Trends in long-term oxygen therapy for COPD in Denmark from 2001 to 2010

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KEYWORDS
COPD; Oxygen therapy; Survival; Quality control

Summary
Objectives: To evaluate changes in demographics, incidence, prevalence, treatment modalities, and survival of COPD patients on long-term oxygen therapy (LTOT) from year 2001 –2010 in Denmark.
Methods: All 14,965 COPD patients with COPD treated LTOT in Denmark in the period 2001 –2010.
Results: During the study period, the incidence and prevalence of COPD patients on LTOT increased from 30.5 to 32.2 per 100.000, and from 42.0 to 48.1 per 100.000, respectively. Mean age of patients increased from 73.4 to 74.8 years, \( P < 0.001 \). An increasing number of patients were prescribed LTOT in connection with discharge after hospitalisation for an exacerbation (2001 vs. 2010: 76.5% vs. 91.7%, \( P < 0.001 \)); were prescribed oxygen 15–24 h/day (85.8% vs. 89.5%, \( P < 0.001 \)); had mobile oxygen (56.4% vs. 94.2%, \( P < 0.001 \), and stopped LTOT alive within 6 months (20.6% vs. 30.8%, \( P < 0.001 \)). Ninety-nine percent of the patients received oxygen concentrator or liquid oxygen with no change in the study period (\( P = 0.66 \)).

The median survival on LTOT increased insignificantly from 16.5 to 17.8 months (\( P = 0.12 \)). Women had a lower risk of dying compared with men, with an adjusted hazard ratio of 0.81 (95% confidence interval (CI) 0.78–0.84), \( P < 0.001 \). During the study period, the risk of death for women, compared to men, decreased significantly with a hazard ratio of 0.978 (95% CI: 0.964–0.992) per calendar year.
Conclusions: The incidence of COPD patients on LTOT in Denmark has levelled off during recent years, and the quality of prescribing LTOT and follow up has improved. Women had better survival than men, and this difference has increased during the study period.

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Two randomised studies in the early 80‘ties showed that long-term oxygen therapy (LTOT) under certain circumstances improved survival in hypoaxaemic patients with COPD [1,2]. Since then, LTOT has been widely accepted, and the incidence and prevalence have increased steadily [3–5]. Previous studies have shown that adherence to criteria for LTOT was poor – especially when non-pulmonary specialists including general practitioners were responsible for the treatment [6–9]. Studies on survival of COPD patients on LTOT have reported median survival that varies between approximately 2 years [10,11] and 4 years [2,12]. Information on treatment modalities, adherence to guidelines for LTOT, incidence, prevalence, and mortality stem primarily from older or small studies [3,4,7,13].

In this study of all Danes on LTOT during the first decade of the 21st century, we aimed to evaluate the most recent trends in treatment modalities, incidence, prevalence, and of COPD patients on LTOT.

Methods

Collection of information

The Danish Oxygen Register covers more than 99% of the Danish population, which comprises about 5.4 million inhabitants [4]. In the period from 01.01.2001 to 31.12.2010, 16,250 treatment episodes in 14,965 different COPD patients have been registered. The oxygen suppliers provide information on patients on home oxygen therapy, their prescriptions, and possible termination of therapy. The National Health Services Central Register provided information on diagnosis for LTOT and on vital status up to 31 December 2011. Following coding according to ICD 10 was used to diagnose COPD when LTOT was initiated: either J41–J44 as the primary diagnosis or J96 as the primary diagnosis combined with J41–J44 as the secondary diagnosis. In general, the diagnosis of COPD in Denmark has high validity [14]. Survival rates were calculated in 14,535 patients who started LTOT for the first time in the study period. The mean observation time of this group of patients was 6.0 years (1.0–11.0 years). The regional Ethical Committees and the Data Inspection Board have approved the study.

Guidelines and organization of home oxygen therapy in Denmark

The recommended guidelines for prescribing domiciliary oxygen in Denmark are in line with European guidelines and have not been changed during the study period [15]. In general, only specialists in internal medicine or respiratory medicine can prescribe LTOT. GPs are advised not to prescribe LTOT, but to refer potential patients to the local hospital. The prescribing doctor can choose between large gas cylinders, liquid oxygen or a concentrator alone or combined with small portable gas cylinders. In cases of a large consumption of oxygen, the suppliers will recommend concentrator or liquid oxygen on economic grounds. Liquid oxygen became available in July 1995. It is recommended for the most mobile patients. Due to high weight, liquid oxygen can’t be delivered to patients living in blocks of flats without a lift. In general, the price per day for liquid oxygen is double that of a concentrator, and the price for a concentrator combined with small gas cylinders is in between. All costs of oxygen treatment, including consumption of electricity by oxygen concentrators, are covered by the local hospital.

Statistical analyses

Kaplan Maier test was employed to compare cumulative proportion of mortality. Cox regression model was used to determine whether the year of start of LTOT and gender were individual predictors of survival, and whether there was an interaction between calendar year and gender. The covariates in the multivariate models were age and prescribed oxygen 15–24 h per day. The results of regression analyses are given in terms of estimated relative risks (hazard ratios) with corresponding 95% confidence intervals (CI). The chi-squared and two sample t-tests were used as appropriate to compare differences between groups. Logistic and linear regression analyses were used to test for trends with calendar year as categorical variable. A two-sided p-value of <0.05 was considered significant. Analyses were performed with the statistical package for the social sciences (SPSS) ver. 13.0 (SPSS Inc., Chicago, USA).

Results

Incidence and prevalence of COPD patients on LTOT

On the 31st of December 2001, a total of 2247 COPD patients (42.0 per 100,000 inhabitants) received LTOT (Fig. 1). During the following 9 years, the number of patients on LTOT has increased constantly to reach a prevalence of 48.1 per 100,000 in 2010. Correspondingly, the incidence of oxygen therapy increased insignificantly from 30.5 to 32.2 per 100,000 (Fig. 1).

Patients’ characteristics and treatment modalities

The majority of COPD patients were women and older than 70 years of age (Table 1, Fig. 2). During the study period, the mean age of patients who started LTOT in the study period increased from 73.4 (SD = 9.0) years to 74.8 (9.7) years, p < 0.001 (Table 2). Most of the COPD patients were prescribed oxygen therapy by a hospital doctor immediately after an acute hospitalization, and the number of prescriptions from general practitioners was continuously declining towards zero during the study period. An increasing number of the COPD patients were prescribed oxygen at least 15 h daily and had delivered oxygen concentrator and mobile oxygen, whereas, in general, the oxygen flow remained low (<1.5 L/minute) (Table 2, Fig. 2).

Small, but statistically significant, differences were seen between men and women (Table 1). Compared to men, women started LTOT more often in connection with hospitalization and more often stopped LTOT within the first six months. Women were prescribed a lower oxygen flow than men and the treatment was more often specified to take place for 15–24 h per day.
Mortality

Through the study period, 9377 (64.5%) deaths were observed, and the median survival for the patients increased insignificantly from 16.5 to 17.8 months ($p = 0.12$) (Table 1). The median survival increased from 17.9 to 21.6 months in women ($p = 0.029$), but decreased from 15.5 to 14.0 months in men ($p = 0.61$). Patients who started LTOT in the outpatient clinic had a better survival than patients who started LTOT in connection with a hospital admission (median survival 22.6 months versus 17.1 months; $P < 0.001$).

Females had a lower risk of death compared with males, with a hazard ratio of 0.81 (95% confidence interval (CI) 0.78–0.84), $p < 0.001$, using Cox proportional hazard regression adjusted for age and prescribed oxygen for 15–24 h per day. During the study period, the risk of death for women compared to men decreased significantly with a hazard ratio of 0.978 (95% CI: 0.964–0.992) per calendar year (Fig. 3).

Discussion

This study evaluates temporal trends in LTOT for COPD in Denmark during the period 2001 to 2010. We describe incidence, prevalence, patient characteristics, treatment modalities, adherence to criteria for correctly prescribed oxygen, and survival in all Danish COPD patients on LTOT. The increase in the annual incidence of LTOT in COPD patients has levelled off during the study period. From 1995 to 2001 the incidence increased from 20.5 to 30.5 per 100.000, thereafter only to increase insignificantly to 32.2 per 100.000 the following nine years [4]. An increasing number of clinically unstable COPD patients who had oxygen therapy prescribed immediately after a hospitalisation may explain some of the increase in the incidence. Slightly improved survival could also have contributed to the increase in prevalence.

In general, data on prevalence of home oxygen therapy outside Denmark are either old or based on regional inventories. According to The French Oxygen Register, the

Table 1  Patients’ characteristics, treatment modalities, and survival in COPD patients who started LTOT for the first time in the study period.

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Males</th>
<th>Females</th>
<th>P-value for difference between males and females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (%)</td>
<td>14,535</td>
<td>5836 (40.2)</td>
<td>8699 (59.8)</td>
<td>NA</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>74.1 (9.2)</td>
<td>74.3 (9.3)</td>
<td>74.0 (9.2)</td>
<td>0.10</td>
</tr>
<tr>
<td>Started LTOT within one week after</td>
<td>85.2</td>
<td>83.2</td>
<td>86.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>discharge from hospital, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescribed LTOT by a general practitioner, %</td>
<td>2.4</td>
<td>3.1</td>
<td>1.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prescribed oxygen at least 15 h/day, %</td>
<td>89.9</td>
<td>88.3</td>
<td>91.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oxygen concentrator or liquid oxygen, %</td>
<td>93.0</td>
<td>92.7</td>
<td>93.2</td>
<td>0.23</td>
</tr>
<tr>
<td>Liquid oxygen, %</td>
<td>5.5</td>
<td>5.7</td>
<td>5.3</td>
<td>0.34</td>
</tr>
<tr>
<td>Mobile oxygen, %</td>
<td>66.1</td>
<td>65.8</td>
<td>66.2</td>
<td>0.67</td>
</tr>
<tr>
<td>Oxygen flow, L/minute, mean (SD)</td>
<td>1.48 (0.8)</td>
<td>1.56 (0.9)</td>
<td>1.42 (0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stopped LTOT alive within 6 months, %</td>
<td>25.5</td>
<td>22.4</td>
<td>27.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Survival, months, median (95%-CI)</td>
<td>18.0 (17.4–18.6)</td>
<td>15.0 (14.3–15.8)</td>
<td>20.4 (19.5–21.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI: Confidence interval.

*Among patients who were alive at least six months.
prevalence of COPD patients on LTOT in France was about 28 per 100,000 in 1992 [16], and The Swedish Oxygen Register reported an incidence of approximately 7.4 per 100,000 and a prevalence of 24 per 100,000 in 2000 [3]. When LTOT is prescribed to clinically unstable patients, about 30–50% of the patients don’t fulfil the hypoxaemia criteria at re-evaluation at 2–3 months [2,17]. Therefore, reassessment is recommended after 1–3 months treatment [15]. Accordingly, we found that an increasing number of patients stopped LTOT shortly after starting this treatment, indicating that blood gases had improved, and that LTOT was no longer needed. Supporting an improving quality of LTOT in Denmark, we also found an increasing number of patients with correctly prescribed oxygen (15–24 h per day).

We observed that an increasing proportion of our patients had access to mobile oxygen devices. There could be at least three explanations for this change. More patients could have been supplied with small cylinders as back up for an oxygen concentrator, or the doctors have become more liberal in prescribing mobile oxygen, and finally, patients could actually be more mobile and need portable oxygen regularly. However, increasing age of patients on LTOT and no significant improvement in survival do not support the notion of increased mobility among the patients.

A minority of our patients had liquid oxygen, and this has not changed over time. Similarly, only 2–3% of Swedish patients on LTOT have liquid oxygen [13].

![Figure 2 Trends in patients' characteristics and treatment modalities in COPD patients who started long-term oxygen therapy during 2001–2010.](image)

**Table 2 Patients’ characteristics, treatment modalities, and survival in COPD patients on LTOT: changes between patients who started LTOT 2001 and 2010.**

<table>
<thead>
<tr>
<th></th>
<th>Started 2001</th>
<th>Started 2010</th>
<th>P-level for difference between 2001 and 2010</th>
<th>P-level for trend in the period 2001 to 2010d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (%)</td>
<td>1632</td>
<td>1779</td>
<td>0.13b</td>
<td></td>
</tr>
<tr>
<td>Females, %</td>
<td>59.5</td>
<td>60.1</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>73.4 (9.0)</td>
<td>74.8 (9.7)</td>
<td>&lt;0.001</td>
<td>B = 0.21; P &lt; 0.001</td>
</tr>
<tr>
<td>Started LTOT within one week after discharge from hospital, %</td>
<td>76.5</td>
<td>91.7</td>
<td>&lt;0.001</td>
<td>B = 0.11; P &lt; 0.001</td>
</tr>
<tr>
<td>Prescribed LTOT by a general practitioner, %</td>
<td>3.9</td>
<td>0.3</td>
<td>&lt;0.001</td>
<td>B = −0.18; P &lt; 0.001</td>
</tr>
<tr>
<td>Prescribed oxygen at least 15 h/day, %</td>
<td>85.8</td>
<td>89.5</td>
<td>0.001</td>
<td>B = 0.09; P &lt; 0.001</td>
</tr>
<tr>
<td>Oxygen concentrator or liquid oxygen, %</td>
<td>98.8</td>
<td>99.0</td>
<td>0.66</td>
<td>B = 0.01; P = 0.38</td>
</tr>
<tr>
<td>Liquid oxygen, %</td>
<td>4.6</td>
<td>3.6</td>
<td>0.14</td>
<td>B = −0.03; P = 0.005</td>
</tr>
<tr>
<td>Mobile oxygen, %</td>
<td>56.4</td>
<td>94.2</td>
<td>&lt;0.001</td>
<td>B = 0.11; P &lt; 0.001</td>
</tr>
<tr>
<td>Oxygen flow, L/minute, mean (SD)</td>
<td>1.40 (0.7)</td>
<td>1.50 (0.8)</td>
<td>&lt;0.001</td>
<td>B = 0.01; P &lt; 0.001</td>
</tr>
<tr>
<td>Stopped LTOT alive within 6 monthsa, %</td>
<td>20.6</td>
<td>30.8</td>
<td>&lt;0.001</td>
<td>B = 0.05; P &lt; 0.001</td>
</tr>
<tr>
<td>Survival, months, median (95%-CI)</td>
<td>16.5 (14.8–18.2)</td>
<td>17.8 (15.8–19.8)</td>
<td>0.18c</td>
<td>Hazard ratio 1.00 (0.99–1.01); P = 0.40</td>
</tr>
</tbody>
</table>

CI: Confidence interval.

a Among patients who were alive at least six months.

b Chi²-test used to compare incidences.

c Log Rang test.

d Logistic regression, linear regression, and Cox regression models (per calendar years).
In accordance with data from The Swedish Oxygen Register, we found that the age of the patients on LTOT and the prescribed oxygen flow are increasing [18]. The increasing age of patients and the slightly higher incidence of COPD patients on LTOT may be explained by a "wave" of birth cohorts with high prevalence of COPD rolling over Denmark, which has been suggested by previous Danish studies [19,20]. Although the prescribed oxygen flow is increasing, it’s still significantly lower than in the randomised clinical trials, where flows in the range 1.5–2.5 L/minute were used [1,2].

In contrast to most other countries, more females than males are on LTOT in Denmark and Sweden [13]. We observed small but statistically significant differences between women and men on LTOT: Women started more often LTOT immediately after hospitalisation and stopped more often LTOT within 6 months. They were more often prescribed oxygen at least 15 h per day and a lower flow of oxygen. Finally, women had better survival, and this difference increased significantly during the study period.

Co-morbidities are common in COPD patients on LTOT – especially cardiovascular diseases, which contribute to the high mortality seen in these patients [21]. A Spanish study compared two cohorts of COPD patients after hospital discharge from 1996 to 7 and 2003–4, and found improved long-term survival rates, even after adjusting for covariates [22]. The authors suggested that better management and treatment of COPD and co-morbidities was responsible for the better prognosis. In our study period, better treatment of COPD hospitalised patients has also been documented in Denmark [19]. In addition, we had expected survival of our LTOT patients to improve during the study period due to better treatment of cardiovascular co-morbidities. However, we showed that better survival over time was only observed in females, and to our knowledge this trend in gender related survival among COPD patients has not previously been demonstrated. Another explanation for better survival in females in the study period may be the tendency of starting LTOT in women with less severe COPD or less co-morbidity. Unfortunately, we have no information on co-morbidities, lung function, smoking status, blood gases, actual use of oxygen, and medical treatment of COPD and co-morbidities to evaluate potential changes over time in males and females.

Although survival of our COPD patients has improved slightly, it is still substantially lower than in other countries. The median survival of our patients was 17.8 months compared to 24–36 months in other studies [10–13]. Most of our patients started LTOT in an unstable clinical condition right after a hospital admission, which was related to high mortality. In contrast, only 18% of the Swedish COPD patients initiated LTOT during an exacerbation [3]. We believe that different practice in initiating LTOT (stable or unstable condition) may at least partly explain the higher mortality in our patients compared to patients in the other studies.

In conclusions, the incidence of COPD patients on LTOT in Denmark has levelled of during recent years and the quality of the prescription of LTOT and of the follow up of has improved. Women had better survival than men, and this difference has increased during the study period.

Conflict of interest
The work has been seen and approved by the authors Thomas Ringbaek and Peter Lange. For both authors, there is no conflict of interest.

References


