Diabetes, preadmission morbidity, and intensive care: population-based Danish studies of prognosis

PhD Dissertation

Christian Fynbo Christiansen

Health
Aarhus University

Department of Clinical Epidemiology, Aarhus University Hospital
Department of Anesthesiology and Intensive Care, Aarhus University Hospital

Supervisors

Henrik Toft Sørensen, MD, PhD, DMSc, professor (main supervisor)
Department of Clinical Epidemiology
Aarhus University Hospital, Denmark

Else Tønnesen, MD, DMSc, professor (project supervisor)
Department of Anesthesiology and Intensive Care
Aarhus University Hospital, Denmark

Steffen Christensen, MD, PhD (co-supervisor)
Department of Anesthesiology and Intensive Care
Aarhus University Hospital, Denmark

Evaluation committee

Bodil Steen Rasmussen, MD, PhD, clinical associate professor
Department of Anesthesiology and Intensive Care
Aarhus University Hospital, Aalborg, Denmark

Hans Flaatten, MD, PhD, professor
Department of Anesthesia and Intensive Care
Haukeland University Hospital, Bergen, Norway

Finn Erland Nielsen, MD, DMSc
Danish Prison and Probation Service, Copenhagen, Denmark

Preface

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

I would like to express my gratefulness to all those who made this work possible. First of all, I would like to thank Henrik Toft Sørensen for teaching me clinical epidemiology, for great mentorship, for the never-ending ideas, and for his persistent support throughout these years. I am grateful to Steffen Christensen for introducing me to the department and to the challenges of intensive care epidemiology, for his enthusiastic support, and for all the fruitful discussions. My sincere thanks go to Else Tønnesen for introducing me to research when I was as research-year student almost 10 years ago. Her untiring enthusiasm and positive attitude have inspired me during these years, and it has been a pleasure to be a part of her team. I would like to thank Martin Berg Johansen for sharing his excellent statistical skills and for his never-ending help with statistical challenges. I would like to thank James M. O'Brien for his valuable comments and suggestions regarding the diabetes and metformin studies.

My sincere thanks go to all my colleagues at the Department of Clinical Epidemiology for creating a pleasant and stimulating environment, and to my colleagues at the Departments of Anesthesiology and Intensive Care for the inspiring discussions across research areas and for pleasant company during conferences and meetings.

My warmest thanks go to my wife Anja and our children William and Ida. This work was not possible without their enduring patience, understanding, and support.

This work was made possible through financial support from the Korning foundation, the Danish Medical Research Council (Grant 271-05-0511), and from the Clinical Epidemiology Research Foundation, Denmark. The Department of Clinical Epidemiology is a member of the Danish Centre for Strategic Research in Type 2 Diabetes (Danish Research Council, Grants no. 09-075724 and 10-079102).

This thesis is based on the following papers:

I. The impact of pre-admission morbidity level on 3-year mortality after intensive care: a Danish cohort study. *Acta Anaesthesiol Scand. 2011;55(8):962-70.*

II. Type 2 Diabetes and One-year Mortality in Intensive Care Unit Patients: A Population-based Cohort Study. *Submitted.*

III. Preadmission Metformin use and Mortality among Intensive Care Patients with Diabetes: A Cohort Study. *In manuscript.*

List of abbreviations

APACHE	Acute Physiology and Chronic Health Evaluation
CCI	Charlson Comorbidity Index
CI	Confidence interval
CRS	Civil Registration System
DNRP	Danish National Registry of Patients
HbA1c	Hemoglobin A1c
HR	Hazard ratio
ICD	International Classification of Diseases
ICU	Intensive care unit
MRR	Mortality rate ratio
RCT	Randomized clinical trial
SAPS	Simplified Acute Physiology Score
SMR	Standardized mortality ratio
SOFA	Sequential Organ Failure Assessment score

Contents

1 Introduction

Intensive care units (ICUs) comprise a central part of the health care system, caring for critically ill patients in the hospitals. There are more than 30,000 ICU admissions in Denmark each year.[1] The ICUs require extensive staffing day and night and advanced technology.[2, 3] An ICU admission in Europe typically costs approximately 3000 USD,[4] but twofold more in the US, where up to 20% of hospital costs are allocated to intensive care.[5] Given the limited resources in the health care system, the cost-effectiveness of intensive care treatment is therefore important, and data on the prognosis of intensive care patients with different preadmission characteristics are needed to understand the safety of intensive care treatment, to identify patients who will benefit from intensive care, and thereby to guide ethical considerations regarding who should be offered intensive care admission.[6, 7]

The global population is ageing, with life expectancy raising from 64 years in 1990 to 68 years in 2009.[8] In Denmark, it is expected that the population over age 65 will increase during the next 20 years from 934,000 in 2011 to 1,350,000 in 2031.[9] Despite some elderly being refused ICU admission,[10] the number of very old patients admitted is increasing dramatically.[11] Many elderly patients have one or more chronic diseases that may leave them more prone to critical illness and potentially worsen the prognosis of their critical illnesses. In the USA, approximately 45% of the population has at least one chronic condition, but this prevalence is as high as 85% in those aged 65 or older.[12] Consequently, the proportion of persons with chronic conditions is expected to increase steadily in decades to come.[12] Importantly, even patients with severe chronic diseases, such as cancer, may benefit from intensive care, and patients that would not have been offered intensive care a few decades ago are now admitted to ICUs.[13-15] This change in ICU triage contributes to the increased proportion of elderly patients and patients with chronic diseases in ICUs during the last decades.[15]

One of the most frequent chronic diseases, diabetes, affected 153 million people worldwide in 1980 and 347 million people in 2008.[16] This epidemic rise in diabetes prevalence is primarily due to an increase in type 2 diabetes. Prevalence is expected to

further increase by 50% over the next 20 years[17] because of increased life expectancy and increasing prevalence of obesity, which are both risk factors for type 2 diabetes.[18, 19] Type 2 diabetes is commonly complicated by cardiovascular and kidney diseases that potentially worsen the outcome of critical ill patients admitted to an ICU. On the other hand, patients with type 2 diabetes may receive pharmacological treatments that have potential beneficial effects during critical illness. While morbidity is frequently assessed during or shortly before current hospitalization, there is a need for studies that address *preadmission morbidity*, including the impact of chronic diseases such as type 2 diabetes diagnosed several years before ICU admission.[20, 21]

The aim of the three studies in this thesis was to examine the impact on mortality of preadmission morbidity level (Study I), type 2 diabetes (Study II), and preadmission metformin use (Study III) in ICU patients.

1.1 Clinical epidemiological aspects of intensive care research

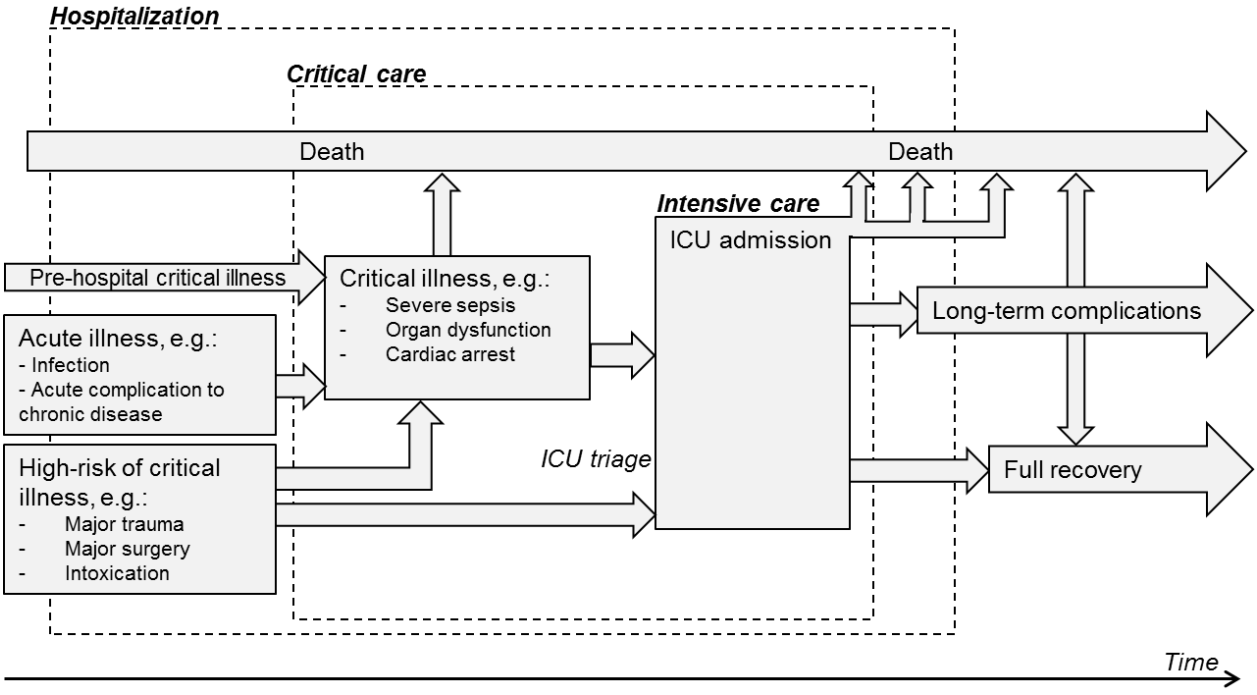
1.1.1 Introduction to intensive care

The first ICU in Denmark was established in 1953 during the polio epidemic.[22] The year before, in 1952, the Danish anesthesiologist Bjørn Ibsen treated the first polio patients with acute respiratory failure with tracheotomy and manual positive-pressure ventilation. The prognosis improved substantially for these patients, with in-hospital mortality decreasing from 87% to 40%.[23] He realized that it was necessary to have a special ward with technical equipment and trained nurses and physicians in order to observe and treat patients 24 hours a day.[24] The successful treatment of patients with respiratory failure in these new ICUs was soon extended to other patient groups. Consequently, patients who previously died of respiratory failure now survived. These patients often had multiple organ dysfunction caused by major trauma or severe sepsis.[25, 26] This, together with the improved medical and surgical treatments may explain the increasing complexity of the treatment of intensive care patients, and today intensive care units offer high-technology treatment to a wide range of patients with manifest or threatening organ-dysfunction.

1.1.2 The definition of an ICU patient

The term *intensive care* is usually restricted to patients admitted to the ICU, while *critical care* may be considered a more broad term that also includes critically ill patients outside the ICUs, e.g., on medical wards and coronary care units.[27] ICUs thus take care of critically ill patients, but not all patients with critical illness are in an ICU.[28] (Figure 1-1) Patients can be critically ill at hospital admission and be almost immediately admitted to the ICU, or can develop critical illness during hospitalization, for example due to urinary tract infection. Patients may also be admitted to the ICU for monitoring if they are at high-risk of developing critical illness, for example after major trauma or major surgery including cardiac surgery.

Figure 1-1. The relationship between critical care and intensive care.



A study population included in a cohort study of ICU patients is thus defined simply by presence at a geographical location within the hospital, and this differs from other clinical epidemiological studies that define cohorts by a disease, an exposure, or an outcome.[29]

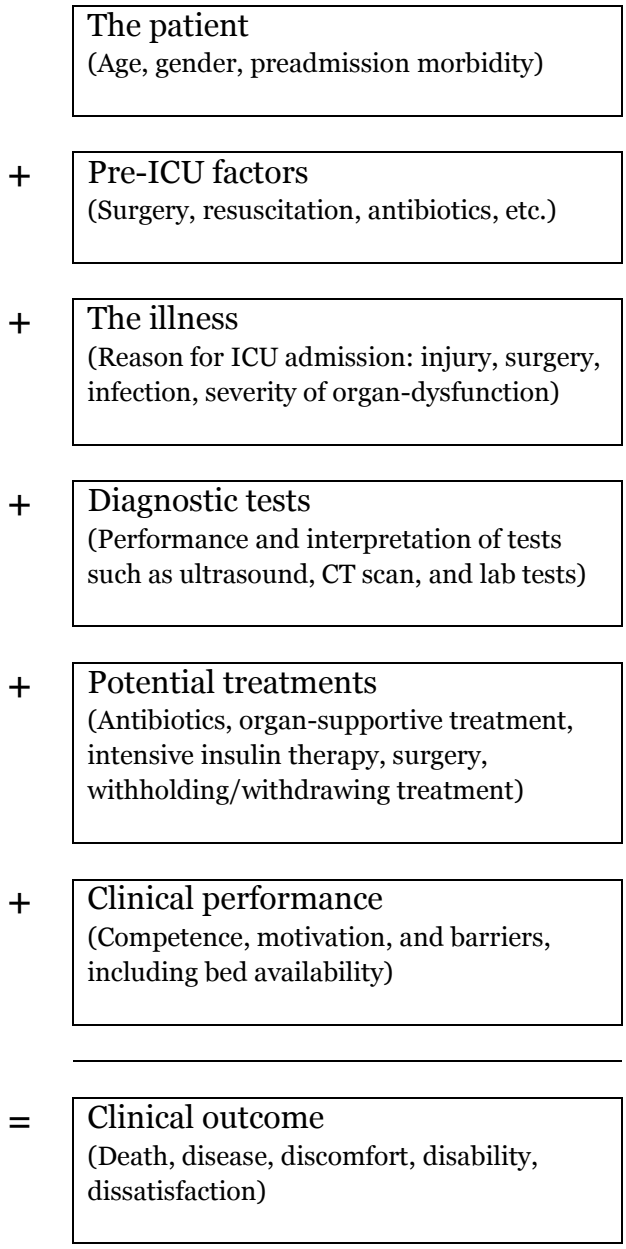
Patients in the ICU are not defined by having a particular disease (*index disease*), but rather by having manifest organ dysfunction or being at high-risk of developing organ dysfunction that requires intensive monitoring or treatment. Common organ dysfunctions in patients admitted to general ICUs include respiratory, cardiovascular, cerebral, and renal dysfunction. The expected prognosis with and without intensive care is central for triage, and at least 25% of patients considered for ICU admission are rejected because they are considered to be either too ill or too healthy to benefit from an ICU admission.[30, 31] According to US guidelines, specific diagnoses and physiological abnormalities may justify ICU admission,[32] but there are still considerable difference in triage based on individual clinical judgment and ICU capacity.[7] The lack of a European consensus may explain why the yearly number of ICU admissions in Europe ranges from 216 per 100,000 citizens in the UK to 2,353 per 100,000 citizens in Germany.[4] In Denmark, there are approximately 603 ICU admissions per 100,000 citizens (33,361 ICU admissions in 2010 within a population of 5,534,738).[1] There are no Danish guidelines for ICU admission, although the Danish National Board of Health provides some overall principles that should help the ICUs to define local admission criteria.[2] ICU patients thus comprise a heterogeneous cohort with regard to current disease (*index disease*), reason for ICU admission, preadmission morbidity, and severity of illness. These differences, often collectively denoted *case-mix,* complicate international comparisons.

1.1.3 Studying prognosis of ICU patients

Prognosis can be defined as the prediction of the outcome of an illness, an essential concept in clinical medicine.[33, 34] Death is the most widely used outcome measure in studies of ICU prognosis, but other relevant long-term outcomes of ICU admission include persistent organ dysfunction such as chronic renal failure, readmission with somatic disease, psychiatric illness, return to previous functional level, and quality of life.[35, 36] Prognostic knowledge is important in order to inform patients and their relatives, to understand the clinical course of the illness, and to guide clinical decision making.

Figure **1-2** describes factors that may influence the outcome.

Figure 1-2. Determinants of the outcome of intensive care. (Modified from *Sackett*[37])



Patient characteristics, including age and preadmission morbidity, may influence the prognosis, and a description of this influence constitutes the primary aim of this thesis. Other factors that may influence prognosis include pre-hospital and in-hospital treatment before ICU admission, e.g., early goal-directed therapy in the emergency room[38] or early

initiation of antibiotic therapy in sepsis.[39] Prognosis is also influenced by the severity of illness and reason for ICU admission. Both diagnostic tests and treatments (e.g., organ support, surgery, and medical treatment) are complicated by the critical illness and influence on the outcome. Naturally, the outcome also depends on any decision to withheld or withdraw therapy in the ICU.[7] Finally, the clinical performance of the personnel and the organization of the ICUs and bed availability would also influence outcome.

1.1.4 Prediction versus etiological studies on prognosis

Prognostic studies can be divided in prediction studies and etiological studies, but there is an overlap in many studies.[33] While data collection and analyses are almost similar, the aims are different. The aim of a prediction study is to predict outcome for future patients based on a number of available variables (e.g. at time of ICU admission) that not necessarily influence the outcome. A prediction study should be developed within one cohort and validated in another.[33, 40-42] Results from a prediction study could help defining high-risk groups and may guide clinical decision making, although they should not be used alone to decide treatment in individual patients. Classic examples of prediction studies used in ICU patients include severity of illness scores, such as the Acute Physiology And Chronic Health Evaluation (APACHE), and simplified acute physiology score (SAPS) scores developed to predict risk of in-hospital death.[43-45]

In contrast, the etiological (or causal) study has a well-defined hypothesis about a potential causal association between an exposure and an outcome. The association may be confounded by other variables, which should be considered and handled appropriately in order to provide valid estimates of a potential causal association. As an example, a cohort study of ICU patients with septic shock hypothesized that early combination antibiotic therapy was associated with lower 28-day mortality compared with monotherapy.[39] The two intervention groups differed with regard to age, preexisting diseases, co-interventions, infection site, etc. After this confounding was handled, the hazard ratio moved from 0.57 (95% CI: 0.51–0.63) to 0.77 (95% CI: 0.67-0.88).

Data on prognostic factors may improve our understanding of critical illness in ICU patients, may help us define risk groups, and may guide the design of subsequent clinical trials.[34] The three studies in this thesis are designed as etiological (causal) studies.

1.1.5 Observational studies versus randomized clinical trials

The randomized clinical trial (RCT) is commonly considered the gold standard in clinical research and superior to non-randomized (observational) studies when the outcome is effect of an intervention.[46] But not all research questions can be answered in a trial, including our question about the prognostic impact of morbidity level and diabetes. Even when an intervention could be studied in a randomized design, observational studies can often be a reasonable alternative, especially when the outcomes are negative effects or adverse events.[47] The randomized assignment of an intervention prevents confounding and information bias if the trial is adequately large, but with the heterogeneity of ICU patients, this often requires inclusion of thousands of ICU patients for all confounders to be equal or requires several restrictions of the study cohort to make it homogenous. Randomized trials are therefore very expensive and may have limited generalizability. Results from RCTs with restricted ICU populations are often difficult to reproduce.[48] As an example, the beneficial effect of intensive insulin therapy in a single-center study of mainly surgical ICU patients[49] could not be reproduced in subsequent multi-center studies.[50, 51]

In contrast to RCTs, observational studies may better reflect daily practice, and if confounding and bias are adequately handled, these may have advantages in the ICU population,[48] as summarized in Table 1-1 below. Another advantage is the possibility to study exposure prior to critical illness, such as preadmission metformin use, which is otherwise only possible to study in randomized studies of patients that are expected to be admitted to the ICU after major surgery.

In conclusion, the RCT is still the gold standard in studies of the causal effects of interventions, although application of RCTs in the ICU population is hampered by the heterogeneity of ICU patients. Well-designed observational studies are feasible alternatives and have advantages in ICU populations, for example, by representing an unrestricted, real-life setting.

Table 1-1. Strengths and limitations of randomized trials and observational studies. (modified from *Sørensen et al.*[47])

	Randomized clinical trial	**Observational study**
Study population	Typically restricted by exclusion criteria	Typically all ICU patients
Ethics	Informed consent needed	Ethical concerns limited as there are no interventions
Cost	High	Low if existing data are used
Heterogeneity	Reduced by restriction	More heterogeneous
Exposure	1-2 interventions	No limits
Exposure assignment	Randomly assigned	Non-randomly assigned (observed)
Blinding	Possible	Impossible
Outcome measures	Well-defined	Depend on available data
Rare outcome	Cost-intensive, typically not feasible	Larger studies are more feasible
Selection bias	Can be a problem if eligible patients differs from non-eligible, e.g. by inclusion of selected ICUs	Depend on completeness of ICU registration and follow-up
Information bias	No major problem	Depend on data quality
Confounding	Limited. Confounders equal distributed in large studies	Unmeasured and residual confounding may be a major problem
Generalizability	Difficult and only to the restricted patient population. Reproducibility in less restrictive ICU populations often fails.	Good (to similar ICUs) because the population typically includes all ICU patients.

1.2 Background and existing literature

1.2.1 Preadmission morbidity level among ICU patients

Chronic diseases are increasingly common, also among ICU patients.[15] Several scores developed to predict in-hospital mortality, for example the APACHE[43] and the SAPS scores,[44, 52] include severe chronic diseases, such as metastatic cancer, severe heart failure, and liver cirrhosis. The importance of chronic diseases was also underlined by the recent PREDICT study in which the widely used Charlson Comorbidity Index (CCI) was found to be one of the most important predictors of long-term mortality.[53] We previously found that the CCI together with age and gender may be almost as good in predicting 30-day mortality as the APACHE II, SAPS II, and SAPS III scores.[54] In 2003, an expert panel proposed the PIRO concept (acronym for Predisposition, Infection/Insult, Response, Organ Failure) and acknowledged that preadmission chronic disease may affect the prognosis of severe sepsis.[19, 28] This concept was proposed to be used in severe sepsis, like the TNM classification in cancer.[19, 55] The concept has recently been applied as a prediction model in which predisposing factors for death include age, gender, congestive failure, pulmonary disease, diabetes, malignancy, and renal disease.[26, 56]

Despite the predictive importance of chronic diseases, there are very few prognostic studies addressing the influence of preadmission morbidity level and specific chronic diseases on mortality among ICU patients, and the terminology is conflicting. *Comorbidity* is probably the most widely used term and is defined as the presence of one or more diseases that exist together with an index disease.[21] However, the ICU population is not characterized by a single index disease because ICU patients have many different diseases, some being complications to underlying chronic diseases. We therefore used the term *preadmission morbidity level* to describe the burden of chronic diseases including diagnoses within five years before, but not during, the index hospitalization.

We assessed preadmission morbidity level using the CCI.[20, 57, 58] The advantage of a comorbidity index is the ability to summarize several diseases into a single score.[59, 60] This is widely used to control for confounding in observational studies, but can also be used as the exposure or outcome.[59, 60] Originally, the aim of the CCI was to predict one-year mortality.[57] It was developed using records from 559 medical patients admitted to a New

York hospital during one month in 1984 and validated using a historic cohort of 685 breast cancer patients.[57] The final CCI included 19 diseases weighted according to the integer of the coefficients from the regression model. The included diseases are presented in Figure 1-3. While the original index used medical record data, it has subsequently been adapted to administrative databases using ICD-8, ICD-9, and ICD-10.[20, 58] This application to administrative databases is an important strength, also for critical care research.[61]

Figure 1-3. Diseases included in the Charlson Comorbidity Index.[57]

Disease	Score
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Connective tissue disease	1
Peptic ulcer disease	1
Mild liver disease	1
Diabetes type 1 and type 2	1
Hemiplegia	2
Moderate to severe renal disease	2
Diabetes with end organ damage, type 1 and type 2	2
Any tumor	2
Leukemia	2
Lymphoma	2
Moderate to severe liver disease	3
Metastatic solid tumor	6
Acquired Immunodeficiency Syndrome (AIDS)	6

1.2.1.1 Existing literature on the mortality impact of preadmission morbidity level among ICU patients compared with the general population

Data on the prognostic impact of preadmission morbidity level are needed not only to understand the clinical course in ICU patients, but also to plan the needed ICU capacity in the future. To better understand the impact of morbidity on prognosis in ICU patients, it is relevant to compare the impact with the prognostic impact of morbidity in the general population. No previous studies have undertaken such a comparison and we therefore separately reviewed the literature examining: 1) mortality following ICU admission compared with mortality in the general population, 2) the mortality in ICU patients with different CCI levels.

We first identified studies comparing mortality among ICU patients with mortality in the general population. Medline was searched using the following query: ("Intensive Care"[Mesh] OR "Critical Care"[Mesh]) AND "mortality"[Mesh] AND "general population".

This gave 16 hits, with three of them relevant. Review of the reference lists of these papers and papers citing these revealed another five studies. (Table 1-2)

Table 1-2. Studies comparing mortality in ICU patients with survival in the general population.

Author, publication year, reference	Country	N	Design	Patients	Setting, study period	Follow-up time	Outcome measure of interest	Result
Timmers TK, 2011 [62]	The Netherlands	1,822	Cohort study	Surgical ICU patient, ≥ 18 years	Surgical ICU in a single hospital, 1995–2000	Up to 10 years	10-year mortality	51% in ICU patients and 27% in general population with same age and sex distribution
Wright JC, 2003 [63]	Scotland	2,104	Cohort study	All ICU patients (no neurosurgical and pediatric patients <16 years)	Single ICU, 1985–1992,	5-12 years	Mortality, standardized mortality ratio (SMR)	5-year mortality 47.1% in ICU patients. Overall SMR = 3.4 (using age- and sex-specific death rates in the general population). SMR was highest within the first years, but close to 1.0 after 4 years.
Niskanen M, 1996 [64]	Finland	12,180	Cohort study	Adult ICU patients ≥ 15 years	25 ICUs (~ 75% of ICU admissions in Finland), 1987	4-5 years	Mortality, SMR	5-year mortality 40.1%. SMR = 3.3 (95% CI: 3.0–3.4), but mortality in ICU patients paralleled the general population after 2 years.
Williams TA, 2008 [65]	Australia	19,921	Cohort study	ICU patients alive at hospital discharge	Single ICU, 1987–2002	Up to 15 years	SMR	First year SMR = 2.9 (95% CI: 2.7–3.1), subsequent year SMR ~1.5 (during the remaining follow-up period)

Table 1-2. Studies comparing mortality in ICU patients with survival in the general population.

Author, publication year, reference	Country	N	Design	Patients	Setting, study period	Follow-up time	Outcome measure of interest	Result
(continued…)								
Flaatten H, 2001 [66]	Norway	219	Cohort study	All ICU patients	Single ICU, 1987	12 years	Survival estimates, survival difference	12-year survival 48.4% in ICU patients and 77.7% in the general population. Survival difference was 6.3% (95%CI: -0.7%–13.4%) in the period after 2 years of follow-up.
Zaren B, 1989 [67]	Sweden	980	Cohort study	All adult ICU patients ≥ 15 years, >1 hour in the ICU	Single general ICU, 1983	2 years	Survival estimates, relative survival rate	One month survival 84.9%, one-year survival 73.6%. Observed vs. expected survival was 0.85 (95% CI: 0.83–0.87) for 0-1 month, 0.92 (95% CI: 0.90–0.94) for months 1–6, 0.96 (95% CI: 0.94–0.97) for months 6–12 and very similar thereafter.
Dragsted L, 1990 [68]	Denmark	926	Cohort study	ICU patients surviving to hospital discharge	Single ICU, 1979-1983	5 years	Relative mortality	5-year mortality 5 times higher in ICU patients than general population
Wunsch H, 2010 [69]	USA	35,308	Cohort study	ICU patients surviving to hospital discharge	Medicare sample, 2003	3 years	Mortality, hazard ratio (HR) for death	3-year mortality was 39.5% in ICU patients and 14.9% in general population cohort (adjusted HR = 2.39, 95% CI: 2.31–2.48).

The table illustrates that there are conflicting results from the eight studies that examined whether ICU admission was a predictor of long-term mortality. Four Nordic studies with sample sizes ranging from 236 to 12,180 ICU patients consistently reported increased mortality from 6 months to 2 years after intensive care compared with the general population, but not thereafter.[64, 66-68] A Scottish study found that mortality among patients who had received care in an ICU was comparable to the general population after 4 years.[63] A recent US cohort study that followed elderly ICU patients for up to 3 years found increased 3-year mortality among ICU patients who survived until hospital discharge, compared with the general population.[69] An Australian study found persistently increased mortality for up to 15 years among ICU patients discharged alive.[65] Also, a Dutch study including surgical ICU patients found approximately two-fold increased mortality during the 10-year study period.[62] Although preadmission morbidity has an important impact on mortality among ICU patients, only one of the studies compared morbidity levels with the population comparison cohort and found markedly higher morbidity level among ICU patients.[69]

We therefore did a supplementary literature search to identify studies on CCI level and mortality among ICU patients. We searched Medline using the following queries:

- ("Intensive Care"[Mesh] OR "Critical Care"[Mesh]) AND "Chronic disease"[Mesh] AND "Mortality"[Mesh] (25 hits)
- ("Intensive Care"[Mesh] OR "Critical Care"[Mesh]) AND "Comorbidity"[Mesh] AND "Mortality"[Mesh] (65 hits)
- ("Intensive Care"[Mesh] AND "Critical Care"[Mesh]) AND "Chronic Disease"[Mesh] (119 hits)
- ("Intensive Care"[Mesh] AND "Critical Care"[Mesh]) AND "Comorbidity"[Mesh] (131 hits)
- ("Intensive Care"[Mesh] OR "Intensive Care Units"[Mesh]) AND "Mortality"[Mesh] AND ("Chronic Disease"[Mesh] OR "Comorbidity"[Mesh]) 241 hits

Only three studies were found relevant after review of titles and abstracts.[53, 65, 70] Two of these were causal studies and one was a prediction study. Another causal study was found

in the reference list of another study.[71] All found high CCI to be associated with an increased mortality. (Table 1-3)

An Australian cohort study on long-term prognosis of 22,980 ICU patients found a CCI score of 0 in 55% of the ICU patients, 1–2 in 33%, and 3 or more in 12% of ICU patients, using diagnoses recorded within 5 years before ICU admission.[70] ICU patients with a CCI of 3 or more had markedly increased 1- and 3-year mortality compared with patients with a CCI of 0.[70] In the study including the 19,921 of the ICU patients who survived to hospital discharge, CCI was a predictor for mortality after adjustment for confounders including age and gender.[65] Also in the PREDICT study, a high CCI score of 5 or more was an important predictor of long-term mortality.[53] Another Australian single-center study of 2,022 ICU patients found that the excess hazard for post-discharge death compared with the general Australian population increased with increasing CCI level.[71]

To summarize, mortality was markedly higher in ICU patients compared to the general population, at least for the first years after the ICU stay. Among ICU patients, preadmission morbidity was associated with a markedly higher long-term mortality rate.

1.2.1.2 Limitations of the existing literature

Most previous studies included data that are now 10 to 25 years old; a period in which treatment of chronic diseases has changed dramatically as has the composition of ICU patients. The results may therefore not be applicable today. Only one study included data on preadmission morbidity in the general population comparison cohort, but none of the previous studies examined potential interaction, i.e., whether preadmission morbidity had the same impact on mortality in ICU patients as it did in the general population.

Table 1-3. Studies on the impact of preadmission morbidity level on mortality in ICU patients. (CCI: Charlson Comorbidity Index)

Author, publication year	Country	N	Design	Patients	Setting, study period	Follow-up time	Outcome measure of interest	Result
Williams TA, 2006 [70]	Australia	22,980	Cohort study	All ICU patients	Single ICU, 1987–2002	Up to 15 years	Survival estimates	1-year survival 86.6% for CCI = 0, 84.8% for CCI = 1–2, and 67.9% for CCI = 3+. Corresponding 3-year survival was 83.1% (CCI = 0), 78.8% (CCI = 1–2), 58.1% (CCI = 3+).
Ho KM, 2008 [53]	Australia	11,930	Cohort study (prediction study)	ICU patients surviving >5 days	Single ICU, 1989–2002	Up to 15 years	Hazard ratio (HR) for death	HR for CCI 5 vs. 0 was 2.15 after adjustment for other predictors.
Williams TA, 2008 [65]	Australia	19,921	Cohort study	ICU patients alive at hospital discharge	Single ICU, 1987–2002	Up to 15 years	Hazard ratio for death	Adjusted HR for CCI = 3+ was 2.67 (95% CI: 2.45–2.90), and 1.48 (95% CI: 1.39–1.57) for CCI = 1–2, both compared to CCI = 0. The corresponding adjusted HRs restricted to 1 year post discharge was 3.98 (95 %CI: 3.38–4.68) and 2.02 (95% CI: 1.73–2.35), respectively.
Ghelani D, 2009 [71]	Australia	2,022	Cohort study	All ICU patients	Single ICU, 1993–1999	4.2–9.6 years	Excess hazard ratio (compared with general population)	Compared to CCI = 0, excess HR for CCI = 1 was 2.1 (95%CI: 1.9–2.3), for CCI = 2: 3.7 (95% CI: 3.3–4.1), CCI = 3: 3.9 (95% CI: 3.1–4.8).

1.2.2 Type 2 diabetes and mortality among ICU patients

Almost 10% of the world population has diabetes,[16] but among ICU patients the prevalence may be as high as 19%.[72] Still, this prevalence of diabetes in ICU patients may be overestimated by misclassification of stress hyperglycemia as diabetes during current hospitalization.[73] The relative prevalence was, however, confirmed by our finding of more than a two-fold higher prevalence of a prior hospital diagnosis of diabetes in ICU patients compared with the general population (Study I).[74] Diabetes is most often a comorbidity in ICU patients and is only occasionally the reason for ICU admission, for example in patients with severe diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome.[75]

Diabetes is associated with immune dysfunction[76, 77] and hypercoagulation,[78, 79] which may contribute to the increased risk of acute kidney injury,[80] cardiovascular events,[81-83] pneumonia,[84] and in some studies also bacteremia.[85-87] All these conditions may lead to ICU admission. In contrast, the attenuated immune response may potentially protect against organ dysfunction including acute lung injury, which is characterized by an overwhelming inflammatory response.[88-91]

Despite a potentially increased risk of critical illness, data on the effect of diabetes on outcome of critical illness are limited and conflicting. Diabetes is associated with increased mortality in patients with specific critical illnesses such as myocardial infarction,[92, 93] cardiac surgery,[94] and complicated peptic ulcer,[95] while such an association is less clear in patients with burns,[96] trauma,[97] pneumonia,[98, 99], sepsis,[86, 100] and bacteremia.[86, 101, 102] During the last 10 years, several studies examined the prognostic impact of hyperglycemia and therapeutic effects of intensive insulin therapy in ICU patients, both of which seem to have less impact in patients with diabetes than in patients without diabetes.[103-106] These topics are, however, beyond the scope of this thesis.

Type 2 diabetes is commonly complicated by micro- and macrovascular complications, including chronic kidney disease[107, 108] and cardiovascular disease,[81] that may affect the outcome of critical illness. End-stage renal disease is associated with a poor prognosis among ICU patients.[109-111] This may be mediated through an increased risk of acute kidney

injury,[80] although the mortality of patients with acute kidney injury is not further increased by end-stage renal disease.[112, 113] Heart failure may also be a predictor of increased mortality in ICU patients.[114] Indeed, both diabetes and heart failure are associated with increased 90-day mortality in ICU patients with end-stage renal disease.[111]

A recent systematic review and meta-analysis of observational and interventional studies included 141 studies that described short-term mortality in adult ICU patients and provided data on diabetes.[72] Thirty-day (28- or 30-day) mortality was reported in 20 of the studies (19,040 patients), but the overall odds ratio for death was still imprecise (OR = 1.19, 95% CI: 0.96–1.47), while it was more clearly increased in surgical ICU patients (OR = 1.62, 95% CI: 1.13–2.34). The wide confidence intervals may be explained by the heterogeneity of the included studies, and the use of a random effects model.[115] Only one of the included studies specifically aimed at studying the impact of diabetes,[116] and the meta-analysis therefore relied primarily on studies that did not control for confounding. Importantly, any misclassification of diabetes status in the included studies would also bias the overall result of the meta-analysis.

1.2.2.1 Existing literature on the effect of diabetes on mortality among ICU patients

In the literature review, we focused on studies that had the primary aim of studying the impact of diabetes on mortality among ICU patients. We searched Medline using the following query:

- ("Intensive Care"[Mesh] OR "Intensive Care Units"[Mesh]) AND "Diabetes Mellitus"[Mesh] AND "Mortality"[Mesh]

A total of 65 articles were identified, and titles and abstracts were reviewed to identify studies examining the effect of diabetes on mortality in ICU patients. We did not include prediction studies, studies on intensive insulin therapy, and studies on the prognostic impact of glucose level. We found three studies that specifically examined the overall impact of diabetes on mortality in ICU patients. (Table 1-4)

Table 1-4. Studies on the impact of diabetes on mortality in ICU patients.

Author, publication year, reference	Country	N	Design	Patients, data source	Setting, study period	Follow-up time	Outcome measure of interest	Result
Stegenga, 2010[117]	Multinational (11 countries)	830	Cohort study	Patients with severe sepsis included in a previous trial[118]	164 centers, July 1998–June 2000	Up to 90 days	28- and 90-day mortality	28-day mortality: 31.4% in diabetic and 30.5% in non-diabetic patients 90-day mortality: 39.1% and 39.0%
Graham, 2010[116]	USA	1,509,890 + 36,414	Cohort study	Patients aged 18 years or older without acute diabetic complications. Identified in University Health System database (UHC) + Mayo cohort	130 centers, January 2003–December 2006 (1999–2007 for Mayo cohort)	To hospital discharge	In-hospital mortality, age-adjusted odds ratio	Mortality in diabetic patients was 8.8% and in non-diabetic 9.7% in the UHC cohort and 10.3% vs. 9.7% in the Mayo cohort. Adjusted OR = 0.79 (95% CI: 0.78–0.80) in the UHC and 1.01 (95% CI: 0.92–1.11) in the Mayo cohort.
Vincent, 2010[119]	24 European countries	3,147	Cohort study	Adult ICU patients included in the Sepsis Occurrence in Acutely ill Patients (SOAP) study	198 centers, 1 – 15 May 2002	To hospital discharge but no longer than 28 days	Hospital mortality, adjusted hazard ratio (HR)	Hospital mortality, 28% in insulin-treated diabetic ICU patients and 24% in other ICU patients. Adjusted HR = 0.78 (95% CI: 0.58–1.07)

A US cohort study including more than 1.5 million ICU patients, primarily included from the University Health System Consortium's benchmarking database, reported in-hospital mortality of 8.8% in diabetics and 9.7% in nondiabetics, corresponding to an age-adjusted odds ratio of 0.79.[116] However, the age-adjusted odds ratio was 1.01 (95% CI: 0.92–1.11) in a subcohort of patients in the Mayo Clinic.[116] In a European study of 3,147 patients from 198 ICUs, insulin-treated diabetes was associated with slightly increased crude in-hospital mortality (28% vs. 24%, corresponding to a crude relative mortality risk of 1.17). The hazard ratio for hospital mortality within 28 days was 0.78 (95% CI: 0.58–1.07) after adjustment for age, liver cirrhosis, SAPS II score, and mechanical ventilation.[119] A multinational cohort study included 830 patients with severe sepsis from the control arm of a multicenter trial conducted in 1998–2000.[117, 118] The 28-day mortality rates were very similar in diabetic (31.4%) and nondiabetic patients (30.5%).[117]

In conclusion, the previous three studies found no association between diabetes and mortality among intensive care patients. This finding was surprising because diabetes patients were older and had a greater severity of illness at ICU admission.[116, 117, 119] Suggested mechanisms include protective biological effects of diabetes and antidiabetic treatment,[89, 120] miscoding of diabetes, or better care of diabetes patients during both acute critical illness and chronic disease.[116]

1.2.2.2 Limitations of the existing literature

The earlier studies were limited by lack of data regarding diabetes type and complications [116, 117, 119], lack of hemoglobin A1c (HbA1c) data to identify diabetes [116, 117, 119], adjustment for factors influenced by diabetes (intermediate steps in the causal pathway),[119] and potential selection bias due to restricted inclusion criteria.[117] Finally, the two larger studies reported only in-hospital mortality,[116, 119] and none had long-term follow-up beyond 90 days.[116, 117, 119] None were conducted within a uniform population-based hospital setting.[116, 117, 119]

1.2.3 Metformin treatment of type 2 diabetes and mortality among ICU patients

1.2.3.1 Metformin

Metformin is an oral antidiabetic drug used in the treatment of type 2 diabetes.[121, 122] The use increased dramatically after 1998, when the UK Prospective Diabetes Study (UKPDS) found reduced all-cause mortality and cardiovascular event rate among metformin users compared with users of other antidiabetic drugs including sulfonylurea.[123, 124]

Metformin has pleiotropic effects.[121, 125] The hypoglycemic effect of metformin is mediated through reduced glucotoxicity in pancreatic islet cells, increased peripheral glucose uptake, and decreased hepatic gluconeogenesis.[126] Metformin also has anti-inflammatory effects, such as decreased neutrophil activation and attenuation of mitochondrial derived reactive oxygen species after exposure to bacterial lipopolysaccharide (LPS) in vitro.[120] LPS infusion induces a systemic inflammatory response like sepsis.[127] In mice exposed to LPS, metformin reduces severity of acute lung injury, release of proinflammatory cytokines, expression of adhesion molecule genes, and mortality.[120, 128-130] The potential anticoagulant and vascular effects of metformin include increased fibrinolysis, reduction in coagulation factors VII and XIII, stabilization of platelet function, and increased post-ischemic blood flow.[131]

Hyperinflammation and procoagulation are central to the pathogenesis of sepsis and multiple organ dysfunction, which are common among intensive care patients.[89, 127, 132] Because sepsis is characterized by an early phase of immune activation followed by a phase of immune suppression, we would expect that the anti-inflammatory effect of metformin would be beneficial if the drug is administered before or early after onset of critical illness.[127, 133, 134]

Treatment with metformin after onset of critical illness is usually avoided because of the feared risk of lactic acidosis, and metformin is therefore often discontinued on admission to hospital.[125] The suggested mechanism behind lactic acidosis is inhibition of

gluconeogenesis, which has lactate as one of its substrates.[135] However, the fear of lactic acidosis arose with the previously used phenformin (a predecessor of metformin) that, in contrast to metformin, increased peripheral lactate production. Although lactic acidosis is reported in metformin users, the rate is reported to be as low as 4.3 per 100,000 person-years, which may actually be similar to the situation in other type 2 diabetic patients (5.4 per 100,000 person-years).[136] We only found four (0.2%) metformin users with a primary diagnosis of lactic acidosis (Study II). Is has been suggested that metformin may be safely used in conditions like mild to moderate chronic kidney failure, a condition in which metformin use was also considered to be associated with increased risk of lactic acidosis.[137]

There are limited clinical data on metformin use before and during critical illness. Metformin decreases insulin sensitivity when added to intensive insulin therapy.[138] A potential cardioprotective effect[139] may explain the decreased mortality and complications after coronary intervention.[140] However, metformin has no major impact on mortality following acute myocardial infarction.[141-143] In Denmark, most patients with acute myocardial infarction are treated in coronary care units outside the ICUs. In contrast to patients with acute myocardial infarction, ICU patients often have severe systemic inflammation, and any anti-inflammatory properties of metformin may have beneficial effects in these patients.

1.2.3.2 Existing literature on metformin and mortality among ICU patients

The primary aim of the literature search was to identify studies on the impact of metformin on mortality in ICU patients. We did not include case reports on lactic acidosis.

We searched Medline using the following query:

- ("Intensive Care"[Mesh] OR "Intensive Care Units"[Mesh]) AND "Metformin"[Mesh]

This revealed nine hits. There were no human studies on the impact of metformin on mortality among ICU patients. Only one had some relevance by showing that the combination of intensive insulin therapy with metformin decreased insulin resistance, but the study did not include mortality as an outcome.[138]

Next, we widened the search to include sepsis patients and perioperative patients, because these patients are commonly admitted to the ICU.

We searched using the following Medline query:

- "Sepsis"[Mesh] AND "Metformin"[Mesh]

This revealed four hits, none of which were relevant. Three were animal studies, and one was a case-report of lactic acidosis.

- ("General Surgery"[Mesh] OR "Surgical Procedures, Operative"[Mesh]) AND "Metformin"[Mesh]

This search revealed 163 hits, but after review of these, only one human study was relevant. (Table 1-5)

Duncan et al. included 1,284 diabetic patients who underwent cardiac surgery between 1994 and 2004 from a registry at the Cleveland Clinic in Ohio, USA.[144] Among these, 524 received metformin preoperatively, i.e., until the night before surgery. After propensity score matching of 443 metformin users to 443 non-users, mortality was 0.7% in metformin-treated and 1.4% in non-metformin treated, corresponding to an odds ratio of 0.5 (95% CI: 0.1–2.0). Also, cardiac complications were less frequent in metformin-treated patients (0.5% vs. 1.4%, OR = 0.3 (95% CI: 0.1–1.7)). There was no evidence of metabolic acidosis in metformin-treated patients. The main limitation of the study is the imprecise estimates that hamper interpretation of the data.

In conclusion, metformin has potential beneficial anti-inflammatory effects in ICU patients and may be associated with reduced complications and mortality after cardiac surgery.

1.2.3.3 Limitations of the existing literature

There are no previous studies on the impact of metformin treatment on mortality among ICU patients. The only study on preadmission metformin use before cardiac surgery provided only imprecise in-hospital mortality estimates because of the low number of outcomes.

Table 1-5. The study on preadmission metformin use and prognosis among cardiac surgery patients.

Author, publication year, reference	Country	N	Design	Patients	Setting, study period	Follow-up time	Outcome measure of interest	Results
Duncan AI, 2007 [144]	USA	1,284 (884 in matched analysis)	Cohort study, propensity score matched	Patients receiving oral antidiabetic drugs who were hospitalized the day of cardiac surgery	Single center, 1994–2004	To hospital discharge	In-hospital mortality, complications (cardiac, renal, respiratory, neurological, infection)	Mortality 0.7% vs. 1.4%, OR = 0.5 (95% CI: 0.1–2.0). Overall OR for complications 0.4 (95% CI: 0.2–0.8)

2 Aims of the thesis

- To examine the prevalence of preadmission morbidity in ICU patients and in an age- and sex-matched sample of the general population. Furthermore, to examine the impact of preadmission morbidity on mortality within 3 years of ICU admission compared with the impact of morbidity on mortality in the general population. (Study I)
- To examine the impact of uncomplicated and complicated type 2 diabetes on mortality in ICU patients. Additionally, to examine how covariates influenced the association. (Study II)
- To examine the association between preadmission metformin use and mortality in ICU patients. Additionally, to examine how covariates influenced the association. (Study III)

3 Patients and methods

3.1 Setting

We conducted the three studies within the population of Northern Denmark (Central Denmark Region and North Denmark Region), a mixed rural-urban area with approximately 1.8 million citizens (approximately 33% of the Danish Population).

Denmark has a national tax-supported health care system. All acute care is provided by public hospitals and none of the few private hospitals in Denmark have intensive care units.

3.2 Data sources

We obtained data from existing population-based registries and databases. All Danish citizens are assigned a unique personal identifier (the civil registration number or CPR number) at birth or immigration.[145] This allowed unambiguous electronically linkage of the data sources described below.[146]

3.2.1 The Intensive Care Cohort of Northern Denmark

We assembled a cohort of all adult patients aged 15 years or older living in Northern Denmark admitted to an ICU in the study period from 1 January 2005 to 31 December 2010, using the Danish National Registry of Patients (DNRP). (Characteristics of the cohort are illustrated in Table 3-1) The study period was chosen because data on intensive care were not registered routinely before 2005.[147] We restricted the cohort to patients who lived in the study area, because we wanted complete medical, laboratory, and prescription history that were only available in the study area.

There are 17 ICUs in this area. Nine are highly specialized or multidisciplinary (general) ICUs located at Aarhus University Hospital in Aarhus and Aalborg, and eight are multidisciplinary ICUs at regional hospitals in Horsens, Randers, Silkeborg, Holstebro, Herning, Hjørring, Viborg, Thisted, and Hobro.

We identified the patients first ICU admission in the study period by a procedure code for ICU admission (Danish procedure codes NABB or NABE) registered in the DNRP. Date

of ICU admission was defined as the date of procedure coding. We also included procedure codes for any treatments with mechanical ventilation, renal replacement therapy (acute dialysis or hemofiltration), or inotropes/vasoactive drugs. The reason for ICU admission was considered surgical if the patient had a surgical procedure registered in the DNRP on day of ICU admission or within 7 days before.[44] All other patients were considered medical ICU patients. We defined diagnostic category by the first-listed diagnosis during current hospitalization as a proxy for ICU admission diagnosis. The cohort is described in Table 3-1.

Table 3-1. Characteristics of the 46,630 adult patients admitted to ICUs in Northern Denmark 2005–2010.

	15–39 years	40–59 years	60–79 years	80+ years	Total
	n = 7,197 (%)	n = 11,229 (%)	n = 21,546 (%)	n = 6,658 (%)	n = 46,630 (%)
Charlson Comorbidity Index					
0	6,390 (88.8)	7,200 (64.1)	10,111 (46.9)	3,184 (47.8)	26,885 (57.7)
1–2	588 (8.2)	2,793 (24.9)	7,909 (36.7)	2,507 (37.7)	13,797 (29.6)
3+	219 (3.0)	1,236 (11.0)	3,526 (16.4)	967 (14.5)	5,948 (12.8)
Preadmission diabetes					
Type 1 diabetes	189 (2.6)	146 (1.3)	1 (<0.1)	0 (0.0)	336 (0.7)
Type 2 diabetes	143 (2.0)	1,094 (9.7)	3,861 (17.9)	1,072 (16.1)	6,170 (13.2)
Diagnostic category (current admission)					
Pneumonia	67 (0.9)	285 (2.5)	695 (3.2)	301 (4.5)	1,348 (2.9)
Infectious diseases excluding pneumonia	723 (10.0)	1,013 (9.0)	1,600 (7.4)	593 (8.9)	3,929 (8.4)
Diabetes	127 (1.8)	110 (1.0)	91 (0.4)	29 (0.4)	357 (0.8)
Endocrinology excluding diabetes	98 (1.4)	263 (2.3)	230 (1.1)	59 (0.9)	650 (1.4)
Cardiovascular diseases	360 (5.0)	2,679 (23.9)	7,425 (34.5)	1,642 (24.7)	12,106 (26.0)
Respiratory diseases	145 (2.0)	482 (4.3)	1,652 (7.7)	541 (8.1)	2,820 (6.1)
Gastrointestinal and liver disease	310 (4.3)	1,092 (9.7)	2,158 (10.0)	1,260 (18.9)	4,820 (10.3)
Cancer	250 (3.5)	1,504 (13.4)	3,734 (17.3)	696 (10.5)	6,184 (13.3)
Trauma and poisoning	2,721 (37.8)	2,007 (17.9)	1,754 (8.1)	888 (13.3)	7,370 (15.8)
Other	2,396 (33.3)	1,794 (16.0)	2,207 (10.2)	649 (9.8)	7,046 (15.1)
ICU admission type					
Medical	3,514 (48.8)	4,436 (39.5)	7,053 (32.7)	2,622 (39.4)	17,625 (37.8)
Surgical	3,683 (51.2)	6,793 (60.5)	14,493 (67.3)	4,036 (60.6)	29,005 (62.2)

3.2.2 The Danish National Registry of Patients (DNRP)

The DNRP includes data on all hospital admissions since 1977 and also on outpatient clinic visits and emergency room visits since 1995. It is mandatory to report to the DNRP, which is used, i.a., to monitor health care and to assess the Danish diagnosis-related groups (DRG). DRG is a measure of health care costs and is used by the state and between hospital owners (the regions) to reimburse hospitals.

Data for each hospital contact include civil registration number, date of admission and discharge, date and type of surgery, major treatments and procedures, one primary diagnosis (main reason for the hospitalization) and up to 19 secondary diagnoses.[148] Diagnoses are assigned by discharging physicians according to the International Classification of Diseases 8th edition (ICD-8) until 1993 and the 10th edition (ICD-10) thereafter. The 9th edition (ICD-9) was never used in Denmark. Surgical procedures are coded according to The Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures.[149]

Procedures and treatments are coded according to a Danish classification of treatments. ICU admission and important treatments during this admission are coded using these codes. These codes are typically assigned by the intensive care physicians and entered by secretary staff at the intensive care unit, but the referring ward (e.g. the surgical or medical ward) is legally responsible for the coding. Data are entered into a local patient administrative system that automatically transfers data to regional servers and thence to the DNRP at the Danish National Board of Health. There are several checks of data, which may cause 1 to several months of delay from data entry to data are available in the DNRP.

3.2.3 The Civil Registration System (CRS)

The Danish Civil Registration system is an administrative registry that keeps track of vital status, marital status, and residential address for all Danish Citizens. It was established in 1968 and is updated daily.[145] We used the CRS to secure that patients were residents of the study area, to obtain data on their marital status as a marker for socioeconomic status, and to obtain complete follow-up data for death or emigration.

3.2.4 The Prescription Database of Northern Denmark

The Danish health care system provides partial reimbursement for prescribed drugs. All Danish pharmacies are equipped with an electronic accounting system that allows reimbursement when the drug is dispensed to the patient. Data from this system in Northern Denmark are transferred to a research database at Aarhus University. Data include civil registration number, drug dispensing date, drug name, Anatomical Therapeutics Chemical Classification System (ATC) code, total package size, and package item number. The database is complete for the study area since 1998, except for a small area in the southern part of Central Denmark Region that was not included in the database until 2007.[150]

3.2.5 The Clinical Laboratory Information Systems

The laboratory information systems used at the hospitals in the study area are the backbone of daily clinical work used to order tests and to display the results online for the clinicians. All tests performed in hospitals laboratories are included, i.e., all tests among hospital in- or outpatients and virtually all tests from general practice (with the exception of hemoglobin, C-reactive protein, and blood glucose that are usually analyzed at the GPs' own clinic as point-of-care testing).[151] Data include civil registration number, date of test, test name, test code (local analysis number and/or code according to IUPAC, International Union for Pure and Applied Chemistry), and unit. The database currently includes data in the former North Jutland County from 1997 through 2008 and in the former Aarhus County from 2000 through 2010. Although the entire Central Denmark Region is now included in the database, this was not uniformly covered throughout the study period for our studies. All data are merged into the regional registries of health and morbidity hosted at Department of Clinical Epidemiology, Aarhus University.

3.3 Study design

All three studies were designed as cohort studies.

3.4 Study population, exposure, outcome, and confounders

3.4.1 Study populations

We included adult patients admitted to the ICUs in Northern Denmark from 1 January 2005 to 31 December 2008 in Study I, and through 31 December 2010 in Study II and Study III. Studies I and III included adults 15 years or older, while Study II included only patients aged 40 years or older in order to have more similar age profile of type 2 diabetes patients and patients without diabetes.

Study I also included an age- and gender-matched comparison cohort. For Studies II and III we required that the patients should have lived in the study area for at least 2 years in order to have sufficient preadmission laboratory and prescription data.

3.4.2 Validation of ICU coding

We validated the registration of ICU admissions in the DNRP in a random sample of 50 patients per year in 2005–2008 (150 patients in total) at one of the hospitals within the Aarhus University Hospital network. Specifically, we used the hospital records to confirm the occurrence and date of ICU admissions. Among the 150 patients registered in the DNRP with an ICU admission, 148 were identified with an ICU admission in the local hospital records, that is, a positive predictive value (PPV) of 98.7% (95%CI: 95.3%–99.8%). The date of first ICU code corresponded to the day of ICU admission in all patients except one, who was admitted to the recovery room at date of coding but transferred to the ICU the following day.

3.4.3 Exposure

In Study I, the exposure was both ICU admission and preadmission morbidity level in order to study any different effect of preadmission morbidity in ICU patients compared with the general population. Preadmission morbidity level was assessed by the CCI,

including diagnoses from the DNRP within 5 years before ICU admission. The DNRP coding of the conditions included in the CCI is accurate.[58]

In Study II, the exposure was type 2 diabetes. We defined diabetic patients as patients with either 1) a previous hospital diagnosis of diabetes since 1977, *or* 2) any prescription for an antidiabetic drug since 1998, or 3) a HbA1c level elevated of 6.5% or more within the year before ICU admission.[98, 152] Patients were considered to have type 2 diabetes, and not type 1 diabetes, if they were diagnosed with diabetes after age 30, if they were diagnosed before age 30 but did not fill prescriptions for insulin within one year before admission, or if they had ever filled a prescription for an oral antidiabetic drug.[98] Because metformin is also used to treat polycystic ovarian syndrome (PCOS), metformin users with a history of PCOS were considered nondiabetic if they lacked a diabetes diagnosis and had never been prescribed another antidiabetic drug (n = 3).[142] Because major micro- and macro-vascular complications of diabetes may affect prognosis, we further segregated type 2 diabetic patients according to preadmission history of kidney disease and heart disease, comprising myocardial infarction and heart failure. We did not include complications like diabetic retinopathy or neuropathy because these were expected to have minimal impact on mortality in ICU patients. Because a diagnosis of diabetes may be preceded by heart and kidney complications, we included patients in the analysis if they were initially diagnosed with kidney or heart disease within 1 year before receiving the first type 2 diabetes diagnosis or antidiabetic prescription and before the index hospitalization. Diabetes was thus divided into five subcategories: no diabetes, uncomplicated type 2 diabetes, type 2 diabetes with heart disease but without kidney disease, type 2 diabetes with kidney disease but without heart disease, and type 2 diabetes with both heart and kidney disease.

In Study III, the exposure was preadmission metformin use, defined as any filled prescription for metformin within 90 days before ICU admission. To address different severities of diabetes, patients were divided in metformin monotherapy users that only received metformin, and metformin combination therapy users that also received any other oral antidiabetic drug or insulin within this 90-day preadmission period. Confounding by indication, i.e., reason for metformin prescription, may influence our findings. To address this, we did several additional analyses. First, we did a comparison of metformin monotherapy users with sulfonylurea monotherapy users because these groups

may be more homogeneous with regard to indication for treatment. Next, we divided metformin users in current (prescription filled within 0–90 days before ICU admission), recent (91–365 days), former (1–5 years), and never users (>5 years or no prescription). If the association was confounded by chronic disease or life-style factors present during these periods, we would expect an association in current, recent, and former users, when compared to no users. We further divided current users in new- and long-term users, as new-users may provide a more true drug effect because long-term users may be more healthy as they had to tolerate side effects to continue treatment.[153] As a sensitivity analysis, we changed the time window for capturing metformin prescriptions from 90 days before admission to 180 and 365 days before.

3.4.4 Outcome

The outcome in the studies was all-cause death after ICU admission, and the regression analyses were based on time to death. Mortality was defined as probability of death within each of the predefined time periods.

Deaths after ICU admission may occur while the patient is in the ICU, after ICU discharge but before hospital discharge, or after hospital discharge.[154] Because in-hospital and ICU mortality are influenced by local transferal and discharge patterns, we used the fixed time periods to assess mortality.[155]

Study I included mortality for up to 3 after ICU admission, segregated in the following periods: day 0–30, day 31–365, day 366–3 years. This was done to address changes in relative mortality during follow-up. Study II included more recent data, and follow-up for mortality was therefore limited to 1 year, segregated into day 0 – 30 and day 31–365 after ICU admission. Study III included only 30-day mortality, because we were interested in the short-term effect of preadmission metformin use.

3.4.5 Potential confounding factors

Several factors associated with mortality that are not in the causal pathway, may be unequal distributed across exposure groups and are therefore potential confounders.[156]

We used the CRS to obtain data on age, sex, and marital status. Through the DNRP, we obtained data on preadmission diseases, current primary diagnosis (diagnostic category), and surgical procedures performed. In Study I, we simply divided diagnostic category according to chapters in the ICD-10, while in studies II and III infectious diseases were extracted from the organ-specific chapters.

For Study III, we obtained data from the prescription database on preadmission use of statins, beta-blockers, and low-dose aspirin. We assessed acute organ dysfunction on the day of ICU admission as defined by the Sequential Organ Failure Assessment (SOFA) score's criteria for kidney, liver, and coagulation system dysfunction.[157] We defined organ dysfunction as any organ-specific score above 0. We assessed this score by blood test data (creatinine, bilirubin, and platelet count) from the laboratory database.[151] The analysis of organ dysfunction was restricted to the part of the study area covered by the database (67.4% of the study cohort). For patients without routine measurement on day of ICU admission, we computed the mean of the values the day before and the day after ICU admission.[157] Still, some patients in the area with laboratory coverage had missing data for all 3 days (creatinine n=198 (4.8%), bilirubin 2,173 (55.3%), platelet count 632 (15.3%)). These tests are usually performed on minor indication, and we therefore assumed that missing tests represented normal values as previously done elsewhere.[158]

3.5 Statistical analyses

In all three studies, follow-up started on day of ICU admission and continued to death (event of interest), to loss of follow-up (e.g., due to emigration), or to the end of follow-up, whichever came first. Follow-up was restricted to 3 years in Study I, to 1 year in Study II, and 30 days in Study III.

3.5.1 Mortality (Studies I, II, III)

We assessed mortality (1 – survival probability) and 95% confidence intervals (CI) in each of the time periods by the Kaplan-Meier method, which account for censoring, and plotted the cumulative mortality curves.

3.5.2 Standardization (Study I)

In Study I, each ICU patient was matched by age and sex to 10 individuals from the general population using the CRS. We did not match on Charlson Comorbidity level, because this was one of the exposures of interest. Therefore the age and sex distributions within each Charlson Comorbidity level were different in ICU patients compared with the general population. Furthermore, the age and sex matching was violated during follow-up because of persons dying. To allow comparison of mortality in the time periods at each morbidity level, we therefore used direct standardization to adjust the Kaplan-Meier estimates at each comorbidity level and time period to the age and sex distribution of the general population cohort.[159]

3.5.3 Interaction risk (Study I)

Death after ICU admission may be either from the critical illness or from preadmission morbidity. ICU patients with preadmission morbidity may have reduced physiological reserves and may thereby be more susceptible to progression of organ dysfunction and death. The mortality in ICU patients would thus depend on preadmission morbidity. Such interaction of two causal factors is denoted *biological interaction*, which should not be confused with *statistical interaction* that is specific for a given statistical model and just implies that an observed effect depends on the level of another factor for a particular outcome measure (corresponds to *effect-measure modification* when all bias is adequately controlled).[156, 160]

We addressed this potential *biological interaction* by computing the *interaction risk* using the age- and sex-standardized mortality estimates.[156, 161, 162] As shown in the expression below, we subtracted the standardized mortality difference between ICU patients with moderate/high (CCI+) and low (CCI-) preadmission morbidity from the mortality difference between general population cohort members (pop) with moderate/high and low index morbidity:

$$\textit{Interaction risk} = (R_{(ICU,CCI+)} - R_{(ICU,CCI-)}) - (R_{(pop,CCI+)} - R_{(pop,CCI-)})$$

The overall difference constitutes the excess mortality or *interaction risk* caused by the *biological interaction* of critical illness and preadmission morbidity on mortality, i.e., the

mortality that cannot be explained by the sum of mortality from critical illness and preadmission morbidity.[156]

3.5.4 Propensity score adjusted and matched analysis (Study III)

Factors that affect treatment choice may confound non-randomized studies of interventions. There is an ongoing development of methods that aim to reduce confounding, and these include methods based on propensity score. The indication for using propensity score-based analyses in our study is the ability to include several covariates into a single score, which is more robust when there are few outcomes per covariate.[163, 164] In our study, the propensity score thus describe the probability of being treated with metformin given the measured covariate pattern.[163] We computed the propensity score in a multivariate logistic regression model that included age, sex, marital status (five levels), diabetes duration 5 years or more, HbA1c of 8% or more, concurrent cardiovascular drug use (low-dose aspirin, beta-blockers, statins), preadmission diseases (myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, liver disease, moderate/severe renal disease, cancer, metastatic cancer, diabetic retinopathy, diabetic nephropathy, hypertension, obesity, alcoholism), diagnostic category, and medical/surgical admission type, and organ dysfunction at ICU admission (renal, liver, and coagulation). These variables were assumed to be associated with the outcome, which is the most important criterion for including the variable in the estimation of the propensity score.[165]

First, we used the propensity score to adjust for confounding in a Cox regression model, both overall and in subgroups. Next, we used the propensity score to match each metformin user to the non-user with the closest propensity score (nearest-neighbor-matching) within a maximum range of +/- 0.025. Matching was thereby possible in 91.5% of metformin users. We found covariates well balanced after the matching, as assessed by an absolute standardized difference for each covariate of less than 0.1.[166]

3.5.5 Cox proportional hazard regression analysis (Studies I, II, III)

We used Cox proportional hazards regression (Cox regression) with 95% confidence intervals (CIs) in the three studies to compute hazard ratios for death.[167] The computed

hazard ratios were interpreted as mortality rate ratios (MRRs). We assumed proportional hazards, i.e., that the MRRs did not change within each time period of follow-up. This assumption was checked graphically in each of the three studies by log(-log) plots and found reasonable.

We adjusted for potential confounders using multivariate Cox regression.[168]

In Study I, we used Cox regression to compare mortality rates at different preadmission morbidity levels within ICU patients and to compare mortality rate in ICU patients with those in the general population. We adjusted the analyses for age group and sex, and among ICU patients also for medical/surgical admission type.

In Study II, we adjusted for age and sex in the primary analysis, but a second analysis also included marital status, medical/surgical admission type, diagnostic category, dementia, chronic pulmonary disease, connective tissue disease, liver disease, cancer, metastatic cancer, alcoholism, and obesity.

In Study III, we adjusted for the following potential confounders: age, sex, marital status (five levels), diabetes duration 5 years or more, HbA1c of 8% or more, concurrent cardiovascular drug use (low-dose aspirin, beta-blockers, statins), preadmission diseases (myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, liver disease, moderate/severe renal disease, cancer, metastatic cancer, diabetic retinopathy, diabetic nephropathy, hypertension, obesity, alcoholism), diagnostic category, and medical/surgical admission type. Because acute organ dysfunction may be a part of the causal pathway (and thereby not a confounder) variables concerning organ dysfunction were only adjusted for in an additional analysis, but used in computing the propensity score. (See section 3.5.4) We used a stratified Cox regression analysis in the propensity score-matched analysis to take the matching into account.

3.5.6 Stratified analyses (Studies I, II, III)

All three studies included analyses stratified by covariates that represented subgroups of ICU patients. We did these analyses because the effect of the exposure may differ between these groups of ICU patients, i.e., there may be an *effect measure modification*.[156]

Study I included analyses stratified by subgroups of ICU patients according to medical and surgical admission type.

Study II included analyses stratified by age group, sex, diagnostic category, medical/surgical admission type, and according to mechanical ventilation.

Study III included stratified analyses by age group, sex, diagnostic category, medical/surgical admission type, HbA1c <8%/≥ 8%, and according to the presence of preadmission kidney or pulmonary disease.

4 Results

4.1 Study I: The preadmission morbidity level study

Study I included 28,172 ICU patients and 281,671 age- and sex-matched persons from the general population. Among ICU patients, 56.8% were men, 60.6% were surgical patients, and the median age was 63 years.

4.1.1 Prevalence of morbidity

Among ICU patients, 14.4% had a high morbidity level, 34.1% had a moderate, and 51.5% had a low morbidity level. The general population had markedly lower morbidity levels, with 3.7% having high, 16.2% moderate, and 80.1% having a low morbidity level.

All morbidities, except dementia, were more common among ICU patients. The prevalence of diabetes was more than two-fold higher in ICU patients, but the most marked difference was in the prevalence of metastatic cancer and liver disease, which were both approximately six-fold higher in ICU patients than in the general population.

4.1.2 Mortality

The 30-day mortality was 26.7% in ICU patients with a high morbidity level, 18.4% in a moderate, and 10.8% in ICU patients with a low morbidity level. Also 31–365 day mortality was higher in patients with a high morbidity level (27.8%) compared with moderate (15.5%) and low morbidity levels (5.7%). The 1–3 year mortality was very similar: 30.4%, 17.4%, and 6.4% in the three groups. (Table 4-1)

The MRRs were increased throughout the study period in patients with high and moderate morbidity levels compared with patients with a low morbidity level. The relative impact was, however, most pronounced after 30 days. (Table 4-1)

Despite a higher absolute mortality of medical ICU patients, the relative impact of preadmission morbidity level was very similar in medical and surgical ICU patients.

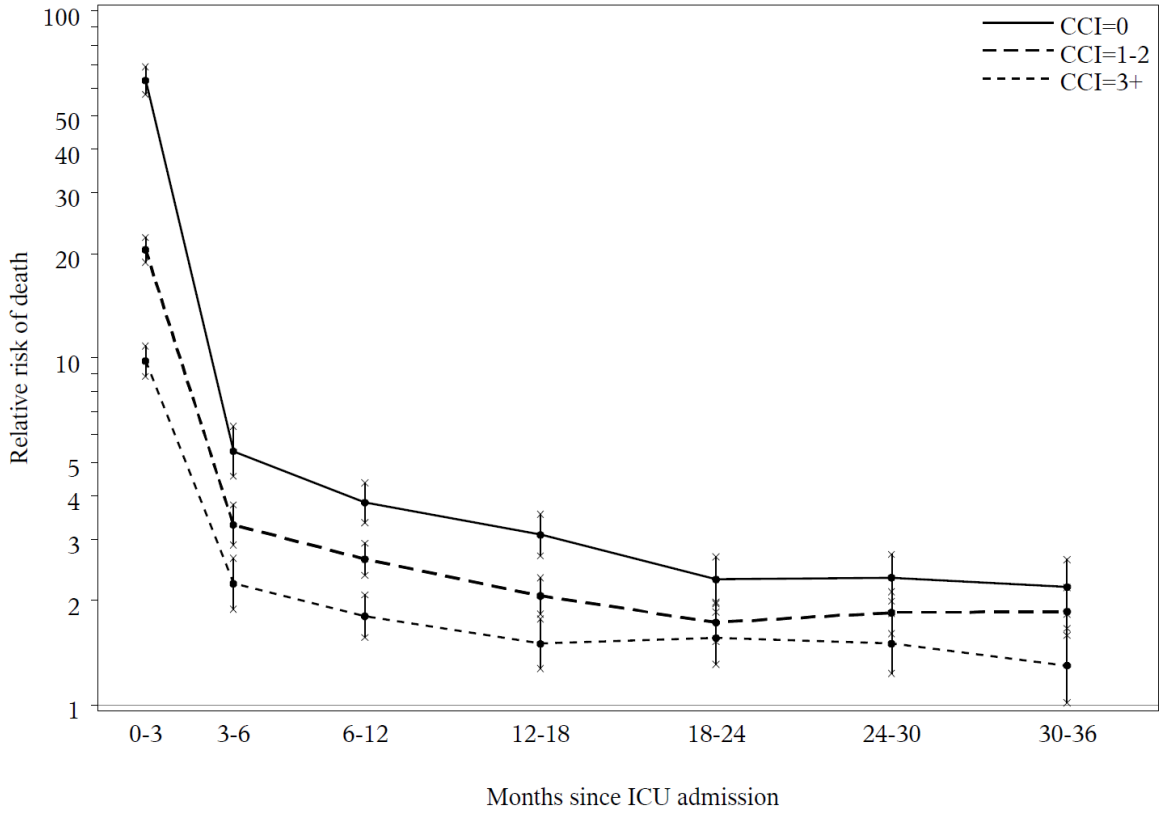
Table 4-1. Mortality and mortality rate ratio (MRR) for ICU patients within 0–30 days, 31–365 days, and 1–3 years after ICU admission for the three preadmission morbidity levels among patients who were alive at the beginning of these periods (Charlson Comorbidity Index (CCI) score = 0, 1–2, or 3+).

		N at period start	Mortality % (95%CI)	Crude MRR (95%CI)		Adjusted MRR* (95%CI)	
Day 0–30	CCI = 0	14,514	10.8% (10.3%–11.3%)	1.00	(Ref.)	1.00	(Ref.)
	CCI = 1–2	9,598	18.4% (17.6%–19.2%)	1.77	(1.65–1.89)	1.30	(1.21–1.39)
	CCI = 3+	4,060	26.7% (25.3%–28.0%)	2.67	(2.47–2.88)	1.86	(1.71–2.01)
Day 31–365	CCI = 0	12,944	5.7% (5.4%–6.2%)	1.00	(Ref.)	1.00	(Ref.)
	CCI = 1–2	7,832	15.5% (14.7%–16.3%)	2.83	(2.58–3.10)	2.10	(1.92–2.31)
	CCI = 3+	2,977	27.8% (26.3%–29.5%)	5.50	(4.98–6.07)	3.93	(3.55–4.35)
Day 366–3 years	CCI = 0	12,173	6.4% (5.9%–6.8%)	1.00	(Ref.)	1.00	(Ref.)
	CCI = 1–2	6,612	17.4% (16.5%–18.4%)	2.91	(2.65–3.20)	2.16	(1.96–2.38)
	CCI = 3+	2,142	30.4% (28.4%–32.4%)	5.54	(4.97–6.17)	3.96	(3.55–4.43)

* Adjusted for age group, sex, and medical/surgical admission type.

As expected, mortality was markedly higher in ICU patients than in the general population within the first months after ICU admission, but it remained elevated throughout the study period for all three preadmission morbidity levels. (Figure 4-1)

Figure 4-1. Relative risk of death (mortality rate ratio) among ICU patients compared with the general population cohort at each morbidity level and for up to 3 years, adjusted for age and sex, with 95% confidence intervals.



4.1.3 Interaction risk

We found an interaction between increased morbidity level and ICU admission. Morbidity added more to the absolute mortality in ICU patients than it did in the general population. This interaction risk in the first 30-day period was 3.1% (95% CI: 2.2%–4.0%) for moderate and 10.5% (95% CI: 8.7%–12.3%) for high morbidity, but remained elevated throughout the 3-year follow-up. Even ICU patients with a low morbidity level had a higher 1–3 year mortality of 8.7% compared with 4.4% in the general population.

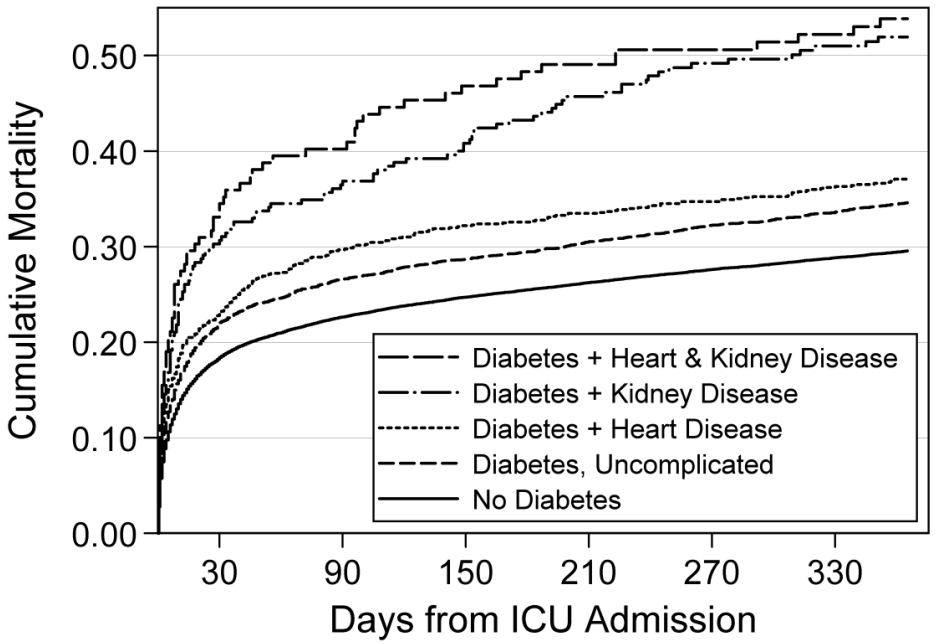
4.2 Study II: The diabetes study

Among 39,286 ICU patients over 40 years of age, 6,027 (15.3%) had type 2 diabetes, which was complicated by chronic heart disease in 1,103 (18.3%), by kidney disease in 261 (4.3%), and by both in 142 (2.4%).

The median age was 70 years in patients with type 2 diabetes and 67 years in other ICU patients. There were slightly more men among the type 2 diabetic patients (60.3%) than among other ICU patients (56.9%). Patients with type 2 diabetes were more likely to have a previous diagnosis of other lifestyle-associated diseases, such as chronic pulmonary disease, liver disease, and obesity. Cancer was slightly more frequent in patients without type 2 diabetes.

Thirty-day mortality was 22.9% (95% CI: 21.9%–24.0%) in type 2 diabetic patients and 18.4% (95% CI: 18.0%–18.8%) in other ICU patients. Mortality in type 2 diabetic patients ranged from 22.1% among those without complications to 34.5% among those with diabetes complicated by both heart and kidney disease. (Figure 4-2 and Table 4-2)

Figure 4-2. Cumulative 1-year mortality among intensive care patients without diabetes, patients with uncomplicated type 2 diabetes, and patients with type 2 diabetes complicated by heart and/or kidney disease.



Age- and sex-adjusted MRR was 1.18 (95% CI: 1.11–1.25). (Table 4-2) Type 2 diabetes complicated by heart disease was also associated with a slight mortality increase [adjusted MRR 1.12 (95% CI: 0.99–1.27)], while diabetes patients with chronic kidney disease had markedly increased mortality compared with patients without diabetes [adjusted MRR with kidney disease 1.65 (95% CI: 1.32–2.05), adjusted MRR with both kidney and heart disease 1.66 [95% CI: 1.26–2.21]). Duration of diabetes had no impact on mortality. Stratified analyses revealed that the association was most pronounced in patients aged 60 years or older and in patients that were not mechanically ventilated.

The long-term mortality from day 31 to day 365 after ICU admission was 17.3% (95% CI: 16.2%–18.5%) among type 2 diabetic patients and 13.7% (95% CI: 13.2%–14.1%) among other ICU patients. The 31–365-day mortality was approximately 30% in type 2 diabetic patients with kidney disease (Table 4-2). The adjusted long-term MRR was 1.20 (95% CI 1.11–1.30), and peaked at 2.25 (95% CI: 1.71–2.96) in type 2 diabetic patients with kidney disease. (Table 4-2)

Table 4-2. Thirty-day and 31–365-day mortality and mortality rate ratio (MRR) in type 2 diabetic patients with/without history of heart and kidney disease.

	N	30-day mortality			31 – 365 day mortality		
Diabetes status and complications		**Mortality, % (95%CI)**	**Crude MRR (95%CI)**	**Adjusted* MRR (95%CI)**	**Mortality, % (95%CI)**	**Crude MRR (95%CI)**	**Adjusted* MRR (95%CI)**
No diabetes	33,259	18.4 (18.0–18.8)	1.00 (ref.)	1.00 (ref.)	13.7 (13.2–14.1)	1.00 (ref.)	1.00 (ref.)
Type 2 diabetes	6,027	22.9 (21.9–24.0)	1.28 (1.20–1.35)	1.18 (1.11–1.25)	17.3 (16.2–18.5)	1.29 (1.19–1.40)	1.20 (1.11–1.30)
- Without complications	4,521	22.1 (20.9–23.3)	1.22 (1.14–1.31)	1.16 (1.08–1.24)	16.1 (14.9–17.4)	1.18 (1.08–1.30)	1.12 (1.02–1.23)
- With heart disease†	1,103	23.0 (20.6–25.6)	1.29 (1.14–1.46)	1.12 (0.99–1.27)	18.3 (15.8–21.2)	1.40 (1.19–1.66)	1.22 (1.03–1.44)
- With kidney disease‡	261	30.7 (25.5–36.7)	1.79 (1.43–2.23)	1.65 (1.32–2.05)	30.7 (24.3–38.3)	2.43 (1.85–3.20)	2.25 (1.71–2.96)
- With heart† and kidney disease‡	142	34.5 (27.3–43.0)	2.06 (1.56–2.73)	1.66 (1.26–2.21)	29.6 (21.1–40.3)	2.39 (1.62–3.51)	1.91 (1.30–2.81)

† Heart diseases comprise myocardial infarction and congestive heart failure.

‡ Kidney diseases comprised chronic kidney disease.

* Adjusted for age and sex

4.3 Study III: The metformin study

We included 6,170 type 2 diabetic patients within the cohort of 46,630 adult ICU patients. Among included patients, 827 (13.4%) were metformin monotherapy users, 1,101 (17.8%) metformin combination therapy users, and 4,242 (68.8%) were non-users of metformin.

Compared with non-users, both groups of metformin users had less preadmission morbidity including cardiovascular, liver, renal and pulmonary disease. However, metformin combination therapy users were more likely to have diabetic nephropathy and retinopathy, long diabetes duration, high preadmission HbA1c level, compared with non-users. Metformin users more frequently received concurrent cardiovascular drugs. There were only slight differences in proportion admitted to the ICU after surgery (64% of metformin monotherapy users, 62% of metformin combination therapy users, and 59% of non-users). Preadmission characteristics were equally distributed in the propensity-score matched cohorts.

Compared with non-users, metformin monotherapy and combination therapy users were less likely to have renal, liver, and coagulation system dysfunction on day of ICU admission.

The 30-day mortality was 16.9% in metformin monotherapy users, 18.0% in metformin combination therapy users, and 25.0% in non-users. Among non-users, the mortality was very similar in users of sulfonylurea, insulin, other/combination therapy, and in those who not take antidiabetic medications.

Compared with non-users, the adjusted MRR was 0.79 (95% CI: 0.66–0.95) in metformin monotherapy users and 0.83 (95% CI: 0.71–0.97) in metformin combination therapy users. Further adjustment for organ dysfunction had no influence on the overall estimate. Estimates were very similar after adjustment for propensity score. In the propensity score matched cohorts, the unadjusted MRR was 0.85 (95% CI; 0.73–1.00) for metformin users compared with non-user. Stratified analyses revealed very similar results across subgroups of ICU patients, although the estimates were imprecise.

The association was restricted to current users of metformin [adjusted MRR = 0.81 (95% CI: 0.71–0.93) compared with never users], with no association found in recent [adjusted MRR = 1.01 (95% CI: 0.81–1.27)] and former metformin users [adjusted MRR = 1.04 (95% CI: 0.85–1.26)]. The decreased mortality was less pronounced in new users [aMRR = 0.90 (95% CI: 0.58–1.41)] than in long-term metformin users [aMRR = 0.81 (95% CI: 0.71–0.93)].

In a direct comparison of metformin monotherapy users (n = 827) with sulfonylurea monotherapy users (n = 799), the mortality decrease was less pronounced in the adjusted analysis [adjusted MRR = 0.87 (95% CI: 0.69–1.10)], but very similar in the propensity score adjusted analysis [MRR = 0.77 (95% CI: 0.61–0.96)].

Changing the metformin exposure window to 180 days increased the number of metformin users from 1,928 to 2,149, without substantial change of the estimates [adjusted MRR = 0.83 (95% CI: 0.73–0.94)]. Similarly, use of a 1-year window did not markedly change the estimates (adjusted MRR = 0.85 (95% CI: 0.75–0.95) among 2,310 metformin users compared with non-users).

Table 4-3. Thirty-day mortality and mortality rate ratios (MRRs) for metformin monotherapy, metformin combination therapy, and non-metformin users among type 2 diabetics admitted to intensive care units in Northern Denmark.

	n	30-day mortality, % (95% CI)	Crude MRR (95%CI)	Adjusted MRR (95%CI)	Propensity score adjusted MRR (95%CI)
Overall analysis					
Metformin users	1,928	17.5 (15.9–19.3)	0.67 (0.59–0.76)	0.81 (0.71–0.92)	0.84 (0.74–0.96)
Metformin monotherapy	827	16.9 (14.5–19.6)	0.64 (0.54–0.77)	0.79 (0.66–0.95)	0.80 (0.67–0.96)
Metformin combination therapy	1,101	18.0 (15.8–20.4)	0.69 (0.59–0.80)	0.83 (0.71–0.97)	0.88 (0.75–1.03)
Metformin non-user	4,242	25.0 (23.7–26.3)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Propensity score matched cohorts					
Metformin users	1,765	18.0 (16.3–19.8)	0.85 (0.73–1.00)	0.82 (0.68–0.99)	0.86 (0.72–1.02)
Metformin non-user	1,765	20.7 (18.9–19.8)	1.00 (Ref.)	1.00 (Ref.)	1.00 (ref.)
Monotherapy comparison					
Metformin monotherapy	827	16.9 (14.5–19.6)	0.63 (0.51–0.78)	0.87 (0.69–1.10)	0.77 (0.61–0.96)
Sulfonylurea monotherapy	799	25.4 (22.6–28.6)	1.00 (Ref.)	1.00 (Ref.)	1.00 (ref.)

5 Discussion

5.1 Methodological considerations

We examined potential causal associations between preadmission exposures and mortality after ICU admission in the three cohort studies. Several potential study limitations should be considered before any found association can be considered a causal association.[29] First, bias from selective inclusion of ICU patients or from erroneous information about the exposure or outcome should be excluded. Second, the statistical precision of the estimated association should be examined, e.g. by 95% confidence interval, in order to reassure that the association could not have occurred by chance (i.e., exclude type I error). However, statistically imprecise estimates from small ICU studies cannot be used to exclude any association (type II error). Third, given the heterogeneity of ICU patients, differences between exposure groups are very common, and these potential confounders should be adequately measured and controlled for. Any effect of unmeasured confounding can hardly be excluded in non-randomized studies, and the final interpretation about causality should therefore be cautious.

Chance, or better random error, is unlike to explain our findings. The large number of patients included in the three studies yielded statistically precise estimates of the associations with narrow 95% confidence intervals. However, the stratified analyses gave less certain results for subgroups of ICU patients.

Selection and information bias are systemic errors from the study design, which, in contrast to confounding, cannot be corrected for by statistical analyses. Bias and confounding will be discussed in further detail in the sections below.

As with all other research data, data quality is also important for the applicability of existing data sources.[169-171] Data in the applied large population-based databases were routinely collected independent of the studies, thereby limiting certain types of bias at the expenses of inability to expand the number of variables collected.[171] The value of existing data sources depend on the completeness of registration, the accuracy of data, the size of the data source, the registration period, the data availability, the data format, and the

possibility of record linkage.[169, 170] Several of these issue are outlined in the description of the databases in section 3.2, but further addressed below.

5.1.1 Selection bias

Selection bias is a systematic error that arises if the association between an exposure and an outcome is different in patients included in the study compared to those not included.[156]

We included almost all ICU patients in a well-defined population with virtually complete follow-up. We included only the first ICU admission in the study period, and patients included early in the study period may have had an ICU admission just before study start. Except for a very few potential re-admissions, a history of ICU admission is not expected to influence the outcome markedly. Registration of ICU admissions in the DNRP is considered to be approximately 95% complete,[1] but approximately 1% of adults registered as admitted to an ICU were not actually admitted.[74] We find it unlikely that any registration error regarding ICU admission would depend on preadmission morbidity level (Study I), diabetes (Study II), or preadmission metformin treatment (Study III). And even if it did, the proportion miscoded would be small and any selection bias would be minimal.

The reason for ICU admission may, however, differ between exposure groups, but this should be considered confounding by indication for ICU admission and not selection bias.[172] This is important because confounding can be controlled for in the statistical analysis as described in section 5.1.3. However, one should still be aware that indications for ICU admission caused by the exposure could be a part of the causal pathway, and adjustment may attenuate the estimate of a causal association mediated through this. As an example, diabetes may increase the risk of acute kidney injury or severe sepsis, which may both be reasons for ICU admission. Therefore, we undertook analyses both with and without adjustment for reason for ICU admission to allow careful interpretation. Additionally, we provided stratified analyses on reason for admission because this may reveal different effects with different reasons for ICU admission, i.e., effect-measure modification, which would have been overlooked if simply included in an adjusted regression model.

5.1.2 Information bias

Information bias arises if data about the exposure (morbidity level, diabetes, and metformin use) is measured erroneous and dependent on the outcome (time to death) or vice versa.[156]

The exposures in these studies are measured on dichotomous or categorical scales, and any error would result in a misclassification. If the misclassification of the exposure is associated with death, such misclassification will be differential. If not, it is non-differential. Differential misclassification may lead to unpredictable information bias, while non-differential misclassification of dichotomous variables will bias the results towards the null.

In Study I, exposure is preadmission morbidity level at three levels assessed by the CCI. We used all inpatient and outpatient clinic diagnoses to assess this, and the diagnostic coding is known to be accurate.[58] We included diagnoses within a 5-year period before index admission because we assumed that patients having one of these chronic diseases would have at least one hospital contact during the period. Still, patients may have been diagnosed as having a chronic disease either before that or had the diagnosis assigned by their general practitioner without hospital contact. Such misclassification will be non-differential because it is independent of mortality during or after the index admission. Because there are three exposure groups, it is more difficult to judge the direction of any bias. We would, however, expect that any incomplete or inaccurate data on preadmission chronic diseases would tend to overestimate the mortality at the lower preadmission morbidity levels, thereby leading to a potential underestimation of the effect of a high preadmission morbidity level. It is also a limitation that the CCI does not take into account the time from diagnosis to index admission, e.g., patients having a cancer diagnosis 5 years before ICU admission may be cured, whereas patients with diabetes or kidney disease may have experienced disease progression during such a period. Furthermore, the index was developed more than 25 years ago and an update of the weighting of the 19 included conditions may be appropriate.[173]

In Study II, exposure is type 2 diabetes diagnosed or treated at any time before index admission. We were able to identify diabetes by in- or outpatient diagnoses, prescriptions

for antidiabetic drugs, and elevated HbA1c levels. Still, there are a considerable number of patients in the population with unrecognized diabetes, and in addition HbA1c measurements were not available for the entire study area. Therefore, there might be some misclassification of diabetic patients as non-diabetics, but it is not expected to be associated with time to death and therefore non-differential. Our estimates would therefore be conservative, as any bias would be towards the null. Although diagnostic coding of heart and kidney diseases is valid,[58] we neither estimated the glomerular filtration rate to assess severity of kidney dysfunction nor assessed the severity of heart disease, which ranged from uncomplicated myocardial infarction to severe congestive heart failure. We also assumed that heart and kidney diseases diagnosed in the period from 1 year before diagnosis of type 2 diabetes until the current hospitalization could be ascribed to diabetes. However, there may be exceptions, such as patients who become diabetic when their glomerulonephritis was treated with glucocorticoids. In addition, any impact of undiagnosed heart disease may have biased our results regarding type 2 diabetes with heart disease towards the null. Misclassifications between type 1 and type 2 diabetes would be few, and they are not expected to have any major influence on our results.

In Study III, the exposure is preadmission use of metformin. We used filled prescriptions as a proxy for drug use, and any non-adherence would most likely bias our estimates towards the null when comparing metformin users with non-users. Patients who filled their prescription more than 90 days before index admission, but were still taking the drug would also tend to bias our results towards the null. Metformin users with numerous hospitalizations within the 90 days may not have filled a prescription, and this could actually be associated with an increased mortality rate, thereby causing differential misclassification, which could potentially bias our results towards a more beneficial effect in metformin users. This is unlikely to have any major impact, as our estimates were virtually unchanged by expanding the exposure window from 90 to 180 and to 365 days.

The outcome in the three studies was time to death. Time to death is measured accurately in the CRS,[145] and we were thus able to follow patients using the CRS. We had complete follow-up for death in all except 59 (0.1%) patients who emigrated and three patients who disappeared during follow-up. Information bias from misclassification of death is therefore unlikely.

5.1.3 Confounding

Confounding is a systematic error that leads us to confuse the effect of an exposure with the effect of another variable, the confounder. Confounding is only relevant to consider in causal models like ours, but not in prediction models. In contrast to information and selection bias, confounding can be accounted for not only in the study design (e.g., by randomization, restriction, or matching) but also during analyses of data (e.g., by standardization, stratification, or in multivariate regression models).[156] It may be necessary to use more than one of the methods to reduce residual confounding. Matching in cohort studies may reduce confounding from factors present at the start of follow-up, whereas matching in case-control studies may actually introduce bias.[174]

By definition, a confounder must be associated with both the outcome (death) and the exposure (morbidity level, diabetes, metformin) and should not a part of the causal pathway (i.e., an intermediate step).[175] Consequently, complications during intensive care admission that occur after the exposure of interest should not be considered confounders, and adjustment for these may bias the result. In our studies, treatment during the ICU stay with mechanical ventilation, renal replacement therapy, and inotropes or vasopressors may be markers of an underlying complication and are therefore not considered as confounders. Also, adjustment for severity of illness scores may be problematic if the exposure of interest precedes and potentially causes its effect through increased severity of illness. Confounding is more obvious with variables clearly present before hospitalization, e.g., age, gender, and preadmission morbidity, and these may actually also be useful alternatives to risk adjustment with severity of illness scores.[54, 61]

Non-randomized studies of interventions, such as drug use, are prone to confounding due to the reason for prescription of the drug or intervention, i.e., confounding by indication.[176, 177] In general, the decision to initiate and adhere to a specific intervention is complex and affected by the health care system, the physician, and the patient.[176] Residual confounding can therefore hardly be fully excluded in non-randomized studies, especially when the intervention is used in the prevention of the outcome. For instance, the use of a pulmonary artery catheter, which is used to monitor the most severely ill patients at highest risk of dying, may itself cause severe complications. It can thus be challenging to adjust for confounding by indication, e.g., by severity of illness. This may explain why a

previous cohort study found increased mortality in patients with a pulmonary artery catheter compared with patients without.[178] In contrast, a randomized trial found no mortality difference.[179] A cohort study actually reached the same conclusion after balancing potential confounders by propensity score matching.[180] Also non-randomized studies on ICU treatments not directly related to the outcome may be hampered by confounding by indication. For example, a study found use of haloperidol in the first days after ICU admission to be associated with decreased hospital mortality in mechanically ventilated patients, but confounder adjustment may not adequately have adjusted for the differences between treated and non-treated. These differences that include comorbidity, reason for admission, and severity of agitation may actually be associated with recovery.[181]

In Study I, the association between preadmission morbidity level and mortality could be confounded by age and gender, which may be associated with both morbidity level and mortality. We handled this potential confounding by standardization and by adjustment in a multivariate regression analysis. The importance of especially age as a confounder is underlined by the clear decrease in mortality rate ratios (MRRs) after adjustment. To account for any different effect in medical and surgical patients, we further adjusted for admission type. However, stratification provided more information by showing that although surgical patients had a lower absolute mortality, the relative impact of preadmission morbidity level was similar in medical and surgical patients.

In Study II, we restricted the study to patients aged over 40 to reduce confounding by age and further adjusted for age in the multivariate regression analysis. The challenge in diabetes is that many diseases may be considered as complications to diabetes rather than confounders. Therefore, we considered separately diabetes patients with heart and/or kidney disease, which represent major macrovascular and microvascluar complications. To address a potential confounding effect, we did an analysis in which diseases not directly caused by diabetes, e.g. chronic pulmonary disease, were controlled for. Adjustment for these further decreased MRRs, especially in diabetic patients with kidney disease, which indicates potential residual confounding.

In Study III, several potential confounders influence the indication and contraindication for metformin prescription and outcome. The most important

contraindications include severe liver or renal disease or severe congestive heart failure. We adjusted for these and a wide range of variables, but can still not exclude any effect of unmeasured or residual confounding, e.g. from life-style factors like smoking, diet, exercise, and obesity. However, except for obesity, there is little difference in life-style factors between metformin users and users of other antidiabetic drugs.[182] Although obesity was found associated with decreased mortality in some studies of ICU patients,[183, 184] it is unlikely to fully explain our findings because we found no association between preadmission metformin and mortality in recent and former metformin users who are likely to have same prevalence of obesity.

5.2 Comparison with the existing literature

This section includes a discussion of the findings in relation to previous studies mentioned in section 1.2.

5.2.1 Study I: The preadmission morbidity level study

Our study confirms previous research with regard to the prevalence of preadmission morbidity level and its impact on mortality. Additionally, our study extends previous research by providing data about the mortality in ICU patients compared with a general population cohort, and adds to the previous research by comparing this mortality impact within different preadmission morbidity levels and by including an analysis of interaction between ICU admission and preadmission morbidity level.

We found a prevalence of morbidity level that was very similar to an Australian study reporting a prevalence of 12% for a high, 33% for a moderate, and 55% for a low morbidity level.[70] Mortality was, however, lower in that study, with a cumulative 3-year mortality of 41.9% for patients with a severe, 21.2% for a moderate, and 16.9% for a low morbidity level.[70] The less pronounced effect of morbidity on absolute mortality, compared with our findings, may be explained by differences in the ICU populations because the Australian studies included only 31% medical patients and a large proportion of cardiac surgery patient with a low mortality.[65] The different case-mix may largely be explained by the fact that the Australian studies included ICU patients back to 1987, as it is known that the case-mix of ICU patients has changed considerable since then.[15]

The relative impact on long-term mortality was close to our findings. Among ICU patients who survived 1 year after hospital discharge, the adjusted hazard ratios were 1.48 (95% CI: 1.39–1.57) for those with a moderate and 2.67 (95% CI: 2.45–2.90) for those with a severe morbidity level compared with a low morbidity level during follow-up for up to 15 years.[65] Also in an Australian prediction study, a very high morbidity level (CCI ≥ 5) was associated with a two-fold increased mortality.[53] The excess hazard with increasing CCI level found in another Australian study is in accordance with our finding of an interaction between ICU admission and CCI level; however the study relied on life tables for the general population and had therefore no data on CCI in the general population.[71]

Our findings on long-term mortality in ICU patients compared with the general population were supported by a recently published US cohort study on 35,308 elderly ICU survivors, who had persistently elevated mortality during a 3-year follow-up compared with the general population.[69] Also, analyses from the aforementioned Australian cohort study showed increased mortality for up to 15 years after ICU discharge, compared with the general population.[65] In a Scottish cohort study, survival was increased during the first 3 years but became comparable with that in the general population 4 years after ICU discharge.[63] We did not have a long enough follow-up time to confirm these findings. In contrast, both a Finnish and a Norwegian cohort study found that survival was comparable with the general population after 2 years.[64, 66] Actually, the Norwegian study found a mortality difference of 6.3% (95% CI: -0.7–13.4), and the imprecise estimate may be explained by small study size (N = 219). The previous studies did not describe whether they accounted for the change in age and sex composition of the cohorts during follow-up of the cohorts, e.g., elderly fragile ICU patients may die during the hospitalization, leaving the ICU cohort younger than the general population comparison cohort. We accounted for this by age and sex standardization at the start of each time period of follow-up. The US study was the only study that compared preadmission morbidity level in ICU patients with that in the general population. They found preadmission morbidity, as assessed by Elixhauser score, in as many as 84.3% of ICU patients, but only 41% of the general population. The high prevalence may be explained by the use of the Elixhauser score that includes more (30 vs. 19) and less severe conditions (such as obesity and uncomplicated hypertension) than the CCI,[185] and by differences in registration praxis the US and European health care

system. Importantly, we compared mortality in ICU patients with the general population and cannot distinguish the impact of ICU admission from the impact of hospitalization. As expected, the impact of ICU admission is less pronounced when compared with hospitalized patients.[69, 71, 186]

Our study thus confirmed that almost half of ICU patients have preadmission morbidity that is associated with a markedly worsened prognosis. Our study was the first to demonstrate that the increased mortality of ICU patients compared with the general population was present at all preadmission morbidity levels, and that preadmission morbidity had more impact on mortality in ICU patients than it did in the general population.

5.2.2 Study II: The diabetes study

Our study extends previous studies by having more detailed diabetes data and by reporting mortality for up to 1-year, while previous studies only reported short-term mortality, mainly in-hospital mortality. In contrast to our study, the previous studies found no association between diabetes and short-term mortality after ICU admission. In the large US study, diabetes was associated with a decreased in-hospital mortality in the overall cohort [age-adjusted odds ratio 0.79 (95% CI: 0.78–0.80)], but with similar mortality in one of the included centers that used nurses to assess diabetes status on admission instead of registry diagnosis [age-adjusted odds ratio 1.01 (95% CI: 0.92–1.11)].[116] The European multicenter study of 3,147 patients from 198 ICUs found slightly higher in-hospital mortality in patients with insulin-treated diabetes (28% vs. 24%), but diabetes was not a predictor for mortality after adjustment for age, liver cirrhosis, SAPS II score, and mechanical ventilation [hazard ratio 0.78 (95% CI 0.58–1.07)].[119] In a cohort of 830 patients with severe sepsis from the control group of an international multicenter trial, the 28-day mortality was very similar in patients with and without diabetes (31.4% vs. 30.5%),[117] but type 2 diabetic patients with severe chronic complications may have been excluded by one of several exclusion criteria in the original trial.[118]

Several issues may explain the different findings, including bias from the selection of study participants, bias from inaccurate diabetes information, uncontrolled confounding, or chance. Reported diabetes prevalence in previous studies ranged from

7.2% [119] to 22.7% [117]. Importantly, identification of diabetes by insulin treatment, chart review, or registration during index hospitalization could bias the results towards no association if diabetes was underreported in patients with other and more severe diagnoses, or if non-diabetic patients with stress hyperglycemia during their current ICU admission were registered as having diabetes.[187] Importantly, the largest two of the previous studies reported only in-hospital mortality. This outcome is sensitive to discharge and transferal patterns.[155] This potential problem is supported by a recent meta-analysis that found no effect of diabetes on in-hospital mortality but a statistically non-significant increase in 30-day mortality that was very similar to our overall estimate [odds ratio 1.19 (95% CI 0.96–1.47)].

5.2.3 Study III: The metformin study

Our study was the first to examine the association between preadmission metformin use and mortality among ICU patients. Generally seen, there are only very limited data on metformin use and outcome of critical illness. A US cohort study compared 1,284 cardiac surgery patients who received preadmission oral antidiabetic drugs with patients who did not. In a propensity score-matched analysis, metformin users had less postoperative morbidity, including infections (0.7% vs. 3.2%). Mortality was non-significantly decreased (0.7% vs. 1.4%).[144] An Iranian randomized trial of 21 patients with systemic inflammatory response syndrome examined the clinical effect of metformin during treatment in the ICU and found a decrease in proinflammatory cytokines and reduced insulin requirements when metformin was added to intensive insulin therapy.[138] However, the study did not include data on clinical outcomes. The findings in our study can also be compared with findings in experimental animal studies that found metformin treatment to be associated with decreased mortality in mice with lipopolysaccharide (LPS)-induced acute lung injury or endotoxemia.[120, 128] These effects were mediated through attenuation of the proinflammatory response and included a decrease in proinflammatory cytokines such as TNF-α and IL-1β and decreased neutrophil activation through mitochondrial inhibition.[120, 128] The hyperinflammatory response is central part of the pathogenesis in the early phase of sepsis and organ dysfunction,[127] and early metformin treatment may have beneficially modulated this response, although evidence is still very limited.

6 Main conclusions

The following conclusions are based on the research questions raised on page 25.

6.1 Study I: The preadmission morbidity level study

We found that 14.4% of ICU patients had a high and 34.1% had a moderate preadmission morbidity level and that these levels were associated with a worsened prognosis compared with ICU patients with a low preadmission morbidity level. High and moderate morbidity were less frequent in the general population and had less impact on mortality. ICU patients had increased mortality for up to 3 years after ICU admission compared with the general population, regardless of the morbidity level.

6.2 Study II: The diabetes study

We found that ICU patients with type 2 diabetes had 20% higher mortality than other ICU patients for up to 1 year after ICU admission. The effect of type 2 diabetes was most pronounced in those with chronic kidney disease, whereas there was no further increase in mortality in diabetic patients with heart disease.

6.3 Study III: The metformin study

We found that preadmission use of metformin, as monotherapy and in combination with other antidiabetic drugs, was associated with decreased 30-day mortality compared with other type 2 diabetic patients in the ICU. The association could not be explained by the lower rate of renal, liver, and coagulation system dysfunction.

7 Perspective

This thesis examined the mortality impact of chronic diseases, including diabetes, diagnosed before current hospitalization. This contrasts with most previous research on intensive care outcomes that have focused mainly on the acute critical illness itself. The potential implications of this thesis for patients, physicians, health care planners, and the society are summarized in Figure 7-1.

Figure 7-1. Potential implications of this thesis.

Patient related

- Improved counseling of patient/relatives about prognosis in patients with preadmission morbidity

Physician related

- Awareness of the increased mortality in ICU patients with preadmission morbidity, including type 2 diabetes, may potentially prevent complications and deaths
- Knowledge about prognosis of patients with preadmission morbidity and diabetes may add to improved ICU triage
- The impact of preadmission metformin on mortality may direct attention to anti-inflammatory therapy before admission and during the early phase of critical illness
- Metformin should not necessarily be discontinued routinely on hospital admission given the potential beneficial effects during the early phase of critical illness

Health care system related

- With the increased prevalence of preadmission morbidity, including diabetes, more ICU beds may be required if the increased mortality also represents longer and more complicated ICU stays
- Primary prevention of chronic diseases including diabetes may reduce mortality from critical illness
- Tertiary prevention of kidney disease in diabetes patients may reduce mortality from critical illness

Society related

- The increased mortality for several years after ICU admission, compared with the general population, contribute to public health burden
- Primary prevention of chronic diseases may reduce mortality from critical illness considerably because of the interaction between ICU admission and preadmission morbidity level

This thesis also demonstrated the unique opportunities provided by doing clinical epidemiological research in intensive care patients recruited through use of Danish registries and databases. The availability of unambiguous individual-level linkage allowed us to have complete data on preadmission morbidity and on mortality.

This thesis does, however, raise following questions:

1. ICU patients comprise a heterogeneous cohort, and there is further need to examine whether associations between chronic diseases and outcome are different in disparate groups of ICU patients, i.e., whether there are effect-measure modifications.
2. Can patients at high risk of death be identified earlier and death thereby prevented by earlier ICU admission?
3. What is the mechanism behind the increased mortality in ICU patients with chronic diseases including diabetes?
4. Does chronic diseases including diabetes and preadmission metformin treatment influence ICU admission rate?
5. What is the impact of specific chronic diseases with different severities?
6. What is the impact of preadmission chronic diseases on other and potentially treatable long-term outcomes, including readmissions, persistent organ dysfunction, return to work, and somatic and psychiatric illness?
7. How frequently are oral antidiabetic drugs continued during hospitalization and what is the impact of in-hospital metformin use on the frequency of lactic acidosis and outcome in ICU patients?

These questions could be addressed by:

1. Studies examining the influence of reason for ICU admission, including type of any preadmission surgery, on the association between chronic diseases and outcome, e.g., by stratification or restriction to subgroups of ICU patients based on reason for admission, including type of surgery before ICU admission.

2. Studies of critical illness outside the ICU could help identifying high-risk groups that may benefit from earlier ICU admission.
3. More detailed clinical data about in-hospital complications and severity of illness that may help us identify the underlying mechanisms behind the increased mortality and redirect preventive initiatives towards these.
4. Studies of risk factors for ICU admission could be conducted within cohorts of all or particular groups of hospitalized patients, e.g., patients with specific surgical procedures, which would be feasible using large databases. Given the complexity of ICU triage, it would also be of interest to study patients that were considered for ICU admission but were rejected.
5. More detailed data on severity of preadmission chronic diseases should be obtained. For example estimated glomerular filtration rate in chronic kidney disease, ejection fraction in heart failure, or pharmacological treatment steps in patients with diseases like chronic obstructive pulmonary disease or heart failure.
6. Studies of other long-term outcomes of ICU patients compared with other hospitalized patients and the general population can be conducted using data available from the Danish registries and databases.
7. In-hospital medication data are needed to address whether oral antidiabetic are discontinued on hospital admission and to examine any impact of other treatment during hospitalization, including the ICU stay.

In order to address these questions, it will be necessary to supplement existing data with more detailed clinical data. Such data could be obtained from manual data collection, from data in the newly implemented electronic medical records, and from nationwide clinical databases, such as the Danish Intensive Care Database, that are becoming increasingly complete.

The overall aim for future studies would be to improve the outcome for Danish intensive care patients. As illustrated in Figure 1-2 on page 5, there are several determinants of prognosis, and efforts should be directed to all of these to improve prognosis. At the patient level, prevention of chronic disease and its complications may

potentially decrease death from critical illness. Early identification and treatment of exacerbations of chronic diseases, sepsis, and other serious medical and surgical complications in the wards may potentially reduce the number of ICU admissions and decrease the severity of illness on ICU admission. Prognosis may also be improved by improved diagnostics during the ICU stay, including technically improvements with better diagnostic imaging and biochemical characterization of the critical illness by biomarkers. Many clinicians and ICU studies focus primarily on the clinical performance, e.g., bed availability, avoidance of adverse events, and treatment during the ICU stay, such as organ supportive treatment, antibiotic treatment, and immune modulating therapy. But this is, as illustrated, only one of the determinants of the outcome.

The hope is that this thesis will contribute to an improved understanding of the prognosis of ICU patients with preadmission morbidity, including diabetes, and that it will foster the suggested future research.

8 Summary

The intensive care units (ICUs) comprise a central and resource demanding part of the health care system with more than 30,000 admissions in Denmark each year. An understanding of the clinical course of ICU patients is needed for clinical decision making and for future planning of ICU capacity. With the increased life expectancy, more elderly with chronic diseases are expected to be admitted to the ICUs. It is therefore crucial to know the prognosis of patients with an increased preadmission morbidity level in general as well as in patients with specific diseases such as diabetes.

This thesis included three cohort studies on mortality among ICU patients based on data from the Danish National Registry of Patients, the Danish Civil Registration System, and the prescription and laboratory databases covering Northern Denmark.

The aims of this thesis were to examine: 1) whether preadmission morbidity level was associated with increased mortality following ICU admission and whether the impact was more pronounced than in the general population, 2) whether preadmission type 2 diabetes with and without major diabetic complications was associated with increased mortality, 3) whether metformin was associated with a decreased mortality in ICU patients with type 2 diabetes.

Study I included all 28,172 adult patients admitted to an ICU in Northern Denmark in 2005–2008. Preadmission morbidity level was assessed by the Charlson Comorbidity Index (CCI) Score: 51.5% had a low morbidity level (CCI = 0), 34.1% had a moderate (CCI = 1–2), and 14.4% had a high morbidity level (CCI = 3+). The 30-day mortalities at these levels were 10.8%, 18.4%, and 26.7%, respectively. Compared with patients with a low morbidity level, the age- and sex-adjusted 30-day mortality was 30% higher in patients with a moderate morbidity level and 86 % higher in patients with a high morbidity level. The 3-year mortality in the three groups was 21.3%, 43.1%, and 63.2%, respectively. Morbidity level was lower in an age- and gender-matched general population cohort that included 281,671 persons and had less impact on mortality throughout the follow-up period.

Study II included 39,286 ICU patients aged over 40 who were admitted during 2005–2010. Type 2 diabetes was prevalent in 15.3%. In 18.3% of these, diabetes was complicated by heart disease, 4.3% by kidney diseases, and 2.4% by both. The 30-day mortality was 22.9% in type 2 diabetic patients and 18.4% in non-diabetic patients, corresponding to a 18% increased mortality after adjustment. Mortality was 65% higher in diabetes patients with kidney disease compared with patients without diabetes. Mortality was also increased from day 31 up to 1 year and was 17.3% in type 2 diabetic patients and 13.7% in nondiabetics patients, corresponding to 20% increased mortality after adjustment.

Study III included 6,170 adult ICU patients with type 2 diabetes. Within 90 day before ICU admission, 13.4% of these filled a prescription for metformin only, while 17.8% received metformin in combination with one or more other antidiabetic drugs. The 30-day mortality was 16.9% in metformin monotherapy users, 18.0% in metformin combination therapy users, and 25.0% in non-users. After adjustment, mortality was decreased 21% in metformin monotherapy users and 17% in metformin combination therapy users, both compared with non-users. The association could be due to a pharmacological effect of metformin, although unmeasured differences in patient characteristics between metformin users and non-users could influence the results

In conclusion, this thesis showed that ICU patients with increased preadmission morbidity levels had markedly worsened short- and long-term prognosis compared with the general population. Also, type 2 diabetes was associated with a worsened prognosis, especially when complicated by kidney disease. Preadmission metformin use was, however, associated with a decreased mortality among type 2 patients admitted to the ICU.

9 Dansk resume

Intensivafdelingerne udgør en central og ressourcekrævende del af sundhedssystemet med mere end 30.000 intensivindlæggelser i Danmark hvert år. Forståelse af det kliniske forløb hos intensivpatienter er nødvendig for den kliniske beslutningsproces og for fremtidig planlægning af intensivafdelingernes kapacitet. Idet der er øget forventet levetid i befolkningen, vil vi forvente at flere ældre med kroniske sygdomme fremover bliver indlagt på intensivafdelingerne. Det er derfor vigtigt at kende prognosen for patienter med generelt forøget morbiditetsniveau, samt for patienter med specifikke sygdomme såsom diabetes.

Denne afhandling indeholder tre kohortestudier omkring dødelighed blandt intensivpatienter og bygger på data fra Landspatientregisteret, CPR-registeret, samt recept- og laboratoriedatabaserne i Region Midtjylland og Region Nordjylland (nordlige Danmark).

Formålet med afhandlingen var at undersøge: 1) Hvorvidt morbiditetsniveau forud for indlæggelsen var forbundet med øget dødelighed efter intensivindlæggelse og hvorvidt påvirkningen var mere udtalt end i befolkningen generelt, 2) Hvorvidt forudgående type 2 diabetes med og uden betydelige diabetiske komplikationer var forbundet med øget dødelighed, og 3) Hvorvidt forudgående metformin var forbundet med nedsat mortalitet hos intensivpatienter med type 2 diabetes.

Studie I inkluderede 28.172 patienter indlagt på intensivafdelinger i det nordlige Danmark i 2005-2008. Forudgående morbiditetsniveau blev fastlagt vha. Charlson komorbiditetsindex score. I alt 51,5 % havde lavt morbiditetsniveau, 34,1 % havde moderat og 14,4 % havde højt morbiditetsniveau. 30-dages mortaliteten in disse grupper var henholdsvis 10,8 %, 18,4 % og 26,7 %. Sammenlignet med patienter med lavt morbiditetsniveau, var den alders- og kønsjusterede 30-dages dødelighed 30 % højere hos patienter med moderat morbiditetsniveau og 86 % højere hos patienter med højt morbiditetsniveau. 3-års dødeligheden i de tre grupper var henholdsvis 21,3 %, 43,1 %, og 63,2 %. Morbiditetsniveauet var lavere hos de 281.671 personer inkluderet i den alders- og kønsmatchede befolkningskohorte og morbiditet havde mindre indflydelse på dødeligheden under hele opfølgningstiden.

Studie II inkluderede 39.286 intensivpatienter over 40 år indlagt i 2005-2010. I alt 15,3 % havde type 2 diabetes. Af disse, var 18,3 % kompliceret af hjertesygdom, 4,3 % af nyresygdom og 2,4 % af begge. 30-dages dødeligheden var 22,9 % blandt type 2 diabetespatienter og 18,4 % in ikke-diabetiske patienter. Efter justering, svarede dette til 18 % forøget dødelighed. Hos type 2 diabetes patienter med nyresygdom var dødeligheden dog 65 % højere end hos patienter uden diabetes. Dødeligheden fra dag 31 og op til 1 år var 17,3 % hos type 2 diabetespatienter og 13,7 % hos øvrige patienter, sv.t. 20 % øget dødelighed efter justering.

Studie III inkluderede 6,170 intensivpatienter med type 2 diabetes. I perioden 90 dage op til intensivindlæggelse indløste 13,4 % en recept på metformin som monoterapi, medens 17,8 % fik metformin i kombination med et andet antidiabetisk lægemiddel. 30-dages dødeligheden var 16,9 % hos patienter med metformin som monoterapi, 18,0 % hos patienter med metformin som kombinationsterapi og 25,0 % blandt ikke-brugere. Efter justering for køn og alder var der stadig en 21% lavere dødelighed blandt metformin monoterapi brugere og en 17% lavere dødelighed blandt metformin kombinationsterapi brugere, sammenlignet med ikke-brugere. Den fundne association kan være en famakologisk effekt, men umålte forskelle i patientkarakteristika kan have påvirket resultaterne.

Samlet set har studierne vist, at intensivpatienter med forudgående morbiditet har en betydelig forværret kort- og langtidsprognose sammenlignet med betydningen i befolkningen generelt. Også type 2 diabetes var forbundet med en øget dødelighed, særligt hos patienter med samtidig kronisk nyresygdom. Metformin brug var derimod associeret med nedsat dødelighed blandt intensivpatienter med type 2 diabetes.

10 References

1. Dansk Intensiv Database (DID). Årsrapport 2010. 2011. Danish. Available from: http://www.did1.dk/upl/9124/DIDrsrapport2010.pdf

2. Sundhedsstyrelsen. Intensiv terapi - definitioner, dokumentation og visitationsprincipper. 2006. Danish. Available from: http://www.sst.dk/publ/Publ2006/PLAN/Intensiv_terapi/Intensiv_terapi.pdf

3. Valentin A, Ferdinande P. Recommendations on basic requirements for intensive care units: structural and organizational aspects. Intensive Care Med 2011;37(10):1575-1587.

4. Wunsch H, Angus DC, Harrison DA et al. Variation in critical care services across North America and Western Europe. Crit Care Med 2008;36(10):2787-2789.

5. Halpern NA, Pastores SM. Critical care medicine in the United States 2000-2005: an analysis of bed numbers, occupancy rates, payer mix, and costs. Crit Care Med 2010;38(1):65-71.

6. Edbrooke DL, Minelli C, Mills GH et al. Implications of ICU triage decisions on patient mortality: a cost-effectiveness analysis. Crit Care 2011;15(1):R56.

7. Curtis JR, Vincent JL. Ethics and end-of-life care for adults in the intensive care unit. Lancet 2010;376(9749):1347-1353.

8. World Health Organization. WORLD HEALTH STATISTICS 2011. Part II Global Health Indicators. Life expectancy and mortality. 2011

9. Statistics Denmark. Statbank Denmark [Internet]. 2011. Available from: http://www.statistikbanken.dk/

10. Garrouste-Org, Timsit JF, Montuclard L et al. Decision-making process, outcome, and 1-year quality of life of octogenarians referred for intensive care unit admission. Intensive Care Med 2006;32(7):1045-1051.

11. Bagshaw SM, Webb SA, Delaney A et al. Very old patients admitted to intensive care in Australia and New Zealand: a multi-centre cohort analysis. Crit Care 2009;13(2):R45.

12. Anderson G, Horvath J. The growing burden of chronic disease in America. Public Health Rep 2004;119(3):263-270.

13. Lecuyer L, Chevret S, Thiery G, Darmon M, Schlemmer B, Azoulay E. The ICU trial: a new admission policy for cancer patients requiring mechanical ventilation. Crit Care Med 2007;35(3):808-814.

14. Azoulay E, Soares M, Darmon M, Benoit D, Pastores S, Afessa B. Intensive care of the cancer patient: recent achievements and remaining challenges. Ann Intensive Care 2011;1(1):5.

15. Williams TA, Ho KM, Dobb GJ, Finn JC, Knuiman MW, Webb SA. Changes in case-mix and outcomes of critically ill patients in an Australian tertiary intensive care unit. Anaesth Intensive Care 2010;38(4):703-709.

16. Danaei G, Finucane MM, Lu Y et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. Lancet 2011;378(9785):31-40.

17. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010;87(1):4-14.

18. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature 2001;414(6865):782-787.

19. Angus DC, Burgner D, Wunderink R et al. The PIRO concept: P is for predisposition. Crit Care 2003;7(3):248-251.

20. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45(6):613-619.

21. Valderas JM, Starfield B, Sibbald B, Salisbury C, Roland M. Defining comorbidity: implications for understanding health and health services. Ann Fam Med 2009;7(4):357-363.

22. Reisner-Senelar L. The birth of intensive care medicine: Bjorn Ibsen's records. Intensive Care Med 2011;37(7):1084-1086.

23. Lassen HC. A preliminary report on the 1952 epidemic of poliomyelitis in Copenhagen with special reference to the treatment of acute respiratory insufficiency. Lancet 1953;1(6749):37-41.

24. Ibsen B. The anaesthetist's viewpoint on the treatment of respiratory complications in poliomyelitis during the epidemic in Copenhagen, 1952. Proc R Soc Med 1954;47(1):72-74.

25. Bone RC, Balk RA, Cerra FB et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101(6):1644-1655.

26. Ferreira AM, Sakr Y. Organ dysfunction: general approach, epidemiology, and organ failure scores. Semin Respir Crit Care Med 2011;32(5):543-551.

27. Vincent JL, Singer M. Critical care: advances and future perspectives. Lancet 2010;376(9749):1354-1361.

28. Angus DC, Carlet J. Surviving intensive care: a report from the 2002 Brussels Roundtable. Intensive Care Med 2003;29(3):368-377.

29. Fletcher RH, Fletcher SW. Clinical Epidemiology - The Essentials. Fourth ed. Philadelphia: Lippincott Williams & Wilkins; 2005.

30. Sprung CL, Geber D, Eidelman LA et al. Evaluation of triage decisions for intensive care admission. Crit Care Med 1999;27(6):1073-1079.

31. Howe DC. Observational study of admission and triage decisions for patients referred to a regional intensive care unit. Anaesth Intensive Care 2011;39(4):650-658.

32. Guidelines for intensive care unit admission, discharge, and triage. Task Force of the American College of Critical Care Medicine, Society of Critical Care Medicine. Crit Care Med 1999;27(3):633-638.

33. Moons KG, Royston P, Vergouwe Y, Grobbee DE, Altman DG. Prognosis and prognostic research: what, why, and how? BMJ 2009;338:b375.

34. Altman DG. Systematic reviews of evaluations of prognostic variables. BMJ 2001;323(7306):224-228.

35. Desai SV, Law TJ, Needham DM. Long-term complications of critical care. Crit Care Med 2011;39(2):371-379.

36. Wunsch H, Angus DC. The puzzle of long-term morbidity after critical illness. Crit Care 2010;14(1):121.

37. Sackett DL, Haynes RB, Guyatt GH, Tugwell P. Clinical Epidemiology: A Basic Science for Clinical Medicine. Second ed. Boston: Little, Brown and Company; 1991.

38. Rivers E, Nguyen B, Havstad S et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345(19):1368-1377.

39. Kumar A, Zarychanski R, Light B et al. Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity-matched analysis. Crit Care Med 2010;38(9):1773-1785.

40. Altman DG, Vergouwe Y, Royston P, Moons KG. Prognosis and prognostic research: validating a prognostic model. BMJ 2009;338:b605.

41. Moons KG, Altman DG, Vergouwe Y, Royston P. Prognosis and prognostic research: application and impact of prognostic models in clinical practice. BMJ 2009;338:b606.

42. Royston P, Moons KG, Altman DG, Vergouwe Y. Prognosis and prognostic research: Developing a prognostic model. BMJ 2009;338:b604.

43. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13(10):818-829.

44. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993;270(24):2957-2963.

45. Strand K, Flaatten H. Severity scoring in the ICU: a review. Acta Anaesthesiol Scand 2008;52(4):467-478.

46. Wulff HR, Gøtzsche PC. Rationel klinik. 5th ed. Copenhagen: Munksgaard Danmark; 2007.

47. Sorensen HT, Lash TL, Rothman KJ. Beyond randomized controlled trials: a critical comparison of trials with nonrandomized studies. Hepatology 2006;44(5):1075-1082.

48. Vincent JL. We should abandon randomized controlled trials in the intensive care unit. Crit Care Med 2010;38(10 Suppl):S534-S538.

49. van den BG, Wouters P, Weekers F et al. Intensive insulin therapy in the critically ill patients. N Engl J Med 2001;345(19):1359-1367.

50. Brunkhorst FM, Engel C, Bloos F et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008;358(2):125-139.

51. Finfer S, Chittock DR, Su SY et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360(13):1283-1297.

52. Moreno RP, Metnitz PG, Almeida E et al. SAPS 3--From evaluation of the patient to evaluation of the intensive care unit. Part 2: Development of a prognostic model for hospital mortality at ICU admission. Intensive Care Med 2005;31(10):1345-1355.

53. Ho KM, Knuiman M, Finn J, Webb SA. Estimating long-term survival of critically ill patients: the PREDICT model. PLoS ONE 2008;3(9):e3226.

54. Christensen S, Johansen MB, Christiansen CF, Jensen R, Lemeshow S. Comparison of Charlson comorbidity index with SAPS and APACHE scores for prediction of mortality following intensive care. Clin Epidemiol 2011;3:203-211.

55. Levy MM, Fink MP, Marshall JC et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med 2003;29(4):530-538.

56. Howell MD, Talmor D, Schuetz P, Hunziker S, Jones AE, Shapiro NI. Proof of principle: The predisposition, infection, response, organ failure sepsis staging system. Crit Care Med 2011;39(2):322-327.

57. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373-383.

58. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sorensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. BMC Med Res Methodol 2011;11(1):83.

59. Schneeweiss S, Maclure M. Use of comorbidity scores for control of confounding in studies using administrative databases. Int J Epidemiol 2000;29(5):891-898.

60. Lash TL, Mor V, Wieland D, Ferrucci L, Satariano W, Silliman RA. Methodology, design, and analytic techniques to address measurement of comorbid disease. J Gerontol A Biol Sci Med Sci 2007;62(3):281-285.

61. Needham DM, Scales DC, Laupacis A, Pronovost PJ. A systematic review of the Charlson comorbidity index using Canadian administrative databases: a perspective on risk adjustment in critical care research. J Crit Care 2005;20(1):12-19.

62. Timmers TK, Verhofstad MH, Moons KG, Leenen LP. Long-term survival after surgical intensive care unit admission: fifty percent die within 10 years. Ann Surg 2011;253(1):151-157.

63. Wright JC, Plenderleith L, Ridley SA. Long-term survival following intensive care: subgroup analysis and comparison with the general population. Anaesthesia 2003;58(7):637-642.

64. Niskanen M, Kari A, Halonen P. Five-year survival after intensive care--comparison of 12,180 patients with the general population. Finnish ICU Study Group. Crit Care Med 1996;24(12):1962-1967.

65. Williams TA, Dobb GJ, Finn JC et al. Determinants of long-term survival after intensive care. Crit Care Med 2008;36(5):1523-1530.

66. Flaatten H, Kvale R. Survival and quality of life 12 years after ICU. A comparison with the general Norwegian population. Intensive Care Med 2001;27(6):1005-1011.

67. Zaren B, Bergstrom R. Survival compared to the general population and changes in health status among intensive care patients. Acta Anaesthesiol Scand 1989;33(1):6-12.

68. Dragsted L, Qvist J, Madsen M. Outcome from intensive care. IV. A 5-year study of 1308 patients: long-term outcome. Eur J Anaesthesiol 1990;7:51-62.

69. Wunsch H, Guerra C, Barnato AE, Angus DC, Li G, Linde-Zwirble WT. Three-year outcomes for Medicare beneficiaries who survive intensive care. JAMA 2010;303(9):849-856.

70. Williams TA, Dobb GJ, Finn JC et al. Data linkage enables evaluation of long-term survival after intensive care. Anaesth Intensive Care 2006;34(3):307-315.

71. Ghelani D, Moran JL, Sloggett A, Leeson RJ, Peake SL. Long-term survival of intensive care and hospital patient cohorts compared with the general Australian population: a relative survival approach. J Eval Clin Pract 2009;15(3):425-435.

72. Siegelaar SE, Hickmann M, Hoekstra JB, Holleman F, DeVries JH. The effect of diabetes on mortality in critically ill patients: a systematic review and meta-analysis. Crit Care 2011;15(5):R205.

73. Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. Lancet 2009;373(9677):1798-1807.

74. Christiansen CF, Christensen S, Johansen MB, Larsen KM, Tonnesen E, Sorensen HT. The impact of pre-admission morbidity level on 3-year mortality after intensive care: a Danish cohort study. Acta Anaesthesiol Scand 2011;55(8):962-970.

75. Kearney T, Dang C. Diabetic and endocrine emergencies. Postgrad Med J 2007;83(976):79-86.

76. Alexiewicz JM, Kumar D, Smogorzewski M, Klin M, Massry SG. Polymorphonuclear leukocytes in non-insulin-dependent diabetes mellitus: abnormalities in metabolism and function. Ann Intern Med 1995;123(12):919-924.

77. Marhoffer W, Stein M, Maeser E, Federlin K. Impairment of polymorphonuclear leukocyte function and metabolic control of diabetes. Diabetes Care 1992;15(2):256-260.

78. Grant PJ. Diabetes mellitus as a prothrombotic condition. J Intern Med 2007;262(2):157-172.

79. Carr ME. Diabetes mellitus: a hypercoagulable state. J Diabetes Complications 2001;15(1):44-54.

80. Hsu CY, Ordonez JD, Chertow GM, Fan D, McCulloch CE, Go AS. The risk of acute renal failure in patients with chronic kidney disease. Kidney Int 2008;74(1):101-107.

81. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. JAMA 2002;287(19):2570-2581.

82. Movahed MR, Hashemzadeh M, Jamal M. Increased prevalence of ventricular fibrillation in patients with type 2 diabetes mellitus. Heart Vessels 2007;22(4):251-253.

83. Movahed MR, Hashemzadeh M, Jamal MM. The prevalence of pulmonary embolism and pulmonary hypertension in patients with type II diabetes mellitus. Chest 2005;128(5):3568-3571.

84. Kornum JB, Thomsen RW, Riis A, Lervang HH, Schonheyder HC, Sorensen HT. Diabetes, glycemic control, and risk of hospitalization with pneumonia: a population-based case-control study. Diabetes Care 2008;31(8):1541-1545.

85. Thomsen RW, Hundborg HH, Lervang HH, Johnsen SP, Schonheyder HC, Sorensen HT. Risk of community-acquired pneumococcal bacteremia in patients with diabetes: a population-based case-control study. Diabetes Care 2004;27(5):1143-1147.

86. Schuetz P, Castro P, Shapiro NI. Diabetes and sepsis: preclinical findings and clinical relevance. Diabetes Care 2011;34(3):771-778.

87. Michalia M, Kompoti M, Koutsikou A et al. Diabetes mellitus is an independent risk factor for ICU-acquired bloodstream infections. Intensive Care Med 2009;35(3):448-454.

88. Yang Y, Salam ZH, Ong BC, Yang KS. Respiratory dysfunction in patients with sepsis: protective effect of diabetes mellitus. Am J Crit Care 2011;20(2):e41-e47.

89. Honiden S, Gong MN. Diabetes, insulin, and development of acute lung injury. Crit Care Med 2009;37(8):2455-2464.

90. Moss M, Guidot DM, Steinberg KP et al. Diabetic patients have a decreased incidence of acute respiratory distress syndrome. Crit Care Med 2000;28(7):2187-2192.

91. Esper AM, Moss M, Martin GS. The effect of diabetes mellitus on organ dysfunction with sepsis: an epidemiological study. Crit Care 2009;13(1):R18.

92. Hansen HH, Joensen AM, Riahi S, Malczynski J, Molenberg D, Ravkilde J. Short and long-term outcome in diabetic patients with acute myocardial infarction in the invasive era. Scand Cardiovasc J 2007;41(1):19-24.

93. Jensen LO, Maeng M, Thayssen P et al. Influence of Diabetes Mellitus on Clinical Outcomes Following Primary Percutaneous Coronary Intervention in Patients With ST-Segment Elevation Myocardial Infarction. Am J Cardiol 2011;Dec 5. [Epub ahead of print].

94. Brown JR, Edwards FH, O'Connor GT, Ross CS, Furnary AP. The diabetic disadvantage: historical outcomes measures in diabetic patients undergoing cardiac surgery -- the pre-intravenous insulin era. Semin Thorac Cardiovasc Surg 2006;18(4):281-288.

95. Thomsen RW, Riis A, Christensen S, Norgaard M, Sorensen HT. Diabetes and 30-day mortality from peptic ulcer bleeding and perforation: a Danish population-based cohort study. Diabetes Care 2006;29(4):805-810.

96. Dahagam CK, Mora A, Wolf SE, Wade CE. Diabetes does not influence selected clinical outcomes in critically ill burn patients. J Burn Care Res 2011;32(2):256-262.

97. Ahmad R, Cherry RA, Lendel I et al. Increased hospital morbidity among trauma patients with diabetes mellitus compared with age- and injury severity score-matched control subjects. Arch Surg 2007;142(7):613-618.

98. Kornum JB, Thomsen RW, Riis A, Lervang HH, Schonheyder HC, Sorensen HT. Type 2 diabetes and pneumonia outcomes: a population-based cohort study. Diabetes Care 2007;30(9):2251-2257.

99. Vardakas KZ, Siempos II, Falagas ME. Diabetes mellitus as a risk factor for nosocomial pneumonia and associated mortality. Diabet Med 2007;24(10):1168-1171.

100. Schuetz P, Jones AE, Howell MD et al. Diabetes is not associated with increased mortality in emergency department patients with sepsis. Ann Emerg Med 2011;58(5):438-444.

101. Thomsen RW, Hundborg HH, Lervang HH, Johnsen SP, Schonheyder HC, Sorensen HT. Diabetes mellitus as a risk and prognostic factor for community-acquired bacteremia due to enterobacteria: a 10-year, population-based study among adults. Clin Infect Dis 2005;40(4):628-631.

102. Thomsen RW, Hundborg HH, Lervang HH, Johnsen SP, Sorensen HT, Schonheyder HC. Diabetes and outcome of community-acquired pneumococcal bacteremia: a 10-year population-based cohort study. Diabetes Care 2004;27(1):70-76.

103. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab 2002;87(3):978-982.

104. Christiansen C, Toft P, Jorgensen HS, Andersen SK, Tonnesen E. Hyperglycaemia and mortality in critically ill patients. A prospective study. Intensive Care Med 2004;30(8):1685-1688.

105. Egi M, Bellomo R, Stachowski E et al. Blood glucose concentration and outcome of critical illness: the impact of diabetes. Crit Care Med 2008;36(8):2249-2255.

106. van den BG, Wilmer A, Milants I et al. Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. Diabetes 2006;55(11):3151-3159.

107. Ritz E, Orth SR. Nephropathy in patients with type 2 diabetes mellitus. N Engl J Med 1999;341(15):1127-1133.

108. de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J. Temporal trends in the prevalence of diabetic kidney disease in the United States. JAMA 2011;305(24):2532-2539.

109. Bagshaw SM, Uchino S. End-stage kidney disease patients in the intensive care unit. Nephrol Dial Transplant 2009;24(6):1714-1717.

110. Hutchison CA, Crowe AV, Stevens PE, Harrison DA, Lipkin GW. Case mix, outcome and activity for patients admitted to intensive care units requiring chronic renal dialysis: a secondary analysis of the ICNARC Case Mix Programme Database. Crit Care 2007;11(2):R50.

111. Bell M, Granath F, Schon S, Lofberg E, Ekbom A, Martling CR. End-stage renal disease patients on renal replacement therapy in the intensive care unit: short- and long-term outcome. Crit Care Med 2008;36(10):2773-2778.

112. Khosla N, Soroko SB, Chertow GM et al. Preexisting chronic kidney disease: a potential for improved outcomes from acute kidney injury. Clin J Am Soc Nephrol 2009;4(12):1914-1919.

113. Rocha E, Soares M, Valente C et al. Outcomes of critically ill patients with acute kidney injury and end-stage renal disease requiring renal replacement therapy: a case-control study. Nephrol Dial Transplant 2009;24(6):1925-1930.

114. Higgins TL, Estafanous FG, Loop FD et al. ICU admission score for predicting morbidity and mortality risk after coronary artery bypass grafting. Ann Thorac Surg 1997;64(4):1050-1058.

115. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. BMJ 1997;315(7121):1533-1537.

116. Graham BB, Keniston A, Gajic O, Trillo Alvarez CA, Medvedev S, Douglas IS. Diabetes mellitus does not adversely affect outcomes from a critical illness. Crit Care Med 2010;38(1):16-24.

117. Stegenga ME, Vincent JL, Vail GM et al. Diabetes does not alter mortality or hemostatic and inflammatory responses in patients with severe sepsis. Crit Care Med 2010;38(2):539-545.

118. Bernard GR, Vincent JL, Laterre PF et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001;344(10):699-709.

119. Vincent JL, Preiser JC, Sprung CL, Moreno R, Sakr Y. Insulin-treated diabetes is not associated with increased mortality in critically ill patients. Crit Care 2010;14(1):R12.

120. Zmijewski JW, Lorne E, Zhao X et al. Mitochondrial respiratory complex I regulates neutrophil activation and severity of lung injury. Am J Respir Crit Care Med 2008;178(2):168-179.

121. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. Ann Intern Med 2002;137(1):25-33.

122. Nathan DM, Buse JB, Davidson MB et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009;32(1):193-203.

123. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352(9131):854-865.

124. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359(15):1577-1589.

125. Hundal RS, Inzucchi SE. Metformin: new understandings, new uses. Drugs 2003;63(18):1879-1894.

126. Nyenwe EA, Jerkins TW, Umpierrez GE, Kitabchi AE. Management of type 2 diabetes: evolving strategies for the treatment of patients with type 2 diabetes. Metabolism 2011;60(1):1-23.

127. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. N Engl J Med 2003;348(2):138-150.

128. Tsoyi K, Jang HJ, Nizamutdinova IT et al. Metformin inhibits HMGB1 release in LPS-treated RAW 264.7 cells and increases survival rate of endotoxaemic mice. Br J Pharmacol 2011;162(7):1498-1508.

129. Bergheim I, Luyendyk JP, Steele C et al. Metformin prevents endotoxin-induced liver injury after partial hepatectomy. J Pharmacol Exp Ther 2006;316(3):1053-1061.

130. Hattori Y, Suzuki K, Hattori S, Kasai K. Metformin inhibits cytokine-induced nuclear factor kappaB activation via AMP-activated protein kinase activation in vascular endothelial cells. Hypertension 2006;47(6):1183-1188.

131. Grant PJ. Beneficial effects of metformin on haemostasis and vascular function in man. Diabetes Metab 2003;29(4 Pt 2):6S44-6S52.

132. Levi M, van der Poll T. Inflammation and coagulation. Crit Care Med 2010;38(2 Suppl):S26-S34.

133. Boomer JS, To K, Chang KC et al. Immunosuppression in Patients Who Die of Sepsis and Multiple Organ Failure. JAMA 2011;306(23):2594-2605.

134. Toft P, Tonnesen E. Immune-modulating interventions in critically ill septic patients: pharmacological options. Expert Rev Clin Pharmacol 2011;4(4):491-501.

135. Cusi K, Consoli A, DeFronzo RA. Metabolic effects of metformin on glucose and lactate metabolism in noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab 1996;81(11):4059-4067.

136. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev 2010;(4):CD002967.

137. Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. Diabetes Care 2011;34(6):1431-1437.

138. Ansari G, Mojtahedzadeh M, Kajbaf F et al. How does blood glucose control with metformin influence intensive insulin protocols? Evidence for involvement of oxidative stress and inflammatory cytokines. Adv Ther 2008;25(7):681-702.

139. Calvert JW, Gundewar S, Jha S et al. Acute metformin therapy confers cardioprotection against myocardial infarction via AMPK-eNOS-mediated signaling. Diabetes 2008;57(3):696-705.

140. Kao J, Tobis J, McClelland RL et al. Relation of metformin treatment to clinical events in diabetic patients undergoing percutaneous intervention. Am J Cardiol 2004;93(11):1347-50, A5.

141. Mellbin LG, Malmberg K, Norhammar A, Wedel H, Ryden L. The impact of glucose lowering treatment on long-term prognosis in patients with type 2 diabetes and myocardial infarction: a report from the DIGAMI 2 trial. Eur Heart J 2008;29(2):166-176.

142. Horsdal HT, Johnsen SP, Sondergaard F, Rungby J. Type of preadmission glucose-lowering treatment and prognosis among patients hospitalised with myocardial infarction: a nationwide follow-up study. Diabetologia 2008;51(4):567-574.

143. Lamanna C, Monami M, Marchionni N, Mannucci E. Effect of metformin on cardiovascular events and mortality: a meta-analysis of randomized clinical trials. Diabetes Obes Metab 2011;13(3):221-228.

144. Duncan AI, Koch CG, Xu M et al. Recent metformin ingestion does not increase in-hospital morbidity or mortality after cardiac surgery. Anesth Analg 2007;104(1):42-50.

145. Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. Dan Med Bull 2006;53(4):441-449.

146. Frank L. Epidemiology. When an entire country is a cohort. Science 2000;287(5462):2398-2399.

147. Dansk Intensiv Database (DID). Anvendelse af Landspatientregisteret til monitorering af kvaliteten af intensiv terapi i Danmark. 2009 . Danish. Available from: http://www.did1.dk/upl/8821/DIDLPR12.pdf.

148. Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull 1999;46(3):263-268.

149. NOMESCO Classification of Surgical Procedures. 1.15 ed. Copenhagen: Nordic Medico-Statistical Committee; 2010.

150. Ehrenstein V, Antonsen S, Pedersen L. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. Clin Epidemiol 2010;2:273-279.

151. Grann AF, Erichsen R, Nielsen AG, Froslev T, Thomsen RW. Existing data sources for clinical epidemiology: The clinical laboratory information system (LABKA) research database at Aarhus University, Denmark. Clin Epidemiol 2011;3:133-138.

152. Standards of medical care in diabetes--2011. Diabetes Care 2011;34 Suppl 1:S11-S61.

153. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol 2003;158(9):915-920.

154. Flaatten H. Long-term outcomes after intensive care. In: Kuhlen R, Moreno R, Ranieri M, Rhodes A, editors. 25 Years of Progress and Innovation in Intensive Care Medicine. Berlin: Medizinisch Wissenschaftliche Verlagsgesellschaft; 2007:419-427.

155. Watson RS, Angus DC. Assessing Outcomes in Critical Care. Journal of Intensive Care Medicine 2002;17:103-111.

156. Rothman KJ. Epidemiology: an introduction. 1st ed. New York: Oxford University Press; 2002.

157. Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA 2001;286(14):1754-1758.

158. Venkata C, Sampathkumar P, Afessa B. Hospitalized patients with 2009 H1N1 influenza infection: the Mayo Clinic experience. Mayo Clin Proc 2010;85(9):798-805.

159. Kirkwood BR, Sterne JAC. Standardization. Essential Medical Statistics. Second edition ed. Malden, USA: Blackwell Science Ltd; 2003:263-271.

160. Greenland S, Lash TL, Rothman KJ. Concepts of Interaction. Modern Epidemiology. Third ed. Lippincott William & Wilkins; 2008:71-83.

161. Jepsen P, Vilstrup H, Andersen PK, Lash TL, Sorensen HT. Comorbidity and survival of Danish cirrhosis patients: a nationwide population-based cohort study. Hepatology 2008;48(1):214-220.

162. Lash TL, Johansen MB, Christensen S et al. Hospitalization rates and survival associated with COPD: a nationwide Danish cohort study. Lung 2011;189(1):27-35.

163. Glynn RJ, Schneeweiss S, Sturmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. Basic Clin Pharmacol Toxicol 2006;98(3):253-259.

164. Sturmer T, Joshi M, Glynn RJ, Avorn J, Rothman KJ, Schneeweiss S. A review of the application of propensity score methods yielded increasing use, advantages in specific settings, but not substantially different estimates compared with conventional multivariable methods. J Clin Epidemiol 2006;59(5):437-447.

165. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Sturmer T. Variable selection for propensity score models. Am J Epidemiol 2006;163(12):1149-1156.

166. Normand ST, Landrum MB, Guadagnoli E et al. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. J Clin Epidemiol 2001;54(4):387-398.

167. Hosmer DW, Lemeshow S, May S. Applied Survival Analysis: Regression Modeling of Time to Event Data. 2nd ed. Wiley-Interscience Publication; 2008.

168. Greenland S. Modeling and variable selection in epidemiologic analysis. Am J Public Health 1989;79(3):340-349.

169. Sorensen HT. Regional administrative health registries as a resource in clinical epidemiology. International Journal of Risk and Safety in Medicine 1997;10(1):1-22.

170. Sorensen HT, Sabroe S, Olsen J. A framework for evaluation of secondary data sources for epidemiological research. Int J Epidemiol 1996;25(2):435-442.

171. Sørensen HT, Baron JA. Registries and medical databases. In: Olsen J, Saracci R, Trichopoulos D, editors. Teaching epidemiology. Third ed. Oxford: Oxford University Press; 2010:455-466.

172. Rothman KJ, Greenland S, Lash TL. Validity in Epidemiologic Studies. Modern Epidemiology. Third ed. Lippincott William & Wilkins; 2008:128-147.

173. Quan H, Li B, Couris CM et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol 2011;173(6):676-682.

174. Rothman KJ, Greenland S, Lash TL. Design Strategies to Improve Study Accuracy. Modern Epidemiology. Third ed. Lippincott William & Wilkins; 2008:168-182.

175. Rothman KJ. Epidemiology - An introduction, pp. 94-111. Oxford University Press; 2002.

176. Brookhart MA, Sturmer T, Glynn RJ, Rassen J, Schneeweiss S. Confounding control in healthcare database research: challenges and potential approaches. Med Care 2010;48(6 Suppl):S114-S120.

177. Csizmadi I, Collet J-P, Boivin J-P. Bias and Confounding in Pharmacoepidemiology. In: Strom BL, editor. Pharmacoepidemiology. West Sussex: John Wiley; 2005:791-809.

178. Connors AF, Jr., Speroff T, Dawson NV et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. JAMA 1996;276(11):889-897.

179. Harvey S, Harrison DA, Singer M et al. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. Lancet 2005;366(9484):472-477.

180. Sakr Y, Vincent JL, Reinhart K et al. Use of the pulmonary artery catheter is not associated with worse outcome in the ICU. Chest 2005;128(4):2722-2731.

181. Milbrandt EB, Kersten A, Kong L et al. Haloperidol use is associated with lower hospital mortality in mechanically ventilated patients. Crit Care Med 2005;33(1):226-229.

182. Horsdal HT, Ulrichsen SP, Thomsen RW, Norgaard M, Larsen FB, Sorensen HT. Lifestyle Profile among Users of Antidiabetic Treatments. Pharmacoepidemiology and Drug Safety 20, S292. 2011. [Abstract]

183. Oliveros H, Villamor E. Obesity and mortality in critically ill adults: a systematic review and meta-analysis. Obesity (Silver Spring) 2008;16(3):515-521.

184. O'Brien JM, Jr., Phillips GS, Ali NA, Lucarelli M, Marsh CB, Lemeshow S. Body mass index is independently associated with hospital mortality in mechanically ventilated adults with acute lung injury. Crit Care Med 2006;34(3):738-744.

185. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care 1998;36(1):8-27.

186. Keenan SP, Dodek P, Chan K et al. Intensive care unit admission has minimal impact on long-term mortality. Crit Care Med 2002;30(3):501-507.

187. Jencks SF, Williams DK, Kay TL. Assessing hospital-associated deaths from discharge data. The role of length of stay and comorbidities. JAMA 1988;260(15):2240-2246.

Study I

Acta Anaesthesiol Scand 2011; **55**: 962–970
Printed in Singapore. All rights reserved

ACTA ANAESTHESIOLOGICA SCANDINAVICA
doi: 10.1111/j.1399-6576.2011.02480.x

The impact of pre-admission morbidity level on 3-year mortality after intensive care: a Danish cohort study

C. F. Christiansen[1,2], S. Christensen[1], M. B. Johansen[1], K. M. Larsen[2], E. Tønnesen[2] and H. T. Sørensen[1]
Departments of [1]Clinical Epidemiology and [2]Anaesthesiology and Intensive Care Medicine, Aarhus University Hospital, Aarhus, Denmark

Background: Chronic diseases are common among intensive care unit (ICU) patients and may worsen their prognosis. We examined the prevalence and impact of pre-admission/index morbidity among ICU patients compared with a general population cohort.
Methods: Our study encompassed all 28,172 adult patients admitted to ICUs in northern Denmark in 2005–2007 and 281,671 age- and sex-matched individuals from the general population. We used a nationwide hospital registry to obtain a 5-year history of 19 chronic diseases and computed Charlson Comorbidity Index (CCI) for each study participant and grouped them into low (CCI = 0), moderate (CCI = 1–2), and high (CCI = 3+) morbidity levels. We computed mortality and mortality rate ratios (MRRs) adjusted for confounders, and compared the mortality between ICU patients and the general population cohort.
Results: Low, moderate, and high pre-admission morbidity levels were present in 51.5%, 34.1%, and 14.4% of ICU patients, respectively. In these groups, 30-day mortality was 10.8%, 18.4%, and 26.7%, respectively. Three-year mortality was 21.3%, 43.1%, and 63.2%, respectively. The adjusted 30-day MRR was 1.30 [95% confidence intervals (CI): 1.21–1.39] and 1.86 (95% CI: 1.71–2.01) for ICU patients with moderate and high morbidity levels, both compared with a low morbidity level. The general population had a lower morbidity level and mortality at all morbidity levels throughout the study period. Interaction between ICU admission and high morbidity level added 5.1% to the mortality during the second and third year of follow-up.
Conclusion: A high pre-admission morbidity level was frequent among ICU patients and associated with a worsened prognosis. Morbidity had more impact on mortality among ICU patients compared with a general population cohort.

Accepted for publication 25 May 2011

With the aging of the population, more fragile elderly people with high levels of pre-admission morbidity will be admitted to intensive care units (ICU).[1–4] Currently, almost half of ICU patients have a history of pre-admission morbidity, and their morbidity levels are increasing steadily.[4,5] Although a high pre-admission morbidity level is a strong predictor for poor long-term prognosis and is associated with increased mortality during ICU stays and within 1 year post-discharge,[5–7] data are lacking on the impact of pre-admission morbidity among ICU patients compared with the general population.

Data comparing the prognosis of ICU patients with that of the general population are limited and conflicting. Only seven studies have examined this topic.[7–13] Four Nordic studies with sample sizes ranging from 236 to 12,180 ICU patients consistently reported increased mortality from 6 months to 2 years after intensive care compared with the general population, but not thereafter.[8–11] A Scottish study found that mortality among patients who had received care in an ICU was comparable to the general population after 4 years.[12] A recent US cohort study that followed elderly ICU patients for up to 3 years found slightly increased long-term mortality among ICU patients who survived until hospital discharge, compared with the general population.[13] In contrast, an Australian study found persistently increased mortality for up to 15 years among ICU patients discharged alive.[7]

Although pre-admission morbidity has an important impact on mortality among ICU patients, only one study compared morbidity levels with a population comparison cohort.[13] No attempts have been made to clarify the effect of pre-admission

The study findings was presented orally at the Acta Award Competition at the 30th Congress of the Scandinavian Society of Anesthesiology and Intensive Care Medicine, Odense, Denmark, 12 June 2009.

morbidity on long-term mortality, including whether mortality among ICU patients without chronic diseases is similar to that of the general population. Such data are needed to understand and potentially prevent death after intensive care.

We therefore compared the prevalence of pre-admission morbidity among ICU patients with morbidities in an age- and sex-matched general population comparison cohort. We also assessed and compared the mortality patterns among ICU patients with different pre-admission morbidity levels. Finally, we examined how pre-admission morbidity levels influenced mortality for up to 3 years after ICU admission compared with the influence of morbidity in the general population.

Materials and methods

Study design and setting

We conducted this cohort study in northern Denmark (the Central Denmark Region and the North Denmark Region) within a population of 1.8 million people (approximately 33% of the Danish population). The study area is mixed rural–urban and includes 17 ICUs: eight highly specialized units at university hospitals and nine multidisciplinary units at regional hospitals. All Danish citizens have access to the national tax-supported public health service, which includes all ICUs in Denmark. We linked the population-based registries described below using the unique civil registration number assigned to every Danish citizen at birth.[14]

ICU patients

We used the Danish National Registry of Patients (DNRP) to identify first-time ICU admissions between 1 January 2005 and 31 December 2007, among patients aged 15 years or older.

The DNRP contains data on all discharges from all non-psychiatric hospitals since 1977 and on emergency room and outpatient clinic visits since 1995. It includes information on patients' civil registration numbers, dates of admission and discharge, surgical procedures, procedure codes, one primary diagnosis (main reason for hospital admission), and up to 19 secondary diagnoses coded by physicians according to the *International Classification of Diseases* (ICD) (8th edition until the end of 1993, 10th edition thereafter).[15,16]

We used the DNRP to identify ICU patients by the procedure codes for intensive care observation/therapy (NABE and NABB) and defined the date of first ICU admission as the first day an intensive care code was used. Admission type was considered surgical if the patient had surgical procedures on the day of ICU admission or within 7 days before. We obtained data from the DNRP on the primary diagnosis for the current ICU stay and categorized these into major disease groups (see Appendix 1).

We validated ICU codes for a random sample of 50 patients per year in the study period (150 patients in total), who had a first-time admission to ICUs at one of the hospitals within Aarhus University Hospital. Specifically, we used hospital records to confirm the occurrence and date of ICU admissions.

General population comparison cohort

For each ICU patient, we used the Danish Civil Registration System (CRS) to sample 10 age- and sex-matched persons from the general population who were alive on the date that the ICU patient was admitted (the index date).[14]

The general population cohort allowed us to compare the prevalence of pre-admission/index morbidity and mortality in ICU patients with that in the general population, and further to study whether the level of pre-admission/index morbidity influenced the mortality difference between ICU patients and the general population cohort.

Pre-admission/index morbidity level

We used the DNRP to obtain data on previous diagnoses of the 19 diseases in the Charlson Comorbidity Index (CCI) within five years before the current ICU admission date and index date in the general population cohort. The CCI score was computed from the sum of weights for the 19 diseases (see Appendix 2 for ICD-10 codes). The CCI was originally developed to assess comorbidity based on medical record data,[17] but has subsequently been validated for use with administrative data including that for ICU patients.[18,19] We divided morbidity levels on the ICU admission date/index date into three groups: low (CCI score 0), moderate (CCI score 1 or 2), and high (CCI score 3 or more).

Mortality

We used the CRS to obtain data on mortality up to 3 years after the ICU admission date/index date. Since 1968, the CRS has recorded all changes in vital status and migration for the entire Danish population.

Statistical analysis

The baseline characteristics of the ICU cohort were described in contingency tables. The prevalence of pre-admission/index morbidity was described for the ICU cohort and the population cohort and compared with prevalence ratios and prevalence differences, both with 95% confidence intervals (95% CI). Patients were followed from the date of ICU admission until the date of death, emigration, 1 January 2010, whichever came first. We computed Kaplan–Meier estimates with 95% CI. We plotted survival functions for ICU patients with low, moderate, and high pre-admission morbidity levels and described mortality estimates for the entire 3-year period and within three time periods: 0–30 days (period of acute illness), 31–365 days (post-acute phase), and 366 days to 3 years after ICU admission (post-hospital period).

We used Cox proportional hazard regression analysis to estimate hazard ratios (HRs) as a measure of mortality rate ratios (MRRs) in the three time periods for moderate and high pre-admission morbidity levels compared with a low pre-admission morbidity level. We adjusted MRRs for age group, sex, and admission type (surgical/medical) and also stratified based on medical/surgical admission. The assumption of proportional hazards was checked graphically and found to be reasonable for all three time periods. We also used Cox proportional hazard regression analysis to compare survival in ICU patients with survival in the general population cohort for each morbidity level in 3-month periods, adjusted for age (time-scale), sex, and admission type.

Over the course of the study period, age and sex distributions may have differed among subgroups of patients with different pre-admission morbidity levels; e.g., fragile elderly patients with high pre-admission morbidity levels may have died soon after ICU admission. In order to compare the risk of death in three time periods, we adjusted mortality through direct standardization of the Kaplan–Meier estimates to the age and sex distribution of the general population cohort.

We compared the impact of pre-admission/index morbidity levels among ICU patients and the general population cohort by subtracting the mortality difference between ICU patients with and without pre-admission morbidity from the mortality difference between general population cohort members with and without index morbidity. The overall difference constitutes the excess mortality or *interaction risk* caused by the interaction of critical illness and pre-admission morbidity on mortality, i.e., the mortality that cannot be explained by the sum of mortality from critical illness and pre-admission morbidity.[20]

All statistical analyses were performed using Stata software (version 10.1; StataCorp LP, College Station, TX). The study was approved by the Danish Data Protection Agency (record no. 2009-41-3987).

Results

Descriptive data

We identified 28,172 ICU patients in the 3-year study period and 281,671 general population comparison cohort members (10 for 28,124 ICU patients, nine for 47 ICU patients, and eight for the last ICU patient). Among ICU patients, 56.8% were men, the median age was 63 years (interquartile range: 48–74 years), and 17,060 (60.6%) were surgical patients (Table 1). The most common primary diagnoses during the hospital stay were cardiovascular diseases, trauma/poisoning, and cancer (Table 1). Most cancer patients were surgical patients (90.2%), and the most common cancer sites were the lung, colon, rectum, and prostate.

Prevalence of pre-admission/index morbidity in ICU patients and in the general population

A high pre-admission morbidity level was present in 4060 (14.4%) ICU patients, a moderate pre-admission morbidity level in 9598 (34.1%) patients, and a low level in 14,514 patients (51.5%). Patients with a moderate or a high pre-admission morbidity level were older and were more likely to be men (Table 1). The morbidity level was substantially lower in the general population cohort: a high index morbidity level was present in 10,414 persons (3.7%), a moderate pre-admission morbidity level in 45,736 persons (16.2%), and a low pre-admission morbidity level in 225,521 persons (80.1%) (data not shown).

The most common pre-admission/index morbidities were cardiovascular diseases, chronic pulmonary disease, diabetes, and cancer (Table 2). Compared with the general population cohort, ICU patients had an approximately threefold higher prevalence of major cardiovascular diseases, chronic pulmonary diseases, and cancer. The prevalence of metastatic cancer was 6.2-fold higher and liver diseases was 5.6–8.8-fold higher in the ICU cohort compared with the general population

Table 1

Characteristics of intensive care unit (ICU) patients and the general population comparison cohort

	ICU patients				Population comparison cohort
	Charlson Comorbidity Index score			Total 28,172 (100%)	Total 281,671 (100%)
	0 14,514 (51.5%)	1–2 9598 (34.1%)	3+ 4060 (14.4%)		
Age group (years)					
15–39	4010 (27.6)	554 (5.8)	154 (3.8)	4718 (16.7)	47,205 (16.8)
40–59	4107 (28.3)	2097 (21.9)	879 (21.7)	7083 (25.1)	70,651 (25.1)
60–79	4946 (34.1)	5450 (56.8)	2377 (58.5)	12,773 (45.3)	127,868 (45.4)
80+	1451 (10.0)	1497 (15.6)	650 (16.0)	3598 (12.8)	35,947 (12.8)
Gender					
Female	6546 (45.1)	4068 (42.4)	1566 (38.6)	12,180 (43.2)	121,784 (43.2)
Male	7968 (54.9)	5530 (57.6)	2494 (61.4)	15,992 (56.8)	159,887 (56.8)
Type of admission					
Medical	5856 (40.4)	3573 (37.2)	1683 (41.5)	11,112 (39.4)	–
Surgical	8658 (59.7)	6025 (62.8)	2377 (58.5)	17,060 (60.6)	–
Primary diagnosis during current hospital admission					
Infectious diseases	271 (1.9)	246 (2.6)	149 (3.7)	666 (2.4)	–
Endocrinology including diabetes	384 (2.7)	211 (2.2)	90 (2.2)	685 (2.4)	–
Cardiovascular diseases	3286 (22.6)	3038 (31.7)	984 (24.2)	7308 (25.9)	–
Respiratory diseases	969 (6.7)	1324 (13.8)	517 (12.7)	2810 (10.0)	–
Gastrointestinal and liver diseases	1983 (13.7)	1141 (11.9)	562 (13.8)	3686 (13.1)	–
Cancer and other neoplasm	1273 (8.8)	1634 (17.0)	985 (24.3)	3892 (13.8)	–
Trauma and poisoning	3375 (23.3)	840 (8.8)	242 (6.0)	4457 (15.8)	–
Other	2973 (20.5)	1164 (12.1)	531 (13.1)	4668 (16.6)	–

Table 2

Morbidity in ICU patients before admission and before index date in the population comparison cohort

Diseases included in the Charlson Comorbidity Index	ICU patients, n (%)	Population comparison cohort, n (%)	Prevalence ratio (95% CI)	Prevalence difference (95% CI)
	28,172 (100%)	281,671 (100%)		
Myocardial infarction	1825 (6.5)	5632 (2.0)	3.2 (3.1, 3.4)	4.5% (4.2, 4.8)
Congestive heart failure	1977 (7.0)	6734 (2.4)	2.9 (2.8, 3.1)	4.6% (4.3, 4.9)
Peripheral arterial disease	2039 (7.2)	6061 (2.2)	3.4 (3.2, 3.5)	5.1% (4.8, 5.4)
Cerebrovascular disease	2441 (8.7)	12,483 (4.4)	2.0 (1.9, 2.0)	4.2% (3.9, 4.6)
Dementia	220 (0.8)	2637 (0.9)	0.8 (0.7, 1.0)	−0.2% (−0.3, −0.05)
Chronic pulmonary disease	3308 (11.7)	10,887 (3.9)	3.0 (2.9, 3.2)	7.9% (7.5, 8.3)
Connective tissue disease	763 (2.7)	3859(1.4)	2.0 (1.8, 2.1)	1.3% (1.1, 1.5)
Peptic ulcer disease	1060 (3.8)	3642 (1.3)	2.9 (2.7, 3.1)	2.5% (2.2, 2.7)
Mild liver disease	590 (2.1)	1073 (0.4)	5.5 (5.0, 6.1)	1.7% (1.5, 1.9)
Moderate-to-severe liver disease	235 (0.8)	270 (0.1)	8.7 (7.3, 10.3)	0.7% (0.6, 0.8)
Diabetes without organ damage	2067 (7.3)	8563 (3.0)	2.4 (2.3, 2.5)	4.3% (4.0, 4.6)
Diabetes with organ damage	1258 (4.5)	4562 (1.6)	2.8 (2.6, 2.9)	2.8% (2.6, 3.1)
Hemiplegia	140 (0.5)	318 (0.1)	4.4 (3.6, 5.4)	0.4% (0.3, 0.5)
Moderate-to-severe renal disease	865 (3.1)	2154 (0.8)	4.0 (3.7, 4.3)	2.3% (2.1, 2.5)
Cancer	3502 (12.4)	11,488 (4.1)	3.0 (2.9, 3.2)	8.4% (8.0, 8.7)
Metastatic cancer	642 (2.3)	1042 (0.4)	6.2 (5.6, 6.8)	1.9% (1.7, 2.1)
Leukemia	133 (0.5)	453 (0.2)	2.9 (2.4, 3.6)	0.3% (0.2, 0.4)
Lymphoma	245 (0.9)	789 (0.3)	3.1 (2.7, 3.6)	0.6% (0.5, 0.7)
AIDS	15 (0.05)	96 (0.03)	1.6 (0.9, 2.7)	0.01% (−0.01, 0.05)

cohort. Only dementia was less common among ICU patients. In the two cohorts, absolute differences in prevalence were the greatest for chronic pulmonary disease and cancer (Table 2).

Mortality

Thirty-day mortality was 10.8% (95% CI: 10.3–11.3) among ICU patients with a low pre-admission morbidity level, 18.4% (95% CI: 17.6–19.2) among

patients with a moderate pre-admission morbidity level, and 26.7% (95% CI: 25.3–28.0%) for patients with a high level (Fig. 1 and Table 3). Thirty-day mortality ranged from 2.4% in patients aged 15–39 years with a low pre-admission morbidity level to 42.8% in patients aged 80 years and over with a high pre-admission morbidity level. In all age groups, mortality was about 10% higher in patients with high pre-admission morbidity compared with patients with low pre-admission morbidity (data not shown).

Among patients surviving 30 days, mortality 31–365 days after ICU admission was 5.7% (95% CI: 5.4–6.2%) for patients with a low pre-admission morbidity level, 15.5% (95% CI: 14.7–16.3%) for patients with a moderate morbidity level, and 27.8% (95% CI: 26.3–29.5%) for patients with a high morbidity level. If patients survived the first year after ICU admission, mortality in the second and third years was 6.4% (95% CI: 5.9–6.8%), 17.4% (95% CI: 16.5–18.4%), and 30.4% (95% CI: 28.4–32.4%), respectively, among patients with the three pre-admission morbidity levels.

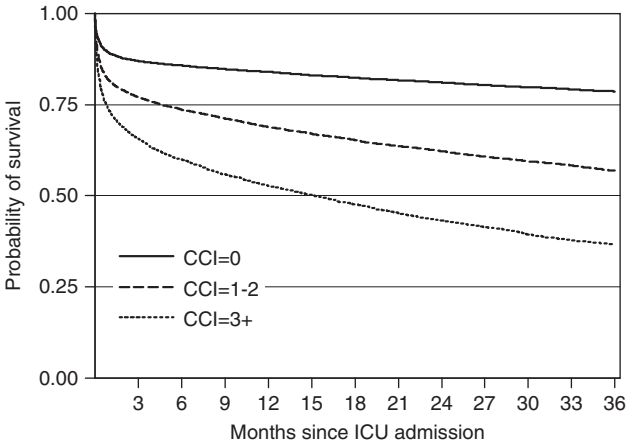


Fig. 1. Three-year survival curves among intensive care unit (ICU) patients with low, moderate, and high pre-admission morbidity levels [——= low morbidity level/Charlson Comorbidity Index score (CCI) = 0, – – = moderate pre-admission morbidity level/ CCI = 1–2, ····· = high pre-admission morbidity level/CCI = 3+].

The mortality within the first three years after ICU admission was 21.3% (95% CI: 20.7–22.0%), 43.1% (95% CI: 42.1–44.1%), and 63.2% (95% CI: 61.7–64.8%) in the three morbidity levels (Table 3).

Compared with ICU patients with a low pre-admission morbidity level, the adjusted 30-day MRR was 1.30 (95% CI: 1.21–1.39) for ICU patients with moderate morbidity and 1.86 (95% CI: 1.71–2.01) for ICU patients with high morbidity (Table 3). The impact of a moderate or a high pre-admission morbidity level was even stronger for the period from 31 to 365 days after ICU admission [MRR = 2.10 (95% CI: 1.92–2.31) for moderate morbidity, MRR = 3.93 (95% CI: 3.55–4.35) for high morbidity]. Very similar associations were found from day 366 to 3 years after ICU admission (Table 3).

While the absolute mortality was higher in medical patients than surgical ICU patients (e.g. overall 30-day mortality 21.6% vs. 11.8%), an increased pre-admission morbidity level was associated with a similar relative mortality increase in medical and surgical ICU patients. The 30-day adjusted MRRs for medical patients were 1.41 (95% CI:

Table 3

Mortality and mortality rate ratio (MRR) for intensive care unit (ICU) patients within the first 30 days, 31–365 days, and 1–3 years for the three pre-admission morbidity levels among patients who were alive at the beginning of these periods (Charlson Comorbidity Index score = 0, 1–2, or 3)

	n at period start	Mortality (%) (95% CI)	Crude MRR (95% CI)		Adjusted MRR (95% CI)*	
Day 0–30						
CCI = 0	14,514	10.8% (10.3%, 11.3%)	1.00	(Ref.)	1.00	(Ref.)
CCI = 1–2	9598	18.4% (17.6%, 19.2%)	1.77	(1.65, 1.89)	1.30	(1.21, 1.39)
CCI = 3+	4060	26.7% (25.3%, 28.0%)	2.67	(2.47, 2.88)	1.86	(1.71, 2.01)
Day 31–365						
CCI = 0	12,944	5.7% (5.4%, 6.2%)	1.00	(Ref.)	1.00	(Ref.)
CCI = 1–2	7832	15.5% (14.7%, 16.3%)	2.83	(2.58, 3.10)	2.10	(1.92, 2.31)
CCI = 3+	2977	27.8% (26.3%, 29.5%)	5.50	(4.98, 6.07)	3.93	(3.55, 4.35)
Day 366–3 years						
CCI = 0	12,173	6.4% (5.9%, 6.8%)	1.00	(Ref.)	1.00	(Ref.)
CCI = 1–2	6612	17.4% (16.5%, 18.4%)	2.91	(2.65, 3.20)	2.16	(1.96, 2.38)
CCI = 3+	2142	30.4% (28.4%, 32.4%)	5.54	(4.97, 6.17)	3.96	(3.55, 4.43)
0–3 years						
CCI = 0	14,514	21.3% (20.7%, 22.0%)	1.00	(Ref.)	1.00	(Ref.)
CCI = 1–2	9598	43.1% (42.1%, 44.1%)	2.29	(2.18, 2.40)	1.69	(1.62, 1.78)
CCI = 3+	4060	63.2% (61.7%, 64.8%)	3.92	(3.72, 4.13)	2.78	(2.63, 2.93)

*Adjusted for age group, sex, and type of admission (surgical/medical).

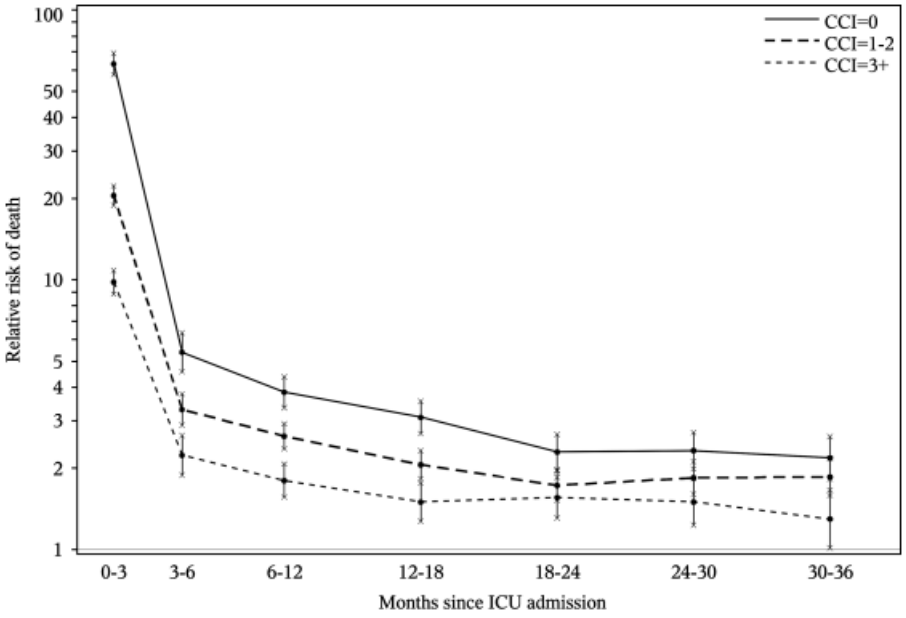


Fig. 2. Relative risk (mortality rate ratio) of death among intensive care unit (ICU) patients compared with the general population cohort for up to 3 years, adjusted for age and sex, with 95% confidence intervals [—— = low morbidity level/Charlson Comorbidity Index score (CCI) = 0, – – = moderate pre-admission morbidity level/CCI = 1–2, ····· = high pre-admission morbidity level/CCI = 3+].

1.28–1.55) for moderate pre-admission morbidity and 1.81 (95% CI: 1.63–2.02) for high morbidity. The adjusted 30-day MRRs for surgical patients were 1.21 (95% CI: 1.10–1.34) for moderate pre-admission morbidity and 1.94 (95% CI 1.73–2.18) for high morbidity, compared with a low pre-admission morbidity level (data not shown).

Compared with the general population cohort, mortality was most markedly increased during the first 3 months after ICU admission, but remained elevated throughout the 3-year period (Fig. 2).

The impact on mortality of the interaction between critical illness and pre-admission morbidity level

Compared with the general population cohort, mortality was increased among ICU patients throughout the study period, even among patients with a low pre-admission morbidity level. The standardized mortality rate during the second and third year of follow-up was 8.7% in ICU patients with low pre-admission morbidity, but only 4.4% in the general population cohort (i.e. risk difference 4.3%) (Table 3).

Morbidity before admission/index date increased mortality more in ICU patients than in the general population, e.g., during the second and third year of follow-up, high morbidity on the index date added 15.8% to mortality in the general population, but high pre-admission morbidity added 20.9% to mortality in ICU patients, i.e., mortality was 5.1% higher than expected (the interaction risk) (Table 4). The interaction risk was the highest for young patients.

Validation of ICU admission and treatment coding

Among a sample of 150 patients registered in the DNRP with an ICU admission, 148 were identified with an ICU admission in the local hospital records, i.e. the PPV was 98.7% (95% CI: 95.3–99.8%). The date of the first ICU code corresponded to the day of ICU admission in all patients except one, who was admitted to the recovery room at date of coding but transferred to the ICU the following day.

Discussion

This large population-based study found that nearly half of the ICU patients had moderate or high pre-admission morbidity. Also, virtually all specific chronic diseases examined were more common in the ICU patients than in the general population comparison cohort. Pre-admission morbidity among ICU patients was associated with markedly increased short- and long-term mortality. Throughout the 3-year study period, ICU patients had persistently higher mortality compared with the general population cohort. A higher level of morbidity before the ICU admission date/index date had a greater impact on mortality among ICU patients than on mortality in the general population comparison cohort.

Table 4

Standardized mortality and interaction risk by preadmission/index morbidity level (Charlson Comorbidity Index scores of 0, 1–2, or 3+) in intensive care unit (ICU) patients compared with the general population cohort.

	Preadmission/ index morbidity level	Standardized mortality ICU patients, % (95% CI)*		Standardized mortality Population comparison cohort, % (95% CI)*		Risk difference (ICU patients – population comparison cohort) (%)	Interaction risk (%) (95% CI)†	
Day 0–30	CCI = 0	12.9	(12.3%, 13.5%)	0.1	(0.1%, 0.1%)	12.8	–	
	CCI = 1–2	16.3	(15.6%, 17.0%)	0.4	(0.3%, 0.4%)	15.9	3.1	(2.2%, 4.0%)
	CCI = 3+	24.7	(23.0%, 26.4%)	1.4	(1.2%, 1.6%)	23.3	10.5	(8.7%, 12.3%)
Day 31–365	CCI = 0	7.7	(7.2%, 8.2%)	1.5	(1.5%, 1.6%)	6.2	–	
	CCI = 1–2	14.2	(13.5%, 15.0%)	4.1	(4.0%, 4.3%)	10.1	3.9	(3.0%, 4.9%)
	CCI = 3+	26.9	(24.8%, 29.0%)	11.2	(10.4%, 12.1%)	15.7	9.5	(7.1%, 11.8%)
Day 366–3 years	CCI = 0	8.7	(8.1%, 9.4%)	4.4	(4.4%, 4.5%)	4.3	–	
	CCI = 1–2	16.7	(15.8%, 17.6%)	9.2	(8.9%, 9.5%)	7.5	3.2	(2.1%, 4.4%)
	CCI = 3+	29.6	(27.1%, 32.2%)	20.2	(18.8%, 21.6%)	9.4	5.1	(2.1%, 8.1%)
0–3 years	CCI = 0	25.4	(24.7%, 26.2%)	5.9	(5.8%, 6.0%)	19.5	–	
	CCI = 1–2	38.4	(37.4%, 39.4%)	12.8	(12.6%, 13.1%)	25.6	6.0	(4.8%, 7.3%)
	CCI = 3+	60.2	(58.1%, 62.2%)	29.4	(27.8%, 30.9%)	30.8	11.3	(8.6%, 13.9%)

*Standardized to the age and sexdistribution of the population comparison cohort.
†As an example, the 30-day interaction risk in patients with a high pre-admission morbidity level was computed as the difference in mortality in ICU patients with a low and a high preadmission morbidity level, i.e., 11.8% (24.7–12.9%), minus the difference in mortality in the general population cohort with a low and a high index morbidity level, i.e., 1.3% (1.4–0.1%). The interaction risk is thereby 11.8–1.3% = 10.5%.

Our study extends previous research by showing that a moderate or a high pre-admission morbidity level was common among ICU patients and had a major impact on mortality.[5–7] Our study is also the first to compare the effect of the pre-admission/ index morbidity on mortality among ICU patients and a general population cohort. An Australian cohort study on the long-term prognosis of ICU patients included 22,980 patients admitted to a single ICU between 1987 and 2002.[5] Forty-five percent of the ICU patients in that study had a moderate or a severe pre-admission morbidity level, only a few percent lower than that observed in our study. Mortality was lower and the pre-admission morbidity level affected mortality less than that in our study, probably because the case-mix was different. Our findings were supported by a recently published US cohort study on 35,308 elderly ICU survivors, who had persistently elevated mortality during a 3-year follow-up compared with the general population.[13] Similarly, analyses from the Australian cohort study cited above showed increased mortality for up to 15 years after ICU discharge, compared with the general population.[7] In contrast, both a Finnish and a Norwegian cohort study found that survival was comparable with the general population after 2 years.[8,9] In a Scottish cohort study, survival was comparable with that in the general population 4 years after ICU discharge.[12]

Our study made use of routinely collected data in a population-based hospital setting with complete follow-up. In Denmark, public hospitals care for all patients with acute critical illness, including those requiring intensive care, thereby limiting referral, diagnostic, and other information biases.[14] Still, our study has several limitations. Its findings depend on the quality of coding for intensive care and comorbidities. It is mandatory to report to the DNRP and coding should follow the regulations by the National Board of Health. The chronic diseases included in the Charlson Index are accurately coded in the DNRP, with high PPVs.[21] We used 5-year registry history of in- and outpatient diagnoses to secure completeness of hospital diagnoses. The CCI score has proved to be a valid predictor of mortality and a good tool for risk adjustment.[18,19] We found a high PPV of ICU admissions registered in the DNRP and the number of admissions was stable in the 3 years included in this study, thereby indicating consistent registration. Still, we cannot rule out that some ICU patients admitted for short stays were not registered in the DNRP.

We had limited data on the exact mechanism behind the associations we observed. Patients with pre-admission morbidity may have more serious illness at the time of ICU admission, but we lacked data on severity of illness. It is possible that patients with a high pre-admission morbidity level

will have an increased severity of illness score, e.g. Simplified Acute Physiology (SAPS) II score. This could either be from older age, severe morbidity, or abnormal physiological variables, which are all included in the score. Patients with chronic organ dysfunction may be prone to acute organ dysfunction, e.g., chronic kidney disease is a strong risk factor for acute kidney injury and thereby an increased SAPS II score.[22] We found a markedly higher prevalence of most chronic diseases in the ICU patients than in the general population comparison cohort, indicating that these diseases may be risk factors for critical illness, or at least for admission to an ICU. However, this finding should be interpreted with caution because it may depend on the likelihood for intensive care admission. For instance, treatment may be withheld in elderly ICU patients with high pre-admission morbidity,[23] thereby leading to increased mortality, but patients with the highest morbidity, such as metastatic cancer, may not even be admitted to an ICU. Future studies are needed to clarify the mechanisms underlying the markedly increased mortality among ICU patients, focusing on the impact of individual chronic diseases on ICU prognosis.

This study underscores the need for the assessment of pre-admission chronic diseases in ICU patients because they are common and have a major impact on mortality. Although the influence of moderate and high pre-admission morbidity was most pronounced within the first month after ICU admission, excess mortality persisted for up to 3 years, indicating the need for a long-term follow-up of critically ill patients.

In conclusion, we found that pre-admission/index morbidity was more common among ICU patients than in the general population cohort. Pre-admission morbidity was associated with markedly increased mortality for up to 3 years after ICU admission. The general population had a lower morbidity level and mortality at all morbidity levels throughout the study period. Finally, pre-admission/index morbidity had a greater impact on mortality in ICU patients compared with the general population cohort.

Acknowledgements

This research was made possible through financial support from the Clinical Epidemiology Research Foundation, Denmark, from the Korning Foundation, and from the Danish Medical Research Council (Grant 271-05-0511). The funding institutions had no influence on the study.

Conflicts of interest: The authors have no conflicts of interest with regard to the current study.

Reference

1. Kvale R, Flaatten H. Changes in intensive care from 1987 to 1997 – has outcome improved? A single centre study. Intensive Care Med 2002; 28: 1110–16.
2. Flaatten H. Intensive care in the very old: are we prepared? Acta Anaesthesiol Scand 2007; 51: 519–21.
3. Laake JH, Dybwik K, Flaatten HK, Fonneland IL, Kvale R, Strand K. Impact of the post-World War II generation on intensive care needs in Norway. Acta Anaesthesiol Scand 2010; 54: 479–84.
4. Williams TA, Ho KM, Dobb GJ, Finn JC, Knuiman MW, Webb SA. Changes in case-mix and outcomes of critically ill patients in an Australian tertiary intensive care unit. Anaesth Intensive Care 2010; 38: 703–09.
5. Williams TA, Dobb GJ, Finn JC, Knuiman M, Lee KY, Geelhoed E, Webb SA. Data linkage enables evaluation of long-term survival after intensive care. Anaesth Intensive Care 2006; 34: 307–15.
6. Ho KM, Knuiman M, Finn J, Webb SA. Estimating long-term survival of critically ill patients: the PREDICT model. PLoS ONE 2008; 3: e3226.
7. Williams TA, Dobb GJ, Finn JC, Knuiman M, Geelhoed E, Lee KY, Webb SA. Determinants of long-term survival after intensive care. Crit Care Med 2008; 36: 1523–30.
8. Niskanen M, Kari A, Halonen P. Five-year survival after intensive care–comparison of 12,180 patients with the general population. Finnish ICU Study Group. Crit Care Med 1996; 24: 1962–67.
9. Flaatten H, Kvale R. Survival and quality of life 12 years after ICU. A comparison with the general Norwegian population. Intensive Care Med 2001; 27: 1005–11.
10. Zaren B, Bergstrom R. Survival compared to the general population and changes in health status among intensive care patients. Acta Anaesthesiol Scand 1989; 33: 6–12.
11. Dragsted L. Outcome from intensive care. A five year study of 1,308 patients. Dan Med Bull 1991; 38: 365–74.
12. Wright JC, Plenderleith L, Ridley SA. Long-term survival following intensive care: subgroup analysis and comparison with the general population. Anaesthesia 2003; 58: 637–42.
13. Wunsch H, Guerra C, Barnato AE, Angus DC, Li G, Linde-Zwirble WT. Three-year outcomes for Medicare beneficiaries who survive intensive care. JAMA 2010; 303: 849–56.
14. Frank L. Epidemiology. When an entire country is a cohort.. Science 2000; 287: 2398–9.
15. Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull 1999; 46: 263–68.
16. Nickelsen TN. [Data validity and coverage in the Danish National Health Registry A literature review]. Ugeskr Laeger 2001; 164: 33–37.
17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40: 373–78.
18. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992; 45: 613–19.

19. Needham DM, Scales DC, Laupacis A, Pronovost PJ. A systematic review of the Charlson comorbidity index using Canadian administrative databases: a perspective on risk adjustment in critical care research. J Crit Care 2005; 20: 12–29.
20. Rothman KJ. Measuring interactions. In: Epidemiology – an introduction. Rothman KJ., ed. New York: Oxford University Press Inc, 2002:168–80.
21. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sorensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson Comorbidity Index conditions in the population-based Danish National Registry of Patients. BMC Med Res Methodol 2011; 11: 83.
22. Hsu CY, Ordonez JD, Chertow GM, Fan D, McCulloch CE, Go AS. The risk of acute renal failure in patients with chronic kidney disease. Kidney Int 2008; 74: 101–07.
23. Curtis JR, Vincent JL. Ethics and end-of-life care for adults in the intensive care unit. Lancet 2010; 376: 1347–53.

Address:
Christian Fynbo Christiansen
Department of Clinical Epidemiology
Aarhus University Hospital
Olof Palmes Alle 43-45
DK-8200 Aarhus C
Denmark
e-mails: cc@dce.au.dk, cfc@dadlnet.dk

Appendix 1: Diagnostic codes by disease group

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)
Other (ICD-10: all codes not included in other categories)

Appendix 2: Diagnoses included in the Charlson Comorbidity Index and corresponding ICD-10 codes

	Charlson Comorbidity Index disease	ICD-10 code	Score
1	Myocardial infarction	I21;I22;I23	1
2	Congestive heart failure	I50; I11.0; I13.0; I13.2	1
3	Peripheral vascular disease	I70; I71; I72; I73; I74; I77	1
4	Cerebrovascular disease	I60-I69; G45; G46	1
5	Dementia	F00-F03; F05.1; G30	1
6	Chronic pulmonary disease	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3	1
7	Connective tissue disease	M05; M06; M08; M09;M30;M31; M32; M33; M34; M35; M36; D86	1
8	Ulcer disease	K22.1; K25-K28	1
9	Mild liver disease	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0	1
10	Diabetes type 1 Diabetes type 2	E10.0, E10.1; E10.9 E11.0; E11.1; E11.9	1
11	Hemiplegia	G81; G82	2
12	Moderate-to-severe renal disease	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61	2
13	Diabetes with end organ damage Type 1 Type 2	 E10.2-E10.8 E11.2-E11.8	2
14	Any tumor	C00-C75	2
15	Leukemia	C91-C95	2
16	Lymphoma	C81-C85; C88; C90; C96	2
17	Moderate-to-severe liver disease	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85	3
18	Metastatic solid tumor	C76-C80	6
19	AIDS	B21-B24	6

Study II

Type 2 Diabetes and One-year Mortality in Intensive Care Unit Patients: A Population-based Cohort Study

Short running title: Mortality in ICU patients with diabetes

Authors: Christian F Christiansen[1,2], MD; Martin B Johansen[1], MSc; Steffen Christensen[1,2], MD, PhD; James M O'Brien[3],MD; Else Tønnesen[2], MD, DMSc; Henrik Toft Sørensen[1], MD, PhD, DMSc.

Affiliations:

[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus N, Denmark

[2]Department of Anesthesiology and Intensive Care, Aarhus University Hospital, Aarhus C, Denmark

[3] Department of Internal Medicine, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Center for Critical Care, The Ohio State University Medical Center, Columbus, Ohio, USA

Corresponding author: Christian Fynbo Christiansen, MD, Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Alle 43-45, 8200 Aarhus N. Denmark. Phone: +45 871 68063. Fax: +45 871 67215. E-mail address: cc@dce.au.dk

Key words: Diabetes mellitus type 2, intensive care, intensive care unit, cohort studies, mortality, heart diseases, kidney diseases

Word count: 3,518 + abstract 240; Tables: 2; Figures: 2

ABSTRACT

OBJECTIVE— To examine whether type 2 diabetes complicated by chronic heart and/or kidney disease is associated with increased mortality among intensive care unit (ICU) patients.

RESEARCH DESIGN AND METHODS— We used population-based medical databases to assemble a cohort of all patients aged 40 years or older admitted to ICUs in Northern Denmark during 2005–2010. Type 2 diabetes was identified by a filled prescription for an antidiabetic drug, previous hospital diagnosis of diabetes, or elevated hemoglobin A1c measurement. Patients were grouped according to history of heart and kidney disease. We estimated 30-day and 31–365-day mortality. Age- and sex-adjusted mortality rate ratios (MRRs) were computed using Cox regression.

RESULTS— Among 39,286 ICU patients, 6,027 (15.3%) had type 2 diabetes, which was complicated by chronic heart disease in 1,103 (18.3%), by kidney disease in 261 (4.3%), and by both in 142 (2.4%). Thirty-day mortality was 22.9% in patients with type 2 diabetes and 18.4% in other patients, corresponding to an overall 30-day adjusted MRR of 1.18 (95% CI 1.11–1.25). MRR was similar for type 2 diabetes patients with heart disease, but higher for diabetic patients with kidney disease (adjusted MRR 1.65 [1.32–2.05]). Mortality was also increased during the 31–365-day period (adjusted MRR 1.20 [1.11–1.30]), and most pronounced in diabetic patients with kidney disease.

CONCLUSIONS— ICU patients with type 2 diabetes had higher mortality than other ICU patients for up to one year. The impact was most pronounced in those with chronic kidney disease.

INTRODUCTION

Diabetes is associated with an increased risk of chronic micro- and macrovascular complications such as chronic kidney and heart disease (1-3), as well as specific critical illnesses such as acute renal failure (4), infections (5-7), and acute cardiovascular events (2,8,9), which may lead to intensive care unit (ICU) admission. Diabetes also influences prognosis in patients with complicated peptic ulcer (10) and myocardial infarction (11), while data are conflicting in patients with trauma (12), pneumonia (13,14), and bacteremia (15,16). These conditions are common among ICU admission.

A recent systematic review and meta-analysis extracted data about diabetes and mortality in adult ICU patients from 141 studies, and concluded that diabetes was not associated with ICU or in-hospital mortality (17). However, only 20 of the included studies reported 30-day mortality among 19,040 ICU patients. Diabetes was associated with a statistically non-significant 20% increase in 30-day mortality, and with a 60% increase in 30-day mortality in surgical ICU patients (17).

Examining the impact of diabetes on mortality following intensive care unit (ICU) admission was the primary aim in only three studies (18-20). These studies each included from 830 to 1.5 million patients, and observed that diabetes was not associated with short-term mortality (18-20). This finding was surprising because diabetes patients were older and had higher severity of illness at ICU admission (18-20). Suggested mechanisms include protective biological effects of diabetes and antidiabetic treatment (21-23), misclassification of diabetes, or better care for diabetes patients during both acute critical illness and chronic disease (19). These studies were limited by lack of data regarding diabetes type and complications (18-20), lack of hemoglobin A1c (HbA1c) to identify diabetes (18-20), and potential selection bias due to restricted inclusion criteria (18). Finally, the two larger studies

only reported in-hospital mortality (19,20). None were conducted within a uniform population-based hospital setting (18-20).

There is a need for a large population-based study to provide reliable estimates of the prognostic impact of type 2 diabetes, including major diabetic complications. With the increasing prevalence of type 2 diabetes and the high costs of intensive care, any prognostic impact of type 2 diabetes may have important implications for the management of high-risk diabetes patients and for the implementation of preventive initiatives.

We therefore undertook a large population-based cohort study to examine whether type 2 diabetes, including chronic heart and kidney complications, was associated with increased mortality for up to one year after ICU admission.

RESEARCH DESIGN AND METHODS

We conducted this cohort study among patients living in Northern Denmark, a region with a mixed rural and urban population of approximately 1.8 million (approximately 33% of the entire Danish population). Included individuals had to have lived in the study area for at least two years for sufficient preadmission data to exist regarding antidiabetic drug prescriptions.

Denmark has a tax-supported health care system that guarantees unfettered access to medical care for all residents, as well as partial reimbursement of the costs of the majority of prescribed drugs. All acute care, including intensive care therapy, is provided by public hospitals. There are 17 ICUs in Northern Denmark, including eight highly specialized units at university hospitals and nine multidisciplinary units at regional hospitals. All Danish citizens receive a unique personal identification number (CPR number) at birth or upon immigration that allows unambiguous linkage among all Danish medical databases.

Identification of patients in intensive care units

We used the Danish National Registry of Patients (DNRP) to identify all patients aged 40 years or older with at least one admission to an ICU in the study region between 1 January 2005 and 31 December 2010 (24). We did not include patients younger than 40 years because type 2 diabetes is less frequent in this age group. We focused on type 2 diabetes because type 1 diabetes patients comprise a different group of younger patients who were admitted to the ICU more frequently because of acute diabetes-related complications.

The DNRP has documented more than 99% of all non-psychiatric hospital admissions in Denmark since 1977, and outpatient clinic and emergency room visits since 1995 (25). DNRP records comprise routinely collected data from the hospitals, including dates of admission and discharge, one primary diagnosis (the main reason for hospitalization), and up to 19 secondary diagnoses, treatments, and procedures, including valid data regarding intensive care observation/therapy (24). Data are registered routinely at the hospital level and electronically transferred to the DNRP for quality monitoring and reimbursement of hospital costs. Diagnoses are coded according to the International Classification of Diseases, 8^{th} revision (ICD-8) through 1993, and the 10^{th} revision (ICD-10) since 1994. We defined diagnostic category by the first-listed diagnosis during current hospitalization as a proxy for ICU admission diagnosis. The first-listed diagnosis in the registry is assigned by the discharging physician and is the most important diagnosis during the hospitalization. Surgical ICU admission was defined by the performance of any surgical procedure on the day of ICU admission or within seven days before admission (26). We also obtained data regarding mechanical ventilation, non-invasive ventilation, and treatment with inotropes or vasopressors from the DNRP.

Diabetes data

For each ICU patient, we searched the DNRP for any previous diabetes diagnosis since 1977 (see Supplemental Table S1 for ICD-8 and ICD-10 codes). Because not all patients received their diabetes diagnosis at a hospital, we also identified patients with any previous filled prescription for an antidiabetic drug, including insulin and oral antidiabetic drugs (see Supplemental Table S2 for Anatomical Therapeutical Chemical [ATC] codes). Pharmacies in the region are equipped with an electronic accounting system that is used to secure reimbursement from the National Health Service. For each prescription, data are transferred to the prescription database at Aarhus University. Data include the patient's unique identification number, the date of dispensing, and the amount and type of drug prescribed according to the ATC classification system (27). Because metformin is also used to treat polycystic ovarian syndrome (PCOS), metformin users with a history of PCOS were considered nondiabetic if they lacked a diabetes diagnosis and had never been prescribed another antidiabetic drug (n = 3) (28).

To capture diabetic patients treated by general practitioners with dietary and lifestyle changes only, we also included patients with a HbA1c measurement at the diagnostic level for diabetes (i.e., an HbA1c value of 6.5% or greater, as defined in the American Diabetes Association's guidelines) (29). We obtained these data from a laboratory database, which included results of HbA1c tests performed in the main part of the study area (30).

We defined patients as having type 2 diabetes, and not type 1 diabetes, if they were diagnosed with diabetes after age 30, if they were diagnosed before age 30 but did not fill

prescriptions for insulin within one year before admission, or if they had ever filled a prescription for an oral antidiabetic drug (5).

Because major micro- and macrovascular complications of diabetes may affect prognosis, we further segregated type 2 diabetes patients according to preadmission history of chronic kidney disease and heart disease, including myocardial infarction and heart failure. The relevant ICD codes are provided in the Supplemental Table S1. Because a diabetes diagnosis may be preceded by these complications, we included patients in the analysis if they were initially diagnosed with kidney or heart disease within one year before receiving the first diabetes diagnosis or antidiabetic prescription and before the index hospitalization. Diabetes was thus divided into five subcategories: no diabetes, uncomplicated type 2 diabetes, type 2 diabetes with heart disease but without kidney disease, type 2 diabetes with kidney disease but without heart disease, and type 2 diabetes with both heart and kidney disease.

Mortality

Data regarding vital status, including the exact date of death or emigration, were obtained from the Danish Civil Registration System, which includes daily updated data regarding vital status (dead or alive), marital status, and place of residence for all Danes (31).

Potential confounders

We used all inpatient and outpatient diagnoses in the DNRP within five years before ICU admission to identify other preadmission morbidity, including chronic pulmonary disease,

connective tissue disease, liver disease, cancer, and metastatic cancer, which are all known to have prognostic impacts in the Charlson Comorbidity Index (32,33). We also included obesity and alcoholism defined as alcoholism-related disease or prescription for disulfiram (see Supplemental Table S1 and S2 for ICD-10 and ATC codes). We obtained demographic data from the Danish Civil Registration System.

Statistical analyses

We followed patients for up to one year, from the day of their first ICU admission during the study period until death (event), censoring at emigration, or 1 January 2011, whichever came first. Covariates, including demographic variables and preadmission morbidity, were tabulated by type 2 diabetes status and diabetic complications.

The Kaplan-Meier life table method was used to estimate 30-day and 31-365-day mortality. Kaplan-Meier curves were plotted with respect to type 2 diabetes status and diabetic complications.

To compare mortality rates, we used a Cox proportional hazards regression analysis to compute age- and sex-adjusted 30-day and 31-365-day hazard ratios as estimates of the corresponding mortality rate ratios (MRRs) for patients with type 2 diabetes in each group of diabetic complications, compared with other ICU patients. The assumption of proportional hazards was checked graphically and found appropriate. We also examined mortality according to duration of type 2 diabetes, because patients with long-standing diabetes may have more severe chronic end-organ damage. Duration of type 2 diabetes was defined as years elapsed from the first diabetes diagnosis or the first prescription for an antidiabetic drug.

To address the impact of potential confounders other than age and sex, we conducted a second analysis that was further adjusted for other preadmission chronic disease, diagnostic category, medical/surgical admission type, and marital status (i.e., all variables listed in Table 1 excepting ICU treatments). We also repeated the analyses excluding patients identified using only HbA1c criteria (n = 568), because they may have had more mild diabetes.

To address the potentially different effects of type 2 diabetes in subgroups (effect measure modification), we stratified the analyses by age group, sex, diagnostic category (including the following non-endocrinology disease groups: pneumonia, other infectious disease, cardiovascular, respiratory, gastrointestinal/liver, cancer, trauma/poisoning, and other diseases), treatment with mechanical ventilation, and surgical/medical admission type. (see Supplemental Table S1 for diagnostic codes)

All analyses were conducted using the software package Stata, version 10.1 (StataCorp, College Station, TX, USA). The study was approved by the Danish Data Protection Agency.

RESULTS

Descriptive data

The study cohort consisted of 39,286 patients aged 40 years or older admitted to ICUs in Northern Denmark during the six-year study period. Among these, 6,027 (15.3%) had type 2 diabetes and 33,259 (84.7%) did not have diabetes. Diabetes was identified by a previous inpatient or outpatient hospital diagnosis in 4,475 patients (74.2%), by a prescription for antidiabetic drugs alone in 960 patients (15.9%), and by an elevated HbA1c test alone in 568 patients (9.4%). Most of the ICU patients with type 2 diabetes did not have a history of heart

or kidney disease (n = 4,521, 75.0%); 1,103 (18.3%) had comorbid heart disease alone, 260 (4.3%) had comorbid kidney disease alone, and 142 (2.4%) had both of these complications.

The median age was 70 years in patients with type 2 diabetes and 67 years in other ICU patients. There were slightly more men among the type 2 diabetes patients (60.3%) than among other ICU patients (56.9%) (Table 1). Patients with type 2 diabetes were more likely to have a previous diagnosis of other lifestyle-associated diseases, such as chronic pulmonary disease, liver disease, and obesity. Cancer was slightly more frequent in patients without type 2 diabetes. There was no major difference in marital status between the two groups (Table 1).

Type 2 diabetes patients with previous heart disease were older (median age, 72 years) and more had chronic pulmonary disease. Surprisingly, more than 90% of patients with kidney complications also had chronic pulmonary disease (Table 1). Mechanical ventilation was provided in approximately 40% of both uncomplicated type 2 diabetes patients and other ICU patients, and renal replacement therapy was provided in 3% of uncomplicated type 2 diabetes patients and more than 20% of patients with kidney complication, compared with 4% of other ICU patients. Treatment with inotropes or vasopressors was also more frequent among type 2 diabetes patients with heart and/or kidney disease (Table 1). Most type 2 diabetes patients with kidney complications were non-surgical ICU patients (Table 1).

Mortality

Thirty-day mortality was 22.9% (95% CI 21.9%–24.0%) in type 2 diabetes patients and 18.4% (95% CI 18.0%–18.8%) in other ICU patients. Mortality in type 2 diabetes patients ranged from 22.1% among those without complications to 34.5% among those with diabetes

complicated by both heart and kidney disease. Type 2 diabetes was also associated with increased mortality compared with other patients after age and sex adjustment, adjusted MRR was 1.18 (95% CI 1.11–1.25). Additionally, type 2 diabetes complicated by heart disease was associated with a slight mortality increase (adjusted MRR 1.12 [95% CI 0.99–1.27]). Type 2 diabetes patients with chronic kidney disease had markedly increased mortality compared with patients without diabetes, both when kidney disease was the only complication [adjusted MRR 1.65 [95% CI 1.32–2.05]) and when combined with heart disease (MRR 1.66 [95% CI 1.26–2.21]). Duration of diabetes had no impact on mortality (Table 2).

Additional adjustment for other chronic diseases, diagnostic category, surgical/medical admission, and marital status decreased the overall MRR without changing the conclusion (adjusted MRR 1.12 [95% CI 1.05–1.19]). Additionally, in diabetes subcategories the estimates moved further towards one: adjusted MRR for uncomplicated diabetes was 1.12 (95% CI 1.05–1.20); 1.09 (95% CI 0.96–1.23) if complicated by heart disease; 1.17 (95% CI 0.92–1.50) if complicated by kidney disease; and 1.17 (95% CI 0.87–1.58) if complicated by both heart and kidney disease.

The long-term mortality from day 31 to day 365 after ICU admission was 17.3% (95% CI 16.2%–18.5%) among type 2 diabetes patients and 13.7% (95% CI 13.2%–14.1%) among other ICU patients. Mortality rose to approximately 30% in type 2 diabetes patients with kidney disease (Fig. 1 and Table 2). The adjusted long-term MRR was 1.20 (95% CI 1.11–1.30), and peaked at 2.25 (95% CI 1.71–2.96) in type 2 diabetes patients with kidney disease (Table 2).

Among the 6,027 type 2 diabetes patients, 568 (9.4%) were included only because of an HbA1c test result indicating diabetes. Excluding these patients did not affect the overall

estimates (overall 30-day MRR 1.18 [95% CI 1.11–1.25] and overall 31-365–day MRR 1.19 [95% CI 1.09–1.29]).

Stratified analyses

The effect of type 2 diabetes on mortality was primarily in patients aged 60 years or older. There were no sex-associated differences (Fig. 2).

Type 2 diabetes had no impact on mortality in ICU patients hospitalized because of infectious diseases, including pneumonia, and cardiovascular disease. The estimates were close to the overall result for patients admitted with cancer, respiratory diseases, gastrointestinal/liver disease, and trauma/poisoning (Fig. 2).

Overall, there were no major differences in the impact of type 2 diabetes among surgical (adjusted MRR 1.17 [95% CI 1.07–1.27]) and medical ICU patients (adjusted MRR 1.11 [95% CI 1.02–1.20]) (Fig. 2). The association was less pronounced in patients treated with mechanical ventilation (adjusted MRR 1.06 [95% CI 0.98–1.15]) than in patients not receiving mechanical ventilation (adjusted MRR 1.29 [95% CI 1.19–1.41]) (Fig. 2).

DISCUSSION

This is the first study to report one-year mortality among intensive care patients with type 2 diabetes. During the entire follow-up period, the mortality rate was 20% higher among ICU patients with type 2 diabetes than among other ICU patients. The excess risk was most pronounced in diabetic patients with chronic kidney disease, while preadmission heart disease

did not further increase mortality. The impact of type 2 diabetes was primarily in patients aged 60 years or older.

In contrast to our findings, the three previous studies observed no increased short-term mortality among intensive care patients with diabetes. A cohort study conducted in the United States that included more than 1.5 million ICU patients from an administrative database reported in-hospital mortality of 8.8% in diabetic patients and 9.7% in other ICU patients, corresponding to an age-adjusted odds ratio of 0.79 (95% CI 0.78–0.80) in the overall cohort, and 1.01 (95% CI 0.92–1.11) in 36,414 patients in which diabetes history was obtained by nurses at ICU admission (19). In a European study of 3,147 patients from 198 ICUs, insulin-treated diabetes was associated with slightly increased crude in-hospital mortality (28% vs. 24%, corresponding to a relative mortality risk of 1.17), which is compatible with our finding; however, the hazard ratio for in-hospital mortality within 28 days was 0.78 (95% CI 0.58–1.07) after adjustment for age, liver cirrhosis, SAPS II score, and mechanical ventilation (20). Adjustment for factors influenced by diabetes may have biased any true association towards the null. Another cohort study included 830 patients with severe sepsis from the control group of an international multicenter trial conducted in 1998–2000 (18). Although the 28-day mortality rates were very similar in ICU patients with and without diabetes (31.4% vs. 30.5%), type 2 diabetes patients with severe chronic complications may have been excluded by one of several exclusion criteria in the trial (34).

Very similar to our finding, a recent meta-analysis observed that an unadjusted odds ratio for death within 30 days of ICU admission was 1.19 (95% CI 0.96–1.47) in diabetes patients compared with other ICU patients. In contrast to our finding, diabetes was associated with markedly increased mortality in surgical patients (OR 1.62 [95% CI 1.13–2.34]);

however, the study may have included patients admitted only for postoperative recovery, because mortality was as low as 2.5% in surgical ICU patients (17).

In summary, several issues may explain the varied findings, including bias from the selection of study participants, bias from inaccurate diabetes information, uncontrolled confounding, or chance. Reported diabetes prevalence in previous studies ranged from 7.2% (20) to 22.7% (18). Importantly, identification of diabetes by insulin-treatment, chart review, or registration during index hospitalization could bias the results towards no association if diabetes was underreported in patients with other and more severe diagnoses, or if non-diabetic patients with stress hyperglycemia during their current ICU admission were registered as having diabetes (35).

The present study was conducted in a population-based hospital setting within a uniform health care system with little racial or socioeconomic diversity. However, several issues must be considered in the interpretation of our data. We relied on routine registrations to identify ICU admissions. The registrations of ICU admissions in the DNRP are considered approximately 95% complete and 99% accurate (24), thereby limiting selection bias. We also had complete follow-up for death and accurate data regarding diabetes before the index hospitalization, which limits information bias (6), and undetected diabetes patients will bias our results towards no association. Although diagnostic coding of heart and kidney diseases is valid (33), we did not estimate the glomerular filtration rate to assess severity of kidney dysfunction. We also assumed that heart and kidney diseases diagnosed in the period from one year before diagnosis of type 2 diabetes until the current hospitalization could be ascribed to diabetes. However, there may be exceptions, such as patients who become diabetic when their glomerulonephritis is treated with glucocorticoids. In addition, any impact of undiagnosed heart disease may have biased our results regarding type 2 diabetes with heart

disease towards the null. Finally, we cannot rule out effects from unmeasured confounding by lifestyle factors such as smoking and body mass index, as our estimates decreased slightly when further adjusted for a previous diagnosis of lifestyle-associated chronic diseases, including chronic pulmonary disease, alcoholism, and obesity.

Several mechanisms may explain our findings. First, preclinical studies suggest that diabetes is associated with immune dysfunction, endothelial dysfunction, and procoagulation (7), which may increase risk and worsen prognosis of critical illness, including sepsis and organ dysfunction, although clinical data are conflicting (23,36). Second, clinical awareness of critical complications in diabetes patients may lead to earlier ICU admission with milder acute illness; however, previous studies do not support this hypothesis, as they observed higher severity of illness in diabetes patients (18-20,36). Third, type 2 diabetes patients often receive preadmission cardioprotective drugs, such as statins and betablockers, which may affect the prognosis of critical illness and explain how coexisting heart disease was not associated with any further mortality risk (37,38). Fourth, antidiabetic drugs may have anti-inflammatory and anti-coagulative effects that may be beneficial during critical illness (21), although the potential beneficial effect of intensive insulin therapy is not observed in ICU patients with diabetes (39).

This study demonstrates that type 2 diabetes may affect the clinical course of ICU patients, and those with chronic kidney disease may be at particularly high risk, which may be of interest both in the clinical setting and for planning preventive initiatives. However, our observational study used existing data and we had limited clinical data to explore underlying mechanisms such as severity of illness. Equal access to health care in Denmark strengthens the study's internal validity at the expense of generalizability to other and more diverse health care systems.

In conclusion, ICU patients with type 2 diabetes experienced higher mortality than other ICU patients for up to one year after ICU admission. The impact was most pronounced in those with chronic kidney disease.

ACKNOWLEDGMENTS

Author contributions: C.F.C. researched data and wrote the manuscript. M.B.J. researched data, contributed to discussion, and reviewed/edited the manuscript. H.T.S., S.C., J.M.O., and E.T. contributed to discussion and reviewed/edited the manuscript.

Guarantor: C.F.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibilities for the integrity of the data and the accuracy of the data analysis.

Funding/financial support: This research received financial support from the Danish Medical Research Council (Grant 271-05-0511) and from the "Klinisk Epidemiologisk Forskningsfond", Denmark. The Department of Clinical Epidemiology is a member of the Danish Center for Strategic Research in Type 2 Diabetes (Danish Research Council, Grants no. 09-075724 and 10-079102). The funders had no influence on the present study.

Prior abstract publication: The preliminary study findings were presented orally in the Abstract Award Winning Session at the European Society of Intensive Care Medicine (ESICM) Annual Meeting 2010, Barcelona, Spain, 12 October 2010. Abstract published in *Intensive Care Med. 2010 Sep; 36(Suppl 2):S205*.

Conflicts of interest: C.F., M.B.J., S.C., E.T., and H.T.S. did not report receiving fees, honoraria, grants or consultancies. J.M.O received fees and grants for other studies, but have no conflicts of interest in relation to the present study. The Department of Clinical Epidemiology is, however, involved in studies with funding from various companies as research grants to (and administered by) Aarhus University. None of these studies have any relation to the present study.

References

1. Ritz E, Orth SR. Nephropathy in patients with type 2 diabetes mellitus. N Engl J Med 1999;341:1127-1133.

2. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. JAMA 2002;287:2570-2581.

3. de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J. Temporal trends in the prevalence of diabetic kidney disease in the United States. JAMA 2011;305:2532-2539.

4. Hsu CY, Ordonez JD, Chertow GM, Fan D, McCulloch CE, Go AS. The risk of acute renal failure in patients with chronic kidney disease. Kidney Int 2008;74:101-107.

5. Kornum JB, Thomsen RW, Riis A, Lervang HH, Schonheyder HC, Sorensen HT. Diabetes, glycemic control, and risk of hospitalization with pneumonia: a population-based case-control study. Diabetes Care 2008;31:1541-1545.

6. Thomsen RW, Hundborg HH, Lervang HH, Johnsen SP, Schonheyder HC, Sorensen HT. Risk of community-acquired pneumococcal bacteremia in patients with diabetes: a population-based case-control study. Diabetes Care 2004;27:1143-1147.

7. Schuetz P, Castro P, Shapiro NI. Diabetes and sepsis: preclinical findings and clinical relevance. Diabetes Care 2011;34:771-778.

8. Movahed MR, Hashemzadeh M, Jamal M. Increased prevalence of ventricular fibrillation in patients with type 2 diabetes mellitus. Heart Vessels 2007;22:251-253.

9. Movahed MR, Hashemzadeh M, Jamal MM. The prevalence of pulmonary embolism and pulmonary hypertension in patients with type II diabetes mellitus. Chest 2005;128:3568-3571.

10. Thomsen RW, Riis A, Christensen S, Norgaard M, Sorensen HT. Diabetes and 30-day mortality from peptic ulcer bleeding and perforation: a Danish population-based cohort study. Diabetes Care 2006;29:805-810.

11. Hansen HH, Joensen AM, Riahi S, Malczynski J, Molenberg D, Ravkilde J. Short and long-term outcome in diabetic patients with acute myocardial infarction in the invasive era. Scand Cardiovasc J 2007;41:19-24.

12. Ahmad R, Cherry RA, Lendel I, Mauger DT, Service SL, Texter LJ, Gabbay RA. Increased hospital morbidity among trauma patients with diabetes mellitus compared with age- and injury severity score-matched control subjects. Arch Surg 2007;142:613-618.

13. Kornum JB, Thomsen RW, Riis A, Lervang HH, Schonheyder HC, Sorensen HT. Type 2 diabetes and pneumonia outcomes: a population-based cohort study. Diabetes Care 2007;30:2251-2257.

14. Vardakas KZ, Siempos II, Falagas ME. Diabetes mellitus as a risk factor for nosocomial pneumonia and associated mortality. Diabet Med 2007;24:1168-1171.

15. Thomsen RW, Hundborg HH, Lervang HH, Johnsen SP, Schonheyder HC, Sorensen HT. Diabetes mellitus as a risk and prognostic factor for community-acquired bacteremia due to enterobacteria: a 10-year, population-based study among adults. Clin Infect Dis 2005;40:628-631.

16. Thomsen RW, Hundborg HH, Lervang HH, Johnsen SP, Sorensen HT, Schonheyder HC. Diabetes and outcome of community-acquired pneumococcal bacteremia: a 10-year population-based cohort study. Diabetes Care 2004;27:70-76.

17. Siegelaar SE, Hickmann M, Hoekstra JB, Holleman F, DeVries JH. The effect of diabetes on mortality in critically ill patients: a systematic review and meta-analysis. Crit Care 2011;15:R205.

18. Stegenga ME, Vincent JL, Vail GM, Xie J, Haney DJ, Williams MD, Bernard GR, van der Poll T. Diabetes does not alter mortality or hemostatic and inflammatory responses in patients with severe sepsis. Crit Care Med 2010;38:539-545.

19. Graham BB, Keniston A, Gajic O, Trillo Alvarez CA, Medvedev S, Douglas IS. Diabetes mellitus does not adversely affect outcomes from a critical illness. Crit Care Med 2010;38:16-24.

20. Vincent JL, Preiser JC, Sprung CL, Moreno R, Sakr Y. Insulin-treated diabetes is not associated with increased mortality in critically ill patients. Crit Care 2010;14:R12.

21. Honiden S, Gong MN. Diabetes, insulin, and development of acute lung injury. Crit Care Med 2009;37:2455-2464.

22. Zmijewski JW, Lorne E, Zhao X, Tsuruta Y, Sha Y, Liu G, Siegal GP, Abraham E. Mitochondrial respiratory complex I regulates neutrophil activation and severity of lung injury. Am J Respir Crit Care Med 2008;178:168-179.

23. Moss M, Guidot DM, Steinberg KP, Duhon GF, Treece P, Wolken R, Hudson LD, Parsons PE. Diabetic patients have a decreased incidence of acute respiratory distress syndrome. Crit Care Med 2000;28:2187-2192.

24. Christiansen CF, Christensen S, Johansen MB, Larsen KM, Tonnesen E, Sorensen HT. The impact of pre-admission morbidity level on 3-year mortality after intensive care: a Danish cohort study. Acta Anaesthesiol Scand 2011;55:962-970.

25. Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull 1999;46:263-268.

26. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993;270:2957-2963.

27. Ehrenstein V, Antonsen S, Pedersen L. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. Clin Epidemiol 2010;2:273-279.

28. Horsdal HT, Johnsen SP, Sondergaard F, Rungby J. Type of preadmission glucose-lowering treatment and prognosis among patients hospitalised with myocardial infarction: a nationwide follow-up study. Diabetologia 2008;51:567-574.

29. Standards of medical care in diabetes--2011. Diabetes Care 2011;34 Suppl 1:S11-S61.

30. Grann AF, Erichsen R, Nielsen AG, Froslev T, Thomsen RW. Existing data sources for clinical epidemiology: The clinical laboratory information system (LABKA) research database at Aarhus University, Denmark. Clin Epidemiol 2011;3:133-138.

31. Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. Dan Med Bull 2006;53:441-449.

32. Needham DM, Scales DC, Laupacis A, Pronovost PJ. A systematic review of the Charlson comorbidity index using Canadian administrative databases: a perspective on risk adjustment in critical care research. J Crit Care 2005;20:12-19.

33. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sorensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. BMC Med Res Methodol 2011;11:83.

34. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJ, Jr. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001;344:699-709.

35. Jencks SF, Williams DK, Kay TL. Assessing hospital-associated deaths from discharge data. The role of length of stay and comorbidities. JAMA 1988;260:2240-2246.

36. Slynkova K, Mannino DM, Martin GS, Morehead RS, Doherty DE. The role of body mass index and diabetes in the development of acute organ failure and subsequent mortality in an observational cohort. Crit Care 2006;10:R137.

37. Christensen S, Thomsen RW, Johansen MB, Pedersen L, Jensen R, Larsen KM, Larsson A, Tonnesen E, Sorensen HT. Preadmission statin use and one-year mortality among patients in intensive care - a cohort study. Crit Care 2010;14:R29.

38. Christensen S, Johansen MB, Tonnesen E, Larsson A, Pedersen L, Lemeshow S, Sorensen HT. Preadmission beta-blocker use and 30-day mortality among patients in intensive care: a cohort study. Crit Care 2011;15:R87.

39. van den BG, Wilmer A, Milants I, Wouters PJ, Bouckaert B, Bruyninckx F, Bouillon R, Schetz M. Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. Diabetes 2006;55:3151-3159.

Table 1—Characteristics of intensive care patients with and without type 2 diabetes and among type 2 diabetes patients according to history of heart and kidney disease

	No diabetes	Type 2 diabetes				
		All	Major diabetes-related complications†			
			No	Heart disease	Kidney disease	Heart+kidney disease
	n = 33,259 (%)	n = 6,027 (%)	n = 4,521 (%)	n = 1,103 (%)	n = 261 (%)	n = 142 (%)
Age group						
40–59 years	9,989 (30.0)	1,094 (18.2)	910 (20.1)	128 (11.6)	44 (16.9)	12 (8.5)
60–79 years	17,684 (53.2)	3,861 (64.1)	2,846 (63.0)	743 (67.4)	173 (66.3)	99 (69.7)
80+ years	5,586 (16.8)	1,072 (17.8)	765 (16.9)	232 (21.0)	44 (16.9)	31 (21.8)
Age, median (IQR*)	67 (57-76)	70 (62-77)	69 (61-77)	72 (65-78)	71 (63-77)	74 (68-78)
Sex						
Female	14,328 (43.1)	2,393 (39.7)	1,845 (40.8)	402 (36.5)	98 (37.6)	48 (33.8)
Male	18,931 (56.9)	3,634 (60.3)	2,676 (59.2)	701 (63.6)	163 (62.5)	94 (66.2)
Marital status						
Married	18,283 (55.0)	3,093 (51.3)	2,323 (51.4)	570 (51.7)	127 (48.7)	73 (51.4)
Never married	3,587 (10.8)	617 (10.2)	472 (10.4)	96 (8.7)	35 (13.4)	14 (9.9)
Divorced	4,567 (13.7)	905 (15.0)	700 (15.5)	147 (10.4)	34 (13.0)	24 (16.9)
Widowed	6,744 (20.3)	1,407 (23.3)	1,021 (22.6)	290 (26.3)	65 (24.9)	31 (21.8)
Unknown	78 (0.2)	5 (0.1)	5 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Other preadmission morbidity‡						
Dementia	337 (1.0)	68 (1.1)	44 (1.0)	14 (1.3)	4 (1.5)	6 (4.2)
Chronic pulmonary disease	906 (2.7)	631 (10.5)	180 (4.0)	78 (7.1)	239 (91.6)	134 (94.4)
Connective tissue disease	945 (2.8)	243 (4.0)	147 (3.3)	65 (5.9)	22 (8.4)	9 (6.3)
Liver disease	769 (2.3)	202 (3.4)	170 (3.8)	23 (2.1)	7 (2.7)	2 (1.4)
Cancer	5,189 (15.6)	801 (13.3)	645 (14.3)	112 (10.2)	34 (13.0)	10 (7.0)
Metastatic cancer	840 (2.5)	109 (1.8)	92 (2.0)	14 (1.3)	2 (0.8)	1 (0.7)
Alcoholism	2,458 (7.4)	399 (6.6)	323 (7.1)	46 (4.2)	21 (8.1)	9 (6.3)
Obesity	620 (1.9)	603 (10.0)	395 (8.7)	152 (13.8)	35 (13.4)	21 (14.8)

	No diabetes	Type 2 diabetes				
		All	Major diabetes-related complications†			
			No	Heart disease	Kidney disease	Heart+kidney disease
	n = 33,259 (%)	n = 6,027 (%)	n = 4,521 (%)	n = 1,103 (%)	n = 261 (%)	n = 142 (%)
ICU admission type						
Medical	11,620 (34.9)	2,408 (40.0)	1,796 (39.7)	416 (37.7)	123 (47.1)	73 (51.4)
Surgical	21,639 (65.1)	3,619 (60.0)	2,725 (60.3)	687 (62.3)	138 (52.9)	69 (48.6)
Intensive care treatments						
Mechanical ventilation	13,224 (39.8)	2,569 (42.6)	1,886 (41.7)	542 (49.1)	99 (37.9)	42 (29.6)
Renal replacement therapy	1,240 (3.7)	394 (6.5)	261 (5.8)	47 (4.3)	57 (21.8)	29 (20.4)
Treatment with inotropes/vasopressors	9,216 (27.7)	1,938 (32.2)	1,410 (31.2)	386 (35.0)	101 (38.7)	41 (28.9)

† First diagnosed from one year before first diabetes diagnosis/antidiabetic prescription until the current hospital admission.
‡ Any diagnosis within five years before the current hospital admission
* IQR = interquartile range

Table 2—Thirty-day and 31–365-day mortality and mortality rate ratio (MRR), including type 2 diabetes patients with/without history of heart and kidney disease, as well as diabetes duration

	N	30-day			31–365day-mortality		
		Mortality, % (95%CI)	Crude MRR (95%CI)	Adjusted* MRR (95%CI)	Mortality, % (95%CI)	Crude MRR (95%CI)	Adjusted* MRR (95%CI)
Diabetes status and complications							
No diabetes	33,259	18.4 (18.0–18.8)	1.00 (ref.)	1.00 (ref.)	13.7 (13.2–14.1)	1.00 (ref.)	1.00 (ref.)
Type 2 diabetes	6,027	22.9 (21.9–24.0)	1.28 (1.20–1.35)	1.18 (1.11–1.25)	17.3 (16.2–18.5)	1.29 (1.19–1.40)	1.20 (1.11–1.30)
Without complications	4,521	22.1 (20.9–23.3)	1.22 (1.14–1.31)	1.16 (1.08–1.24)	16.1 (14.9–17.4)	1.18 (1.08–1.30)	1.12 (1.02–1.23)
With heart disease†	1,103	23.0 (20.6–25.6)	1.29 (1.14–1.46)	1.12 (0.99–1.27)	18.3 (15.8–21.2)	1.40 (1.19–1.66)	1.22 (1.03–1.44)
With kidney disease‡	261	30.7 (25.5–36.7)	1.79 (1.43–2.23)	1.65 (1.32–2.05)	30.7 (24.3–38.3)	2.43 (1.85–3.20)	2.25 (1.71–2.96)
With heart† and kidney disease‡	142	34.5 (27.3–43.0)	2.06 (1.56–2.73)	1.66 (1.26–2.21)	29.6 (21.1–40.3)	2.39 (1.62–3.51)	1.91 (1.30–2.81)
Diabetes duration							
0–2 years	1,849	21.9 (20.1–23.9)	1.00 (ref.)	1.00 (ref.)	18.1 (16.1–20.2)	1.00 (ref.)	1.00 (ref.)
3–5 years	1,101	21.6 (19.2–24.1)	0.98 (0.84–1.15)	1.02 (0.87–1.19)	16.2 (13.8–18.9)	0.89 (0.72–1.10)	0.90 (0.73–1.11)
6–10 years	1,396	24.2 (22.0–26.5)	1.11 (0.96–1.28)	1.09 (0.94–1.25)	16.8 (14.6–19.3)	0.93 (0.77–1.14)	0.90 (0.74–1.10)
>10 years	1,681	23.8 (21.8–25.9)	1.10 (0.96–1.26)	1.06 (0.92–1.21)	17.8 (15.7–20.1)	0.99 (0.82–1.19)	0.95 (0.79–1.14)

† Heart diseases included myocardial infarction and congestive heart failure.
‡ Kidney diseases included chronic kidney disease.
* Adjusted for age and sex

FIGURES

Figure 1—Cumulative one-year mortality among intensive care patients without diabetes, patients with uncomplicated type 2 diabetes, and patients with type 2 diabetes complicated by heart and/or kidney disease.

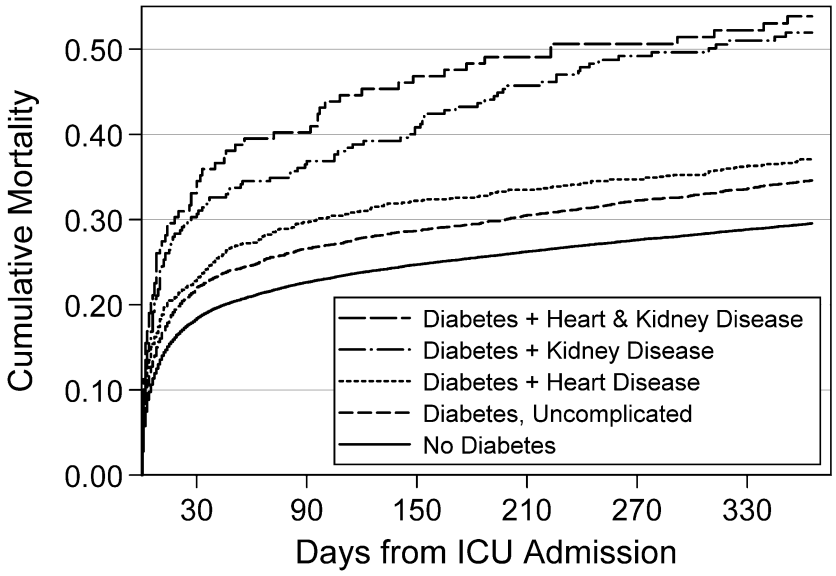
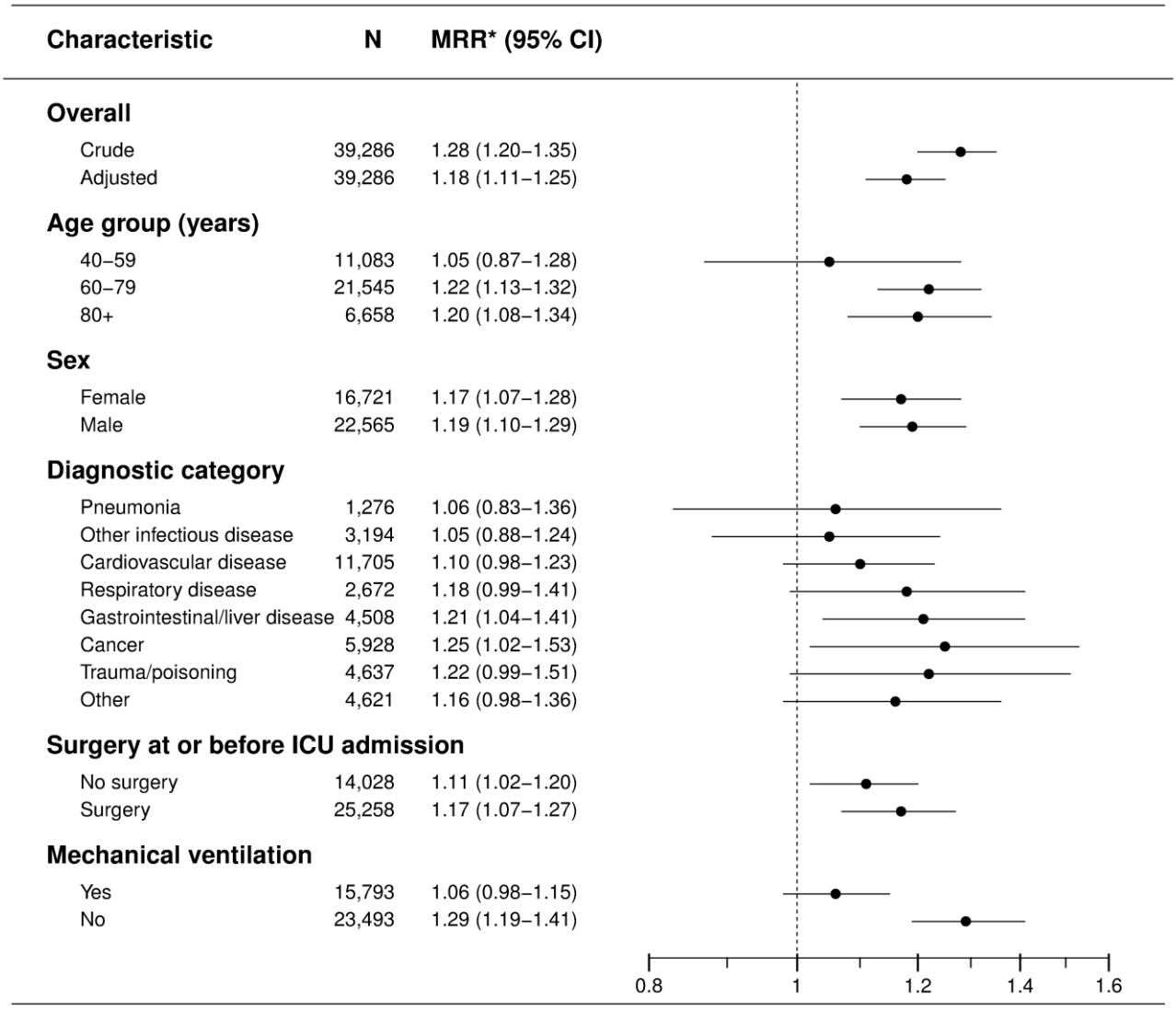


Figure 2—Thirty-day mortality rate ratio (MRR) comparing type 2 diabetes patients with other ICU patients, stratified by age, sex, diagnostic category (main reason for hospitalization), surgery at or before intensive care unit (ICU) admission, and mechanical ventilation.



ONLINE-ONLY SUPPLEMENTAL MATERIAL

Supplemental Table S1. International Classification of Diseases, 8th (ICD-8) and 10th revision (ICD-10) diagnosis codes.

	ICD-8	ICD-10
Diabetes	249, 250	E10-E14, O24 (except O24.4), G63.2, H36.0, N08.3
Chronic kidney disease	249.02, 250.02, 403-404, 580-584, 590.09, 593.20, 753.10, 753.19	N00-N01, N03-N05, N07, N08 N11, N14-N16, N18-N19, N26, N27, I12, I13, I15.0, I15.1, Q61.1-Q61.4, E10.2, E11.2, E14.2
Heart disease (myocardial infarction and heart failure)	410, 427.09, 427.10, 427.11, 427.19, 428.99, 782.49	I21, I22, I23, I50, I11.0, I13.0, I13.2
Obesity	-	E66
Alcoholism**	-	F10 (except F10.0), G31.2, G62.1, G72.1, I 42.6, K29.2, K86.0, Z72.1
Polycystic ovarian syndrome	-	E28.2
Diagnostic category		
Pneumonia	-	J12-J18, A48.1, A70.9
Infectious diseases excluding pneumonia	-	A00-B99 (without A48.1, A70.9), G00-G07, I00-I02, I30.1, I32.0, I33, I38, I40.0, J00-J06, J36, J39.0, J10-J11, J20-J22, J85.1, J86, K35, K37, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.9, K67, K75.0, K75.1, K80.0, K80.3, K80.4, K81.0, K81.9, K83.0, L00-L03, L05-L08, M00, M01, M86, N10, N12, N15.1, N30, N39.0, N41, N45, N70-N77
Diabetes	-	E10-E14, O24 (except O24.4), G63.2, H36.0, N08.3
Endocrinology excluding diabetes	-	E00-E90 (without E10-E14)
Cardiovascular diseases	-	I00-I99 without I00-I02, I30.1, I32.0, I33, I38, I40.0
Respiratory diseases	-	J00-J99 without J00-J06, J36, J39.0, J10-J11, J12-J18, J20-J22, J85.1, J86
Gastrointestinal and liver disease	-	K00-K99 without , K35, K37, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.9, K67, K75.0, K75.1, K80.0, K80.3, K80.4, K81.0, K81.9, K83.0
Cancer	-	C00-D89
Trauma and poisoning	-	S00-T98
Other	-	all codes not included in other categories

Supplemental Table S2. Anatomical Therapeutical Chemical (ATC) codes for included drugs.

	ATC-code
Antidiabetic drugs (insulin, oral antidiabetic drug)	A10A, A10B
Disulfiram	N07BB01

Study III

Preadmission Metformin use and Mortality among Intensive Care Patients with Diabetes: A Cohort Study

Running title: Metformin use and Mortality among ICU Patients

Authors: Christian F Christiansen[1,2], MD; Martin B Johansen[1], MSc; Steffen Christensen[1,2], MD, PhD; James M O'Brien[3], MD; Else Tønnesen[2], MD, DMSc; Henrik Toft Sørensen[1], MD, PhD, DMSc.

Affiliations:

[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

[2]Department of Anesthesiology and Intensive Care, Aarhus University Hospital, Aarhus, Denmark

[3]Center for Critical Care, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, The Ohio State University Medical Center, Columbus, Ohio, USA

Corresponding author: Christian F Christiansen, Aarhus University Hospital, Department of Clinical Epidemiology, Olof Palmes Alle 43−45, 8200 Aarhus N, Denmark. Phone +45 87168063. Fax +45 87167215. E-mail: cc@dce.au.dk

Key words: Cohort studies; diabetes mellitus type 2; intensive care; metformin; mortality.

Word count: 2,504 + abstract 250.

Abstract

Rationale: Metformin has anti-inflammatory and anti-thrombotic effects that may improve the outcome of critical illness, but clinical data are limited.

Objectives: To examine the impact of preadmission metformin use on mortality among intensive care patients with type 2 diabetes.

Methods: Cohort study of type 2 diabetic patients admitted to intensive care units in Northern Denmark (population~1.8 million) in 2005−2010. By individual-level linkage of medical databases, diabetes was identified by previous diabetes hospital diagnoses, filled prescriptions for antidiabetic drugs, or elevated hemoglobin A1c. Metformin use was identified by filled prescriptions within 90 days before admission. Covariates included among others surgery, preadmission morbidity, diabetes duration, and organ dysfunction. We computed 30-day mortality and adjusted mortality rate ratios adjusted for covariates in the overall cohort and after propensity score matching.

Measurements and Main Results: Among 6,170 type 2 diabetes patients (13.2% of all ICU patients), 827 (13.4%) used metformin as monotherapy and 1,101 (17.8%) in combination with other antidiabetic drugs. Metformin users had less comorbidity and less organ dysfunction upon ICU admission. The 30-day mortality was 16.9% among metformin monotherapy users, 18.0% among metformin combination therapy users, and 25.0% among non-users. The adjusted mortality rate ratio was 0.79 (95% confidence interval (CI): 0.66−0.95) for metformin monotherapy users and 0.83 (95% CI: 0.71−0.97) for metformin combination therapy users, compared to non-users. Adjustment for organ dysfunction had no influence on the estimates. Propensity score matched analyses revealed similar estimates.

Conclusions: Preadmission metformin use was associated with a reduced mortality among intensive care patients with diabetes.

Introduction

Metformin is a widely used drug in the treatment of patients with type 2 diabetes.[1;2] The use of metformin increased dramatically after 1998, when the UK Prospective Diabetes Study (UKPDS) found reduced all-cause mortality and cardiovascular event rate among metformin users compared with users of other antidiabetic drugs.[3;4] Despite this, treatment with metformin is generally not recommended during hospitalization because of the potential risk of lactic acidosis reported in patients with severe kidney, liver, or heart disease, and after major surgery.[5-7] The low observed rate of lactic acidosis in acutely ill patients should be balanced against the possible beneficial effects of metformin.[8]

Metformin has pleiotropic effects.[9] The hypoglycemic effect of metformin is mediated through increased glucose sensitivity in pancreatic islet cells, increased peripheral glucose utilization, and decreased hepatic gluconeogenesis.[10] In addition, experimental animal studies found that metformin has anti-inflammatory and anti-thrombotic effects that may influence the outcome of critical illness by attenuating the development and progression of acute organ dysfunction, such as acute lung injury.[11-13]

Only few human studies have examined the effect of metformin in relation to critical illness. A clinical trial of 21 intensive care unit (ICU) patients found anti-inflammatory properties of metformin when added to intensive insulin therapy.[14] In a cohort of 1,284 diabetes patients who underwent cardiac surgery, preadmission metformin was associated with a more than 50% decreased post-operative morbidity rate, including infections, and with a substantial decrease in inpatient mortality.[15] Any potential impact may, however, be limited to conditions with an early phase of high-grade inflammation,[16;17] as metformin use was not associated with mortality in patients with acute myocardial

infarction.[18-20] Still, no data exist on the impact of metformin on mortality after intensive care admission.

Examination of the association between preadmission metformin use and mortality following ICU admission may promote understanding of disease processes and may elucidate future therapeutic targets. We therefore examined whether preadmission metformin use was associated with decreased 30-day mortality among ICU patients with type 2 diabetes. Some of the results of this study have been previously reported in the form of an abstract.[21]

Methods

This cohort study included type 2 diabetes patients living in Northern Denmark who were admitted to one of the 17 ICUs in the region between January 1, 2005 and December 31, 2010.[22] Data collection was based on unambiguous individual-level linkage between medical registries and databases,[23-25] using a unique person identifier assigned to each Danish citizen.[26;27] For methodological details, see the online supplement.

Intensive care patients with type 2 diabetes

We identified type 2 diabetic patients using a previously validated algorithm including any previous inpatient or outpatient clinic diagnosis of diabetes after age 30, or any filled prescription for an oral antidiabetic drug.[28] We further included patients diagnosed before age 30 if they had not filled any prescriptions for insulin within a year before admission, and patients with HbA1c level of 6.5% or more within a year before admission.[5] Non-diabetic patients with metformin-treated polycystic ovarian syndrome were excluded (n = 15).[19]

Preadmission metformin use

We identified all prescriptions for antidiabetics including metformin through a complete population-based prescription database.[23] Metformin use was defined by a filled prescription within 90 days before admission.[29]

Covariates

We used the Sequential Organ Failure Assessment (SOFA) score to assess organ-specific dysfunction of kidney, liver, or coagulation system.[25;30]

We obtained demographic data on age, sex, and marital status, and diagnoses from hospital contacts with chronic diseases within five years before the current admission.[31] We also included data on preadmission prescriptions for low-dose aspirin, beta-blockers, and statins.[23;32-34]

Statistical analyses

We described covariates and the rate of organ dysfunction in contingency tables.

We had complete follow-up from date of ICU admission until date of death, or to censoring at emigration.[26] Thirty-day mortality was assessed by the Kaplan-Meier method. We used a Cox proportional hazards regression analysis to compute hazard ratios (mortality rate ratios) adjusted for the covariates (age, sex, marital status, preadmission diseases, concurrent drug use, diabetes duration, HbA1c level, diagnostic category, and surgical/medical admission

type). We also stratified the analyses according to these covariates.[35] In an additional analysis we also adjusted for organ dysfunction despite that it may be in the causal pathway.[36]

We did several other additional analyses to support the main analyses. Propensity score adjusted and matched analyses were used to improve the adjustment for the likelihood for getting metformin.[37;38] Propensity score matching of metformin users with non-users was possible in 1,765 (91.5%) patients within a range of +/- 0.025. Covariates were adequately balanced after matching.[39] Current (prescription 0−90 days before ICU admission), recent (91−365 days), and former use (1−5 years) of metformin were compared with never use to provide evidence of timing of any drug effect. Current users were further divided in new and long-term users.[40] We also compared metformin monotherapy with sulfonylurea monotherapy because these groups may have comparable and easier controllable type 2 diabetes. Last, we extended the exposure window from 90 to 180 and 365 days to assess sensitivity of the cut point. For methodological details and codes, see the online supplement.

All analyses were conducted using the software package Stata, version 10.1. The study was approved by the Danish Data Protection Agency.

Results

The study included 6,170 adult type 2 diabetes patients, corresponding to 13.2% of 46,630 adult patients admitted to the ICUs. Among type 2 diabetic patients, 827 (13.4%) were metformin monotherapy users, 1,101 (17.8%) used metformin in combination with other anti-diabetic drugs, and 4,242 (68.3%) were non-users.

Descriptive data are presented in Table 1a. A larger proportion of metformin monotherapy and combination therapy users were younger than 80 years compared with non-users. Both groups of metformin users also had less preadmission morbidity, including cardiovascular, liver, renal, and chronic pulmonary diseases. Diabetic nephropathy and retinopathy were more common in metformin combination therapy users and non-users than in metformin monotherapy users. Long diabetes duration (5 years or more) and high preadmission glucose level (hemoglobin A1c greater than 8%) were more common in metformin combination therapy users and less common in metformin monotherapy users compared to non-users. Cardiovascular drugs, particular statins, were more frequently prescribed in metformin users than in non-users. (Table 1a)

The primary diagnosis, registered for the current hospitalization, only differed slightly, with a larger proportion of metformin users admitted because of cardiovascular disease and a smaller proportion with infectious disease. (Table 1b) Sixty-four percent of metformin monotherapy users and 62% of metformin combination therapy users had surgical reason for ICU admission, compared to 59% of non-users. (Table 1b) Four (0.2%) of the metformin users had a primary diagnosis of lactic acidosis. (Data not shown)

Organ dysfunction and organ supportive treatment

Organ dysfunction at day of ICU admission, as evidenced by abnormal creatinine levels, bilirubin levels, and platelet counts, was less common in both metformin monotherapy users and metformin combination therapy users, compared with non-users. As expected, there was virtually no difference after propensity score matching because admission organ dysfunction was included in the score. (Table 1b)

Metformin users were more frequently treated with mechanical ventilation (48% vs. 39%), but there was virtually no difference in use of inotropes/vasopressors and renal replacement therapy. (Table 1b) When comparing the propensity score matched cohorts, all these intensive care treatments were slightly more common among metformin users. (Table 1b)

Mortality

Mortality data are presented in Table 2. Thirty-day mortality was 16.9% in metformin monotherapy users, 18.0% in metformin combination therapy users, and 25.0% in non-users. There were no major mortality differences between non-users who did not get antidiabetic drugs and users of sulfonylurea, insulin, or other/combination therapy. (Table 2)

The mortality rate in metformin users were decreased in both monotherapy [adjusted MRR (aMRR) = 0.79 (95% CI: 0.66−0.95)] and combination therapy users [aMRR = 0.83 (95% CI: 0.71−0.97)] compared to non-users after adjustment for age, sex, marital status, diabetes duration, high preadmission HbA_{1c}, preadmission morbidity, concurrent cardiovascular medication, diagnostic category, and medical/surgical admission type. (Table 2) Further adjustment for organ dysfunction on ICU admission had no influence on the combined estimate for metformin use [aMRR = 0.79 (95% CI: 0.67−0.94)]. (Table 2) The propensity score adjusted analysis gave virtually the same estimates [metformin monotherapy: aMRR = 0.80 (95% CI: 0.67−0.96); metformin combination therapy: aMRR = 0.88 (95% CI: 0.75−1.03)].

In the propensity score matched cohorts, 30-day mortality was 18.0% in metformin users combined and 20.7% in non-users, corresponding to an unadjusted MRR of 0.85 (95% CI:

0.73−1.00). As expected, further adjustment for variables originally included in the propensity score only slightly changed the estimate [aMRR = 0.82 (95% CI: 0.68−0.99)]. (Table 2)

Among all 6,170 patients, 1,928 (31.2%) were current, 382 (6.2%) were recent, 483 (7.8%) were former, and 3,377 (54.7%) were never users of metformin. Compared to never users of metformin, current use was associated with decreased mortality rate [aMRR = 0.81 (95% CI: 0.71−0.93)], while no such association was found in recent [aMRR = 1.01 (95% CI: 0.81−1.27)] and former users [aMRR = 1.04 (95% CI: 0.85−1.26)]. Among current users, 111 were new-users and 1,817 were long-term users. The decreased mortality was less pronounced in new users [aMRR = 0.90 (95% CI: 0.58−1.41)] than in long-term metformin users [aMRR = 0.81 (95% CI: 0.71−0.93)].

The comparison of metformin monotherapy (n=827) with sulfonylurea monotherapy (n=799) revealed a slightly less pronounced association with an aMRR of 0.87 (95% CI: 0.69−1.10) but very similar in the propensity score adjusted analysis with a aMRR of 0.77 (95% CI: 0.61−0.96). (Table 2)

Changing the antidiabetic drug capture window from 90 to 180 or 365 days before ICU admission slightly increased the number of metformin users without changing the estimates considerably. (Data not shown)

Stratified analyses

Figure 1 illustrates the results of the stratified analyses. The mortality decrease was most pronounced in patients aged 60−79 years and in males, which include the groups that most commonly used metformin. Although the estimates were imprecise in subgroups, the

protective effect of metformin was most evident in those with a primary diagnosis of septicemia and other infectious diseases, and in patients with cancer. The mortality reduction was almost similar in medical and surgical ICU patients. The estimates were also very similar in patients with high/low preadmission hemoglobin A1c, and in those with and without chronic pulmonary disease.

Discussion

This was the first study to address the association between preadmission metformin use and outcome after ICU admission. Both use of metformin as monotherapy and in combination with other antidiabetic drugs was associated with a decreased 30-day mortality compared to non-use. The association persisted after adjustment for different admission pattern, organ dysfunction, and other potential confounders. Results were confirmed in a propensity score matched analysis.

There are only very limited data on metformin use and outcome of critical illness. A US cohort study compared 1,284 cardiac surgery patients who received preadmission oral antidiabetic drugs with patients who did not. In a propensity score matched analysis metformin users had less postoperative morbidity, including infections (0.7% vs. 3.2%). Mortality was non-significantly decreased (0.7% vs. 1.4%).[15] An Iranian randomized trial of 21 patients with systemic inflammatory response syndrome examined the clinical effect of metformin during treatment in the ICU and found a decrease in pro-inflammatory cytokines and reduced insulin requirements when metformin was added to intensive insulin therapy.[14] However, the study did not include data on clinical outcomes.

Our study also translate findings from experimental animal studies that found metformin treatment to be associated with decreased mortality in lipopolysaccharide induced acute lung injury or endotoxemia.[11;13] These effects were mediated through attenuation of the pro-inflammatory response including a decrease in pro-inflammatory cytokines such as TNF-α and IL-1β and decreased neutrophil activation through mitochondrial inhibition.[11;13] The hyperinflammatory response is a central part of the pathogenesis in the early phase of sepsis and organ dysfunction,[16] and early metformin treatment may have beneficially modulated this response. Beside the anti-inflammatory effects, the pleiotropic effects of metformin include fibrinolytic effects that may prevent microvasuclar thrombosis by reducing the level of plasminogen activator.[12] We did not have clinical data to support the previous animal studies indicating a lower rate of acute lung injury.[13] Actually, we found an increased rate of mechanical ventilation in metformin users compared with non-users, but we have no data on the indication and this might be imbalanced despite propensity score matching.

Any effect of preadmission metformin in our study was most likely through mediation of the early response to critical illness, because metformin will often be switched to insulin at hospital admission. We can only speculate on any prolonged anti-inflammatory and anticoagulative effect after discontinuation.

Several issues should be considered in the interpretation of our data. We had accurate data on ICU admissions, prescription data, and death during follow-up which limit information and selection bias. We used prescriptions for antidiabetic drugs as a proxy for current use, but any non-compliance would most likely bias our estimates towards no association. We also included patients not receiving antidiabetic drugs in the comparison group of non-users. This is unlikely to bias our results as we found virtually the same mortality as in the other non-users, probably because this group comprised a mix of mild and

non-compliant diabetes patients. We had data on routine biochemical parameters, but lacked data on cardiovascular, respiratory, and cerebral dysfunction to compute the entire SOFA score or other severity-of-illness scores. Our assumption that missing biochemical variables are normal is generally accepted but may not be entirely true.[41]

Metformin users were more often admitted after surgery; however, we found virtually the same association in medical and surgical ICU patients. Metformin is contraindicated in patients with severe congestive heart failure, or with severe liver or renal disease and should be used with caution in patients aged 80 years or older and in patients with chronic obstructive pulmonary disease.[5;6;42] We adjusted for age and these diseases, but unmeasured differences may still influence our findings. We adjusted for diagnosed life-style related diseases, such as chronic pulmonary disease, obesity, alcohol-related disease, and cardiovascular disease. Unmeasured life-style factors are unlikely to explain our findings because there are no major difference in smoking, diet, and physical activity between users of different antidiabetic drugs in Denmark.[43] This is also confirmed by the similar results when analyses were stratified in patients with and without chronic pulmonary disease. Obesity is, however, more frequent in metformin users and may be associated with lowered mortality in ICU patients.[44;45] However, a true drug effect was supported by the fact that the decreased mortality was restricted to current metformin users while no such association was found in recent or former users, who are expected to be very similar with regard to indication for drug prescription including obesity.

Although ICU patients may benefit from preadmission use of metformin, the effect and safety of metformin treatment initiation and continuation in patients who are already critically ill remain to be clarified. Routinely discontinuation of metformin at hospitalization may not be warranted. The non-randomized allocation of metformin treatment

may give rise to uncontrolled confounding, but altogether our analyses support a potential causal association between preadmission metformin use and decreased mortality.

In conclusion, preadmission metformin use was associated with decreased 30-day mortality among ICU patients with type 2 diabetes.

Acknowledgements

Conflict of interest statement: C.F.C., M.B.J., S.C., E.T., and H.T.S. did not report receiving fees, honoraria, grants or consultancies. J.M.O. had no conflict of interest in relation to this study. The Department of Clinical Epidemiology is, however, involved in studies with funding from various companies as research grants to (and administered by) Aarhus University. None of these studies have any relation to the present study.

Author contributions: H.T.S. and C.F.C. conceived the idea and designed the study together with J.M.O. and S.C. Data were analyzed by C.F.C. and M.B.J., and C.F.C. wrote the first draft. All authors interpreted data and revised the manuscript critically. All authors approved the final version.

Financial support: This research received financial support from the Danish Medical Research Council (Grant 271-05-0511) and from the Clinical Epidemiology Research Foundation, Denmark. The Department of Clinical Epidemiology is a member of the Danish Center for Strategic Research in Type 2 Diabetes (Danish Research Council, Grant no. 09-075724 and 10-079102). The funding sources had no influence on the study.

Table 1a. Patient characteristics in metformin users and non-users (overall and after propensity score matching).

	All type 2 diabetic ICU patients (n=6,170)				Propensity score matched patients	
	Metformin monotherapy users n=827 (%)	*Metformin combination therapy users n=1,101(%)*	All Metformin users n=1,928 (%)	Non-users n=4,242 (%)	Metformin users n=1,765(%)	Non-users n=1,765 (%)
Age group						
15−39	18 (2.2)	14 (1.3)	32 (1.7)	111 (2.6)	31 (1.8)	30 (1.7)
40−59	147 (17.8)	211 (19.2)	358 (18.6)	736 (17.4)	325 (18.4)	315 (17.9)
60−79	563 (68.1)	765 (69.5)	1,328 (68.9)	2,533 (59.7)	1,200 (68.0)	1,205 (68.3)
80+	99 (12.0)	111 (10.1)	210 (10.9)	862 (20.3)	209 (11.8)	215 (12.2)
Sex						
Female	325 (39.3)	416 (37.8)	741 (38.4)	1,747 (41.2)	688 (39.0)	685 (38.8)
Male	502 (60.7)	685 (62.2)	1,187 (61.6)	2,495 (58.8)	1,077 (61.1)	1,080 (61.2)
Marital status						
Married	462 (55.9)	619 (56.2)	1,081 (56.1)	2,070 (48.8)	980 (55.5)	990 (56.1)
Never married	82 (9.9)	127 (11.5)	209 (10.8)	475 (11.2)	181 (10.3)	185 (10.5)
Divorced	120 (14.5)	148 (13.4)	268 (13.9)	648 (15.3)	251 (14.2)	231 (13.1)
Widowed	163 (19.7)	206 (18.7)	369 (19.1)	1,038 (24.5)	352 (19.9)	358 (20.3)
Unknown	0 (0.0)	1 (0.1)	1 (0.1)	11 (0.3)	1 (0.1)	1 (0.1)
Preadmission diseases						
Myocardial infarction	66 (7.9)	123 (11.2)	180 (9.3)	492 (11.6)	175 (9.9)	168 (9.5)
Heart failure	71 (8.6)	118 (10.7)	189 (9.8)	665 (15.7)	184 (10.4)	190 (10.8)
Peripheral vascular disease	72 (8.7)	116 (10.5)	188 (9.8)	603 (14.2)	187 (10.6)	182 (10.3)
Cerebrovascular disease	94 (11.4)	107 (9.7)	201 (10.4)	635 (15.0)	198 (11.2)	192 (10.9)
Chronic pulmonary disease	24 (2.9)	56 (5.1)	80 (4.2)	562 (13.3)	80 (4.5)	78 (4.4)
Liver disease	17 (2.1)	13 (1.2)	30 (1.6)	180 (4.2)	30 (1.7)	31 (1.8)
Moderate to severe renal disease	15 (1.8)	30 (2.7)	45 (2.3)	434 (10.2)	45 (2.5)	48 (2.7)
Cancer	103 (12.5)	125 (11.4)	228 (11.8)	582 (13.7)	223 (12.6)	235 (13.3)
Metastatic cancer	15 (1.8)	23 (2.1)	38 (2.0)	73 (1.7)	33 (1.9)	33 (1.9)
Diabetic retinopathy	26 (3.1)	105 (9.5)	131 (6.8)	369 (8.7)	128 (7.3)	117 (6.6)
Diabetic nephropathy	10 (1.2)	39 (3.5)	49 (2.5)	319 (7.5)	49 (2.8)	53 (3.0)
Hypertension	302 (36.5)	396 (36.0)	698 (36.2)	1,524 (35.9)	623 (35.3)	625 (35.4)
Obesity	98 (11.9)	153 (13.9)	251 (13.0)	381 (9.0)	202 (11.4)	199 (11.3)
Alcoholism	35 (4.2)	30 (2.7)	65 (3.4)	350 (8.3)	65 (3.7)	60 (3.4)
Diabetes duration > 5 years	255 (30.8)	769 (69.9)	1,024 (53.1)	2,088 (49.2)	907 (51.4)	946 (53.6)
Hemoglobin A1c* ≥ 8%	79 (9.6)	273 (24.8)	352 (18.3)	691 (16.3)	313 (17.7)	336 (19.0)
Concurrent drug use						
Low-dose aspirin	349 (42.2)	459 (41.7)	808 (41.9)	1,474 (34.8)	696 (39.4)	699 (39.6)
Beta-blockers	319 (38.6)	452 (41.1)	771 (40.0)	1,587 (37.4)	692 (39.2)	709 (40.2)
Statins	518 (62.6)	727 (66.0)	1,245 (64.6)	1,875 (44.2)	1,083 (61.4)	1,094 (62.0)

*Available in 4,365 (70.7%).

Table 1b. Characteristics of current hospitalization and ICU stay including primary diagnosis (diagnostic category), surgery, organ dysfunction, and ICU treatments in metformin users and non-users (overall and after propensity score matching).

	All type 2 diabetic ICU patients (n=6,170)				**Propensity score matched patients**	
	Metformin monotherapy users n=827(%)	*Metformin combination therapy users n=1,101(%)*	All Metformin users n=1,928 (%)	Non-users n=4,242 n (%)	Metformin users (n=1,765) n (%)	Non-users (n=1,765) N (%)
Diagnostic category						
Pneumonia	20 (2.4)	36 (3.3)	56 (2.9)	172 (4.1)	54 (3.1)	55 (3.1)
Septicemia	27 (3.3)	25 (2.3)	52 (2.7)	144 (3.4)	50 (2.8)	48 (2.7)
Other infectious diseases	36 (4.4)	57 (5.2)	93 (4.8)	271 (6.4)	91 (5.2)	86 (4.9)
Diabetes	6 (0.7)	24 (2.2)	30 (1.6)	149 (3.5)	30 (1.7)	42 (2.4)
Endocrinology excl. diabetes	12 (1.5)	27 (2.5)	39 (2.0)	73 (1.7)	34 (1.9)	31 (1.8)
Cardiovascular diseases	292 (35.3)	411 (37.3)	703 (36.5)	1,205 (28.4)	623 (35.3)	616 (34.9)
Respiratory diseases	63 (7.6)	94 (8.5)	157 (8.1)	289 (6.8)	130 (7.4)	130 (7.4)
Gastrointestinal and liver diseases	91 (11.0)	101 (9.2)	192 (10.0)	524 (12.4)	187 (10.6)	177 (10.0)
Cancer and other neoplasm	102 (12.3)	112 (10.2)	214 (11.1)	494 (11.7)	206 (11.7)	229 (13.0)
Trauma and poisoning	81 (9.8)	94 (8.5)	175 (9.1)	342 (8.1)	155 (8.8)	148 (8.4)
Other	97 (11.7)	120 (10.9)	217 (11.3)	579 (13.7)	205 (11.6)	203 (11.5)
Surgical ICU admission	531 (64.2)	685 (62.2)	1,216 (63.1)	2,480 (58.5)	1,112 (63.0)	1,103 (62.5)
Organ dysfunction on day of ICU admission*						
SOFA − Renal score ≥ 1 (Creatinine ≥ 110 µmol/L)	151 (18.3)	236 (21.4)	387 (20.1)	1,258 (29.7)	374 (21.2)	377 (21.4)
SOFA − Liver ≥ 1 (Bilirubin ≥ 20 µmol/L)	36 (4.4)	56 (5.1)	92 (4.8)	355 (8.4)	88 (5.0)	87 (4.9)
SOFA − Coagulation ≥ 1 (Platelet count < 150 x10^9/L)	113 (13.7)	167 (15.2)	280 (14.5)	772 (18.2)	271 (15.4)	260 (14.7)
ICU treatments						
Mechanical ventilation	394 (47.6)	539 (49.0)	933 (48.4)	1,664 (39.2)	837 (47.4)	764 (43.3)
Renal replacement therapy	56 (6.8)	67 (6.1)	123 (6.4)	279 (6.6)	112 (6.4)	86 (4.9)
Treatment with inotropes/vasopressors	280 (33.9)	369 (33.5)	649 (33.7)	1,304 (30.7)	605 (34.3)	524 (29.7)

*Subsample of 4,156 (67.4%) with laboratory database coverage.

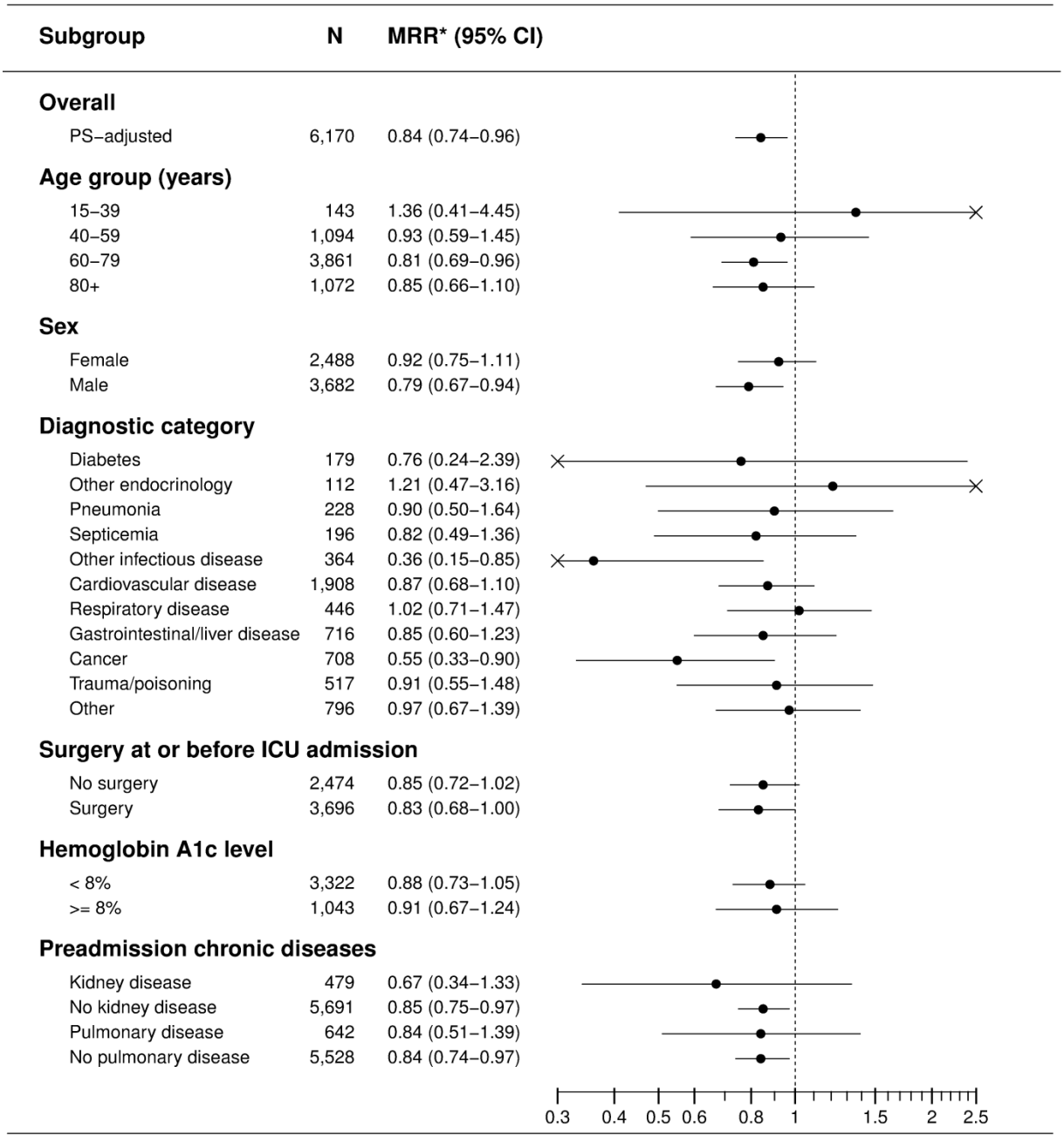
SOFA = the Sequential Organ Failure Assessment score

Table 2. 30-day mortality and mortality rate ratios (MRRs) for metformin users and non-users among type 2 diabetics admitted to intensive care units in Northern Denmark.

	n	30-day mortality, % (95% CI)	Crude MRR (95%CI)	Adjusted* MRR (95%CI)	Propensity score adjusted MRR (95%CI)
Overall analysis					
Metformin users	**1,928**	**17.5 (15.9−19.3)**	**0.67 (0.59−0.76)**	**0.81 (0.71−0.92)**	**0.84 (0.74−0.96)**
Metformin monotherapy	827	16.9 (14.5−19.6)	0.64 (0.54−0.77)	0.79 (0.66−0.95)	0.80 (0.67−0.96)
Metformin combination therapy	1,101	18.0 (15.8−20.4)	0.69 (0.59−0.80)	0.83 (0.71−0.97)	0.88 (0.75−1.03)
Metformin non-user	**4,242**	**25.0 (23.7−26.3)**	**1.00 (ref.)**	**1.00 (ref.)**	**1.00 (ref.)**
- *Sulfonylurea monotherapy*	799	25.4 (22.6−28.6)	−	−	−
- *Insulin monotherapy*	1,160	26.1 (23.6−28.7)	−	−	−
- *Other/combination*	189	23.8 (18.4−30.6)	−	−	−
- *No pharmacotherapy*	2,094	24.3 (22.5−26.2)	−	−	−
Subsample with laboratory data (n=4,156)					
Metformin users	1,325	14.8 (12.9−16.9)	0.62 (0.52−0.73)	0.79 (0.66−0.93)	0.85 (0.71−1.01)
Metformin users, adjusted for admission organ dysfunction	1,325	14.8 (12.9−16.9)	0.62 (0.52−0.73)	0.79 (0.67−0.94)	−
Metformin non-users	2,831	22.8 (21.5−24.4)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Propensity score matched cohorts					
Metformin users	1,765	18.0 (16.3−19.8)	0.85 (0.73−1.00)	0.82 (0.68−0.99)	0.86 (0.72−1.02)
Metformin non-user	1,765	20.7 (18.9−19.8)	1.00 (Ref.)	1.00 (Ref.)	1.00 (ref.)
Monotherapy comparison					
Metformin monotherapy	827	16.9 (14.5−19.6)	0.63 (0.51−0.78)	0.87 (0.69−1.10)	0.77 (0.61−0.96)
Sulfonylurea monotherapy	799	25.4 (22.6−28.6)	1.00 (Ref.)	1.00 (Ref.)	1.00 (ref.)

*Adjusted for all variables in Table 1a and 1b, except organ dysfunction and ICU treatments.

Figure 1. Adjusted mortality rate ratios (MRRs) in metformin users compared with non-users stratified by subgroups of type 2 diabetes patients admitted to intensive care units in Northern Denmark.



* Adjusted for propensity score (PS)

References

1. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. *Ann.Intern.Med* 2002;137:25-33.

2. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009;32:193-203.

3. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854-865.

4. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N.Engl.J.Med.* 2008;359:1577-1589.

5. Standards of medical care in diabetes--2011. *Diabetes Care* 2011;34 Suppl 1:S11-S61.

6. Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. *Diabetes Care* 2011;34:1431-1437.

7. Seidowsky A, Nseir S, Houdret N, Fourrier F. Metformin-associated lactic acidosis: a prognostic and therapeutic study. *Crit Care Med.* 2009;37:2191-2196.

8. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane.Database.Syst.Rev.* 2010;CD002967.

9. Hundal RS, Inzucchi SE. Metformin: new understandings, new uses. *Drugs* 2003;63:1879-1894.

10. Nyenwe EA, Jerkins TW, Umpierrez GE, Kitabchi AE. Management of type 2 diabetes: evolving strategies for the treatment of patients with type 2 diabetes. *Metabolism* 2011;60:1-23.

11. Tsoyi K, Jang HJ, Nizamutdinova IT, Kim YM, Lee YS, Kim HJ, Seo HG, Lee JH, Chang KC. Metformin inhibits HMGB1 release in LPS-treated RAW 264.7 cells and increases survival rate of endotoxaemic mice. *Br.J.Pharmacol.* 2011;162:1498-1508.

12. Grant PJ. Beneficial effects of metformin on haemostasis and vascular function in man. *Diabetes Metab* 2003;29:6S44-6S52.

13. Zmijewski JW, Lorne E, Zhao X, Tsuruta Y, Sha Y, Liu G, Siegal GP, Abraham E. Mitochondrial respiratory complex I regulates neutrophil activation and severity of lung injury. *Am.J.Respir.Crit Care Med.* 2008;178:168-179.

14. Ansari G, Mojtahedzadeh M, Kajbaf F, Najafi A, Khajavi MR, Khalili H, Rouini MR, Ahmadi H, Abdollahi M. How does blood glucose control with metformin influence intensive insulin protocols? Evidence for involvement of oxidative stress and inflammatory cytokines. *Adv.Ther.* 2008;25:681-702.

15. Duncan AI, Koch CG, Xu M, Manlapaz M, Batdorf B, Pitas G, Starr N. Recent metformin ingestion does not increase in-hospital morbidity or mortality after cardiac surgery. *Anesth.Analg.* 2007;104:42-50.

16. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. *N.Engl.J.Med.* 2003;348:138-150.

17. Toft P, Tonnesen E. Immune-modulating interventions in critically ill septic patients: pharmacological options. *Expert.Rev Clin.Pharmacol.* 2011;4:491-501.

18. Mellbin LG, Malmberg K, Norhammar A, Wedel H, Ryden L. The impact of glucose lowering treatment on long-term prognosis in patients with type 2 diabetes and myocardial infarction: a report from the DIGAMI 2 trial. *Eur.Heart J.* 2008;29:166-176.

19. Horsdal HT, Johnsen SP, Sondergaard F, Rungby J. Type of preadmission glucose-lowering treatment and prognosis among patients hospitalised with myocardial infarction: a nationwide follow-up study. *Diabetologia* 2008;51:567-574.

20. Lamanna C, Monami M, Marchionni N, Mannucci E. Effect of metformin on cardiovascular events and mortality: a meta-analysis of randomized clinical trials. *Diabetes Obes.Metab* 2011;13:221-228.

21. Christiansen CF, Johansen MB, Christensen S, O'Brien JM, Tonnesen E, Sorensen HT. Type 2 diabetes, antidiabetics and mortality among intensive care patients: a Danish cohort study. Intensive Care Med 36[S2], S205. 2010. [Abstract]

22. Christiansen CF, Christensen S, Johansen MB, Larsen KM, Tonnesen E, Sorensen HT. The impact of pre-admission morbidity level on 3-year mortality after intensive care: a Danish cohort study. *Acta Anaesthesiol Scand* 2011;55:962-970.

23. Ehrenstein V, Antonsen S, Pedersen L. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. *Clin.Epidemiol.* 2010;2:273-279.

24. Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan.Med.Bull.* 1999;46:263-268.

25. Grann AF, Erichsen R, Nielsen AG, Froslev T, Thomsen RW. Existing data sources for clinical epidemiology: The clinical laboratory information system (LABKA) research database at Aarhus University, Denmark. *Clin.Epidemiol.* 2011;3:133-138.

26. Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan.Med.Bull.* 2006;53:441-449.

27. Frank L. Epidemiology. When an entire country is a cohort. *Science* 2000;287:2398-2399.

28. Kornum JB, Thomsen RW, Riis A, Lervang HH, Schonheyder HC, Sorensen HT. Type 2 diabetes and pneumonia outcomes: a population-based cohort study. *Diabetes Care* 2007;30:2251-2257.

29. Horsdal HT, Sondergaard F, Johnsen SP, Rungby J. Antidiabetic treatments and risk of hospitalisation with myocardial infarction: a nationwide case-control study. *Pharmacoepidemiol.Drug Saf* 2011;20:331-337.

30. Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA* 2001;286:1754-1758.

31. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sorensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC.Med.Res.Methodol.* 2011;11:83.

32. Christensen S, Thomsen RW, Johansen MB, Pedersen L, Jensen R, Larsen KM, Larsson A, Tonnesen E, Sorensen HT. Preadmission statin use and one-year mortality among patients in intensive care - a cohort study. *Crit Care* 2010;14:R29.

33. Christensen S, Johansen MB, Tonnesen E, Larsson A, Pedersen L, Lemeshow S, Sorensen HT. Preadmission beta-blocker use and 30-day mortality among patients in intensive care: a cohort study. *Crit Care* 2011;15:R87.

34. Winning J, Neumann J, Kohl M, Claus RA, Reinhart K, Bauer M, Losche W. Antiplatelet drugs and outcome in mixed admissions to an intensive care unit. *Crit Care Med.* 2010;38:32-37.

35. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993;270:2957-2963.

36. Greenland S. Modeling and variable selection in epidemiologic analysis. *Am.J.Public Health* 1989;79:340-349.

37. Glynn RJ, Schneeweiss S, Sturmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. *Basic Clin.Pharmacol.Toxicol.* 2006;98:253-259.

38. Sturmer T, Joshi M, Glynn RJ, Avorn J, Rothman KJ, Schneeweiss S. A review of the application of propensity score methods yielded increasing use, advantages in specific

settings, but not substantially different estimates compared with conventional multivariable methods. *J Clin.Epidemiol.* 2006;59:437-447.

39. Normand ST, Landrum MB, Guadagnoli E, Ayanian JZ, Ryan TJ, Cleary PD, McNeil BJ. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. *J Clin.Epidemiol.* 2001;54:387-398.

40. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am.J.Epidemiol.* 2003;158:915-920.

41. Venkata C, Sampathkumar P, Afessa B. Hospitalized patients with 2009 H1N1 influenza infection: the Mayo Clinic experience. *Mayo Clin.Proc.* 2010;85:798-805.

42. Calabrese AT, Coley KC, DaPos SV, Swanson D, Rao RH. Evaluation of prescribing practices: risk of lactic acidosis with metformin therapy. *Arch.Intern.Med.* 2002;162:434-437.

43. Horsdal, H. T., S. P. Ulrichsen, R. W. Thomsen, M. Norgaard, F. B. Larsen, and H. T. Sorensen. Lifestyle Profile among Users of Antidiabetic Treatments. Pharmacoepidemiology and Drug Safety 20, S292. 2011. [Abstract]

44. Oliveros H, Villamor E. Obesity and mortality in critically ill adults: a systematic review and meta-analysis. *Obesity.(Silver.Spring)* 2008;16:515-521.

45. O'Brien JM, Jr., Phillips GS, Ali NA, Lucarelli M, Marsh CB, Lemeshow S. Body mass index is independently associated with hospital mortality in mechanically ventilated adults with acute lung injury. *Crit Care Med* 2006;34:738-744.

SUPPLEMENTARY MATERIALS:

Methods in details

We conducted this cohort study among persons with type 2 diabetes who were admitted to an ICU in Northern Denmark between January 1, 2005 and December 31, 2010.[22] Data collection was based on unambiguous individual-level linkage between medical registries and databases using the unique Danish Civil Registration number (CPR-number) assigned to each Danish citizen at birth or upon immigration.[26] Denmark provides tax-financed health care, including partial reimbursement of drugs, including antidiabetic drugs, for all Danish citizens. All ICUs in Denmark are located in public hospitals. Northern Denmark has 17 ICUs, including eight units in university hospitals and nine multidisciplinary units in regional hospitals.

Intensive care patients with type 2 diabetes

We used the Danish National Registry of Patients (DNRP) to identify adult persons (aged 15+) who were admitted to an ICU during the study period (n=46,630). We required that study participants should have lived in the area for at least two years, in order to ensure a complete history of laboratory and prescription data. Virtually all admissions to Danish hospitals since 1977 and outpatient clinic visits since 1995 are registered in the DNRP.[24] Data include CPR number, dates of hospital admission and discharge, one primary diagnosis (main reason for hospitalization), up to 19 secondary diagnoses, surgical procedures, and major treatments. Diagnoses are coded according to the International Classification of Diseases, 8th edition (ICD-8) until 1993 and 10th edition (ICD-10) thereafter. Registration of intensive care therapy is considered accurate and virtually complete since 2005.[22]

We defined diabetic patients as patients with either 1) a previous hospital diagnosis of diabetes since 1977, *or* 2) any prescription for an antidiabetic drug since 1998, *or* 3) a hemoglobin A1c level elevated of 6.5% or more within the year before ICU admission. Patients were considered to have type 2 diabetes, and not type 1 diabetes, if they were diagnosed with diabetes after age 30, diagnosed under age 30 but had not filled any prescriptions for insulin within the year before admission, or if they had ever filled a prescription for an oral antidiabetic drug. Non-diabetic patients with metformin-treated polycystic ovarian syndrome were excluded (n = 15).[19]

We used the DNRP to identify all inpatient and outpatient clinic diagnosis of diabetes mellitus. (See Appendix for ICD-10 codes). Because general practitioners' diagnoses are not included in the DNRP, we also identified patients who filled any prescription for an antidiabetic drug since 1998, when the prescription database was established.[23] All filled prescriptions in Denmark are registered to ensure partial reimbursement at the time of dispensing. The prescription database covering Northern Denmark includes date of dispensing, type of drug according to the Anatomical Therapeutical Classification (ATC) system, and total amount dispensed.[23] To identify patients treated only by diet and lifestyle changes, we also obtained data on hemoglobin A1c tests. Type 2 diabetes DM was defined using the definition by the American Diabetes Association, i.e., 6.5% or more.[5] We defined severe diabetes as any hemoglobin A1c measurement at or above 8% in the year before ICU admission and by diabetes duration of more than five years from the first diagnosis or antidiabetic prescription. The laboratory database partly covers the study area and includes HbA1c measurements on 4,365 (70.7%) of the type 2 diabetes patients.[25]

Preadmission metformin use

For each intensive care patient with type 2 diabetes, we searched for any metformin prescription dispensed within 90 days prior to the current ICU admission and categorized metformin users in metformin monotherapy, and metformin combination therapy when combined with insulin or any other oral antidiabetic drug. All other ICU patients with type 2 diabetes were defined as metformin non-users. The 90-day period was chosen because prescriptions are rarely issued for more than three months.[29] This choice of exposure window was challenged by extending the exposure window from 90 to 180 and 365 days to assess sensitivity of the cut point.

Acute organ dysfunction

Because any effect of metformin may be mediated through decreased severity of organ dysfunction, we assessed acute organ dysfunction on the day of ICU admission as defined by the Sequential Organ Failure Assessment (SOFA) score´s criteria for kidney, liver, and coagulation system dysfunction.[30] We defined organ dysfunction as any organ-specific score above 0 at the day of ICU admission assessed by creatinine, bilirubin, and platelets using data on blood test results from a clinical laboratory database.[25] The database includes virtually all in- and outpatient blood tests and covers the former counties of Aarhus and North Jutland (67% of the study population). The analyses of organ dysfunction were therefore restricted to this part of the study area.

For patients without routine measurement at day of ICU admission, we computed the mean of the values the day before and the day after ICU admission.[30] Still, some patients in the area with laboratory coverage had missing data for all three days [creatinine n=200 (4.8%),

bilirubin 2,184 (52.6%), platelet count 640 (15.4%)]. Missing tests were assumed normal because they are usually performed on minor indication.[41]

We obtained data from the DNRP on any organ supportive treatment with mechanical ventilation, renal replacement therapy, and inotropes/vasopressors during the ICU admission in the entire study population.

Mortality

We followed patients using the Danish Civil Registration system (DCRS) to the date of death or emigration. DCRS data include vital status, residence, and marital status, updated daily.[26]

Covariates

We used the DCRS to obtain demographic data on age, sex, and marital status as a marker of social status. We retrieved data from the DNRP on relevant in- and outpatient hospital contacts with preadmission morbidity diagnoses within five years before the current admission.

In order to study possible differential impacts of metformin use in subgroups of ICU patients, we obtained data from the DNRP on the diagnostic category defined by primary diagnosis during the current hospitalization; used as a surrogate for ICU admission diagnosis. Surgical ICU admission was defined as any surgical procedures performed on the day of ICU admission or within seven days beforehand.[35]

Because cardiovascular drug use may affect prognosis following intensive care, we obtained information from the prescription database on concurrent prescriptions for low-dose aspirin within 90 days, beta-blockers within 120 days, and statins within 120 days before ICU admission reflecting typical prescription durations.[32-34]

Statistical analyses

We obtained contingency tables for demography, preadmission morbidity, diabetes characteristics, concurrent drug use, and primary diagnoses during the current hospitalization for metformin monotherapy users, metformin combination therapy users, all metformin users combined, and non-users. In the subgroup with laboratory data coverage, the rate of organ dysfunction was described as the percentage of patients with biochemical evidence of organ dysfunction or who received organ supportive treatment.

We followed patients from date of ICU admission until date of death, or to censoring at emigration. Thirty-day mortality among metformin users and non-users was assessed by Kaplan-Meier estimates. We used a Cox proportional hazards regression analysis to compute hazard ratios comparing mortality in metformin users with that in non-users, and adjusted for the potential confounders listed in Table 1. We stratified the analyses by covariates that were considered most important. Further adjustment for organ dysfunction was performed in the subgroup of the study area where laboratory data is available. We did not adjust for treatment during ICU admission because the effect may be mediated through these complications.[36] The hazard ratios are estimates of the mortality rate ratios (MRRs). Linearity of age and the assumption of proportional hazards was checked graphically and found appropriate.

We also did analyses with propensity score adjustment and matching, because these may be more robust as we have few outcomes per covariate.[37;38] The propensity score is the probability of being metformin user. We computed the propensity score in a multivariate logistic regression model including all variables in table 1a and 1b (except ICU treatment data), i.e., marital status, each preadmission morbidity, medical/surgical admission type, and

organ dysfunction on ICU admission. We first did the Cox regression adjusted for the propensity score. Next, we matched each metformin user with the non-user who had the closest propensity score within a range of no more than +/- 0.025. Matching was possible in 1,765 (91.5%) of metformin users. This leaved the covariates well balanced, as confirmed by an absolute standardized difference below 0.1.[39] (Table 1a and 1b) We used Cox regression with stratification to matched pairs to compute MRRs unadjusted and adjusted for the all variables included in the primary model in case of any imbalance.

We stratified the overall analyses in subgroups of ICU patients to elucidate whether patient characteristics influenced the result. We also compared metformin monotherapy with sulfonylurea monotherapy because these patients may have more similar indication for treatment.

To examine any temporary effect associated with the indication for metformin treatment rather than the pharmacological effect, we categorized metformin users as current users (0−90 days before ICU admission), recent users (91−365 days before ICU admission), former users (1−5 years before ICU admission), and never users (no prescriptions within 5 years before ICU admission). Current users were further categorized into new users (with their first prescription filled 0−90 days before current ICU admission) and long-term users (with filled prescriptions for metformin more than 91 days prior to ICU admission).[40]

All analyses were conducted using the software package Stata, version 10.1 (StataCorp, College Station, TX, USA). The study was approved by the Danish Data Protection Agency. Informed consent was not required.

Appendix

Preadmission morbidity. Diagnosis codes according to the International Classification of Diseases, 8th (ICD-8) and 10th revision (ICD-10).

	ICD-8	ICD-10
Diabetes	249, 250	E10−E14, O24 (except O24.4), G63.2, H36.0, N08.3
Myocardial infarction	*	I21, I22, I23
Congestive heart failure	*	I50, I11.0, I13.0, I13.2
Kidney disease (Moderate to severe renal disease)	*	I12, I13, N00−N05, N07, N11, N14, N18−N19, Q61
Dementia	*	F00−F03, F05.1, G30
Chronic pulmonary diseases	*	J40−J47, J60−J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3
Connective tissue disease	*	M05, M06, M08, M09,M30,M31, M32, M33, M34, M35, M36, D86
Liver disease	*	B18, K70.0−K70.3, K70.9, K71, K73, K74, K76.0 B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85
Cancer (solid tumor, leukemia, lymphoma)	*	C00−C75 (without C44) C91−C95 C81−C85, C88, C90, C96
Metastatic cancer	*	C76−C80
Obesity	*	E66
Alcoholism	*	F10 (except F10.0), G31.2, G62.1, G72.1, I 42.6, K29.2, K86.0, Z72.1 (Or prescription for disulfiram. See drug code below)
Polycystic ovarian syndrome	*	E28.2
Diabetic retinopathy	*	H36.0, E10.3, E11.3, E12.3, E13.3, E14.3
Diabetic nephropathy	*	N08.3, E10.2, E11.2, E12.2, E13.2, E14.2

*Not applicable because only morbidity within five years before admission was included. (Covered by ICD-10)

Primary diagnosis during current hospitalization (diagnostic category), according to the International Classification of Diseases, 10th edition.

	ICD-10
Pneumonia	J12−J18, A48.1, A70.9
Septicemia	A39.2, A40, A41, A42.7, B37.7
Infectious diseases excluding pneumonia	A00−B99 (without A48.1, A70.9), G00−G07, I00−I02, I30.1, I32.0, I33, I38, I40.0, J00−J06, J36, J39.0, J10−J11, J20−J22, J85.1, J86, K35, K37, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.9, K67, K75.0, K75.1, K80.0, K80.3, K80.4, K81.0, K81.9, K83.0, L00−L03, L05−L08, M00, M01, M86, N10, N12, N15.1, N30, N39.0, N41, N45, N70−N77
Diabetes	E10−E14, O24 (except O24.4), G63.2, H36.0, N08.3
Endocrinology excluding diabetes	E00−E90 (without E10−E14)
Cardiovascular diseases	I00−I99 without I00−I02, I30.1, I32.0, I33, I38, I40.0
Respiratory diseases	J00−J99 without J00−J06, J36, J39.0, J10−J11, J12−J18, J20−J22, J85.1, J86
Gastrointestinal and liver disease	K00−K99 without K35, K37, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.9, K67, K75.0, K75.1, K80.0, K80.3, K80.4, K81.0, K81.9, K83.0
Cancer	C00−D89
Trauma and poisoning	S00−T98
Other	all codes not included in other categories
Lactic acidosis	E87.2A
Surgical procedures	
Surgery	All surgical codes (K-codes) in the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures.

Drug codes according to Anatomical Therapeutic Classification (ATC).

Drug name (generic)	**ATC code**
All antidiabetic drugs	A10A, A10B
- Insulin	A10A
- Metformin	A10BA02
- Sulfonylureas	A10BB, A10BC
- Other antidiabetic drugs	A10B without A10BA02, A10BB, A10BC
Low-dose aspirin	B01AC06
Beta-blockers	C07
Statins	C10AA
Disulfiram	N07BB01

Blood test codes (Nomenclature for Properties and Units (NPU)-CODES and local analysis codes):

Blood test	**NPU/analysis code**
HbA1c	NPU03835, DNK35249, AAB00091, AAA00740, AAB00061, NPU02307, NPU27300, AAB00092
Creatinine, highest	NPU18016, NPU01807
Platelets, lowest	NPU03568
Bilirubin, highest	NPU 01370

ICU treatment codes:

Treatment	**Danish treatment code**
Mechanical ventilation (respirator)	BGDA0
Acute dialysis	BJFD0
Treatment with inotropes or vasopressors	BFHC92A, BFHC92B, BFHC92C, BFHC92D, BFHC92E, BFHC93A, BFHC93B, BFHC93C, BFHC95

Reports/PhD theses from Department of Clinical Epidemiology

1. Ane Marie Thulstrup: Mortality, infections and operative risk in patients with liver cirrhosis in Denmark. Clinical epidemiological studies. *2000*.

2. Nana Thrane: Prescription of systemic antibiotics for Danish children. *2000*.

3. Charlotte Søndergaard. Follow-up studies of prenatal, perinatal and postnatal risk factors in infantile colic. *2001*.

4. Charlotte Olesen: Use of the North Jutland Prescription Database in epidemiological studies of drug use and drug safety during pregnancy. *2001*.

5. Yuan Wei: The impact of fetal growth on the subsequent risk of infectious disease and asthma in childhood. *2001*.

6. Gitte Pedersen. Bacteremia: treatment and prognosis. *2001*.

7. Henrik Gregersen: The prognosis of Danish patients with monoclonal gammopathy of undertermined significance: register-based studies. *2002*.

8. Bente Nørgård: Colitis ulcerosa, coeliaki og graviditet; en oversigt med speciel reference til forløb og sikkerhed af medicinsk behandling. *2002*.

9. Søren Paaske Johnsen: Risk factors for stroke with special reference to diet, Chlamydia pneumoniae, infection, and use of non-steroidal anti-inflammatory drugs. *2002*.

10. Elise Snitker Jensen: Seasonal variation of meningococcal disease and factors associated with its outcome. *2003*.

11. Andrea Floyd: Drug-associated acute pancreatitis. Clinical epidemiological studies of selected drugs. *2004*.

12. Pia Wogelius: Aspects of dental health in children with asthma. Epidemiological studies of dental anxiety and caries among children in North Jutland County, Denmark. *2004*.

13. Kort-og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Nordjyllands, Viborg og Århus amter 1985-2003. *2004*.

14. Reimar W. Thomsen: Diabetes mellitus and community-acquired bacteremia: risk and prognosis. *2004*.

15. Kronisk obstruktiv lungesygdom i Nordjyllands, Viborg og Århus amter 1994-2004. Forekomst og prognose. Et pilotprojekt. *2005*.

16. Lungebetændelse i Nordjyllands, Viborg og Århus amter 1994-2004. Forekomst og prognose. Et pilotprojekt. *2005*.

17. Kort- og langtidsoverlevelse efter indlæggelse for nyre-, bugspytkirtel- og leverkræft i Nordjyllands, Viborg, Ringkøbing og Århus amter 1985-2004. *2005*.

18. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Nordjyllands, Viborg, Ringkøbing og Århus amter 1995-2005. *2005*.

19. Mette Nørgaard: Haematological malignancies: Risk and prognosis. *2006*.

20. Alma Becic Pedersen: Studies based on the Danish Hip Arthroplastry Registry. *2006*.

    Særtryk: Klinisk Epidemiologisk Afdeling - De første 5 år. *2006*.

21. Blindtarmsbetændelse i Vejle, Ringkjøbing, Viborg, Nordjyllands og Århus Amter. *2006*.

22. Andre sygdommes betydning for overlevelse efter indlæggelse for seks kræftsygdomme i Nordjyllands, Viborg, Ringkjøbing og Århus amter 1995-2005. *2006*.

23. Ambulante besøg og indlæggelser for udvalgte kroniske sygdomme på somatiske hospitaler i Århus, Ringkjøbing, Viborg, og Nordjyllands amter. *2006*.

24. Ellen M Mikkelsen: Impact of genetic counseling for hereditary breast and ovarian cancer disposition on psychosocial outcomes and risk perception: A population-based follow-up study. *2006*.

25. Forbruget af lægemidler mod kroniske sygdomme i Århus, Viborg og Nordjyllands amter 2004-2005. *2006*.

26. Tilbagelægning af kolostomi og ileostomi i Vejle, Ringkjøbing, Viborg, Nordjyllands og Århus Amter. *2006*.

27. Rune Erichsen: Time trend in incidence and prognosis of primary liver cancer and liver cancer of unknown origin in a Danish region, 1985-2004. *2007*.

28. Vivian Langagergaard: Birth outcome in Danish women with breast cancer, cutaneous malignant melanoma, and Hodgkin's disease. *2007*.

29. Cynthia de Luise: The relationship between chronic obstructive pulmonary disease, comorbidity and mortality following hip fracture. *2007*.

30. Kirstine Kobberøe Søgaard: Risk of venous thromboembolism in patients with liver disease: A nationwide population-based case-control study. *2007*.

31. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Region Midtjylland og Region Nordjylland 1995-2006. *2007*.

32. Mette Skytte Tetsche: Prognosis for ovarian cancer in Denmark 1980-2005: Studies of use of hospital discharge data to monitor and study prognosis and impact of comorbidity and venous thromboembolism on survival. *2007*.

33. Estrid Muff Munk: Clinical epidemiological studies in patients with unexplained chest and/or epigastric pain. *2007*.

34. Sygehuskontakter og lægemiddelforbrug for udvalgte kroniske sygdomme i Region Nordjylland. *2007*.

35. Vera Ehrenstein: Association of Apgar score and postterm delivery with neurologic morbidity: Cohort studies using data from Danish population registries. *2007*.

36. Annette Østergaard Jensen: Chronic diseases and non-melanoma skin cancer. The impact on risk and prognosis. *2008*.

37. Use of medical databases in clinical epidemiology. *2008*.

38. Majken Karoline Jensen: Genetic variation related to high-density lipoprotein metabolism and risk of coronary heart disease. *2008*.

39. Blodprop i hjertet - forekomst og prognose. En undersøgelse af førstegangsindlæggelser i Region Nordjylland og Region Midtjylland. *2008*.

40. Asbestose og kræft i lungehinderne. Danmark 1977-2005. *2008*.

41. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Region Midtjylland og Region Nordjylland 1996-2007. *2008*.

42. Akutte indlæggelsesforløb og skadestuebesøg på hospiter i Region Midtjylland og Region Nordjylland 2003-2007. Et pilotprojekt. *Ikke publiceret*.

43. Peter Jepsen: Prognosis for Danish patients with liver cirrhosis. *2009*.

44. Lars Pedersen: Use of Danish health registries to study drug-induced birth defects – A review with special reference to methodological issues and maternal use of non-steroidal anti-inflammatory drugs and Loratadine. *2009*.

45. Steffen Christensen: Prognosis of Danish patients in intensive care. Clinical epidemiological studies on the impact of preadmission cardiovascular drug use on mortality. *2009*.

46. Morten Schmidt: Use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs and risk of cardiovascular events and death after intracoronary stenting. *2009*.

47. Jette Bromman Kornum: Obesity, diabetes and hospitalization with pneumonia. *2009*.

48. Theis Thilemann: Medication use and risk of revision after primary total hip arthroplasty. *2009*.

49. Operativ fjernelse af galdeblæren. Region Midtjylland & Region Nordjylland. 1998-2008. *2009*.

50. Mette Søgaard: Diagnosis and prognosis of patients with community-acquired bacteremia. *2009*.

51. Marianne Tang Severinsen. Risk factors for venous thromboembolism: Smoking, anthropometry and genetic susceptibility. *2010*.

52. Henriette Thisted: Antidiabetic Treatments and ischemic cardiovascular disease in Denmark: Risk and outcome. *2010*.

53. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme. Region Midtjylland og Region Nordjylland 1997-2008. *2010*.

54. Prognosen efter akut indlæggelse på Medicinsk Visitationsafsnit på Nørrebrogade, Århus Sygehus. *2010*.

55. Kaare Haurvig Palnum: Implementation of clinical guidelines regarding acute treatment and secondary medical prophylaxis among patients with acute stroke in Denmark. *2010*.

56. Thomas Patrick Ahern: Estimating the impact of molecular profiles and prescription drugs on breast cancer outcomes. *2010*.

57. Annette Ingeman: Medical complications in patients with stroke: Data validity, processes of care, and clinical outcome. *2010*.

58. Knoglemetastaser og skeletrelaterede hændelser blandt patienter med prostatakræft i Danmark. Forekomst og prognose 1999-2007. *2010*.

59. Morten Olsen: Prognosis for Danish patients with congenital heart defects - Mortality, psychiatric morbidity, and educational achievement. *2010*.

60. Knoglemetastaser og skeletrelaterede hændelser blandt kvinder med brystkræft i Danmark. Forekomst og prognose 1999-2007. *2010*.

61. Kort- og langtidsoverlevelse efter hospitalsbehandlet kræft. Region Midtjylland og Region Nordjylland 1998-2009. *2010*.

62. Anna Lei Lamberg: The use of new and existing data sources in non-melanoma skin cancer research. *2011*.

63. Sigrún Alba Jóhannesdóttir: Mortality in cancer patients following a history of squamous cell skin cancer – A nationwide population-based cohort study. *2011*.

64. Martin Majlund Mikkelsen: Risk prediction and prognosis following cardiac surgery: the EuroSCORE and new potential prognostic factors. *2011*.

65. Gitte Vrelits Sørensen: Use of glucocorticoids and risk of breast cancer: a Danish population-based case-control study. *2011*.

66. Anne-Mette Bay Bjørn: Use of corticosteroids in pregnancy. With special focus on the relation to congenital malformations in offspring and miscarriage. *2012*.

67. Marie Louise Overgaard Svendsen: Early stroke care: studies on structure, process, and outcome. *2012*.