF (range: 12-31), and the number needed to treat was 4.4 (range: 3.1-7.8). In total 49 patients developed AF, 38 in the active arm and 11 in the placebo arm (P < 0.001) (N = 242).

Adverse effects were observed in 10 patients, equally distributed in both trial arms.

A five-day prophylactic regimen had been chosen because, in itself, it did not alter the LOS. Accordingly, it was possible to detect whether LOS was influenced by occurrence of AF and the possible cost benefits of using amiodarone as a prophylactic agent to prevent it.

The hypothesis of this sub-study was that a regime combining intravenous bolus and five days of oral amiodarone prophylaxis would reduce the LOS and consequently reduce healthcare costs. The aim was therefore to find out whether the implemented prophylactic regimen was cost-effective.
PATIENTS AND METHODS

Out of about 1.5 million inhabitants in Western Denmark, approximately 150 persons are referred annually to Aarhus University Hospital to undergo surgery for lung cancer. Informed consent was obtained from all eligible patients who were screened and consecutively enrolled for participation in the PASCART trial [15]. Inclusion criteria were (i) elective lobectomy/pneumonectomy, (ii) age above 18 years, (iii) willingness to participate and (iv) provision of informed consent. Exclusion criteria were: (i) previous heart or lung surgery, (ii) resting heart rate below 40 beats per minute, (iii) hypotension with systolic blood pressure below 80 mmHg, (iv) atrial-ventricular blockage of any degree or sick sinus syndrome, (v) pre-operative atrial fibrillation or flutter, (vi) known previous atrial fibrillation or flutter lasting more than one month, (vii) hepatic dysfunction (alanine–amino-transferase level more than twice the normal upper limit), (viii) hyperthyroidism, (ix) pregnancy, (x) breastfeeding, (xi) undergoing treatment with monoaminoxidase inhibitors (MAOI), (xii) QTc interval longer than 440 ms for men and 460 ms for women or (xiii) known adverse reactions to amiodarone.

The regional scientific ethics committee approved the study. The study complied with the Helsinki II declaration and all patients consented to participate; further, it was conducted according to the standards of Good Clinical Practice and was monitored and approved by the Good Clinical Practice-unit at Aarhus University Hospital.

Patients

Two hundred and fifty-four eligible, consecutively enrolled patients undergoing elective lung cancer surgery were included from September 2008 to March 2011: a total number of 386 patients were enlisted during that period but 144 were excluded from the study. The trial flow chart is shown in Fig. 1. Based on a computerized, prospective randomization schedule, they were assigned to receive either the intervention (amiodarone) or placebo. Randomization was performed in variable blocks and stratified by age (≤65 years and >65 years) and pre-operative use of β-blockers. All patients receiving β-blockers pre-operatively continued their treatment throughout the study.

Figure 1: Trial flow chart.
Each patient received a randomization number, which was recorded and sent by fax to the pharmacy at Aarhus University Hospital, along with the patient’s Civil Registration Number. The pharmacy decoded the number, prepared the appropriate infusion and pills and forwarded them— together with a sealed, opaque envelope containing the randomization assignment, to the Department of Cardiothoracic and Vascular Surgery. Baseline characteristics are shown in Table 1.

**Table 1: Baseline characteristics of patients undergoing lung cancer surgery**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Amiodarone group n = 122</th>
<th>Control group n = 120</th>
<th>Fisher’s exact test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, median (minimum–maximum)</td>
<td>66 (46–82)</td>
<td>67 (35–84)</td>
<td>0.44 (8.80)</td>
</tr>
<tr>
<td>Pre-operative use of β-blockers</td>
<td>17 (14%)</td>
<td>14 (12%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Male</td>
<td>60 (49%)</td>
<td>56 (47%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>21 (17%)</td>
<td>16 (13%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Hypertension</td>
<td>48 (39%)</td>
<td>35 (29%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13 (11%)</td>
<td>8 (7%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Current smoker</td>
<td>43 (35%)</td>
<td>47 (39%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>13 (11%)</td>
<td>11 (9%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>2 (2%)</td>
<td>2 (2%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hgb (mmol/l), median (minimum–maximum)</td>
<td>8.3 (5.8–9.9)</td>
<td>8.2 (5.6–10.4)</td>
<td>0.86 (0.88)</td>
</tr>
<tr>
<td>Creatinine (μmol/l), median (minimum–maximum)</td>
<td>66 (33–278)</td>
<td>66 (7–163)</td>
<td>0.21 (24.72)</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone (mU/l), median (minimum–maximum)</td>
<td>1 (0–6)</td>
<td>1 (0–14)</td>
<td>0.52 (1.43)</td>
</tr>
</tbody>
</table>

n: Number; SD: Standard deviation.

### Study design

This was a randomized, controlled, double-blinded trial following the recommendations of the CONSORT Statement, while the analysis of the costs was estimated retrospectively [16].

### Intervention

The morning after surgery, at the intensive care unit, each patient received a bolus infusion containing 300 mg of amiodarone or placebo (dextrose 5% in water) over 20 min at 8 a.m., together with the first 600 mg dose of oral amiodarone or placebo. The oral administration dose of 600 mg amiodarone/placebo was given twice a day, at 8 a.m. and at 6 p.m., for five days.

The patients continued their regular medication until the day of surgery and resumed it at the intensive care unit on the first postoperative day.

### Atrial fibrillation and surgery

Atrial fibrillation was defined as fast, irregular, eddy current activation of the atrium, with neutralization of its contractions. The treatment algorithm followed standard procedures at Aarhus University Hospital or, following transfer, the guidelines at the department in charge of the patient.

All operations were performed under general anaesthesia, with propofol and fentanyl combined with epidural morphine analgesia through an anterior muscle, sparing thoracotomy or video-assisted thoracoscopic surgery (VATS). All patients were intubated with a Carlens double-lumen tube [15].

During surgery, and until discharge from the intensive care unit, the patients were under continuous telemetry monitoring. The following morning, patients were transferred to the ward around 10 a.m.; telemetry monitoring was disconnected; the patients’ heart rhythm was then observed by standard 12-lead electrocardiogram (ECG) and monitored in a continuous report formula. If clinical suspicion of atrial fibrillation or prolonged QT interval was raised, an ECG was obtained. If atrial fibrillation was documented, the study drug was discontinued and the department’s appropriate treatment was initiated. No patients developed prolonged QT interval in this trial, which is why no further action was taken regarding QT prolongation. If patients were transferred to their local hospitals, discharge summaries were collected from those hospitals.

On postoperative day 30, each patient was contacted by a study physician and asked whether or not he/she had developed clinical AF. At the same time, each was asked to contact his or her own physician to obtain an ECG, which was sent to the study group.

### Endpoints

The endpoints of this sub-analysis were:

(a) costs
(b) LOS at Aarhus University Hospital.
(c) combined LOS at Aarhus University Hospital and local hospital.
(d) LOS at the intensive care unit (ICU) and intermediary unit at Aarhus University Hospital.
(e) occurrence of postoperative atrial fibrillation

LOS was defined as time from surgery to discharge.

### Resource costs and statistical analysis

The economic analysis, conducted from the payer’s perspective, included medical costs associated with lung surgery and its...
complications. All costs were measured in 2012 Danish Kroner (DKK) and converted into Euros (€1.00 ≈ DKK 7.8). Perioperative (defined as from admission at the specialist department to the day of discharge to the local hospital) cost for each patient was estimated from resource utilization data collected in the PASCART trial. Total costs were a function of resources consumed (routine and ICU lengths of stay, blood products, utilization acquired) and complications (postoperative stroke, postoperative AMI or in-hospital death). All data on resource usage were collected from the patient records. Unit costs were based on market prices and hospital accounts, where upper and lower limits were applied with 20% margins (Table 2) to perform one-way sensitivity analysis.

Comparison of the endpoints in the two groups was performed using intention-to-treat analysis. The data were analysed using the Stata 9© package (StataCorp, College Station, Texas, USA). Differences in costs and LOS were analysed with unpaired student’s t-test, as a normal probability plot was conducted showing that the data followed normal distribution. Characteristics in Tables 1 and 3 were compared with Fisher’s exact test. A one-way sensitivity analysis was performed to test whether changes in the input cost data could change the results of the study.

RESULTS

Demographics and perioperative data for the patients in each group are shown in Tables 1 and 3. There were no significant differences between the two prophylactic groups. LOS did not alter significantly between the two groups, in terms of intensive care, intermediary unit, ward or overall hospitalization, although the occurrence of atrial fibrillation was lower in the amiodarone group (9 vs. 32%, P < 0.001) (Table 4). All patients were discharged from Aarhus University Hospital in sinus rhythm. The nurse and doctor time spent on a patient with AF was approximately 30 min and, since fewer patients in the amiodarone group developed AF, the cost per patient was lower in the amiodarone group. There were no significant differences between the groups in respect of intensive care treatment (P = 0.49), intermediate care treatment (P = 0.41), treatment on the ward at Aarhus University Hospital (P = 0.51) or at the local hospitals (P = 0.81) (Table 5).

Based on unit costs and the observed usage of healthcare (Table 5), the mean total costs were also similar in the two prophylactic arms, with a mean cost of €7288 per patient (P = 0.23); respectively €8040 (5764–10 315) in the prophylactic arm and €6524 (5544–7504) in the placebo arm.
Patients remaining in sinus rhythm, who incurred a mean cost of stay, with a mean cost of QT interval in this trial. Pulmonary toxicity was found. No patients developed prolonged be traced to the active prophylactic regime. Furthermore no pul-
no difference between the two groups and no side-effects could
that led to discontinuation of the study medication. There was
possible side-effects (bradycardia, hypotension, AV blockage)
or persistent stroke. Five patients in each group experienced
an acute myocardial infarction. No patients developed transient
wide range of cost assumptions.

One-way sensitivity analysis based on Table 2 demonstrated
between the two prophylactic arms, with
been the same but with no immediately obvious difference
study, the calculated average cost per patient would still have
severe illness, which was not found to correlate with amiodarone
administration. If those patients had been excluded from the

Three patients (two in the amiodarone group and one in the
placebo group) were hospitalized for more than 30 days due to
severe illness, which was not found to correlate with amiodarone
administration. If those patients had been excluded from the

One-way sensitivity analysis based on Table 2 demonstrated
that the prophylactic regime entailed the same cost under a
wide range of cost assumptions.

One patient in the placebo group died during the trial, due to
an acute myocardial infarction. No patients developed transient
or persistent stroke. Five patients in each group experienced
possible side-effects (bradycardia, hypotension, AV blockage)
that led to discontinuation of the study medication. There was
no difference between the two groups and no side-effects could
be traced to the active prophylactic regime. Furthermore no pul-
monary toxicity was found. No patients developed prolonged QT
interval in this trial.

Patients experiencing AF had a more expensive postoperative
stay, with a mean cost of €9799 (6882–12 716), compared with
patients remaining in sinus rhythm, who incurred a mean cost of
€6650 (5284–8016) (P = 0.046).

**COMMENT**

In this randomized, placebo-controlled trial, we observed a sig-
nificant reduction in the occurrence of AF by applying a cost-
neutral regime of postoperative amiodarone prophylaxis, which
was not prone to cause any severe side-effects.

Furthermore, when looking at expenditure without focussing
on in hospital stay, the studied regime was cost-neutral due to
increased postoperative care needs for those patients developing
AF, which equalled the expense for the prophylactic regime.

If potential high-risk patients could be selected, this regime
might prove to be cost-beneficial, as it has been shown to minim-
ize the risk of AF, which was shown to extend the in-hospital stay
and expenditure. Several attempts have been made to identify
high-risk patients in terms of perioperative TEE, previous AF, etc.
So far, only age has been found to be a consistent prognostic
factor. Our study indicates that patients, doctors, nurses and
administrators all benefit from introduction of the proposed
prophylactic regime. Patients avoid episodes of AF, blood sam-
ping, insecurity and the risk of embolism attacks. Doctors, nurses
and bio-analysts need not allocate additional time to the
patients. The hospital might save money and resources in respect
of treating complications of AF, such as apoplexy or other
embolus attacks.

**Table 4:** Length of hospital stay and occurrence of atrial fibrillation according to type of treatment with 95% confidence intervals

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Amiodarone (n = 122)</th>
<th>Placebo (n = 120)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS at Aarhus University Hospital, days: mean (95% CI)</td>
<td>8.5 (6.7–10.4)</td>
<td>7.3 (6.7–7.8)</td>
<td>0.21</td>
</tr>
<tr>
<td>LOS at Aarhus University Hospital and local hospital, days: mean (95% CI)</td>
<td>10.6 (8.4–12.7)</td>
<td>9.3 (8.0–10.5)</td>
<td>0.30</td>
</tr>
<tr>
<td>LOS at intermediary unit Aarhus University Hospital, hours: mean (95% CI)</td>
<td>17.2 (1.9–36.4)</td>
<td>16.5 (8.1–25.0)</td>
<td>0.78</td>
</tr>
<tr>
<td>LOS at intensive care unit Aarhus University Hospital, hours: mean (95% CI)</td>
<td>39.3 (19.5–59.2)</td>
<td>26.3 (18.6–33.9)</td>
<td>0.24</td>
</tr>
<tr>
<td>Occurrence of atrial fibrillation</td>
<td>11 (9%)</td>
<td>38 (32%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Occurrence of symptomatic atrial fibrillation</td>
<td>3 (3%)</td>
<td>11 (9%)</td>
<td>0.029</td>
</tr>
</tbody>
</table>

LOS: Length of stay.

**Table 5:** Average cost (€) per patient according to treatment arm

<table>
<thead>
<tr>
<th>Intervention in € (patients)</th>
<th>Intention-to-treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone prophylaxis with liver and thyroid parameters</td>
<td>28.08 (122)</td>
</tr>
<tr>
<td>Extra blood samples</td>
<td>1.56 (11)</td>
</tr>
<tr>
<td>Nurse and doctor time spend</td>
<td>2.33 (11)</td>
</tr>
<tr>
<td>Amiodarone 24 h infusion</td>
<td>0.76 (2)</td>
</tr>
<tr>
<td>X-ray examinations</td>
<td>0.33 (3)</td>
</tr>
<tr>
<td>Direct current conversion</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Bolus infusion initiating atrial fibrillation treatment</td>
<td>0.32 (3)</td>
</tr>
<tr>
<td>Oral treatment of diagnosed atrial fibrillation</td>
<td>0.97 (11)</td>
</tr>
<tr>
<td>Cost at the intensive care unit: mean (95% CI)</td>
<td>2663 (1570–3756)</td>
</tr>
<tr>
<td>Cost at the intermediate care unit: mean (95% CI)</td>
<td>533 (101–965)</td>
</tr>
<tr>
<td>Cost of stay at the ward: mean (95% CI)</td>
<td>697 (335–1059)</td>
</tr>
<tr>
<td>Cost of stay at the intermediate care unit: mean (95% CI)</td>
<td>2946 (1059–3350)</td>
</tr>
<tr>
<td>Cost of stay at local hospital: mean (95% CI)</td>
<td>852 (278–1370)</td>
</tr>
<tr>
<td>Total cost</td>
<td>8040 (5764–10 315)</td>
</tr>
</tbody>
</table>

P-value
Limitations of this research are that any costing studies carry the risk of being relevant only regionally and not being universally applicable, by reason of the enormous variability in health-care delivery models adopted throughout the world. More importantly, the clinical decision-making process and resource allocation is arbitrary, subjective and territorial to the point that they are only specific to the institution.

The strength of our study is that it is a blinded, randomized, controlled trial, carried out without changing the normal routines on the ward. A potential problem with the study is that data on resource usage were collected retrospectively from the patient records and lack of precision in the hospital accounts may bias the unit cost estimates.

Only one other randomized study [17] has so far been published regarding amiodarone prophylaxis against AF following pulmonary resection, where Tisdale et al. concluded that amiodarone prophylaxis significantly reduces the incidence of AF after anatomic pulmonary resection and is associated with a significant reduction in length of intensive care unit stay; but that study was limited by the lack of a double-blinded, placebo-controlled design, which is why the present study is the first to satisfy those criteria.

This prophylactic regimen is therefore a good, feasible, economical and practical way of reducing the risk of postoperative atrial fibrillation among patients undergoing surgery for lung cancer.

Conflict of interest: none declared.

REFERENCES