# Prognosis of Danish patients in intensive care

## Clinical epidemiological studies on the impact of preadmission cardiovascular drug use on mortality

PhD dissertation

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Report no. 45

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**PREFACE**

This PhD thesis was carried out during my employment at the Department of Clinical Epidemiology, Aarhus University Hospital, Denmark.

I would like to express my sincere gratitude to all those people who made this work possible. First of all, I thank Professor Henrik Toft Sørensen for outstanding mentorship; for patiently teaching me clinical epidemiology, for sharing his creative ideas; and for his trust and unfaltering support at all times. I am grateful to Lars Pedersen for his enthusiastic support and valuable suggestions and for his enormous amount of work in creating the high-quality databases at the Department for Clinical Epidemiolog. I wish to thank Professors Anders Larsson and Else Tønnesen for their never failing engagement and constructive feed-back and for sharing their profound clinical knowledge.

My sincere thanks go to statistician Martin B. Johnsen for sharing his excellent statistical skills and for the comprehensive work with the analysis for the studies in this thesis. I thank Miriam Grijota for initial help with the statin study.

I would like to thank Kim M. Larsen and Reinhold Jensen for their help with establishing the Aarhus University Intensive Care Cohort and for their valuable comments and suggestions on clinical issues. I am grateful to Stanley Lemeshow for a lot of guidance and thoughtful advice for the comorbidity study. I thank Christian Fynbo Christiansen for great help collecting data for the comorbidity stud and for numerous inspiring discussions and Reimar W. Thomsen for very helpful advice and great in-put for the statin study.

I express my sincere gratitude to all my colleagues and friends at the Department of Clinical Epidemiology for creating a pleasant and inspiring working atmosphere. Special thanks to Søren Påske Johnsen for his guidance and support when I first started at the department. I also want to thank everybody in the research group at the Department of Anesthesiology and Intensive, Aarhus University Hospital, for the many inspiring discussions and great company at conferences and seminars.

Finally, my warmest thanks go to my family, Katrine, Mathilde and Josefine for their support, understanding and patience.

This work was made possible through financial support from the Western Danish Research Forum for Health Sciences (Vestdansk Forskningsforum), from the Danish Medical Research Council (Grant 271-05-0511), and from “Klinisk Epidemiologisk Forskningsfond”, Denmark.

**This thesis is based on the following papers**

I. Comparison of SAPS and APACHE scores with the Charlson Comorbidity Index for prediction of mortality following intensive care. *Final draft*

II. Preadmission statin use and one-year mortality among intensive care patients- A cohort study. *Submitted*

III. Pre-admission beta-blocker use and risk of death among intensive care patients- A cohort study. *Final draft*

**CONTENT**

## 1. INTRODUCTION

In Denmark, the specialty of intensive care medicine began in Copenhagen in the early 1950's, when, during the poliomyelitis epidemic, patients were treated with tracheotomy and prolonged manual ventilation, which resulted in a reduction of mortality from 87 to 40 percent [1]. Since then, intensive care medicine has developed into a highly specialized medical discipline with a wide array of high-technology treatment strategies and specially developed drugs for the care of critically ill patients. In the USA, approximately 30% of hospital budgets are used for 5 to 8 percent of all hospitalized patients that are treated in intensive care units (ICUs) [2;3].

During the past few decades, there have been improvements in treatment strategies and supportive measures for ICU patients. Nevertheless, the prognosis does not seem to have substantially improved for general ICU patients; however, only very limited data exist on this issue [4-8]. One reason for the apparent lack of improvement in the prognosis of general ICU patients may be the change in attitude towards patients that transfer to the ICU. Previously, very old patients and patients with severe comorbidity that had a relatively short life expectancy were not transferred to the ICU; however, recently, there seems to have been a shift toward offering intensive care also to these patients[8;9]. This shift may have masked any improvements in prognosis that may have occurred over the last few decades.

Understanding the complex clinical course of ICU patients is essential for potentially reducing morbidity and mortality [10]. Maybe the best way to examine the clinical course of general ICU patients is through studies based on large longitudinal databases, and therefore, such databases are important for determining ways to improve the prognosis of ICU patients.

### *1.1 Clinical epidemiological studies of intensive care medicine*

Population epidemiology is defined as the study of the distribution, determinants, and frequency of disease in human populations [11]. Clinical epidemiology can be defined similarly: one part is descriptive and focuses on the distribution and outcome variation of diseases, and a second part is analytical and focuses on identifying important determinants of outcomes of diagnostic and therapeutic interventions [12 13]. It follows that clinical epidemiology deals with individual patients in a broad sense. An important purpose of clinical epidemiology is to apply valid epidemiological methods to clinical studies in order to avoid being misled by systematic error or chance. Over the

last 2-3 decades, the importance of observational studies has increased due to the development of new study designs and biostatistical models that provide better controls for confounding factors [14;15].

In the following sections, we will discuss some of the main challenges and advantages of clinical epidemiological studies of ICU patients.

### *1.1.1 Study population*

In contrast to most other study populations, ICU patients are not defined by a particular condition or treatment. The definition of an ICU patient is a patient that requires admission to a highly specialized unit at the hospital. ICU study populations, therefore, comprise very heterogeneous populations, ranging from older patients to newborns and from patients with chronic diseases, like chronic obstructive pulmonary disease or congestive heart failure, to patients with acute conditions, like severe infections, trauma, or respiratory distress. This is illustrated by the distribution of diagnostic groups and comorbidity among the different age groups within the Aarhus University Intensive Care Cohort (AUICC). This cohort represents all admissions between 1999 and 2007 to the ICUs at Aarhus University Hospital (table 1.1.1).

The broad definition of ICU patients has two major implications for clinical epidemiological studies. First, the large variations in clinical indications for transferral to the ICU, the large age span, the vast variety of treatments or interventions, and the complexity of the disease processes make it difficult to control for confounding in observational studies. Second, the study population is difficult to clearly define which is an inherent challenge in all ICU studies since it makes generalizability difficult to assess[11;16]

Table 1.1.1 Diagnostic categories and comorbidity among Danish ICU patients in the Aarhus University Intensive Care Cohort.

| | Age Group | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 45-54 | | 55-64 | | 65-74 | | 75-84 | | 85+ | | Overall | |
| | N | % | N | % | N | % | N | % | N | % | N | % |
| Overall | 2190 | 100.00 | 3378 | 100.00 | 3675 | 100.00 | 2718 | 100.00 | 522 | 100.00 | 12483 | 100.00 |
| Diagnostic category | | | | | | | | | | | | |
| . Cancer | 292 | 13.33 | 597 | 17.67 | 586 | 15.95 | 271 | 9.97 | 24 | 4.60 | 1770 | 14.18 |
| . Diabetes | 29 | 1.32 | 52 | 1.54 | 35 | 0.95 | 35 | 1.29 | 8 | 1.53 | 159 | 1.27 |
| . Cardiovascular | 492 | 22.47 | 909 | 26.91 | 1218 | 33.14 | 901 | 33.15 | 108 | 20.69 | 3628 | 29.06 |
| . Respiratory | 147 | 6.71 | 277 | 8.20 | 385 | 10.48 | 315 | 11.59 | 57 | 10.92 | 1181 | 9.46 |
| . Gastrointestinal | 219 | 10.00 | 321 | 9.50 | 337 | 9.17 | 359 | 13.21 | 114 | 21.84 | 1350 | 10.81 |
| . Trauma/poisoning | 448 | 20.46 | 399 | 11.81 | 310 | 8.44 | 261 | 9.60 | 101 | 19.35 | 1519 | 12.17 |
| . Other | 508 | 23.20 | 728 | 21.55 | 729 | 19.84 | 517 | 19.02 | 98 | 18.77 | 2580 | 20.67 |
| Comorbidity | | | | | | | | | | | | |
| Ischemic Heart Disease | | | | | | | | | | | | |
| . Yes | 93 | 4.25 | 325 | 9.62 | 612 | 16.65 | 504 | 18.54 | 74 | 14.18 | 1608 | 12.88 |
| Congestive Heart Failure | | | | | | | | | | | | |
| . Yes | 87 | 3.97 | 287 | 8.50 | 517 | 14.07 | 525 | 19.32 | 103 | 19.73 | 1519 | 12.17 |
| Peripheral Vascular Disease | | | | | | | | | | | | |
| . Yes | 112 | 5.11 | 309 | 9.15 | 561 | 15.27 | 453 | 16.67 | 66 | 12.64 | 1501 | 12.02 |
| Cerebrovascular Disease | | | | | | | | | | | | |
| . Yes | 180 | 8.22 | 432 | 12.79 | 611 | 16.63 | 520 | 19.13 | 118 | 22.61 | 1861 | 14.91 |
| COPD | | | | | | | | | | | | |
| . Yes | 230 | 10.50 | 503 | 14.89 | 768 | 20.90 | 591 | 21.74 | 83 | 15.90 | 2175 | 17.42 |
| Diabetes | | | | | | | | | | | | |
| . Yes | 149 | 6.80 | 339 | 10.04 | 489 | 13.31 | 309 | 11.37 | 49 | 9.39 | 1335 | 10.69 |
| Cancer | | | | | | | | | | | | |
| Yes | 349 | 15.94 | 769 | 22.76 | 893 | 24.30 | 598 | 22.00 | 91 | 17.43 | 2700 | 21.63 |
| Renal Disease | | | | | | | | | | | | |
| . Yes | 86 | 3.93 | 202 | 5.98 | 236 | 6.42 | 196 | 7.21 | 19 | 3.64 | 739 | 5.92 |
| Alcoholism-related Diseases | | | | | | | | | | | | |
| . Yes | 549 | 25.07 | 534 | 15.81 | 263 | 7.16 | 84 | 3.09 | 12 | 2.30 | 1442 | 11.55 |

*1.1.2 Internal validity and generalizability*

High internal validity in terms of limited or no influence of bias or confounding is essential for the interpretation of epidemiological studies. It makes little sense to use results from a study with low internal validity for generalizations to other settings[11].

As mentioned the large heterogeneities inherent in ICU populations may lead to difficulties in controlling for confounding factors. Restricting study participation with inclusion or exclusion criteria is an effective way to prevent confounding by the factors for which it is employed. This is probably one of the reasons that studies regarding ICU interventions often focus on patients with specific, well-defined critical illnesses, like sepsis or acute renal failure [17-21], or on medical vs. surgical ICU patients [22;23]. However, restriction may have drawbacks, because findings from studies that are restricted to well-defined ICU patient subgroups may not be generalizable to other ICU patients. This point was illustrated in two recent prominent examples from intensive care medicine. In two randomized controlled trials (RCTs), Van Den Berghe et al found that intensive insulin therapy had different effects on mortality and complication rates between medical ICU patients and surgical ICU patients at the same hospital, although patients were treated according to the same insulin therapy protocol[22;23]. The PROWESS trial showed reduced mortality conferred by activated protein-C therapy in patients with severe sepsis; however the results could not be confirmed in the subsequent ADDRESS trial, which included patients with less severe sepsis [24;25]. This exemplifies the complexity of generalizing findings from one subgroup of ICU patients to other ICU settings even in studies with high internal validity. Use of large health care databases for ICU studies may overcome some of these problems because they have sufficient sample sizes for analysis of several subgroups of ICU patients and at the same time can provide data for general ICU patients.

*1.1.3 Study design*

Two main types of study designs can be used to examine the associations between interventions and ICU outcome: 1) experimental studies, primarily Randomized Controlled Trials (RCTs); and 2) non-experimental, observational studies [11;12].

For several reasons, there is a great lack of RCT-based evidence in intensive care medicine. As previously discussed, ICU patients are very heterogeneous; often they have multiple diseases with different etiologies, severe comorbidity, and a need for advanced treatments that require continuous

monitoring and changes in dose and duration. These heterogeneities make it difficult to obtain perfect randomization in RCTs without one or more imbalanced covariates between intervention groups; thus large study populations are needed to eliminate confounding [15;26]. The heterogeneity also makes it difficult to standardize treatments, as required in RCTs, and to maintain randomized assignments without unintended cross-over between intervention groups. Blinding patients and researchers is commonly used to reduce the risk of information bias in RCTs; but in ICU patients, it is very difficult to obtain complete blinding; for example, in practice, it is impossible for the physicians to be blinded to ventilator settings, or to "*early goal directed therapy"* [27]. In addition, it is ethically complicated in RCTs to study truly life-saving ICU interventions, including mechanical ventilation for respiratory failure and vasopressors for severe shock [28]. Although beyond the scope of the thesis, it would be important to discuss the arguments for whether it is ethically acceptable to randomize patients to treatments that may have severe adverse effects, or that may even increase mortality, in the search for new beneficial interventions; as it was seen in a large RCT of growth hormone treatment for critically ill adults[29]. Most RCTs are costly in terms of time and money, and this limits the number of interventions that can be examined. Many RCTs are sponsored by pharmaceutical companies or medical device manufacturers who aim to demonstrate the effect of a new product. Therapies without commercial interest are rarely evaluated in large RCTs [15]. In RCTs, the intervention groups should be compared using an *intention- to- treat* analysis, implying that the groups should be compared according to initial assignments, because analyzing according to actual treatment may eliminate randomization and introduce confounding. The drawback of the intention-to-treat analysis is that cross-over between two intervention groups during follow-up usually leads to an underestimation of the treatment effect. Due to these practical, ethical, and methodological limitations of RCTs for studies in ICU patients, the use of observational study designs is increasing for studies in the ICU setting[18;28;30].

There are three main types of observational study designs: the cohort design, the case-control design, and the cross-sectional design[12]. All studies in this thesis were conducted as cohort studies. The main advantage of a cohort study is that it allows for direct assessment of absolute risks and risk differences between exposure groups; therefore, the cohort study allows for computation of the number needed to treat and the number needed to harm [16]. For studies on rare complications that require detailed clinical data only obtainable by review of medical records, a case-control study

nested within an existing cohort of ICU patients is a very efficient study design[16]. Cross sectional and case-control studies are often used to validate diagnostic tests and procedures[12].

The costs and complexity associated with primary data collection for large observational studies have prompted an increase in the use of registries and databases as alternative data sources[31]; however, using data from existing registries has both strengths and limitations[32;33]. A strength of registries is that they often include data on large study populations that have been followed for long time periods and therefore allows for studies of rare exposures, infrequent outcomes, and long-term effects. Registries often retain data on multiple exposures and outcomes and, to a certain extent, on potential confounding factors. Data in registries are often collected prospectively and independent of any subsequent study; thus, the risk of some types of information bias, e.g., recall bias of drug exposure, is reduced[33]. When the data are complete, they reflect daily clinical practice far better than the data obtained in a RCT. Also, the time and money cost is much lower than that for studies that use primary data collection. Of note, registries that collect data for administrative purposes can also be used for continuous monitoring of the quality of care in ICUs[34]. A limitation for the use of existing registries is the fact that the researcher often does not have any influence on whether data is collected on key variables; in particular, life style factors, which are potential confounding factors in many etiological studies and may improve prediction in prediction studies. Also, it may be difficult to assess the validity of the included variables[32]. Finally, systematic errors in the data collection or handling of data in the registry may introduce severe biases and, therefore, thorough validation of the data is improtant[32].

In this thesis, we used registry-based data; thus, the studies were historical cohort studies. The data were collected prospectively and independent of future studies; thus, the studies should be considered prospective by design.

### *1.1.4 Etiologic vs. prediction studies*

There are two main types of observational outcome studies, etiological studies and prediction studies[11]. Unfortunately, inconsistent and confusing terminology has been used across the literature regarding etiological and prediction studies[10;11;35]. In this thesis, the terms are defined as follows: A) The purpose of *etiological studies* is to evaluate the causal role of one or more *prognostic factors* while simultaneously controlling for the possible confounding effects of other factors.

Etiological studies are therefore always based on a given hypothesis. It also follows that a prognostic factor for ICU patients is defined as an exposure or characteristic of a patient that is casually related to the outcome of intensive care. B) The purpose of *prediction studies* is to estimate risk based on information from *risk predictors*. The result from a prediction study is a model that can be used to predict a person's risk for an outcome; e.g. APACHE or SAPS scores were developed to predict the risk of in-hospital death for individual ICU patients, based on a number of covariates available within the first 24 hours in the ICU[36;37]. There are two main consequences of these important, but often overlooked, differences between the two types of studies. First, confounding is specific for a particular hypothesis, and thus, confounding is an important issue in etiological studies. In contrast, prediction studies have no underlying hypothesis, thus, it is not relevant to discuss confounding. Second, in etiological studies, all covariates included as potential confounders should fulfill the criteria for being potential confounders. In contrast, prediction studies include all covariates that improve prediction. This distinction is especially important for factors that are effects of the exposure under study; in etiological studies, exposure effects should not be included in the analysis, because a bias may be introduced when controlling for these factors; however, in prediction studies, these factors may improve prediction, and thus should be included in the statistical model[11].

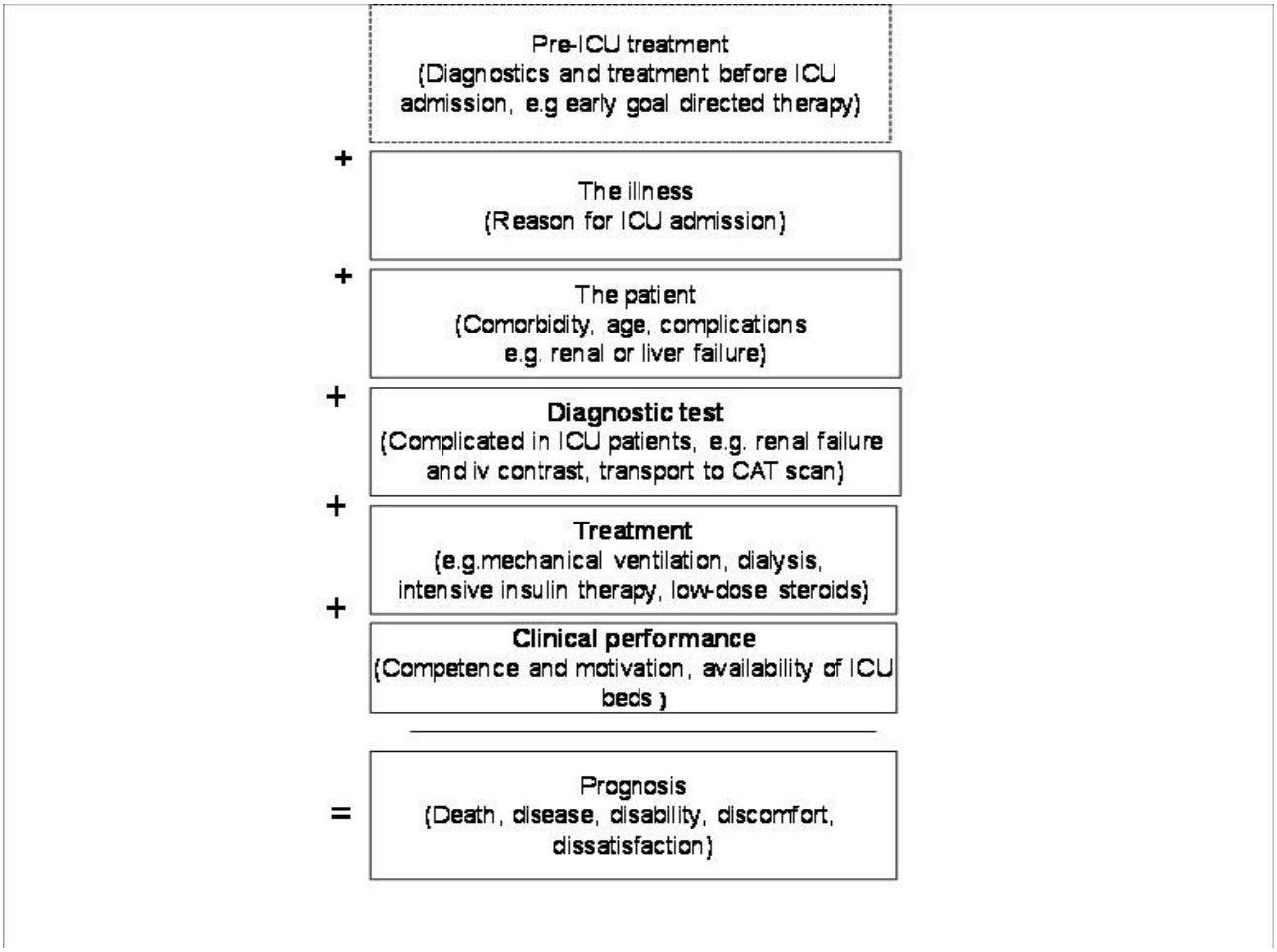
### *1.1.5 Prognostic factors of ICU outcome*

Traditionally, studies on prognostic factors for ICU patients have focused on subgroups of patients with specific conditions, like severe sepsis/septic shock or acute renal failure[38-40], or on patients with specific interventions, like blood transfusions or intensive insulin therapy [18;22;23]. In contrast, little data exist on prognostic factors for general ICU patients. A Medline search on "Epidemiology"[Mesh] AND "Intensive Care"[Mesh] AND "Prognosis"[Mesh] revealed "no items found".

A wide range of factors may influence the prognosis of ICU patients [41]. Figure 1.1.1 displays examples of factors that are likely to play a role in the prognosis for ICU patients. As in most other medical specialties, the focus of intensive care research has been on identifying *treatments* that may improve outcome. However, few intensive care interventions have been shown to reduce mortality in general ICU patients. In fact, there is more evidence on treatments that should be avoided than treatments that should be used [28]. Even the landmark findings by Van den Berghe et al on intensive

insulin therapy have recently been challenged [22;23;40], as has the highly promoted finding by Annane and colleagues on the beneficial effects of low-dose glucocorticoids in severe sepsis [17;42;43]. Because many patients are diagnosed and initially stabilized in the emergency room or in the wards before being transferred to the ICU, the prognosis of ICU patients is affected by the pre-ICU treatment. For example, a late diagnosis of sepsis leading to delayed treatment would most likely affect the prognosis of a patient following ICU admission.

Figure 1.1.1 Factors that may determine the prognosis of ICU patients[41].



## *1.2 Terminology*

The terminology used in intensive care medicine is not entirely consistent. In this section we define some of the key terms used in this thesis.

An intensive care unit (ICU) is defined as a specially staffed and equipped hospital ward dedicated to the observation and treatment of life-threatening illnesses and complications[44]. Three levels of adult ICUs can be defined. Level I, typically available in small district hospitals, can provide mechanical ventilator support and basic cardiovascular monitoring for a limited period of time. Level II can provide a high standard of general intensive care, including multisystem life-support. Level III can provide all aspects of intensive care and is often only available at major referral or university hospitals. All the studies in this thesis are based on data from level III ICUs. The term "general ICU patients" is defined as all the patients treated in the ICUs.

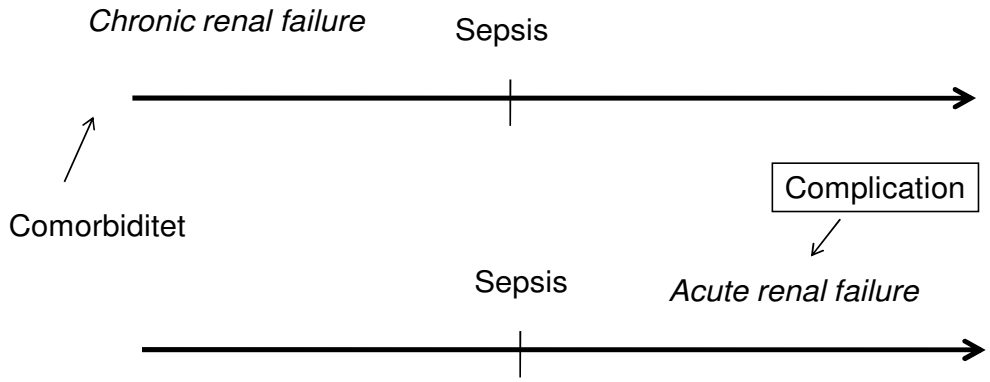
Intensive care is defined as highly specialized care provided to in-hospital patients with life-threatening conditions that require comprehensive care and constant monitoring. The care is usually provided for several days and is usually administered in ICUs. In contrast, critical care is defined as the care provided to severely ill patients during a medical emergency or crisis. Critical care is often provided for a relatively short time period and does not necessarily require an ICU. Critical care and intensive care are often used interchangeably in the literature.

## *1.3 Background and existing literature*

### *1.3.1 Comorbidity in ICU studies*

Comorbidity has been defined as "any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient with an index disease under study"[45;46]. Of note, a comorbidity cannot be a complication to the index disease under study [47;48] ; e.g. acute kidney injury in ICU patients with sepsis is not regarded a comorbidity; but chronic renal failure in a ICU patient with sepsis is considered a comorbidity (figure 1.3.1). In ICU patients, it may be difficult to distinguish complications from comorbidity.

Figure 1.3.1 Complications versus comorbidity, an example.




A concern in registry-based research of prognostic factors is that the lack of key variables may hinder control for confounding[31;32]. It is difficult to collect valid detailed clinical data, such as required for APACHE and SAPS scores, in a standardized way over a long period of time. Also, since routinely collected data reflect daily clinical practice, some clinical data is only collected in databases when there is an indication by an underlying condition; e.g., laboratory tests, blood pressure, heart rate, and urinary output are only measured when there is an underlying condition that indicates a need for these tests.

In observational ICU studies physiology-based severity of illness scoring systems are frequently used to control for confounding. These systems include the Simplified Acute Physiology Scores (SAPS), the Acute Physiology and Chronic Health Evaluations (APACHE), and the Mortality Probability Models (MPM). The systems are based on a summary score consisting of measures of physiological derangement in combination with demographics, comorbidity, and reason for ICU admission and were developed to predict in-hospital mortality.

Although predicting mortality and controlling for confounding are two entirely different entities, the ability to predict mortality is important for the ability to control for confounding. Therefore, comparisons of the ability to predict mortality between registry-based comorbidity scores and traditionally used physiology-based scores (e.g., APACHE and SAPS scores) are important for the

interpretation of etiological studies based on administrative database that does not contain data on severity of illness score.

Single scores that summarize comorbidity are particularly useful in studies using large health care databases, because a large number of variables are reduced into a manageable set of proxy variables [49]. The most widely used comorbidity index is the Charlson Comorbidity Index (CCI)[50;51]. In calculating the CCI score, a weight (1 to 6) is assigned to each of 19 comorbid disease categories and the score is the sum of these weights. The CCI was developed to predict the one year mortality of 604 medical patients at a US hospital in 1984. The comorbidity of study patients was identified by review of medical records. The weight of each comorbid condition was then derived from the relative risk of one year mortality from a proportional hazard regression model.

The CCI has subsequently been validated for the ability to discriminate between survivors and non-survivors in a number of different settings and for different outcomes with acceptable results [51;52]. The CCI has also been adapted for use with International Classification of Disease (ICD) discharge diagnosis [53-55]. However, the CCI also has several limitations that may limit its predictive performance and its use in control for confounding: 1) the index was developed in 1984 and the prognosis, and thus the weights, for a number of diseases (e.g., AIDS) have changed dramatically in current clinical practice. 2) The prognosis for some comorbid diseases may vary between settings, but this is not reflected in the use of fixed weights used in the CCI, and 3) no index disease was defined; because confounding is specific for each hypothesis this may limit the ability of the CCI to control for confounding in etiological studies. 4) A number of diseases that may be predictors of ICU mortality are not included in the CCI, including alcoholism, heart valve diseases, and psychiatric disease.

*Existing literature*

Limited data exist on the performance of the CCI score in predicting mortality in ICU patients.

We conducted a Medline search with the following query:

(("Intensive Care"[Mesh] OR "Intensive Care Units"[Mesh]) AND "Comorbidity"[Mesh]) AND "Prognosis"[Mesh]

The same key terms were used for searches in the Scopus and the Cochrane Library databases. There was no time limit in the literature searches, and all references from identified articles were also searched for relevant information. A total of 98 articles were identified, but just four studies examined the performance of comorbidity scores in predicting mortality in ICU patients (Table 1.3.1).

In a US study including more than 17,000 ICU patients from Veterans Affairs Medical Centers, Johnston *et al.* found that the 30 comorbidity variables included in the Elixhauser Index generated from administrative databases discriminated between in-hospital survivors and non-survivors (c-statistic = 0.598) better than the chronic health evaluation component of the APACHE score (c-statistic = 0.568)[56]. When combined with other clinical data (laboratory data, principal diagnosis, age, and admission source), the discrimination of the Elixhauser Index was excellent (c-statistic = 0.874). In a 1996 US study of 201 ICU patients, the Charlson Index showed moderate discriminating ability for in-hospital mortality (c-statistic = 0.67)[57]. Ho *et al.* found that the Charlson Index had poor predictive performance for short-term mortality among 24,303 ICU patients in Western Australia (c-statistic = <0.610)[58]. This study did not combine the Charlson Index score with other administrative data. A 2006 Canadian study on 1,603 ICU patients found that APACHE II predicted in-hospital survival better than the Charlson Index (c-statistics = 0.77 vs. 0.69)[59].

*Other studies including comorbidity in prediction models*

Recently, an Australian study including more than 11,000 ICU patients found that in a prediction model of 1 year, 5 year, and 15 year mortality, age and comorbidity as measured by the CCI were the most important determinants of prognosis. The c-statictis of the full PREDICT model was 0.757 (95% CI: 0.745-0.769); however, no data on the performance of the CCI without APACHE II score in the model was presented[60]. In the SUPPORT Prognostic Model study, Knaus et al, developed a prediction model of 180 day mortality for ICU patients (c-statistics 0.79) primarily based on diagnosis and physiological variables; however, did not include a comorbidity score in their model[61].

*Limitations of existing literature*

To our knowledge, no data exist that assess the ability of comorbidity scores to predict one-year mortality of ICU patients without physiological variables included in the model. Models based on administrative databases from different health care systems may have different abilities to predict mortality due to differences in the validity and availability of data; thus, generalizability between studies may be poor. Some studies used secondary diagnoses of the index hospitalization or review of medical records to identify comorbidity; this may have lead to substantial underreporting of comorbidity. Also, a secondary diagnosis may have included complications to the index disease, which should not be considered comorbidity.

Table 1.3.1. Studies comparing the performance of comorbidity scoring systems and physiology-based scoring systems in predicting mortality in ICU patients.

| Author, year, country | Study design | Setting | Comorbidity scoring system | Data source | Sample size | Measure of interest* | Result |
|---|---|---|---|---|---|---|---|
| Johnston et al,[56] 2001, USA | Cohort study | Veterans Affairs Medical Centers, 1996-1997 | Elixhauser Index[62] alone and in combination* with age, laboratory results, admission source | Hospital registries, administrative data, discharge diagnosis. | 17,893 patients from 43 ICUs | c-statistics (in-hospital mortality) | c-statistics comorbidity score alone 0.598, in combination with* 0.870<br>APACHE 0.874 |
| Ho et al[58], 2007, Australia | Cohort study | Royal Perth Hospital 1987-2002 | Charlson comorbidity Index and in combination** with APACHE score without chronic health evaluation | Hospital registries, discharge diagnosis | 24303 ICU patients | c-statistics (in-hospital mortality) | c-statistics Charlson alone <0.610, in combination with ** 0.831<br>APACHE 0.832 |
| Norena et al[59], 2006, Canada | Cohort study | Single 13 bed ICU, 1998-2003 | Charlson Comorbidity Index in combination*** with age, gender, source of admission, socioeconomic variables | Hospital registries, discharge diagnosis | | c-statistics (in-hospital mortality) | c-statistics Charlson in combination with ***0.69, APACHE 0.77 |
| Poses et al[57], 1996, USA | Cohort study | Single center ICU, 1987 | Charlson Comorbidity Index | Review of medical records | 201 ICU patients | c-statistics (in-hospital mortality) | c-statistics Charlson Index 0.67<br>APACHE 0.87 |

*C-statistics (area under ROC curve) is a measure of the model's ability to discriminate between survivors and non-survivors (c-statistics=0.5: no discrimination, c-statistics 0.7-0.8: acceptable discrimination, c-statistics 0.8-0.9: excellent discrimination, c-statistics: >0.9 outstanding discrimination)[63]

### *1.3.2 Cardiovascular drug use and intensive care*

ICU patients have a high prevalence of cardiovascular comorbidity; they are often admitted due to acute cardiovascular conditions, like myocardial infarction; and they often suffer from cardiovascular complications during the ICU stay. We therefore focused our on the association between two interventions known to reduce mortality due to cardiovascular disease and mortality following intensive care: preadmission statin use and preadmission beta-blocker use.

#### ***Statin use and prognosis in ICU patients***

*Background*

Hydroxymethylglutaryl-CoA Reductase Inhibitors (statins) are widely used lipid-lowering drugs that have been shown to be effective in reducing cardiovascular events in patients with arteriosclerosis [64-66] . In addition to the lipid-lowering effects, there is substantial experimental evidence that statins have important anti-inflammatory, anti-thrombotic, and immuno-modulating effects independent of lowering lipids [67-69]; these are often referred to as the pleiotropic effect of statins.

*Pathophysiology*

As recently reviewed by Terblanche et al, the pleiotropic effects of statins are primarily mediated through an inhibition of the Hydroxymethylglutaryl-CoA Reductase (HMG-CoA), an important mediator of intracellular inflammatory signaling pathways [69]. Inhibition of the HMG-CoA reductase by statins leads to an overall reduction of circulating pro-inflammatory cytokines during critical illness, and this is believed to reduce the systemic pro-inflammatory response[70;71]. These immuno-modulating effects may be beneficial during the initial "hyper-immune" phase of critical illness[72]. The reduction in circulating pro-inflammatory cytokines also causes reductions in platelet aggregation and stress on the endothelium, which may in turn reduce the risk of thrombosis [73;74]. Experimental animal studies have reported that different statin types may have different immuno-modulating effects; however, results are contradictory and the clinical implications of these differences need to be fully elucidated [75;76].

*Clinical effects*

The effect of statins in preventing cardiovascular disease has been demonstrated in large randomized controlled trials[65]; however, only limited data exist on whether the pleiotropic effects of statins found in experimental studies translate into clinical beneficial effects in critically ill patients. Observational studies have described associations between the use of statins and the risk of severe infections [77-79], cancer [80-82], deep venous thrombosis[73;74;83], dementia [84], neurological disease[85], and immune-mediated diseases like rheumatoid arthritis[86]; most studies report beneficial effects of statins. Similarly, several observational, but no RCT, studies examined whether statin use was associated with reduced mortality in patients after severe infections, (like sepsis) [87-91], in patients with trauma [92], in patients undergoing major surgery [93;94] and in patients with chronic obstructive pulmonary disease [95]. Statins also have side effects, including myalgia, liver function test elevations, and rhabdomyolysis; however, large meta-analyses of randomized controlled trials have shown that serious adverse events are rare with statin therapy[96].

ICU patients have a high prevalence of cardiovascular disease, a high prevalence of complications with major surgery and severe infections, and varying degrees of the systemic inflammatory response syndrome. Therefore, statins may reduce mortality in general ICU patients.

*Existing literature*

Very limited data exist on the association between statin use and the prognosis of intensive care patients.

We conducted a Medline search with the following query:

"Intensive Care"[Mesh]) OR "Intensive Care Units"[Mesh] OR "Critical illness" [Mesh] OR "sepsis" [Mesh]OR "Critical Care"[Mesh] AND "Mortality"[Mesh] AND "Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh]

The same key terms were used to search the Scopus and the Cochrane Library databases. There was no time limit in the literature searches, and all references from identified articles were also searched for relevant information. Three studies examined the association between statin use and mortality of general ICU patients (table 1.3.2).

A 2006 German observational study of 120 ICU patients with multiple organ dysfunction syndrome (MODS) included 40 patients that used statin and found a significantly reduced 28-day mortality among statin users compared with non-users (hazard ratio 0.53 [95% CI: 0.29-0.99]) [97]. In contrast, a 2006 Spanish study of 438 patients that had been mechanically ventilated for more than 96 hours, included 38 (8.7%) patients that used statin; they found significantly increased in-hospital mortality among statin users compared with non-users (in-hospital mortality: statin use 61%, no use: 42%, [p=0.03]) [98]. In a 2009 US study, Kor et al reported that they found no significant difference in ICU and in-hospital mortality between statin users and other ALI/ARDS patients[99]; however, they reported statistically imprecise risk estimates of 0.82 (95% CI: 0.36-1.89) and 0.62 (95% CI: 0.29-1.32), respectively. These may indicate a quite substantially reduced mortality among statin users. Of note, statin use was defined in three different ways in the three studies: as statin treatment while in the ICU[97], prehospital use that was continued while in the ICU[98], and prehospital and/or in-hospital use[99].

*Limitations of the existing literature*

First, the lack of adjustment for important confounding factors, including the use of other cardiovascular drugs and socio-economic factors, makes the results difficult to interpret [100]. Second, the study populations were highly selected. They included patients with MODS, ALI/ARDS or patients mechanically ventilated for more than 96 hours. These criteria may hinder generalization to other general ICU patients because the effect of statins may be different between these subgroups of very severely ill patients and other ICU patients. Third, the relatively small sample sizes gave rise to statistically imprecise risk estimates, which complicated the interpretation. The latter problem was particularly true for the study by Kor et al. No data was found on mortality for ICU patients using specific types of statins.

Table 1.3.2

| Author, year, country | Study design | Setting | Data source | Measure of interest | Result |
|---|---|---|---|---|---|
| Schmidt et al[97], Germany, 2005 | Cohort study | Single ICU,<br>120 MODS patients<br>(40 statin users) | Manual review of medical records | 28-day mortality comparing statin users and non-users | HR 0.53 (95% CI:0.29-0.99) |
| Fernandez et al[98], Spain, 2005 | Cohort study | Single ICU,<br>438 patients, MV>96 hours<br>(38 statin users) | Manual review of medical records | Hospital mortality | 61% among statin users, 42% among non-users (p=0.03) |
| Kor et al[99], USA, 2009 | Cohort study | Three ICUs<br>178 patients with ALI/ARDS<br>(45 statin users) | Medical databases and medical records | ICU and hospital mortality | ICU mortality: Statin users 20% vs. non-users 23% [OR:0.82 (0.36-1.89)]<br>Hospital mortality: Statin users 27% vs. non-users 37% [OR:0.62 (0.29-1.32)] |

*Statins and sepsis outcome*

The majority of studies on statin effects on the prognosis of critically ill patients were conducted for patients with bacteremia/sepsis [88-90;101;102]. Three studies reported substantially reduced in-hospital or 30-day mortality among statin users compared with non-users [88;89;101]. In contrast, Thomsen et al found no difference in the 30-day mortality following bacteremia between Danish statin users and

non-users, but they did find reduced mortality for the 30 to 180 days following bacteremia in statin users [90]. Yang et al, in a Taiwanese cohort study, found no reduced sepsis-related mortality among sepsis patients taking statins[102]. However, none of these studies examined ICU patients exclusively, and generalization to critically ill patients without infections may be complicated.

***Beta-blocker use and prognosis in ICU patients***

*Background*

Beta-blockers are primarily used to treat cardiovascular diseases, but they are also used to treat migraine and hyperthyroidism. Beta-blockers have been shown to reduce re-infarction rates and mortality following myocardial infarction[103;104] and to improve cardiac function and reduce mortality in chronic heart failure patients [105]. Some evidence exists that beta-blockers reduced the risk of perioperative cardiac complications and mortality in high-risk patients undergoing major surgery[106-110], although this evidence has recently been challenged [111;112]. Beta-blockers also have side effects of bronchoconstriction and heart failure following acute administration; however, these side effects are rare during chronic use[113;114].

*Pathophysiology*

A shift in metabolism towards a hypermetabolic state occurs during critical illness that is primarily mediated through a catecholamine surge and sympathetic activation during the early phase of critical illness[115;116]. Attenuation of these harmful metabolic changes by blocking beta-adrenergic stimulation of the catecholamine surge has been suggested to be the underlying biological mechanism for the reduced mortality observed in beta-blocker users that were hospitalized after severe trauma and burns [117-119].

Key mediators of the immune system have been shown to express beta-adrenergic receptors[120;121] . In vitro studies have suggested that beta-blockers promoted a number of potentially beneficial immuno-modulating effects [122] ; however, the full extent of these effects is far from elucidated in critically ill patients.

ICU patients are characterized by a high prevalence of cardiovascular disease, a high risk of cardiovascular complications, severe hypermetabolic disturbances, and a hyper-inflammatory response. Therefore beta-blocker therapy may have beneficial effects in ICU patients[123].

*Existing literature*

Virtually no data exist on the association between beta-blocker use and prognosis following intensive care.

We conducted a Medline search with the following queries:

"Adrenergic beta-Antagonists"[Mesh] AND "Mortality"[Mesh] AND "Intensive Care Unit"[Mesh]

"Adrenergic beta-Antagonists"[Mesh] AND "Mortality"[Mesh] AND "Intensive Care Unit"[Mesh]

"Adrenergic beta-Antagonists"[Mesh] AND "Mortality"[Mesh] AND "Critically ill"[Mesh]

The same key terms were used for searches in the Scopus and the Cochrane Library databases. There was no time limit in the literature search, and all references from identified articles were also searched for relevant information. No studies were identified, however, a number of studies exist on the prognostic effect of beta-blocker use in patients with diseases or undergoing procedures related to ICU admission.

*Effects in non-ICU patients*

Data from a number of observational studies and RCTs have suggested that beta-blockers reduced perioperative mortality in patients undergoing major non-cardiac surgery, but no studies have reported separate data for ICU patients [107;108;124]. In contrast, the recent POISE trial found that acute administration of high-dose beta-blocker therapy perioperatively was associated with a reduced risk of myocardial infarction but an increased risk of total mortality[111]. The increased total mortality was at least in part due to more deaths due to sepsis or infections among beta-blocker users compared to non-users; in contrast, there were no differences in deaths due to multiple organ failure or cardiogenic shock or heart failure. Less than 30% of POISE participants were transferred to an ICU. A US observational study of 4,117 trauma patients found that beta-blocker use was associated with reduced mortality[117]. The authors suggested that beta-blocker use led to an attenuation of the detrimental effects of hyper-metabolism and increased tissue oxygen consumption related to severe trauma. Beta-blockers have also been reported to have beneficial effects in patients with severe burns, apparently by decreasing energy expenditure and muscle catabolism [118;125].

*Limitations of the existing literature*

To our knowledge, no data have been published on beta-blockers as a prognostic factor for general ICU patients. Nevertheless, experimental data and data from sub-groups of ICU patients suggest that this inexpensive and fairly safe treatment may reduce mortality among these patients.

*1.4 Conclusion of literature review*

Limited data exist on the use of administrative data for predicting the in-hospital mortality, 30-day and one-year mortality of ICU patients. Studies on the performance of administrative data in predicting mortality are needed because large health care databases that have no data on the conventionally used physiology-based scoring systems are increasingly used to study and monitor ICU outcomes.

There are a few studies on whether preadmission use of statins or beta-blockers is associated with mortality following ICU admission. However, the interpretations of the results were limited by methodological weaknesses, including potential uncontrolled confounding by comorbidity and concurrent use of other cardiovascular drugs. The relatively small sample sizes did not allow for clinically meaningful subgroup analysis. Because statins and beta-blockers have relatively few adverse effects, are cheap, and are readily available, any reduction in mortality associated with use of these drugs would have substantial public and clinical implications.

Using data from large health care databases may help overcome some of the limitations in the existing literature; large study populations can be identified, and this may allow meaningful sub-group analysis; preadmission drug use can be determined with negligible risk of recall bias, no influences of surveillance bias, or loss to follow up [31].

## 2. AIMS

The aims of this thesis were to study prognostic factors for ICU patients and to determine whether scoring systems based on administrative data could predict mortality in ICU patients. Specifically, the following questions were addressed:

1. Can the Charlson Comorbidity Index, based on administrative data, predict mortality in ICU patients at least as well as the physiology-based scoring systems? (Study I)

2. Is preadmission statin use associated with mortality in general ICU patients? (Study II)

3. Is preadmission beta-blocker use associated with mortality in general ICU patients? (Study III)

## 3. SUBJECTS AND METHODS

### *3.1 Data sources*

#### *3.1.1 Aarhus University Intensive Care Cohort*

As part of this PhD project, we established an ICU database based on administrative data at the Department of Clinical Epidemiology, Aarhus University Hospital, Denmark. As part of the standard ICU clinical practice at Aarhus University Hospital, data were recorded on the use of mechanical ventilation, use of renal replacement therapy, dates of ICU admission and discharge, and civil registration numbers for all patients treated in the ICUs. The data were recorded by ICU physicians and entered into hospital registries. From the hospital registries, we identified all ICU patients and electronically entered data into the *Aarhus University Intensive Care Cohort* (AUICC)**.**

The creation of the AUICC and the studies conducted based on the database were approved by the Danish Data Protection Agency (record number 2005-41-4782) and the Aarhus University Hospital Registry Board.

We previously validated information on renal replacement therapy in the AUICC. We reviewed all medical records of patients registered with renal replacement therapy in 2004 and 2005 at Aarhus Hospital and found that renal replacement therapy had a very high positive predictive value of 94% in the AUICC (98 of 105 registered cases were correct).

To obtain further information on each ICU patient, we linked the AUICC to a number of population-based medical databases (described below; figure 3.1.1). From the year 1968, every Danish citizen has been assigned a unique civil registry number encoding their gender, and date of birth[126]. This unique personal identifier is included in all Danish administrative registries and medical databases and allows accurate linkage between databases.

#### *3.1.2 The National Registry of Patients*

Since 1977, for each non-psychiatric hospital admission (and, since 1995, for all hospital outpatient and emergency room visits), the National Registry of Patients (NRP) has recorded the patient civil registration number, the dates of admission and discharge, and up to 20 discharge diagnoses,

classified according to the *International Classification of Diseases* (ICD), 8th revision (10th revision after the end of 1993)[127]. All coding is done at discharge by the physician treating the patient. The NRP covers more than 99.5% of all admissions to Danish non-psychiatric acute care hospitals. A number of diagnoses and procedures in the NRP have been validated with acceptable results [128;129].

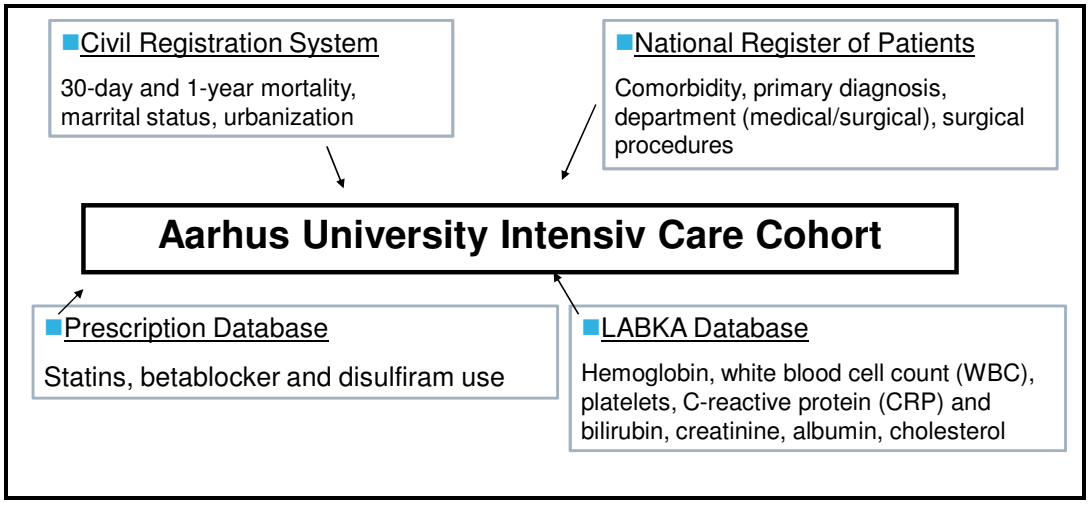
### *3.1.3 Prescription database*

Since 1998, a prescription database has tracked all prescriptions for reimbursable drugs dispensed at all pharmacies in the regions of North Jutland and Aarhus with complete coverage [130;131]. For each filled prescription, the following information is transferred electronically from the pharmacies to the prescription databases: the patient civil registration number, the type and amount of drug prescribed according to the Anatomical Therapeutic Chemical (ATC) classification system, and the date the prescription was filled. Drugs that are not reimbursed and drugs available without prescriptions are not registered. The structure of the database ensures high validity and completeness of the data.

### *3.1.4 Laboratory Database (LABKA)*

All the blood tests analyzed in hospital laboratories in Aarhus and North Jutland County are registered in the LABKA system. The system contains data on the patient civil registration number, the test name and IUPAC-code, the result, the measurement unit, the dates of ordering and carrying out the analysis, and a code for the hospital department or the general practitioner (GP) that ordered the test. Because the system is used in every clinic at the hospitals, the completeness for ICU patients is expected to be very high. However, we did not include data on arterial blood gas tests in our studies, because these are often analyzed in the ICUs, which do not report data to the LABKA system.

Figure 3.1.1 Aarhus University Intensive Care Cohort




*3.1.5 The Civil Registration System*

Since 1968, the Civil Registration System (CRS) has been updated on a daily basis. The CRS contains information for the entire Danish population on migration and changes in vital status, including exact date of death [126]. The register also includes, among other variables, marital status (including spouse), citizenship, kinship, profession, and declaration of incapacity.

*3.1.6 Clinical database for ICU patients at Skejby Hospital*

Since 2004, detailed physiological data and treatment data for all ICU patients admitted to the ICU at Skejby Hospital has been electronically collected in a computerized patient data management system (PICIS). The system electronically collects a wide range of data from mechanical ventilators, arterial blood gas analyzers, and includes detailed data on drug infusion, body temperature, blood pressure and heart rate, and urinary output.

*3.1.7 Medical records*

For study I, we collected data on the Glasgow Coma Scale score, surgery, reason for ICU admission, and comorbidity through review of medical records of all study patients. By Danish law, hospitals are required to store medical records for at least 10 years. At Skejby Hospital, all medical records from 2000 to the present were electronically available.

*3.2 Study populations*

*3.2.1 All adult ICU patients at Skejby Hospital in 2007 (study I)*

In study 1 (comorbidity study), we identified all individuals over 15 years old that had been admitted to the ICU at Skejby Hospital in 2007. A total of 864 ICU admissions were identified; however, we included only first-time ICU admissions in 2007, and did not include coronary care patients and cardiac surgery or other patients admitted for planned post-operative observations for less than 24 hours as defined in the original physiology-based models [36;132;133]. Thus, 469 patients were analyzed further. Because some of the clinical data were obtained from medical records, we confirmed that all the selected ICU patients had been in the ICU during the study period.

*3.2.2 All adult ICU patients at Aarhus University Hospital (Study II and III)*

In studies II and III, the study populations were based on the AUICC.

For study II (statin study), we identified all patients with a first ICU admission between 2001 and 2007. Because statins are rarely used by patients under 45 years old, we included only ICU patients over 45. We also did not include patients that were admitted for less than 24 hours of planned postoperative observation. The study population totaled 12,483 eligible ICU patients with a first ICU admission during the study period.

For study III (beta-blocker study), we identified all patients with a first ICU admission between 1999 and 2005. We defined two different data collection periods based on the initial availability of computerized ICU data records: January 1, 1999 – December 31, 2005 for patients treated in Aarhus and Skejby Hospitals, and January 1, 2001 – December 31, 2005 for patients treated in Aalborg Hospital. For study III (beta-blocker study), we did not include patients that were admitted for less than 24 hours of planned postoperative observation. Patients under 45 years old were also excluded because beta-blockers are rarely prescribed to patients in this age group in Denmark [134]. The study cohort encompassed 9,515 eligible ICU patients with a first ICU admission during the study period.

### *3.3 Exposure, outcomes, and confounding factors*

#### *3.3.1. Exposure*

Exposure can, in its most general sense, be defined as a potential causal charateristic[16]. Examples of exposures include: treatments or interventions, patient characteristics like genotype, age, or gender, or a disease, including comorbidity. It follows that in etiological cohort studies, exposure is the prognostic factor under study, which can be present (exposed cohort) or absent (unexposed cohort) in the study population[11].

*Study I*

In study I (comorbidity study), we used the Charlson Comorbidity Index (CCI) to estimate comorbidity levels among study patients. We utilized a version of the Deyo ICD-9 adaptation of the CCI[51;53], modified for use with ICD-8 and ICD-10 discharge codes. Using the National Registry of Patients, we identified all the post-1977 hospital diagnoses of study patients, and used them to compute a CCI score for each patient. The scores were included as continuous variables in the analysis. In order to include the comorbidity categories separately in the regression model, we reduced the number of categories in a secondary analysis. We therefore defined 10 separate clinically relevant categories based on the original 19 comorbid disease categories in the Charlson Index.

We obtained data on the physiology-based scores of SAPS II, SAPS III, and APACHE II through review of medical records. Two reviewers (SC and CFC) went through all 469 medical records and grouped the patients according to the reasons for ICU admission. The reasons for admission included surgical, medical, acute, or elective. We computed the Glasgow Coma Scale score, identified comorbidity (as defined in the scoring systems), and manually retrieved data from the computerized patient data management system on blood pressure, heart rate, renal function, mechanical ventilation, PaCO2, PaO2, pH, and data from LABKA on hemoglobin, white blood cell count, and creatinine. We used the original definitions of all variables in the APACHE II, SAPS II, and SAPS III systems. The Glasgow Coma scale (GCS) score is difficult to assess based on review of medical records[135]. In cases where no data on the GCS score were available in the medical

records or in cases where the patient was sedated upon ICU admission, we assumed a normal GCS score (=15), as defined in the original definitions[36].

*Study II*

For study II (statin study), we used the prescription database to identify preadmission statin users. We defined current statin use as at least one filled prescription for statins within 125 days of ICU admission. The 125-day period allowed us to capture most current statin users, because in Denmark, few statin prescriptions are expected to last more than 125 days[134].

Adherence to statin therapy may be a marker for overall better health, and thus, is associated with better prognosis. This may introduce "adherence bias" and "healthy user bias"[136]. In long-term statin users, the intervention (statin use) may have influenced the prevalence of potential confounding factors; for example, statin use may have reduced the risk of cardiovascular disease among ICU patients. Adjusting for cardiovascular disease to control for confounding seems reasonable in a study on the association between statin use and mortality; however, if long-term statin use reduced the risk of cardiovascular disease, it may also be considered an effect of statin use, and therefore should not be controlled for[11]. One way to deal with these difficulties is to include only new statin users in the analysis, because any effects of adherence or an effect on potential confounding factors should be negligible[137]. We therefore distinguished among "new" and "long-term" current statin users, defined as those that had filled their first statin prescription within the 125 days before ICU admission, or earlier than 125 days, respectively. For a subanalysis we defined statin use as at least one filled prescription within 90 days of ICU admission.

Statin users may have been more frequently hospitalized before ICU admission than other patients. Because no prescriptions were filled during hospitalization, misclassification of statin use may have occurred if current statin use is defined as a filled prescription within 125 days before the ICU admission [138]. We therefore used the National Registry of Patients to identify the number of days that study patients were hospitalized within the 125 days before ICU admission (0 days, 1-10 days,11-25 days, >25 days).

*Study III*

For study III (beta-blocker study), we defined current beta-blocker use as at least one filled prescription for beta-blockers within 125 days before ICU admission. Again, the 125-day period allowed us to capture most current beta-blockers users, because in Denmark few beta-blocker prescriptions are expected to last more than 125 days[134]. As for study II, in study III, we distinguished between subgroups of "new" and "long-term" beta-blocker users, defined as those who had filled their first ever beta-blocker prescription within the 125 days before ICU admission, or earlier than 125 days, respectively[137]. We also categorized patients according to the type of the last prescribed beta-blocker before the ICU admission (cardio-selective, non-selective, non-selective combined with alpha-adrenergic blocker). For a subanalysis we defined current beta-blocker use as at least one filled prescription within 60 days of ICU admission.

### *3.3.2 Mortality*

The outcome in all studies was risk of death, defined as the proportion of ICU patients that died in-hospital (study I), within 30 days after ICU admission (studies I, II, and III), and within one year after ICU admission (studies I and II). In this thesis, the risk of death, or cumulative mortality proportion, is referred to as mortality[11]. We obtained data on death for all study patients through the Danish Civil Registration System[126].

We did not attempt to determine the cause of death because we believe this is extremely difficult in ICU patients that die from very complicated diseases and failure of multiple organ systems. This is particularly true in studies, like the once in this thesis, based on historical data.

### *3.3.3 Confounding factors*

There are a number of potential prognostic factors for ICU patients, other than the ones under study, that also may have affected the choice of treatment with statins or beta-blockers[41]. We therefore adjusted for a wide range of these potential confounding factors in studies II and III. Data on the potential confounding factors were obtained through the National Register of Patients (e.g. diagnosis, comorbidity, surgery, department), prescription databases (e.g. use of cardiovascular drugs), LABKA (e.g. hemoglobin, white blood cell count), and the civil registration system (marital status, urbanization).

### *3.4 Statistical analysis*

#### *3.4.1 Prediction model (study 1)*

For each endpoint (in-hospital, 30-day, and 1-year mortality) logistic regressions models were constructed for the following combinations of variables: (1) CCI score; (2) CCI score, age, gender; (3) CCI score, age, gender, surgical/medical status; (4) CCI score, age, gender, surgical/medical status, social factors; (5) CCI score, age, gender, surgical/medical status, social factors, mechanical ventilation and dialysis; (6) CCI score, age, gender, surgical/medical status, social factors, mechanical ventilation and dialysis, primary diagnosis; (7) 10 separate comorbidity groups; (8) 10 comorbidity groups in combination with age, gender, surgical/medical status, social factors, mechanical ventilation and dialysis, primary diagnosis; (9) SAPS II; (10) SAPS III; and (11) APACHE II.

We computed Spearman rank correlation coefficients as a measure of correlation between comorbidity scores and physiology-based scoring systems.

We used Hosmer-Lemeshow goodness-of-fit statistics to assess model *calibration* except for the model including CCI only and the model including the 10 separate comorbidity groups only. Because of the limited number of observed and expected deaths in the higher deciles of risk in these models Pearsons chi-square statistics was used.

For all models, c-statistics (area under the ROC curve) were calculated as a measure of *discrimination* between survivors and non-survivors[63]. The interpretation of the c-statistics is: c-statistics 0.5 indicate chance discrimination, c-statistics 0.7-0.8 indicate acceptable discrimination, c-statistics 0.8-0.9 indicate excellent discrimination, and c-statistics: >0.9 indicate outstanding discrimination[63].

*3.4.2 Propensity score analysis (studies II and III)*

A propensity score analysis potentially improves control for confounding in observational studies although there is little evidence that a propensity score analysis can outperform a conventional regression analysis [139].

For the propensity score analyses, we generated a multivariable logistic regression model that predicted beta-blocker use or statin use among ICU patients based on their covariate profile. The propensity score (e.g. the probability of beta-blocker use or statin use) was then computed for each ICU patient. We used a greedy matching algorithm to match each beta-blocker user and statin user with the non-user that had the closest propensity score. All matches were within a maximum matching range of ±0.025 in propensity scores. All beta-blocker users and all statin users could be matched to a non-user. To determine whether the propensity score matching achieved adequate balance between exposure groups for all covariates, we computed, for each covariate, the absolute standardized difference in propensity score between users and non-users. The propensity score matching decreased the absolute standardized differences of each covariate to values below 0.1, indicating that an adequate balance was achieved in both study II (statin study) and study III (beta-blocker study).

*3.4.3 Cox proportional hazards regression analysis (study II)*

Associations between the exposure variables and risk of death in study II were expressed as mortality rate ratios (MRR) and 95% confidence intervals (CI), and were derived from a Cox proportional hazards regression analysis.

In assessing statin use (study II) as a prognostic factor for ICU patients, we adjusted in the model for diagnostic category; age group; department (medical/surgical); level of Charlson score; alcoholism-related diseases; surgery (yes/no); need for mechanical ventilation or renal replacement therapy; current use of ACE-inhibitors, low-dose aspirin or beta-blockers; and marital status (married, divorced, widowed, never married, or unknown).

*3.4.4 Conditional logistic regression analysis (study III)*

For study III (beta-blocker study), the association between preadmission beta-blocker use and risk of death was expressed as the odds ratio (OR) with 95% confidence intervals, and was derived from

logistic regression models. Because the patients had been matched with propensity score matching, we used conditional logistic regression.

To control for confounders, we used the propensity score matched dataset, computed the OR of deaths within 30 days after ICU admission, for users of beta-blockers compared with non-users.

*3.4.5 Sub analyses*

For studies II and III (statin and beta-blocker studies), we performed several additional analyses to further explore the associations found.

For study II (statin study), we performed separate analyses for subgroups that were defined by the admitting department, surgery, presence of mechanical ventilation, renal replacement therapy, and by whether the patient was a former, new, or long-term statin user. To further control for confounding, we repeated the analysis for patients with similar underlying diseases that indicated statin use (cardiovascular diseases and diabetes) and excluded patients unlikely to be treated with statins (cancer patients and alcoholic patients). We also performed separate analyses for users of simvastatin, atorvastatin, pravastatin, or other statins, and for users of non-statin lipid-lowering agents.

For study III (beta-blocker study), we performed separate analyses for subgroups that were defined by the admitting department, mechanical ventilation, dialysis, surgery, renal replacement therapy, and by whether the patient was a new or long-term beta-blocker user. We also performed separate analyses for users of selective or non-selective beta-blockers.

In studies II and III, we used Wald statistics to compare MRRs between different types of statins and between different types of beta-blockers[140].

## 4. RESULTS

Below follows a summary of the main results from the three studies.

*4.1 Study I (comorbidity study)*

For study I, we identified a total of 469 ICU patients that were admitted to the ICU for the first time at Skejby Hospital, Aarhus University Hospital in 2007.

The correlations between the CCI score and the physiology-based scores were poor (table 4.1). However, the correlations between the three physiology-based scores were moderate to high.

Table 4.1. Correlations between scoring systems (Spearman's rank correlation coefficient, *p*-values)

| | **SAPS II** | **SAPS III** | **APACHE II** |
|---|---|---|---|
| **Charlson score** | 0.124 | 0.082 | 0.228 |
| | (*p*=0.0074) | (*p*=0.0750) | (*p*<0.0001) |
| **SAPS II** | -- | 0.691 | 0.770 |
| | | (*p*<0.0001) | (*p*<0.0001) |
| **SAPS III** | | -- | 0.659 |
| | | | (*p*<0.0001) |

The Hosmer-Lemeshow goodness-of-fit statistics varied between models and outcomes; however, supported model fit of all models for 30-day and 1-year mortality. For in-hospital mortality p-values<0.05 for the models including CCI, age and gender, surgical/medical status, social factors, and the full CCI indicated poor calibration.

When the model included only the CCI score, it performed poorly in discriminating between survivors and non-survivors during hospitalization ( c-statistic = 0.53 [95% CI: 0.46-0.59]), within 30 days of ICU admission (c-statistic = 0.52 [95% CI: 0.46-0.57]), and within one year of ICU admission (c-statistic = 0.58 [ 95% CI: 0.53-0.63]) (Table 4.2.1). When the CCI score was combined with age, gender, social factors, surgical/medical status, mechanical ventilation/dialysis,

and primary diagnosis, the discrimination of the regression model improved substantially, with c-statistics of 0.75 (95% CI: 0.69-0.81) for in-hospital mortality, 0.75 (95% CI: 0.70-0.80) for 30-day mortality, and 0.72 (95% CI: 0.68-0.77) for one-year mortality. The physiology-based scores were comparable to the CCI in combination with administrative data for discriminating between short-term survivors and non-survivors. C-statistics for one year mortality was 0.70 (95% CI: 0.66-0.75) for SAPS II, 0.69 (95% CI: 0.64-0.73) for SAPS III, and 0.69 (95% CI: 0.64-0.73) for APACHE II.

*4.2 Study II (statin study)*

For study II, we identified 12,483 first-time ICU patients between 2001 and 2007; of these, 1,882 (15.1%) were current statin users. Statin users were more likely to be male and had a higher prevalence of comorbidity than non-users, as expected in particular for cardiovascular diseases and diabetes. Alcoholism-related diseases and cancer were less prevalent among statin users than among non-users.

Throughout the follow-up period, statin users had considerably lower risk of death than statin non-users (figure 4.2.1).

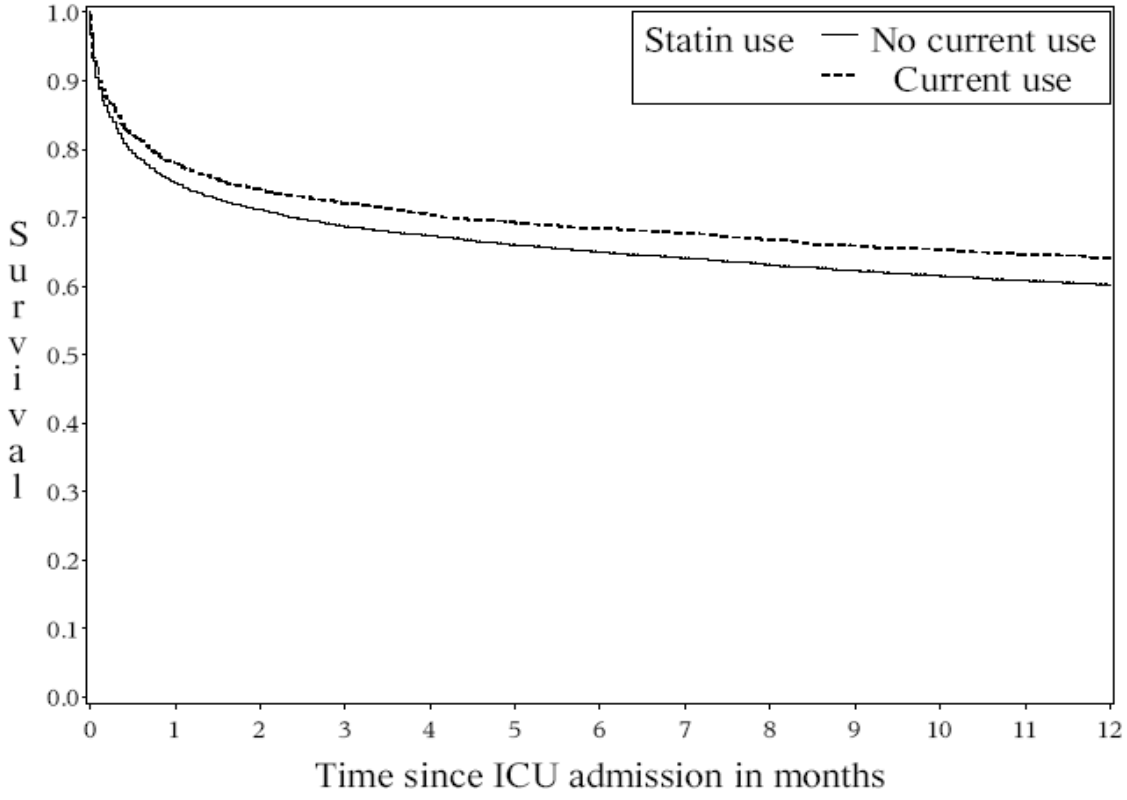
Table 4.2.1 C-statistics (area under ROC curve) as measure of discrimination between surviviors and non-surviviors (in-hospital, 30-day and 1-year mortality).

| **Score/measure** | **Outcome (c-statistic, 95% confidence interval)** | | |
|---|---|---|---|
| | In-hospital mortality | 30-day mortality | 1-year mortality |
| Charlson score | 0.53 (0.46-0.59) | 0.52 (0.46-0.57) | 0.58 (0.53-0.63) |
| Charlson score, age and gender | 0.65 (0.58-0.71) | 0.65 (0.59-0.71) | 0.65 (0.60-0.70) |
| Charlson score, age and gender, surgical/medical status | 0.67 (0.60-0.74) | 0.67 (0.61-0.73) | 0.66 (0.61-0.71 |
| Charlson score, age and gender, surgical/medical status, social factors | 0.69 (0.62-0.75) | 0.70 (0.64-0.75) | 0.68 (0.63-0.73) |
| Charlson score, age and gender, surgical/medical status, social factors, mechanical ventilation and dialysis | 0.72 (0.65-0.78) | 0.73 (0.68-0.78) | 0.71 (0.67-0.76) |
| Charlson score, age and gender, surgical/medical status, social factors, mechanical ventilation and dialysis, primary diagnosis | 0.75 (0.69-0.81) | 0.75 (0.70-0.80) | 0.72 (0.68-0.77) |
| Ten separate comorbidity groups* | 0.59 (0.52-0.66) | 0.58 (0.52-0.64) | 0.63 (0.58-0.68) |
| Ten comorbidity groups*, with age, gender, surgical/medical status, social factors, mechanical ventilation and dialysis, primary diagnosis | 0.75 (0.69-0.81) | 0.76 (0.71-0.81) | 0.75 (0.70-0.79) |
| SAPS II | 0.75 (0.69-0.81) | 0.72 (0.67-0.75) | 0.70 (0.66-0.75) |
| SAPS III | 0.69 (0.63-0.76) | 0.68 (0.63-0.74) | 0.69 (0.64-0.73) |
| APACHE II | 0.69 (0.63-0.76) | 0.68 (0.63-0.74) | 0.69 (0.64-0.73) |

* Please see text for details.

Of note, the c-statistics were nearly the same for in-hospital, 30-day, and 1-year mortality within the different categories of comorbidity measures.

Figure 4.2.1 Kaplan Meier survival curve for statin users and non-users. Aarhus University Intensive Care Cohort (2001-2007).




The risk of death within 30-days after ICU admission was 22.1% among statin users and 25.0% among non-users, corresponding to a crude MRR of 0.85 (95% CI: 0.76-0.96) (table 4.2.1). After controlling for potential confounders, the 30-day MRR was 0.77 (0.69-0.86). For all diagnostic categories except diabetes, and infectious diseases statin use was associated with a reduced risk of death (figure 4.2.2). For different types of statins, the MRRs differed, with the lowest MRR estimates observed among users of simvastatin; however, the differences between statin types failed to reach statistical significance ($p$=0.42, Wald statistics for difference between MRRs).

The one-year risk of death was 36.4% among statin users and 39.9% among non-users. The crude MRR was 0.84 (95% CI: 0.76-0.93), but the MRR decreased to 0.79 (0.73-0.87) after adjustment for confounding factors (table 4.2.1). The one-year reduction in risk of death was most pronounced

for simvastatin, although the differences between statin types were not statistically significant ($p$=0.35, Wald statistics for difference between MRRs). The mortality reduction remained robust in all diagnostic categories, but some of the risk estimates were statistically imprecise due to the relatively small patient numbers in the sub-cohorts.

Table 4.2.1. Cumulative 30 day and 365 day mortality and the corresponding crude and adjusted mortality rate ratios (MRR).

| | **Number (N)** | **Mortality (%)** | **Crude MRR (95% CI)** | **Adjusted MRR (95% CI)#** |
|---|---|---|---|---|
| ***0-30 days*** | | | | |
| Statin use | 1,882 | 22.1% | 0.85 (0.76-0.96) | 0.77 (0.69-0.86) |
| No statin use | 11,313 | 25.0% | 1 -- | 1 -- |
| ***0-365 days*** | | | | |
| Statin use | 1,882 | 36.4% | 0.84 (0.76-0.93) | 0.79 (0.73-0.87) |
| No statin use | 11,313 | 39.9% | 1 -- | 1 -- |

**#** Adjusted by Cox proportional hazards for age group, gender, medical/surgical department, diagnosis, Charlson index score and alcoholism-related disease, surgical status, renal replacement therapy and mechanical ventilation, current use of ACE-inhibitors, beta-blockers and low-dose aspirin, and marital status.

Figure 4.2.2. Adjusted 30-day mortality rate ratios (MRRs) associated with preadmission statin use; overall and within different patient subgroups.

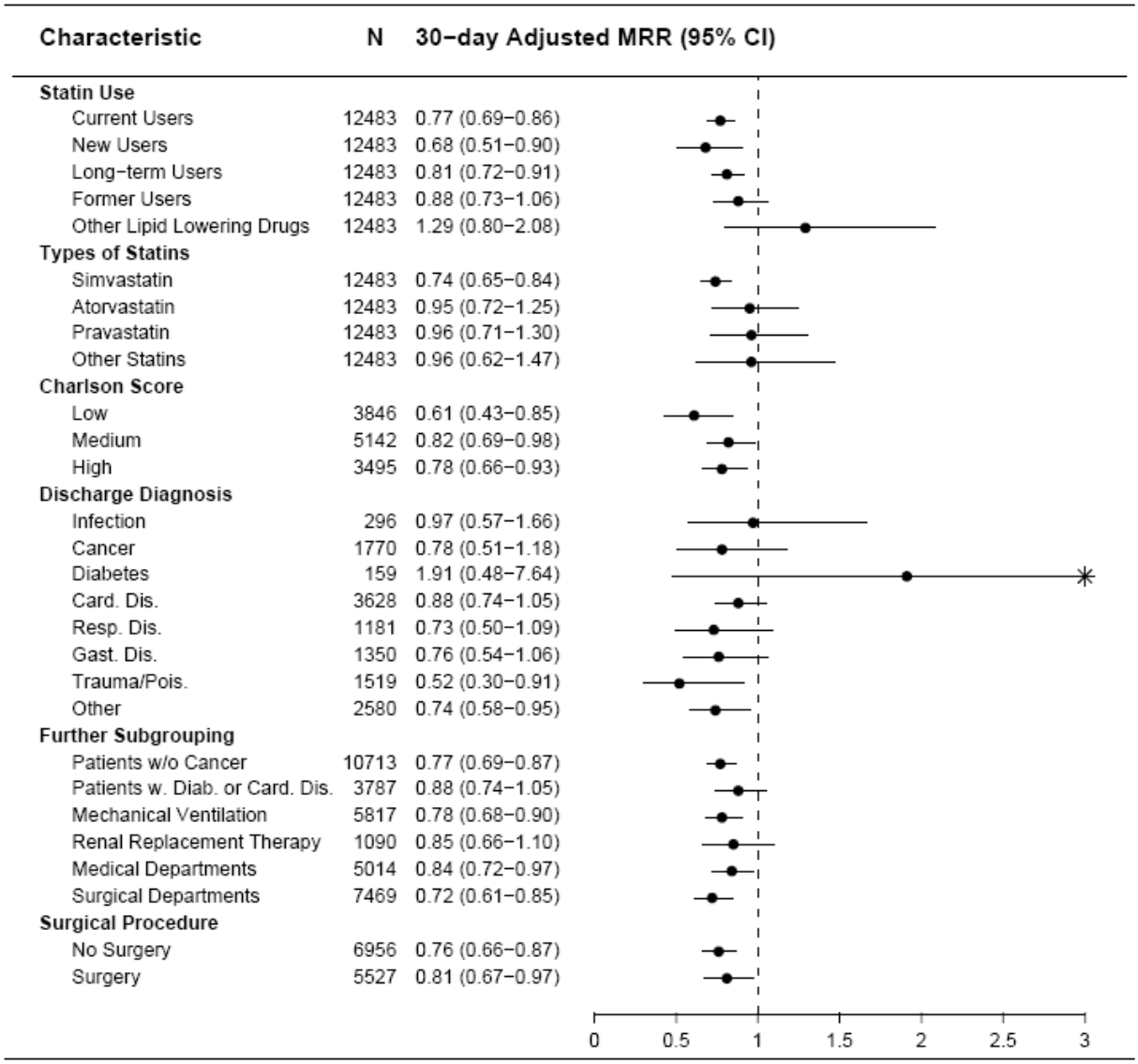
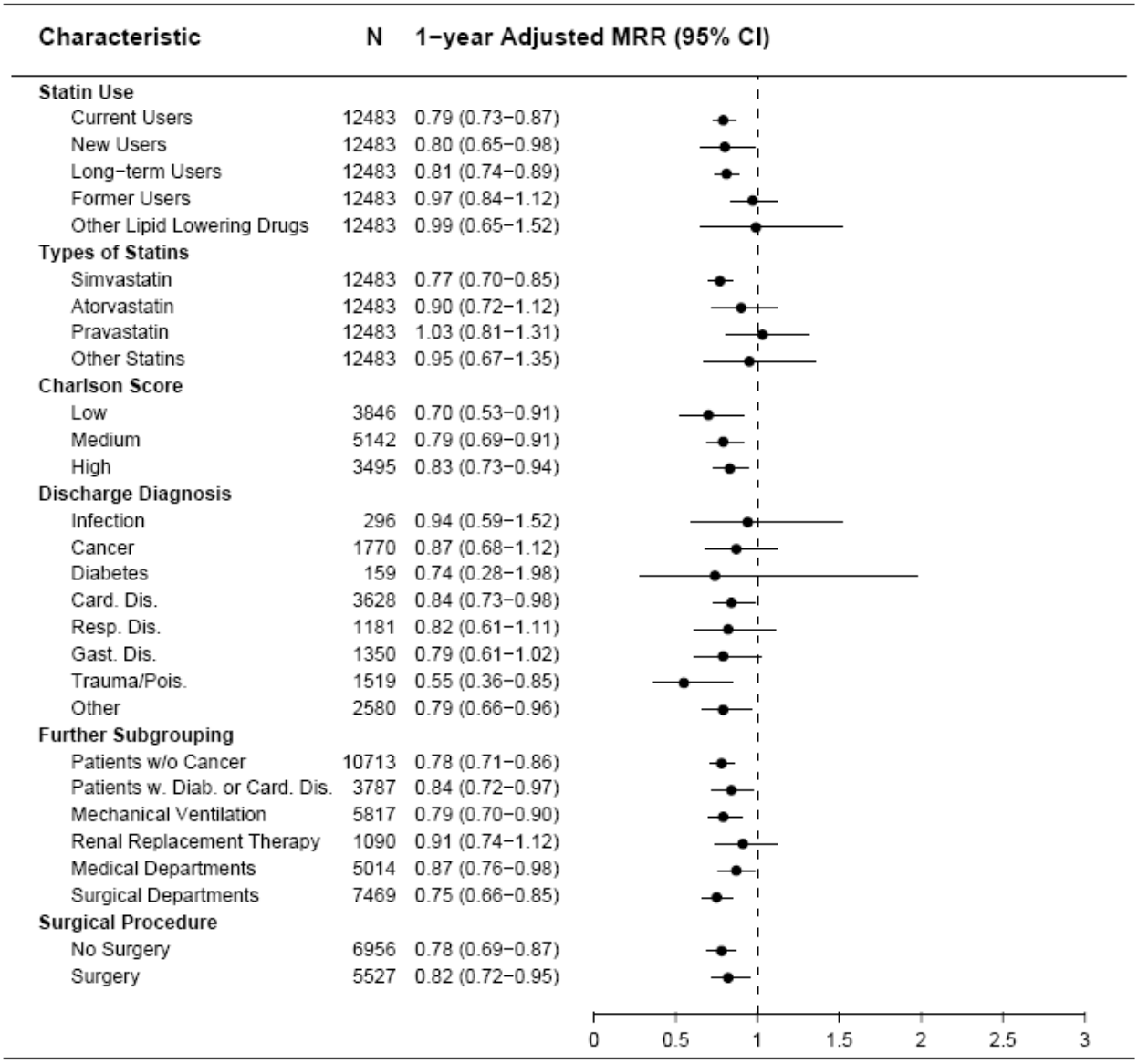


Figure 4.2.3. Adjusted one-year mortality rate ratios (MRRs) associated with preadmission statin use; overall and within different patient subgroups.



As part of several subanalyses, we performed separate analyses after excluding patients with cancer and alcoholism-related diseases and included only patients with indications for statins (i.e., patients with diabetes or cardiovascular disease), and stratified the analysis according to surgery/no surgery and the primary diagnosis. The association between statin use and risk of death was consistent and robust. Defining statin use as at least one redeemed prescription within 90 days of ICU admission had no major impact on the risk estimate.

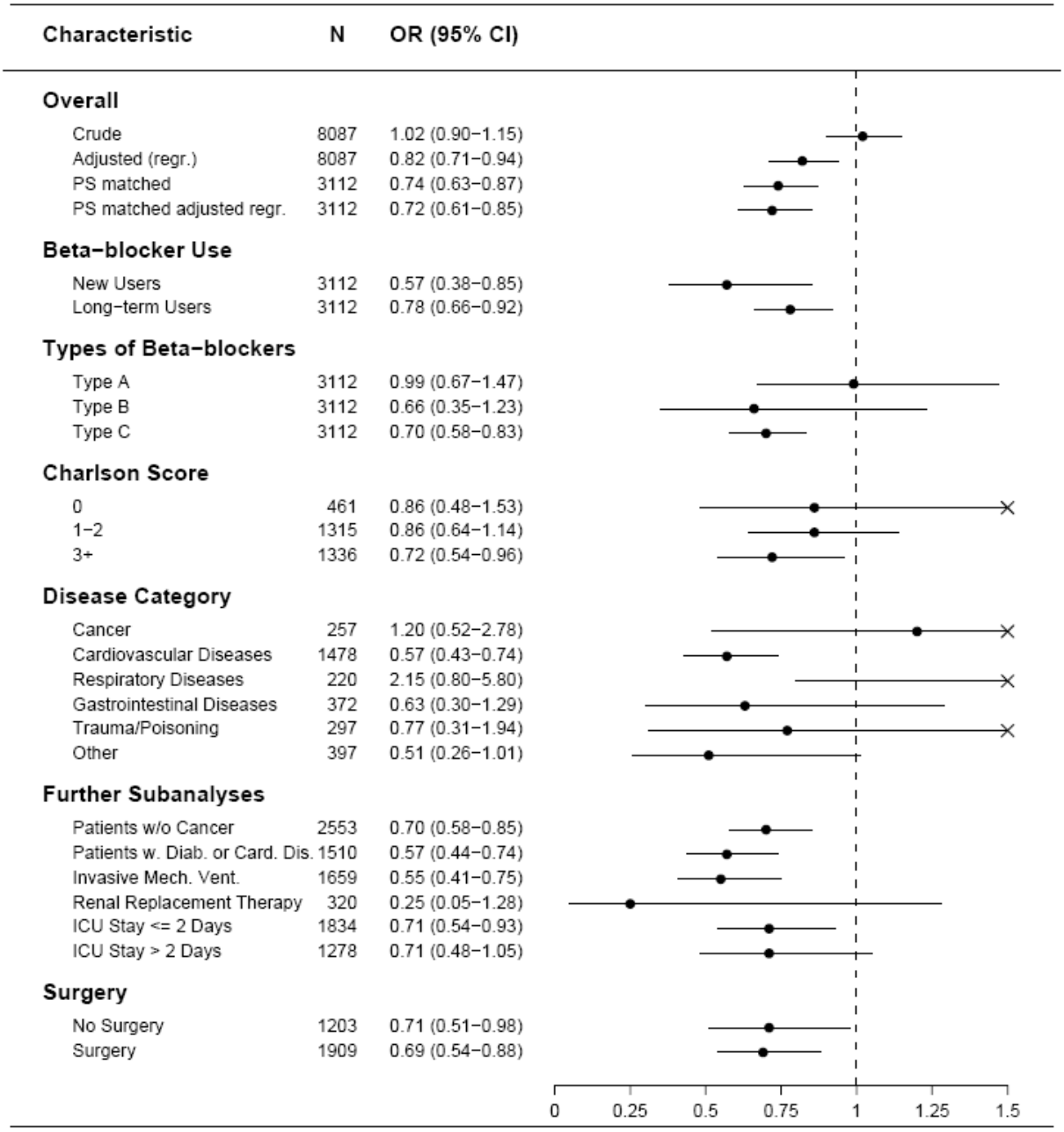
Of note, we found similar reductions in risk of death among new and long-term statin users, while former statin use and current use of other lipid-lowering drugs were not associated with reduced risk.

*4.3 Study III (beta-blocker study)*

Among 8,087 first-time ICU patients admitted between 1999 and 2005, 1,556 (19.2%) were current users of beta-blockers at the time of admission. Beta-blocker users were older and had as expected higher levels of comorbidity than non-users; moreover, substantially more beta-blocker users than non-users were also taking other cardiovascular drugs (statins, low-dose aspirin, ACE-inhibitors).

Of the entire cohort, 25.7% of beta-blocker users died within 30 days after ICU admission compared with 24.5 % of non-users. After propensity score matching, mortality among beta-blocker users was, as expected, unchanged (25.7%) whereas 31.4% died among non-users. In the propensity score analysis, the OR of death within 30 days after ICU admission among beta-blocker users was 0.74 (95% CI: 0.63–0.87) compared with non-users (figure 4.3.1). The OR for death of use of non-selective beta-blockers was 0.99 (95% CI: 0.67-1.47) and 0.66 (95% CI: 0.35-1.23) and 0.70 (95% CI: 0.58-0.83) for use of non-selective beta-blockers combined with alpha-adrenergic blocker and 0.70 (95% CI: 0.58-0.83) for use of cardio-selective beta-blockers (RR 0.69 (95% CI: 0.56-0.85)). We found reduced OR estimates in most (cardiovascular diseases, gastrointestinal diseases, trauma/poisoning, others) but not all (cancer, respiratory diseases) diagnostic groups. Beta-blocker use was associated with reduced risk of death among patients treated with invasive mechanical ventilation [OR: 0.55 (95% CI: 0.44-0.75)] and among those treated with renal replacement therapy [OR: 0.25 (95% CI: 0.05-1.28)]. Defining beta-blocker use as at least one redeemed prescription within 60 days of ICU admission had no major impact on the risk estimate.

Figure 4.3.1. Overall and subgroup relative risk estimates of death within 30 days after ICU admission for beta-blocker users and non-users.




Type A: Non-selective beta-blockers; type B: non-selective beta-blocker combined with alpha-adrenergic blocker; type C: cardio-selective beta-blocker

# 5. DISCUSSION

## *5.1 Methodological considerations*

The overall aim of etiological studies is to provide valid estimates of relative risk for the outcome[41]. In contrast, the aim of prediction studies is to develop a model that predicts risk of outcome for the individual patient[11]. In the assessing the validity of findings from observational studies, three alternative explanations for the findings have to be examined: bias, confounding, and random error[41].

Bias and confounding are systematic errors. Bias is mainly prevented by the design of a study, while confounding can be prevented in the design and controlled for in the analysis. Under certain circumstances, it is possible to control for information bias of categorical variables when the sensitivity and specificity of the misclassified variable is known[141]. The latter is rarely the case, and researchers are then forced to use sensitivity analyses to estimate the impact of misclassification on the risk estimates.

Any reduction in systematic error will improve the validity of a study. Reduction of random error, assessed by 95% confidence intervals as presented in the *Results* section, will increase precision in our studies.

### *5.1.1 Bias and confounding*

Although many specific types of biases have been proposed, there are two main categories of bias: selection bias and information bias[11].

*Selection bias*

In cohort studies, selection bias can arise from the method of selecting study participants or from factors that influence study participation.

Loss to follow-up is the main potential source of selection bias in cohort studies. Selection bias occurs when the loss to follow-up is related to both the exposure and the outcome, and when the loss to follow-up is high[11]. We used the Civil Registration System to obtain data on death. Because this system is highly complete, the loss to follow-up was negligible in our studies.

Selection bias can also occur when the choice of exposure category is related to the outcome. An association between exposure and the threshold for ICU admission may introduce selection bias; for example, if statin use was associated with a lower threshold for admission to the ICU and with reduced mortality, then this may explain at least part of our findings. However, the laboratory test results indicated that there were no major differences in severity of illness between statin users and non-users at ICU admission (table 5.1.1).

Table 5.1.1 Laboratory findings of statin users and non-users in the AUICC; 2001-2006.

| **Laboratory findings, median (IQR)*** | Statin user | No statin use |
|---|---|---|
| Hemoglobin (ref: female: 7.4-9.6 mmol/l, male:8.4-10.8 mmol/l) | 7.10 (6.30-8.20) | 7.30 (6.40-8.30) |
| Creatinine (ref: 60-125 µmol/l) | 106.5 (80-165) | 93 (70-138) |
| Bilirubin (ref: 4-21 mmol/l) | 10 (7-16) | 12 (8-20) |
| C-reactive protein (ref: < 10 mg/l) | 80 (15-250) | 97 (21-279) |
| White blood cell count | | |
| (ref: 4.0-11.0 x $10^9$ / l) | 12.2 (8.8-16.0) | 12.3 (9.0-16.7) |
| Total cholesterol (ref: 3.0-6.7 mmol/l) | 4.6 (3.9-5.5) | 5.0 (4.1-5.9) |

* For the subcohort of patients admitted between 2001 and 2006. The highest test result on the day of ICU admission or the following day are shown for creatinine, bilirubin C-reactive protein, and white blood cell count; the lowest test results are shown for hemoglobin and albumin. For cholesterol, the most recent recorded value within one year before ICU admission is shown.

For study III (beta-blocker study), we included in the main analysis only patients with complete laboratory data. This may have introduced a selection bias if the mortality among beta-blocker users without complete laboratory data differed from that of beta-blocker users with complete laboratory data. A sub-analysis that included patients with and those without complete laboratory data (and without adjustment for laboratory data in the analysis) showed a result similar to the main analysis; this indicated that this type of selection bias was not a major problem in this study.

*Information bias*

Information bias may occur when there is systematic error in the measurement of exposure or outcome. The measurement error is often referred to as misclassification for categorical variables. Misclassification can be either *differential* (the exposure status is misclassified differentially between outcome statuses, or vice versa) or *non-differential* (the exposure status is misclassified independently of outcome status, or vice versa)[11]. Differential misclassification may lead to an over- or underestimation of the true association. In comparisons between two exposure groups, non-differential misclassification would most likely attenuate the relative risk towards the null. When more than two exposure groups are compared, non-differential misclassification may lead to either overestimation or underestimation of the relative risk, depending on the categories to which patients are misclassified.

The outcome in all three studies was death, which was ascertained from the Civil Registration System. Therefore, information bias from errors in outcome assessment is unlikely[126].

For *study I* (comorbidity study), we identified the comorbidities included in the CCI by hospital diagnosis registered in the National Register of Patients before the date of ICU admission. The validity of the hospital diagnosis registered in the National Register of Patients is variable, but it is generally high for most major diseases, including diabetes, myocardial infarction, chronic obstructive pulmonary disease, and cancer. An ongoing validation study at the Department of Clinical Epidemiology, Aarhus University Hospital, has found that the positive predictive values for all disease categories in the CCI are higher than 0.9 (unpublished data). Any misclassification of the comorbidity level would most likely have reduced our ability to discriminate between survivors and non-survivors. While the study design called for the reviewers of medical records to be blinded to the study endpoint, in practice it was not possible to obtain perfect blinding for in-hospital mortality. This may have improved the ability of the physiology-based scores to discriminate between survivors and non-survivors. We used the original definitions of all variables in the APACHE II, SAPS II, and SAPS III systems. The Glasgow Coma Scale (GCS) score is difficult to assess based on review of medical records[135]. When no data on the GCS score was available in the medical record, or when the patient was sedated on ICU admission, we assumed a normal GCS score (=15). Although this was part of the original definition, it may have reduced the ability to discriminate between survivors and non-survivors.

For *studies II and III* (*statin and beta-blocker studies*), we defined statin use and beta-blocker use by filled prescriptions. Using a filled prescription as a proxy for actual drug use may not always be entirely appropriate. However, in Denmark, adherence to statin therapy is high, and any non-adherence would most likely have attenuated the relative risk estimates towards unity. Although there are no data on the adherence to beta-blocker use in Denmark, the beneficial clinical effects of beta-blockers and the co-payment requirement would be expected to increase adherence. Any non-adherence would most likely have attenuated the relative risk estimates towards unity, and therefore is unlikely to explain our findings.

Using filled prescriptions as a proxy for drug use may also result in immeasurable time bias[138]. In the statin study, we found that less than 9% of statin users had been hospitalized for more than 25 days in the 125 day exposure defining period, and almost the same proportion of non-users had been hospitalized for more than 25 days. Therefore, because statin prescriptions are not expected to last more than 100 days, it seems unlikely that immeasurable time bias can explain our findings. This is supported by the fact that less than 3% of all statins in Denmark are used in hospitals[134].

For studies II and III, we used a 125 day time window to define current use of statins and beta-blockers, respectively. This may have lead to misclassification of exposure, because we may have classified as current users patients that had stopped the medication before admission to the ICU. However, using a 90 day exposure defining time window in the statin study and a 60 day window in the beta-blocker study had virtually no influence on the relative risk estimates; this indicated that this type of information bias had limited influence on our results.

*5.1.2.3 Confounding*

Confounding, or simply the mixing of effects, is an important issue in etiological studies[16]. To influence the association between exposure and outcome, a confounding factor must affect the outcome, and its presence must be imbalanced between exposure groups[11]. A third and important requirement for confounding factors is that the confounder cannot be an effect of the exposure[11]. In the etiological studies (studies II and III) in this thesis, we controlled for confounding in both study design and analysis.

We used administrative data from existing registries to control for confounding. Generally, any lack of specificity in these routinely recorded data may have reduced our ability to completely remove

confounding. Therefore, uncontrolled confounding in studies II and III (statin and beta-blocker studies) may have attenuated our relative mortality estimates towards the null. Apart from the lack of specificity of recorded data, the main disadvantage of register-based studies is the lack of data on potential confounding factors, like life style factors [33]. In the etiological studies in this thesis, we used comorbidity, including cancer, ischemic heart disease, and chronic obstructive pulmonary disease as proxy measures of smoking; this, at least in part, controlled for confounding by smoking and other life style factors.

In *study II (statin study*), we restricted the analysis to ICU patients over 45 years old because otherwise, age might have confounded the associations; particularly because statins are only rarely prescribed to patients under 45 years old. Despite control for a wide range of covariates reflecting comorbidity, current disease status, concurrent use of other medications, and social factors in the analysis and several sub-analyses, residual and unmeasured confounding may still have influenced the observed associations. *Confounding by indication* can influence all observational studies of drug effects because the prevalence of the underlying disease that indicated the drug is obviously different between exposed and unexposed participants[142]. However, in study II, we controlled for most of the indications for statin therapy in the analysis. Moreover, in sub-analyses, we restricted the groups to include only patients that had underlying diseases that often require statin prescriptions (diabetes and cardiovascular disease). These restrictions did not materially alter the risk estimates. Also, cardiovascular disease, which is the main indication for statin therapy, is associated with increased mortality in most critical illnesses and thus confounding by cardiovascular disease is unlikely to explain the reduced mortality among statin user[143]. Finally, we found no reduction in mortality among former statin users with similar underlying diseases as currents user. Thus, confounding by indication seems unlikely to explain the beneficial effects of statins found in our study.

The *healthy user bias*, or confounding by lifestyle factors and frailty, is an important issue in observational studies of the beneficial effects of any medication given for prevention of disease, including statins[136]. The concern is that patients with statin prescriptions that are able to adhere to the treatment may have an overall better health status and thus, a lower risk of death, than other patients. We used several approaches to assess the impact of the healthy user bias on our risk estimates. We found almost similar risk estimates for new and long-term statin users; this indicated

that adherence was not a marker for an overall better risk profile. We adjusted for measures of social factors and comorbidity; again this had only limited impact on our results. Also, there are limited socioeconomic differences between statin users and non-users in Denmark[144]. Moreover, during the study period, statins were primarily prescribed for symptomatic cardiovascular disease, which is associated with increased mortality[143]. Taken together, these observations indicate that a potential healthy user bias is unlikely to explain the entire beneficial effect of statins in our data.

As mentioned earlier, a very important requirement for confounding factors is that the confounder cannot be an effect of the exposure[11]. Controlling for an effect of the intervention may potentially lead to an underestimation of the true effect of the intervention. In studies on the association between statin use and mortality, the effect of statins was believed to be caused by beneficial immune-modulating effects that reduced physiological derangements. Thus, adjustment for physiological variables or severity of disease in a study on the association between statin use and mortality may result in an underestimation of the true beneficial effect of statin use. We therefore did not control for laboratory data, including hemoglobin, creatinine, liver function test, white blood cell count, or C-reactive protein in the analysis.

In *study III (beta-blocker study)*, confounding by indication from cardiovascular disease may have affected the results. However, cardiovascular disease is associated with increased mortality in ICU patients[143] and therefore, confounding by underlying diseases most likely would have attenuated our relative risk estimates towards the null and would not explain our findings. This is reflected in the unmatched, uncontrolled analysis that showed no association between beta-blocker use and mortality. As mentioned above, residual confounding by incomplete control for indications for beta-blocker use may have reduced our ability to completely remove confounding, and thus, may have attenuated the adjusted relative risk estimates towards the null.

## 6. MAIN CONCLUSIONS

Based on the results obtained and our considerations of potential bias and confounding in the three studies, we drew the following conclusions:

*Study I (comorbidity study)*

This study provides evidence that the Charlson Comorbidity Index, based on routinely collected hospital data in combination with other readily available administrative data, performed at least as well as the physiology-based scoring systems in predicting mortality of ICU patients.

*Study II (Statin study)*

We found that preadmission statin use was associated with considerably reduced risk of death within 30 days and one year following ICU admission. The reduced risk of death seemed most pronounced for simvastatin. The associations observed could be a biological effect of statins, but unmeasured differences in the characteristics of statin users and non-users cannot be entirely ruled out.

*Study III (beta-blocker study)*

We found that preadmission use of beta-blockers was associated with reduced risk of death within 30 days following ICU admission.

## 7. INTERPRETATION AND CLINICAL IMPLICATIONS

The following section will discuss the findings of the studies in this thesis in relation to the existing literature and the clinical implications of our findings.

### *7.1 Study 1 (comorbidity study)*

To our knowledge, this study was the first to examine how well comorbidity scores could predict mortality within one year after ICU admission.

Our findings for in-hospital mortality extend data from four previous studies that examined the performance of comorbidity scores in predicting in-hospital mortality among ICU patients, as discussed in section 1.2.1. In a large US study, Johnston et al. found that the Elixhauser Comorbidity Index could discriminate better between in-hospital survivors and non-survivors (c-statistic = 0.700) than the chronic health evaluation component of the APACHE score (c-statistic = 0.568)[56]. When combined with other clinical data, the discrimination of the Elixhauser Index was excellent (c-statistic = 0.874); however, some of the data used are not readily available in other settings; particularly laboratory data, which accounted for 67.7% of the model's unique attributable chi square. It is also important to note that using data from Veterans Affairs Medical Centres primarily treating elderly men, may limit generalization to other settings.

In a 1996 US study of 201 ICU patients, the Charlson Comorbidity Index (CCI) showed a moderate discriminating ability for in-hospital mortality (c-statistic = 0.67)[57]. However, in that study, data on comorbidity were collected by chart reviews, and the CCI was not combined with other administrative data. Ho et al. found that the CCI had poor predictive performance for short-term mortality among 24,303 ICU patients in Western Australia (c-statistic = <0.610)[58]. Again, that study did not combine the CCI score with other administrative data, but they did combine the CCI with the acute physiology evaluation part of APACHE. A 2006 Canadian study of 1,603 ICU patients found that APACHE II predicted in-hospital survival better than the Charlson Index (c-statistics = 0.77 vs. 0.69, respectively)[59]. Moreover, both the APACHE II score and the CCI remained independent predictors of in-hospital mortality even after adjustment for demographics, source of admission, socioeconomic factors, and primary diagnosis.

In our study the physiology-based scoring systems performed less well in predicting in-hospital mortality than previously reported[145]. We used prospectively collected physiological data from an electronic database which reduced the risk of information bias. However, some clinical variables such as the Glasgow Coma Scale (GCS) score were obtained from medical records. GCS scores were missing in a number of these records and by assuming that patients with missing values had normal GCS scores we may have underestimated the SAPS and APACHE scores [135]. Also, the majority of patients in our study were stabilized in the emergency department before arrival at the ICU. This may also have lead us to underestimate the SAPS and APACHE scores. We did not include patients admitted for planned post-operative observation for less than 24 hours but may still have included some coronary care patients who by definition were not included in the original physiology-based scores. This may have led to an underestimation of the predictive performance of the physiology-based scores.

*Implications*

We found that the CCI and the physiology-based scores were equivalent at predicting mortality. This supports the use of the CCI in etiological studies based on data from large health care databases, particularly when the physiology-based score is missing or of poor validity. Our study, for the first time, showed that the CCI can also be used to predict long-term mortality of ICU patients. This is an important consideration in the design of studies on long-term outcome of intensive care.

*7.2 Study II (statin study)*

Our findings in study II are consistent with the increasing evidence that statins may reduce mortality in patients with severe infections, including sepsis [88-90;101;102]. However, limited and conflicting data exist on the association between statin use and mortality among general ICU patients. No data exist on the effect of statins on long-term risk of death among ICU patients, nor whether specific types of statins have different effects.

Consistent with our findings, a 2006 German cohort study of 120 ICU patients with multiple organ dysfunction syndrome found that statin use was associated with substantially reduced in-hospital mortality (MRR= 0.53 [95% CI: 0.29-0.99]) [97]. Furthermore, a recent US study among patients with ALI/ARDS found reduced ICU mortality and in-hospital mortality among statin users (OR ICU

mortality 0.82 [95% CI: 0.36-1.89] and OR in-hospital mortality 0.62 [95% CI: 0.29-1.32]); however, the latter study had a relatively small study population (N=178); thus, the imprecision in the risk estimates hindered a clear interpretation[99]. In contrast, a 2006 Spanish observational study of 438 patients that had been mechanically ventilated for over 96 hours reported a higher in-hospital mortality among statin users (61%) compared to non-users (42%; OR=2.30 [95% CI: 1.08-4.89]) [98].

The interpretation of the existing studies was limited by the inclusion of highly selected patients and the lack of adjustment for important confounders, including comorbidity and use of other cardiovascular drugs. In all three studies, statin use was defined as the use of statins at and/or during ICU admission; this means that statins may have been initiated after the patient was hospitalized and thus, before the patient became critically ill.

*Clinical implications*

We studied preadmission use of statins; this means that patients were using statins before they became critically ill. There are two mechanisms by which preadmission statin use may reduce mortality. First, statins may reduce the risk of severe illness; e.g., statins may reduce the risk of progression from sepsis to severe sepsis or septic shock. Second, statins may reduce mortality among severely ill patients by reducing the risk of complications like cardiovascular disease. An interesting question is whether statins should be initiated at ICU admission in patients that are not previously treated with statins; however, since we had no data on in-hospital drug use our study did not address that question. A limitation of our study was the lack of data on the use of statins during the ICU stay and on statin use during follow-up. However, if we had included data on statin use during follow-up, we would have introduced bias, because only survivors could fill prescriptions for statins.

*7.3 Study III (beta-blocker study)*

This study was the first to examine the association between the use of beta-blockers and mortality in general ICU patients. However, a number of previous studies have examined the effect of beta-blocker use in patients with specific diseases or patients undergoing procedures that are often related to ICU admission. In line with our findings, those studies presented evidence that beta-blockers reduced perioperative mortality in patients undergoing major non-cardiac surgery[107-110]; however, the recent POISE trial found that acute perioperative administration of high-dose beta-

blocker therapy was associated with an increased risk of all-cause mortality[111]. Also in line with our findings, a US observational study among 4,117 trauma patients found that beta-blocker use was associated with reduced mortality[117] and beta-blockers have also been reported to have beneficial effects in patients with severe burns[118].

*Clinical Implications*

Our data suggest a potential for reducing mortality by beta-adrenergic blockage. A limitation of the beta-blocker study was the lack of data on in-hospital beta-blocker use and on the use of beta-blockers during follow-up. However, if we had included data on beta-blocker use after ICU discharge, we would have introduced bias, because only survivors can fill prescriptions. We could not exclude the possibility that long-term beta-blocker use may have resulted in an up-regulation of beta-receptors, as has been described in asthma patients[113]. An up-regulation of beta-receptors may have benefited patients that required beta-stimulation to main adequate tissue perfusion. Acute initiation of beta-blockers does not lead to an up-regulation of beta-receptors and may therefore not have the same mortality reducing effect as chronic beta-blocker use. An interesting question is therefore whether beta-blockers should be acutely initiated in the ICU in patients not previously treated with beta-blockers. Our study did not address that question. There is concern that some of the potentially beneficial effects of beta-blockers in critically ill patients may by outweighed by a decreased oxygen supply and decreased tissue perfusion because of reduced cardiac output in patients treated with beta-blockers [123]. Therefore, it is too premature to recommend beta-blocker therapy to all ICU patients. Further studies are needed to determine the safety and effect of beta-blocker treatment for ICU patients not previously treated with beta-blockers.

## 8. PERSPECTIVES

Identifying predictors of prognosis is important for understanding the clinical course of ICU patients and thus improve the outcome. The existing knowledge on such predictors has several limitations. Most ICU studies are restricted to patients with specific critical illness syndromes and are restricted to short-term follow-up such as in-hospital mortality. ICU patients have many different diseases and the underlying disease process in ICU patients is complex. For example a patient with a well-defined critical illness syndrome such as severe sepsis may also have transient acute kidney injury one day and septic shock and acute lung injury the next, complicated by pulmonary embolism. Therefore studies on the clinical course of ICU patients must cover a large spectrum of patients with a number of different outcomes. Such complexity cannot be handled within the framework of a clinical trial or a single cohort study restricted to a subgroup of ICU patients. Moreover many studies have only focused on clinical predictions and not on etiologic research. Large ICU databases may overcome some of these problems since they cover a large number of patients with multiple outcomes. The Danish health care system provides an ideal setting for creating large population-based ICU databases. The ongoing work of establishing a nation-wide Danish database for ICU patients will provide access to such large population-based data and is in part originated from this PhD thesis [34]. Civil registration numbers make it possible to unambiguously link medical databases and administrative registries, and thereby, build large cohorts with detailed longitudinal data that include among others complete hospital history, data on comorbidity, and complete long-term follow-up data. With the creation of the AUICC database and the process of designing, analyzing, and interpreting the studies in this thesis, we have shown that ICU studies based on Danish health care databases can be properly conducted, provided careful evaluations of biases and confounding are included.

Our studies, however, also exposed some of the weaknesses in Danish health care databases for ICU research. The main weakness is the lack of clinical data. In the AUICC, we included laboratory data, hospital diagnoses and surgical procedures, prescription data, and mortality data. Still, we lacked data such as number and severity of organ failure and in-hospital treatments including in-hospital medication use. Since 2005, in-hospital medication use has been electronically recorded at all hospitals in our region and can in the future be added to the AUICC. In addition, it is now possible to establish electronic links between the AUICC and databases containing diagnostic procedures such as ultrasonography and X-rays. In the future, more ICUs will establish information

systems that can electronically collect clinical data, including blood pressure and heart rate, and electronic medical records will be available for data on indications for treatments and severity of illness. These improvements will allow more detailed characterizations of ICU patients than those possible today.

It is important to note that longitudinal data on the complex clinical course of ICU patients that will include multiple repeated measurements and missing values are difficult to analyze with conventional study designs and statistical models. It will therefore be necessary to develop new study designs and to develop statistical models and analyses that can handle this vast amount of complex longitudinal data. Such work has now been initiated by the Department of Clinical Epidemiology.

## 9. SUMMARY

Understanding the clinical course of general ICU patients is important for improving prognosis. One way of improving our knowledge of the complex clinical course of ICU patients is to conduct observational studies based on existing data in large health care databases.

This thesis includes one prediction study and two etiological (analytical) studies that were based on data from the Aarhus University Intensive Care Cohort (AUICC), the regional prescription database, the LAKBA laboratory database, the Danish National Registry of Patients, and the Danish Civil Registration System, in addition to a manual review of medical records. The aims of this thesis were: (1) to determine whether the Charlson Comorbidity Index based on administrative data could perform as well as physiology-based scoring systems in predicting mortality in ICU patients (study I); (2) to examine the association between preadmission statin use and mortality following ICU admission (study II); and (3) to examine the association between preadmission beta-blocker use and mortality following ICU admission (study III).

Some concern has been raised regarding the lack of clinical data in health care databases, and whether this would hinder sufficient control for confounding in studies of prognostic factors for ICU patients. In study I (comorbidity study), we found that the Charlson Comorbidity Index, based on data from the Danish National Registry of Patients in combination with other readily available administrative data, performed at least as well as physiological-based scores (APACHE, SAPS) in predicting ICU mortality. This was true for in-hospital, 30-day, and one-year survival.

Statins and beta-blockers have been suggested to have beneficial effects in critically ill patients; however, very limited and conflicting data exist on whether statin use and beta-blocker use are associated with reduced mortality following intensive care. In study II (statin study), we found that statin users had a reduced risk of death within 30 days of ICU admission (22.1% among users vs. 25.0% among non-users, adjusted MRR=0.77 [95% CI: 0.69-0.86]). Statin users also had a reduced risk of death within one-year after admission to the ICU (36.4% among users vs. 39.9% among non-users, adjusted MRR=0.79 [95% CI: 0.73-0.87]). The largest reductions in 30-day and one-year risks of death were observed among users of simvastatin. The observed associations could be due to the pharmacological effects of statins, but we could not rule out influence on our results from

unmeasured differences in patient characteristics between statin users and non-users. In study III (beta-blocker study), we found that preadmission beta-blocker use was associated with reduced risk of death within 30 days of ICU admission (OR of death 0.74 [95% CI: 0.63−0.87]). Future studies are needed to examine the safety of beta-blocker use in severely ill ICU patients that require beta-stimulation to maintain adequate tissue perfusion.

The studies in this thesis have shown that, provided a careful evaluation of biases and confounding, observational studies of ICU patients based on large health care database can be properly conducted and may contribute to a better understanding of the clinical course of ICU patients.

## 10. DANSK RESUME

Prognosen for patienter indlagt på intensivafdeling har været stort set uændret gennem de seneste årtier. Observationelle studier baseret på eksisterende registre kan med fordel anvendes til identifikation af faktorer associeret med dårlig prognose, og dermed faktorer hvor nye behandlinger potentielt kan bedre prognosen. En af svaghederne ved observationelle studier er den mulige indflydelse af confounding. I observationelle studier af kritisk syge patienter anvendes traditionelt score systemer for sværhedsgrad af sygdom (f.eks. APACHE, SAPS score). Disse er primært baseret på kliniske fysiologiske variable som blodtryk, puls og nyrefunktion. Data på disse scorer er imidlertid vanskelige rutinemæssigt at indsamle og validiteten af sådanne data i administrative registre kan derfor være dårlig. I studie I sammenligner vi evnen til at prædiktere død for en komorbiditets-score (Charlson Indekset) i kombination med andre administrative data med de mest anvendte fysiologiske scorer. Vi finder, at Charlson Indekset i kombination med andre administrative data prædiktere kort- og langtidsprognosen lige så godt som avancerede score systemer for sværhedsgrad af sygdom.

En del patienter indlægges på intensivafdeling på grund af akutte kardiovaskulære tilstande, og kroniske kardiovaskulære sygdomme er hyppige blandt intensivpatienter, ligesom mange får kardiovaskulære komplikationer under indlæggelsen på intensivafdeling. Statiner og beta-blokkere, som begge anvendes til forebyggelse og beta-blokker også i behandling af kardiovaskulære sygdomme, er vist at reducere dødeligheden og komplikationsfrekvensen ved kardiovaskulære sygdomme. Både statiner og beta-blokkere har derudover potentielt gavnlige immunmodulerende effekter ved kritisk sygdom. Imidlertid foreligger der meget begrænset viden om effekten af statin og beta-blokker behandling på mortaliteten blandt intensivpatienter. I studie II og III undersøger vi således associationen mellem statin og beta-blokker brug inden indlæggelsen og død indenfor 30 dage (statin og beta-blokker) og 1 år (statin) efter indlæggelsen på intensivafdeling. Vi finder, at statin brug er associeret med betydeligt reduceret 30-dages dødelighed [22.1% blandt statin brugere vs. 25.0% blandt ikke-brugere, justeret MRR=0.77 (95% CI: 0.69-0.86)] og 1-års dødelighed [36.4% blandt statin brugere vs. 39.9% blandt ikke-brugere, justeret MRR=0.79 (95% CI: 0.73-0.87)]. På trods af de entydige fund kan vi dog ikke fuldstændigt udelukke, at forskelle i patient karakteristika mellem statin brugere og ikke-brugere har indflydelse på resultaterne. I studie III

finder vi, at beta-blokker brug er associeret med reduceret 30-dages dødelighed efter indlæggelse på intensivafdeling [OR 0.74 (95% CI: 0.63–0.87)]. Der er dog fortsat behov for yderligere undersøgelser af blandt andet bivirkningsprofilen af beta-blokker behandling til svært syge patienter som kræver beta-stimulation i form af inotropika og vasopressor behandling for at opretholde sufficient perifer cirkulation.

Samlet har vores studier vist, at observationelle studier baseret på eksisterende registre kan bidrage med væsentlig viden om prognose og prognostiske faktorer for intensivpatienter såfremt fejlkilder i form af bias og confounding behandles og diskuteres korrekt.

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# Comparison of Charlson Comorbidity Index with SAPS and APACHE Scores for prediction of mortality following intensive care

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**Abstract**

*Background*

Limited data exist on the performance of comorbidity scores in predicting mortality of intensive care unit (ICU) patients. We examined the performance of the Charlson Comorbidity Index (CCI) and three physiology-based scores in predicting short- and long-term mortality following intensive care.

*Methods*

We identified all adult patients (n=469) with a first admission to the ICU at Skejby University Hospital, Denmark. We obtained data on APACHE II, SAPS II and SAPS III scores from medical databases and medical records. Data on CCI score and complete follow-up for mortality within one year was obtained from medical databases. We computed goodness-of-fit statistics and c-statistics (area under ROC curve) as measures of model calibration and discrimination, respectively.

*Results*

Goodness-of-fit statistics supported model fit for 30-day and 1-year mortality of the CCI score combined with other administrative data, but not for in-hospital mortality. Combining the CCI score with other administrative data revealed c-statistics of 0.75 (95% CI: 0.69-0.81) for in-hospital mortality, 0.75 (95% CI: 0.70-0.80) for 30-day mortality and 0.72 (95% CI: 0.68-0.77) for one-year mortality. There were no major differences in c-statistics between physiology-based and the CCI combined with other administrative data.

*Conclusion*

The CCI combined with administrative data predict short- and long-term mortality for ICU patients as well as physiology-based scores.

Key words: Charlson Index, comorbidity, epidemiology, mortality, prediction

Running header: Performance of scoring systems to predict mortality of ICU patients

## Introduction

Within intensive care medicine, limited evidence is available from randomized controlled trials (RCTs) [1]. Patients in intensive care units (ICUs) are characterized by multiple diseases with different etiologies, severe comorbidity, and a constant change in advanced treatments such as dialysis and mechanical ventilation. The complex clinical course of ICU patients makes it difficult to standardize treatment as required in RCTs and to maintain randomized assignments. In addition, it is ethically questionable to study truly life-saving ICU interventions, including mechanical ventilation for respiratory failure and vasopressors for severe shock, in RCTs [1]. Therefore large health care databases are increasingly used to study outcomes of ICU interventions [1-6].

The validity of observational studies depends on the ability to control for confounding, among other factors, and this may be imperfect in studies based on medical databases. In observational ICU studies based on primary data collection physiology-based severity of illness scoring systems are frequently used to control for confounding. The physiology-based scoring systems include the Simplified Acute Physiology Scores (SAPS) [7], the Acute Physiology and Chronic Health Evaluations (APACHE) [8], and the Mortality Probability Models (MPM) [9]. These systems were developed to predict in-hospital mortality based on a summary score consisting of measures of physiological derangement in combination with demographics, comorbidity, and reason for ICU admission. Although predicting mortality and controlling for confounding are two entirely different entities[10], the performance in predicting mortality is important for the ability to control for confounding.

Comorbidity is an important confounding factor in many ICU studies[11;12]. The Charlson Comorbidity Index (CCI) [13;14], developed to predict one-year mortality among medical patients, is among the most frequently used measures of comorbidity[15]. However, only four studies examined the performance of comorbidity scores in predicting mortality in critically ill patients [12;16-18]. The studies either did not combine the comorbidity score with other readily available administrative data[12;18] or included special study populations such as patients from Veteran Affairs hospitals[12]. All studies were restricted to in-hospital mortality[12;16-18].

To address these limitations, we compared the performance of the CCI alone and in combination with other readily available administrative data with that of three physiology-based scoring systems (APACHE II, SAPS II and SAPS III) in predicting short-term mortality (in-hospital and 30-day) and long-term mortality (one-year) in a cohort of Danish ICU patients.

## Methods

The study population included all patients older than 15 years of age admitted to the ICU at Skejby University Hospital, Denmark, between 1 January 2007 and 31 December 2007. We included only first-time ICU admission during the study period. We did not include in the cohort coronary care patients, or cardiac surgery patients and other patients admitted for planned postoperative observation of less than 24 hours as defined in the original physiology-based models[7;9;19]. The 14-bed facility is a highly specialized university-affiliated surgical/medical tertiary unit serving as both a primary and referral ICU. Its patients include those with severe respiratory insufficiency requiring extracorporeal membrane oxygenation and patients undergoing organ transplantation. The nurse to patient ratio is 1:1. Patients are admitted from departments of thoracic surgery or cardiology, as well as from departments of infectious diseases, gynecology and obstetrics, nephrology, and urology.

### *Comorbidity*

We obtained data on comorbidity from the Danish National Registry of Patients (NRP). For all hospital admissions to Danish acute care hospitals since 1977 and, since 1995, for all hospital outpatient and emergency room visits, the NRP has recorded the patient's civil registration number, dates of admission and discharge, up to 20 surgical procedures, and up to 20 discharge diagnoses classified according to the International Classification of Diseases (ICD), 8th revision until the end of 1993 and 10th revision thereafter [20]. All hospital diagnoses were coded by the physician treating the patient at the time of hospital discharge. Since 2005 treatments such as mechanical ventilation and dialysis also have been registered.

We used the CCI to estimate comorbidity levels among study patients [13]. In calculating the CCI, a weight (1 to 6) is assigned to each of 19 comorbid disease categories and the score is the sum of these weights. We used a version of the Deyo ICD-9 adaptation of the CCI[15], modified for use with ICD-8 and ICD-10 discharge codes (see Appendix for details). Using the NRP, we identified all study patients' post-1977 hospital diagnoses registered before the date of ICU admission. The score was included as a continuous covariate in the analysis. In order to include comorbidity categories separately in the regression model, we had to reduce the number of categories. We therefore defined 10 separate clinically relevant comorbidity categories based on the original 19 comorbid disease categories in the Charlson Index (see Appendix for details).

*Other administrative data*

We used the NRP to identify the primary hospital diagnosis for all hospital stays that included ICU care and grouped patients into eight diagnostic categories: infectious diseases; endocrinology including diabetes; cardiovascular diseases; respiratory diseases; gastrointestinal and liver diseases; cancer; trauma and poisoning; and others (details on ICD codes are provided in the Appendix). Using the NRP, we also obtained information on surgical procedures performed on all study patients. We defined surgical patients as patients who underwent surgery within 7 days before ICU admission and medical patients as those who had no surgery within 7 days before ICU admission[7]. Data on mechanical ventilation and dialysis/hemofiltration in the ICU were obtained from the NRP. Through the Civil Registration System we obtained data on marital status (married, divorced, widowed, never married, or unknown) and urbanization (city, town, provincial town) as measures of social status [21].

*Physiology-based scores*

To obtain data on physiology-based scores, two reviewers (SC, CFC) reviewed all medical records for study patients. Data on physiological variables were obtained from a computerized patient data management system (PICIS) that prospectively collects a wide range of clinical information, including detailed data on

mechanical ventilation, body temperature, and blood pressure and heart rate. From a computerized laboratory database we obtained the laboratory data included in the physiology-based scores [haemoglobin, white blood cell count and creatinine/urea]. All clinical data were reviewed which allowed us to avoid including invalid data from the computerized databases. Data on reason for ICU admission were obtained from medical records. We used the original definitions of all variables in the APACHE II, SAPS II and SAPS III systems. The Glasgow Coma Scale (GCS) score is difficult to assess based on review of medical records [22]. We assumed a normal GCS score (=15) if the GCS score was not described in the medical record and if the patient was sedated upon ICU admission. While the study design called for the reviewers to be blinded to the study endpoint, in practice it was not possible to obtain perfect blinding for in-hospital mortality.

*Record linkage and mortality*

Since 1968 every Danish citizen has received at birth a unique personal identifier, the civil registration number, encoding gender and date of birth. This number is included in all Danish registries and permits accurate linkage between registries [21]. The Danish Civil Registration System provides information on vital status and residence for the entire Danish population, updated daily since 1968. Using this database, we were able to track the study outcomes, *i.e.*, in-hospital mortality, 30-day mortality and 1-year mortality, following the date of first ICU admission.

*Statistical analysis*

We used medians and inter-quartile ranges (IQRs) to describe the distribution of covariates. We computed Spearman's rank correlation coefficients for correlation between scores.

For each endpoint (in-hospital, 30-day and 1-year mortality) logistic regressions models were constructed for the following combinations of variables: (1) CCI score; (2) CCI, age, gender; (3) CCI, age, gender, surgical/medical status; (4) CCI, age, gender, surgical/medical status, social factors; (5) CCI, age, gender, surgical/medical status, social factors, mechanical ventilation and dialysis; (6) CCI, age, gender, surgical/medical status, social factors, mechanical ventilation and dialysis, primary diagnosis; (7) 10 separate

comorbidity groups; (8) 10 comorbidity groups in combination with age, gender, surgical/medical status, social factors, mechanical ventilation and dialysis, primary diagnosis; (9) SAPS II; (10) SAPS III; (11) APACHE 2.

We used Hosmer-Lemeshow goodness-of-fit statistics to assess model calibration except for the model including CCI only and the model including the 10 separate comorbidity groups only. Because of the limited number of observed and expected deaths in the higher deciles of risk in these models Pearsons chi-square statistics was used.

For all models c-statistics (area under ROC curve) were calculated as a measure of discrimination between survivors and non-survivors. C-statistics range from 0 to 1, with 1 indicating perfect discrimination and 0.5 indicating a chance discrimination; a c-statistic between 0.7 and 0.8 is considered a good discrimination, and c-statistics > 0.8 as an excellent discrimination[23].

**Results**

We identified 469 first-time adult ICU patients during the study period. The majority of patients (66.9%) were older than 60 years of age, and 298 (63.5%) patients had surgery within 7 days before ICU admission (Table 1). Cardiovascular diagnoses were the primary diagnoses for the majority of patients (58.9%). Median CCI score was 2 (interquartile range (IQR) 1-3), and median score was 16 (IQR 11-21) for APACHE II, 36 (IQR 26-47) for SAPS II, and 57 (IQR 45-66) for SAPS III.

*Correlation*

The correlation was poor between CCI score and SAPS scores and only slightly better for the CCI and APACHE II scores (Table 2). The correlation between the physiology-based scores was moderate to high.

*Calibration*

The correspondence of mortality predicted from the multivariable model including the CCI in combination with other administrative data and observed mortality was good for the lower deciles of mortality risk for 30-

day mortality, and slightly poorer for in-hospital and one-year mortality (Figure 1). The relatively low number of patients and outcomes in the higher deciles of risk limited the interpretation of model calibration in these groups. The Hosmer-Lemeshow goodness-of-fit statistics varied between models and outcomes; however, supported model fit of all models for 30-day and 1-year mortality (table 3). For in-hospital mortality low p-values for the models including the CCI, age and gender, surgical/medical status, social factors, and the full CCI model indicated poor calibration.

*Discrimination*

The model including only the CCI performed poorly in discriminating between survivors and non-survivors of the current hospitalization [c-statistic = 0.53 (95% CI: 0.46-0.59)], as well as within 30 days [c-statistic = 0.52 (95% CI: 0.46-0.57)] and one year of ICU admission [c-statistic = 0.58 (95% CI: 0.53-0.63)] (Table 4). Adding age, gender, social factors, surgical/medical status, mechanical ventilation/dialysis, and primary diagnosis to the CCI score in a multivariable model improved the discrimination substantially, with c-statistics of 0.75 (95% CI: 0.69-0.81) for in-hospital mortality, 0.75 (95% CI: 0.70-0.80) for 30-day mortality and 0.72 (95% CI: 0.68-0.77) for one-year mortality. Physiology-based scores discriminated as well as the CCI in combination with administrative data between short-term survivors and non-survivors. C-statistics for one year mortality was 0.70 (95% CI: 0.66-0.75) for SAPS II, 0.69 (95% CI: 0.64-0.73) for SAPS III, and 0.69 (95% CI: 0.64-0.73) for APACHE II. Including 10 comorbidity groups as separate covariates in the regression model only slightly improved discrimination compared with the CCI [c-statistic for 30-day mortality = 0.76 (95% CI: 0.71-0.81)]. Of note, c-statistics were almost nearly the same for in-hospital, 30-day, and 1-year mortality within the same categories of comorbidity measures.

## Discussion

In this study of 469 critically ill ICU patients we found that the CCI combined with other readily available administrative data performed as well as physiology-based scoring systems in predicting in-hospital and 30-

day mortality. The CCI and physiology-based scoring systems can be used to predict one-year mortality following intensive care.

Very limited data exist on how well comorbidity scores and physiology-based scores predict long-term mortality of ICU patients. Recently, an Australian study including more than 11,000 ICU patients found that in a prediction model (PREDICT) of 1 year, 5 year, and 15 year mortality, age and comorbidity as measured by the CCI were the most important determinants of prognosis[24]. The c-index of the full PREDICT model was 0.757 (95% CI: 0.745-0.769); however, no data on the performance of the CCI without APACHE II score in the model was presented. In the SUPPORT Prognostic Model study, Knaus et al, developed a prediction model of 180 day mortality for ICU patients (c-statistics 0.79) primarily based on diagnosis and physiological variables; however, did not include a comorbidity score in their model[25]. Our findings for in-hospital mortality extend data from four previous studies that examined the performance of comorbidity scores in predicting in-hospital mortality among ICU patients [12;16-18]. In a US study including more than 17,000 ICU patients from Veterans Affairs Medical Centers, Johnston *et al.* found that the 30 comorbidity variables included in the Elixhauser Index generated from administrative databases discriminated better between in-hospital survivors and non-survivors (c-statistic = 0.700), compared with the chronic health evaluation component of the APACHE score (c-statistic = 0.568) [12]. The Elixhauser Index uses 30 comorbidity variables separately and allows each variable to influence the outcome independently; unlike the Charlson Index, it does not use fixed weights. When combined with other clinical data (laboratory data, principal diagnosis, age, and admission source) the discrimination of the Elixhauser Index was excellent (c-statistic = 0.874); however, some of the data used are not readily available in other settings--particularly laboratory data, which accounted for 67.7% of the model's unique attributable chi square. Model calibration was not reported. In a 1996 US study of 201 general ICU patients, the CCI showed moderate discriminating ability for in-hospital mortality (c-statistic = 0.67)[18]. Data on comorbidity were collected by chart review and the CCI was not combined with other administrative data. Ho *et al.* found that the CCI had poor predictive performance for short-term mortality among 24,303 ICU patients in Western Australia (c-statistic = <0.610)

[16]. This study also did not combine the CCI with other administrative data. A 2006 Canadian study among 1603 ICU patients found that APACHE II predicted in-hospital survival better than the CCI (c-statistics = 0.77 vs 0.69). Even after adjustment for demographics, source of admission, socioeconomic factors, and primary diagnosis, both the APACHE II score and the CCI score remained independent predictors of in-hospital mortality[17].

In our study the physiology-based scoring systems performed less well in predicting in-hospital mortality than previously reported[26]. In an assessment of the performance of APACHE, SAPS and MPM in 22 general ICUs in Scotland, Livingstone *et al.* found good to excellent discrimination for all three scoring systems, with c-statistics ranging between 0.785 and 0.854[27]. We obtained data on physiological variables from computerized databases containing prospectively collected data which reduced the risk of information bias. However, some clinical variables, in particular the Glasgow Coma Scale (GCS) score, were missing in a number of medical records and by assuming that patients with missing values had normal GCS scores we may have underestimated the SAPS and APACHE scores [22]. Also, the majority of patients in our study was admitted from emergency departments or following surgery and therefore was stabilized before arrival at the ICU. This may also have lead us to underestimate the SAPS and APACHE scores. We did not include patients admitted for planned post-operative observation for less than 24 hours but may still have included some cardiac patients who by definition were not included in the original physiology-based scores. This may have led to an underestimation of the predictive performance of the physiology-based scores.

Despite advantages of physiology-based scoring systems in assessing ICU performance, the systems have limitations when used to control for confounding. To influence the association between exposure and outcome, a confounding factor must effect the outcome and must be unequally distributed between exposure groups[10]. Physiology-based scores predict outcome (mortality) but may not be unequally distributed between exposure groups and physiology-based scores are therefore not necessarily confounding factors. A third (and important) requirement for confounding factors is that the confounder cannot be an effect of the exposure[10]. Interventions that potentially affect mortality of ICU patients most likely do so by reducing physiological

derangement; thus physiology scores based on covariates collected after the intervention is initiated may be regarded an effect of the intervention. Controlling for a physiology-based score may under these circumstances introduce bias[10]. Generally, since confounding factors are defined by exposure-confounder and confounder-outcome associations, potential confounding factors are specific for the hypothesis under study. Thus, assigning predetermined weights to the covariates included in the systems may limit the ability to control for confounding. This holds for both physiology-based scoring systems and for the Charlson Index. Still, in the present study the prediction model including ten separate comorbidity categories performed only slightly better than the CCI, which used predetermined weights.

Based on our results, the CCI combined with other routinely collected data from administrative medical databases seem to perform at least as well as physiology-based scores in predicting mortality. However, the performance of administrative data largely depends on the completeness and validity of the data. Our access to high-quality population-based medical databases, linked using a unique personal identifier, may explain the good overall performance of the administrative data in our study. Whether the CCI in combination with administrative data perform as well as physiology-based scores in predicting mortality in other settings therefore remain to be clarified.

In conclusion, our study demonstrates that the CCI in combination with other readily available administrative healthcare data can be used to predict in-hospital and 30-day mortality. The CCI in combination with other readily available data and physiology-based scores can be used predicted one-year mortality following intensive care.

Table 1. Characteristics of 469 adult ICU patients, Skejby Hospital, Denmark 2007.

| | | Number | % |
|---|---|---|---|
| **Gender** | Women | 158 | 33.7% |
| | Men | 311 | 66.3% |
| **Age group** | 15-45 | 47 | 10.0% |
| | 45-60 | 108 | 23.0% |
| | 61-75 | 192 | 40.9% |
| | 76+ | 122 | 26.0% |
| **Surgical/medical status*** | Medical | 171 | 36.5% |
| | Surgical | 298 | 63.5% |
| **Primary diagnosis** | Infectious disease | 18 | 3.8% |
| | Cancer | 40 | 8.5% |

| | | | |
|---|---|---|---|
| | Diabetes | 2 | 0.4% |
| | Cardiovascular disease | 276 | 58.9% |
| | Respiratory disease | 40 | 8.5% |
| | Gastrointestinal disease | 11 | 2.4% |
| | Trauma/poisoning | 5 | 1.1% |
| | Other | 77 | 16.4% |
| **Mechanical ventilation** | | 320 | 68.2% |
| **Dialysis** | | 126 | 26.9% |
| **Marital status** | Married | 275 | 58.6% |
| | Divorced | 59 | 12.6% |
| | Widow(er) | 49 | 10.5% |
| | Never married | 84 | 17.9% |
| | Unknown | 2 | 0.4% |

| | | | |
|---|---|---|---|
| **Urbanization** | Provincial town | 186 | 39.7% |
| | Town | 153 | 32.6% |
| | City | 130 | 27.7% |

* Surgery within 7 days before ICU admission

Table 2. Correlation between scoring systems (Spearmans rank coefficient)

| | **SAPS II** | **SAPS III** | **APACHE II** |
|---|---|---|---|
| **Charlson score** | 0.124 | 0.082 | 0.228 |
| | ($p$=0.0074) | ($p$=0.0750) | ($p$<0.0001) |
| **SAPS II** | -- | 0.691 | 0.770 |
| | | ($p$<0.0001) | ($p$<0.0001) |
| **SAPS III** | | -- | 0.659 |
| | | | ($p$<0.0001) |

Table 3. Model calibration assessed by Hosmer-Lemeshow goodness-of-fit statistics (H-L goodness-of-fit) and Pearson chi-square.

| Score/measure | In-hospital mortality | | | 30-day mortality | | | !-year mortality | | |
|---|---|---|---|---|---|---|---|---|---|
| | H-L goodness-of-fit* | DF** | p-value | H-L goodness-of-fit* | DF** | p-value | H-L goodness-of-fit* | DF** | p-value |
| **Charlson score*** | 14.35* | 9 | 0.11 | 8.97* | 9 | 0.44 | 15.61* | 9 | 0.08 |
| **Charlson score, age and gender** | 9.33 | 8 | 0.32 | 6.91 | 8 | 0.55 | 8.06 | 8 | 0.43 |
| **Charlson score, age and gender, surgical/medical status** | 8.32 | 8 | 0.40 | 11.66 | 8 | 0.17 | 9.13 | 8 | 0.33 |
| **Charlson score, age and gender, surgical/medical status, social factors** | 18.73 | 8 | 0.02 | 2.69 | 8 | 0.95 | 4.10 | 8 | 0.85 |
| **Charlson score, age and gender, surgical/medical status, social factors, mechanical ventilation and dialysis** | 7.86 | 8 | 0.45 | 10.23 | 8 | 0.25 | 12.12 | 8 | 0.15 |
| **Charlson score, age and gender, surgical/medical status, social factors, mechanical ventilation and dialysis, primary diagnosis** | 20.25 | 8 | 0.01 | 9.07 | 8 | 0.34 | 10.48 | 8 | 0.23 |
| **Ten separate comorbidity groups*** | 85.30* | 92 | 0.68 | 85.49* | 92 | 0.67 | 106.12* | 92 | 0.15 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Ten comorbidity groups, with age, gender, surgical/medical status, social factors, mechanical ventilation and dialysis, primary diagnosis** | 8.71 | 8 | 0.37 | 8.89 | 8 | 0.35 | 7.38 | 8 | 0.50 |
| **SAPS II** | 5.08 | 10 | 0.89 | 3.49 | 10 | 0.97 | 1.58 | 10 | 1.00 |
| **SAPS III** | 9.39 | 10 | 0.50 | 10.89 | 10 | 0.37 | 11.55 | 10 | 0.32 |
| **APACHE II** | 13.69 | 10 | 0.19 | 12.65 | 10 | 0.24 | 8.12 | 10 | 0.62 |

* Pearson chi-square (see text for details), **DF= degrees of freedom;

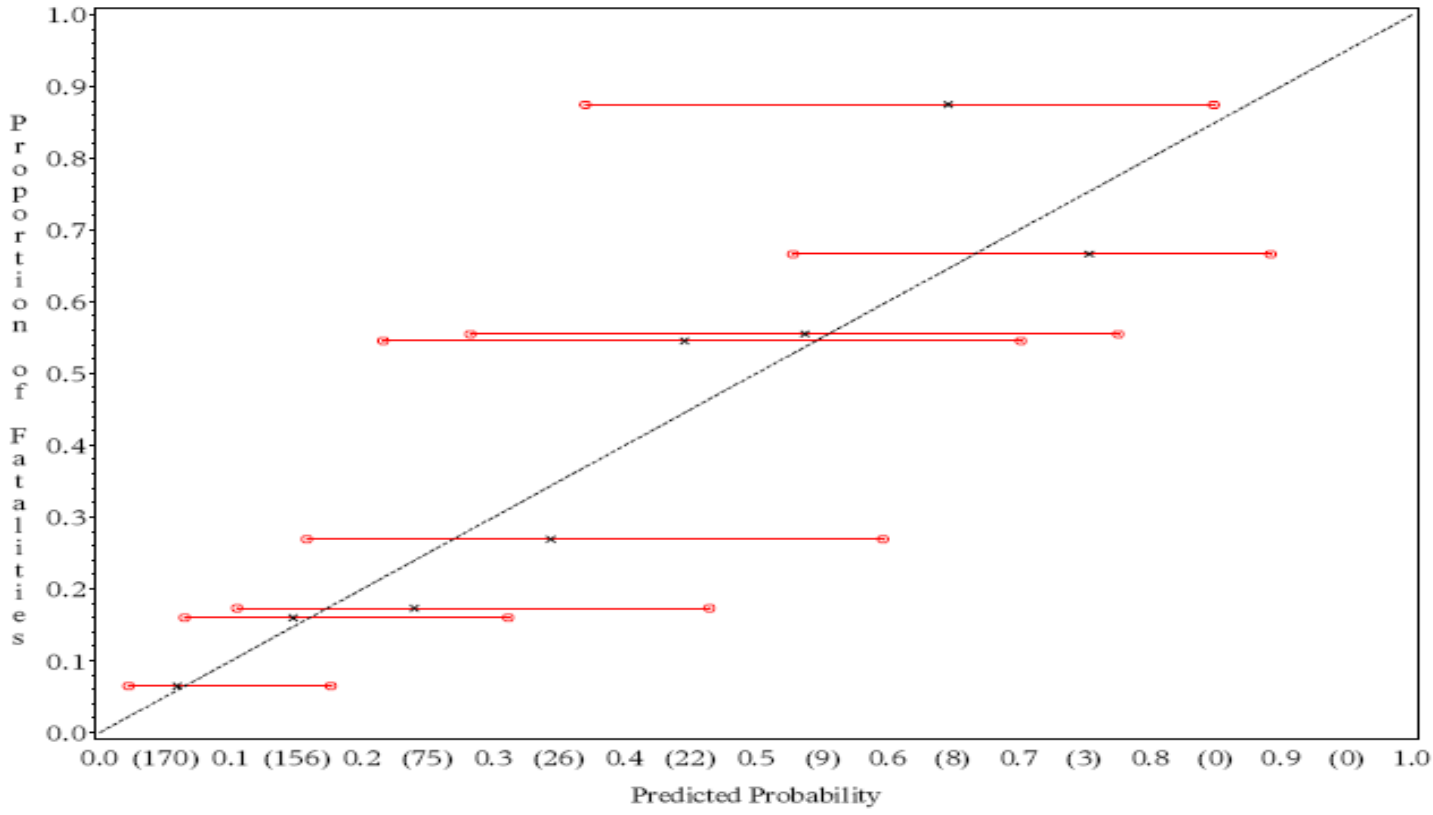
Table 4. C-statistics (area under ROC curve) as measure of discrimination between surviviors and non-surviviors (in-hospital, 30-day and 1-year mortality).

| Score/measure | Outcome (c-statistic, 95% confidence interval) | | |
|---|---|---|---|
| | **In-hospital mortality** | **30-day mortality** | **1-year mortality** |
| **Charlson score** | 0.53 (0.46-0.59) | 0.52 (0.46-0.57) | 0.58 (0.53-0.63) |
| **Charlson score, age and gender** | 0.65 (0.58-0.71) | 0.65 (0.59-0.71) | 0.65 (0.60-0.70) |
| **Charlson score, age and gender, surgical/medical status** | 0.67 (0.60-0.74) | 0.67 (0.61-0.73) | 0.66 (0.61-0.71 |
| **Charlson score, age and gender, surgical/medical status, social factors** | 0.69 (0.62-0.75) | 0.70 (0.64-0.75) | 0.68 (0.63-0.73) |
| **Charlson score, age and gender, surgical/medical status, social factors, mechanical ventilation and dialysis** | 0.72 (0.65-0.78) | 0.73 (0.68-0.78) | 0.71 (0.67-0.76) |
| **Charlson score, age and gender, surgical/medical status, social factors, mechanical ventilation and dialysis, primary diagnosis** | 0.75 (0.69-0.81) | 0.75 (0.70-0.80) | 0.72 (0.68-0.77) |
| **Ten separate comorbidity groups*** | 0.59 (0.52-0.66) | 0.58 (0.52-0.64) | 0.63 (0.58-0.68) |
| **Ten comorbidity groups*, with age, gender, surgical/medical status, social factors, mechanical ventilation and dialysis, primary diagnosis** | 0.75 (0.69-0.81) | 0.76 (0.71-0.81) | 0.75 (0.70-0.79) |
| **SAPS II** | 0.75 (0.69-0.81) | 0.72 (0.67-0.75) | 0.70 (0.66-0.75) |

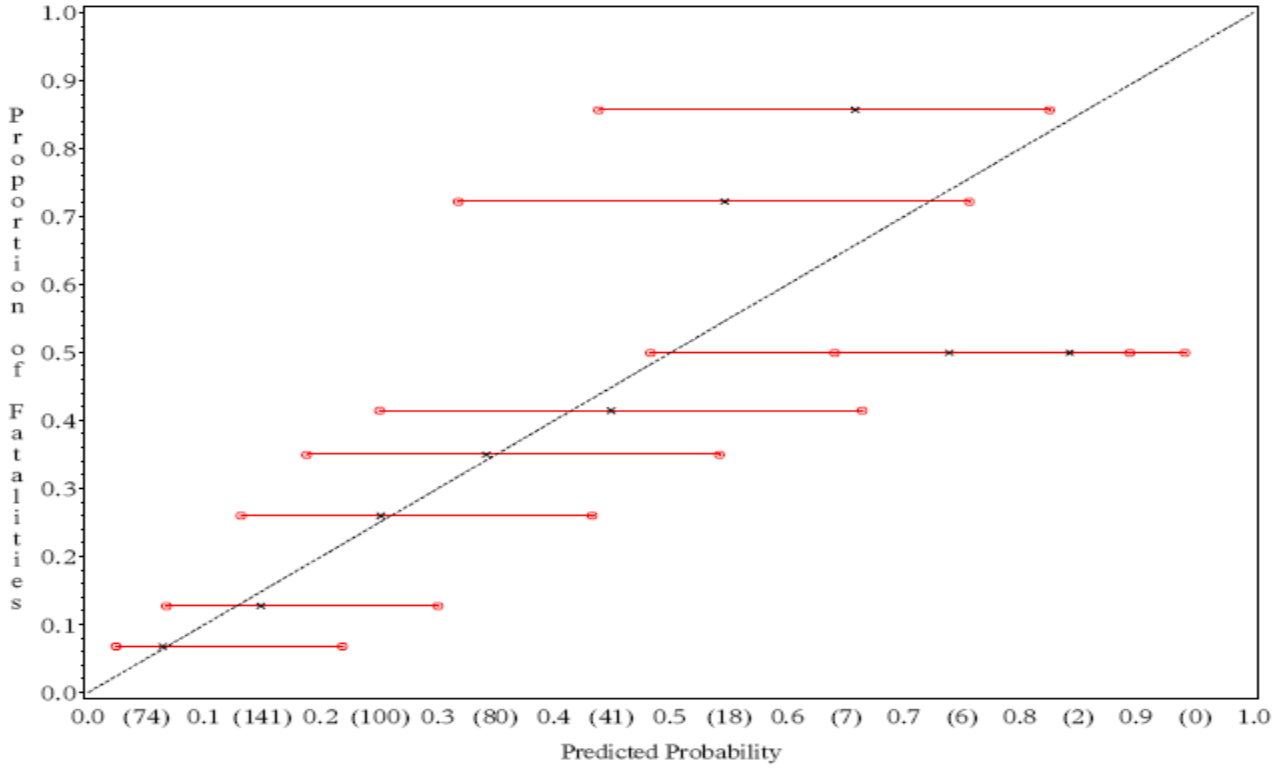
| | | | |
|---|---|---|---|
| **SAPS III** | 0.69 (0.63-0.76) | 0.68 (0.63-0.74) | 0.69 (0.64-0.73) |
| **APACHE II** | 0.69 (0.63-0.76) | 0.68 (0.63-0.74) | 0.69 (0.64-0.73) |

* See text for details

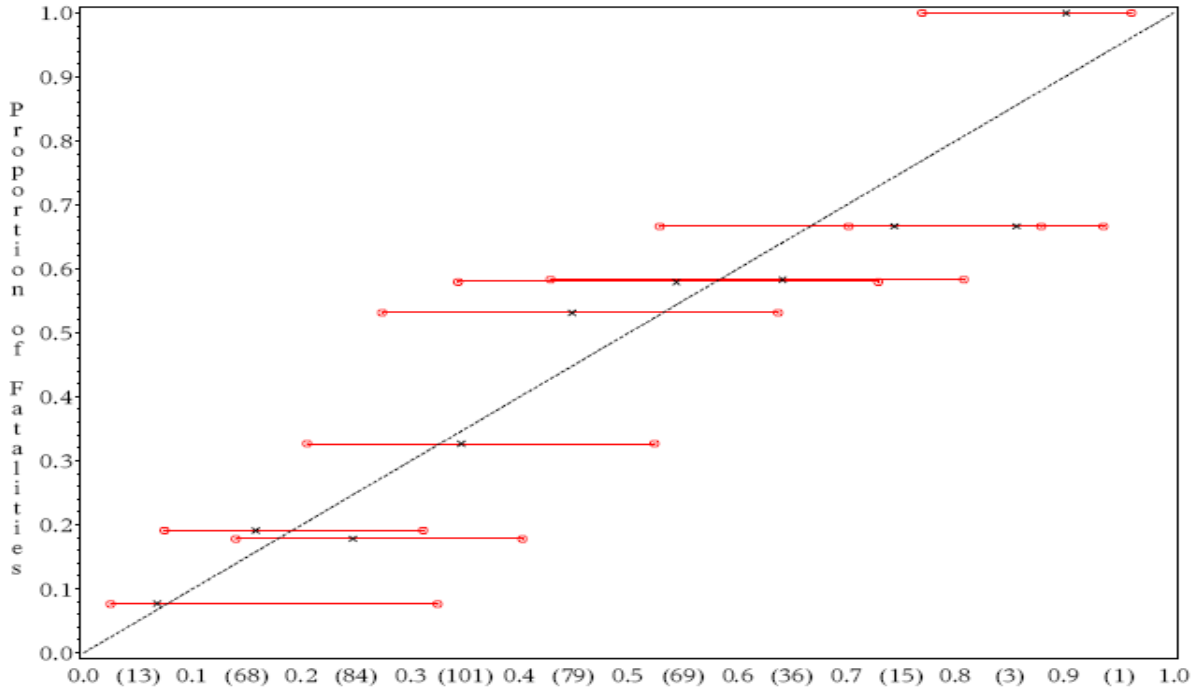
Figure 1. Model calibration (predicted mortality vs. actual mortality).The number in parenthesis is the number of patients in each decile.



**30-day mortality**




**1-year mortality**

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**APPENDIX**

**1. Charlson Comorbidity Index and comorbidity groups.**

| | Charlson comorbidity category | Number of patients (%) | 30-day mortality | ICD-8 | ICD-10 | Charlson Score | Comorbidity groups |
|---|---|---|---|---|---|---|---|
| 1 | Myocardial infarction | 111(23.7%) | 22.2% | 410 | I21;I22;I23 | 1 | Myocardial infarction |
| 2 | Congestive heart failure | 86 (18.3%) | 20.5% | 427.09;427.10; 427.11;427.19; 428.99; 782.49 | I50; I11.0; I13.0; I13.2 | 1 | Congestive heart failure |
| 3 | Peripheral vascular disease | 92 (19.6%) | 17.1% | 440; 441; 442; 443; 444; 445 | I70; I71; I72; I73; I74; I77 | 1 | Peripheral vascular disease |
| 4 | Cerebrovascular disease | 70 (14.9%) | 14.5% | 430-438 | I60-I69; G45; G46 | 1 | Cerebrovascular disease |
| 5 | Dementia | 5 (1.1%) | 2.6% | 290.09-290.19; 293.09 | F00-F03; F05.1; G30 | 1 | - |
| 6 | Chronic pulmonary disease | 94(20.0%) | 23.1% | 490-493; 515-518 | J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3 | 1 | Chronic pulmonary disease |
| 7 | Connective tissue disease | 27(5.8%) | 5.1% | 712; 716; 734; 446; 135.99 | M05; M06; M08; M09;M30;M31; M32; M33; M34; M35; M36; D86 | 1 | - |
| 8 | Ulcer disease | 48(10.2%) | 10.6% | 530.91; 530.98; 531-534 | K22.1; K25-K28 | 1 | Peptic ulcer disease |
| 9 | Mild liver disease | 15 (3.2%) | 3.4% | 571; 573.01; 573.04 | B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0 | 1 | Liver disease |
| 10 | Diabetes type1 | 52 (11.1%) | 7.7% | 249.00;249.06; | E10.0, E10.1; | 1 | Diabetes |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | 249.07; 249.09 | E10.9 | | |
| | Diabetes type2 | | | 250.00;250.06; 250.07; 250.09 | E11.0; E11.1; E11.9 | | |
| 11 | Hemiplegia | 1 (0.2%) | - | 344 | G81; G82 | 2 | - |
| 12 | Moderate to severe renal disease | 60 (12.8%) | 11.1% | 403; 404; 580-583;584;590.09; 593.19; 753.10-753.19; 792 | I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61 | 2 | Renal disease |
| 13 | Diabetes with end organ damage type1 | 38 (8.1%) | 6.8% | 249.01-249.05; 249.08 | E10.2-E10.8 | 2 | Diabetes |
| | type2 | | | 250.01-250.05; 250.08 | E11.2-E11.8 | | |
| 14 | Any tumor | 74 (15.8%) | 17.1% | 140-194 | C00-C75 | 2 | Cancer |
| 15 | Leukemia | 3 (0.6%) | 1.7% | 204-207 | C91-C95 | 2 | Cancer |
| 16 | Lymphoma | 5 (1.1%) | 0.8% | 200-203;275.59 | C81-C85; C88; C90; C96 | 2 | Cancer |
| 17 | Moderate to severe liver disease | 5 (1.1%) | 0.9% | 070.00; 070.02; 070.04; 070.06; 070.08; 573.00; 456.00-456.09 | B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85 | 3 | Liver disease |
| 18 | Metastatic solid tumor | 2 (0.4%) | 1.7% | 195-198; 199 | C76-C80 | 6 | Cancer |
| 19 | AIDS | 1 (0.2%) | - | 079.83 | B21-B24 | 6 | - |

**2. Diagnostic categories**

Infectious diseases (ICD-10:A00-B99), endocrinology including diabetes (ICD-10:E00-E90), cardiovascular diseases (ICD-10: I00-I99), respiratory diseases (ICD-10: J00-J99), gastrointestinal and liver disease (ICD-10: K00-K99), cancer (ICD-10:C00-D89), trauma and poisoning (ICD-10: S00-T98) and others (ICD-10: all codes not included in other categories)

# Preadmission statin use and one-year mortality among intensive care patients

## A cohort study

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**Abstract**

*Objective*

Statins reduce risk of cardiovascular events and have pleiotropic effects; both may reduce mortality in critically ill patients. We examined whether statin use was associated with risk of death in general intensive care unit (ICU) patients.

*Design*

Cohort study, using medical databases in Denmark.

*Setting*

Three multidisciplinary highly specialized ICUs within the Aarhus University Hospital network (2001-2007).

Participants: All (n=12,483) first-time ICU patients more than 45 years of age.

*Main outcome measures*

30-day, and one-year mortality and mortality rate ratios (MRR) comparing statin users and non-users, adjusted for potential confounders (demographics, use of other cardiovascular drugs, comorbidity, markers of social status, diagnosis, and surgery).

*Results*

1882 (14.3%) ICU patients were current statin users. Statin users had a reduced risk of death within 30 days of ICU admission [users: 22.1% vs. non-users 25.0%; adjusted MRR=0.77 (95% conficence interval (CI): 0.69 to 0.86)]. Statin users also had a reduced risk of death within one year after admission to the ICU [users: 36.4% vs. non-users 39.9%; adjusted MRR=0.79 (95% CI: 0.73 to 0.86)]. Reduced risk of death associated

with current statin use remained robust in various subanalyses and in an analysis using propensity score matching. Former use of statins and current use of non-statin lipid-lowering drugs were not associated with reduced risk of death.

*Conclusion*

Preadmission statin use was associated with reduced risk of death following intensive care. The associations seen could be a pharmacological effect of statins, but unmeasured differences in characteristics of statin users and non-users cannot be entirely ruled out.

## Introduction

There is substantial evidence that statins --widely used lipid-lowering drugs-- are effective in reducing major cardiovascular events and mortality in patients with arteriosclerotic disease, diabetes and hypercholesterolemia [1-4]. Experimental studies reported evidence that statins may also have anti-inflammatory, anti-thrombotic and immuno-modulating effects independent of lowering lipids, also referred to as pleiotropic properties [5;6]. The pleiotropic properties may differ between individual statins, in particular between lipophilic and hydrophilic statins [7-9].

In line with the experimental findings observational studies have reported a risk reduction [10-12] and profound improvements in the outcome of critical illnesses such as severe infections among statin users [13-17]. Beneficial effects in terms of reduced morbidity and mortality of statins have also been reported among patients with chronic obstructive pulmonary disease, renal failure and in patients undergoing cardiac or major non-cardiac surgery [18-21].

Patients in intensive care have a high prevalence of cardiovascular diseases, severe infections and thrombotic complications, and almost all ICU patients suffer from the systemic inflammatory response syndrome [22;23]. Statins could thus have beneficial effects on mortality following ICU admission. The three existing studies on this issue reported conflicting results and were limited by small and highly selected study populations such as patients with multiple organ dysfunction syndrome or ALI/ARDS, and assessed mortality only while in the hospital [24-26]. Since intensive care treatment is common, expensive and often ends in death, any beneficial effect of statins in this setting has major clinical and public health implications.

We conducted a large cohort study, based on more than 12,000 ICU patients, to examine the extent to which preadmission statin use overall and by specific agent was associated with risk of death in the year following ICU admission.

## Methods

*Setting*

We conducted this cohort study based on prospectively collected data obtained from medical databases in northern Denmark between January 1, 2001 and December 31, 2007. The Danish national health care system provides the entire Danish population with unrestricted access to tax-supported public health services and all critically ill patients receive care in public hospitals [27].

Since 1968 every Danish citizen has received at birth a unique civil registration number from the Danish Civil Registration System. This number permits accurate linkage across all Danish registries [28].

The study population comprised all patients admitted for the first time to an ICU in one of three hospitals within the Aarhus University Hospital network (Aalborg, Aarhus and Skejby Hospitals) [29]. All ICUs are highly specialized multidisciplinary units serving both as primary and referral ICUs. Their patients include those with severe respiratory failure requiring extracorporeal membrane oxygenation and patients undergoing organ transplantation.

*Intensive care data*

ICU patients were identified using a research database (Aarhus University Intensive Care Cohort (AUICC)). Data on use of mechanical ventilation, use of renal replacement therapy, dates of ICU admission and discharge, and civil registration numbers for all patients treated in the three ICUs are recorded by ICU physicians as part of standard department clinical practice and are routinely entered into AUICC. We did not include in the cohort patients who were admitted for planned postoperative observation of less than 24 hours and did not include patients younger than 45 years of age, a group that is rarely prescribed statins [30]. The study cohort totaled 12,483 eligible ICU patients with a first ICU admission during the study period.

*Preadmission use of statins*

We used a prescription database covering the entire region since 1998 to identify statin users. The database contain data, transferred electronically from all pharmacies in the region, on types and dosages of all reimbursed drugs prescribed, customers' civil registration numbers, and redemption dates [31]. We defined current statin use as at least one filled prescription for statins within 125 days before ICU admission (for details on ATC codes, see Appendix) [17]. The 125-day period allowed us to capture most current statin users, because in Denmark few statin prescriptions are expected to last more than 125 days [17;30]. Among current statin users, we distinguished "new" and "long-term" statin users as those who had filled their first statin prescription within 125 days before ICU admission, or earlier than 125 days, respectively [32].

Statin users may have been more frequently hospitalized during the exposure defining period before ICU admission than non-users. Since no prescriptions are filled during hospitalizations this may lead to misclassification of statin use [33]. We therefore used the Danish National Registry of Patients (NRP) to identify the number of days that study patients were hospitalized within the 125 days before ICU admission (0 days, 1-10 days,11-25 days, >25 days).

*Other prognostic factors*

We identified the main diagnosis for the admission requiring intensive care through the Danish National Registry of Patients (NRP). The NRP covers all hospitalizations in Denmark since 1977 and all out-patient hospital visits since 1995 [34]. We grouped patients into eight disease categories: infectious diseases; endocrinology including diabetes; cardiovascular diseases; respiratory diseases; gastrointestinal and liver diseases; cancer; trauma and poisoning; and others (for details on ICD codes, see Appendix). We also identified the department that transferred the patient to the ICU (surgical/medical). Using the NRP, we obtained information on surgical procedures in the seven days before ICU admission and classified patients

as surgical and medical (no surgery within seven days before ICU admission) [35]. To control for comorbidity we computed the Charlson comorbidity score based on the entire previous discharge history and defined three comorbidity levels: low (score of 0), medium (1-2), and high (≥ 3)) [36]. The index includes 19 major disease categories and has been validated as a predictor of mortality [37;38]. We also retrieved information on alcoholism-related disorders, and prescriptions for disulfiram (ICD and ATC codes are provided in the Appendix). For the subcohort of patients admitted between 2001 and 2006 we collected data on hemoglobin, white blood cell count (WBC), platelets, C-reactive protein (CRP) and bilirubin on ICU admission and on the most recent total cholesterol level recorded within 6 months before ICU admission from laboratory databases. We retrieved prescription data on current use of ACE-inhibitors, beta-blockers, and low-dose aspirin, as these drugs may confound studies on clinical effects of statins [18;39] and on current use of non-statin lipid lowering drugs as these drugs are given on almost the same indications as statins but lack the pleiotropic effects [e.g. niacin, bile acid binding resin and fibric acid derivatives]. As a measure of social status, we obtained data on marital status at the time of ICU admission from the CRS [28].

*Mortality data*

We accessed data from the Civil Registration System, which contains complete information for the entire Danish population on migration and changes in vital status, including exact date of death, updated on a daily basis [28].

*Statistical analysis*

Follow-up began on the date of first-time ICU admission and continued until death, migration, 365 days after ICU admission or December 31 2008, whichever came first. We computed Kaplan Meier curves and life table estimates for mortality at 30 days and one year for the following variables: preadmission statin use; primary diagnosis; age group; gender; department (medical/surgical); level of Charlson score; alcoholism-related diseases; surgery within 7 days (yes/no); need for mechanical ventilation or renal replacement

therapy; current use of ACE-inhibitors, low-dose aspirin or beta-blockers; marital status (married, divorced, widowed, never married, or unknown).

We used Cox proportional hazards regression to compute mortality rate ratios (MRRs) for statin users compared with non-users, controlling for all covariates in table 1 and 2, except mechanical ventilation, dialysis, and laboratory data as we considered these potential effects of the intervention [40]. We did separate analyses for subgroups defined according to admitting department, surgery, presence of mechanical ventilation, renal replacement therapy, and for former, new, and long-term statin users. Since the pleiotropic effects may vary between types of statins we also did a separate analysis for users of the lipophilic simvastatin, and the hydrophilic atorvastatin, and pravastatin and used Wald statistics to compute p-values for the difference in MRR between types of statins.

To assess possible unmeasured confounding by indication for statin treatment we restricted the analysis to patients with a previous diagnosis of ischemic or unspecified stroke, atherosclerosis, ischemic heart disease, or diabetes mellitus. We also repeated the analysis after excluding patients with cancer and for users of non-statin lipid-lowering agents. Details on ICD codes are provided in the Appendix.

To further control for confounding we conducted a supplementary analysis using propensity score matching [41;42]. We generated a multivariable logistic regression model that predicted statin use among ICU patients based on the covariate profile listed in tables 1 and 2, except laboratory data and mechanical ventilation and dialysis, and computed the propensity score for all ICU patients. We then matched each statin user with one non-user using a greedy matching algorithm. All statin users could be matched to a non-user. Propensity score matching decreased the absolute standardized differences of each covariate to values below 0.1 indicating that an adequate balance was achieved. We then used Cox regression analysis to compute 30 day and one-year MRR in the matched cohort.

The assumptions of proportional hazards in all Cox regression models were assessed graphically and found appropriate. All analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC).

The study was approved by the Danish Data Protection Agency (record number 2005-41-4782) and the Aarhus University Hospital Registry Board.

## Results

*Descriptive data*

We identified 12,483 first-time ICU patients older than 45 years. Of these, 1,882 (15.1%) were current statin users on admission (Table 1). Statin users were more likely to be male, and had higher levels of comorbidity than other ICU patients. Diabetes and cardiovascular diseases were as expected more prevalent among statin users than among non-users, whereas cancer and alcoholism-related diseases were less common. Statin users were more frequently users of ACE-inhibitors, beta-blockers or low-dose aspirin than non-users (Table 2). At ICU admission, statin users had higher average blood levels of creatinine, similar WBC count and slightly lower levels of C-reactive protein than non-users.

A total of 151 (8.0%) statin users and 917 (8.7%) non-users were hospitalized for more than 25 days during the 125 days before ICU admission.

*30-day mortality*

Throughout the follow-up period, statin users had considerably lower risk of death than statin non-users (figure 1). The risk of death within 30-days after ICU admission was 22.1% among statin users and 25.0% among non-users, corresponding to a crude MRR of 0.85 (95% CI: 0.76-0.96) (table 3). After control for

potential confounders the 30-day MRR was 0.76 (95% CI: 0.68-0.85). For all diagnostic categories, except diabetes and infection diseases, statin use was associated with a reduced risk of death (figure 2). The MRRs seemed lower for users of simvastatin [MRR=0.74 (95% CI: 0.65-0.84)] than for other types of statins [atorvastatin MRR=0.95 (95% CI: 0.72-1.25); pravastatin MRR=0.96 (95% CI: 0.71-1.30)]; however, the differences were not statistically significant (p=0.42).

Exclusion of patients with cancer from the analysis or restriction to patients with cardiovascular diseases or diabetes left the decreased MRRs for statins virtually unchanged. Of note the risk of death seemed not to be reduced by non-statin lipid lowering drug use [MRR=1.29 (95% CI: 0.80-2.08)] or by former statin use [MRR=0.88 (95% CI: 0.73-1.06)]. For new and long-term statin users the adjusted MRRs were 0.68 (95% CI: 0.51-0.90) and 0.81 (95% CI: 0.72-0.91), respectively.

Further stratified analyses showed an adjusted 30-day MRR of 0.81 (95% CI: 0.67-0.97) among ICU patients who had surgery within 7 days of ICU admission, and 0.76 (95% CI: 0.66-0.87) among ICU patients who had no surgery within 7 days.

The propensity score matched analysis yielded a MRR similar to the estimates from the conventional Cox regression analysis [adjusted MRR 0.71 (95% CI: 0.61-0.83)].

*One year mortality*

The one-year risk of death was 36.4% among statin users vs. 39.9% among non-users; crude MRR was 0.84 (95% CI: 0.76-0.93) decreasing to 0.79 (95% CI: 0.73-0.87) after controlling for confounding factors. The one-year reduction in risk of death remained robust in all diagnostic categories and seemed most pronounced for simvastatin [simvastatin: MRR= 0.77 (95% CI: 0.70-0.85); atorvastatin: MRR=0.90 (95% CI: 0.72-1.12); pravastatin: MRR=1.03 (95% CI: 0.81-1.31)]; however, the difference between statins did not reach statistical significance (p=0.35). The reduction in risk of death associated with statin use remained virtually unchanged when analyses were restricted to patients without cancer or to patients with cardiovascular disease or diabetes (figure 3). MRR among new and long-term statin users were 0.80 (95% CI: 0.65-0.98)

and 0.81 (95% CI: 0.74-0.89), respectively. Former statin use and use of non-statin lipid lowering drugs was not to be associated with reduced risk of death within one year of ICU admission.

The propensity score matched analysis yielded an adjusted MRR of 0.70 (95% CI: 0.62-0.80).

## Discussion

In this large cohort study we found that preadmission statin use was associated with considerably reduced risk of death among ICU patients. The reduced risk of death remained robust in various subgroup analyses, including among new- and long-term statin users. We found no clear association between former statin use and non-statin lipid-lowering drug use and risk of death which supports a causal association between statin use and reduced risk of death among ICU patients.

*Existing data*

Increasing evidence exist that statins may reduce mortality in patients with severe infections including sepsis [13-17] but limited and conflicting data exist on the association between statin use and in-hospital/30-day mortality among general ICU patients. In a 2006 German cohort study of 120 ICU patients with multiple organ dysfunction syndrome, Schmidt et al reported that statin use was associated with substantially reduced in-hospital mortality [MRR= 0.53 (95% CI: 0.29-0.99], a result consistent with our findings [25]. Also, in line with our findings a recent US study among 178 patients with acute lung injury/adult respiratory distress syndrome (ALI/ARDS) found reduced ICU and in-hospital mortality among statin users [OR for ICU mortality 0.82 (95% CI: 0.36-1.89), OR for in-hospital mortality 0.62 (95% CI: 0.29-1.32)]; however, the relatively small study population hindered a clear interpretation of the risk estimates [26]. In contrast, a 2006 Spanish observational study of 438 patients mechanically ventilated for more than 96 hours reported higher in-hospital mortality among statin users (61%) than non-users (42%) [OR=2.30 (95% CI: 1.08-4.89)] [24]. All studies included highly selected subgroups of ICU patients and did not adjust for important covariates such

as comorbidity and use of other cardiovascular drugs. To our knowledge no former data exist on the effect of statins on long-term risk of death among ICU patients.

The biological mechanisms underlying our observations are not yet entirely understood. However, the high prevalence of systemic inflammatory response syndrome and/or severe infections among ICU patients may increase the risk of fatal venous and arterial thrombotic events by inducing endothelial dysfunction and atherosclerotic plaque instability [43-45]. There is strong experimental evidence that statins have beneficial effects on platelet function, coagulation, fibrinolysis, and plaque formation, as well as inhibitory effects on endothelial dysfunction [46-49]. Also, statins have immuno-modulating effects that may be beneficial during the initial "hyper-immune" phase of critical illness [5;23]. Differences in these pleiotropic properties between lipophilic and hydrophilic statins may explain the differences between individual statins suggested by our data [7-9].

*Limitations*

We conducted this study within a tax-financed National Health Service system with free access to health care which largely removed referral bias. We had complete and independently collected data on preadmission statin use and one-year mortality which limited the risk of information and surveillance bias. The relatively large number of ICU patients enabled robust analysis on several ICU subgroups showing consistent results.

The validity of our findings depends ultimately on accurate registration of statin use and ability to control for confounding. The completeness and nature of the prescription database used makes the measurement of filled prescriptions for statins highly valid [31]. In Denmark adherence to statin therapy is high, and any influence of non-compliance should therefore be minor, potentially attenuating our mortality estimates towards unity [51]. Since few statin users were hospitalized for more than 25 days during the 125 days before ICU admission, misclassification of statin use because of more frequent previous hospitalizations most likely had little influence on our results [33]. We had access to data on a large number of prospectively collected

covariates from databases with high validity for surgical procedures, diagnosis codes, and laboratory data. Still, any lack of specificity in routinely recorded data may have reduced our ability to completely remove confounding and most likely would attenuate our findings towards the null. Severe confounding by socioeconomic differences between statin users and non-users is unlikely given the tax-financed Danish public health care system [52]. This is supported by a recent study which found similar reduced risk of all-cause mortality among statin users and non-users when comparing results from the randomised 4S study with results from an observational study based on prescription data [53].

Statins may exert their potential beneficial effects by improving immune dysfunction caused by critical illness. Surrogate physiological measures of severity of illness and inflammation, e.g. C-reactive protein and white blood cell count, may thus be in the pathway between statin use and mortality and therefore do not fulfil the criteria for being confounding factors [40;54]. We therefore did not adjust for physiological measures, including laboratory data, in the analysis.

*Conclusion*

In this large cohort study preadmission use of statins was associated with reduced risk of death within 30 days and one year in general ICU patients. The associations seen could be a pharmacological effect of statin use; however, it remains to be fully clarified whether differences in characteristics of statin users and non-users may explain at least part of the associations found.

**Funding**

This work was made possible through financial support from the Danish Medical Research Council (Grant 271-05-0511), and from "Klinisk Epidemiologisk Forskningsfond", Denmark. The sponsors had no influence on study design and the collection, analysis, and interpretation of data and the writing of the article and the decision to submit it for publication

**Contributors**

SC, RWT, AL, ET and HTS conceived the study idea. SC and HTS designed the study. RJ and KML collected the data. SC, HTS, MBJ and LP analysed the data. All authors interpreted the findings. SC and RWT reviewed the literature. SC wrote the first draft and all authors edited the manuscript and approved the final version. SC is the guarantor.



**Competing Interest Statement**

All authors declare that the answer to the questions on your competing interest form are all No and therefore have nothing to declare.

**What is already known on this topic:**

In experimental studies statins have shown to have anti-inflammatory, anti-thrombotic and immuno-modulating effects independent of lowering lipids which may reduce mortality from critical illness.

In observational studies statin use has been associated with reduced mortality following major surgery and severe infections.

**What this study adds:**

Preadmission statin use is associated with reduced short- and long-term mortality following intensive care.

The beneficial effects may be most pronounced for users of simvastatin.

**APPENDIX: ICD and ATC Codes**

Disease categories

Infectious diseases (ICD-10:A00-B99), endocrinology including diabetes (ICD-10:E00-E90), cardiovascular diseases (ICD-10: I00-I99), respiratory diseases (ICD-10: J00-J99), gastrointestinal and liver disease (ICD-10: K00-K99), cancer (ICD-10:C00-D89), trauma and poisoning (ICD-10: S00-T98) and others (ICD-10: all codes not included in other categories)

Alcoholism-related disorders

ICD-8: 291, 303, 979, 980,571.09, 571.10, 577.10

ICD-10: G62.1, G72.1, G31.2, I42.6, F10, K29.2, K70, K86.0, Z72.1, R78.0, T51

AND/OR

Previous prescriptions of disulfiram (ATC: N07BB01)

Ischemic or unspecified stroke

ICD-8: 433-434; ICD-10: I63-I64, I69.3, I69.4, I69.8

Atherosclerosis

ICD-8: 440, ICD-10: I70

Ischemic heart disease

ICD-8: 410-440, ICD-10: I20-I25

Diabetes

ICD-8: 249-250, ICD-10: E10-E11

Cancer

ICD-8:140-194, 195-198, 199, 200-203, 204-207, 275.59;

ICD-10: C00-C75, C76-C80, C81-C85, C88, C90, C91-C95, C96

Medications (ATC codes)

Simvastatin: C10AA01, B04AB01

Atorvastatin: C10AA05, B04AB05

Pravastatin: C10AA03, B04AB03

Other statins: C10AA0X, B04AB0X, not included in other categories.

ACE-inhibitors: C09

Beta-blockers: C07

Low-dose aspirin: N02BA01

Non-statin lipid lowering drugs [niacin, bile acid binding resin and fibric acid derivatives]: C10AD

Table 1: Baseline characteristics by preadmission statin use among 12,483 ICU patients, Aarhus University Hospital, Denmark 2001-2007.

| | Statin use<br>N (%) | No statin use<br>N (%) |
|---|---|---|
| **Overall** | 1882 (14.3%) | 10,601 (85.7%) |
| **Age group** | | |
| 45-60 | 373 (19.8%) | 3725 (35.1%) |
| 61-75 | 1095 (58.2%) | 4421 (41.7%) |
| 76+ | 414 (22.0 %) | 2455 (23.2%) |
| **Gender** | | |
| Male | 1193 (63.4%) | 6085 (57.4%) |
| Female | 689 (36.6%) | 4516 (42.6%) |
| **Comorbidity score*** | | |
| Low | 283 (15.0%) | 3563 (33.6%) |
| Medium | 862 (45.8%) | 4280 (40.4%) |
| High | 737 (39.2%) | 2758 (26.0%) |

| | | |
|---|---|---|
| **Comorbidity diagnosis** | | |
| Ischemic heart disease | 658 (35.0%) | 950 (9.0%) |
| Congestive heart failure | 406 (21.6%) | 1113 (10.5%) |
| Peripheral vascular disease | 451 (24.0%) | 1050 (9.9%) |
| Cerebrovascular disease | 468 (24.9%) | 1393 (13.1%) |
| COPD | 339 (18.0%) | 1836 (17.3%) |
| Diabetes | 456 (24.2%) | 879 (8.3%) |
| Cancer | 299 (15.9%) | 2401 (22.5%) |
| Renal disease | 171 (9.0%) | 586 (5.4%) |
| Alcoholism-related diseases | 137 (7.3%) | 1305 (12.3%) |
| **Cardiovascular drug use** | | |
| ACE inhibitors | 1003 (53.3%) | 1860 (17.6%) |
| Beta blockers | 983 (52.2%) | 1706 (16.1%) |

| | | |
|---|---|---|
| Low-dose aspirin | 336 (17.9%) | 674 (6.4%) |
| **Marital status** | | |
| Married | 1141 (60.6%) | 5664 (53.4%) |
| Divorced | 251 (13.3%) | 1512 (14.3%) |
| Widow(er) | 345 (18.3%) | 2033 (19.2%) |
| Never married | 139 (7.4%) | 1135 (10.7%) |
| Unknown | 6 (0.3%) | 257 (2.4%) |

*Level of Charlson comorbidity index. See text for details.

** Patients may have more than one comorbidity.

Table 2. Characteristics associated with the current hospitalization of 12,483 ICU patients with and without preadmission statin use, Aarhus University Hospital, Denmark, 2001-2007.

| | **Statin use** N (%) | **No statin use** N (%) |
|---|---|---|
| **Department** | | |
| Medical | 771 (41.0%) | 4243 (40.0%) |
| Surgical | 1111 (59.0%) | 6358 (60.0%) |
| **Main diagnosis** | | |
| Infections | 43 (2.3%) | 253 (2.4%) |
| Cancer | 163 (8.7%) | 1607 (15.2%) |
| Diabetes | 30 (1.6%) | 129 (1.2%) |
| Cardiovascular | 800 (42.5%) | 2828 (26.7%) |
| Respiratory | 132 (7.0%) | 1049 (9.9 %) |
| Gastrointestinal | 163 (8.7%) | 1187 (11.2%) |
| Trauma/poisoning | 136 (7.2%) | 1383 (13.1%) |
| Other | 415 (22.0%) | 2165 (20.4%) |
| **Surgical status at ICU admission** | | |

| | | |
|---|---|---|
| Surgery within 7 days | 199 (10.6%) | 1347 (12.7%) |
| **Mechanical ventilation** | | |
| Yes | 1021 (54.3%) | 4796 (45.3%) |
| **Renal replacement therapy** | | |
| Yes | 223 (11.9%) | 867 (8.2%) |
| **Laboratory findings, median (IQR)*** | | |
| Hemoglobin (ref; female: 7.4-9.6 mmol/l, male:8.4-10.8 mmol/l) | 7.10 (6.30-8.20) | 7.30 (6.40-8.30) |
| Creatinine (ref 60-125 µmol/l) | 106.5 (80-165) | 93 (70-138) |
| Bilirubin (ref 4-21 mmol/l) | 10 (7-16) | 12 (8-20) |
| C-reactive protein (ref < 10 mg/l) | 80 (15-250) | 97 (21-279) |
| White blood cell count (ref 4.0-11.0 x $10^9$ / l) | 12.2 (8.8-16.0) | 12.3 (9.0-16.7) |
| Total cholesterol (ref 3.0-6.7 mmol/l) | 4.6 (3.9-5.5) | 5.0 (4.1-5.9) |

* For the subcohort of patients admitted between 2001 and 2006. Highest test result on day of ICU admission or the following day for creatinine, bilirubin C-reactive protein and white blood cell count and the lowest test results for hemoglobin. For cholesterol closets record value within one year before ICU admission.

Table 3. Cumulative 0-30 and 31-365 day mortality and corresponding crude and adjusted mortality rate ratios (MRR).

| | **Number (N)** | **Mortality (%)** | **Crude MRR (95% CI)** | **Adjusted MRR (95% CI)#** |
|---|---|---|---|---|
| ***0-30 days*** | | | | |
| Statin use | 1882 | 22.1% | 0.85 (0.76-0.96) | 0.76 (0.68-0.85) |
| No statin use | 11,313 | 25.0% | 1 -- | 1 -- |
| ***0-365 days*** | | | | |
| Statin use | 1882 | 36.4% | 0.84 (0.76-0.93) | 0.78 (0.71-0.84) |
| No statin use | 11,313 | 39.9% | 1 -- | 1 -- |

**#** Adjusted by Cox proportional hazards for age group, gender, medical/surgical department, diagnosis, Charlson index score and alcoholism-related disease, surgery within 7 days, current use of ACE-inhibitors, beta-blockers and low-dose aspirin and marital status.

Figure 1. One year survival curve of 1881 statin users and 10,601 non-users.

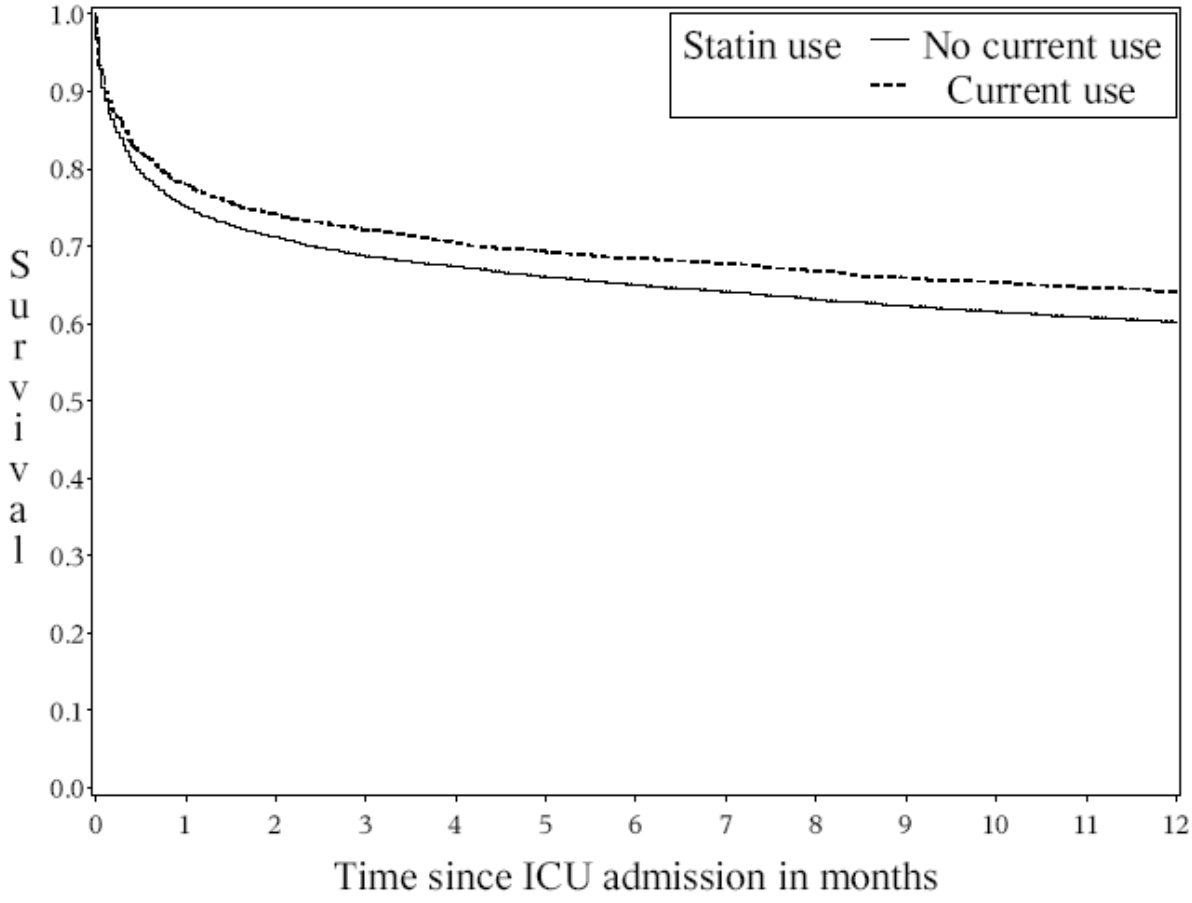


Figure 2: Adjusted 30-day mortality rate ratios (MRRs) associated with preadmission statin use overall and within different patient subgroups.

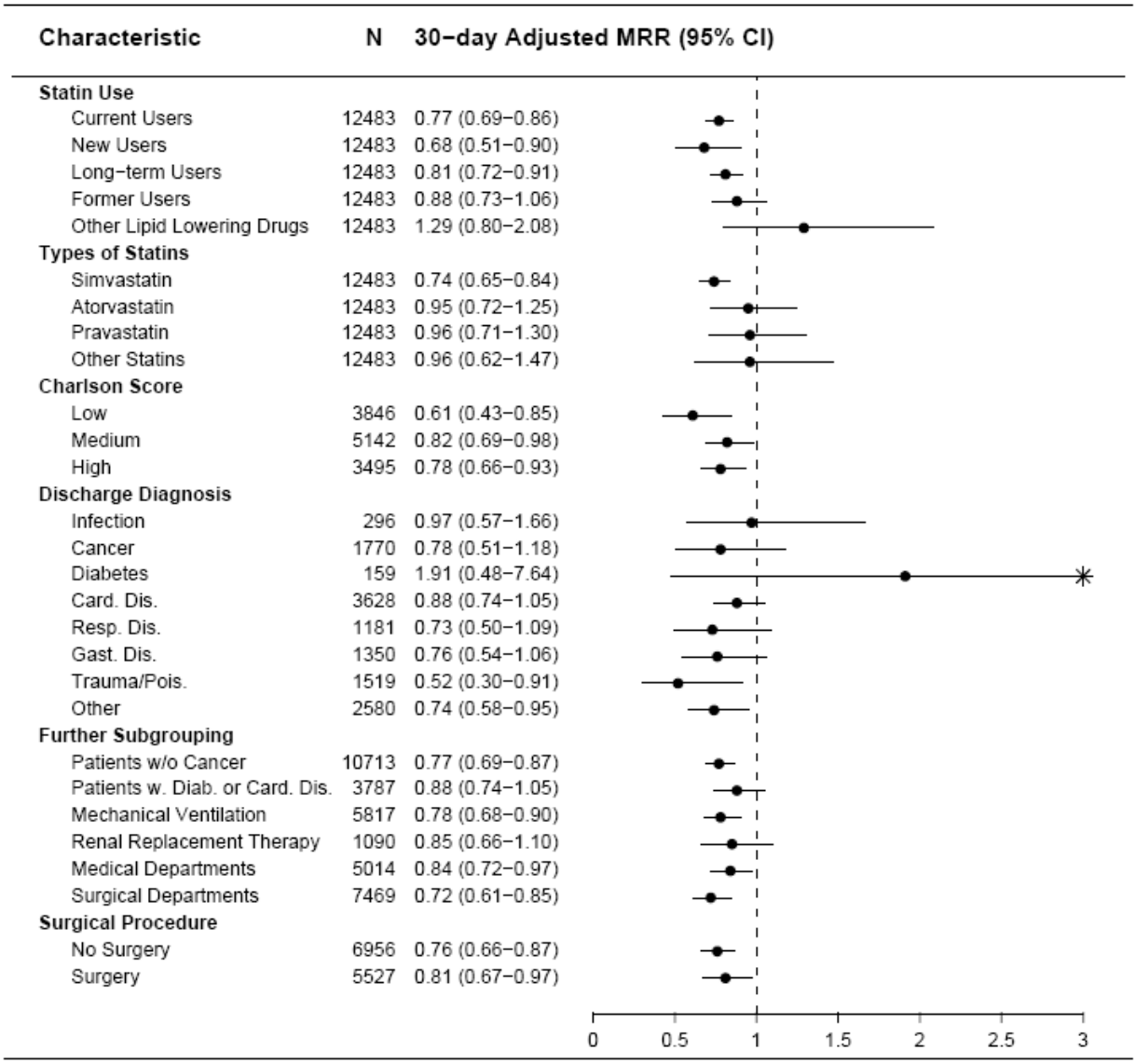
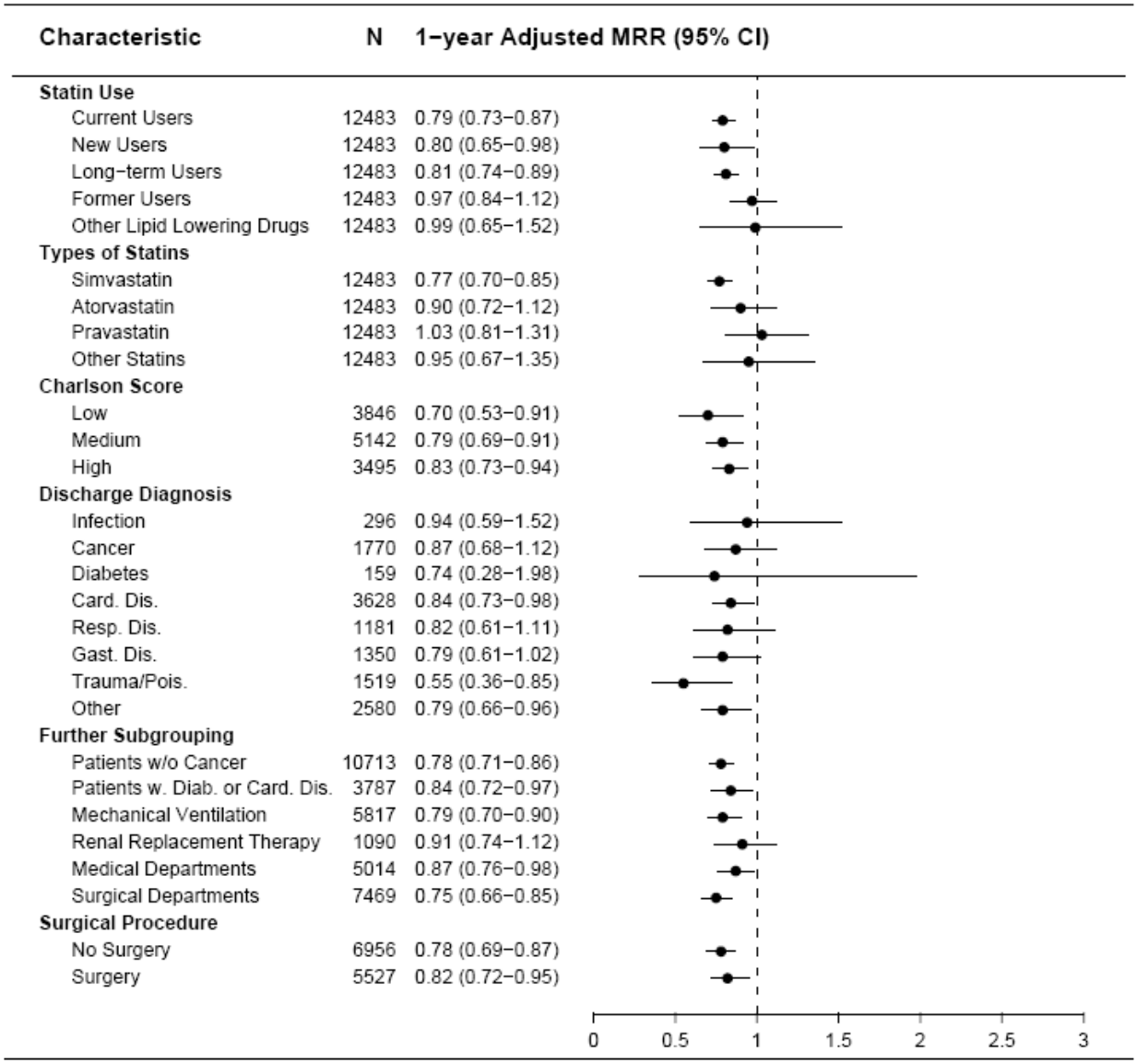


Figure 3: Adjusted one-year mortality rate ratios (MRRs) associated with preadmission statin use overall and within different patient subgroups.



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# Pre-admission beta-blocker use and 30-day mortality among patients in intensive care: a cohort study

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*Acknowledgments:*

This work was made possible through financial support from the Danish Medical Research Council (Grant 271-05-0511), and from "Klinisk Epidemiologisk Forskningsfond", Denmark.

*Running title:* Betablockers and outcome of intensive care

*Word count:* 2138 (abstract 191)

*Tables*: 1, Figures: 1

*Key words:* Intensive care, mortality, metabolism, adrenergic beta-antagonists, critical illness, critical care

**Abstract**

*Introduction*

Beta-blockers have cardio-protective, metabolic and immuno-modulating effects which may beneficial in patients in intensive care. We examined whether preadmission beta-blocker use was associated with 30-day mortality following intensive care.

*Methods*

For this cohort study we identified 8087 patients older than 45 years of age admitted for the first time at three multidisciplinary Intensive Care Units (ICUs) within the Aarhus University Hospital network, Denmark between 1999 and 2005. Data on beta-blocker use, use of other cardiovascular medications, diagnosis, comorbidity, surgery, markers of socio-economic status, data on laboratory tests at ICU admission, and complete follow for mortality were obtained from medical databases. In a propensity score analysis based on the entire covariate profile of study patients we matched all 1,556 beta-blocker users (19.2% of the entire cohort) with 1,556 non-users. We computed mortality of death within 30-days following ICU admission for beta-blocker users and non-users, and odds ratio (OR) of death as a measure of relative risk using conditional logistic regression.

*Results*

In the propensity matched analysis 30-day mortality was 25.7% among beta-blocker users and 31.4% among non-users corresponding to an OR of beta-blocker users compared with non-users of 0.74 (95% CI: 0.63–0.87). The OR was 0.69 (95 % CI: 0.54–0.88) for surgical ICU patients and 0.71 (95% CI: 0.51–0.98) for medical ICU patients. The OR for new users of beta-blockers was 0.57 (95% CI: 0.38-0.85) and 0.78 (95% CI: 0.66-0.92) for long-term users. Among users of non-selective beta-blockers OR was 0.99 (95% CI: 0.67-1.47) and 0.66 (95% CI: 0.35-1.23) among users of non-selective beta-blocker combined with alpha-

adrenergic blocker and OR 0.70 (95% CI: 0.58-0.83) for cardio-selective beta-blockers. Including all 8087 ICU patients in a conventional regression analysis revealed an adjusted OR of 0.78 (95% CI: 0.68-0.91)].

*Conclusions*

In general ICU patients preadmission use of beta-blockers is associated with reduced mortality within 30 days following ICU admission.

***Introduction***

Beta-blockers are widely used to treat cardiovascular diseases and has been shown to reduce re-infarction rates and mortality following myocardial infarction [1;2]. In patients with chronic heart failure beta-blockers improve cardiac function and reduce mortality [3;4]. Evidence from observational studies and randomized controlled trials exist that beta-blockers may reduce the risk of perioperative cardiac complications and mortality in high-risk patients undergoing major surgery, although this has recently been challenged [5-12].

During critical illness the whole body metabolism is shifted towards a hypermetabolic state primarily in terms of increased resting energy expenditure, rapid muscle loss and hyperglycemia [13-15]. The shift in metabolism is mainly mediated through a catecholamine surge and sympathetic activation during the early phase of critical illness [16]. Attenuation of the hypermetabolic state of critical illness has been associated with reduced mortality [16-18]. Blocking the beta-adrenergic stimulation of the catecholamine surge has been suggested as the underlying biological mechanism for the reduced mortality observed in beta-blocker users hospitalized with severe trauma and burns [18-21].

Key mediators of the immune system have beta-adrenergic receptors [22;23] and in vitro studies have suggested a number of potential beneficial immuno-modulating effects of beta-blockers [24]; however, the full extent of these effects in critically ill patients are far from elucidated.

Among intensive care unit (ICU) patients the prevalence of cardiovascular complications is high [25;26], and a large proportion of ICU patients has cardiovascular comorbidities. Most ICU patients are in a hypermetabolic state and have varying degrees of the systemic inflammatory response syndrome. For these reasons preadmission beta-blocker use may be associated with improved prognosis in ICU patients. On the other hand beta-blockade may have detrimental effects in patients who need beta-stimulation to maintain adequate tissue perfusion.

Since virtually no data exist on the association between beta-blocker use and mortality in ICU patients we examined whether and to what extend preadmission beta-blocker use was associated with mortality within 30-days after ICU admission.

***Methods***

*Setting*

We conducted this cohort study based on prospectively collected data obtained from population-based medical databases in Northern Denmark. The study population consisted of all patients admitted for the first time to an ICU in one of three hospitals within the Aarhus University Hospital network during the study period. The ICUs are highly specialized multidisciplinary tertiary units serving as both primary and referral ICUs and together they cover all major medical specialties. The nurse patient ratio is 1:1. For study purposes, two different data collection periods were defined, based on the initial availability of computerized ICU data records: January 1, 1999 – December 21, 2005 for patients treated in Aarhus and Skejby Hospitals, and January 1, 2001 – December 31, 2005 for patients treated in Aalborg Hospital.

*ICU patients*

A research database at the University of Aarhus contain data on all admissions to the ICU's at Aarhus, Aalborg and Skejby Hospitals including patient civil registration numbers, dates of ICU admission and discharge, use of mechanical ventilation, and use of renal replacement therapy. We did not include patients in the cohort who were admitted for planned postoperative observation of less than 24 hours. Patients younger than 45 years of age were also not included because betablockers are rarely prescribed to patients in this age group in Denmark (23). This left 9,515 first-time ICU patients for further analysis. We included only patients with complete laboratory data in the main analysis. The study cohort thus encompassed 8087 patients (85% of the entire cohort) eligible ICU patients with a first ICU admission during the study period.

*Preadmission use of beta-blockers*

We collected data on all prescriptions filled by study patients since 1997 through a prescription database that contains data, transferred electronically from all pharmacies in the region, on customers' civil registration numbers, types and dosages of drugs prescribed, and redemption dates [27]. We defined current beta-blocker use as at least one filled prescription for beta-blockers within 125 days before ICU admission (for details on ATC codes, see Appendix). The 125-day period allowed us to capture most current beta-blockers users, because in Denmark few beta-blockers prescriptions are expected to last more than 125 days. In a sub-analysis we repeated the analysis after defining current use as redemption of at least one prescription within 60 days before ICU admission. Since including prevalent users in the analysis may have introduced bias we identified subgroups of "new" and "long-term" current beta-blocker users as those who had filled their first ever beta-blocker prescription within or more than 125 days before ICU admission, respectively [28]. We also categorized patients according to type of last prescribed beta-blocker before ICU admission (cardio-selective, non-selective, non-selective combined with alpha-adrenergic blocker).

*Other prognostic factors*

We identified the primary diagnosis, i.e. the first listed diagnosis in the discharge record, for the admission during which the patients were transferred to the ICUs through the Danish National Register of Patients (NRP) [29] and grouped patients into eight disease categories: infectious diseases; endocrinology (including diabetes); cardiovascular diseases; respiratory diseases; gastrointestinal and liver diseases; cancer; trauma and poisoning; and others. We classified patients as 'medical' or 'surgical' according to whether they had any surgery performed within 7 days of ICU admission. To control for comorbidity we computed the Charlson comorbidity score based on the entire previous discharge history since 1977 and defined three comorbidity levels: low (score of 0), medium (1-2), and high ($\geq 3$) [30]. Alcoholism-related disease was defined as either previous hospital diagnosis of alcoholism-related diseases (e.g. alcoholic liver disease) or redemption of prescription for disulfiram. We also retrieved information on filled prescriptions for other cardiovascular drugs including ACE-inhibitors, statins, and low-dose aspirin. From hospital laboratory databases we obtained data on the lowest level of hemoglobin, and the highest level of white blood cell count

(WBC), C-reactive protein (CRP), and creatinine registered within 2 days before or after ICU admission. We were able to retrieve all laboratory data for 8087 patients (85% of the entire cohort). As a measure of social status, we obtained data on urbanization and marital status at the time of ICU admission from the Danish Civil Registration System (CRS) [31].

*Mortality data*

To asses deaths and migration in our cohort, we accessed data from the Danish CRS [31]. The CRS contains information for the entire Danish population on migration and changes in vital status, including exact date of death, updated on a daily basis.

*Statistical analysis*

Follow-up began on the date of first-time ICU admission and continued until death, migration, 30 days after ICU admission or December 31 2006, whichever came first. We computed life table estimates for the mortality of death within 30 days.

In the main analysis we included the 8087 (85.0% of the entire cohort) ICU patients with complete laboratory data available. In a secondary analysis we included all 9,515 ICU patients and then did not control for laboratory data.

For the propensity score analysis we generated a multivariable logistic regression model that predicted beta-blocker use among ICU patients based on the covariate profile listed in table 1 and computed the propensity score (i.e. the probability of beta-blocker use) for all ICU patients. We used a greedy matching algorithm to match each beta-blocker user with the one non-user with the closest propensity score, within a maximum matching range of ±0.025. All beta-blocker users could be matched to a non-user. The propensity score matching decreased the absolute standardized differences of each covariate to values below 0.1 indicating that an adequate balance was achieved.

We then used conditional logistic regression to compute the odds ratio (OR) as a measure of relative risk of death within 30 days after ICU admission for users of beta-blockers compared with non-users in the propensity score matched cohort. We did separate analyses for subgroups defined according to admitting department, mechanical ventilation, dialysis, type of surgery, renal replacement therapy, and for users of selective and non-selective betablockers, and new and long-term beta-blockers use. We also in the propensity matched analysis controlled for all included covariates using conditional logistic regression.

To assess possible unmeasured confounding by indication for beta-blockers primarily in terms of cardiovascular diseases treated by general practitioners only we restricted analysis to patients previously hospitalized with cardiovascular diseases or diabetes. In a supplementary analysis we used logistic regression analysis to compute the OR of death for users of beta-blockers compared with non-users in the unmatched dataset, controlling for covariates listed in table 1. Finally, to assess the influence of excluding ICU patients with missing laboratory data from the analysis, we repeated the logistic regression model including all 9515 ICU patients and controlling for covariates listed in table 1, except laboratory data.

All analyses were performed using SAS version 9.1.1 (SAS Institute Inc, Cary, NC).

The study was approved by the Danish Data Protection Agency and the Aarhus University Hospital Registry Board.

***Results***

*Descriptive data*

Among the 8087 first-time ICU patients included in the main analysis, 1556 (19.2%) were current users of beta-blockers on admission (Table 1). Users of beta-blockers were generally older than non-users and had higher levels of comorbidity. Beta-blocker users were as expected more often users of other cardiovascular drugs including statins (30.1% vs. 6.4%), ACE-inhibitors (40.7% vs. 14.6%), and low-dose aspirin (21.6%

vs. 7.3%) than non-users. Propensity score matching balanced out these differences between beta-blocker users and non-users (table 1).

*Mortality*

The unadjusted risk of death within 30-days of ICU admission among beta-blocker users was 25.7% of beta-blocker users and 24.5 % among non-users [OR 1.02 (95% CI: 0.90-1.15)] (figure 1). In the propensity score analysis the risk of death was 25.7% among beta-blocker users and 31.4% among non-users corresponding to an OR among beta-blocker users of 0.74 (95% CI: 0.63–0.87) compared with non-users. Further adjustment in a logistic regression model for the variables included in the propensity score analysis left the RR estimate virtually unchanged.

The OR for death of use of non-selective beta-blockers was 0.99 (95% CI: 0.67-1.47) and 0.66 (95% CI: 0.35-1.23) and 0.70 (95% CI: 0.58-0.83) for use of non-selective beta-blockers combined with alpha-adrenergic blocker and 0.70 (95% CI: 0.58-0.83) for use of cardio-selective beta-blockers (RR 0.69 (95% CI: 0.56-0.85)). We found decreased ORs in most diagnostic categories, except for patients admitted with cancer or respiratory diseases; however, relatively few patients in these categories left the risk estimates statistically imprecise. The decreased OR of beta-blocker use was 0.57 (95% CI: 0.38-0.85) for new beta-blocker users and 0.78 (95% CI: 0.66-0.92) for long-term users. Restricting analysis to patients with diabetes or cardiovascular comorbidities revealed an OR of 0.57 (95% CI: 0.44-0.74). Among patients treated with invasive mechanical ventilation the OR for death of beta-blocker use was 0.55 (95% CI: 0.44-0.75) and OR was 0.25 (95% CI: 0.05-1.28) among those treated with renal replacement therapy.

Using a 60 day exposure window to define current beta-blocker use decreased the number of current users to revealed an OR of death of 0.74 (95% CI: 0.60-0.91).

***Discussion***

In this cohort study we found that preadmission use of beta-blockers was associated with reduced mortality within 30 days following ICU admission.

To our knowledge no data exist on whether beta-blockers use is associated with mortality in general ICU patients. However, a number of studies exist on beta-blocker use in patients with diseases or undergoing surgery which regularly require ICU admission. In line with our findings several studies reported that beta-blocker use may reduce perioperative mortality in patients undergoing major non-cardiac surgery, but no study reported separate data for ICU patients [5;8;9;32]. In contrast, the recent POISE randomized controlled trial reported that acute administration of high-dose beta-blocker therapy perioperatively was associated with a reduced risk of myocardial infarction but an increased risk of total mortality [10]. Of note, sepsis and other infections were more common causes of death among beta-blocker users than among non-users whereas there were no differences between users and non-users in deaths due to multiple organ failure, cardiogenic shock, or heart failure. Less than 30% of POISE participants were transferred to an ICU. In line with our findings a US observational study among 4117 trauma patients found that beta-blocker use was associated with reduced in-hospital mortality[19]. The authors speculated whether beta-blocker use lead to an attenuation of the detrimental effects of hyper-metabolism and increased tissue oxygen consumption related to severe trauma. Beta-blocker use has also been reported to have beneficial effects in patients with severe burns, apparently by decreasing energy expenditure and muscle catabolism[18;20].

We evaluated the effect of preadmission beta-blocker use in a large population of general ICU patients which yielded robust estimates in a large number of sub-analyses. The use of prospectively recorded data from independent medical databases with complete follow-up, limited the risk of recall, selection or surveillance bias. The completeness and nature of the prescription database used makes the measurement of preadmission beta-blocker use virtually complete[27]. Changing the exposure defining period from 125 days before ICU admission to 60 days had virtually no impact on our risk estimates. Thus, any influence of bias from

misclassification of beta-blocker due to length of exposure defining period as well as from immeasurable time bias should be minor[33;34]. The lack of random assignment of beta-blocker use may have introduced confounding. Beta-blockers are prescribed for cardiovascular diseases which are associated with an increased mortality in ICU patients and confounding by underlying diseases may have attenuated our relative risk estimates towards the null. We controlled for a wide range of covariates using both propensity score analysis and conventional regression analysis. In analyses restricted to patients with cardiovascular comorbidities and to patients admitted with cardiovascular diseases beta-blocker use was not associated with reduced mortality. Thus, residual confounding by indications of beta-blocker use is unlikely to explain our findings. Still, any lack of specificity in routinely recorded data may have reduced our ability to completely remove confounding and may have attenuated the relative risk estimates towards the null. We lacked data on in-hospital beta-blocker use which may have lead to an underestimation of the true beneficial effect of beta-blocker use.

In asthma patients long-term beta-blocker use have been reported to result in an up-regulation of beta-receptors[35]. An up-regulation of beta-receptors may be beneficial in ICU patients that require beta-stimulation to main adequate tissue perfusion. We had no data on in-hospital beta-blocker use and therefore did not address the question of whether beta-blockers initiated immediately before ICU admission is associated with mortality. However, we found more pronounced mortality reductions in new than in long-term beta-blocker users. A concern is that some of the potentially beneficial effects of beta-blockers in critically ill patients may be outweighed by a decreased oxygen supply and decreased tissue perfusion because of reduced cardiac output[21]. Further studies are therefore needed to provide data on the safety of beta-blocker treatment in ICU patients who require beta-stimulation to maintain an adequate tissue perfusion and on the effect of acutely initiated beta-blocker therapy at ICU admission.

In conclusion, preadmission beta-blocker use is associated with reduced 30-day mortality in general ICU patients.

## APPENDIX

*ATC-codes for betablockers:*

Type A: Non-selective ('C07AA02' 'C07AA03' 'C07AA05' 'C07AA06' 'C07AA07' 'C07AA16')

Type B: Non-selective combined with alpha-adrenergic blocker ('C07AG01' 'C07AG02')

Type C: Cardio-selective ('C07AB02' 'C07AB03' 'C07AB04' 'C07AB05' 'C07AB07' 'C07AB09')

Table 1. Characteristics of ICU patients, Aarhus University Hospital, 1999-2005.

| | **Overall** | | **Propensity score matched cohorts** | |
|---|---|---|---|---|
| | **No current use of betablockers N (%)** | **Current use of betablockers N(%)** | **No current use of betablockers N(%)** | **Current use of betablockers N (%)** |
| *Overall* | 6531 (80.8%) | 1556 (19.2%) | 1556 (-) | 1556 (-) |
| ***Age group*** | | | | |
| 46-60 | 2100 (32.2%) | 344 (22.1%) | 307 (19.7%) | 344 (22.1%) |
| 60-75 | 2880 (44.1%) | 740 (47.6%) | 790 (50.7%) | 740 (47.6%) |
| 75+ | 1551 (23.7%) | 472 (30.3%) | 459 (29.5%) | 472 (30.3%) |
| ***Gender*** | | | | |
| Female | 2796 (42.8%) | 598 (38.4%) | 623 (40.0%) | 598 (38.4%) |
| Male | 3735 (57.1%) | 958 (61.6%) | 933 (60.0%) | 958 (61.6%) |
| ***Diagnostic category*** | | | | |
| Infectious disease | 152 (2.3%) | 37 (2.4%) | 22 (1.4%) | 37 (2.4%) |
| Cancer | 1200 (18.4%) | 143 (9.2%) | 114 (7.3%) | 143 (9.2%) |

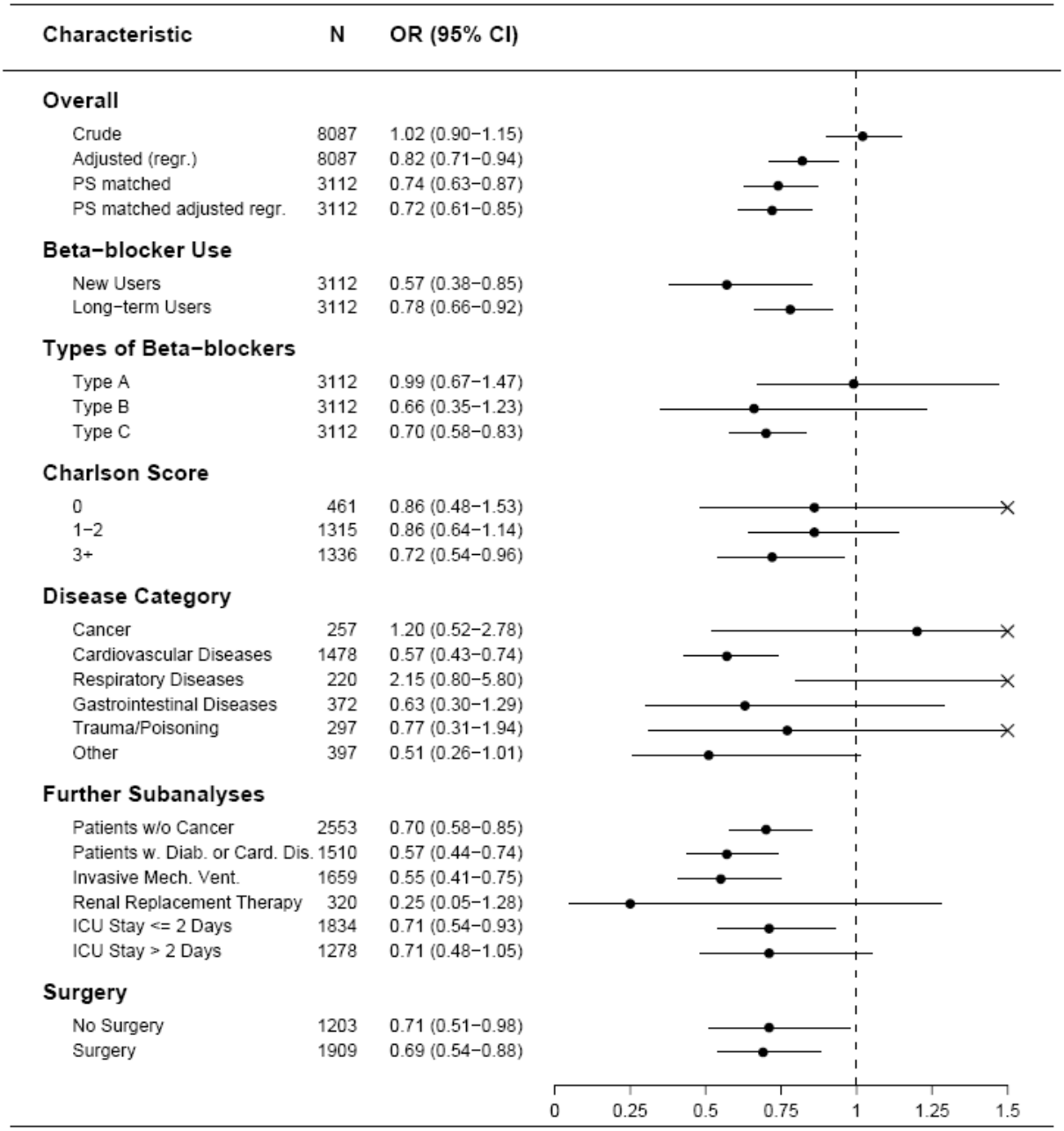
| | | | | |
|---|---|---|---|---|
| Diabetes | 88 (1.4%) | 18 (1.2%) | 14 (0.8%) | 18 (1.2%) |
| Cardiovascular | 1812 (27.7%) | 722 (46.4%) | 756 (48.6%) | 722 (46.4%) |
| Respiratory | 753 (11.5%) | 117 (7.5%) | 103 (6.6%) | 117 (7.5%) |
| Gastrointestinal | 797 (12.2%) | 176 (11.3%) | 196 (12.6%) | 176 (11.3%) |
| Trauma/poisoning | 834 (12.8%) | 137 (8.8%) | 160 (10.3%) | 137 (8.8%) |
| Others | 895 (13.7%) | 206 (13.2%) | 191 (12.3%) | 206 (13.2%) |
| ***Surgery within 7 days*** | | | | |
| No surgery | 2829 (43.3%) | 611 (39.3%) | 592 (38.1%) | 611 (39.7%) |
| Surgery | 3702 (56.7%) | 945 (60.7%) | 964 (62.0%) | 945 (60.7%) |
| ***Comorbidity*** | | | | |
| *Charlson score* | | | | |
| 0 | 1880 (28.8%) | 237 (15.2%) | 224 (14.4%) | 237 (15.2 %) |
| 1-2 | 2740 (42.0%) | 649 (41.7%) | 666 (42.8%) | 649 (41.7%) |
| 3+ | 1911 (29.3%) | 670 (43.1%) | 666 (42.8%) | 670 (43.1%) |
| *Alcoholism-related disorders* | 696 (10.7%) | 160 (10.3%) | 150 (9.6%) | 160 (10.3%) |

| | | | | |
|---|---|---|---|---|
| ***Preadmission drug use*** | | | | |
| *ACE-inhibitors* | 954 (14.6%) | 633 (40.7%) | 644 (41.4%) | 633 (40.7%) |
| *Statins* | 415 (6.4%) | 469 (30.1%) | 436 (28.0%) | 469 (30.1%) |
| *Low-dose aspirin* | 477 (7.3%) | 336 (21.6%) | 311 (20.0%) | 366 (21.6%) |
| ***Marital status*** | | | | |
| Married | 2729 (41.8%) | 671 (43.1%) | 652 (41.9%) | 671 (43.1%) |
| Never married | 476 (7.3%) | 91 (5.7%) | 88 (5.7%) | 91 (5.9%) |
| Divorced | 665 (10.2%) | 128 (8.2%) | 129 (8.3%) | 128 (8.2%) |
| Widow | 910 (13.4%) | 246 (15.8%) | 243 (15.6%) | 246 (15.8%) |
| Unknown | 1751 (26.8%) | 420 (27.0%) | 444 (28.5%) | 420 (27.0%) |
| ***Laboratory data**** | | | | |
| *Hemoglobin* | | | | |
| Low | 3049 (47.7%) | 805 (51.8%) | 771 (49.6%) | 805 (51.7%) |
| High | 3482 (53.4%) | 751 (48.2%) | 785 (50.4%) | 751 (48.3%) |
| *Leukocytes* | | | | |
| Low | 3244 (49.7%) | 787 (50.6%) | 737 (47.4%) | 787 (50.6%) |
| High | 3287 (50.3%) | 769 (49.4%) | 819 (52.6%) | 769 (49.4%) |

| | | | | |
|---|---|---|---|---|
| *C-reactive protein* | | | | |
| Low | 3318 (50.8%) | 723 (46.8%) | 703 (45.2%) | 723 (46.8%) |
| High | 3213 (49.2%) | 833 (53.2%) | 453 (54.8%) | 833 (53.2%) |
| *Creatinine* | | | | |
| Low | 3458 (53.0%) | 577 (37.1%) | 645 (41.5%) | 577 (37.1%) |
| High | 3073 (47.1%) | 979 (62.9%) | 911 (58.6%) | 979 (62.9%) |

*Laboratory data were categorized into two groups based on the medians.

Figure 1. Overall and subgroup odds ratios (OR) for death within 30 days after ICU admission among beta-blocker users and non-users.




Type A: Non-selective beta-blockers; type B: non-selective beta-blocker combined with alpha-adrenergic blocker; type C: cardio-selective beta-blocker

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