Causes and Treatment of Chronic Respiratory Failure
Experience of a National Register

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To Jonas, Helena, Emma and Ulla,
my dear family!
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ABSTRACT

Causes and treatment of chronic respiratory failure - experience of a national register

Long-term oxygen therapy (LTOT) or home mechanical ventilation (HMV) can improve survival time in chronic respiratory failure. A national quality register could be an aid to identifying risk markers and optimizing therapy for respiratory failure.

Aims: •To identify risk markers for chronic respiratory failure, especially when triggered by chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF). •To predict sex-related differences in the future need of LTOT for COPD and to study sex related survival rate in COPD patients starting LTOT. •To investigate if HMV is more effective than LTOT alone in treating chronic respiratory failure caused by kyphoscoliosis. •To evaluate the use of quality indicators in LTOT.

Methods: Swedish national registers for LTOT and HMV were established in 1987 and 1996 respectively. They were reconstructed in 2004 to form the web-based register Swedevox. Indications for LTOT were based on the guidelines from the Swedish Society for Respiratory Medicine. The incidence and prevalence of LTOT for COPD were measured annually from 1987 to 2000, and the future need for LTOT was estimated on the basis of the frequency of ever smoking in Sweden in 2001 in different age groups. A postal questionnaire on occupational exposures was completed by 181 patients with severe pulmonary fibrosis who started LTOT between 1997 and 2000, and by 757 controls. Odds ratios (ORs) were calculated. Time to death was evaluated in kyphoscoliotic patients starting HMV or LTOT alone in 1996-2004. Ten quality indicators were defined and evaluated based on data from patients starting LTOT in 1987-2005.

Results: The incidence each year of LTOT in COPD patients increased more rapidly in women than in men (from 2.0 and 2.8/100,000 in 1987 to 7.6 and 7.1/100,000 in 2000 respectively, (p < 0.001)). Women ran a 1.9 times higher risk than men to develop chronic hypoxemia from COPD and had a higher survival rate during LTOT. In men, IPF was associated with exposure to birch dust with an OR 2.7, (95% confidence interval (CI) 1.30–5.65) and with hardwood dust, OR 2.7 (95% CI 1.14–6.52). Patients with kyphoscoliosis showed a better survival rate with HMV than with LTOT alone with a hazard ratio of 0.30 (95%CI 0.18-0.51), adjusted for age, sex, concomitant respiratory diseases, and blood gas levels. There were improvements in the following eight quality indicators for LTOT: access to LTOT, PaO2 ≤ 7.3 kPa without oxygen, no current smoking, low number of thoracic deformity patients without concomitant HMV, LTOT > 16 hours of oxygen/day, mobile oxygen equipment, reassessment of hypoxemia when LTOT was not started in a stable state COPD, and avoidance of continuous oral steroids in COPD. There was a decline in the indicator PaO2 > 8 kPa on oxygen. First-year survival rate in COPD was unchanged.

Conclusions: The incidence and prevalence of LTOT increase more rapidly in women than in men. Survival rate during LTOT in COPD is better in women than in men. Exposure to birch and hardwood dust may contribute to the risk of IPF in men. Survival rate in patients with kyphoscoliosis was three times better with HMV than with LTOT alone. The national quality register for LTOT showed improvements in eight out of ten quality indicators. Levels for excellent quality in the indicators are suggested.

Key words: Chronic obstructive pulmonary disease; pulmonary fibrosis; kyphoscoliosis; respiratory failure; sex; smoking; occupation; survival; long-term oxygen therapy; mechanical ventilation.
SAMMANFATTNING PÅ SVENSKA


Målsättning: • Att identifiera riskmarkörer för kronisk andningssvikt orsakad av kroniskt obstruktiv lungsjukdom (KOL) eller idiopatisk lungfibros (IPF). • Att förutsäga könsrelaterade skillnader vad gäller behov av LTOT mot KOL inom en nära framtid och att studera könsrelaterade skillnader i överlevnad hos KOL-patienter, vilka påbörjar LTOT. • Att studera om HMV är effektivtare än enbart LTOT vid behandling av kronisk andningssvikt orsakad av kyfoskolios. • Att utvärdera effekten av ett nationellt kvalitetsregister och att föreslå utmärkt kvalitet på kvalitetsindikatorer vid LTOT.


Resultat: Det årliga antalet påbörjade LTOT hos KOL-patienter ökade snabbare hos kvinnor än hos män (från 2,0 och 2,8/100 000 under 1987 till 7,6 och 7,1/100,000 under 2000 respektive (p < 0,001)). Kvinnor löpte en 1,9 gånger högre risk än män att utveckla kronisk syrebrist på grund av KOL. Allt fler kvinnor med KOL beräknas påbörja LTOT under de närmaste åren och ännu fler kommer att ha pågående LTOT på grund av KOL. Hos män var IPF associerat med exponering för björkdamm, OR 2,7, (95 % konfidensintervall (CI) 1,30–5,65) och med damm av ädelträ, OR 2,7 (95 % CI 1,14–6,52). Patienter med kyfoskolios, vilka erhöll HMV, hade bättre överlevnadsgrad än de som behandlades med enbart syrgas med en riskkvot på 0,30 (95 % CI 0,18–0,51), korrigerat för ålder, kön, samtigrations lungsjukdom samt blodgasnivåer. Det blev förbättring i följande åtta kvalitetsindikatorer.
för LTOT: Tillgång till LTOT, arteriellt syretryck (PaO₂) ≤ 7,3 kPa med luftandning, ingen pågående rökning, HMV till alla kyfoskoliospatienter som erhåller LTOT, > 16 timmar med syrgas per dygn, portabel syrgasutrustning, omprövning av indikationen för LTOT, om den har påbörjats när KOL inte var i stabil fas samt undvikande av underhållsbehandling med kortisontabletter vid KOL. Det blev minskning i indikatorn PaO₂ > 8 kPa vid andning av syrgas. Överlevnadsgraden första året vid KOL var oförändrad. Under 2005 förmådde > 80 % av länen uppfylla fyra kriterier för LTOT.

**Slutsatser:** Påbörjade behandlingar med LTOT och pågående LTOT ökar snabbare hos kvinnor än hos män. Överlevnaden vid LTOT på grund av KOL är bättre hos kvinnor än hos män. Exponering för damm av björk och ädelträ kan bidra till ökad risk för IPF hos män. Kyfoskoliospatienter hade tre gånger bättre överlevnad med HMV än med enbart syrgas. Det nationella kvalitetsregistret för LTOT visade förbättring i åtta av tio kvalitetsindikatorer. Nivåer föreslås för utmärkt kvalitet för de tio indikatorerna.
CAUSES AND TREATMENT OF CHRONIC RESPIRATORY FAILURE
– EXPERIENCE OF A NATIONAL REGISTER

ORIGINAL PAPERS

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    Respir Med 2007; 101:2207-2212

III  Gustafson T, Franklin KA, Midgren B, Pehrsson K, Ranstam J, Ström K. Survival of patients with kyphoscoliosis receiving mechanical ventilation or oxygen at home.
    Chest 2006; 130:1828-1833

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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>ERS</td>
<td>European Respiratory Society</td>
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<tr>
<td>FEV$_1$</td>
<td>Forced expiratory volume in one second</td>
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<td>FVC</td>
<td>Forced vital capacity</td>
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<tr>
<td>HMV</td>
<td>Home mechanical ventilation</td>
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<tr>
<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>IPF</td>
<td>Idiopathic pulmonary fibrosis</td>
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<tr>
<td>ILD</td>
<td>Interstitial lung disease</td>
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<tr>
<td>kPa</td>
<td>kilopascal</td>
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<td>LTOT</td>
<td>Long-term oxygen therapy</td>
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<td>MRC</td>
<td>Medical Research Council</td>
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<td>NOTT</td>
<td>Nocturnal Oxygen Therapy Trial</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>PaCO$_2$</td>
<td>Arterial carbon dioxide tension</td>
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<tr>
<td>PaO$_2$</td>
<td>Arterial oxygen tension</td>
</tr>
<tr>
<td>PF</td>
<td>Pulmonary fibrosis</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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INTRODUCTION

Chronic respiratory failure
Chronic respiratory failure (arterial partial pressure of oxygen (PaO₂) < 8.0 kPa, with or without arterial partial pressure of carbon dioxide (PaCO₂) > 6.7 kPa while breathing air at sea level),¹ is a serious complication of several pulmonary diseases, chronic obstructive pulmonary disease (COPD) being the most common of them.²⁻⁵ Other major causes include interstitial lung disease (ILD), pulmonary vascular disease and damage to the lungs and bronchi after pulmonary tuberculosis.²⁻⁵ Chronic respiratory failure can also be caused by thoracic deformity, such as kyphoscoliosis and sequelae after pulmonary tuberculosis. In thoracic deformity, hypoventilation with carbon dioxide retention requires special attention.²,³,⁶ Hypoxemia, the main component of respiratory failure, is the result of various combinations of four mechanisms: ventilation-perfusion inequality, hypoventilation, diffusion impairment and shunt, of which ventilation-perfusion inequality is the most important.⁷,⁸ Hypoxemia is dangerous, since it results in tissue hypoxia, causing damage to the internal organs.⁷

Long-term oxygen therapy
The consequence of chronic hypoxemia in COPD is a poor prognosis with reduced time to death.⁹ Oxygen has been used in the treatment of pulmonary diseases since the 1920s.¹⁰,¹¹ Long-term administration of oxygen (LTOT) to COPD patients with respiratory failure was introduced in the 1950s, based on the results of some largely observational studies with small numbers of subjects.¹²,¹³

The results of two large randomised controlled studies confirmed the improvements in survival time after LTOT in COPD patients with severe chronic hypoxemia.¹⁴,¹⁵ The Nocturnal Oxygen Therapy Trial (NOTT) from the US randomised 203 patients with COPD and hypoxemia (PaO₂ ≤ 7.3 kPa or PaO₂ ≤ 7.9 kPa together with pulmonary hypertension or polycythemia) to nocturnal oxygen of 12 hours per 24 hours or continuous oxygen for 24 hours per day. After a mean of 19 months (range 12-24 months), the mortality was 1.94 times higher (p = 0.01) in the nocturnal oxygen group vs. continuous oxygen.
In the British study from the Medical Research Council (MRC), oxygen for at least 15 hours per day at a flow rate of 2 l/min or higher if required to reach a PaO₂ of > 8 kPa was...
compared with no oxygen at all in 87 COPD patients with PaO$_2$ between 5.3 and 8.0 kPa. Most patients were men and 37% were smokers. At 5 years of follow-up, 19/42 patients had died in the oxygen group vs. 30/45 patients in the control group. There was no effect on mortality in men within 500 days.

Later, a study in Poland demonstrated that LTOT had no influence on survival time in COPD patients with mild-moderate hypoxemia, which so far is the only performed study in that area. There was no difference in cumulative survival time over three years between LTOT and no oxygen in 135 COPD patients with PaO$_2$ between 7.4 and 8.7 kPa. These controlled trials on hypoxemic COPD constitute the scientific evidence for several recommendations on the use of LTOT.$^{1,17-21}$

Long-term oxygen therapy is one of the two interventions with positive prognostic effects in COPD, the other being smoking cessation.$^{22-25}$ LTOT actually doubles survival time when administered continuously to severely hypoxemic COPD patients.$^{14,15}$ In contrast, a large recently published study did not clearly show that the combination of inhaled steroid and long-acting beta-2-agonist had life-prolonging effects on COPD.$^{26}$

There is no evidence that LTOT has effects in terms of survival time in other underlying conditions with chronic hypoxemia than COPD. Still, oxygen is believed to reduce dyspnoea and to attenuate the harmful effect of hypoxemia on the internal organs.$^{27}$ Therefore oxygen is recommended when hypoxemia occurs in patients with idiopathic pulmonary fibrosis (IPF) and pulmonary hypertension (PAH) or other disease processes with similar indications as in COPD.$^{2,21,28}$

Despite the doubling of survival time with LTOT administered for chronic severe hypoxemia in COPD, survival time during LTOT is poor, particularly in pulmonary fibrosis and pulmonary hypertension.$^{3-5}$ In COPD, the excess mortality attributable to hypoxemia is eliminated by LTOT$^{29}$ but the mortality attributable to severe obstruction and cardiovascular disease associated with COPD remains.$^{30}$ Therefore, identifying risk markers for chronic respiratory failure and hypoxemia is an important task for improving prevention.

Furthermore, the survival time benefit is only observed in patients with severe hypoxemia.$^{14-16}$ Therefore, it is essential to have adequate patient selection criteria for LTOT. The survival
benefit was doubled when continuous oxygen therapy was administered, as compared with nocturnal treatment. Adequate LTOT, including hours of oxygen use and oxygenation, is also essential to obtain maximum benefit. Adequate LTOT is also decisive to obtain improvements in quality of life.31

A small improvement in quality of life is obtained with LTOT in hypoxemic COPD, but quality of life remains poor during LTOT.31-34 To obtain the benefit of improving quality of life, mobile equipment is decisive for patients active outside home.31 Dyspnoea at exertion can be incapacitating in respiratory failure and oxygen has a limited effect on this symptom.35-38

The aims of this thesis were to study sex as a risk factor for hypoxemic COPD and occupational exposure as a risk factor for pulmonary fibrosis with severe hypoxemia, to identify whether HMV or LTOT is the best treatment in kyphoscoliosis with respiratory failure and to evaluate quality indicators for LTOT. The quality indicators were based on existing evidence and guidelines and our experience of a national register on LTOT.

**Sex-related differences in COPD**

Tobacco smoking and occupational risk factors, as well as malnutrition, poor water supply, sanitation, personal and domestic hygiene, unsafe sexual behaviour, alcohol use, hypertension, physical inactivity, illegal drugs, and air pollution have been identified as major risk factors for death and disability worldwide.39

Tobacco smoking is the dominant risk factor for COPD,19,40,41 after age.42 Smoking is increasing in a global perspective.43 The cigarette consumption per capita worldwide is slowly decreasing, but total smoking has increased continuously over the last decades, mainly owing to population growth. Cigarette consumption is still higher per capita in developed countries, but it is increasing dramatically in the developing part of the world.43 Chronic obstructive pulmonary disease is expected to rise from the twelfth to the fifth leading cause of disability from 1990 to 2020 and from the sixth to the third leading cause of death from 1990 to 2020.44

The tobacco industry has studied smoking patterns and preferred tobacco products among women in detail, and has used this information to make tobacco products specially designed to support recruitment of female smokers.45,46 Tobacco advertising contributes to initiation of
smoking in the population. It is believed that deaths attributable to tobacco use would continue to rise even if comprehensive tobacco control policies were immediately implemented worldwide.

Women are more sensitive than men to the harmful effects of tobacco smoke, according to several studies, and may also be more disposed to developing severe form of COPD. Moreover, in severe COPD the prognosis is worse for women than for men. The effects of long-term oxygen on survival time in women with severe COPD have been less studied than among men. Only 21%-24% of the patients included in previous studies of LTOT and survival time were women.

For many years, the prevalence of COPD has been higher for men than for women. This pattern has been changing in recent years. In Sweden, smoking has decreased gradually since 1980 and since 1990 fewer men than women smoke. In 2005, 14% of men and 18% of women in Sweden were current smokers, or less than 16% of the adults in total. The ratio in a country of prevalence of smoking in younger women to that of older women is thought to be an indicator of the future prevalence of smoking in that country.

The mechanism behind pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is the most common disorder in the group of idiopathic interstitial pneumonias which, in turn, is a subgroup of the diffuse parenchymal lung diseases. The histological pattern is usual interstitial pneumonia (UIP), not specific for IPF. It is a serious disease with poor response to treatment. Idiopathic pulmonary fibrosis is clinically comparable to diffuse interstitial pneumonia (DIP) and nonspecific interstitial pneumonia (NSIP), which carry less severe prognosis than IPF. These are the main alternative interstitial lung diseases (ILD) to IPF. The recommended procedure for differentiation of IPF from the other ILDs is surgical lung biopsy. When it is not possible to perform, the differential diagnosis may rest on accepted major and minor criteria, based on non-invasive techniques. In reality, open lung biopsy is only performed in a small proportion of patients with PF.

The mortality in IPF is high and is increasing. Median survival time is 3-5 years after diagnosis and there is evidence that mortality rates may now be higher than in several
When PF is complicated by respiratory failure, survival time is considerably shorter than in COPD with respiratory failure.\textsuperscript{3,5} Figures for prevalence/incidence are not entirely reliable, owing to a shortage of reports, a low proportion of biopsy verifications of the diagnosis, and reclassification.\textsuperscript{61} The previous highest prevalence (20.2 per 10\textsuperscript{5} in men and 14.3 per 10\textsuperscript{5} in women) and incidence (10.7 per 10\textsuperscript{5} in men and 7.4 per 10\textsuperscript{5} in women per year) was found in a New Mexico county.\textsuperscript{68} A recent survey demonstrated a more than doubling of the incidence between 1990 and 2003 in the United Kingdom.\textsuperscript{64} This increase could not be explained in terms of ageing in the population or improved diagnostic accuracy.

There are several risk factors for IPF, including genetic predisposition and environmental agents.\textsuperscript{61} The knowledge about potentially harmful occupational exposures is largely based on six case-control studies in three countries.\textsuperscript{69-74} According to a meta-analysis of these studies,\textsuperscript{65} there are significant associations between six types of exposure and IPF: ever smoking (1.58 [1.27–1.97]), agriculture/farming (1.65 [1.20–2.26]), livestock (2.17 [1.28–3.68]), wood dust (1.94 [1.34–2.81]), metal dust (2.44 [1.74–3.40]), and stone/sand (1.97 [1.09–3.55]). There is no study from northern Europe on occupational exposure in patients with PF where, for example, occupational exposure to soft wood may be frequent.

**Respiratory failure in kyphoscoliosis**

In respiratory failure, ventilation-perfusion mismatch, reduced area for gas diffusion and alveolar hypoventilation contribute in varying proportions to this physiological disturbance, depending on the underlying disease.\textsuperscript{7,8} Kyphoscoliosis causes impaired ventilatory mechanics, which may result in considerable alveolar hypoventilation, especially during sleep.\textsuperscript{75-79} It has been demonstrated that breathing at low lung volumes often leads to airway obstruction.\textsuperscript{80-82} Many of these patients therefore have both a restrictive and obstructive respiratory disorder and may develop both hypercapnia and hypoxemia in varying combinations. Therefore, the selection criteria for both LTOT and for HMV are often fulfilled. The respiratory and cardiac failure caused by kyphoscoliosis results in a poor prognosis.

Several studies suggest that early initiation of HMV in kyphoscoliotic patients may prevent the onset of overt respiratory failure.\textsuperscript{83,84} The mechanisms for the effect seem to be improved respiratory drive,\textsuperscript{85,86} improved respiratory muscle function,\textsuperscript{87-89} but not necessarily affecting of sleep architecture.\textsuperscript{90} Consequently, there is a positive effect on daytime blood gases from
INTRODUCTION

HMV during the night to patients with hypoventilation, which is observed early in the treatment. The benefits of HMV as compared with LTOT has recently been shown in a small retrospective follow-up by Buyse et al. 

Earlier studies comparing LTOT with HMV in patients with severe thoracic spine deformity are either short-term or retrospective, and small in terms of number of subjects. Randomised controlled trials on this issue are generally considered ethically difficult to justify.

According to figures from quality registers in Sweden and France, LTOT is prescribed for a substantial number of patients with respiratory failure caused by kyphoscoliosis. In the Swedish Oxygen Register the annual number of new patients with kyphoscoliosis registered when starting LTOT remained stable since 1987. This was a matter of concern, since the Swedish Society of Respiratory Medicine has recommended HMV for these patients since 1993. Since several patients with severe thoracic spine deformity are prescribed LTOT without concomitant HMV we found it important to compare the impact on survival time of the different treatment modes in a large patient group.

Quality in long-term oxygen therapy

The main goal of LTOT in relation to hypoxemic COPD is to improve survival time. To attain this goal, patient selection and performance are of utmost importance. Long-term oxygen therapy is effective in COPD with severe hypoxemia. This treatment method is complicated, and the portable oxygen is fairly expensive. Therefore, it is important to assure the quality of LTOT with use of a number of appropriate quality parameters, and guidelines constitute the first step in this direction.

Guidelines on LTOT

The indications for LTOT are described in a number of guidelines, among them the Global Strategy for the Diagnosis, Management, and Prevention of COPD, and in the statement from the American Thoracic Society (ATS) and the European Respiratory Society (ERS). Guidelines consist of patient selection criteria and criteria for performance of LTOT.

According to the guidelines from the Swedish Society of Respiratory Medicine, LTOT is indicated for patients with:

- chronic hypoxemia owing to COPD or other diseases,
• a stable disease course on optimum medical therapy for at least three weeks, and
• arterial oxygen tension (PaO$_2$) when breathing room air $\leq$ 7.3 kPa ($<$ 7.0-7.5 kPa before 1993) or signs of cor pulmonale or haematocrit $> 50 \%$ plus room air PaO$_2$ of 7.4-8 kPa (around 7.5 kPa before 1993).

The prescription of LTOT to current smokers is discouraged.

Arterial blood gas samples are taken with the patient at rest and after having breathed air for a minimum of 20 minutes. Arterial blood gas samples are taken on oxygen after having breathed the prescribed flow of oxygen for a minimum of twenty minutes.

**Performance of LTOT**

According to the Swedish guidelines, oxygen should be prescribed as many hours as possible per day, preferably 24 hours.$^{21}$ A resting PaO$_2$ of above 8 kPa when breathing oxygen is recommended.

The stationary oxygen supply through the concentrator should be supplemented with mobile equipment in patients with outdoor activity.

Reassessment of the indication for LTOT should be performed after one and three months, when LTOT is initiated owing to an exacerbation of COPD.$^{20}$

**Quality indicators**

*Patient selection criteria*

Access to LTOT – Given above, it is important to identify and provide LTOT to patients who fulfil the selection criteria. In the mid 1980s there were large variations in the number of LTOT patients among the different counties in Sweden, which caused concern among respiratory physicians and was the rationale for the start of the Swedish Oxygen Register in 1987.$^{2}$

Level of hypoxemia – Contrary to severe hypoxemia, patients with mild to moderate hypoxemia should not be prescribed long-term oxygen, unless the hypoxemia is accompanied by pulmonary hypertension or raised haematocrit levels.$^{1,17-19}$ Consequently, the selection of appropriate patients should be essential in LTOT.$^{14-16}$

Smoking - According to the Swedish guidelines for LTOT, current smoking is an obstacle to prescription of LTOT, because of the risk that ongoing smoking will jeopardize the treatment...
results. Cigarette smoking has been shown to inhibit the benefits of oxygen on secondary polycythemia, and a previous study demonstrated association between continued smoking during LTOT and increased mortality. There is also a risk of fire accidents, of which there are a few reports.

Kyphoscoliosis - Since alveolar hypoventilation is an important pathophysiological mechanism when kyphoscoliosis is the reason for chronic hypoxemia, oxygen alone is insufficient as therapy in these patients. Instead, HMV during the night is often recommended as the first treatment, since it has favourable physiological effects, including improved daytime blood gases. Many patients with kyphoscoliosis and respiratory failure receive supplemental oxygen especially those who also have concomitant respiratory disease, but the mortality is higher when oxygen is given without concomitant HMV, according to data from a large French register and a Belgian retrospective follow-up study.

Performance of LTOT

Correction of hypoxemia – The target for resting arterial oxygen tension is chosen from the procedure in the NOTT and the MRC studies, where the subjects were given a flow rate of oxygen sufficient to reach PaO₂ 60-80 mmHg (equal to 5.3-8.0 kPa) and 60 mmHg, respectively. The level of oxygen in the arterial blood has to be raised to alleviate hypoxia in the body tissues, and the results of LTOT thus depend on adherence to adequate achievement of arterial oxygenation. In some patients, retention of carbon dioxide can make it difficult to reach adequate oxygenation with the oxygen supply.

Treatment time per day – Appropriate duration of treatment with oxygen per day is also important for the outcome of LTOT, according to the findings in the NOTT and the MRC studies. Oxygen should be supplied for at least 15 hours per day, and the effects on survival time are increased if the treatment time is extended beyond that, up to 24 hours per day.

Portable oxygen equipment – The possibilities of reaching appropriate treatment time increases if the patient has suitable equipment. For this purpose, addition of portable oxygen equipment to the stationary equipment has a positive effect in patients who spend time outside their home.
Reassessment of LTOT after initiation during COPD exacerbation – It is often necessary to start LTOT during recovery from an exacerbation of COPD instead of awaiting the stable level of oxygenation. Some patients will then experience improved arterial oxygen levels during a three-month period, making LTOT no longer needed. Under those circumstances, recent guidelines recommend a recheck of arterial blood gases after 30-90 days.19,100,101

Concomitant treatment
Avoidance of continuous oral glucocorticosteroids in COPD – Temporary treatment with oral glucocorticosteroids in acute exacerbations has beneficial effects on recovery time, lung function and hypoxemia1,19 but long-term treatment with oral glucocorticosteroids is not recommended in COPD, because no treatment effects have been shown and there are serious side effects.1 An association has been found between oral steroid medication and increased mortality in female LTOT patients3,102 and higher mortality in LTOT patients with high body mass index receiving oral glucocorticosteroids has also been demonstrated.103

Results of treatment
Survival time – According to the results from the NOTT and MRC studies, LTOT can double survival time in COPD patients with severe hypoxemia.14,15 Those studies were performed on selected patients, who were younger and had fewer co-morbidities than the average patients who have later received LTOT.104 The survival time in COPD patients may be lower in clinical practice than in the randomised controlled trials,14,15 according to the findings of an Australian study,104 where the patients were older and had multiple co-morbidities. However, when selected according to similar criteria as in the NOTT and MRC studies, survival time in Swedish COPD patients receiving LTOT was similar.102,105

Implementing guidelines for management of LTOT are recognized as being difficult.106,107 Adherence to the LTOT guidelines varies in different countries and different areas in the countries.3,98,108-110 A national register provides a basis for evaluation and subsequent improvement.
AIMS

The objectives of this thesis were to identify possible strategies for the prevention and postponement of the development of chronic respiratory failure as well as to assure the quality of treatment of chronic respiratory failure.

The specific aims were
- To identify risk markers for chronic respiratory failure, particularly female sex in chronic obstructive pulmonary disease and occupational exposure in pulmonary fibrosis.

- To predict the future incidence and prevalence of chronic hypoxemia in chronic obstructive pulmonary disease on the basis of sex-related prevalence in smoking.

- To study sex related survival time in COPD patients who start LTOT.

- To identify the best treatment of chronic respiratory failure caused by kyphoscoliosis, comparing home mechanical ventilation or long-term oxygen alone.

- To evaluate the effects of a national quality assurance register and to suggest levels for excellent quality for quality indicators in long-term oxygen therapy.
MATERIAL AND METHODS

STUDY DESIGN
Paper I: Register study of cohorts as well as cross-sectional data
Paper II: Retrospective case control study
Paper III: Cohort study
Paper IV: Prevalence study on county level and national level

STUDY POPULATIONS

The Swedish Oxygen Register
The Swedish Oxygen Register was established in 1987 with the two main purposes of gaining knowledge of treatment effects and long-term prognosis in LTOT and improving the quality of LTOT in chronic hypoxemia. The principal quality aspects were to optimize: access to therapy, adherence to national guidelines for LTOT and performance of LTOT. The register is used for a prospective cohort study of patients receiving oxygen for chronic hypoxemia at the start of LTOT, including patients who were already on LTOT when the register was established. The LTOT patients are reported from the responsible physicians at the Swedish centers for LTOT, one or more in each Swedish county. Follow up is recorded one year after inclusion.

Specially trained physicians and nurses are responsible for the LTOT in each county, which is the relevant unit. Annual meetings are held for reporting of the results from the register, for training, and thereby to achieve gradual improvements in LTOT. The statistics from the register are also annually distributed in written forms.

A large number of variables for each patient are were registered at inclusion, when their LTOT is started. A selection of these variables has been registered since the start of the Register and others during limited periods.
Table 1. Registered data in patients receiving LTOT (selection)

<table>
<thead>
<tr>
<th>Inclusion record form</th>
<th>Follow up record form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swedish census registration number</td>
<td>Swedish census registration number</td>
</tr>
<tr>
<td>Sex</td>
<td>County</td>
</tr>
<tr>
<td>County</td>
<td>Number of in-hospital days</td>
</tr>
<tr>
<td>Arterial blood gas tensions</td>
<td>Reason of withdrawal of oxygen</td>
</tr>
<tr>
<td>PaO₂ (air)</td>
<td>Date for withdrawal of oxygen</td>
</tr>
<tr>
<td>PaCO₂ (air)</td>
<td></td>
</tr>
<tr>
<td>PaO₂ (oxygen)</td>
<td></td>
</tr>
<tr>
<td>PaCO₂ (oxygen)</td>
<td></td>
</tr>
<tr>
<td>Cause(s) of hypoxemia</td>
<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
</tr>
<tr>
<td>Current medication</td>
<td></td>
</tr>
<tr>
<td>Presence of ankle oedema</td>
<td></td>
</tr>
<tr>
<td>WHO performance status</td>
<td></td>
</tr>
<tr>
<td>FEV₁ and FVC</td>
<td></td>
</tr>
<tr>
<td>Oxygen therapy</td>
<td></td>
</tr>
<tr>
<td>Equipment</td>
<td></td>
</tr>
<tr>
<td>Prescribed flow rate</td>
<td></td>
</tr>
<tr>
<td>Prescribed daily treatment time</td>
<td></td>
</tr>
</tbody>
</table>

FEV₁: forced expiratory volume in one second; FVC: forced vital capacity

Figure 1. Causes of hypoxemia in patients receiving LTOT 1987-2005 according to sex.
Register coverage
Sweden had a population of 8.4 million in 1987 and 9.1 million in 2006. The register covers approximately 85% of the LTOT patients. The coverage is internally validated with surveys to the reporting centers about every other year. Four of the 24 counties were unable to report all LTOT patients to the register, owing to shortages of staff during some part of the period 1987-2000.

Data from the Swedish Oxygen Register were used in Papers I-IV.

The Swedish Home Ventilator Register
The Swedish HMV Register was established 1996 with the purpose of allowing international and national comparisons of indications, dissemination of methods and results. All the Departments of Respiratory Medicine and all other medical units prescribing oxygen or home mechanical ventilation in all Swedish counties report all patients who start HMV, and they are then followed prospectively with survival time as a primary outcome. Among the data registered is Swedish census registration number, sex, arterial blood gas tensions when breathing air, and presence of a concomitant respiratory disease.

Register coverage
The Register covers at least 90% of the Swedish patients treated with HMV according to repeated internal validations.

Data from the Swedish HMV Register were used in Paper III.

In November 2004, the Swedish Oxygen Register and the Swedish HMV Register were reconstructed and merged to form the Swedevox Register, which is entirely web-based.

The Swedish Oxygen Register and the Swedish HMV Register were approved by all regional ethic committees and by the Swedish Data Inspection Board. The registers were funded by the Swedish National Board of Health and Welfare as national quality assurance registers.

The Causes of Death Register is kept by the Swedish National Board of Health and Welfare, and comprises all deceased Swedish citizens during a calendar year. Among the information in the register are Swedish census registration numbers, cause or causes of death, time of
death and results of autopsy if performed. The International Classification of Diseases (ICD) is used for classification of causes of death.

Official statistics in Sweden are produced by the government agency Statistics Sweden, or *Statistiska centralbyråns* (SCB), housing the Swedish Population Register, which also contains information about date of death for people living in Sweden.

**Data analyses**
In Paper I, we analysed data from the Swedish Oxygen Register, comparing this data with the dates of death from the Swedish Causes of Death Register. In Papers III and IV, we analysed data from the Swedish Oxygen and HMV registers with dates of death from the Swedish Population Register. In the COPD patients in Paper IV, we investigated the survival rates during the first year of LTOT, adjusted for age and sex. We also analysed the age-adjusted overall survival according to the year of starting LTOT and sex.

**Statistical methods**
The Chi-squared test was used in Papers I and III for comparisons of categorical data.

The Student’s t-test was used in Paper I for comparisons of continuous data.

Analyses of variance were used in Paper III for comparison analyses of continuous data.

Cox regression analysis was used in Paper I to analyse time to death adjusted for age, in Paper III to assess the effects of treatment method on survival rate and in Paper IV to assess first-year and overall survival rates standardised for sex and age 70 years.

The Mantel-Haenszel chi-squared test was used in Paper II to calculate odds ratios for PF and IPF.

Linear regression analyses were used for adjustment of age and other confounders in time-trend analyses of continuous variables in Paper I.

Logistic regression analysis was used in Paper I for age-adjusted analyses of category variables and in Paper II to adjust for overlapping exposures between occupations.
The photograph in the printed version has been removed in the electronic version

Figure 2. Young girls smoking cigarettes
PAPER I – Sex-related differences in LTOT in COPD

Patient population
We included all LTOT patients aged 18 and over with hypoxemia attributable to COPD who were registered between 1 January 1987 and 31 December 2000 (n=5,689). We acquired the vital statistics on each patient through 31 December 2003 and the dates of death from the Causes of Death Register at the Swedish National Board of Health and Welfare.

Women were slightly younger than men at the start of LTOT (p < 0.001). The mean age of both sex increased during the study years. In 1987, the mean age of the women was 66 ± 8 years and that of the men 67 ± 9 years. In 2000, the mean age of women had increased to 73 ± 9 years (p < 0.001) and the mean age of men to 74 ± 8 years (p < 0.001). Seventy-three per cent of the women and 70% of the men had PaO₂ ≥ 7.3 kPa at the onset of oxygen therapy. Three hundred and ninety-four patients were excluded since they were registered in the four counties that withdrew from the study for part of the time. They did not differ in age and sex from the included patients.

Mean arterial PaO₂ was slightly lower and mean PaCO₂ was higher in women than in men when starting oxygen therapy. Mean PaCO₂ at the start of treatment gradually decreased in men from 1987 to 2000, but remained stable in women.

Table 2. Baseline characteristics of COPD patients at start of LTOT.

<table>
<thead>
<tr>
<th></th>
<th>Women n = 2,894</th>
<th>Men n = 2,795</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>70 ± 9</td>
<td>72 ± 9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PaO₂ (kPa)</td>
<td>6.6 ± 1.0</td>
<td>6.7 ± 0.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PaCO₂ (kPa)</td>
<td>6.6 ± 1.2</td>
<td>6.1 ± 1.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PaO₂ (oxygen) (kPa)</td>
<td>9.0 ± 1.1</td>
<td>9.0 ± 1.2</td>
<td>0.95</td>
</tr>
<tr>
<td>PaCO₂ (oxygen) (kPa)</td>
<td>6.9 ± 1.2</td>
<td>6.4 ± 1.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FEV₁ (liters)</td>
<td>0.6 ± 0.3</td>
<td>1.0 ± 0.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FVC (liters)</td>
<td>1.4 ± 0.5</td>
<td>2.1 ± 0.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Peripheral oedema (%)</td>
<td>58</td>
<td>52</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Smoking history (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>4</td>
<td>3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Past</td>
<td>85</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>11</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented in per cent or as the means ± SD
The predicted incidence and prevalence of the need for LTOT was calculated from the frequency of ever smoking in Sweden in 2001 in different age groups, according to Statistics Sweden:

Table 3. Ever smoking in men and women according to age in 2001.

<table>
<thead>
<tr>
<th>Age</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>16-24</td>
<td>23.5</td>
<td>30.1</td>
</tr>
<tr>
<td>25-34</td>
<td>33.6</td>
<td>37.9</td>
</tr>
<tr>
<td>35-44</td>
<td>43.4</td>
<td>52.4</td>
</tr>
<tr>
<td>45-54</td>
<td>63.9</td>
<td>59.5</td>
</tr>
<tr>
<td>55-64</td>
<td>69.9</td>
<td>54.0</td>
</tr>
<tr>
<td>65-74</td>
<td>64.1</td>
<td>41.8</td>
</tr>
<tr>
<td>75-84</td>
<td>66.3</td>
<td>30.3</td>
</tr>
</tbody>
</table>

In the prediction of future need for LTOT, we assumed that age at the start of treatment for men and women would be the same as in 2000 and that the relation between the prevalence and incidence would continue to be the same as from 1987 to 2000.

The incidence of LTOT was calculated as in the following example:
The mean percentage of ever smoking in Sweden in women in the age group of 64-84 years old of was 36.4% in 2001. This age group corresponds closely to the age range of women receiving oxygen in 2000 (73 ±9 years). Five years later, in 2006, there would thus be 41.8% of women who had ever smoked among women in the age group for starting LTOT, and the incidence of LTOT was therefore calculated as being 1.15 times higher (41.8/36.4) in 2006 than in 2000 (when the incidence was 7.65 per 100,000) which would have been 8.78 per 100,000. Fifteen years later, in 2016, the incidence would be 1.48 times higher (54.0/36.4) than in 2000.

Prevalence of LTOT was calculated as in the following example:
We first calculated the annual quotient between prevalence and incidence which, in women, was 2.76 per 100,000 in 1988 and 3.47 per 100,000 in 2000. The mean increase for every year
was 0.054. The prevalence of oxygen in the year of 2006 was therefore calculated as the predicted incidence in 2006 (in women: 8.78 per 100,000) multiplied by the expected quotient in 2006 i.e. the quotient in 2000 plus 6 x 0.054 (in women 3.79 per 100,000). This gave an expected prevalence of 8.78 x 3.79 = 33.28 per 100,000 in women in the year of 2006. The mathematical model is therefore: Expected prevalence year X = expected incidence year X x ((prevalence year 2000/incidence year 2000) + (X-2000 x ((prevalence year 2000/incidence 2000) – (prevalence year 1987/incidence 1987))/13)).
The photograph in the printed version has been removed in the electronic version

Figure 3. Inside a timber industry.
PAPER II - Occupation and pulmonary fibrosis

We included as cases all patients (n=241) registered when starting LTOT for chronic hypoxemia triggered by PF between 1 February 1997 and 4 April 2000. In the analysis, we divided the cases into two groups, namely all cases (the PF sample), and a restricted sample of cases (the IPF sample), after exclusion of all subjects with known aetiology of their fibrosis.

The data from the Oxygen Register and the questionnaires did not allow verification of IPF according to accepted major and minor criteria. When identifying the IPF patients we therefore excluded all patients with host susceptibility or known external agents. We then assumed that the remaining patients had IPF, being the largest group of the idiopathic interstitial pneumonias serious enough to cause chronic respiratory failure.

We selected as controls a random sample (n=1,000) from the general population of Sweden with the same age range as the cases. We sent an extensive postal questionnaire to the cases and the controls, described below.

The questionnaire was completed by 193 PF patients (cases). Twelve (6%) were excluded due to erroneous diagnosis in the Oxygen Register. Hence, 181 subjects were included in the PF sample. From this sample we excluded 27 subjects because of rheumatoid arthritis (n=14), scleroderma (n=4), Sjögren’s syndrome (n=2) and other diseases such as systemic sclerosis and systemic lupus erythematosus (n=7). An additional 14 cases were excluded because of known aetiology, viz. asbestosis (n=6), silicosis (n=5), and irradiation or drug-induced PF (n=3). Hence, 140 cases were included in the IPF sample. Of the 1,000 controls being sent the questionnaire, 757 responded.

For each patient answering the questionnaire, the responsible physician was sent a questionnaire about drugs used the ten years before debut of the disease, any irradiation treatment, year of first symptoms and diagnosis, investigations performed, grounds for diagnosis and the physician’s opinion of the possible aetiology of the PF. In the IPF sample, 75 had been examined with high resolution computer tomography of the lungs and ten had lung biopsy, open or video assisted.
These are the baseline data for the cases and controls with regard to age and smoking status.

Table 4. Description of the study population. The cases were the subjects in the PF sample (n=181), where the IPF sample (n=140) was included.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td>n=114</td>
<td>74.4</td>
<td>64.2</td>
<td>72.0</td>
<td>63.4</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=349</td>
<td>64.2</td>
<td></td>
<td>63.4</td>
<td></td>
</tr>
<tr>
<td>Never-smokers (%)</td>
<td>15.7</td>
<td>38.7</td>
<td>54.5</td>
<td>52.6</td>
</tr>
<tr>
<td>Ex-smokers (%)</td>
<td>80.6</td>
<td>46.2</td>
<td>43.8</td>
<td>27.4</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>3.7</td>
<td>15.1</td>
<td>1.7</td>
<td>20.0</td>
</tr>
</tbody>
</table>

Figure 4. Flow chart showing the selection of cases and controls for the study.

The postal questionnaire sent to the cases and controls included details about their occupation, specific occupational exposure, drugs used and smoking habits. The wording of the items in the questionnaire was as follows, covering 29 different types of occupational exposure:
Table 5. Questions about occupational exposure in the questionnaire.

**Have you ever been exposed to**
- welding fumes?
- mineral dust?
- coal dust or graphite dust?
- man-made mineral fibres?
- ceramics dust?
- asbestos?
- grain dust?
- flour dust?
- dust from pine or fir?
- dust from birch?
- dust from hardwood?
- paper dust?
- textile dust?
- radiation?
- fire fumes?
- engine exhausts?
- irritating gases (ammonia, chlorine dioxide, chlorine gas, sulphur dioxide)?
- environmental tobacco smoke?

**Have you worked with**
- grinding, polishing, milling, turning or other processing of metals?
- soldering?
- blasting?
- chrome-platering or nickel-platering?
- birds?
- moldy hay or straw?
- solvents?
- cutting oils/fluids?
- rapid glues (Loctite®, cyanoacrylates or Omnifit®)?

**Have you worked as a** dentist, dental technician or dental nurse?

The cases and referents were divided into the following three groups according to year of birth: 1906–1923, 1924–1936 and 1937–1969. The cases were diagnosed in 1968–1999. We further divided them into three groups according to their year of diagnosis, as follows: 1968–1986 (41%), 1987–1993 (28%) and 1994–1999 (31%).

Relevant exposure was exposure that had occurred before the onset of PF, approximated as the year of diagnosis. It was also necessary to define an anchor point in time for each control. Hence, in each birth year group the controls were randomly assigned to a year of diagnosis group. The number of controls allocated to each year of diagnosis group was weighted by the number of actual cases. Each control was then assigned the mid-year in his or her year of diagnosis group as the anchor year.
Subjects had to report exposure five years or more before diagnosis to be classified as exposed. Consequently, exposure occurring during the 5-year period immediately prior to the diagnosis was not included in the analysis. Exposures were merged into five categories in the final analysis: occupational, organic dust, wood dust, inorganic dust, and metal dust.

Two groups of cases were analysed, the whole group of cases (the PF sample) and the restricted sample (the IPF sample). The cases and controls were stratified for sex, age group, and birth year group. Odds ratios (ORs) were calculated. Only exposure categories with five or more exposed cases were considered in the final analysis.

Figure 5. A woman with kyphoscoliosis.

*The photograph in the printed version has been removed in the electronic version*
PAPER III – Ventilation or oxygen in kyphoscoliosis

All men and women with respiratory failure caused by non-paralytic kyphoscoliosis, i.e. scoliosis not related to neuromuscular disorders, registered when starting LTOT or HMV between 1 January 1996 and 31 December 2004 were included (n=244). We acquired the vital statistics before 15 February 2006 and the dates of death from the Swedish Population Register.

The mean age of all patients was 69 ± 11 years. One hundred and sixty-seven were women and 77 were men. Twenty-seven of the 100 patients who received HMV also received supplementary oxygen therapy. Three patients were ventilated via tracheostomy and the rest with nasal or oro-nasal masks. Mechanical ventilation was prescribed during sleep, i.e. for less than eight hours to 75% of the patients and for more than 12 hours to only two per cent of patients. All of 144 patients who received oxygen therapy alone were prescribed oxygen for 16 to 24 hours per day. Five patients who started with oxygen alone and later received supplementary mechanical ventilation were grouped according to the initial treatment.

Table 6. Baseline characteristics of patients with kyphoscoliosis starting treatment with home mechanical ventilation or oxygen in Sweden, 1996-2004.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HMV (n = 100)</th>
<th>LTOT alone (n = 144)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.4±12.7</td>
<td>73.5±8.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Women (%)</td>
<td>68</td>
<td>69</td>
<td>0.95</td>
</tr>
<tr>
<td>Concomitant respiratory disease (%)</td>
<td>33</td>
<td>65</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PaO2 (kPa)</td>
<td>7.5±1.7</td>
<td>6.4±0.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PaCO2 (kPa)</td>
<td>7.6±1.2</td>
<td>6.9±1.3</td>
<td>0.002</td>
</tr>
</tbody>
</table>
The photograph in the printed version has been removed in the electronic version

Figure 6. A man with portable oxygen equipment.
PAPER IV - Quality in long-term oxygen therapy

We prospectively followed all registered adults starting LTOT for chronic hypoxemia before 1 January 2006 until death or 31 December 2006 (n=12,187). We did not include patients receiving LTOT for a short period as part of palliative treatment for cancer of the lung, whether primary or secondary.

Our quality indicators

Patient selection criteria

From 1987 and onwards:
- Access to LTOT as the number of LTOT patients per 100,000 inhabitants
- Percentage of patients with PaO₂ ≤ 7.3 kPa when breathing air, daytime at rest
- Percentage of patients who are not current smokers

From 1993 and onwards:
- Small number of patients with thoracic deformity without concomitant HMV

Performance of LTOT

From 1987 and onwards:
- Percentage of patients with PaO₂ > 8 kPa when breathing oxygen
- Percentage of patients with prescribed dosage of oxygen > 16 hours per day

1989-2004:
- Percentage of patients with access to mobile oxygen equipment, registered at follow-up after one year

From 2002 and onwards:
- Percentage of COPD patients with reassessment of hypoxemia when breathing air if LTOT was not started in a stable state, registered at follow up after one year

Concomitant treatment:

1987-1989 and from 1995 and onwards:
- Percentage of COPD patients without continuous oral glucocorticosteroids

Result of treatment: First-year survival rate in COPD

1987-2004:
- First-year survival rate among COPD patients
Use of quality indicators
The county level of achievement for each quality indicator was given for comparisons with the national level reached by all participating centers in the annual reports and from the start of the web-based Swedevox register. With the individual levels obtained from these centers as guidance, a recommended level of achievement was chosen as a marker of excellent quality, according to the individual levels obtained from the centers, e.g. XX% of patients have PaO$_2$ > 8 kPa when breathing oxygen (Table 14).

Each quality indicator was analysed by comparing data from 1987 and 2005, or at some other start and end year, as described above.

Table 7. Baseline characteristics of patients starting LTOT 1987-2005.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No patients</td>
<td>12 187</td>
</tr>
<tr>
<td>% men</td>
<td>49</td>
</tr>
<tr>
<td>Age, years</td>
<td>71±9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cause(s) of hypoxaemia, no patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>8446</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>1431</td>
</tr>
<tr>
<td>Thoracic deformity</td>
<td>605</td>
</tr>
<tr>
<td>Pulmonary vascular disease</td>
<td>461</td>
</tr>
<tr>
<td>Sequelae of pulmonary tuberculosis</td>
<td>262</td>
</tr>
<tr>
<td>Other causes</td>
<td>982</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arterial blood gas tensions, kPa</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO$_2$ (air)</td>
<td>6.6±1.0</td>
</tr>
<tr>
<td>PaCO$_2$ (air)</td>
<td>6.2±1.3</td>
</tr>
<tr>
<td>PaO$_2$ (oxygen)</td>
<td>9.0±1.3</td>
</tr>
<tr>
<td>PaCO$_2$ (oxygen)</td>
<td>6.5±1.3</td>
</tr>
</tbody>
</table>
Figure 7. Age of COPD patients at the start of LTOT according to starting year and sex.
RESULTS

PAPER I – Sex-related differences in LTOT in COPD

Observed and predicted incidence and prevalence

The incidence of LTOT increased among women from 2.0/100,000 in 1987 to 7.6/100,000 in 2000 (p < 0.001), and among men from 2.8/100,000 in 1987 to 7.1/100,000 in 2000 (p < 0.001). From 1997 and onwards, more women than men started LTOT each year.

Figure 8. Incidence of COPD patients starting LTOT according to start year and sex.

The prevalence of women on LTOT increased more rapidly than that of men. In 1987, 50% of the COPD patients were women, and in 2000, 58%. Among the women, the prevalence of LTOT increased from 5.5/100,000 in 1986 to 26.5/100,000 in 2000 (p < 0.001), and among the men LTOT prevalence rose from 5.7/100,000 to 19.3/100,000 during the observation period (p < 0.001).
Results

Figure 9. Prevalence of COPD patients starting LTOT according to start year and sex.

Risk for need of LTOT in women

In the age group receiving oxygen, i.e. ages 65-84 years, the overall frequency of ever smoking in Sweden was 36.4% in women and 65.0% in men in 2001.112 The incidence of LTOT for the indication COPD was, however, slightly higher in women in 2000, indicating that women with COPD ran a 1.9 times higher risk of needing LTOT to treat respiratory failure. The frequency of ever smoking decreased with age among women, while the opposite trend was seen in men (Table 3).

Future perspectives

We predict that the incidence and prevalence of LTOT will increase in women from 2006 to 2036, since smoking frequency is increasing among middle-aged women and since smoking women have a high risk of developing end-stage COPD requiring oxygen therapy.
Figure 10. Registered and predicted incidence of COPD patients receiving LTOT according to year and sex. The dotted lines indicate the predicted incidence.

We also predict that about 70% of patients on oxygen in 2026 will be women, with a prevalence of 61 per 100,000 women as compared with 29 per 100,000 men.

Figure 11. Registered and predicted prevalence of COPD patients receiving LTOT according to year and sex. The dotted lines indicate the predicted prevalence.
**RESULTS**

**Hours of oxygen and survival time**

In 1987, 42% of patients were prescribed oxygen from compressed gas cylinders and 58% were prescribed oxygen from concentrators. The percentage of patients using concentrators rose rapidly, to 97% in 2000. Liquid oxygen was prescribed in 2-3% of patients after 1993, when it was introduced in Sweden. Slightly more men than women were prescribed oxygen for \( \geq 20 \) hours per day, \( p=0.041 \). Two percent of women were prescribed oxygen for less than 15 hours per day, 60% for 15-17 hours per day, 9% for 18-19 hours per day and 29% for 20-24 hours per day. In the case of men, 2% were prescribed oxygen for less than 15 hours per day, 59% for 15-17 hours per day, 8% for 18-19 hours per day and 31% for 20-24 hours per day.

The median (1\(^{st}\) and 3\(^{rd}\) quartile) survival time after the start of treatment was 2.8 (2.6-2.9) years in women and 2.0 (1.9-2.1) years in men (Figure 12). First-year survival rate was 77\% (95% CI 75-79\%) in women and 69\% (95% CI 67-71\%) in men. The relative risk of death for men vs. women was 1.21 (95% CI 1.14-1.28) according to a Cox regression adjusted for age. In patients who were withdrawn from LTOT within one year from the start of treatment, death was the reason for withdrawal in 88\% of women and 91\% of men. Improvement in oxygenation breathing ambient air, and non-compliance were other reasons for withdrawal during the first year of treatment.

Figure 12. Survival rate in men and women receiving LTOT 1987 -2000.
RESULTS

PAPER II - Occupation and pulmonary fibrosis

Subjects with occupational exposure had an increased risk for PF, but not for IPF. Exposure to wood dust increased the risk for PF but not for IPF. There was no increased risk for either PF or IPF in relation to exposure to metal dust.

Table 8. Odds ratio, stratified by sex, year of diagnosis, birth year and smoking, for the PF sample (n=181) and the IPF sample (n=140) according to occupational exposure.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>PF sample</th>
<th>IPF sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n*</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>Any occupational exposure</td>
<td>123</td>
<td>1.6 1.06–2.37</td>
</tr>
<tr>
<td>Organic dust</td>
<td>69</td>
<td>1.4 0.98–2.12</td>
</tr>
<tr>
<td>Wood dust</td>
<td>34</td>
<td>1.7 1.03–2.95</td>
</tr>
<tr>
<td>Inorganic dust</td>
<td>57</td>
<td>1.2 0.79–1.97</td>
</tr>
<tr>
<td>Metal dust</td>
<td>37</td>
<td>1.0 0.62–1.69</td>
</tr>
</tbody>
</table>

When stratifying the analyses for sex, we observed the highest risks of developing PF among men. Exposure to wood dust among men doubled the risk of developing PF.

Table 9. Odds ratio, stratified by year of diagnosis, birth year and smoking, for the PF sample divided into men (n=114) and women (n=67), according to occupational exposure.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Men, PF</th>
<th>Women, PF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n* OR 95% CI</td>
<td>n* OR 95% CI</td>
</tr>
<tr>
<td>Any occupational exposure</td>
<td>89 1.7 0.95–3.12</td>
<td>34 1.5 0.84–2.55</td>
</tr>
<tr>
<td>Organic dust</td>
<td>54 1.7 1.04–2.70</td>
<td>15 1.1 0.56–2.10</td>
</tr>
<tr>
<td>Wood dust</td>
<td>33 2.1 1.18–3.65</td>
<td>– n.a. –</td>
</tr>
<tr>
<td>Inorganic dust</td>
<td>54 1.4 0.84–2.23</td>
<td>– n.a. –</td>
</tr>
<tr>
<td>Metal dust</td>
<td>34 1.1 0.62–1.79</td>
<td>– n.a. –</td>
</tr>
</tbody>
</table>

We then analysed the risks of developing PF and IPF according to all the detailed exposures. These analyses were performed in men and women together, and were restricted to exposures affecting five or more cases. The exposure categories are not mutually exclusive. An increased risk of PF was associated with exposure to mineral dust, birds, flour dust, dust from pine or fir, birch dust, hardwood dust and fire fumes. In cases of IPF the exposures giving
increased risk were only birch dust and hardwood dust. The OR for flour dust and IPF were just below significance level.
Table 10. Odds ratio for the PF sample and the IPF sample according to occupational exposure, stratified by sex. Only exposures with five or more exposed cases were considered. Number of controls exposed for each occupational exposure, divided into men and women.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>PF (n=181)</th>
<th>IPF (n=140)</th>
<th>Controls, men (n=349)</th>
<th>Controls, women (n=408)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>OR 95% CI</td>
<td>n</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>Welding fumes</td>
<td>24</td>
<td>1.1 0.64–1.78</td>
<td>15</td>
<td>0.8 0.42–1.42</td>
</tr>
<tr>
<td>Grinding, polishing, milling or turning or other processing of metals</td>
<td>22</td>
<td>1.0 0.57–1.64</td>
<td>15</td>
<td>0.8 0.43–1.44</td>
</tr>
<tr>
<td>Soldering</td>
<td>13</td>
<td>0.9 0.47–1.65</td>
<td>9</td>
<td>0.7 0.31–1.38</td>
</tr>
<tr>
<td>Blasting</td>
<td>7</td>
<td>3.2 1.10–9.32</td>
<td>–</td>
<td>n.a.</td>
</tr>
<tr>
<td>Mineral dust</td>
<td>27</td>
<td>2.4 1.39–4.06</td>
<td>14</td>
<td>1.4 0.74–2.72</td>
</tr>
<tr>
<td>Coal dust or graphite dust</td>
<td>11</td>
<td>1.8 0.83–3.82</td>
<td>9</td>
<td>1.8 0.80–4.07</td>
</tr>
<tr>
<td>Artificial mineral fibres</td>
<td>22</td>
<td>1.2 0.67–2.00</td>
<td>14</td>
<td>0.8 0.45–1.57</td>
</tr>
<tr>
<td>Asbestos</td>
<td>26</td>
<td>1.2 0.72–2.00</td>
<td>15</td>
<td>0.8 0.44–1.47</td>
</tr>
<tr>
<td>Birds</td>
<td>16</td>
<td>2.3 1.22–4.34</td>
<td>10</td>
<td>1.7 0.82–3.62</td>
</tr>
<tr>
<td>Moldy hay or straw</td>
<td>12</td>
<td>1.4 0.68–2.68</td>
<td>8</td>
<td>1.1 0.50–2.48</td>
</tr>
<tr>
<td>Grain dust</td>
<td>17</td>
<td>1.3 0.70–2.21</td>
<td>12</td>
<td>1.1 0.57–2.15</td>
</tr>
<tr>
<td>Flour dust</td>
<td>18</td>
<td>2.1 1.14–3.76</td>
<td>13</td>
<td>1.9 0.98–3.74</td>
</tr>
<tr>
<td>Pine or fir dust</td>
<td>32</td>
<td>2.1 1.31–3.47</td>
<td>20</td>
<td>1.4 0.82–2.52</td>
</tr>
<tr>
<td>Birch dust</td>
<td>16</td>
<td>2.6 1.32–5.18</td>
<td>13</td>
<td>2.4 1.18–4.92</td>
</tr>
<tr>
<td>Hardwood dust</td>
<td>10</td>
<td>2.4 1.05–5.69</td>
<td>9</td>
<td>2.5 1.06–5.89</td>
</tr>
<tr>
<td>Source</td>
<td>No.</td>
<td>Mean</td>
<td>CI</td>
<td>No.</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>-----</td>
<td>------</td>
<td>--------------</td>
<td>-----</td>
</tr>
<tr>
<td>Paper dust</td>
<td>9</td>
<td>1.3</td>
<td>0.60–2.91</td>
<td>6</td>
</tr>
<tr>
<td>Textile dust</td>
<td>13</td>
<td>1.4</td>
<td>0.74–2.72</td>
<td>10</td>
</tr>
<tr>
<td>Radiation</td>
<td>6</td>
<td>0.9</td>
<td>0.36–2.28</td>
<td>5</td>
</tr>
<tr>
<td>Solvents</td>
<td>28</td>
<td>1.3</td>
<td>0.79–2.05</td>
<td>19</td>
</tr>
<tr>
<td>Fire fumes</td>
<td>8</td>
<td>2.9</td>
<td>1.10–7.58</td>
<td>5</td>
</tr>
<tr>
<td>Engine exhausts</td>
<td>24</td>
<td>0.9</td>
<td>0.54–1.50</td>
<td>15</td>
</tr>
<tr>
<td>Irritating gases (ammonia, chlorine dioxide, chlorine, sulphur dioxide)</td>
<td>13</td>
<td>1.5</td>
<td>0.79–3.00</td>
<td>10</td>
</tr>
<tr>
<td>Environmental tobacco smoke</td>
<td>53</td>
<td>1.0</td>
<td>0.71–1.45</td>
<td>40</td>
</tr>
<tr>
<td>Cutting oils/fluids</td>
<td>8</td>
<td>1.0</td>
<td>0.43–2.23</td>
<td>5</td>
</tr>
<tr>
<td>Rapid glues (Loctite®, cyanoacrylates or Omnifit®)</td>
<td>6</td>
<td>1.0</td>
<td>0.37–2.45</td>
<td>6</td>
</tr>
</tbody>
</table>
When we analyzed men and women separately with five or more exposed subjects to a group, risks remained increased for IPF in men exposed to birch dust \((\text{OR} 2.7, 95\% \text{ CI} 1.30–5.65)\) and hardwood dust \((\text{OR} 2.7, 95\% \text{ CI} 1.14–6.52)\). Men with IPF also had an increased OR associated with birds \((\text{OR} 2.7, 95\% \text{ CI} 1.00–7.06)\). There was no increased risk for any of the exposure subgroups in women.

Ten patients with PF reported occupational exposure to hardwood dust. There was also information about occupations in the questionnaire. The occupations with the longest duration of exposure to hardwood dust were wood products machine operator, forester, cabinet makers, machine operator, telephone service worker and blacksmith. There were also two carpenters and two subjects who did not report their occupation.

We also analysed the material using a latency period of 10 years instead of 5 years, with similar results. The same exposures were associated with increased risks, but the risks were slightly higher. In order to explore a cohort effect, we ran the analyses with the population divided into two groups according to the mean birth year, 1930. We found no clear indication of any cohort effect.

With the logistic regression models, we observed similar results. Exposure to organic dust (and wood dust) increased the risk of PF, especially among men. No significant associations were found when we modelled IPF as the dependent outcome.

### Table 11. Logistic regression models for the PF sample giving odds ratios (and 95% confidence intervals) adjusted for sex, smoking, year of birth and year of diagnosis.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>All PF patients ((n=181))</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inorganic dust</td>
<td>1.1 (0.70–1.68)</td>
<td>1.1 (0.70–1.83)</td>
<td>0.55 (0.12–2.53)</td>
</tr>
<tr>
<td>Organic dust</td>
<td>1.5 (1.00–2.15)</td>
<td>1.7 (1.06–2.8)</td>
<td>1.2 (0.60–2.22)</td>
</tr>
<tr>
<td>Metal dust</td>
<td>0.98 (0.61–1.58)</td>
<td>0.97 (0.58–1.63)</td>
<td>0.82 (0.17–3.82)</td>
</tr>
<tr>
<td>Wood dust</td>
<td>1.9 (1.12–3.15)</td>
<td>2.1 (1.22–3.75)</td>
<td>0.50 (0.06–4.11)</td>
</tr>
</tbody>
</table>
PAPER III – Ventilation or oxygen in kyphoscoliosis

More patients started LTOT alone than HMV during the whole study period (Figure 13). Figure 13. The annual number of patients starting HMV or LTOT 1996-2004.

Thirty-two of the 100 (32%) patients on home mechanical ventilation and 110 of the 144 (76%) patients on oxygen therapy alone had died at follow-up. Age above 70 years, suffering from concomitant respiratory disease, low PaO₂ and low PCO₂ were related to an increased risk of early death in the univariate analysis.

Table 12. Univariate analysis of relative risk of death among patients with kyphoscoliosis.

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical ventilation vs.</td>
<td>0.22</td>
<td>0.15-0.33</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>oxygen therapy alone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt; 70 years</td>
<td>3.34</td>
<td>2.31-4.82</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Concomitant respiratory disease</td>
<td>2.43</td>
<td>1.72-3.44</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.33</td>
<td>0.93-1.93</td>
<td>0.118</td>
</tr>
<tr>
<td>PaO₂ (mm Hg)*</td>
<td>0.97</td>
<td>0.96-0.99</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)*</td>
<td>0.98</td>
<td>0.96-0.99</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

*Continuous variables
Table 13. Multivariate analyses of relative risk of death among patients with kyphoscoliosis.

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen therapy alone</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home mechanical ventilation</td>
<td>0.30</td>
<td>0.18-0.51</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age &gt; 70 years</td>
<td>2.63</td>
<td>1.74-3.98</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.27</td>
<td>0.85-1.92</td>
<td>0.24</td>
</tr>
<tr>
<td>Concomitant respiratory disease</td>
<td>1.43</td>
<td>0.96-2.12</td>
<td>0.078</td>
</tr>
<tr>
<td>PaO\textsubscript{2} (mm Hg)</td>
<td>0.99</td>
<td>0.97-1.02</td>
<td>0.70</td>
</tr>
<tr>
<td>PaCO\textsubscript{2} (mm Hg)</td>
<td>0.99</td>
<td>0.98-1.02</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Patients treated with HMV experienced better survival rate than patients treated with oxygen alone, even when adjusting for age, sex, concomitant respiratory diseases and blood gases.

Figure 14. Cumulative proportion of surviving patients receiving HMV or LTOT alone.
RESULTS

Survival time was longer in patients with a concomitant disease receiving mechanical ventilation than in patients without a concomitant respiratory disease on oxygen therapy (p=0.03):

Figure 15. Cumulative proportion of surviving patients receiving HMV or LTOT alone, subdivided according to the presence of concomitant respiratory disease.
RESULTS

PAPER IV - Quality in long-term oxygen therapy

Quality indicators at national level

We found improvements in eight of the ten quality indicators. The achievement of adequate oxygenation (PaO₂ > 8 kPa) when breathing oxygen was impaired and first-year survival rate was unchanged.

Table 14. Achieved performance at national level in ten quality indicators according to the proposed levels for excellent quality, first and latest-year of use of indicator.

<table>
<thead>
<tr>
<th>Quality indicator</th>
<th>Proposed excellent quality level</th>
<th>Achieved performance level first-year cohort Year</th>
<th>Achieved performance level latest-year cohort Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient selection criteria</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Access to LTOT (patients/100,000 inhabitants)</td>
<td>&gt; 30</td>
<td>1987) 7</td>
<td>2005) 31</td>
</tr>
<tr>
<td>2. PaO₂ ≤ 7.3 kPa (% of patients)</td>
<td>&gt; 85</td>
<td>1987) 76</td>
<td>2005) 85</td>
</tr>
<tr>
<td>4. LTOT patients with thoracic wall deformity without HMV (n)</td>
<td>None</td>
<td>1993) 30</td>
<td>2005) 5</td>
</tr>
<tr>
<td><strong>Performance of LTOT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. PaO₂ &gt; 8 kPa on oxygen (% of patients)</td>
<td>&gt; 90</td>
<td>1987) 86</td>
<td>2005) 80</td>
</tr>
<tr>
<td>6. More than 16 hours per day (% of patients)</td>
<td>&gt; 95</td>
<td>1987) 91</td>
<td>2005) 97</td>
</tr>
<tr>
<td>8. Reassessment of LTOT one to three months after initiation during a COPD exacerbation (% of patients)</td>
<td>&gt; 95</td>
<td>2002) 0</td>
<td>2005) 30</td>
</tr>
<tr>
<td><strong>Concomitant treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Avoidance of continuous oral glucocorticosteroids in COPD (% of patients)</td>
<td>≥ 80</td>
<td>1987) 54</td>
<td>2005) 81</td>
</tr>
<tr>
<td><strong>Result of treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. First-year survival rate in COPD patients</td>
<td>&gt; 0.65</td>
<td>1987) 0.73</td>
<td>2004) 0.75</td>
</tr>
</tbody>
</table>

Access to therapy increased in terms of the number of patients on LTOT and there was a decrease in the variations among the counties. On 1 January 1987, the number of ongoing patients on LTOT varied between 1.3 and 19.6 per 100,000 (a factor of 15) in the different counties, whereas on 31 December 2005 it varied between 21.0 and 76.0 per 100,000 (a factor
of 3.6.) At national level, the total number of LTOT cases increased from 565 to 2,871 per these dates.

The dominant underlying diseases for respiratory failure were COPD and PF.

Figure 16. Number of new patients (n) with long-term oxygen therapy in 1987-2005 divided by reasons for hypoxemia.  
- : Chronic obstructive pulmonary disease;  
- : Pulmonary fibrosis;  
- : Thoracic cage deformity;  
- : Other diseases.

The first-year survival rate in COPD patients did not change.

Figure 17. First-year survival rate in patients with COPD according to year of start of LTOT.
County quality achievement

At the end of the study period, all the counties reached our proposed excellent quality levels for first-year survival rate, the prescription of oxygen for more than 16 hours per day, 90% for LTOT to non-smokers and 80% for providing the patients with mobile equipment. Conversely, only 25% of the counties managed to reach the quality levels for the reassessment of LTOT one to three months after initiation during a COPD exacerbation and 25% for \( \text{PaO}_2 > 8 \) kPa on oxygen. For this quality indicator, there was a decline in achievement among the counties. There were improvements in the other quality indicators, apart from avoiding LTOT to current smokers, which emerged as unchanged.

Table 15. Achievement among the counties (%) in excellent quality level by quality indicator, first and latest-year of use of indicator.

<table>
<thead>
<tr>
<th>Proposed excellent quality level</th>
<th>Counties achieving excellent quality level first and latest-year of use of indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient selection criteria</strong></td>
<td>Year</td>
</tr>
<tr>
<td>&gt; 30 patients/100,000 inhabitants with access to LTOT</td>
<td>1987) 0</td>
</tr>
<tr>
<td>&gt; 85% of patients with ( \text{PaO}_2 \leq 7.3 ) kPa</td>
<td>1987) 35</td>
</tr>
<tr>
<td>≥ 95% of patients who were non-smokers</td>
<td>1987) 90</td>
</tr>
<tr>
<td>HMV to all patients with thoracic wall deformity</td>
<td>1993) 30</td>
</tr>
<tr>
<td><strong>Performance of LTOT</strong></td>
<td></td>
</tr>
<tr>
<td>&gt; 90% of patients with ( \text{PaO}_2 &gt; 8 ) kPa on oxygen</td>
<td>1987) 50</td>
</tr>
<tr>
<td>&gt; 90% of patients with more than 16 hours per day</td>
<td>1987) 70</td>
</tr>
<tr>
<td>&gt; 50% of patients with mobile oxygen equipment</td>
<td>1989) 60</td>
</tr>
<tr>
<td>&gt; 95% of patients with reassessment of LTOT one to three months after initiation during a COPD exacerbation</td>
<td>2002) 0</td>
</tr>
<tr>
<td><strong>Concomitant treatment</strong></td>
<td></td>
</tr>
<tr>
<td>≥ 80% of COPD patients without continuous oral glucocorticosteroids</td>
<td>1987) 25</td>
</tr>
<tr>
<td><strong>Result of treatment</strong></td>
<td></td>
</tr>
<tr>
<td>&gt; 0.65 first-year survival rate in COPD patients</td>
<td>1987) 70</td>
</tr>
</tbody>
</table>
DISCUSSION OF METHODOLOGY

A national quality assurance register, as the Swedish Oxygen Register and the Swedish Home Mechanical Ventilation Register, now merged to become Swedevox, offers the advantage of following the diagnosis and treatment outcome in the vast majority of patients over a long period of time, making it possible to compare the medical service among the reporting units.

There are two major drawbacks to register studies: patients are not randomised to treatment mode and there is no control group. The treatments among the patients in a register are decided on the basis of the preferences of the doctor and patient. However, there is also an advantage: the patients in the registers do not represent a small selected group, but rather the majority of the Swedish patients as in this case treated with LTOT and HMV. Therefore, a study based on data from the Swedish Oxygen Register gives different information than the NOTT and MRC studies, since many of our patients would have been excluded from those studies.

A quality register runs the risk of bias from under-reporting. For the Oxygen Register, an external validation comparing patient registrations with data from manufacturers and pharmacies was performed in 1986-1987. This validation showed that the coverage of the register was 85%. Later, an internal validation of the coverage of registration was performed approximately every second year by sending questionnaires to participating clinics.

We do not believe that there were selective reporting losses to the Oxygen Register, since the interruptions in reporting applies to the entire counties, and were caused by shortages of staff. For example from 1987 until 2000, in periods there were no reports from four counties. We have not performed any analysis of dropout rates, but we advised the units against reporting only surviving patients, when average coverage reporting resumed from a county.

The unique Swedish census registration numbers enable linkage with other registers that are important for follow up and analyses, especially the Swedish Population Register for vital status. This system may not altogether cover follow up correctly, owing to some difficulties in the census registration number system. Statistics Sweden estimates, for example, that some 4,000 personal identification numbers are annually “recycled” from a small number of persons. Also, some people emigrate without informing the authorities. Consequently, it is
sometimes difficult to obtain the correct date of death. Before the introduction of the web-based registration system in 2004, the register forms occasionally contained an erroneous census registration number. The patients have been known and followed by the reporting clinic, which have reported the date of death or date of withdrawal for other reasons for these patients. The number of erroneous census registration numbers was less than 1%. In all, we believe that the cases without follow up have been few and may only have resulted in negligible errors. Data collection is promoted by the uniformly organised medical care system in Sweden and by the good quality of official statistics related to medical diagnoses, treatments and causes of deaths.

**How to improve quality of LTOT**

One of the main objectives for a quality assurance register is to promote the improvement of quality of care, e.g. patient selection and performance of treatment by feedback to the reporting centers. To achieve this goal we have held annual meetings for the responsible physicians and nurses since the start of the Swedish Oxygen Register 1987, where they also received reports on the Swedish Home Mechanical Ventilation Register since its start in 1996. Since 2004, data from the merged register Swedevox is entirely web-based, and the reporting clinics have continuous access to their reported data. The annual reports and quality indicators are accessible to each participating clinic and, when relevant, to the public. Some indicators from small counties are subject to large annual variation and are therefore not accessible to the public on an annual basis.
DISCUSSION OF MAIN RESULTS

Sex-related differences in LTOT in COPD

Our results indicate that over the next 20 years there will be an increasing female dominance in patients receiving LTOT for chronic hypoxemia attributable to COPD. We estimate that in Sweden in 2026, more than twice as many women as men will be on LTOT to treat COPD with chronic hypoxemia. This assumption is based on our findings that incidence and prevalence of LTOT increased among women as compared with men over 15 years, and on the present smoking habits of middle-aged women and men. We believe that the increase in prevalence of LTOT in women as compared with men will be more pronounced than the increase in incidence, since we found significantly lower mortality after start of LTOT in women than men in our study.

Several studies have demonstrated that women are more sensitive than men to the harmful effect of tobacco smoke. It has long been known that there are sex-related differences in the natural behaviour of the airways during a person’s life span, both in biological and socio-cultural respects. Starting smoking in childhood is especially serious, since it increases the likelihood of becoming a persistent adult smoker, and thus the risk of developing obstructive airway disease. Moreover, lung function develops more slowly in smoking girls than in smoking boys, and women who begin to smoke in childhood experience a greater risk of lung function reduction and obstructive airway disease later than men who smoke from childhood.

Women may also be more susceptible than men to the development of severe COPD. A study of patients with severe, early onset COPD revealed that current or ex-smoking female first-degree relatives of these patients had a greater risk of reduction of FEV₁ and of relevant response to bronchodilator than male relatives. Analysis of data in two independent population studies showed that smoking women ran a higher risk than smoking men of needing admittance to hospital for COPD, but this finding was not reproduced in the Confronting COPD International Survey. A Spanish investigation of COPD patients who attended a pulmonary clinic, 53 FEV₁-matched men and women, showed that the women were younger and smoked less than the men. The women had more exacerbations in the last year, poorer performance in walking distance and worse quality-of-life scores than the
DISCUSSION

Our new finding indicates that smoking women are substantially more likely than smoking men to develop respiratory failure that necessitates LTOT. We found a higher survival rate in women than in men after the start of LTOT. First-year survival rate was 77% (95% CI 75–79%) and 69% (95% CI 67–71%), respectively, and median survival rate was 2.8 years in women and 2.0 years in men. Similar survival data were noted in an Australian study of 249 men and 256 women with COPD or chronic airflow limitation treated with long-term oxygen. Their overall first-year survival rate was 75% and median survival rate was 28 months in women and 22 months in men. Three other studies reported higher survival rates after the onset of oxygen therapy. Miyamoto et al. found, in a large study, a mean survival rate of 5.2 ± 0.2 years among women and 4.8 ± 0.2 in men after the start of LTOT. Their first-year survival rates were 93.3% for women and 90.0% for men. In a study by Chailleux et al. on the French quality register ANTADIR Observatory, the mean survival time for COPD patients on LTOT was three years. Machado et al. found, in contrast to several other authors, a higher risk of death among women than men with oxygen-dependent COPD.

When interpreting these results, patient selection and sex distribution among patients should be taken into account. Women represented 51% of the subjects both in our study and in the study by Crockett et al., while only 25% of the participants were women in the Japanese study.

The similarity in the results between our study and the Australian study can partly be explained by the fact that all patients receiving LTOT were included in these studies, in contrast to the studies by Chailleux et al and Miyamoto et al., who excluded patients for various reasons and had higher survival rates.

When patients with a poor WHO performance status were excluded from the Swedish Oxygen Register, similar survival time as in the randomized controlled studies and in the studies on Japanese and French LTOT patients was found.

On the other hand, the daily hours of oxygen use should also affect the survival time, according to the results in the “NOTT” study, where treatment 24 hours per day was more effective than 12 hours per day. In the Japanese study, 63% of the patients were prescribed oxygen for at least 20 hours per day, as compared with only 30% of the patients in our study. This could very well contribute to the lower survival rate for our patients. The lower survival...
rate in our material probably depends both on the inclusion of all patients, regardless of performance status, and the shorter treatment time with oxygen per 24 hour period.

The mathematical model used to predict the future incidence and prevalence of LTOT in COPD is based on two assumptions: the age at the start of LTOT is stable and quitting smoking will not affect the model. The mean age at the start of LTOT increased gradually in the period 1987-2005. We are happy enough to have a high smoking cessation rate. A high cessation rate in patient cohorts reaching the age of 60-80 years during the period 2007-2035 will probably reduce or postpone the onset of chronic hypoxemia and need of LTOT in this group.

As previously mentioned, the national ratio of prevalence of smoking in younger women to that of older women is thought to be an indicator of the future prevalence of smoking in that country. Despite this uncertainty, the increased sensitivity of the female lung to tobacco smoke and the high numbers of smoking women will lead to an increased need for LTOT in the future, which will probably be even more pronounced worldwide than in Sweden, if our predictions prove correct.

*Methodological considerations*

The future incidence and prevalence of LTOT in COPD may develop in other directions than predicted if various conditions turn out to be other than anticipated using our method. Lower incidence and prevalence may occur if smoking decreases more rapidly than we believe and if prevention and treatment of COPD improves more rapidly than it has so far. The prevalence of LTOT may increase if cardiovascular mortality continues to decrease, if the attention to respiratory failure increases and if the LTOT becomes more effective with increased hours of oxygen per day.
Occupation and pulmonary fibrosis

We report the association in men between IPF and exposure to birch dust and hardwood dust as the main finding in our case-control study. The risk of IPF with these exposures was more than doubled, and the risk of PF, without exclusion of cases with other probable reason for fibrosis, was doubled in men with exposure to unspecified wood dust. In addition to birch dust and hardwood dust, the patients with PF, men and women together, also had increased odds ratios for blasting, mineral dust, birds, flour dust, and dust from pine or fir and fire fumes.

We studied a different selection of cases than in the previous case-control studies, namely severe PF including IPF as the largest subgroup. In this procedure, we could estimate the risk of the studied exposures in the patients with already known external cause of their PF, asbestos being the most common, and other diseases known to be associated with PF, rheumatoid arthritis being the largest group. The previous case-control studies on risk of environmental exposures did not include patients with other forms of ILD than IPF. We found associations with more exposures in PF than in IPF, namely: blasting, mineral dust, birds, flour dust, dust from pine or fir, birch dust, hardwood dust and fire fumes. The increased odds ratios for blasting and mineral dust might represent undiagnosed silicosis. It is also possible that some of the patients with known cause of PF actually had IPF, since IPF is the most common of the idiopathic interstitial pneumonias. The cohort we studied was a national sample of PF patients in advanced stage with chronic hypoxemia. They represent 8-9% of the Swedish patients with ongoing LTOT for chronic hypoxemia, the second largest group after COPD. As expected, the majority of the PF patients in our study, 77%, had IPF. The fibrosis in PF patients was explained by external agents in 8% and by association with other disease in 15%. Yet it is possible that some of the remaining 23% also had IPF, since IPF is not only the most common ILD but also the most serious one. The diagnosis of IPF was based on other data than lung biopsy in the majority of our patients, as in a recent study from the UK on incidence and mortality of IPF.

The main difference between our results and those of previous studies of environmental exposure in IPF was that we did not find an increased risk with exposure to metal dust as was found in five other case-control studies. In a UK study on standardised mortality ratios, no association with exposure to metal dust was found. The patients in our cohort may have been less severely exposed to dust from hard metal and they may have had less
harmful working environments than the patients in previous studies. A difference in patient selection may also have played a role. Our patients represented a national sample and were not recruited from a specific region, as in two of the other case-control studies.69,71

Methodological considerations

The cases in the PF sample, which included the IPF sample, were selected in the sense that they represented a late stage in the disease and that current smoking was an exclusion criterion, when they were prescribed LTOT. On the other hand, the cases were recruited from the whole country, and can thus be assumed to be representative of Swedish patients with IPF, with knowledge of the poor prognosis of that disease. In a retrospective case-control study like this one, there is a risk of recall bias. People with a disease may be more inclined to recall certain exposures than control persons without the disease.125 This problem could be solved by interviews from experts to achieve higher accuracy, but for practical and financial reasons that is not possible in a large study like this.126 Among people with respiratory disorders, higher sensitivity and lower specificity have been demonstrated than in persons without respiratory problems to self-reported dust or gas exposure.127 For common exposures, as in our study, bias in terms of sensitivity is more important than bias specificity to cause misclassification.128 We have found support for the validity of the self-reported exposures when comparing with details about occupations among the ten patients who reported exposure to dust from hardwood. An even more accurate check of validity of the reported exposures could be achieved by using a job exposure matrix, as in a recent study on adult asthma incidence.129
Ventilation or oxygen in kyphoscoliosis

The results of our prospective study from two national quality assurance registers suggest that HMV is a more effective improver of survival rates than LTOT alone in patients with respiratory failure owing to kyphoscoliosis. Our results also indicate that survival rate is not influenced by the degree of hypoxemia or hypercapnia, once corrected with HMV or a combination of HMV with LTOT. The presence of concomitant respiratory disease, in 66% of the patients, mainly COPD, does not seem to have as negative an impact on survival time as found in two previous studies.\textsuperscript{5,6}

There is abundant documentation on the effectiveness and uses of mechanical ventilation in kyphoscoliosis.\textsuperscript{83,89,92,130} It’s utility has also been demonstrated in a French survey.\textsuperscript{5} Consequently, home mechanical ventilation and not LTOT is the recommended treatment for hypercapnic respiratory failure, as seen in kyphoscoliosis.\textsuperscript{97} There is no documentation that supports treatment with oxygen to these patients. The reasons for which a considerable proportion of the Swedish kyphoscoliotic patients are treated with LTOT instead of HMV might be that the responsible physicians have assessed the concomitant disease as mainly responsible for the respiratory failure, and the hypoxemia has been regarded as more serious than the hypercapnia. However, our results show that this treatment strategy is erroneous in patients with kyphoscoliosis and respiratory failure. The hypoventilation or impending hypoventilation is the greatest risk factor and should always be corrected first.

Concomitant respiratory disease is common in patients with kyphoscoliosis\textsuperscript{5,6} and this may be partly explained as an airway complication attributable to small lung volume.\textsuperscript{80,81} Recent research demonstrates that a restriction of lung volume and chronic breathing at low lung volumes might increase the rate of stress generation in airway smooth muscle,\textsuperscript{82} as has also been demonstrated in mechanical strain in cultured airway smooth muscle cells.\textsuperscript{131} In obese patients there is an increased prevalence of wheezing and airway hyperresponsiveness\textsuperscript{81,132-134} and several studies have observed an association between high body mass index and asthma.\textsuperscript{135-141} Patients with kyphoscoliosis breathe at low lung volumes, which might explain the high frequency of airway disease in patients with kyphoscoliosis and respiratory failure,\textsuperscript{80} as in patients with lung function affected by chronic cervical spinal cord injury.\textsuperscript{142} Furthermore, airway obstruction in kyphoscoliosis can also be caused by bronchial torsion secondary to the thoracic deformity.\textsuperscript{143}
Among the kyphoscoliotic patients treated with LTOT, 54% had a diagnosis of COPD, and only 75% of these patients with kyphoscoliosis and COPD had ever smoked. This finding supports the hypothesis that the kyphoscoliosis or relatively low lung volumes might explain some of the airways disease diagnosed as COPD and thought to motivate LTOT. Improvement in vital capacity and arterial blood gas oxygen has been shown to occur when patients with kyphoscoliosis are treated with nocturnal nasal intermittent positive pressure ventilation.

The strongest confounding factor in our study was the older mean age in the LTOT group. When entered in a multiple regression analysis, age and treatment turned out to have independent impacts on survival time. When considered alone, hypoxemia and concomitant respiratory disease was associated with poorer survival time, but since these factors were closely related to advanced age, they lost their statistical significance when entered in the multivariate analysis. Moreover, survival time was not affected by levels of carbon dioxide or vital capacity. No effect of initial PaO₂ is expected, since both therapies aim at correcting hypoxemia. Since nocturnal mechanical ventilation corrects daytime hypercapnia, which was most pronounced in the HMV groups, any negative effect of hypercapnia on survival time is abolished by this treatment. The prognosis for patients with a combination of HMV and LTOT was about the same as with HMV alone, which is in accordance with the results of Buyse et al. in a study on a smaller patient material.

Methodological considerations
A joint register would have strengthened our results, but since the two registers have been supervised by the same scientific society and in most instances receive reports from the same clinicians, we believe that our results give a true description of the outcome for the two treatment modalities. Our study is not randomised or controlled, which would probably not be ethically possible in relation to this problem. The patients were actually selected for one of the studied treatment methods. Patients prescribed LTOT and HMV differed at the start of treatment for respiratory failure, the main difference being that patients prescribed LTOT had a mean age of twelve years older. They also had more pronounced hypoxemia and less hypoventilation or hypercapnia than the patients prescribed HMV. They also had slightly higher vital capacity. Clearly, LTOT was selected for a subset of patients with more hypoxemia than explained by hypoventilation only, and hypercapnia was an indication for starting HMV. Yet the results of this study demonstrate that when the main disease is a severe
thoracic spine deformity, patients receiving HMV have a better outcome than patients on LTOT, and our results add support to the consensus statement on therapy in kyphoscoliosis.97
Quality in long-term oxygen therapy

We found improvement in eight of the ten quality indicators which we had selected for follow up during the 19 years of quality registration. Patient selection was improved regarding access to therapy, and there was an increase in the proportion of patients with severe hypoxemia and a decrease in the proportion of current smokers. There were improvements both on the national level and in the individual counties. Yet, there was a worsening in terms of achieving the treatment goal of oxygenation with supplementary oxygen. That quality indicator was poorly fulfilled at the end of the observation period as was the activity of reassessment of LTOT when it was started during an exacerbation of COPD. However, the latter quality indicator was introduced late in the observation period and improvement might have been slow. From the start of the study the register data was used for feedback to the responsible physicians and nurses in annual reports and at training meetings. In this way, the register has served as a benchmarking tool for quality assurance, as can be seen in that there were improvements in most of the quality indicators.

Patient selection in LTOT

Initiation of LTOT increased considerably during the study, almost entirely on the indication of COPD. The reason for this is probably increased attention to patients requiring LTOT and the time course of smoking habits rather than selection of patients with doubtful indications, since the proportion of patients with severe hypoxemia increased. A Danish study showed increased prevalence of LTOT to COPD patients from 27 per 100,000 inhabitants in 1994 to 42 per 100,000 in 2000. The highest prevalence was found in the counties where general practitioners took part in the prescription of LTOT, and the adherence to the criteria for the treatment was lower in those counties. In our study, all responsible physicians, mainly pulmonologists, were specially trained for LTOT. We found a fourfold variation between the counties in the incidence of LTOT prescriptions in 2005. Differences in attention could possibly contribute to this, but the differences are probably caused by variations in respiratory failure owing to smoking related diseases, as can be seen by the fact that there was also a fourfold variation in the incidence of lung cancer in Sweden, according to the Cancer Register of the National Board of Health and Welfare.

There was an adherence to the indicator severe hypoxemia when breathing room air of 76% in the patients who were prescribed LTOT from the beginning of the study, and this rose to 85%. The adherence to the Swedish guidelines for LTOT is likely to have been higher, since some
of the patients with PaO₂ > 7.3 kPa probably had pulmonary hypertension or polycythemia as an additional reason for LTOT. In a Danish study on COPD patients receiving LTOT, 462 of 822 (56%) patients had adherence to the criteria for hypoxemia. There were no data on PaO₂ on room air in 169 of the patients and there was adherence to the hypoxemia criteria in 70.6% of the other 653 patients. The limit at which LTOT is effective in treating hypoxemia is addressed as a research field in a recent NHLBI workshop report. The report emphasizes that the average use of oxygen was only 13.5 hours per day in the study by Górecka et al., which may have lowered the possibility of establishing an effect on survival time in mild to moderate hypoxemia, and that LTOT might have other effects than prolonged survival time in these patients.

The Swedish guidelines include a strong recommendation that LTOT should be avoided in patients who have not stopped smoking. The reason is that smoking probably interferes with the treatment result and that there is a risk of fire accidents. Current smokers have increased mortality during LTOT, but it is still possible that LTOT is beneficial on survival time in these patients. This is an ethical issue for further investigation according to the NHLBI workshop. At the end of our study, as many as 99% of the patients were non-smokers when starting LTOT. This adherence to guidelines for LTOT has varied in other countries between 49% in the US and 93% in Turkey. Other examples of proportion of non-smoking LTOT patients are 79% in Denmark and 86% in Scotland.

When respiratory failure is caused by deformity of the thoracic cage, LTOT is often prescribed, especially when there is a concomitant respiratory disorder. However, HMV is physiologically more effective in these patients. Home mechanical ventilation alone is sufficient in some cases, but LTOT alone results in a poorer survival rate. After the presentation of the results of Paper III, the prescription of LTOT alone to patients with deformity of the thoracic cage dwindled to a few registered cases annually in Sweden.

**Performance of LTOT**
Attaining the desired level of PaO₂ when breathing oxygen was the only quality indicator that decreased during the study (from 86% to 80%). This was not explained by insufficient PaO₂ in the patients with PF, in whom it can otherwise be difficult to reach appropriate oxygenation levels. Nor was it explained by an increase in the mean PaCO₂ from 1987 to 2005 on oxygen
in the LTOT patients. Yet another explanation could be insufficient titration of the oxygen dosage, owing to shortening of the times for in-hospital treatment. In previous studies, the adherence to improvement of the arterial oxygenation guidelines when breathing oxygen was, for example, 45% in a Scottish study and 90% in an Australian study.\textsuperscript{110,150}

Prescription of oxygen for more than 16 hours per day was high from the start in our study, and improved further. It is possible that this was influenced by increased usage of portable oxygen equipment.\textsuperscript{98,99,151} In a Greek study, only 27% of the patients with LTOT used oxygen for more than 15 hours daily, as compared with 65% of the patients in a Danish study.\textsuperscript{99,152}

We have studied the prescribed treatment time per day, rather than use of oxygen in reality, since compliance has been deemed too difficult to follow in our large patient material, and would seriously affect the possibilities for the staffs to report to the register. In an early observation in the Swedish Oxygen Register, measuring of oxygen cylinder use and reading of concentrator meters showed that approximately 70% of patients used oxygen for 15 hours or more per day.\textsuperscript{3} Compliance of 65% with the treatment time > 15 hours per day was demonstrated in both a Danish and a Dutch study.\textsuperscript{99,153} The use of mobile oxygen equipment influenced compliance in both of these studies.

Adequate treatment time per day is important to the effects of LTOT in terms of survival times,\textsuperscript{14,15} and mobile oxygen equipment has been shown to be important to enable patients with outdoor activity, to have improved compliance.\textsuperscript{98} The use of mobile oxygen equipment increased from 48% to 65% of the patients in our study between 1989 and 2004. The corresponding figures have been between 20% and 67% in other countries.\textsuperscript{153-155} During the same period, the oxygen equipment has also undergone developments, with lightweight cylinders and demand pulsing delivery devices, making it easy to handle.\textsuperscript{156} We did not measure the patients’ use of their mobile equipment, but according to the results in previous studies, there is reason to suppose some degree of reduced compliance with the use of the equipment.\textsuperscript{151,153}

When severe hypoxemia occurs during an exacerbation of COPD, it may often be necessary to initiate LTOT despite there not being a stable phase in the underlying disease. Reversal of hypoxemia may take several weeks so initiating LTOT earlier has become more common with earlier discharges from hospital.\textsuperscript{19,100,101} This early LTOT has been prescribed in such cases for several years, and lately it has also been recommended in some guidelines.\textsuperscript{19,20}
DISCUSSION

When LTOT is started during an exacerbation of COPD, it is recommended that the indication be reassessed after one to three months. During the few years when we registered adherence to the guidelines for this indicator, it increased from zero to 30% of the relevant patients. In a Danish study from 1995, only 39% of the patients were followed up properly after initiation of LTOT and the corresponding figure was 61% in a localised British district in 1986-1987. Those studies dealt with all patients who received LTOT, and to our knowledge, there is no other study of the follow up of only patients starting LTOT during an exacerbation of COPD.

Concomitant treatment

A few studies have demonstrated increased mortality in COPD patients, associated with maintenance therapy with oral glucocorticosteroids. In the study by Ström, female COPD patients had increased mortality; in Ringbaek’s study the increased mortality was limited to overweight COPD patients, while the increase in mortality was found to be dose dependent for oral steroids in the study by Schols. Attention has been paid to this risk since many years in Swedish COPD patients and the use of oral glucocorticosteroids decreased from 46% to 19% during our study period. In some of these elderly patients, the indication for corticosteroid maintenance therapy may well be other diseases than COPD.

Results of treatment

In our 19 year observation of COPD patients receiving LTOT, we found a stable level of the first-year survival rate. We chose that measure for practical reasons. When comparing with the national Causes of Death Register data, we did not find any significant change in overall survival. It might be expected that improvements over the years in the performance of LTOT would lead to somewhat improved survival times. One explanation for the fact that this did not occur is probably that the patients have become steadily older at start of LTOT, which could, in turn, be a result of improved overall care, with postponement of respiratory failure. The decrease of smoking in the population during recent decades can also have influenced the later start of respiratory failure. It is also possible that the prescription of oxygen for a minimum of 16 hours per day results in many patients not striving to use oxygen for up to 24 hours per day. A continuous treatment 23-24 hours per day probably improves survival times more than 15-16 hours per day in COPD patients with severe hypoxemia. Patients in our study were older and patients with a very poor performance status or concomitant disease
were not excluded as in the NOTT and MRC studies, a fact that probably affected our survival statistics.

Methodological considerations
We chose the ten quality indicators as a proposed instrument for accessing improvement of LTOT, based on published evidence: PaO$_2$ $\leq$ 7.3 kPa on air, HMV to patients with thoracic deformity, PaO$_2$ > 8 kPa on oxygen, more than 16 hours of oxygen per day and reassessment of LTOT if started during a COPD exacerbation, and early results on data from our register concerning access to LTOT, non-smoking status and avoidance of continuous oral glucocorticosteroids in COPD. The suggested levels for excellent quality of the indicators are based on the results in the individual counties and reflect the current disease panorama and guidelines. Changes in epidemiology and scientific progress will lead to a need for revision of the levels for excellent quality.
CONCLUSIONS

Our results contribute to knowledge for preventing and postponing chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF) and to improved quality of treatment of respiratory failure.

Specific conclusions:
- Women with COPD experience a more rapid increase in incidence and prevalence for long-term oxygen therapy (LTOT) than men with COPD.

- Exposure to wood dust, especially dust from birch and hardwood, may be a risk marker in men for developing IPF.

- A substantial increase in the need for oxygen therapy will probably occur in women in the immediate coming years.

- When they receive LTOT for COPD with severe hypoxemia, women have better survival rates than men.

- Patients with kyphoscoliosis treated with home mechanical ventilation have better survival rate than those treated with oxygen alone.

- We found improvements in eight of our ten quality indicators during 19 years of quality registration. We propose a model for the quality assurance of LTOT, using indicators with levels for excellent quality, based on our estimation of current knowledge.
FUTURE PERSPECTIVES

The two most important therapeutic implications of our studies are:
- Do not treat patients with respiratory failure due to kyphoscoliosis with oxygen alone.
- Encourage COPD patients with chronic hypoxemia to use the oxygen for as many hours as possible during the every day and night.

The demonstrated female dominance in the increase of incidence and prevalence of LTOT together with the increase in smoking in women as compared with men will constitute a strong argument for increased efforts regarding smoking prevention and cessation. It is important to target women for information and other measures to counteract the efforts by the tobacco industry to recruit female smokers. Our model for prediction of future need for LTOT can be validated by analyzing the future incidence and prevalence of LTOT.

The finding of wood dust as a probable risk marker for idiopathic pulmonary fibrosis (IPF) will contribute to relevant preventive actions in manufacturing industries as well as in handicrafts and private carpentries. It will be important to follow the future incidence of IPF, and if it rises, it may be justifiable to repeat a case control study based on quality register data on risk markers for IPF. We also aim to evaluate cigarette smoking as a risk marker for IPF by studying data on IPF patients reported to the Swedevox Register.

Home mechanical ventilation (HMV) is the first line treatment when respiratory failure occurs in patients with kyphoscoliosis. In selected cases, this treatment may be supplemented with oxygen. After the presentation of Paper III to the participating centers the number of new patients prescribed LTOT without HMV dropped to a few elderly patients who could not learn to accept HMV. However, it is necessary to use data from the Swedevox Register to assure that the prescription of LTOT without HMV to kyphoscoliotic patients stays on a low level.

Evaluation of the implementation of the quality indicators for LTOT will serve as an instrument for improvement of performance and outcome of LTOT. Scientific re-evaluation of several of the indicators must be undertaken regularly to decide whether they should remain as indicators or whether adjustments are needed. The optimal treatment time per 24
hours and the possible effect of LTOT in mild to moderate hypoxemia are areas that would need further evidence.

Impaired health related quality of life is a very important aspect of respiratory failure and the effect of LTOT has, so far, only been explored in a sample of our LTOT patients. Since 2006 we have included a short generic instrument for health related quality of life measurement at the start and after the end of the first year of LTOT. The development of a Swedish version of a specific instrument for health related quality of life in respiratory failure will facilitate a better evaluation of the impact of treatment including the impact on LTOT in this aspect.

The levels for excellent quality also need continuous updating according to new knowledge and the changing epidemiology of respiratory failure.
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